

FORM 7-A
THE PATENTS ACT, 1970
(39 OF 1970)
AND
THE PATENTS RULE, 2003
REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT
[Section 25(1); Rule 55]

We, CANCER PATIENTS AID ASSOCIATION (CPAA), a registered NGO, having its Registered Office at 5, Malhotra House, Opposite GPO, Mumbai – 400 001 hereby give representation by way of opposition to the grant of patent in respect of amended 42 claims of National Phase Patent Application No. 2007/DELNP/2007 having filing date of March 15, 2007 by Genentech Inc. and Curis, Inc.



On the grounds

Section 25(1)(b) - Prior publication

Section 25(1)(c) – Prior claiming

Section 25(1)(d) - Prior public knowledge or public use in India

Section 25(1)(e) – Obviousness and lack of inventive step

Section 25(1)(f) - Not an invention or the invention not patentable

Section 25(1)(g) – Does not sufficiently and clearly describe the invention

Detailed grounds of opposition and evidence in the form of Exhibits (Exhibits A to H) thereof are attached herewith.

Our address for services in India is Gopakumar Nair Associates, 3rd Floor, 'Shivmangal', Next to Big Bazaar, Akurli Road, Kandivli (East), Mumbai - 400 101, Maharashtra, India.
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Dated this 30th day of June, 2017

Dr. GOPAKUMAR G. NAIR

Regn. No: IN/PA 509

Agent for the Opponent

GOPAKUMAR NAIR ASSOCIATES

To,
The Controller of Patents,
The Patents Office, Delhi

IPO DELHI 04-07-2017 15:18

BEFORE THE CONTROLLER OF PATENTS AT DELHI

IN THE MATTER of Sec. 25(1)
of The Patents Act; 1970,
as amended up to
The Patents (Amendment) Act, 2005

And

IN THE MATTER of Rule 55
of The Patents Rules, 2003,
as amended upto
the Patents (Amendment) Rules, 2016

And

IN THE MATTER OF
National Phase Patent
Application No. 2007/DELNP/2007
filed by Genentech Inc. and Curis Inc.
on March 15, 2007 claiming
priority from September 02, 2004

..... APPLICANT

And

IN THE MATTER OF:
Pre-grant representation by way of opposition
Filed by the CANCER PATIENTS AID ASSOCIATION
A registered NGO, having its registered office at
5, Malhotra House, Opposite GPO, Mumbai – 400 001

..... OPPONENT

STATEMENT OF FACTS/ EVIDENCE

1. It is respectfully submitted on behalf of Cancer Patients Aid Association (CPAA), a charitable non-governmental organization registered under the Societies Registration Act, 1860 in January 1970 and under the Bombay Public Trusts Act, 1940 in February its main 1970, having registered office at 5, Malhotra House, Opposite GPO, Mumbai – 400 001 (hereinafter referred to as “Opponent”) that a representation by way of opposition is being made against the grant of patent application titled: “*PYRIDYL INHIBITORS OF HEDGEHOG SIGNALLING*”, filed by the Applicant Genentech Inc. and Curis Inc., having their office I DNA way, South San Franscico, California 94080-4990, USA, and 61 Moulton Street, Cambridge, MA 02138, USA, bearing Indian Patent Application No. 2007/DELNP/2007.

It is submitted by the Opponent as follows:

LOCUS STANDI

2. That Representation by way of Opposition can be made by any person, in writing under Sec. 25(1) of The Patents Act, 1970. Notwithstanding, the Opponent submits that they are interested (under Sec.2(1)(t)) in the field of the present invention and have *locus standi* to initiate the present Pre-grant Opposition proceedings. The Opponent has real and substantial interest in the aforesaid patent application being opposed.
3. The Opponent had filed a pre-grant opposition to the present application on January 3, 2017. However, the Applicant made an application to amend the claims on January 12, 2017, pursuant to which the claims were amended.

The Opponent is therefore, filing this Pre-Grant Opposition against the amended claims of Applicant.

JURISDICTION

4. The patent application has been filed by Genentech Inc. and Curis Inc. at the Patent Office in Delhi, therefore, the Patent Controller has the jurisdiction to hear this Pre-grant Opposition in Delhi. The Pre-grant Opposition is being filed on Form-7A under Section 25 (1) Of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005 and Rule 55 (1) of the Patents Rules, 2003 as amended by the Patents (Amendment) Rules, 2016. Any submission made or evidence adduced with specific reference to any subsection of Section 25(1) may be treated as being made without prejudice to other submissions made elsewhere in this Representation by way of Opposition.
5. The Opponent submits that the grant of the impugned patent application reciting amended Claims 1 to 42 is being opposed by availing strong and valid grounds provided under Section 25(1) of the Patent Act 1970 (amended up to date by the Patents (Amendment) Act, 2005), hereinafter referred to as "the Act" and are consequently filing the present representation/ Pre-grant Opposition to the impugned patent application.

BACKGROUND

6. The impugned patent application is for pyridine derivatives as inhibitors of hedgehog signalling. However, both pyridine derivatives and hedgehog signalling have been known for decades. There is no inventive step, and

the compounds for which the patent is claimed do not constitute an invention and hence not patentable.

Use of Pyridine derivatives

7. Pyridine base was first isolated in 1846 by Anderson, the structure was determined by William Korner in 1869 and James Dewar in 1871, independently. It was found that pyridine has been derived from benzene and its structure might be obtained by replacing a CH moiety with a nitrogen atom. In 1876, William Ramsay synthesized pyridine compound by combining acetylene and hydrogen cyanide.
8. Thereafter since 1930 pyridine has been an interesting compound for treatment of various ailments. Nitrogen containing six membered aromatic pyridine and its derivatives abundantly exist in nature and have played a vital role in the field of heterocyclic chemistry. Such compounds are widely used for medicinal science. There is no novelty, as pyridine and its derivatives are known for use in medicine, including as anti-cancer agents.
9. Compounds of pyrazoline, pyridine and pyrimidine were found to have excellent activity against tumour cells. Many ligands derived from pyridine when coupled with metals, acetyl, etc. have exhibited high cytotoxicity proved to be effective as an anti-cancer agent.

Hedgehog signalling and cancer

10. The Hedgehog (Hh) gene was initially discovered by Christiane Nusslein – Volhard and Eric F. Weischaus in 1980 in their screen for mutations that disrupt the *Drosophila* larval body plan.

11. The Hh proteins have since been recognized as key mediators of fundamental processes in vertebrate embryonic development playing a crucial role in controlling cell fate, patterning, proliferation, survival and differentiation of many regions [Ingham and McMahon, 2001].
12. The Hedgehog (Hh) signalling pathway is an important signalling pathway, playing critical role in regulation of cell growth, embryonic development, tissue patterning and angiogenesis process. The Hedgehog (Hh) proteins comprise a group of secreted proteins that regulate cell growth, differentiation and survival. They are involved in organogenesis, and have been shown to promote adult stem cell proliferation. The Hh signalling pathway has been recognised as an important therapeutic target in cancer, as it has been seen that in adults, mutation and deregulation of this pathway plays a key role in proliferation and differentiation leading to tumourigenesis or tumour growth acceleration in a wide variety of tissues [Dahmane et al 1997; Taylor et al 2002].
13. Usually, Hh signalling pathway is inactive in adults. Inappropriate activation of the Hh signalling pathway has been implicated in the development of several types of cancers. Aberrant activation of Hh pathway has been implicated in a variety of human tumor types such as basal cell carcinoma (BCC), medulloblastoma (MB), rhabdomyosarcoma (RMS), leukemia, lymphoma, pancreatic, hepatocellular, gastric, esophageal, lung, colorectal, prostate, ovarian, melanoma and glioblastoma. Scientific evidence shows that mutations in the Hh signalling components are the essential reason for the development of BCC and MB, while cancers such as pancreatic, hepatocellular, gastric, esophageal, lung,

colorectal, prostate, ovarian, melanoma, glioblastoma, leukemia and lymphoma have been linked to hyperactive Hh signalling. Therefore, Hh signalling pathway has been regarded as an attractive target and Hh inhibitors for treatment of cancers.

14. The active chemical identified in the corn lily, cyclopamine, was shown to inhibit the Hh pathway by binding to and inactivating the Smoothed (SMO) transmembrane receptor protein [Cooper et al 1998; Chen et al 2002]. Since then more potent derivatives have been synthesised.
15. The teratogenic effects of jervine and cyclopamine are due to their specific inhibitions of vertebrate cellular responses to the Hedgehog (Hh) of secreted growth factors [Cooper et al 1998; Incardona et al, 1998], as first suggested by similarities between the *Vertarum* induced development malformations and holoprosencephaly like abnormalities associated with loss of *Sonic hedgehog* (*Shh*) function [Chiang et al 1996; Rossler et al, 1996].
16. Plants of the genus *Veratrum* have been used as folk remedies for generations [Namba 1993; Levetin and McMahon 1996]. The jervine family of alkaloids constitutes a majority of the *Veratrum* secondary metabolites [Fried and Klingsberg 1953] used for the treatment of hypertension and cardiac disease. *Veratrum Californicum* was linked to congenital deformities in sheep during the 1950s [Binns et al, 1962], that raised the possibility that jerkin alkaloids are also potent teratogens. Research in the U.S. Department of Agriculture showed that jervine and

cyclopamine (11-deoxojervine) given during gestation can induce deformities [Keeler and Binns, 1965].

17. Sporadic Basal Cell Carcinoma (BCC) is the most common type of malignant cancer. Familial BCC and a fraction of sporadic BCCs have lost their function of Patched (Ptc) function, a Sonic Hedgehog (Shh) receptor, that acts negatively on the signalling pathway. Over expression of Shh can induce BCCs in mice [23 October 1997, Nature Vol.389]. Abnormal activation of Hh is known to push BCC, and therefore inhibitors of Hh pathway are important to stem the disease.
18. The major carcinogenic factor for BCC is exposure to sunlight and causes tumours on the face, head, neck, etc. The ligand dependant hedgehog pathway such as Ptc and SMO lead to constitutive activation of the Hh pathway independently of Hh ligand. The Hh pathway is an important regulator of embryogenesis that has also been implicated in tumour development. As all Hh signalling through the canonical pathway required Smoothed (SMO), small molecules such as GDC-0449 (Vismodegib) that inhibit SMO function, block the Hh pathway regardless of ligand. Vismodegib is a drug based on cyclopamine and pyridine derivatives that has been known and has been claimed prior to the priority date of the Applicant herein.
19. What is claimed in the present patent application, is known, obvious to a person skilled in the art, lacks novelty and inventive step.

PATENT APPLICANT'S MAIN CONTENTION

20. The Patent Applicant, Genentech Inc. and Curis Inc. filed the patent application on March 15, 2007. The application claims priority to provisional patent application 60/607, 367 and the PCT international filing date is September 2, 2005. Priority date of the application is **September 2, 2004**. Publication date is August 17, 2007. Bibliographic page alongwith **amended claims** of impugned National Phase Patent Application No. 2007/DELNP/2007 retrieved from the Indian Patent Office website is enclosed as **Annexure 1**.
21. The impugned application now recites 42 claims commencing with broad and infinite Markush claims without any claim for industrial application or indications for medicinal use even though pyridyl inhibitors of hedgehog signalling, used as a pharmaceutical medicine for the treatment of basal cell carcinoma is mentioned in the specification. The compounds claimed in the impugned patent application are **markush structures** with many possible substitutions which can lead to many possible compounds. The description consists of markush structures with as many as **320 possible compounds** with their structures as described. The applicant also claims the **salt or solvate forms** of the compounds, the pharmaceutical compositions and the process of making the compounds. The biological assay methods for hedgehog pathway signalling inhibition are described in the specification, though not claimed.
22. The Applicant is claiming the use of pyridyl inhibitors with prodrugs, with anti-cancer drugs, with radiation, UV rays. The compounds of the

impugned patent application are alleged to be used to cure all types of cancer and tumours, inflammation, depilatory therapy etc.

23. The Applicant uses Negishi coupling procedure [See Acc. Chem. Res. 1982, 15, 34-348], and Suzuki coupling procedure that have been known prior to the priority date of the Application [See J. Am. Chem. Soc. 1998, 120, 9722-9723, Old David &ors.; "Highly Active catalyst for palladium-catalyzed cross coupling reactions: room temperature Suzuki Coupling and Amination of unactivated aryl chlorides"]; and [See Akira Suzuki, "Recent advances in cross coupling reactions of organoboron derivatives with organic electrophiles, 1995-1998, Journal of organometallic chemistry 576 (1999) 147-168]. There is no inventive step. The Applicant is using iron reduction, amide bond formation, sulphonic acids, sulphonamide benzoic acid, bromine, et al. Mixing, purifying, coupling processes are used – all those have been known, contain no inventive step and are obvious to a person skilled in the art.
24. The patent applicant seeks a patent on known structures and compounds, where there is no novelty, no inventive step, and that are obvious to a person skilled in the art. The patent application should therefore be dismissed *in toto*.
25. The compounds represented by markush formula I are described in claims 1 - 8, 23, 32, 33 and claim 35.
26. The compounds represented by markush formula Ib are described in claims 9-15, 16-18, 20, 21, 22, 24-28, 29-31, 34, 36-40.

27. Compound with a definite structure is at claim 19.

28. The preparation of pharmaceutical composition comprising compounds claimed in claim 1 is claimed at claim 41.

29. The process of making the compounds of formula 1b'' is claimed at claim 42.

30. The Opponent is filing this opposition as the claims of the Applicant are not a genuine therapeutic invention, lacks novelty, lacks inventive step and is obvious to a person skilled in the art. The compounds as claimed in the impugned patent application have been known earlier and claimed in other patent applications prior to the priority date of the Applicant. The patent application does not show any novel structures of compounds and does not use any inventive step. The structures claimed in the impugned patent application are obvious to a person skilled in the art. The prior art annexed to the present Pre-grant Opposition shows that the compounds were known prior to the priority date of the impugned patent application filed by the Applicant. The application is not patentable under Section 3(d) and grounds of Opposition have been laid down hereinbelow as being under sections 25(1).

31. The Opponent further states that the right to health as guaranteed under Article 21 of the Constitution of India is paramount, and medicines required for the treatment of cancer, including basal cell carcinoma, ought to be made available at affordable prices to the people in the country. Wrongfully granting a patent to the Applicant would breach the right to life

of many patients with cancer who ought to obtain medicines at affordable prices. The price of Erivedge (Vismodegib) in the USA is about \$75,000 for the treatment course. This price is way beyond the reach of people in India. This is a monopolistic price, and if the patent is wrongly granted, it would prevent competition that could have otherwise helped to bring down the prices of the drugs, allowing people to get the drugs at an affordable price.

PRE-GRANT OPPOSITION ON THE FOLLOWING GROUNDS

32. *Section 25(1): Opposition to the patent where the application has been published but not granted.* The following grounds and evidence sets out the basis of the opposition to the application. It is submitted that the impugned patent application claiming invention is not an invention within the meaning of Section 2(1)(j) of the Patents Act, as well as does not involve an inventive step as defined under section 2(1)(ja), as it is obvious to a person skilled in the art, and is not a new invention as defined under section 2(1)(l) as it has been anticipated by publication before the date of filing of the patent application with complete specification and its priority date therein.
33. In any event, no patent ought to be granted on the present application, and the Opponent is opposing all the claims for pyridyl inhibitors of hedgehog signalling. Under section 3(d) derivatives, salts, esters, etc. of known substances are not patentable under the Indian law. Pyridyl is a derivative of pyridine, whose properties and significance are known in science. For this reason alone pyridyl inhibitors of hedgehog signalling are not

patentable under the Patents Act in India, and the present patent application should be dismissed.

34. The Opponent is filing this pre-grant opposition on the grounds stated in Section 25(1) of the Patents Act. The primary grounds of opposition are under Section 25(1)(b), that the invention so far claimed has been published before the priority date of the claim; Section 25(1)(c), as the invention so claimed is prior claimed; Section 25(1)(d), as the methods of making the derivatives and coupling and linking them are all known and their properties are known; Section 25(1)(e) as the invention so claimed is obvious and clearly does not involve an inventive step; Section 25(1)(f) as the invention so claimed is not patentable in India under the Patents Act. And Section 25(1)(g) is also attracted as the claims in the patent application are all markush claims and it does not sufficiently and clearly describe the alleged invention.

35. The primary grounds of opposition under section 25(1) that the invention so far claimed has been published and claimed before the priority date of the claim in the following list of applications and documents filed herewith.

(a) Exhibit A: GB 2276163 A, filed by Glaxo Group Limited, published on September 21, 1994, bearing filing date as March 17, 1993; for "Pyridine compounds".

(b) Exhibit B: WO9502580A1, filed by BASF AG, published on January 26, 1995; priority date of July 16, 1993; for "Substituted 2 – phenyl pyridines with herbicidal action". There is a corresponding German application DE 4323916 A1, filed by BASF AG, published on January

19, 1995; date of filing shown as July 16, 1993; for “Substituted 2 – phenyl pyridines” that may be referred to if required.

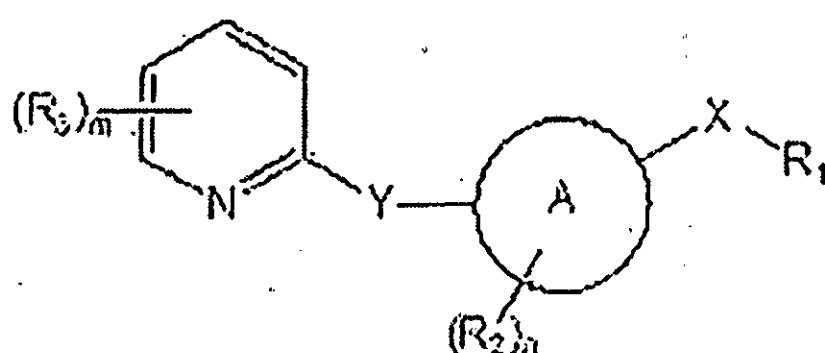
- (c) Exhibit C: US 2004/043903 A1, filed by Puhl et.al bearing priority date of November 22, 2000 published on March 2, 2004; for “2-aryl 5 – trifluoromethyl pyridines”. There is an identical application WO 2002 42275 A1, filed by BASF Aktiengesellschaft, bearing international publication date as May 30, 2002, bearing priority date of November 22, 2000; for “2-aryl 5 – trifluoromethyl pyridines” that may be referred to as and when required.
- (d) Exhibit D: WO 03/068747 A1 filed by Smithkline Beecham Corporation, published on August 21, 2003, bearing a priority date of February 12, 2002 for “Nicotinamide Derivatives useful as P38 inhibitors.”
- (e) Exhibit E: WO 03/032970 A1 filed by Glaxo Group Limited, published on April 24, 2003, bearing a priority date of October 17, 2001 for “5-carbamoyl-2 – methyl-1, 1-biphenyl-4 carboxamide derivatives and their use as P38 kinase inhibitors.”
- (f) Exhibit F: WO 2005/085227 A1 filed by Smithkline Beecham Corporation, published on September 15, 2005, bearing priority date of March 2, 2004 for “Inhibitors of AKT activity.”
- (g) Exhibit G: WO 2005/033288 A2 filed by The John Hopkins University, published on April 14, 2005, bearing priority date of September 29, 2003 for “**Hedgehog Pathway antagonists**”
- (h) Exhibit H: WO 2004/058176 A2 filed by Pharmacia Corporation, published on July 15, 2004, bearing priority date of December 20, 2002 for “Acyclic pyrazole compounds for the inhibition of mitogen activated protein kinase – activated protein kinase – 2.”

36. The Opponent states that none of the claims of the Applicant should be deemed accepted, unless the same are specifically admitted/accepted herein. The Opponent opposes all the claims of the Applicant and states that the Patent Application should be dismissed *in toto*.

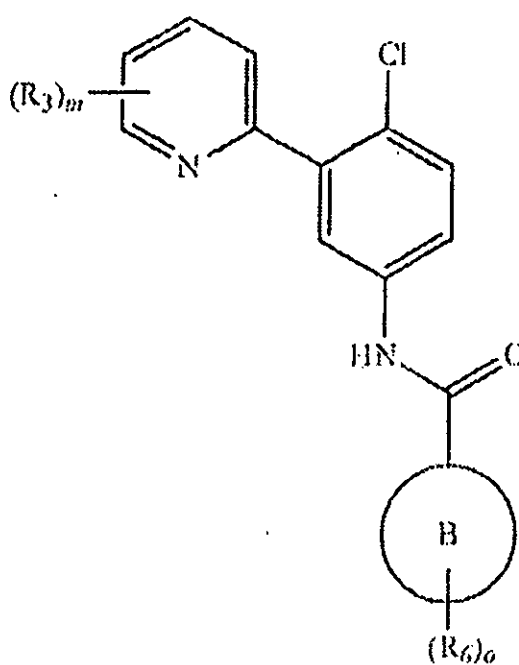
37. The grounds of opposition of claims 1 to 42 are primarily based on provisions of Section 3 and Section 25(1) of the Patents Act, 2005 as specified hereto.

38. The Opponent states that the Applicant has made claims for the following structures, which have been known for many decades prior to the priority date of the impugned patent application, and is obvious to a person skilled in the art, thus, no claim for a patent can be made by the Applicant.

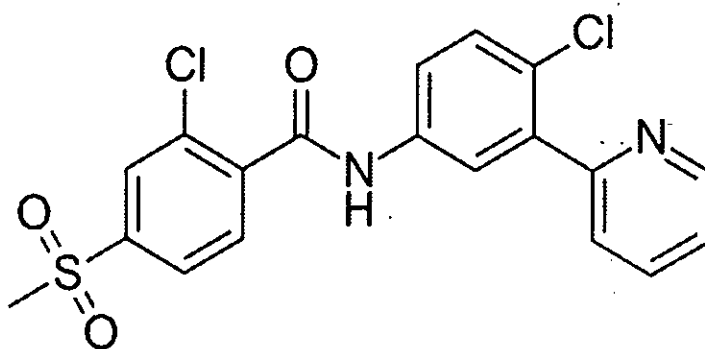
(a) The compound at claim 1 mentions the structure:



(b) The specific genus structure has been claimed at claim 20 by the Applicant as:



(c) The main structure of the compound (Vismodegib) is at claim 19:



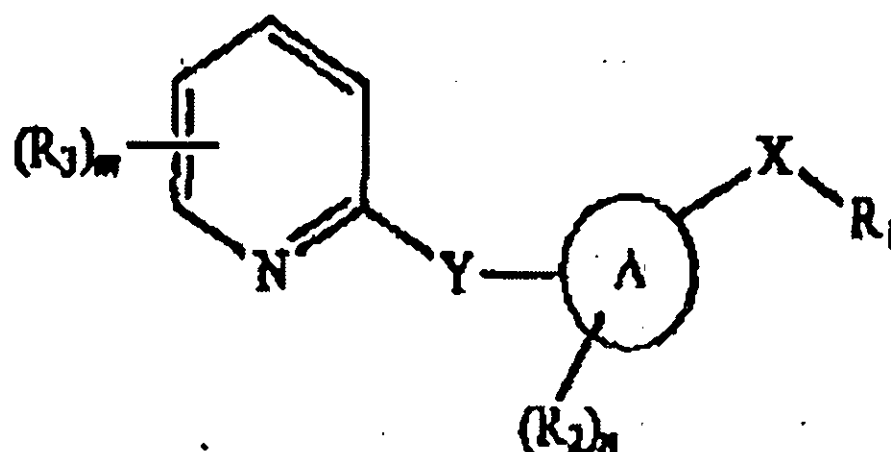
39. As it can be seen that the structure as claimed by the Applicant can be described as a **pyridine ring to which a phenyl ring is attached, specifically at the ortho position, and this ring is further substituted with an ortho halogen group and at the para position to this halo is the -NHCO- substitution attached to a phenyl ring.** The prior art documents annexed to this opposition specifically show such substitutions and disclose the similarities between the claimed structure in the present application and the prior art documents annexed to this pre-grant opposition.

GROUND OF OPPOSITION

The Opponent now deals with following relevant grounds of Pre-grant opposition under Sec. 25(1) substantiated with facts disclosed in the prior art documents.

a. Section 25(1)(b):Lack of Novelty/ Prior publication

- (i) The Opponent submits that the impugned patent application is ineligible for grant of patent under Section 25(1)(b) of the Patents Act, 1970.
- (ii) The basic scaffold / skeletal structure of the compounds claimed in the impugned patent application is as below :-



**Basic skeletal structure claimed in amended Claim 1 of
the impugned patent Application No. 2007/DELNP/2007**

Wherein

A is substituted benzene;

X is NR_4CO or $NR_4C(S)$;

Y is absent;

R₁ is aryl or heteroaryl, each of which is optionally substituted with hydroxyl, halogen, amino, carboxyl, amidino, guanidino, carbonyl, nitro, cyano, acyl, alkyl, haloalkyl, sulfonyl, sulfinyl, alkoxy, alkylthio, carbamoyl, acylamino, sulfamoyl, sulfonamide, a carbocycle or a heterocycle; wherein said amino, amidino, alkyl, acyl, sulfonyl, sulfinyl, alkoxy, alkylthio, carbamoyl, acylamino, sulfamoyl, sulphonamide, carbocycle and heterocycle substituent is optionally substituted with halogen, haloalkyl, hydroxyl, carboxyl, carbonyl, or an amino, alkyl, alkoxy, acyl, sulfonyl, sulfinyl, phosphinate, carbocycle or heterocycle that is optionally substituted with hydroxyl, carboxyl, carbonyl, amino, halogen, haloalkyl, alkyl, alkoxy, alkylthio, sulfonyl, sulfinyl, acyl, a carbocycle or a heterocycle;

R₂ is halogen or alkyl substituted with halogen and an R₂ is in the o-position on said A benzene relative to pyridyl;

R₃ is halogen, hydroxyl, carboxyl, alkyl, acyl, alkoxy, alkoxycarbonyl, carbamoyl, alkylsulfide, sulfinyl, sulfonyl, a carbocycle or a heterocycle wherein each alkyl, acyl, alkoxy, alkoxycarbonyl, carbamoyl, alkylsulfide, sulfinyl, sulfonyl, carbocycle and heterocycle is optionally substituted with hydroxyl, halogen, amino, nitro, alkyl, acyl, sulfonyl or alkoxy;

R₄ is H or alkyl;

m is 0-3;

n is 1-3;

or a salt or solvate thereof

wherein

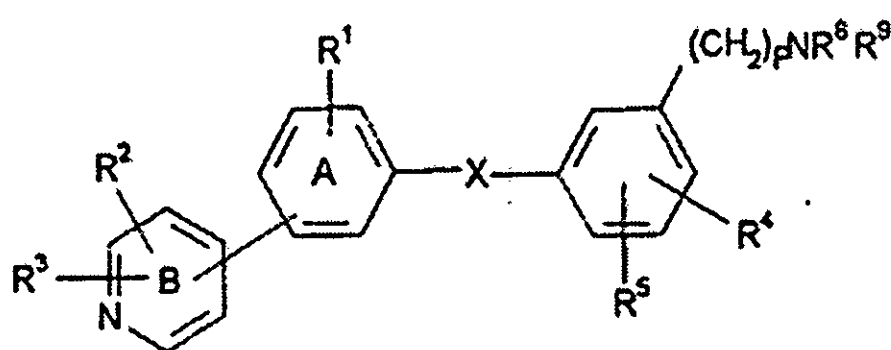
aryl, in each case, has upto 14 carbon atoms,

heteroaryl, in each case, is a mono-, bi-, or tricyclic aromatic ring system having from 5 to about 14 ring atoms where at least one ring is a 5-, 6-, or 7-membered ring containing from one to four heteroatoms selected from the group nitrogen, oxygen and sulfur,

- (iii) The impugned invention is clearly described and anticipated in the document at **Exhibit A (GB 2276163 A)** dated 1993, "Pyridine compounds" that included the pyridine ring to which a phenyl ring is attached. It further describes the substitution with a halogen group and para to this halo is a -NHCO- substitution followed by a ring, similar to what is

claimed in the impugned patent application.

- (iv) The structure claimed in the 1993 patent application at **Exhibit A** clearly describes and claims the genus structure of the present application [See pages 1-23 and 52 of **Exhibit A** hereto]:-



As per the claims in Exhibit A hereto - R¹ represents a hydrogen atom or a halogen atom or a C₁₋₆alkyl or C₁₋₆alkoxy group; the substitution has been envisaged as 2-position; and also indicates halo or alkyl substitution of this ring; thereby destroying novelty of the Applicant in the present application; X represents -CONH-, -NHCO-, -CH₂NH- or -NHCH₂. Clearly NHCO, as claimed by the Applicant in the present application has already been known and described in **Exhibit A**, in 1993, thereby demolishing claims of novelty and inventive step of the Applicant.

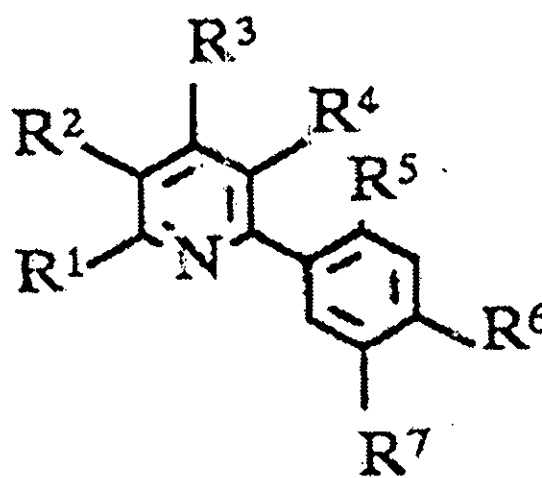
- (v) Thus, the genus/basic markush of the structure as claimed in the present application has been anticipated and described at **Exhibit A** to this pre grant opposition.
- (vi) Physiological accepted salts and solvates of the structure have also been claimed in the document at **Exhibit A**,

thereby displaying a complete lack of novelty in the present application of the Applicant, and demolishing claim 41 of pharmaceutical composition, as the same have already been disclosed at pages 7 to 9 of **Exhibit A**.

(vii) With regards to biological activity, although **Exhibit A** discusses some other therapeutic category, the claims state “Compounds as claimed in Claim 1 for use in therapy” indicating a general therapeutic application, that is not exhaustive but inclusive.

(viii) The impugned invention herein is also anticipated in the document annexed hereto as **Exhibit B**, viz. WO 95/02580 published on January 26, 1995 with a priority date of July 16, 1993 titled “Substituted 2- phenylpyridines with herbicidal action”.

(ix) **Exhibit B** discloses and claims the following structure with substitutions [See pages 1-5 and 82-86 of **Exhibit B** hereto]:



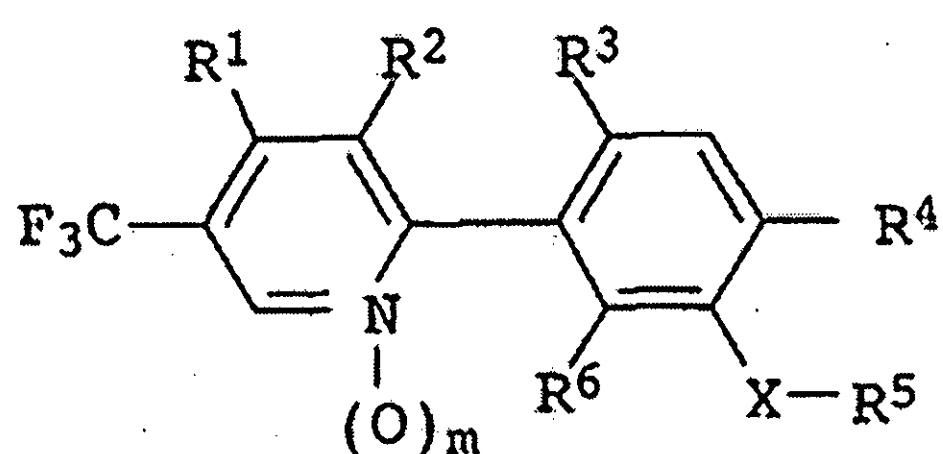
A pyridine ring is attached to a phenyl ring; the point of attachment of the phenyl ring is specifically 2-position of the pyridine ring. This is the same as the genus claimed by the

Applicant herein in the present application. Further, the phenyl ring, at **Exhibit B** hereto, has halo substitution and a -NHCO- or NHC(S) substitution which is in turn attached to a terminal phenyl ring which is claimed in amended claim 1 of the impugned patent application.

- (x) At pages 2-5 of **Exhibit B**, the same type of substitution pattern R^5 has been claimed to be hydrogen or halogen. R^7 has been claimed to be $-NR^{11}(CO-R^{12})$ (apart from many other substitutions) wherein R^{11} encompasses hydrogen and alkyl (covering hydrogen and methyl, similar to the claims of the applicant herein); R^{12} encompasses phenyl, and phenyl can be unsubstituted or carry one to three radicals selected from the group comprising halogen, nitro, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio and C_1-C_4 -haloalkyl R^7 is also claimed to be substituted as $-CS-N(R^9.R^{10})$, wherein R^9 and R^{10} , independently of one another are hydrogen, alkyl, phenyl, where the phenyl ring in each case can be unsubstituted or carry one to three radicals selected from the group comprising halogen, nitro, cyano, C_1-C_4 -alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio and C_1-C_4 -haloalkyl. The said substitutions clearly fall within those claimed in the impugned patent application. Hence all the essential groups/substituents disclosed in **Exhibit B** overlaps with the groups/substituents of the Markush structure claimed in the impugned patent application.

(xi) Thus, both **Exhibits A and B** hereto endanger the novelty of all of the Applicant's claims due to prior publication of the genus structure which is same, identical and similar to the compound claimed in the present Application, including the salt and solvate forms..

(xii) The impugned invention is clearly anticipated by the disclosure made in **Exhibit C** (US 2004 /0043903) hereto, for "2-aryl-5- trifluoromethylpyridines". The document at **Exhibit C** claims the following general structure:-



As per the claims [See **Exhibit C** at pages 50 to 52], R^1 is NH_2 or CH_3 , R^2 is Halogen and R^3 is Hydrogen or Halogen; X can be a chemical bond and R^5 encompasses $-N(Y-R^7)-CO-Z-R^8$. This is similar and identical to the structure claimed by the Applicant herein, thereby not making their alleged invention new or novel.

(xiii) The document at **Exhibit C** also demonstrates the compound consisting of a pyridine ring that is attached to a phenyl ring; the point of attachment of the phenyl ring is specifically 2-position of the pyridine ring. The phenyl ring has halo substitution and a $-NHCO-$ substitution which is

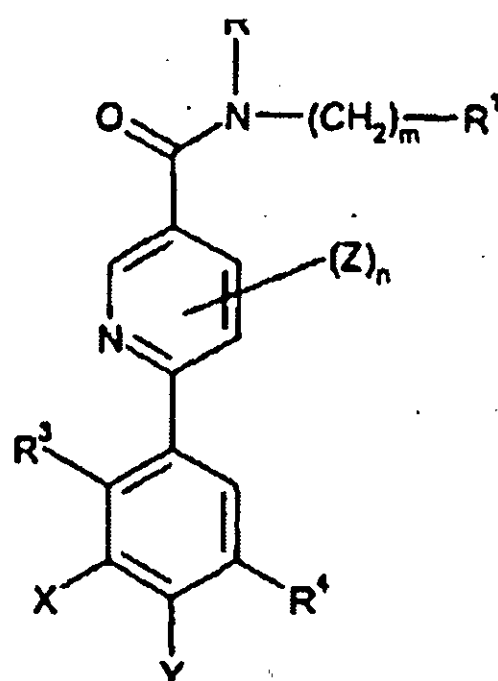
in turn attached to a terminal phenyl ring. This is the same as the genus claimed by the Applicant herein in the present application and contains the same type of substitution pattern as the Applicant herein is claiming.

(xiv) The document at **Exhibit C** also relates to the use of the compounds and the salts thereof, thereby demolishing all the claims of the Applicant herein due to lack of novelty and prior publication, invoking Section 25(1)(b) of the Patents Act.

(xv) The impugned invention is also clearly anticipated by the teachings of WO 2003/068747(**Exhibit D**). The Opponent brings forth below the detailed study of the prior art, WO 2003/068747(**Exhibit D**) vis-à-vis the impugned patent application for invoking Section 25(1)(b) of the Patents Act, 1970. The document, hereto annexed and marked as "**Exhibit D**", WO 03/068747 A1, consists of the relevant portions of the complete specification. The said prior art document filed by Smithkline Beecham Corporation was published on August 21, 2003, bearing a priority date of February 12, 2002 titled "*Nicotinamide Derivatives useful as P38 inhibitors*", i.e. pyridine derivatives, useful as p38 kinase inhibitors, and salts of compounds destroys the novelty of the impugned patent application. The said document is published before the priority date of the impugned patent application and was publicly known in

India before the priority date in India. The compounds and claims described in **Exhibit D** render the claims in the present application clearly devoid of novelty.

- (xvi) **Exhibit D** claims Nicotinamide derivatives in Claim 1 having formula :-



- (xvii) The Opponent states that the Markush structure claimed in the impugned patent application is identical to that claimed and disclosed in the prior art, WO'747. The substituents claimed in the impugned patent application wholly encompass the substituents disclosed and taught in the said prior art. A person skilled in the art would be easily motivated to arrive at the impugned invention by merely substituting the obvious and known groups taught in the prior art using routine trial and error experimentation and retaining the activity claimed in the prior art which is also the subject matter of the impugned patent application.

- (xviii) Example 1 at page 35 of **Exhibit D** discloses a formula for pyridine derivatives which falls within the Markush structure claimed in Claim 1 of the impugned patent application. The

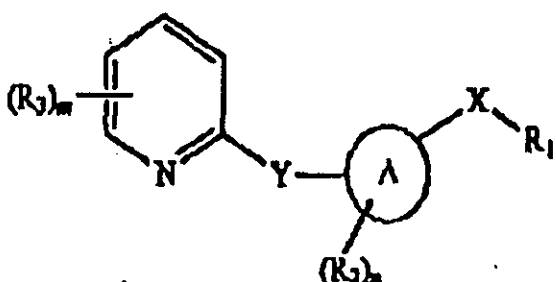
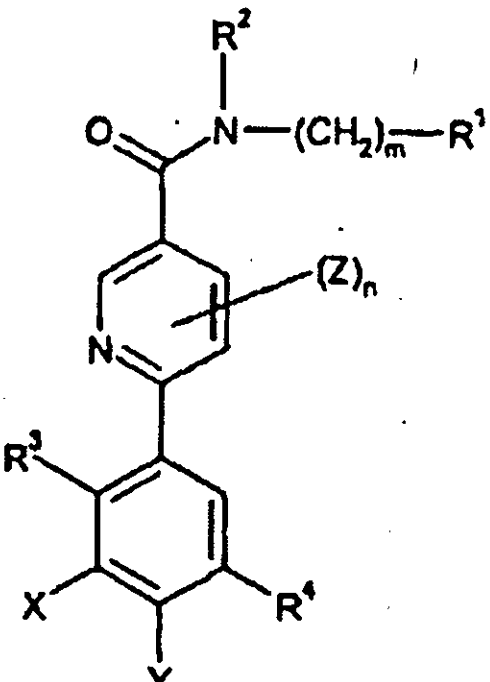
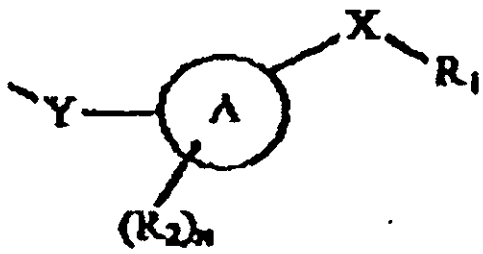
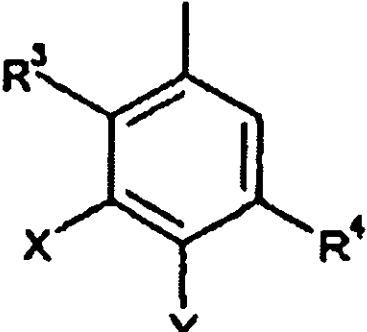
salts encompassing within the term "pharmaceutically acceptable salt" and solvates of the broadly claimed compounds are also disclosed in the prior art, WO'747. Page 10, lines 26 and 27 of WO'747 states "*The compounds can be made by standard chemistry*". **Exhibit D** discloses pyridyl, alkyl, heteroaryl, halogen, etc. at pages 1 to 9 of **Exhibit D** that have been claimed by the Applicant in the impugned patent application.

(xix) Pages 9-10 and 13 to 21 of **Exhibit D** teaches various processes for manufacturing compounds broadly claimed in the Markush structure as well as salt and solvate forms of the compound including pharmaceutically acceptable salts.

(xx) Pages 22-23 of **Exhibit D** discloses various disease conditions including cancer and its type that can be treated by claimed pyridines and its derivatives. Examples of pyridine derivatives have been disclosed in the prior art, WO'747. Pyridine derivatives disclosed at pages 35-53 and 68-70 of **Exhibit D** falls within application. The impugned patent application claims similar pyridine derivatives having substitutions of alkyl groups, halogen and hydroxy, chloro or methyl, oxygen, sulphur, etc. that have already been taught and disclosed in the prior art, WO'747.

(xxi) For better understanding of the Ld. Controller, the Opponent provides the following tabular chart which implies unequivocal lack of novelty in the compounds claimed in the

impugned patent application vis-à-vis the prior art,
WO2003/068747.

<p>Impugned Patent Application 2007/DELNP/2007</p>	<p>Prior art WO 2003/068747 (Exhibit D)</p>	<p>Comments</p>
		<p>The backbone structure / basic scaffold claimed in the impugned patent application and the basic skeletal structure disclosed in the prior art WO'747 are identical to each other</p>
 <p>Claim 1 <i>A is substituted benzene;</i> <i>X is NR₄CO or NR₄C(S);</i> <i>R₄=hydrogen;</i> <i>Y is absent</i> <i>R₁ = aryl or heteroaryl, each of which is optionally substituted with alkyl, alkoxy,</i></p>	 <p>Claim 1 <i>X and Y = hydrogen</i> <i>R⁴=NH-CO-R⁷</i> <i>R⁷= -(CH₂)_r-heteroaryl optionally substituted by R¹³ and/or R¹⁴-(CH₂)_r-phenyl optionally substituted r is selected from 0, 1 and 2</i></p>	<p>The substituents claimed in the impugned patent application superimpose and encompass the substituents disclosed in the prior art WO'747.</p>

<p><i>halogen.....</i></p> <p><i>R₁ = substituted phenyl or substituted pyridyl (Claim 2)</i></p> <p><i>R₂=halogen or alkyl substituted with halogen</i></p> <p><i>R₂= o-position on said A benzene relative to pyridyl;</i></p>	<p><i>R₁₃ is selected from C₁₋₆ alkyl, C₁₋₆alkoxy, halogen.....</i></p> <p><i>R₁₄ is selected from C₁₋₆ alkyl, C₁₋₆alkoxy, halogen.....</i></p> <p><i>R₃ = chloro or methyl</i></p>	
<div data-bbox="348 1257 784 1506" data-label="Chemical-Block"> </div> <p><i>Claim 1</i></p> <p><i>R₃ = halogen</i></p> <p><i>R₃ = carbamoyl or R₃ = acyl , wherein acyl is substituted with amino</i></p> <p><i>R₃ = heterocycle optionally substituted with acyl</i></p> <p><i>R₃ = acyl and heterocycle optionally substituted with alkyl</i></p>	<div data-bbox="956 1225 1295 1570" data-label="Chemical-Block"> </div> <p><i>Claim 1</i></p> <p><i>Z = halogen</i></p> <p><i>m = 0,</i></p> <p><i>R¹ = hydrogen</i></p> <p><i>R² = hydrogen</i></p> <p><i>(CH₂)_mR¹ and R² together with nitrogen atom to which they are bond form four to six membered heterocyclic ring</i></p> <p><i>(CH₂)_mR¹ and R² together with nitrogen atom to which they are bond form four to six membered heterocyclic ring optionally substituted of upto three C₁₋₆ alkyl groups</i></p>	<p>The substituents claimed in the impugned patent application superimpose and encompass the substituents disclosed in the prior art WO'747.</p>

(xxii) The document hereto annexed and marked as "**Exhibit E**" is **WO 03/032970 A1** containing the relevant portions of the complete specification, filed by Glaxo Group Limited and published on April 24, 2003, bearing a priority date of October 17, 2001 titled "*5-carbamoyl-2'-methyl-1,1-biphenyl-4 carboxamide derivatives and their use as P38 kinase inhibitors*" The document discloses the essential elements of the invention as claimed in the impugned patent application, thereby destroying novelty. There is inherent anticipation that has been expressly, implicitly and inherently disclosed in the prior art document exhibited with the present Pre-grant Opposition.

(xxiii) The document at **Exhibit E** discloses the heteroaryl ring that refers to a monocyclic 5 to 7 membered unsaturated hydrocarbon ring containing at least one heteroatom selected from oxygen, nitrogen and sulphur. The examples referred at **Exhibit E** disclose pyridyl, pyridazinyl, and the derivatives of pyridine amongst others and demolishes the claims of the patent applicant [See pages 1 to 7 of **Exhibit E**].

(xxiv) The salt and solvate form and the pharmaceutically compositions or pharmaceutically acceptable salts and solvents of the compounds too have been disclosed in **Exhibit E**, thereby covering the entire range of claims made by the Applicant, rendering the impugned invention not patentable due to prior publication and prior claiming. [See

Pages 8 to 37 and pages 48 to 52 of **Exhibit E**]. The use of the compound for treatment of cancer has also been disclosed and claimed in the said application at Exhibit E. Methods of preparation of the compounds have also been disclosed [See pages 24-46 of **Exhibit E**].

- (xxv) In the absolute absence of novelty, the alleged invention fails to qualify patentability criteria. As such, Claims 1 to 42 of the impugned Patent Application No. 2007/DELNP/2007 merits to be rejected in the light of anticipation from prior art documents (**Exhibits A to E**) individually thereby impacting novelty of the impugned invention which is evident from the elaborative explanation given above under Section 25(1)(b) of the Patents Act, 1970.

b. Section 25(1)(c): Prior claiming

- (i) It is stated that the invention claimed in the impugned complete specification is published after the priority date of the Applicant's claim, but claim of the priority date is earlier than that of the Applicant's claim.
- (ii) The document hereto annexed and marked as "**Exhibit F**" is **WO 2005/085227 A1**, consists of the relevant portions, filed by Smithkline Beecham Corporation, published on September 15, 2005, bearing priority date of March 02, 2004 for "Inhibitors of AKT activity". This document discloses pyridine compounds, the use of the compounds as inhibitors

of PKB/AKT kinase activity and in the treatment of cancer and arthritis. The document demolishes all the claims, i.e. claims 1 to 42 made by the Applicant, and thus the application should be rejected.

(iii) The document at **Exhibit F** discloses pyridine compounds used for the treatment of cancer. [See pages 1, 7 of **Exhibit F**]. **Exhibit F**, for instance, claims and discloses the compounds possessing benzene ring substituted with halogen and -NHCO- linkage which is further substituted by heteroaryl group. The said substituted benzene ring is further attached to substituted pyridinyl moiety (Claims at page 170-194 of **Exhibit F**). Thus all the essential groups/substituents disclosed in **Exhibit F** substantially overlaps with the groups/ substituents of the Markush structure claimed in the impugned patent application. The document at **Exhibit F** also discloses the pharmaceutically acceptable salts, hydrates, solvates and pro-drugs thereof with varied substituent [see pages 33-37 of **Exhibit F**].

(iv) The pharmaceutical compositions of the compounds, including pyridine derivatives used as AKT inhibitors for treatment of cancer have been disclosed in the document at **Exhibit F** [See pages 74-75 of **Exhibit F**]. The pyridine compounds have been claimed, and their salt forms and pharmaceutical compositions have also been claimed in the document at **Exhibit F** [See pages 170 to 177 of **Exhibit F**].

Thus, the disclosures in **Exhibit F** render all the claims in the present application to lose its priority and novelty.

- (v) The document hereto annexed and marked as "**Exhibit G**" is **WO 2005/033288 A2**, consists of the relevant portions of the complete specification and claims, filed by The John Hopkins University, published on April 14, 2005, bearing priority date of September 29, 2003 for "Hedgehog Pathway antagonists." The document reveals pyridine compounds used to treat disease conditions through inhibition of hedgehog signalling pathways. The document demolishes all the claims 1 to 42 of the Applicant, and even though it was published later than the priority date of the Applicant, it has a priority date before the priority date of the Applicant. Thus, the present patent application should be rejected *in toto*.

- (vi) The document at **Exhibit G** discloses pyridine compounds used for inhibiting hedgehog signalling pathway, including the salt forms and pharmaceutically acceptable salts thereof [see pages 1 to 5 of **Exhibit G**]. Examples of pyridine compounds have been disclosed at **Exhibit G** [See page 11 of **Exhibit G**]. This renders the impugned invention obvious to a person skilled in the art and anticipates the inherent disclosure made in the document.

(vii) The document at **Exhibit G** reveals the compound that antagonizes hedgehog functioning i.e. by antagonizing hedgehog, patched or smoothened activity that can be used for treating or preventing basal cell carcinoma or other hedgehog pathway disorders. The document also reveals the use of pyridine compounds for cancerous tumours. [see page 19 to 21 of **Exhibit G**. Also refer pages 22 to 26 and pages 60 to 62 and 67 of **Exhibit G** for detailed information on hedgehog functioning].

(viii) Pyridine compounds have been disclosed at **Exhibit G** that include not only the salt forms but also pyridine compounds as hedgehog inhibitors used for treatment of cancer, more particularly basal cell carcinoma. The Applicant claims pyridine inhibitors of hedgehog signalling for treatment of basal cell carcinoma, and thus the claims of the Applicant in the impugned patent application are not patentable as it is not an invention and has been claimed earlier to the priority date of the Applicant. [See pages 35 to 42 of **Exhibit G**].

(ix) The document at **Exhibit G** also reveals details of the pharmaceutical compositions of the compounds, methods of administering the drug, and the combination of the composition with pro drugs and other anti-cancer agents. The claims in the present application are similar to those at **Exhibit G**, all of which have been known in science and to a person skilled in the art and does not involve an inventive

step. The document at **Exhibit G** clearly states that the compound is a hedgehog antagonist. [See pages 80 to 98 of **Exhibit G**, including pages 96, 97]. The claims at **Exhibit G** demolish the novelty of the claims of the impugned patent application. Pyridyl compounds are claimed along with the salt forms and pharmaceutically acceptable compositions for treating basal cell carcinomas amongst other disorders. The claims at **Exhibit G** also contain combination of the compounds with anti-cancer agents. [See pages 99 to 106 and pages 120 to 126 of **Exhibit G**]. This document at **Exhibit G** alone is enough to demolish the claims of the Applicant. The Opponent therefore submits that the invention claimed in the impugned patent application was very well prior known in the art at the time of filing the impugned patent application.

- (x) In view of the foregoing, it is therefore submitted that the impugned patent application ought to be dismissed under Section 25(1)(c) of the Act.

c. **Section 25(1)(d) : Prior public knowledge or public use in India**

- (i) It is stated that the invention so far claimed in Claims 1 to 42 of the impugned patent application was publicly known before the priority date of these claims. As can be seen from the prior art documents (**Exhibits A to H**) cited in the present Pre-grant Opposition, there exists prior public knowledge of alleged invention claimed in the impugned patent application prior to the priority date of said patent

application.

- (ii) Claims 1 to 42 of the impugned patent application, therefore, ought to be rejected on the ground of prior public knowledge under Section 25(1)(d) of the Act.

d. Section 25(1)(e): Obviousness and lack of inventive step

- (i) The invention so far claimed is obvious and does not involve an inventive step, having regard to the matter published herein and what has been used and disclosed prior to the priority date mentioned in the present patent application of the Applicant.
- (ii) The Opponent submits that the alleged invention clearly lacks an inventive step and is obvious to a person of ordinary skill in the art. As such the Indian Patent Application No. 2007/DELNP/2007 is ineligible for grant of a patent under Sec. 25(1)(e) of the Patents Act, 1970.
- (iii) The document hereto annexed and marked as “**Exhibit E**” is **WO 03/032970 A1** containing relevant portions of the complete specification, filed by Glaxo Group Limited and published on April 24, 2003, bearing a priority date of October 17, 2001 titled “*5-carbamoyl-2'-methyl-1,1-biphenyl-4 carboxamide derivatives and their use as P38 kinase inhibitors*” The document discloses the essential elements of the invention as claimed in the impugned patent

application, thereby destroying novelty as well as inventive step. There is inherent anticipation that has been expressly, implicitly and inherently disclosed in the prior art document exhibited with the present Pre-grant Opposition.

(iv) The document at **Exhibit E** discloses the heteroaryl ring that refers to a monocyclic 5 to 7 membered unsaturated hydrocarbon ring containing at least one heteroatom selected from oxygen, nitrogen and sulphur. The examples referred at **Exhibit E** disclose pyridyl, pyridazinyl and the derivatives of pyridine amongst others and demolishes the claims of the patent applicant made at claims 1 to 7 and 9 to 42 [See pages 1 to 7 of **Exhibit E**].

(v) The salt and solvate form and the pharmaceutical compositions or pharmaceutically acceptable salts and solvents of the compounds too have been disclosed in **Exhibit E**, thereby covering the entire range of claims made by the Applicant in the impugned patent application, rendering the impugned invention not patentable due to prior publication and prior claiming. [See Pages 8 to 37 and pages 48 to 52 of **Exhibit E**]. The use of the compound for treatment of cancer has also been disclosed and claimed in the said application at **Exhibit E**. Methods of preparation of the compounds have also been disclosed [See pages 24-46 of **Exhibit E**].

(vi) The document hereto annexed and marked as "**Exhibit H**" is WO 2004/058176 A2, is the relevant portions of the complete specification, filed by Pharmacia Corporation, published on July 15, 2004, bearing priority date of December 20, 2002 for "*Acyclic pyrazole compounds for the inhibition of mitogen activated protein kinase – activated protein kinase – 2*". This document explains that the Mitogen activated protein kinases are members of conserved signal transduction pathways that activate transcription factors, translation factors and other target molecules in response to a variety of extracellular signals. The ability to regulate signal transduction via the pathways could lead to development of treatments and preventive therapies for diseases associated with it, including cancer, autoimmune diseases, etc. [See page 1 of **Exhibit H**].

(vii) The document at **Exhibit H** also discloses pyridine compounds, the pharmaceutical compositions of such compounds, the salt forms of the compounds, thus demolishing the claims 1 to 42 made by the Applicant of novelty, invention and inventive steps. [See pages 46 to 50 (as a sample, though all the examples of pyridine are given from pages 45 to 70) of **Exhibit H**. Also see pages 166 to 170 of **Exhibit H**].

(viii) The document at **Exhibit H** also lists the types of diseases that the compounds could be used for, that include all types

of cancers, the methods of preparation of the compounds have been stated in great detail in the document, and the claims reveal therapeutic composition of compounds. [See attached hereto are pages 171 to 180, and pages 260-261 of **Exhibit H**. Leave maybe granted to file the entire document as and when required.] The document at **Exhibit H** published prior to the priority date of the present application, makes the impugned invention so claimed by the Applicant, obvious to a person skilled in the art, and clearly reveal that the present patent application does not involve an inventive step.

(ix) It is further submitted that a person skilled in the art on combining the prior art documents cited herein can achieve a reasonable expectation of success and easily arrive at the impugned invention claimed in the Patent Application No. 2007/DELNP/2007.

(x) The evidence as adduced herein above are clearly admissible under Sec. 25(1)(e) of the Patents Act, 1970 for determining absolute lack of inventive step and clearly indicating obviousness. The impugned patent application merits to be rejected *in toto*.

e. Section 25(1)(f): Not an invention within the meaning of the Patents Act.

(i) It has been shown by the prior art documents annexed in the

present Pre-grant Opposition that the complete specification and the amended claims do not constitute an invention. The impugned invention so far claimed is neither a new product nor a new process, does not involve an inventive step and is not capable of industrial application. There is no technical advancement as compared to existing knowledge, and the invention so claimed is obvious to a person skilled in the art.

- (ii) The product and processes have been known and are obvious to a person skilled in the art, and thus the present application does not meet the test prescribed under Sections 2(1)(j) and 2(1)(ja) of the Patents Act and hence the application ought to be dismissed *in limine*.

Section 3(d): Lack of therapeutic efficacy and mere use of known process

- (i) The Opponent strongly submits that the impugned invention falls within the ambit of Section 3(d) and hence is not patentable. The definition of Section 3(d) read alongwith explanation is relevant and validly applicable for the impugned subject matter.
- (ii) Sec. 3(d) of the Act reads as “the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process,

machine or apparatus unless such known process results in a new product or employs at least one new reactant” is not patentable under the Act.

Explanation:- For the purpose of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy.”

(iii) It is an established position of the law that if a discovery is made from a known substance, a duty is cast upon the patent applicant to show that the discovery had resulted in the enhancement of a known efficacy of that substance [See *Novartis AG v. Union of India and others*, (2007), 4 MLJ 1153, page 15]. The Hon’ble Intellectual Property Appellate Board has also held in *Novartis AG v. Union of India and Others*, IPAB, 26.06.2009, at pages 178 and 179, that “efficacy” in Sec. 3(d) means therapeutic efficacy.

(iv) It is pertinent to note that the alleged Applicant has merely employed and substituted the known prior art elements/substituents/groups in the basic scaffold disclosed and taught in the prior art documents (**Exhibits A to H**) in order to arrive at the impugned invention. The prior art documents additionally teaches that the pyridyl compounds

disclosed therein inhibit the hedgehog signaling pathway and are useful in the treatment of hyperproliferative diseases and angiogenesis mediated diseases which is also the subject matter of the impugned invention. From the teachings and disclosures in **Exhibits A to H**, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the compounds claimed in the impugned patent application retaining the identical backbone structure / basic scaffold as well as the activity of the compounds claimed therein.

- (v) It is further pertinent to note that the pyridyl compounds/ pyridine derivatives broadly claimed in the impugned patent application are structurally and functionally similar to the pyridyl compounds/ pyridine derivatives broadly claimed in the said prior art documents. Hence the Applicant is under the obligation to provide enhanced therapeutic efficacy data in comparison to the prior art products. The Applicant has conveniently ignored to demonstrate enhanced therapeutic efficacy of all the claimed products in comparison to the prior art products. Hence the claimed compounds shall be considered to be the same substance and clearly falls within the ambit of Section 3(d) of the Patents Act, 1970. The Opponent would like to bring to the kind attention of the Hon'ble Board that the validity of Section 3(d) has been upheld by the Supreme Court in the recent judgment (Civil Appeal Nos. 2706-2716 of 2013 in *Novartis vs. Union of*

India) pronounced on April 1, 2013 wherein it was adjudged that a new form of known substance is outside the purview of the definition of "invention" if the said new form of a known substance does not pass the test of efficacy required under Section 3(d) of the Patents Act, 1970. The compounds claimed in the impugned patent application are new form (derivative) of a known substance lacking enhanced therapeutic efficacy, hence cannot be regarded as non-patentable invention under Section 3(d), in view of disclosure in the prior art documents (**Exhibits A to H**).

- (vi) Further, the process for preparing the claimed compound are also disclosed in the cited prior art documents. It is also pertinent to note that no invention resides in claiming process for preparing the compounds broadly claimed in independent Claim 1 which are found to be *prima facie* obvious and devoid of novelty.
- (vii) In view of the above, Claims 1 to 42 are liable to be rejected under Sec. 25(1)(f) read with Sec. 3(d) of the Patents Act, 1970 being a derivative of a known substance (pyridine) lacking enhanced therapeutic efficacy and mere use of a known process without resulting into a new and improved product.

Section 3(e): Pharmaceutical Composition – Mere Admixture

- (i) The Opponent further strongly submits that the impugned

invention falls within the ambit of Sec. 3(e).

(ii) Sec. 3(e) of the Act reads as "a substance obtained by mere admixture resulting only in aggregation of the properties of the components thereof or a process for producing such substance" is not patentable under the Act.

(iii) It is pertinent to note that the pharmaceutical composition as claimed by the Applicant in amended Claim 41 is nothing but a mere admixture containing compounds covered in Markush structure claimed in amended Claim 1. Though the amended claim 41 does not recite other ingredients to be employed in preparing pharmaceutical composition, specific mention of the use of inert carrier, diluent or excipient to be admixed with claimed compounds is made in the specification at page 65 wherein it is stated "*The invention also includes pharmaceutical compositions or medicaments containing the compounds of the invention and a therapeutically inert carrier, diluent or excipient, as well as methods of using the compounds of the invention to prepare such compositions and medicaments*". Hence the pharmaceutical composition claimed in amended Claim 41 is a mere admixture falling within the ambit of Section 3(e) of the Act.

(iv) Mere workshop (laboratory) demonstrations, devoid of ingenuity, do not qualify for grant of a patent. A

pharmaceutical composition claimed in the impugned patent application, being a mere admixture, results only in the aggregation of the properties of the components. Further the Applicant has failed to demonstrate any synergy in the claimed pharmaceutical composition. Additionally, the prior art documents **(Exhibits A to H)** clearly teaches the pharmaceutical composition comprising pyridyl compound. Hence the pharmaceutical composition claimed in amended Claim 41 of the impugned patent application falls within the ambit of Section 3(e) of the Patents Act, 1970.

- (v) Point 4.6.9, Page 64 of Draft Manual of Patent Practice and Procedure cites a below mentioned case pertaining to Sec. 3(e):-

In the matter of an application for Patent No. 63/Bom/75 (Decisions on Patents and Designs, Vol.1, published by The Patent Office Technical Society p.17), Hindustan Lever Limited, applied for patent for an invention relating to an antiperspirant composition. It was held by the Controller that an admixture having only the aggregation of the individual properties of the components thereof is not an invention within the meaning of the Act and is thus not patentable, a process for producing such an admixture is also not patentable.

- (vi) Consequently, the amended dependent Claim 41 of the impugned patent application reciting pharmaceutical

composition comprising compounds claimed in claim 1 (pyridyl compounds) are heavily attracted and impacted by Section 3(e) and hence not patentable under Section 25(1)(f) of the Patents Act, 1970.

- (vii) In view of the foregoing grounds of Opposition, the Opponent vehemently submits that the alleged invention, being prior known and prior disclosed subject matter, is not a patentable invention within the meaning of the (Indian) Patents Act, 1970. As such, the impugned patent application is liable to be rejected under Section 25(1)(f) read with Section 2(1)(j), Section 2(1)(ja), Section 3(d) and Section 3(e) of The Patents Act, 1970.

f. Section 25(1)(g): the complete specification does not sufficiently and clearly describe the invention.

- (i) The impugned complete specification discloses 320 compounds, and claims Markush structure for the said compounds. Markush claims raise issues concerning sufficiency of disclosure. The amended claims in the application are complex and excessively broad. Such claims disguise the true nature of the invention and cover compounds that lack activity as indicated in the impugned patent application.
- (ii) The compounds covered by the Markush claims determine a combination of variations that can give rise to an infinite set

of alternatives, as is seen in the impugned patent application. The variations include the substituents based on alternative values for R-group, position variation depending on the point of attachment and frequency variation due to multiple occurrences of groups and homology variation depending on the attached groups (eg. Alkyl, methyl, ethyl, etc.). The impugned patent application has these varied and many sets of alternatives that prevents a clear description of the invention so claimed. For this reason the application ought to be rejected *in toto* under Section 25(1)(g) of the Act.

40. It is submitted by the Opponent that all the above-mentioned prior art documents annexed to the present Pre-grant Opposition destroy the novelty of the impugned invention so claimed by the Applicant. The information in the prior art documents disclose the essential elements of the impugned invention. Novelty is destroyed when the essential elements have been disclosed, even if the details of executing the invention, or clear description of its properties or method of making it were not disclosed. However, in the present case, novelty is destroyed as what is claimed has been claimed in earlier documents and applications that have a priority date prior to the priority date of the impugned patent application.

41. In *Enercon (India) Limited v. Aloys Wobben* ORA/6/2009/PT/CH, ORDER (No. 18 of 2013) the Intellectual Property Appellate Board of India noted that novelty may be denied on the basis of 'inherent anticipation'. It stated: "*the prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or*

inherent, in the single anticipating prior art..... it is not necessary that inherent anticipation requires that a person of ordinary skill in the art at the time would have recognized the inherent disclosure. But it is necessary that the result is a necessary consequence of what was deliberately intended in the invention." Thus, the novelty in the present application is destroyed by all prior art documents cited herein.

42. It is further submitted that the inventive step claims in the present application are destroyed as what is claimed and described is obvious to a person skilled in the art, i.e. there is reasonable expectation of success embedded in the prior art which motivates a skilled person to arrive at the impugned claimed invention. Obviousness cannot be avoided by showing some degree of unpredictability in the art, so long as there was a reasonable probability of success through disclosures provided in the prior art documents. Obviousness does not require absolute predictability of success. All that is required is reasonable expectation of success in the matter of pharmaceutical inventions. All the prior art documents annexed to this Opposition provide a reasonable predictability of success and are obvious to a person skilled in the art.

43. The Opponent humbly submits that the prior art documents annexed to the present Pre-grant opposition and also those cited in the FER demolish all the amended claims of the impugned patent application, rendering the amended claims devoid of novelty, inventive step and obvious to a person skilled in the art. The Opponent states that grant of patents to the Applicant in other jurisdictions cannot tantamount to a grant of a patent in India. The Indian law is different from the laws in other jurisdictions and care has

been taken by the law makers not to allow patents for pharmaceutical products that are not genuinely inventive or that are known earlier, or obvious to a person skilled in the art. The law specifically prohibits grant of patents for derivatives of known substances and also prevents abuse of the patent process by laying down grounds for opposition that prevent undeserving patents from being granted.

44. The Opponent states that the impugned patent Application No. 2007/DELNP/2007 falls within the category of non-patentable inventions as described in Section 3(d) and Section 3(e) of the Patents act, and also lack invention and inventive step as described under Section 2(1)(j) and 2(1)(ja) of the Patents Act, 1970. The said impugned patent application ought to be rejected *in toto* under Section 25(1) read with Section 3(d) and Section 3(e) of the Patents Act.

45. **Prayers**

Having established non-patentability of the impugned invention and having adduced supporting evidence for each of the above grounds of Opposition, Opponent prays for the following reliefs:

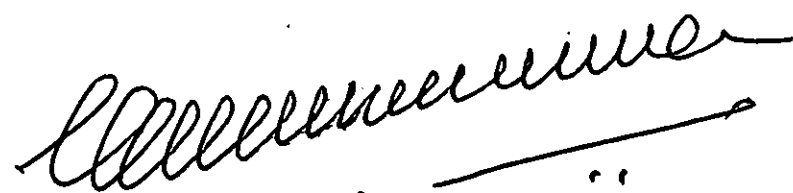
- a. That the Applicant's Patent Application No. 2007/DELNP/2007 having filed, with original claims as well as amended claims, be rejected *in toto* and the grant of Patent to the Applicant be refused.
- b. That the Opponent be granted leave to file further arguments and evidence against the impugned application.
- c. That copy of the reply of the Applicants and evidence, if any, be forwarded to the Opponent along with amendment to claims, if any;

- d. That the Opponent be granted leave to file response/rejoinder to the reply and the evidence of the Applicants.
- e. That the Opponent should be given an opportunity to oppose the amended claims, if any.
- f. That the Opponent be granted hearing in this case.
- g. Such other and further relief/s be granted to the Opponent, as the Ld. Controller may deem fit in the facts and circumstances of this case.
- h. That the Opponent be awarded costs.

All communications relating to these proceedings may be sent to the following address in India:-

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Dated this 30th day of June, 2017



Dr. GOPAKUMAR G. NAIR
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To,
The Controller of Patents
The Patent Office
Delhi.

Before the Patent Controller At Delhi

Pre-grant Opposition of National Phase Patent Application No. 2007/DELNP/2007

In the matter of

Cancer Patients Aid Association

..... Opponent

And

Genentech Inc. and Curis Inc.

..... Applicant

S. No.	Documents Relied Upon	Page Nos.
1.	Annexure 1 - Bibliographic page and amended Claims of National Phase Patent Application No. 2007/DELNP/2007	1-10
2.	Exhibit A: GB 2276163 A	11-35
3.	Exhibit B: WO 95/02580 A1	36-51
4.	Exhibit C: US 2004/0043903 A1	52-104
5.	Exhibit D: WO 03/068747 A1	105-151
6.	Exhibit E: WO 03/032970 A1	152-203
7.	Exhibit F: WO 2005/085227 A1	204-261
8.	Exhibit G: WO 2005/033288 A2	262-323
9.	Exhibit H: WO 2004/058176 A2	324-368

(12) PATENT APPLICATION PUBLICATION

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(51) International classification :C07D 213/40
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 Filing Date :NA
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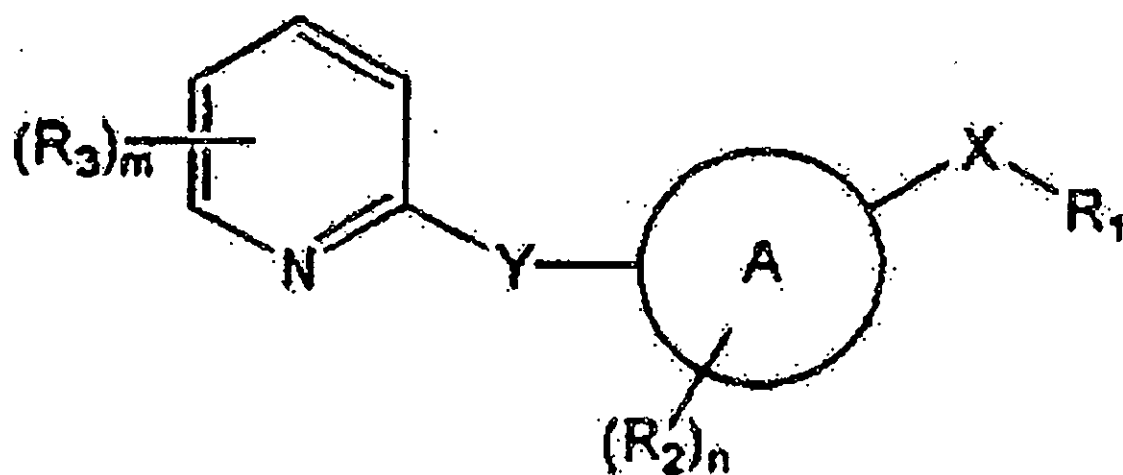
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11)MICHAEL DINA

(57) Abstract :

The invention provides novel inhibitors of hedgehog signaling that are useful as a therapeutic agents for treating malignancies where the compounds have the general formula I: wherein A, X, Y, R₁, R₂, R₃, R₄ and n are as described herein.



FORM 2
THE PATENTS ACT 1970
[39 OF 1970]
&
THE PATENTS (AMENDMENT) RULES, 2006
COMPLETE SPECIFICATION

2007 DELNP 2007

15 MAR 2007

[See Section 10; rule 13]

"PYRIDYL INHIBITORS OF HEDGEHOG SIGNALLING"

GENENTECH INC., a US corporation of 1 DNA Way, South San Francisco,
California 94080-4990, USA; and CURIS INC., a US corporation of 61
Moulton Street, Cambridge, MA 02138, USA;

ORIGINAL

The following specification particularly describes the invention and the
manner in which it is to be performed:

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PYRIDYL INHIBITORS OF HEDGEHOG SIGNALLING

This application claims priority to provisional patent application 60/607,367 filed on 02 September 2004.

FIELD OF THE INVENTION

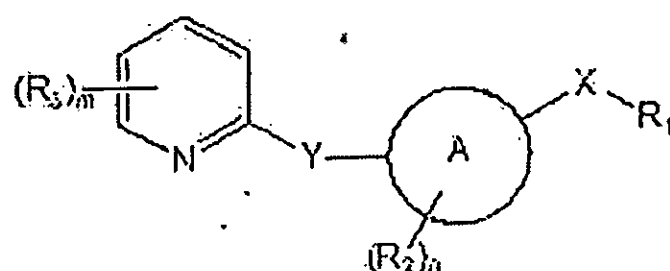
The present invention relates to organic compounds useful for therapy and/or prophylaxis in a mammal, in particular to pyridyl compounds that inhibit the hedgehog signaling pathway and are useful in the treatment of hyperproliferative diseases and angiogenesis mediated diseases.

BACKGROUND OF THE INVENTION

Hedgehog (Hh) protein was first identified in *Drosophila melanogaster* as a segment-polarity gene involved in embryo patterning (Nusslein-Volhard et al., Roux. Arch. Dev. Biol. 193: 267-282 (1984)). Three orthologs of *Drosophila* hedgehog (Sonic, Desert and Indian) were later identified to occur in all vertebrates including fish, birds and mammals. Desert hedgehog (DHH) is expressed principally in the testes, both in mouse embryonic development and in the adult rodent and human; Indian hedgehog (IHH) is involved in bone development during embryogenesis and in bone formation in the adult; and, Sonic hedgehog (SHh) is expressed at high levels in the notochord and floor plate of developing vertebrate embryos. In vitro explant assays as well as ectopic expression of SHh in transgenic animals have shown that SHh plays a key role in neuronal tube patterning (Echelard et al., supra.; Ericson et al., Cell 81: 747-56 (1995); Marti et al., Nature 375: 322-5 (1995); Krauss et al., Cell 75, 1432-44 (1993); Riddle et al., Cell 75: 1401-16 (1993); Roelink et al., Cell 81:445-55 (1995); Hynes et al., Neuron 19: 15-26 (1997)). Hh also plays a role in the development of limbs (Krauss et al., Cell 75: 1431-44 (1993); Laufer et al., Cell 79, 993-1003 (1994)), somites (Fan and Tessier-Lavigne, Cell 79, 1175-86 (1994); Johnson et al., Cell 79: 1165-73 (1994)), lungs (Bellusci et al., Develop. 124: 53-63 (1997) and skin (Oro et al., Science 276:

We claim:

1. A compound of formula I:



wherein

A is substituted benzene;

X is $\text{NR}_4\text{C}(\text{O})$ or $\text{NR}_4\text{C}(\text{S})$;

Y is absent;

R_1 is aryl or heteroaryl, each of which is optionally substituted with hydroxyl, halogen, amino, carboxyl, amidino, guanidino, carbonyl, nitro, cyano, acyl, alkyl, haloalkyl, sulfonyl, sulfinyl, alkoxy, alkylthio, carbamoyl, acylamino, sulfamoyl, sulfonamide, a carbocycle or a heterocycle; wherein said amino, amidino, alkyl, acyl, sulfonyl, sulfinyl, alkoxy, alkylthio, carbamoyl, acylamino, sulfamoyl, sulfonamide, carbocycle and heterocycle substituent is optionally substituted with, halogen, haloalkyl, hydroxyl, carboxyl, carbonyl, or an amino, alkyl, alkoxy, acyl, sulfonyl, sulfinyl, phosphinate, carbocycle or heterocycle that is optionally substituted with hydroxyl, carboxyl, carbonyl, amino, halogen, haloalkyl, alkyl, alkoxy, alkylthio, sulfonyl, sulfinyl, acyl, a carbocycle or a heterocycle;

R_2 is halogen, or alkyl substituted with halogen and an R_2 is in the o-position on said A benzene relative to pyridyl;

R_3 is halogen, hydroxyl, carboxyl, alkyl, acyl, alkoxy, alkoxycarbonyl, carbamoyl, alkylsulfide, sulfinyl, sulfonyl, a carbocycle or a heterocycle wherein each alkyl, acyl, alkoxy, alkoxycarbonyl, carbamoyl, alkylsulfide, sulfinyl, sulfonyl, carbocycle and heterocycle is optionally substituted with hydroxyl, halogen, amino, nitro, alkyl, acyl, sulfonyl or alkoxy;

R_4 is H or alkyl;

m is 0-3;

n is 1-3;

or a salt or solvate thereof;

wherein

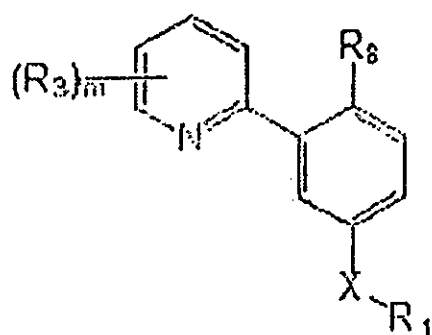
aryl, in each case, has up to 14 carbon atoms,

heteroaryl, in each case, is a mono-, bi-, or tricyclic aromatic ring system having from 5 to about 14 ring atoms where at least one ring is a 5-, 6- or 7-membered ring containing from one to four heteroatoms selected from the group nitrogen, oxygen, and sulfur,

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alkyl, in each case, has up to 12 carbon atoms,
acyl, in each case, is of the formula $-C(O)-R$ in which R is H, alkyl, a carbocycle, a heterocycle, carbocycle-substituted alkyl or heterocycle-substituted alkyl,
alkoxy, in each case, has up to 12 carbon atoms,
carbamoyl, in each case, is of the formula $-C(O)N(R)_2$ in which R is H, hydroxyl, alkoxy, alkyl, a carbocycle, a heterocycle, carbocycle-substituted alkyl or alkoxy, or heterocycle-substituted alkyl or alkoxy
carbocycle, in each case, is a mono-, bi-, or tricyclic aliphatic ring having 3 to 14 carbon atoms which may be saturated or unsaturated, aromatic or non-aromatic, and heterocycle, in each case, is a mono-, bi-, or tricyclic, saturated or unsaturated, aromatic or non-aromatic ring having from 5 to about 14 ring atoms, where the ring atoms are carbon and at least one heteroatom selected from nitrogen, sulfur and oxygen.

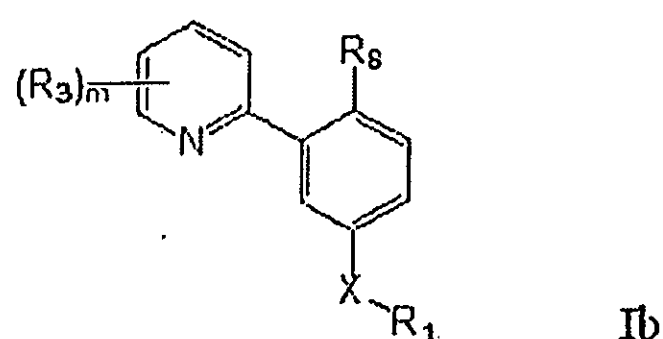
2. The compound as claimed in claim 1, wherein R_4 is H or methyl.
3. The compound as claimed in claim 2, wherein R_4 is H.
4. The compound as claimed in claim 1, wherein R_1 is substituted phenyl or substituted pyridyl.
5. The compound as claimed in claim 4, wherein R_1 is substituted phenyl.
6. A compound as claimed in claim 4, wherein R_3 is absent or methyl, ring A is o-chlorophenyl, and X is $-NHC(O)-$.
7. A compound as claimed in claim 4, wherein R_1 is substituted phenyl or pyridyl comprises $-SO_2-$.
8. A compound as claimed in claim 4, wherein ring A is o-chlorophenyl, X is $-NHC(O)-$, and R_1 is substituted phenyl or substituted pyridyl which comprises $-SO_2-$.
9. The compound as claimed in claim 4, wherein A is



Ib

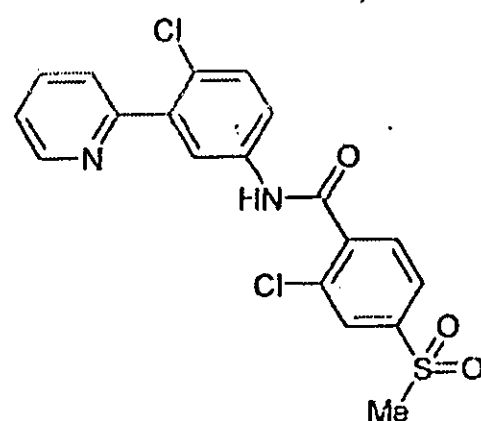
10. The compound as claimed in claim 4, wherein R_2 is Cl.

11. The compound as claimed in claim 4, wherein X is $\text{NR}_4\text{C(O)}$.
12. The compound as claimed in claim 4, wherein R_3 is methyl or F.
13. The compound as claimed in claim 4, wherein R_3 is methyl and m is 1 or 2.
14. The compound as claimed in claim 4, wherein m is 0.
15. A compound as claimed in claim 1, wherein said compound is of formula Ib



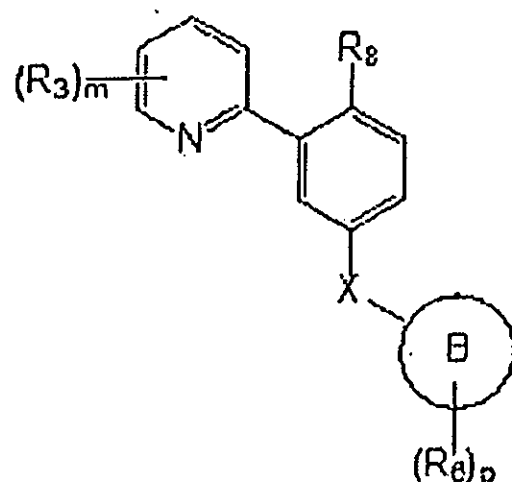
wherein R_3 is methyl,
 R_8 is halogen or alkyl substituted with halogen;
X is $\text{NR}_4\text{C(O)}$,
m is 0-3,
 R_4 is H or alkyl, and
 R^1 is aryl or heteroaryl, each of which is optionally substituted.

16. A compound as claimed in claim 14, wherein R_8 is halogen and R_1 is substituted phenyl or substituted pyridyl.
17. A compound as claimed in claim 16, wherein R_4 is H, m is 0 and R_8 is Cl.
18. A compound as claimed in claim 16, wherein said substituted phenyl or pyridyl R_1 group comprises $-\text{SO}_2-$.
19. A compound as claimed in claim 16, wherein said compound is of the formula



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20. A compound as claimed in claim 16, wherein said compound is of the formula Ib'

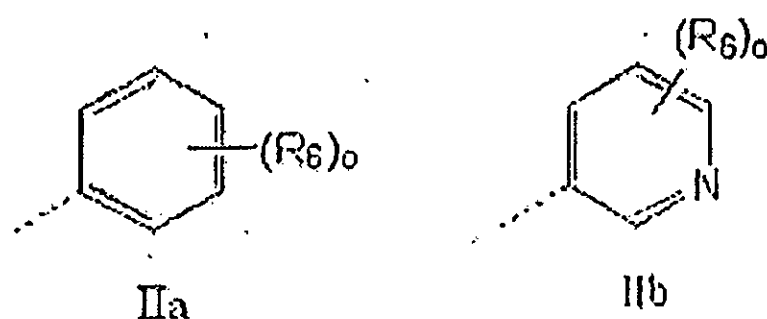


Ib'

wherein ring B is phenyl or pyridyl, o is 1-3, and each R_6 independently is hydroxyl, halogen, amino, carboxyl, amidino, guanidino, carbonyl, nitro, cyano, acyl, alkyl, haloalkyl, sulfonyl, sulfinyl, alkoxy, alkylthio, carbamoyl, acylamino, sulfamoyl, sulfonamide, a carbocycle or a heterocycle; wherein said amino, amidino, alkyl, acyl, sulfonyl, sulfinyl, alkoxy, alkylthio, carbamoyl, acylamino, sulfamoyl, sulfonamide, carbocycle and heterocycle substituent is optionally substituted with, halogen, haloalkyl, hydroxyl, carboxyl, carbonyl, or an amino, alkyl, alkoxy, acyl, sulfonyl, sulfinyl, phosphinate, carbocycle or heterocycle that is optionally substituted with hydroxyl, carboxyl, carbonyl, amino, halogen, haloalkyl, alkyl, alkoxy, alkylthio, sulfonyl, sulfinyl, acyl, a carbocycle or a heterocycle.

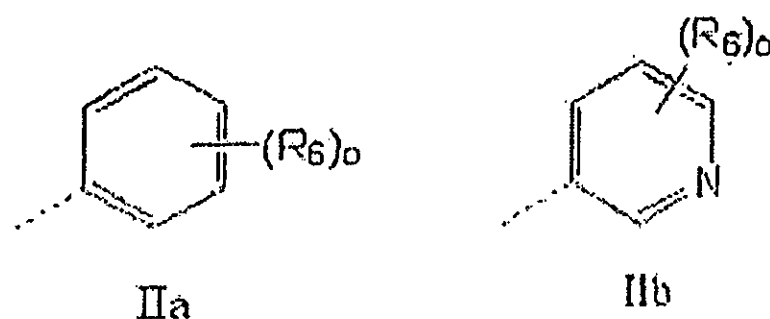
21. A compound as claimed in claim 20, wherein at least one R_6 is an optionally substituted sulfonyl.
22. A compound as claimed in claim 20, wherein carbocycle is a mono-, bi-, or tricyclic ring having 3 to 14 carbon atoms which can be saturated or unsaturated aliphatic or aromatic and heterocycle is a mono-, bi-, or tricyclic ring which is saturated or unsaturated, or aromatic, having from 5 to about 14 ring atoms, where the ring atoms are carbon and from 1 to 4 heteroatoms which are nitrogen, sulfur or oxygen.
23. A compound as claimed in claim 1, wherein R_1 is thiophene, isoxazole, benzothiadiazole, pyrimidine, pyrazole, phenyl or pyridine.
24. A compound as claimed in claim 21, wherein m is 0.
25. A compound as claimed in claim 21, wherein R_8 is Cl.
26. A compound as claimed in claim 21, wherein o is 2.

27. A compound as claimed in claim 21, wherein one R_6 is Cl.
28. A compound as claimed in claim 21, wherein m is 0, o is 2, R_8 is Cl, one R_6 is Cl and one R_6 is an optionally substituted sulfonyl.
29. A compound as claimed in claim 15, wherein m is 0 or 1.
30. A compound as claimed in claim 20, wherein R_6 is independently in each instance halogen or optionally substituted alkyl, alkoxy, carbonyl, a heterocycle, alkylamino, arylamino, alkylcarbamoyl, alkylsulfamoyl or sulfonyl.
31. A compound as claimed in claim 21, wherein R_6 is independently in each instance halogen or optionally substituted alkyl, alkoxy, carbonyl, a heterocycle, alkylamino, arylamino, alkylcarbamoyl, alkylsulfamoyl or sulfonyl.
32. A compound as claimed in claim 1, wherein R_1 is not naphthyl.
33. A compound as claimed in claim 1, wherein R_1 is of formula IIa or IIb:



wherein R_6 is independently in each instance optionally substituted alkyl, halogen, alkoxy, carbonyl, a heterocycle, alkylamino, arylamino, alkylcarbamoyl, alkylsulfamoyl or sulfonyl; and o is 1-3.

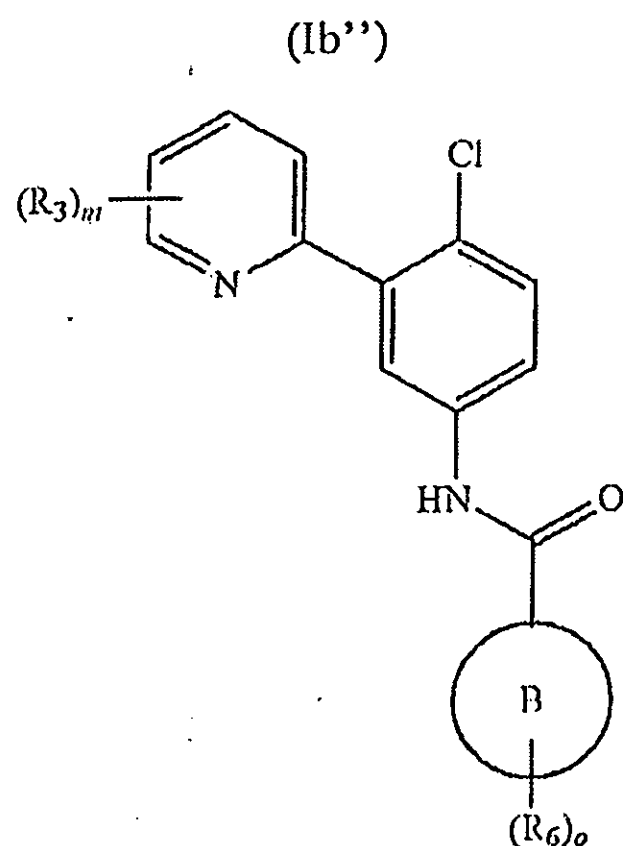
34. A compound as claimed in claim 15, wherein R_1 is of formula IIa or IIb:



wherein R_6 is independently in each instance halogen or optionally substituted alkyl, alkoxy, carbonyl, a heterocycle, alkylamino, arylamino, alkylcarbamoyl, alkylsulfamoyl or sulfonyl; and o is 1-3.

35. A compound as claimed in claim 33, wherein R_1 is of formula IIa.

36. A compound as claimed in claim 34, wherein R_1 is of formula IIa.
37. A compound as claimed in claim 34, wherein R_8 is halogen and R_1 is substituted phenyl or substituted pyridyl.
38. A compound as claimed in claim 37, wherein R_4 is H, m is 0 and R_8 is Cl.
39. A compound as claimed in claim 37, wherein said substituted phenyl or pyridyl R_1 group comprises $-SO_2-$.
40. A compound as claimed in claim 34, wherein R_1 is substituted phenyl or substituted pyridyl, R_3 is absent or is methyl, ring A is o-chlorophenyl, and X is $-NHC(O)-$.
41. The compound as claimed in claim 1 as and when used for preparing a pharmaceutical composition.
42. A process for preparing a compound as claimed in claim 1, wherein said compound is of formula Ib''



wherein

ring B is aryl or heteroaryl, each of which is optionally substituted

R_3 is halogen, hydroxyl, carboxyl, alkyl, acyl, alkoxy, alkoxycarbonyl, carbamoyl, alkylsulfide, alkylsulfinyl, alkylsulfonyl, a carbocycle or a heterocycle wherein each alkyl, acyl, alkoxy, alkoxycarbonyl, carbamoyl, alkylsulfide, alkylsulfinyl, alkylsulfonyl, carbocycle and heterocycle is optionally substituted with hydroxyl, halogen, amino, nitro, alkyl, acyl, alkylsulfonyl or alkoxy;

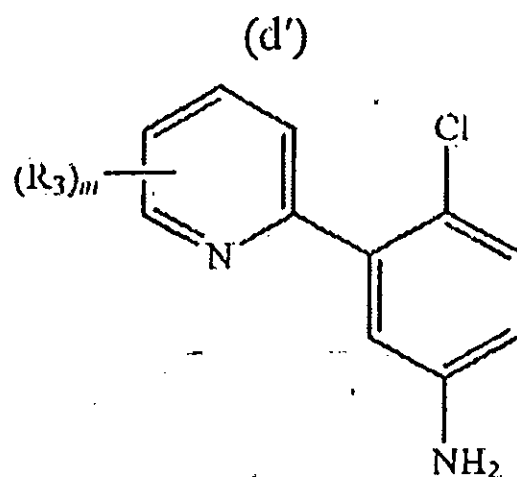
R_6 in each instance is independently hydroxyl, halogen, amino, carbonyl, nitro, cyano, acyl, alkyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, alkoxy, alkylcarbamoyl, alkanoylamine, alkylsulfamoyl, alkylsulfonamide, a carbocycle or a

heterocycle; wherein said amino, alkyl, carbonyl, acyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, alkoxy, alkylcarbamoyl, alkanoylamine, alkylsulfamoyl, alkylsulfonamide, carbocycle and heterocycle substituent is optionally substituted with amino, halogen, hydroxyl, carbonyl, or a carbocycle or heterocycle that is optionally substituted with hydroxyl, amino, halogen, haloalkyl, alkyl, alkoxy or acyl;

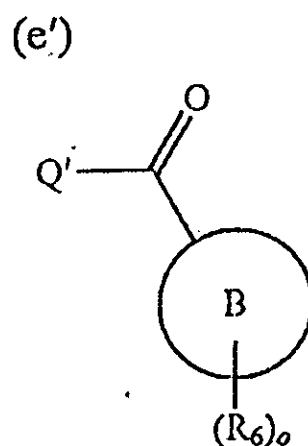
o is 0-3; and

m is 0-3;

comprising reacting a compound of formula (d')



with a compound of formula (e')



wherein Q' is halogen, OH or OR wherein R is an activating group, to yield said compound of formula Ib'', and, optionally, forming a salt or solvate thereof.

Dated this 15/03/2007



[JITESH KUMAR]

IN/PA-1134

OF REMFRY & SAGAR

ATTORNEY OF THE APPLICANTS

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(21) Application No 9305509.3

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C07D 213/04, A61K 31/44

(52) UK CL (Edition M)

C2C CAA CKH CKJ CKN CKZ CLG C1530 C215 C22Y
C220 C246 C25Y C250 C251 C270 C280 C281 C29X
C29Y C30Y C31Y C311 C314 C32Y C322 C323 C338
C34Y C342 C351 C355 C36Y C360 C361 C362 C364
C365 C366 C367 C368 C45Y C455 C57Y C603 C610
C62X C620 C623 C624 C628 C63X C630 C65X C650
C652 C658 C660 C662 C678 C680 C697 C699 C80Y
C800 C802
U1S S1318 S2413 S2414 S2415 S2417 S2418

(56) Documents Cited

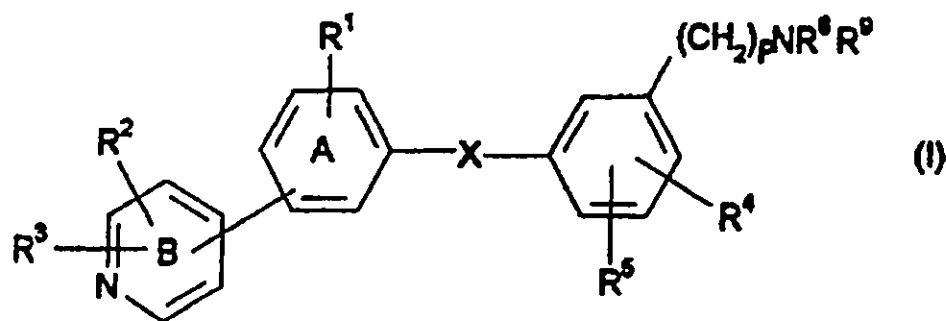
None

(58) Field of Search

UK CL (Edition M) C2C CKH CKJ CLG CNJ
INT CL⁵ C07D
ONLINE DATABASES: CAS ONLINE

(54) Pyridine compounds.

(57) Compounds of the formula (I):-



or a physiologically acceptable salt or solvate thereof, in which

R¹ represents a hydrogen atom or a halogen atom or a C₁₋₆alkyl or C₁₋₆alkoxy group;R² and R³, which may be the same or different, each independently represent a hydrogen atom or a halogen atom, or a C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkoxy, hydroxy, -CN, -NO₂, -CO₂R⁶, -COR⁶, -CONR⁶R⁷ or -(CH₂)_mOC(O)C₁₋₄alkyl group;R⁴ and R⁵, which may be the same or different, each independently represent a hydrogen atom or a halogen atom, or a hydroxy, C₁₋₆alkoxy or C₁₋₆alkyl group;R⁶, R⁷, R⁸ and R⁹, which may be the same or different, each independently represent a hydrogen atom or a C₁₋₆alkyl group;or -NR⁶R⁷ forms a saturated heterocyclic ring which has 5 or 6 ring members which, when there are 6 ring members, may optionally contain in the ring one oxygen or sulphur atom;X represents -CONH-, -NHCO-, -CH₂NH- or -NHCH₂-;

m represents zero or an integer from 1 to 3; and

p represents an integer from 2 to 4;

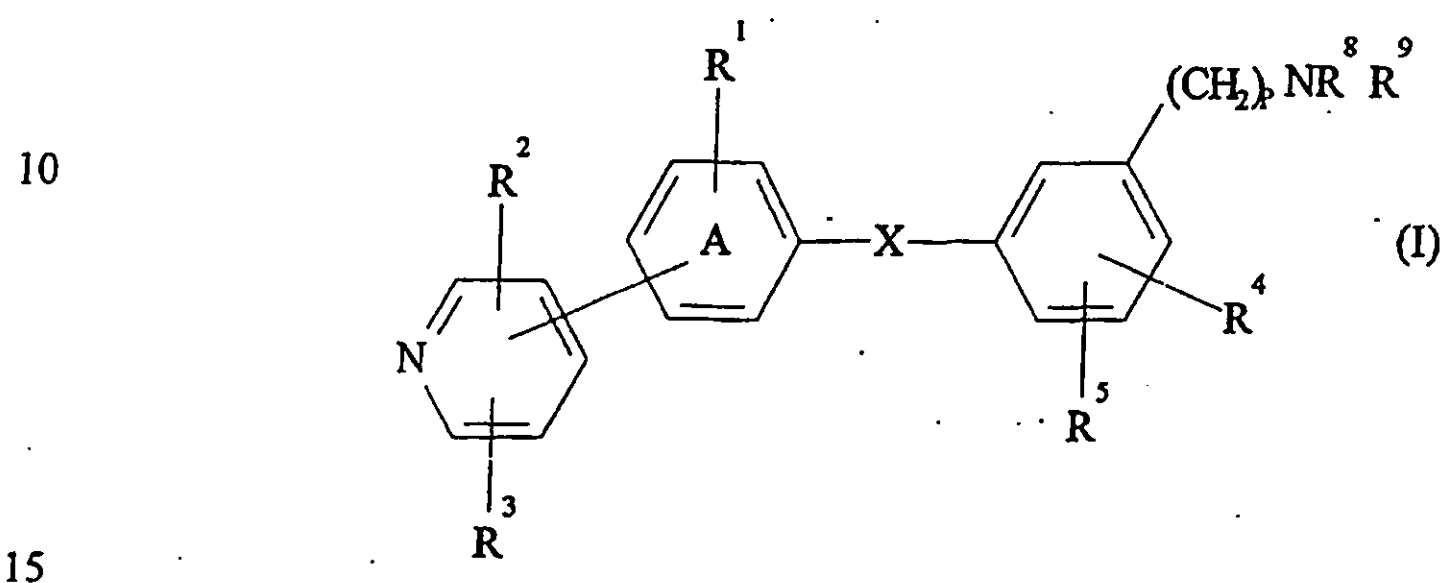
are 5-HT_{1D} antagonists useful in the treatment of CNS disorders, endocrine disorders and sexual dysfunction.

GB 2 276 163 A

CHEMICAL COMPOUNDS

This invention relates to novel aniline and benzanilide derivatives, to processes for their preparation, and to pharmaceutical compositions containing them.

5 According to the present invention there is provided compounds of the general formula (I) :-



or a physiologically acceptable salt or solvate thereof, in which

R^1 represents a hydrogen atom or a halogen atom or a C_{1-6} alkyl or C_{1-6} alkoxy group;

20 R^2 and R^3 , which may be the same or different, each independently represent a hydrogen atom or a halogen atom, or a C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkoxy C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, -CN, -NO₂, -CO₂R⁶, -COR⁶, -CONR⁶R⁷ or -(CH₂)_mOC(O)C₁₋₄alkyl group;

R^4 and R^5 , which may be the same or different, each independently represent a hydrogen atom or a halogen atom, or a hydroxy, C_{1-6} alkoxy or C_{1-6} alkyl group;

R^6 , R^7 , R^8 and R^9 , which may be the same or different, each independently represent a hydrogen atom or a C_{1-6} alkyl group;

25 or -NR⁶R⁷ forms a saturated heterocyclic ring which has 5 or 6 ring members which, when there are 6 ring members, may optionally contain in the ring one oxygen or sulphur atom;

X represents -CONH-, -NHCO-, -CH₂NH- or -NHCH₂-;

m represents zero or an integer from 1 to 3; and

p represents an integer from 2 to 4.

It is to be understood that the present invention encompasses all geometric and optical isomers of the compounds of general formula (I) and their mixtures including the racemic mixtures thereof.

Physiologically acceptable salts of the compounds of formula (I) include acid addition salts formed with inorganic or organic acids (for example hydrochlorides, hydrobromides, sulphates, phosphates, benzoates, naphthoates, hydroxynaphthoates, p-toluenesulphonates, methanesulphonates, sulphamates, ascorbates, tartrates, citrates, oxalates, maleates, salicylates, fumarates, succinates, lactates, glutarates, glutaconates, acetates or tricarballates) and, where appropriate, inorganic base salts such as alkali metal salts (for example sodium salts).

In the compounds of formula (I), the term "C₁₋₆alkyl" or "C₁₋₆alkoxy" as a group or part of a group means that the group is straight or branched and consists of 1 to 6 carbon atoms. Examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy. The term "halogen" within the definition of R² means fluorine, chlorine, bromine or iodine.

Within the above definition, when -NR⁶R⁷ represent a saturated heterocyclic ring, these contain 5 or 6 ring members, one of which (when there are 6 ring members) may be an oxygen or a sulphur atom. Suitable heterocyclic groups are a pyrrolidinyl, piperidinyl, morpholinyl or thiomorpholinyl group.

The pyridinyl ring may preferably be attached in the meta or more particularly the para position of the phenyl ring A relative to the group X.

When the pyridinyl ring is substituted by a single atom or group as defined above where possible the substituent is preferably attached in a position meta or para to the phenyl ring A in general formula (I). When the pyridinyl ring is substituted by two atoms or groups as defined above where possible one substituent is preferably attached in the position para to, and the other is in a position ortho to the phenyl ring A in general formula (I).

A preferred group of compounds of general formula (I) is that wherein the pyridinyl ring is substituted by one or two substituents as defined in general formula (I) wherein

one substituent is in the position para to the phenyl ring A in general formula (I) the second substituent is in the position ortho to the phenyl ring A in general formula (I).

Another preferred group of compounds of general formula (I) is that wherein the pyridinyl ring is substituted by a single substituent as defined in general formula (I) wherein said substituent is in the position para to the phenyl ring A in general formula (I).

Another preferred group of compounds of general formula (I) is that wherein the pyridinyl ring is attached at the 3-position, or more preferably at the 4-position.

Another preferred group of compounds of general formula (I) is that wherein R^2 and/or R^3 each independently represent a hydrogen atom or a C_{1-6} alkyl, especially methyl, group. Particularly preferred are those compounds wherein R^2 and/or R^3 on the pyridinyl ring is in a position ortho to the bond to the phenyl ring A in general formula (I).

A further preferred group of compounds of general formula (I) is that wherein R^1 is a hydrogen atom, a halogen atom, especially a fluorine atom, or a group selected from C_{1-3} alkyl, especially methyl, and C_{1-3} alkoxy, especially methoxy.

Another preferred group of compounds of general formula (I) is that wherein R^1 is attached at a position ortho to the pyridinyl ring on the phenyl ring A in general formula (I).

Another preferred group of compounds of general formula (I) is that wherein R^4 is attached in the para-position relative to the group X.

A further preferred group of compounds of general formula (I) is that wherein R^4 is a halogen atom, especially a fluorine or chlorine atom, or a hydroxy or C_{1-6} alkoxy, especially methoxy, group.

Also preferred is the group of compounds of general formula (I) wherein R^5 is a hydrogen atom or a fluorine atom.

A yet further preferred group of compounds of general formula (I) is that wherein R^8 and R^9 each represent a C_{1-6} alkyl, especially methyl, group.

Also preferred is the group of compounds of general formula (I) wherein X is -NHCO- or -CONH-.

Another preferred group of compounds of general formula (I) is that wherein p is 3.

Preferred compounds of general formula (I) include:

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2-methoxy-N,N-dimethyl-5-[[[4-(4-pyridinyl)phenyl]amino]methyl]benzenepropanamine;
 3-[3-(dimethylamino)propyl]-4-methoxy-N-[4-(2-pyridinyl)phenyl]benzamide;
 4-methoxy-3-[3-[methylamino]propyl]-N-[4-(4-pyridinyl)phenyl]benzamide;
 3-[3-(dimethylamino)propyl]-N-[4-[6-(1-hydroxyethyl)-3-pyridinyl]phenyl]-4-
 5 methoxybenzamide;
 4-bromo-3-[3-(dimethylamino)propyl]-N-[4-(4-pyridinyl)phenyl]benzamide;
 and their physiologically acceptable salts and solvates.

Particularly preferred compounds of general formula (I) include:

3-[3-(dimethylamino)propyl]-4-methoxy-N-[4-(4-pyridinyl)phenyl]benzamide;
 10 3-[3-(dimethylamino)propyl]-4-hydroxy-N-[4-(4-pyridinyl)phenyl]benzamide;
 3-[3-(dimethylamino)propyl]-N-[4-[2-(hydroxymethyl)-5-pyridinyl]phenyl]-4-
 methoxybenzamide;
 5-[4-[[3-[3-(dimethylamino)propyl]-4-methoxybenzoyl]amino]phenyl]-2-
 pyridinemethanol acetate (ester);
 15 3-[3-(dimethylamino)propyl]-4-methoxy-N-[4-(3-methyl-4-pyridinyl)phenyl]benzamide;
 and their physiologically acceptable salts and solvates.

5-Hydroxytryptamine (serotonin) is a neurotransmitter which is widely distributed within the central nervous system (CNS), platelets and the gastrointestinal tract. Changes in transmission in serotonergic pathways in the CNS are known to modify, for example,
 20 mood, psychomotor activity, appetite, memory and blood pressure. Release of 5-hydroxytryptamine from platelets can mediate vasospasm while changes in free 5-hydroxytryptamine levels in the gastrointestinal tract can modify secretion and motility.

Abundant pharmacological studies have led to the discovery of multiple types of receptors for 5-hydroxytryptamine, thus providing a molecular basis to the diversity of its
 25 actions. These receptors are classed as 5-HT₁, 5-HT₂ and 5-HT₃, with 5-HT₁ receptors being sub-classified as 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D} and 5-HT_{1D}(like) receptors. The identification of these classes and sub-classes of receptor is based mainly on radioligand binding studies.

Compounds having a selective antagonist action at 5-HT_{1D} receptors such as those
 30 described herein may exhibit a beneficial effect on subjects suffering from CNS disorders.

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In the present specification, a 5-HT_{1D} antagonist is a non-naturally occurring (synthetic) compound that specifically and selectively antagonises 5-HT_{1D} receptors, i.e. blocks the specific actions of 5-hydroxytryptamine mediated by 5-HT_{1D} receptors. Such compounds may be identified by a high level of affinity ($pK_i \geq 8$) in the *in vitro* human cortex and guinea-pig striatum radioligand binding assays described by Hoyer *et al*,
 5 Neuroscience Letters, 1988, 85, p357-362. Activity at 5-HT_{1D} receptors may be confirmed *in vivo* using the guinea pig rotation model described by G A Higgins *et al*, Br. J. Pharmacol., 1991, 102, p305-310.

The affinity of a compound for 5-HT_{1A}, 5-HT_{1C} and/or 5-HT₂ receptors is measured
 10 using the *in vitro* tests described in the following publications:

5-HT _{1A}	Gozlan <i>et al</i> , Nature, 1983, <u>305</u> , p140-142
5-HT _{1C}	Pazos <i>et al</i> , Eur. J.Pharmacol., 1984, <u>106</u> , p531-538
5-HT ₂	Humphrey <i>et al</i> , Br. J. Pharmacol, 1988, <u>94</u> , p1123-1132
15	(rabbit aorta model).

Thus, for example, compounds of the present invention have been shown to inhibit 5-hydroxytryptamine induced contraction of the dog isolated saphenous vein and to antagonise the 5-hydroxytryptamine induced inhibition of neurotransmission in central and
 20 peripheral neurones.

5-HT_{1D} antagonists, and in particular the compounds of the present invention, may therefore be of use in the treatment of CNS disorders such as mood disorders, including depression, seasonal affective disorder and dysthymia; anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive
 25 disorder and post-traumatic stress disorder; memory disorders, including dementia, amnesic disorders and age-associated memory impairment; and disorders of eating behaviour, including anorexia nervosa and bulimia nervosa. Other CNS disorders include Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias, as well as other psychiatric disorders.

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5-HT_{1D} antagonists, and in particular compounds of the present invention, may also be of use in the treatment of endocrine disorders such as hyperprolactinaemia, the treatment of vasospasm (particularly in the cerebral vasculature) and hypertension, as well as disorders in the gastrointestinal tract where changes in motility and secretion are involved. They may also be of use in the treatment of sexual dysfunction.

Therefore, according to a second aspect of the invention, we provide a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in therapy.

According to a further aspect of the present invention, we therefore provide a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment of the aforementioned disorders.

According to another aspect of the invention, we provide the use of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a therapeutic agent for the treatment of the aforementioned disorders.

According to a further aspect of the invention, we provide, a method of treating the aforementioned disorders which comprises administering an effective amount to a patient in need of such treatment of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof.

In particular, according to another aspect of the present invention, we provide a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment or prophylaxis of depression.

It will be appreciated that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents such as tricyclic antidepressants (e.g. amitriptyline, dothiepin, doxepin, trimipramine, butriptyline, clomipramine, desipramine, imipramine, iprindole, lofepramine, nortriptyline or protriptyline), monoamine oxidase inhibitors (e.g. isocarboxazid, phenelzine or tranylcyclopramine) or 5-HT reuptake inhibitors (e.g. fluvoxamine, sertraline, fluoxetine or paroxetine), and/or antiparkinsonian agents such as dopaminergic antiparkinsonian agents (e.g. levodopa, preferably in combination with a peripheral decarboxylase inhibitor e.g. benserazide or carbidopa), or a

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dopamine agonist (e.g. bromocriptine, lysuride or pergolide). It is to be understood that the present invention covers the use of a compound of general formula (I) or a physiologically acceptable salt or solvate thereof in combination with one or more other therapeutic agents.

5 Thus there is provided in a further or alternative aspect of the present invention a compound of general formula (I) or a physiologically acceptable salt or solvate thereof and an antidepressant agent in the presence of each other in the human or non-human animal body for use in the treatment of the aforementioned disorders.

10 While it is possible that a compound of general formula (I) may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

15 The compounds of general formula (I) and their physiologically acceptable salts and solvates may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions comprising at least one compound of general formula (I) or a physiologically acceptable salt or solvate thereof. Such compositions may be presented for use in a conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

20 Thus, the compositions according to the invention may be formulated for oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation. Oral administration is preferred.

25 Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, sugar, microcrystalline cellulose maize-starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid
30 preparations may be in the form of, for example, aqueous or oily suspensions, solutions,

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emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methylcellulose, glucose/sugar syrup, gelatin, hydroxypropyl methylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; and preservatives, for example, methyl or propyl p-hydroxybenzoates or sorbic acid. The compositions may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The composition according to the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

For administration by inhalation either orally or nasally the compositions according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or from a nebuliser. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation the compositions according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder

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composition may be presented in unit dosage form in, for example, capsules or cartridges of e.g. gelatin, or blister packs from which the powder may be administered with the aid of an inhaler or insufflator.

The pharmaceutical formulations according to the invention may also contain other
5 active ingredients such as antimicrobial agents, or preservatives.

The compositions according to the invention may be prepared by mixing the various ingredients using conventional means.

It will be appreciated that the amount of a compound of general formula (I) required for use in treatment will vary not only with the particular compound selected but also with
10 the route of administration, the nature of the condition being treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician or veterinarian. In general, however, a proposed dose of the compounds of the invention for administration in man is 0.5 to 1000mg, preferably 1 to 200mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

15 The compounds of the invention may be prepared by a number of processes as described in the following. In describing the processes which may be used for preparing the compounds of general formula (I) or intermediates useful in the preparation thereof, any of R^1 - R^9 , m and p in the various formulae are as defined in general formula (I) unless otherwise stated.

20 It will be appreciated that in the following methods for the preparation of compounds of general formula (I), for certain reaction steps it may be necessary to protect various reactive substituents in the starting materials for a particular reaction and subsequently to remove the protecting group. Such protection and subsequent deprotection may be particularly pertinent where R^6 , R^7 , R^8 , and/or R^9 in intermediates used to prepare
25 compounds of general formula (I) are hydrogen atoms. Standard protection and deprotection procedures can be employed, for example formation of a phthalimide (in the case of a primary amine), benzyl, trityl, benzyloxycarbonyl or trichloroethoxycarbonyl derivatives. Subsequent removal of the protecting group is achieved by conventional procedures. Thus a phthalimide group may be removed by treatment with hydrazine or a
30 primary amine, for example methylamine. Benzyl or benzyloxycarbonyl groups may be

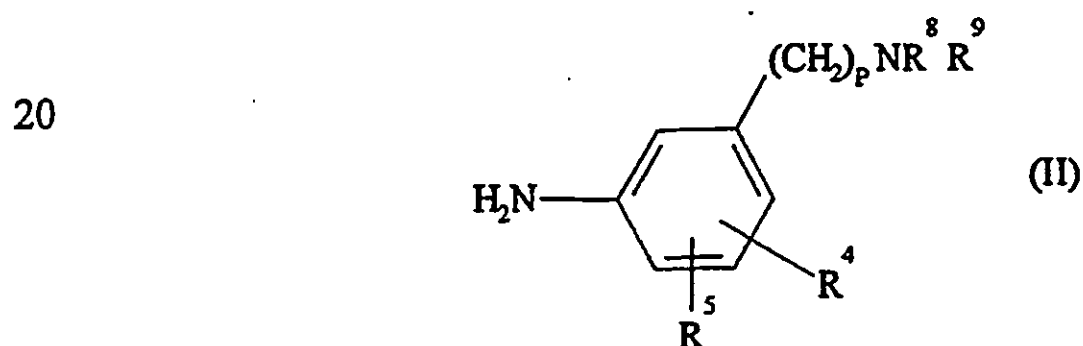
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removed by hydrogenolysis in the presence of a catalyst e.g. palladium, and trichloroethoxycarbonyl derivatives may be removed by treatment with zinc dust. Trityl groups may be removed under acidic conditions using standard procedures.

It may also be necessary in some cases to protect carboxylic acid groups (e.g. as esters) or aldehyde or ketone groups (e.g. as acyclic or cyclic acetals or ketals or as thioacetals or thioketals). Subsequent removal of these protecting groups is achieved by conventional procedures. Thus for example alkyl esters may be removed under conditions of acidic or basic hydrolysis, benzyl esters may be removed by hydrogenolysis in the presence of a catalyst e.g. palladium. Acyclic or cyclic acetals or ketals may be removed under conditions of acidic hydrolysis and thioacetals and thioketals may be removed using a mercuric salt.

Hydroxyl groups may also need protection and these may be adequately protected under amenable conditions as their esters or trialkylsilyl, tetrahydropyran and benzyl ethers. Such derivatives may be deprotected by standard procedures.

According to one general process (1A), the compounds of general formula (I) in which X represents the group $-\text{CONH}-$, may be prepared by a carbonylation reaction involving an aniline (II)



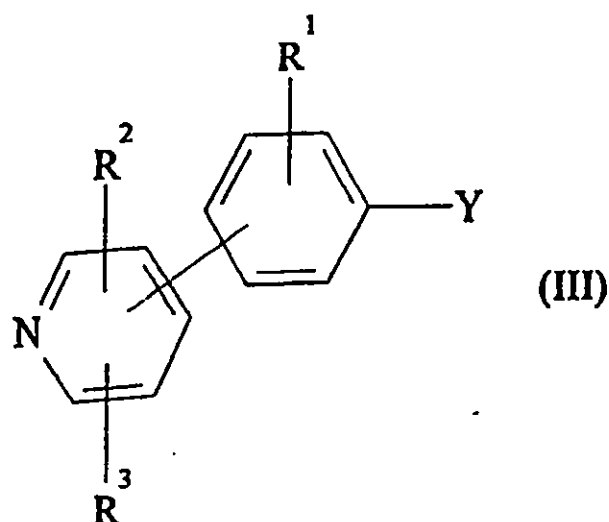
(where R^4 , R^5 , R^8 , R^9 and p are as defined in general formula (I)) and a halophenyl compound (III)

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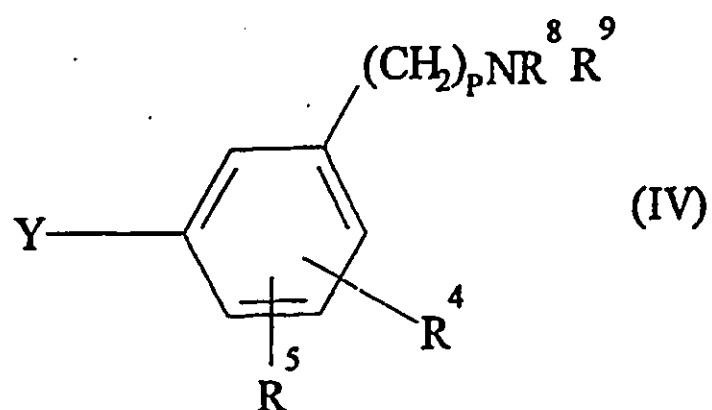
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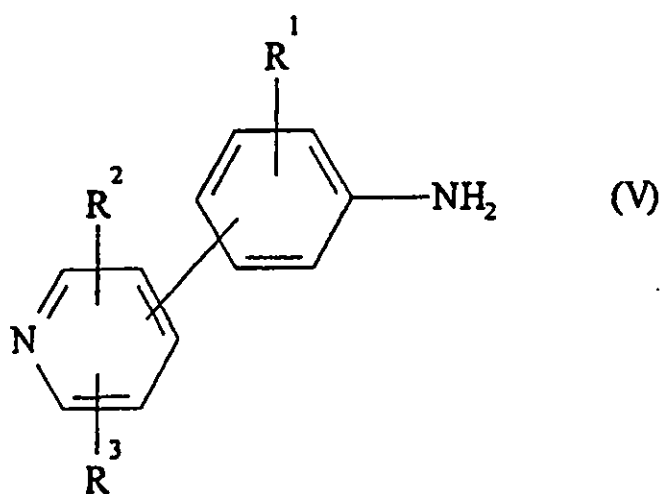


(where R^1 , R^2 and R^3 are as defined in general formula (I) and Y is a bromine or iodine atom or the group $-\text{OSO}_2\text{CF}_3$).

Alternatively, according to the general process (1B), the compounds of general formula (I), in which X represents the group $-\text{NHCO}-$, may be prepared by a carbonylation reaction involving a halophenyl compound (IV)



(where R^4 , R^5 , R^8 , R^9 and p are as defined in general formula (I) and Y represents a bromine or iodine atom or the group $-\text{OSO}_2\text{CF}_3$) and an aniline of formula (V)



(where R^1 , R^2 and R^3 are as defined in general formula (I)).

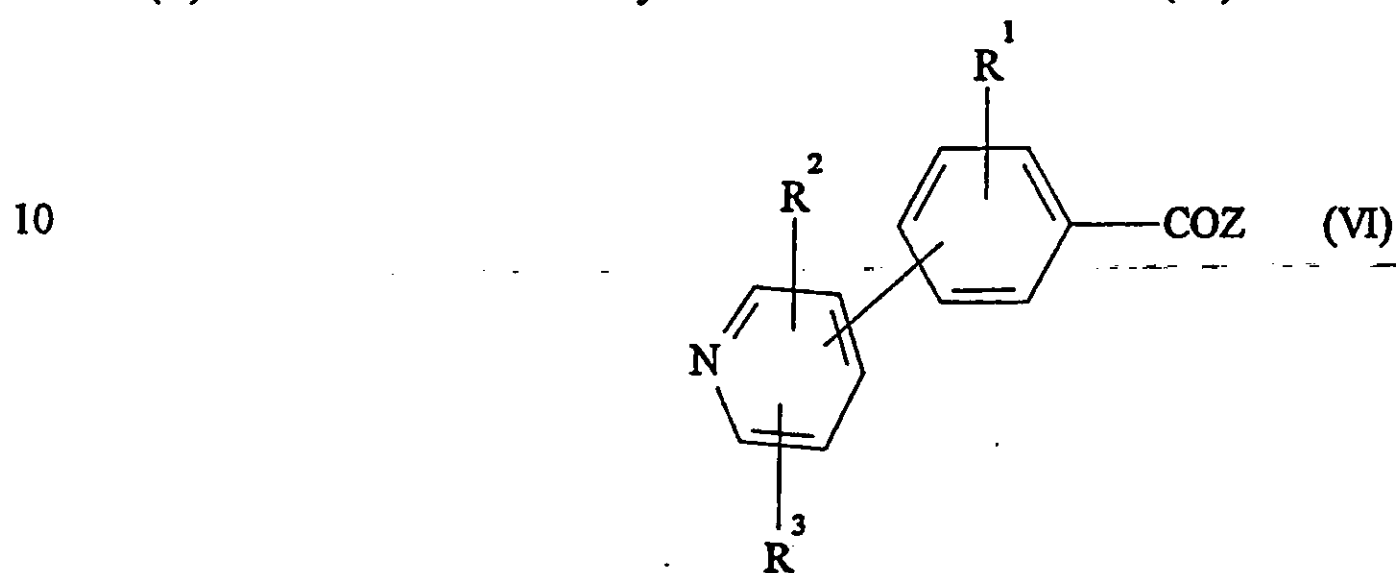
Both reactions take place, for example, in the presence of carbon monoxide using a palladium salt as a catalyst. The reaction is effected in the presence of a suitable base e.g. a trialkylamine such as triethylamine or tri-*n*-butylamine and may be conducted in a

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suitable solvent such as an amide e.g. dimethylformamide or a nitrile e.g. acetonitrile at a temperature within the range of -10°C to $+150^{\circ}\text{C}$.

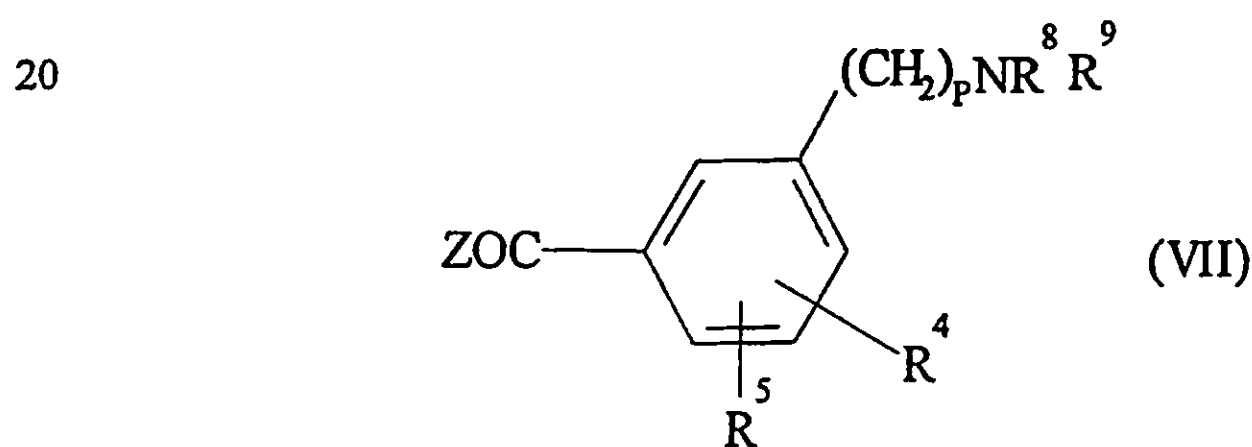
Suitable palladium salts for the reaction include triarylphosphine palladium (II) salts such as bis(triphenylphosphine)palladium (II) chloride.

- 5 According to another general process (2A), the compounds of general formula (I), in which X represents the group $-\text{CONH}-$, may be prepared by reacting an aniline of formula (II) with an activated carboxylic acid derivative of formula (VI)



(where Z is a leaving group).

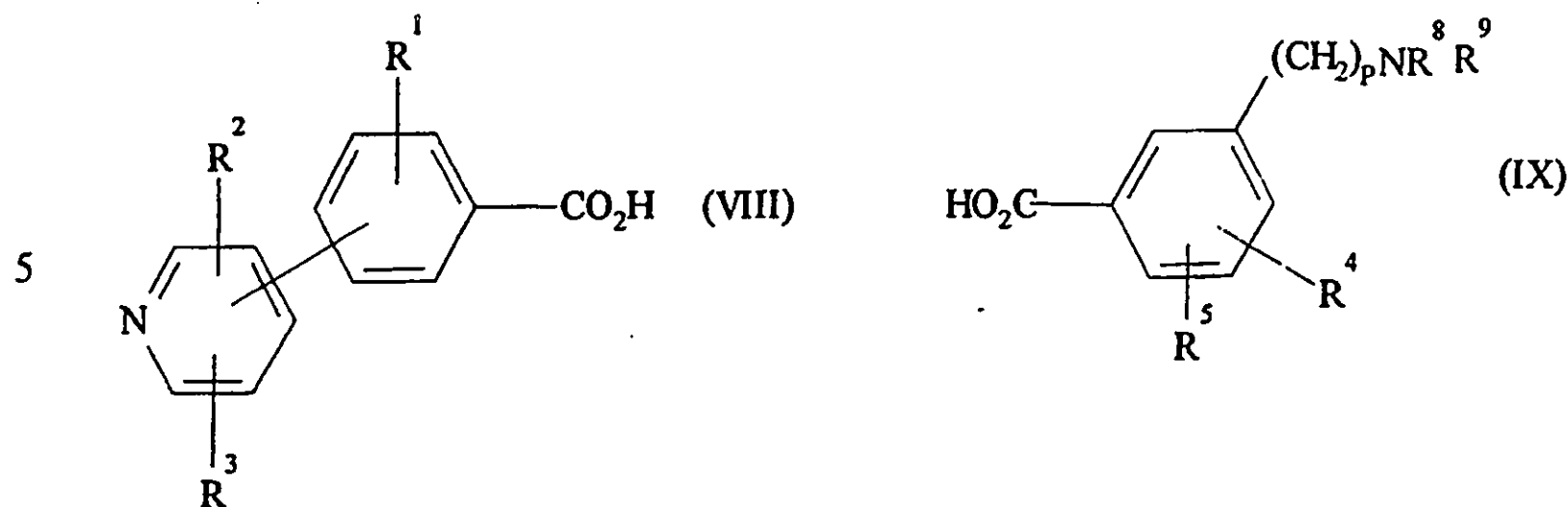
Alternatively, according to the general process (2B), the compounds of general formula (I), in which X represents the group $-\text{NHCO}-$, may be prepared by reacting an aniline of formula (V) with an activated carboxylic acid derivative of formula (VII)



(where Z is a leaving group).

Suitable activated carboxylic acid derivatives represented in formulae (VI) and (VII) include acyl halides (e.g. acid chlorides) and acid anhydrides including mixed anhydrides. These activated derivatives may be formed from the corresponding acids of formulae

(VIII) or (IX)



10 respectively, by well known procedures. For example, acid chlorides may be prepared by reaction with phosphorus pentachloride, thionyl chloride or oxalyl chloride and acid anhydrides may be prepared by reaction with an appropriate acid anhydride (e.g. trifluoroacetic anhydride), an acid chloride (e.g. acetyl chloride), an alkyl or aralkyl haloformate (e.g. ethyl or benzyl chloroformate) or methanesulphonyl chloride.

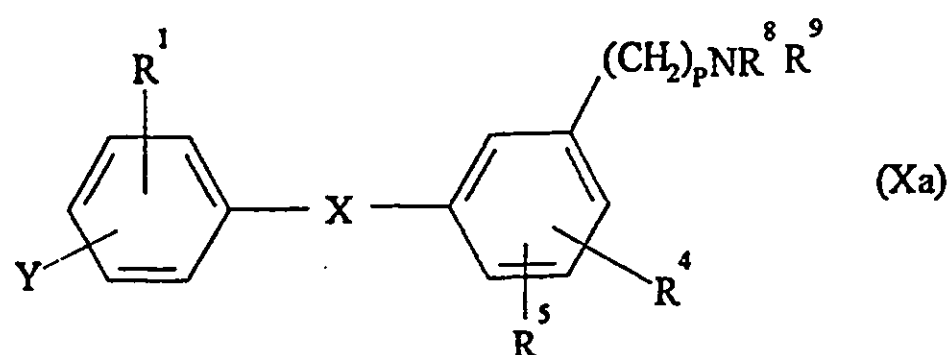
15 Activated carboxylic acid derivatives of formulae (VI) and (VII) may also be prepared *in situ* by the reaction of the corresponding acids of formulae (VIII) and (IX), respectively, with a coupling reagent such as 1,1'-carbonyldiimidazole, dicyclohexylcarbodiimide or diphenylphosphorylazide.

20 The conditions under which the activated carboxylic acid derivatives of formulae (VI) and (VII) are formed and subsequently reacted with the anilines of formulae (II) and (V), respectively, will depend upon the nature of the activated derivative. However, in general the reaction between the compounds (II) and (VI), or (V) and (VII), may be carried out in a non-aqueous medium such as, for example, dimethylformamide, tetrahydrofuran, acetonitrile or a halohydrocarbon such as dichloromethane at a temperature within the range -25°C to +120°C. The reaction may optionally be carried out in the presence of a
25 base such as triethylamine or pyridine and the base may also be used as the solvent for reaction.

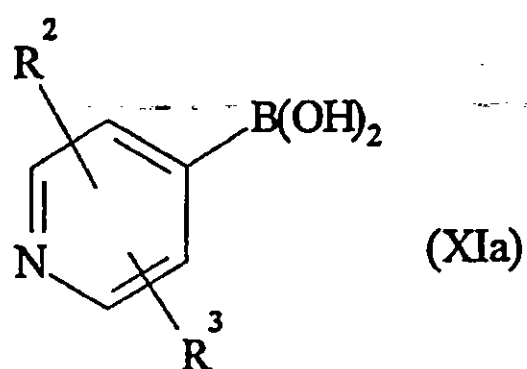
Where acid chlorides are used, the reaction may be carried out using the Schotten-Baumann technique in the presence of a suitable base, for example, aqueous sodium hydroxide, conveniently at a temperature between 0°C and 100°C, for example,
30 room temperature.

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According to another general process (3A), the compounds of general formula (I) may be prepared by treating a compound of formula (Xa)

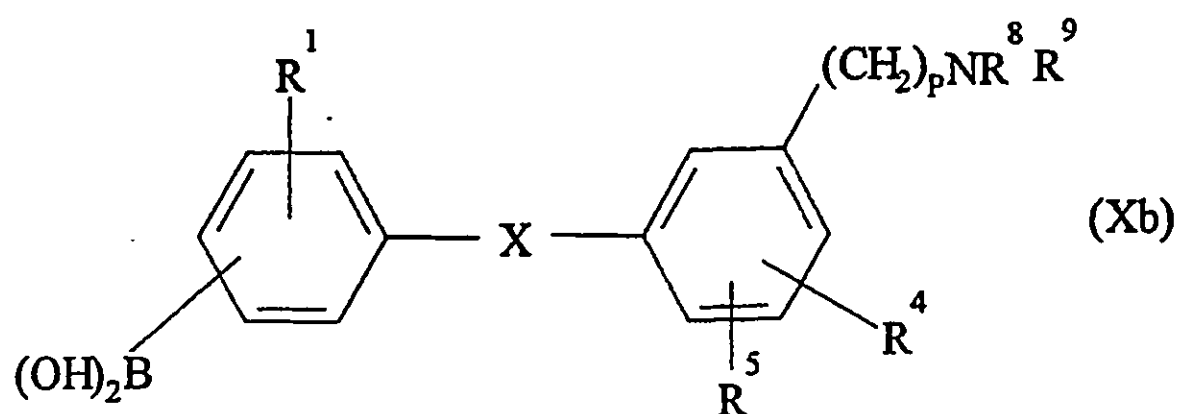


(where Y represents a bromine or iodine atom or the group $-\text{OSO}_2\text{CF}_3$) with a compound of formula (XIa)

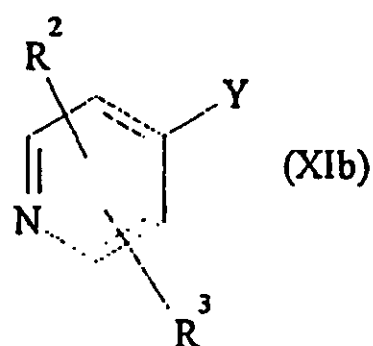


or an ester, an anhydride or a salt (e.g. lithium) thereof.

Alternatively, according to the general process (3B), the compounds of general formula (I) may be prepared by treating a compound of formula (Xb)



or an ester, an anhydride or a salt (e.g. lithium) thereof, with a compound of formula (XIb)

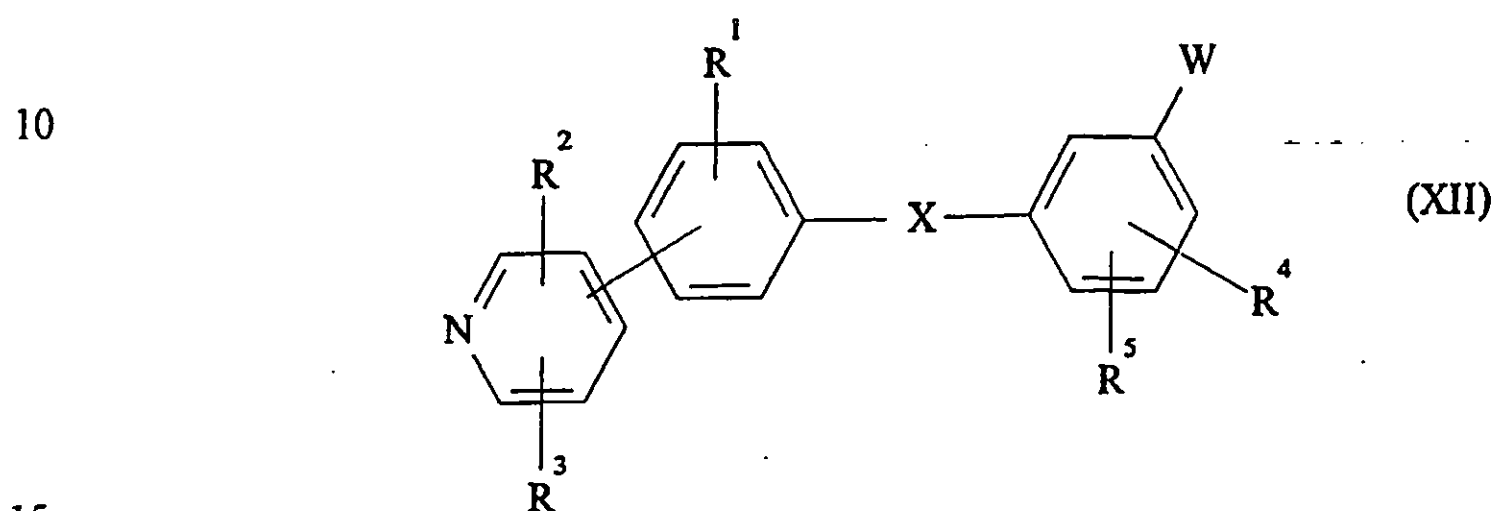


where Y represents a bromine or iodine atom or the group $-\text{OSO}_2\text{CF}_3$.

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Both reactions may be effected in the presence of a transition metal catalyst such as $(\text{Ph}_3\text{P})_4\text{Pd}$ (where Ph represents phenyl) in a suitable solvent such as an ether (e.g. 1,2-dimethoxyethane or tetrahydrofuran) in the presence or absence of water, or an aromatic hydrocarbon (e.g. benzene). The reaction is preferably carried out in the presence of a base such as an alkali or alkaline earth metal carbonate (e.g. sodium carbonate) at a suitable temperature up to reflux.

According to another general process (4), the compounds of general formula (I) may be prepared by reducing a compound of formula (XII)



(where W represents a group convertible to the group $-(\text{CH}_2)_p\text{NR}^8\text{R}^9$ under reducing conditions).

Examples of the type of group W which may be converted into the group $-(\text{CH}_2)_p\text{NR}^8\text{R}^9$ are: $-(\text{CH}_2)_{p-1}\text{CN}$, $-(\text{CH}_2)_{p-1}\text{CHO}$, and when p is 3, $-\text{C}\equiv\text{CCN}$, $-\text{CH}=\text{CHCN}$, $-\text{CH}=\text{CHCHO}$, $-\text{CH}=\text{CHCH}_2\text{NR}^8\text{R}^9$ or $-\text{C}\equiv\text{CCH}_2\text{NR}^8\text{R}^9$. When W contains an aldehyde as defined above, the conversion is carried out in the presence of an appropriate amine of formula NHR^8R^9 . When W contains a nitrile as defined above, the conversion may be carried out in the presence of an amine of formula NHR^8R^9 , with the proviso that R^8 and R^9 do not both represent a hydrogen atom, in order to obtain a secondary or tertiary amine of general formula (I).

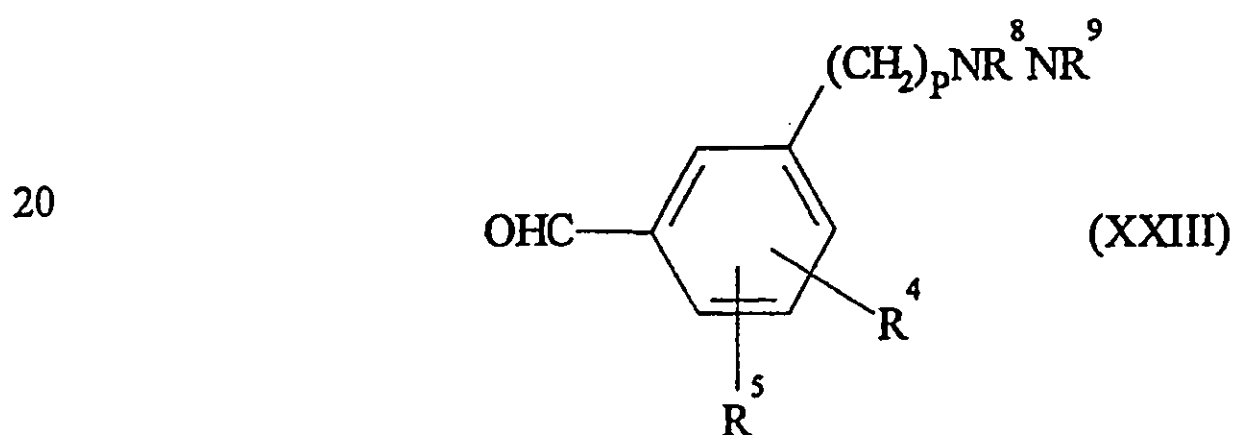
The reaction may be effected using an alkali or alkaline earth metal borohydride, e.g. sodium borohydride, or hydrogen and a metal catalyst such as palladium or platinum or oxides thereof. The reaction may be carried out at a temperature between 0°C and 100°C , conveniently at room temperature, and preferably in a solvent.

Suitable solvents for chemical reduction include ethers e.g. tetrahydrofuran, or alcohols e.g. ethanol. Suitable solvents for catalytic reduction include alcohols e.g. ethanol, ethers e.g. dioxan, amides e.g. dimethylformamide or a mixture of solvents e.g. ethanol/dimethylformamide.

- 5 According to another general process (5), the compounds of general formula (I) in which X represents either of the groups $\text{-NHCH}_2\text{-}$ or $\text{-CH}_2\text{NH-}$ may be prepared by reduction of the corresponding compounds of general formula (I) in which X represents the groups -NHCO- or -CONH- , respectively, except that the reaction cannot be used to prepare compounds in which R^2 and/or R^3 represents another group reducible under the
- 10 reaction conditions, for example, CONR^6R^7 , CO_2H , COR^6 , CN , NO_2 or $\text{-(CH}_2\text{)}_m\text{OC(O)C}_{1-4}\text{alkyl}$.

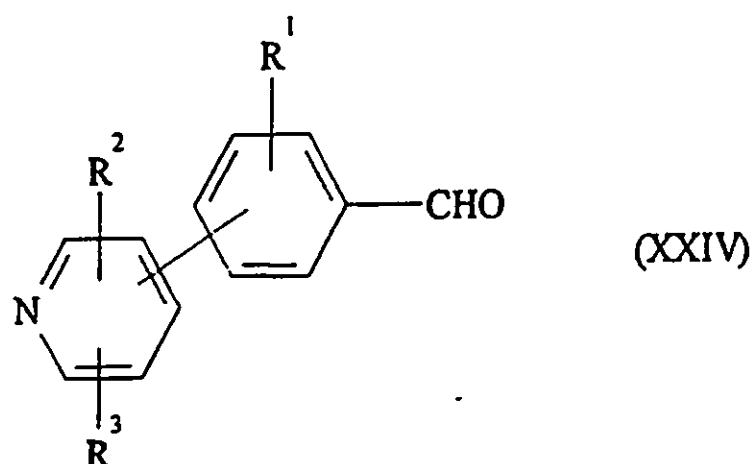
The reduction may be effected using a suitable metal hydride such as lithium aluminium hydride in a solvent e.g. an ether (such as tetrahydrofuran) at a temperature in the range of -10°C to $+100^\circ\text{C}$.

- 15 According to another general process (6A), the compounds of general formula (I) in which X represents the group $\text{-NHCH}_2\text{-}$ may be prepared by reacting an aniline of formula (V) with an aldehyde of formula (XXIII)



under reducing conditions.

- 25 Alternatively, according to general process (6B), the compounds of general formula (I) in which X represents the group $\text{-CH}_2\text{NH-}$ may be prepared by reacting an aniline of formula (II) with an aldehyde of formula (XXIV)



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under reducing conditions.

Both reactions may conveniently take place in the presence of a solvent such as an alcohol e.g. methanol or ethanol using for example a hydride reducing agent such as an alkali or alkaline earth metal borohydride (e.g. sodium borohydride or sodium cyanoborohydride). The reactions may be carried out at a temperature in the range from 0° to 60°C , conveniently at room temperature.

Compounds of general formula (I) in which R^2 , R^3 , R^4 and R^5 have a particular meaning may be converted into another compound of the invention by standard methods of interconversion.

For instance, when R^2 and/or R^3 represents a hydroxy or alkoxy group and/or when R^4 and/or R^5 represents hydroxy or alkoxy these groups may be interchanged by standard methods of O-alkylation or O-dealkylation. Thus, for example, a compound in which R^4 represents hydroxy may be prepared by treating a corresponding compound in which R^4 represents methoxy with a reagent system capable of removing the methyl group e.g. a mercaptide such as sodium ethylmercaptide in a solvent such as dimethylformamide, lithium iodide in collidine, boron tribromide in a halohydrocarbon solvent e.g. methylene chloride or molten pyridine hydrochloride.

When R^2 represents a hydroxymethyl group this may be converted by oxidation into a corresponding compound of general formula (I) in which R^2 represents a group COR^6 (where R^6 is a hydrogen atom) or CO_2H . Thus, for example, oxidation may be effected using a suitable oxidising agent such as a manganese oxidising agent (e.g. manganese dioxide) in a solvent such as an ether (e.g. 1,4-dioxan) at a suitable temperature up to

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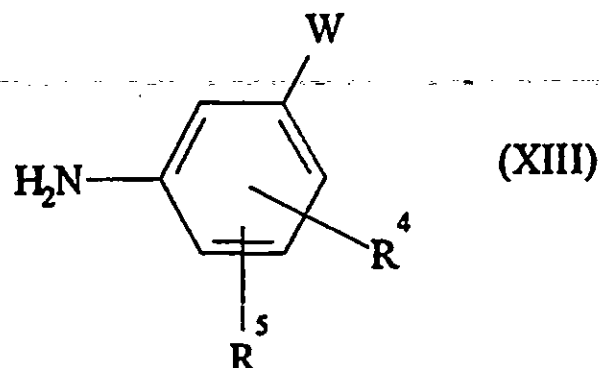
reflux, a chromium oxidising agent (e.g. Jones reagent) or pyridinium dichromate in a suitable solvent such as a halohydrocarbon (e.g. methylene chloride).

When R^2 represents an aldehyde group this may be converted by oxidation into a corresponding compound of general formula (I) in which R^2 represents a group CO_2H .

Thus, for example, oxidation may be effected using a suitable oxidising agent such as a source of silver (I) (e.g. silver nitrate) in aqueous alkali optionally in the presence of a cosolvent such as an alcohol (e.g. methanol).

Intermediates of formula (II) may be prepared by reduction of a compound of formula (XIII)

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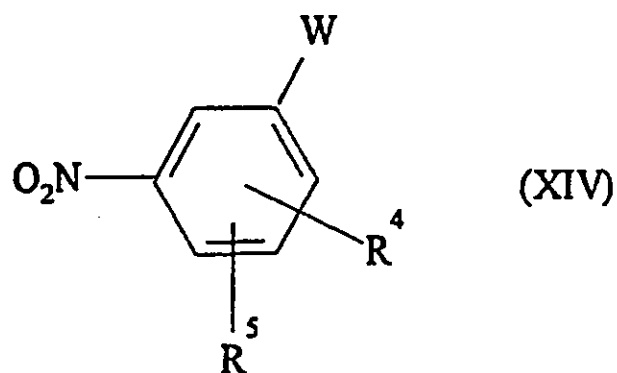


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(where W is as defined in formula (XII)) under the reducing conditions described for process (4).

Compounds of formula (XIII) may be prepared by reduction of the corresponding nitro compounds of formula (XIV)

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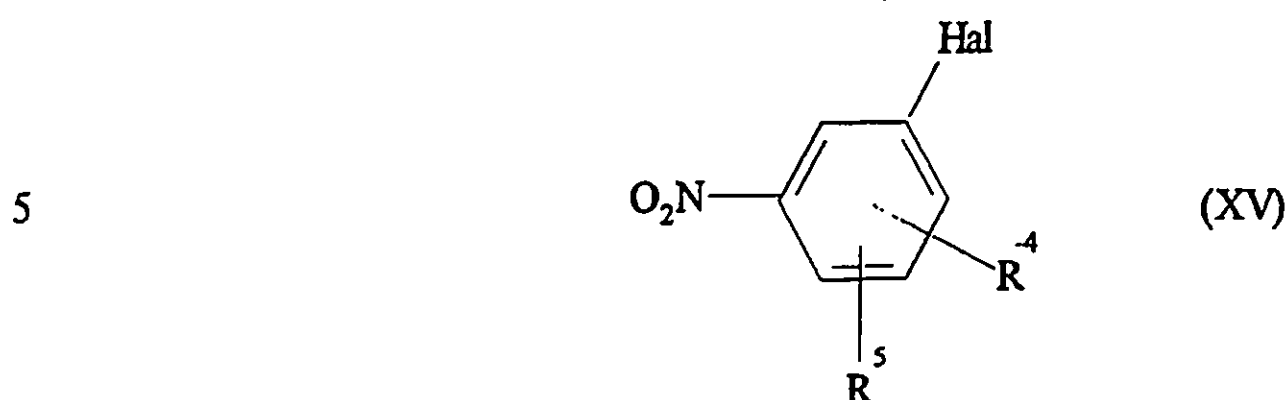
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Suitable reducing conditions include, for example, catalytic hydrogenation using a metal catalyst such as palladium oxide on a support such as charcoal, optionally in a solvent such as an alcohol (e.g. ethanol) or an ether (e.g. tetrahydrofuran). Under such conditions, the group W may also be reduced and hence the intermediates of formula (II) may be prepared directly from the compounds of formula (XIV) without prior isolation of the compounds of formula (XIII).

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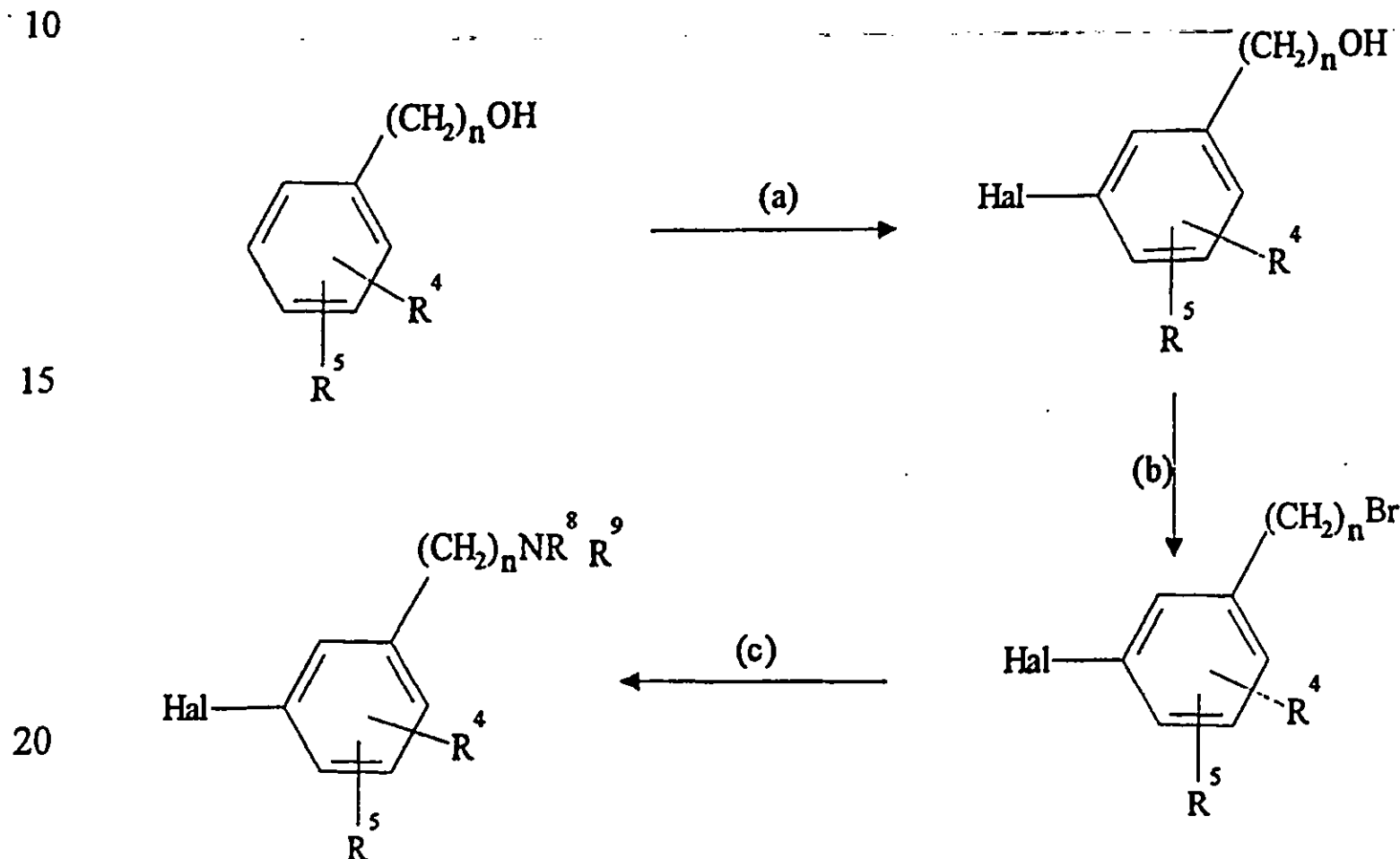
29

The nitro compounds of formula (XIV) may be prepared from the corresponding halo compounds of formula (XV)



(where Hal is bromine or iodine) using standard methodology.

Intermediates of formula (IV) may be prepared by the following reaction sequence:



Step (a) is carried out using suitable halogenating conditions, for example, when Hal represents iodine the iodine atom may be introduced using iodine monochloride in a solvent such as methylene chloride;

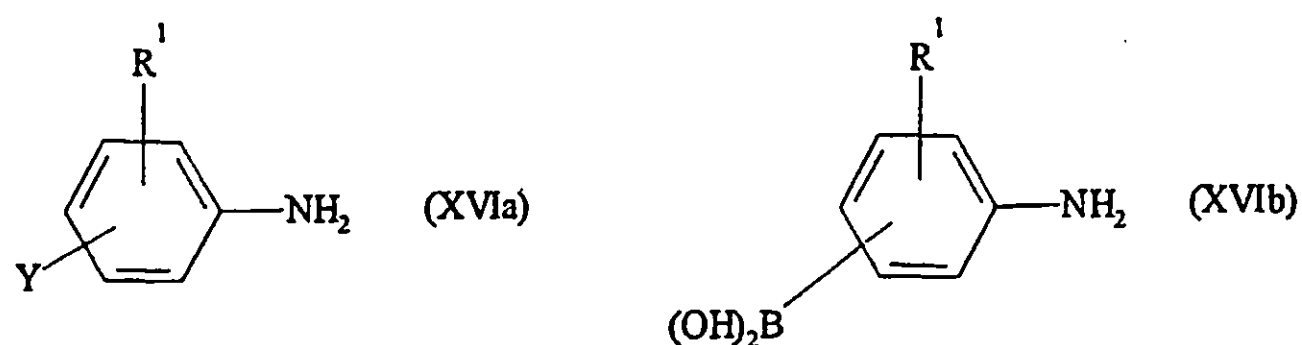
step (b) is carried out under standard brominating conditions such as using phosphorous tribromide in a halohydrocarbon solvent or using carbon tetrabromide in the presence of triphenylphosphine; and

step (c) is carried out using an amine R^8R^9NH in a suitable solvent such as ethanol, preferably in the presence of a base;

30

with the proviso that either R^4 or R^5 is a directing group (i.e. fluorine, chlorine, hydroxy, C_{1-6} alkoxy or C_{1-6} alkyl) in a position either ortho or para to the group $-(CH_2)_nOH$.

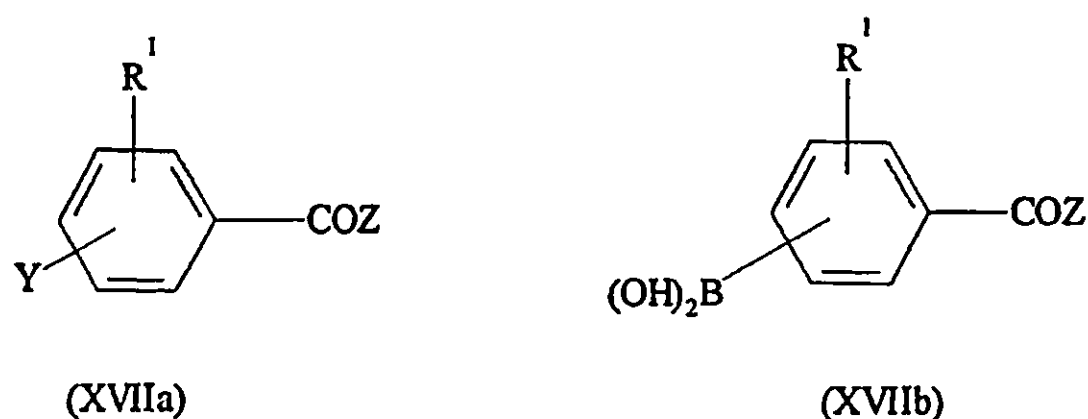
Intermediates of formula (V) may be prepared by reaction of a compound of formula (XIa) or (XIb) with a compound of formula (XVIa) or (XVIb), respectively,



10 according to the method of general process (3).

Intermediates of formula (II) or (V) may also be prepared from the corresponding carboxylic acid of formula (IX) or (VIII), respectively, using conventional procedures (e.g. by Curtius rearrangement).

15 Intermediates of formula (Xa) and (Xb), in which X is $-CONH-$, may be prepared by reaction of a compound of formula (II) with a compound of formula (XVIIa) or (XVIIb), respectively,

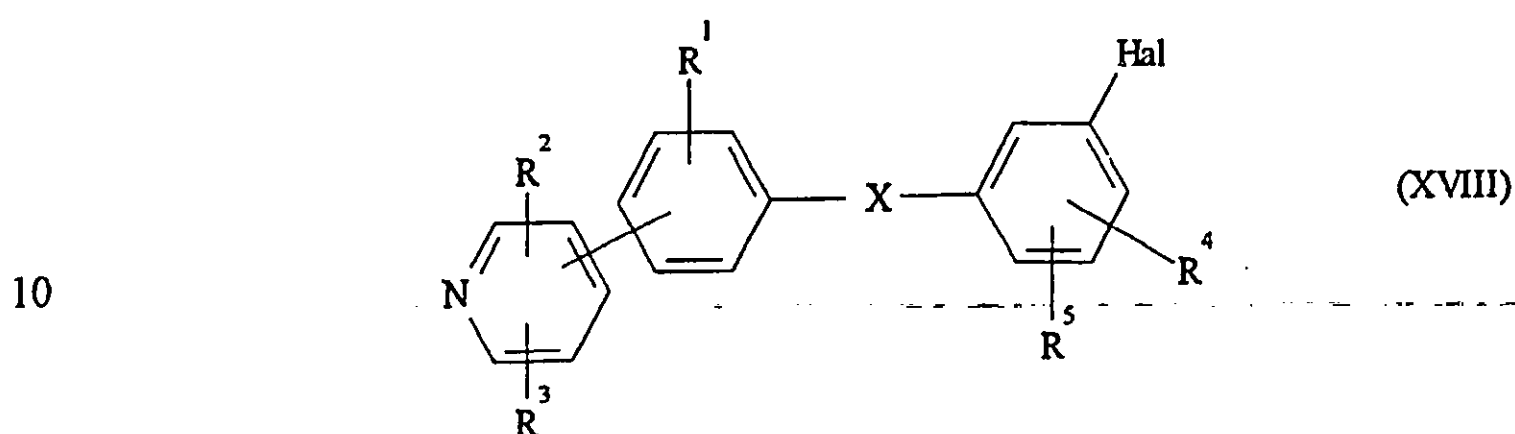


25 according to the method of general process (2).

Intermediates of formulae (Xa) and (Xb), in which X is $-NHCO-$, may be prepared by reaction of a compound of formula (VII) with a compound of formula (XVIa) or (XVIb), respectively, according to the method of general process (2).

Intermediates of formula (XII), in which X is -CONH-, may be prepared by reaction of a compound of formula (XIII) with a compound of either formula (III) or (VI) according to the method of general process (1) or (2), respectively.

Alternatively, intermediates of formula (XII), in which W is -CH=CHCHO, -CH=CHCN, -CH=CHCH₂NR⁸R⁹ or -C≡CCH₂NR⁸R⁹, may be prepared from a compound of formula (XVIII)



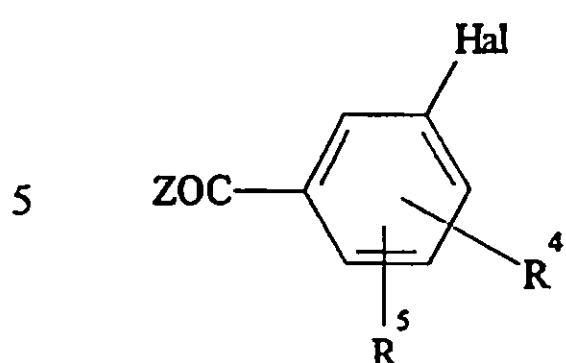
(wherein Hal is the only bromine or iodine atom in the molecule) by reaction with an alkene: H₂C=CHCHO, H₂C=CHCH₂NR⁸R⁹ or H₂C=CHCN; or an alkyne: HC≡CCH₂NR⁸R⁹.

15 The reaction may be effected in the presence of a palladium reagent and preferably in the presence of a base. The palladium reagent may be, for example, a palladium salt derived from an organic acid (e.g. an acetate) or derived from an inorganic acid (e.g. a chloride or bromide), a palladium complex such as a triarylphosphine palladium complex (e.g. triphenylphosphine or tri(2-methylphenyl)phosphine palladium complex), or a finely divided palladium metal such as palladium on charcoal. The triarylphosphine palladium complex may be generated *in situ* by reacting a palladium salt (e.g. palladium acetate) with the appropriate triarylphosphine.

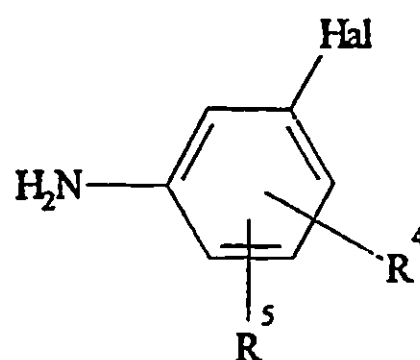
20 Suitable bases include tertiary amines (e.g. triethylamine or tri-n-butylamine) or alkali metal (e.g. sodium or potassium) carbonates, bicarbonates and acetates.

25 The reaction may be effected in the presence or absence of a solvent. Suitable solvents include nitriles (e.g. acetonitrile), amides (e.g. dimethylformamide, N-methylpyrrolidinone) and water. The reaction may conveniently be carried out at a temperature between room temperature and 200°C, preferably between 50°C and 160°C.

Compounds of formula (XVIII) may be prepared by the reaction of a compound of formula (V) or (VI) with a compound of formula (XIX) or (XX), respectively,



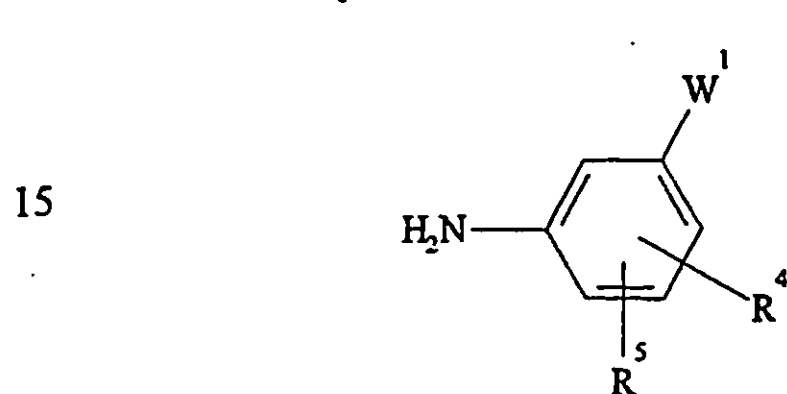
(XIX)



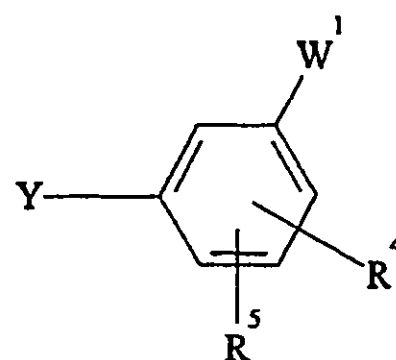
(XX)

according to the method of general process (2).

10 Alternatively, intermediates of formula (XII) in which W is $-(CH_2)_{p-1}CN$ or $-(CH_2)_{p-1}CHO$ may be prepared by the reaction of a compound of formula (III) or (V) with a compound of formula (XXI) or (XXII), respectively,



(XXI)



(XXII)

20 (wherein W^1 represents $-(CH_2)_{p-1}CN$ or $-(CH_2)_{p-1}CHO$), according to the method of general process (1).

Intermediates of formulae (XXI) and (XXII) in which W^1 contains a nitrile group may be prepared from the corresponding halo (e.g. bromo) compound using standard methodology.

25 It will be appreciated that, where necessary, a halogen substituent may be converted into a carboxyl group using standard methodology thus, for example, compounds of formula (VIII) or (IX) may be prepared from an intermediate of formula (III) or (IV), respectively, by lithiation using, for example, n-butyl lithium followed by quenching with carbon dioxide.

The boronic acid intermediates of formulae (Xb), (XIa), (XVIb) and (XVIIb) or their esters, anhydrides or salts may be used *in situ* under the conditions described above for general process (3).

5 The aldehydes of formula (XXIII) or (XXIV) may be prepared from an intermediate of formula (IV) or (III), respectively, by lithiation using, for example, n-butyl lithium followed by formylation using, for example, dimethylformamide.

Intermediates of formulae (III), (XIa), (XIb), (XV), (XVIa), (XVIb), (XVIIa), (XVIIb), (XIX) and (XX) are either known compounds or may be prepared by standard methodology or methods analogous to those described herein.

10 Physiologically acceptable acid addition salts of the compounds of general formula (I) may be prepared by treating the corresponding free base with a suitable acid using conventional methods. Thus, for example, a generally convenient method of forming the acid addition salts is to mix appropriate quantities of the free base and the acid in an appropriate solvent e.g. an alcohol such as ethanol or an ester such as ethyl acetate.

15 Inorganic basic salts of compounds of general formula (I) may be prepared by treating the corresponding acid of general formula (I) (i.e. a compound of general formula (I) in which R^2 and/or R^3 represents the group CO_2H) with a suitable base using conventional methods.

20 Salts of compounds of general formula (I) may also be converted into different physiologically acceptable salts of compounds of general formula (I) using conventional methods.

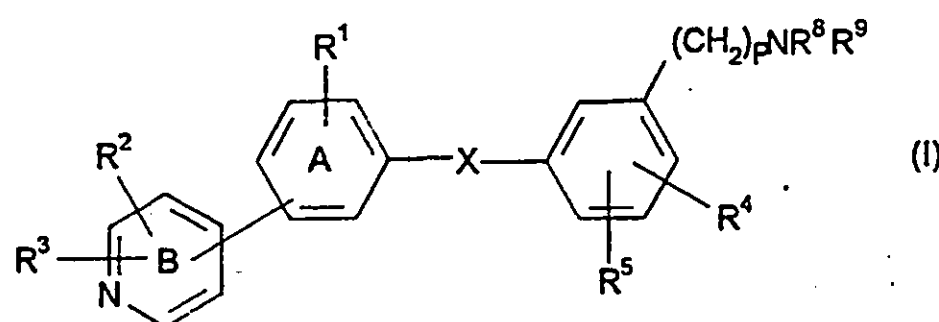
25 The invention is illustrated but not limited by the following examples in which temperatures are in $^{\circ}C$. Thin layer chromatography (T.l.c.) was carried out on silica plates. 'Dried' refers to drying using sodium sulphate or magnesium sulphate unless otherwise stated. Flash column chromatography (FCC) was carried out on silica gel (Merck 9385) unless otherwise stated. Short path column chromatography (SPC) was carried out on silica gel (Merck 7747) unless otherwise stated.

The following solvent systems were used: System A - dichloromethane:ethanol:0.88 ammonia; System B - dichloromethane:ethanol; System C - hexane:diethyl ether; System

Claims

1. Compounds of the general formula (I) :-

5



or a physiologically acceptable salt or solvate thereof, in which

R^1 represents a hydrogen atom or a halogen atom or a C_{1-6} alkyl or C_{1-6} alkoxy group;

10 R^2 and R^3 , which may be the same or different, each independently represent a hydrogen atom or a halogen atom, or a C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkoxy C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, -CN, -NO₂, -CO₂R⁶, -COR⁶, -CONR⁶R⁷ or -(CH₂)_mOC(O) C_{1-4} alkyl group;

15 R^4 and R^5 , which may be the same or different, each independently represent a hydrogen atom or a halogen atom, or a hydroxy, C_{1-6} alkoxy or C_{1-6} alkyl group;

R^6 , R^7 , R^8 and R^9 , which may be the same or different, each independently represent a hydrogen atom or a C_{1-6} alkyl group;

20 or -NR⁶R⁷ forms a saturated heterocyclic ring which has 5 or 6 ring members which, when there are 6 ring members, may optionally contain in the ring one oxygen or sulphur atom;

X represents -CONH-, -NHCO-, -CH₂NH- or -NHCH₂-;

m represents zero or an integer from 1 to 3; and

p represents an integer from 2 to 4.

25

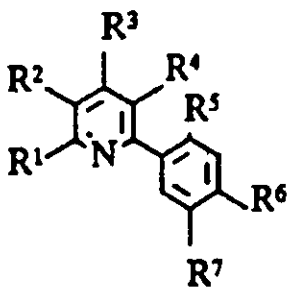
2. Compounds as claimed in Claim 1 for use in therapy.



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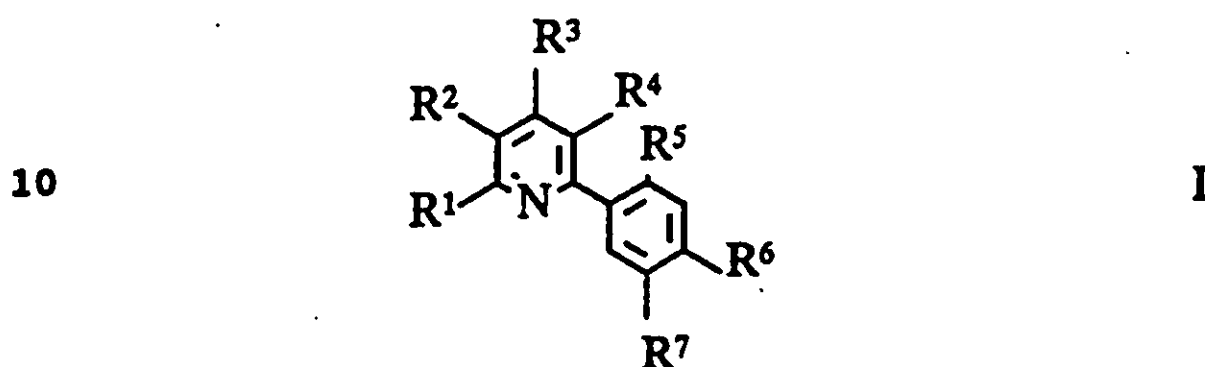
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(54) Title: SUBSTITUTED 2-PHENYLPYRIDINES WITH HERBICIDAL ACTION <div style="text-align: center;">  <p>(I)</p> </div> (57) Abstract <p>Substituted 2-phenylpyridines have formula (I) wherein R¹, R³ = H, halogen, alkyl, haloalkyl, alkoxyalkyl, alkoxy, alkoxyalkoxy, OH, haloalkoxy, alkylcarbonyloxy, haloalkylcarbonyloxy, SH, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, CHO, CN, CO₂H, alkoxycarbonyl, alkoxyalkoxycarbonyl, haloalkoxycarbonyl, alkylcarbonyl, haloalkylcarbonyl, alkoxyalkylcarbonyl, CONH₂, alkylaminocarbonyl, dialkylaminocarbonyl, pyrrolidinylcarbonyl, piperidylcarbonyl, morpholinylcarbonyl, NO₂, NH₂, alkylamino, dialkylamino, pyrrolidinyl, piperidinyl, morpholinyl, alkylcarbonylamino, haloalkylcarbonylamino, alkylsulfonylamino; R² = halogen, CN, NO₂, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio, haloalkylthio; or R¹ + R² or R² + R³ = trimethylene or tetramethylene chain; R⁴ = halogen, alkyl, haloalkyl, alkoxyalkyl, alkoxy, alkoxyalkoxy, OH, haloalkoxy, alkylcarbonyloxy, haloalkylcarbonyloxy, SH, alkylthio, alkylsulfinyl, alkylsulfonyl, haloalkylthio, haloalkylsulfinyl, haloalkylsulfonyl, CHO, CN, CO₂H, alkoxycarbonyl, alkoxyalkoxycarbonyl, haloalkoxycarbonyl, alkylcarbonyl, haloalkylcarbonyl, alkoxyalkylcarbonyl, NO₂, NH₂, alkylamino, dialkylamino, pyrrolidinyl, piperidinyl, morpholinyl, alkylcarbonylamino, haloalkylcarbonylamino, alkylsulfonylamino; R⁵ = hydrogen or halogen; R⁶ = halogen, CN, NO₂, OH, CF₃, C₁-C₆-alkyl, C₁-C₄-alkoxy; R⁷ = various radicals; and the N-oxides of (I) and the agriculturally utilizable salts of (I) where these exist, excepting those compounds (I) where R² is C₁-C₄-alkoxy and R¹ and/or R³ is carboxyl or the salt, ester or amide thereof. Use: herbicides; desiccation/defoliation of plants.</p>		

36

SUBSTITUTED 2-PHENYLPYRIDINES WITH HERBICIDAL ACTION

The present invention relates to novel substituted 2-phenylpyridines of the formula I



15

in which the variables have the following meanings:

- R¹, R³, independently of one another, hydrogen, halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkoxy-C₁-C₄-alkoxy, hydroxyl, C₁-C₄-haloalkoxy, (C₁-C₅-alkyl)carbonyloxy, (C₁-C₅-haloalkyl)carbonyloxy, SH, C₁-C₄-alkylthio, C₁-C₄-alkylsulfinyl, C₁-C₄-alkylsulfonyl, C₁-C₄-haloalkylthio, C₁-C₄-haloalkylsulfinyl, C₁-C₄-haloalkylsulfonyl, formyl, cyano, hydroxycarbonyl, (C₁-C₄-alkoxy)carbonyl, C₁-C₄-alkoxy-(C₁-C₄-alkoxy)carbonyl, (C₁-C₄-haloalkoxy)carbonyl, (C₁-C₄-alkyl)carbonyl, (C₁-C₄-haloalkyl)carbonyl, C₁-C₄-alkoxy-(C₁-C₄-alkyl)carbonyl, CONH₂, (C₁-C₄-alkyl)amino-carbonyl, di-(C₁-C₄-alkyl)aminocarbonyl, pyrrolidinylcarbonyl, piperidinylcarbonyl, morpholinylcarbonyl, nitro, amino, C₁-C₄-alkylamino, di-(C₁-C₄-alkyl)amino, pyrrolidinyl, piperidinyl, morpholinyl, (C₁-C₄-alkyl)carbonylamino, (C₁-C₄-haloalkyl)carbonylamino or C₁-C₄-alkylsulfonylamino;
- 35 R²
halogen, cyano, nitro, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, or C₁-C₄-haloalkylthio

- 40 or together with R¹ or with R³ a trimethylene or tetramethylene chain;

- R⁴
halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkoxy-C₁-C₄-alkoxy, hydroxyl, C₁-C₄-haloalkoxy, (C₁-C₅-alkyl)carbonyloxy, (C₁-C₅-haloalkyl)carbonyloxy, SH, C₁-C₄-alkylthio,

2

C₁-C₄-alkylsulfinyl, C₁-C₄-alkylsulfonyl, C₁-C₄-haloalkylthio, C₁-C₄-haloalkylsulfinyl, C₁-C₄-haloalkylsulfonyl, formyl, cyano, hydroxycarbonyl, (C₁-C₄-alkoxy)carbonyl, C₁-C₄-alkoxy-(C₁-C₄-alkoxy)carbonyl, (C₁-C₄-haloalkoxy)carbonyl, 5 (C₁-C₄-alkyl)carbonyl, (C₁-C₄-haloalkyl)carbonyl, C₁-C₄-alkoxy-(C₁-C₄-alkyl)carbonyl, nitro, amino, C₁-C₄-alkylamino, di-(C₁-C₄-alkyl)amino, pyrrolidinyl, piperidinyl, morpholinyl, (C₁-C₄-alkyl)carbonylamino, (C₁-C₄-haloalkyl)carbonylamino or C₁-C₄-alkylsulfonylamino;

10

R⁵

hydrogen or halogen;

R⁶

15 halogen, cyano, nitro, hydroxyl, trifluoromethyl, C₁-C₆-alkyl or C₁-C₄-alkoxy;

R⁷chlorine, bromine, iodine, cyano, nitro, C₁-C₈-alkyl,

20 C₂-C₈-alkenyl, C₂-C₈-alkynyl, C₁-C₈-haloalkyl, C₂-C₈-haloalkenyl, C₂-C₈-haloalkynyl, -(C₁-C₈-alkylene)-O-R⁸, -(C₂-C₈-alkenylene)-O-R⁸, -(C₂-C₈-alkynylene)-O-R⁸, -(C₁-C₈-alkylene)-S-R⁸,

-(C₂-C₈-alkenylene)-S-R⁸; -(C₂-C₈-alkynylene)-S-R⁸,-(C₁-C₈-alkylene)-SO-R⁸, -(C₂-C₈-alkenylene)-SO-R⁸,

25 -(C₂-C₈-alkynylene)-SO-R⁸, -(C₁-C₈-alkylene)-SO₂-R⁸,

-(C₂-C₈-alkenylene)-SO₂-R⁸; -(C₂-C₈-alkynylene)-SO₂-R⁸, -O-R⁸,-S-R⁸, -SO-R⁸, -SO₂-R⁸, chlorosulfonyl, -SO₂-O-R⁸, -SO₂-N(R⁹, R¹⁰),-SO₂-NR⁹(CO-R¹²), -N(R⁹, R¹⁰), -NR¹¹(CO-R¹²), -NR¹¹(SO₂-R¹³),-N(SO₂-R¹³)(SO₂-R¹⁴), -N(SO₂-R¹³)(CO-R¹²), -NH-CO-O-R⁸, -O-CO-NH-R⁹,

30 -O-CO-R¹², -NH-CO-NH-R⁹, -O-CS-N(C₁-C₄-alkyl)₂, -O-CS-NH₂,

cyano-C₁-C₄-alkyl, -CO-O-R⁸, -CO-O-N=C(R²⁶, R²⁷), -CO--CH₂-O-N=C(R³⁰, R³¹), -CO-O-C(R²⁸, R²⁹)-CH₂-O-N=C(R³⁰, R³¹),-CO-N(R⁹, R¹⁰), -CS-N(R⁹, R¹⁰), -CO-NH-SO₂-(C₁-C₄-alkyl),isoxazolidinylcarbonyl, formyl, -CO-R¹⁵,

35 hydroxycarbonyl-C₁-C₆-alkyl, (C₁-C₆-alkoxy)carbonyl-C₁-C₆-alkyl,

-C(R¹⁵)=C(R¹⁶)-CHO, -C(R¹⁵)=C(R¹⁶)-CO-O-R⁸,-C(R¹⁵)=C(R¹⁶)-CO-N(R⁹, R¹⁰), -C(R¹⁵)=C(R¹⁶)-CO-R¹⁷, -CH=N-O-R⁸,-CH(XR¹⁸, YR¹⁹), -CH₂-CH(halogen)-CO-O-R⁸,-CH₂-CH(halogen)-CO-N(R⁹, R¹⁰), -CH₂-CH(halogen)-CO-(C₁-C₄-alkyl),

40 -CH₂-CH(halogen)-CN, -C(C₁-C₄-alkoxy)=N-O-R⁸,

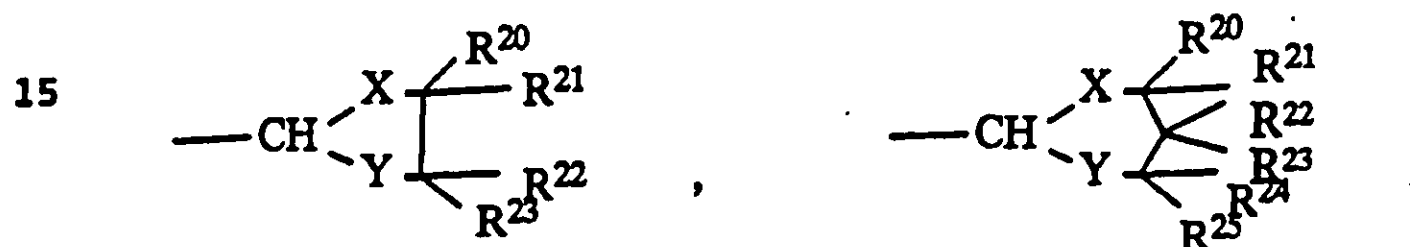
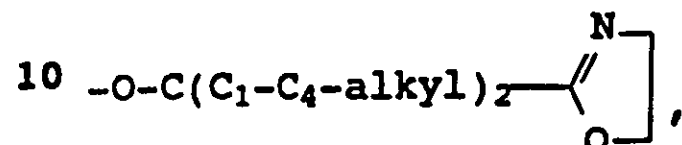
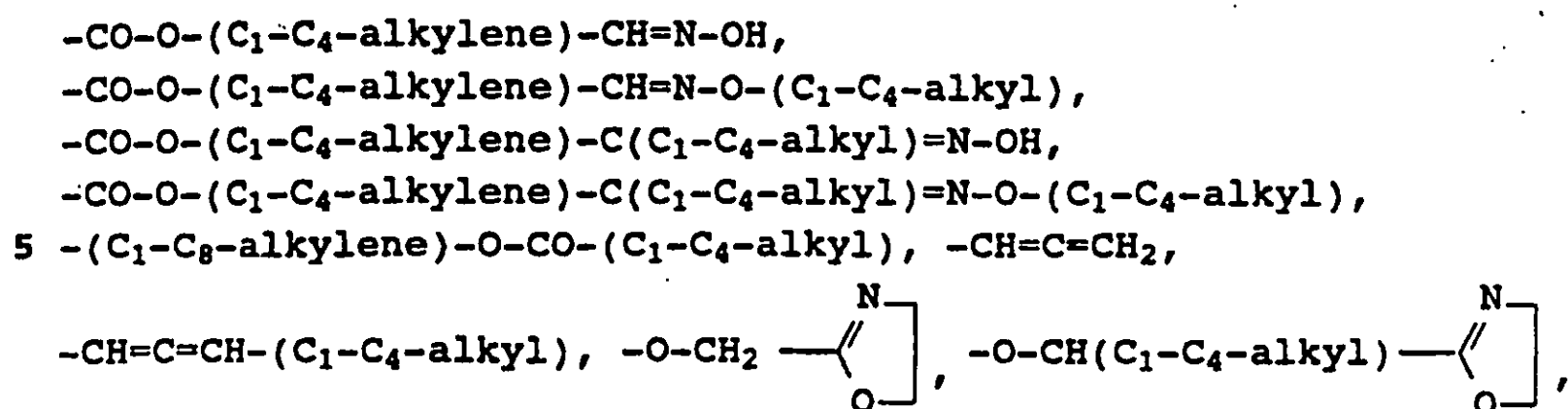
-C(R¹⁵)=C(R¹⁶)-C(C₁-C₄-alkoxy)=N-O-R⁸, -CH=CH-CH=CH-CO-O-R⁸,-C(R⁵)=-C(R¹⁵)=N-O-R⁸, -CO-OCH=N-OH, -CO-

45

OCH=N-O-(C₁-C₄-alkyl), -CO-OC(C₁-C₄-alkyl)=N-OH,-CO-OC(C₁-C₄-alkyl)=N-O-(C₁-C₄-alkyl),

38

3



- 20 5- or 6-membered heteroaryl with one to three hetero atoms selected from a group comprising one or two nitrogen atoms and one oxygen or sulfur atom, it being possible for each heteroaromatic ring atom which can be substituted to carry, if desired, a radical selected from the group comprising nitro,
 25 halogen, $\text{C}_1-\text{C}_4\text{-alkyl}$, $\text{C}_1-\text{C}_4\text{-alkoxy}$, $\text{C}_1-\text{C}_4\text{-alkylthio}$ und $(\text{C}_1-\text{C}_4\text{-alkoxy})\text{carbonyl}$;

 R^8

- hydrogen, $\text{C}_1-\text{C}_8\text{-alkyl}$, $\text{C}_1-\text{C}_8\text{-haloalkyl}$, $\text{C}_4-\text{C}_7\text{-cycloalkyl}$, which in
 30 turn can carry one to three $\text{C}_1-\text{C}_3\text{-alkyl}$ radicals, $\text{C}_3-\text{C}_6\text{-alkenyl}$, $\text{C}_5-\text{C}_7\text{-cycloalkenyl}$, which in turn can carry one to three $\text{C}_1-\text{C}_3\text{-alkyl}$ radicals, $\text{C}_3-\text{C}_6\text{-haloalkenyl}$, cyano- $\text{C}_1-\text{C}_8\text{-alkyl}$, $\text{C}_3-\text{C}_6\text{-alkynyl}$, $\text{C}_2-\text{C}_8\text{-alkoxyalkyl}$, 2-tetrahydrofuranyl- $\text{C}_1-\text{C}_8\text{-alkyl}$, 3-oxetanyl, 3-thietanyl, carboxyl- $\text{C}_1-\text{C}_6\text{-alkyl}$, $(\text{C}_1-\text{C}_8\text{-alkoxy})\text{carbonyl}-\text{C}_1-\text{C}_6\text{-alkyl}$, $(\text{C}_1-\text{C}_6\text{-alkoxy})\text{carbonyl}-(\text{C}_3-\text{C}_7\text{-Cycloalkyl})$, $\text{C}_1-\text{C}_4\text{-alkoxy}-(\text{C}_1-\text{C}_4\text{-alkoxy})\text{carbonyl}-\text{C}_1-\text{C}_6\text{-alkyl}$, cyclopropylmethyl, (1-methylthiocyclopropyl)methyl, $-\text{CH}(\text{SH})-\text{CO}-\text{OH}$,
 $-\text{CH}(\text{SH})-\text{CO}-(\text{C}_1-\text{C}_8\text{-alkoxy})$, $-\text{CH}(\text{C}_1-\text{C}_8\text{-alkylthio})-\text{COOH}$,
 $-\text{CH}(\text{C}_1-\text{C}_4\text{-alkylthio})-\text{CO}-(\text{C}_1-\text{C}_8\text{-alkoxy})$, $-\text{CH}_2-\text{CO}-\text{N}(\text{R}^9)-\text{R}^{10}$,
 40 $-\text{CH}(\text{C}_1-\text{C}_4\text{-alkyl})-\text{CO}-\text{N}(\text{R}^9)-\text{R}^{10}$, $\text{C}(\text{C}_1-\text{C}_4\text{-alkyl})_2-\text{CO}-\text{N}(\text{R}^9)-\text{R}^{10}$,
 $-\text{CH}_2-\text{CO}-\text{N}(\text{R}^9)-\text{SO}_2-(\text{C}_1-\text{C}_4\text{-alkyl})$,
 $-\text{CH}(\text{C}_1-\text{C}_4\text{-alkyl})-\text{CO}-\text{N}(\text{R}^9)-\text{SO}_2-(\text{C}_1-\text{C}_4\text{-alkyl})$,
 $-\text{C}(\text{C}_1-\text{C}_4\text{-alkyl})_2-\text{CO}-\text{N}(\text{R}^9)-\text{SO}_2-(\text{C}_1-\text{C}_4\text{-alkyl})$, $-\text{S}-\text{CO}-\text{NH}_2$,
 $-\text{S}-\text{CO}-\text{N}(\text{C}_1-\text{C}_4\text{-alkyl})-(\text{C}_1-\text{C}_4\text{-alkyl})$,
 45 $-\text{CH}_2-\text{CO}-\text{O}-(\text{C}_1-\text{C}_6\text{-alkylene})-\text{COOH}$,
 $-\text{CH}_2-\text{CO}-\text{O}-(\text{C}_1-\text{C}_6\text{-alkylene})-\text{CO}-(\text{C}_1-\text{C}_6\text{-alkoxy})$,
 $-\text{C}(\text{C}_1-\text{C}_4\text{-alkyl})_2-\text{CO}-\text{O}-(\text{C}_1-\text{C}_6\text{-alkylene})-\text{COOH}$,

39

4

- C(C₁-C₄-alkyl)₂-CO-O-(C₁-C₄-alkylene)-CO-(C₁-C₆-alkoxy),
 -CH(C₁-C₄-alkyl)-CO-O-(C₁-C₆-alkylene)-COOH,
 -CH(C₁-C₄-alkyl)-CO-O-(C₁-C₆-alkylene)-CO-(C₁-C₆-alkoxy),
 C₃-C₉-(α -alkylalkylidene)iminooxy-C₁-C₆-alkyl, phenyl,
 5 phenyl-C₁-C₆-alkyl, phenyl-C₃-C₆-alkenyl, phenyl-C₃-C₆-alkynyl or
 phenoxy-C₁-C₆-alkyl, where the phenyl ring can in each case be
 unsubstituted or carry one to three radicals selected from the
 group comprising halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-alkoxy,
 C₁-C₄-alkylthio, C₁-C₄-haloalkyl and C₂-C₆-alkenyl, 5- or
 10 6-membered heteroaryl, heteroaryl-C₁-C₆-alkyl,
 heteroaryl-C₃-C₆-alkenyl, heteroaryl-C₃-C₆-alkynyl or
 heteroaryloxy-C₁-C₆-alkyl, where the heteroaryl radical in each
 case contains one to three hetero atoms selected from a group
 comprising one or two nitrogen atoms and one oxygen or sulfur
 15 atom, and it being possible for each heteroaromatic ring atom
 which can be substituted also to carry, if desired, a radical
 selected from the group comprising hydroxyl, halogen, C₁-C₄-alkyl,
 C₁-C₄-alkoxy, C₁-C₄-alkylthio and C₁-C₄-haloalkyl;
- 20 R⁹ and R¹⁰ independently of one another,
 hydrogen, C₁-C₈-alkyl, C₂-C₈-alkenyl, C₃-C₈-alkynyl,
 C₁-C₈-haloalkyl, C₁-C₄-alkoxy-C₁-C₄-alkyl,
 C₁-C₄-alkylthio-C₁-C₄-alkyl, cyano-C₁-C₈-alkyl,
 carboxyl-C₁-C₄-alkyl, (C₁-C₄-alkoxy)carbonyl-C₁-C₄-alkyl,
 25 (C₁-C₆-alkoxy)carbonyl- (C₃-C₇-cycloalkyl),
 C₁-C₄-alkylsulfonyl-C₁-C₄-alkyl, C₃-C₈-cycloalkyl, C₁-C₆-alkoxy,
 (C₃-C₆-cycloalkoxy)carbonyl-C₁-C₄-alkyl,
 C₁-C₄-alkoxy-(C₁-C₄-alkoxy)carbonyl-C₁-C₄-alkyl, phenyl,
 phenyl-C₁-C₄-alkyl, where the phenyl ring can in each case be
 30 unsubstituted or carry one to three radicals selected from the
 group comprising halogen, nitro, cyano, C₁-C₄-alkyl, C₁-C₄-alkoxy,
 C₁-C₄-alkylthio, C₁-C₄-haloalkyl and C₂-C₆-alkenyl, 5- or
 6-membered heteroaryl or heteroaryl-C₁-C₄-alkyl, where the
 heteroaryl radical contains one to three hetero atoms selected
 35 from a group comprising one or two nitrogen atoms and one oxygen
 or sulfur atom, and it being possible for each heteroaromatic
 ring atom which can be substituted also, if desired, to carry a
 radical selected from the group comprising hydroxyl, halogen,
 C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio and C₁-C₄-haloalkyl;
- 40 or
- R⁹ and R¹⁰ together a tetramethylene, pentamethylene or
 ethyleneoxyethylene chain, it being possible for each chain to
 45 carry, if desired, a (C₁-C₆-alkoxy)carbonyl radical;

40

5

R¹¹

hydrogen, C₁-C₄-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl,
C₁-C₄-alkoxy-C₁-C₄-alkyl, sodium, potassium, calcium, magnesium,
ammonium or ammonium which is substituted by one to four

- 5 C₁-C₄-alkyl- or benzyl radicals and can, if desired, carry one to three further C₁-C₄-alkyl radicals;

R¹²

hydrogen, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₄-alkoxy-

- 10 C₁-C₄-alkyl, C₃-C₇-cycloalkyl, which can in turn carry one to three radicals selected from the group comprising halogen, C₁-C₄-alkyl, C₁-C₄-alkoxy and C₁-C₄-alkylthio, phenyl or phenyl-C₁-C₆-alkyl, where the phenyl ring can in each case be unsubstituted or carry one to three radicals selected from the
15 group comprising halogen, nitro, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio and C₁-C₄-haloalkyl;

R¹³ and R¹⁴, independently of one another,

- C₁-C₄-alkyl, phenyl or thienyl, where the phenyl or thienyl
20 radical can be unsubstituted or carry one to three radicals selected from the group comprising halogen, nitro, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio and C₁-C₄-haloalkyl;

R¹⁵, R¹⁶ and R¹⁷, independently of one another,

- 25 hydrogen, halogen, C₁-C₄-alkyl, C₂-C₄-alkenyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy-C₁-C₄-alkyl or C₁-C₄-alkylthio-C₁-C₄-alkyl;

R¹⁸ and R¹⁹, independently of one another,

C₁-C₈-alkyl, C₁-C₄-alkoxy-C₁-C₄-alkyl or C₁-C₈-haloalkyl;

30

R²⁰, R²¹, R²², R²³, R²⁴ and R²⁵, independently of one another,

hydrogen, cyano, C₁-C₈-alkyl, C₁-C₄-alkoxy-C₁-C₄-alkyl,
halo-C₁-C₈-alkyl, C₁-C₈-alkoxy, C₁-C₄-alkoxy-C₁-C₄-alkoxy, -CO-
O-R⁸, -CO-N(R⁹, R¹⁰), -CO-R¹⁵, -S-R⁸, -SO₂-R⁸, -O-CO-R¹² or

- 35 C₃-C₇-cycloalkyl, which can in turn carry from one to three radicals selected from the group comprising halogen, C₁-C₄-alkyl, C₁-C₄-alkoxy and C₁-C₄-alkylthio;

R²⁶

- 40 C₁-C₆-alkyl, C₁-C₆-alkylthio, C₁-C₆-alkoxycarbonyl or C₁-C₆-alkoxycarbonyl-C₁-C₄-alkyl;

R²⁷

C₁-C₆-alkyl, trifluoromethyl, C₁-C₆-alkoxy-C₁-C₄-alkyl,

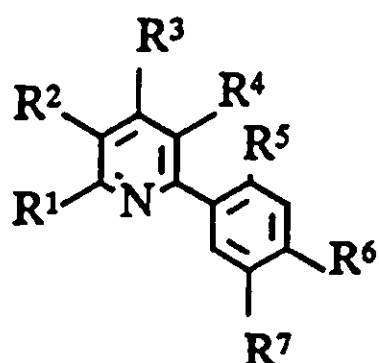
- 45 C₂-C₇-alkoxycarbonyl-C₁-C₄-alkyl,
di-(C₁-C₆-alkoxycarbonyl)-C₁-C₄-alkyl, C₃-C₆-cycloalkyl,
C₁-C₆-alkoxy, C₁-C₆-alkylthio, C₁-C₆-alkanoyl,

We claim:

1. A substituted 2-phenylpyridine of the formula I

5

10



I

- 15 in which the variables have the following meanings:

20 R^1, R^3 , independently of one another,
 hydrogen, halogen, C_1 - C_4 -alkyl, C_1 - C_4 -haloalkyl, C_1 - C_4 -alkoxy-
 C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, C_1 - C_4 -alkoxy- C_1 - C_4 -alkoxy, hydroxyl,
 C_1 - C_4 -haloalkoxy, (C_1 - C_5 -alkyl)carbonyloxy, (C_1 - C_5 -
 haloalkyl)carbonyloxy, SH, C_1 - C_4 -alkylthio, C_1 - C_4 -alkyl-
 sulfinyl, C_1 - C_4 -alkylsulfonyl, C_1 - C_4 -haloalkylthio, C_1 - C_4 -
 haloalkylsulfinyl, C_1 - C_4 -haloalkylsulfonyl, formyl, cyano,
 hydroxycarbonyl, (C_1 - C_4 -alkoxy)carbonyl, C_1 - C_4 -alkoxy-
 25 (C_1 - C_4 -alkoxy)carbonyl, (C_1 - C_4 -haloalkoxy)carbonyl,
 (C_1 - C_4 -alkyl)carbonyl, (C_1 - C_4 -haloalkyl)carbonyl, C_1 - C_4 -
 alkoxy-(C_1 - C_4 -alkyl)carbonyl, $CONH_2$, (C_1 - C_4 -alkyl)amino-
 carbonyl, di-(C_1 - C_4 -alkyl)aminocarbonyl, pyrrolidinylcarbonyl,
 piperidinylcarbonyl, morpholinylcarbonyl, nitro, amino,
 30 C_1 - C_4 -alkylamino, di-(C_1 - C_4 -alkyl)amino, pyrrolidinyl,
 piperidinyl, morpholinyl, (C_1 - C_4 -alkyl)carbonylamino,
 (C_1 - C_4 -haloalkyl)carbonylamino or C_1 - C_4 -alkylsulfonylamino;

35 R^2
 halogen, cyano, nitro, C_1 - C_4 -alkyl, C_1 - C_4 -haloalkyl, C_1 - C_4 -
 alkoxy, C_1 - C_4 -haloalkoxy, C_1 - C_4 -alkylthio, or C_1 - C_4 -haloalkyl-
 thio

40 or together with R^1 or with R^3 a trimethylene or tetramethy-
 lene chain;

45 R^4
 halogen, C_1 - C_4 -alkyl, C_1 - C_4 -haloalkyl, C_1 - C_4 -alkoxy-
 C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, C_1 - C_4 -alkoxy- C_1 - C_4 -alkoxy, hydroxyl,
 C_1 - C_4 -haloalkoxy, (C_1 - C_5 -alkyl)carbonyloxy, (C_1 - C_5 -halo-
 alkyl)carbonyloxy, SH, C_1 - C_4 -alkylthio, C_1 - C_4 -alkylsulfinyl,
 C_1 - C_4 -alkylsulfonyl, C_1 - C_4 -haloalkylthio, C_1 - C_4 -haloalkyl-

42

83

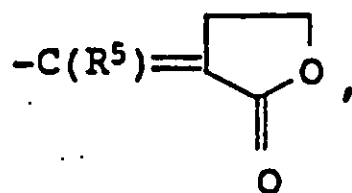
sulfinyl, C₁-C₄-haloalkylsulfonyl, formyl, cyano, hydroxy-carbonyl, (C₁-C₄-alkoxy)carbonyl, C₁-C₄-alkoxy-(C₁-C₄-alkoxy)carbonyl, (C₁-C₄-haloalkoxy)carbonyl, (C₁-C₄-alkyl)-carbonyl, (C₁-C₄-haloalkyl)carbonyl, C₁-C₄-alkoxy-

5 (C₁-C₄-alkyl)carbonyl, nitro, amino, C₁-C₄-alkylamino, di-(C₁-C₄-alkyl)amino, pyrrolidinyl, piperidinyl, morpholinyl, (C₁-C₄-alkyl)carbonylamino, (C₁-C₄-haloalkyl)carbonylamino or C₁-C₄-alkylsulfonylamino;

10 R⁵
hydrogen or halogen;

R⁶
halogen, cyano, nitro, hydroxyl, trifluoromethyl, C₁-C₆-alkyl
15 or C₁-C₄-alkoxy;

R⁷
chlorine, bromine, iodine, cyano, nitro, C₁-C₈-alkyl,
C₂-C₈-alkenyl, C₂-C₈-alkynyl, C₁-C₈-haloalkyl, C₂-C₈-halo-
20 alkenyl, C₂-C₈-haloalkynyl, -(C₁-C₈-alkylene)-O-R⁸,
-(C₂-C₈-alkenylene)-O-R⁸, -(C₂-C₈-alkynylene)-O-R⁸,
-(C₁-C₈-alkylene)-S-R⁸, -(C₂-C₈-alkenylene)-S-R⁸; -(C₂-C₈-
alkynylene)-S-R⁸, -(C₁-C₈-alkylene)-SO-R⁸, -(C₂-C₈-
alkenylene)-SO-R⁸, -(C₂-C₈-alkynylene)-SO-R⁸, -(C₁-C₈-
25 alkylene)-SO₂-R⁸, -(C₂-C₈-alkenylene)-SO₂-R⁸; -(C₂-C₈-
alkynylene)-SO₂-R⁸, -O-R⁸, -S-R⁸, -SO-R⁸, -SO₂-R⁸, chlorosulfo-
nyl, -SO₂-O-R⁸, -SO₂-N(R⁹, R¹⁰), -SO₂-NR⁹(CO-R¹²), -N(R⁹, R¹⁰),
-NR¹¹(CO-R¹²), -NR¹¹(SO₂-R¹³), -N(SO₂-R¹³)(SO₂-R¹⁴),
-N(SO₂-R¹³)(CO-R¹²), -NH-CO-O-R⁸, -O-CO-NH-R⁹, -O-CO-R¹²,
30 -NH-CO-NHR⁹, -O-CS-N(C₁-C₄-alkyl)₂, -O-CS-NH₂, cyano-
C₁-C₄-alkyl, -CO-O-R⁸, -CO-O-N=C(R²⁶, R²⁷), -CO-O-
CH₂-O-N=C(R³⁰, R³¹), -CO-O-C(R²⁸, R²⁹)-CH₂-O-N=C(R³⁰, R³¹),
-CO-N(R⁹, R¹⁰), -CS-N(R⁹, R¹⁰), -CO-NH-SO₂-(C₁-C₄-alkyl), isoxa-
zolidinylcarbonyl, formyl, -CO-R¹⁵, hydroxycarbonyl-
35 C₁-C₆-alkyl, (C₁-C₆-alkoxy)carbonyl-C₁-C₆-alkyl,
-CR¹⁵=C(R¹⁶)-CHO, -C(R¹⁵)=C(R¹⁶)-CO-O-R⁸,
-C(R¹⁵)=C(R¹⁶)-CO-N(R⁹, R¹⁰), -C(R¹⁵)=C(R¹⁶)-CO-R¹⁷, -CH=N-O-R⁸,
-CH(XR¹⁸, YR¹⁹), -CH₂-CH(halogen)-CO-O-R⁸, -CH₂-CH-
(halogen)-CO-N(R⁹, R¹⁰), -CH₂-CH(halogen)-CO-(C₁-C₄-alkyl),
40 -CH₂-CH(halogen)-CN, -C(C₁-C₄-alkoxy)=N-O-R⁸,
-C(R¹⁵)=C(R¹⁶)-C(C₁-C₄-alkoxy)=N-O-R⁸, -CH=CH-CH=CH-CO-O-R⁸,
-C(R⁵)=



45 OCH=N-O-(C₁-C₄-alkyl), -CO-OC(C₁-C₄-alkyl)=N-OH, -CO-
OC(C₁-C₄-alkyl)=N-O-(C₁-C₄-alkyl), -CO-O-(C₁-C₄-

43

84

alkylene)-CH=N-OH, -CO-O-(C₁-C₄-alkylene)-CH=N-O-(C₁-C₄-alkyl),
 -CO-O-(C₁-C₄-alkylene)-C(C₁-C₄-alkyl)=N-OH, -CO-O-(C₁-C₄-
 alkylene)-C(C₁-C₄-alkyl)=N-O-(C₁-C₄-alkyl), -(C₁-C₈-
 alkylene)-O-CO-(C₁-C₄-alkyl), -CH=C=CH₂,

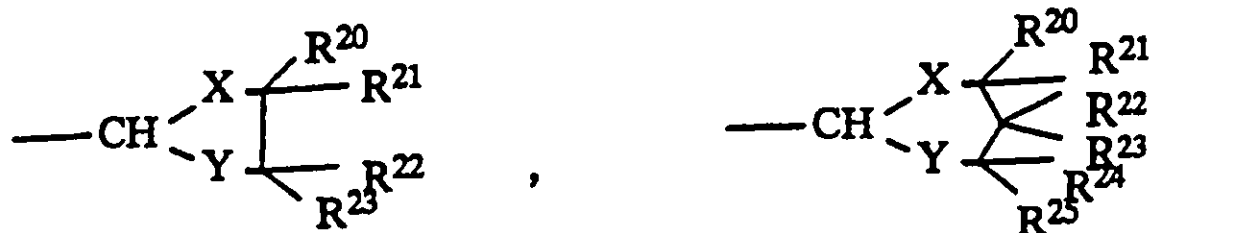
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-CH=C=CH-(C₁-C₄-alkyl), -O-CH₂- $\begin{array}{c} \text{N} \\ \parallel \\ \text{O} \end{array}$, -O-

10

CH(C₁-C₄-alkyl)- $\begin{array}{c} \text{N} \\ \parallel \\ \text{O} \end{array}$, -O-C(C₁-C₄-alkyl)₂- $\begin{array}{c} \text{N} \\ \parallel \\ \text{O} \end{array}$,

15



20

5- or 6-membered heteroaryl with one to three hetero atoms
 selected from a group comprising one or two nitrogen atoms
 and one oxygen or sulfur atom, it being possible for each
 heteroaromatic ring atom which can be substituted to carry,
 if desired, a radical selected from the group comprising
 nitro, halogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio und
 (C₁-C₄-alkoxy)carbonyl;

25

R⁸

30

hydrogen, C₁-C₈-alkyl, C₁-C₈-haloalkyl, C₄-C₇-cycloalkyl,
 which in turn can carry one to three C₁-C₃-alkyl radicals,
 C₃-C₆-alkenyl, C₅-C₇-cycloalkenyl, which in turn can carry one
 to three C₁-C₃-alkyl radicals, C₃-C₆-haloalkenyl, cyano-
 C₁-C₈-alkyl, C₃-C₆-alkynyl, C₂-C₈-alkoxyalkyl, 2-tetrahydro
 furanyl-C₁-C₈-alkyl; 3-oxetanyl, 3-thietanyl, carboxyl-
 C₁-C₆-alkyl, (C₁-C₈-alkoxy)carbonyl-C₁-C₆-alkyl, (C₁-C₆-al-
 koxy)carbonyl-(C₃-C₇-Cycloalkyl), C₁-C₄-alkoxy-(C₁-C₄-al-
 koxy)carbonyl-C₁-C₆-alkyl, cyclopropylmethyl, (1-methylthio-
 cyclopropyl)methyl, -CH(SH)-CO-OH, -CH(SH)-CO-(C₁-C₈-alkoxy),
 -CH(C₁-C₈-alkylthio)-COOH, -CH(C₁-C₄-alkylthio)-CO-(C₁-C₈-al-
 koxy), -CH₂-CO-N(R⁹)-R¹⁰, -CH(C₁-C₄-alkyl)-CO-N(R⁹)-R¹⁰,
 C(C₁-C₄-alkyl)₂-CO-N(R⁹)-R¹⁰, -CH₂-CO-N(R⁹)-SO₂-(C₁-C₄-alkyl),
 -CH(C₁-C₄-alkyl)-CO-N(R⁹)-SO₂-(C₁-C₄-alkyl),
 -C(C₁-C₄-alkyl)₂-CO-N(R⁹)-SO₂-(C₁-C₄-alkyl), -S-CO-NH₂, -S-
 CO-N(C₁-C₄-alkyl)-(C₁-C₄-alkyl), -CH₂-CO-O-(C₁-C₆-alky-
 lene)-COOH,

45

-CH₂-CO-O-(C₁-C₆-alkylene)-CO-(C₁-C₆-alkoxy),
 -C(C₁-C₄-alkyl)₂-CO-O-(C₁-C₆-alkylene)-COOH,
 -C(C₁-C₄-alkyl)₂-CO-O-(C₁-C₄-alkylene)-CO-(C₁-C₆-alkoxy),

-CH(C₁-C₄-alkyl)-CO-O-(C₁-C₆-alkylene)-COOH,
 -CH(C₁-C₄-alkyl)-CO-O-(C₁-C₆-alkylene)-CO-(C₁-C₆-alkoxy),
 C₃-C₉-(α -alkylalkylidene)iminooxy-C₁-C₆-alkyl, phenyl,
 phenyl-C₁-C₆-alkyl, phenyl-C₃-C₆-alkenyl, phenyl-C₃-C₆-alkynyl
 5 or phenoxy-C₁-C₆-alkyl, where the phenyl ring can in each case
 be unsubstituted or carry one to three radicals selected from
 the group comprising halogen, nitro, cyano, C₁-C₄-alkyl,
 C₁-C₄-alkoxy, C₁-C₄-alkylthio, C₁-C₄-haloalkyl and C₂-C₆-
 alkenyl, 5- or 6-membered heteroaryl, heteroaryl-C₁-C₆-alkyl,
 10 heteroaryl-C₃-C₆-alkenyl, heteroaryl-C₃-C₆-alkynyl or
 heteroaryloxy-C₁-C₆-alkyl, where the heteroaryl radical in
 each case contains one to three hetero atoms selected from a
 group comprising one or two nitrogen atoms and one oxygen or
 sulfur atom, and it being possible for each heteroaromatic
 15 ring atom which can be substituted also to carry, if desired,
 a radical selected from the group comprising hydroxyl,
 halogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio and
 C₁-C₄-haloalkyl;

20 R⁹ and R¹⁰
 hydrogen, C₁-C₈-alkyl, C₂-C₈-alkenyl, C₃-C₈-alkynyl, C₁-C₈-
 haloalkyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₁-C₄-alkylthio-
 C₁-C₄-alkyl, cyano-C₁-C₈-alkyl, carboxyl-C₁-C₄-alkyl,
 (C₁-C₄-alkoxy)carbonyl-C₁-C₄-alkyl, (C₁-C₆-alkoxy)carbonyl-
 25 (C₃-C₇-cycloalkyl), C₁-C₄-alkylsulfonyl-C₁-C₄-alkyl,
 C₃-C₈-cycloalkyl, C₁-C₆-alkoxy, (C₃-C₆-cycloalkoxy)carbonyl-
 C₁-C₄-alkyl, C₁-C₄-alkoxy-(C₁-C₄-alkoxy)carbonyl-C₁-C₄-alkyl,
 phenyl, phenyl-C₁-C₄-alkyl, where the phenyl ring can in each
 case be unsubstituted or carry one to three radicals selected
 30 from the group comprising halogen, nitro, cyano, C₁-C₄-alkyl,
 C₁-C₄-alkoxy, C₁-C₄-alkylthio, C₁-C₄-haloalkyl and C₂-C₆-
 alkenyl, 5- or 6-membered heteroaryl oder heteroaryl-
 C₁-C₄-alkyl, where the heteroaryl radical contains one to
 three hetero atoms selected from a group comprising one or
 35 two nitrogen atoms and one oxygen or sulfur atom, and it
 being possible for each heteroaromatic ring atom which can be
 substituted also, if desired, to carry a radical selected
 from the group comprising hydroxyl, halogen, C₁-C₄-alkyl,
 C₁-C₄-alkoxy, C₁-C₄-alkylthio and C₁-C₄-haloalkyl;

40

or

45

R⁹ and R¹⁰ together a tetramethylene, pentamethylene or
 ethyleneoxyethylene chain, it being possible for each chain
 to carry, if desired, a (C₁-C₆-alkoxy)carbonyl radical;

R¹¹

45

86

hydrogen, C₁-C₄-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, sodium, potassium, calcium, magnesium, ammonium or ammonium which is substituted by one to four C₁-C₄-alkyl- or benzyl radicals and can, if desired, carry one to three further C₁-C₄-alkyl radicals;

R¹²

hydrogen, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₃-C₇-cycloalkyl, which can in turn carry one to three radicals selected from the group comprising halogen, C₁-C₄-alkyl, C₁-C₄-alkoxy and C₁-C₄-alkylthio, phenyl or phenyl-C₁-C₆-alkyl, where the phenyl ring can in each case be unsubstituted or carry one to three radicals selected from the group comprising halogen, nitro, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio and C₁-C₄-haloalkyl;

R¹³ and R¹⁴, independently of one another,

C₁-C₄-alkyl, phenyl or thienyl, where the phenyl or thienyl radical can be unsubstituted or carry one to three radicals selected from the group comprising halogen, nitro, C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio and C₁-C₄-haloalkyl;

R¹⁵, R¹⁶ and R¹⁷, independently of one another,

hydrogen, halogen, C₁-C₄-alkyl, C₂-C₄-alkenyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy-C₁-C₄-alkyl or C₁-C₄-alkylthio-C₁-C₄-alkyl;

R¹⁸ and R¹⁹, independently of one another,

C₁-C₈-alkyl, C₁-C₄-alkoxy-C₁-C₄-alkyl or C₁-C₈-haloalkyl;

R²⁰, R²¹, R²², R²³, R²⁴ and R²⁵, independently of one another, hydrogen, cyano, C₁-C₈-alkyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, halo-C₁-C₈-alkyl, C₁-C₈-alkoxy, C₁-C₄-alkoxy-C₁-C₄-alkoxy, -CO-O-R⁸, -CO-N(R⁹, R¹⁰), -CO-R¹⁵, -S-R⁸, -SO₂-R⁸, -O-CO-R¹² or C₃-C₇-cycloalkyl, which can in turn carry from one to three radicals selected from the group comprising halogen, C₁-C₄-alkyl, C₁-C₄-alkoxy and C₁-C₄-alkylthio;

R²⁶

C₁-C₆-alkyl, C₁-C₆-alkylthio, C₁-C₆-alkoxycarbonyl or C₁-C₆-alkoxycarbonyl-C₁-C₄-alkyl;

R²⁷

C₁-C₆-alkyl, trifluoromethyl, C₁-C₆-alkoxy-C₁-C₄-alkyl, C₂-C₇-alkoxycarbonyl-C₁-C₄-alkyl, di-(C₁-C₆-alkoxycarbonyl)-C₁-C₄-alkyl, C₃-C₆-cycloalkyl, C₁-C₆-alkoxy, C₁-C₆-alkylthio, C₁-C₆-alkanoyl, C₁-C₆-alkoxycarbonyl, 2-furyl or phenyl which can be unsubstituted or in turn carry one to

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three radicals selected from the group comprising halogen, C₁-C₄-alkyl and C₁-C₄-alkoxy;

or

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R²⁶ and R²⁷ together with the carbon to which they are bonded a cyclopentane or cyclohexane ring which can in turn, if desired, carry one to three C₁-C₄-alkyl radicals;

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R²⁸

hydrogen or C₁-C₄-alkyl;

R²⁹

hydrogen, C₁-C₄-alkyl, phenyl or benzyl;

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R³⁰

hydrogen or C₁-C₆-alkyl;

R³¹

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C₁-C₆-alkyl, C₃-C₆-cycloalkyl or phenyl;

X and Y, independently of one another, oxygen or sulfur;

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and the N-oxides of I and the agriculturally utilizable salts of I where these exist,

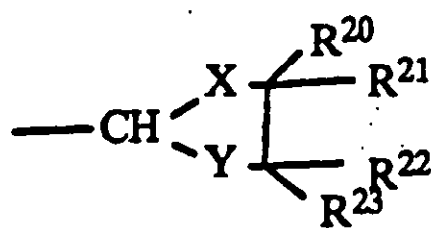
excepting those compounds I where R² is C₁-C₄-alkoxy and R¹ and/or R³ is carboxyl, its salt, ester or amide.

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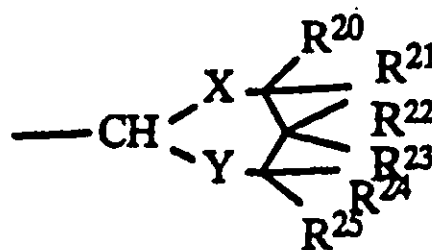
2. A substituted 2-phenylpyridine of the formula 1 as claimed in claim 1, where R¹ and R³ are hydrogen or halogen, R² is halogen, C₁-C₄-haloalkyl with one to five halogen atoms or C₁-C₄-haloalkoxy with one to five halogen atoms, R⁴ is halogen, R⁵ is hydrogen, fluorine or chlorine, R⁶ is chlorine and R⁷ is -O-R⁸, -S-R⁸, -NR¹¹-SO₂R¹³, -COOR⁸, -CR¹⁵=CR¹⁶-COOR⁸, -CH=N-O-R⁸, -CH(X-R¹⁸)(X-R¹⁹), -CH₂-CH(Cl)-COOR⁸, -SO₂NR⁹R¹⁰,

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3. The use of a substituted 2-phenylpyridine of the formula I, its N-oxide and/or agriculturally utilizable salt, as claimed in claim 1, as herbicide or for the desiccation and/or defoliation of plants.
- 5
4. A herbicidal composition containing a herbicidally effective amount of at least one substituted 2-phenylpyridine of the formula I or its N-oxide or agriculturally utilizable salt, as claimed in claim 1, and at least one inert liquid and/or
- 10 solid carrier and, if desired, at least one adjuvant.
5. A composition for the desiccation and/or defoliation of plants, containing an amount, which has desiccant and/or defoliant activity, of at least one substituted 2-phenyl-
- 15 pyridine of the formula I or its N-oxide or its agriculturally utilizable salt, as claimed in claim 1, and at least one inert liquid and/or solid carrier and, if desired, at least one adjuvant.
- 20 6. A process for the production of herbicidal compositions, which comprises mixing a herbicidally effective amount of at least one substituted 2-phenylpyridine of the formula I or its N-oxide or its agriculturally utilizable salt, as claimed in claim 1, and at least one inert liquid and/or solid
- 25 carrier and, if desired, at least one adjuvant.
7. The process for the production of desiccant and/or defoliant compositions, which comprises mixing an amount, which has defoliant and/or desiccant activity, of at least one substi-
- 30 tuted 2-phenylpyridine of the formula I or its N-oxide or its agriculturally utilizable salt, as claimed in claim 1, and at least one inert liquid and/or solid carrier and, if desired, at least one adjuvant.
- 35 8. A method for controlling unwanted plant growth, which comprises allowing a herbicidally effective amount of at least one substituted 2-phenylpyridine of the formula I', where I' corresponds to formula I as claimed in claim 1 without the disclaimer, and R⁴ can additionally be aminocarbonyl,
- 40 (C₁-C₄-alkyl)aminocarbonyl, di-(C₁-C₄-alkyl)aminocarbonyl, pyrrolidinylcarbonyl, piperidinylcarbonyl or morpholinylcarbonyl, or its N-oxide or agriculturally utilizable salt, to act on plants, their habitat or on seeds.
- 45 9. A method for the desiccation and defoliation of plants, which comprises allowing an amount, which has defoliant and/or desiccant activity, of at least one substituted 2-phenylpyri-

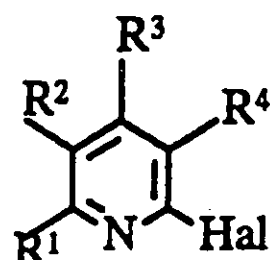
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dine of the formula I', where I' corresponds to formula I as claimed in claim 1 without the disclaimer, and R⁴ can additionally be aminocarbonyl, (C₁-C₄-alkyl)aminocarbonyl, di-(C₁-C₄-alkyl)aminocarbonyl, pyrrolidinylcarbonyl, piperidylcarbonyl or morpholinylcarbonyl, or its N-oxide or agriculturally utilizable salt, to act on plants.

10. A method as claimed in claim 9, wherein cotton is defoliated.

11. A process for the preparation of substituted 2-phenylpyridines of the formula I as claimed in claim 1, which comprises reacting a 2-halopyridine of the formula II

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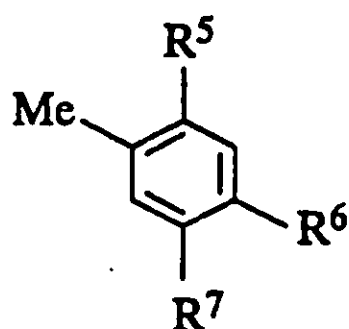


II

20 where Hal is chlorine or bromine,

in the presence of a transition metal catalyst with an organometallic compound of the formula III

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III

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35 where Me is magnesium bromide, zinc bromide, zinc chloride, tin tri(C₁-C₈-alkyl), lithium, copper or B(OR³³)(OR³⁴) where R³³ and R³⁴ are, independently of one another, hydrogen or C₁-C₄-alkyl or together are ethylene or propylene.

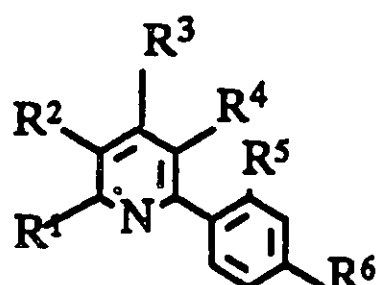
40 12. A process as claimed in claim 11, wherein Me in compound III is B(OH)₂.

13. The use of phenylpyridines of the formula IV

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IV

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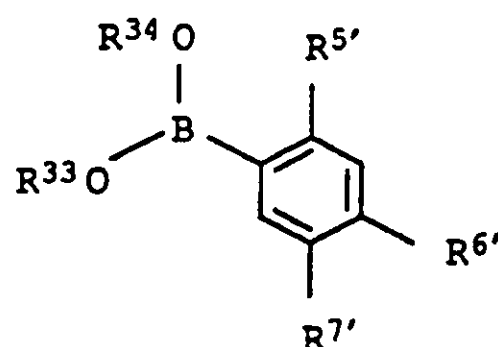
in which the substituents R^1 to R^6 have the appropriate meanings for the substituted 2-phenylpyridines of the formula I as claimed in claim 1,

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as intermediates for the preparation of the compounds I.

14. The use of aromatic boronic acids or esters thereof of the formula IIIa

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IIIa

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where

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$R^{5'}$ is hydrogen, fluorine or chlorine;

R^6 is halogen, hydroxyl or C_1 - C_4 -alkoxy;

$R^{7'}$ is hydrogen, C_1 - C_4 -alkyl or C_1 - C_4 -alkoxy;

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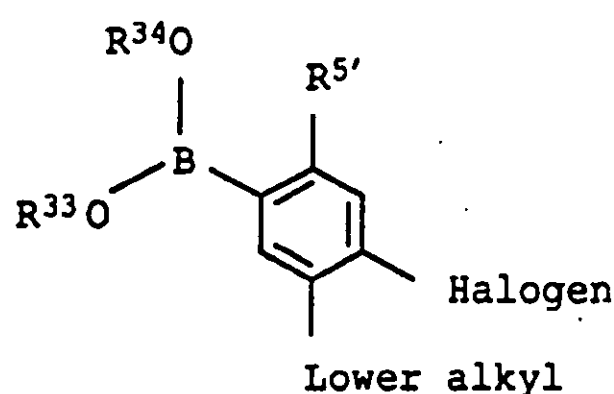
R^{33} and R^{34} are, independently of one another, hydrogen or C_1 - C_4 -alkyl or together are ethylene or propylene

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as intermediates for the preparation of substituted 2-phenylpyridines of the formula I as claimed in claim 1.

15. An aromatic boronic acid or ester thereof of the formula IIIa'

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IIIa'

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where

$R^{5'}$ is hydrogen, fluorine or chlorine;

5 halogen is a halogen atom;

lower alkyl is C_1 - C_4 -alkyl and

10 R^{33} and R^{34} are, independently of one another, hydrogen or C_1 - C_4 -alkyl or together are ethylene or propylene.

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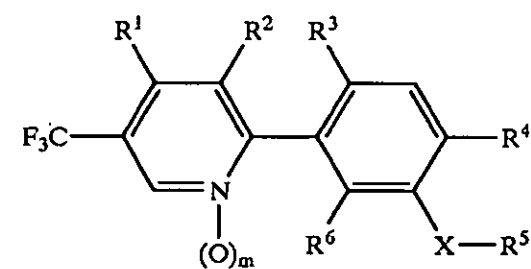


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(19) **United States**(12) **Patent Application Publication**
Puhl et al.(10) **Pub. No.: US 2004/0043903 A1**
(43) **Pub. Date: Mar. 4, 2004**(54) **2-ARYL-5-TRIFLUOROMETHYLPYRIDINES**(52) **U.S. Cl. 504/244; 546/286; 546/329**(76) **Inventors: Michael Puhl, Lampertheim (DE);
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(DE)**(57) **ABSTRACT**

The present invention relates to 2-aryl-5-trifluoromethylpyridines of the formula I

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Publication Classification(51) **Int. Cl.⁷ A01N 43/40; C07D 213/84**in which the variables m, R¹, R², R³, R⁴, R⁵, R⁶ and X have the meanings given in claim 1, and their agriculturally tolerated salts.

Moreover, the invention relates to the use of compounds I and their salts as herbicides and/or for the desiccation and/or defoliation of plants, to herbicidal compositions and compositions for the desiccation and/or defoliation of plants comprising the compounds I and/or their salts as active substances.

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2-ARYL-5-TRIFLUOROMETHYLPYRIDINES

[0001] The present invention relates to 2-aryl-5-trifluoromethylpyridines, to their pyridine N-oxides and their agriculturally useful salts, and to their use as herbicides, desiccants or defoliants.

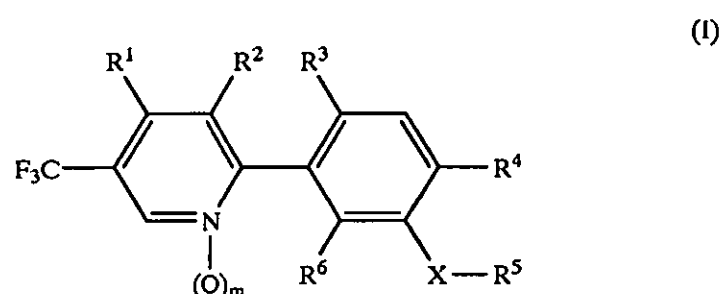
[0002] Herbicidally active 2-aryl-5-trifluoromethylpyridines have been described on several occasions in the prior art (see, for example, DE 4323916, WO 95/02580, WO 95/02590, WO 96/21645, WO 96/21646, WO 96/21647, WO 96/21645, WO 97/06143, WO 97/11059, WO 97/30059, WO 98/07700 and WO 99/06394).

[0003] The prior-art 2-aryl-5-trifluoromethylpyridines leave something to be desired in some cases with regard to their activity and/or selectivity with respect to harmful plants. Moreover, there is a constant need to provide novel herbicidally active substances to avoid the possibility of resistance build-up against known herbicides.

[0004] It was an object of the present invention to provide novel herbicides by means of which harmful plants can be controlled better than hitherto. Advantageously, the novel herbicides should have a high activity with regard to harmful plants. Moreover, crop plant tolerance is desired.

[0005] We have found that this object is achieved, surprisingly, by 2-aryl-5-trifluoromethylpyridines, their N-oxides and their agriculturally useful salts which have a particularly high herbicidal activity when they have an amino group or a methyl group in the 4-position of the pyridine ring, a halogen atom being attached in the 3-position and the 6-position being unsubstituted.

[0006] Accordingly, the present invention relates to 2-aryl-5-trifluoromethylpyridines of the formula I



[0007] in which the variables m, R¹, R², R³, R⁴, R⁵, R⁶ and X have the following meanings:

[0008] m is 0 or 1,

[0009] X is a chemical bond, a methylene, 1,2-ethylene, propane-1,3-diyl, ethene-1,2-diyl or ethyne-1,2-diyl chain, or an oxymethylene or thiomethylene chain bonded to the phenyl ring via the hetero atom, it being possible for all chains to be unsubstituted or to have attached to them one or two substituents, in each case selected from the group consisting of cyano, carboxyl, halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, (C₁-C₄-alkoxy)carbonyl, di(C₁-C₄-alkyl)amino and phenyl;

[0010] R¹ is NH₂ or CH₃;

[0011] R² is halogen;

[0012] R³ is hydrogen or halogen;

[0013] R⁴ is halogen, cyano, OH, C₁-C₄-alkoxy or C₁-C₄-alkoxycarbonyl-C₁-C₄-alkoxy;

[0014] R⁵ is hydrogen, nitro, cyano, halogen, halosulfonyl, N₃, —O—Y—R⁷, —O—CO—Y—R⁷, —N(Y—R⁷)(Z—R⁸), —N(Y—R⁷)—SO₂—Z—R⁸, —N(SO₂—Y—R⁷)(SO₂—Z—R⁸), —N(Y—R⁷)—CO—Z—R⁸, —N(Y—R⁷)(O—Z—R⁸), —S—Y—R⁷, —SO—Y—R⁷, —SO₂—Y—R⁷, —SO₂—O—Y—R⁷, —SO₂—N(Y—R⁷)(Z—R⁸), —CO—Y—R⁷, —C(=NOR⁹)—Y—R⁷, —C(=NOR⁹)—O—Y—R⁷, —CO—O—Y—R⁷, —CO—S—Y—R⁷, —CO—N(Y—R⁷)(Z—R⁸), —CO—N(Y—R⁷)(O—Z—R⁸) or —PO(O—Y—R⁷)₂;

[0015] R⁶ is hydrogen or

[0016] R⁴ and X—R⁵ or X—R⁵ and R⁶ are a 3- or 4-membered chain whose chain members, in addition to carbon, can have 1, 2 or 3 hetero atoms selected from among nitrogen, oxygen and sulfur atoms, which hetero atoms can be unsubstituted or can have attached to them, in turn, one, two or three substituents, and whose members can also encompass one or two nonadjacent carbonyl, thiocarbonyl or sulfonyl groups,

[0017] Y, Z independently of one another are:

[0018] a chemical bond, a methylene or ethylene group which can be unsubstituted or can have attached to it one or two substituents, in each case selected from the group consisting of carboxyl, C₁-C₄-alkyl, C₁-C₄-haloalkyl, (C₁-C₄-alkoxy)carbonyl and phenyl;

[0019] R⁷, R⁸ independently of one another are:

[0020] hydrogen, C₃-C₈-cycloalkyl-C₁-C₄-alkyl, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₂-C₆-alkenyl, C₂-C₆-haloalkenyl, C₂-C₆-alkynyl, C₂-C₆-haloalkynyl, —CH(R¹⁰)(R¹¹), —C(R¹⁰)(R¹¹)—CN, —C(R¹⁰)(R¹¹)—halogen, —C(R¹⁰)(R¹¹)—OR¹², —C(R¹⁰)(R¹¹)—N(R¹²)R¹³, —C(R¹⁰)(R¹¹)—N(R¹²)—OR¹³, —C(R¹⁰)(R¹¹)—SR¹², —C(R¹⁰)(R¹¹)—SO—R¹², —C(R¹⁰)(R¹¹)—SO₂—R¹², —C(R¹⁰)(R¹¹)—SO₂—OR¹², —C(R¹⁰)(R¹¹)—SO₂—N(R¹²)R¹³, —C(R¹⁰)(R¹¹)—CO—R¹², —C(R¹⁰)(R¹¹)—C(=NOR¹⁴)—R¹², —C(R¹⁰)(R¹¹)—CO—OR¹², —C(R¹⁰)(R¹¹)—CO—SR¹², —C(R¹⁰)(R¹¹)—CO—N(R¹²)R¹³, —C(R¹⁰)(R¹¹)—CO—N(R¹²)—OR¹³, —C(R¹⁰)(R¹¹)—PO(OR¹²)₂, C₃-C₈-cycloalkyl which can contain a carbonyl or thiocarbonyl ring member,

[0021] phenyl or 3-, 4-, 5-, 6- or 7-membered heterocyclyl which can contain a carbonyl or thiocarbonyl ring member,

[0022] it being possible for each cycloalkyl ring, for the phenyl ring and for each heterocyclyl ring to be unsubstituted or to have attached to it one, two, three or four substituents, in each case selected from the group consisting of cyano, nitro, amino, hydroxyl, carboxyl, halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, C₁-C₄-haloalkylthio, C₁-C₄-alkylsulfonyl, C₁-C₄-haloalkylsulfonyl, (C₁-C₄-alkyl)carbonyl, (C₁-C₄-haloalkyl)carbonyl, (C₁-C₄-alkyl)carbonyloxy, (C₁-

C₄-haloalkyl)carbonyloxy, (C₁-C₄-alkoxy)carbonyl and di(C₁-C₄-alkyl)amino;

[0023] R⁹ is hydrogen, C₁-C₆-alkyl, C₁-C₄-alkoxycarbonyl-C₁-C₄-alkoxy, C₄-C₈-cycloalkyl-C₁-C₄-alkyl, C₁-C₆-haloalkyl, C₂-C₆-alkenyl, C₂-C₆-haloalkenyl, C₂-C₆-alkynyl, C₂-C₆-haloalkynyl, C₃-C₈-cycloalkyl, phenyl or phenyl-C₁-C₄-alkyl;

[0024] where the variables R¹⁰ to R¹⁴ have the following meanings:

[0025] R¹⁰, R¹¹ independently of one another are

[0026] hydrogen, C₁-C₄-alkyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₁-C₄-alkylthio-C₁-C₄-alkyl, (C₁-C₄-alkoxy)carbonyl-C₁-C₄-alkyl or phenyl-C₁-C₄-alkyl, it being possible for the phenyl ring to be unsubstituted or to have attached to it one to three substituents, in each case selected from the group consisting of cyano, nitro, carboxyl, halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl and (C₁-C₄-alkoxy)carbonyl;

[0027] R¹², R¹³ independently of one another are

[0028] hydrogen, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₂-C₆-alkenyl, C₂-C₆-haloalkenyl, C₂-C₆-alkynyl, C₂-C₆-haloalkynyl, C₃-C₈-cycloalkyl, C₃-C₈-cycloalkyl-C₁-C₄-alkyl, phenyl, phenyl-C₁-C₄-alkyl, 3- to 7-membered heterocyclyl or heterocyclyl-C₁-C₄-alkyl, it being possible for each cycloalkyl and each heterocyclyl ring to contain a carbonyl or thiocarbonyl ring member, and where each cycloalkyl ring, the phenyl ring and each heterocyclyl ring can be unsubstituted or have attached to it one, two, three or four substituents, in each case selected from the group consisting of cyano, nitro, amino, hydroxyl, carboxyl, halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, C₁-C₄-haloalkylthio, C₁-C₄-alkylsulfonyl, C₁-C₄-haloalkylsulfonyl, (C₁-C₄-alkyl)carbonyl, (C₁-C₄-haloalkyl)carbonyl, (C₁-C₄-alkyl)carbonyloxy, (C₁-C₄-haloalkyl)carbonyloxy, (C₁-C₄-alkoxy)carbonyl and di(C₁-C₄-alkyl)amino;

[0029] R¹⁴ is hydrogen, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₂-C₆-alkenyl, C₂-C₆-haloalkenyl, C₂-C₆-alkynyl, C₂-C₆-haloalkynyl, C₃-C₈-cycloalkyl, C₁-C₄-alkoxy-carbonyl-C₁-C₄-alkyl, phenyl or phenyl-C₁-C₄-alkyl;

[0030] and the agriculturally useful salts of I.

[0031] Furthermore, the invention relates to:

[0032] the use of compounds I and their salts as herbicides and/or for the desiccation and/or defoliation of plants,

[0033] herbicidal compositions and compositions for the desiccation and/or defoliation of plants comprising the compounds I and/or their salts as active substances,

[0034] intermediates for the preparation of the compounds I

[0035] processes for the preparation of herbicidal compositions and compositions for the desiccation and/or defoliation of plants using the compounds I, and

[0036] methods of controlling undesired vegetation (harmful plants) and for the desiccation and/or defoliation of plants with the compounds I and/or their salts.

[0037] The compounds of the formula I can form geometric isomers, for example E/Z isomers, in the substituents. The invention relates not only to the pure isomers, but also to their mixtures. Moreover, the compounds of the formula I can have one or more chiral centers in the substituents, in which case they are present as enantiomer or diastereomer mixtures. The invention relates to the pure enantiomers and diastereomers and also to their mixtures.

[0038] Suitable among agriculturally useful salts are especially the salts of those cations and the acid addition salts of those acids whose cations, or anions, do not adversely affect the herbicidal action of the compounds I. Thus, suitable cations are, in particular, the ions of the alkali metals, preferably sodium and potassium, of the alkaline earth metals, preferably calcium, magnesium and barium, and of the transition metals, preferably manganese, copper, zinc and iron, and the ammonium ion which, if desired, can have attached to it one to four C₁-C₄-alkyl substituents and/or a phenyl or benzyl substituent, preferably diisopropylammonium, tetramethylammonium, tetrabutylammonium, trimethylbenzylammonium, furthermore phosphonium ions, sulfonium ions, preferably tri(C₁-C₄-alkyl)sulfonium and sulfoxonium ions, preferably tri(C₁-C₄-alkyl)sulfoxonium.

[0039] Anions of useful acid addition salts are mainly chloride, bromide, fluoride, hydrogen sulfate, sulfate, dihydrogen phosphate, hydrogen phosphate, phosphate, nitrate, hydrogen carbonate, carbonate, hexafluorosilicate, hexafluorophosphate, benzoate, and the anions of C₁-C₄-alkanoic acids, preferably formate, acetate, propionate and butyrate. They can be formed by reacting I with an acid of the anion in question, preferably hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid or nitric acid.

[0040] The organic moieties mentioned in the definition of the substituents R¹, R², R⁴, R⁷ to R¹⁸ or as radicals on cycloalkyl rings, phenyl rings or heterocyclic rings or on X, Y and Z constitute, like the meaning halogen, collective terms for individual enumerations of the individual group members. All carbon chains, i.e. all alkyl, haloalkyl, phenylalkyl, cycloalkylalkyl, alkoxy, haloalkoxy, alkylthio, haloalkylthio, alkylsulfinyl, haloalkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, alkenyl, haloalkenyl, alkynyl and haloalkynyl groups and corresponding moieties in larger groups such as alkoxycarbonyl, phenylalkyl, cycloalkylalkyl, alkoxycarbonylalkyl etc. can be straight-chain or branched, the prefix C_n-C_m in each case indicating the possible number of carbon atoms in the group. Halogenated substituents preferably have attached to them one, two, three, four or five identical or different halogen atoms. The meaning halogen denotes in each case fluorine, chlorine, bromine or iodine.

[0041] Other examples of meanings are:

[0042] —C₁-C₄-alkyl: CH₃, C₂H₅, n-propyl, CH(CH₃)₂, n-butyl, CH(CH₃)—C₂H₅, CH₂—CH(CH₃)₂ and C(CH₃)₃;

[0043] —C₁-C₄-haloalkyl: a C₁-C₄-alkyl radical as mentioned above which is partially or fully substituted by fluorine, chlorine, bromine and/or iodine,

i.e., for example, CH_2F , CHF_2 , CF_3 , CH_2Cl , dichloromethyl, trichloromethyl, chlorofluoromethyl, dichlorofluoromethyl, chlorodifluoromethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 2-iodoethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-chloro-2-fluoroethyl, 2-chloro-2,2-difluoroethyl, 2,2-dichloro-2-fluoroethyl, 2,2,2-trichloroethyl, C_2F_5 , 2-fluoropropyl, 3-fluoropropyl, 2,2-difluoropropyl, 2,3-difluoropropyl, 2-chloropropyl, 3-chloropropyl, 2,3-dichloropropyl, 2-bromopropyl, 3-bromopropyl, 3,3,3-trifluoropropyl, 3,3,3-trichloropropyl, 2,2,3,3,3-pentafluoropropyl, heptafluoropropyl, 1-(fluoromethyl)-2-fluoroethyl, 1-(chloromethyl)-2-chloroethyl, 1-(bromomethyl)-2-bromoethyl, 4-fluorobutyl, 4-chlorobutyl, 4-bromobutyl or nonafluorobutyl;

[0044] $\text{C}_1\text{-C}_6\text{-alkyl}$: $\text{C}_1\text{-C}_4\text{-alkyl}$ as mentioned above and also, for example, n-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, 1-ethylpropyl, n-hexyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl or 1-ethyl-2-methylpropyl, preferably methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1,1-dimethylethyl, n-pentyl or n-hexyl;

[0045] $\text{C}_1\text{-C}_6\text{-haloalkyl}$: a $\text{C}_1\text{-C}_6\text{-alkyl}$ radical as mentioned above which is partially or fully substituted by fluorine, chlorine, bromine and/or iodine, i.e., for example, one of the radicals mentioned under $\text{C}_1\text{-C}_4\text{-haloalkyl}$ and also 5-fluoro-1-pentyl, 5-chloro-1-pentyl, 5-bromo-1-pentyl, 5-iodo-1-pentyl, 5,5,5-trichloro-1-pentyl, undecafluoropentyl, 6-fluoro-1-hexyl, 6-chloro-1-hexyl, 6-bromo-1-hexyl, 6-iodo-1-hexyl, 6,6,6-trichloro-1-hexyl or dodecafluorohexyl;

[0046] phenyl- $\text{C}_1\text{-C}_4\text{-alkyl}$: benzyl, 1-phenylethyl, 2-phenylethyl, 1-phenylprop-1-yl, 2-phenylprop-1-yl, 3-phenylprop-1-yl, 1-phenylbut-1-yl, 2-phenylbut-1-yl, 3-phenylbut-1-yl, 4-phenylbut-1-yl, 1-phenylbut-2-yl, 2-phenylbut-2-yl, 3-phenylbut-2-yl, 4-phenylbut-2-yl, 1-(phenylmethyl)eth-1-yl, 1-(phenylmethyl)-1-(methyl)eth-1-yl or 1-(phenylmethyl)prop-1-yl, preferably benzyl or 2-phenylethyl;

[0047] heterocycl- $\text{C}_1\text{-C}_4\text{-alkyl}$: heterocyclmethyl, 1-heterocyclylethyl, 2-heterocyclylethyl, 1-heterocyclylprop-1-yl, 2-heterocyclylprop-1-yl, 3-heterocyclylprop-1-yl, 1-heterocyclylbut-1-yl, 2-heterocyclylbut-1-yl, 3-heterocyclylbut-1-yl, 4-heterocyclylbut-1-yl, 1-heterocyclylbut-2-yl, 2-heterocyclylbut-2-yl, 3-heterocyclylbut-2-yl, 4-heterocyclylbut-2-yl, 1-(heterocyclylmethyl)eth-1-yl, 1-(heterocyclylmethyl)-1-(methyl)eth-1-yl or 1-(heterocyclylmethyl)prop-1-yl, preferably heterocyclylmethyl or 2-heterocyclylethyl;

[0048] $\text{C}_1\text{-C}_4\text{-alkoxy}$: OCH_3 , OC_2H_5 , n-propoxy, $\text{OCH}(\text{CH}_3)_2$, n-butoxy, $\text{OCH}(\text{CH}_3)\text{—C}_2\text{H}_5$, $\text{OCH}_2\text{—CH}(\text{CH}_3)_2$ or $\text{OC}(\text{CH}_3)_3$, preferably OCH_3 , OC_2H_5 or $\text{OCH}(\text{CH}_3)_2$;

[0049] $\text{C}_1\text{-C}_4\text{-haloalkoxy}$: a $\text{C}_1\text{-C}_4\text{-alkoxy}$ radical as mentioned above which is partially or fully substituted

by fluorine, chlorine, bromine and/or iodine, i.e., for example, OCH_2F , OCHF_2 , OCF_3 , OCH_2Cl , $\text{OCH}(\text{Cl})_2$, $\text{OC}(\text{Cl})_3$, chlorofluoromethoxy, dichlorofluoromethoxy, chlorodifluoromethoxy, 2-fluoroethoxy, 2-chloroethoxy, 2-bromoethoxy, 2-iodoethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, 2-chloro-2-fluoroethoxy, 2-chloro-2,2-difluoroethoxy, 2,2-dichloro-2-fluoroethoxy, 2,2,2-trichloroethoxy, OC_2F_5 , 2-fluoropropoxy, 3-fluoropropoxy, 2,2-difluoropropoxy, 2,3-difluoropropoxy, 2-chloropropoxy, 3-chloropropoxy, 2,3-dichloropropoxy, 2-bromopropoxy, 3-bromopropoxy, 3,3,3-trifluoropropoxy, 3,3,3-trichloropropoxy, 2,2,3,3,3-pentafluoropropoxy, $\text{OCF}_2\text{—C}_2\text{F}_5$, 1-(CH_2F)-2-fluoroethoxy, 1-(CH_2Cl)-2-chloroethoxy, 1-(CH_2Br)-2-bromoethoxy, 4-fluorobutoxy, 4-chlorobutoxy, 4-bromobutoxy or nonafluorobutoxy, preferably OCHF_2 , OCF_3 , dichlorofluoromethoxy, chlorodifluoromethoxy or 2,2,2-trifluoroethoxy;

[0050] $\text{C}_1\text{-C}_4\text{-alkylthio}$: SCH_3 , SC_2H_5 , n-propylthio, $\text{SCH}(\text{CH}_3)_2$, n-butylthio, $\text{SCH}(\text{CH}_3)\text{—C}_2\text{H}_5$, $\text{SCH}_2\text{—CH}(\text{CH}_3)_2$ or $\text{SC}(\text{CH}_3)_3$, preferably SCH_3 or SC_2H_5 ;

[0051] $\text{C}_1\text{-C}_4\text{-haloalkylthio}$: a $\text{C}_1\text{-C}_4\text{-alkylthio}$ radical as mentioned above which is partially or fully substituted by fluorine, chlorine, bromine and/or iodine, i.e., for example, SCH_2F , SCHF_2 , SCH_2Cl , $\text{SCH}(\text{Cl})_2$, $\text{SC}(\text{Cl})_3$, SCF_3 , chlorofluoromethylthio, dichlorofluoromethylthio, chlorodifluoromethylthio, 2-fluoroethylthio, 2-chloroethylthio, 2-bromoethylthio, 2-iodoethylthio, 2,2-difluoroethylthio, 2,2,2-trifluoroethylthio, 2-chloro-2-fluoroethylthio, 2-chloro-2,2-difluoroethylthio, 2,2-dichloro-2-fluoroethylthio, 2,2,2-trichloroethylthio, SC_2F_5 , 2-fluoropropylthio, 3-fluoropropylthio, 2,2-difluoropropylthio, 2,3-difluoropropylthio, 2-chloropropylthio, 3-chloropropylthio, 2,3-dichloropropylthio, 2-bromopropylthio, 3-bromopropylthio, 3,3,3-trifluoropropylthio, 3,3,3-trichloropropylthio, $\text{SCH}_2\text{—C}_2\text{F}_5$, $\text{SCF}_2\text{—C}_2\text{F}_5$, 1-(CH_2F)-2-fluoroethylthio, 1-(CH_2Cl)-2-chloroethylthio, 1-(CH_2Br)-2-bromoethylthio, 4-fluorobutylthio, 4-chlorobutylthio, 4-bromobutylthio or $\text{SCF}_2\text{—CF}_2\text{—C}_2\text{F}_5$, preferably SCHF_2 , SCF_3 , dichlorofluoromethylthio, chlorodifluoromethylthio or 2,2,2-trifluoroethylthio;

[0052] $\text{C}_1\text{-C}_4\text{-alkoxy-}\text{C}_1\text{-C}_4\text{-alkyl}$: $\text{C}_1\text{-C}_4\text{-alkyl}$ which is substituted by $\text{C}_1\text{-C}_4\text{-alkoxy}$ as mentioned above, i.e., for example, $\text{CH}_2\text{—OCH}_3$, $\text{CH}_2\text{—OC}_2\text{H}_5$, n-propoxymethyl, $\text{CH}_2\text{—OCH}(\text{CH}_3)_2$, n-butoxymethyl, (1-methylpropoxy)methyl, (2-methylpropoxy)methyl, $\text{CH}_2\text{—OC}(\text{CH}_3)_3$, 2-(methoxy)ethyl, 2-(ethoxy)ethyl, 2-(n-propoxy)ethyl, 2-(1-methylethoxy)ethyl, 2-(n-butoxy)ethyl, 2-(1-methylpropoxy)ethyl, 2-(2-methylpropoxy)ethyl, 2-(1,1-dimethylethoxy)ethyl, 2-(methoxy)propyl, 2-(ethoxy)propyl, 2-(n-propoxy)propyl, 2-(1-methylethoxy)propyl, 2-(n-butoxy)propyl, 2-(1-methylpropoxy)propyl, 2-(2-methylpropoxy)propyl, 2-(1,1-dimethylethoxy)propyl, 3-(methoxy)propyl, 3-(ethoxy)propyl, 3-(n-propoxy)propyl, 3-(1-methylethoxy)propyl, 3-(n-butoxy)propyl, 3-(1-methylpropoxy)propyl, 3-(2-methylpropoxy)propyl, 3-(1,1-dimethylethoxy)propyl, 2-(methoxy)butyl,

2-(ethoxy)butyl, 2-(n-propoxy)butyl, 2-(1-methylethoxy)butyl, 2-(n-butoxy)butyl, 2-(1-methylpropoxy)butyl, 2-(2-methylpropoxy)butyl, 2-(1,1-dimethylethoxy)butyl, 3-(methoxy)butyl, 3-(ethoxy)butyl, 3-(n-propoxy)butyl, 3-(1-methylethoxy)butyl, 3-(n-butoxy)butyl, 3-(1-methylpropoxy)butyl, 3-(2-methylpropoxy)butyl, 3-(1,1-dimethylethoxy)butyl, 4-(methoxy)butyl, 4-(ethoxy)butyl, 4-(n-propoxy)butyl, 4-(1-methylethoxy)butyl, 4-(n-butoxy)butyl, 4-(1-methylpropoxy)butyl, 4-(2-methylpropoxy)butyl or 4-(1,1-dimethylethoxy)butyl, preferably $\text{CH}_2\text{—OCH}_3$, $\text{CH}_2\text{—OC}_2\text{H}_5$, 2-methoxyethyl or 2-ethoxyethyl;

[0053] $\text{C}_1\text{—C}_4\text{-alkylthio—C}_1\text{—C}_4\text{-alkyl}$: $\text{C}_1\text{—C}_4\text{-alkyl}$ which is substituted by $\text{C}_1\text{—C}_4\text{-alkylthio}$ as mentioned above, i.e., for example, $\text{CH}_2\text{—SCH}_3$, $\text{CH}_2\text{—SC}_2\text{H}_5$, n-propylthiomethyl, $\text{CH}_2\text{—SCH}(\text{CH}_3)_2$, n-butylthiomethyl, (1-methylpropylthio)methyl, (2-methylpropylthio)methyl, $\text{CH}_2\text{—SC}(\text{CH}_3)_2$, 2-(methylthio)ethyl, 2-(ethylthio)ethyl, 2-(n-propylthio)ethyl, 2-(1-methylethylthio)ethyl, 2-(n-butylthio)ethyl, 2-(1-methylpropylthio)ethyl, 2-(2-methylpropylthio)ethyl, 2-(1,1-dimethylethylthio)ethyl, 2-(methylthio)propyl, 2-(ethylthio)propyl, 2-(n-propylthio)propyl, 2-(1-methylethylthio)propyl, 2-(n-butylthio)propyl, 2-(1-methylpropylthio)propyl, 2-(2-methylpropylthio)propyl, 2-(1,1-dimethylethylthio)propyl, 3-(methylthio)propyl, 3-(ethylthio)propyl, 3-(n-propylthio)propyl, 3-(1-methylethylthio)propyl, 3-(n-butylthio)propyl, 3-(1-methylpropylthio)propyl, 3-(2-methylpropylthio)propyl, 3-(1,1-dimethylethylthio)propyl, 2-(methylthio)butyl, 2-(ethylthio)butyl, 2-(n-propylthio)butyl, 2-(1-methylethylthio)butyl, 2-(n-butylthio)butyl, 2-(1-methylpropylthio)butyl, 2-(2-methylpropylthio)butyl, 2-(1,1-dimethylethylthio)butyl, 3-(methylthio)butyl, 3-(ethylthio)butyl, 3-(n-propylthio)butyl, 3-(1-methylethylthio)butyl, 3-(n-butylthio)butyl, 3-(1-methylpropylthio)butyl, 3-(2-methylpropylthio)butyl, 3-(1,1-dimethylethylthio)butyl, 4-(methylthio)butyl, 4-(ethylthio)butyl, 4-(n-propylthio)butyl, 4-(1-methylethylthio)butyl, 4-(n-butylthio)butyl, 4-(1-methylpropylthio)butyl, 4-(2-methylpropylthio)butyl or 4-(1,1-dimethylethylthio)butyl, preferably $\text{CH}_2\text{—SCH}_3$, $\text{CH}_2\text{—SC}_2\text{H}_5$, 2-methylthioethyl or 2-ethylthioethyl;

[0054] $(\text{C}_1\text{—C}_4\text{-alkyl})\text{carbonyl}$: CO—CH_3 , $\text{CO—C}_2\text{H}_5$, $\text{CO—CH}_2\text{—C}_2\text{H}_5$, $\text{CO—CH}(\text{CH}_3)_2$, n-butylcarbonyl, $\text{CO—CH}(\text{CH}_3)\text{—C}_2\text{H}_5$, $\text{CO—CH}_2\text{—CH}(\text{CH}_3)_2$ or $\text{CO—C}(\text{CH}_3)_3$, preferably CO—CH_3 or $\text{CO—C}_2\text{H}_5$;

[0055] $(\text{C}_1\text{—C}_4\text{-haloalkyl})\text{carbonyl}$: a $(\text{C}_1\text{—C}_4\text{-alkyl})\text{carbonyl}$ radical as mentioned above which is partially or fully substituted by fluorine, chlorine, bromine and/or iodine, i.e., for example, $\text{CO—CH}_2\text{F}$, CO—CHF_2 , CO—CF_3 , $\text{CO—CH}_2\text{Cl}$, $\text{CO—CH}(\text{Cl})_2$, $\text{CO—C}(\text{Cl})_3$, chlorofluoromethylcarbonyl, dichlorofluoromethylcarbonyl, chlorodifluoromethylcarbonyl, 2-fluoroethylcarbonyl, 2-chloroethylcarbonyl, 2-bromoethylcarbonyl, 2-iodoethylcarbonyl, 2,2-difluoroethylcarbonyl, 2,2,2-trifluoroethylcarbonyl, 2-chloro-2-fluoroethylcar-

bonyl, 2-chloro-2,2-difluoroethylcarbonyl, 2,2-dichloro-2-fluoroethylcarbonyl, 2,2,2-trichloroethylcarbonyl, $\text{CO—C}_2\text{F}_5$, 2-fluoropropylcarbonyl, 3-fluoropropylcarbonyl, 2,2-difluoropropylcarbonyl, 2,3-difluoropropylcarbonyl, 2-chloropropylcarbonyl, 3-chloropropylcarbonyl, 2,3-dichloropropylcarbonyl, 2-bromopropylcarbonyl, 3-bromopropylcarbonyl, 3,3,3-trifluoropropylcarbonyl, 3,3,3-trichloropropylcarbonyl, 2,2,3,3,3-pentafluoropropylcarbonyl, $\text{CO—CF}_2\text{—C}_2\text{F}_5$, 1-(CH_2F)-2-fluoroethylcarbonyl, 1-(CH_2Cl)-2-chloroethylcarbonyl, 1-(CH_2Br)-2-bromoethylcarbonyl, 4-fluorobutylcarbonyl, 4-chlorobutylcarbonyl, 4-bromobutylcarbonyl or nonafluorobutylcarbonyl, preferably CO—CF_3 , $\text{CO—CH}_2\text{Cl}$, or 2,2,2-trifluoroethylcarbonyl;

[0056] $(\text{C}_1\text{—C}_4\text{-alkyl})\text{carbonyloxy}$: O—CO—CH_3 , $\text{O—CO—C}_2\text{H}_5$, $\text{O—CO—CH}_2\text{—C}_2\text{H}_5$, $\text{O—CO—CH}(\text{CH}_3)_2$, $\text{O—CO—CH}_2\text{—CH}_2\text{—C}_2\text{H}_5$, $\text{O—CO—CH}(\text{CH}_3)\text{—C}_2\text{H}_5$, $\text{O—CO—CH—CH}(\text{CH}_3)_2$ or $\text{O—CO—C}(\text{CH}_3)_3$, preferably O—CO—CH_3 or $\text{O—CO—C}_2\text{H}_5$;

[0057] $(\text{C}_1\text{—C}_4\text{-haloalkyl})\text{carbonyloxy}$: a $(\text{C}_1\text{—C}_4\text{-alkyl})\text{carbonyl}$ radical as mentioned above which is partially or fully substituted by fluorine, chlorine, bromine and/or iodine, i.e., for example, $\text{O—CO—CH}_2\text{F}$, O—CO—CHF_2 , O—CO—CF_3 , $\text{O—CO—CH}_2\text{Cl}$, $\text{O—CO—CH}(\text{Cl})_2$, $\text{O—CO—C}(\text{Cl})_3$, chlorofluoromethylcarbonyloxy, dichlorofluoromethylcarbonyloxy, chlorodifluoromethylcarbonyloxy, 2-fluoroethylcarbonyloxy, 2-chloroethylcarbonyloxy, 2-bromoethylcarbonyloxy, 2-iodoethylcarbonyloxy, 2,2-difluoroethylcarbonyloxy, 2,2,2-trifluoroethylcarbonyloxy, 2-chloro-2-fluoroethylcarbonyloxy, 2-chloro-2,2-difluoroethylcarbonyloxy, 2,2-dichloro-2-fluoroethylcarbonyloxy, 2,2,2-trichloroethylcarbonyloxy, $\text{O—CO—C}_2\text{F}_5$, 2-fluoropropylcarbonyloxy, 3-fluoropropylcarbonyloxy, 2,2-difluoropropylcarbonyloxy, 2,3-difluoropropylcarbonyloxy, 2-chloropropylcarbonyloxy, 3-chloropropylcarbonyloxy, 2,3-dichloropropylcarbonyloxy, 2-bromopropylcarbonyloxy, 3-bromopropylcarbonyloxy, 3,3,3-trifluoropropylcarbonyloxy, 3,3,3-trichloropropylcarbonyloxy, 2,2,3,3,3-pentafluoropropylcarbonyloxy, heptafluoropropylcarbonyloxy, 1-(CH_2F)-2-fluoroethylcarbonyloxy, 1-(CH_2Cl)-2-chloroethylcarbonyloxy, 1-(CH_2Br)-2-bromoethylcarbonyloxy, 4-fluorobutylcarbonyloxy, 4-chlorobutylcarbonyloxy, 4-bromobutylcarbonyloxy or nonafluorobutylcarbonyloxy, preferably O—CO—CF_3 , $\text{O—CO—CH}_2\text{Cl}$ or 2,2,2-trifluoroethylcarbonyloxy;

[0058] $(\text{C}_1\text{—C}_4\text{-alkoxy})\text{carbonyl}$: CO—OCH_3 , $\text{CO—OC}_2\text{H}_5$, n-propoxycarbonyl, $\text{CO—OCH}(\text{CH}_3)_2$, n-butoxycarbonyl, $\text{CO—OCH}(\text{CH}_3)\text{—C}_2\text{H}_5$, $\text{CO—OCH}_2\text{—CH}(\text{CH}_3)_2$ or $\text{CO—OC}(\text{CH}_3)_3$, preferably CO—OCH_3 or $\text{CO—OC}_2\text{H}_5$;

[0059] $(\text{C}_1\text{—C}_4\text{-alkoxy})\text{carbonyl—C}_1\text{—C}_4\text{-alkyl}$: $\text{C}_1\text{—C}_4\text{-alkyl}$ which is substituted by $(\text{C}_1\text{—C}_4\text{-alkoxy})\text{carbonyl}$ as mentioned above, i.e., for example, methoxy-

carbonylmethyl, ethoxycarbonylmethyl, n-propoxycarbonylmethyl, (1-methylethoxycarbonyl)methyl, n-butoxycarbonylmethyl, (1-methylpropoxycarbonyl)methyl, (2-methylpropoxycarbonyl)methyl, (1,1-dimethylethoxycarbonyl)methyl, 1-(methoxycarbonyl)ethyl, 1-(ethoxycarbonyl)ethyl, 1-(n-propoxycarbonyl)ethyl, 1-(1-methylethoxycarbonyl)ethyl, 1-(n-butoxycarbonyl)ethyl, 2-(methoxycarbonyl)ethyl, 2-(ethoxycarbonyl)ethyl, 2-(n-propoxycarbonyl)ethyl, 2-(1-methylethoxycarbonyl)ethyl, 2-(n-butoxycarbonyl)ethyl, 2-(1-methylpropoxycarbonyl)ethyl, 2-(2-methylpropoxycarbonyl)ethyl, 2-(1,1-dimethylethoxycarbonyl)ethyl, 1-(methoxycarbonyl)-1-methylethyl, 1-(ethoxycarbonyl)-1-methylethyl, 1-(n-propoxycarbonyl)-1-methylethyl, 1-(1-methylethoxycarbonyl)-1-methylethyl, 1-(n-butoxycarbonyl)-1-methylethyl, 2-(methoxycarbonyl)propyl, 2-(ethoxycarbonyl)propyl, 2-(n-propoxycarbonyl)propyl, 2-(1-methylethoxycarbonyl)propyl, 2-(n-butoxycarbonyl)propyl, 2-(1-methylpropoxycarbonyl)propyl, 2-(2-methylpropoxycarbonyl)propyl, 2-(1,1-dimethylethoxycarbonyl)propyl, 3-(methoxycarbonyl)propyl, 3-(ethoxycarbonyl)propyl, 3-(n-propoxycarbonyl)propyl, 3-(1-methylethoxycarbonyl)propyl, 3-(n-butoxycarbonyl)propyl, 3-(1-methylpropoxycarbonyl)propyl, 3-(2-methylpropoxycarbonyl)propyl, 3-(1,1-dimethylethoxycarbonyl)propyl, 2-(methoxycarbonyl)-butyl, 2-(ethoxycarbonyl)-butyl, 2-(n-propoxycarbonyl)-butyl, 2-(1-methylethoxycarbonyl)-butyl, 2-(n-butoxycarbonyl)-butyl, 2-(1-methylpropoxycarbonyl)-butyl, 2-(2-methylpropoxycarbonyl)-butyl, 2-(1,1-dimethylethoxycarbonyl)-butyl, 3-(methoxycarbonyl)-butyl, 3-(ethoxycarbonyl)-butyl, 3-(n-propoxycarbonyl)-butyl, 3-(1-methylethoxycarbonyl)-butyl, 3-(n-butoxycarbonyl)-butyl, 3-(1-methylpropoxycarbonyl)-butyl, 3-(2-methylpropoxycarbonyl)-butyl, 3-(1,1-dimethylethoxycarbonyl)-butyl, 4-(methoxycarbonyl)-butyl, 4-(ethoxycarbonyl)-butyl, 4-(n-propoxycarbonyl)-butyl, 4-(1-methylethoxycarbonyl)-butyl, 4-(n-butoxycarbonyl)-butyl, 4-(1-methylpropoxycarbonyl)-butyl, 4-(2-methylpropoxycarbonyl)-butyl or 4-(1,1-dimethylethoxycarbonyl)-butyl, preferably methoxycarbonylmethyl, ethoxycarbonylmethyl, 1-(methoxycarbonyl)ethyl or 1-(ethoxycarbonyl)ethyl;

[0060] (C₁-C₄-alkoxy)carbonyl-C₁-C₄-alkoxy:

C₁-C₄-alkoxy which is substituted by (C₁-C₄-alkoxy)carbonyl as mentioned above, i.e., for example, methoxycarbonylmethoxy, ethoxycarbonylmethoxy, n-propoxycarbonylmethoxy, (1-methylethoxycarbonyl)methoxy, n-butoxycarbonylmethoxy, (1-methylpropoxycarbonyl)methoxy, (2-methylpropoxycarbonyl)methoxy, (1,1-dimethylethoxycarbonyl)methoxy, 1-(methoxycarbonyl)ethoxy, 1-(ethoxycarbonyl)ethoxy, 1-(n-propoxycarbonyl)ethoxy, 1-(1-methylethoxycarbonyl)ethoxy, 1-(n-butoxycarbonyl)ethoxy,

2-(methoxycarbonyl)ethoxy, 2-(ethoxycarbonyl)ethoxy, 2-(n-propoxycarbonyl)ethoxy, 2-(1-methylethoxycarbonyl)ethoxy, 2-(n-butoxycarbonyl)ethoxy, 2-(1-methylpropoxycarbonyl)ethoxy, 2-(2-methylpropoxycarbonyl)ethoxy, 2-(1,1-dimethylethoxycarbonyl)ethoxy, 1-(methoxycarbonyl)-1-methylethoxy, 1-(ethoxycarbonyl)-1-methylethoxy, 1-(n-propoxycarbonyl)-1-methylethoxy, 1-(1-methylethoxycarbonyl)-1-methylethoxy, 1-(n-butoxycarbonyl)-1-methylethoxy, 2-(methoxycarbonyl)propoxy, 2-(ethoxycarbonyl)propoxy, 2-(n-propoxycarbonyl)propoxy, 2-(1-methylethoxycarbonyl)propoxy, 2-(n-butoxycarbonyl)propoxy, 2-(1-methylpropoxycarbonyl)propoxy, 2-(2-methylpropoxycarbonyl)propoxy, 2-(1,1-dimethylethoxycarbonyl)propoxy, 3-(methoxycarbonyl)propoxy, 3-(ethoxycarbonyl)propoxy, 3-(n-propoxycarbonyl)propoxy, 3-(1-methylethoxycarbonyl)propoxy, 3-(n-butoxycarbonyl)propoxy, 3-(1-methylpropoxycarbonyl)propoxy, 3-(2-methylpropoxycarbonyl)propoxy, 3-(1,1-dimethylethoxycarbonyl)propoxy, 2-(methoxycarbonyl)-butoxy, 2-(ethoxycarbonyl)-butoxy, 2-(n-propoxycarbonyl)-butoxy, 2-(1-methylethoxycarbonyl)-butoxy, 2-(n-butoxycarbonyl)-butoxy, 2-(1-methylpropoxycarbonyl)-butoxy, 2-(2-methylpropoxycarbonyl)-butoxy, 2-(1,1-dimethylethoxycarbonyl)-butoxy, 3-(methoxycarbonyl)-butoxy, 3-(ethoxycarbonyl)-butoxy, 3-(n-propoxycarbonyl)-butoxy, 3-(1-methylethoxycarbonyl)-butoxy, 3-(n-butoxycarbonyl)-butoxy, 3-(1-methylpropoxycarbonyl)-butoxy, 3-(2-methylpropoxycarbonyl)-butoxy, 3-(1,1-dimethylethoxycarbonyl)-butoxy, 4-(methoxycarbonyl)-butoxy, 4-(ethoxycarbonyl)-butoxy, 4-(n-propoxycarbonyl)-butoxy, 4-(1-methylethoxycarbonyl)-butoxy, 4-(n-butoxycarbonyl)-butoxy, 4-(1-methylpropoxycarbonyl)-butoxy, 4-(2-methylpropoxycarbonyl)-butoxy, 4-(1,1-dimethylethoxycarbonyl)-butoxy, preferably methoxycarbonylmethoxy, ethoxycarbonylmethoxy, 1-(methoxycarbonyl)ethoxy or 1-(ethoxycarbonyl)ethoxy;

[0061] (C₁-C₄-alkoxy)carbonyl-C₁-C₄-alkylthio:

C₁-C₄-alkylthio which is substituted by (C₁-C₄-alkoxy)carbonyl as mentioned above, i.e., for example, methoxycarbonylmethylthio, ethoxycarbonylmethylthio, n-propoxycarbonylmethylthio, (1-methylethoxycarbonyl)methylthio, n-butoxycarbonylmethylthio, (1-methylpropoxycarbonyl)methylthio, (2-methylpropoxycarbonyl)methylthio, (1,1-dimethylethoxycarbonyl)methylthio, 1-(methoxycarbonyl)ethylthio, 1-(ethoxycarbonyl)ethylthio, 1-(n-propoxycarbonyl)ethylthio, 1-(1-methylethoxycarbonyl)ethylthio, 1-(n-butoxycarbonyl)ethylthio, 2-(methoxycarbonyl)ethylthio, 2-(ethoxycarbonyl)ethylthio, 2-(n-propoxycarbonyl)ethylthio, 2-(1-methylethoxycarbonyl)ethylthio, 2-(n-butoxycarbonyl)ethylthio, 2-(1-methylpropoxycarbonyl)ethylthio, 2-(2-methylpropoxycarbonyl)ethylthio, 2-(1,1-dimethylethoxycarbonyl)ethylthio, 2-(methoxycarbonyl)propylthio,

2-(ethoxycarbonyl)propylthio, 2-(n-propoxycarbonyl)propylthio, 2-(1-methylethoxycarbonyl)propylthio, 2-(n-butoxycarbonyl)propylthio, 2-(1-methylpropoxycarbonyl)propylthio, 2-(2-methylpropoxycarbonyl)propylthio, 2-(1,1-dimethylethoxycarbonyl)propylthio, 3-(methoxycarbonyl)propylthio, 3-(ethoxycarbonyl)propylthio, 3-(n-propoxycarbonyl)propylthio, 3-(1-methylethoxycarbonyl)propylthio, 3-(n-butoxycarbonyl)propylthio, 3-(1-methylpropoxycarbonyl)propylthio, 3-(2-methylpropoxycarbonyl)propylthio, 3-(1,1-dimethylethoxycarbonyl)propylthio, 2-(methoxycarbonyl)butylthio, 2-(ethoxycarbonyl)butylthio, 2-(n-propoxycarbonyl)butylthio, 2-(1-methylethoxycarbonyl)butylthio, 2-(n-butoxycarbonyl)butylthio, 2-(1-methylpropoxycarbonyl)butylthio, 2-(2-methylpropoxycarbonyl)butylthio, 2-(1,1-dimethylethoxycarbonyl)butylthio, 3-(methoxycarbonyl)butylthio, 3-(ethoxycarbonyl)butylthio, 3-(n-propoxycarbonyl)butylthio, 3-(1-methylethoxycarbonyl)butylthio, 3-(n-butoxycarbonyl)butylthio, 3-(1-methylpropoxycarbonyl)butylthio, 3-(2-methylpropoxycarbonyl)butylthio, 3-(1,1-dimethylethoxycarbonyl)butylthio, 4-(methoxycarbonyl)butylthio, 4-(ethoxycarbonyl)butylthio, 4-(n-propoxycarbonyl)butylthio, 4-(1-methylethoxycarbonyl)butylthio, 4-(n-butoxycarbonyl)butylthio, 4-(1-methylpropoxycarbonyl)butylthio, 4-(2-methylpropoxycarbonyl)butylthio, or 4-(1,1-dimethylethoxycarbonyl)butylthio, preferably methoxycarbonylmethylthio, ethoxycarbonylmethylthio, 1-(methoxycarbonyl)ethylthio or 1-(ethoxycarbonyl)ethylthio;

[0062] C_1 - C_4 -alkylsulfinyl: $SO-CH_3$, $SO-C_2H_5$, $SO-CH_2-C_2H_5$, $SO-CH(CH_3)_2$, n-butylsulfinyl, $SO-CH(CH_3)-C_2H_5$, $SO-CH_2-CH(CH_3)_2$ or $SO-C(CH_3)_3$, preferably $SO-CH_3$ or $SO-C_2H_5$;

[0063] C_1 - C_4 -haloalkylsulfinyl: a C_1 - C_4 -alkylsulfinyl radical as mentioned above which is partially or fully substituted by fluorine, chlorine, bromine and/or iodine, i.e., for example, $SO-CH_2F$, $SO-CHF_2$, $SO-CF_3$, $SO-CH_2Cl$, $SO-CH(Cl)_2$, $SO-C(Cl)_3$, chlorofluoromethylsulfinyl, dichlorofluoromethylsulfinyl, chlorodifluoromethylsulfinyl, 2-fluoroethylsulfinyl, 2-chloroethylsulfinyl, 2-bromoethylsulfinyl, 2-iodoethylsulfinyl, 2,2-difluoroethylsulfinyl, 2,2,2-trifluoroethylsulfinyl, 2-chloro-2-fluoroethylsulfinyl, 2-chloro-2,2-difluoroethylsulfinyl, 2,2-dichloro-2-fluoroethylsulfinyl, 2,2,2-trichloroethylsulfinyl, $SO-C_2F_5$, 2-fluoropropylsulfinyl, 3-fluoropropylsulfinyl, 2,2-difluoropropylsulfinyl, 2,3-difluoropropylsulfinyl, 2-chloropropylsulfinyl, 3-chloropropylsulfinyl, 2,3-dichloropropylsulfinyl, 2-bromopropylsulfinyl, 3-bromopropylsulfinyl, 3,3,3-trifluoropropylsulfinyl, 3,3,3-trichloropropylsulfinyl, $SO-CH_2-C_2F_5$, $SO-CF_2-C_2F_5$, 1-(fluoromethyl)-2-fluoroethylsulfinyl, 1-(chloromethyl)-2-chloroethylsulfinyl, 1-(bromomethyl)-2-bromoethylsulfinyl, 4-fluorobutylsulfinyl,

4-chlorobutylsulfinyl, 4-bromobutylsulfinyl or nonafluorobutylsulfinyl, preferably $SO-CF_3$, $SO-CH_2Cl$ or 2,2,2-trifluoroethylsulfinyl;

[0064] C_1 - C_4 -alkylsulfonyl: SO_2-CH_3 , $SO_2-C_2H_5$, $SO_2-CH_2-C_2H_5$, $SO_2-CH(CH_3)_2$, n-butylsulfonyl, $SO_2-CH(CH_3)-C_2H_5$, $SO_2-CH_2-CH(CH_3)_2$ or $SO_2-C(CH_3)_3$, preferably SO_2-CH_3 or $SO_2-C_2H_5$;

[0065] C_1 - C_4 -haloalkylsulfonyl: a C_1 - C_4 -alkylsulfonyl radical as mentioned above which is partially or fully substituted by fluorine, chlorine, bromine and/or iodine, i.e., for example, SO_2-CH_2F , SO_2-CHF_2 , SO_2-CF_3 , SO_2-CH_2Cl , $SO_2-CH(Cl)_2$, $SO_2-C(Cl)_3$, chlorofluoromethylsulfonyl, dichlorofluoromethylsulfonyl, chlorodifluoromethylsulfonyl, 2-fluoroethylsulfonyl, 2-chloroethylsulfonyl, 2-bromoethylsulfonyl, 2-iodoethylsulfonyl, 2,2-difluoroethylsulfonyl, 2,2,2-trifluoroethylsulfonyl, 2-chloro-2-fluoroethylsulfonyl, 2-chloro-2,2-difluoroethylsulfonyl, 2,2-dichloro-2-fluoroethylsulfonyl, 2,2,2-trichloroethylsulfonyl, $SO_2-C_2F_5$, 2-fluoropropylsulfonyl, 3-fluoropropylsulfonyl, 2,2-difluoropropylsulfonyl, 2,3-difluoropropylsulfonyl, 2-chloropropylsulfonyl, 3-chloropropylsulfonyl, 2,3-dichloropropylsulfonyl, 2-bromopropylsulfonyl, 3-bromopropylsulfonyl, 3,3,3-trifluoropropylsulfonyl, 3,3,3-trichloropropylsulfonyl, $SO_2-CH_2-C_2F_5$, $SO_2-CF_2-C_2F_5$, 1-(fluoromethyl)-2-fluoroethylsulfonyl, 1-(chloromethyl)-2-chloroethylsulfonyl, 1-(bromomethyl)-2-bromoethylsulfonyl, 4-fluorobutylsulfonyl, 4-chlorobutylsulfonyl, 4-bromobutylsulfonyl or nonafluorobutylsulfonyl, preferably SO_2-CF_3 , SO_2-CH_2Cl or 2,2,2-trifluoroethylsulfonyl;

[0066] di(C_1 - C_4 -alkyl)amino: $N(CH_3)_2$, $N(C_2H_5)_2$, N,N-dipropylamino, $N[CH(CH_3)_2]_2$, N,N-dibutylamino, N,N-di(1-methylpropyl)amino, N,N-di(2-methylpropyl)amino, $N[C(CH_3)_3]_2$, N-ethyl-N-methylamino, N-methyl-N-propylamino, N-methyl-N-(1-methylethyl)amino, N-butyl-N-methylamino, N-methyl-N-(1-methylpropyl)amino, N-methyl-N-(2-methylpropyl)amino, N-(1,1-dimethylethyl)-N-methylamino, N-ethyl-N-propylamino, N-ethyl-N-(1-methylethyl)amino, N-butyl-N-ethylamino, N-ethyl-N-(1-methylpropyl)amino, N-ethyl-N-(2-methylpropyl)amino, N-ethyl-N-(1,1-dimethylethyl)amino, N-(1-methylethyl)-N-propylamino, N-butyl-N-propylamino, N-(1-methylpropyl)-N-propylamino, N-(2-methylpropyl)-N-propylamino, N-(1,1-dimethylethyl)-N-propylamino, N-butyl-N-(1-methylethyl)amino, N-(1-methylethyl)-N-(1-methylpropyl)amino, N-(1-methylethyl)-N-(2-methylpropyl)amino, N-(1,1-dimethylethyl)-N-(1-methylethyl)amino, N-butyl-N-(1-methylethyl)amino, N-butyl-N-(2-methylpropyl)amino, N-butyl-N-(1,1-dimethylethyl)amino, N-(1-methylpropyl)-N-(2-methylpropyl)amino, N-(1,1-dimethylethyl)-N-(1-methylpropyl)amino or N-(1,1-dimethylethyl)-N-(2-methylpropyl)amino, preferably $N(CH_3)_2$ or $N(C_2H_5)_2$;

[0067] di(C_1 - C_4 -alkyl)aminocarbonyl: e.g. N,N-diethylaminocarbonyl, N,N-diethylaminocarbonyl,

N,N-di(1-methylethyl)aminocarbonyl, N,N-dipropylaminocarbonyl, N,N-dibutylaminocarbonyl, N,N-di(1-methylpropyl)aminocarbonyl, N,N-di(2-methylpropyl)aminocarbonyl, N,N-di(1,1-dimethylethyl)aminocarbonyl, N-ethyl-N-methylaminocarbonyl, N-methyl-N-propylaminocarbonyl, N-methyl-N-(1-methylethyl)aminocarbonyl, N-butyl-N-methylaminocarbonyl, N-methyl-N-(1-methylpropyl)aminocarbonyl, N-methyl-N-(2-methylpropyl)aminocarbonyl, N-(1,1-dimethylethyl)-N-methylaminocarbonyl, N-ethyl-N-propylaminocarbonyl, N-ethyl-N-(1-methylethyl)aminocarbonyl, N-butyl-N-ethylaminocarbonyl, N-ethyl-N-(1-methylpropyl)aminocarbonyl, N-ethyl-N-(2-methylpropyl)aminocarbonyl, N-ethyl-N-(1,1-dimethylethyl)aminocarbonyl, N-(1-methylethyl)-N-propylaminocarbonyl, N-Butyl-N-propylaminocarbonyl, N-(1-methylpropyl)-N-propylaminocarbonyl, N-(2-methylpropyl)-N-propylaminocarbonyl, N-(1,1-dimethylethyl)-N-propylaminocarbonyl, N-butyl-N-(1-methylethyl)aminocarbonyl, N-(1-methylethyl)-N-(1-methylpropyl)aminocarbonyl, N-(1-methylethyl)-N-(2-methylpropyl)aminocarbonyl, N-(1,1-dimethylethyl)-N-(1-methylethyl)aminocarbonyl, N-butyl-N-(1-methylpropyl)aminocarbonyl, N-butyl-N-(2-methylpropyl)aminocarbonyl, N-butyl-N-(1,1-dimethylethyl)aminocarbonyl, N-(1-methylpropyl)-N-(2-methylpropyl)aminocarbonyl, N-(1,1-dimethylethyl)-N-(1-methylpropyl)aminocarbonyl or N-(1,1-dimethylethyl)-N-(2-methylpropyl)aminocarbonyl;

[0068] di(C₁-C₄-alkyl)aminocarbonyl-C₁-C₄-alkyl: C₁-C₄-alkyl which is monosubstituted by di(C₁-C₄-alkyl)aminocarbonyl, for example di(C₁-C₄-alkyl)aminocarbonylmethyl, 1- or 2-di(C₁-C₄-alkyl)aminocarbonylethyl, 1-, 2- or 3-di(C₁-C₄-alkyl)aminocarbonylpropyl;

[0069] di(C₁-C₄-alkyl)aminocarbonyl-C₁-C₄-alkoxy: C₁-C₄-alkoxy which is monosubstituted by di(C₁-C₄-alkyl)aminocarbonyl, for example di(C₁-C₄-alkyl)aminocarbonylmethoxy, 1- or 2-di(C₁-C₄-alkyl)aminocarbonylethoxy, 1-, 2- or 3-di(C₁-C₄-alkyl)aminocarbonylpropoxy;

[0070] di(C₁-C₄-alkyl)aminocarbonyl-C₁-C₄-alkylthio: C₁-C₄-alkylthio which is monosubstituted by di(C₁-C₄-alkyl)aminocarbonyl, for example di(C₁-C₄-alkyl)aminocarbonylmethylthio, 1- or 2-di(C₁-C₄-alkyl)aminocarbonylethylthio, 1-, 2- or 3-di(C₁-C₄-alkyl)aminocarbonylpropylthio;

[0071] C₂-C₆-alkenyl: vinyl, prop-1-en-1-yl, allyl, 1-methylethenyl, 1-buten-1-yl, 1-buten-2-yl, 1-buten-3-yl, 2-buten-1-yl, 1-methylprop-1-en-1-yl, 2-methylprop-1-en-1-yl, 1-methylprop-2-en-1-yl, 2-methylprop-2-en-1-yl, n-penten-1-yl, n-penten-2-yl, n-penten-3-yl, n-penten-4-yl, 1-methylbut-1-en-1-yl, 2-methylbut-1-en-1-yl, 3-methylbut-1-en-1-yl, 1-methylbut-2-en-1-yl, 2-methylbut-2-en-1-yl, 3-methylbut-2-en-1-yl, 1-methylbut-3-en-1-yl, 2-methylbut-3-en-1-yl, 3-methylbut-3-en-1-yl, 1,1-

dimethylprop-2-en-1-yl, 1,2-dimethylprop-1-en-1-yl, 1,2-dimethylprop-2-en-1-yl, 1-ethylprop-1-en-2-yl, 1-ethylprop-2-en-1-yl, n-hex-1-en-1-yl, n-hex-2-en-1-yl, n-hex-3-en-1-yl, n-hex-4-en-1-yl, n-hex-5-en-1-yl, 1-methylpent-1-en-1-yl, 2-methylpent-1-en-1-yl, 3-methylpent-1-en-1-yl, 4-methylpent-1-en-1-yl, 1-methylpent-2-en-1-yl, 2-methylpent-2-en-1-yl, 3-methylpent-2-en-1-yl, 4-methylpent-2-en-1-yl, 1-methylpent-3-en-1-yl, 2-methylpent-3-en-1-yl, 3-methylpent-3-en-1-yl, 4-methylpent-3-en-1-yl, 1-methylpent-4-en-1-yl, 2-methylpent-4-en-1-yl, 3-methylpent-4-en-1-yl, 4-methylpent-4-en-1-yl, 1,1-dimethylbut-2-en-1-yl, 1,1-dimethylbut-3-en-1-yl, 1,2-dimethylbut-1-en-1-yl, 1,2-dimethylbut-2-en-1-yl, 1,2-dimethylbut-3-en-1-yl, 1,3-dimethylbut-1-en-1-yl, 1,3-dimethylbut-2-en-1-yl, 1,3-dimethylbut-3-en-1-yl, 2,2-dimethylbut-3-en-1-yl, 2,3-dimethylbut-1-en-1-yl, 2,3-dimethylbut-2-en-1-yl, 2,3-dimethylbut-3-en-1-yl, 3,3-dimethylbut-1-en-1-yl, 3,3-dimethylbut-2-en-1-yl, 1-ethylbut-1-en-1-yl, 1-ethylbut-2-en-1-yl, 1-ethylbut-3-en-1-yl, 2-ethylbut-1-en-1-yl, 2-ethylbut-2-en-1-yl, 2-ethylbut-3-en-1-yl, 1,1,2-trimethylprop-2-en-1-yl, 1-ethyl-1-methylprop-2-en-1-yl, 1-ethyl-2-methylprop-1-en-1-yl or 1-ethyl-2-methylprop-2-en-1-yl;

[0072] C₂-C₆-haloalkenyl: C₂-C₆-alkenyl as mentioned above which is partially or fully substituted by fluorine, chlorine and/or bromine, i.e., for example, 2-chlorovinyl, 2-chloroallyl, 3-chloroallyl, 2,3-dichloroallyl, 3,3-dichloroallyl, 2,3,3-trichloroallyl, 2,3-dichlorobut-2-enyl, 2-bromoallyl, 3-bromoallyl, 2,3-dibromoallyl, 3,3-dibromoallyl, 2,3,3-tribromoallyl and 2,3-dibromobut-2-enyl, preferably C₃— or C₄-haloalkenyl;

[0073] C₂-C₆-alkynyl: ethynyl and C₃-C₆-alkynyl such as prop-1-yn-1-yl, prop-2-yn-1-yl, n-but-1-yn-1-yl, n-but-1-yn-3-yl, n-but-1-yn-4-yl, n-but-2-yn-1-yl, n-pent-1-yn-1-yl, n-pent-1-yn-3-yl, n-pent-1-yn-4-yl, n-pent-1-yn-5-yl, n-pent-2-yn-1-yl, n-pent-2-yn-4-yl, n-pent-2-yn-5-yl, 3-methylbut-1-yn-3-yl, 3-methylbut-1-yn-4-yl, n-hex-1-yn-1-yl, n-hex-1-yn-3-yl, n-hex-1-yn-4-yl, n-hex-1-yn-5-yl, n-hex-1-yn-6-yl, n-hex-2-yn-1-yl, n-hex-2-yn-4-yl, n-hex-2-yn-5-yl, n-hex-2-yn-6-yl, n-hex-3-yn-1-yl, n-hex-3-yn-2-yl, 3-methylpent-1-yn-1-yl, 3-methylpent-1-yn-3-yl, 3-methylpent-1-yn-4-yl, 3-methylpent-1-yn-5-yl, 4-methylpent-1-yn-1-yl, 4-methylpent-2-yn-4-yl or 4-methylpent-2-yn-5-yl, preferably prop-2-yn-1-yl;

[0074] C₂-C₆-haloalkynyl: C₂-C₆-alkynyl as mentioned above which is partially or fully substituted by fluorine, chlorine and/or bromine, i.e., for example, 1,1-difluoroprop-2-yn-1-yl, 1,1-difluorobut-2-yn-1-yl, 4-fluorobut-2-yn-1-yl, 4-chlorobut-2-yn-1-yl, 5-fluoropent-3-yn-1-yl or 6-fluorohex-4-yn-1-yl, preferably C₃— or C₄-haloalkynyl;

[0075] C₃-C₈-cycloalkyl: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl;

[0076] C₃-C₈-cycloalkyl which contains a carbonyl or thiocarbonyl ring member, for example cyclobutanon-2-yl, cyclobutanon-3-yl, cyclopentanon-2-yl, cyclopentanon-3-yl, cyclohexanon-2-yl, cyclohex-

anon-4-yl, cycloheptanon-2-yl, cyclooctanon-2-yl, cyclobutanethion-2-yl, cyclobutanethion-3-yl, cyclopentanethion-2-yl, cyclopentanethion-3-yl, cyclohexanethion-2-yl, cyclohexanethion-4-yl, cycloheptanethion-2-yl or cyclooctanethion-2-yl, preferably cyclopentanon-2-yl or cyclohexanon-2-yl;

[0077] C₃-C₈-cycloalkyl-C₁-C₄-alkyl: cyclopropylmethyl, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclopropylprop-1-yl, 2-cyclopropylprop-1-yl, 3-cyclopropylprop-1-yl, 1-cyclopropylbut-1-yl, 2-cyclopropylbut-1-yl, 3-cyclopropylbut-1-yl, 4-cyclopropylbut-1-yl, 1-cyclopropylbut-2-yl, 2-cyclopropylbut-2-yl, 3-cyclopropylbut-2-yl, 4-cyclopropylbut-2-yl, 1-(cyclopropylmethyl)eth-1-yl, 1-(cyclopropylmethyl)-1-(methyl)eth-1-yl, 1-(cyclopropylmethyl)prop-1-yl, cyclobutylmethyl, 1-cyclobutylethyl, 2-cyclobutylethyl, 1-cyclobutylprop-1-yl, 2-cyclobutylprop-1-yl, 3-cyclobutylprop-1-yl, 1-cyclobutylbut-1-yl, 2-cyclobutylbut-1-yl, 3-cyclobutylbut-1-yl, 4-cyclobutylbut-1-yl, 1-cyclobutylbut-2-yl, 2-cyclobutylbut-2-yl, 3-cyclobutylbut-2-yl, 4-cyclobutylbut-2-yl, 1-(cyclobutylmethyl)eth-1-yl, 1-(cyclobutylmethyl)-1-(methyl)eth-1-yl, 1-(cyclobutylmethyl)prop-1-yl, cyclopentylmethyl, 1-cyclopentylethyl, 2-cyclopentylethyl, 1-cyclopentylprop-1-yl, 2-cyclopentylprop-1-yl, 3-cyclopentylprop-1-yl, 1-cyclopentylbut-1-yl, 2-cyclopentylbut-1-yl, 3-cyclopentylbut-1-yl, 4-cyclopentylbut-1-yl, 1-cyclopentylbut-2-yl, 2-cyclopentylbut-2-yl, 3-cyclopentylbut-2-yl, 4-cyclopentylbut-2-yl, 1-(cyclopentylmethyl)eth-1-yl, 1-(cyclopentylmethyl)-1-(methyl)eth-1-yl, 1-(cyclopentylmethyl)prop-1-yl, cyclohexylmethyl, 1-cyclohexylethyl, 2-cyclohexylethyl, 1-cyclohexylprop-1-yl, 2-cyclohexylprop-1-yl, 3-cyclohexylprop-1-yl, 1-cyclohexylbut-1-yl, 2-cyclohexylbut-1-yl, 3-cyclohexylbut-1-yl, 4-cyclohexylbut-1-yl, 1-cyclohexylbut-2-yl, 2-cyclohexylbut-2-yl, 3-cyclohexylbut-2-yl, 4-cyclohexylbut-2-yl, 1-(cyclohexylmethyl)eth-1-yl, 1-(cyclohexylmethyl)-1-(methyl)eth-1-yl, 1-(cyclohexylmethyl)prop-1-yl, cycloheptylmethyl, 1-cycloheptylethyl, 2-cycloheptylethyl, 1-cycloheptylprop-1-yl, 2-cycloheptylprop-1-yl, 3-cycloheptylprop-1-yl, 1-cycloheptylbut-1-yl, 2-cycloheptylbut-1-yl, 3-cycloheptylbut-1-yl, 4-cycloheptylbut-1-yl, 1-cycloheptylbut-2-yl, 2-cycloheptylbut-2-yl, 3-cycloheptylbut-2-yl, 4-cycloheptylbut-2-yl, 1-(cycloheptylmethyl)eth-1-yl, 1-(cycloheptylmethyl)-1-(methyl)eth-1-yl, 1-(cycloheptylmethyl)prop-1-yl, cyclooctylmethyl, 1-cyclooctylethyl, 2-cyclooctylethyl, 1-cyclooctylprop-1-yl, 2-cyclooctylprop-1-yl, 3-cyclooctylprop-1-yl, 1-cyclooctylbut-1-yl, 2-cyclooctylbut-1-yl, 3-cyclooctylbut-1-yl, 4-cyclooctylbut-1-yl, 1-cyclooctylbut-2-yl, 2-cyclooctylbut-2-yl, 3-cyclooctylbut-2-yl, 4-cyclooctylbut-2-yl, 1-(cyclooctylmethyl)eth-1-yl, 1-(cyclooctylmethyl)-1-(methyl)eth-1-yl or 1-(cyclooctylmethyl)prop-1-yl, preferably cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl or cyclohexylmethyl;

[0078] C₃-C₈-cycloalkyl-C₁-C₄-alkyl which contains a carbonyl or thiocarbonyl ring member, for example cyclobutanon-2-ylmethyl, cyclobutanon-3-ylmethyl, cyclopentanon-2-ylmethyl, cyclopentanon-3-ylmethyl, cyclohexanon-2-ylmethyl, cyclohexanon-4-ylmethyl, cycloheptanon-2-ylmethyl, cyclooctanon-2-ylmethyl, cyclobutanethion-2-ylmethyl, cyclobutanethion-3-ylmethyl, cyclopentanethion-2-ylmethyl, cyclopentanethion-3-ylmethyl, cyclohexanethion-2-ylmethyl, cyclohexanethion-4-ylmethyl,

cycloheptanethion-2-ylmethyl, cyclooctanethion-2-ylmethyl, 1-(cyclobutanon-2-yl)ethyl, 1-(cyclobutanon-3-yl)ethyl, 1-(cyclopentanon-2-yl)ethyl, 1-(cyclopentanon-3-yl)ethyl, 1-(cyclohexanon-2-yl)ethyl, 1-(cyclohexanon-4-yl)ethyl, 1-(cycloheptanon-2-yl)ethyl, 1-(cyclooctanon-2-yl)ethyl, 1-(cyclobutanethion-2-yl)ethyl, 1-(cyclobutanethion-3-yl)ethyl, 1-(cyclopentanethion-2-yl)ethyl, 1-(cyclopentanethion-3-yl)ethyl, 1-(cyclohexanethion-2-yl)ethyl, 1-(cyclohexanethion-4-yl)ethyl, 1-(cycloheptanethion-2-yl)ethyl, 1-(cyclooctanethion-2-yl)ethyl, 2-(cyclobutanon-2-yl)ethyl, 2-(cyclobutanon-3-yl)ethyl, 2-(cyclopentanon-2-yl)ethyl, 2-(cyclopentanon-3-yl)ethyl, 2-(cyclohexanon-2-yl)ethyl, 2-(cyclohexanon-4-yl)ethyl, 2-(cycloheptanon-2-yl)ethyl, 2-(cyclooctanon-2-yl)ethyl, 2-(cyclobutanethion-2-yl)ethyl, 2-(cyclobutanethion-3-yl)ethyl, 2-(cyclopentanethion-2-yl)ethyl, 2-(cyclopentanethion-3-yl)ethyl, 2-(cyclohexanethion-2-yl)ethyl, 2-(cyclohexanethion-4-yl)ethyl, 2-(cycloheptanethion-2-yl)ethyl, 2-(cyclooctanethion-2-yl)ethyl, 3-(cyclobutanon-2-yl)propyl, 3-(cyclobutanon-3-yl)propyl, 3-(cyclopentanon-2-yl)propyl, 3-(cyclopentanon-3-yl)propyl, 3-(cyclohexanon-2-yl)propyl, 3-(cyclohexanon-4-yl)propyl, 3-(cycloheptanon-2-yl)propyl, 3-(cyclooctanon-2-yl)propyl, 3-(cyclobutanethion-2-yl)propyl, 3-(cyclobutanethion-3-yl)propyl, 3-(cyclopentanethion-2-yl)propyl, 3-(cyclopentanethion-3-yl)propyl, 3-(cyclohexanethion-2-yl)propyl, 3-(cyclohexanethion-4-yl)propyl, 3-(cycloheptanethion-2-yl)propyl, 3-(cyclooctanethion-2-yl)propyl, 4-(cyclobutanon-2-yl)butyl, 4-(cyclobutanon-3-yl)butyl, 4-(cyclopentanon-2-yl)butyl, 4-(cyclopentanon-3-yl)butyl, 4-(cyclohexanon-2-yl)butyl, 4-(cyclohexanon-4-yl)butyl, 4-(cycloheptanon-2-yl)butyl, 4-(cyclooctanon-2-yl)butyl, 4-(cyclobutanethion-2-yl)butyl, 4-(cyclobutanethion-3-yl)butyl, 4-(cyclopentanethion-2-yl)butyl, 4-(cyclopentanethion-3-yl)butyl, 4-(cyclohexanethion-2-yl)butyl, 4-(cyclohexanethion-4-yl)butyl, 4-(cycloheptanethion-2-yl)butyl or 4-(cyclooctanethion-2-yl)butyl, preferably cyclopentanon-2-ylmethyl, cyclohexanon-2-ylmethyl, 2-(cyclopentanon-2-yl)ethyl or 2-(cyclohexanon-2-yl)ethyl.

[0079] 3- to 7-membered heterocyclyl is understood as meaning not only saturated, partially or fully unsaturated, but also aromatic, heterocycles with one, two or three hetero atoms, the hetero atoms being selected from among nitrogen atoms, oxygen and sulfur atoms. Saturated 3- to 7-membered heterocyclyl may also contain a carbonyl or thiocarbonyl ring member.

[0080] Examples of saturated heterocycles which may contain a carbonyl or thiocarbonyl ring member are:

[0081] oxiranyl, thiranyl, aziridin-1-yl, aziridin-2-yl, diaziridin-1-yl, diaziridin-3-yl, oxetan-2-yl, oxetan-3-yl, thietan-2-yl, thietan-3-yl, azetidin-1-yl, azetidin-2-yl, azetidin-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothiophen-2-yl, tetrahydrothiophen-3-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, 1,3-dioxolan-2-yl, 1,3-dioxolan-4-yl, 1,3-oxathiolan-2-yl, 1,3-oxathiolan-4-yl, 1,3-oxathiolan-5-yl, 1,3-oxazolidin-2-yl, 1,3-oxazolidin-3-yl, 1,3-oxazolidin-4-yl, 1,3-oxazolidin-5-yl, 1,2-oxazolidin-2-yl,

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1,2-oxazolidin-3-yl, 1,2-oxazolidin-4-yl, 1,2-oxazolidin-5-yl, 1,3-dithiolan-2-yl, 1,3-dithiolan-4-yl, tetrahydropyrazol-1-yl, tetrahydropyrazol-3-yl, tetrahydropyrazol-4-yl, tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, tetrahydrothiopyran-2-yl, tetrahydrothiopyran-3-yl, tetrahydrothiopyran-4-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, 1,3-dioxan-2-yl, 1,3-dioxan-4-yl, 1,3-dioxan-5-yl, 1,4-dioxan-2-yl, 1,3-oxathian-2-yl, 1,3-oxathian-4-yl, 1,3-oxathian-5-yl, 1,3-oxathian-6-yl, 1,4-oxathian-2-yl, 1,4-oxathian-3-yl, morpholin-2-yl, morpholin-3-yl, morpholin-4-yl, hexahydropyridazin-1-yl, hexahydropyridazin-3-yl, hexahydropyridazin-4-yl, hexahydropyrimidin-1-yl, hexahydropyrimidin-2-yl, hexahydropyrimidin-4-yl, hexahydropyrimidin-5-yl, piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, hexahydro-1,3,5-triazin-1-yl, hexahydro-1,3,5-triazin-2-yl, oxepan-2-yl, oxepan-3-yl, oxepan-4-yl, thiepan-2-yl, thiepan-3-yl, thiepan-4-yl, 1,3-dioxepan-2-yl, 1,3-dioxepan-4-yl, 1,3-dioxepan-5-yl, 1,3-dioxepan-6-yl, 1,3-dithiepan-2-yl, 1,3-dithiepan-4-yl, 1,3-dithiepan-5-yl, 1,3-dithiepan-6-yl, 1,4-dioxepan-2-yl, 1,4-dioxepan-7-yl, hexahydroazepin-1-yl, hexahydroazepin-2-yl, hexahydroazepin-3-yl, hexahydroazepin-4-yl, hexahydro-1,3-diazepin-1-yl, hexahydro-1,3-diazepin-2-yl, hexahydro-1,3-diazepin-4-yl, hexahydro-1,4-diazepin-1-yl and hexahydro-1,4-diazepin-2-yl.

[0082] Examples of unsaturated heterocycles which may contain a carbonyl or thiocarbonyl ring member are:

[0083] dihydrofuran-2-yl, 1,2-oxazolin-3-yl, 1,2-oxazolin-5-yl, 1,3-oxazolin-2-yl.

[0084] Examples of aromatic heterocyclyl are the 5- and 6-membered aromatic, heterocyclic radicals, for example furyl such as 2-furyl and 3-furyl, thienyl such as 2-thienyl and 3-thienyl, pyrrolyl such as 2-pyrrolyl and 3-pyrrolyl, isoxazolyl such as 3-isoxazolyl, 4-isoxazolyl and 5-isoxazolyl, isothiazolyl such as 3-isothiazolyl, 4-isothiazolyl and 5-isothiazolyl, pyrazolyl such as 3-pyrazolyl, 4-pyrazolyl and 5-pyrazolyl, oxazolyl such as 2-oxazolyl, 4-oxazolyl and 5-oxazolyl, thiazolyl such as 2-thiazolyl, 4-thiazolyl and 5-thiazolyl, imidazolyl such as 2-imidazolyl and 4-imidazolyl, oxadiazolyl such as 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl and 1,3,4-oxadiazol-2-yl, thiadiazolyl such as 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl and 1,3,4-thiadiazol-2-yl, triazolyl such as 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl and 1,2,4-triazol-4-yl, pyridinyl such as 2-pyridinyl, 3-pyridinyl and 4-pyridinyl, pyridazinyl such as 3-pyridazinyl and 4-pyridazinyl, pyrimidinyl such as 2-pyrimidinyl, 4-pyrimidinyl and 5-pyrimidinyl, furthermore 2-pyrazinyl, 1,3,5-triazin-2-yl and 1,2,4-triazin-3-yl, in particular pyridyl, pyrimidyl, furanyl and thienyl.

[0085] Examples of fused rings are, in addition to phenyl, the abovementioned heteroaromatic groups, in particular pyridine, pyrazine, pyridazine, pyrimidine, furan, dihydrofuran, thiophene, dihydrothiophene, pyrrole, dihydropyrrole, 1,3-dioxolane, 1,3-dioxolan-2-one, isoxazole, oxazole, oxazolinone, isothiazole, thiazole, pyrazole, pyrazoline, imidazole, imidazolinone, dihydroimidazole, 1,2,3-triazole, 1,1-dioxodihydroisothiazole, dihydro-1,4-dioxine, pyridone, dihydro-1,4-oxazine, dihydro-1,4-oxazin-2-one, dihydro-1,4-oxazin-3-one, dihydro-1,3-oxazine, dihydro-1,3-thiazin-2-one, dihydro-1,4-thiazine, dihydro-1,4-thiazin-2-one, dihydro-1,4-thiazin-3-one, dihydro-1,3-thiazine and dihydro-1,3-thiazin-2-one, which, in turn, can have one, two or

three substituents. Examples of suitable substituents on the fused ring are the meanings given hereinbelow for R^{15} , R^{16} , R^{17} and R^{18} .

[0086] With regard to the use of the 2-aryl-5-trifluoromethylpyridines I as herbicides or desiccants/defoliant, those compounds I are preferred in which R^2 is fluorine or chlorine. R^1 is preferably methyl. Furthermore preferred compounds I are those in which the variables R^3 and R^4 have the following meanings, in each case alone or in combination:

[0087] R^3 is hydrogen, chlorine or, in particular, fluorine,

[0088] R^4 is halogen, preferably chlorine, and cyano.

[0089] In the compounds in which R^6 is hydrogen and $X-R^7$ together with R^4 do not form a chain (hereinbelow compounds IA), X , R^4 and R^5 independently of one another and preferably together have the following preferred meanings:

[0090] R^4 is chlorine or cyano,

[0091] X is a chemical bond, methylene, ethane-1,2-diyl, ethene-1,2-diyl which can be unsubstituted or have attached to it a substituent selected from among C_1 - C_4 -alkyl, specifically methyl, or halogen, specifically chlorine, for example 1- or 2-chloroethane-1,2-diyl, 1- or 2-chloroethene-1,2-diyl, 1- or 2-bromoethane-1,2-diyl, 1- or 2-bromoethene-1,2-diyl, 1- or 2-methylethane-1,2-diyl, 1- or 2-methylethene-1,2-diyl, in particular a chemical bond, 1- or 2-chloroethane-1,2-diyl, 1- or 2-chloroethene-1,2-diyl, 1- or 2-bromoethane-1,2-diyl, 1- or 2-methylethane-1,2-diyl. If X is substituted ethane-1,2-diyl, ethene-1,2-diyl, the substituent is preferably attached to the carbon atom which is adjacent to the group R^5 ;

[0092] R^5 is hydrogen, fluorine, nitro, chlorosulfonyl, $-O-Y-R^7$, $-O-CO-Y-R^7$, $-N(Y-R^7)$ ($Z-R^8$), $-N(Y-R^7)-SO_2-Z-R^8$, $-N(SO_2-Y-R^7)(SO_2-Z-R^8)$, $-S-Y-R^7$, $-SO_2-N(Y-R^7)(Z-R^8)$, $-C(=NOR^9)-Y-R^7$, $-C(=NOR^9)Y-R^7$, $-C(Y-R^7)PO(O-Y-R^7)$ or $-CO-N(Y-R^7)(Z-R^8)$, in particular $-O-Y-R^7$, $-S-Y-R^7$, $-N(Y-R^7)-SO_2-Z-R^8$ or $-C(Y-R^7)$,

[0093] especially preferably $-CO-O-Y-R^7$ and $-O-Y-R^7$.

[0094] The variables R^7 , R^8 , R^9 , Y , Z mentioned in the definition of the variables R^5 preferably have the following meanings:

[0095] Y , Z independently of one another are a chemical bond or methylene;

[0096] R^7 , R^8 independently of one another are

[0097] hydrogen, C_1 - C_4 -haloalkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, $-CH(R^{10})(R^{11})$, C_1 - C_4 -alkoxy- C_1 - C_4 -alkyl, $-C(R^{10})(R^{11})-N(R^{12})R^{13}$, $-C(R^{10})(R^{11})-CO-OR^{12}$, $-C(R^{10})(R^{11})-CO-N(R^{12})R^{13}$, C_3 - C_8 -cycloalkyl or phenyl, it being possible for the cycloalkyl ring and the phenyl ring to be unsubstituted or to have attached to it one or two substituents, in each case selected from the group consisting of cyano, nitro, halogen, C_1 - C_4 -

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alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylsulfonyl, (C₁-C₄-alkyl)carbonyl, (C₁-C₄-alkyl)carbonyloxy and (C₁-C₄-alkoxy)carbonyl;

[0098] in particular hydrogen, C₁-C₆-haloalkyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, —CH(R¹⁰)(R¹¹), —C(R¹⁰)(R¹¹)—CO—OR¹², —C(R¹⁰)(R¹¹)—CO—N(R¹²)R¹³, phenyl or C₃-C₈-Cycloalkyl, especially preferably hydrogen, C₁-C₆-alkyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, —C(R¹⁰)(R¹¹)—CO—OR¹², or C₃-C₈-Cycloalkyl.

[0099] In this context, the variables R¹⁰, R¹¹, R¹² and R¹³ independently of one another preferably have the meanings stated hereinbelow:

[0100] R¹⁰ is hydrogen or C₁-C₄-alkyl, specifically methyl or ethyl;

[0101] R¹¹ is hydrogen or C₁-C₄-alkyl, specifically methyl or ethyl;

[0102] R¹², R¹³ independently of one another are hydrogen, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₈-cycloalkyl, C₃-C₈-cycloalkyl-C₁-C₄-alkyl, or C₁-C₄-alkoxy-C₁-C₄-alkyl, in particular hydrogen or C₁-C₆-alkyl;

[0103] R⁹ is C₁-C₆-alkyl, C₁-C₄-alkoxycarbonyl-C₁-C₄-alkyl, C₂-C₆-alkenyl, in particular methyl or ethyl.

[0104] In a further preferred embodiment R⁷ and R⁸ independently of one another are C₃-C₈-cycloalkyl-C₁-C₄-alkyl or C₁-C₆-alkyl.

[0105] R⁵ is very especially preferably C₃-C₄-alkynyloxy, C₁-C₄-alkoxy, C₃-C₄-alkenyloxy, OCH(R¹⁹)—COOR²⁰, CO—OR²¹ or COO—CH(R²²)COOR²³, where

[0106] R¹⁹, R²² independently of one another are hydrogen or C₁-C₄-alkyl,

[0107] R²⁰, R²¹, R²³ independently of one another are C₁-C₄-alkyl, C₃-C₆-alkenyl, C₃-C₆-alkynyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy-C₁-C₄-alkyl;

[0108] in particular when X is a single bond.

[0109] Those compounds IA in which X is a single bond and R⁵ is COO—CH(R²²)COOR²³, where R²² and R²³ independently of one another are C₁-C₄-alkyl, have a very particularly high activity, in particular when the carbon atom to which the group R²² is attached is in S configuration.

[0110] R⁴ and XR⁵ or XR⁵ and R⁶ in formula I may also form a 3- or 4-membered chain which, in addition to carbon, can have 1, 2 or 3, preferably 2, hetero atoms selected from among nitrogen, oxygen and sulfur atoms, which chain can be unsubstituted or, in turn, have attached to it one, two or three substituents and whose members can also encompass one or two nonadjacent carbonyl, thiocarbonyl or sulfonyl groups. Such compounds are termed compounds IB and IC hereinbelow.

[0111] Examples are compounds IB where R⁴ together with X—R⁵ in formula I are a chain of the formulae: —O—C(R¹⁵, R¹⁶)—N—CO—N(R¹⁷)—, —S—C(R¹⁵, R¹⁶)—CO—N(R¹⁷)—, —O—C(R¹⁵, R¹⁶)—CS—N(R¹⁷)—, —S—C(R¹⁵, R¹⁶)—CS—N(R¹⁷)—,

—N=C(R¹⁸)—O— or —N=C(R¹⁸)—S— (compounds IB) in which the variables n, R¹⁵ to R¹⁸ have the following meanings:

[0112] n is 0 or 1, in particular 1,

[0113] R¹⁵, R¹⁶ independently of one another are

[0114] hydrogen, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₂-C₆-alkenyl, C₂-C₆-haloalkenyl, C₂-C₆-alkynyl, C₂-C₆-haloalkynyl, C₃-C₈-cycloalkyl, phenyl or phenyl-C₁-C₄-alkyl;

[0115] R¹⁷ is hydrogen, hydroxyl, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₂-C₆-alkenyl, C₂-C₆-haloalkenyl, C₂-C₆-alkynyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₃-C₆-alkenyloxy, C₃-C₆-alkynyloxy, C₁-C₄-alkylsulfonyl, C₁-C₄-haloalkylsulfonyl, C₁-C₄-alkylcarbonyl, C₁-C₄-haloalkylcarbonyl, C₁-C₄-alkoxycarbonyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₁-C₄-alkoxycarbonyl-C₁-C₄-alkyl, C₁-C₄-alkoxycarbonyl-C₁-C₄-alkoxy, mono- and di(C₁-C₄-alkyl)aminocarbonyl, mono- and di(C₁-C₄-alkyl)aminocarbonyl-C₁-C₄-alkoxy, phenyl, phenyl-C₁-C₄-alkyl, C₃-C₈-cycloalkyl, C₃-C₈-cycloalkyl-C₁-C₄-alkyl, 3-, 4-, 5-, 6- or 7-membered heterocyclyl, 3-, 4-, 5-, 6- or 7-membered heterocyclyl-C₁-C₄-alkyl, preferably 5- or 6-membered, preferably saturated, heterocyclyl which has in each case one or two, preferably one, ring hetero atom selected from among oxygen, nitrogen or sulfur;

[0116] R¹⁸ is hydrogen, halogen, cyano, amino, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₂-C₆-alkenyl, C₂-C₆-haloalkenyl, C₂-C₆-alkynyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₃-C₆-alkenyloxy, C₃-C₆-alkynyloxy, C₁-C₄-alkylamino, di(C₁-C₄-alkyl)amino, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, C₁-C₄-haloalkylthio, C₁-C₄-alkylsulfinyl, C₁-C₄-haloalkylsulfinyl, C₁-C₄-alkylsulfonyl, C₁-C₄-haloalkylsulfonyl, C₁-C₄-alkylcarbonyl, C₁-C₄-haloalkylcarbonyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₁-C₄-alkoxycarbonyl, C₁-C₄-alkoxycarbonyl-C₁-C₄-alkyl, C₁-C₄-alkoxycarbonyl-C₁-C₄-alkoxy, C₁-C₄-alkoxy-carbonyl-C₁-C₄-alkylthio, di(C₁-C₄-alkyl)aminocarbonyl, di(C₁-C₄-alkyl)aminocarbonyl-C₁-C₄-alkyl, di(C₁-C₄-alkyl)aminocarbonyl-C₁-C₄-alkoxy, di(C₁-C₄-alkyl)aminocarbonyl-C₁-C₄-alkylthio, C₃-C₈-cycloalkyl, phenyl, phenyl-C₁-C₄-alkyl, C₃-C₈-cycloalkyl-C₁-C₄-alkyl, 3-, 4-, 5-, 6- or 7-membered, preferably 5- or 6-membered, preferably saturated, heterocyclyl which has one or two, preferably one, ring hetero atom selected from among oxygen, nitrogen or sulfur.

[0117] The variables R¹⁵ to R¹⁸ preferably have the following meanings:

[0118] R¹⁵, R¹⁶ independently of one another are hydrogen or methyl;

[0119] R¹⁷ is hydrogen, hydroxyl, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₃-C₆-alkenyloxy, C₃-C₆-alkynyloxy, C₁-C₄-alkoxycarbonyl-C₁-C₄-alkyl, C₁-C₄-alkoxycarbonyl-C₁-C₄-alkoxy, C₃-C₈-cycloalkyl, C₃-C₈-cycloalkyl-C₁-C₄-alkyl or phenyl-C₁-C₄-alkyl or 3-, 4-, 5- or 6-membered, preferably 5- or

6-membered, preferably saturated, heterocyclyl which has one ring hetero atom selected from among oxygen, nitrogen or sulfur;

[0120] R^{18} is hydrogen, halogen, amino, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -haloalkenyl, C_2 - C_6 -alkynyl, C_1 - C_4 -alkoxy, C_3 - C_6 -alkenyloxy, C_3 - C_6 -alkynyloxy, C_1 - C_4 -alkylamino, di(C_1 - C_4 -alkyl)amino, C_1 - C_4 -alkylthio, C_1 - C_4 -alkoxycarbonyl- C_1 - C_4 -alkyl, C_1 - C_4 -alkoxycarbonyl- C_1 - C_4 -alkoxy, C_1 - C_4 -alkoxycarbonyl- C_1 - C_4 -alkylthio, C_3 - C_8 -cycloalkyl, phenyl, phenyl- C_1 - C_4 -alkyl, C_3 - C_8 -cycloalkyl- C_1 - C_4 -alkyl, 3-, 4-, 5- or 6-membered, preferably 5- or 6-membered, preferably saturated, heterocyclyl which has one ring hetero atom selected from among oxygen, nitrogen or sulfur.

[0121] Especially preferred among the compounds IB are those compounds in which R^4 together with $X-R^5$ is a chain of the formula $-O-[C(R^{15})(R^{16})]_n-CO-N(R^{17})-$, $-S-[C(R^{15})(R^{16})]_n-CO-N(R^{17})-$ where $n=0$ or 1. R^{15} and R^{17} in particular have the meanings mentioned as being preferred. Among them, very especially preferred compounds IB are those in which the nitrogen atom of the chain $-O-C(R^{16})(R^{15})-CO-N(R^{17})-$ or $-S-C(R^{16})(R^{15})-CO-N(R^{17})-$ is bonded to the carbon atom of the phenyl ring in formula I which has the group $X-R^5$ attached to it (meta position relative to the pyridine group). R^{16} in these chains is preferably hydrogen. In the compounds IB, R^3 is preferably halogen and in particular fluorine, or else hydrogen.

[0122] Examples of compounds IC are those compounds of the formula I in which R^6 together with $X-R^5$ is a chain of the formulae: $-O-(C(R^{15}, R^{16}))_n-CO-N(R^{17})-$, $-S-(C(R^{15}, R^{16}))_n-CO-N(R^{17})-$ where $n=0$ or 1, $-N=C(R^{18})-O-$ or $-N=C(R^{18})-S-$ (compounds IC).

[0123] In this context, the variables R^{15} to R^{18} have the meanings mentioned above, in particular the meanings mentioned as preferred. Preferred amongst these compounds are in particular those in which R^6 together with $X-R^5$ is a chain of the formula $-N=C(R^{18})-O-$ or of the formula $-N=C(R^{18})-S-$.

[0124] In these compounds, the nitrogen atom of the chain is preferably bonded to the C atom of the phenyl ring in formula I which has the $X-R^5$ group attached to it. In the compounds IC, R^3 is preferably fluorine or hydrogen. R^4 is preferably chlorine or cyano.

[0125] The 2-aryl-5-trifluoromethylpyridines according to the invention can be employed both as pyridines, where m assumes the value 0, or as pyridine-N-oxides, i.e. compounds of the formula I where $m=1$.

[0126] Especially preferred are the compounds of the formula IAa (compounds IA where $m=0$, $R^1=CH_3$ and $R^2=Cl$, $R^3=F$ and $R^4=Cl$) in which the variable $X-R^5$ has the abovementioned meanings, in particular the meanings mentioned in each case one line of Table 1 (compounds IAa.1-IAa.232).

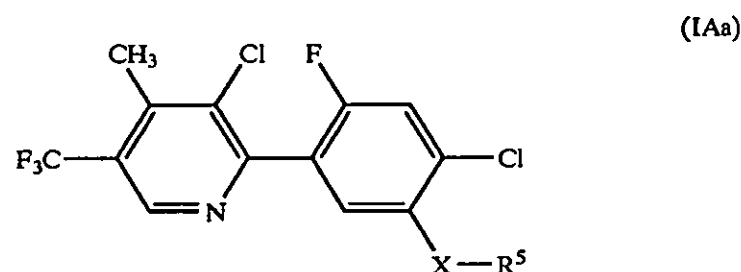


TABLE 1

No.	X-R ⁵
1	H
2	OH
3	OCH ₃
4	OCH ₂ CH ₃
5	OCH ₂ CH ₂ Cl
6	OCH ₂ CH ₂ OCH ₃
7	OCH ₂ CH ₂ SCH ₃
8	OCH(CH ₃) ₂
9	OCH ₂ CH=CH ₂
10	OCH ₂ CCH
11	OCH(CH ₃)CCH
12	O-cyclopentyl
13	OCH ₂ COOH
14	OCH ₂ COOCH ₃
15	OCH ₂ COOCH ₂ CH ₃
16	OCH ₂ COOCH ₂ CH ₂ Cl
17	OCH ₂ COOCH ₂ CH ₂ OCH ₃
18	OCH ₂ COOCH ₂ CH ₂ SCH ₃
19	OCH ₂ COOCH(CH ₃) ₂
20	OCH ₂ COOCH ₂ CH=CH ₂
21	OCH ₂ COOCH ₂ CCH
22	OCH ₂ COOCH ₂ COOCH ₃
23	OCH ₂ CONH ₂
24	OCH ₂ CONHCH ₃
25	OCH ₂ CON(CH ₃) ₂
26	OCH ₂ CONH(OCH ₃)
27	OCH ₂ CON(CH ₃)(OCH ₃)
28	OCH ₂ CONHCH ₂ COOCH ₃
29	OCH ₂ CON(CH ₃)CH ₂ COOCH ₃
30	OCH ₂ CONHCH(CH ₃)COOCH ₃
31	OCH ₂ CON(CH ₃)CH(CH ₃)COOCH ₃
32	OCH(CH ₃)COOH
33	OCH(CH ₃)COOCH ₃
34	OCH(CH ₃)COOCH ₂ CH ₃
35	OCH(CH ₃)COOCH ₂ CH ₂ Cl
36	OCH(CH ₃)COOCH ₂ CH ₂ OCH ₃
37	OCH(CH ₃)COOCH ₂ CH ₂ SCH ₃
38	OCH(CH ₃)COOCH(CH ₃) ₂
39	OCH(CH ₃)COOCH ₂ CH=CH ₂
40	OCH(CH ₃)COOCH ₂ CCH
41	OCH(CH ₃)COOCH ₂ COOCH ₃
42	OCH(CH ₃)CONH ₂
43	OCH(CH ₃)CONHCH ₃
44	OCH(CH ₃)CON(CH ₃) ₂
45	OCH(CH ₃)CONH(OCH ₃)
46	OCH(CH ₃)CON(CH ₃)(OCH ₃)
47	OCH(CH ₃)CONHCH ₂ COOCH ₃
48	OCH(CH ₃)CON(CH ₃)CH ₂ COOCH ₃
49	OCH(CH ₃)CONHCH(CH ₃)COOCH ₃
50	OC(CH ₃) ₂ COOCH ₂ CH=CH ₂
51	OC(CH ₃) ₂ COOCH ₂ CCH
52	OC(CH ₃) ₂ COOCH ₂ COOCH ₃
53	SH
54	SCH ₃
55	SCH ₂ CH ₃
56	SCH ₂ CH ₂ Cl
57	SCH ₂ CH ₂ OCH ₃
58	SCH(CH ₃) ₂
59	SCH ₂ CH=CH ₂
60	SCH ₂ CCH

TABLE 1-continued

No.	X-R ⁵
61	SCH(CH ₃)CCH
62	S—cyclopentyl
63	SCH ₂ COOH
64	SCH ₂ COOCH ₃
65	SCH ₂ COOCH ₂ CH ₃
66	SCH ₂ COOCH ₂ CH ₂ Cl
67	SCH ₂ COOCH ₂ CH ₂ OCH ₃
68	SCH ₂ COOCH(CH ₃) ₂
69	SCH ₂ COOCH ₂ CH=CH ₂
70	SCH ₂ COOCH ₂ CCH
71	SCH ₂ COOCH ₂ COOCH ₃
72	SCH(CH ₃)COOCH ₃
73	SCH(CH ₃)COOCH ₂ CH ₃
74	SCH(CH ₃)COOCH ₂ CH=CH ₂
75	SCH(CH ₃)COOCH ₂ CCH ₃
76	SCH(CH ₃)COOCH ₂ COOCH ₃
77	SCH ₂ CONH ₂
78	SCH ₂ CONHCH ₃
79	SCH ₂ CON(CH ₃) ₂
80	SCH ₂ CONHCH ₂ COOCH ₃
81	NO ₂
82	NHOH
83	NH ₂
84	N ₃
85	NHCH ₃
86	N(CH ₃) ₂
87	NCH(CH ₃) ₂
88	NHCH ₂ CH=CH ₂
89	N(CH ₃)CH ₂ CCH
90	N(CH ₃)CH ₂ CH=CH ₂
91	N(CH ₃)CH ₂ CCH
92	N(CH ₃)CH(CH ₃)CCH
93	NHCH ₂ COOCH ₃
94	NHCH ₂ COOCH ₂ CH ₃
95	NHCH ₂ COOCH ₂ CH ₂ Cl
96	NHCH ₂ COOCH ₂ CH ₂ OCH ₃
97	NHCH ₂ COOCH ₂ CH=CH ₂
98	NHCH ₂ COOCH ₂ CCH
99	N(CH ₃)CH ₂ COOCH ₃
100	N(CH ₃)CH ₂ COOCH ₂ CH ₃
101	N(CH ₃)CH ₂ COOCH ₂ CH ₂ Cl
102	N(CH ₃)CH ₂ COOCH ₂ CH ₂ OCH ₃
103	N(CH ₃)CH ₂ COOCH ₂ CH=CH ₂
104	N(CH ₃)CH ₂ COOCH ₂ CCH
105	NHCH(CH ₃)COOCH ₃
106	NHCH(CH ₃)COOCH ₂ CH ₃
107	NHCH(CH ₃)COOCH ₂ CH ₂ Cl
108	NHCH(CH ₃)COOCH ₂ CH ₂ OCH ₃
109	NHCH(CH ₃)COOCH ₂ CH=CH ₂
110	NHCH(CH ₃)COOCH ₂ CCH
111	N(CH ₃)CH(CH ₃)COOCH ₃
112	N(CH ₃)CH(CH ₃)COOCH ₂ CH ₃
113	N(CH ₃)CH(CH ₃)COOCH ₂ CH ₂ Cl
114	N(CH ₃)CH(CH ₃)COOCH ₂ CH ₂ OCH ₃
115	N(CH ₃)CH(CH ₃)COOCH ₂ CH=CH ₂
116	N(CH ₃)CH(CH ₃)COOCH ₂ CCH
117	NHSO ₂ CH ₃
118	NHSO ₂ CH ₂ Cl
119	N(SO ₂ CH ₃) ₂
120	NHSO ₂ CH ₂ CH ₃
121	N(SO ₂ CH ₂ CH ₃) ₂
122	N(CH ₃)SO ₂ CH ₃
123	N(CH ₃)SO ₂ CH ₂ CH ₃
124	COOH
125	COCl
126	COOCH ₃
127	COOCH ₂ CH ₃
128	COOCH ₂ CH ₂ Cl
129	COOCH ₂ CH ₂ OCH ₃
130	COOCH ₂ CH ₂ SCH ₃
131	COOCH(CH ₃) ₂
132	COOCH ₂ CH=CH ₂
133	COOCH ₂ CCH
134	COOCH ₂ COOH

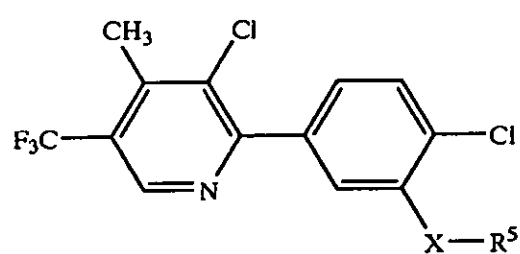
TABLE 1-continued

No.	X-R ⁵
135	COOCH ₂ COOCH ₃
136	COOCH ₂ COOCH ₂ CH ₃
137	COOCH ₂ COOCH ₂ CH ₂ Cl
138	COOCH ₂ COOCH ₂ CH ₂ OCH ₃
139	COOCH ₂ COOCH ₂ CH ₂ SCH ₃
140	COOCH ₂ COOCH ₂ CH=CH ₂
141	COOCH ₂ COOCH ₂ CCH
142	COOCH(CH ₃)COOH
143	COOCH(CH ₃)COOCH ₃
144	COOCH(CH ₃)COOCH ₂ CH ₃
145	COOCH(CH ₃)COOCH ₂ CH ₂ Cl
146	COOCH(CH ₃)COOCH ₂ CH ₂ OCH ₃
147	COOCH(CH ₃)COOCH ₂ CH ₂ SCH ₃
148	COOCH(CH ₃)COOCH ₂ CH=CH ₂
149	COOCH(CH ₃)COOCH ₂ CCH
150	COOC(CH ₃) ₂ COOH
151	COOC(CH ₃) ₂ COOCH ₃
152	COOC(CH ₃) ₂ COOCH ₂ CH ₃
153	COOC(CH ₃) ₂ COOCH ₂ CH=CH ₂
154	COOC(CH ₃) ₂ COOCH ₂ CCH
155	CONH ₂
156	CONHCH ₃
157	CON(CH ₃) ₂
158	CONH(OCH ₃)
159	CON(CH ₃)(OCH ₃)
160	CONHCH ₂ COOCH ₃
161	CONHCH ₂ COOCH ₂ CH ₃
162	CONHCH ₂ COOCH ₂ CH ₂ Cl
163	CONHCH ₂ COOCH ₂ CH ₂ OCH ₃
164	CONHCH ₂ COOCH ₂ CH=CH ₂
165	CONHCH ₂ COOCH ₂ CCH
166	CON(CH ₃)CH ₂ COOCH ₃
167	CON(CH ₃)CH ₂ COOCH ₂ CH ₃
168	CON(CH ₃)CH ₂ COOCH ₂ CH ₂ Cl
169	CON(CH ₃)CH ₂ COOCH ₂ CH ₂ OCH ₃
170	CON(CH ₃)CH ₂ COOCH ₂ CH=CH ₂
171	CON(CH ₃)CH ₂ COOCH ₂ CCH
172	CONHCH(CH ₃)COOCH ₃
173	CONHCH(CH ₃)COOCH ₂ CH ₃
174	CONHCH(CH ₃)COOCH ₂ CH ₂ Cl
175	CONHCH(CH ₃)COOCH ₂ CH ₂ OCH ₃
176	CONHCH(CH ₃)COOCH ₂ CH=CH ₂
177	CONHCH(CH ₃)COOCH ₂ CCH
178	CON(CH ₃)CH(CH ₃)COOCH ₃
179	CON(CH ₃)CH(CH ₃)COOCH ₂ CH ₃
180	CON(CH ₃)CH(CH ₃)COOCH ₂ CH ₂ Cl
181	CON(CH ₃)CH(CH ₃)COOCH ₂ CH ₂ OCH ₃
182	CON(CH ₃)CH(CH ₃)COOCH ₂ CH=CH ₂
183	CON(CH ₃)CH(CH ₃)COOCH ₂ CCH
184	CONHSO ₂ CH ₃
185	CONHSO ₂ CH ₂ CH ₃
186	CH ₂ OH
187	CHO
188	CH=NOH
189	CH=NOCH ₃
190	CH=NOCH ₂ CH ₃
191	CH=NOCH ₂ COOCH ₃
192	CH=NOCH ₂ COOCH ₂ CH ₃
193	CH=NOCH(CH ₃)COOCH ₃
194	C(=NOCH ₃)(OCH ₃)
195	C(=NOCH ₃)(OCH ₂ COOCH ₃)
196	C(=NOH)CH ₃
197	C(=NOCH ₃)CH ₃
198	CH ₂ CHClCOOH
199	CH ₂ CHClCOOCH ₃
200	CH ₂ CHClCOOCH ₂ CH ₃
201	CH ₂ CHClCOOCH ₂ CH ₂ Cl
202	CH ₂ CHClCOOCH ₂ CH ₂ OCH ₃
203	CH ₂ CHClCOOCH ₂ COOCH ₃
204	CH ₂ CHClCONH ₂
205	CH ₂ CHClCONHCH ₃
206	CH ₂ CHClCON(CH ₃) ₂
207	CH ₂ CHClCONCH ₂ COOCH ₃
208	CH=CHCOOH

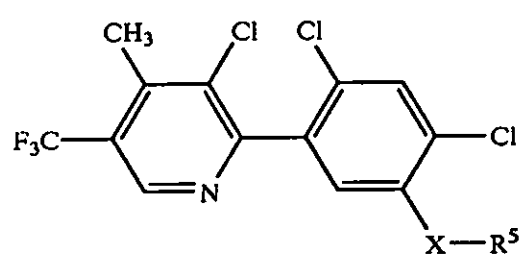
TABLE 1-continued

No.	X-R ⁵
209	CH=CHCOOCH ₃
210	CH=CHCOOCH ₂ CH ₃
211	CH=CClCOOH
212	CH=CClCOOCH ₃
213	CH=CClCOOCH ₂ CH ₃
214	CH=CClCOOCH ₂ CH ₂ Cl
215	CH=CClCOOCH ₂ CH ₂ OCH ₃
216	CH=CClCOOCH ₂ COOCH ₃
217	CH=CClCONH ₂
218	CH=CClCONHCH ₃
219	CH=CClCON(CH ₃) ₂
220	CH=CClCONHCH ₂ COOCH ₃
221	CH=CBrCOOH
222	CH=CBrCOOCH ₃
223	CH=CBrCOOCH ₂ CH ₃
224	CH=CBrCOOCH ₂ CH ₂ Cl
225	CH=CBrCOOCH ₂ CH ₂ OCH ₃
226	CH=CBrCOOCH ₂ COOCH ₃
227	CH=C(CH ₃)COOH
228	CH=C(CH ₃)COOCH ₃
229	CH=C(CH ₃)COOCH ₂ CH ₃
230	CH=C(CH ₃)COOCH ₂ CH ₂ Cl
231	CH=C(CH ₃)COOCH ₂ CH ₂ OCH ₃
232	CH=C(CH ₃)COOCH ₂ COOCH ₃

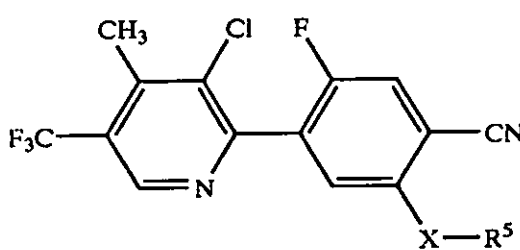
[0127] Especially preferred are, moreover, the compounds of the formulae IAb to IAq mentioned hereinbelow, in which the variable X—R⁵ has the abovementioned meanings, in particular the meanings mentioned in in each case one line of Table 1 (compounds IAb.1-IAb.232 to IAq.1-IAq.232).



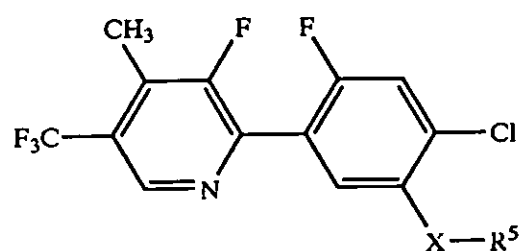
(IAb)



(IAc)

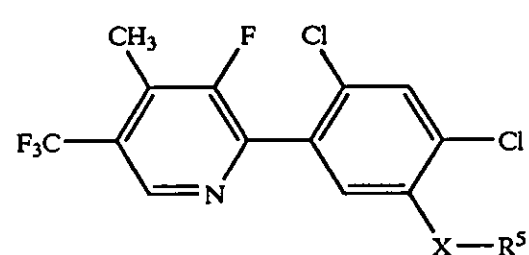


(IAd)

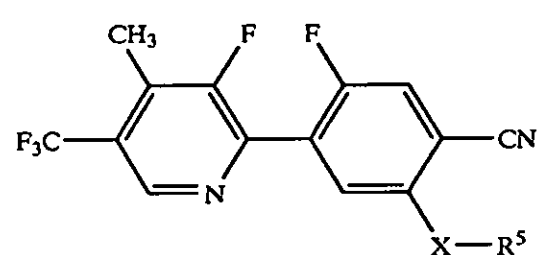


(IAe)

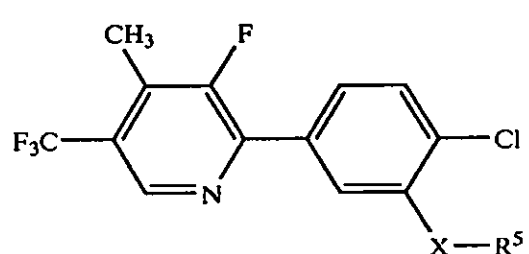
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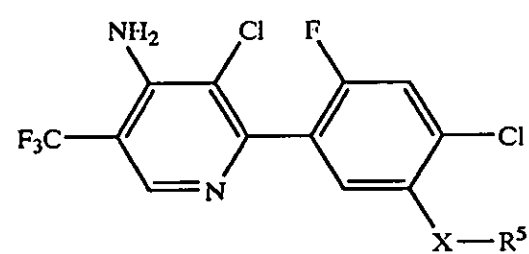
(IAf)



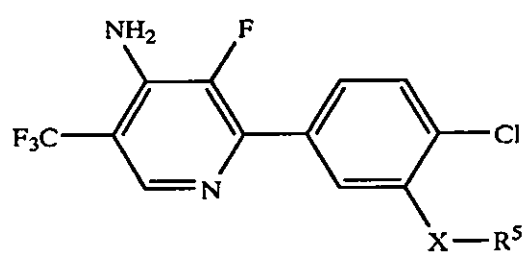
(IAg)



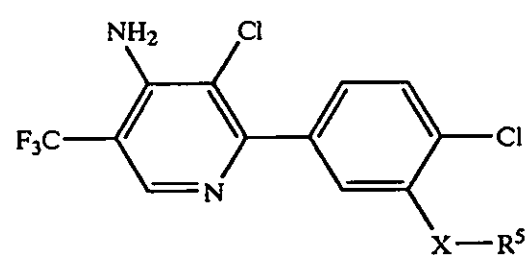
(IAh)



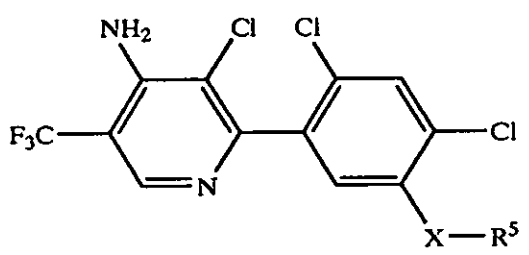
(IAi)



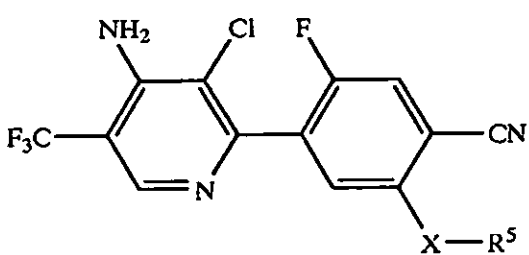
(IAj)



(IAk)

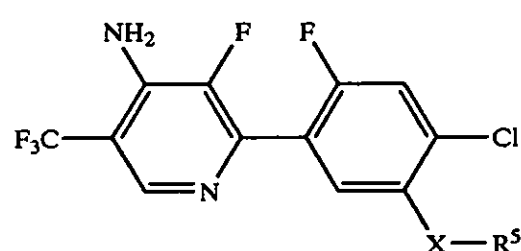


(IAm)

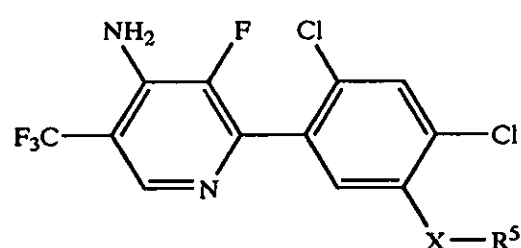


(IAN)

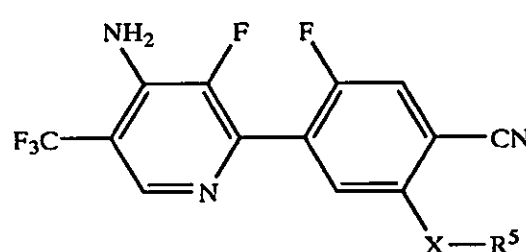
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(IAo)



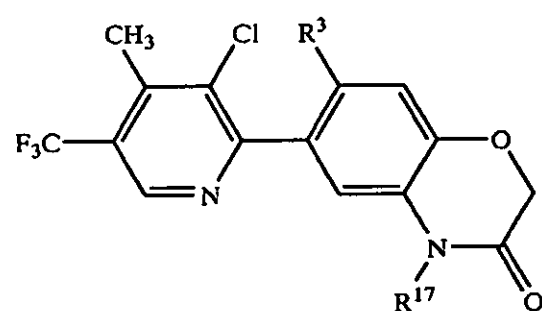
(IAp)



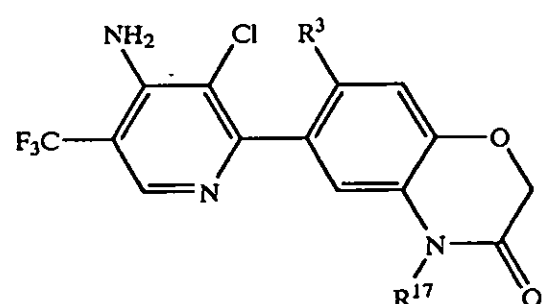
(IAq)

[0128] Among the compounds of the formulae IAa to Ia, the compounds of the formulae IAa to IAh, in particular the compounds of the formulae IAa and Ia, are especially preferred, in particular those where X is a single bond and R⁵ is —CO—O—Y—R⁷ and —O—Y—R⁷ and is especially preferably C₃-C₄-alkynyloxy, OCH(R¹⁹)—COOR²⁰, CO—OR²¹ or COO—CH(R²²)COOR²³, where R⁷, R¹⁹ to R²³ have the abovementioned meanings.

[0129] Especially preferred are, moreover, the compounds of the formulae IBa to IBf mentioned hereinbelow in which the variables R³ and R¹⁷ have the abovementioned meanings, in particular the meanings mentioned in in each case one line of Table 2 (compounds IBa.1-IBa.108 to IBf.1-IBf.108).

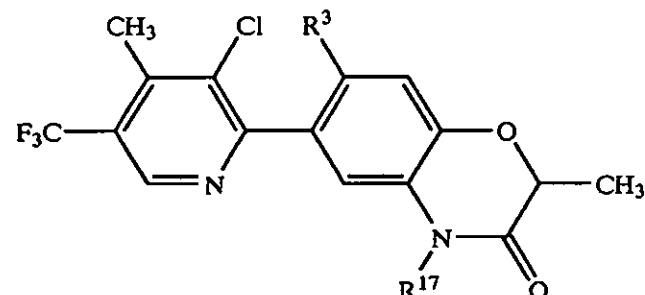


(IBa)

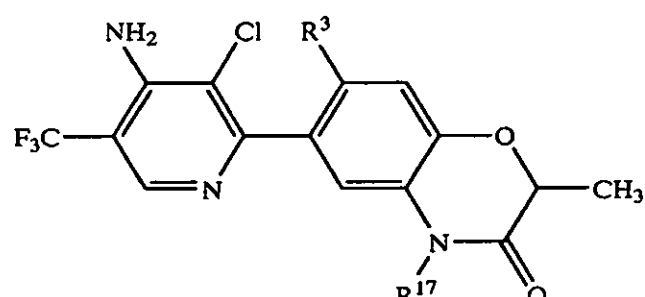


(IBb)

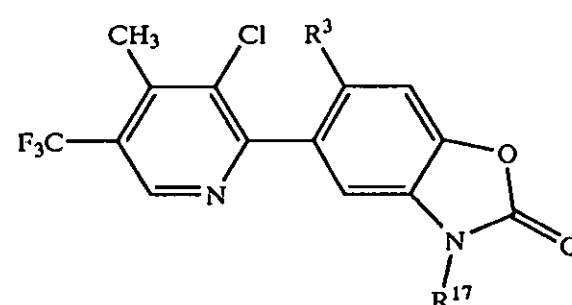
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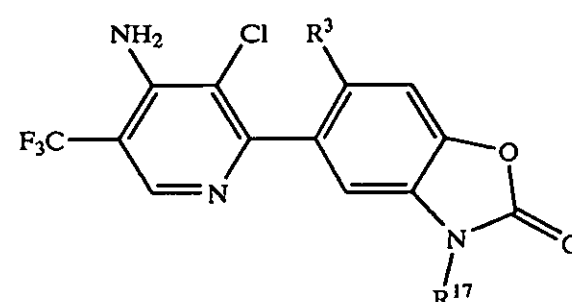
(IBc)



(IBd)



(IBe)



(IBf)

TABLE 2

No.	R ³	R ¹⁷
1	F	H
2	F	CH ₃
3	F	CH ₂ F
4	F	CHF ₂
5	F	CH ₂ OCH ₃
6	F	CH ₂ SCH ₃
7	F	CH ₂ —COOCH ₃
8	F	CH ₂ —COOC ₂ H ₅
9	F	CH(CH ₃)—COOCH ₃
10	F	CH(CH ₃)—COOC ₂ H ₅
11	F	CH ₂ CH ₃
12	F	CH ₂ CH ₂ Cl
13	F	CH ₂ CH ₂ OCH ₃
14	F	CH ₂ CH ₂ SCH ₃
15	F	n—C ₃ H ₇
16	F	CH(CH ₃) ₂
17	F	n—C ₄ H ₉
18	F	CH(CH ₃)—C ₂ H ₅
19	F	CH ₂ —CH(CH ₃) ₂
20	F	CH ₂ —(cyclo—C ₃ H ₉)
21	F	CH ₂ —CH=CH ₂
22	F	CH ₂ —CH=CH—CH ₃
23	F	CH(CH ₃)—CH=CH ₂
24	F	CH ₂ —C≡CH
25	F	CH ₂ —C≡C—CH ₃
26	F	CH(CH ₃)—C≡CH

TABLE 2-continued

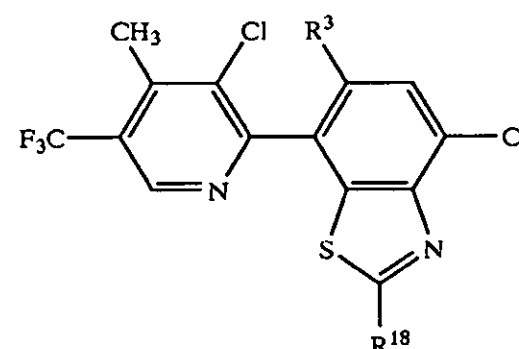
No.	R ³	R ¹⁷
27	F	CH ₂ -phenyl
28	F	OH
29	F	O-CH ₃
30	F	O-CH ₂ F
31	F	O-CHF ₂
32	F	O-CH ₂ OCH ₃
33	F	O-CH ₂ SCH ₃
34	F	O-CH ₂ -COOCH ₃
35	F	O-CH ₂ -COOC ₂ H ₅
36	F	O-CH(CH ₃)-COOCH ₃
37	F	O-CH(CH ₃)-COOC ₂ H ₅
38	F	O-CH ₂ CH ₃
39	F	O-CH ₂ CH ₂ Cl
40	F	O-CH ₂ CH ₂ OCH ₃
41	F	O-CH ₂ CH ₂ SCH ₃
42	F	O-n-C ₃ H ₇
43	F	O-CH(CH ₃) ₂
44	F	O-n-C ₄ H ₉
45	F	O-CH(CH ₃)-C ₂ H ₅
46	F	O-CH ₂ -CH(CH ₃) ₂
47	F	O-CH ₂ -(cyclo-C ₅ H ₉)
48	F	O-CH ₂ -CH=CH ₂
49	F	O-CH ₂ -CH=CH-CH ₃
50	F	O-CH(CH ₃)-CH=CH ₂
51	F	O-CH ₂ -C≡CH
52	F	O-CH ₂ -C≡C-CH ₃
53	F	O-CH(CH ₃)-C≡CH
54	F	O-CH ₂ -phenyl
55	H	H
56	H	CH ₃
57	H	CH ₂ F
58	H	CHF ₂
59	H	CH ₂ OCH ₃
60	H	CH ₂ SCH ₃
61	H	CH ₂ -COOCH ₃
62	H	CH ₂ -COOC ₂ H ₅
63	H	CH(CH ₃)-COOCH ₃
64	H	CH(CH ₃)-COOC ₂ H ₅
65	H	CH ₂ CH ₃
66	H	CH ₂ CH ₂ Cl
67	H	CH ₂ CH ₂ OCH ₃
68	H	CH ₂ CH ₂ SCH ₃
69	H	n-C ₃ H ₇
70	H	CH(CH ₃) ₂
71	H	n-C ₄ H ₉
72	H	CH(CH ₃)-C ₂ H ₅
73	H	CH ₂ -CH(CH ₃) ₂
74	H	CH ₂ -(cyclo-C ₅ H ₉)
75	H	CH ₂ -CH=CH ₂
76	H	CH ₂ -CH=CH-CH ₃
77	H	CH(CH ₃)-CH=CH ₂
78	H	CH ₂ -C≡CH
79	H	CH ₂ -C≡C-CH ₃
80	H	CH(CH ₃)-C≡CH
81	H	CH ₂ -phenyl
82	H	OH
83	H	O-CH ₃
84	H	O-CH ₂ F
85	H	O-CHF ₂
86	H	O-CH ₂ OCH ₃
87	H	O-CH ₂ SCH ₃
88	H	O-CH ₂ -COOCH ₃
89	H	O-CH ₂ -COOC ₂ H ₅
90	H	O-CH(CH ₃)-COOCH ₃
91	H	O-CH(CH ₃)-COOC ₂ H ₅
92	H	O-CH ₂ CH ₃
93	H	O-CH ₂ CH ₂ Cl
94	H	O-CH ₂ CH ₂ OCH ₃
95	H	O-CH ₂ CH ₂ SCH ₃
96	H	O-n-C ₃ H ₇
97	H	O-CH(CH ₃) ₂
98	H	O-n-C ₄ H ₉
99	H	O-CH(CH ₃)-C ₂ H ₅
100	H	O-CH ₂ -CH(CH ₃) ₂

TABLE 2-continued

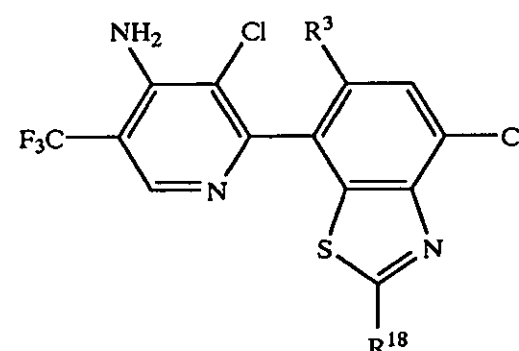
No.	R ³	R ¹⁷
101	H	O-CH ₂ -(cyclo-C ₅ H ₉)
102	H	O-CH ₂ -CH=CH ₂
103	H	O-CH ₂ -CH=CH-CH ₃
104	H	O-CH(CH ₃)-CH=CH ₂
105	H	O-CH ₂ -C≡CH
106	H	O-CH ₂ -C≡C-CH ₃
107	H	O-CH(CH ₃)-C≡CH
108	H	O-CH ₂ -phenyl

[0130] Especially preferred are, moreover, the compounds of the formulae ICa to ICh mentioned hereinbelow in which the variables R³ and R¹⁸ have the abovementioned meaning, in particular the meaning mentioned in in each case one line of Table 3 (compounds ICa.1-ICa.351 to ICh.1-ICh.351).

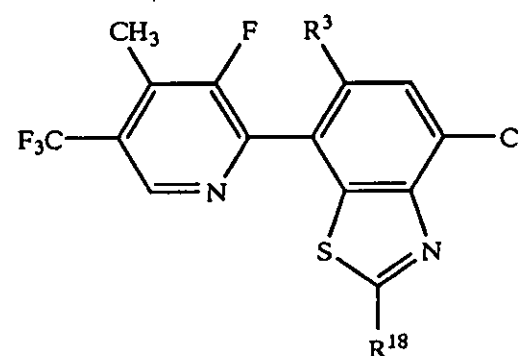
(ICa)



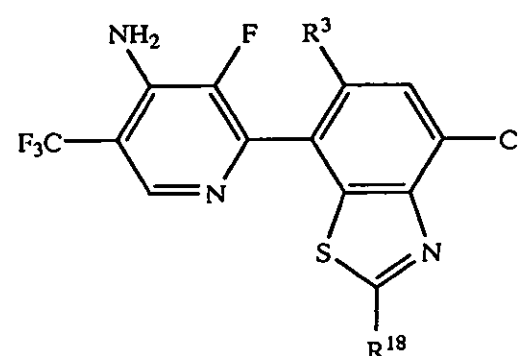
(ICh)



(ICc)



(ICd)



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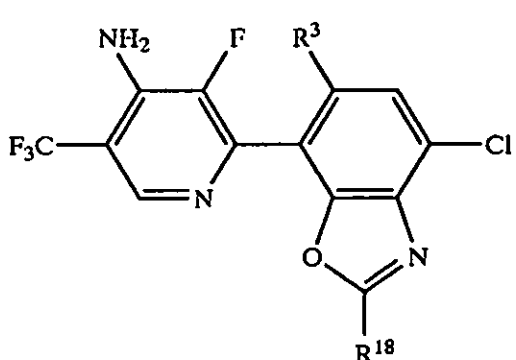
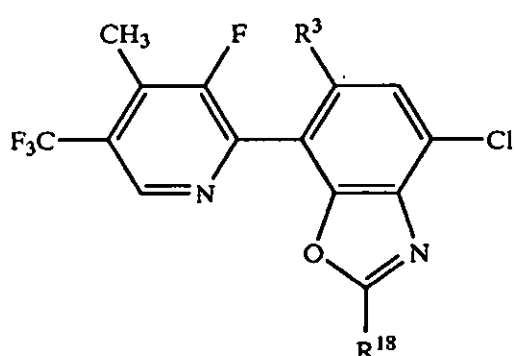
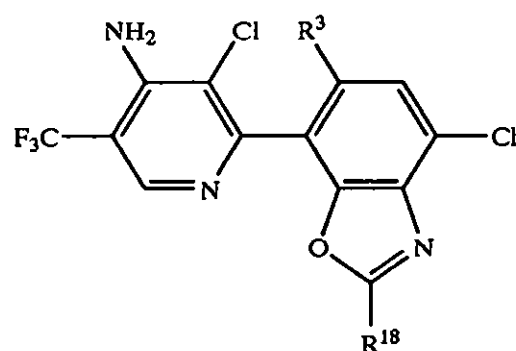
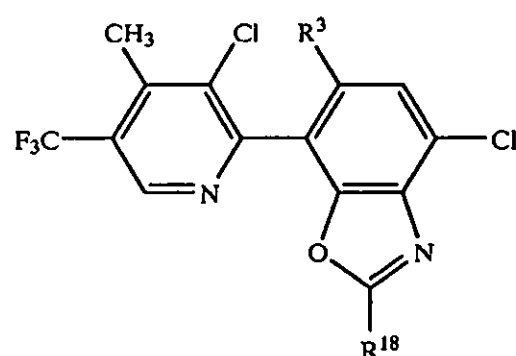


TABLE 3

No.	R ³	R ¹⁸
1	F	H
2	F	CH ₃
3	F	CH ₂ CH ₃
4	F	CH ₂ CH ₂ CH ₃
5	F	CH ₂ CH ₂ CH ₂ CH ₃
6	F	CH(CH ₃) ₂
7	F	CHCH ₃ CH ₂ CH ₃
8	F	C(CH ₃) ₃
9	F	CH ₂ -cyclopropyl
10	F	cyclopropyl
11	F	CH ₂ CH=CH ₂
12	F	CH ₂ CH=CH ₂
13	F	CH ₂ C≡CH
14	F	CH ₂ OCH ₃
15	F	CH ₂ CH ₂ OCH ₃
16	F	CH ₂ CN
17	F	CH ₂ F
18	F	CH ₂ Cl
19	F	CF ₃
20	F	CH ₂ COOCH ₃

TABLE 3-continued

(ICe)	No.	R ³	R ¹⁸
	21	F	CH ₂ COOCH ₂ CH ₃
	22	F	CH ₂ CON(CH ₃) ₂
	23	F	CH ₂ CH ₂ CO ₂ CH ₃
	24	F	CH ₂ CH ₂ CO ₂ CH ₂ CH ₃
	25	F	CH ₂ CHClCO ₂ CH ₃
	26	F	CH ₂ CHClCOOCH ₂ CH ₃
	27	F	CH ₂ CH ₂ PO(OCH ₃) ₂
	28	F	CH ₂ CH ₂ PO(OCH ₂ CH ₃) ₂
	29	F	CH ₂ CHClPO(OCH ₃) ₂
	30	F	CH ₂ CHClPO(OCH ₂ CH ₃) ₂
(ICf)	31	F	phenyl
	32	F	NO ₂
	33	F	F
	34	F	Cl
	35	F	Br
	36	F	OCH ₃
	37	F	OCH ₂ CH ₃
	38	F	OCH ₂ CH ₂ CH ₃
	39	F	OCH(CH ₃) ₂
	40	F	OCH ₂ CH ₂ CH ₂ CH ₃
	41	F	OC(CH ₃) ₃
	42	F	OCH ₂ CH=CH ₂
(ICg)	43	F	OCH ₂ CH=CHCH ₃
	44	F	OCH(CH ₃)CH=CH ₂
	45	F	OCH ₂ C≡CH
	46	F	OCH(CH ₃)C≡CH
	47	F	OCH ₂ OCH ₃
	48	F	OCH ₂ CH ₂ OCH ₃
	49	F	OCH ₂ CN
	50	F	OCH ₂ F
	51	F	OCH ₂ CF ₃
	52	F	OCH ₂ COOCH ₃
	53	F	OCH ₂ COOCH ₂ CH ₃
	54	F	OCH ₂ COOCH ₂ CO ₂ CH ₃
(ICi)	55	F	OCH ₂ CON(CH ₃) ₂
	56	F	OCHCH ₃ COOCH ₃
	57	F	OCHCH ₃ COOCH ₂ CH ₃
	58	F	OCH ₂ COOCH ₂ COOCH ₃
	59	F	OCH ₂ PO(OCH ₃) ₂
	60	F	OCH ₂ PO(OCH ₂ CH ₃) ₂
	61	F	OCH ₂ CH ₂ PO(OCH ₃) ₂
	62	F	OCH ₂ CH ₂ PO(OCH ₂ CH ₃) ₂
	63	F	O-phenyl
	64	F	NH ₂
	65	F	NHCH ₃
	66	F	N(CH ₃) ₂
	67	F	NHCH ₂ CH ₃
	68	F	N(CH ₂ CH ₃) ₂
	69	F	NHCH ₂ CH ₂ CH ₃
	70	F	N(CH ₂ CH ₂ CH ₃) ₂
	71	F	NHCH(CH ₃) ₂
	72	F	N(CH(CH ₃) ₂) ₂
	73	F	NHCH ₂ CH=CH ₂
	74	F	N(CH ₂ CH=CH ₂) ₂
	75	F	NHCH ₂ CH=CHCH ₃
	76	F	N(CH ₂ CH=CHCH ₃) ₂
	77	F	NHCH ₂ C≡CH
	78	F	N(CH ₂ C≡CH) ₂
	79	F	NHCH ₂ COOCH ₃
	80	F	NHCH ₂ COOCH ₂ CH ₃
	81	F	NHCH ₂ COOCH ₂ CO ₂ CH ₃
	82	F	NCH ₃ CH ₂ COOCH ₃
	83	F	NCH ₃ CH ₂ COOCH ₂ CH ₃
	84	F	NCH ₃ CH ₂ COOCH ₂ CO ₂ CH ₃
	85	F	NCH ₃ CH(CH ₃)CO ₂ CH ₃
	86	F	SH
	87	F	SCH ₃
	88	F	SCH ₂ CH ₃
	89	F	SCH ₂ CH ₂ CH ₃
	90	F	SCH(CH ₃) ₂
	91	F	SCH ₂ CH ₂ CH ₂ CH ₃
	92	F	SC(CH ₃) ₃
	93	F	SC ₂ CH=CH ₂
	94	F	SCH ₂ CH=CHCH ₃

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TABLE 3-continued

No.	R ³	R ¹⁸
95	F	SCH(CH ₃)CH=CH ₂
96	F	SCH ₂ C≡CH
97	F	SCH(CH ₃)C≡CH
98	F	SCH ₂ OCH ₃
99	F	SCH ₂ CH ₂ OCH ₃
100	F	SCH ₂ CN
101	F	SCH ₂ F
102	F	SCH ₂ CF ₃
103	F	SCH ₂ COOCH ₃
104	F	SCH ₂ COOCH ₂ CH ₃
105	F	SCH ₂ CON(CH ₃) ₂
106	F	SCHCH ₃ COOCH ₃
107	F	SCH ₂ PO(OCH ₃) ₂
108	F	SCH ₂ PO(OCH ₂ CH ₃) ₂
109	F	SCH ₂ CH ₂ PO(OCH ₃) ₂
110	F	SCH ₂ CH ₂ PO(OCH ₂ CH ₃) ₂
111	F	SCHCH ₃ COOCH ₂ CH ₃
112	F	SCH ₂ COOCH ₂ COOCH ₃
113	F	S—phenyl
114	F	S(O)CH ₃
115	F	S(O)CH ₂ CH ₃
116	F	S(O) ₂ CH ₃
117	F	S(O) ₂ CH ₂ CH ₃
118	Cl	H
119	Cl	CH ₃
120	Cl	CH ₂ CH ₃
121	Cl	CH ₂ CH ₂ CH ₃
122	Cl	CH ₂ CH ₂ CH ₂ CH ₃
123	Cl	CH(CH ₃) ₂
124	Cl	CHCH ₃ CH ₂ CH ₃
125	Cl	C(CH ₃) ₃
126	Cl	CH ₂ —cyclopropyl
127	Cl	cyclopropyl
128	Cl	CH ₂ CH=CH ₂
129	Cl	CH ₂ CH ₂ CH=CH ₂
130	Cl	CH ₂ C≡CH
131	Cl	CH ₂ OCH ₃
132	Cl	CH ₂ CH ₂ OCH ₃
133	Cl	CH ₂ CN
134	Cl	CH ₂ F
135	Cl	CH ₂ Cl
136	Cl	CF ₃
137	Cl	CH ₂ COOCH ₃
138	Cl	CH ₂ COOCH ₂ CH ₃
139	Cl	CH ₂ CON(CH ₃) ₂
140	Cl	CH ₂ CH ₂ CO ₂ CH ₃
141	Cl	CH ₂ CH ₂ CO ₂ CH ₂ CH ₃
142	Cl	CH ₂ CHClCO ₂ CH ₃
143	Cl	CH ₂ CHClCOOCH ₂ CH ₃
144	Cl	CH ₂ CH ₂ PO(OCH ₃) ₂
145	Cl	CH ₂ CH ₂ PO(OCH ₂ CH ₃) ₂
146	Cl	CH ₂ CHClPO(OCH ₃) ₂
147	Cl	CH ₂ CHClPO(OCH ₂ CH ₃) ₂
148	Cl	phenyl
149	Cl	NO ₂
150	Cl	F
151	Cl	Cl
152	Cl	Br
153	Cl	OCH ₃
154	Cl	OCH ₂ CH ₃
155	Cl	OCH ₂ CH ₂ CH ₃
156	Cl	OCH(CH ₃) ₂
157	Cl	OCH ₂ CH ₂ CH ₂ CH ₃
158	Cl	OC(CH ₃) ₃
159	Cl	OCH ₂ CH=CH ₂
160	Cl	OCH ₂ CH=CHCH ₃
161	Cl	OCH(CH ₃)CH=CH ₂
162	Cl	OCH ₂ C≡CH
163	Cl	OCH(CH ₃)C≡CH
164	Cl	OCH ₂ OCH ₃
165	Cl	OCH ₂ CH ₂ OCH ₃
166	Cl	OCH ₂ CN
167	Cl	OCH ₂ F
168	Cl	OCH ₂ CF ₃

TABLE 3-continued

No.	R ³	R ¹⁸
169	Cl	OCH ₂ COOCH ₃
170	Cl	OCH ₂ COOCH ₂ CH ₃
171	Cl	OCH ₂ COOCH ₂ CO ₂ CH ₃
172	Cl	OCH ₂ CON(CH ₃) ₂
173	Cl	OCHCH ₃ COOCH ₃
174	Cl	OCHCH ₃ COOCH ₂ CH ₃
175	Cl	OCH ₂ COOCH ₂ COOCH ₃
176	Cl	OCH ₂ PO(OCH ₃) ₂
177	Cl	OCH ₂ PO(OCH ₂ CH ₃) ₂
178	Cl	OCH ₂ CH ₂ PO(OCH ₃) ₂
179	Cl	OCH ₂ CH ₂ PO(OCH ₂ CH ₃) ₂
180	Cl	O—phenyl
181	Cl	NH ₂
182	Cl	NHCH ₃
183	Cl	N(CH ₃) ₂
184	Cl	NHCH ₂ CH ₃
185	Cl	N(CH ₂ CH ₃) ₂
186	Cl	NHCH ₂ CH ₂ CH ₃
187	Cl	N(CH ₂ CH ₂ CH ₃) ₂
188	Cl	NHCH(CH ₃) ₂
189	Cl	N(CH(CH ₃) ₂) ₂
190	Cl	NHCH ₂ CH=CH ₂
191	Cl	N(CH ₂ CH=CH ₂) ₂
192	Cl	NHCH ₂ CH=CHCH ₃
193	Cl	N(CH ₂ CH=CHCH ₃) ₂
194	Cl	NHCH ₂ C≡CH
195	Cl	N(CH ₂ C≡CH) ₂
196	Cl	NHCH ₂ COOCH ₃
197	Cl	NHCH ₂ COOCH ₂ CH ₃
198	Cl	NHCH ₂ COOCH ₂ CO ₂ CH ₃
199	Cl	NCH ₃ CH ₂ COOCH ₃
200	Cl	NCH ₃ CH ₂ COOCH ₂ CH ₃
201	Cl	NCH ₃ CH ₂ COOCH ₂ CO ₂ CH ₃
202	Cl	NCH ₃ CH(CH ₃)CO ₂ CH ₃
203	Cl	SH
204	Cl	SCH ₃
205	Cl	SCH ₂ CH ₃
206	Cl	SCH ₂ CH ₂ CH ₃
207	Cl	SCH(CH ₃) ₂
208	Cl	SCH ₂ CH ₂ CH ₂ CH ₃
209	Cl	SC(CH ₃) ₃
210	Cl	SC ₂ CH=CH ₂
211	Cl	SC ₂ CH=CHCH ₃
212	Cl	SCH(CH ₃)CH=CH ₂
213	Cl	SCH ₂ C≡CH
214	Cl	SCH(CH ₃)C≡CH
215	Cl	SCH ₂ OCH ₃
216	Cl	SCH ₂ CH ₂ OCH ₃
217	Cl	SCH ₂ CN
218	Cl	SCH ₂ F
219	Cl	SCH ₂ CF ₃
220	Cl	SCH ₂ COOCH ₃
221	Cl	SCH ₂ COOCH ₂ CH ₃
222	Cl	SCH ₂ CON(CH ₃) ₂
223	Cl	SCHCH ₃ COOCH ₃
224	Cl	SCH ₂ PO(OCH ₃) ₂
225	Cl	SCH ₂ PO(OCH ₂ CH ₃) ₂
226	Cl	SCH ₂ CH ₂ PO(OCH ₃) ₂
227	Cl	SCH ₂ CH ₂ PO(OCH ₂ CH ₃) ₂
228	Cl	SCHCH ₃ COOCH ₂ CH ₃
229	Cl	SCH ₂ COOCH ₂ COOCH ₃
230	Cl	S—phenyl
231	Cl	S(O)CH ₃
232	Cl	S(O)CH ₂ CH ₃
233	Cl	S(O) ₂ CH ₃
234	Cl	S(O) ₂ CH ₂ CH ₃
235	H	H
236	H	CH ₃
237	H	CH ₂ CH ₃
238	H	CH ₂ CH ₂ CH ₃
239	H	CH ₂ CH ₂ CH ₂ CH ₃
240	H	CH(CH ₃) ₂
241	H	CHCH ₃ CH ₂ CH ₃
242	H	C(CH ₃) ₃

TABLE 3-continued

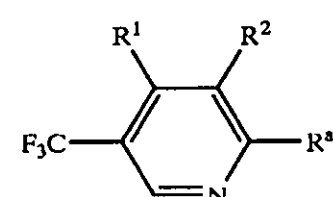
No.	R ³	R ¹⁸
243	H	CH ₂ -cyclopropyl
244	H	cyclopropyl
245	H	CH ₂ CH=CH ₂
246	H	CH ₂ CH ₂ CH=CH ₂
247	H	CH ₂ C≡CH
248	H	CH ₂ OCH ₃
249	H	CH ₂ CH ₂ OCH ₃
250	H	CH ₂ CN
251	H	CH ₂ F
252	H	CH ₂ Cl
253	H	CF ₃
254	H	CH ₂ COOCH ₃
255	H	CH ₂ COOCH ₂ CH ₃
256	H	CH ₂ CON(CH ₃) ₂
257	H	CH ₂ CH ₂ CO ₂ CH ₃
258	H	CH ₂ CH ₂ CO ₂ CH ₂ CH ₃
259	H	CH ₂ CHClCO ₂ CH ₃
260	H	CH ₂ CHClCOOCH ₂ CH ₃
261	H	CH ₂ CH ₂ PO(OCH ₃) ₂
262	H	CH ₂ CH ₂ PO(OCH ₂ CH ₃) ₂
263	H	CH ₂ CHClPO(OCH ₃) ₂
264	H	CH ₂ CHClPO(OCH ₂ CH ₃) ₂
265	H	phenyl
266	H	NO ₂
267	H	F
268	H	Cl
269	H	Br
270	H	OCH ₃
271	H	OCH ₂ CH ₃
272	H	OCH ₂ CH ₂ CH ₃
273	H	OCH(CH ₃) ₂
274	H	OCH ₂ CH ₂ CH ₂ CH ₃
275	H	OC(CH ₃) ₃
276	H	OCH ₂ CH=CH ₂
277	H	OCH ₂ CH=CHCH ₃
278	H	OCH(CH ₃)CH=CH ₂
279	H	OCH ₂ C≡CH
280	H	OCH(CH ₃)C≡CH
281	H	OCH ₂ OCH ₃
282	H	OCH ₂ CH ₂ OCH ₃
283	H	OCH ₂ CN
284	H	OCH ₂ F
285	H	OCH ₂ CF ₃
286	H	OCH ₂ COOCH ₃
287	H	OCH ₂ COOCH ₂ CH ₃
288	H	OCH ₂ COOCH ₂ CO ₂ CH ₃
289	H	OCH ₂ CON(CH ₃) ₂
290	H	OCHCH ₃ COOCH ₃
291	H	OCHCH ₃ COOCH ₂ CH ₃
292	H	OCH ₂ COOCH ₂ COOCH ₃
293	H	OCH ₂ PO(OCH ₃) ₂
294	H	OCH ₂ PO(OCH ₂ CH ₃) ₂
295	H	OCH ₂ CH ₂ PO(OCH ₃) ₂
296	H	OCH ₂ CH ₂ PO(OCH ₂ CH ₃) ₂
297	H	O-phenyl
298	H	NH ₂
299	H	NHCH ₃
300	H	N(CH ₃) ₂
301	H	NHCH ₂ CH ₃
302	H	N(CH ₂ CH ₃) ₂
303	H	NHCH ₂ CH ₂ CH ₃
304	H	N(CH ₂ CH ₂ CH ₃) ₂
305	H	NHCH(CH ₃) ₂
306	H	N(CH(CH ₃) ₂) ₂
307	H	NHCH ₂ CH=CH ₂
308	H	N(CH ₂ CH=CH ₂) ₂
309	H	NHCH ₂ CH=CHCH ₃
310	H	N(CH ₂ CH=CHCH ₃) ₂
311	H	NHCH ₂ C≡CH
312	H	N(CH ₂ C≡CH) ₂
313	H	NHCH ₂ COOCH ₃
314	H	NHCH ₂ COOCH ₂ CH ₃
315	H	NHCH ₂ COOCH ₂ CO ₂ CH ₃
316	H	NCH ₃ CH ₂ COOCH ₃

TABLE 3-continued

No.	R ³	R ¹⁸
317	H	NCH ₃ CH ₂ COOCH ₂ CH ₃
318	H	NCH ₃ CH ₂ COOCH ₂ CO ₂ CH ₃
319	H	N(CH ₃)CH(CH ₃)CO ₂ CH ₃
320	H	SH
321	H	SCH ₃
322	H	SCH ₂ CH ₃
323	H	SCH ₂ CH ₂ CH ₃
324	H	SCH(CH ₃) ₂
325	H	SCH ₂ CH ₂ CH ₂ CH ₃
326	H	SC(CH ₃) ₃
327	H	SCH ₂ CH=CH ₂
328	H	SCH ₂ CH=CHCH ₃
329	H	SCH(CH ₃)CH=CH ₂
330	H	SCH ₂ C≡CH
331	H	SCH(CH ₃)C≡CH
332	H	SCH ₂ OCH ₃
333	H	SCH ₂ CH ₂ OCH ₃
334	H	SCH ₂ CN
335	H	SCH ₂ F
336	H	SCH ₂ CF ₃
337	H	SCH ₂ COOCH ₃
338	H	SCH ₂ COOCH ₂ CH ₃
339	H	SCH ₂ CON(CH ₃) ₂
340	H	SCHCH ₃ COOCH ₃
341	H	SCH ₂ PO(OCH ₃) ₂
342	H	SCH ₂ PO(OCH ₂ CH ₃) ₂
343	H	SCH ₂ CH ₂ PO(OCH ₃) ₂
344	H	SCH ₂ CH ₂ PO(OCH ₂ CH ₃) ₂
345	H	SCHCH ₃ COOCH ₂ CH ₃
346	H	SCH ₂ COOCH ₂ COOCH ₃
347	H	S-phenyl
348	H	S(O)CH ₃
349	H	S(O)CH ₂ CH ₃
350	H	S(O) ₂ CH ₃
351	H	S(O) ₂ CH ₂ CH ₃

[0131] The 2-aryl-5-trifluoromethylpyridines, their N-oxides and their salts can be prepared analogously to the preparation of the 2-aryl-5-trifluoromethylpyridines, which are known from the prior art cited at the outset.

[0132] Preferred procedure for this purpose is to couple a suitably substituted pyridine of the formula II

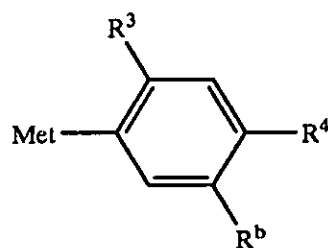


(II)

[0133] in which the variables R¹ and R² have the above-mentioned meanings, or R¹ is a protected amino group, and

[0134] R^a is halogen or S(O)_k-phenyl where k is 0, 1 or 2

[0135] with an organometallic compound of the formula III



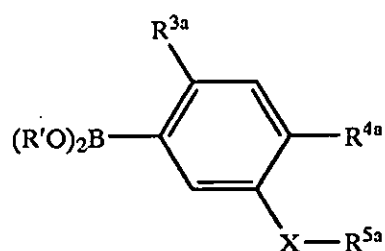
(III)

[0136] where Met is a metal atom or a semimetal or a radical bonded via a metal atom or semimetal atom, R³ and R⁴ have the abovementioned meanings and R^b is a substituent which is compatible with the metal atom or the semimetal which can be converted by known methods into one of the groups X—R⁵, or is a group X—R⁵ which is compatible with the metal or the semimetal. The reaction of II with III is preferably carried out in the presence of catalytically active amounts of a transition metal of the VIIIb group of the periodic system, for example Ni or Pd, it being possible for the metal to be employed as such, in doped or supported form, as a complex compound or as a salt.

[0137] Examples of suitable groups Met are, in particular, Mg-Hal and Zn-Hal, where Hal is halogen, and —B(OR')₂, where R' is hydrogen or C₁-C₁₀-alkyl.

[0138] Examples of suitable radicals R^b are the groups X—R⁵ mentioned hereinbelow, where X has the abovementioned meanings and R⁵ is selected from among hydrogen, cyano, halogen, —O—Y—R⁷, —O—CO—Y—R⁷, —N(Y—R⁷)(Z—R⁸), —S—Y—R⁷, —CO—Y—R⁷, —CO—O—Y—R⁷, —CO—N(Y—R⁷)(Z—R⁸), —CO—N(Y—R⁷)(O—Z—R⁸) and —PO(O—Y—R⁷)₂; with the abovementioned meanings of Y, Z, R⁷ and R⁸. R^b is, in particular, hydrogen, C₁-C₄-alkyl, halogen, a group —O—Y—R⁷ or a group —CO—O—Y—R⁷.

[0139] The above-defined pyridines of the formula II where R^a is OH, C₁-C₄-alkoxy or benzyloxy (compounds VI, VII, IX and X described hereinbelow and N-protected derivatives of II where R¹=NH₂) and the boronic acid compounds of the formula IIIa



(IIIa)

[0140] in which X is a single bond and the variables R', R^{3a}, R^{4a} and R^{5a} have the following meanings:

[0141] R' is hydrogen or C₁-C₁₀-alkyl or two radicals R' form a chain of the formula —CH₂—CH₂— or —CH₂—CH₂—CH₂;

[0142] R^{3a} is hydrogen or halogen;

[0143] R^{4a} is halogen or C₁-C₄-alkoxy;

[0144] R^{5a} is hydrogen, cyano, halogen, —O—Y—R^{7a}, —O—CO—Y—R⁷, —S—Y—R^{7a}, —CO—O—Y—

R⁷ or —PO(O—Y—R^{7a})₂; where R^{7a} is a group —C(R¹⁰)(R¹¹)—CO—OR¹² and Y, R⁷, R¹⁰, R¹¹ and R¹² have the abovementioned meanings;

[0145] or R^{4a} is CN and R^{5a} has the following meaning:

[0146] R^{5a} is cyano, halogen, —O—Y—R⁷, —O—CO—Y—R⁷, —S—Y—R⁷, —CO—O—Y—R⁷ or —PO(O—Y—R⁷)₂; where Y and R⁷ have the abovementioned meanings;

[0147] are novel and, being important intermediates for the preparation of the 2-aryl-5-trifluoromethylpyridines of the formula I according to the invention, are likewise subject matter of the present invention. In the boronic acids IIIa, X and Y are preferably single bonds. Especially important intermediates among the boronic acid derivatives IIIa are those compounds in which R^{4a} is chlorine and X—R^{5a} is CN, —O—Y—R^{7a}, —O—CO—Y—R⁷ or —CO—O—Y—R⁷. In these formulae, R⁷ has the abovementioned meanings and in this case is especially preferably C₁-C₄-alkyl or C₁-C₄-alkyloxycarbonyl-C₁-C₄-alkyl. R^{7a} is preferably a C₁-C₄-alkyloxycarbonyl-C₁-C₄-alkyl radical. If R^{4a} is CN, then X—R^{5a} is preferably cyano, halogen, —O—Y—R⁷, —O—CO—Y—R⁷ or —CO—O—Y—R⁷. R⁷ in this case preferably represents C₁-C₄-alkyl or C₁-C₄-alkyloxycarbonyl-C₁-C₄-alkyl.

[0148] To prepare the compounds I according to the invention, it is preferred to react a chloropyridine derivative (compound II where R^a=Cl) with a phenylboronic acid or boronic acid ester (compound III where Met=B(OH)₂ or B(OR')₂) or with a Grignard compound (compound III where Met=Hal-Mg, for example Cl—Mg) or with a zinc compound (compound III where Met=Hal-Zn, in particular Cl—Zn) in the presence of catalytically active amounts of a palladium or nickel compound and in the event of boronic acid coupling additionally in the presence of a base in an organic solvent or in a mixture of an organic solvent with water at ambient temperature or elevated temperatures.

[0149] The processes and conditions for such reactions are known to the skilled worker and can be found for example in the reviews by F. Diederich, P. J. Stang (Ed.) Metal-catalyzed Cross-coupling Reactions, Wiley-VCH-Verlag Weinheim 1998, W. A. Herrmann et al., Angew. Chem. 39, 2000, p. 1602, or W. A. Herrmann et al., "Applied Homogeneous Catalysis with Organometallic Compounds" Wiley-VCH 1996, p. 764, and in WO 95/02580, WO 95/02590, WO 98/11070, EP 972765-A1 and the prior art stated therein.

[0150] Suitable palladium catalysts are, in addition to palladium carboxylates such as palladium(II) acetate, also palladium/phosphane complexes such as tetrakis(triphenylphosphane)palladium, totriphenylphosphanepalladium(II) chloride, to (1,2-diphenylphosphanoethane)palladium(II) chloride, to (1,3-diphenylphosphanopropane)palladium(II) chloride, to (1,4-diphenylphosphanobutane)palladium(II) chloride and to (diphenylphosphano)ferrocenylpalladium(II) chloride. However, palladium halides such as palladium(II) chloride may also be reacted in situ with phosphine ligands to give the catalytically active complexes. Examples of suitable phosphine ligands are arylphosphanes which are unsubstituted or substituted in the ortho, meta or para position by

halogen, alkyl and/or SO_3H , such as triphenylphosphine, 1,2-bis(diphenylphosphano)ethane, 1,3-bis(diphenylphosphano)propane, 1,4-bis(diphenylphosphano)butane, to (diphenylphosphano)ferrocene, hetarylphosphanes such as trisfurylphosphine or trispyridylphosphine. Corresponding platinum catalysts are also suitable.

[0151] Suitable Ni catalysts are nickel(II) acetyl acetonate, alone or in conjunction with the abovementioned phosphine ligands, or Ni(II) acetyl acetonate with imidazolium carbene ligands, and complexes of nickel(II) salts with the abovementioned phosphine ligands, for example to (triphenylphosphine)nickel(II) chloride, [1,3-bis(diphenylphosphano)propane]nickel(II) chloride, [1,4-bis(diphenylphosphano)butane]nickel(II) chloride and [bis(diphenylphosphano)ferrocene]nickel(II) chloride.

[0152] The catalyst is usually employed in a substoichiometric amount, preferably from 0.001-0.8 equivalents and especially preferably from 0.01 to 0.5 equivalents, based on the pyridine II employed.

[0153] The molar ratio of compound II to compound III is preferably in the range of from 0.95:1 to 1:1.5.

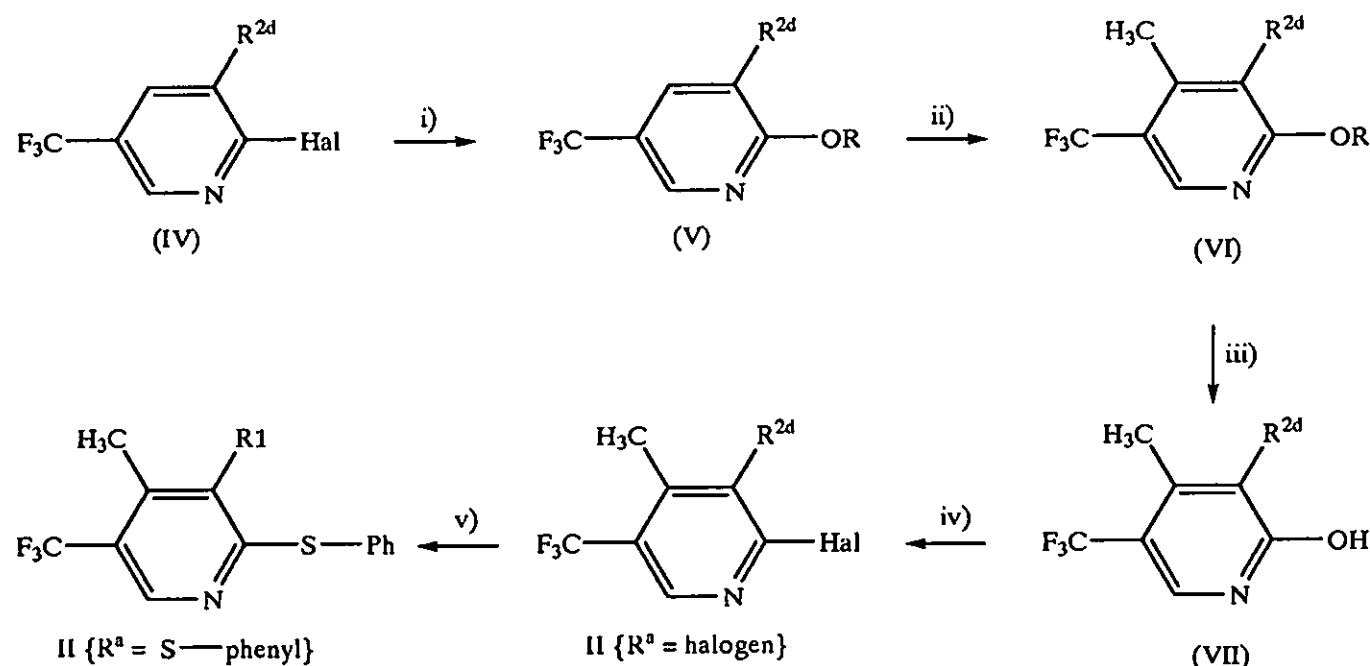
approximately 5:1 to 1:5, preferably in a ratio of approximately 2:1 to 1:2, and in particular of approximately 1:1.

[0156] The reaction temperature is usually above the melting point and can be up to the boiling point of the solvent. It is preferably in the range between 50 and 150° C.

[0157] Moreover, the compounds I according to the invention can also be obtained by coupling the corresponding 2-pyridinyl sulfoxides (compounds II where $\text{R}^a=\text{S}(\text{O})_k\text{R}^b$) or 2-pyridinyl sulfones (compounds II where $\text{R}^a=\text{S}(\text{O})_2\text{R}^b$) with a phenyl-Grignard compound III (compound III where $\text{Met}=\text{Mg-Hal}$). The reaction can be carried out analogously to the procedures described in JP 2000080082, WO 98 54137, WO 98 11069, WO 98/11070 and WO 98/11072, so that reference is made herewith to the disclosure of these publications.

[0158] The compounds of the formula II which are required for the preparation of the 2-aryl-5-trifluoromethylpyridines I according to the invention can be prepared starting from the commercially available dichloropyridines IV ($\text{Hal}=\text{Cl}$, $\text{R}^{2d}=\text{Cl}$, CAS-No.: 69045-84-7, $\text{Hal}=\text{R}^{2d}=\text{F}$, CAS-No.: 89402-42-6) following the schemes 1 and 2 hereinbelow.

Scheme 1: Preparation of pyridines II where $\text{R}^1 = \text{CH}_3$



[0154] If required, suitable bases are alkali metal hydroxides, alkaline earth metal hydroxides, alkali metal (hydrogen) carbonates and alkali metal (hydrogen) phosphates such as NaOH , NaHCO_3 , Na_2CO_3 , KHCO_3 , K_2CO_3 , $\text{Ba}(\text{OH})_2$, K_3PO_4 , alkali metal alkoxides, alkaline earth metal alkoxides, thallium alkoxides and transition metal alkoxides such as sodium ethoxide and thallium ethoxide. Alkali metal fluorides such as potassium fluoride, cesium fluoride, ammonium fluorides and tetrabutylammonium fluoride are also suitable as bases. The base is usually employed in an approximately stoichiometric amount or in an up to 10-fold excess, based on compound II.

[0155] Suitable solvents are organic solvents such as DMF, dimethylacetamide, toluene, tetrahydrofuran (THF), dioxane and dimethoxyethane. In the event of boronic acid coupling, the abovementioned solvents may also be employed in a mixture with water, for example in a ratio of

[0159] In scheme 1, R^{2d} is halogen, in particular fluorine or chlorine. Hal is also halogen, in particular fluorine or chlorine. R is C_1 - C_{10} -alkyl or benzyl. R^b has the abovementioned meanings.

[0160] In accordance with scheme 1, the pyridine compounds V are first prepared by reacting the dihalopyridines IV with alcohols ROH in the presence of bases or by reacting IV with the corresponding alkoxides (step i)). Such reactions are known in principle and described, for example, in Tome et al. Tetrahedron Lett. 34 (41) 1993 p. 6639, Gerster et al. J. Org. Chem. 31 1966 p. 3259 and in WO 98/11069, which are herewith referred to.

[0161] Surprisingly, the introduction of the methyl group in the 4-position of the pyridine ring in step ii) can be carried out by a two-step reaction sequence comprising first the

metalation, in particular lithiation, of the 4-position and subsequently the reaction of the pyridine anion thus obtained with an electrophilic methylating agent. An undesired halogen-metal exchange or the formation of undesired isomers or adducts in the 6-position is not observed. This procedure opens up for the first time a route for the preparation of the compounds II and thus for the preparation of the compounds I. The compounds II and the methods illustrated in schemes 1 and 2 are therefore also subject matter of the present invention.

[0162] This procedure has not been described as yet in the prior art, even though examples of regioselective metalations on pyridine derivatives are found occasionally in the literature. EP-A 0953566, for example, describes the derivatization of 2-alkoxy-5-trifluoromethylpyridines by metalation of the 4-position of the pyridine ring in the vicinity of a trifluoromethyl group using sterically demanding lithium amide bases. However, this publication does not teach that such a metalation is possible in pyridines which have a halogen atom bonded to the pyridine ring without a halogen-metal exchange taking place. In accordance with the prior art, this would have been expected owing to the ortho-directing effect of the alkoxy group (see JOC 1990, 55 p. 69).

[0163] To carry out the lithiation, the pyridine derivative V is usually reacted, in step ii), with at least one equivalent of an organolithium compound, for methyl lithium, n-butyl lithium or sec-butyl lithium, or with a lithium amide such as lithium diisopropylamide or lithium-2,2,6,6-tetramethylpiperidine (LiTMP) in an aprotic, preferably etherial, organic solvent such as tetrahydrofuran or methyl tert-butyl ether. As a rule, the reaction is carried out at temperatures of below -30°C ., preferably in the range of -120°C . to -40°C ., and in particular in the range of from -75°C . to -60°C . To carry out the methylation, 1 to 20 equivalents, preferably 1 to 10 equivalents, of an electrophilic methylating agent are subsequently added. In some cases it may be advantageous to add the lithiated pyridine to a solution of electrophilic methylating agent.

[0164] Suitable as electrophilic methylating agents are a multiplicity of customary methylating agents such as methyl halides, preferably methyl chloride, methyl bromide, methyl iodide, furthermore dimethyl sulfate, methyl tosylate and methyl triflate.

[0165] Starting with the 2-alkoxy-4-methyl-5-trifluoromethylpyridines VI obtained in step ii), the halopyridines II are then prepared in a two-step synthesis sequence comprising an ether cleavage of the pyridine IV in step iii) and the subsequent conversion of the resulting hydroxypyridine VII or the tautomeric pyridone in step iv) into the halogen compound, in particular into the chlorine compound II {R^a=halogen, in particular chlorine}.

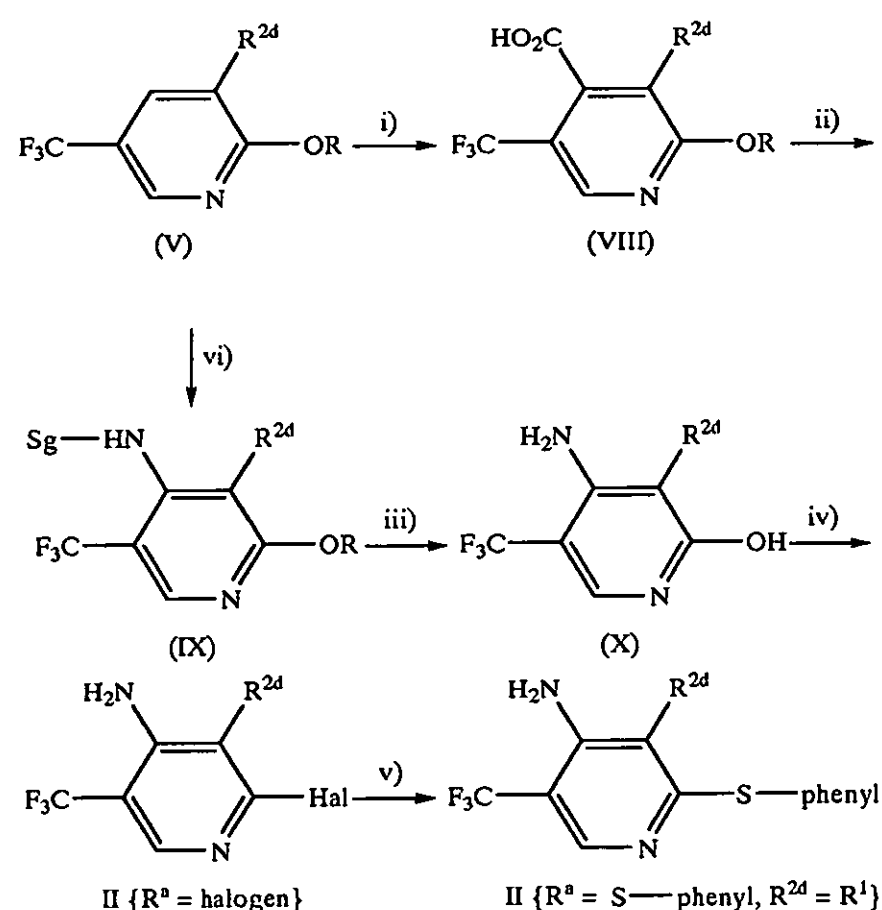
[0166] To carry out the ether cleavage in step iii), the pyridine compound VI is treated with a strong Lewis acid such as, for example, boron tribromide, trimethylsilyl iodide or a hydrohalic acid such as concentrated hydrobromic acid, depending on the radical R. If R in formula VI is benzyl, the ether cleavage can also be carried out by means of hydrogenolysis, for example by treating VI with hydrogen in the presence of a transition metal catalyst such as palladium or platinum on active charcoal or Raney nickel. The conditions for this procedure follow the methods known from protec-

tion-group chemistry as are described, for example, in Kocienski et al. "Protecting Groups", Thieme Verlag 1994.

[0167] The subsequent conversion of the hydroxypyridine VII in step iv), which, depending on the solvent, may also be present in the form of the tautomeric pyridone, is known to the skilled worker in principle and is generally carried out by reacting VII with a Lewis-acidic halogenating agent such as phosgene, thionyl chloride, phosphorus oxychloride or phosphorus(V) chloride. To this end, the halogenating agent is employed in equimolar amounts or in an up to 10-fold excess in an inert organic solvent such as chloroform, dichloroethane, toluene or in very large excess as the solvent. As a rule, the reaction temperatures range from 20°C . to 120°C ., preferably from 40°C . to 100°C ., very especially preferably from 40°C . to 80°C . As regards further details on steps iii) and iv), reference is made at this point to EP-A 72777, in particular the examples, which apply analogously to steps iii) and iv) of Scheme 1.

[0168] The thiopyridines II can then be prepared analogously to processes known from the literature by reacting chloropyridines II with thiols R^bSH in the presence of a base or of a catalyst. As regards the reaction conditions for these reactions, reference is made to WO 98/11072, WO 98/11070, WO 98/11069 and WO 98/54137, WO 98/54139 and JP 2000080082. The further oxidation to give the sulfoxides II {R^a=SO-phenyl} or the sulfones II {R^a=SO₂-phenyl} can also be carried out analogously to the publications mentioned herein.

Scheme 2: Preparation of pyridines II where R¹ = NH₂



[0169] In Scheme 2, R^{2d} is halogen, in particular fluorine or chlorine. Hal is also halogen, in particular fluorine or chlorine. R is C₁-C₁₀-alkyl or benzyl. R^b has the abovementioned meanings. Sg is hydrogen or a protecting group.

[0170] The preparation of the aminopyridines II (R¹=NH₂) is similar to the preparation of the methylpy-

ridines II ($R^1=CH_3$). First, an alkoxy pyridine compound V is metalated, in particular lithiated, in step i) and subsequently reacted with CO_2 or a carbonic acid derivative to give the carboxylic acid VIII. As regards step i), what has been said for step ii) in Scheme 1 applies analogously.

[0171] Using known processes, the carboxylic acid VIII is then converted in step ii) into the amine IX ($Sg=H$) or a suitably protected derivative IX. The methods of converting carboxylic acid derivatives into amines are known to the skilled worker as Hofmann, Curtius and Schmidt degradation. As regards the conditions for the reaction, reference is made for example to Houben-Weyl *Organo-Stickstoff-Verbindungen* IV, Vol. E16d Part 2, pages 1160-1167, Thieme Verlag Stuttgart.

[0172] Steps iii), iv) and v) of Scheme 2 are then carried out analogously to the steps described in Scheme 1. If Sg is a protecting group, that is to say other than hydrogen, Sg is generally eliminated under ether cleavage conditions (step iii) in Schemes 1 and 2). When oxidizing the aminomercaptopyrindines II ($R^1=NH_2$, $R^a=S-R^b$), it may be necessary to introduce a protecting group at the amino group before the oxidation. Suitable protecting groups are, for example, acetyl and benzyloxycarbonyl.

[0173] Moreover, the aminopyridines II can be prepared by lithiating compound V and subsequently reacting the lithiated pyridine with an electrophilic aminating reagent such as tosyl azide, phosphinyl azide, t-butylvinyl azide, hydroxylamine or 2,4-dinitrophenyl hydroxylamine ether (Scheme 2, step vi)). These methods are known to the skilled worker and described, for example, in K. Krohn, *Electrophilic Amination*, in Mulzer, Altenbach, Braun, Krohn, Reissig (editors) "Organic Synthesis Highlights" VCH 1991, p. 45; Kozikowski et al. *Tetrahedron Lett.* 30 (33) 1989, p. 4613.

TABLE 4a

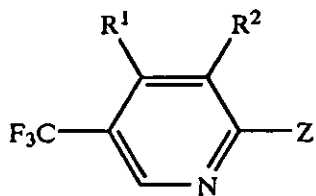
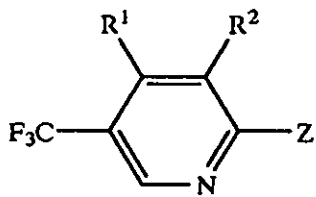
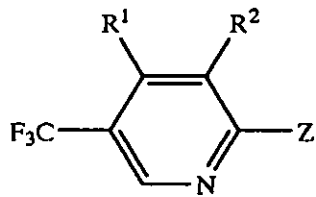
Intermediates of Scheme 1			
			
Compound	R^1	R^2	Z
V.1	H	Cl	OCH_2Ph
V.2	H	Cl	OCH_3
V.3	H	Cl	OCH_2CH_3
V.4	H	Cl	$OCH(CH_3)_2$
V.5	H	F	OCH_2Ph
V.6	H	F	OCH_3
V.7	H	F	OCH_2CH_3
V.8	H	F	$OCH(CH_3)_2$
VI.1	CH_3	Cl	OCH_2Ph
VI.2	CH_3	Cl	OCH_3
VI.3	CH_3	Cl	OCH_2CH_3
VI.4	CH_3	Cl	$OCH(CH_3)_2$
VII.1	CH_3	Cl	OH
II.1	CH_3	Cl	Cl
VI.5	CH_3	F	OCH_2Ph
VI.6	CH_3	F	OCH_3
VI.7	CH_3	F	OCH_2CH_3
VI.8	CH_3	F	$OCH(CH_3)_2$
VII.2	CH_3	F	OH
II.2	CH_3	F	Cl

TABLE 4a-continued

Intermediates of Scheme 1			
			
Compound	R^1	R^2	Z
II.3	CH_3	Cl	S-phenyl
II.4	CH_3	F	S-phenyl
II.5	CH_3	Cl	S(O)-phenyl
II.6	CH_3	F	S(O)-phenyl
II.7	CH_3	Cl	S(O) ₂ -phenyl
II.8	CH_3	F	S(O) ₂ -phenyl

[0174]

TABLE 4b

Intermediates of Scheme 2			
			
Compound	R^1	R^2	Z
VIII.1	COOH	Cl	OCH_2Ph
VIII.2	COOH	Cl	OCH_2Ph
IX.1	tert-butoxycarbonyl-NH	Cl	OCH_2Ph
IX.2	tert-butoxycarbonyl-NH	Cl	OCH_2Ph
X.1	NH_2	F	OH
X.2	NH_2	F	OH
II.9	NH_2	Cl	Cl
II.10	NH_2	F	Cl
II.11	NH_2	Cl	S-phenyl
II.12	NH_2	F	S-phenyl
II.13	NH_2	Cl	S(O)-phenyl
II.14	NH_2	F	S(O)-phenyl
II.15	NH_2	Cl	S(O) ₂ -phenyl
II.16	NH_2	F	S(O) ₂ -phenyl

[0175] Some of the compounds III required for synthesizing the 2-aryl-5-trifluoromethylpyridines I are known from the literature or can generally be prepared by known methods, preferably from the corresponding halogen compounds.

[0176] Some of the boronic acids which are especially suitable for preparing the 2-aryl-5-trifluoromethylpyridines I according to the invention (compounds III where $Met=B(OR)_2$) are known from the literature, for example 2-fluoro-4-chloro-5-methoxyphenylboronic acid (CAS-No.: 153122-60-2), 2-fluoro-4-chlorophenylboronic acid (CAS-No.: 160591-91-3) or 2-fluoro-4-methoxyphenylboronic acid (CAS-No.: 162101-31-7).

[0177] Moreover, they can be prepared analogously to known methods by reacting the corresponding phenyl-Grignard compounds (compound III where $Met=Mg-Hal$) with boric esters (see, for example, Houben-Weyl, Vol. 13, Part 3a, pages 616-654, Thieme Verlag 1982).

[0178] Usually, the preparation of the phenyl-Grignard compounds required for this purpose is carried out as

described therein, starting from the corresponding phenyl bromide, and reacting it with magnesium or a second Grignard reagent. The reaction temperatures required for this purpose only make it possible to obtain those Grignard compounds in which the group R^4 or R^b in formula III is a radical which does not react with a Grignard compound.

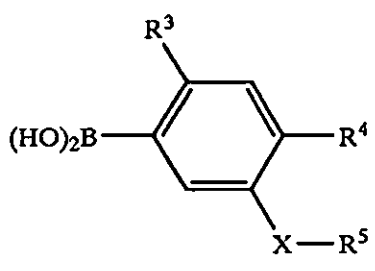
[0179] Surprisingly, it has been found that phenyl-Grignard compounds III (compounds III where $Met=Mg-Hal$) can be scavenged at low temperatures using borates $(R'O)_3B$. To this end, the corresponding phenyl iodides are first converted into Grignard compounds. The reaction of functionalized aromatic iodides to give Grignard reagents is known, in principle, from the literature (see, for example, Knochel et al, *Angew. Chem.* 1998, 110, p. 1801 and DE-A 19836408) and is usually carried out by reacting the phenyl iodides with other Grignard compounds. The conversion of the resulting phenyl-Grignard compounds III into the boronic acids IIIa is then carried out at low temperatures, i.e. below $0^\circ C$., in particular at $-10^\circ C$. and below, that is to say at temperatures at which a series of groups which are reactive toward Grignard compounds, such as carboxylate, amide and nitrile groups, are not yet attacked. Thus, in this manner, even those boronic compounds IIIa (compound IIIa where $Met=B(OR')_2$) which have a substituent which is reactive toward Grignard compounds can be prepared for the first time. Accordingly, the present invention also relates to the above-defined phenylboronic acid compounds of the formula IIIa. Depending on work-up and storage, these compounds can either exist only as monomeric boronic acids or as its trimer boroxine or else as mixtures and employed in the reactions described at the outset.

[0180] To prepare the boronic acid compounds (compound III where $Met=B(OR')_2$), the corresponding iodides are first converted into the corresponding phenyl-Grignard compound by means of another Grignard compound. Suitable for this purpose are, in particular, alkyl Grignard compounds, for example C_1 - C_4 -alkylmagnesium halides, in particular the bromides such as methylmagnesium bromide or isopropylmagnesium bromide. For this purpose, the iodide is usually reacted at temperatures of between $-78^\circ C$. and $0^\circ C$., preferably at $-60^\circ C$. to $0^\circ C$. and very especially preferably at $-50^\circ C$. to $-10^\circ C$. with an approximately equivalent amount, for example 1 to 1.05 equivalents, of a Grignard compound, preferably isopropylmagnesium bromide or isopropylmagnesium chloride, in an inert organic solvent, preferably an ether such as diethyl ether, tetrahydrofuran, dioxane, dimethoxyethane, methyl-tert-butyl ether or mixtures of these. The Grignard compound is subsequently scavenged at these temperatures using boric esters, preferably lower alkyl esters, very especially trimethyl borate. Work-up under acidic aqueous conditions then yields boronic acid or its trimer; or else, work-up under neutral conditions gives the esters of boronic acid ($R' \neq H$).

[0181] Some of the iodides required for the preparation of the boronic acids III are known from the literature (for example 2-fluoro-4-chloro-5-carboisopropoxy-1-iodobenzene, CAS-No.: 264927-52-8), 2-fluoro-4-chloro-5-methoxy-1-iodobenzene (CAS-No.: 174913-22-5), 2-fluor-4-chloro-1-iodobenzene (CAS-No.: 6797-79-1) or can be prepared analogously to these methods (see also Houben-Weyl Vol. 5/4, p. 639 et seq.).

[0182] Some boronic acids according to the invention which can be prepared via this route are mentioned by way of example in Table 5:

TABLE 5

(IIIa)			
			
Compound	R^3	R^4	$X-R^5$
IIIa.1	H	Cl	CO_2CH_3
IIIa.2	F	Cl	CO_2CH_3
IIIa.3	Cl	Cl	CO_2CH_3
IIIa.4	H	Cl	$CO_2CH_2CH_3$
IIIa.5	F	Cl	$CO_2CH_2CH_3$
IIIa.6	Cl	Cl	$CO_2CH_2CH_3$
IIIa.7	H	Cl	$CO_2CH(CH_3)_2$
IIIa.8	F	Cl	$CO_2CH(CH_3)_2$
IIIa.9	Cl	Cl	$CO_2CH(CH_3)_2$
IIIa.10	H	CN	OCH_3
IIIa.11	F	CN	OCH_3
IIIa.12	Cl	CN	OCH_3
IIIa.13	H	CN	F
IIIa.14	F	CN	F
IIIa.15	Cl	CN	F

[0183] Moreover, the compounds of the formula I according to the invention can be prepared by derivatizing other 2-aryl-5-trifluoromethylpyridines.

[0184] I For example, compounds IA, where $X-R^5$ is a group $O-Y-R^7$ can be obtained from the respective methoxy compound IA ($X-R^5=OCH_3$) by first cleaving the methyl ether and then alkylating the resulting phenol compound IA ($X-R^5=OH$) with a suitable alkylating agent $L-Y-R^7$, in which L is a nucleophilically displaceable leaving group, for example a halogen atom, an arylsulfonate group, a sulfate group or similar, preferably in the presence of a base.

[0185] Suitable for cleaving the methyl ethers are strong Lewis acids such as boron tribromide and also hydrohalic acids such as HBr or HI.

[0186] Preferably, the methoxy compound is reacted with 1 to 5 equivalents of the Lewis acid in an aprotic organic solvent, preferably a chlorohydrocarbon such as dichloromethane, chloroform or 1,2-dichloroethane. The reaction temperature is usually above the melting point and can be as high as the boiling point of the solvent. It is preferably in the range of from $0^\circ C$. to $50^\circ C$. Further methods and conditions for ether cleavage are described in Kocienski, "Protecting Groups", Thieme Verlag Stuttgart 1994. The alkylation of the phenol compound IA ($X-R^5=OH$) is carried out analogously to methods known from the literature (see, for example, *Organikum*, VEB Berlin 1988, Chapter D2, *Org. Synth. Coll. Vol. III* 1955, 140 and *Org. Reactions*, 2, 1944, 26).

[0187] II The compounds IA where $X-R^5$ is NO_2 , $NHOH$ or NH_2 can be prepared from the compounds of the formula IA where $R^6=X-R^5=H$ by nitration and subsequent reduction. If appropriate, an amino group R^1 will previously be protected in the known fashion.

[0188] Suitable nitrating reagents are, for example, nitric acid in various concentrations, also concentrated and fuming

nitric acid, mixtures of sulfuric acid and nitric acid, also salts of nitric acid, e.g. potassium nitrate, in a mixture with sulfuric acid, also acetyl nitrates and alkyl nitrates.

[0189] The reaction can either be carried out without a solvent in an excess of the nitrating reagent or in an inert solvent or diluent, suitable substances being, for example, water, mineral acids, organic acids, halohydrocarbons such as methylene chloride, anhydrides such as acetic anhydride, and mixtures of these.

[0190] The starting compound IA $\{R^6=XR^5=H\}$ and nitrating reagent are expediently employed in approximately equimolar amounts; as regards the conversion of the starting compound, it may be advantageous to use the nitrating reagent in an excess up to approximately 10 times the molar amount based on IA. When carrying out the reaction without solvent in the nitrating reagent, the latter is present in an even larger excess.

[0191] The reaction temperature is normally -100°C . to 200°C ., preferably -30°C . to 50°C .

[0192] The compounds IA where $R^6=H$ and $XR^5=NO_2$ can then be reduced to give compounds IA where $X-R^5=NH_2$ or $-NHOH$:



[0193] As a rule, the reduction will be carried out by reacting the nitro compound with a metal such as iron, zinc or tin under acidic reaction conditions or else with a complex hydride such as lithium aluminum hydride and sodium borohydride, the reduction being carried out in the solid state or in a solvent or diluent. Depending on the reducing agent used, suitable diluents are, for example, water, alcohols such as methanol, ethanol and isopropanol or ethers such as diethyl ether, methyl tert-butyl ether, dioxane, tetrahydrofuran and ethylene glycol dimethyl ether.

[0194] When carrying out the reduction with a metal, the process is preferably carried out in the absence of a solvent in an inorganic acid, in particular in concentrated or dilute hydrochloric acid, or in a liquid organic acid such as acetic acid or propionic acid. However, the acid can also be diluted with an inert solvent, for example one of those mentioned above. The reduction with complex hydrides is preferably carried out in a solvent, for example an ether or an alcohol.

[0195] The nitro compound IA $\{X-R^5=NO_2\}$ and the reducing agent are frequently employed in approximately equimolar amounts; to optimize the course of the reaction, it may be advantageous to use one of the two components in an excess of up to approximately 10 times the molar amount.

[0196] The amount of acid is not critical. In order to reduce the starting compound as completely as possible, it is expedient to employ at least an equivalent amount of acid. Frequently, the acid is employed in excess, based on the nitro compound IA $\{X-R^5=NO_2\}$.

[0197] The reaction temperature is generally in the range of from -30°C . to 200°C ., preferably in the range of from 0°C . to 80°C .

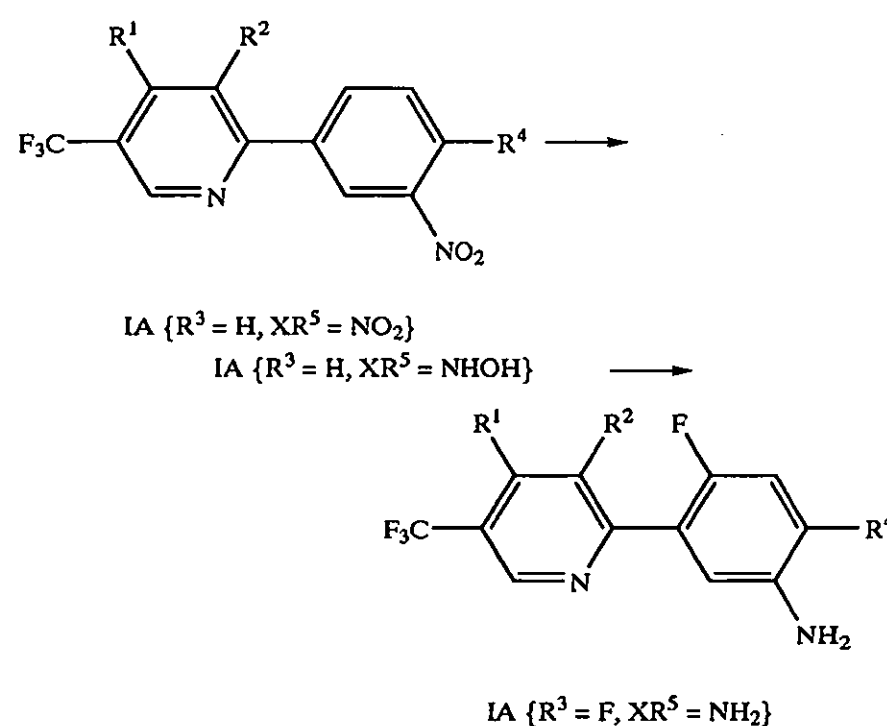
[0198] For work-up, the reaction mixture is, as a rule, diluted with water and the product is isolated by filtration,

crystallization or extraction with a solvent which is largely immiscible with water, for example with ethyl acetate, diethyl ether or methylene chloride. If desired, the product can subsequently be purified as usual.

[0199] The nitro group of the compounds IA $\{X-R^5=NO_2\}$ can also be hydrogenated catalytically using hydrogen. Catalysts which are suitable for this purpose are, for example, Raney nickel, palladium on charcoal, palladium oxide, platinum and platinum oxide, an amount of from 0.05 to 10.0 mol % of catalyst, based on the compound to be reduced, generally being sufficient. The process is either carried out in the absence of a solvent or in an inert solvent or diluent, for example in acetic acid, a mixture of acetic acid and water, ethyl acetate, ethanol or in toluene. After the catalyst has been removed, the reaction solution can be worked up as customary to give the product. The hydrogenation can be effected under normal hydrogen pressure or under elevated hydrogen pressure.

[0200] The resulting amino compounds, in turn, can be reacted with known electrophiles, for example with alkyl-sulfonyl halides or with the corresponding anhydrides to give the sulfonamides, or with alkyl halides to give the secondary or tertiary anilines.

[0201] Compounds IA in which R^3 is hydrogen and $X-R^5$ is NHOH can be converted into the corresponding 2-(2'-fluoro-5'-aminophenyl)pyridines ($R^3=F$, $X-R^5=NH_2$) by means of Bamberger rearrangement with HF as fluorine source. This reaction can be carried out analogously to the method described in WO 97/34872 (see following scheme).



[0202] To this end, a nitro compound IA $\{R^3=H, XR^5=NO_2\}$ is first hydrogenated on a platinum catalyst or a sulfur- or selenium-doped palladium catalyst in the presence of a morpholine compound, and the resulting hydroxylamine IA $\{R^3=H, XR^5=NHOH\}$ is then reacted with hydrogen fluoride, yielding the fluoroamino compound $\{R^3=F, XR^5=NH_2\}$. Owing to further details on the reaction conditions, reference is made herewith to the contents of WO 97/34872.

[0203] III Further compounds I can be prepared from the 2-(5'-aminophenyl)pyridines I ($X-R^5=NH_2$) by means of their diazonium salts:

- [0204] $X-R^5$ =cyano or halogen {for example by Sandmeyer reaction: cf., for example, Houben-Weyl, Methoden der Organischen Chemie [Methods in organic chemistry], Georg Thieme Verlag Stuttgart, Vol. 5/4, 4th Edition 1960, p. 438 et seq.},
- [0205] $X-R^5$ =hydroxyl {for example by boiling down with phenol: cf., for example, Org. Synth. Coll. Vol. 3 (1955), p. 130},
- [0206] $X-R^5$ =mercapto or C_1 - C_6 -alkylthio {cf., in this context, for example Houben-Weyl, Methoden der Organischen Chemie, Georg Thieme Verlag Stuttgart, Vol. E11 1984, pp. 43 and 176},
- [0207] $X-R^5$ =halosulfonyl {cf. in this context, for example, Houben-Weyl, Methoden der Organischen Chemie, Georg Thieme Verlag Stuttgart, Vol. E11 1984, p. 1069 et seq.},
- [0208] $X-R^5$ =for example $-CH_2-CH(halogen)-CO-O-Y-R^8$, $-CH=C(halogen)-CO-O-Y-R^7$, $-CH_2-CH(halogen)-PO-(O-Y-R^7)_2$, $-CH=C(halogen)-CO-(O-Y-R^7)_2$ {these are generally products of a Meerwein arylation; cf. in this context, for example, C. S. Rondestedt, Org. React. 11, 189 (1960) and H. P. Doyle et al., J. Org. Chem. 42, 2431 (1977)}.
- [0209] The respective diazonium salt of IA $\{X-R^5=N_2^+\}$ is prepared, as a rule, in a manner known per se by reacting IA $\{X-R^7=NH_2\}$ with a nitrite such as sodium nitrite or potassium nitrite in an aqueous acid solution, for example in hydrochloric acid, hydrobromic acid or sulfuric acid.
- [0210] To prepare the diazonium salt IA $\{X-R^5=N_2^+\}$, the amino compound IA $\{X-R^5=NH_2\}$ can be reacted with a nitrous ester such as tert-butyl nitrite and isopentyl nitrite under anhydrous conditions, for example in hydrogen chloride-containing glacial acetic acid, in absolute alcohol, in dioxane or tetrahydrofuran, in acetonitrile or in acetone.
- [0211] The conversion of the resulting diazonium salt into the corresponding compound IA where $X-R^5$ =cyano, chlorine, bromine or iodine is especially preferably carried out by treatment with a solution or suspension of a copper(I) salt such as copper(I) cyanide, copper(I) chloride, copper(I) bromide and copper(I) iodide, or with an alkali metal salt solution.
- [0212] The conversion of the resulting diazonium salt into the corresponding hydroxy compound IA $\{X-R^5=hydroxyl\}$ is expediently carried out by treating the diazonium salt IA with an aqueous acid, preferably sulfuric acid. The addition of a copper(II) salt such as copper(II) sulfate can have an advantageous effect on the course of the reaction. In general, this reaction is carried out at from 0° C. to 100° C., preferably at the boiling point of the reaction mixture.
- [0213] Compounds IA where $X-R^5$ =mercapto, C_1 - C_6 -alkylthio or halosulfonyl are obtained, for example, by reacting the corresponding diazonium salt of IA with hydrogen sulfide, an alkali metal sulfide, a dialkyl disulfide such as dimethyl disulfide, or with sulfur dioxide.
- [0214] The Meerwein arylation is usually the reaction of the diazonium salts with alkenes or alkynes. The alkene or alkyne is preferably employed in an excess up to approximately 3000 mol % based on the amount of the diazonium salt. Thus, for example, the reaction of the diazonium salt IA $\{X-R^5=N_2^+\}$ with acrylic esters of the formula $H_2C=CH-COO-Y-R^7$, preferably in the presence of copper salts such as Cu(I) halide or Cu(II) halide, for example Cu(I)Cl or Cu(II)Cl₂, yields compounds I where $X-R^5=H_2C-CH(Hal)-COO-Y-R^7$.
- [0215] The above-described reactions of the diazonium salt IA $\{X-R^5=N_2^+\}$ can be carried out, for example, in water, in aqueous hydrochloric acid or hydrobromic acid, in a ketone such as acetone, diethyl ketone and methyl ethyl ketone, in a nitrile such as acetonitrile, in an ether such as dioxane and tetrahydrofuran, or in an alcohol such as methanol and ethanol.
- [0216] Unless otherwise stated for the individual reactions, the reaction temperatures are normally from -30° C. to 50° C.
- [0217] All reactants are preferably employed in approximately stoichiometric amounts, with an excess of one or the other component of up to approximately 3000 mol % also being advantageous.
- [0218] The mercapto compounds IA $\{X-R^5=SH\}$ can also be obtained by reducing the compounds IA where $X-R^7$ =halosulfonyl which are described hereinbelow. Examples of reducing agents which can be used are transition metals such as iron, zinc and tin (cf., in this context, for example "The Chemistry of the Thiol Group", John Wiley, 1974, p. 216).
- [0219] IV Halosulfonation of 4-aryl-1-difluoromethoxyimidazoles IA, where XR^5 is hydrogen:
- $$IA \{XR^5 = H\} \longrightarrow IA \{XR^5 = -SO_2-halogen\}$$
- [0220] The halosulfonation can be carried out without solvent in an excess of sulfonating reagent or in an inert solvent/diluent, for example in a halogenated hydrocarbon, an ether, an alkyl nitrile or a mineral acid.
- [0221] Chlorosulfonic acid constitutes both the preferred reagent and a suitable solvent.
- [0222] The sulfonating reagent is normally employed in slightly substoichiometric amounts (of up to approximately 95 mol %) or in an excess of 1 to 5 times the molar amount based on the starting compound IA (where $X-R^5=H$). If the process is carried out without inert solvent, an even larger excess may also be expedient.
- [0223] The reaction temperature is normally between 0° C. and the boiling point of the reaction mixture.
- [0224] For work-up, the reaction mixture is treated with, for example, water, whereupon the product can be isolated as usual. The halosulfonated compounds IA $\{X-R^5=SO_2C_1\}$, in turn, are valuable starting materials for compounds IA where $X-R^5=SH$, $S-Y-R^7$, SO_2OYR^7 and $SO_2-N(Y-R^7)(Z-R^8)$.
- [0225] The compounds I where $X-R^5=CO-Y-R^7$ are advantageously prepared from 2-(5'-alkoxycarbonylphenyl)pyridines I $\{X-R^5=CO_2Rx$ where $R^x=C_1$ - C_4 -alkyl}.

The latter can be obtained in a particularly efficient manner by the above-described coupling of pyridines II with boronic acids IIIa.

[0226] To this end, the following choice of procedures exists:

[0227] Hydrolyzing the ester group CO_2R_x to give the free acid, converting the acid into its mixed anhydride with formic acid or carbonic acid and reducing the anhydride with borohydrides such as NaBH_4 or reducing the free acid directly with borane adducts such as the BH_3 /dimethyl sulfide complex or the BH_3 /THF complex to give the alcohol IA $\{\text{X}-\text{R}^5=\text{CH}_2\text{OH}\}$ and oxidizing the alcohol I to give the aldehyde IA $\{\text{X}-\text{R}^5=\text{CHO}\}$.

[0228] Preparation of the acid chloride IA $\{\text{X}-\text{R}^5=\text{COCl}\}$ via free acid and reduction with complex hydrides at low temperature to give the aldehyde directly.

[0229] The skilled worker is sufficiently familiar with the methods required for this purpose, for example Larock "Comprehensive Organic Transformations" VCH 1989 Weinheim or Fuhrhop, Penzlin, "Organic Synthesis" VCH Verlag Weinheim 1986.

[0230] The 2-(3'-formylphenyl)pyridines IA $\{\text{X}-\text{R}^5=\text{CHO}\}$ obtained in this manner can then be reacted further analogously to the processes described in EP-A 240569 and DE-A 3904082, for example in a Wittig reaction. Thus, for example pyridylcinnamic acids/pyridylcinnamic esters IA $\{\text{X}-\text{R}^5=\text{CH}=\text{CH}-\text{COO}-\text{Y}-\text{R}^7$ or $\text{CH}=\text{C}(\text{R}_z)-\text{COO}-\text{Y}-\text{R}^7$ where $\text{R}^z=\text{halogen}$ or C_{1-4} -alkyl} can be prepared. The phosphonium salts, phosphonates or phosphorus ylides required as reactants for this purpose are known or can be synthesized in a manner known per se {cf., in this context, for example Houben-Weyl, Methoden der Organischen Chemie, Vol. E1, pp. 636 et seq. and Vol. E2, pp. 345 et seq., Georg Thieme Verlag Stuttgart 1982; Chem. Ber. 95, 1962, 3993}.

[0231] The 2-(3'-formylphenyl)pyridines IA can also be converted into compounds IA where $\text{X}-\text{R}^5=\text{CO}-\text{Y}-\text{R}^7$ in a manner known per se, for example by reacting them with a suitable organometallic compound $\text{Me}-\text{Y}-\text{R}^7$ where Me is a base metal, preferably lithium or magnesium, and subsequently oxidizing the resulting alcohols (cf., for example, J. March, Advanced

[0232] Organic Chemistry, 3rd ed., John Wiley, New York 1985, pp. 816 et seq. and 1057 et seq.).

[0233] The compounds IA where $\text{X}-\text{R}^5=\text{CO}-\text{Y}-\text{R}^7$, in turn, can be reacted further in a Wittig reaction in the manner described above for the aldehydes.

[0234] Further possibilities of preparing other 2-aryl-5-trifluoromethylpyridines IA from compounds IA where $\text{X}-\text{R}^5=\text{formyl}$ include aldol condensation, which is known per se, and Knoevenagel or Perkin condensation reactions. Suitable conditions for these processes can be found, for example, in Nielson, Org. React. 16, 1968, 1 et seq. {aldol condensation}; Org. React. 15, 1967, 204 et seq. {Knoevenagel condensation} and Johnson, Org. React. 1, 1942, 210 et seq. {Perkin condensation}.

[0235] The compounds IA where $\text{X}-\text{R}^5=\text{CO}-\text{Y}-\text{R}^7$ can also be converted into their corresponding oximes

$\text{X}-\text{R}^5=\text{C}(\text{YR}^7)(=\text{NOR}^9)$ in a manner known per se {cf. in this context, for example, Houben-Weyl, Methoden der Organischen Chemie, Georg Thieme Verlag Stuttgart, Vol. 10/4, 4th Edition 1968, p. 55 et seq. and p. 73 et seq.}.

[0236] VI The compounds of the formula IB where XR^5 and R^4 form a chain of the formula $-\text{O}-(\text{CR}^{15}, \text{R}^{16})_k\text{CON}(\text{R}^{17})-$ or $-\text{S}-(\text{CR}^{15}, \text{R}^{16})_k\text{CON}(\text{R}^{17})-$ can be prepared by coupling, as described above, a halopyridine II with a corresponding boronic acid III (compound III where $\text{Met}=\text{B}(\text{OR}^1)_2$, where R^4 , together with $\text{X}-\text{R}^5$, is $\text{O}-\text{C}(\text{R}^{15}, \text{R}^{16})_k-\text{CO}-\text{N}(\text{R}^{17})-$ or $-\text{S}-(\text{CR}^{15}, \text{R}^{16})_k\text{CON}(\text{R}^{17})-$). A further preparation method starts from the aminophenols IA $\{\text{R}^4=\text{OH}$ and $\text{X}-\text{R}^5=\text{NH}_2$ or $\text{R}^4=\text{NH}_2$ and $\text{X}-\text{R}^5=\text{OH}\}$ or aminothiophenols IA $\{\text{R}^4=\text{SH}$ and $\text{X}-\text{R}^5=\text{NH}_2$ or $\text{R}^4=\text{NH}_2$ and $\text{X}-\text{R}^5=\text{SH}\}$, which are cyclized by known methods (see, for example, U.S. Pat. No. 4,798,620, WO 95/02590, WO 98/07720) using α -halocarboxylic acids or their esters or derivatives of similar reactivity to give the compounds IB (for example in analogy with synthesis scheme 6 of WO 98/07720). The amino(thio)phenols IA required can be prepared by the methods described under II.

[0237] Table 6 shows examples of preferred aminophenols of the formula IAr where R^1 , R^2 and R^3 have the above-mentioned meanings, in particular meanings stated in Table 6:

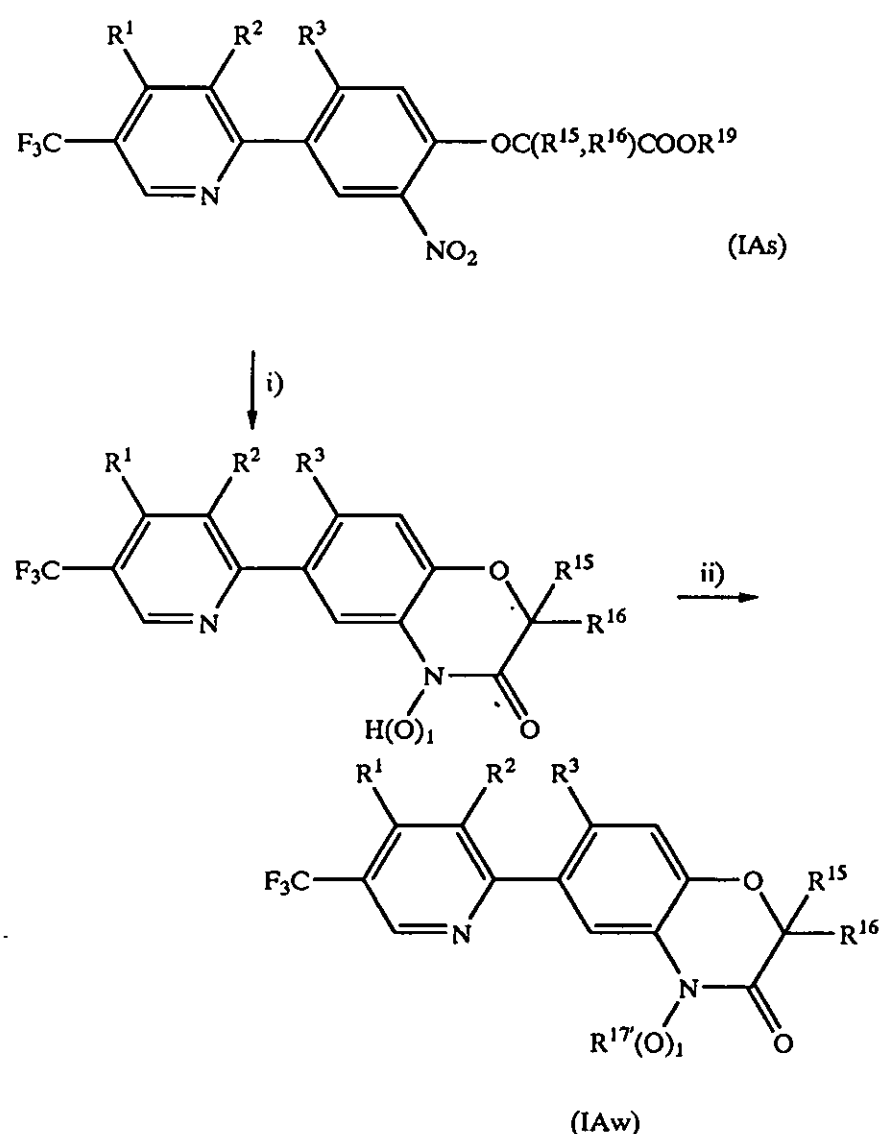
TABLE 6

	R^1	R^2	R^3
IAr.1	CH_3	F	F
IAr.2	CH_3	F	Cl
IAr.3	CH_3	Cl	F
IAr.4	CH_3	Cl	Cl

[0238] The compounds IB which can be obtained in this manner, in which R^{17} is hydrogen, can be reacted with an alkylating agent $\text{R}^{17'}-\text{L}$ by methods known per se as are described, for example, in WO 95/02590, WO 98/07700 and the prior art described therein, in Sicker et al. Tetrahedron 52, 1996, 10389 or in DE-A 19508590. L is a nucleophilically displaceable leaving group such as halogen, arylsulfonate, triflate or sulfate, or an isocyanate group. $\text{R}^{17'}$ is, for example, C_1 - C_6 -alkyl, C_1 - C_6 -haloalkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -haloalkenyl, C_2 - C_6 -alkynyl, C_1 - C_4 -alkylsulfonyl, C_1 - C_4 -haloalkylsulfonyl, C_1 - C_4 -alkylcarbonyl, C_1 - C_4 -haloalkylcarbonyl, C_1 - C_4 -alkoxycarbonyl, C_1 - C_4 -alkoxy- C_1 - C_4 -alkyl, C_1 - C_4 -alkoxycarbonyl- C_1 - C_4 -alkyl, mono- and di(C_1 - C_4 -alkyl)aminocarbonyl- C_1 - C_4 -alkyl, phenyl- C_1 - C_4 -alkyl, C_3 - C_8 -cycloalkyl, C_3 - C_8 -cycloalkyl- C_1 - C_4 -alkyl, 3-, 4-, 5-, 6- or 7-membered heterocyclyl- C_1 - C_4 -alkyl. If L is a nucleophilically displaceable leaving group, the reaction with the alkylating agent $\text{R}^{17'}-\text{L}$ is, as a rule, carried out in the presence of a base.

[0239] The compounds I in which the radicals $X-R^5$ and R^4 form a chain of the formula $-O-C(R^{15}, R^{16})-CO-NR^{17}-$ or $-S-C(R^{15}, R^{16})-CO-NR^{17}-$ can also be obtained by reductive cyclization of nitrophenoxycarboxylic acid derivatives of the formula IAs or of corresponding nitrothiophenoxycarboxylic acid derivatives. In the case of the nitrophenoxycarboxylic acid derivatives IAs, compounds IB are first formed in which $X-R^5$ and R^4 form a chain of the formula $-O-C(R^{15}, R^{16})-CO-N(O)_lH-$ where $l=0$ or 1 . These can subsequently be functionalized. An example of such a synthesis sequences is shown in Scheme 3:

Scheme 3:



[0240] In the formula IAw in Scheme 3, $R^1, R^2, R^3, R^{15}, R^{16}$ and R^{17} have the abovementioned meanings. R^{19} is alkyl having, preferably, 1 to 4 C atoms, in particular methyl or ethyl. The variable l is 0 or 1. In Scheme 3, step i) is the reductive cyclization and step ii) is the above-described reaction with the electrophile $L-R^{17}$.

[0241] The nitro(thio)phenoxyalkanecarboxylic acid derivatives IAs can be prepared and cyclized reductively to give the compounds IB for example in analogy to the prior art stated in Böger, "Peroxidizing Herbicides", Springer Verlag, Berlin 1999, p. 32, or in analogy with the methods described by Sicker et al., Synthesis, 1989, p. 211; Atkinson et al. J. Org. Chem. 56, (1991) p. 1788; Coutts et al. J. Chem. Soc., 1963, S. 4610, U.S. Pat. No. 3,862,180, WO 95/02590 and the literature cited therein, DE-A 19508590, Sicker et al. J. Het. Chem. 31, 1994, p.801, WO 98/07720 and international application PCT/EP 00/08639. Table 7 shows

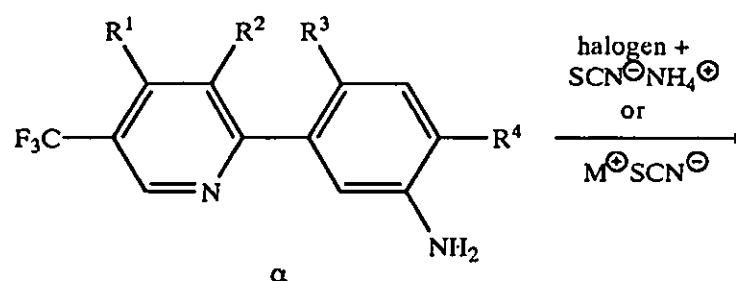
examples of preferred nitrophenoxycarboxylic acid derivatives of the formula IAs where R^{15} and R^{16} are hydrogen and R^1, R^2, R^3 and R^{19} have the abovementioned meanings, in particular the meanings mentioned in Table 7, and which are of particular importance as intermediates for the preparation of compound B:

TABLE 7

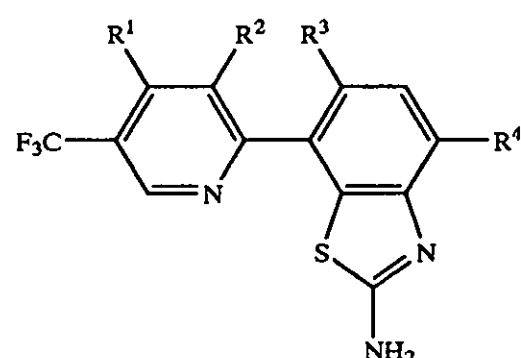
	R^1	R^2	R^3	R^{19}
IAs.1	CH ₃	F	F	CH ₃
IAs.2	CH ₃	F	F	CH ₂ CH ₃
IAs.3	CH ₃	F	Cl	CH ₃
IAs.4	CH ₃	F	Cl	CH ₂ CH ₃
IAs.5	CH ₃	Cl	F	CH ₃
IAs.6	CH ₃	Cl	F	CH ₂ CH ₃
IAs.7	CH ₃	Cl	Cl	CH ₃
IAs.8	CH ₃	Cl	Cl	CH ₂ CH ₃
IAs.9	NH ₂	F	F	CH ₃
IAs.10	NH ₂	F	F	CH ₂ CH ₃
IAs.11	NH ₂	F	Cl	CH ₃
IAs.12	NH ₂	F	Cl	CH ₂ CH ₃
IAs.13	NH ₂	Cl	F	CH ₃
IAs.14	NH ₂	Cl	F	CH ₂ CH ₃
IAs.15	NH ₂	Cl	Cl	CH ₃
IAs.16	NH ₂	Cl	Cl	CH ₂ CH ₃

[0242] VII 4- or 8-(5'-Trifluoromethylpyridyl)benzazoles of the formula IC (compounds IC where $X-R^5$ and R^6 are a chain $-N=C(R^{18})-O-$ or $-N=C(R^{18})-S-$) can be obtained in various ways, in particular by one of the following processes (see also WO 98/27090 and WO 99/55702, whose technical teaching can be applied to the preparation of the compounds IC):

[0243] A Reaction of a (3-aminophenyl)-5-trifluormethylpyridine of the formula IA ($X-R^5=NH_2$) with halogen and ammonium thiocyanate or with an alkali metal thiocyanate or alkaline earth metal thiocyanate in accordance with the following scheme:

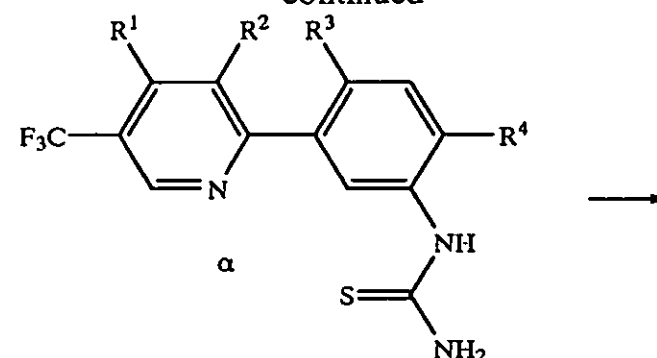


-continued



IC {XR⁵ + R⁶
—N=C(NH₂)—S—
bonded to α
via the sulfur}

-continued



IA {X—R⁵ =
NH—C(S)—NH₂}

IC {XR⁵ + R⁶

—N=C(NH₂)—S—
bonded to α via the sulfur}

[0244] M[⊕]=alkali metal ion or ½ alkaline earth metal ion

[0245] Preferred halogen is chlorine or bromine; among the alkali metal thiocyanates and alkaline earth metal thiocyanates, sodium thiocyanate is preferred.

[0246] As a rule, the process is carried out in an inert solvent/diluent, for example in a hydrocarbon such as toluene and hexane, in a halogenated hydrocarbon such as dichloromethane, in an ether such as tetrahydrofuran, in an alcohol such as ethanol, in a carboxylic acid such as acetic acid, or in an aprotic solvent such as dimethylformamide, acetonitrile and dimethyl sulfoxide.

[0247] The reaction temperature is usually above the melting point and can be up to the boiling point of the solvent. It is preferably in the range of from 0 to 150° C.

[0248] To achieve as high as possible a yield of product of interest, halogen and ammonium thiocyanate, or alkali metal thiocyanate/alkaline earth metal thiocyanate, are employed in equimolar amounts or in an excess of up to approximately 5 times the molar amount based on the amount of (3-aminophenyl)-5-trifluoromethylpyridine IA {X—R⁵=NH₂}.

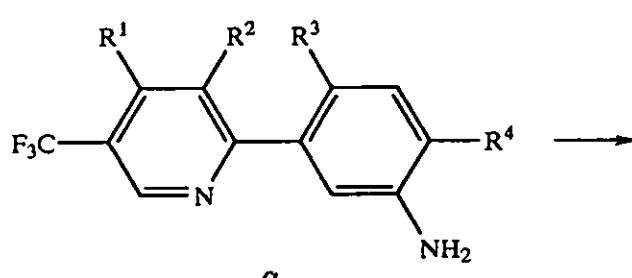
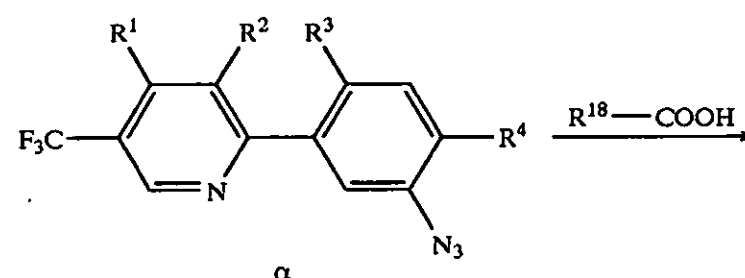
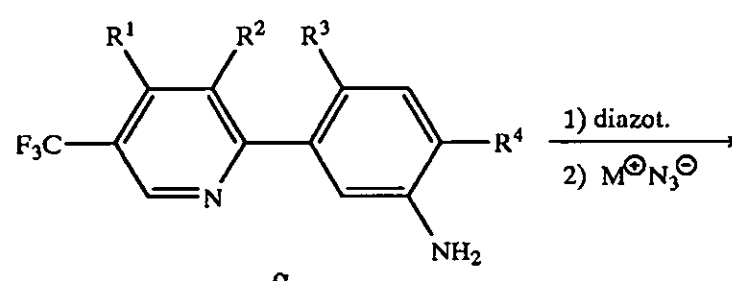
[0249] A variant of the process consists in first reacting the (3-aminophenyl)-5-trifluoromethylpyridine IA {X—R⁵=NH₂} with ammonium thiocyanate or an alkali metal thiocyanate or alkaline earth metal thiocyanate to give a thiourea IA {X—R⁵=NH—C(S)—NH₂}

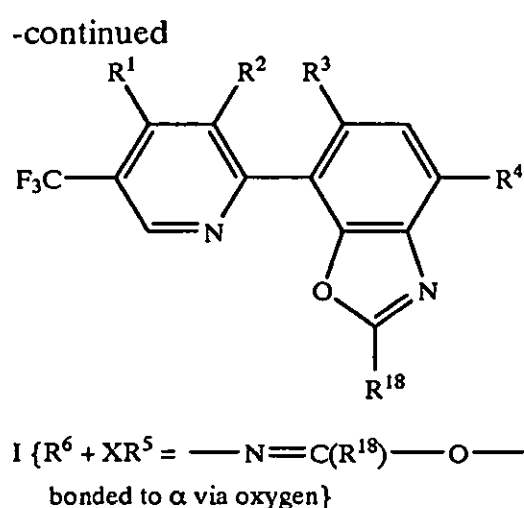
[0250] and subsequently to convert the thiourea IA {X—R⁵=NH—C(S)—NH₂} into 8-(5'-trifluoromethylpyridyl)benzothiazole IA {X—R⁵+R⁴=—N=C(NH₂)—S—} by treatment with halogen. The amino group in the 2-position on the thiazole radical can be functionalized in a known manner, for example via its diazonium compound (R¹⁸=N₂⁺).

[0251] The compounds of the formula IC in which R⁶ and X—R⁵ are a chain —S—C(R¹⁸)=N— with the nitrogen being bonded via the α carbon atom can be prepared analogously.

[0252] B Diazotization of a (3-aminophenyl)-5-trifluoromethylpyridine IA {R⁶=H, X—R⁵=NH₂}, conversion of the respective diazonium salt into a (3-azidophenyl)-5-trifluoromethylpyridine IA {R⁶=H, X—R⁵=N₃} and its reaction with a carboxylic acid R¹⁸COOH or a derivative thereof in accordance with scheme 4 hereinbelow, giving rise to a compound IC in which R⁶ and X—R⁵ are a chain —O—C(R¹⁸)=N— with the oxygen being bonded via the a carbon atom.

Scheme 4:





[0253] M[⊕] is an alkali metal ion or ½ alkaline earth metal ion.

[0254] What has been said above also applies to the diazotization process. The conversion into the aryl azide IA {R⁶=H, X—R⁵=N₃} is preferably carried out by reacting the diazonium compounds {R⁶=H, X—R⁵=N₂⁺} with an alkali metal azide or alkaline earth metal azide such as sodium azide or by reaction with trimethylsilyl azide.

[0255] The reaction of the azides IA {R⁶=H, X—R⁵=N₃} with a carboxylic acid as shown in Scheme 4 is either carried out in an inert solvent, for example an ether such as tetrahydrofuran and dioxane, an aprotic solvent such as dimethylformamide and acetonitrile, a hydrocarbon such as toluene and hexane, a halogenated hydrocarbon such as dichloromethane, or without a solvent in an excess of the carboxylic acid R¹⁸—COOH. In the latter case, the addition of a mineral acid such as phosphoric acid may be helpful.

[0256] The reaction is preferably carried out at elevated temperature, for example at the boiling point of the reaction mixture.

[0257] VIII If desired, the 2-aryl-5-trifluoromethylpyridines of the formula I where m=0 can be converted by oxidation on the nitrogen to give the pyridine-N-oxides of the formula I where m=1, which also have a herbicidal and desiccant/defoliant action.

[0258] The oxidation of the pyridines to give the N-oxides can be carried out in analogy to known methods, for example by the methods described by A. Albini, S. Pietra in "Heterocyclic N-Oxides" CRC-Press Inc, Boca Raton USA 1991; Mosher et al. Org. Synth. Coll Vol. IV, 1963 page 828; Taylor et al., Org. Synth. Coll Vol. IV, 1963 page 704; Bell et al., Org. Synth. 69, 226, 1990; and JP 20000191644.

[0259] Oxidants which are customary for converting the pyridines I into their N-oxides are, for example, peracetic acid, trifluoroperacetic acid, perbenzoic acid, meta-chloropero benzoic acid, magnesium monopero-phthalate, 1,2-dicarboxylic acid derivatives in general, sodium perborate, oxone (contains peroxodisulfate), pertungstic acid, hydrogen peroxide, methyltrioxorhenium. These reagents can be used alone or as a mixture.

[0260] The oxidation is preferably carried out in a solvent or diluent. Suitable solvents are water, sulfuric acid, carboxylic acids such as, for example, acetic acid, and halogenated solvents such as, for example, dichloromethane and chloroform, or else mixtures of the above.

[0261] The reaction is normally carried out in a temperature range of from 0° C. to the boiling point of the solvent, preferably up to 150° C.

[0262] The oxidants are normally employed in at least equimolar amounts, frequently in a large excess of, for example, up to 5 equivalents based on the pyridine I to be oxidized.

[0263] In the case of the 4-aminopyridines I {R¹=NH₂} it may be necessary to protect the amino nitrogen and then to eliminate the protecting group when the reaction has ended, depending on the oxidant. Protecting groups which are suitable for this purpose and the conditions suitable for their introduction and elimination are found in Kocienski, "Protecting Groups", Thieme Verlag Stuttgart 1994. Examples of suitable protecting groups which may be mentioned are benzyloxycarbonyl and fluorenylmethoxycarbonyl.

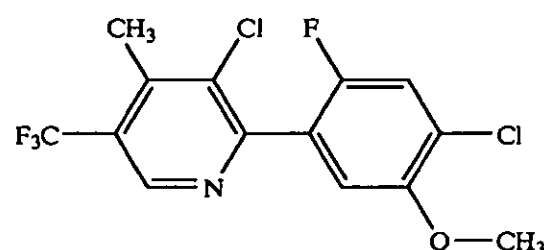
[0264] The examples which follow are intended to illustrate the invention in greater detail without imposing any limitation.

PREPARATION EXAMPLES

Example 1

Preparation of 2-(2-fluoro-4-chloro-5-methoxyphenyl-1-yl)-3-chloro-4-methyl-5-trifluoromethylpyridine (IAa.3)

[0265]



[0266] 1.1 2-Benzyloxy-3-chloro-5-trifluoromethylpyridine

[0267] 21.6 g (0.20 mol) of benzyl alcohol were added to a solution of 43.2 g (0.20 mol) of 2,3-dichloro-5-trifluoromethylpyridine in 250 ml of DMF, followed by the portionwise addition of 22.4 g (0.20 mol) of potassium tert-butoxide. The reaction mixture was stirred overnight, introduced into 11 of saturated ammonium chloride solution and then extracted three times using in each case 300 ml of methyl tert-butyl ether. After the combined organic phases had been washed with water and dried over sodium sulfate, the solvent was removed in vacuo. This gave 54.1 g of 2-benzyloxy-3-chloro-5-trifluoromethylpyridine, which was reacted in the next step without further purification.

[0268] ¹H NMR (CDCl₃): δ (ppm)=8.3 (s, 1H), 7.8 (m, 1H), 7.5 to 7.3 (m, 5H), 5.5 (s, 2H).

[0269] 1.2 2-Benzyloxy-3-chloro-4-methyl-5-trifluoromethylpyridine

[0270] 57 ml of a butyllithium solution (1.3 M in hexane) were added dropwise at -70° C. to a solution of 20.0 g (0.07 mol) of 2-benzyloxy-3-chloro-5-trifluoromethylpyridine of

Example 1.1 in 100 ml of THF, and stirring was continued for 30 minutes at -70°C . This solution was subsequently added dropwise at -70°C . to a solution of 29.6 g (0.21 mol) of methyl iodide in 100 ml of THF, and stirring was continued for 90 minutes at -70°C .

[0271] After heating to -10°C ., 200 ml of a saturated ammonium chloride solution were added, the mixture was diluted with 200 ml of a saturated sodium chloride solution and extracted three times using in each case 200 ml of methyl tert-butyl ether. After drying of the combined organic phases, the mixture was concentrated, yielding 20.4 g of 2-benzyloxy-3-chloro-4-methyl-5-trifluoromethylpyridine of 90% purity.

[0272] ^1H NMR (CDCl_3): δ (ppm)=8.3 (s, 1H), 7.5 to 7.3 (m, 5H), 5.5 (s, 2H), 2.5 (s, 3H).

[0273] 1.3 2-Hydroxy-3-chloro-4-methyl-5-trifluoromethylpyridine

[0274] 15.5 g (0.14 mol) of trimethylsilyl chloride were added to 21.4 g (0.14 mol) of sodium iodide in 250 ml of acetonitrile, the mixture was stirred for 15 minutes, and a solution of 28.7 g (0.095 mol) of 2-benzyloxy-3-chloro-4-methyl-5-trifluoromethylpyridine of Example 1.2 in 50 ml of acetonitrile was subsequently added dropwise at room temperature. The mixture was then stirred for 1 hour at 50°C . After removal of the solvent in vacuo, ice-cold water was carefully added to the residue, and the mixture was extracted three times using in each case 200 ml of methyl tert-butyl ether. The combined organic phases were dried over sodium sulfate and the solvent was removed in vacuo. Chromatography of the residue on silica gel with cyclohexane/ethyl acetate (4/1, v/v) yielded 17.4 g of 2-hydroxy-3-chloro-4-methyl-5-trifluoromethylpyridine of m.p. 204 to 205°C .

[0275] ^1H NMR (CDCl_3): δ (ppm)=8.8 (s, 1H), 2/5 (s, 3H).

[0276] 1.4 2,3-Dichloro-4-methyl-5-trifluoromethylpyridine

[0277] 14.4 g (0.068 mol) of 2-hydroxy-3-chloro-4-methyl-5-trifluoromethylpyridine of Example 1.3 in 100 ml of phosphorus oxychloride were heated for 3 hours at 75°C . The reaction mixture was subsequently added dropwise to 1.5 l of water/300 ml of methylene chloride with stirring, the organic phase was then separated off, and the aqueous phase was extracted twice more with in each case 300 ml of methylene chloride. After the combined organic phases had been dried, these were concentrated in vacuo, and the crude product was distilled in vacuo (b.p. 78 to 80°C . at 16 mm). This gave 9.4 g of 2,3-dichloro-4-methyl-5-trifluoromethylpyridine.

[0278] ^1H NMR (CDCl_3): δ (ppm)=8.5 (s, 1H), 2.6 (s, 3H).

[0279] 1.5 2-(2-Fluoro-4-chloro-5-methoxyphenyl-1-yl)-3-chloro-4-methyl-5-trifluoromethylpyridine

[0280] 4.5 g (0.019 mol) of the dichloropyridine of Example 1.4, 4.0 g (0.019 mol) of 2-fluoro-4-chloro-5-methoxyphenylboronic acid, 1.1 g (0.001 mol) of tetrakis(triphenylphosphine) palladium and 12.0 g of sodium hydrogencarbonate in 150 ml of THF and 150 ml of water were refluxed for 20 hours with stirring. After cooling, the phases were separated, the aqueous phase was extracted twice using

in each case 100 ml of methyl tert-butyl ether, and the combined organic phases were dried over sodium sulfate and concentrated in vacuo. Chromatography of the residue on silica gel with cyclohexane/ethyl acetate (100:1, v/v) yielded 2.4 g of 2-(2-fluoro-4-chloro-5-methoxyphenyl-1-yl)-3-chloro-4-methyl-5-trifluoromethylpyridine.

[0281] ^1H NMR (CDCl_3): δ (ppm)=8.8 (s, 1H), 7.3 (d, 1H), 7.0 (d, 1H), 3.9 (s, 3H), 2.6 (s, 3H).

Example 2

2-(2-Fluoro-4-chloro-5-hydroxyphenyl)-3-chloro-4-methyl-5-trifluoromethylpyridine (compound IAa.2)

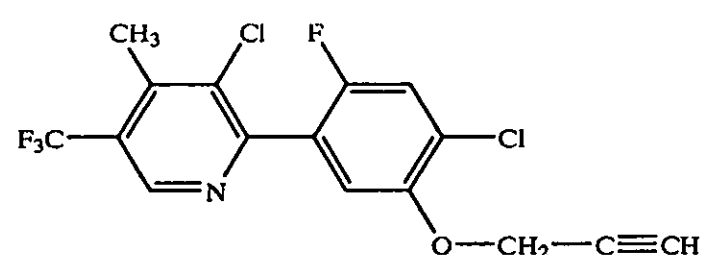
[0282] 27 ml (0.027 mol) of a boron tribromide solution (1 M in methylene chloride) were added dropwise at 0°C . to a solution of 2.4 g (0.007 mol) of the pyridine of Example 1.5 in 50 ml of dichloromethane. After the reaction mixture had been stirred for two hours at room temperature, ice-cold water was added, and the phases were subsequently separated. The aqueous phase was extracted twice using in each case 100 ml of methylene chloride. The combined organic phases were dried and concentrated in vacuo. This gave 2 g of 2-(2-fluoro-4-chloro-5-hydroxyphenyl)-3-chloro-4-methyl-5-trifluoromethylpyridine.

[0283] ^1H NMR (CDCl_3): δ (ppm)=8.8 (s, 1H), 7.2 (d, 1H), 7.0 (s, 1H), 2.5 (s, 3H).

Example 3

2-(2-Fluoro-4-chloro-5-propargyloxyphenyl)-3-chloro-4-methyl-5-trifluoromethylpyridine (Compound IAa.10)

[0284]



[0285] 0.37 g (2.6 mmol) of potassium carbonate and 0.23 g (19.4 mmol) of propargyl bromide were added in succession to a solution of 0.6 g (1.7 mmol) of the phenol of Example 2 in 10 ml of dimethylformamide (DMF). The mixture was stirred for 4 hours at room temperature. The reaction mixture was subsequently introduced into ice-cold water and the mixture was extracted three times with methyl tert-butyl ether. The combined organic phases were washed with water and dried over sodium sulfate. Chromatography on silica gel with cyclohexane/ethyl acetate (9/1, v/v) gave 0.62 g of the title compound of m.p. 95 to 98°C .

[0286] ^1H NMR (CDCl_3): δ (ppm)=8.8 (s, 1H), 7.3 (d, 1H), 7.1 (d, 1H), 4.8 (d, 2H), 2.6 (s, 3H), 2.5 (t, 1H).

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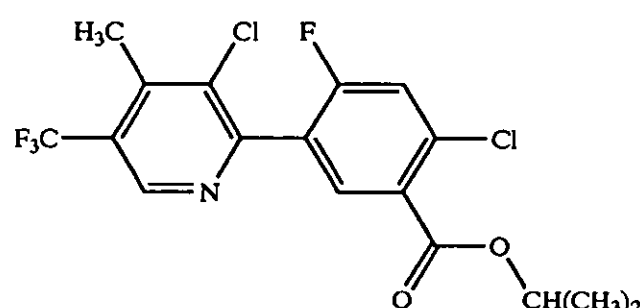
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Example 4

2-(2-Fluoro-4-chloro-5-isopropoxycarbonylphenyl-1-yl)-3-chloro-4-methyl-5-trifluoromethylpyridine (IAa.131)

[0287]



[0288] 4.1 Isopropyl 2-chloro-4-fluoro-5-iodobenzoate

[0289] 20.0 g (0.086 mol) of isopropyl 2-chloro-4-fluoro-5-aminobenzoate (CAS-No. 86819-51-4) were introduced into 100 ml of concentrated hydrochloric acid at 0° C., and a solution of 6.6 g (0.095 mol) of sodium nitrite in 20 ml of water was added dropwise at 0 to 5° C. Stirring was continued for 1 hour at 0° C., a solution of 2.6 g (0.043 mol) of urea in 20 ml of water was then added dropwise and the mixture was stirred for a further 15 minutes. The reaction mixture was subsequently added dropwise to a solution of 17.2 g (0.1 mol) of potassium iodide in 30 ml of water. The mixture was first allowed to come to room temperature and was subsequently warmed for 30 minutes at 60 to 70° C. After cooling, the mixture was extracted three times with in each case 200 ml of methylene chloride, and the combined organic phases were dried over sodium sulfate and concentrated. This gave 27.6 g of isopropyl 2-chloro-4-fluoro-5-iodobenzoate of m.p. 38 to 43° C.

[0290] ¹H NMR (CDCl₃): δ (ppm)=8.2 (d, 1H), 7.2 (d, 1H), 5.2 (sept, 1H), 1.4 (d, 6H).

[0291] 4.2 2-Fluoro-4-chloro-5-isopropoxycarbonylphenylboronic Acid

[0292] 7.7 ml (0.015 mol) of an isopropylmagnesium chloride solution (2 M in ether) were added dropwise at -40° C. to a solution of 5.0 g (0.015 mol) of the iodide of Example 4.1 in 30 ml of methyl tert-butyl ether, and stirring was then continued for 1 hour at -40° C. A solution of 4.6 g (0.043 mol) of trimethyl borate in 10 ml of THF was subsequently added dropwise, stirring was continued for 1 hour at -40° C., and the mixture was allowed to come to room temperature. The mixture was treated with 50 ml of 10% strength hydrochloric acid and extracted three times with in each case 50 ml of methyl tert-butyl ether, and the combined organic phases were dried over sodium sulfate and subsequently concentrated. Recrystallization from n-hexane yielded 2.5 g of 2-fluoro-4-chloro-5-isopropoxycarbonylphenylboronic

acid of m.p. 176 to 180° C., which in some cases also contained some trimeric boron oxine.

[0293] ¹H NMR (d₆-DMSO): δ (ppm)=8.4 (br, 2H), 8.0 (d, 1H), 7.4 (d, 1H), 5.2 (sept, 1H), 1.4 (d, 6H).

[0294] 4.3 2-(2-Fluoro-4-chloro-5-isopropoxycarbonylphenyl)-3-chloro-4-methyl-5-trifluoromethylpyridine

[0295] 1.8 g (7.7 mmol) of the pyridine of Example 1.4 and 2 g (7.7 mmol) of the boronic acid of Example 4.2 were reacted analogously to the procedure described in Example 1.5, yielding 1.0 g of the title compound.

[0296] ¹H NMR (CDCl₃): δ (ppm)=8.8 (s, 1H), 8.0 (d, 1H), 7.3 (d, 1H), 5.3 (sept, 1H), 2.6 (s, 3H), 1.4 (d, 6H).

Example 5

2-(2-Fluoro-4-chloro-5-nitrophenyl)-3-chloro-4-methyl-5-trifluoromethylpyridine (Compound IAa.81)

[0297] 1.87 g (29.6 mmol) of 100% strength nitric acid were added dropwise at 0 to 5° C. to a solution of 8.0 g (24.7 mmol) of 2-(2-fluoro-4-chlorophenyl-1-yl)-3-chloro-4-methyl-5-trifluoromethylpyridine (prepared analogously to the procedure described in Example 1.5 starting from the pyridine of Example 1.4 and 2-fluoro-4-chlorophenylboronic acid) in 100 ml of concentrated sulfuric acid, and stirring was continued for 3 hours at this temperature. The reaction mixture was subsequently introduced into 500 ml of ice-cold water and the mixture was extracted three times with in each case 200 ml of ethyl acetate. After the combined organic phases had been dried over sodium sulfate and the solvent had been removed, the residue which remained was filtered through a short silica gel column (eluent cyclohexane/ethyl acetate=4/1, (v/v)). This gave 3.8 g of 2-(2-fluoro-4-chloro-5-nitrophenyl-1-yl)-3-chloro-4-methyl-5-trifluoromethylpyridine.

[0298] ¹H NMR (CDCl₃): δ (ppm)=8.8 (s, 1H), 8.2 (d, 1H), 7.4 (d, 1H), 2.6 (s, 3H).

Example 6

2-(2-Fluoro-4-chloro-5-nitrophenyl)-3-chloro-4-methyl-5-trifluoromethylpyridine (Compound IAa.83)

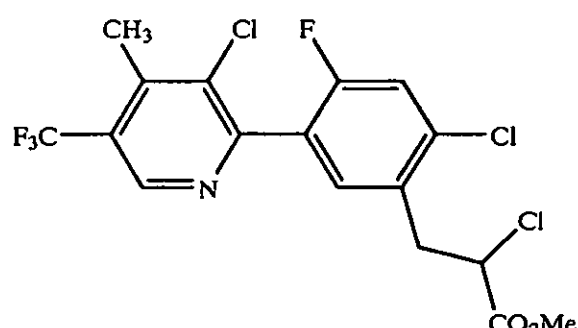
[0299] 2.3 g of iron powder were refluxed in 600 ml of 100% strength acetic acid and a solution of 3.8 g (10.3 mmol) of the product of Example 5 in 40 ml of methanol were added dropwise. The mixture was then warmed for 2 hours at 80° C., and the methanol was subsequently removed. Approximately 500 ml of ethyl acetate were added, and the mixture was introduced into ice-cold water. The ethyl acetate phase was removed and the aqueous phase was extracted twice more with in each case 200 ml of ethyl acetate. After the combined organic phases had been dried over sodium sulfate, the solvent was removed in vacuo. This gave 3.0 g of the amino compound which was reacted further without further purification.

[0300] ¹H NMR (CDCl₃): δ (ppm)=8.8 (s, 1H), 7.2 (d, 1H), 6.8 (d, 1H), 4.2 (br, 2H), 2.6 (s, 3H).

Example 7

2-(2-Fluoro-4-chloro-5-(2-chloro-2-carbomethoxyethyl)-phenyl)-3-chloro-4-methyl-5-trifluoromethylpyridine (IAa.199)

[0301]



[0302] A mixture of 0.91 g (8.9 mmol) of tert-butyl nitrite, 0.51 g (5.9 mmol) of methyl acrylate and 0.99 g (7.3 mmol) of CuCl in 50 ml of acetonitrile was treated with 2.0 g (5.9 mmol) of 2-(2-fluoro-4-chloro-5-aminophenyl-1-yl)-3-chloro-4-methyl-5-trifluoromethylpyridine, and the mixture was stirred for 10 hours at 0° C. After the solvent had been removed, the residue was chromatographed on silica gel with cyclonhexane/ethyl acetate (1/1, v/v), yielding 0.22 g of the title compound.

[0303] ¹H NMR (CDCl₃): δ (ppm)=8.8 (s, 1H), 7.4 (d, 1H), 7.2 (d, 1H), 4.6 (m, 1H), 3.8 (s, 3H), 3.5 (m, 1H), 3.3 (m, 1H), 2.6 (s, 3H).

Example 8

2-(2-Fluoro-4-chloro-5-hydroxycarbonylphenyl-1-yl)-3-chloro-4-methyl-5-trifluoromethylpyridine (IAa.124)

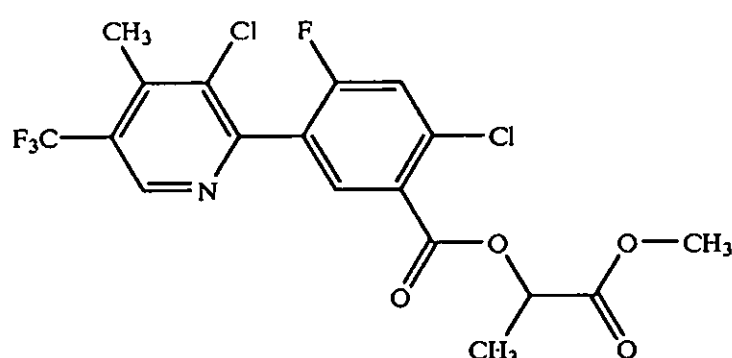
[0304] 0.6 g of 2-(2-fluoro-4-chloro-5-isopropoxycarbonylphenyl)-3-chloro-4-methyl-5-trifluoromethylpyridine of Example 4.3 was refluxed for 3 hours in 40 ml of glacial acetic acid together with concentrated hydrochloric acid. The mixture was subsequently evaporated to dryness in vacuo. This gave the title compound in quantitative yield.

[0305] ¹H NMR (CDCl₃): δ (ppm)=8.8 (s, 1H), 8.2 (d, 1H), 7.4 (d, 1H), 2.6 (s, 3H).

Example 9

2-[2-Fluoro-4-chloro-5-(2-methoxycarbonylpropionyl)-carbonylphenyl-1-yl]-3-chloro-4-methyl-5-trifluoromethylpyridine (compound IAa.143 as R enantiomer and as S enantiomer)

[0306]



[0307] 0.5 g (1.3 mmol) of the acid of Example 8 was treated with 5 ml of thionyl chloride and the mixture was subsequently refluxed for 3 hours. After cooling, excess

thionyl chloride was removed in vacuo, and the resulting acid chloride (IAa.125) was dissolved in 5 ml of methylene chloride.

[0308] This solution of the acid chloride (IAa.125) was added dropwise to a solution of 0.16 g of methyl R-lactate in 10 ml of methylene chloride and 0.16 g of triethylamine, and the mixture was stirred for 8 hours with addition of a catalytic amount of DMAP. Removal of the solvent in vacuo and subsequent chromatography of the residue on silica gel with cyclohexane/ethyl acetate (95:5, v/v) yielded 0.47 g of the title compound (R enantiomer).

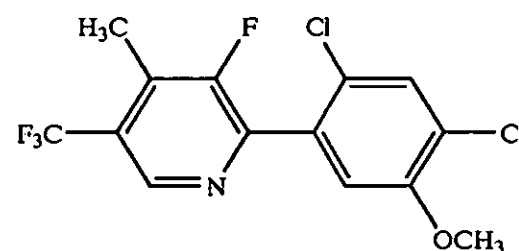
[0309] The experiment was repeated with the difference that the same amount of methyl S-lactate was employed instead of methyl R-lactate, yielding 0.42 g of the S enantiomer.

[0310] ¹H NMR (CDCl₃): δ (ppm)=8.8 (s, 1H), 8.1 (d, 1H), 7.4 (d, 1H), 5.4 (q, 1H), 3.8 (s, 3H), 2.6 (s, 3H), 1.6 (d, 3H).

Example 10

Preparation of 2-(2,4-dichloro-5-methoxyphenyl)-fluoro-4-methyl-5-trifluoromethylpyridine (IAf.3)

[0311]



[0312] 10.1 2-Benzyloxy-3-fluoro-5-trifluoromethylpyridine

[0313] The procedure as described in Example 1.1 was followed, and 13 g of 2-benzyloxy-3-fluoro-5-trifluoromethylpyridine were prepared starting from 9.9 g of 2,3-difluoro-5-trifluoromethylpyridine.

[0314] ¹H NMR (CDCl₃): δ (ppm)=8.3 (s, 1H), 7.6 to 7.3 (m, 6H), 5.5 (s, 2H).

[0315] 10.2 2-Benzyloxy-3-fluoro-4-methyl-5-trifluoromethylpyridine

[0316] 8.1 g of 2-benzyloxy-3-fluoro-4-methyl-5-trifluoromethylpyridine were prepared starting from 9.4 g (36.5 mmol) of the pyridine of Example 10.1 analogously to the procedure described in Example 1.2.

[0317] ¹H NMR (CDCl₃): δ (ppm)=8.1 (s, 1H), 7.5 to 7.3 (m, 5H), 5.5 (s, 2H), 2.4 (s, 3H).

[0318] 10.3 2-Hydroxy-3-fluoro-4-methyl-5-trifluoromethylpyridine

[0319] 3.8 g of 2-hydroxy-3-fluoro-4-methyl-5-trifluoromethylpyridine were prepared starting from 8.0 g (28.07 mmol) of the pyridine of Example 10.2 analogously to the procedure described in Example 1.3.

[0320] ¹H NMR (CDCl₃): δ (ppm)=13.0 (br, 1H), 7.6 (s, 1H), 2.4 (s, 3H).

[0321] 10.4 2-Chloro-3-fluoro-4-methyl-5-trifluoromethylpyridine

[0322] 3.7 g of 2-chloro-3-fluoro-4-methyl-5-trifluoromethylpyridine were prepared starting from 3.8 g (19.5 mmol) of the pyridine of Example 10.3 analogously to the procedure described in Example 1.4.

[0323] ^1H NMR (CDCl_3): δ (ppm)=8.4 (s, 1H), 2.5 (s, 3H).

[0324] 10.5 2,4-Dichloro-5-methoxyphenylboronic Acid

[0325] 20.8 g (6.8 mmol) of 2,4-dichloro-5-methoxyiodobenzene (CAS-No. 189138-40-7) were converted into the boronic acid with 36.4 ml (7.3 mmol) of an isopropylmagnesium chloride solution (2 M in ether) and 21.4 g of trimethyl borate analogously to the procedure described in Example 4.2. This gave 11.1 g of 2,4-dichloro-5-methoxyphenylboronic acid.

[0326] ^1H NMR (d_6 -DMSO): δ (ppm)=8.4 (br, 2H), 7.4 (s, 1H), 7.1 (s, 1H), 3.9 (s, 3H).

[0327] 10.6 2-(2,4-Dichloro-5-methoxyphenyl-1-yl)-3-fluoro-4-methyl-5-trifluoromethylpyridine

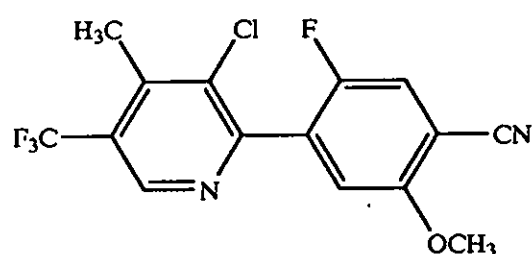
[0328] This was prepared analogously to the procedure described in Example 1.5. Starting from 3.7 g (17.3 mmol) of the pyridine of Example 10.4 and 3.8 g (17.3 mmol) of the boronic acid of Example 10.5 in dimethoxyethane/water (4:1, v/v) in the presence of 0.8 mmol of [1,2-bis(diphenylphosphine)butane]palladium(II) chloride as catalyst, 2.8 g of 2-(2,4-dichloro-5-methoxyphenyl-1-yl)-3-fluoro-4-methyl-5-trifluoromethylpyridine were obtained.

[0329] ^1H NMR (CDCl_3): δ (ppm)=8.7 (s, 1H), 7.5 (s, 1H), 7.0 (s, 1H), 3.9 (s, 3H), 2.6 (s, 3H).

Example 11

Preparation of 2-(2-fluoro-4-cyano-5-methoxyphenyl)-3-chloro-4-methyl-5-trifluoromethylpyridine (IAd.3)

[0330]



[0331] 11.1 2-Fluoro-4-cyano-5-methoxyphenylboronic Acid

[0332] 10 ml (20.3 mmol) of a solution of isopropylmagnesium chloride (2 M in ether) were added dropwise at -40°C . with stirring to 5.3 g (19.1 mmol) of 2-methoxy-4-iodo-5-fluorobenzonitrile (obtainable analogously to Example 4.1 from 2-fluoro-4-cyano-5-methoxyaniline) in 50 ml methyl tert-butyl ether and 20 ml of THF, and stirring was continued for 1 hour. 6.0 g (57.4 mmol) of trimethyl borate were subsequently added dropwise, stirring of the mixture was continued for 1 hour at -40°C . and the mixture was allowed to afterreact overnight at room temperature with stirring.

The mixture was subsequently treated with 50 ml of saturated ammonium chloride solution, diluted with saturated sodium chloride solution and extracted three times with in each case 100 ml of ethyl acetate. After drying of the combined organic phases over sodium sulfate and concentrating the solution, the residue was digested in n-hexane and the solid was filtered off with suction. The mother liquor was subsequently diluted with ethyl acetate and extracted three times with 5% strength NaOH solution. The combined aqueous phases were acidified with 10% strength hydrochloric acid and subsequently extracted three more times with in each case 50 ml of ethyl acetate. In total, 1.6 g of a colorless solid of m.p. 213 to 214°C . were isolated. Depending on the work-up, it was possible that the product also contained the trimer boron oxine, which, however, reacted further like the desired boronic acid.

[0333] ^1H NMR (d_6 -DMSO): δ (ppm)=8.7 (br, 2H), 7.6 (d, 1H), 7.4 (d, 1H), 3.9 (s, 3H).

[0334] 11.2 2-(2-Fluoro-4-cyano-5-methoxyphenyl-1-yl)-3-chloro-4-methyl-5-trifluoromethylpyridine

[0335] The title compound was prepared analogously to the procedure described in Example 1.5. Starting from 1.8 g (7.7 mol) of the pyridine of Example 1.4 and 1.5 g (7.7 mmol) of the cyanoboronic acid of Example 11.1, 1.0 g of the title compound of m.p. 108 to 109°C . were obtained.

[0336] ^1H NMR (CDCl_3): δ (ppm)=8.8 (s, 1H), 7.4 (d, 1H), 7.0 (d, 1H), 4.0 (s, 3H), 2.6 (s, 3H).

Example 12

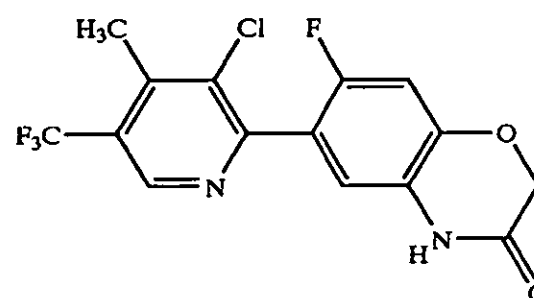
2-[2-Fluoro-4-(methoxycarbonyl)methoxy-5-nitrophenyl]-3-chloro-4-methyl-5-trifluoromethylpyridine (Comp. Ias.5)

[0337] 2-(2,4-Difluorophenyl)-3-chloro-4-methyl-5-trifluoromethylpyridine was prepared analogously to Example 1.5. This compound was nitrated analogously to the protocol of Example 5 yielding 2-(2,4-difluoro-5-nitrophenyl)-3-chloro-4-methyl-5-trifluoromethylpyridine. The nitro compound was then reacted with methyl glycolate in dioxane in the presence of potassium fluoride as base to give the title compound.

Example 13

7-(3-Chloro-4-methyl-5-trifluoromethylpyridin-2-yl)-6-fluoro-2H-1,4-benzoxazin-3-one (IBa.1)

[0338]



[0339] 2.4 g (5.7 mmol) of the nitrophenyl ester Iaw.5 of Example 12 were dissolved in 150 ml of methanol, 1 g of Pt (5% on charcoal) was added, and the mixture was treated

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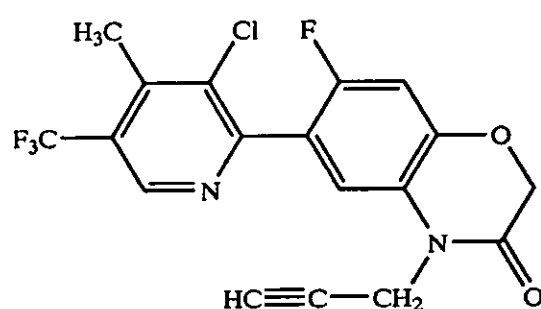
with 0.0171 mol H₂ (1 bar). The reaction mixture was subsequently filtered through kieselguhr in order to remove the catalyst and concentrated. The residue was taken up in 25 ml of DMF and 1.7 g (12.2 mmol) of K₂CO₃ were added. To complete the cyclization, the mixture was then stirred for 2 hours at 70° C. The mixture was then diluted with 150 ml of water and extracted three times with in each case 100 ml of methyl tert-butyl ether, and the combined organic phases were dried over sodium sulfate. Concentration gave 1.7 g of 7-(3-chloro-4-methyl-5-trifluoromethylpyridin-2-yl)-6-fluoro-2H-1,4-benzoxazin-3-one, which was directly reacted further.

[0340] ¹H NMR (CDCl₃): δ (ppm)=9.5 (br, 1H), 8.8 (s, 1H), 6.9 (d, 1H), 6.8 (d, 1H), 4.5 (s, 2H), 2.6 (s, 3H).

Example 14

7-(3-Chloro-4-methyl-5-trifluoromethylpyridin-2-yl)-6-fluoro-4-propargyl-2H-1,4-benzoxazin-3-one (IBa.24)

[0341]



[0342] 0.23 g (1.66 mmol) of potassium carbonate and then 0.18 g (1.5 mmol) of propargyl bromide were added to a solution of 0.5 g (1.4 mmol) of Example 13 in 10 ml of DMF. The mixture was stirred at room temperature until TLC revealed no further change. For work-up, the reaction mixture was poured into water and the product which precipitated was filtered off with suction. Washing of the residue with water gave 0.45 g of 7-(3-chloro-4-methyl-5-trifluoromethylpyridin-2-yl)-6-fluoro-4-propargyl-2H-1,4-benzoxazin-3-one of m.p. 156 to 157° C.

[0343] ¹H NMR (CDCl₃): δ (ppm)=8.8 (s, 1H), 7.2 (d, 1H), 6.8 (d, 1H), 4.7 (m, 4H), 2.6 (s, 3H), 2.2 (t, 1H).

Example 15

2-(2-Fluoro-4-chloro-5-azidophenyl)-3-chloro-4-methyl-5-trifluoromethylpyridine (IAa.84)

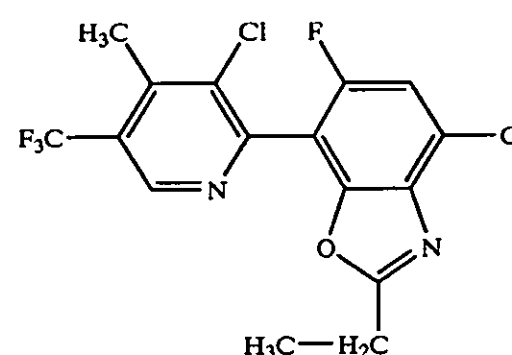
[0344] 1.75 g (17.0 mmol) of tert-butyl nitrite were added dropwise at 5° C. to a solution of 5.5 g (16.2 mmol) of the aniline of Example 6 in 60 ml of trifluoroacetic acid. After 40 minutes at this temperature, 1.58 g (24.3 mmol) of sodium azide were added portionwise. Stirring was continued for 1 hour at 0 to 5° C. and for 2 hours at room temperature, and the reaction mixture was introduced into 500 ml of ice-cold water and extracted three times with in each case 200 ml of methylene chloride. The combined organic phases were washed twice with in each case 100 ml of water, once with 100 ml of 5% strength sodium hydroxide solution and again with 100 ml of water, dried over magnesium sulfate and concentrated. This gave 4.2 g of the title compound IAa.84

[0345] ¹H NMR (CDCl₃): δ (ppm)=8.8 (s, 1H), 7.3 (m, 2H), 2.6 (s, 3H).

Example 16

4-Chloro-7-[3-chloro-4-methyl-5-(trifluoromethyl)-2-pyridinyl]-2-ethyl-6-fluoro-1,3-benzoxazole (ICe.3)

[0346]



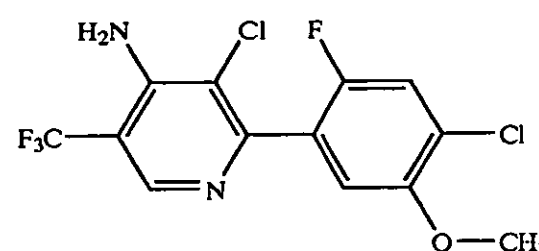
[0347] 1.5 g of the azide of Example 15 were treated with 30 ml of propionic acid and the mixture was refluxed for 7 hours. The reaction mixture was subsequently poured into 200 ml of ice-cold water and neutralized with 5% strength sodium hydroxide solution. The mixture was extracted three times with in each case 100 ml of ethyl acetate, the combined organic phases were dried over sodium sulfate and the solvent was removed in vacuo. Chromatography on silica gel with cyclohexane/ethyl acetate (10/1, v/v) yielded 0.25 g of the title compound.

[0348] ¹H NMR (CDCl₃): δ (ppm)=8.8 (s, 1H), 7.3 (s, 1H), 3.0 (q, 2H), 2.6 (s, 3H), 1.4 (t, 3H).

Example 17

2-(2-Fluoro-4-chloro-5-methoxyphenyl-1-yl)-3-chloro-4-amino-5-trifluoromethylpyridine (IAi.3)

[0349]



[0350] 17.1 2-Benzyloxy-3-chloro-4-carboxy-5-trifluoromethylpyridine

[0351] 41 ml (53.3 mmol) of a 1.3 M butyllithium solution in n-hexane was added dropwise -75° C. to a solution of 14.5 g (43.7 mmol) of 2-benzyloxy-3-chloro-5-trifluoromethylpyridine of Example 1.1 in approximately 200 ml of THF and stirring was continued at this temperature for 1 hour. This solution was then added dropwise at -75° C. to 100 ml of a saturated solution of carbon dioxide in THF. After the addition had ended, carbon dioxide was passed in within 1 hour. The mixture was defrosted to -10° C., 100 ml of saturated ammonium chloride solution were added, the

mixture was diluted with saturated sodium chloride solution, and the organic phase was subsequently separated off. The aqueous phase was then extracted twice more with in each case approximately 200 ml of methyl tert-butyl ether and the combined organic phases were washed with water. After drying of the organic phase over sodium sulfate and concentrating the solution, 14.7 g of 2-benzyloxy-3-chloro-4-carboxy-5-trifluoromethylpyridine were obtained.

[0352] ^1H NMR (d_6 -DMSO): δ (ppm)=8.3 (s, 1H), 7.4 to 7.2 (m, 5H), 5.5 (s, 2H).

[0353] 17.2 2-Benzyloxy-3-chloro-4-(N-tert-butoxycarbonyl)amino-5-trifluoromethylpyridine

[0354] 4.63 g (45.9 mmol) of triethylamine and 12.0 g (43.7 mmol) of diphenylphosphoryl azide were added to 14.5 g (43.7 mmol) of the acid of Example 17.1 in 180 ml tert-butanol, and the mixture was stirred for 10 hours at room temperature. The mixture was subsequently concentrated and the residue was chromatographed on silica gel using cyclohexane/ethyl acetate. This gave 10.3 g of 2-benzyloxy-3-chloro-4-(N-tert-butoxycarbonyl)amino-5-trifluoromethylpyridine.

[0355] ^1H NMR (CDCl_3): δ (ppm)=9.3 (br, 1H), 8.5 (s, 1H), 7.5 to 7.3 (m, 5H), 5.5 (s, 2H), 1.4 (s, 9H).

[0356] 17.3 2-Hydroxy-3-chloro-4-amino-5-trifluoromethylpyridine

[0357] 7.2 g (66.3 mmol) of trimethylsilyl chloride were added dropwise to 9.9 g of sodium iodide in 120 ml of acetonitrile. After 20 minutes, a solution of 10.7 g of the amide of Example 9.2 in 80 ml of acetonitrile was added. The reaction mixture was stirred for 2 hours at 50° C. The mixture was subsequently concentrated in vacuo, the residue was introduced into ice-cold water, and the mixture was extracted three times with in each case 200 ml of ethyl acetate. The aqueous phase was brought to pH 7 using 5% strength sodium hydroxide solution and reextracted twice with ethyl acetate. The combined organic phases were

subsequently washed with 100 ml of water. After drying of the organic phase over sodium sulfate and concentration, chromatography of the crude product on silica gel using cyclohexane/ethyl acetate (gradient 5/1 to 1/2, v/v) yielded 4.5 g of 2-hydroxy-3-chloro-4-amino-5-trifluoromethylpyridine.

[0358] ^1H NMR (CDCl_3): δ (ppm)=11.5 (br, 1H), 7.6 (s, 1H), 6.4 (s, 2H).

[0359] 7.4 2,3-Dichloro-4-amino-5-trifluoromethylpyridine

[0360] 3.6 g (16.9 mmol) of the hydroxypyridine of Example 17.3 was stirred for 2 hours at 75° C. with 50 ml of phosphoryl chloride, excess phosphoryl chloride was removed on a rotary evaporator, and the residue was treated with water. The mixture was subsequently extracted three times with in each case 50 ml of methylene chloride, the organic phase was dried over sodium sulfate, and the solvent was removed in vacuo.

[0361] This gave 3.0 g of 2,3-dichloro-4-amino-5-trifluoromethylpyridine.

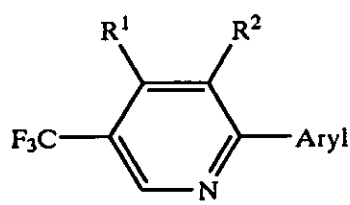
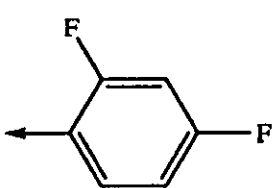
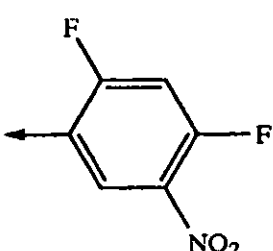
[0362] ^1H NMR (d_6 -DMSO): δ (ppm)=8.2 (s, 1H), 7.2 (s, 2H).

[0363] 17.5 2-(2-Fluoro-4-chloro-5-methoxyphenyl-1-yl)-3-chloro-4-amino-5-trifluoromethylpyridine

[0364] Analogously to the procedure described in Example 1.5, 2.0 g (8.7 mmol) of the aminochloropyridine of Example 17.4 were treated with 2-fluoro-4-chloro-5-methoxyphenylboronic acid. Chromatography of the crude product on silica gel with cyclohexane/ethyl acetate (15/1, v/v) gave 1.0 g of the title compound.

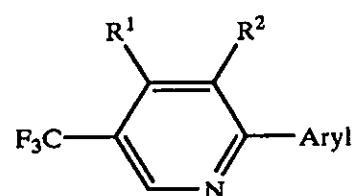
[0365] ^1H NMR (d_6 -DMSO): δ (ppm)=8.4 (s, 1H), 7.6 (d, 2H), 7.2 (d, 2H), 3.9 (s, 3H). The NH_2 signal is located broadly under the H_2O signal.

[0366] The compounds of the following Examples 19 to 77 were prepared analogously.

				
Ex.	R ¹	R ²	Aryl	^1H NMR
19	CH ₃	Cl		(CDCl_3) 8.8 (s, 1 H), 7.4 (m, 1 H), 6.8 (m, 2 H), 2.6 (s, 3 H),
20	CH ₃	Cl		(CDCl_3) 8.8 (s, 1 H), 8.3 (m, 1 H), 7.2 (m, 1 H), 2.6 (s, 3 H).

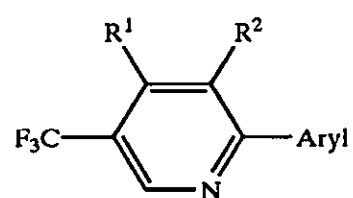
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Ex.	R^1	R^2	Aryl	1H NMR	m.p.
21	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 7.3 (d, 1 H), 7.0 (d, 1 H), 4.7 (s, 2 H), 4.2 (q, 2 H), 2.6 (s, 3 H), 1.3 (t, 3 H).	72 to 73° C.
22	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 7.2 (d, 1 H), 7.0 (d, 1 H), 4.8 (q, 1 H), 3.8 (s, 3 H), 2.6 (s, 3 H), 1.7 (d, 3 H).	
23	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 7.2 (d, 1 H), 7.0 (d, 1 H), 5.8 to 5.1 (m, 2 H), 4.8 (q, 1 H), 4.6 (m, 2 H), 2.6 (s, 3 H), 1.7 (d, 3 H).	
24	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 7.2 (d, 1 H), 7.0 (d, 1 H), 4.8 (q, 1 H), 4.2 (m, 2 H), 3.7 (m, 2 H), 2.6 (s, 3 H), 1.7 (d, 3 H).	
25	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 7.2 (d, 1 H), 7.0 (d, 1 H), 4.8 (q, 1 H), 4.3 (m, 2 H), 3.4 (m, 2 H), 3.3 (s, 3 H), 2.6 (s, 3 H), 1.7 (d, 3 H).	

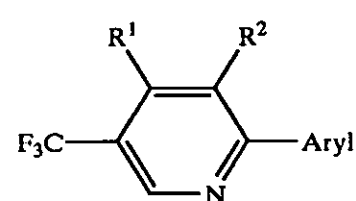
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Ex.	R ¹	R ²	Aryl	¹ H NMR	m.p.
26	CH ₃	Cl		(CDCl ₃) 8.8 (s, 1 H), 7.2 (d, 1 H), 7.0 (d, 1 H), 4.5 (sept, 1 H), 2.6 (s, 3H), 1.4 (d, 6 H)	
27	CH ₃	Cl		(CDCl ₃) 8.8 (s, 1 H), 7.3 (d, 1 H), 7.1 (d, 1 H), 4.8 (s, 2 H), 2.6 (s, 3H)	136 to 137° C.
28	CH ₃	Cl		(CDCl ₃) 8.8 (s, 1 H), 7.2 (d, 1 H), 7.0 (d, 1 H), 6.0 (m, 1 H), 5.5 to 5.3 (m, 2 H), 4.6 (m, 2 H), 2.6 (s, 3 H)	79 to 80° C.
29	CH ₃	Cl		(CDCl ₃) 8.8 (s, 1 H), 7.2 (d, 1 H), 7.0 (d, 1 H), 4.3 (m, 2 H), 3.9 (m, 2 H), 2.6 (s, 3 H)	97 to 98° C.
30	CH ₃	Cl		(CDCl ₃) 8.8 (s, 1 H), 7.3 to 7.1 (m, 2 H), 4.9 (m, 1 H), 2.6 (s, 3 H), 2.5 (s, 1 H), 1.8 (d, 3 H)	71 to 73° C.
31	CH ₃	Cl		(CDCl ₃) 8.8 (s, 1 H), 7.4 (d, 1 H), 7.0 (d, 1 H), 4.8 (m, 1 H), 2.6 (s, 3 H), 2.0 to 1.6 (m, 8 H)	

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Ex.	R^1	R^2	Aryl	1H NMR	m.p.
32	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 8.0 (d, 1 H), 7.4 (d, 1 H), 3.9 (m, 2 H), 2.6 (s, 3 H).	150 to 152° C.
33	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 8.1 (d, 1 H), 7.4 (d, 1 H), 4.6 (m, 2 H), 3.8 (m, 2 H), 2.6 (s, 3 H).	
34	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 8.1 (d, 1 H), 7.4 (d, 1 H), 6.0 (m, 1 H), 5.5 to 5.2 (m, 2 H), 4.8 (d, 2 H), 2.6 (s, 3 H).	
35	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 8.1 (d, 1 H), 7.4 (d, 1 H), 4.9 (d, 2 H), 2.6 (s, 3 H), 2.5 (t, 1 H).	
36	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 8.0 (d, 1 H), 7.4 (d, 1 H), 5.9 (mc, 1 H), 5.4 to 5.2 (m, 2 H), 4.6 (m, 2 H), 2.6 (s, 3 H), 1.7 (s, 6 H).	

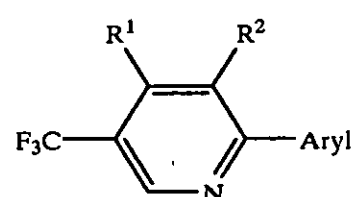
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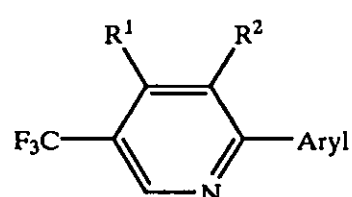
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Ex.	R ¹	R ²	Aryl	¹ H NMR	m.p.
37	CH ₃	Cl		(CDCl ₃) 8.8 (s, 1 H), 7.9 (d, 1 H), 7.3 (d, 1 H), 6.9 (br, 1 H), 4.3 (d, 2 H), 3.8 (s, 3 H), 2.6 (s, 3 H), 2.5 (t, 1 H).	104 to 105° C.
38	CH ₃	Cl		(CDCl ₃) 8.8 (s, 1 H), 8.0 (d, 1 H), 7.3 (d, 1 H), 6.5 to 6.0 (br, 2 H), 2.6 (s, 3 H), 2.5 (t, 1 H).	183 to 184° C.
39	CH ₃	Cl		(CDCl ₃) 8.8 (s, 1 H), 7.4 (s, 1 H), 6.9 (s, 1 H), 4.6 (m, 2 H), 2.6 (s, 3H).	201 to 203° C.
40	CH ₃	Cl		(CDCl ₃) 8.8 (s, 1 H), 7.4 (s, 1 H), 6.8 (s, 1 H), 4.8 (q, 1 H), 3.8 (s, 3 H), 2.6 (s, 3 H), 1.7 (d, 3 H).	
41	CH ₃	Cl		(CDCl ₃) 8.8 (s, 1 H), 7.5 (s, 1 H), 7.0 (s, 1 H), 4.8 (d, 2 H), 2.6 (t, 1H), 2.5 (s 3 H).	95 to 96° C.
42	CH ₃	F		(CDCl ₃) 8.7 (s, 1 H), 7.5 (s, 1 H), 6.9 (s, 1 H), 4.8 (q, 1 H), 3.8 (s, 3 H), 2.5 (s, 3 H), 1.7 (d, 3 H).	

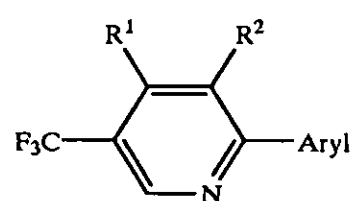
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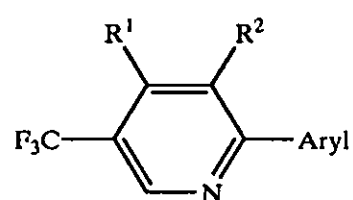
Ex.	R ¹	R ²	Aryl	¹ H NMR	m.p.
43	CH ₃	F	 A benzene ring with chlorine atoms at the 2 and 4 positions, and a -COOCH ₂ C≡CH group at the 1 position.	(CDCl ₃) 8.7 (s, 1 H), 7.57 (s, 1 H), 7.0 (s, 1 H), 4.8 (d, 2 H), 2.6 (t, 1 H), 2.5 (s, 3 H).	69 to 70° C.
44	CH ₃	F	 A benzene ring with a fluorine atom at the 4 position, a chlorine atom at the 2 position, and an -NH-SO ₂ CH ₃ group at the 1 position.	(CDCl ₃) 8.8 (s, 1 H), 7.7 (d, 1 H), 7.3 (d, 1 H), 7.1 (br, 1 H), 3.0 (s, 3 H), 2.6 (t, 1 H), 2.5 (s, 3 H).	138 to 139° C.
45	CH ₃	F	 A benzene ring with a fluorine atom at the 4 position, a chlorine atom at the 2 position, and an -NH-SO ₂ CH ₃ group at the 1 position.	(CDCl ₃) 8.8 (s, 1 H), 7.7 (d, 1 H), 7.6 (br, 1 H), 7.3 (d, 1 H), 3.2 (q, 2 H), 2.6 (t, 1 H), 2.5 (s, 3 H), 1.4 (t, 3 H).	142 to 146° C.
46	CH ₃	F	 A benzene ring with a fluorine atom at the 4 position, a nitro group (-NO ₂) at the 2 position, and a -CO ₂ Me group at the 1 position.	(CDCl ₃) 8.8 (s, 1 H), 8.1 (d, 1 H), 6.8 (d, 1 H), 4.9 (s, 1 H), 3.8 (s, 3 H), 2.6 (s, 3 H).	
47	CH ₃	F	 A benzene ring with a fluorine atom at the 4 position, and a -CO ₂ Et group at the 1 position.	(CDCl ₃) 8.8 (s, 1 H), 7.2 (d, 1 H), 6.8 (d, 1 H), 4.8 (s, 2 H), 4.2 (q, 2 H), 2.6 (s, 3 H), 1.4 (t, 3 H).	107 to 109° C.
48	CH ₃	F	 A benzene ring with a fluorine atom at the 4 position, and a -CO ₂ iPr group at the 1 position.	(CDCl ₃) 8.8 (s, 1 H), 7.2 (d, 1 H), 6.8 (d, 1 H), 4.8 (s, 2 H), 4.5 (sept, 1 H), 2.6 (s, 3 H), 1.3 (d, 6 H).	113 to 114° C.

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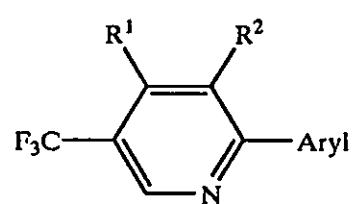
Ex.	R^1	R^2	Aryl	1H NMR	m.p.
49	CH_3	F		($CDCl_3$) 8.8 (s, 1 H), 7.0 (d, 1 H), 6.8 (d, 1 H), 4.5 (s, 2 H), 4.0 (q, 2 H), 2.6 (s, 3 H), 1.4 (t, 3 H).	127 to 128° C.
50	CH_3	F		($CDCl_3$) 8.8 (s, 1 H), 7.1 (d, 1 H), 6.9 (d, 1 H), 4.5 (sept, 1 H), 2.6 (s, 3 H), 1.6 (d, 6 H).	
51	CH_3	F		($CDCl_3$) 8.8 (s, 1 H), 7.2 (d, 1 H), 3.2 (sept, 1 H), 2.6 (s, 3 H), 1.4 (d, 6 H).	
52	CH_3	F		($CDCl_3$) 8.8 (s, 1 H), 7.2 (d, 1 H), 6.9 (d, 1 H), 2.6 (s, 3 H), 2.2 (m 1, 1.4 to 1.2 (m, 4 H).	
53	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 7.2 (d, 1 H), 7.0 (d, 1 H), 5.1 (q, 1 H), 3.8 (s, 3 H), 2.6 (s, 3H), 1.8 (d, 2 H).	

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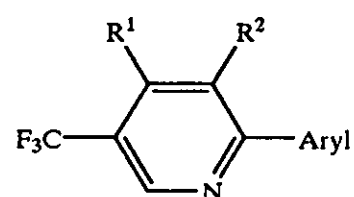
Ex.	R^1	R^2	Aryl	1H NMR	m.p.
54	CH_3	Cl		(d_6 -DMSO) 8.8 (s, 1 H), 7.5 (d, 1 H), 7.2 (d, 1 H), 4.8 (s, 1 H), 2.7-2.6 (m, 4H).	
55	NH_2	Cl		(d_6 -DMSO) 8.6 (s, 1 H), 8.1 (br, 1 H), 7.6 (d, 1 H), 7.1 (d, 1 H), NH_2 broad	
56	NH_2	Cl		(d_6 -DMSO) 8.4 (s, 1 H), 7.6 (d, 1 H), 7.3 (d, 1 H), 7.0 (br, 2 H), 4.9 (d, 2 H), 3.6 (t, 1 H).	115 to 118° C.
57	NH_2	Cl		($CDCl_3$) 8.5 (s, 1 H), 7.3 (d, 1 H), 7.0 (d, 1 H), 5.4 (br, 2 H), 4.7 (q, 2 H), 3.8 (s, 3 H), 1.7 (d, 3 H).	
58	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 7.4 (d, 1 H), 7.0 (d, 1 H), 4.2 (q, 2 H), 2.6 (s, 3 H), 1.5 (t, 3 H).	
59	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 7.3 (d, 1 H), 7.0 (d, 1 H), 5.2 (s, 1 H), 5.1 (s, 1 H), 4.4 (s, 2 H), 2.6 (s, 3 H).	

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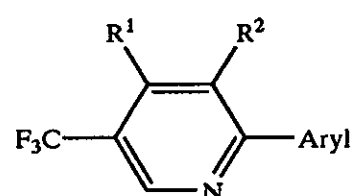
Ex.	R^1	R^2	Aryl	1H NMR	m.p.
60	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 8.5 (d, 1 H), 7.6 (br. s., 1 H), 7.2 (d, 1 H), 2.6 (s, 3 H), 2.2 (s, 3 H).	
61	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 7.3 (d, 1 H), 7.0 (d, 1 H).	
62	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 7.2 (d, 1 H), 7.0 (d, 1 H), 4.6 (s, 2 H), 3.8 (s, 3 H), 2.6 (s, 3 H).	
63	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 7.2 (d, 1 H), 7.0 (d, 1 H), 5.2 (q, 1 H), 4.7 (m, 2 H), 3.7 (s, 3 H), 2.6 (s, 3 H), 1.3 (d, 3 H).	
64	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 8.0 (d, 1 H), 7.4 (d, 1 H), 5.2 (m, 1 H), 2.6 (s, 3 H), 1.7 (d, 3 H), 1.8 to 1.6 (m, 1 H), 1.4 (d, 3 H), 1.0 (t, 3 H).	

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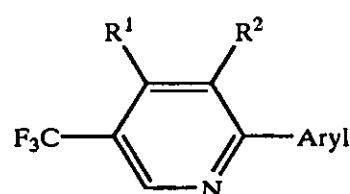
Ex.	R ¹	R ²	Aryl	¹ H NMR	m.p.
65	CH ₃	Cl		(CDCl ₃) 8.8 (s, 1 H), 8.0 (d, 1 H), 7.4 (d, 1 H), 5.0 (m, 1 H), 2.6 (s, 3 H), 2.0 (m, 1 H), 1.3 (d, 3 H), 1.0 (d, 6 H).	
66	CH ₃	Cl		(CDCl ₃) 8.8 (s, 1 H), 8.0 (d, 1 H), 7.4 (d, 1 H), 5.4 (m, 1 H), 2.6 (s, 3 H), 2.0 to 1.5 (m 8 H).	
67	CH ₃	Cl		(CDCl ₃) 8.8 (s, 1 H), 8.0 (d, 1 H), 7.4 (d, 1 H), 5.1 (m, 1 H), 2.6 (s, 3 H), 2.0 to 1.5 (m, 10 H).	
68	CH ₃	Cl		(CDCl ₃) 8.8 (s, 1 H), 8.0 (d, 1 H), 7.4 (d, 1 H), 6.7 (m, 1 H), 2.6 (s, 3 H), 2.5 (s, 1 H), 1.6 (d, 3 H).	
69	CH ₃	Cl		(CDCl ₃) 8.8 (s, 1 H), 8.0 (d, 1 H), 7.4 (d, 1 H), 4.2 (d 2 H), 2.6 (s, 3 H), 1.3 (m, 1 H), 1.6 to 1.4 (m, 4 H).	

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Ex.	R^1	R^2	Aryl	1H NMR	m.p.
70	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 8.0 (d, 1 H), 7.4 (d, 1 H), 4.1 (d 2 H), 2.6 (s, 3 H), 1.3 (m, 1 H), 2.1 (m, 1 H), 1.0 (d, 6 H).	
71	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 8.0 (d, 1 H), 7.4 (d, 1 H), 4.0 (s, 2 H), 2.6 (s, 3 H), 1.0 (s, 9 H).	
72	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 8.1 (d, 1 H), 7.5 to 7.2 (m, 6 H), 5.4 (s 2 H), 2.6 (s, 3 H).	
73	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 7.8 (d, 1 H), 7.3 (d, 1 H), 6.4 (br. s, 1 H), 6.0 (m, 1 H), 5.4 to 5.2 (m, 2 H), 4.1 (m, 2 H), 2.6 (s, 3 H).	
74	CH_3	Cl		($CDCl_3$) 8.8 (s, 1 H), 7.8 (d, 1 H), 7.3 (d, 1 H), 6.5 (br. s, 1 H), 4.3 (m, 2 H), 2.6 (s, 3 H), 2.3 (m, 1 H).	

-continued



Ex.	R ¹	R ²	Aryl	¹ H NMR	m.p.
75	CH ₃	Cl	 A benzene ring with a fluorine atom at the 4-position and a chlorine atom at the 2-position, attached to a carbonyl group.	(CDCl ₃) 8.8 (s, 1 H), 7.8 (d, 1 H), 7.4 (d, 1 H), 5.9 (mc, 1 H), 5.4 to 5.2 (m, 2 H), 4.6 (m, 2 H), 2.6 (s, 3 H), 1.7 (s, 6 H).	
76	CH ₃	Cl	 A benzene ring with a fluorine atom at the 4-position and a chlorine atom at the 2-position, attached to a carbonyl group.	(CDCl ₃) 8.8 (s, 1 H), 7.8 (d, 1 H), 7.4 (d, 1 H), 6.1 (br. d, 1 H), 4.3 (m, 1 H), 2.6 (s, 3 H), 1.3 (d, 6 H).	
77	CH ₃	Cl	 A benzene ring with a fluorine atom at the 4-position and a chlorine atom at the 2-position, attached to a carbonyl group.	(CDCl ₃) rotamer mixture: 8.8 (s, 1 H), 7.8 (d, 1 H), 7.3 (d, 1 H), 5.0 (m, 0.5 H), 4.8 (m, 0.5 H), 3.0 (s, 1.5 H), 2.8 (s, 1.5 H), 2.6 (s, 3 H), 1.2 (m, 6 H).	

[0367] The compounds I and their agriculturally useful salts, not only as isomer mixtures, but also in the form of the pure isomers, are suitable as herbicides. The herbicidal compositions comprising I effect very good control of vegetation on noncrop areas, especially at high application rates. In crops such as wheat, rice, maize, soybeans and cotton, they act against broad-leaved weeds and grass weeds without substantially harming the crop plants. This effect is observed especially at low application rates.

[0368] Depending on the application method in question, the compounds I or compositions comprising them can also be employed in a further number of crop plants for eliminating undesired plants. Examples of suitable crops are the following:

[0369] *Allium cepa*, *Ananas comosus*, *Arachis hypogaea*, *Asparagus officinalis*, *Beta vulgaris* spec. altissima, *Beta vulgaris* spec. rapa, *Brassica napus* var. *napus*, *Brassica napus* var. *napobrassica*, *Brassica rapa* var. *silvestris*, *Camellia sinensis*, *Carthamus tinctorius*, *Carya illinoensis*, *Citrus limon*, *Citrus sinensis*, *Coffea arabica* (*Coffea canephora*, *Coffea liberica*), *Cucumis sativus*, *Cynodon dactylon*, *Daucus carota*, *Elaeis guineensis*, *Fragaria vesca*,

Glycine max, *Gossypium hirsutum*, (*Gossypium arboreum*, *Gossypium herbaceum*, *Gossypium vitifolium*), *Helianthus annuus*, *Hevea brasiliensis*, *Hordeum vulgare*, *Humulus lupulus*, *Ipomoea batatas*, *Juglans regia*, *Lens culinaris*, *Linum usitatissimum*, *Lycopersicon lycopersicum*, *Malus* spec., *Manihot esculenta*, *Medicago sativa*, *Musa* spec., *Nicotiana tabacum* (*N. rustica*), *Olea europaea*, *Oryza sativa*, *Phaseolus lunatus*, *Phaseolus vulgaris*, *Picea abies*, *Pinus* spec., *Pisum sativum*, *Prunus avium*, *Prunus persica*, *Pyrus communis*, *Ribes sylvestre*, *Ricinus communis*, *Saccharum officinarum*, *Secale cereale*, *Solanum tuberosum*, *Sorghum bicolor* (*S. vulgare*), *Theobroma cacao*, *Trifolium pratense*, *Triticum aestivum*, *Triticum durum*, *Vicia faba*, *Vitis vinifera*, *Zea mays*.

[0370] In addition, the compounds I can also be used in crops which tolerate the effect of herbicides owing to breeding, including recombinant methods.

[0371] Moreover, the 3-halo-2-phenylpyridines and their agriculturally useful salts are also suitable for the desiccation and/or defoliation of plants.

[0372] As desiccants, they are suitable in particular for desiccating the aerial parts of crop plants such as potato,

oilseed rape, sunflower and soybeans. This makes possible the full mechanization of the harvest of these important crop plants.

[0373] Also of economic interest are:

[0374] the dehiscence of fruit concentrated over a period of time, or the reduction in their adherence to the plant, for example in the case of citrus fruit, olives or other species and varieties of pomaceous fruit, stone fruit and hard-shelled fruit, since this facilitates the harvest of these fruits, and

[0375] the controlled removal of the foliage of useful plants, in particular cotton (defoliation).

[0376] The dehiscence which is promoted by the use of compounds of the formula I according to the invention and their agriculturally useful salts is based on the formation of abscission tissue between the fruit organ or leaf organ and the shoot organ of the plants. The defoliation of cotton is of very particular economic interest since it facilitates harvesting. At the same time, the shortening of the period of time within which the individual plants mature leads to an increased quality of the harvested fiber material.

[0377] The compounds I or the compositions comprising them can be applied for example in the form of directly sprayable aqueous solutions, powders, suspensions, also highly-concentrated aqueous, oily or other suspensions or dispersions, emulsions, oil dispersions, pastes, dusts, materials for spreading or granules by means of spraying, atomizing, dusting, spreading, pouring or treating the seed or mixing with the seed. The use forms depend on the intended purpose; in any case, they should guarantee the finest possible distribution of the active ingredients according to the invention. The herbicidal compositions comprise a herbicidally active amount of at least one compound of the formula I or of an agriculturally useful salt of I and auxiliaries conventional in the formulation of crop protection products.

[0378] Inert additives which are suitable are essentially the following:

[0379] Mineral oil fractions of medium to high boiling point, such as kerosene or diesel oil, furthermore coal tar oils and oils of vegetable or animal origin, aliphatic, cyclic and aromatic hydrocarbons, for example paraffin, tetrahydronaphthalene, alkylated naphthalenes or their derivatives, alkylated benzenes or their derivatives, alcohols such as methanol, ethanol, propanol, butanol, cyclohexanol, ketones such as cyclohexanone, or strongly polar solvents, for example amines such as N-methylpyrrolidone, or water.

[0380] Aqueous use forms can be prepared from emulsion concentrates, suspensions, pastes, wettable powders or water-dispersible granules by adding water. To prepare emulsions, pastes or oil dispersions, the 3-halo-2-phenylpyridines, as such or dissolved in an oil or solvent, can be homogenized in water by means of wetter, adhesive, dispersant or emulsifier. However, it is also possible to prepare concentrates composed of active substance, wetter, adhesive, dispersant or emulsifier and, if appropriate, solvent or oil, which concentrates are suitable for dilution with water.

[0381] Suitable surface-active substances are the alkali metal salts, alkaline earth metal salts, ammonium salts of aromatic sulfonic acids, for example lignosulfonic acid, phenolsulfonic acid, naphthalenesulfonic acid and dibutyl-naphthalenesulfonic acid, and of fatty acids, alkylsulfonates and alkylarylsulfonates, of alkyl sulfates, lauryl ether sulfates and fatty alcohol sulfates, and salts of sulfated hexa-, hepta- and octadecanols and of fatty alcohol glycol ethers, condensates of sulfonated naphthalene and its derivatives with formaldehyde, condensates of naphthalene or of the naphthalenesulfonic acids with phenol and formaldehyde, polyoxyethylene octylphenol ether, ethoxylated isooctyl-, octyl- or nonylphenol, alkylphenyl polyglycol ethers, tributylphenyl polyglycol ether, alkylaryl polyether alcohols, isotridecyl alcohol, fatty alcohol/ethylene oxide condensates, ethoxylated castor oil, polyoxyethylene alkyl ethers or polyoxypropylene alkyl ethers, lauryl alcohol polyglycol ether acetate, sorbitol esters, lignin-sulfite waste liquors or methylcellulose.

[0382] Powders, materials for spreading and dusts can be prepared by mixing or concomitantly grinding the active substances together with a solid carrier.

[0383] Granules, for example coated granules, impregnated granules, and homogeneous granules can be prepared by binding the active ingredients to solid carriers. Solid carriers are mineral earths such as silicas, silica gels, silicates, talc, kaolin, limestone, lime, chalk, bole, loess, clay, dolomite, diatomaceous earth, calcium sulfate, magnesium sulfate, magnesium oxide, ground synthetic materials, fertilizers such as ammonium sulfate, ammonium phosphate, ammonium nitrate, ureas, and products of vegetable origin such as cereal meal, tree bark meal, wood meal and nutshell meal, cellulose powders or other solid carriers.

[0384] The concentrations of the active ingredients I in the ready-to-use preparations can be varied within wide ranges. In general, the formulations comprise 0.001 to 98% by weight, preferably 0.01 to 95% by weight, of at least one active ingredient. In this context, the active ingredients are employed in a purity of from 90% to 100%, preferably 95% to 100% (according to NMR spectrum).

[0385] For example, the compounds I according to the invention can be formulated as follows:

[0386] I 20 parts by weight of the compound No. IAa.3 are dissolved in a mixture composed of 80 parts by weight of alkylated benzene, 10 parts by weight of the adduct of 8 to 10 mol of ethylene oxide and 1 mol of oleic acid N-monoethanolamide, 5 parts by weight of calcium dodecylbenzenesulfonate and 5 parts by weight of the adduct of 40 mol of ethylene oxide and 1 mol of castor oil. Pouring the solution into 100,000 parts by weight of water and finely distributing it therein gives an aqueous dispersion comprising 0.02% by weight of the active ingredient.

[0387] II 20 parts by weight of the compound No. IAa.10 are dissolved in a mixture composed of 40 parts by weight of cyclohexanone, 30 parts by weight of isobutanol, 20 parts by weight of the adduct of 7 mol of ethylene oxide and 1 mol of isooctylphenol and 10 parts by weight of the adduct of 40 mol of ethylene oxide and 1 mol of castor oil. Pouring the solution into 100,000 parts by weight of water and finely distributing it therein gives an aqueous dispersion comprising 0.02% by weight of the active ingredient.

[0388] III 20 parts by weight of the active ingredient No. IAa.131 are dissolved in a mixture composed of 25 parts by weight of cyclohexanone, 65 parts by weight of a mineral oil fraction of boiling point 210 to 280° C. and 10 parts by weight of the adduct of 40 mol of ethylene oxide and 1 mol of castor oil. Pouring the solution into 100,000 parts by weight of water and finely distributing it therein gives an aqueous dispersion comprising 0.02% by weight of the active ingredient.

[0389] IV 20 parts by weight of the active ingredient No. IAa.143 are mixed thoroughly with 3 parts by weight of sodium diisobutyl naphthalenesulfonate, 17 parts by weight of the sodium salt of a lignosulfonic acid from a sulfite waste liquor and 60 parts by weight of pulverulent silica gel, and the mixture is ground in a hammer mill. Finely distributing the mixture in 20,000 parts by weight of water gives a spray mixture comprising 0.1% by weight of the active ingredient.

[0390] V 3 parts by weight of the active ingredient No. IAi.10 are mixed with 97 parts by weight of finely divided kaolin. This gives a dust comprising 3% by weight of the active ingredient.

[0391] VI 20 parts by weight of the active ingredient No. IBa.24 are mixed intimately with 2 parts by weight of calcium dodecylbenzenesulfonate, 8 parts by weight of fatty alcohol polyglycol ether, 2 parts by weight of the sodium salt of a phenol/urea/formaldehyde condensate and 68 parts by weight of a paraffinic mineral oil. This gives a stable oily dispersion.

[0392] VII 1 part by weight of the compound No. IBa.11 is dissolved in a mixture composed of 70 parts by weight of cyclohexanone, 20 parts by weight of ethoxylated isooctylphenol and 10 parts by weight of ethoxylated castor oil. This gives a stable emulsion concentrate.

[0393] VIII 1 part by weight of the compound No. ICe.3 is dissolved in a mixture composed of 80 parts by weight of cyclohexanone and 20 parts by weight of Wettol® EM 31 (nonionic emulsifier based on ethoxylated castor oil). This gives a stable emulsion concentrate.

[0394] The application of the herbicidal compositions or of the active ingredients can be effect pre-emergence, post-emergence or together with the seed of a crop plant. There is also the possibility of applying the herbicidal compositions or active ingredients by sowing the seed, of a crop plant, which has been pretreated with the herbicidal compositions or active ingredients. If the active ingredients are less well tolerated by specific crop plants, application techniques can be used in which the herbicidal compositions are sprayed with the aid of the spraying apparatus in such a way that the leaves of the sensitive crop plants come into as little contact as possible with the active ingredients, while these reach the leaves of undesired plants growing underneath the crop plants, or the naked soil (post-directed, lay-by).

[0395] Depending on the intended aim, the season, the target plants and the growth stage, the application rates of active ingredient are from 0.001 to 3.0, preferably 0.01 to 1.0 kg/ha of active substance (a.s.) per ha.

[0396] To widen the spectrum of action and to achieve synergistic effects, the 3-halo-2-phenylpyridines can be mixed, and applied jointly, with numerous representatives of other groups of herbicidally or growth-regulatory active

ingredients. Examples of suitable components in mixtures are 1,2,4-thiadiazoles, 1,3,4-thiadiazoles, amides, amino-phosphoric acid and its derivatives, aminotriazoles, anilides, (het)aryloxyalkanoic acids and their derivatives, benzoic acid and its derivatives, benzothiadiazinones, 2-aryloxy-1,3-cyclohexanediones, 2-hetaryloxy-1,3-cyclohexanediones, hetaryl aryl ketones, benzyloxazolidinones, meta-CF₃-phenyl derivatives, carbamates, quinolinecarboxylic acid and its derivatives, chloroacetanilides, cyclohexenone oxime ether derivatives, diazines, dichloropropionic acid and its derivatives, dihydrobenzofurans, dihydrofuran-3-ones, dinitroanilines, dinitrophenols, diphenyl ethers, dipyridyls, halocarboxylic acids and their derivatives, ureas, 3-phenyluracils, imidazoles, imidazolinones, N-phenyl-3,4,5,6-tetrahydrophthalimides, oxadiazoles, oxiranes, phenols, aryloxy- or heteroaryloxyphenoxypropionic esters, phenylacetic acid and its derivatives, phenylpropionic acid and its derivatives, pyrazoles, phenylpyrazoles, pyridazines, pyridinecarboxylic acid and its derivatives, pyrimidyl ethers, sulfonamides, sulfonylureas, triazines, triazinones, triazolinones, triazolecarboxamides, uracils.

[0397] Moreover, it may be advantageous to employ the compounds I, alone or in combination with other herbicides, as a mixture with yet further crop protection agents, for example with agents for controlling pests or phytopathogenic fungi or bacteria. Also of interest is the miscibility with mineral salt solutions which are employed for alleviating nutritional and trace element deficiencies. Nonphyto-toxic oils and oil concentrates may also be added.

USE EXAMPLES

[0398] The herbicidal action of the 3-halo-5-trifluoromethyl-2-phenylpyridines of the formula I was demonstrated by greenhouse 5 experiments:

[0399] The culture containers used were plastic pots with loamy sand with approximately 3.0% humus as substrate. The seeds of the test plants were sown separately for each species.

[0400] In the case of the pre-emergence treatment, the active ingredients which were suspended or emulsified in water were applied directly after sowing by means of finely distributing nozzles. The containers were irrigated gently to promote germination and growth and subsequently covered with translucent plastic hoods until the plants had rooted. This cover causes uniform germination of the test plants provided this was not adversely affected by the active ingredients.

[0401] For the purposes of the post-emergence treatment, the test plants were first grown to a height of 3 to 15 cm, depending on the growth habit, and only then treated with the active ingredients which were suspended or emulsified in water. To this end, the test plants were either sown directly and grown on in the same containers, or else they were first grown separately as seedlings and then transplanted into the experimental containers a few days prior to treatment. The application rate for the post-emergence treatment was 31.3, 15.6, 7.8 and/or 3.9 g of a.s./ha.

[0402] The plants were kept at temperatures of 10-25° C. or 20-35° C., depending on the species. The experimental period extended over 2 to 4 weeks. During this time, the plants were tended, and their response to the individual regimes were evaluated.

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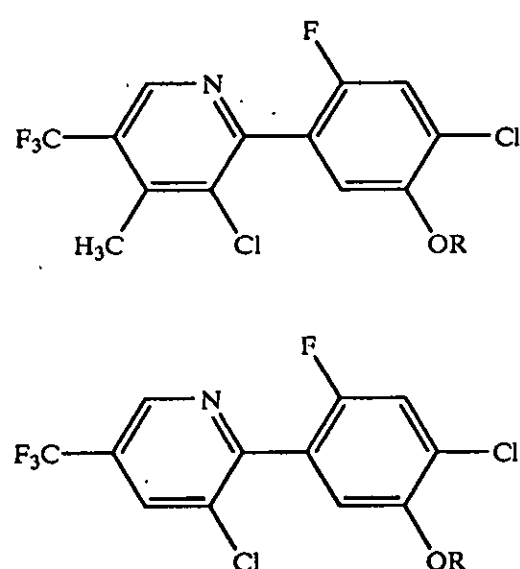
[0403] For the evaluation, a scale of 0 to 100 was used. 100 means no emergence of the plants, or complete destruction of at least the aerial parts, and 0 means no damage or normal course of growth.

[0404] The plants used in the greenhouse experiments consisted of the following species:

Bayercode	Common name
ECHCG	barnyardgrass
SETFA	giant foxtail
BIDPI	hairy beggarlicks
CHEAL	lambsquarters
BRAPL	alexandergrass

[0405] The compounds I according to the invention which were tested were No. IAa.3 (Example 1) and IAa.10 (Example 3) and the corresponding compounds No. 1.501 (Comparative Example VA) and 1.512 (Comparative Example VB) of WO 95/02580.

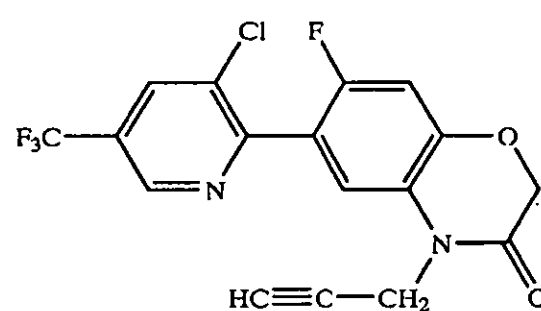
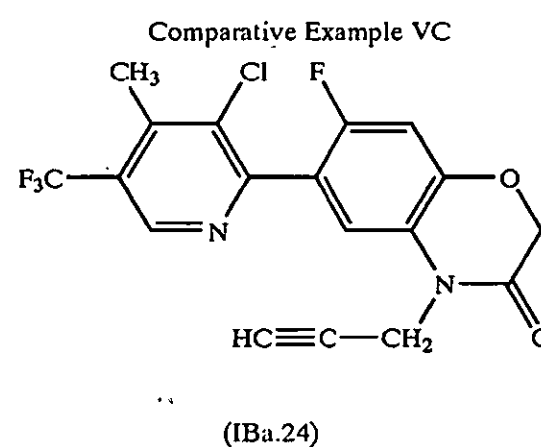
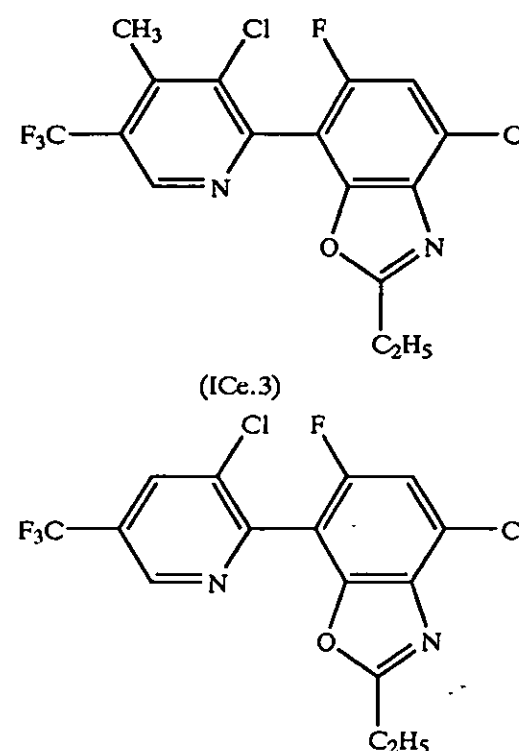
[0406] Other compounds I according to the invention which were tested were No. ICe.3 (Example 16) and IBa.24 (Example 14) and the corresponding compounds No. Iz.003 (Comparative Example VC) of WO 99/06394 and the compound No. Ih.005 (Comparative Example VD) of WO 95/02590.



[0407] Compound according Comparative Example to the invention

R = CH ₃	No. IAa.3,	VA
R = CH ₂ C≡CH	No. IAa.10,	VB

[0408]



[0409] The post-emergence herbicidal action found is compiled in Tables 8 and 9.

TABLE 8

Application rate	IAa.3		VA		IAa.10		VB	
[g/ha a.s.]	31.3	15.6	31.3	15.6	7.8	3.9	7.8	3.9
	Harmful plant/action							
ECHCG	100	90	80	30	85	70	70	50
SETFA	100	95	80	70	98	98	90	80
BIDPI	60	60	40	35	100	100	70	40
CHEAL	100	100	98	90	100	100	100	100

[0410]

TABLE 9

Application rate	ICe.3		VC		IBa.24		VD	
[g/ha a.s.]	7.8	3.9	7.8	3.9	3.9	1.9	3.9	1.9
	Harmful plant/action							
BRAPL	90	80	55	40	—	—	—	—
SETFA	100	100	95	90	100	70	90	60
BIDPI	100	100	55	50	100	100	55	50

[0411] At application rates of 31.3 and 15.6 g of a.s./ha, compound No. IAa.3, applied post-emergence, showed a considerably better action against the harmful plants ECHCG, SETFA, BIDPI and CHEAL than Comparative Example VA.

[0412] At application rates of 7.8 and 3.9 g of a.s./ha, compound No. IAa.10, applied post-emergence, showed a considerably better action against the harmful plants ECHCG, SETFA and BIDPI than Comparative Example VB.

[0413] At application rates of 7.8 and 3.9 g of a.s./ha, compound No. ICe.3, applied post-emergence, showed a considerably better action against the harmful plants BRAPL, SETFA and BIDPI than Comparative Example VC.

[0414] At application rates of 3.9 and 1.9 g of a.s./ha, compound No. IBa.24, applied post-emergence, showed a considerably better action against the harmful plants SETFA and BIDPI than Comparative Example VD.

Use Examples (Desiccant/Defoliant Activity)

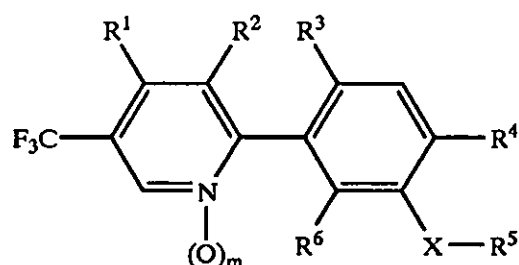
[0415] The test plants used were young cotton plants with 4 leaves (without cotyledons) which had been grown under greenhouse conditions (relative atmospheric humidity 50 to 70%; day/night temperature 27/20° C.).

[0416] The young cotton plants were subjected to leaf treatment to runoff point with aqueous preparations of the active ingredient (with addition of 0.15% by weight of the fatty alcohol alkoxide Plurafac® LF 700, based on the spray mixture). The amount of water applied corresponded to 1000 l/ha (converted). After 13 days, the number of shed leaves and the degree of defoliation were determined in %.

[0417] No leaves were shed in the case of the untreated control plants.

We claim:

1. A 2-aryl-5-trifluoromethylpyridine of the formula I



in which the variables m, R¹, R², R³, R⁴, R⁵, R⁶ and X have the following meanings:

m is 0 or 1,

X is a chemical bond, a methylene, 1,2-ethylene, propane-1,3-diyl, ethene-1,2-diyl or ethyne-1,2-diyl chain, or an oxymethylene or thiamethylene chain bonded to the phenyl ring via the hetero atom, it being possible for all chains to be unsubstituted or to have attached to them one or two substituents, in each case selected from the group consisting of cyano, carboxyl, halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, (C₁-C₄-alkoxy)carbonyl, di(C₁-C₄-alkyl)amino and phenyl;

R¹ is NH₂ or CH₃;

R² is halogen;

R³ is hydrogen or halogen;

R⁴ is halogen, cyano, OH, C₁-C₄-alkoxy or C₁-C₄-alkoxy-carbonyl-C₁-C₄-alkoxy;

R⁵ is hydrogen, nitro, cyano, halogen, halosulfonyl, N₃, —O—Y—R⁷, —O—CO—Y—R⁷, —N(Y—R⁷)(Z—R⁸), —N(Y—R⁷)—SO₂—Z—R⁸, —N(SO₂—Y—R⁷)(SO₂—Z—R⁸), —N(Y—R⁷)—CO—Z—R⁸, —N(Y—R⁷)(O—Z—R⁸), —S—Y—R⁷, —SO—Y—R⁷, —SO₂—Y—R⁷, —SO₂—O—Y—R⁷, —SO₂—N(Y—R⁷)(Z—R⁸), —CO—Y—R⁷, —C(=NOR⁹)—Y—R⁷, —C(=NOR⁹)—O—Y—R⁷, —CO—O—Y—R⁷, —CO—S—Y—R⁷, —CO—N(Y—R⁷)(Z—R⁸), —CO—N(Y—R⁷)(O—Z—R⁸) or —PO(O—Y—R⁷)₂;

R⁶ is hydrogen; or

R¹ and X—R⁵ or X—R⁵ and R⁶ are a 3- or 4-membered chain whose chain members, in addition to carbon, can have 1, 2 or 3 hetero atoms selected from among nitrogen, oxygen and sulfur atoms, which hetero atoms can be unsubstituted or can have attached to them, in turn, one, two or three substituents, and whose members can also encompass one or two nonadjacent carbonyl, thiocarbonyl or sulfonyl groups,

Y, Z independently of one another are:

a chemical bond, a methylene or ethylene group which can be unsubstituted or can have attached to it one or two substituents, in each case selected from the group consisting of carboxyl, C₁-C₄-alkyl, C₁-C₄-haloalkyl, (C₁-C₄-alkoxy)carbonyl and phenyl;

R⁷, R⁸ independently of one another are:

hydrogen, C₃-C₈-cycloalkyl-C₁-C₄-alkyl, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₂-C₆-alkenyl, C₂-C₆-haloalkenyl, C₂-C₆-alkynyl, C₂-C₆-haloalkynyl, —CH(R¹⁰)(R¹¹), —C(R¹⁰)(R¹¹)—CN, —C(R¹⁰)(R¹¹)—halogen, —C(R¹⁰)(R¹¹)—OR¹², —C(R¹⁰)(R¹¹)—N(R¹²)R¹³, —C(R¹⁰)(R¹¹)—N(R¹²)—OR¹³, —C(R¹⁰)(R¹¹)—SR¹², —C(R¹⁰)(R¹¹)—SO—R¹², —C(R¹⁰)(R¹¹)—SO₂—R¹², —C(R¹⁰)(R¹¹)—SO₂—OR¹², —C(R¹⁰)(R¹¹)—SO₂—N(R¹²)R¹³, —C(R¹⁰)(R¹¹)—CO—R¹², —C(R¹⁰)(R¹¹)—C(=NOR¹⁴)—R¹², —C(R¹⁰)(R¹¹)—CO—OR¹², —C(R¹⁰)(R¹¹)—CO—SR¹², —C(R¹⁰)(R¹¹)—CO—N(R¹²)R¹³, —C(R¹⁰)(R¹¹)—CO—N(R¹²)—OR¹³, —C(R¹⁰)(R¹¹)—PO(OR¹²)₂,

C₃-C₈-cycloalkyl which can contain a carbonyl or thiocarbonyl ring member,

phenyl or 3-, 4-, 5-, 6- or 7-membered heterocycl which can contain a carbonyl or thiocarbonyl ring member, it being possible for each cycloalkyl ring, for the phenyl ring and for each heterocycl ring to be unsubstituted or to have attached to it one, two, three or four substituents, in each case selected from the group consisting of cyano, nitro, amino, hydroxyl, carboxyl, halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, C₁-C₄-haloalkylthio, C₁-C₄-alkylsulfonyl, C₁-C₄-haloalkylsulfonyl, (C₁-C₄-alkyl)carbonyl, (C₁-C₄-haloalkyl)carbonyl, (C₁-C₄-alkyl)carbonyloxy, (C₁-C₄-haloalkyl)carbonyloxy, (C₁-C₄-alkoxy)carbonyl and di (C₁-C₄-alkyl) amino;

R⁹ is hydrogen, C₁-C₆-alkyl, C₁-C₄-alkoxycarbonyl-C₁-C₄-alkyl, C₄-C₈-cycloalkyl-C₁-C₄-alkyl, C₁-C₆-haloalkyl, C₂-C₆-alkenyl, C₂-C₆-haloalkenyl, C₂-C₆-alkynyl, C₂-C₆-haloalkynyl, C₃-C₈-cycloalkyl, phenyl or phenyl-C₁-C₄-alkyl;

where the variables R¹⁰ to R¹⁴ have the following meanings:

R¹⁰, R¹¹ independently of one another are

hydrogen, C₁-C₄-alkyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₁-C₄-alkylthio-C₁-C₄-alkyl, (C₁-C₄-alkoxy)carbonyl-C₁-C₄-alkyl or phenyl-C₁-C₄-alkyl, it being possible for the phenyl ring to be unsubstituted or to have attached to it one to three substituents, in each case selected from the group consisting of cyano, nitro, carboxyl, halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl and (C₁-C₄-alkoxy)carbonyl;

R¹², R¹³ independently of one another are

hydrogen, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₂-C₆-alkenyl, C₂-C₆-haloalkenyl, C₂-C₆-alkynyl, C₂-C₆-haloalkynyl, C₃-C₈-cycloalkyl, C₃-C₈-cycloalkyl-C₁-C₄-alkyl, phenyl, phenyl-C₁-C₄-alkyl, 3- to 7-membered heterocycl or heterocycl-C₁-C₄-alkyl, it being possible for each cycloalkyl and each heterocycl ring to contain a carbonyl or thiocarbonyl ring member,

and where each cycloalkyl ring, the phenyl ring and each heterocycl ring can be unsubstituted or have attached to it one, two, three or four substituents, in each case selected from the group consisting of cyano, nitro, amino, hydroxyl, carboxyl, halogen, C₁-C₄-alkyl, C₁-C₄-haloalkyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₁-C₄-alkylthio, C₁-C₄-haloalkylthio, C₁-C₄-alkylsulfonyl, C₁-C₄-haloalkylsulfonyl, (C₁-C₄-alkyl)carbonyl, (C₁-C₄-haloalkyl)carbonyl, (C₁-C₄-alkyl)carbonyloxy, (C₁-C₄-haloalkyl)carbonyloxy, (C₁-C₄-alkoxy)carbonyl and di(C₁-C₄-alkyl)amino;

R¹⁴ is hydrogen, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₂-C₆-alkenyl, C₂-C₆-haloalkenyl, C₂-C₆-alkynyl, C₂-C₆-haloalkynyl, C₃-C₈-cycloalkyl, C₁-C₄-alkoxycarbonyl-C₁-C₄-alkyl, phenyl or phenyl-C₁-C₄-alkyl;

or an agriculturally useful salt of I.

2. A 2-aryl-5-trifluoromethylpyridine as claimed in claim 1, where R² is fluorine or chlorine.

3. A 2-aryl-5-trifluoromethylpyridine as claimed in claim 1 or 2, where R³ is hydrogen, fluorine or chlorine.

4. A 2-aryl-5-trifluoromethylpyridine as claimed in any of the preceding claims, where R⁴ is chlorine or cyano and R⁶ is hydrogen.

5. A 2-aryl-5-trifluoromethylpyridine as claimed in any of the preceding claims, where R¹ is methyl.

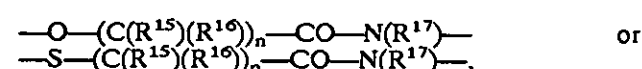
6. A 2-aryl-5-trifluoromethylpyridine as claimed in claim 5, where R² is chlorine, R³ is fluorine, R⁴ is chlorine or cyano and R⁶ is hydrogen.

7. A 2-aryl-5-trifluoromethylpyridine as claimed in claim 6, where X is a single bond and R⁵ is selected from among C₃-C₄-alkynyloxy, OCH(R¹⁹)-COOR²⁰, CO-OR²¹ and COO-CH(R²²)-COOR²³ where

R¹⁹, R²² independently of one another are hydrogen or C₁-C₄-alkyl,

R²⁰, R²¹, R²³ are C₁-C₄-alkyl, C₃-C₄-alkenyl, C₃-C₄-alkynyl, C₁-C₄-haloalkyl or C₁-C₄-alkoxy-C₁-C₄-alkyl.

8. A 2-aryl-5-trifluoromethylpyridine as claimed in any of claims 1 to 3 or 5, where R⁴ together with -X-R⁵ is a chain of the formulae:



where the nitrogen atom of the chain is attached to the C atom which, in formula I, has the group -X-R⁵ attached to it, in which the variables n, R¹⁵ to R¹⁷ have the following meanings:

n is 0 or 1,

R¹⁵, R¹⁶ independently of one another are

hydrogen, C₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-haloalkyl, C₂-C₆-alkenyl, C₂-C₆-haloalkenyl, C₂-C₆-alkynyl, C₂-C₆-haloalkynyl, C₃-C₈-cycloalkyl, phenyl or phenyl-C₁-C₄-alkyl;

R¹⁷ is hydrogen, hydroxyl, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₂-C₆-alkenyl, C₂-C₆-haloalkenyl, C₂-C₆-alkynyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₃-C₆-alkenyloxy, C₃-C₆-alkynyloxy, C₁-C₄-alkylsulfonyl, C₁-C₄-haloalkylsulfonyl, C₁-C₄-alkylcarbonyl, C₁-C₄-haloalkylcarbonyl, C₁-C₄-alkoxycarbonyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₁-C₄-alkoxycarbonyl-C₁-C₄-alkyl, C₁-C₄-alkoxycarbonyl-C₁-C₄-alkoxy, mono- and di(C₁-C₄-alkyl)aminocarbonyl, mono- and di(C₁-C₄-alkyl)aminocarbonyl-C₁-C₄-alkyl, mono- and di(C₁-C₄-alkyl)aminocarbonyl-C₁-C₄-alkoxy, phenyl, phenyl-C₁-C₄-alkyl, C₃-C₈-cycloalkyl, C₃-C₈-cycloalkyl-C₁-C₄-alkyl, 3-, 4-, 5-, 6- or 7-membered heterocycl, 3-, 4-, 5-, 6- or 7-membered heterocycl-C₁-C₄-alkyl which has one or two ring hetero atoms selected from among oxygen, nitrogen or sulfur.

9. A 2-aryl-5-trifluoromethylpyridine as claimed in claim 8, where R³ is fluorine or hydrogen.

10. A 2-aryl-5-trifluoromethylpyridine as claimed in any of claims 1 to 3 or 5, where R⁶ together with -X-R⁵ is a chain of the formulae -N=C(R¹⁸)-O- and -N=C(R¹¹)-S- in which the nitrogen atom of the chain is bonded to the C atom in the phenyl ring of the formula I which has the group X-R⁵ attached to it and where

R¹⁸ is hydrogen, halogen, cyano, amino, C₁-C₆-alkyl, C₁-C₆-haloalkyl, C₂-C₆-alkenyl, C₂-C₆-haloalkenyl, C₂-C₆-alkynyl, C₁-C₄-alkoxy, C₁-C₄-haloalkoxy, C₃-C₆-alkenyloxy, C₃-C₆-alkynyloxy, C₁-C₄-alkylamino, di(C₁-C₄-alkyl)amino, C₁-C₄-haloalkoxy,

C₁-C₄-alkylthio, C₁-C₄-haloalkylthio, C₁-C₄-alkylsulfinyl, C₁-C₄-haloalkylsulfinyl, C₁-C₄-alkylsulfonyl, C₁-C₄-haloalkylsulfonyl, C₁-C₄-alkylcarbonyl, C₁-C₄-haloalkylcarbonyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₁-C₄-alkoxycarbonyl, C₁-C₄-alkoxycarbonyl-C₁-C₄-alkyl, C₁-C₄-alkoxycarbonyl-C₁-C₄-alkoxy, C₁-C₄-alkoxycarbonyl-C₁-C₄-alkylthio, di(C₁-C₄-alkyl) aminocarbonyl, di(C₁-C₄-alkyl) aminocarbonyl-C₁-C₄-alkyl, di(C₁-C₄-alkyl) aminocarbonyl-C₁-C₄-alkoxy, di(C₁-C₄-alkyl) aminocarbonyl-C₁-C₄-alkylthio, C₃-C₈-cycloalkyl, phenyl, phenyl-C₁-C₄-alkyl, C₃-C₈-cycloalkyl-C₁-C₄-alkyl, 3-, 4-, 5-, 6- or 7-membered heterocyclyl which has one or two ring hetero atoms selected from among oxygen, nitrogen or sulfur.

11. A 2-aryl-5-trifluoromethylpyridine as claimed in claim 10, where R³ is fluorine or hydrogen and R⁴ is chlorine or cyano.

12. The use of a 2-aryl-5-trifluoromethylpyridine of the formula I and of its agriculturally useful salts as claimed in claim 1 as herbicides or for the desiccation/defoliation of plants.

13. A composition comprising a herbicidally effective amount of at least one 2-aryl-5-trifluoromethylpyridine of the formula I or of an agriculturally useful salt of I as claimed in claim 1 and at least one inert liquid and/or solid carrier and, if desired, at least one surface-active substance.

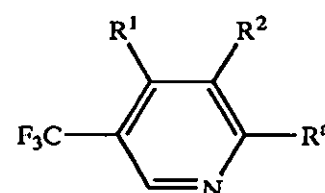
14. A composition for the desiccation and/or defoliation of plants comprising such an amount of at least one 2-aryl-5-trifluoromethylpyridine of the formula I or of an agriculturally useful salt of I as claimed in claim 1 and at least one inert liquid and/or solid carrier and, if desired, at least one surface-active agent that it has a desiccant and/or defoliant action.

15. A method of controlling undesired vegetation, which comprises allowing a herbicidally active amount of at least one 2-aryl-5-trifluoromethylpyridine of the formula I or of an agriculturally useful salt of I as claimed in claim 1 to act on plants, their environment or on seed.

16. A method for the desiccation and/or defoliation of plants, which comprises allowing such an amount of at least one 2-aryl-5-trifluoromethylpyridine of the formula I or of an agriculturally useful salt of I as claimed in claim 1 to act on plants that it has a desiccant and/or defoliant action.

17. A method as claimed in claim 16, wherein cotton is treated.

18. A pyridine compound of the formula II

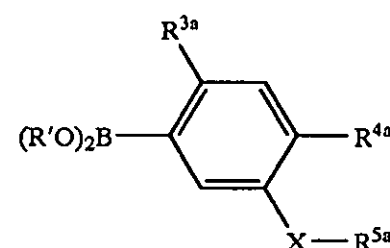


(II)

in which the variables R¹ and R² have the meanings given in claim 1 and

R⁴ is halogen, OH, benzyloxy, C₁-C₄-alkoxy or is S(O)_k-phenyl where k is 0, 1 or 2.

19. A boronic acid compound of the formula IIIa



(IIIa)

in which X is a single bond and the variables R¹, R^{3a}, R^{4a} and R^{5a} have the following meanings:

R¹ is hydrogen or C₁-C₁₀-alkyl or two radicals R¹ together form a chain of the formula —CH₂—CH₂— or —CH₂—CH₂—CH₂—,

R^{3a} is hydrogen or halogen;

R^{4a} is halogen or C₁-C₄-alkoxy;

R^{5a} is hydrogen, cyano, halogen, —O—Y—R^{7a}, —O—CO—Y—R⁷, —S—Y—R^{7a}, —CO—O—Y—R⁷ or —PO(O—Y—R^{7a})₂; where R^{7a} is a group —C(R¹⁰)(R¹¹)—CO—OR¹² and Y, R⁷, R¹⁰, R¹¹ and R¹² have the meanings given in claim 1;

or R^{4a} is CN and R^{5a} have the following meanings:

R^{5a} is cyano, halogen, —O—Y—R⁷, —O—CO—Y—R⁷, —S—Y—R⁷, —CO—O—Y—R⁷ or —PO(O—Y—R⁷)₂; where Y and R⁷ have the meanings given in claim 1.

* * * * *

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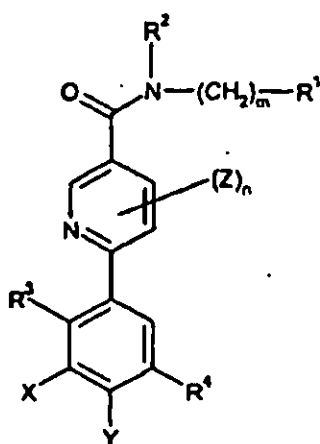
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(54) Title: NICOTINAMIDE DERIVATES USEFUL AS P38 INHIBITORS



(I)

(57) Abstract: Compounds of formula (I), are inhibitors of p38 kinase and are useful in the treatment of conditions or disease states mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38.

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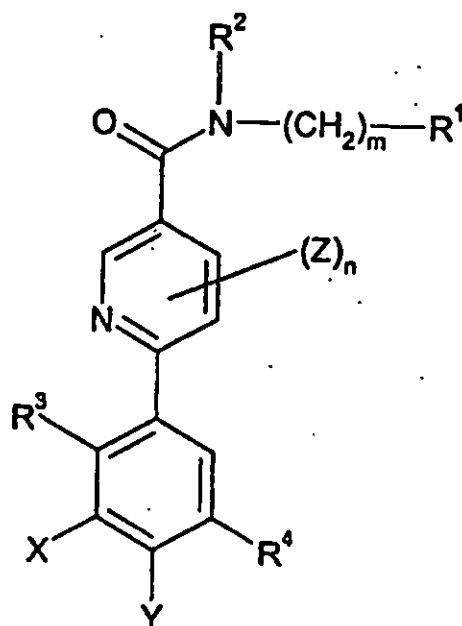
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NICOTINAMIDE DERIVATES USEFUL AS P38 INHIBITORS

This invention relates to novel compounds and their use as pharmaceuticals, particularly as p38 kinase inhibitors, for the treatment of conditions or disease states mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase.

We have now found a group of novel compounds that are inhibitors of p38 kinase.

According to the invention there is provided a compound of formula (I):



(I)

wherein

R^1 is selected from hydrogen, C_{1-6} alkyl optionally substituted by up to three groups selected from C_{1-6} alkoxy, halogen and hydroxy, C_{2-6} alkenyl, C_{3-7} cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups, phenyl optionally substituted by up to three groups selected from R^5 and R^6 , and heteroaryl optionally substituted by up to three groups selected from R^5 and R^6 ,

R^2 is selected from hydrogen, C_{1-6} alkyl and $-(CH_2)_q-C_{3-7}$ cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups, or $(CH_2)_mR^1$ and R^2 , together with the nitrogen atom to which they are bound, form a four- to six-membered heterocyclic ring optionally substituted by up to three C_{1-6} alkyl groups;

R^3 is chloro or methyl;

R^4 is the group $-NH-CO-R^7$ or $-CO-NH-(CH_2)_q-R^8$;

R^5 is selected from C_{1-6} alkyl, C_{1-6} alkoxy, $-(CH_2)_q-C_{3-7}$ cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups, $-CONR^9R^{10}$, $-NHCOR^{10}$, $-SO_2NHR^9$, $-(CH_2)_sNHSO_2R^{10}$, halogen, CN, OH, $-(CH_2)_sNR^{11}R^{12}$, and trifluoromethyl;

R^6 is selected from C_{1-6} alkyl, C_{1-6} alkoxy, halogen, trifluoromethyl and $-(CH_2)_sNR^{11}R^{12}$;

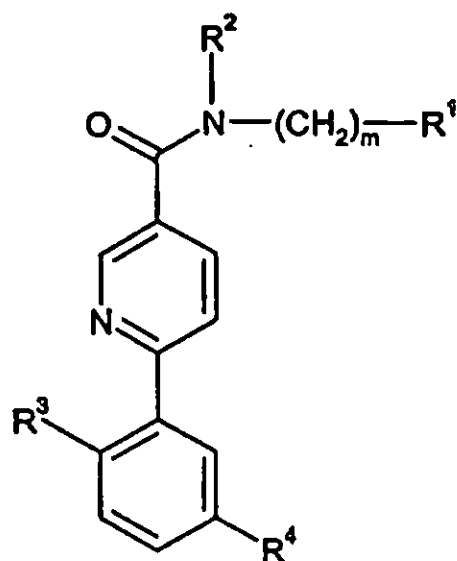
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- R^7 is selected from hydrogen, C_{1-6} alkyl, $-(CH_2)_q-C_{3-7}$ cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups, trifluoromethyl, $-(CH_2)_r$ heteroaryl optionally substituted by R^{13} and/or R^{14} , and $-(CH_2)_r$ phenyl optionally substituted by R^{13} and/or R^{14} ;
- 5 R^8 is selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups, $CONHR^9$, phenyl optionally substituted by R^{13} and/or R^{14} , and heteroaryl optionally substituted by R^{13} and/or R^{14} ;
- R^9 and R^{10} are each independently selected from hydrogen and C_{1-6} alkyl, or R^9 and R^{10} , together with the nitrogen atom to which they are bound, form
- 10 a five- to six-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and $N-R^{15}$, wherein the ring may be substituted by up to two C_{1-6} alkyl groups;
- R^{11} is selected from hydrogen, C_{1-6} alkyl and $-(CH_2)_q-C_{3-7}$ cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups,
- 15 R^{12} is selected from hydrogen and C_{1-6} alkyl, or R^{11} and R^{12} , together with the nitrogen atom to which they are bound, form a five or six-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and $N-R^{15}$;
- R^{13} is selected from C_{1-6} alkyl, C_{1-6} alkoxy, $-(CH_2)_q-C_{3-7}$ cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups, $-CONR^9R^{10}$, $-NHCOR^{10}$, halogen, CN, $-(CH_2)_sNR^{11}R^{12}$, trifluoromethyl, phenyl optionally substituted by one or more R^{14} groups and heteroaryl optionally substituted by one or more R^{14} groups;
- 20 R^{14} is selected from C_{1-6} alkyl, C_{1-6} alkoxy, halogen, trifluoromethyl and $-NR^{11}R^{12}$;
- 25 R^{15} is selected from hydrogen and methyl;
- X and Y are each independently selected from hydrogen, methyl and halogen;
- Z is halogen;
- m is selected from 0, 1, 2, 3 and 4, wherein each carbon atom of the resulting carbon chain may be optionally substituted with up to two groups selected
- 30 independently from C_{1-6} alkyl and halogen;
- n is selected from 0, 1 and 2;
- q is selected from 0, 1 and 2;
- r is selected from 0 and 1; and
- s is selected from 0, 1, 2 and 3.
- 35 According to a further embodiment of the invention there is provided a compound of formula (IA):

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(IA)

wherein R^1 , R^2 , R^3 , R^4 and m are as defined above.

According to one embodiment of the present invention, R^1 is selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl optionally substituted by R^5 and/or R^6 , and heteroaryl optionally substituted by R^5 and/or R^6 , and R^2 is selected from hydrogen, C_{1-6} alkyl and $-(CH_2)_q-C_{3-7}$ cycloalkyl.

In a preferred embodiment, R^1 is selected from C_{1-6} alkyl, for example methyl, ethyl, n-propyl, isopropyl, 1-methylpropyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, 1-ethyl-1-methyl-propyl, n-butyl, isobutyl, 3-methylbutyl, 1,1-dimethylbutyl, 1,3-dimethylbutyl, 3,3-dimethylbutyl, 2-pentyl or 1-methylpentyl, optionally substituted by up to three groups selected from C_{1-6} alkoxy, in particular C_{1-4} alkoxy groups such as methoxy or t-butoxy, halogen, in particular fluorine, and hydroxy; C_{2-6} alkenyl, for example C_{4-6} alkenyl such as 3-methylbut-2-enyl or 1,1-dimethylbut-2-enyl; C_{3-7} cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups, for example cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, in particular cyclopropyl, optionally substituted by one or two C_{1-4} alkyl groups such as methyl or ethyl; phenyl optionally substituted by up to three groups selected from R^5 and R^6 , for example phenyl optionally substituted by up to three substituents, for example one or two substituents, such as C_{1-4} alkyl, in particular methyl, C_{1-4} alkoxy, in particular methoxy, halogen, in particular fluorine or chlorine, trifluoromethyl, $-(CH_2)_sNR^{11}R^{12}$ or $-(CH_2)_sNHSO_2R^{10}$, located on any position on the ring; heteroaryl optionally substituted by up to three groups selected from R^5 and R^6 , for example heteroaryl optionally substituted by one or two substituents, in particular a 5-membered heteroaryl such as furyl, thienyl or thiazolyl optionally substituted by C_{1-4} alkyl, in particular methyl. In a particularly preferred embodiment, R^1 is C_{1-6} alkyl, for example C_{2-5} alkyl, such as ethyl, n-propyl, isopropyl, 1-methylpropyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, n-butyl, isobutyl, 3-methylbutyl or 2-pentyl.

In another preferred embodiment, R^1 is selected from C_{3-7} cycloalkyl, phenyl optionally substituted by R^5 and/or R^6 , and heteroaryl optionally substituted by R^5 and/or R^6 . In a more preferred embodiment, R^1 is selected from C_{3-6} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, in particular cyclopropyl, and phenyl optionally substituted by R^5 and/or R^6 . The phenyl may be optionally substituted by one or two substituents, located on any position on the phenyl ring.

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Preferred substituents for the phenyl include C₁₋₄alkoxy, in particular methoxy, -
(CH₂)₅NR¹¹R¹², and -(CH₂)₅NHSO₂R¹⁰.

In another preferred embodiment, R¹ is selected from C₁₋₆alkyl, for example
n-propyl, 1-methylpropyl, isobutyl, 3-methylbutyl or 2,2-dimethylpropyl, and C₃₋₇
cycloalkyl optionally substituted by one or more C₁₋₆alkyl groups, for example
cyclopropyl optionally substituted by one or two methyl groups.

In a further preferred embodiment, R¹ is selected from C₁₋₆alkyl, for example
methyl, ethyl, n-propyl, isopropyl, 1,1-dimethylpropyl, 1-ethyl-1-methyl-propyl, n-
butyl, isobutyl, 1,1-dimethylbutyl, 1,3-dimethylbutyl, 3,3-dimethylbutyl, 2-pentyl or 1-
methylpentyl, optionally substituted by up to three groups selected from C₁₋₆alkoxy,
in particular C₁₋₄alkoxy groups such methoxy or t-butoxy, halogen, in particular
fluorine, and hydroxy; C₂₋₆alkenyl, for example C₄₋₆alkenyl such as 3-methylbut-2-
enyl or 1,1-dimethylbut-2-enyl; C₃₋₇cycloalkyl optionally substituted by one or more
C₁₋₆alkyl groups, for example, cyclopropyl, cyclopentyl or cyclohexyl, optionally
substituted by one or two ethyl groups; phenyl optionally substituted by up to three
groups selected from R⁵ and R⁶, for example phenyl optionally substituted by up to
three substituents such as C₁₋₄alkyl, in particular methyl, C₁₋₄alkoxy, in particular
methoxy, halogen, in particular fluorine or chlorine and trifluoromethyl, located on
any position on the ring; heteroaryl optionally substituted by up to three groups
selected from R⁵ and R⁶, in particular a 5-membered heteroaryl such as furyl, thienyl
or thiazolyl optionally substituted by C₁₋₄alkyl, in particular methyl.

In a preferred embodiment, R² is selected from hydrogen; C₁₋₄alkyl, in
particular methyl, ethyl, isopropyl or isobutyl; and -(CH₂)_q-C₃₋₆cycloalkyl, in
particular cyclopropyl, -CH₂-cyclopentyl, -(CH₂)₂-cyclopentyl or cyclohexyl.

In another preferred embodiment, R² is selected from hydrogen, C₁₋₄alkyl and
-CH₂-cyclopropyl. More preferably R² is hydrogen.

In a further preferred embodiment, (CH₂)_mR¹ and R², together with the
nitrogen atom to which they are bound, form a four- to six-membered heterocyclic
ring optionally substituted by up to three C₁₋₆alkyl groups, in particular an azetidiny,
pyrrolidiny or piperidiny ring optionally substituted by one or two methyl, ethyl or
propyl groups.

In a preferred embodiment, R³ is methyl.

In a preferred embodiment, R⁴ is the group -CO-NH-(CH₂)_q-R⁸.

In one embodiment of the present invention, R⁵ is selected from C₁₋₆alkyl,
C₁₋₆alkoxy, -(CH₂)_q-C₃₋₇cycloalkyl, -CONR⁹R¹⁰, -NHCOR¹⁰, -SO₂NHR⁹, -
(CH₂)₅NHSO₂R¹⁰, halogen, CN, OH, -(CH₂)₅NR¹¹R¹², and trifluoromethyl.

In a preferred embodiment, R⁵ is selected from C₁₋₄alkyl, in particular
methyl; C₁₋₄alkoxy, in particular methoxy; -(CH₂)₅NHSO₂R¹⁰; halogen, in
particular chlorine or fluorine; -(CH₂)₅NR¹¹R¹²; and trifluoromethyl.

In another preferred embodiment, R⁵ is selected from C₁₋₄alkoxy, in
particular methoxy, -(CH₂)₅NR¹¹R¹², and -(CH₂)₅NHSO₂R¹⁰.

In a further preferred embodiment, R⁵ is selected from C₁₋₄alkyl, in particular
methyl; C₁₋₄alkoxy, in particular methoxy; halogen, in particular chlorine or fluorine;
and trifluoromethyl.

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In a preferred embodiment, R⁶ is selected from C₁₋₄alkyl, in particular methyl, ethyl or propyl; C₁₋₄alkoxy, in particular methoxy; halogen, in particular chlorine or fluorine; and trifluoromethyl.

In a further preferred embodiment, R⁶ is C₁₋₄alkoxy, in particular methoxy.

5 In one embodiment of the present invention, R⁷ is selected from hydrogen, C₁₋₆alkyl, -(CH₂)_q-C₃₋₇cycloalkyl, trifluoromethyl, -(CH₂)_rheteroaryl optionally substituted by R¹³ and/or R¹⁴, and -(CH₂)_rphenyl optionally substituted by R¹³ and/or R¹⁴.

10 In a preferred embodiment, R⁷ is selected from C₁₋₆alkyl, -(CH₂)_q-C₃₋₇cycloalkyl, trifluoromethyl, -(CH₂)_rheteroaryl optionally substituted by R¹³ and/or R¹⁴, and -(CH₂)_rphenyl optionally substituted by C₁₋₆alkyl, C₁₋₆alkoxy, -(CH₂)_q-C₃₋₇cycloalkyl, -CONR⁹R¹⁰, -NHCOR¹⁰, halogen, CN, trifluoromethyl, phenyl optionally substituted by one or more R¹⁴ groups and/or heteroaryl optionally substituted by one or more R¹⁴ groups. In another preferred embodiment, R⁷ is
15 selected from C₁₋₄alkyl, -(CH₂)_q-C₃₋₆cycloalkyl, trifluoromethyl, -(CH₂)_rheteroaryl optionally substituted by R¹³ and/or R¹⁴, and -(CH₂)_rphenyl optionally substituted by C₁₋₆alkyl, C₁₋₆alkoxy, -(CH₂)_q-C₃₋₇cycloalkyl, -CONR⁹R¹⁰, -NHCOR¹⁰, halogen, CN, trifluoromethyl, phenyl optionally substituted by one or more R¹⁴ groups and/or heteroaryl optionally substituted by one or more R¹⁴ groups. In a more
20 preferred embodiment, R⁷ is -(CH₂)_rheteroaryl optionally substituted by R¹³ and/or R¹⁴, in particular a five or six-membered heteroaryl containing at least one heteroatom selected from oxygen, nitrogen and sulfur, for example, pyridinyl optionally substituted by -NR¹¹R¹², furyl or thiophenyl.

In one embodiment of the present invention, R⁸ is selected from hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, CONHR⁹, phenyl optionally substituted by R¹³ and/or R¹⁴, and heteroaryl optionally substituted by R¹³ and/or R¹⁴
25

In a preferred embodiment, R⁸ is selected from C₃₋₇cycloalkyl, CONHR⁹, heteroaryl optionally substituted by R¹³ and/or R¹⁴, and phenyl optionally substituted by C₁₋₆alkyl, C₁₋₆alkoxy, -(CH₂)_q-C₃₋₇cycloalkyl, -CONR⁹R¹⁰, -NHCOR¹⁰,
30 halogen, CN, trifluoromethyl, phenyl optionally substituted by one or more R¹⁴ groups and/or heteroaryl optionally substituted by one or more R¹⁴ groups. In another preferred embodiment, R⁸ is selected from C₃₋₇cycloalkyl, heteroaryl optionally substituted by R¹³ and/or R¹⁴, and phenyl optionally substituted C₁₋₆alkyl, C₁₋₆alkoxy, -(CH₂)_q-C₃₋₇cycloalkyl, -CONR⁹R¹⁰, -NHCOR¹⁰, halogen, CN,
35 trifluoromethyl, phenyl optionally substituted by one or more R¹⁴ groups and/or heteroaryl optionally substituted by one or more R¹⁴ groups. In a more preferred embodiment, R⁸ is selected from C₃₋₆cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, in particular cyclopropyl, heteroaryl optionally substituted by R¹³ and/or R¹⁴, in particular a five or six-membered heteroaryl containing at least
40 one heteroatom selected from nitrogen and sulfur, for example, thiazolyl or thiadiazolyl, and phenyl optionally substituted by heteroaryl. In a particularly preferred embodiment, R⁸ is selected from C₃₋₆cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, in particular cyclopropyl.

In a preferred embodiment, R⁹ is selected from hydrogen and C₁₋₄alkyl.

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In a preferred embodiment, R^{10} is selected from hydrogen and C_{1-4} alkyl, in particular methyl.

In one embodiment, R^{11} is selected from hydrogen, C_{1-6} alkyl and $-(CH_2)_q$ - C_{3-7} cycloalkyl optionally substituted by C_{1-6} alkyl.

5 In a preferred embodiment, R^{11} and R^{12} , together with the nitrogen atom to which they are bound, form a five or six-membered heterocyclic ring optionally further containing one additional heteroatom N- R^{15} .

10 In one embodiment of the present invention, R^{13} is selected from C_{1-6} alkyl, C_{1-6} alkoxy, $-(CH_2)_q$ - C_{3-7} cycloalkyl, $-CONR^9R^{10}$, $-NHCOR^{10}$, halogen, CN, $-(CH_2)_5NR^{11}R^{12}$, trifluoromethyl, phenyl optionally substituted by one or more R^{14} groups and heteroaryl optionally substituted by one or more R^{14} groups;

15 In a preferred embodiment, R^{13} is selected from C_{1-4} alkyl, in particular methyl, C_{1-4} alkoxy, in particular methoxy, halogen, $-(CH_2)_5NR^{11}R^{12}$, phenyl optionally substituted by one or more R^{14} groups and heteroaryl optionally substituted by one or more R^{14} groups. In a more preferred embodiment, R^{13} is selected from $-(CH_2)_5NR^{11}R^{12}$ and heteroaryl optionally substituted by one or more R^{14} groups, in particular a five or six-membered heteroaryl containing at least one nitrogen atom, for example, pyridyl.

20 In a preferred embodiment R^{14} is selected from C_{1-4} alkyl, in particular methyl, C_{1-4} alkoxy, in particular methoxy, and $-NR^{11}R^{12}$.

In a preferred embodiment, R^{15} is methyl.

In a preferred embodiment, X and Y are each independently selected from hydrogen, chlorine and fluorine. In a further preferred embodiment, X is fluorine. In another preferred embodiment, Y is hydrogen.

25 In a preferred embodiment, Z is fluorine.

In one embodiment of the present invention, m is selected from 0, 1, 2, 3 and 4. In another embodiment of the present invention, m is selected from 0, 1, 2, 3 and 4, wherein each carbon atom of the resulting carbon chain may be optionally substituted with up to two groups selected independently from C_{1-6} alkyl.

30 In a preferred embodiment, m is selected from 0, 1, 2 and 3. In a further preferred embodiment, m is selected from 0, 1 and 2, in particular 0 and 1. When the carbon chain of m is substituted, these substituents are preferably one or two methyl groups or fluorine atoms. In one embodiment, the substituents are preferably one or two methyl groups. In another embodiment, the substituents are preferably one or two fluorine atoms.

In a preferred embodiment, n is selected from 0 and 1. In particular, n is 0.

In a preferred embodiment, q is selected from 0 and 1. In particular, q is 0.

In a preferred embodiment, r is 0.

In a preferred embodiment, s is selected from 0 and 1.

40 It is to be understood that the present invention covers all combinations of particular and preferred groups described hereinabove.

Particular compounds according to the invention include those mentioned in the Examples. Specific examples which may be mentioned include:

45 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-cyclopropylmethyl-nicotinamide;

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6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(1-cyclopropylethyl)-nicotinamide;

6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide;

5 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2-methylpropyl)-nicotinamide; and

6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(1-methylpropyl)-nicotinamide.

Further specific examples which may be mentioned include:

10 6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-cyclobutylmethyl-nicotinamide;

6-(5-cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-cyclobutyl-nicotinamide;

6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(2,4,5-trifluorobenzyl)nicotinamide;

15 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(2,5-difluorobenzyl)nicotinamide;

6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(3,4-difluorobenzyl)nicotinamide;

20 N-(3-chlorobenzyl)-6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}nicotinamide;

N-(4-chlorobenzyl)-6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}nicotinamide;

N-(3-chloro-2-fluorobenzyl)-6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}nicotinamide;

25 N-(2-chloro-3,6-difluorobenzyl)-6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}nicotinamide;

6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(2,3-difluoro-4-methylbenzyl)nicotinamide;

30 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(2,3,5-trifluorobenzyl)nicotinamide;

6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(3-fluoro-4-methylbenzyl)nicotinamide;

N-(5-chloro-2-fluorobenzyl)-6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}nicotinamide;

35 N-(2-chlorobenzyl)-6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}nicotinamide;

6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(4-fluorobenzyl)nicotinamide;

40 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(2,3,4-trifluorobenzyl)nicotinamide;

N-benzyl-6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}nicotinamide;

6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-[3-(trifluoromethyl)benzyl]nicotinamide;

45 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(1,1-dimethylbutyl)nicotinamide;

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- N-(4-chloro-2-fluorobenzyl)-6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}nicotinamide;
 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-[4-(trifluoromethyl)benzyl]nicotinamide;
 5 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-[(5-methyl-2-furyl)methyl]nicotinamide;
 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(2,3-difluorobenzyl)nicotinamide;
 N-(3-chloro-4-fluorobenzyl)-6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}nicotinamide;
 10 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(4-methylbenzyl)nicotinamide;
 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-[(3-methylthien-2-yl)methyl]nicotinamide;
 15 N-(3-chloro-2,6-difluorobenzyl)-6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}nicotinamide;
 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(1-ethyl-1-methylpropyl)nicotinamide;
 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(2-fluorobenzyl)nicotinamide;
 20 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(tert-pentyl)nicotinamide; and
 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(3-methylbenzyl)nicotinamide.

25 As used herein, the term "alkyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms. For example, C₁₋₆alkyl means a straight or branched alkyl containing at least 1, and at most 6, carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl and t-butyl. A C₁₋₄alkyl group is preferred, for example methyl, ethyl, isopropyl or t-butyl. The said alkyl groups may be optionally substituted with one or more fluorine atoms for example, trifluoromethyl.

35 As used herein, the term "alkenyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms and containing at least one double bond. For example, C₂₋₆alkenyl means a straight or branched alkenyl containing at least 2, and at most 6, carbon atoms and containing at least one double bond. Examples of "alkenyl" as used herein include, but are not limited to ethenyl, propenyl, 3-methylbut-2-enyl and 1,1-dimethylbut-2-enyl.

40 As used herein, the term "alkoxy" refers to a straight or branched chain alkoxy group, for example, methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy, 2-methylprop-1-oxy, 2-methylprop-2-oxy, pentoxy, or hexyloxy. A C₁₋₄alkoxy group is preferred, for example methoxy or ethoxy.

45 As used herein, the term "cycloalkyl" refers to a non-aromatic hydrocarbon ring containing the specified number of carbon atoms which may optionally contain up to one double bond. For example, C₃₋₇cycloalkyl means a non-aromatic ring

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containing at least three, and at most seven, ring carbon atoms. Examples of "cycloalkyl" as used herein include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A C₃₋₆cycloalkyl group is preferred, for example, cyclopropyl, cyclopentyl or cyclohexyl. The said cycloalkyl groups may be optionally substituted with one or more C₁₋₆alkyl groups, for example one or two methyl groups. In one embodiment, the cycloalkyl groups may be optionally substituted by up to four C₁₋₆alkyl groups, for example one or two C₁₋₆alkyl groups, in particular one or two C₁₋₄alkyl groups such as methyl or ethyl.

As used herein, the terms "heteroaryl ring" and "heteroaryl" refer to a monocyclic five- to seven-membered unsaturated hydrocarbon ring containing at least one heteroatom independently selected from oxygen, nitrogen and sulfur. Preferably, the heteroaryl ring has five or six ring atoms. Examples of heteroaryl rings include, but are not limited to, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl. The said ring may be optionally substituted by one or more substituents independently selected from C₁₋₆alkyl and oxy.

As used herein, the terms "heterocyclic ring" or "heterocyclyl" refer to a monocyclic three- to seven-membered saturated hydrocarbon ring containing at least one heteroatom independently selected from oxygen, nitrogen and sulfur. Preferably, the heterocyclyl ring has five or six ring atoms. Examples of heterocyclyl groups include, but are not limited to, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl, morpholino, tetrahydropyranyl, tetrahydrofuranyl, and thiomorpholino. The said ring may be optionally substituted by one or more substituents independently selected from C₁₋₆alkyl and oxy.

As used herein, the terms "halogen" or "halo" refer to the elements fluorine, chlorine, bromine and iodine. Preferred halogens are fluorine, chlorine and bromine. A particularly preferred halogen is fluorine or chlorine.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) which occur and events that do not occur.

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. All such solvates are included within the scope of the present invention.

Certain compounds of formula (I) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms or may exhibit cis-trans isomerism). The individual stereoisomers (enantiomers and diastereomers) and

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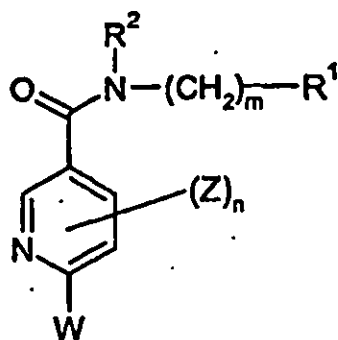
mixtures of these are included within the scope of the present invention. The present invention also covers the individual isomers of the compounds represented by formula (I) as mixtures with isomers thereof in which one or more chiral centres are inverted. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

Salts of the compounds of the present invention are also encompassed within the scope of the invention and may, for example, comprise acid addition salts resulting from reaction of an acid with a basic nitrogen atom present in a compound of formula (I).

Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Representative salts include the following salts: Acetate, Benzenesulfonate, Benzoate, Bicarbonate, Bisulfate, Bitartrate, Borate, Bromide, Calcium Edetate, Camsylate, Carbonate, Chloride, Clavulanate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluceptate, Gluconate, Glutamate, Glycolylarsanilate, Hexylresorcinate, Hydrabamine, Hydrobromide, Hydrochloride, Hydroxynaphthoate, Iodide, Isethionate, Lactate, Lactobionate, Laurate, Malate, Maleate, Mandelate, Mesylate, Methylbromide, Methylnitrate, Methylsulfate, Monopotassium Maleate, Mucate, Napsylate, Nitrate, N-methylglucamine, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Potassium, Salicylate, Sodium, Stearate, Subacetate, Succinate, Tannate, Tartrate, Teoclate, Tosylate, Triethiodide, Trimethylammonium and Valerate. Other salts which are not pharmaceutically acceptable may be useful in the preparation of compounds of this invention and these form a further aspect of the invention.

The compounds of this invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the working Examples.

A compound of formula (I) may be prepared by reacting a compound of (II)

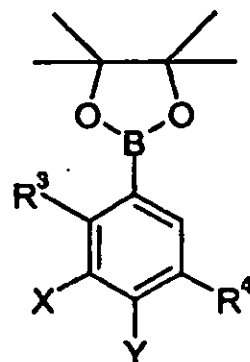


(II)

in which R¹, R², Z, m and n are as hereinbefore defined and W is halogen, in particular bromine or chlorine, with a compound of formula (III)

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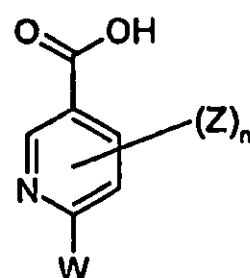
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(III)

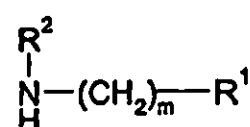
in which R³, R⁴, X and Y are as hereinbefore defined,
in the presence of a catalyst, for example tetrakis(triphenylphosphine)palladium.

- 5 A compound of formula (II) may readily be prepared from a corresponding acid compound of formula (IV)



(IV)

- 10 in which Z, W and n are as hereinbefore defined,
by converting the acid to an activated form of the acid, for example the acid chloride,
by treatment with, for example, thionyl chloride, and then reacting the activated acid
thus formed with an amine compound of formula (V)



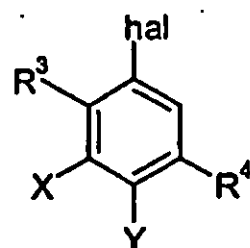
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(V)

in which R¹, R² and m are as hereinbefore defined,
under amide forming conditions.

- 20 Suitable amide forming conditions are well known in the art and include
treating a solution of the acid of formula (IV), or the activated form thereof, in for
example acetone or dichloromethane, with an amine of formula (V) in the presence of
sodium carbonate.

A compound of formula (III) may be prepared by reacting a compound of
formula (VI)



25

(VI)

in which R³, R⁴, X and Y are as hereinbefore defined and hal is halogen, in particular
iodine,

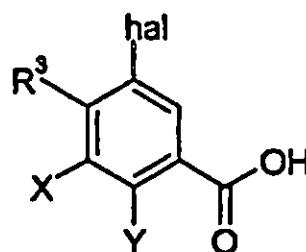
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with bis(pinnacolato)diboron, PdCl₂dppf and potassium acetate in a solvent such as DMF.

Alternatively, when R⁴ is -CO-NH-(CH₂)_q-R⁸, a compound of formula (III) may be prepared by reacting an acid compound of formula (VII)

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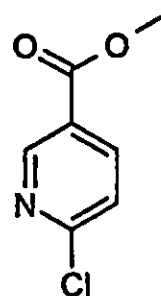
(VII)

in which R³, hal, X and Y are as hereinbefore defined,

with bis(pinnacolato)diboron, PdCl₂dppf and potassium acetate in a solvent such as DMF, and then forming an amide by reaction with an amine compound of formula (V) as hereinbefore defined.

10

A compound of formula (I) may also be prepared by reacting a compound of formula (VIII)



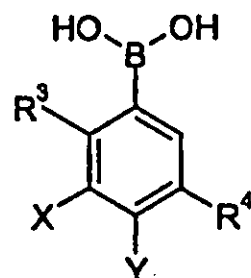
(VIII)

15

with a compound of formula (III) as hereinbefore defined and then reacting the acid thus formed with an amine of formula (V) as hereinbefore defined, under amide forming conditions.

Additionally, a compound of formula (I) may be prepared by reacting a compound of (II) as hereinbefore defined with a compound of formula (IX)

20



(IX)

in which R³, R⁴, X and Y are as hereinbefore defined,

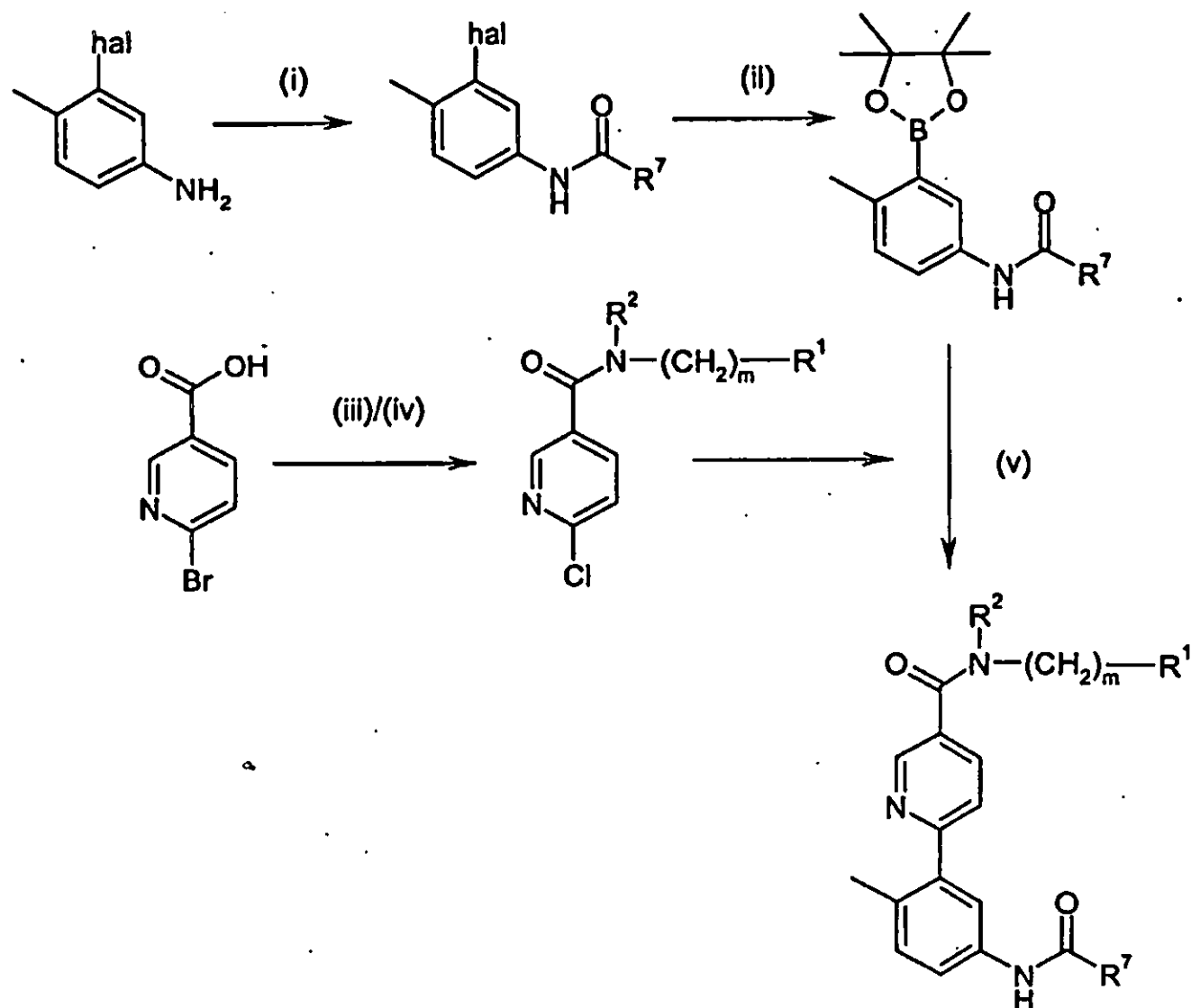
in the presence of a catalyst, for example tetrakis(triphenylphosphine)palladium.

For example, one general method for preparing the compounds of formula (I) comprises the reactions set out in Scheme 1 below.

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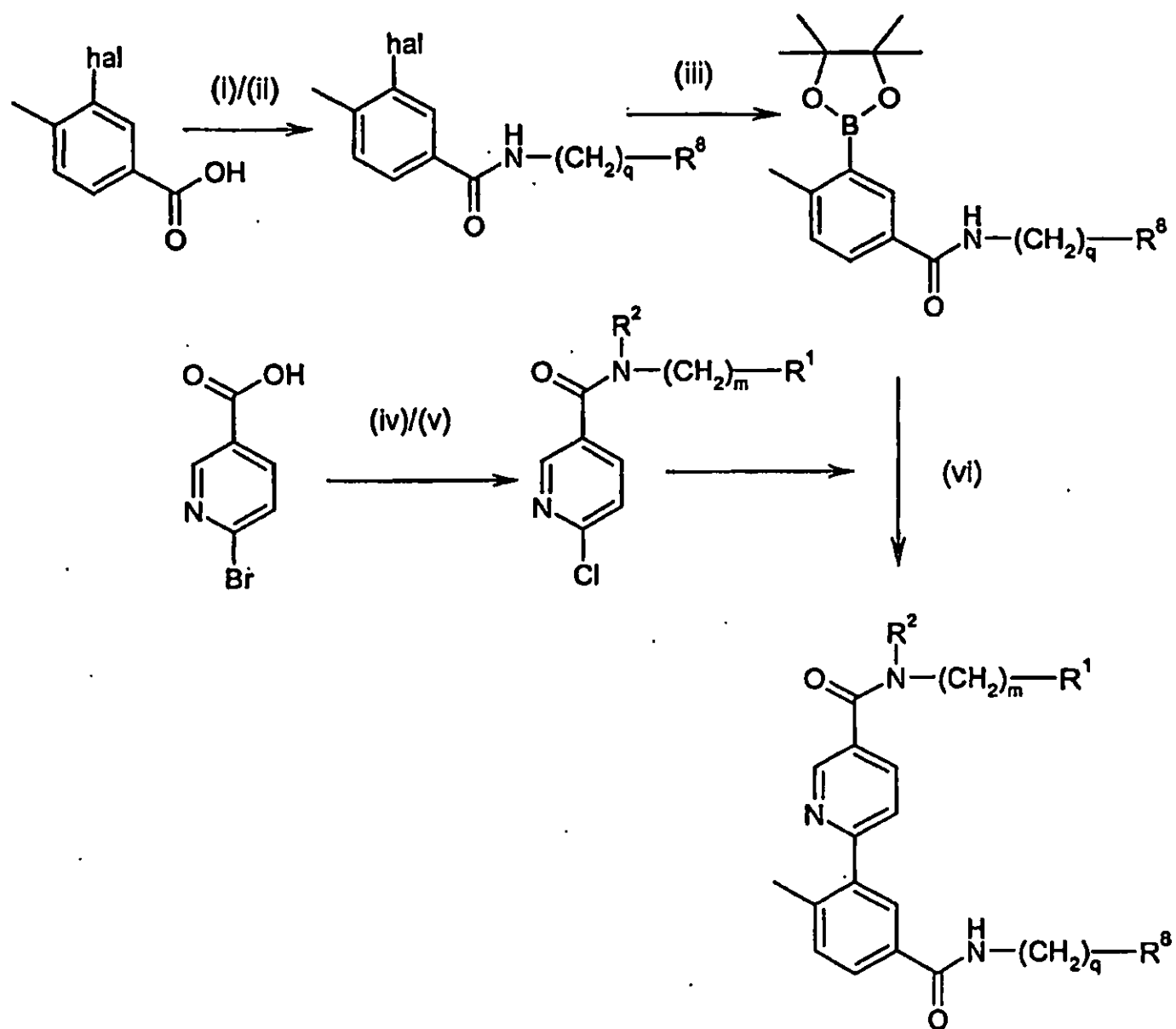
Scheme 1

- i. R^7CO_2H , HATU, DIPEA, DMF.
- ii. Bis(pinacolato)diboron, PdCl₂dppf, KOAc, DMF.
- 5 iii. SOCl₂.
- iv. R¹(CH₂)_mR²NH, Na₂CO₃, acetone.
- v. Na₂CO₃, tetrakis(triphenylphosphine)palladium, propan-2-ol.

For example, another general method for preparing the compounds of formula (I) comprises the reactions set out in Scheme 2 below.

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Scheme 2

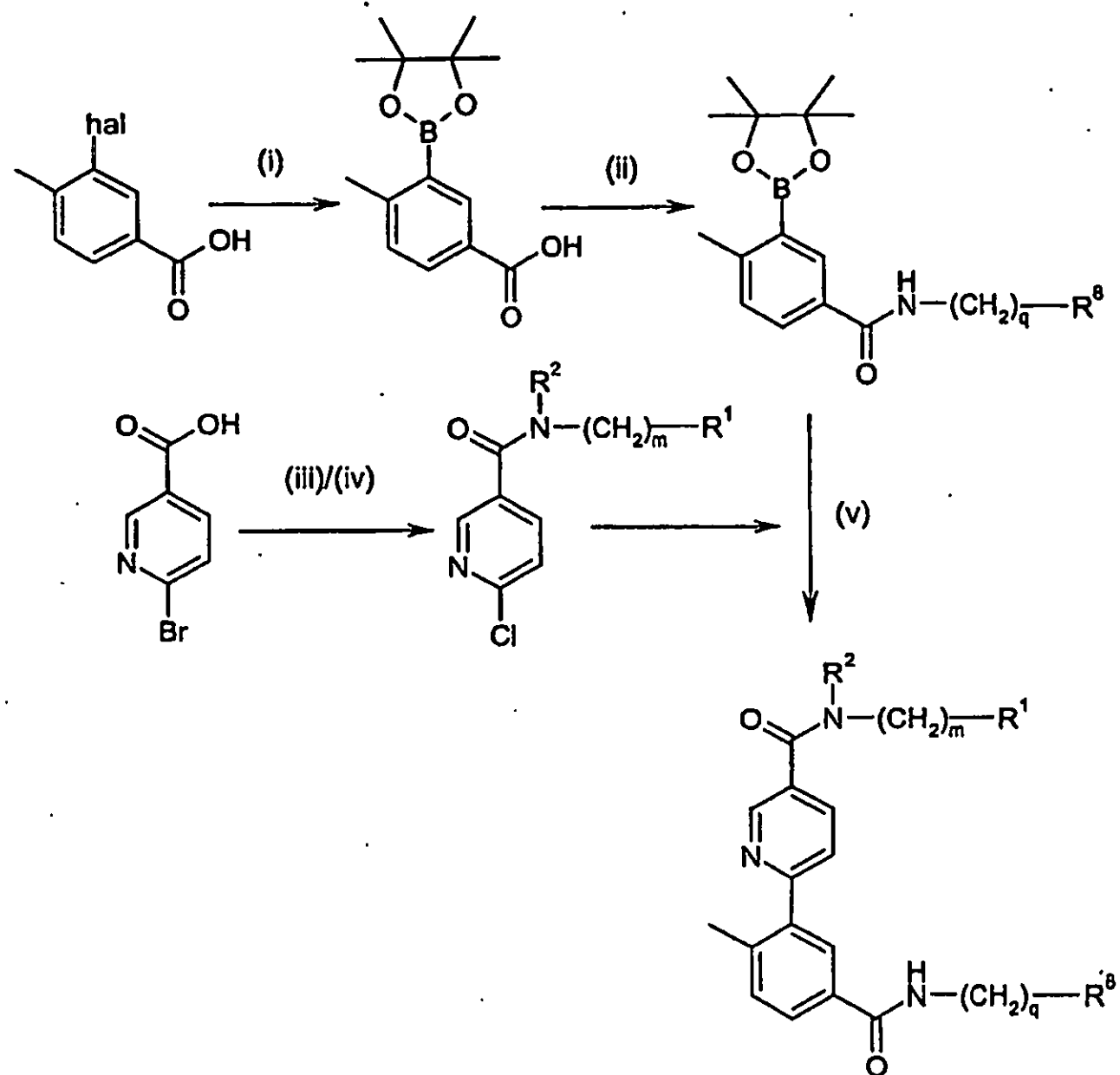
- i. SOCl_2 .
- ii. $\text{R}^8(\text{CH}_2)_q\text{NH}_2$, Na_2CO_3 , acetone.
- 5 iii. Bis(pinnacolato)diboron, PdCl_2dppf , KOAc, DMF.
- iv. SOCl_2 .
- v. $\text{R}^1(\text{CH}_2)_m\text{R}^2\text{NH}$, Na_2CO_3 , acetone.
- vi. Na_2CO_3 , tetrakis(triphenylphosphine)palladium, propan-2-ol.

For example, another general method for preparing the compounds of formula

10 (I) comprises the reactions set out in Scheme 3 below.

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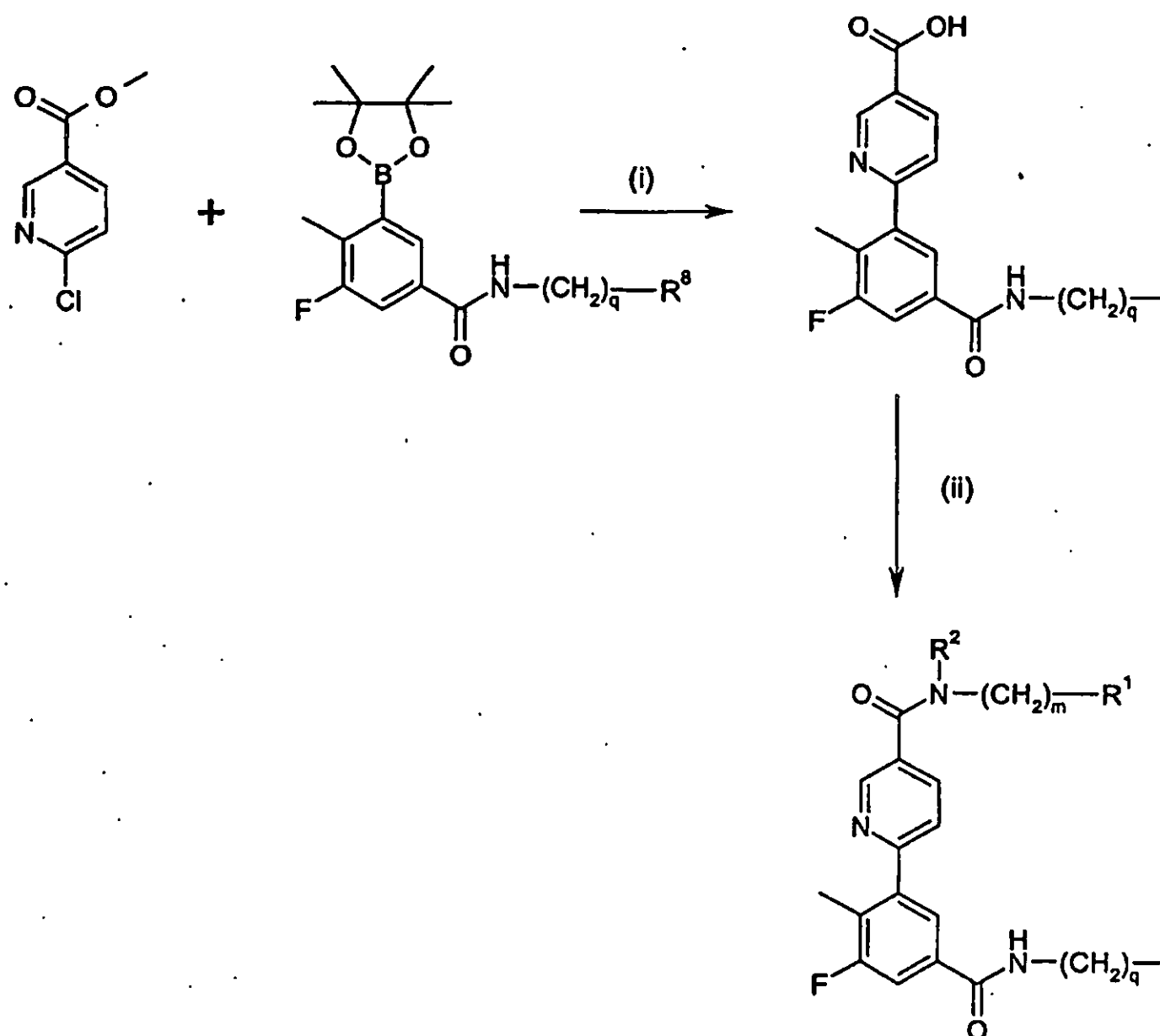
Scheme 3

- i. Bis(pinacolato)diboron, PdCl_2dppf , KOAc, DMF.
- ii. $\text{R}^8(\text{CH}_2)_q\text{NH}_2$, HATU, DIPEA, DMF.
- 5 iii. SOCl_2 .
- iv. $\text{R}^1(\text{CH}_2)_m\text{R}^2\text{NH}$, Na_2CO_3 , DCM.
- v. Na_2CO_3 , tetrakis(triphenylphosphine)palladium, propan-2-ol.

For example, another general method for preparing the compounds of formula (I) comprises the reactions set out in Scheme 4 below.

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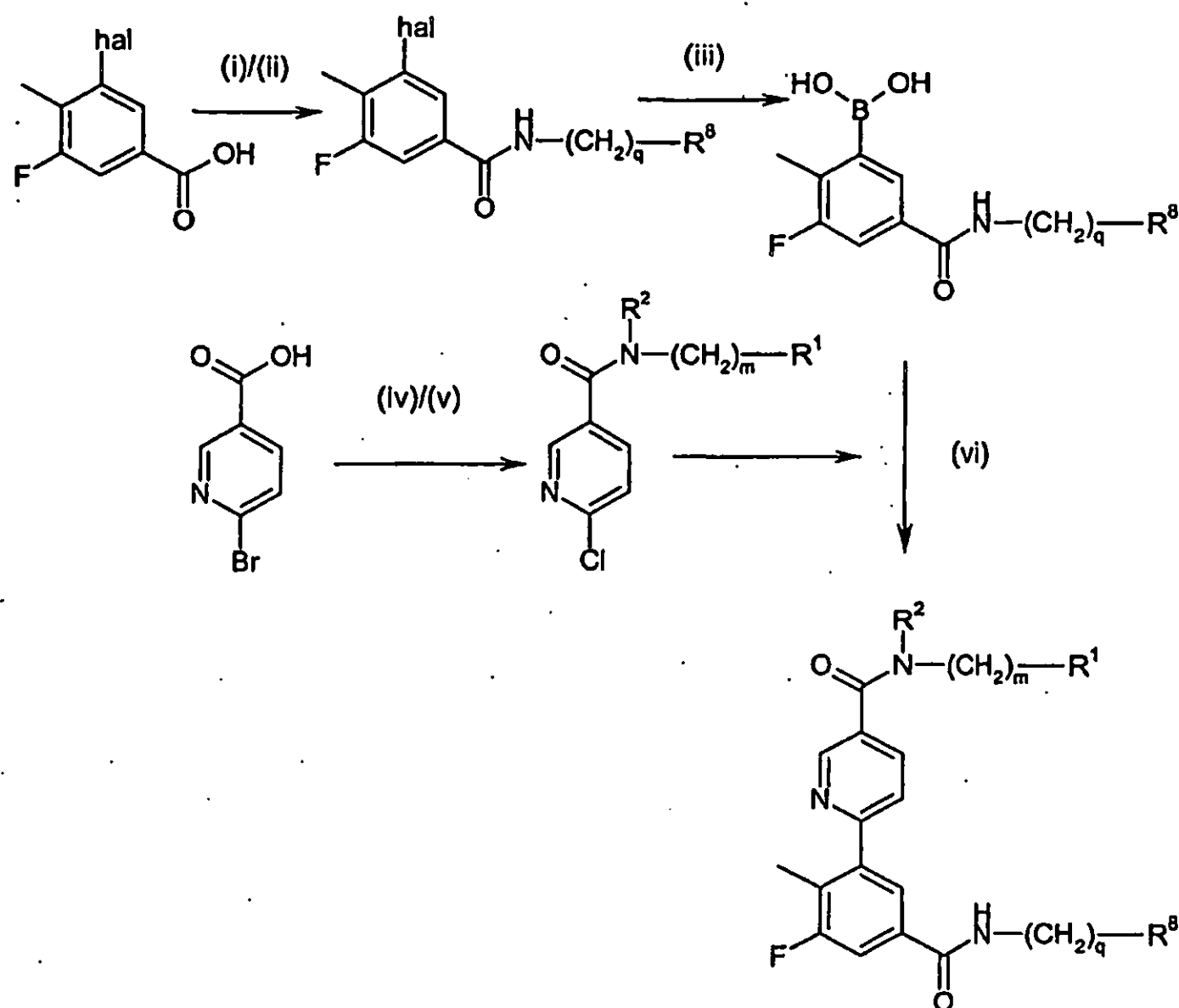
Scheme 4

- i. NaHCO₃, tetrakis(triphenylphosphine)palladium, propan-2-ol.
- 5 ii. R¹(CH₂)_mR²NH, HATU, DIPEA, DMF.

For example, a further general method for preparing the compounds of formula (I) comprises the reactions set out in Scheme 5 below.

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Scheme 5

- i. SOCl_2 .
- 5 ii. $\text{R}^8(\text{CH}_2)_q\text{NH}_2$, Na_2CO_3 , DCM.
- iii. NaH , $n\text{-BuLi}$, THF, $(i\text{PrO})_3\text{B}$.
- iv. SOCl_2 .
- v. $\text{R}^1(\text{CH}_2)_m\text{R}^2\text{NH}$, Na_2CO_3 , DCM.
- 10 vi. NaHCO_3 , tetrakis(triphenylphosphine)palladium, propan-2-ol.

10 Whilst it is possible for the compounds of the present invention to be administered as the new chemical, the compounds of formula (I) are conveniently administered in the form of pharmaceutical compositions. Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I), in admixture with one or more pharmaceutically acceptable carriers, diluents or excipients.

15 The compounds of formula (I) may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration. The pharmaceutical composition may be in a form such that it can effect controlled release of the compounds of formula (I). A particularly preferred method of administration, and corresponding formulation, is oral administration.

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For oral administration, the pharmaceutical composition may take the form of, and be administered as, for example, tablets (including sub-lingual tablets) and capsules (each including timed release and sustained release formulations), pills, powders, granules, elixirs, tinctures, emulsions, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules can be made by preparing a powder mixture as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginat, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

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Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle.

5 Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavor additives such as peppermint oil or saccharin, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of the present invention can also be administered in the form of liposome emulsion delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include

25 polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

The present invention includes pharmaceutical compositions containing 0.1 to 99.5%, more particularly, 0.5 to 90% of a compound of the formula (I) in combination with a pharmaceutically acceptable carrier.

35 Likewise, the composition may also be administered in nasal, ophthalmic, otic, rectal, topical, intravenous (both bolus and infusion), intraperitoneal, intraarticular, subcutaneous or intramuscular, inhalation or insufflation form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. For administration by injection these

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may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative. Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

5 The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly
10 soluble salt.

Alternatively the composition may be formulated for topical application, for example in the form of ointments, creams, lotions, eye ointments, eye drops, ear drops, mouthwash, impregnated dressings and sutures and aerosols, and may contain appropriate conventional additives, including, for example, preservatives, solvents to
15 assist drug penetration, and emollients in ointments and creams. Such topical formulations may also contain compatible conventional carriers, for example cream or ointment bases, and ethanol or oleyl alcohol for lotions. Such carriers may constitute from about 1% to about 98% by weight of the formulation; more usually they will constitute up to about 80% by weight of the formulation.

20 For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, heptafluoropropane, carbon dioxide or other suitable gas. In the
25 case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

The pharmaceutical compositions generally are administered in an amount
30 effective for treatment or prophylaxis of a specific condition or conditions. Initial dosing in human is accompanied by clinical monitoring of symptoms, such symptoms for the selected condition. In general, the compositions are administered in an amount of active agent of at least about 100 µg/kg body weight. In most cases they will be administered in one or more doses in an amount not in excess of about 20 mg/kg body weight per day.
35 Preferably, in most cases, dose is from about 100 µg/kg to about 5 mg/kg body weight, daily. For administration particularly to mammals, and particularly humans, it is expected that the daily dosage level of the active agent will be from 0.1 mg/kg to 10 mg/kg and typically around 1 mg/kg. It will be appreciated that optimum dosage will be determined by standard methods for each treatment modality and indication, taking into
40 account the indication, its severity, route of administration, complicating conditions and the like. The physician in any event will determine the actual dosage which will be most suitable for an individual and will vary with the age, weight and response of the particular individual. The effectiveness of a selected actual dose can readily be determined, for example, by measuring clinical symptoms or standard anti-inflammatory
45 indicia after administration of the selected dose. The above dosages are exemplary of

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the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention. For conditions or disease states as are treated by the present invention, maintaining consistent daily levels in a subject over an extended period of time, e.g., in a maintenance regime, can be particularly beneficial.

In another aspect, the present invention provides a compound of formula (I) for use in therapy.

The compounds of the present invention are generally inhibitors of the serine/threonine kinase p38 and are therefore also inhibitors of cytokine production which is mediated by p38 kinase. Within the meaning of the term "inhibitors of the serine/threonine kinase p38" are included those compounds that interfere with the ability of p38 to transfer a phosphate group from ATP to a protein substrate according to the assay described below.

It will be appreciated that the compounds of the invention may be selective for one or more of the isoforms of p38, for example p38 α , p38 β , p38 γ and/or p38 δ . In one embodiment, the compounds of the invention selectively inhibit the p38 α isoform. In another embodiment, the compounds of the invention selectively inhibit the p38 β isoform. In a further embodiment, the compounds of the invention selectively inhibit the p38 α and p38 β isoforms. Assays for determining the selectivity of compounds for the p38 isoforms are described in, for example, WO 99/61426, WO 00/71535 and WO 02/46158.

It is known that p38 kinase activity can be elevated (locally or throughout the body), p38 kinase can be incorrectly temporally active or expressed, p38 kinase can be expressed or active in an inappropriate location, p38 kinase can be constitutively expressed, or p38 kinase expression can be erratic; similarly, cytokine production mediated by p38 kinase activity can be occurring at inappropriate times, inappropriate locations, or it can occur at detrimentally high levels.

Accordingly, the present invention provides a method for the treatment of a condition or disease state mediated by p38 kinase activity, or mediated by cytokines produced by the activity of p38 kinase, in a subject which comprises administering to said subject a therapeutically effective amount of a compound of formula (I). The compound may be administered as a single or polymorphic crystalline form or forms, an amorphous form, a single enantiomer, a racemic mixture, a single stereoisomer, a mixture of stereoisomers, a single diastereoisomer or a mixture of diastereoisomers.

The present invention also provides a method of inhibiting cytokine production which is mediated by p38 kinase activity in a subject, e.g. a human, which comprises administering to said subject in need of cytokine production inhibition a therapeutic, or cytokine-inhibiting, amount of a compound of the present invention. The compound may be administered as a single or polymorphic crystalline form or forms, an amorphous form, a single enantiomer, a racemic mixture, a single stereoisomer, a mixture of stereoisomers, a single diastereoisomer or a mixture of diastereoisomers.

The present invention treats these conditions by providing a therapeutically effective amount of a compound of this invention. By "therapeutically effective amount" is meant a symptom-alleviating or symptom-reducing amount, a cytokine-

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reducing amount, a cytokine-inhibiting amount, a kinase-regulating amount and/or a kinase-inhibiting amount of a compound. Such amounts can be readily determined by standard methods, such as by measuring cytokine levels or observing alleviation of clinical symptoms. For example, the clinician can monitor accepted measurement scores for anti-inflammatory treatments.

The compounds of the present invention can be administered to any subject in need of inhibition or regulation of p38 kinase or in need of inhibition or regulation of p38 mediated cytokine production. In particular, the compounds may be administered to mammals. Such mammals can include, for example, horses, cows, sheep, pigs, mice, dogs, cats, primates such as chimpanzees, gorillas, rhesus monkeys, and, most preferably, humans.

Thus, the present invention provides methods of treating or reducing symptoms in a human or animal subject suffering from, for example, rheumatoid arthritis, osteoarthritis, asthma, psoriasis, eczema, allergic rhinitis, allergic conjunctivitis, adult respiratory distress syndrome, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, silicosis, endotoxemia, toxic shock syndrome, inflammatory bowel disease, tuberculosis, atherosclerosis, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, epilepsy, multiple sclerosis, aneurism, stroke, irritable bowel syndrome, muscle degeneration, bone resorption diseases, osteoporosis, diabetes, reperfusion injury, graft vs. host reaction, allograft rejections, sepsis, systemic cachexia, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), malaria, leprosy, infectious arthritis, leishmaniasis, Lyme disease, glomerulonephritis, gout, psoriatic arthritis, Reiter's syndrome, traumatic arthritis, rubella arthritis, Crohn's disease, ulcerative colitis, acute synovitis, gouty arthritis, spondylitis, and non articular inflammatory conditions, for example, herniated/ruptured/prolapsed intervertebral disk syndrome, bursitis, tendonitis, tenosynovitis, fibromyalgic syndrome and other inflammatory conditions associated with ligamentous sprain and regional musculoskeletal strain, pain, for example that associated with inflammation and/or trauma, osteopetrosis, restenosis, thrombosis, angiogenesis, cancer including breast cancer, colon cancer, lung cancer or prostatic cancer, which comprises administering to said subject a therapeutically effective amount of a compound of formula (I).

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from rheumatoid arthritis, asthma, psoriasis, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, systemic cachexia, glomerulonephritis, Crohn's disease, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, epilepsy and cancer including breast cancer, colon cancer, lung cancer and prostatic cancer, which comprises administering to said subject a therapeutically effective amount of a compound of formula (I).

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from rheumatoid arthritis, asthma, psoriasis, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, systemic cachexia, glomerulonephritis, Crohn's disease and cancer including

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breast cancer, colon cancer, lung cancer and prostatic cancer, which comprises administering to said subject a therapeutically effective amount of a compound of formula (I).

5 A further aspect of the invention provides a method of treatment of a human or animal subject suffering from rheumatoid arthritis, asthma, chronic pulmonary inflammation, chronic obstructive pulmonary disease, neurodegenerative disease, Alzheimer's disease, Parkinson's disease and epilepsy which comprises administering to said subject a therapeutically effective amount of a compound of formula (I).

10 A further aspect of the invention provides a method of treatment of a human or animal subject suffering from any type of pain including chronic pain, rapid onset of analgesis, neuromuscular pain, headache, cancer pain, acute and chronic inflammatory pain associated with osteoarthritis and rheumatoid arthritis, post operative inflammatory pain, neuropathic pain, diabetic neuropathy, trigeminal neuralgia, post-hepatic neuralgia, inflammatory neuropathies and migraine pain which comprises
15 administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

The compounds of formula (I) may be employed alone or in combination with other therapeutic agents for the treatment of the above-mentioned conditions. In particular, in rheumatoid arthritis therapy, combination with other chemotherapeutic
20 or antibody agents is envisaged. Combination therapies according to the present invention thus comprise the administration of at least one compound of formula (I) and at least one other pharmaceutically active agent. The compound(s) of formula (I) and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately, this may occur separately or
25 sequentially in any order. The amounts of the compound(s) of formula (I) and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. Examples of other pharmaceutically active agents which may be employed in combination with compounds of formula (I) for rheumatoid arthritis therapy include:
30 immunosuppressants such as amtolmetin guacil, mizoribine and rimexolone; anti-TNF α agents such as etanercept, infliximab, diacerein; tyrosine kinase inhibitors such as leflunomide; kallikrein antagonists such as subreum; interleukin 11 agonists such as oprelvekin; interferon beta 1 agonists; hyaluronic acid agonists such as NRD-101 (Aventis); interleukin 1 receptor antagonists such as anakinra; CD8 antagonists such
35 as amiprilose hydrochloride; beta amyloid precursor protein antagonists such as reumacon; matrix metalloprotease inhibitors such as cipemastat and other disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate, sulphasalazine, cyclosporin A, hydroxychloroquine, auranofin, aurothioglucose, gold sodium thiomalate and penicillamine.

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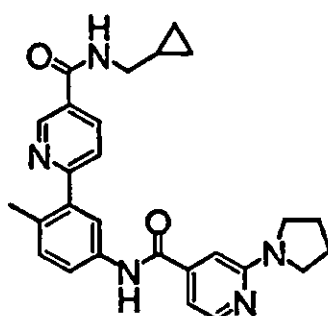
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General Method B

The 2-chloropyridine (0.05mmol), phenyl pinacolborane (0.05mmol), tetrakis(triphenylphosphine) palladium (1mg) and aqueous sodium carbonate (0.25ml) in propan-2-ol (1ml) were heated at 85°C under nitrogen for 18 hours. The cooled
5 reaction was diluted with ethyl acetate (4ml) and methanol (2ml) and filtered through an SCX bond-elut (1g). The product was eluted with 10% ammonia (s.g. 0.88) in methanol. The solvents were evaporated and the residue triturated with ether.

Example 1: N-(3-[5-(Cyclopropylmethyl-carbamoyl)-pyridin-2-yl]-4-methyl-phenyl)-2-pyrrolidin-1-yl-isonicotinamide

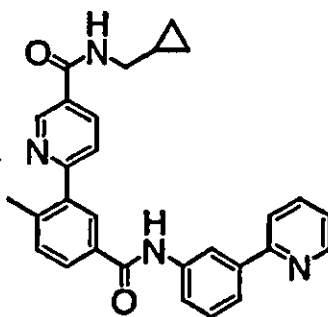


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6-Chloro-N-cyclopropylmethylnicotinamide (Intermediate 1) (25mg, 0.098mmol) and N-[4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-2-pyrrolidin-1-yl-isonicotinamide (Intermediate 18) (30mg, 0.074mmol), aqueous sodium carbonate (2N, 0.5ml) and tetrakis(triphenylphosphine)palladium
15 (4mg) were heated at 80°C in DMF (1ml) for 18hours. The reaction was absorbed onto silica, applied to a bond-elut (10g, silica) and eluted with an ethylacetate/cyclohexane (0 to 100%), then acetone and methanol. The solvent was evaporated from the product fractions under vacuum and the residue triturated with ether to give N-(3-[5-(cyclopropylmethyl-carbamoyl)-pyridin-2-yl]-4-methyl-phenyl)-
20 2-pyrrolidin-1-yl-isonicotinamide as a white solid (20mg). LCMS: retention time 2.42min, MH^+ 456. NMR: δ H [2H_6]-DMSO 10.32,(1H, s), 9.09,(1H, s), 8.82,(1H, t), 8.28,(1H, m), 8.19,(1H, m), 7.85,(1H, t), 7.76,(1H, m), 7.64,(1H, m), 7.31,(1H, m), 6.98,(1H, m), 6.88,(1H, s), 3.43,(4H, m), 3.18,(2H, m), 2.31,(3H, s), 1.95,(4H, m), 1.07,(1H, m), 0.45,(2H, m), 0.25,(2H, m).

25

Example 2: N-Cyclopropylmethyl-6-[2-methyl-5-(3-pyridin-2-yl-phenylcarbamoyl)-phenyl]-nicotinamide

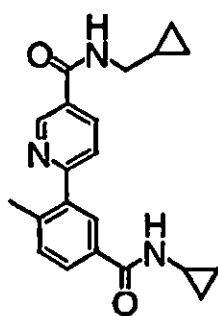


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6-Chloro-N-cyclopropylmethylnicotinamide (Intermediate 1) (18.5mg, 0.073mmol) and 4-methyl-N-(3-pyridin-2-yl-phenyl)-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (Intermediate 6) (30mg, 0.072mmol), aqueous sodium carbonate (2N, 0.5ml) and tetrakis(triphenylphosphine)palladium (4mg) were heated at 90°C in DMF (1ml) for 4hours. The reaction was absorbed onto silica, applied to a bond-elut (5g, silica) and eluted with an ethylacetate/cyclohexane (0 to 100%) and then acetone. The solvent was evaporated from the product fractions under vacuum and the residue triturated with ether to give N-cyclopropylmethyl-6-[2-methyl-5-(3-pyridin-2-yl-phenylcarbamoyl)-phenyl]-nicotinamide as a white solid (20mg). LCMS: retention time 3.18min, MH^+ 463. NMR: δH [2H_6]-DMSO 10.43,(1H, s), 9.14,(1H, s), 8.86,(1H, t), 8.69,(1H, s), 8.53,(1H, s), 8.34,(1H, d), 8.11,(1H, s), 8.01,(1H, d), 7.95-7.89,(3H, m), 7.81-7.78,(2H, m), 7.53-7.46,(2H, m), 7.38,(1H, t), 3.21,(2H, t), 2.44,(3H, s), 1.07,(1H, m), 0.47,(2H, m), 0.27,(2H, m).

Example 3: 6-(5-Cyclopropylcarbamoyl-2-methyl-phenyl)-N-cyclopropylmethyl-nicotinamide

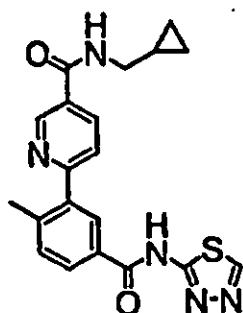


6-Chloro-N-cyclopropylmethylnicotinamide (Intermediate 1) (25.5mg, 0.10mmol) and N-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (Intermediate 8) (30mg, 0.10mmol), aqueous sodium carbonate (2N, 0.5ml) and tetrakis(triphenylphosphine)palladium (4mg) were heated at 90°C in DMF (1ml) for 3hours. The reaction was absorbed onto silica, applied to a bond-elut (5g, silica) and eluted with an ethylacetate/cyclohexane (0 to 100%) and then acetone. The solvent was evaporated from the product fractions under vacuum and the residue triturated with ether to 6-(5-cyclopropylcarbamoyl-2-methyl-phenyl)-N-cyclopropylmethyl-nicotinamide as a cream solid. LCMS: retention time 2.70min, MH^+ 350. NMR: δH [2H_6]-DMSO 9.11,(1H, s), 8.84,(1H, t), 8.48,(1H, d), 8.31,(1H, dd), 7.88,(1H, s), 7.81,(1H, d), 7.70,(1H, d), 7.41,(1H, d), 3.20,(1H, t), 2.86,(1H, m), 2.37,(3H, s), 1.06,(1H, m), 0.69,(2H, m), 0.57,(2H, m), 0.46,(2H, m), 0.26,(2H, m).

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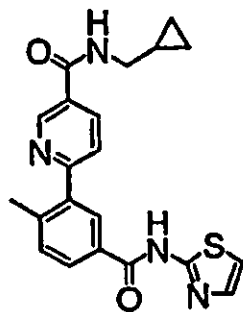
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Example 4: N-Cyclopropylmethyl-6-[5-(thiadiazol-2-ylcarbamoyl)-2-methyl-phenyl]-nicotinamide



N-Cyclopropylmethyl-6-[5-(thiadiazol-2-ylcarbamoyl)-2-methyl-phenyl]-
 5 nicotinamide was prepared from 6-chloro-N-cyclopropylmethylnicotinamide
 (Intermediate 1) and 4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-N-
 (thiadiazol-2-yl)-benzamide (Intermediate 12) using General Method B. LCMS:
 retention time 2.79min, MH^+ 394. NMR: δH [2H_6]-DMSO 13.14,(1H, b), 9.24,(1H,
 s), 9.14,(1H, s), 8.86,(1H, t), 8.35,(1H, d), 8.25,(1H, s), 8.10,(1H, d), 7.82,(1H, d),
 10 7.54,(1H, d), 3.21,(2H, t), 2.46,(3H, s), 1.07,(1H, m), 0.47,(2H, m), 0.27,(2H, m).

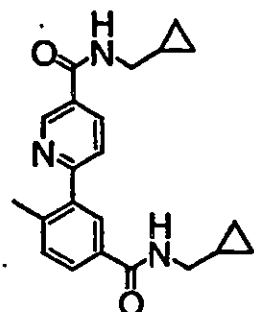
Example 5: N-Cyclopropylmethyl-6-[5-(thiazol-2-ylcarbamoyl)-2-methyl-phenyl]-nicotinamide



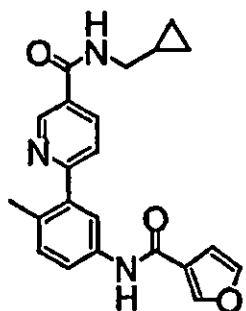
N-Cyclopropylmethyl-6-[5-(thiazol-2-ylcarbamoyl)-2-methyl-phenyl]-
 15 nicotinamide was prepared from 6-chloro-N-cyclopropylmethylnicotinamide
 (Intermediate 1) and 4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-N-
 (thiazol-2-yl)-benzamide (Intermediate 11) using General Method B. LCMS: retention
 time 2.99min, MH^+ 393. NMR: δH [2H_6]-DMSO 12.71,(1H, b), 9.13,(1H, s),
 20 8.86,(1H, t), 8.34,(1H, d), 8.21,(1H, s), 8.07,(1H, d), 7.81,(1H, d), 7.57,(1H, d),
 7.52,(1H, d), 7.29,(1H, d), 3.21,(2H, t), 2.45,(3H, s), 1.07,(1H, m), 0.47,(2H, m),
 0.27,(2H, m).

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Example 6: 6-[5-(Cyclopropylmethylcarbamoyl)-2-methyl-phenyl]-N-cyclopropylmethyl-nicotinamide

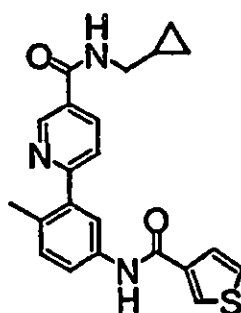
5 6-[5-(Cyclopropylmethyl)carbamoyl-2-methyl-phenyl]-N-cyclopropylmethyl-nicotinamide was prepared from 6-chloro-N-cyclopropylmethylnicotinamide (Intermediate 1) and N-(cyclopropylmethyl)-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (Intermediate 10) using General Method B. LCMS: retention time 2.87min, MH^+ 364. NMR: δH [2H_6]-DMSO 9.10,(1H, s), 8.83,(1H, t), 8.60,(1H, t), 8.30,(1H, dd), 7.92,(1H, s), 7.84,(1H, d), 7.71,(1H, d), 7.41,(1H, d), 3.19,(2H, t), 3.13,(2H, t), 2.37,(3H, s), 1.03,(2H, m), 0.44,(4H, m), 0.23,(4H, m).

Example 7: N-Cyclopropylmethyl-6-[5-(fur-3-ylcarbonylamino)-2-methyl-phenyl]-nicotinamide

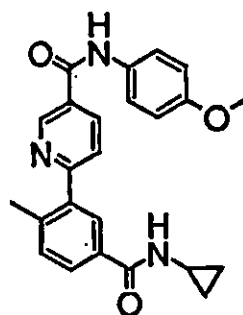
15 N-Cyclopropylmethyl-6-[5-(fur-3-ylcarbonylamino)-2-methyl-phenyl]-nicotinamide was prepared from 6-chloro-N-cyclopropylmethylnicotinamide (Intermediate 1) and N-[4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-3-furamide (Intermediate 13) using General Method B. LCMS: retention time 2.96min, MH^+ 376. NMR: δH [2H_6]-DMSO 9.99,(1H, s), 9.10,(1H, s), 8.83,(1H, t), 8.38,(1H, s), 8.30,(1H, d), 7.80,(2H, s), 7.75,(1H, d), 7.66,(1H, d), 7.30,(1H, d), 3.20,(2H, t), 2.31,(3H, s), 1.06,(1H, m), 0.46,(2H, m), 0.27,(2H, m).

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Example 8: N-Cyclopropylmethyl-6-[2-methyl-5-(thiophen-3-ylcarbonylamino)-phenyl]-nicotinamide

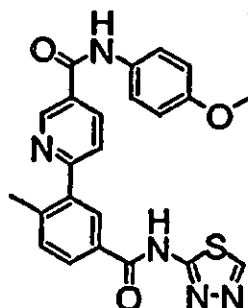
5 N-Cyclopropylmethyl-6-[2-methyl-5-(thiophen-3-ylcarbonylamino)-phenyl]-
 nicotinamide was prepared from 6-chloro-N-cyclopropylmethylnicotinamide
 (Intermediate 1) and N-[4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-
 phenyl]thiophene-3-amide (Intermediate 14) using General Method B. LCMS:
 retention time 3.07min, MH^+ 392. NMR: δH [2H_6]-DMSO 10.11,(1H, s), 9.11,(1H,
 s), 8.83,(1H, t), 8.35,(1H, s), 8.30,(1H, dd), 7.85,(1H, s), 7.78,(1H, d), 7.67-7.63,(3H,
 10 m), 7.31,(1H, d), 3.20,(2H, t), 2.31,(3H, s), 1.06,(1H, m), 0.46,(1H, m), 0.27,(1H, m).

Example 9: 6-(5-Cyclopropylcarbamoyl-2-methyl-phenyl)-N-(4-methoxyphenyl)-nicotinamide

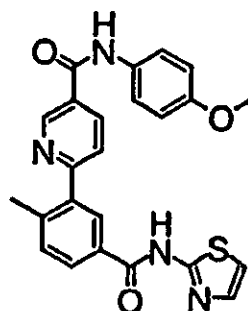
15 6-[5-Cyclopropylcarbamoyl-2-methyl-phenyl]-N-(4-methoxyphenyl)-
 nicotinamide was prepared from 6-chloro-N-(4-methoxyphenyl)nicotinamide
 (Intermediate 2) and N-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-
 [1,3,2]dioxaborolan-2-yl)-benzamide (Intermediate 8) using General Method B.
 LCMS: retention time 2.96min, MH^+ 402. NMR: δH [2H_6]-DMSO 10.38,(1H, s),
 20 9.20,(1H, s), 8.49,(1H, d), 8.40,(1H, dd), 7.91,(1H, s), 7.82,(1H, d), 7.76,(1H, d),
 7.71,(2H, d), 7.43,(1H, d), 6.96,(2H, d), 3.76,(3H, s), 2.87,(1H, m), 2.40,(3H, s),
 0.70,(2H, m), 0.58,(2H, m).

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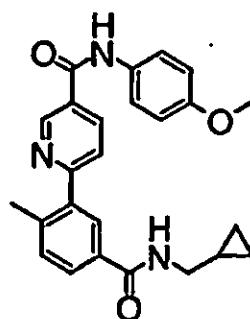
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Example 10: N-(4-Methoxyphenyl)-6-[2-methyl-5-(thiadiazol-2-ylcarbamoyl)-phenyl]-nicotinamide

- 5 N-(4-Methoxyphenyl)-6-[2-methyl-5-(thiadiazol-2-ylcarbamoyl)-phenyl]-
 nicotinamide was prepared from 6-chloro-N-(4-methoxyphenyl)nicotinamide
 (Intermediate 2) and 4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-N-
 (thiadiazol-2-yl)-benzamide (Intermediate 12) using General Method B. LCMS:
 retention time 3.05min, MH^+ 446. NMR: δH [2H_6]-DMSO 13.15,(1H, b), 10.41,(1H,
 s), 9.24,(2H, m), 8.45,(1H, dd), 8.28,(1H, s), 8.11,(1H, d), 7.88,(1H, d), 7.71,(2H, d),
 10 7.56,(1H, d), 6.97,(2H, d), 3.76,(3H, s), 2.48,(3H, s).

Example 11: N-(4-Methoxyphenyl)-6-[2-methyl-5-(thiazol-2-ylcarbamoyl)-phenyl]-nicotinamide

- 15 N-(4-Methoxyphenyl)-6-[2-methyl-5-(thiazol-2-ylcarbamoyl)-phenyl]-
 nicotinamide was prepared from 6-chloro-N-(4-methoxyphenyl)nicotinamide
 (Intermediate 2) and 4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-N-
 (thiazol-2-yl)-benzamide (Intermediate 11) using General Method B. LCMS: retention
 time 3.22min, MH^+ 445. NMR: δH [2H_6]-DMSO 12.72,(1H, s), 10.40,(1H, s),
 20 9.22,(1H, d), 8.44,(1H, dd), 8.24,(1H, s), 8.09,(1H, d), 7.87,(1H, d), 7.71,(2H, d),
 7.58,(1H, d), 7.53,(1H, d), 7.30,(1H, d), 6.97,(2H, d), 3.76,(3H, s), 2.48,(3H, s).

Example 12: 6-(5-Cyclopropylmethylcarbamoyl-2-methyl-phenyl)-N-(4-methoxyphenyl)-nicotinamide

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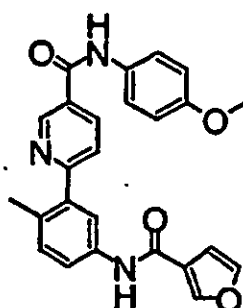
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6-[5-Cyclopropylmethylcarbamoyl-2-methyl-phenyl]-N-(4-methoxyphenyl)-nicotinamide was prepared from 6-chloro-N-(4-methoxyphenyl)nicotinamide (Intermediate 2) and N-cyclopropylmethyl-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (Intermediate 10) using General Method B.

- 5 LCMS: retention time 3.12min, MH^+ 416. NMR: δH [2H_6]-DMSO 10.39,(1H, s), 9.21,(1H, d), 8.63,(1H, t), 8.41,(1H, dd), 7.96,(1H, s), 7.86,(1H, d), 7.79,(1H, d), 7.71,(2H, d), 7.44,(1H, d), 6.96,(2H, d), 3.76,(3H, s), 3.15,(2H, t), 2.41,(3H, s), 1.03,(1H, m), 0.43,(2H, m), 0.23,(2H, m).

10 Example 13: 6-[5-(Fur-3-ylcarbamoylamino)-2-methyl-phenyl]-N-(4-methoxyphenyl)-nicotinamide

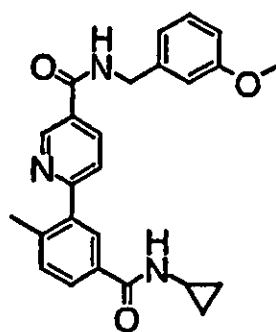


6-[5-(Fur-3-ylcarbamoylamino)-2-methyl-phenyl]-N-(4-methoxyphenyl)-nicotinamide was prepared from 6-chloro-N-(4-methoxyphenyl)nicotinamide

- 15 (Intermediate 2) and N-[4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-3-furamide (Intermediate 13) using General Method B. LCMS: retention time 3.19min, MH^+ 428. NMR: δH [2H_6]-DMSO 10.38,(1H, s), 10.00,(1H, s), 9.19,(1H, s), 8.38,(2H, m), 7.83,(1H, s), 7.80,(1H, s), 7.76,(1H, s), 7.73-7.69,(3H, m), 7.32,(1H, s), 7.01,(1H, s), 6.96,(2H, d), 3.76,(3H, s), 2.34,(3H, s).

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Example 14: 6-(5-Cyclopropylcarbamoyl-2-methyl-phenyl)-N-(3-methoxybenzyl)-nicotinamide



6-[5-Cyclopropylcarbamoyl-2-methyl-phenyl]-N-(3-methoxybenzyl)-nicotinamide was prepared from 6-chloro-N-(3-methoxybenzyl)nicotinamide (Intermediate 3) and N-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-

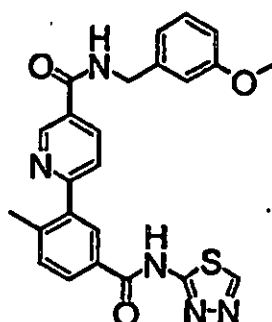
- 25 [1,3,2]dioxaborolan-2-yl)-benzamide (Intermediate 8) using General Method B. LCMS: retention time 2.94min, MH^+ 416. NMR: δH [2H_6]-DMSO 9.29,(1H, t), 9.15,(1H, s), 8.48,(1H, d), 8.35,(1H, d), 7.89,(1H, s), 7.81,(1H, d), 7.72,(1H, d), 7.41,(1H, d), 7.26,(1H, t), 6.93,(2H, m), 6.84,(1H, s), 4.51,(2H, d), 3.75,(3H, s), 2.86,(1H, m), 2.38,(3H, s), 0.69,(2H, m), 0.57,(2H, m).
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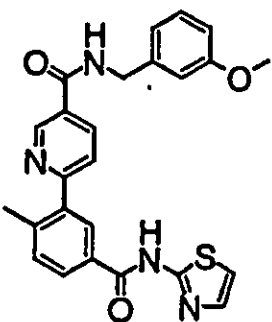
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Example 15: N-(3-Methoxybenzyl)-6-[2-methyl-5-(thiadiazol-2-ylcarbamoyl)-phenyl]-nicotinamide



N-(3-Methoxybenzyl)-6-[2-methyl-5-(thiadiazol-2-ylcarbamoyl)-phenyl]-
 5 nicotinamide was prepared from 6-chloro-N-(3-methoxybenzyl)nicotinamide
 (Intermediate 3) and 4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-N-
 (thiadiazol-2-yl)-benzamide (Intermediate 12) using General Method B. LCMS:
 retention time 3.02min, MH^+ 460. NMR: δH [2H_6]-DMSO 13.14,(1H, b), 9.32,(1H,
 t), 9.24,(1H, s), 9.18,(1H, d), 8.40,(1H, dd), 8.26,(1H, s), 8.10,(1H, d), 7.84,(1H, d),
 10 7.55,(1H, d), 7.27,(1H, t), 6.94,(2H, m), 6.84,(1H, d), 4.53,(2H, d), 3.75,(3H, s),
 2.46,(3H, s).

Example 16: N-(3-Methoxybenzyl)-6-[2-methyl-5-(thiazol-2-ylcarbamoyl)-phenyl]-nicotinamide

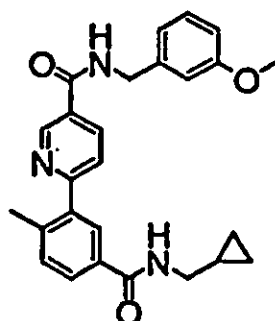


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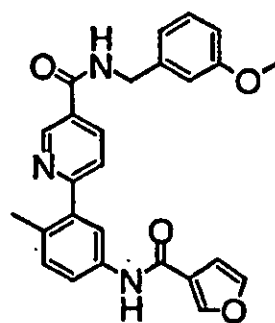
N-(3-Methoxybenzyl)-6-[2-methyl-5-(thiazol-2-ylcarbamoyl)-phenyl]-
 nicotinamide was prepared from 6-chloro-N-(3-methoxybenzyl)nicotinamide
 (Intermediate 3) and 4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-N-
 (thiazol-2-yl)-benzamide (Intermediate 11) using General Method B. LCMS: retention
 20 time 3.20min, MH^+ 459. NMR: δH [2H_6]-DMSO 12.71,(1H, b), 9.31,(1H, t),
 9.17,(1H, d), 8.39,(1H, dd), 8.22,(1H, s), 8.07,(1H, d), 7.83,(1H, d), 7.57,(1H, d),
 7.52,(1H, d), 7.29-7.25,(2H, m), 6.94,(2H, m), 6.84,(1H, d), 4.52,(2H, d), 3.75,(3H, s),
 2.45,(3H, s).

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Example 17: 6-(5-Cyclopropylmethylcarbamoyl-2-methyl-phenyl)-N-(3-methoxybenzyl)-nicotinamide

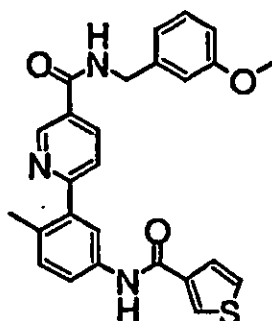
5 6-[5-Cyclopropylmethylcarbamoyl-2-methyl-phenyl]-N-(3-methoxybenzyl)-
 nicotinamide was prepared from 6-chloro-N-(3-methoxybenzyl)nicotinamide
 (Intermediate 3) and N-cyclopropylmethyl-4-methyl-3-(4,4,5,5-tetramethyl-
 [1,3,2]dioxaborolan-2-yl)-benzamide (Intermediate 10) using General Method B.
 LCMS: retention time 3.07min, MH^+ 430. NMR: δH [2H_6]-DMSO 9.30,(1H, t),
 9.16,(1H, d), 8.62,(1H, t), 8.36,(1H, dd), 7.94,(1H, s), 7.85,(1H, d), 7.74,(1H, d),
 10 7.43,(1H, d), 7.27,(1H, t), 6.94-6.92,(2H, m), 6.84,(1H, d), 4.51,(2H, d), 3.75,(3H, s),
 3.14,(2H, t), 2.39,(3H, s), 1.03,(1H, m), 0.43,(2H, m), 0.23,(2H, m).

Example 18: 6-[5-(Fur-3-ylcarbonylamino)-2-methyl-phenyl]-N-(3-methoxybenzyl)-nicotinamide

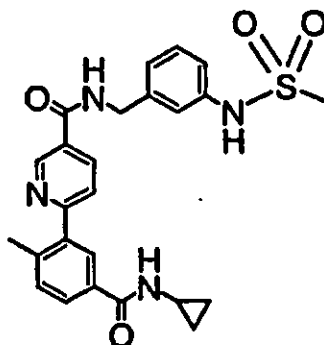
15 6-[5-(Fur-3-ylcarbonylamino)-2-methyl-phenyl]-N-(3-methoxybenzyl)-
 nicotinamide was prepared from 6-chloro-N-(3-methoxybenzyl)nicotinamide
 (Intermediate 3) and N-[4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-
 phenyl]-3-furamide (Intermediate 13) using General Method B. LCMS: retention time
 20 3.17min, MH^+ 442. NMR: δH [2H_6]-DMSO 9.99,(1H, s), 9.29,(1H, t), 9.15,(1H, d),
 8.38,(1H, s), 8.34,(1H, dd), 7.81,(2H, m), 7.75,(1H, d), 7.67,(1H, d), 7.31-7.25,(2H,
 m), 7.00,(1H, s), 6.94,(2H, m), 6.84,(1H, d), 4.51,(2H, d), 3.75,(3H, s), 2.32,(3H, s).

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Example 19: N-(3-Methoxybenzyl)-6-[5-(thiophen-3-ylcarbonylamino)-2-methyl-phenyl]-nicotinamide

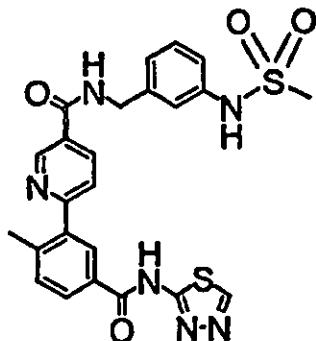
5 N-(3-Methoxybenzyl)-6-[5-(thiophen-3-ylcarbonylamino)-2-methyl-phenyl]-
 nicotinamide was prepared from 6-chloro-N-(3-methoxybenzyl)nicotinamide
 (Intermediate 3) and N-[4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-
 phenyl]thiophene-3-amide (Intermediate 14) using General Method B. LCMS:
 retention time 3.27min, MH^+ 458. NMR: δH [2H_6]-DMSO 10.12,(1H, s), 9.29,(1H, t),
 9.15,(1H, d), 8.35-8.32,(2H, m), 7.86,(1H, s), 7.78,(1H, d), 7.68-7.65,(3H, m), 7.32-
 10 7.24,(2H, m), 6.94,(2H, m), 6.84,(2H, d), 4.51,(2H, d), 3.75,(3H, s), 2.32,(3H, s).

Example 20: 6-(5-Cyclopropylcarbamoyl-2-methyl-phenyl)-N-(3-methylsulphonylaminobenzyl)-nicotinamide

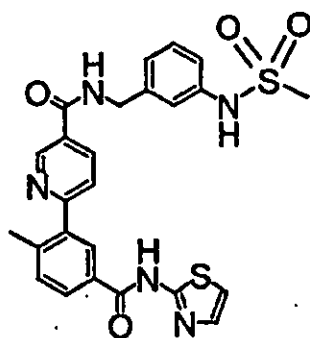
15 6-(5-Cyclopropylcarbamoyl-2-methyl-phenyl)-N-(3-
 methylsulphonylaminobenzyl)-nicotinamide was prepared from 6-chloro-N-(3-
 methylsulphonylaminobenzyl)nicotinamide (Intermediate 4) and N-cyclopropyl-4-
 methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (Intermediate 8)
 using General Method B. LCMS: retention time 2.71min, MH^+ 479. NMR: δH [2H_6]-
 20 DMSO 9.33,(1H, t), 9.15,(1H, s), 8.48-8.33,(3H, m), 7.89,(1H, s), 7.81,(1H, d),
 7.73,(1H, d), 7.41,(1H, d), 7.31,(1H, t), 7.21,(1H, s), 7.10,(2H, m), 4.51,(2H, d),
 2.99,(3H, s), 2.86,(1H, m), 2.38,(3H, s), 0.69,(2H, m), 0.57,(2H, m).

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Example 21: N-(3-Methylsulphonylaminobenzyl)-6-[2-methyl-5-(thiadiazol-2-ylcarbamoyl)-phenyl]-nicotinamide

5 N-(3-Methylsulphonylaminobenzyl)-6-[2-methyl-5-(thiadiazol-2-ylcarbamoyl)-phenyl]-nicotinamide was prepared from 6-chloro-N-(3-methylsulphonylaminobenzyl)nicotinamide (Intermediate 4) and 4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-N-(thiadiazol-2-yl)-benzamide (Intermediate 12) using General Method B. LCMS: retention time 2.80min, MH^+ 523. NMR: δH [2H_6]-DMSO 9.35,(1H, t), 9.17,(2H, m), 8.38,(1H, d), 8.26,(1H, s), 8.09,(1H, d),
 10 7.83,(1H, d), 7.52,(1H, d), 7.31,(1H, t), 7.22,(1H, s), 7.11,(2H, m), 4.52,(2H, d), 2.99,(3H, s), 2.46,(3H, s).

Example 22: N-(3-Methylsulphonylaminobenzyl)-6-[2-methyl-5-(thiazol-2-ylcarbamoyl)-phenyl]-nicotinamide

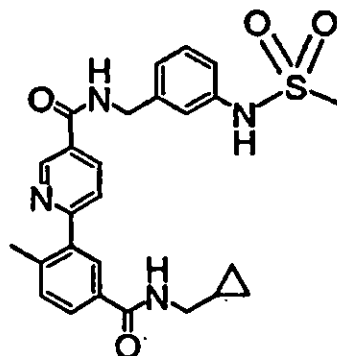
15

N-(3-Methylsulphonylaminobenzyl)-6-[2-methyl-5-(thiazol-2-ylcarbamoyl)-phenyl]-nicotinamide was prepared from 6-chloro-N-(3-methylsulphonylaminobenzyl)nicotinamide (Intermediate 4) and 4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-N-(thiazol-2-yl)-benzamide (Intermediate 11) using General Method B. LCMS: retention time 2.96min, MH^+ 522. NMR: δH [2H_6]-DMSO 10.19,(2H, b), 9.35,(1H, t), 9.17,(1H, s), 8.38,(1H, dd), 8.22,(1H, s), 8.07,(1H, d), 7.84,(1H, d), 7.57,(1H, d), 7.52,(1H, d), 7.31-7.28,(2H, m), 7.22,(1H, s), 7.11,(2H, m), 4.52,(2H, d), 2.99,(3H, s), 2.45,(3H, s).
 20

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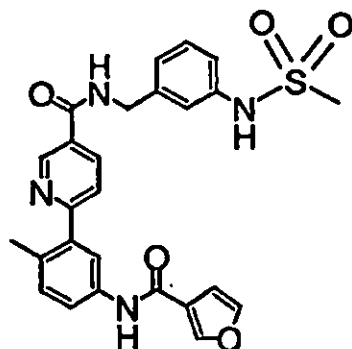
PCT/GB03/00554

Example 23: 6-(5-Cyclopropylmethylcarbamoyl-2-methyl-phenyl)-N-(3-methylsulphonylaminobenzyl)-nicotinamide



5 6-(5-Cyclopropylmethylcarbamoyl-2-methyl-phenyl)-N-(3-methylsulphonylaminobenzyl)-nicotinamide was prepared from 6-chloro-N-(3-methylsulphonylaminobenzyl)nicotinamide (Intermediate 4) and N-cyclopropylmethyl-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (Intermediate 10) using General Method B. LCMS: retention time 2.88min, MH^+ 493. NMR: δH [2H_6]-DMSO 9.34,(1H, t), 9.16,(1H, d), 8.96,(1H, b),
10 8.62,(1H, t), 8.35,(1H, dd), 7.94,(1H, s), 7.85,(1H, d), 7.75,(1H, d), 7.43,(1H, d), 7.31,(1H, t), 7.21,(1H, s), 7.11,(2H, m), 4.52,(2H, d), 3.14,(2H, t), 2.99,(3H, s), 2.39,(3H, s), 1.03,(1H, m), 0.43,(2H, m), 0.23,(2H, m).

15 **Example 24: 6-[5-(Fur-3-ylcarbonylamino)-2-methyl-phenyl]-N-(3-methylsulphonylaminobenzyl)-nicotinamide**



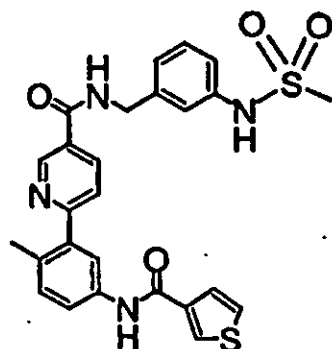
20 6-[5-(Fur-3-ylcarbonylamino)-2-methyl-phenyl]-N-(3-methylsulphonylaminobenzyl)-nicotinamide was prepared from 6-chloro-N-(3-methylsulphonylaminobenzyl)nicotinamide (Intermediate 4) and N-[4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-3-furamide (Intermediate 13) using General Method B. LCMS: retention time 2.93min, MH^+ 505. NMR: δH [2H_6]-DMSO 9.99,(1H, s), 9.32,(1H, t), 9.15,(1H, d), 8.95,(1H, b), 8.38,(1H, s), 8.33,(1H, dd), 7.81,(2H, d), 7.75,(1H, d), 7.68,(1H, d), 7.33-7.30,(2H, m), 7.21,(1H, s),
25 7.11,(2H, m), 7.01,(1H, s), 4.51,(2H, d), 2.99,(3H, s), 2.32,(3H, s).

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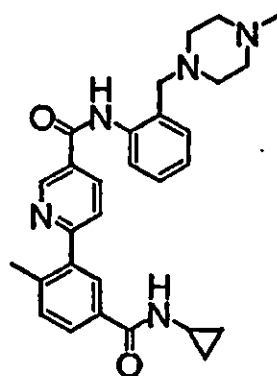
PCT/GB03/00554

Example 25: N-(3-Methylsulphonylaminobenzyl)-6-[5-(thiophen-3-ylcarbonylamino)-2-methyl-phenyl]-nicotinamide



5 N-(3-Methylsulphonylaminobenzyl)-6-[5-(thiophen-3-ylcarbonylamino)-2-methyl-phenyl]-nicotinamide was prepared from 6-chloro-N-(3-methylsulphonylaminobenzyl)nicotinamide (Intermediate 4) and N-[4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]thiophene-3-amide (Intermediate 14) using General Method B. LCMS: retention time 3.03min, MH^+ 521. NMR: δH [2H_6]-DMSO 10.12,(1H, s), 9.33,(1H, t), 9.15,(1H, s), 8.78,(1H, b), 8.36-8.32,(2H, m), 7.86,(1H, s), 7.78,(1H, d), 7.69-7.65,(3H, m), 7.31,(2H, m), 7.21,(1H, s), 7.11,(2H, m), 4.51,(2H, d), 2.99,(3H, s), 2.32,(3H, s).

Example 26: 6-(5-Cyclopropylcarbonyl-2-methyl-phenyl)-N-[2-(4-methylpiperazin-1-ylmethyl)phenyl]-nicotinamide



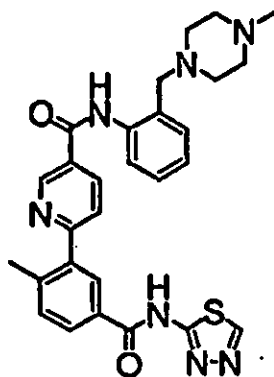
15 6-(5-Cyclopropylcarbonyl-2-methyl-phenyl)-N-[2-(4-methylpiperazin-1-ylmethyl)phenyl]-nicotinamide was prepared from 6-chloro-N-[2-(4-methylpiperazin-1-ylmethyl)phenyl]nicotinamide (Intermediate 5) and N-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (Intermediate 8) using
20 General Method B. LCMS: retention time 2.36min, MH^+ 484. NMR: δH [2H_6]-DMSO 11.70,(1H, b), 9.23,(1H, s), 8.50,(1H, d), 8.38,(1H, d), 8.33,(1H, d), 7.92,(1H, s), 7.83,(2H, m), 7.43,(1H, d), 7.36,(1H, t), 7.29,(1H, d), 7.11,(1H, t), 3.77,(2H, s), 2.87,(1H, m), 2.67-2.24,(11H, m), 2.13,(3H, s), 0.70,(2H, m), 0.58,(2H, m).

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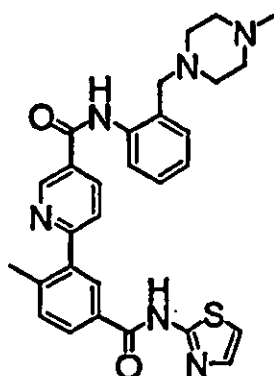
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Example 27: N-[2-(4-Methylpiperazin-1-ylmethyl)phenyl]-6-[2-methyl-5-(thiadiazol-2-ylcarbamoyl)-phenyl]-nicotinamide



5 N-[2-(4-Methylpiperazin-1-ylmethyl)phenyl]-6-[2-methyl-5-(thiadiazol-2-ylcarbamoyl)-phenyl]-nicotinamide was prepared from 6-chloro-N-[2-(4-methylpiperazin-1-ylmethyl)phenyl]nicotinamide (Intermediate 5) and 4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-N-(thiadiazol-2-yl)-benzamide (Intermediate 12) using General Method B. LCMS: retention time 2.43min, MH^+ 528. NMR: δH [2H_6]-DMSO 13.07,(1H, b), 11.74,(1H, s), 9.26,(1H, s), 9.21,(1H, s), 10 8.43,(1H, d), 8.34,(1H, d), 8.29,(1H, s), 8.12,(1H, d), 7.93,(1H, d), 7.56,(1H, d), 7.36,(1H, t), 7.29,(1H, d), 7.11,(1H, t), 3.78,(2H, s), 2.67-2.26,(11H, m), 2.11,(3H, s).

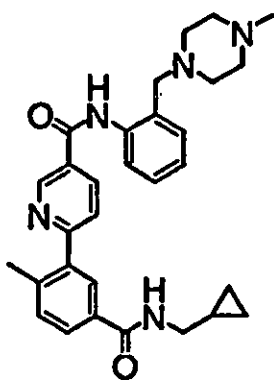
Example 28: N-[2-(4-Methylpiperazin-1-ylmethyl)phenyl]-6-[2-methyl-5-(thiazol-2-ylcarbamoyl)-phenyl]-nicotinamide



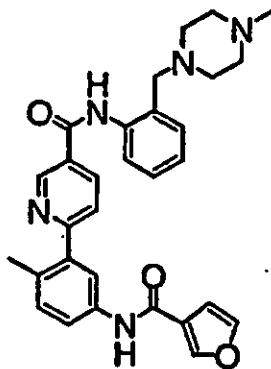
15 N-[2-(4-Methylpiperazin-1-ylmethyl)phenyl]-6-[2-methyl-5-(thiazol-2-ylcarbamoyl)-phenyl]-nicotinamide was prepared from 6-chloro-N-[2-(4-methylpiperazin-1-ylmethyl)phenyl]nicotinamide (Intermediate 5) and 4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-N-(thiazol-2-yl)-benzamide (Intermediate 11) using General Method B. LCMS: retention time 2.53min, MH^+ 527. NMR: δH [2H_6]-DMSO 12.73,(1H, b), 11.70,(1H, b), 9.26,(1H, d), 8.43,(1H, dd), 20 8.33,(1H, d), 8.25,(1H, s), 8.10,(1H, d), 7.93,(1H, d), 7.58,(1H, d), 7.54,(1H, d), 7.36,(1H, t), 7.30,(2H, m), 7.12,(1H, t), 3.78,(2H, s), 2.67-2.25,(11H, b), 2.14,(3H, s).

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Example 29: 6-(5-Cyclopropylmethylcarbamoyl-2-methyl-phenyl)-N-[2-(4-methylpiperazin-1-ylmethyl)phenyl]-nicotinamide

6-(5-Cyclopropylmethylcarbamoyl-2-methyl-phenyl)-N-[2-(4-methylpiperazin-1-ylmethyl)phenyl]-nicotinamide was prepared from 6-chloro-N-[2-(4-methylpiperazin-1-ylmethyl)phenyl]nicotinamide (Intermediate 5) and N-cyclopropylmethyl-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (Intermediate 10) using General Method B. LCMS: retention time 2.46min, MH^+ 498. NMR: δH [2H_6]-DMSO 11.67,(1H, b), 9.24,(1H, s), 8.63,(1H, t), 8.39,(1H, d), 8.32,(1H, d), 7.97,(1H, s), 7.88-7.83,(2H, m), 7.45,(1H, d), 7.36,(1H, t), 7.30,(1H, d), 7.11,(1H, t), 3.77,(2H, s), 3.15,(2H, t), 2.70-2.21,(11H, m), 1.04,(1H, m), 0.43,(2H, m), 0.23,(2H, m).

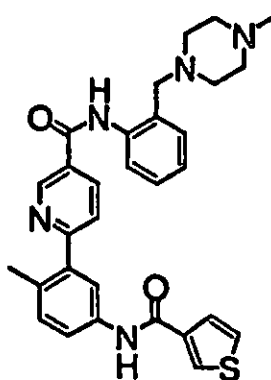
Example 30: 6-[5-(Fur-3-ylcarbonylamino)-2-methyl-phenyl]-N-[2-(4-methylpiperazin-1-ylmethyl)phenyl]-nicotinamide

6-[5-(Fur-3-ylcarbonylamino)-2-methyl-phenyl]-N-[2-(4-methylpiperazin-1-ylmethyl)phenyl]-nicotinamide was prepared from 6-chloro-N-[2-(4-methylpiperazin-1-ylmethyl)phenyl]nicotinamide (Intermediate 5) and N-[4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-3-furamide (Intermediate 13) using General Method B. LCMS: retention time 2.53min, MH^+ 510. NMR: δH [2H_6]-DMSO 11.64,(1H, b), 10.02,(1H, s), 9.23,(1H, s), 8.38,(2H, m), 8.31,(1H, d), 7.86,(1H, s), 7.80,(1H, s), 7.76,(2H, m), 7.38-7.29,(3H, m), 7.11,(1H, t), 7.01,(1H, s), 3.77,(2H, s), 2.66-2.20,(11H, m), 2.16,(3H, s).

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Example 31: N-[2-(4-Methylpiperazin-1-ylmethyl)phenyl]-6-[5-(thiophen-3-ylcarbonylamino)-2-methyl-phenyl]-nicotinamide



- 5 N-[2-(4-Methylpiperazin-1-ylmethyl)phenyl]-6-[5-(thiophen-3-ylcarbonylamino)-2-methyl-phenyl]-nicotinamide was prepared from 6-chloro-N-[2-(4-methylpiperazin-1-ylmethyl)phenyl]nicotinamide (Intermediate 5) and N-[4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]thiophene-3-amide (Intermediate 14) using General Method B. LCMS: retention time 2.58min, MH^+ 526. NMR: δH [2H_6]-DMSO 11.64,(1H, b), 10.14,(1H, s), 9.23,(1H, s), 8.38,(2H, m), 8.31,(1H, d), 7.91,(1H, s), 7.79-7.75,(2H, m), 7.65,(2H, m), 7.38-7.29,(3H, m), 7.11,(1H, t), 3.77,(2H, s), 2.67-2.24,(11H, m), 2.16,(3H, m).
- 10

General Method C

- 15 The 6-chloronicotinamide (25mg), N-cyclopropyl-5-fluoro-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (Intermediate 34, 15mg), tetrakis(triphenylphosphino)palladium (2mg) and aqueous sodium hydrogen carbonate (1M, 0.5ml) were mixed in propan-2-ol (2ml) and heated at reflux for 18 hours. The propan-2-ol was evaporated and the residue diluted with ethylacetate / cyclohexane
- 20 (1:2). The solution was applied to a SPE (Si, 2g) and eluted with ethylacetate / cyclohexane (1:2) and then ethylacetate. The solvent was evaporated from the ethylacetate fraction and the residue triturated with ether to give the desired product as a white solid.
- 25 Examples 32 to 44 may also be prepared using {5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}boronic acid (Intermediate 36) in place of Intermediate 34.

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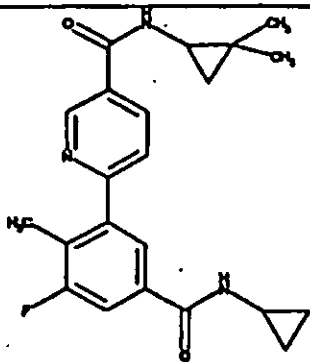
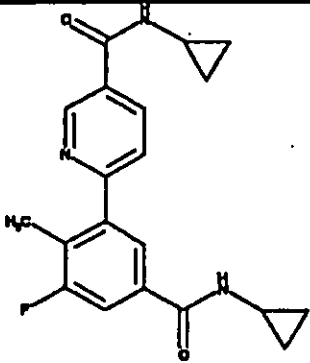
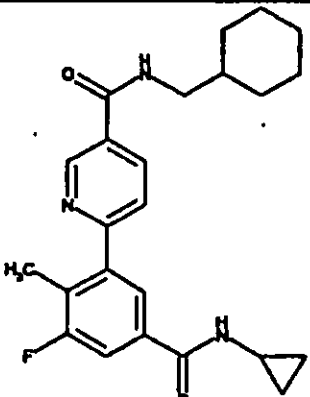
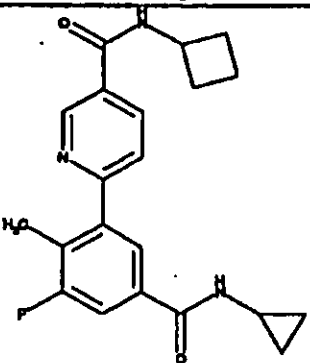
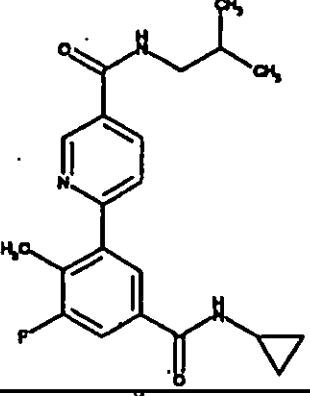
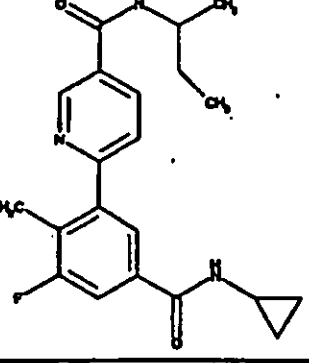
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Compound	Structure	6-Chloronicotinamide	MH ⁺	Retention time (minutes)
Example 32 6-(5-Cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-cyclopropylmethyl-nicotinamide		6-Chloro-N-cyclopropylmethyl nicotinamide (Intermediate 21)	368	2.78
Example 33 6-(5-Cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(3-methylbutyl)-nicotinamide		6-Chloro-N-(3-methylbutyl)nicotinamide (Intermediate 22)	384	3.10
Example 34 6-(5-Cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-cyclobutylmethyl-nicotinamide		6-Chloro-N-cyclobutylmethyl nicotinamide (Intermediate 32)	382	3.01
Example 35 6-(5-Cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(1-cyclopropylethyl)-nicotinamide		6-Chloro-N-(1-cyclopropylethyl)nicotinamide (Intermediate 23)	382	2.95
Example 36 6-(5-Cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylpropyl)-nicotinamide		6-Chloro-N-(2,2-dimethylpropyl)nicotinamide (Intermediate 24)	384	3.01

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Example 37 6-(5-Cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2,2-dimethylcyclopropyl)-nicotinamide		6-Chloro-N-(2,2-dimethylcyclopropyl)nicotinamide (Intermediate 25)	382	2.90
Example 38 6-(5-Cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-cyclopropyl-nicotinamide		6-Chloro-N-cyclopropylnicotinamide (Intermediate 26)	354	2.60
Example 39 6-(5-Cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-cyclohexylmethyl-nicotinamide		6-Chloro-N-cyclohexylmethylnicotinamide (Intermediate 27)	410	3.22
Example 40 6-(5-Cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-cyclobutyl-nicotinamide		6-Chloro-N-cyclobutylnicotinamide (Intermediate 28)	368	2.79
Example 41 6-(5-Cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(2-methylpropyl)-nicotinamide		6-Chloro-N-(2-methylpropyl)nicotinamide (Intermediate 29)	370	2.86
Example 42 6-(5-Cyclopropylcarbamoyl-3-fluoro-2-methyl-phenyl)-N-(1-methylpropyl)-nicotinamide		6-Chloro-N-(1-methylpropyl)nicotinamide (Intermediate 33)	370	2.84

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Example 43 6-(5-Cyclopropylcarbamoyl-3-fluoro-2-methylphenyl)-N-propyl-nicotinamide		6-Chloro-N-propylnicotinamide (Intermediate 30)	356	2.72
Example 44 6-(5-Cyclopropylcarbamoyl-3-fluoro-2-methylphenyl)-N-cyclopentyl-nicotinamide		6-Chloro-N-cyclopentylnicotinamide (Intermediate 31)	382	2.92

General Method D

Intermediate 38 (40 μ mol) in DMF (0.5ml) was treated with HATU (1.12eq) and DIPEA (3eq). On shaking a solution was formed which was added to a solution of amine (1.2 – 2.0eq) in DMF (0.5ml). After shaking the reactions were left overnight at room temperature. The solvent was removed *in vacuo*, the residue dissolved in chloroform (1.0ml) and applied to an SPE (NH₂, 0.5g). The product was eluted with chloroform (1.5ml), ethyl acetate (1.5ml) and methanol/ethyl acetate (1:9, 1.5ml). The solvent was evaporated under vacuum from the product fraction.

10

Compound	Amine	MH ⁺	Retention time (minutes)
Example 45 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(1,3-thiazol-2-ylmethyl)nicotinamide	2-aminomethylthiazole	411	2.79
Example 46 6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-[2-(1,3-thiazol-2-yl)ethyl]nicotinamide	2-(2-aminoethyl)thiazole	425	2.78
Example 47	2-methylbenzylamine	418	3.26

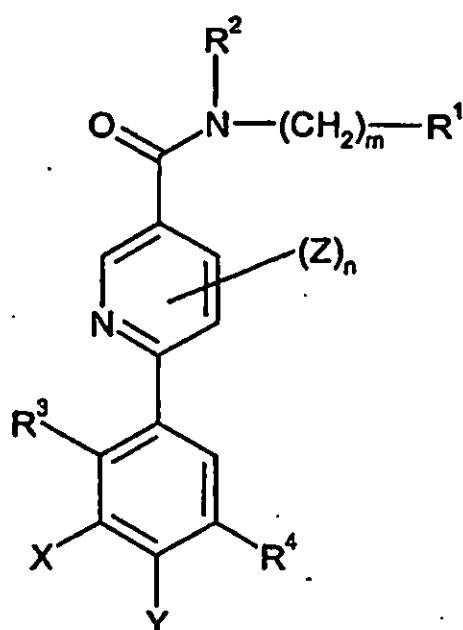
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Claims:

1. A compound of formula (I):



(I)

wherein

R^1 is selected from hydrogen, C_{1-6} alkyl optionally substituted by up to three groups selected from C_{1-6} alkoxy, halogen and hydroxy, C_{2-6} alkenyl, C_{3-7} cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups, phenyl optionally substituted by up to three groups selected from R^5 and R^6 , and heteroaryl optionally substituted by up to three groups selected from R^5 and R^6 ,

R^2 is selected from hydrogen, C_{1-6} alkyl and $-(CH_2)_q-C_{3-7}$ cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups, or $(CH_2)_mR^1$ and R^2 , together with the nitrogen atom to which they are bound, form a four- to six-membered heterocyclic ring optionally substituted by up to three C_{1-6} alkyl groups;

R^3 is chloro or methyl;

R^4 is the group $-NH-CO-R^7$ or $-CO-NH-(CH_2)_q-R^8$;

R^5 is selected from C_{1-6} alkyl, C_{1-6} alkoxy, $-(CH_2)_q-C_{3-7}$ cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups, $-CONR^9R^{10}$, $-NHCOR^{10}$, $-SO_2NHR^9$, $-(CH_2)_sNHSO_2R^{10}$, halogen, CN, OH, $-(CH_2)_sNR^{11}R^{12}$, and trifluoromethyl;

R^6 is selected from C_{1-6} alkyl, C_{1-6} alkoxy, halogen, trifluoromethyl and $-(CH_2)_sNR^{11}R^{12}$;

R^7 is selected from hydrogen, C_{1-6} alkyl, $-(CH_2)_q-C_{3-7}$ cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups, trifluoromethyl, $-(CH_2)_r$ heteroaryl optionally substituted by R^{13} and/or R^{14} , and $-(CH_2)_r$ phenyl optionally substituted by R^{13} and/or R^{14} ;

R^8 is selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups, $CONHR^9$, phenyl optionally substituted by R^{13} and/or R^{14} , and heteroaryl optionally substituted by R^{13} and/or R^{14} ;

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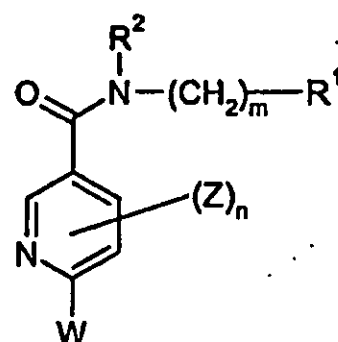
- 5 R^9 and R^{10} are each independently selected from hydrogen and C_{1-6} alkyl, or R^9 and R^{10} , together with the nitrogen atom to which they are bound, form a five- to six-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and $N-R^{15}$, wherein the ring may be substituted by up to two C_{1-6} alkyl groups;
- R^{11} is selected from hydrogen, C_{1-6} alkyl and $-(CH_2)_q-C_{3-7}$ cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups,
- R^{12} is selected from hydrogen and C_{1-6} alkyl, or R^{11} and R^{12} , together with the nitrogen atom to which they are bound,
- 10 form a five or six-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and $N-R^{15}$;
- R^{13} is selected from C_{1-6} alkyl, C_{1-6} alkoxy, $-(CH_2)_q-C_{3-7}$ cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups, $-CONR^9R^{10}$, $-NHCOR^{10}$, halogen, CN, $-(CH_2)_sNR^{11}R^{12}$, trifluoromethyl, phenyl optionally substituted by one
- 15 or more R^{14} groups and heteroaryl optionally substituted by one or more R^{14} groups;
- R^{14} is selected from C_{1-6} alkyl, C_{1-6} alkoxy, halogen, trifluoromethyl and $-NR^{11}R^{12}$;
- R^{15} is selected from hydrogen and methyl;
- X and Y are each independently selected from hydrogen, methyl and halogen;
- 20 Z is halogen;
- m is selected from 0, 1, 2, 3 and 4, wherein each carbon atom of the resulting carbon chain may be optionally substituted with up to two groups selected independently from C_{1-6} alkyl and halogen;
- n is selected from 0, 1 and 2;
- 25 q is selected from 0, 1 and 2;
- r is selected from 0 and 1; and
- s is selected from 0, 1, 2 and 3.
2. A compound according to claim 1 wherein R^1 is selected from C_{1-6} alkyl, C_2 -
- 30 galkenyl, C_{3-7} cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups, phenyl optionally substituted by up to three substituents selected from R^5 and R^6 , heteroaryl optionally substituted by up to three substituents selected from R^5 and R^6 .
3. A compound according to claim 1 or claim 2 wherein R^2 is hydrogen.
- 35 4. A compound according to any one of the preceding claims wherein R^3 is methyl.
5. A compound according to any one of the preceding claims wherein X is
- 40 fluorine.
6. A compound according to any one of the preceding claims wherein R^7 is selected from C_{1-6} alkyl, $-(CH_2)_q-C_{3-7}$ cycloalkyl, trifluoromethyl, $-(CH_2)_r$ heteroaryl optionally substituted by R^{13} and/or R^{14} , and $-(CH_2)_r$ phenyl optionally substituted
- 45 by C_{1-6} alkyl, C_{1-6} alkoxy, $-(CH_2)_q-C_{3-7}$ cycloalkyl, $-CONR^9R^{10}$, $-NHCOR^{10}$,

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halogen, CN, trifluoromethyl, phenyl optionally substituted by one or more R¹⁴ groups and/or heteroaryl optionally substituted by one or more R¹⁴ groups.

7. A compound according to any one of the preceding claims wherein R⁸ is selected from C₃₋₇cycloalkyl, CONHR⁹, heteroaryl optionally substituted by R¹³ and/or R¹⁴, and phenyl optionally substituted by C₁₋₆alkyl, C₁₋₆alkoxy, -(CH₂)_q-C₃₋₇cycloalkyl, -CONR⁹R¹⁰, -NHCOR¹⁰, halogen, CN, trifluoromethyl, phenyl optionally substituted by one or more R¹⁴ groups and/or heteroaryl optionally substituted by one or more R¹⁴ groups.
8. A compound according to claim 1 as defined in any one of Examples 1 to 123.
9. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 8 in admixture with one or more pharmaceutically acceptable carriers, diluents or excipients.
10. A method for treating a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase comprising administering to a patient in need thereof a compound as claimed in any one of claims 1 to 8.
11. A compound as claimed in any one of claims 1 to 8 for use in therapy.
12. Use of a compound as claimed in any one of claims 1 to 8 in the manufacture of a medicament for use in the treatment of a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase.
13. A process for preparing a compound of formula (I) as claimed in any one of claims 1 to 8 which comprises
 - (a) reacting a compound of (II)

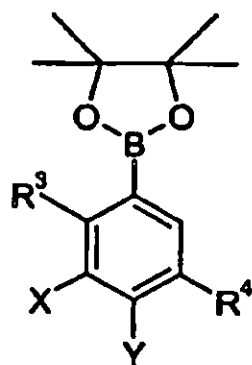


(II)

- 35 in which R¹, R², Z, m and n are as defined in claim 1 and W is halogen, with a compound of formula (III)

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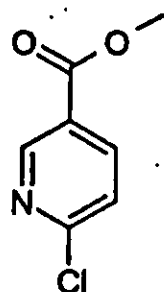


(III)

in which R³, R⁴, X and Y are as defined in claim 1,
in the presence of a catalyst, or

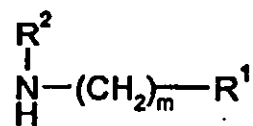
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(b) reacting a compound of formula (VIII)



(VIII)

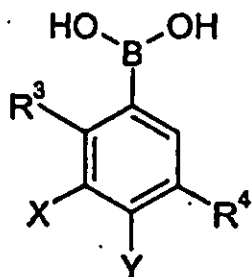
10 with a compound of formula (III) as hereinbefore defined and then reacting the acid
thus formed with an amine of formula (V)



(V)

15 in which R¹, R² and m are as defined in claim 1,
under amide forming conditions, or

(c) reacting a compound of formula (II) as hereinbefore defined with a compound
of formula (IX)



(IX)

20

in which R³, R⁴, X and Y are as defined in claim 1,
in the presence of a catalyst.

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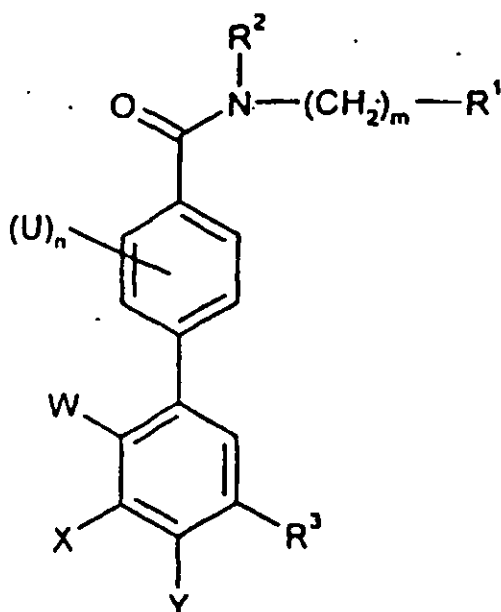
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(54) Title: 5'-CARBAMOYL-2'-METHYL-1,1'-BIPHENYL-4-CARBOXAMIDE DERIVATIVES AND THEIR USE AS P38 KI-
NASE INHIBITORS

(I)

(57) Abstract: Compounds of formula (I) or pharmaceutically acceptable
salts or solvates thereof, and their use as pharmaceuticals, particularly as
p38 kinase inhibitors.

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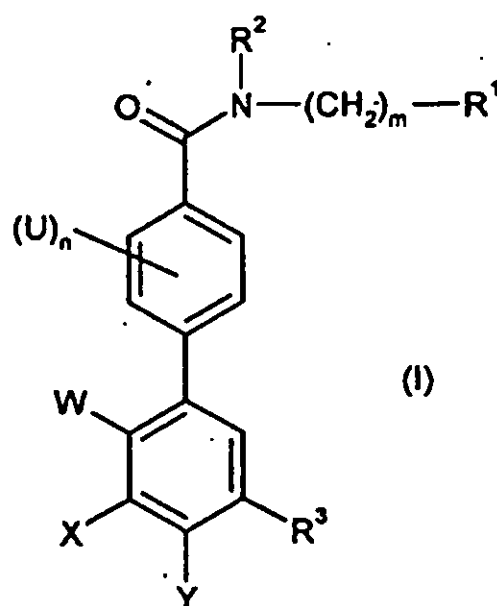
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5'-CARBAMOYL-2'-METHYL-1,1'-BIPHENYL-4-CARBOXAMIDE DERIVATIVES AND THEIR USE AS P38 KINASE INHIBITORS

This invention relates to novel compounds and their use as pharmaceuticals, particularly as p38 kinase inhibitors, for the treatment of certain diseases and conditions.

We have now found a group of novel compounds that are inhibitors of p38 kinase.

According to the invention there is provided a compound of formula (I):



wherein

R^1 is a phenyl group which may be optionally substituted;

R^2 is selected from hydrogen, C_{1-6} alkyl and $-(CH_2)_n-C_{3-7}$ cycloalkyl;

R^3 is the group $-CO-NH-(CH_2)_q-R^4$;

when q is 0 to 2 R^4 is selected from hydrogen, C_{1-6} alkyl, $-C_{3-7}$ cycloalkyl, $CONHR^5$, phenyl optionally substituted by R^7 and/or R^8 , heteroaryl optionally substituted by R^7 and/or R^8 and heterocyclyl optionally substituted by R^7 and/or R^8 ;

and when q is 2 R^4 is additionally selected from C_{1-6} alkoxy, $NHCOR^5$, $NHCONHR^5$, NR^5R^6 , and OH;

R^5 is selected from hydrogen, C_{1-6} alkyl and phenyl wherein the phenyl group may be optionally substituted by up to two substituents selected from C_{1-6} alkyl and halogen;

R^6 is selected from hydrogen and C_{1-6} alkyl;

or R^5 and R^6 , together with the nitrogen atom to which they are bound, form a five- to six-membered heterocyclic or heteroaryl ring optionally containing one additional heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring may be substituted by up to two C_{1-6} alkyl groups;

R^7 is selected from C_{1-6} alkyl, C_{1-6} alkoxy, $-CONR^6R^9$, $-NHCOR^9$, $-SO_2NHR^9$, $-NHSO_2R^9$, halogen, trifluoromethyl, $-Z-(CH_2)_5$ -phenyl optionally substituted by one or more halogen atoms, $-Z-(CH_2)_5$ -heterocyclyl or $-Z-(CH_2)_5$ -heteroaryl wherein the

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heterocyclyl or heteroaryl group may be optionally substituted by one or more substituents selected from C_{1-6} alkyl;

R^8 is selected from C_{1-6} alkyl and halogen;

or when R^7 and R^8 are adjacent to each other they may, together with the carbon atoms to which they are bound, form a five- or six-membered saturated or unsaturated ring to give a fused bicyclic ring system, wherein the ring that is formed by R^7 and R^8 may optionally contain one or two heteroatoms selected from oxygen, nitrogen and sulfur;

R^9 is selected from hydrogen and C_{1-6} alkyl;

U is selected from methyl and halogen;

W is selected from methyl and chlorine;

X and Y are each selected independently from hydrogen, methyl and halogen;

Z is selected from -O- and a bond;

m is selected from 0, 1, 2, 3 and 4, and may be optionally substituted with up to two groups selected independently from C_{1-6} alkyl;

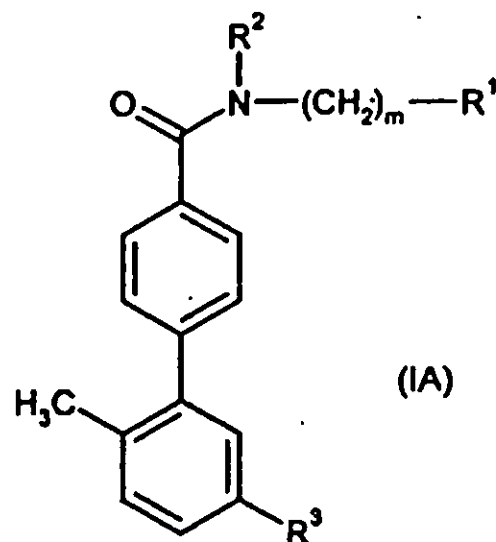
n is selected from 0, 1 and 2;

v is selected from 0, 1 and 2;

q and s are selected from 0, 1 and 2;

or a pharmaceutically acceptable salt or solvate thereof.

According to a further embodiment of the invention there is provided a compound of formula (IA):



wherein R^1 , R^2 , R^3 and m are as defined above, or a pharmaceutically acceptable salt or solvate thereof.

In a preferred embodiment, the molecular weight of a compound of formula (I) does not exceed 1000, more preferably 800, even more preferably 600.

The group R^1 may be optionally substituted by up to three substituents, more preferably one or two substituents, selected independently from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkoxy, trifluoromethyl, benzyloxy, hydroxy, cyano, hydroxy C_{1-6} alkyl, $-(CH_2)_pCO(CH_2)_lNR^{10}R^{11}$, $-(CH_2)_pCO_2R^{10}$, $-(CH_2)_pNR^{10}COR^{11}$, $-(CH_2)_pOCOR^{10}$, -

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- (CH₂)_pOCONR¹⁰R¹¹, -(CH₂)_pNR¹⁰COOR¹¹, -(CH₂)_pCOR¹⁰, -(CH₂)_pSO₂NR¹⁰R¹¹, -(CH₂)_pNR¹⁰SO₂R¹¹, -SO₂R¹⁰, -(CH₂)_pNR¹⁰R¹¹, -O(CH₂)_pNR¹⁰R¹¹, -(CH₂)_pNR¹⁰CO(CH₂)_tNR¹⁰R¹¹, -(CH₂)_pCONR¹⁰SO₂R¹¹, -(CH₂)_pSO₂NR¹⁰COR¹¹ and phenyloxy optionally substituted by a group A; or R¹ may be optionally substituted by two adjacent substituents which, together with the carbon atoms to which they are bound, form a five- or six-membered saturated or unsaturated ring to give a fused bicyclic ring system. The ring that is fused to the phenyl ring may optionally contain one or two heteroatoms selected from oxygen, nitrogen and sulfur. The group R¹ may also be optionally substituted by three, more preferably one or two, C₃₋₇cycloalkyl groups.
- R¹⁰ and R¹¹ are independently selected from hydrogen, C₁₋₆alkyl, trihalomethyl, benzyl, -(CH₂)_rOH, -(CH₂)_rNR¹²R¹³ and phenyl optionally substituted by up to three groups selected from C₁₋₆alkyl and C₁₋₆alkoxy. R¹⁰ and R¹¹ may also be independently selected from C₁₋₆alkyl substituted by up to three, more preferably one or two, hydroxy groups.
- R¹² and R¹³ are independently selected from hydrogen and C₁₋₄alkyl.
- A is selected from halogen, -SO₂NH₂, -SO₂-(4-methyl)piperazinyl, -NR¹⁰COC₁₋₆alkyl and -NR¹⁰SO₂C₁₋₆alkyl.
- p is selected from 0, 1, 2 or 3.
- t is selected from 0, 1, 2 and 3.
- r is selected from 2 or 3.
- The optional substituents on the group R¹, including when the phenyl ring is part of a fused bicyclic system, may be located on any position on the phenyl ring. In a more preferred embodiment, when there is one substituent on the group R¹, that substituent is located on the meta- or para-position relative to the amide linkage. When there are two optional substituents on the group R¹, these substituents preferably occupy the meta- and para-positions relative to the amide linkage.
- Preferred substituents for the group R¹ are halogen, C₁₋₄alkyl, trifluoromethyl, C₁₋₄alkoxy, phenyloxy optionally substituted by the group A, benzyloxy, hydroxy, cyano, -CH₂CH₂OH, -(CH₂)_p-NHCH₃, -(CH₂)_p-N(CH₃)₂, -(CH₂)_pCONR¹⁰R¹¹, -(CH₂)_pCO₂R¹⁰, -(CH₂)_pNR¹⁰COR¹¹, -(CH₂)_pOCOR¹⁰, -(CH₂)_pOCONR¹⁰R¹¹, -(CH₂)_pNR¹⁰COOR¹¹, -(CH₂)_pCOR¹⁰, -(CH₂)_pSO₂NR¹⁰R¹¹, -(CH₂)_pNR¹⁰SO₂R¹¹, -SO₂R¹⁰, -(CH₂)_pNR¹⁰R¹¹, -(CH₂)_pNR¹⁰CONR¹⁰R¹¹ and -(CH₂)_pCONR¹⁰SO₂R¹¹.
- Further preferred substituents for the group R¹ include -CH₂OH.
- More preferred substituents for the group R¹ include halogen, in particular fluorine or chlorine; C₁₋₄alkyl, in particular methyl; C₁₋₄alkoxy, in particular methoxy; hydroxy; cyano; hydroxyC₁₋₄alkyl, in particular -CH₂OH or -CH₂CH₂OH; -(CH₂)_pCO(CH₂)_tNR¹⁰R¹¹, in particular -CONH₂ or -CH₂CONH₂; -(CH₂)_pSO₂NR¹⁰R¹¹, in particular -SO₂NH₂; -(CH₂)_pNR¹⁰SO₂R¹¹, in particular -NHSO₂CH₃ or -CH₂NHSO₂CH₃; -SO₂R¹⁰, in particular -SO₂(CH₂)₂OH; and -(CH₂)_pNR¹⁰R¹¹, in particular -CH₂N(CH₃)₂, -CH₂N(CH₃)(CH₂CH₃) or -NHCH(CH₂OH)₂.

In a preferred embodiment, R^2 is selected from hydrogen, C_{1-4} alkyl and $-CH_2$ -cyclopropyl, more preferably hydrogen. In further preferred embodiment, R^2 is selected from hydrogen, methyl and ethyl.

5 In a preferred embodiment, R^4 is selected from C_{1-4} alkyl, cyclopropyl, $-CH_2$ -cyclopropyl, pyridinyl and phenyl. In further preferred embodiment, R^4 is selected from C_{1-4} alkyl, in particular ethyl or isopropyl; $-C_{3-7}$ cycloalkyl, in particular cyclopropyl, cyclobutyl or cyclopentyl, especially cyclopropyl; phenyl optionally substituted by R^7 and/or R^8 , in particular phenyl optionally substituted by C_{1-4} alkyl, C_{1-4} alkoxy, $-CONH_2$, $-CONHCH_3$, $-NHCOCH_3$, $-SO_2NH_2$, $-NHSO_2CH_3$, halogen, and/or $-Z-(CH_2)_5$ heteroaryl
10 wherein the heteroaryl is preferably pyridyl, pyrimidyl or oxadiazolyl optionally substituted by C_{1-4} alkyl or phenyl optionally substituted with adjacent groups which give a fused bicyclic ring system, especially quinolinyl, isoquinolinyl or tetralonyl; heteroaryl optionally substituted by R^7 and/or R^8 , in particular thienyl, pyridyl or benzofuran optionally substituted by C_{1-4} alkyl and/or $-CONH_2$; and $NHCONHR^5$, in particular where
15 R^5 is phenyl.

In a preferred embodiment, R^5 is selected from hydrogen and C_{1-4} alkyl. In a further preferred embodiment, R^5 is selected from phenyl optionally substituted by C_{1-4} alkyl, in particular methyl.

20 In a preferred embodiment, R^6 is selected from hydrogen and C_{1-4} alkyl. In particular, R^6 is selected from hydrogen or methyl.

In a preferred embodiment, R^7 is selected from C_{1-4} alkyl, $-NHCOCH_3$, pyridinyl, pyrimidinyl and oxadiazolyl. In a further preferred embodiment, R^7 is selected from C_{1-4} alkyl, in particular methyl; C_{1-4} alkoxy, in particular methoxy; $-CONR^8R^9$, in particular $-CONHCH_3$ or $CONH_2$; $-NHCOR^9$, in particular $-NHCOCH_3$; $-SO_2NHR^9$, in particular $-SO_2NH_2$; $-NHSO_2R^9$, in particular $-NHSO_2CH_3$; halogen, in particular chlorine; and $-Z-(CH_2)_5$ heteroaryl wherein the heteroaryl is preferably pyridyl, pyrimidyl or oxadiazolyl
25 optionally substituted by C_{1-4} alkyl.

In a preferred embodiment, R^8 is selected from C_{1-4} alkyl, fluorine and chlorine. In particular, R^8 is selected from methyl and chlorine.

30 In a preferred embodiment, R^9 is selected from hydrogen and methyl.

In a preferred embodiment, R^{10} and R^{11} are independently selected from hydrogen, C_{1-4} alkyl, trifluoromethyl and phenyl. In a further preferred embodiment, R^{10} and R^{11} are independently selected from hydrogen; C_{1-4} alkyl, in particular methyl or t-butyl; or C_{1-4} alkyl substituted by up to three, more preferably one or two, hydroxy groups, in particular 2-hydroxyethyl or 1,3-dihydroxyprop-2-yl.
35

In a preferred embodiment, R^{12} and R^{13} are independently selected from hydrogen, C_{1-4} alkyl and trifluoromethyl.

In a preferred embodiment, W is methyl.

40 In a preferred embodiment, X and Y are each selected independently from hydrogen, chlorine and fluorine. In a further preferred embodiment, X is fluorine.

In a preferred embodiment, Z is a bond.

In a preferred embodiment, m is selected from 0, 1 and 2.

In a preferred embodiment, n is selected from 0 and 1. In particular, n is 0.

In a preferred embodiment, p is selected from 0, 1 and 2.

5 In a preferred embodiment, q is selected from 0 and 1. In one embodiment, q is 0.

In a preferred embodiment, s is selected from 0 and 1.

In a preferred embodiment, t is selected from 0, 1 and 2.

10 It is to be understood that the present invention covers all combinations of particular and preferred groups described hereinabove.

Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable salts and solvates. Specific examples which may be mentioned include:

15 $N^{4'}-(3\text{-Cyanophenyl})-N^3\text{-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide}$;
 $N^{4'}-(3\text{-Cyanophenyl})-6\text{-methyl-}N^3\text{-[3-(2-methylpyrimidin-4-yl)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide}$;
 $N^{4'}-(3\text{-Cyanophenyl})-6\text{-methyl-}N^3\text{-[3-(pyrid-2-yl)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide}$;
 $N^3\text{-cyclopropyl-}N^{4'}-(3\text{-methoxybenzyl})-6\text{-methyl-1,1'-biphenyl-3,4'-dicarboxamide}$;
 20 and $N^3\text{-Cyclopropyl-}N^{4'}-(4\text{-methoxyphenyl})-6\text{-methyl-1,1'-biphenyl-3,4'-dicarboxamide}$.

Further specific examples which may be mentioned include:

25 $N^3\text{-Cyclopropyl-5-fluoro-}N^{4'}-(3\text{-methoxybenzyl})-6\text{-methyl-1,1'-biphenyl-3,4'-dicarboxamide}$;

$N^3\text{-Cyclopropyl-5-fluoro-6-methyl-}N^{4'}\text{-[3-[(methylsulfonyl)amino]benzyl]-1,1'-biphenyl-3,4'-dicarboxamide}$;

30 $N^3\text{-Cyclopropyl-5-fluoro-6-methyl-}N^{4'}\text{-[4-[(methylsulfonyl)amino]phenyl]-1,1'-biphenyl-3,4'-dicarboxamide}$;

$N^3\text{-Cyclopropyl-}N^{4'}-(3\text{-methoxybenzyl})-N^{4'},6\text{-dimethyl-1,1'-biphenyl-3,4'-dicarboxamide}$;

$N^3\text{-Cyclopropyl-}N^{4'}\text{-[2-(4-methoxyphenyl)ethyl]-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide}$;

35 $N^3\text{-Cyclopropyl-6-methyl-}N^{4'}\text{-[3-[(methylsulfonyl)amino]benzyl]-1,1'-biphenyl-3,4'-dicarboxamide}$;

N^{4'}-(3-Bromobenzyl)-N³-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide;

N³-Cyclopropyl-6-methyl-N^{4'}-(4-[(methylsulfonyl)amino]phenyl)-1,1'-biphenyl-3,4'-dicarboxamide;

5 N³-Cyclopropyl-6-methyl-N^{4'}-(4-[(methylsulfonyl)amino]methyl)phenyl)-1,1'-biphenyl-3,4'-dicarboxamide;

N^{4'}-(4-(Aminosulfonyl)benzyl)-N³-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide;

N³-Cyclopropyl-N^{4'}-(3-[(dimethylamino)methyl]benzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide;

10 N³-Cyclopropyl-N^{4'}-(3-[(2-hydroxy-1-(hydroxymethyl)ethyl)amino]benzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide;

N³-Cyclopropyl-N^{4'}-(2-hydroxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide;

15 N^{4'}-(3-(Aminosulfonyl)phenyl)-N³-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide;

N³-Cyclopropyl-N^{4'}-(2,6-difluorobenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide;

N³-Cyclopropyl-N^{4'}-(2,6-dimethoxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide;

20 N^{4'}-Benzyl-N³-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide;

N³-Cyclopropyl-N^{4'}-(4-fluorobenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide;

and

N³-Cyclopropyl-N^{4'}-(2,6-dimethylphenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide.

25 As used herein, the term "alkyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms. For example, C₁₋₆alkyl means a straight or branched alkyl containing at least 1, and at most 6, carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl and t-butyl. A C₁₋₄alkyl group is preferred, for example methyl, ethyl or isopropyl. The said alkyl groups may be optionally substituted with one or more fluorine atoms, for example, trifluoromethyl.

30 As used herein, the term "alkoxy" refers to a straight or branched chain alkoxy group, for example, methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy, 2-methylprop-1-oxy, 2-methylprop-2-oxy, pentoxy, or hexyloxy. A C₁₋₄alkoxy group is preferred, for example methoxy or ethoxy.

35 As used herein, the term "cycloalkyl" refers to a non-aromatic hydrocarbon ring containing the specified number of carbon atoms. For example, C₃₋₇cycloalkyl means a non-aromatic ring containing at least three, and at most seven, ring carbon atoms. Examples of "cycloalkyl" as used herein include, but are not limited to, cyclopropyl,

cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A C₃₋₅cycloalkyl group is preferred, for example cyclopropyl.

As used herein, the terms "heteroaryl ring" and "heteroaryl" refer to a monocyclic five- to seven- membered unsaturated hydrocarbon ring containing at least one heteroatom selected from oxygen, nitrogen and sulfur. Preferably, the heteroaryl ring has five or six ring atoms. Examples of heteroaryl rings include, but are not limited to, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl. A particularly preferred heteroaryl ring is pyridyl. The said ring may be optionally substituted by one or more substituents independently selected from C₁₋₆alkyl and oxy. The terms "heteroaryl ring" and "heteroaryl" also refer to fused aromatic rings comprising at least one heteroatom selected from oxygen, nitrogen and sulfur. Preferably, the fused ring each have five or six ring atoms. Examples of fused aromatic rings include, but are not limited to, indolyl, benzofuranyl and benzothiophenyl, in particular benzofuranyl.

As used herein, the terms "heterocyclic rings" and "heterocyclyl" refer to a monocyclic three- to seven-membered saturated or non-aromatic, unsaturated hydrocarbon ring containing at least one heteroatom selected from oxygen, nitrogen and sulfur. Preferably, the heterocyclyl ring has five or six ring atoms. Examples of heterocyclyl groups include, but are not limited to, aziridinyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolidinyl, pyrazolyl, pyrazolidinyl, piperidyl, piperazinyl, morpholino, and thiomorpholino. The said ring may be optionally substituted by one or more substituents independently selected from C₁₋₆alkyl and oxy.

As used herein, the term "fused bicyclic ring system" refers to a ring system comprising two five- to seven-membered saturated or unsaturated hydrocarbon rings, the ring system optionally containing one or more heteroatoms independently selected from oxygen, nitrogen and sulfur. Preferably, each ring has five or six ring atoms. Examples of suitable fused bicyclic rings include, but are not limited to, naphthyl, indolyl, indolinyl, benzothienyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzodioxanyl, indanyl and tetrahydronaphthyl. Each ring may be optionally substituted with one or more substituents selected from halogen, C₁₋₆alkyl, oxy, -(CH₂)_pNR¹⁰R¹¹, -CO(CH₂)_pNR¹⁰R¹¹, and imidazolyl. Particularly preferred substituents are chlorine, imidazolyl and -CH₂-N(CH₃)₂.

As used herein, the terms "halogen" or "halo" refer to the elements fluorine, chlorine, bromine and iodine. Preferred halogens are fluorine, chlorine and bromine. A particularly preferred halogen is fluorine.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) which occur and events that do not occur.

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. Most preferably the solvent used is water.

Certain compounds of formula (I) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms or may exhibit cis-trans isomerism). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. The present invention also covers the individual isomers of the compounds represented by formula (I) as mixtures with isomers thereof in which one or more chiral centres are inverted. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

Salts of the compounds of the present invention are also encompassed within the scope of the invention and may, for example, comprise acid addition salts resulting from reaction of an acid with a nitrogen atom present in a compound of formula (I).

Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Representative salts include the following salts: Acetate, Benzenesulfonate, Benzoate, Bicarbonate, Bisulfate, Bitartrate, Borate, Bromide, Calcium Edetate, Camsylate, Carbonate, Chloride, Clavulanate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluceptate, Gluconate, Glutamate, Glycolylarsanilate, Hexylresorcinate, Hydrabamine, Hydrobromide, Hydrochloride, Hydroxynaphthoate, Iodide, Isethionate, Lactate, Lactobionate, Laurate, Malate, Maleate, Mandelate, Mesylate, Methylbromide, Methylnitrate, Methylsulfate, Monopotassium Maleate, Mucate, Napsylate, Nitrate, N-methylglucamine, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Potassium, Salicylate, Sodium, Stearate, Subacetate, Succinate, Tannate, Tartrate, Teoclate, Tosylate, Triethiodide, Trimethylammonium and Valerate. Other salts which are not pharmaceutically acceptable may be useful in the preparation of compounds of this invention and these form a further aspect of the invention.

The compounds of this invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are

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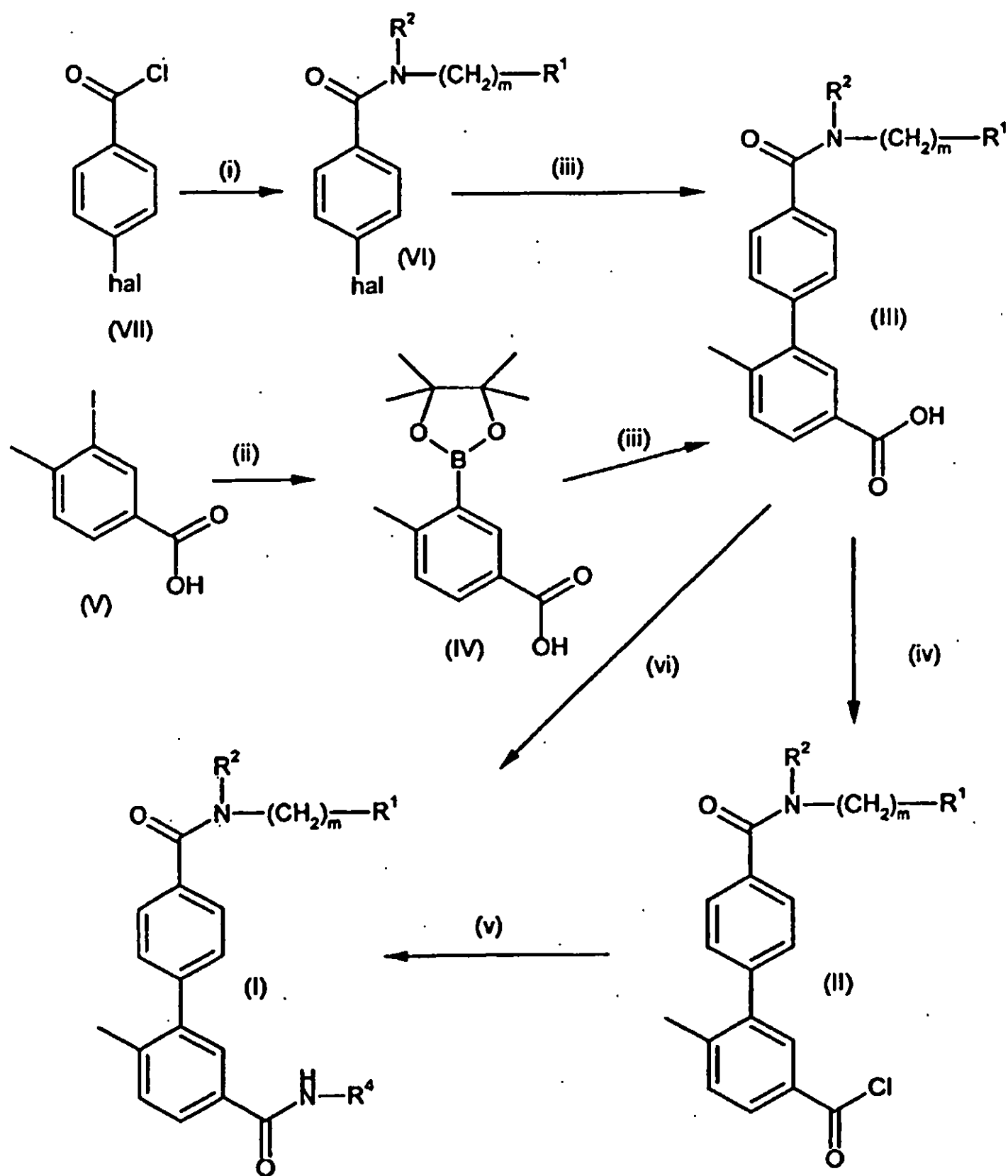
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set out below and then specific compounds of the invention are prepared in the working Examples.

For example, a general method (A) for preparing the compounds of Formula (I) comprises the reactions set out in Scheme 1 below.

5



Scheme 1

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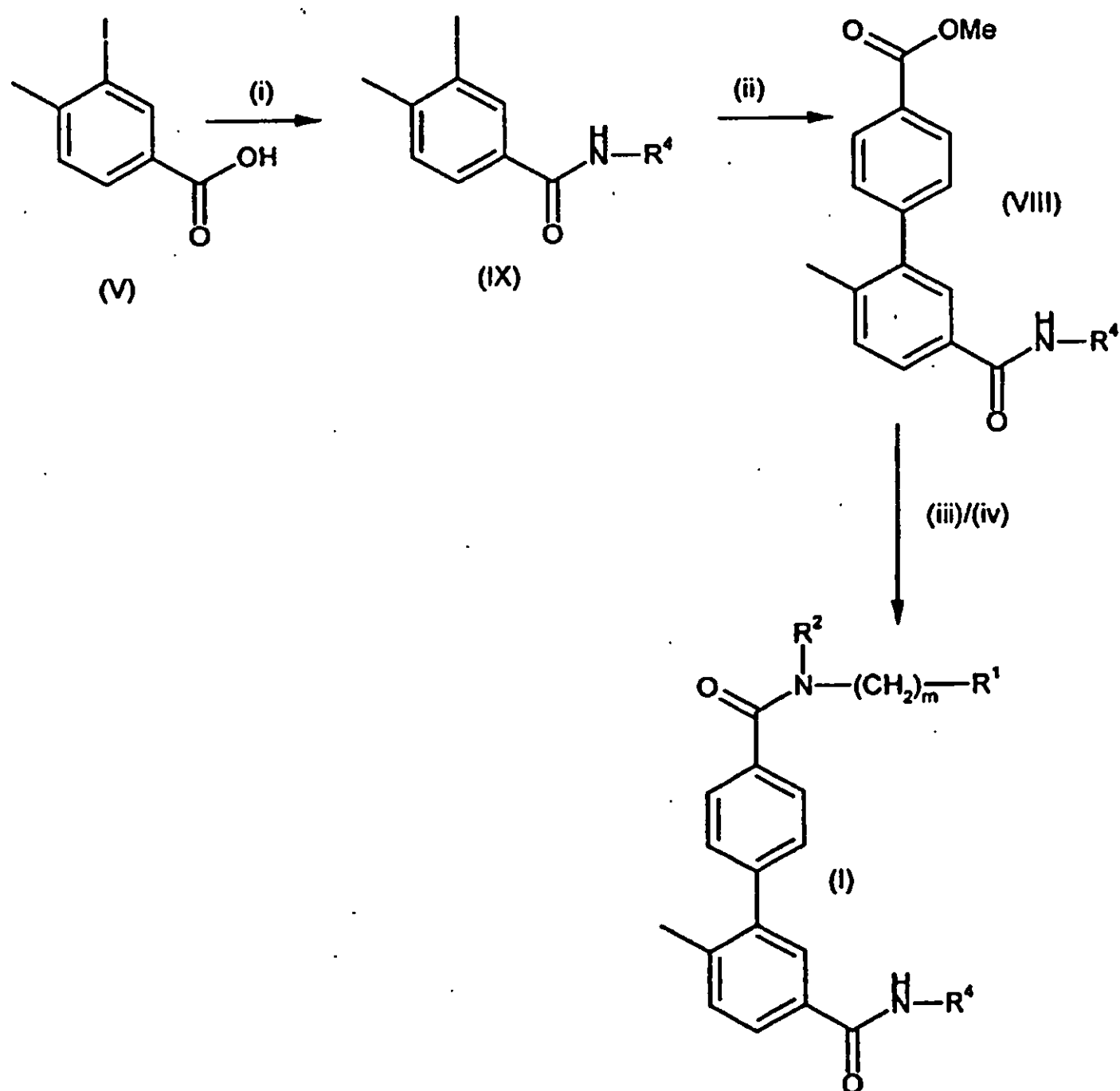
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- (i) $R^1(CH_2)_m N R^2 H$, Et_3N , THF
 - (ii) Bis(pinacolato)diboron, $PdCl_2dppf$, KOAc, DMF
 - (iii) $(Ph_3P)_4Pd$, Na_2CO_3 , DME
 - (iv) $(COCl)_2$, DMF
 - (v) R^4NH_2 , pyridine
 - (vi) R^4NH_2 , PyBOP, HOBT, DIPEA, DMF

For example, a general method (B) for preparing the compounds of Formula (I) comprises the reactions set out in Scheme 2 below.

10



Scheme 2

- 15
- (i) R^4NH_2 , HATU, HOBT, DIPEA, DMF

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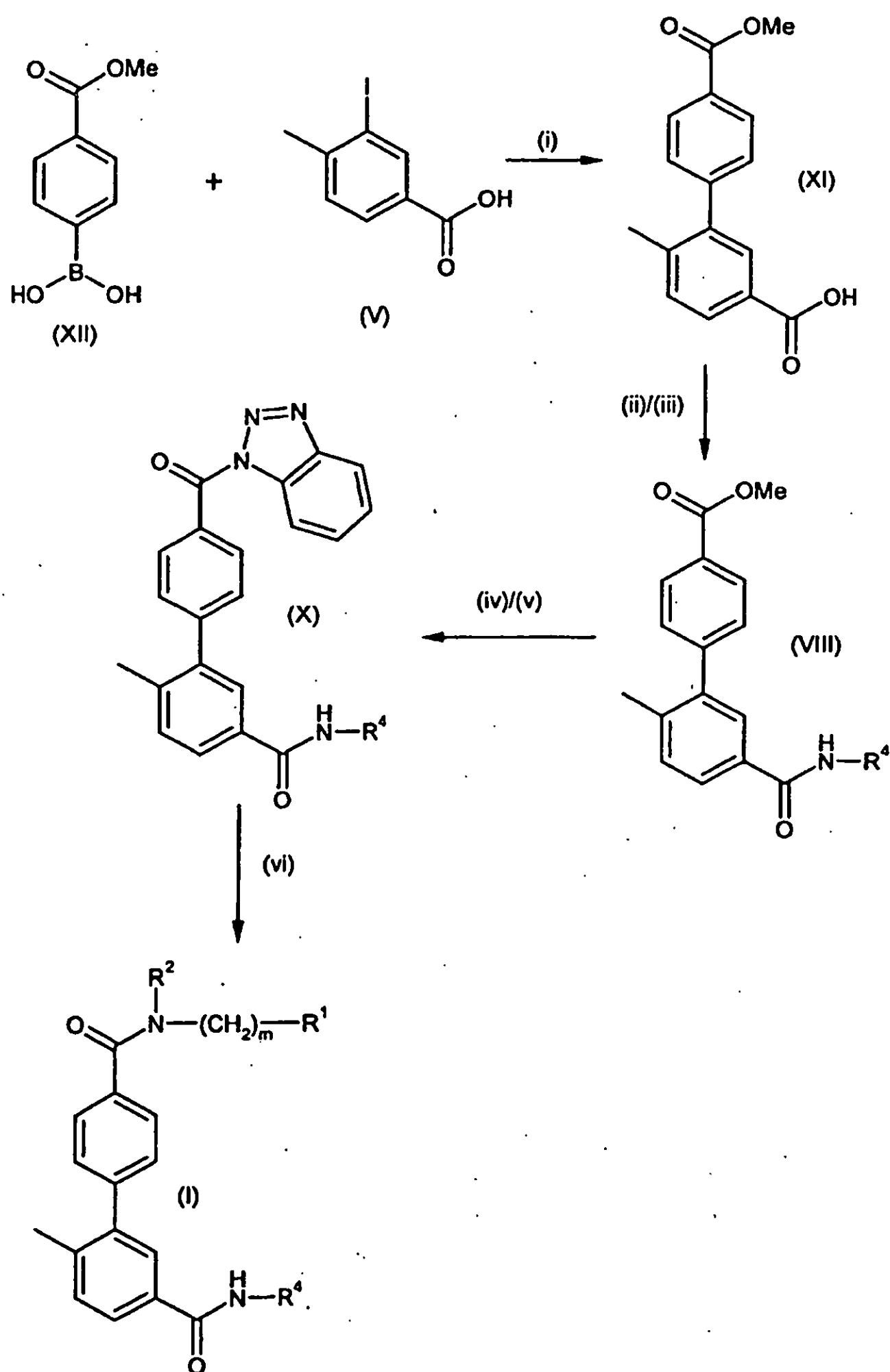
- (ii) (4-Methoxycarbonylphenyl)boronic acid, $(\text{Ph}_3\text{P})_4\text{Pd}$, Na_2CO_3 , DME
- (iii) NaOH , MeOH , H_2O
- (iv) $\text{R}^1(\text{CH}_2)_m\text{N R}^2\text{H}$, HATU, HOBT, DIPEA, THF

- 5 For example, a general method (C) for preparing the compounds of Formula (I) comprises the reactions set out in Scheme 3 below.

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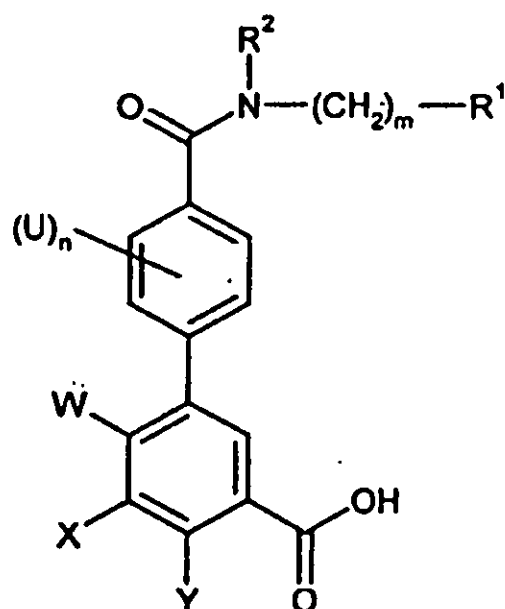
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Scheme 3

- 5
- (i) CsCO_3 , $(\text{Ph}_3\text{P})_4\text{Pd}$, DME
 - (ii) $(\text{COCl})_2$, CHCl_3
 - (iii) R^4NH_2
 - (iv) NaOH , MeOH , H_2O
 - (v) 1-methylsulphonylbenzotriazole, Et_3N , THF, DMF
 - (vi) $\text{R}^1(\text{CH}_2)_m\text{N R}^2\text{H}$, THF

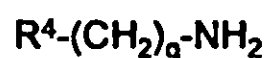
10 Thus, according to the invention there is provided a process for preparing a compound of formula (I) which comprises:

- (a) reacting a compound of formula (XIII)



(XIII)

wherein R^1 , R^2 , U , W , X , Y , m and n are as defined above, with a compound of formula (XIV)



(XIV)

wherein R^4 and q are as defined above, under amide forming conditions (if desired, the acid compound (XIII) may be converted to an activated form of the acid, for example the acid chloride, by treatment with, for example, oxalyl chloride, and then the activated acid thus formed reacted with the amine compound (XIV));

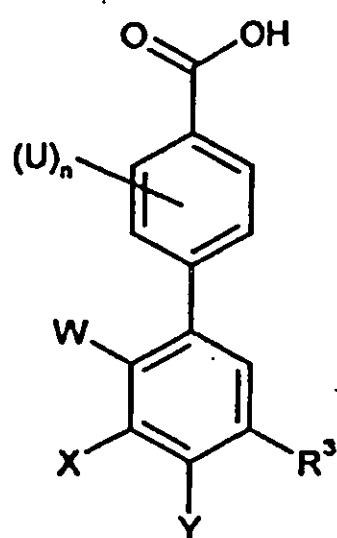
- (b) reacting a compound of formula (XV)

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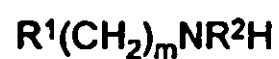
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(XV)

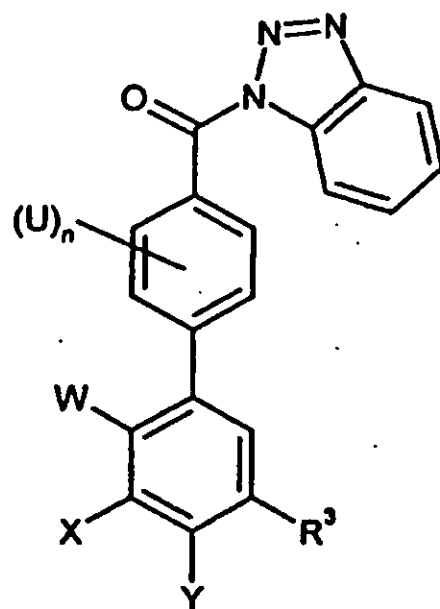
- 5 wherein R^3 , U, W, X, Y and n are as defined above,
with a compound of formula (XVI)



(XVI)

- 10 wherein R^1 , R^2 and m are as defined above,
under amide forming conditions;

- (c) reacting a compound of formula (XVII)



(XVII)

- 15 wherein R^3 , U, W, X, Y and n are as defined above,
with a compound of formula (XVI) as defined above; or

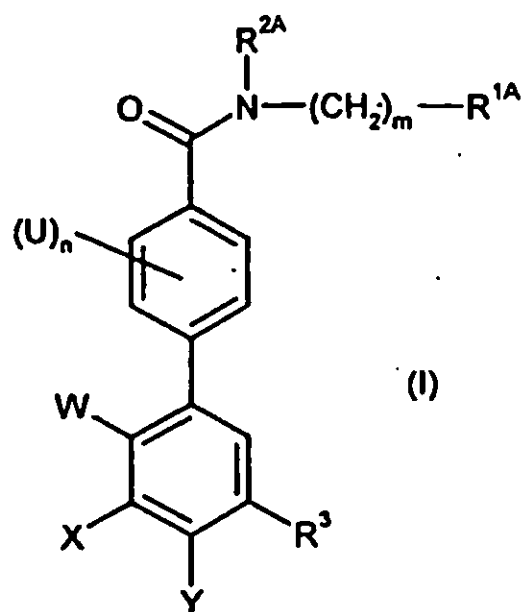
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(d) functional group conversion of a compound of formula (XVIII)



(XVIII)

5

wherein R^3 , U , W , X , Y and n are as defined above and R^{1A} and R^{2A} are R^1 and R^2 as defined above or groups convertible to R^1 and R^2 , to give a compound of formula (I).

10 Suitable amide forming conditions are well known in the art and include treating a solution of the acid, in for example THF, with an amine in the presence of, for example, HOBT, HBTU and DIPEA.

15 Whilst it is possible for the compounds, salts or solvates of the present invention to be administered as the new chemical, the compounds of formula (I) and their pharmaceutically acceptable salts and solvates are conveniently administered in the form of pharmaceutical compositions. Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, in admixture with one or more pharmaceutically acceptable carriers, diluents or excipients.

20 The compounds of formula (I) and their pharmaceutically acceptable salts and solvates may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration. The pharmaceutical composition may be in a form such that it can effect controlled release of the compounds of formula (I) and their pharmaceutically acceptable salts and solvates. A particularly preferred method of administration, and corresponding formulation, is oral administration.

25

For oral administration, the pharmaceutical composition may take the form of, and be administered as, for example, tablets (including sub-lingual tablets) and capsules (each including timed release and sustained release formulations), pills,

powders, granules, elixirs, tinctures, emulsions, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules can be made by preparing a powder mixture as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be

provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additives such as peppermint oil or saccharin, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of the present invention can also be administered in the form of liposome emulsion delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

The present invention includes pharmaceutical compositions containing 0.1 to 99.5%, more particularly, 0.5 to 90% of a compound of the formula (I) in combination with a pharmaceutically acceptable carrier.

Likewise, the composition may also be administered in nasal, ophthalmic, otic, rectal, topical, intravenous (both bolus and infusion), intraperitoneal, intraarticular, subcutaneous or intramuscular, inhalation or insufflation form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative. Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

Alternatively the composition may be formulated for topical application, for example in the form of ointments, creams, lotions, eye ointments, eye drops, ear drops, mouthwash, impregnated dressings and sutures and aerosols, and may contain appropriate conventional additives, including, for example, preservatives, solvents to assist drug penetration, and emollients in ointments and creams. Such topical formulations may also contain compatible conventional carriers, for example cream or ointment bases, and ethanol or oleyl alcohol for lotions. Such carriers may constitute from about 1% to about 98% by weight of the formulation; more usually they will constitute up to about 80% by weight of the formulation.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, heptafluoropropane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

The pharmaceutical compositions generally are administered in an amount effective for treatment or prophylaxis of a specific condition or conditions. Initial dosing in human is accompanied by clinical monitoring of symptoms, such symptoms for the selected condition. In general, the compositions are administered in an amount of active agent of at least about 100 µg/kg body weight. In most cases they will be administered in one or more doses in an amount not in excess of about 20 mg/kg body weight per day. Preferably, in

most cases, dose is from about 100 µg/kg to about 5 mg/kg body weight, daily. For administration particularly to mammals, and particularly humans, it is expected that the daily dosage level of the active agent will be from 0.1 mg/kg to 10 mg/kg and typically around 1 mg/kg. It will be appreciated that optimum dosage will be determined by standard methods for each treatment modality and indication, taking into account the indication, its severity, route of administration, complicating conditions and the like. The physician in any event will determine the actual dosage which will be most suitable for an individual and will vary with the age, weight and response of the particular individual. The effectiveness of a selected actual dose can readily be determined, for example, by measuring clinical symptoms or standard anti-inflammatory indicia after administration of the selected dose. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention. For conditions or disease states as are treated by the present invention, maintaining consistent daily levels in a subject over an extended period of time, e.g., in a maintenance regime, can be particularly beneficial.

In another aspect, the present invention provides a compound of formula (I) or a salt or solvate thereof, for use in therapy.

The compounds of the present invention are generally inhibitors of the serine/threonine kinase p38 and are therefore also inhibitors of cytokine production which is mediated by p38 kinase. Within the meaning of the term "inhibitors of the serine/threonine kinase p38" are included those compounds that interfere with the ability of p38 to transfer a phosphate group from ATP to a protein substrate according to the assay described below.

It will be appreciated that the compounds of the invention may be selective for one or more of the isoforms of p38, for example p38α, p38β, p38γ and/or p38δ. In one embodiment, the compounds of the invention selectively inhibit the p38α isoform. In another embodiment, the compounds of the invention selectively inhibit the p38β isoform. In a further embodiment, the compounds of the invention selectively inhibit the p38α and p38β isoforms. Assays for determining the selectivity of compounds for the p38 isoforms are described in, for example, WO 99/61426, WO 00/71535 and WO 02/46158.

It is known that p38 kinase activity can be elevated (locally or throughout the body), p38 kinase can be incorrectly temporally active or expressed, p38 kinase can be expressed or active in an inappropriate location, p38 kinase can be constitutively expressed, or p38 kinase expression can be erratic; similarly, cytokine production mediated by p38 kinase activity can be occurring at inappropriate times, inappropriate locations, or it can occur at detrimentally high levels.

Accordingly, the present invention provides a method for the treatment of a condition or disease state mediated by p38 kinase activity, or mediated by cytokines produced by the activity of p38 kinase, in a subject which comprises administering to

5 said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof. The compound may be administered as a single or polymorphic crystalline form or forms, an amorphous form, a single enantiomer, a racemic mixture, a single stereoisomer, a mixture of stereoisomers, a single diastereoisomer or a mixture of diastereoisomers.

10 The present invention also provides a method of inhibiting cytokine production which is mediated by p38 kinase activity in a subject, e.g. a human, which comprises administering to said subject in need of cytokine production inhibition a therapeutic, or cytokine-inhibiting, amount of a compound of the present invention. The compound may be administered as a single or polymorphic crystalline form or forms, an amorphous form, a single enantiomer, a racemic mixture, a single stereoisomer, a mixture of stereoisomers, a single diastereoisomer or a mixture of diastereoisomers.

15 The present invention treats these conditions by providing a therapeutically effective amount of a compound of this invention. By "therapeutically effective amount" is meant a symptom-alleviating or symptom-reducing amount, a cytokine-reducing amount, a cytokine-inhibiting amount, a kinase-regulating amount and/or a kinase-inhibiting amount of a compound. Such amounts can be readily determined by standard methods, such as by measuring cytokine levels or observing alleviation of clinical symptoms. For example, the clinician can monitor accepted measurement scores for anti-inflammatory treatments.

20 The compounds of the present invention can be administered to any subject in need of inhibition or regulation of p38 kinase or in need of inhibition or regulation of p38 mediated cytokine production. In particular, the compounds may be administered to mammals. Such mammals can include, for example, horses, cows, sheep, pigs, mice, dogs, cats, primates such as chimpanzees, gorillas, rhesus monkeys, and, most preferably, humans.

25 Thus, the present invention provides methods of treating or reducing symptoms in a human or animal subject suffering from, for example, rheumatoid arthritis, osteoarthritis, asthma, psoriasis, eczema, allergic rhinitis, allergic conjunctivitis, adult respiratory distress syndrome, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, silicosis, endotoxemia, toxic shock syndrome, inflammatory bowel disease, tuberculosis, atherosclerosis, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, epilepsy, multiple sclerosis, aneurism, stroke, irritable bowel syndrome, muscle degeneration, bone resorption diseases, osteoporosis, diabetes, reperfusion injury, graft vs. host reaction, allograft rejections, sepsis, systemic cachexia, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), malaria, leprosy, infectious arthritis, leishmaniasis, Lyme disease, glomerulonephritis, gout, psoriatic arthritis, Reiter's syndrome, traumatic arthritis, rubella arthritis, Crohn's disease, ulcerative colitis, acute synovitis, gouty arthritis, spondylitis,

and non articular inflammatory conditions, for example, herniated/ruptured/prolapsed intervertebral disk syndrome, bursitis, tendonitis, tenosynovitis, fibromyalgic syndrome and other inflammatory conditions associated with ligamentous sprain and regional musculoskeletal strain, pain, for example that associated with inflammation and/or trauma, osteopetrosis, restenosis, thrombosis, angiogenesis, cancer including breast cancer, colon cancer, lung cancer or prostatic cancer, which comprises administering to said subject a therapeutically effective amount of a compound of formula(I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from rheumatoid arthritis, asthma, psoriasis, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, systemic cachexia, glomerulonephritis, Crohn's disease, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, epilepsy and cancer including breast cancer, colon cancer, lung cancer and prostatic cancer, which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from rheumatoid arthritis, asthma, psoriasis, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, systemic cachexia, glomerulonephritis, Crohn's disease and cancer including breast cancer, colon cancer, lung cancer and prostatic cancer, which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from rheumatoid arthritis, neurodegenerative disease, Alzheimer's disease, Parkinson's disease and epilepsy which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from any type of pain including chronic pain, rapid onset of analgesis, neuromuscular pain, headache, cancer pain, acute and chronic inflammatory pain associated with osteoarthritis and rheumatoid arthritis, post operative inflammatory pain, neuropathic pain, diabetic neuropathy, trigeminal neuralgia, post-hepatic neuralgia, inflammatory neuropathies and migraine pain which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by p38 kinase activity.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of a condition or disease state selected from rheumatoid arthritis, osteoarthritis, asthma, psoriasis, eczema, allergic rhinitis, allergic conjunctivitis, adult respiratory distress syndrome, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, silicosis, endotoxemia, toxic shock syndrome, inflammatory bowel disease, tuberculosis, atherosclerosis, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, epilepsy, multiple sclerosis, aneurism, stroke, irritable bowel syndrome, muscle degeneration, bone resorption diseases, osteoporosis, diabetes, reperfusion injury, graft vs. host reaction, allograft rejections, sepsis, systemic cachexia, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), malaria, leprosy, infectious arthritis, leishmaniasis, Lyme disease, glomerulonephritis, gout, psoriatic arthritis, Reiter's syndrome, traumatic arthritis, rubella arthritis, Crohn's disease, ulcerative colitis, acute synovitis, gouty arthritis, spondylitis, and non articular inflammatory conditions, for example, herniated/ruptured/prolapsed intervertebral disk syndrome, bursitis, tendonitis, tenosynovitis, fibromyalgic syndrome and other inflammatory conditions associated with ligamentous sprain and regional musculoskeletal strain, pain, for example that associated with inflammation and/or trauma, osteopetrosis, restenosis, thrombosis, angiogenesis, and cancer including breast cancer, colon cancer, lung cancer or prostatic cancer.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of a condition or disease state selected from rheumatoid arthritis, asthma, psoriasis, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, systemic cachexia, glomerulonephritis, Crohn's disease, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, epilepsy, and cancer including breast cancer, colon cancer, lung cancer and prostatic cancer.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of a condition or disease state selected from rheumatoid arthritis, asthma, psoriasis, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, systemic cachexia, glomerulonephritis, Crohn's disease and cancer including breast cancer, colon cancer, lung cancer and prostatic cancer.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of a condition or disease state selected from rheumatoid

arthritis, neurodegenerative disease, Alzheimer's disease, Parkinson's disease and epilepsy.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of any type of pain including chronic pain, rapid onset of analgesis, neuromuscular pain, headache, cancer pain, acute and chronic inflammatory pain associated with osteoarthritis and rheumatoid arthritis, post operative inflammatory pain, neuropathic pain, diabetic neuropathy, trigeminal neuralgia, post-hepatic neuralgia, inflammatory neuropathies and migraine pain.

The compounds of formula (I) and their salts, solvates and physiologically functional salts and solvates may be employed alone or in combination with other therapeutic agents for the treatment of the above-mentioned conditions. In particular, in rheumatoid arthritis therapy, combination with other chemotherapeutic or antibody agents is envisaged. Combination therapies according to the present invention thus comprise the administration of at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof and at least one other pharmaceutically active agent. The compound(s) of formula (I) or pharmaceutically acceptable salt(s) or solvate(s) thereof and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately, this may occur separately or sequentially in any order. The amounts of the compound(s) of formula (I) or pharmaceutically acceptable salt(s) or solvate(s) thereof and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. Examples of other pharmaceutically active agents which may be employed in combination with compounds of formula (I) and their salts and solvates for rheumatoid arthritis therapy include: immunosuppressants such as amtolmetin guacil, mizoribine and rimexolone; anti-TNF α agents such as etanercept, infliximab, diacerein; tyrosine kinase inhibitors such as leflunomide; kallikrein antagonists such as subreum; interleukin 11 agonists such as oprelvekin; interferon beta 1 agonists; hyaluronic acid agonists such as NRD-101 (Aventis); interleukin 1 receptor antagonists such as anakinra; CD8 antagonists such as amiprilose hydrochloride; beta amyloid precursor protein antagonists such as reumacon; matrix metalloprotease inhibitors such as cipemastat and other disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate, sulphasalazine, cyclosporin A, hydroxychloroquine, auranofin, aurothioglucose, gold sodium thiomalate and penicillamine.

Examples

The following examples are illustrative embodiments of the invention, not limiting the scope of the invention in any way. Reagents are commercially available or are prepared according to procedures in the literature.

LCMS was conducted on a column (3.3cm x 4.6mm ID, 3µm ABZ+PLUS), at a Flow Rate of 3ml/min, Injection Volume of 5µl, at room temperature and UV Detection Range at 215 to 330nm.

5 General method A:

DIPEA (44µl) was added to a mixture of benzoic acid (0.084mmol), HOBT (0.084mmol), PyBOP (0.084mmol) and amine (0.1mmol) in DMF (0.5ml) and the reaction was stirred at room temperature for 17hours. The DMF was evaporated under vacuum and the residue partitioned between DCM (5ml) and aqueous sodium carbonate solution (1M, 5ml). The organic fraction was chromatographed on a silica SPE (5g) eluting with DCM, chloroform, diethyl ether, ethyl acetate, acetonitrile, acetone, ethanol and methanol or DCM/ethanol/ammonia (1:0:0, 300:8:1, 200:8:1, 100:8:1). The product fractions were combined and evaporated to dryness to give the amide.

15 General method B:

DIPEA (44µl) was added to a mixture of benzoic acid (0.084mmol), PyBOP (0.084mmol) and amine (0.1mmol) in DCM (2ml) and the reaction was stirred at room temperature for 18hours. The reaction was washed with aqueous sodium carbonate solution (1M, 2ml) and the organic fraction was chromatographed on a silica SPE (5g) eluting with DCM, chloroform, diethyl ether, ethyl acetate, acetonitrile, acetone, ethanol, methanol and DCM/ethanol/ammonia (20:8:1 then 15:8:1). The product fractions were combined and evaporated to dryness to give the amide.

25 General method C:

Benzoic acid (0.1mmol), HATU (0.1mmol), HOBT (0.1mmol), DIPEA (0.3mmol), and amine (0.1mmol) were mixed in DMF (1ml) and heated for 18hours at 80°C. The solvent was evaporated under vacuum and the residue partitioned between DCM (5ml) and aqueous sodium carbonate (1M, 5ml). The organic phase was reduced to dryness under vacuum and the amide purified as specified in the example.

30 General method D:

Benzoic acid (0.17mmol), HATU (0.2mmol), HOBT (0.17mmol), DIPEA (0.51mmol), and amine (0.2mmol) were mixed in DMF (2ml) and the reaction stirred at room temperature for 24hours. Further portions of amine (0.05mmol) and HATU (0.052mmol) were added and the mixture heated for 18hours at 60°C. The solvent was evaporated under vacuum and the residue partitioned between DCM (5ml) and aqueous sodium carbonate (1M, 5ml). The organic phase was reduced to dryness under vacuum and the amide purified as specified in the example.

Example 1: N⁴-(3-Cyanophenyl)-6-methyl-N³-(pyrid-4-ylmethyl)-1,1'-biphenyl-3,4'-dicarboxamide

- (a) N⁴-(3-Cyanophenyl)-6-methyl-N³-(pyrid-4-ylmethyl)-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-[[[(3-cyanophenyl)amino]carbonyl]-6-methyl-1,1'-biphenyl-3-yl]carboxylic acid and 4-aminomethylpyridine using method A. NMR: δ H [²H₆] – DMSO 10.64,(1H, s), 9.16,(1H, t), 8.49,(2H, d), 8.28,(1H, s), 8.09-8.05,(3H, m), 7.85,(1H, dd), 7.82,(1H, d), 7.61-7.58,(4H, m), 7.46,(1H, d), 7.30,(2H, d), 4.49,(2H, d), 2.31,(3H, s). LCMS: retention time 2.96min, MH⁺447.
- (b) (4'-[[[(3-Cyanophenyl)amino]carbonyl]-6-methyl-1,1'-biphenyl-3-yl]carboxylic acid 4-Bromo-N-(3-cyanophenyl)benzamide (2.0g, 6.64mmol), (3-carboxy-6-methylphenyl)pinnacol borane (1.74g, 6.64mmol), tetrakis(triphenylphosphine)palladium (768mg, 0.664mmol) and aqueous sodium carbonate (1M, 60ml) in DME (120ml) were heated at 90°C for 21h. The organic phase was absorbed onto silica and purified by flash chromatography (silica) eluting with DCM/ethanol/ammonia (40:8:1 then 20:8:1) to give (4'-[[[(3-cyanophenyl)amino]carbonyl]-6-methyl-1,1'-biphenyl-3-yl]carboxylic acid (1.06g, 45%). LCMS: retention time 3.53min, [M-H]⁻355.
- (c) (3-Carboxy-6-methylphenyl)pinnacol borane 3-Iodo-4-methylbenzoic acid (3.34g, 12.74mmol), bis(pinnacolato)diboron (6.47g, 25.48mmol), potassium acetate (6.27g, 63.7mmol), and 1,1'-bis(diphenylphosphino)ferrocene palladium (II) chloride (1.045g, 1.27mmol) in DMF (100ml) were heated at 80°C for 18h. The reaction was concentrated under vacuum and the residue partitioned between ethyl acetate (200ml) and hydrochloric acid (2N, 200ml). The aqueous phase was extracted with ethyl acetate (2 x 150ml). The combined organics were washed with brine (300ml), dried (magnesium sulphate) and absorbed onto silica. Purified by flash chromatography on silica eluting with cyclohexane/ethyl acetate (5:1), the product fractions concentrated under vacuum and triturated with cyclohexane to give (3-carboxy-6-methylphenyl) pinnacol borane (1.81g, 54%). HPLC: retention time 3.54min.
- (d) 4-Bromo-N-(3-cyanophenyl)benzamide 3-Aminobenzonitrile (2.7g, 22.8mmol) and triethylamine (3ml) were dissolved in THF (5ml) and 4-bromobenzoylchloride (22.8mmol) added over 5min. The reaction was stirred at room temperature for 1.5h and then partitioned between ethyl acetate and water. The organic phase was washed with brine, the solvent evaporated under vacuum and the residue triturated with cyclohexane to give 4-bromo-N-(3-cyanophenyl)benzamide (5.3g, 77%). LCMS: retention time 3.58min, MH⁺301/303.

Example 2: N³-(2-Benzofuran-2-ylethyl)-N⁴-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

N³-(2-Benzofuran-2-ylethyl)-N⁴-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 2-(2-aminoethyl)benzofuran using method A. NMR: δ H [²H₆] – DMSO 10.63,(1H, s), 8.69,(1H, t), 8.28,(1H, m), 8.09-8.04,(3H, m), 7.77,(1H, dd), 7.72,(1H, d), 7.60-7.55,(4H, m), 7.52,(1H, m), 7.47,(1H, d), 7.42,(1H, d), 7.23-7.15,(2H, m), 6.65,(1H, s), 3.63,(2H, q), 3.04,(2H, t), 2.29,(3H, s). LCMS: retention time 3.78min, MH⁺500.

Example 3: N⁴-(3-Cyanophenyl)-6-methyl-N³-[2-(3-phenylureido)ethyl]-1,1'-biphenyl-3,4'-dicarboxamide

N⁴-(3-Cyanophenyl)-6-methyl-N³-[2-(3-phenylureido)ethyl]-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 1-(2-aminoethyl)-3-phenylurea using method A. NMR: δ H [²H₆] – DMSO 10.63,(1H, s), 8.60,(1H, t), 8.53,(1H, s), 8.29,(1H, s), 8.07-8.05,(3H, m), 7.81,(1H, dd), 7.77,(1H, s), 7.62-7.56,(4H, m), 7.43,(1H, d), 7.36,(2H, d), 7.18,(2H, t), 6.86,(1H, t), 6.25,(1H, t), 3.30,(4H, m), 2.30,(3H, s). LCMS: retention time 3.45min, MH⁺518.

Example 4: N⁴-(3-Cyanophenyl)-6-methyl-N³-(4-sulphamoylbenzyl)-1,1'-biphenyl-3,4'-dicarboxamide

N⁴-(3-Cyanophenyl)-6-methyl-N³-(4-sulphamoylbenzyl)-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 4-(aminomethyl)benzenesulphonamide using method A. NMR: δ H [²H₆] – DMSO 9.16,(1H, t), 8.28,(1H, s), 8.07-8.05,(3H, m), 7.85,(1H, dd), 7.81,(1H, d), 7.76,(2H, d), 7.59-7.57,(4H, m), 7.48-7.44,(3H, m), 4.52,(2H, d), 2.31,(3H, s). LCMS: retention time 3.46min, MH⁺525.

Example 5: N⁴-(3-Cyanophenyl)-6-methyl-N³-(2-[(4-methylphenyl)amino]carbonyl)ethyl)-1,1'-biphenyl-3,4'-dicarboxamide

N⁴-(3-Cyanophenyl)-6-methyl-N³-(2-[(4-methylphenyl)amino]carbonyl)ethyl)-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 3-amino-N-(4-methylphenyl)propanamide using method A. NMR: δ H [²H₆] – DMSO 10.63,(1H, s), 9.86,(1H, s), 8.63,(1H, t), 8.28,(1H, s), 8.08-8.05,(3H, m), 7.78,(1H, dd), 7.74,(1H, d), 7.60-7.55,(4H, m), 7.46-7.40,(3H, m), 7.06,(2H, d), 3.53,(2H, q), 2.58,(2H, t), 2.29,(3H, s), 2.22,(3H, s). LCMS: retention time 3.54min, MH⁺517.

Example 6: N^{4'}-(3-Cyanophenyl)-6-methyl-N³-[3-[(methylamino)carbonyl]benzyl]-1,1'-biphenyl-3,4'-dicarboxamide

N^{4'}-(3-Cyanophenyl)-6-methyl-N³-[3-[(methylamino)carbonyl]benzyl]-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 3-(aminomethyl)-N-methylbenzamide using method A. NMR: δ H [²H₆] – DMSO 10.63,(1H, s), 9.11,(1H, t), 8.42,(1H, m), 8.28,(1H, m), 8.08-8.05,(3H, m), 7.85,(1H, dd), 7.81,(1H, d), 7.78,(1H, s), 7.68,(1H, d), 7.60-7.58,(4H, m), 7.45,(2H, d), 7.39,(1H, t), 4.51,(2H, d), 2.76,(3H, d), 2.31,(3H, s). LCMS: retention time 3.42min, MH⁺503.

Example 7: N³-(4-Carbamoylbenzyl)-N^{4'}-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

N³-(4-Carbamoylbenzyl)-N^{4'}-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 4-(aminomethyl)benzamide using method A. NMR: δ H [²H₆] – DMSO 10.66,(1H, s), 9.12,(1H, t), 8.28,(1H, m), 8.07-8.05,(3H, m), 7.91,(1H, b), 7.86-7.80,(4H, m), 7.60-7.53,(4H, m), 7.44,(1H, d), 7.36,(2H, d), 7.31,(1H, b), 4.52,(2H, d), 2.31,(3H, s). LCMS: retention time 3.35min, MH⁺489.

Example 8: N^{4'}-(3-Cyanophenyl)-6-methyl-N³-[3-(methylsulphonamido)benzyl]-1,1'-biphenyl-3,4'-dicarboxamide

N^{4'}-(3-Cyanophenyl)-6-methyl-N³-[3-(methylsulphonamido)benzyl]-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and N-[3-(aminomethyl)phenyl]methanesulphonamide using method A. NMR: δ H [²H₆] – DMSO 10.63,(1H, s), 9.72,(1H, s), 9.08,(1H, t), 8.28,(1H, m), 8.08-8.05,(3H, m), 7.84,(1H, dd), 7.80,(1H, d), 7.60-7.58,(4H, m), 7.44,(1H, d), 7.27,(1H, t), 7.16,(1H, m), 7.06,(2H, m), 4.44,(2H, d), 2.95,(3H, s), 2.31,(3H, s). LCMS: retention time 3.39min, MH⁺539.

Example 9: N^{4'}-(3-Cyanophenyl)-N³-cyclopropylmethyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

N^{4'}-(3-Cyanophenyl)-N³-cyclopropylmethyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and cyclopropylmethylamine using method A. NMR: δ H [²H₆] – DMSO 10.63,(1H, s), 8.58,(1H, t), 8.29,(1H, m), 8.09-8.05,(3H, m), 7.81,(1H, dd), 7.76,(1H, d), 7.59-7.57,(4H, m), 7.42,(1H, d), 3.13,(2H, t), 2.30,(3H, s), 1.01,(1H, m), 0.42,(2H, m), 0.21,(2H, m). LCMS: retention time 3.62min, MH⁺410.

Example 10: N^{4'}-(3-Cyanophenyl)-N³-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

5 N^{4'}-(3-Cyanophenyl)-N³-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and cyclopropylamine using method A. NMR: δ H [²H₆] – DMSO 10.62,(1H, s), 8.44,(1H, d), 8.28,(1H, m), 8.09-8.05,(3H, m), 7.77,(1H, dd), 7.72,(1H, d), 7.60-7.56,(4H, m), 7.40,(1H, d), 2.84,(1H, m), 2.29,(3H, s), 0.68,(2H, m), 0.55,(2H, m). LCMS: retention time 3.49min, MH⁺396.

10 Example 11: N^{4'}-(3-Cyanophenyl)-6-methyl-N³-(quinolin-5-ylmethyl)-1,1'-biphenyl-3,4'-dicarboxamide
 15 N^{4'}-(3-Cyanophenyl)-6-methyl-N³-quinolin-5-ylmethyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 5-aminomethylquinoline using method B. NMR: δ H [²H₆] – DMSO 10.64,(1H, s), 9.13,(1H, t), 8.91,(1H, dd), 8.65,(1H, d), 8.27,(1H, m), 8.07-8.04,(3H, m), 7.94,(1H, d), 7.86,(1H, dd), 7.81,(1H, d), 7.72,(1H, m), 7.59-7.56,(6H, m), 7.44,(1H, d), 4.96,(2H, d), 2.30,(3H, s). LCMS: retention time 3.55min, MH⁺497.

20 Example 12: N^{4'}-(3-Cyanophenyl)-6-methyl-N³-tetralon-6-yl-1,1'-biphenyl-3,4'-dicarboxamide
N^{4'}-(3-Cyanophenyl)-6-methyl-N³-tetralon-6-yl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 6-aminotetralone using method C and purified by preparative HPLC. LCMS: retention time 3.74min, MH⁺500.

25 Example 13: N³-(3-Chlorophenyl)-N^{4'}-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide
N³-(3-Chlorophenyl)-N^{4'}-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 3-chloroaniline using method C and purified by preparative HPLC. NMR: δ H [²H₆] – DMSO 10.64,(1H, s), 10.38,(1H, s), 8.29,(1H, m), 8.10-8.06,(3H, m), 7.96,(1H, t), 7.93,(1H, dd), 7.88,(1H, d), 7.71,(1H, m), 7.63,(2H, d), 7.60-7.58,(2H, m), 7.51,(1H, d), 7.37,(1H, t), 7.15,(1H, m), 2.34,(3H, s). LCMS: retention time 3.95min, MH⁺466.

35 Example 14: N³-(2-Carbamoylthiophen-3-yl)-N^{4'}-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide
 40 (a) (4'-{[(3-Cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carbonyl chloride (50mg, 0.13mmol) and 3-aminothiophene-2-carboxamide (19mg, 0.13mmol) in pyridine (1ml) were heated at 70°C for 17h. Water was added to the cooled reaction and the precipitate which formed filtered off and dried to give N³-(2-carbamoylthiophen-3-yl)-N^{4'}-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide (24mg, 38%).

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NMR: δ H [2 H₆] – DMSO 12.46,(1H, s), 10.67,(1H, s), 8.29,(1H, m), 8.11-8.05,(4H, m), 7.88,(1H, dd), 7.80,(1H, d), 7.78,(1H, d), 7.62-7.55,(5H, m), 2.34,(3H, s). LCMS: retention time 3.69min, MH⁺481.

- 5 (b) (4'-{[(3-Cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carbonyl chloride
(4'-{[(3-Cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid
(500mg, 1.4mmol), oxalyl chloride (214mg, 1.68mmol) and DMF (2drops) in DCM
10 (20ml) were stirred at room temperature for 2.5h. The solution was concentrated under vacuum to give (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carbonyl chloride (520mg, 99%). NMR: δ H CDCl₃ 8.24,(2H, d), 8.04,(1H, dd), 7.98,(1H, d), 7.52,(1H, d), 7.46-7.43,(3H, m), 7.31,(1H, m), 7.25,(1H, m), 2.37,(3H, s).

- 15 Example 15: N^{4'}-(3-Cyanophenyl)-N³-(4-methoxyphenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide
(4'-{[(3-Cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carbonyl chloride
(50mg, 0.13mmol) and 4-methoxyaniline (21mg, 0.13mmol) in pyridine (1ml) were heated at 70°C for 17h. Water was added to the cooled reaction, the mixture extracted with ethyl acetate and the organic extract reduced to dryness under vacuum. The
20 residue was purified by chromatography on a silica flash column eluting with DCM/ethanol/ammonia (400:8:1), which after concentration of the product fractions under vacuum and trituration with diethyl ether gave N^{4'}-(3-cyanophenyl)-N³-(4-methoxyphenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide (10mg, 17%). NMR: δ H [2 H₆] – DMSO 10.64,(1H, s), 10.12,(1H, s), 8.29,(1H, s), 8.08,(3H, m), 7.91,(1H, d), 7.87,(1H, s), 7.67-7.58,(6H, m), 7.48,(1H, d), 6.92,(2H, d), 3.73,(3H, s), 2.33,(3H, s).
25 LCMS: retention time 3.71min, MH⁺462.

- Example 16: N³-(2-Chlorophenyl)-N^{4'}-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide
30 N³-(2-Chlorophenyl)-N^{4'}-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 2-chloroaniline using method C. Purified by preparative HPLC. LCMS: retention time 3.93min, MH⁺466.

- 35 Example 17: N^{4'}-(3-Cyanophenyl)-6-methyl-N³-(3-methylpyrid-4-yl)-1,1'-biphenyl-3,4'-dicarboxamide
N^{4'}-(3-Cyanophenyl)-6-methyl-N³-(3-methylpyrid-4-yl)-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 4-amino-3-methylpyridine using method C. Purified by
40 preparative HPLC. NMR: δ H [2 H₆] – DMSO 10.67,(1H, s), 9.99,(1H, s), 8.42,(1H, s),

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8.37,(1H, d), 8.29,(1H, m), 8.09-8.07,(3H, m), 7.93,(1H, dd), 7.88,(1H, d), 7.63,(2H, d), 7.60-7.57,(3H, m), 7.52,(1H, d), 2.35,(3H, s), 2.26,(3H, s). LCMS: retention time 2.99min, MH⁺447.

5 Example 18: N³-(3-Acetylamino)phenyl-N⁴-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

N³-(3-Acetylamino)phenyl-N⁴-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 3'-aminoacetanilide using method C. Purified by preparative HPLC. NMR: δ H [²H₆] – DMSO 10.67,(1H, s), 10.25,(1H, s), 9.96,(1H, s), 8.29,(1H, m), 8.09-8.07,(4H, m), 7.92,(1H, dd), 7.88,(1H, d), 7.63,(2H, d), 7.60-7.58,(2H, m), 7.49,(1H, d), 7.41,(1H, d), 7.30,(1H, d), 7.23,(1H, t), 2.34,(3H, s), 2.03,(3H, s). LCMS: retention time 3.51min, MH⁺489.

15 Example 19: N⁴-(3-Cyanophenyl)-6-methyl-N³-pyrid-3-yl-1,1'-biphenyl-3,4'-dicarboxamide

N⁴-(3-Cyanophenyl)-6-methyl-N³-pyrid-3-yl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 3-aminopyridine using method C. Purified by preparative HPLC. NMR: δ H [²H₆] – DMSO 10.65,(1H, s), 10.44,(1H, s), 8.92,(1H, d), 8.31-8.29,(2H, m), 8.20-8.17,(1H, m), 8.10-8.07,(3H, m), 7.95,(1H, dd), 7.91,(1H, d), 7.63,(2H, d), 7.60-7.58,(2H, m), 7.52,(1H, d), 7.40-7.37,(1H, m), 2.34,(3H, s). LCMS: retention time 3.41min, MH⁺433.

25 Example 20: N⁴-(3-Cyanophenyl)-6-methyl-N³-[3-(2-methylpyrimidin-4-yl)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide

N⁴-(3-Cyanophenyl)-6-methyl-N³-[3-(2-methylpyrimidin-4-yl)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 4-(3-aminophenyl)-2-methylpyrimidine using method C. Purified by preparative HPLC. NMR: δ H [²H₆] – DMSO 10.66,(1H, s), 10.47,(1H, s), 8.76,(1H, d), 8.57,(1H, m), 8.29,(1H, m), 8.10-8.07,(3H, m), 8.05-8.03,(1H, m), 7.97,(1H, dd), 7.95,(1H, d), 7.88,(1H, m), 7.82,(1H, d), 7.65,(2H, d), 7.60-7.58,(2H, m), 7.54-7.50,(2H, m), 2.68,(3H, s), 2.35,(3H, s). LCMS: retention time 3.75min, MH⁺524.

35 Example 21: N⁴-(3-Cyanophenyl)-N³-(isoquinolin-5-yl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

N⁴-(3-Cyanophenyl)-N³-(isoquinolin-5-yl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 5-aminoisoquinoline using method C. Purified by preparative

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HPLC. NMR: δ H [2 H₆] – DMSO 10.66,(1H, s), 10.57,(1H, s), 9.35,(1H, s), 8.52,(1H, d), 8.29,(1H, m), 8.10-8.02,(6H, m), 7.89-7.53,(8H, m), 2.37,(3H, s). LCMS: retention time 3.41min, MH⁺483.

5 Example 22: N⁴-(3-Cyanophenyl)-N³-(isoquinolin-6-yl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

N⁴-(3-Cyanophenyl)-N³-(isoquinolin-6-yl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 6-aminoisoquinoline using method C. Purified by preparative HPLC. NMR: δ H [2 H₆] – DMSO 10.66,(1H, s), 10.63,(1H, s), 9.19,(1H, s), 8.53,(1H, d), 8.43,(1H, d), 8.30,(1H, m), 8.11-8.08,(4H, m), 8.00-7.95,(3H, m), 7.76,(1H, d), 7.65,(2H, d), 7.60-7.59,(2H, m), 7.53,(1H, d), 2.36,(3H, s). LCMS: retention time 3.30min, MH⁺483.

15 Example 23: N⁴-(3-Cyanophenyl)-6-methyl-N³-[4-(pyrid-3-ylmethoxy)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide

(4'-{[(3-Cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carbonyl chloride (50mg, 0.13mmol) and 3-(4-aminophenoxymethyl)pyridine (53mg, 0.26mmol) in pyridine (1ml) were heated at 70°C for 15h. The pyridine was evaporated from the reaction under vacuum and the residue partitioned between ethyl acetate and water. The organic fraction was concentrated under vacuum and purified by preparative HPLC to give N⁴-(3-cyanophenyl)-6-methyl-N³-[4-(pyrid-3-ylmethoxy)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide. NMR: δ H [2 H₆] – DMSO 10.67,(1H, s), 10.15,(1H, s), 8.66,(1H, d), 8.54,(1H, dd), 8.29,(1H, m), 8.09-8.06,(3H, m), 7.91,(1H, dd), 7.87-7.85,(2H, m), 7.68,(2H, d), 7.63-7.58,(4H, m), 7.49,(1H, d), 7.43-7.40,(1H, m), 7.02,(2H, d), 5.13,(2H, s), 2.33,(3H, s). LCMS: retention time 3.58min, MH⁺539.

30 Example 24: N⁴-(3-Cyanophenyl)-6-methyl-N³-(2-methylpyridin-3-yl)-1,1'-biphenyl-3,4'-dicarboxamide

(4'-{[(3-Cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carbonyl chloride (50mg, 0.13mmol) and 3-amino-2-methylpyridine (29mg, 0.26mmol) in pyridine (1ml) were heated at 70°C for 15h. The pyridine was evaporated from the reaction under vacuum and the residue partitioned between ethyl acetate and water. The organic fraction was concentrated under vacuum and purified by preparative HPLC to give N⁴-(3-cyanophenyl)-6-methyl-N³-(2-methylpyridin-3-yl)-1,1'-biphenyl-3,4'-dicarboxamide. NMR: δ H [2 H₆] – DMSO 10.65,(1H, s), 10.08,(1H, s), 8.33,(1H, dd), 8.29,(1H, m), 8.09-8.07,(3H, m), 7.94,(1H, dd), 7.91,(1H, d), 7.73,(1H, dd), 7.63,(2H, d), 7.60-7.58,(2H, m), 7.51,(1H, d), 7.27,(1H, m), 2.43,(3H, s), 2.92,(3H, s). LCMS: retention time 3.21min, MH⁺447.

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Example 25: N³-[4-(Acetylamino)phenyl]-N⁴-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

(4'-[[[(3-Cyanophenyl)amino]carbonyl]-6-methyl-1,1'-biphenyl-3-yl]carbonyl chloride (50mg, 0.13mmol) and 4-(acetylamino)aniline (40mg, 0.26mmol) in pyridine (1ml) were heated at 70°C for 15h. The pyridine was evaporated from the reaction under vacuum and the residue partitioned between ethyl acetate and water. The organic fraction was concentrated under vacuum and purified by preparative HPLC to give N³-[4-(acetylamino)phenyl]-N⁴-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide. LCMS: retention time 3.50min, MH⁺490.

Example 26: N³-(3-Carbamoyl-4-methylphenyl)-N⁴-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

(4'-[[[(3-Cyanophenyl)amino]carbonyl]-6-methyl-1,1'-biphenyl-3-yl]carbonyl chloride (50mg, 0.13mmol) and 5-amino-2-methylbenzamide (40mg, 0.26mmol) in pyridine (1ml) were heated at 70°C for 15h. The pyridine was evaporated from the reaction under vacuum and the residue partitioned between ethyl acetate and water. The organic fraction was concentrated under vacuum and purified by preparative HPLC to give N³-(3-carbamoyl-4-methylphenyl)-N⁴-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide. NMR: δ H [²H₆] – DMSO 10.65,(1H, b), 10.25,(1H, s), 8.29,(1H, s), 8.10-8.07,(3H, m), 7.92,(1H, dd), 7.89,(1H, d), 7.77,(1H, d), 7.74,(1H, dd), 7.69,(1H, b), 7.62,(2H, d), 7.59-7.56,(2H, m), 7.50,(1H, d), 7.36,(1H, b), 7.18,(1H, d), 2.34,(3H, s), 2.31,(3H, s). LCMS: retention time 3.38min, MH⁺489.

Example 27: N⁴-(3-Cyanophenyl)-6-methyl-N³-[3-(pyrid-2-yl)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide

(4'-[[[(3-Cyanophenyl)amino]carbonyl]-6-methyl-1,1'-biphenyl-3-yl]carbonyl chloride (50mg, 0.13mmol) and 2-(3-aminophenyl)pyridine (45mg, 0.26mmol) in pyridine (1ml) were heated at 70°C for 15h. The pyridine was evaporated from the reaction under vacuum and the residue partitioned between ethyl acetate and water. The organic fraction was concentrated under vacuum and purified by preparative HPLC to give N⁴-(3-cyanophenyl)-6-methyl-N³-[3-(pyrid-2-yl)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide. NMR: δ H [²H₆] – DMSO 10.67,(1H, s), 10.39,(1H, s), 8.67,(1H, d), 8.51,(1H, t), 8.30,(1H, m), 8.10-8.07,(3H, m), 7.98-7.87,(5H, m), 7.79,(1H, d), 7.65,(2H, d), 7.60-7.58,(2H, m), 7.51,(1H, d), 7.47,(1H, t), 7.36,(1H, m), 2.35,(3H, s). LCMS: retention time 3.81min, MH⁺509.

Example 28: N⁴-(3-Cyanophenyl)-6-methyl-N³-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide

(4'-[[[(3-Cyanophenyl)amino]carbonyl]-6-methyl-1,1'-biphenyl-3-yl]carbonyl chloride (50mg, 0.13mmol) and 3-(3-aminophenyl)-5-methyl-1,2,4-oxadiazole (47mg, 0.26mmol)

in pyridine (1ml) were heated at 70°C for 15h. The pyridine was evaporated from the reaction under vacuum and the residue partitioned between ethyl acetate and water. The organic fraction was concentrated under vacuum and purified by preparative HPLC to give N³-(3-cyanophenyl)-6-methyl-N³-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide. LCMS: retention time 3.80min, MH⁺514.

Example 29: N³-Cyclopropyl-N⁴-(3-methoxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

N³-Cyclopropyl-N⁴-(3-methoxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from 3'-[(cyclopropylamino)carbonyl]-6'-methyl-1,1'-biphenyl-4-yl)carboxylic acid and 3-methoxybenzylamine using method D. Purified by chromatography on silica, eluting with a toluene/methanol (9:1). NMR: δ H [²H₆] – DMSO 9.11,(1H, t), 8.44,(1H, d), 7.99,(2H, d), 7.76,(1H, dd), 7.70,(1H, d), 7.49,(2H, d), 7.40,(1H, d), 7.26,(1H, m), 6.91,(2H, m), 6.83,(1H, m), 4.49,(2H, d), 3.74,(3H, s), 2.85,(1H, m), 2.28,(3H, s), 0.69,(2H, m), 0.55,(2H, m). LCMS: retention time 3.22min, MH⁺ 415.

Example 30: N³-Cyclopropyl-N⁴-(4-methoxyphenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

N³-Cyclopropyl-N⁴-(4-methoxyphenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from 3'-[(cyclopropylamino)carbonyl]-6'-methyl-1,1'-biphenyl-4-yl)carboxylic acid and 4-methoxyaniline using method D. Purified by chromatography on silica, eluting with a toluene/methanol (19:1). NMR: δ H [²H₆] – DMSO 10.19,(1H, s), 8.44,(1H, d), 8.03,(2H, d), 7.76,(1H, dd), 7.69,(3H, m), 7.52,(2H, d), 7.40,(1H, d), 6.93,(2H, d), 3.74,(3H, s), 2.84,(1H, m), 2.28,(3H, s), 0.68,(2H, m), 0.58,(2H, m). LCMS: retention time 3.26min, MH⁺ 401.

Example 31: N³-Cyclopropyl-5-fluoro-N⁴-(3-methoxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 32: N³-Cyclopropyl-5-fluoro-6-methyl-N⁴-(3-[(methylsulfonyl)amino]benzyl)-1,1'-biphenyl-3,4'-dicarboxamide

Example 33: N³-Cyclopropyl-5-fluoro-6-methyl-N⁴-(4-[(methylsulfonyl)amino]phenyl)-1,1'-biphenyl-3,4'-dicarboxamide

General Method E:

{3'-[(Cyclopropylamino)carbonyl]-5'-fluoro-6'-methyl-1,1'-biphen-4-yl}carboxylic acid (Intermediate 1, 31mg, 0.10mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (21mg, 0.11mmol), HOBT (15mg, 0.11mmol) and the appropriate amine (0.11mmol) were dissolved in DMF (4ml). DIPEA (19 μ l, 0.11mmol) was added to the

solution which was then stirred for 5 hours at 40°C. Ethyl acetate (25ml) and water (25ml) were added. The ethyl acetate layer was separated and washed sequentially with aqueous sodiumhydrogen carbonate and hydrochloric acid (0.5M). The solvent was removed *in vacuo* and the residue was purified by mass-directed HPLC.

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Compound	Amine	MH ⁺	Retention time (minutes)
Example 31	3-methoxybenzylamine	433	3.26
Example 32	N-(3-aminomethylphenyl)methane-sulphonamide	496	3.02
Example 33	N-(4-aminophenyl)methane-sulphonamide	482	3.19

(a) {3'-[(Cyclopropylamino)carbonyl]-5'-fluoro-6'-methyl-1,1'-biphen-4-yl}carboxylic acid (Intermediate 1)

10

3-Bromo-N-cyclopropyl-5-fluoro-4-methylbenzamide (Intermediate 2, 120mg, 0.45mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (111mg, 0.45mmol) and tetrakis(triphenylphosphine) palladium (51mg, 0.045mmol) were dissolved in DME (3ml) and aqueous sodium carbonate (1M, 450μl) was added. The mixture was refluxed at 80°C for 16 hours. Solvent was removed *in vacuo* and the residue was purified by silica biotage chromatography, eluting with 2:1 ethyl acetate:cyclohexane followed by 9:1 ethyl acetate:methanol. To give {3'-[(cyclopropylamino)carbonyl]-5'-fluoro-6'-methyl-1,1'-biphen-4-yl}carboxylic acid (129mg, 91%).

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LCMS: MH⁺ 314, retention time 3.06 min.

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(b) 3-Bromo-N-cyclopropyl-5-fluoro-4-methylbenzamide (Intermediate 2)

3-Fluoro-4-methylbenzoic acid (462mg, 3.0mmol) was added to a stirred mixture of bromine (2.31ml, 45mmol) and iron powder (252mg, 4.5mmol) under nitrogen. The reaction was stirred at 20°C for 4 hours and then left to stand for 16 hours. Sodium thiosulphate solution (200ml) was added and the product was extracted into ethyl acetate (3 x 150ml). Ethyl acetate extracts were combined and evaporated *in vacuo*. The crude product (mixture of isomers) was dissolved in DMF(7ml). Cyclopropylamine (208μl, 3.0mmol), HOBT (405mg, 3.0mmol), 1-(3-dimethylaminopropyl)-3-

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ethylcarbodiimide hydrochloride (575mg, 3.0mmol) and DIPEA (525µl, 3.0mmol) were added to the stirred solution. The reaction was stirred for 5 hours at 20°C. Solvent was removed *in vacuo* and the residue was partitioned between ethyl acetate and water. Combined ethyl acetate extracts were washed sequentially with aqueous sodium hydrogen carbonate and hydrochloric acid (0.5M), then dried (magnesium sulphate). The ethyl acetate was evaporated *in vacuo* and the residue was purified by silica biotage chromatography eluting with cyclohexane:ethyl acetate (6:1) to give 3-bromo-N-cyclopropyl-5-fluoro-4-methylbenzamide (359mg, 44%).
NMR: δH – CDCl₃ 7.68,(1H, s), 7.39,(1H, d), 6.19,(1H, bs), 2.88,(1H, m), 2.36,(3H, d), 0.88,(2H, m), 0.63,(2H, m). LCMS: MH⁺ 272/274, retention time 3.12 min.

Example 34: N³-Cyclopropyl-N⁴-(3-methoxybenzyl)-N⁴,6-dimethyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 35: N³-Cyclopropyl-N⁴-(4-methoxyphenyl)-N⁴,6-dimethyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 36: N³-Cyclopropyl-N⁴-[2-(4-methoxyphenyl)ethyl]-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 37: N³-Cyclopropyl-6-methyl-N⁴-[3-[(methylsulfonyl)amino]benzyl]-1,1'-biphenyl-3,4'-dicarboxamide

Example 38: N³-Cyclopropyl-N⁴-[3-[(dimethylamino)methyl]-1H-indol-5-yl]-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

General Method F:

HATU (65mg, 0.17mmol) was added to a solution of 3'-[(cyclopropylamino)carbonyl]-6'-methyl-biphenyl-4-carboxylic acid (50mg, 0.17mmol) in DMF (2ml). After 5 minutes HOBT (23mg, 0.17mmol), the chosen amine (0.17mmol) and DIPEA (0.087ml, 0.51mmol) were added and the reaction mixture stirred at 80°C under nitrogen for 16 hours. The DMF was removed *in vacuo* and the residue partitioned between DCM (5ml) and aqueous sodium carbonate solution (1M, 5ml). The layers were separated and the organic layer purified by SPE cartridge (Si, 5g) eluting in turn with DCM, chloroform, ether, ethyl acetate, acetonitrile, acetone, ethanol, methanol and DCM:ethanol:ammonia (20:8:1) to give the desired products.

Compound	Amine	MH ⁺	Retention time (minutes)
Example 34	N-(3-methoxybenzyl)-N-methylamine	429	3.26

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Example 35	N-(4-methoxyphenyl)-N-methylamine	415	3.06
Example 36	2-(4-methoxyphenyl)ethylamine	429	3.24
Example 37	N-(3-aminomethylphenyl) methanesulphonamide	478	2.88
Example 38	5-amino-3-(dimethylaminomethyl)-indole	467	2.38

Example 39: N^{4'}-(3-Bromobenzyl)-N³-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

HATU (1.29g, 3.39mmol) was added to a solution of 3'-[(cyclopropylamino)carbonyl]-6'-methyl-biphenyl-4-carboxylic acid (1g, 3.39mmol) in THF (20ml). After 5 minutes HOBT (0.46g, 3.39mmol), 3-bromobenzylamine hydrochloride (0.905g, 4.07mmol) and DIPEA (2.5, 14.24mmol) were added and the reaction mixture stirred at room temperature under nitrogen for 18 hours. The THF was removed *in vacuo*. The residue was partitioned between ethyl acetate (50ml) and water (50ml). The aqueous layer was extracted with ethyl acetate (50ml) and the organic extracts were washed with aqueous sodium carbonate (1M, 50ml), brine (25ml), dried (magnesium sulphate) and the solvent removed *in vacuo* to yield N^{4'}-(3-bromobenzyl)-N³-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide (1.56g, 3.37mmol).
NMR: δ H [²H₆] – DMSO 9.18,(1H, bt), 8.43,(1H, bd), 7.99,(2H,d), 7.77,(1H, dd), 7.70,(1H, d), 7.54,(1H, t), 7.50,(2H, d), 7.46,(1H, dt), 7.39,(1H, d), 7.36,(1H, dt), 7.32,(1H, t), 4.50,(2H, d), 2.85,(1H, m), 2.28,(3H, s), 0.72-0.53,(4H, 2xm). LC/MS: MH⁺ 463/465, retention time 3.36minutes

Example 40: N³-Cyclopropyl-6-methyl-N^{4'}-{4-[(methylsulfonyl)amino]phenyl}-1,1'-biphenyl-3,4'-dicarboxamide

HATU (65mg, 0.17mmol) was added to a solution of 3'-[(cyclopropylamino)carbonyl]-6'-methyl-biphenyl-4-carboxylic acid (50mg, 0.17mmol) in DMF (2ml). After 5 minutes HOBT (23mg, 0.17mmol), N-(4-aminophenyl)methanesulphonamide (0.17mmol) and DIPEA (0.087ml, 0.51mmol) were added and the reaction mixture stirred at room temperature under nitrogen for 18 hours. The reaction was partitioned between ethyl acetate (50ml) and hydrochloric acid (1M, 50ml). The organic layer was washed with aqueous sodium carbonate (1M, 50ml), brine (25ml), dried (magnesium sulphate), and the solvent removed *in vacuo*. The crude material was purified by SPE cartridge (Si, 5g) eluting in turn with DCM:ethanol:ammonia (400:8:1), ethyl acetate, acetonitrile, acetone and ethanol to yield the N³-cyclopropyl-6-methyl-N^{4'}-{4-[(methylsulfonyl)amino]phenyl}-1,1'-biphenyl-3,4'-dicarboxamide.

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LC/MS: MH⁺ 464, retention time 2.96minutesExample 41: N³-Cyclopropyl-6-methyl-N⁴-(4-{[(methylsulfonyl)amino]methyl}phenyl)-1,1'-biphenyl-3,4'-dicarboxamide

- 5 HATU (65mg, 0.17mmol) was added to a solution of 3'-[(cyclopropylamino)carbonyl]-6'-methyl-biphenyl-4-carboxylic acid (50mg, 0.17mmol) in DMF (2ml). After 5 minutes HOBT (23mg, 0.17mmol), N-(4-aminobenzyl)methanesulphonamide (0.17mmol) and DIPEA (0.087ml, 0.51mmol) were added and the reaction mixture stirred at room temperature under nitrogen for 18 hours. The reaction was partitioned between ethyl acetate (50ml) and hydrochloric acid (1M, 50ml). The organic layer was washed with
- 10 aqueous sodium carbonate (1M, 50ml), brine (25ml), dried (magnesium sulphate), and the solvent removed *in vacuo*. The crude material was purified by SPE cartridge (Si, 5g) eluting in turn with DCM:ethanol:ammonia (400:8:1), ethyl acetate, acetonitrile, acetone and ethanol to yield the N³-cyclopropyl-6-methyl-N⁴-(4-
- 15 {[(methylsulfonyl)amino]methyl}phenyl)-1,1'-biphenyl-3,4'-dicarboxamide.
LC/MS: MH⁺ 478, retention time 3.03minutes.

Example 42: N⁴-[4-(Aminosulfonyl)benzyl]-N³-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

- 20 HATU (65mg, 0.17mmol) was added to a solution of 3'-[(cyclopropylamino)carbonyl]-6'-methyl-biphenyl-4-carboxylic acid (50mg, 0.17mmol) in DMF (2ml). After 5 minutes HOBT (23mg, 0.17mmol), 4-(aminomethyl)phenylsulphonamide (0.17mmol) and DIPEA (0.087ml, 0.51mmol) were added and the reaction mixture stirred at room temperature under nitrogen for 18 hours. The DMF was removed *in vacuo* and the residue
- 25 partitioned between DCM (5ml) and aqueous sodium carbonate solution (1M, 5ml). The layers were separated and the organic layer purified by SPE cartridge (Si, 5g) eluting in turn with DCM, chloroform, ether, ethyl acetate, acetonitrile, acetone, ethanol, DCM:ethanol:ammonia (40:8:1) DCM:ethanol:ammonia (20:8:1) and DCM:ethanol:ammonia (10:8:1) to give N⁴-[4-(aminosulfonyl)benzyl]-N³-cyclopropyl-6-
- 30 methyl-1,1'-biphenyl-3,4'-dicarboxamide.
LC/MS: MH⁺ 464, retention time 2.77minutes.

Example 43: N³-Cyclopropyl-N⁴-[3-[(dimethylamino)methyl]benzyl]-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

- 35 HATU (65mg, 0.17mmol) was added to a solution of 3'-[(cyclopropylamino)carbonyl]-6'-methyl-biphenyl-4-carboxylic acid (50mg, 0.17mmol) in DMF (2ml). After 5 minutes HOBT (23mg, 0.17mmol), 3-(dimethylaminomethyl)benzylamine (Intermediate 3, 0.17mmol) and DIPEA (0.087ml, 0.51mmol) were added and the reaction mixture stirred

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at room temperature under nitrogen for 18 hours. The DMF was removed *in vacuo* and the residue partitioned between DCM (5ml) and aqueous sodium carbonate solution (1M, 5ml). The layers were separated and the organic layer purified by SPE cartridge (Si, 5g) eluting in turn with DCM, chloroform, ether, ethyl acetate, acetonitrile, acetone, ethanol, DCM:ethanol:ammonia (40:8:1) DCM:ethanol:ammonia (20:8:1) and DCM:ethanol:ammonia (10:8:1) to give N³-cyclopropyl-N^{4'}-(3-
 5 [(dimethylamino)methyl]benzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide.
 LC/MS: MH⁺ 442, retention time 2.32minutes.

10 (a) 3-(Dimethylaminomethyl)benzylamine (Intermediate 3)

A suspension of (3-dimethylaminomethyl-benzyl)carbamic acid *tert*-butyl ester (Intermediate 4, 0.256g, 1mmol) in hydrogen chloride in dioxane (4N, 4ml) was stirred at room temperature under nitrogen for 2 hours. The solvent was removed *in vacuo* and the residue dissolved in water (6ml). This was washed with ethyl acetate (3x 15ml). The
 15 aqueous layer was basified by addition of aqueous sodium hydroxide (2N) and extracted with ethyl acetate (2x20ml). The combined organic extracts were dried (magnesium sulphate) and the solvent removed *in vacuo* to give 3-(dimethylaminomethyl)benzylamine (0.060g, 0.37mmol).
 20 MS: MH⁺ 165.

(b) (3-Dimethylaminomethylbenzyl)carbamic acid *tert*-butyl ester (Intermediate 4)

A solution of (3-chloromethylbenzyl)carbamic acid *tert* butyl ester (Intermediate 5, 1.55g, 6.06mmol) in THF (15ml) was treated with dimethylamine in THF (2M, 12ml, 24mmol). The mixture was heated under reflux under nitrogen for 6 hours. The solvent was removed *in vacuo* and the residue partitioned between chloroform (50ml) and aqueous sodium hydrogen carbonate (50ml). The organic layer was dried (magnesium sulphate), and the solvent removed *in vacuo* to give the desired product (1.37g, 5.18mmol).
 25 30 MS: MH⁺ 265.

(c) (3-Chloromethylbenzyl)carbamic acid *tert*-butyl ester (Intermediate 5)

Triethylamine (21.27ml, 152.6mmol) was added to a suspension of 3-chloromethylbenzylamine hydrochloride (Intermediate 6, 167.92mmol) in dry THF (180ml). A solution of di-*tert*-butyl dicarbonate (14.75g, 67.58mmol) in dry THF (50ml) was added dropwise at 0°C. Once the addition was complete, the reaction mixture was stirred at room temperature for 18 hours. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in ethyl acetate (250ml) and washed
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with water (150ml). The aqueous layer was extracted with ethyl acetate (50ml). The combined organic extracts were washed with cold hydrochloric acid (1N, 80ml), aqueous sodiumhydrogen carbonate solution (100ml), dried (magnesium sulphate), filtered and concentrated *in vacuo* to give (3-Chloromethylbenzyl)carbamic acid *tert*-butyl ester (12g, 46.9mmol).
 5 MS: MNH_4^+ 273.

(d) 3-Chloromethylbenzylamine hydrochloride (Intermediate 6)

10 Hexamethylenetriamine (27.13g, 0.194mol) was added to a solution of dichloro-m-xylene (34g, 0.194mol) in chloroform (230ml) and the mixture heated at reflux for 30minutes. The cooled reaction was filtered and the filtrate reduced to dryness under vacuum. The residue was dissolved in ethanol (340ml), treated with concentrated hydrochloric acid (32ml) and heated at reflux for 3hours. The reaction was reduced to
 15 4ml under vacuum, diluted with ether (250ml) and filtered to give 3-chloromethylbenzylamine hydrochloride (10.57g).
 MS: MH^+ 156.

20 Example 44: N^3 -Cyclopropyl- N^4 -(3-([2-hydroxy-1-(hydroxymethyl)ethyl]amino)benzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide
 Four drops of 1-methyl-2-pyrrolidinone were added to anhydrous potassium carbonate (45mg, 0.326mmol), copper (I) iodide (5mg, 0.026mmol), N^4 -(3-bromobenzyl)- N^3 -cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide (0.1g, 0.216mmol) and serinol (0.5g, 5.49mmol). The reaction mixture was heated at 200°C in a microwave for 15
 25 minutes. The crude reaction mixture was partitioned between ethyl acetate (10ml) and water (10ml). The aqueous layer was extracted with ethyl acetate (2x10ml). The combined organic extracts were washed with water (2x30ml), brine (30ml), dried (magnesium sulphate) and absorbed onto silica gel. Purification was by SPE cartridge (Si, 5g) eluting with a n ehtyl acetate / cyclohexane gradient (0-100% ethyl acetate) to
 30 give N^3 -cyclopropyl- N^4 -(3-([2-hydroxy-1-(hydroxymethyl)ethyl]amino)benzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide (5mg, 0.011mmol).
 NMR: δH [$^2\text{H}_\text{O}$] – DMSO 9.02,(1H, bt), 8.43,(1H, bd), 8.00,(2H, d) 7.76,(1H, dd), 7.70,(1H, d), 7.48,(2H, d), 7.39,(1H, d), 7.02,(1H, t), 6.59,(1H, bt), 6.48,(2H, bd), 5.25,(1H, d), 4.59,(2H, t), 4.39,(2H, d), 3.53-3.43,(5H, m), 2.83,(1H, m), 2.28,(3H, s),
 35 0.70-0.52,(4H, 2xm). LC/MS: MH^+ 474, retention time 2.68minutes.

Example 45: N^3 -Cyclopropyl- N^4 -(2-hydroxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

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- Example 46: N^{4'}-[3-(Aminosulfonyl)phenyl]-N³-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide
- Example 47: N³-Cyclopropyl-N^{4'}-(2,6-difluorobenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide
- 5 Example 48: N³-Cyclopropyl-N^{4'}-(2,6-dimethoxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide
- Example 49: N^{4'}-Benzyl-N³-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide
- Example 50: N³-Cyclopropyl-N^{4'}-(4-fluorobenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide
- 10 Example 51: N³-Cyclopropyl-N^{4'}-(2,6-dimethylphenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide
- Example 52: N³-Cyclopropyl-N^{4'}-(4-[(ethyl(methyl)amino)methyl]benzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide
- Example 53: N³-Cyclopropyl-N^{4'}-[2-(2-hydroxyethyl)phenyl]-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide
- 15 Example 54: N^{4'}-[3-(Aminocarbonyl)benzyl]-N³-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide
- Example 55: N³-Cyclopropyl-N^{4'}-[4-[(dimethylamino)methyl]benzyl]-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide
- 20 Example 56: N^{4'}-(2-Chlorobenzyl)-N³-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide
- Example 57: N³-Cyclopropyl-N^{4'}-[3-[(2-hydroxyethyl)sulfonyl]phenyl]-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide
- Example 58: tert-Butyl 3-[[[5'-[(cyclopropylamino)carbonyl]-2'-methyl-1,1'-biphenyl-4-yl]carbonyl]amino]benzylcarbamate
- 25 Example 59: N³-Cyclopropyl-N^{4'}-[2-(hydroxymethyl)phenyl]-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide
- Example 60: N³-Cyclopropyl-N^{4'}-(3-[(ethyl(methyl)amino)methyl]benzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide
- 30 Example 61: N³-Cyclopropyl-N^{4'}-(3-hydroxymethylphenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide
- Example 62: N^{4'}-[3-(2-Amino-2-oxoethyl)phenyl]-N³-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

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Example 63: N^{4'}-Benzyl-N³-cyclopropyl-N^{4'}-ethyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 64: N^{4'}-[2-(Aminocarbonyl)benzyl]-N³-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

5 Example 65: N³-Cyclopropyl-N^{4'}-[3-(2-hydroxyethyl)phenyl]-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 66: N³-Cyclopropyl-6-methyl-N^{4'}-[(1R)-1-phenylethyl]-1,1'-biphenyl-3,4'-dicarboxamide

10 General Method G

A solution of {3'-[(cyclopropylamino)carbonyl]-2-methyl-6'-methyl-1,1'-biphen-4-yl}carboxylic acid (50mg, 0.17mmol) in DMF (1ml) was treated with HATU (65mg, 0.17mmol) at room temperature. After 5minutes this was added to a solution of the
15 amine (0.17mmol) and HOBT (23mg, 0.17mmol) in DMF (1ml). DIPEA (87ul, 3eq) was added. The reaction mixture was left at room temperature for 16hrs, then concentrated *in vacuo*.

The residue was dissolved in DCM (1ml) and loaded onto a SPE cartridge (1g, aminopropyl) which had been pre-equilibrated with DCM.
20 Residual sample was washed on with another portion of DCM (0.5ml) , The cartridge was then eluted with: DCM (1x2.5ml), chloroform (1x2.5ml), ethyl acetate (1x2.5ml), and methanol (1x2.5ml). The fractions containing product were isolated by evaporation to give the desired product.

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Compound	Amine	MH ⁺	Retention time (minutes)
Example 45	2-hydroxybenzylamine	401	3.22
Example 46	3-aminophenyl-sulphonamide	450	2.95
Example 47	2,6-difluorobenzylamine	421	3.26
Example 48	2,6-dimethoxybenzyl-amine	445	3.29
Example 49	benzylamine	385	3.24
Example 50	4-fluorobenzylamine	403	3.28
Example 51	2,6-dimethylbenzylamine	399	3.32
Example 52	4-(N-ethyl-N-	456	2.44

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	methylaminomethyl)- benzylamine		
Example 53	2-(2-hydroxyethyl)aniline	415	3.04
Example 54	3-(aminomethyl)- benzamide	428	2.74
Example 55	4-(dimethylaminomethyl)- benzamide	442	2.41
Example 56	2-chlorobenzylamine	419	3.40
Example 57	2-[(3-aminophenyl)- sulphonyl]ethanol	479	3.10
Example 58	3- <i>tert</i> -butoxycarbonyl- aminomethylamine	500	3.47
Example 59	2-(hydroxymethyl)aniline	401	3.46
Example 60	3-(N-ethyl-N-methyl- aminomethyl)benzylamine	456	2.46
Example 61	3-(hydroxymethyl)aniline	401	2.94
Example 62	3-aminophenylacetamide	428	2.80
Example 63	N-benzyl-N-ethylamine	413	3.39
Example 64	2-(aminomethyl)- benzamide	428	2.86
Example 65	3-(2-hydroxyethyl)aniline	415	2.98
Example 66	α -methylbenzylamine	399	3.31

Example 67: N³-Cyclobutyl-N⁴-(3-methoxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

5 Example 68: N³-Ethyl-N⁴-(3-methoxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 69: N³-Ethyl-N⁴-(3-methoxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

10 Example 70: N³-Ethyl-N⁴-(4-methoxyphenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 71: N³-Isopropyl-N⁴-(3-methoxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 72: N³-Cyclopentyl-N⁴-(3-methoxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

General Method H:

5 The acid (0.06mmol), triethylamine (13ul) and 1-(methylsulphonyl)-1H-benzotriazole (12mg, 0.06mmol) were mixed in THF (0.5ml) and heated at reflux for 4 hours. The reaction was concentrated under vacuum and partitioned between chloroform (3ml) and water (2ml) and the organics reduced to dryness under vacuum. The residue was redissolved in THF (0.5ml) and was mixed with the amine (0.06mmol). After 20 hours the reaction was loaded onto an SPE (aminopropyl, 0.5g) and eluted with chloroform to give the desired product.

Compound	Acid	Amine	MH ⁺	Retention time (minutes)
Example 67	{3'-[(Cyclobutylamino)-carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid	3-methoxybenzyl-amine	429	3.42
Example 68	{3'-[(Cyclobutylamino)-carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid	4-methoxyaniline	415	3.47
Example 69	{3'-[(Ethylamino)-carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid	3-methoxybenzyl-amine	403	3.24
Example 70	{3'-[(Ethylamino)-carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid	4-methoxyaniline	389	3.29
Example 71	{3'-[(Isopropylamino)-carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid	3-methoxybenzyl-amine	417	3.34
Example 72	{3'-[(Cyclopentylamino)-	3-methoxybenzyl-	443	3.50

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	carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid	amine		
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(a) {3'-[(Cyclobutylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid (Intermediate 7)

5

Methyl {3'-[(cyclobutylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate (Intermediate 8, 123mg, 0.38mmol) in methanol (2ml) was mixed with aqueous sodium hydroxide (2N, 1ml) and stirred at room temperature for 24hours. The methanol was evaporated, the reaction diluted with water (2ml) and extracted with chloroform (3ml).

10

The aqueous was acidified with hydrochloric acid (2N, 3ml) and extracted with chloroform (2x 4ml). The solvent was evaporated from the organic extracts to give {3'-[(cyclobutylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid (121mg). LC/MS: MH⁺ 310, retention time 3.25minutes.

15

(b) Methyl {3'-[(cyclobutylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate (Intermediate 8)

20

4'-(Methoxycarbonyl)-2-methyl-1,1'-biphenyl-5-carboxylic acid (217mg, 0.80mmol), triethylamine (157ul) and 1-(methylsulphonyl)-1H-benzotriazole (158mg, 0.80mmol) were mixed in THF (3.6ml) and heated at reflux for 18 hours. The reaction was concentrated under vacuum and partitioned between chloroform (9ml) and water (6ml) and the organics reduced to dryness under vacuum. The residue was redissolved in THF (2ml) and was mixed with cyclobutylamine (0.1ml). After 3 hours the reaction was loaded onto an SPE (aminopropyl, 10g) and eluted with chloroform to give methyl {3'-[(cyclobutylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate (123mg). LC/MS: MH⁺ 324, retention time 3.40minutes.

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(c) {3'-[(Ethylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid (Intermediate 9)

30

Methyl {3'-[(ethylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate (Intermediate 10, 0.38mmol) in methanol (2ml) was mixed with aqueous sodium hydroxide (2N, 1ml) and stirred at room temperature for 24hours. The methanol was evaporated, the reaction diluted with water (2ml) and extracted with chloroform (3ml). The aqueous was acidified with hydrochloric acid (2N, 3ml) and extracted with chloroform (2x 4ml). The solvent was evaporated from the organic extracts to give {3'-[(ethylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid .

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LC/MS: MH⁺ 284, retention time 2.99minutes.

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(d) Methyl {3'-[(ethylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate
(Intermediate 10)

- 5 4'-(Methoxycarbonyl)-2-methyl-1,1'-biphenyl-5-carboxylic acid (0.80mmol), triethylamine (157ul) and 1-(methylsulphonyl)-1H-benzotriazole (158mg, 0.80mmol) were mixed in THF (3.6ml) and heated at reflux for 18 hours. The reaction was concentrated under vacuum and partitioned between chloroform (9ml) and water (6ml) and the organics reduced to dryness under vacuum. The residue was redissolved in THF (2ml) and was
10 mixed with ethylamine (0.1ml). After 3 hours the reaction was loaded onto an SPE (aminopropyl, 10g) and eluted with chloroform to give methyl {3'-[(ethylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate.
LC/MS: MH⁺ 298, retention time 3.20minutes.

- 15 (e) {3'-[(isopropylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid
(Intermediate 11)

- Methyl {3'-[(isopropylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate
(Intermediate 12, 0.38mmol) in methanol (2ml) was mixed with aqueous sodium
20 hydroxide (2N, 1ml) and stirred at room temperature for 24hours. The methanol was evaporated, the reaction diluted with water (2ml) and extracted with chloroform (3ml). The aqueous was acidified with hydrochloric acid (2N, 3ml) and extracted with chloroform (2x 4ml). The solvent was evaporated from the organic extracts to give {3'-
25 [(isopropylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid .
LC/MS: MH⁺ 298, retention time 3.11minutes.

(f) Methyl {3'-[(isopropylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate
(Intermediate 12)

- 30 4'-(Methoxycarbonyl)-2-methyl-1,1'-biphenyl-5-carboxylic acid (0.80mmol), triethylamine (157ul) and 1-(methylsulphonyl)-1H-benzotriazole (158mg, 0.80mmol) were mixed in THF (3.6ml) and heated at reflux for 18 hours. The reaction was concentrated under vacuum and partitioned between chloroform (9ml) and water (6ml) and the organics reduced to dryness under vacuum. The residue was redissolved in THF (2ml) and was
35 mixed with isopropylamine (0.1ml). After 3 hours the reaction was loaded onto an SPE (aminopropyl, 10g) and eluted with chloroform to give methyl {3'-[(isopropylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate.
LC/MS: MH⁺ 312, retention time 3.31minutes.

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(g) {3'-[(cyclopentylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid
(Intermediate 13)

5 Methyl {3'-[(cyclopentylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate
(Intermediate 14, 0.38mmol) in methanol (2ml) was mixed with aqueous sodium
hydroxide (2N, 1ml) and stirred at room temperature for 24hours. The methanol was
evaporated, the reaction diluted with water (2ml) and extracted with chloroform (3ml).
The aqueous was acidified with hydrochloric acid (2N, 3ml) and extracted with
10 chloroform (2x 4ml). The solvent was evaporated from the organic extracts to give {3'-
[(cyclopentylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid .
LC/MS: MH⁺ 324, retention time 3.37minutes.

(h) Methyl {3'-[(cyclopentylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate
(Intermediate 14)

15 4'-(Methoxycarbonyl)-2-methyl-1,1'-biphenyl-5-carboxylic acid (0.80mmol), triethylamine
(157ul) and 1-(methylsulphonyl)-1H-benzotriazole (158mg, 0.80mmol) were mixed in
THF (3.6ml) and heated at reflux for 18 hours. The reaction was concentrated under
vacuum and partitioned between chloroform (9ml) and water (6ml) and the organics
20 reduced to dryness under vacuum. The residue was redissolved in THF (2ml) and was
mixed with cyclopentylamine (0.1ml). After 3 hours the reaction was loaded onto an
SPE (aminopropyl, 10g) and eluted with chloroform to give methyl {3'-
[(cyclopentylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate.
LC/MS: MH⁺ 338, retention time 3.52minutes.

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Abbreviations

30	DCM	Dichloromethane
	DIPEA	N,N-Diisopropylethylamine
	DME	Dimethoxyethane
	DMF	Dimethylformamide
	DMSO	Dimethylsulphoxide
35	HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
	HBTU	O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
	HOBT	1-Hydroxybenzotriazole hydrate
	PyBOP	Benzotriazol-1-yl-oxy-tripyrrolidinophosphonium hexafluorophosphate
40	SPE	Solid phase extraction

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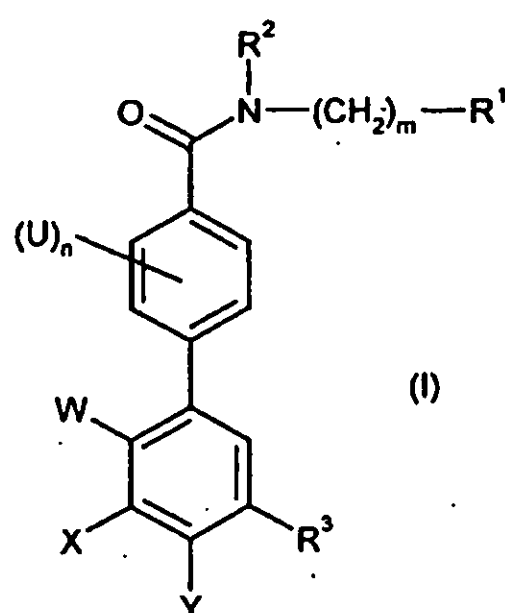
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Claims:

1. A compound of formula (I):



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wherein

- R^1 is a phenyl group which may be optionally substituted;
 R^2 is selected from hydrogen, C_{1-6} alkyl and $-(CH_2)_v-C_{3-7}$ cycloalkyl;
 R^3 is the group $-CO-NH-(CH_2)_q-R^4$;
 when q is 0 to 2 R^4 is selected from hydrogen, C_{1-6} alkyl, $-C_{3-7}$ cycloalkyl, $CONHR^5$, phenyl optionally substituted by R^7 and/or R^8 , heteroaryl optionally substituted by R^7 and/or R^8 and heterocyclyl optionally substituted by R^7 and/or R^8 ;
 and when q is 2 R^4 is additionally selected from C_{1-6} alkoxy, $NHCOR^5$, $NHCONHR^5$, NR^5R^6 , and OH ;
 R^5 is selected from hydrogen, C_{1-6} alkyl and phenyl wherein the phenyl group may be optionally substituted by up to two substituents selected from C_{1-6} alkyl and halogen;
 R^6 is selected from hydrogen and C_{1-6} alkyl;
 or R^5 and R^6 , together with the nitrogen atom to which they are bound, form a five- to six-membered heterocyclic or heteroaryl ring optionally containing one additional heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring may be substituted by up to two C_{1-6} alkyl groups;
 R^7 is selected from C_{1-6} alkyl, C_{1-6} alkoxy, $-CONR^8R^9$, $-NHCOR^9$, $-SO_2NHR^9$, $-NHSO_2R^9$, halogen, trifluoromethyl, $-Z-(CH_2)_s$ -phenyl optionally substituted by one or more halogen atoms, $-Z-(CH_2)_s$ -heterocyclyl or $-Z-(CH_2)_s$ -heteroaryl wherein the heterocyclyl or heteroaryl group may be optionally substituted by one or more substituents selected from C_{1-6} alkyl;
 R^8 is selected from C_{1-6} alkyl and halogen;

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or when R^7 and R^8 are adjacent to each other they may, together with the carbon atoms to which they are bound, form a five- or six-membered saturated or unsaturated ring to give a fused bicyclic ring system, wherein the ring that is formed by R^7 and R^8 may optionally contain one or two heteroatoms selected from oxygen, nitrogen and sulfur;

R^9 is selected from hydrogen and C_{1-6} alkyl;

U is selected from methyl and halogen;

W is selected from methyl and chloro;

X and Y are each selected independently from hydrogen, methyl and halogen;

Z is selected from -O- and a bond;

m is selected from 0, 1, 2, 3 and 4, and may be optionally substituted with up to two groups selected independently from C_{1-6} alkyl;

n is selected from 0, 1 and 2;

v is selected from 0, 1 and 2;

q and s are selected from 0, 1 and 2;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1 wherein R^1 is substituted by one or two substituents selected from halogen, C_{1-4} alkyl, trifluoromethyl, C_{1-4} alkoxy, benzyloxy, hydroxy, cyano, $-CH_2CH_2OH$, $-(CH_2)_pNHCH_3$, $-(CH_2)_pN(CH_3)_2$, $-(CH_2)_pCONR^5R^6$, $-(CH_2)_pCO_2R^5$, $-(CH_2)_pNR^5COR^6$, $-(CH_2)_pOCOR^5$, $-(CH_2)_pOCONR^5R^6$, $-(CH_2)_pNR^5COOR^6$, $-(CH_2)_pCOR^5$, $-(CH_2)_pSO_2NR^5R^6$, $-(CH_2)_pNR^5SO_2R^6$, $-SO_2R^5$, $-(CH_2)_pNR^5R^6$, $-(CH_2)_pNR^5CONR^5R^6$ and $-(CH_2)_pCONR^5SO_2R^6$;

wherein p is selected from 0, 1 and 2; and

R^5 and R^6 are independently selected from hydrogen, C_{1-4} alkyl and phenyl.

3. A compound according to claim 1 wherein R^1 is substituted by one or two substituents selected from halogen, C_{1-4} alkyl, C_{1-4} alkoxy, hydroxy, cyano, hydroxy C_{1-4} alkyl, $-(CH_2)_pCO(CH_2)_iNR^{10}R^{11}$, $-(CH_2)_pNR^{10}COOR^{11}$, $-(CH_2)_pSO_2NR^{10}R^{11}$, $-(CH_2)_pNR^{10}SO_2R^{11}$, $-SO_2R^{10}$, and $-(CH_2)_pNR^{10}R^{11}$.

4. A compound according to any one of the preceding claims wherein R^2 is selected from hydrogen, C_{1-4} alkyl and $-CH_2$ -cyclopropyl.

5. A compound according to claim 4 wherein R^2 is hydrogen.

6. A compound according to any one of the preceding claims wherein m is selected from 0, 1 and 2.

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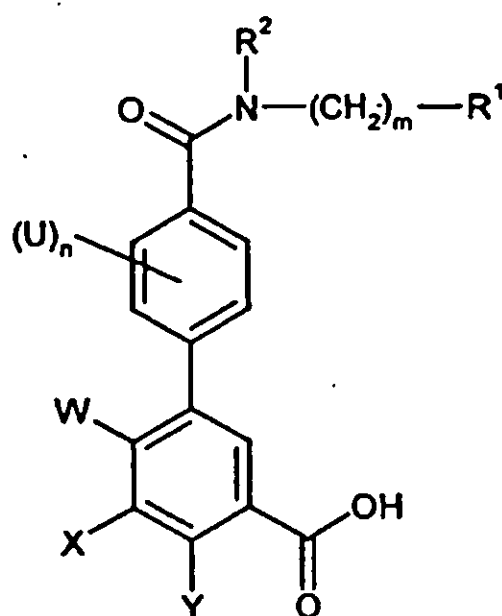
7. A compound according to any one of the preceding claims wherein R^4 is selected from C_{1-4} alkyl, $-C_{3-7}$ cycloalkyl, $CONHR^5$, phenyl optionally substituted by R^7 and/or R^8 , and heteroaryl optionally substituted by R^7 and/or R^8 .

5 8. A compound according to claim 7 wherein R^4 is selected from C_{1-4} alkyl, cyclopropyl, pyridinyl and phenyl.

9. A compound according to claim 1 as defined in any one of Examples 1 to 72, or a pharmaceutically acceptable salt or solvate thereof.

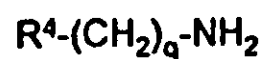
10 10 A process for preparing a compound according to any one of claims 1 to 9 which comprises:

15 (a) reacting a compound of formula (XIII)



(XIII)

20 wherein R^1 , R^2 , U, W, X, Y, m and n are as defined in claim 1, with a compound of formula (XIV)



(XIV)

25 wherein R^4 and q are as defined in claim 1, under amide forming conditions, optionally converting the acid compound (XIII) to an activated form of the acid before reaction with the amine compound (XIV);

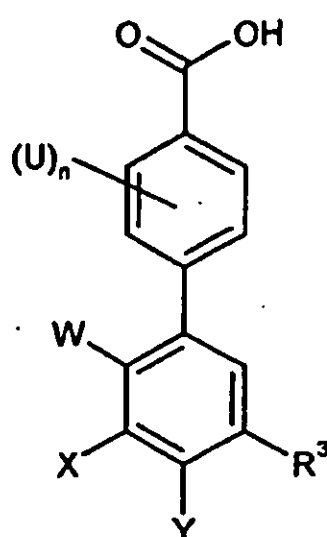
(b) reacting a compound of formula (XV)

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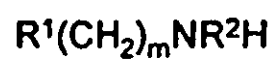
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(XV)

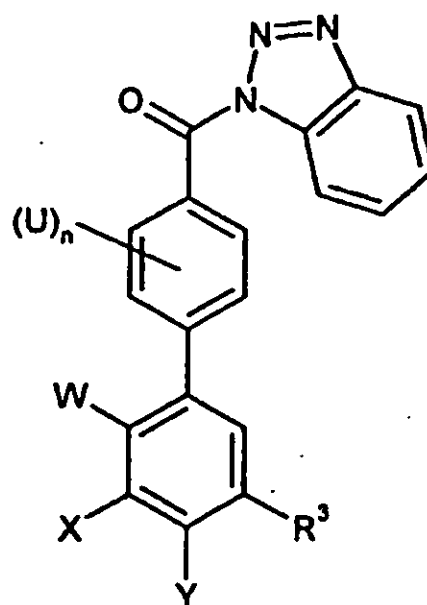
5 wherein R³, U, W, X, Y and n are as defined in claim 1,
with a compound of formula (XVI)



(XVI)

10 wherein R¹, R² and m are as defined in claim 1,
under amide forming conditions;

(c) reacting a compound of formula (XVII)



(XVII)

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wherein R³, U, W, X, Y and n are as defined in claim 1,
with a compound of formula (XVI) as defined above; or

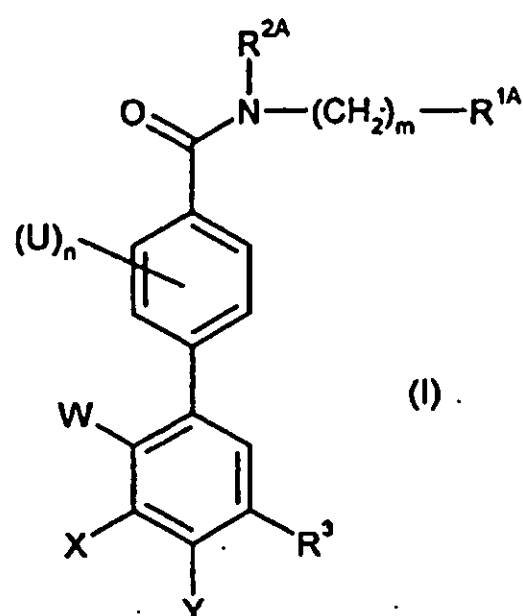
20 (d) functional group conversion of a compound of formula (XVIII)

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(XVIII)

- 5 wherein R^3 , U, W, X, Y and n are as defined in claim 1 and R^{1A} and R^{2A} are R^1 and R^2 as defined in claim 1 or groups convertible to R^1 and R^2 , to give a compound of formula (I).
- 10 11. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt or solvate thereof, in admixture with one or more pharmaceutically acceptable carriers, diluents or excipients.
- 15 12. A method for treating a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase comprising administering to a patient in need thereof a compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt or solvate thereof.
- 20 13. A compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt or solvate thereof for use in therapy.
14. Use of a compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for use in the treatment of a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase.

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Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INHIBITORS OF AKT ACTIVITY

(57) Abstract: Invented are novel pyridine compounds, the use of such compounds as inhibitors of PKB/AKT kinase activity and in the treatment of cancer and arthritis.

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INHIBITORS OF AKT ACTIVITYFIELD OF THE INVENTION

This invention relates to novel pyridine compounds, the use of such
 5 compounds as inhibitors of protein kinase B (hereinafter PKB/Akt, PKB or Akt)
 activity and in the treatment of cancer and arthritis.

BACKGROUND OF THE INVENTION

The present invention relates to pyridine containing compounds that are
 10 inhibitors of the activity of one or more of the isoforms of the serine/threonine
 kinase, Akt (also known as protein kinase B). The present invention also relates to
 pharmaceutical compositions comprising such compounds and methods of using
 the instant compounds in the treatment of cancer and arthritis (Liu et al. Current
Opin. Pharmacology 3:317-22 (2003)).

15 Apoptosis (programmed cell death) plays essential roles in embryonic
 development and pathogenesis of various diseases, such as degenerative neuronal
 diseases, cardiovascular diseases and cancer. Recent work has led to the
 identification of various pro- and anti-apoptotic gene products that are involved in
 the regulation or execution of programmed-cell death. Expression of anti-apoptotic
 20 genes, such as Bcl2 or Bcl-x_L, inhibits apoptotic cell death induced by various
 stimuli. On the other hand, expression of pro-apoptotic genes, such as Bax or Bad,
 leads to programmed cell death (Adams et al. *Science*, 281:1322-1326 (1998)).
 The execution of programmed cell death is mediated by caspase -1 related
 proteinases, including caspase-3, caspase- 7, caspase-8 and caspase-9 etc
 25 (Thornberry et al. *Science*, 281:1312-1316 (1998)).

The phosphatidylinositol 3'-OH kinase (PI3K)/Akt/PKB pathway appears
 important for regulating cell survival/cell death (Kulik et al. *Mol. Cell. Biol.* 17:1595-
 1606 (1997); Franke et al, *Cell*, 88:435-437 (1997); Kauffmann-Zeh et al. *Nature*
 385:544-548 (1997) Hemmings *Science*, 275:628-630 (1997); Dudek et al.,
 30 *Science*, 275:661-665 (1997)). Survival factors, such as platelet derived growth
 factor (PDGF), nerve growth factor (NGF) and insulin-like growth factor-1 (IGF-I),
 promote cell survival under various conditions by inducing the activity of PI3K (Kulik
 et al. 1997, Hemmings 1997). Activated PI3K leads to the production of
 phosphatidylinositol (3,4,5)-triphosphate (PtdIns (3,4,5)-P₃), which in turn binds to,
 35 and promotes the activation of, the serine/ threonine kinase Akt, which contains a
 pleckstrin homology (PH)-domain (Franke et al *Cell*, 81:727-736 (1995); Hemmings
Science, 277:534 (1997); Downward, *Curr. Opin. Cell Biol.* 10:262-267 (1998),

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and/or pharmaceutically acceptable salts, hydrates, solvates and pro-drugs thereof;

further provided that when

5 R¹ is isoquinoline,
R² is not furyl or alkyl.

10 This invention relates to a method of treating cancer, which comprises administering to a subject in need thereof an effective amount of an Akt/PKB inhibiting compound of Formula (I).

This invention relates to a method of treating arthritis, which comprises administering to a subject in need thereof an effective amount of an Akt/PKB inhibiting compound of Formula (I).

15 The present invention also relates to the discovery that the compounds of Formula (I) are active as inhibitors of Akt/PKB.

20 In a further aspect of the invention there is provided novel processes and novel intermediates useful in preparing the presently invented Akt/PKB inhibiting compounds.

25 Included in the present invention are pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the methods of the invention.

Also included in the present invention are methods of co-administering the presently invented Akt/PKB inhibiting compounds with further active ingredients.

DETAILED DESCRIPTION OF THE INVENTION

30 This invention relates to compounds of Formula (I) as described above.

The presently invented compounds of Formula (I) inhibit Akt/PKB activity. In particular, the compounds disclosed herein inhibit each of the three Akt/PKB isoforms.

35 Included among the presently invented compounds of Formula (I) are those having Formula (I):
wherein

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A is selected from: nitrogen, -C-halogen and -CH;

L¹ is selected from the group consisting of a bond, -O-, -N(R⁵)-, -S-, -S(O)-, -S(O₂)-, alkyl, and -N(R⁵)C(O)-;

L² is selected from the group consisting of a bond, -O-, heterocycle, -N(R⁵)-, -N(R⁵)C(O)-, -S-, -S(O)-, -S(O₂)-, and -C(O)N(R⁵)-;

L³ is alkyl, wherein the alkyl is optionally substituted with one or two substituents independently selected from the group consisting of amino, methylamino, dimethylamino, oxo, and hydroxy;

L⁶ is a bond;

R¹ is selected from the group consisting of C₁-C₁₂aryl and substituted C₁-C₁₂aryl;

R² is selected from alkyl, substituted alkyl, halogen, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, and C₁-C₁₂aryl optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, trifluoroalkoxy, C₁-C₁₂aryl, aryloxy, -O(CH₂)_qR³¹, -NHC(O)-NHR⁴¹, -C(O)R⁴³, hydroxy, alkoxy, cycloalkyl, N-acylamino, nitro and halogen,

where q is 1-6,

R³¹ is C₁-C₁₂aryl, cycloalkyl and heterocycle, each of which is optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, acyloxy, amino, methylamino, dimethylamino, N-acylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl,

R⁴¹ is selected from hydrogen, C₁-C₁₂aryl, cycloalkyl and heterocycle, wherein C₁-C₁₂aryl, cycloalkyl and heterocycle are optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, amino, methylamino, dimethylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl,

R⁴³ is selected from C₁-C₁₂aryl, cycloalkyl and heterocycle, each of which is optionally substituted with from 1 to 4 substituents selected from:

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halogen, hydroxyalkyl, alkoxy, amino, methylamino, dimethylamino, hydroxyl, nitro, tetrazole, cyano, oxo and trifluoromethyl,

5 R^3 and R^6 are independently selected from the group consisting of hydrogen, amino, methylamino, dimethylamino, aryl, substituted aryl, heterocycle, substituted heterocycle, cycloalkyl, substituted cycloalkyl, $-S-C_1-C_{12}$ aryl, aryloxy and arylalkoxy; and

10 R^4 is selected from the group consisting of hydrogen and halogen;

where R^5 is selected from the group consisting of hydrogen, $-S(O)_2CH_3$, $-S(O)_2H$ and alkyl;

provided that when,

15 R^1 is azaindazole, substituted azaindazole, 1H-thienopyrazole, substituted 1H-thienopyrazole, benzamide, substituted benzamide, phenylethanone, substituted phenylethanone, thiophene, substituted thiophene, furan or substituted furan,

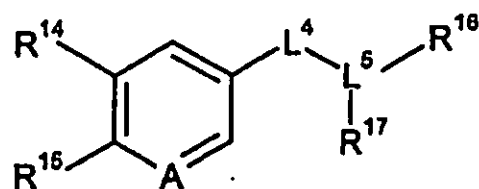
20 R^2 may additionally be hydrogen;

and/or pharmaceutically acceptable salts, hydrates, solvates and pro-drugs thereof;

further provided that when

25 R^1 is isoquinoline,
 R^2 is not furyl or alkyl.

Included among the presently invented compounds of Formula (I) are those having Formula (II):



(II)

30

wherein:

A is selected from nitrogen, $-CF$ and $-CH$;

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- [(1S)-2-[[6-[3,5-difluoro-2-(methoxy)phenyl]-5-(3-methyl-1H-thieno[3,2-c]pyrazol-5-yl)-3-pyridinyl]oxy]-1-(1H-indol-3-ylmethyl)ethyl]amine;
- 2-[5-[[[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy]-3-(3-methyl-1H-thieno[3,2-c]pyrazol-5-yl)-2-pyridinyl]-4,6-difluorophenol;
- 2-[5-[[[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy]-3-(3-methyl-1H-thieno[3,2-c]pyrazol-5-yl)-2-pyridinyl]phenol;
- 2-[5-[[[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy]-3-(3-methyl-1H-thieno[3,2-c]pyrazol-5-yl)-2-pyridinyl]-4-chlorophenol;
- 3-(5-[[[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy]-3-pyridinyl]benzamide;
- 1-[3-(5-[[[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy]-3-pyridinyl]phenyl]ethanone; and
- 5-[[[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy]-2-(3-furanyl)-3,4'-bipyridine-2'-carboxamide
- and/or pharmaceutically acceptable salts, hydrates, solvates and pro-drugs thereof.

Compounds of Formula (I) are included in the pharmaceutical compositions of the invention and used in the methods of the invention.

- By the term "aryl" as used herein, unless otherwise defined, is meant a cyclic or polycyclic aromatic ring containing from 1 to 14 carbon atoms and optionally containing from one to five heteroatoms, provided that when the number of carbon atoms is 1 the aromatic ring contains at least four heteroatoms, when the number of carbon atoms is 2 the aromatic ring contains at least three heteroatoms, when the number of carbons is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom.

- By the term "C₁-C₁₂aryl" as used herein, unless otherwise defined, is meant phenyl, naphthalene, 3,4-methylenedioxyphenyl, pyridine, biphenyl, indazole, quinoline, isoquinoline, azaindazole, 1H-thienopyrazole, pyrimidine, quinazoline, thiophene, furan, pyrrole, pyrazole, imidazole, benzothiophene, benzofuran, isoxazole, indole and tetrazole.

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- The term "substituted" as used herein, unless otherwise defined, is meant that the subject chemical moiety has one or more substituents selected from the group consisting of: $\text{-CO}_2\text{R}^{20}$, $\text{C}_1\text{-C}_{12}\text{aryl}$, $\text{C}_1\text{-C}_{12}\text{aryl amino}$, $\text{C}_1\text{-C}_{12}\text{aryl alkyl}$, cycloalkyl, heterocyclealkyl, $\text{C}_1\text{-C}_{12}\text{aryl}$, cyanoalkylaminoalkyl, $\text{C}_1\text{-C}_{12}\text{aryl}$, -
- 5 $\text{C(O)NHS(O)}_2\text{R}^{20}$, $\text{-NHS(O)}_2\text{R}^{20}$, -NHC(O)-NHR^{41} , hydroxyalkyl, alkoxy, - $\text{C(O)NR}^{21}\text{R}^{22}$, acyloxy, alkyl; R^{42} , $\text{-NR}^{21}\text{R}^{22}$, -C(O)R^{43} , -CHO , $\text{C}_1\text{-C}_{12}\text{aryloxy}$, amino, methylamino, dimethylamino, N-acylamino, hydroxy, $\text{-(CH}_2)_g\text{C(O)OR}^{23}$, $\text{-S(O)}_n\text{R}^{23}$, $\text{-O(CH}_2)_q\text{R}^{31}$, $\text{-O(CH}_2)_y\text{CH(R}^{31})\text{(CH}_2)_z\text{(CH}_3)$, nitro, tetrazole, cyano, oxo, halogen, trifluoromethoxy, trifluoroalkoxy and trifluoromethyl;
- 10 where
- n is 0-2, g is 0-6, q is 1-6, y is 0-6, z is 0-6,
- R^{41} is selected from hydrogen, $\text{C}_1\text{-C}_{12}\text{aryl}$, cycloalkyl and heterocycle, wherein $\text{C}_1\text{-C}_{12}\text{aryl}$, cycloalkyl and heterocycle are optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, amino,
- 15 methylamino, dimethylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl,
- R^{42} is selected from $\text{C}_1\text{-C}_{12}\text{aryl}$, $\text{C}_1\text{-C}_6\text{alkyl}$, cycloalkyl and heterocycle, each of which is substituted with from 1 to 4 substituents selected from: halogen, hydroxyalkyl, alkyl, alkoxy, amino, methylamino, dimethylamino, hydroxy, nitro,
- 20 tetrazole, cyano, oxo and trifluoromethyl,
- R^{43} is selected from $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_1\text{-C}_{12}\text{aryl}$, cycloalkyl and heterocycle, each of which is optionally substituted with from 1 to 4 substituents selected from: halogen, hydroxyalkyl, alkoxy, amino, methylamino, dimethylamino, hydroxyl, nitro, tetrazole, cyano, oxo and trifluoromethyl,
- 25 R^{31} is $\text{C}_1\text{-C}_{12}\text{aryl}$, cycloalkyl and heterocycle, each of which is optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, acyloxy, amino, methylamino, dimethylamino, N-acylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl,
- R^{23} is hydrogen or alkyl,
- 30 R^{20} is selected from hydrogen, $\text{C}_1\text{-C}_4\text{alkyl}$, aryl and trifluoromethyl, and R^{21} and R^{22} are independently selected from hydrogen, $\text{C}_1\text{-C}_4\text{alkyl}$, aryl and trifluoromethyl.

By the term "alkoxy" as used herein is meant -Oalkyl where alkyl is as described herein including -OCH_3 and $\text{-OC(CH}_3)_2\text{CH}_3$.

35

The term "cycloalkyl" as used herein unless otherwise defined, is meant a nonaromatic, unsaturated or saturated, cyclic or polycyclic $\text{C}_3\text{-C}_{12}$.

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Examples of cycloalkyl and substituted cycloalkyl substituents as used herein include: cyclohexyl, 4-hydroxy-cyclohexyl, 2-ethylcyclohexyl, cyclohexene, propyl 4-methoxycyclohexyl, 4-methoxycyclohexyl, 4-carboxycyclohexyl, cyclopropyl, cyclopentene and cyclopentyl.

5 The term "heterocycle," as used herein, unless otherwise defined, is meant a cyclic or polycyclic, non-aromatic, three-, four-, five-, six-, or seven-membered ring containing at least one atom, selected from the group consisting of oxygen, nitrogen, and sulfur. The five-membered rings have zero or one double bond and the six- and seven-membered rings have zero, one, or two double bonds.

10 Examples of heterocyclic groups as used herein include: dihydroisoindolyl, dihydroisoquinolyl, dihydroindolyl, dihydropyridinyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, isoindolyl, morpholyl, piperazinyl, pyrrolidinyl, tetrahydropyridinyl, piperidinyl, thiomorpholyl.

By the term "acyloxy" as used herein is meant -OC(O)alkyl where alkyl is as described herein. Examples of acyloxy substituents as used herein include: -
15 OC(O)CH₃, -OC(O)CH(CH₃)₂ and -OC(O)(CH₂)₃CH₃.

By the term "N-acylamino" as used herein is meant a substituent selected from: -N(H)C(O)alkyl, -N(H)C(O)cycloalkyl and -N(H)C(O)aryl; where alkyl and cycloalkyl are as described herein and aryl is C₁-C₁₂aryl as described herein and
20 where the alkyl, cycloalkyl, and aryl are optionally substituted with from 1 to 4 substituents selected from: halogen, hydroxyalkyl, alkoxy, amino, methylamino, dimethylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl. Examples of N-acylamino substituents as used herein include: -N(H)C(O)CH₃, -N(H)C(O)CH(CH₃)₂ and -N(H)C(O)(CH₂)₃CH₃.

25 By the term "aryloxy" as used herein is meant -Oaryl where aryl is phenyl, naphthyl, 3,4-methylenedioxyphenyl, pyridyl or biphenyl, each of which is optionally substituted with one or more substituents selected from the group consisting of: alkyl, hydroxyalkyl, alkoxy, trifluoromethyl, acyloxy, amino, N-acylamino, hydroxy, -(CH₂)_gC(O)OR²⁵, -S(O)_nR²⁵, nitro, cyano, halogen and protected -OH, where g
30 is 0-6, R²⁵ is hydrogen or alkyl, and n is 0-2. Examples of aryloxy substituents as used herein include: phenoxy, 4-fluorophenyloxy and biphenyloxy.

By the term "heteroatom" as used herein is meant oxygen, nitrogen or sulfur.

35 By the term "halogen" as used herein is meant a substituent selected from bromide, iodide, chloride and fluoride.

By the term "alkyl" and derivatives thereof and in all carbon chains as used herein is meant a linear or branched, saturated or unsaturated hydrocarbon chain,

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and unless otherwise defined, the carbon chain will contain from 1 to 12 carbon atoms. Examples of alkyl and substituted alkyl substituents as used herein include:

- CH₃, -CH₂-CH₃, -CH₂-CH₂-CH₃, -CH(CH₃)₂, -CH₂-CH₂-C(CH₃)₃, -CH₂-CF₃, -C≡C-C(CH₃)₃, -C≡C-CH₂-OH, cyclopropylmethyl, phenylmethyl, -CH₂-
 5 C(CH₃)₂-CH₂-NH₂, -CH₂-C(CH₃)₂-, -C≡C-C₆H₅, -C≡C-C(CH₃)₂-OH, -CH₂-CH(OH)-CH(OH)-CH(OH)-CH(OH)-CH₂-OH, piperidinylmethyl, methoxyphenylethyl, -C(CH₃)₃, -(CH₂)₃-CH₃, -CH₂-CH(CH₃)₂, -CH(CH₃)-CH₂-CH₃, -CH=CH₂, and -C≡C-CH₃.

- By the term "treating" and derivatives thereof as used herein, is meant
 10 prophylactic and therapeutic therapy.

- As used herein, the term "effective amount" and derivatives thereof means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically
 15 effective amount" and derivatives thereof means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological
 20 function.

- Compounds of Formula (I) are included in the pharmaceutical compositions of the invention and used in the methods of the invention. Where a -COOH or -OH group is present, pharmaceutically acceptable esters can be employed, for example methyl, ethyl, pivaloyloxymethyl, and the like for -COOH, and acetate
 25 maleate and the like for -OH, and those esters known in the art for modifying solubility or hydrolysis characteristics, for use as sustained release or prodrug formulations.

- The novel compounds of Formulas I and II are prepared as shown in Schemes 1 through 31 below, or by analogous methods, wherein the 'L' and 'R' substituents are as defined in Formulas I and II respectively and provided that the
 30 'L' and 'R' substituents do not include any such substituents that render inoperative the processes of Schemes 1 through 31. All of the starting materials are commercially available or are readily made from commercially available starting materials by those of skill in the art.

- 35 Ethers such as 1(b) can be prepared by Mitsunobu coupling with hydroxy-pyridines such as 2-chloro-3-bromo-5-hydroxy-pyridine and alcohols such as N-Boc-(2S)-2-amino-3-phenyl-1-propanol (Scheme 1). An aryl moiety such as a 6-(3-

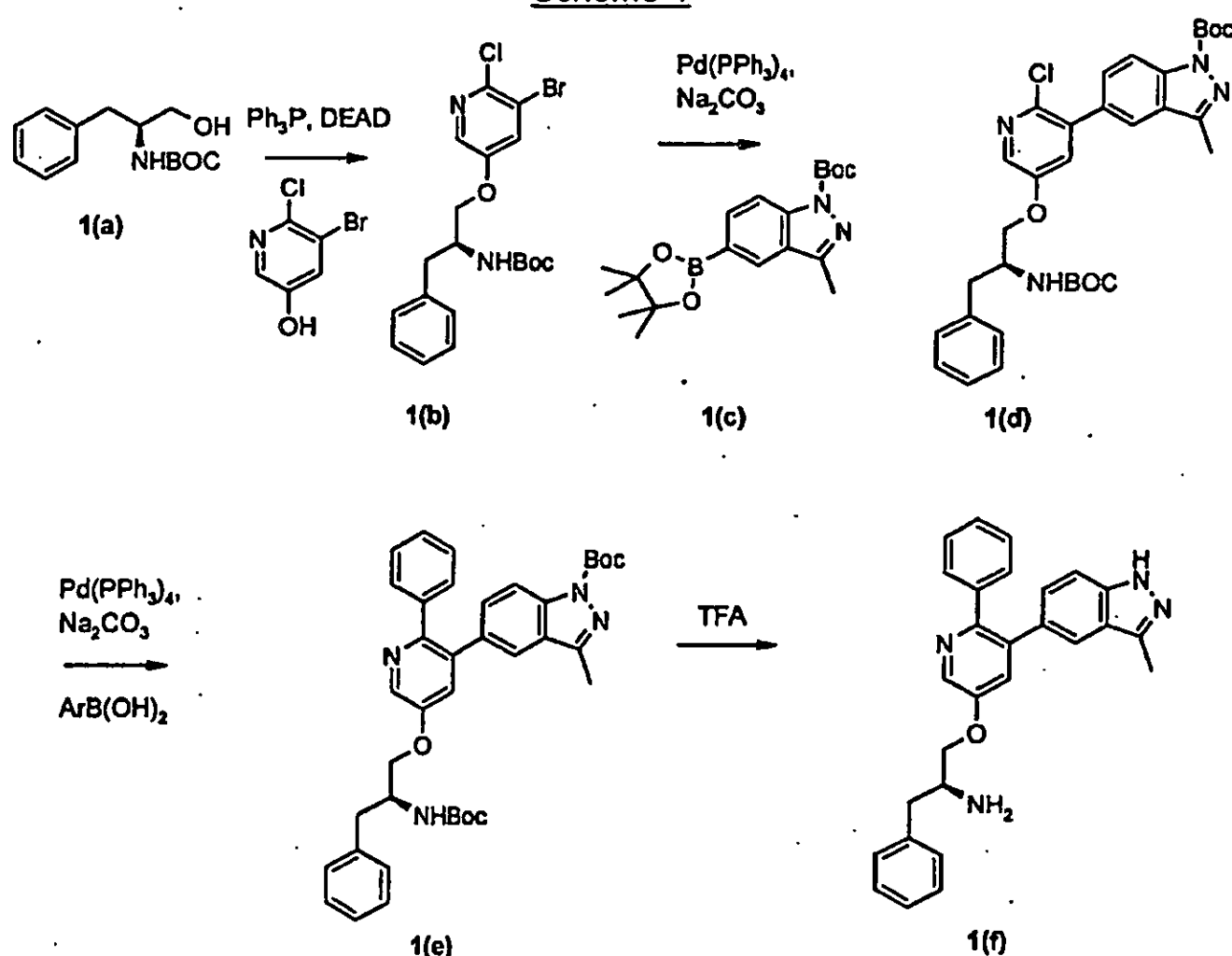
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methylandazole) can be selectively introduced by stoichiometric use of the Suzuki
 reaction (Pd-mediated cross coupling between aryl boronic acids or aryl boronic
 esters and aryl halides or triflates, Chem Rev, 1995, 95(7), 2457-83) or a Stille
 reaction (Pd-mediated cross coupling between aryltrialkylstannanes and aryl
 5 halides or triflates, Angewandte Chemie, International Edition 2004, 43(36),
 4704-4734) to produce intermediates such as 1(d) (Scheme 1). A second aryl
 moiety such as a phenyl group can be introduced at the adjacent position on the
 pyridine by a second Suzuki or Stille reaction forming trisubstituted pyridines such
 as 1(e) (Scheme 1), followed by deprotection steps.

10

Scheme 1



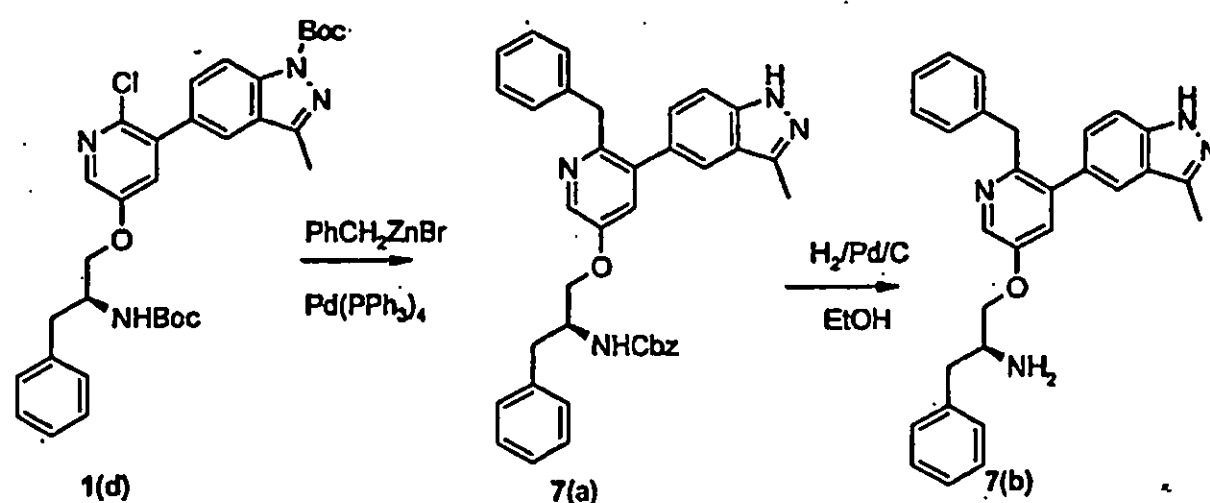
Alternatively, an alkyl or substituted alkyl group such as a benzyl moiety
 can be introduced by Pd-mediated coupling with an organometallic reagent such as
 15 benzyl zinc bromide (Scheme 2) to produce intermediates such as 7(a), followed by
 deprotection steps.

Scheme 2

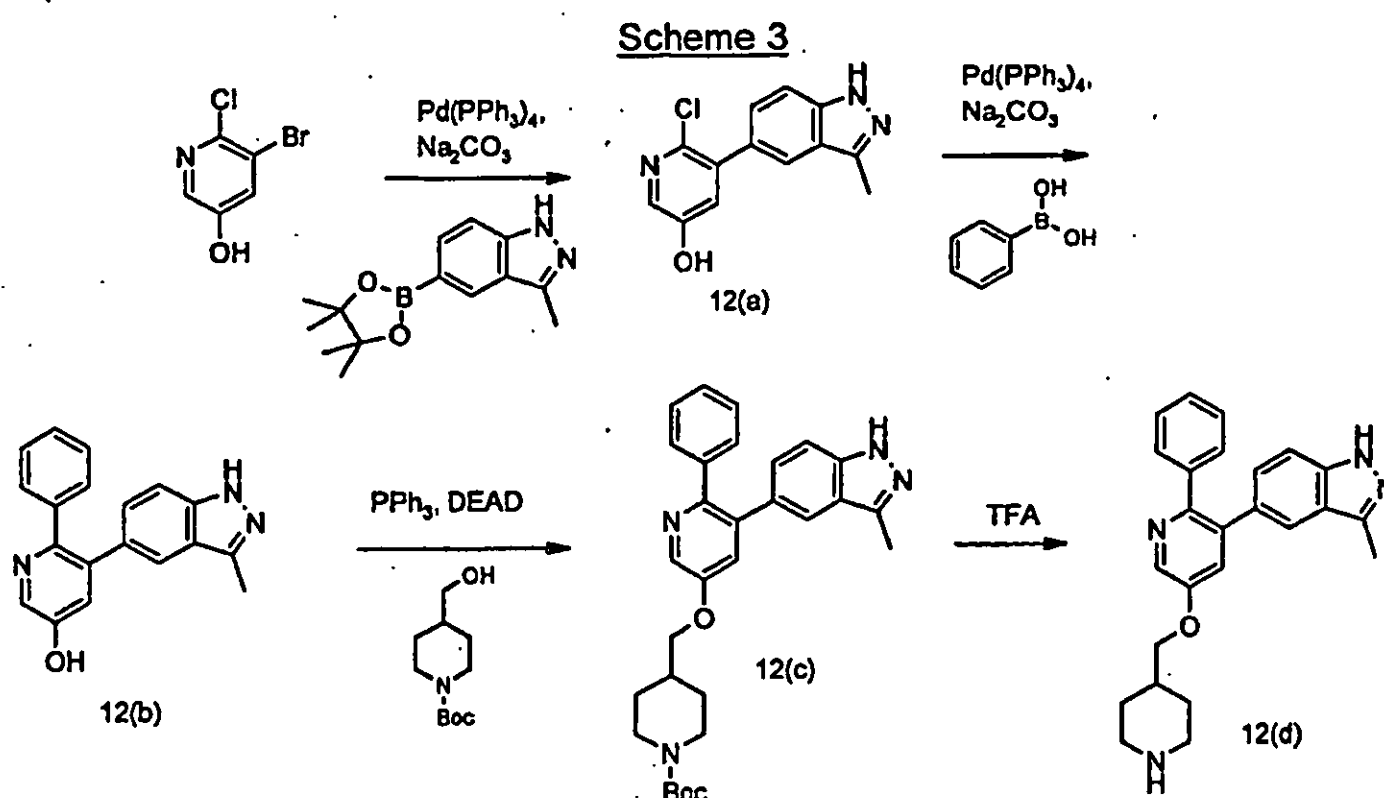
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Alternatively, the Pd-mediated cross coupling steps may precede the etherification or Mitsunobu reaction steps as shown in Scheme 3, followed by
5 deprotection steps.

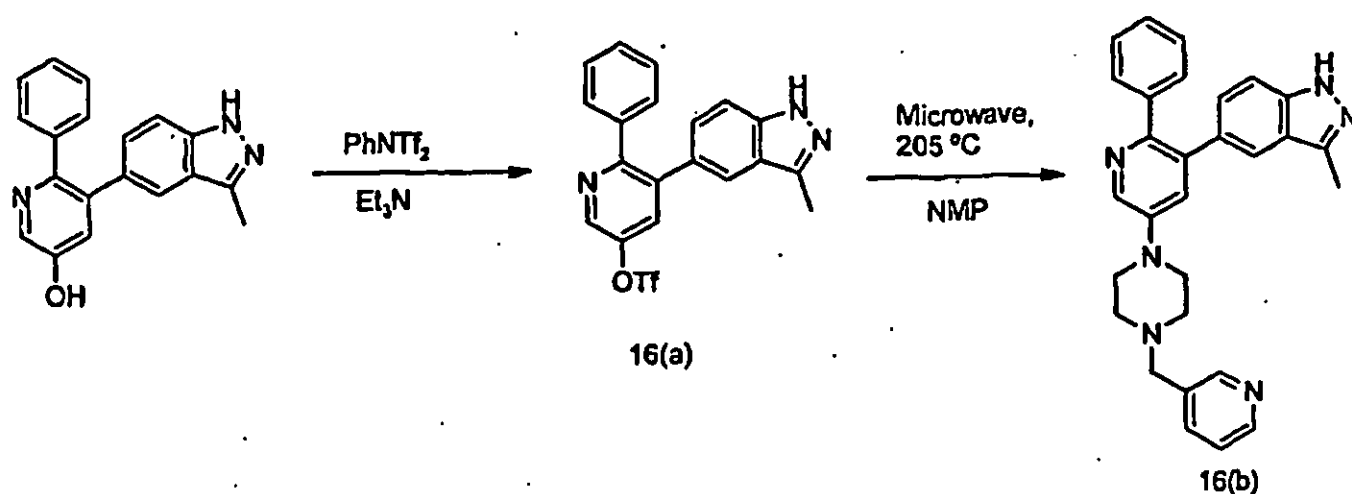


Another variant on the synthesis is to introduce alternative linker groups
10 such as amines in place of ethers as exemplified in Scheme 4. For example, ipso-
addition of an amine such as 1-(3-pyridinylmethyl)piperazine to a pyridine
trifluoromethylsulfonate (triflate or TfO) intermediate such as 16(a) and elimination
under microwave conditions in a solvent such as N-methyl-2-pyrrolidone (NMP)
15 produces amine analogs such as 16(b).

Scheme 4

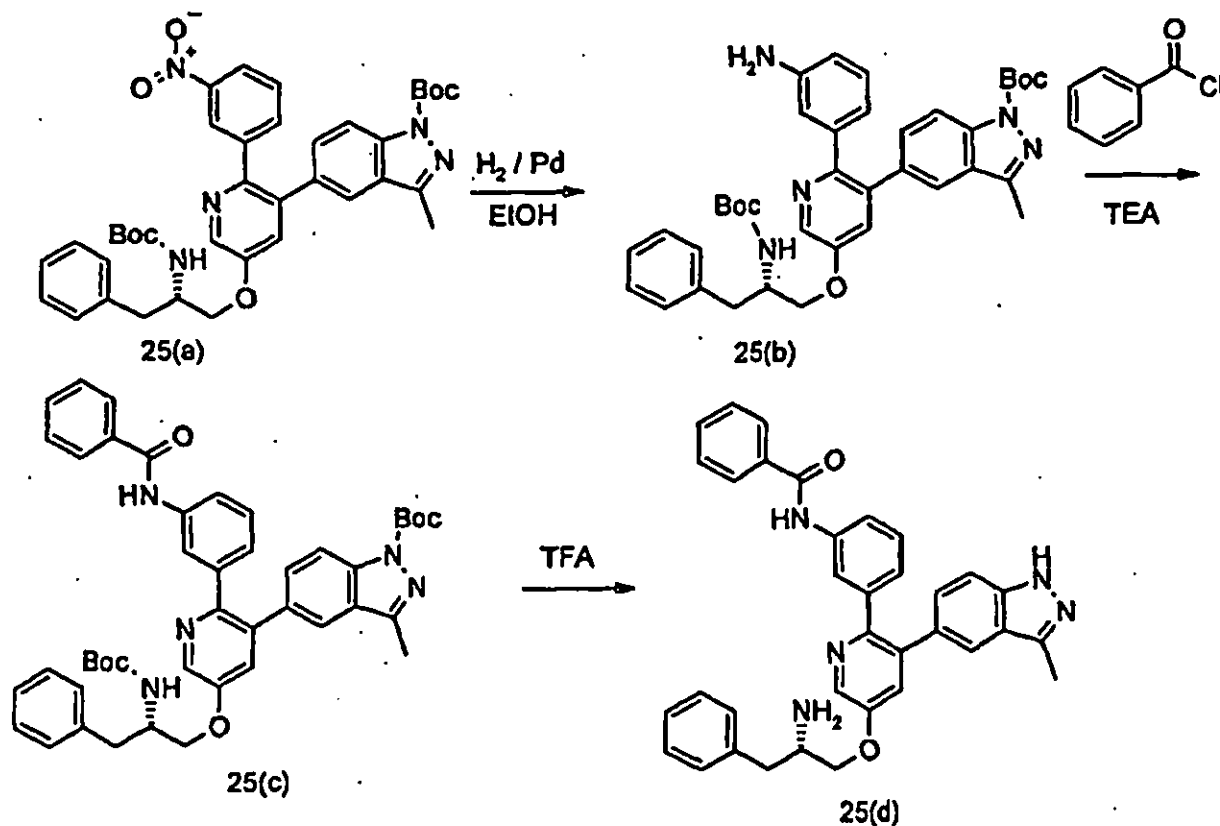
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In addition, the aryl groups on the substituted pyridine may be further functionalized by further reactions such as acylation of a intermediate amines such as 25(b) to form amides such as 25(c) as shown in Scheme 5, followed by deprotection steps.

Scheme 5



10

3-Substituted indazole analogs can be prepared by selective iodination of the parent indazole and Pd-mediated cross coupling steps (Scheme 6).

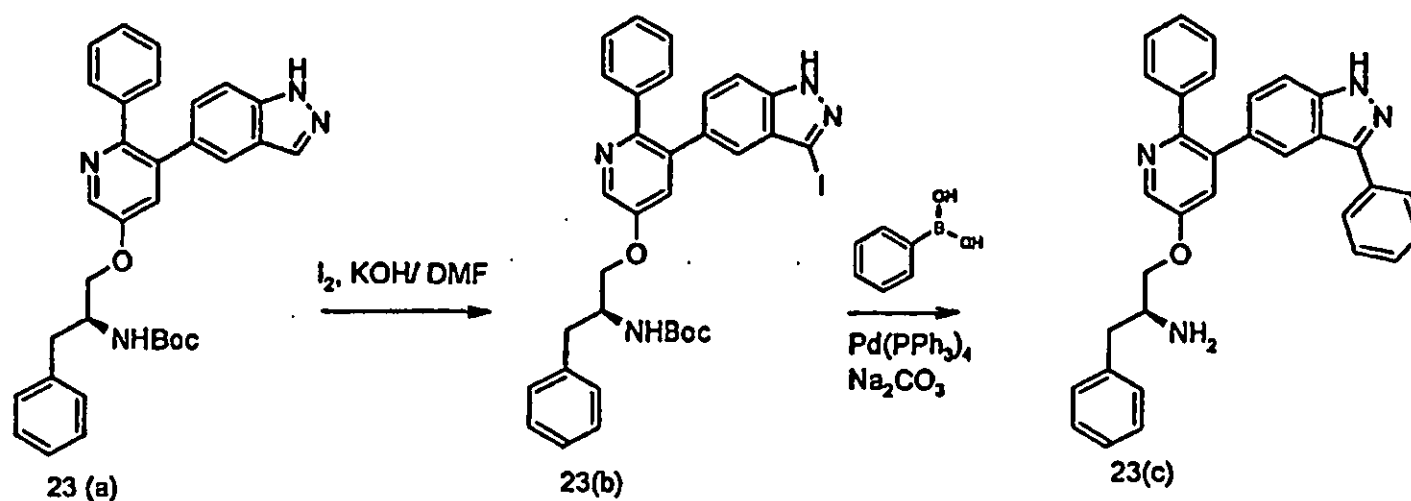
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Scheme 6

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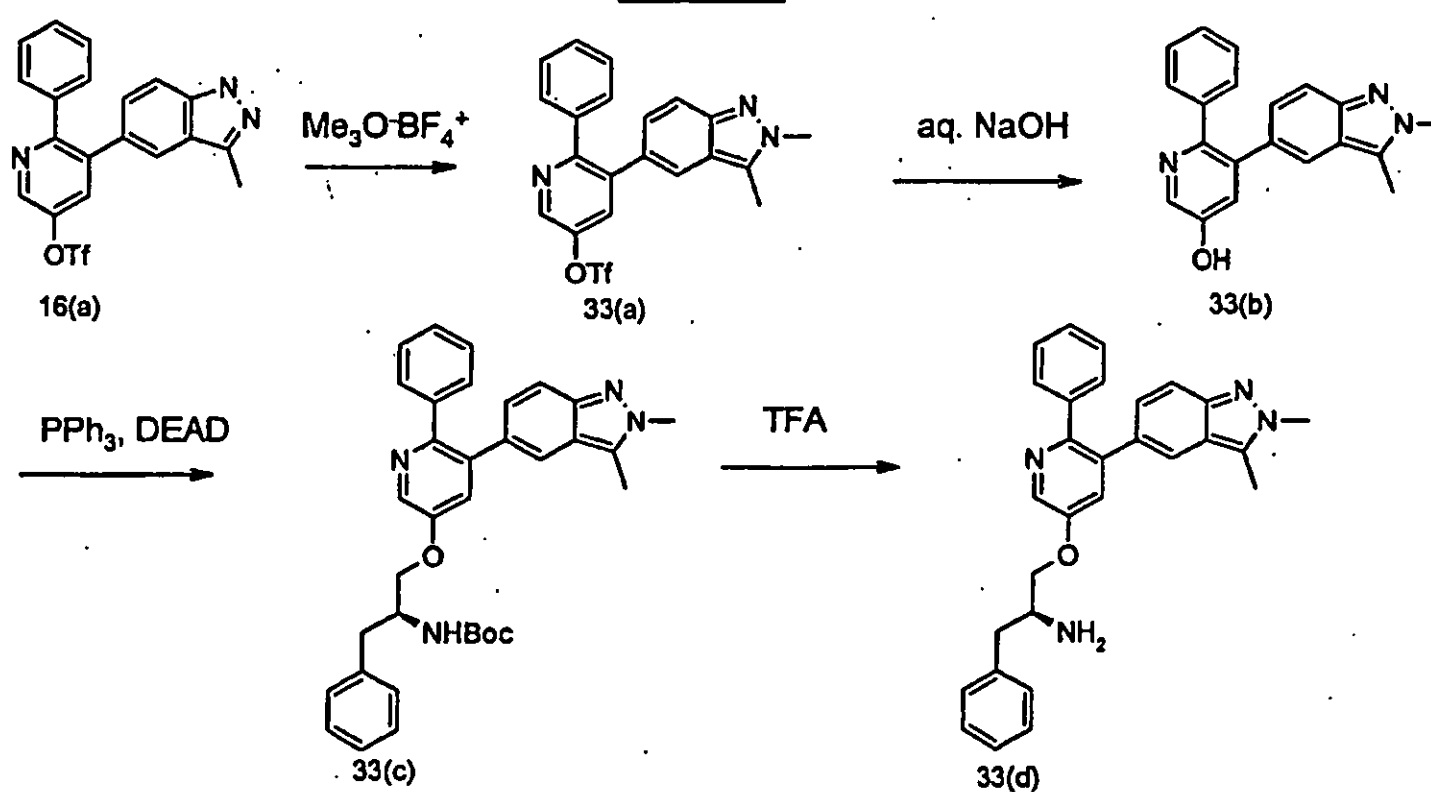
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- Also, *N*-alkylated analogs of the indazole such as 33(d) can be prepared by treating intermediate indazoles such as 16(a) with electrophilic reagents such as Meerwein's reagent followed by a Mitsunobu reaction as described above (Scheme 7), followed by deprotection steps.

Scheme 7



10

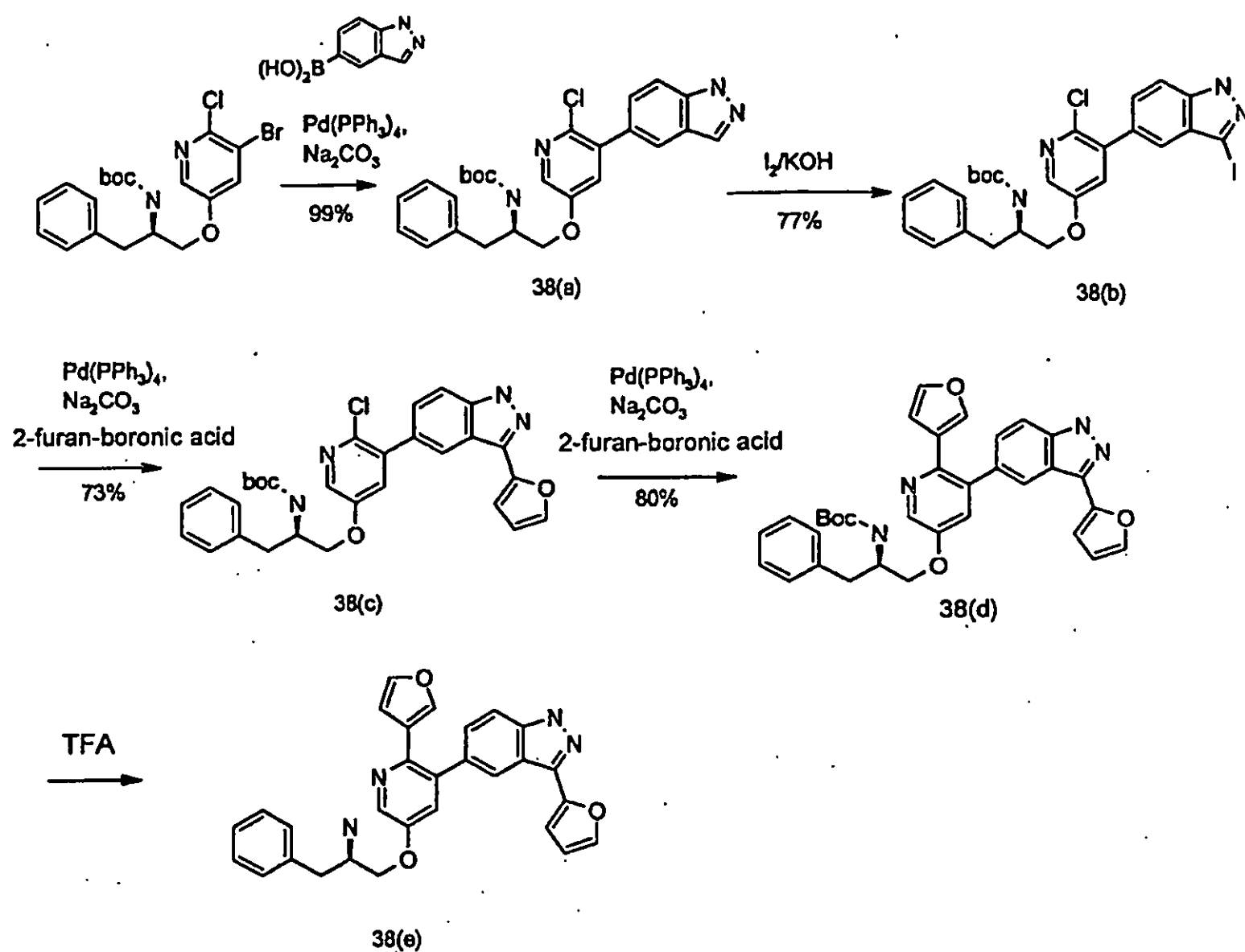
- Indazoles may be further substituted by iodinating the 3-position using an iodinating reagent such as iodine and a base such as potassium hydroxide followed by a Pd-mediated cross coupling step such as Suzuki, Stille, Buchwald/Hartwig (JOC 2000, 65(4), 1158-1174), Negishi (Aus J Chem 2004, 57(1), 107), followed by deprotection steps.

Scheme 8

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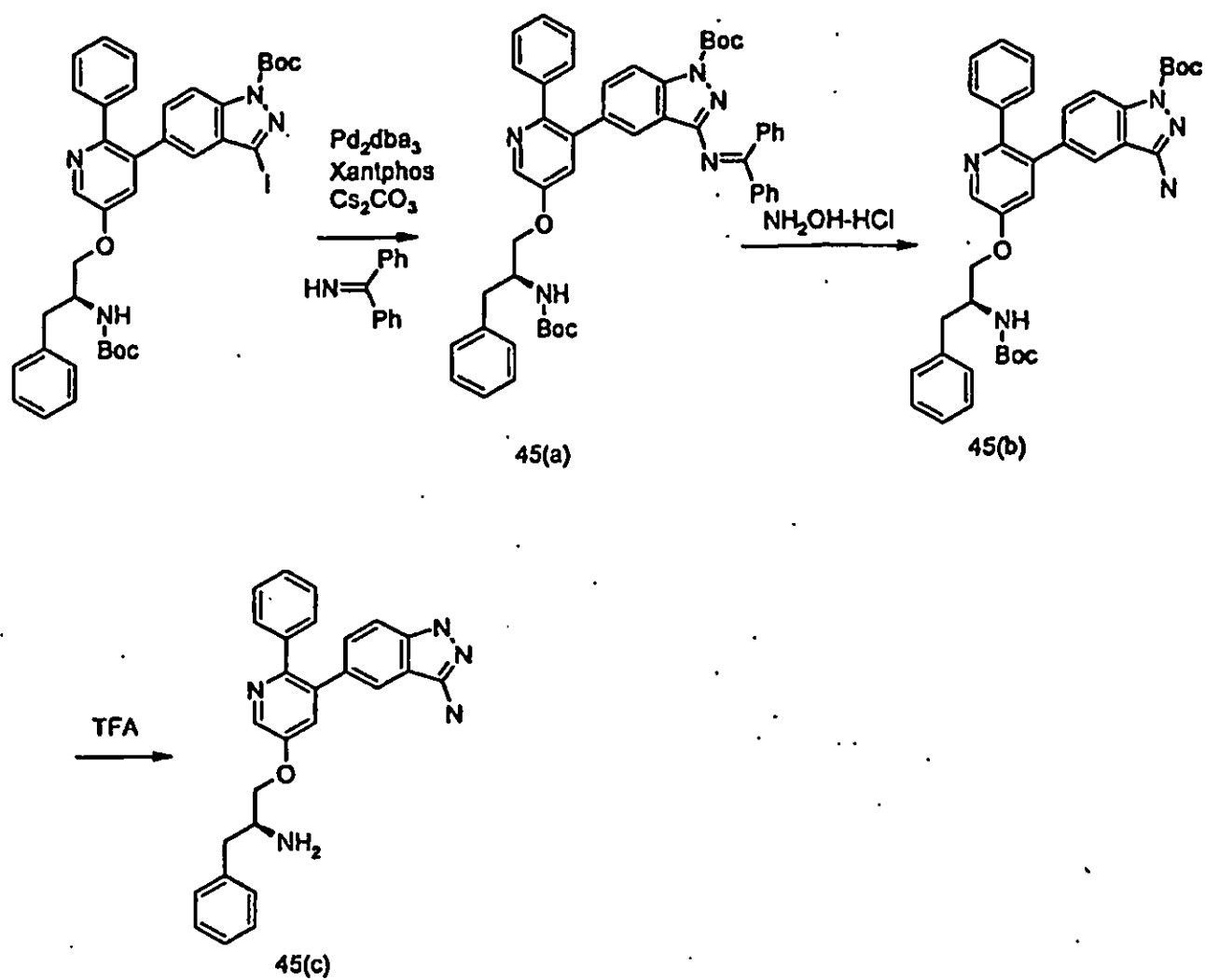
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Scheme 9

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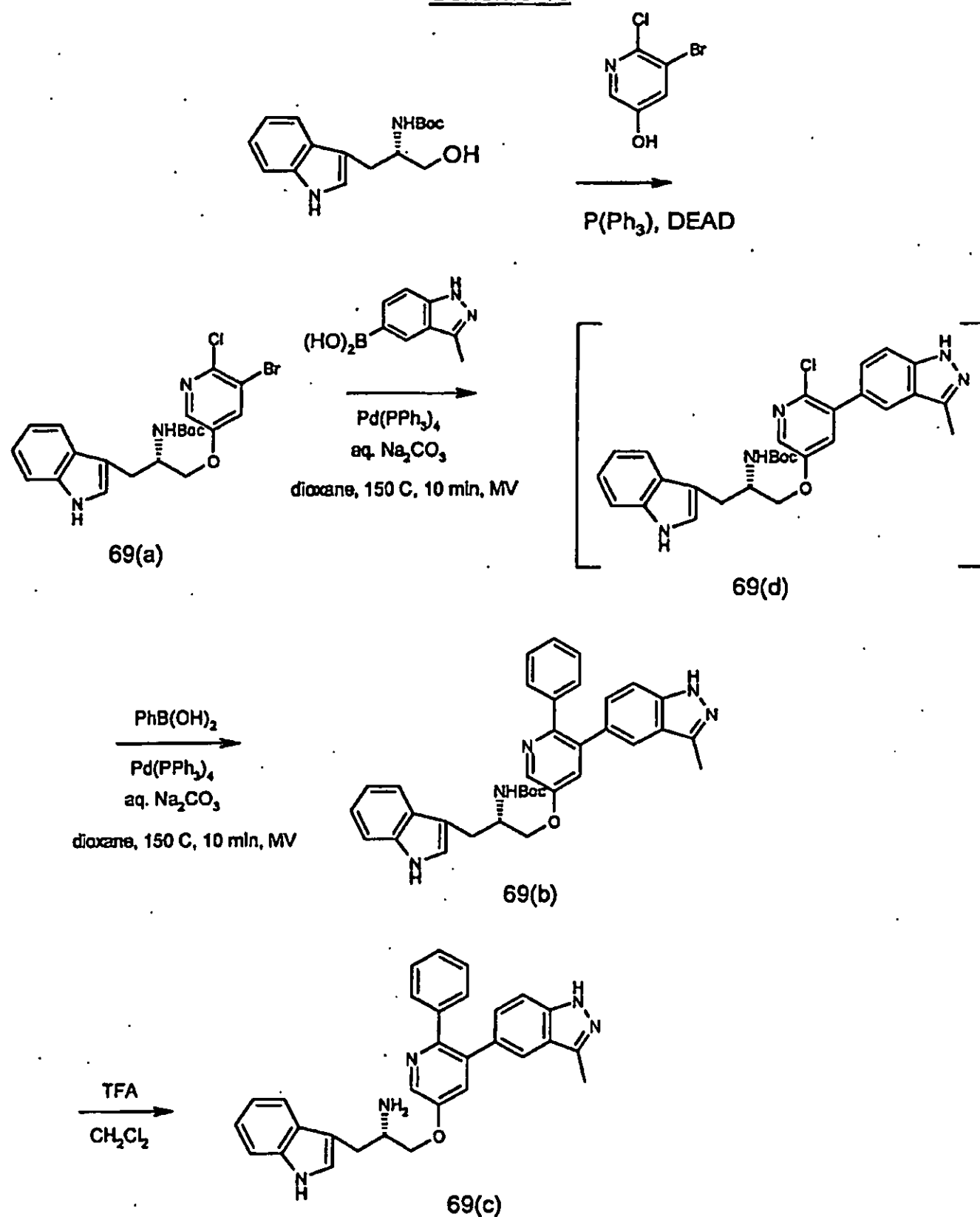


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Ethers such as 69(a) can be prepared by Mitsunobu coupling with hydroxy-pyridines such as 2-chloro-3-bromo-5-hydroxy-pyridine and alcohols such as Boc-(2S)-2-amino-3-(3-indole)-1-propanol (Scheme 10). Then, using Pd-mediated cross coupling methods and deprotection steps, desired compounds such as 69(b) can be prepared.

Scheme 10



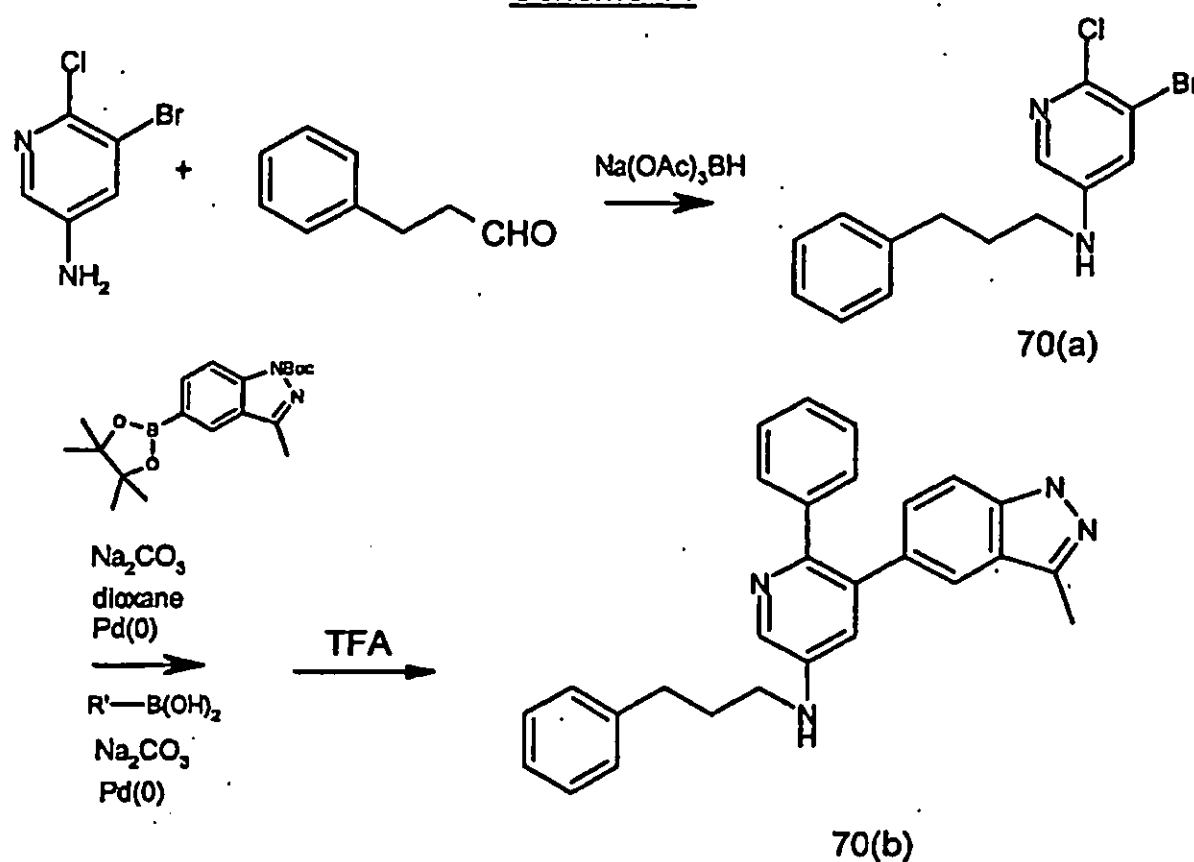
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Amines such as 70(b) can be prepared by reductive amination using aldehydes such as 3-phenyl-propanal and a reducing agent such as triacetoxyborohydride (Scheme 11).

5

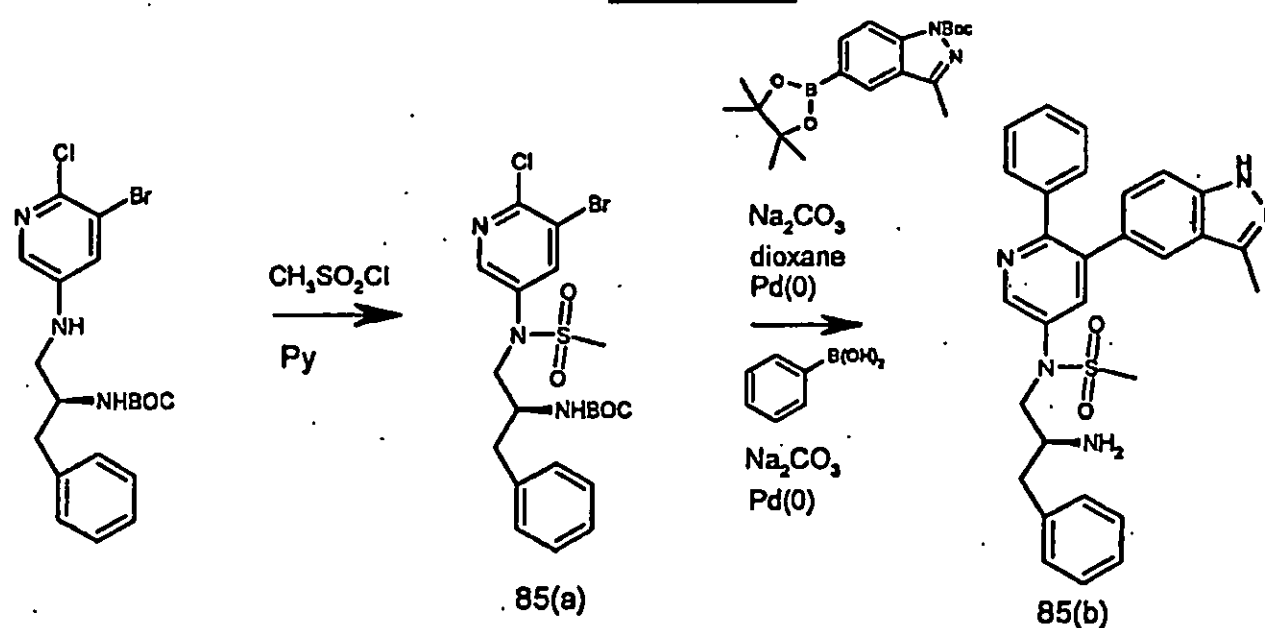
Scheme 11



The amine may be further functionalized with sulfonylating agents such as methylsulfonyl chloride (Scheme 12), followed by Pd-mediated cross coupling and deprotection steps.

10

Scheme 12

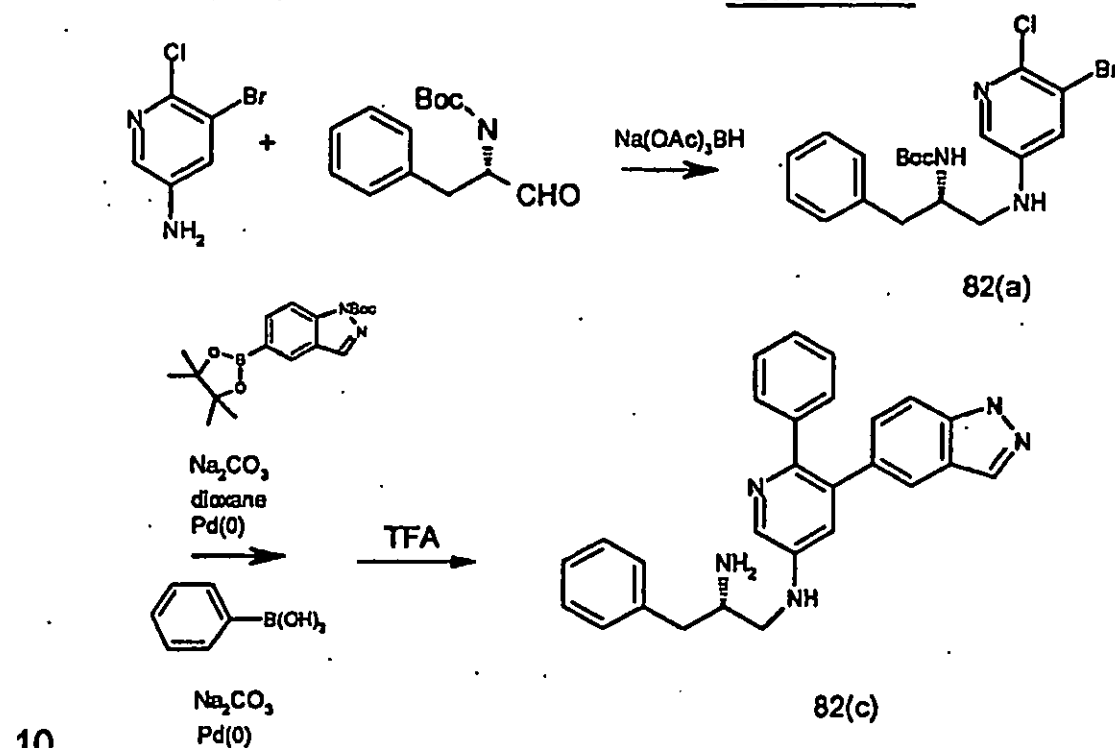


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- Amines such as 82(c) may also be prepared by reductive amination between amines such as 2-chloro-3-bromo-5-amino-pyridine and aldehydes such as 1,1-dimethylethyl [(1*S*)-1-formyl-2-(1*H*-indol-3-yl)ethyl]carbamate with reducing agents such as sodium triacetoxyborohydride or sodium borohydride, followed by
- 5 Pd-mediated cross coupling reactions using the methods of Suzuki, Stille, Buchwald, or Negishi, and final deprotection steps such as Boc removal with trifluoroacetic acid or HCl (Scheme 13).

Scheme 13

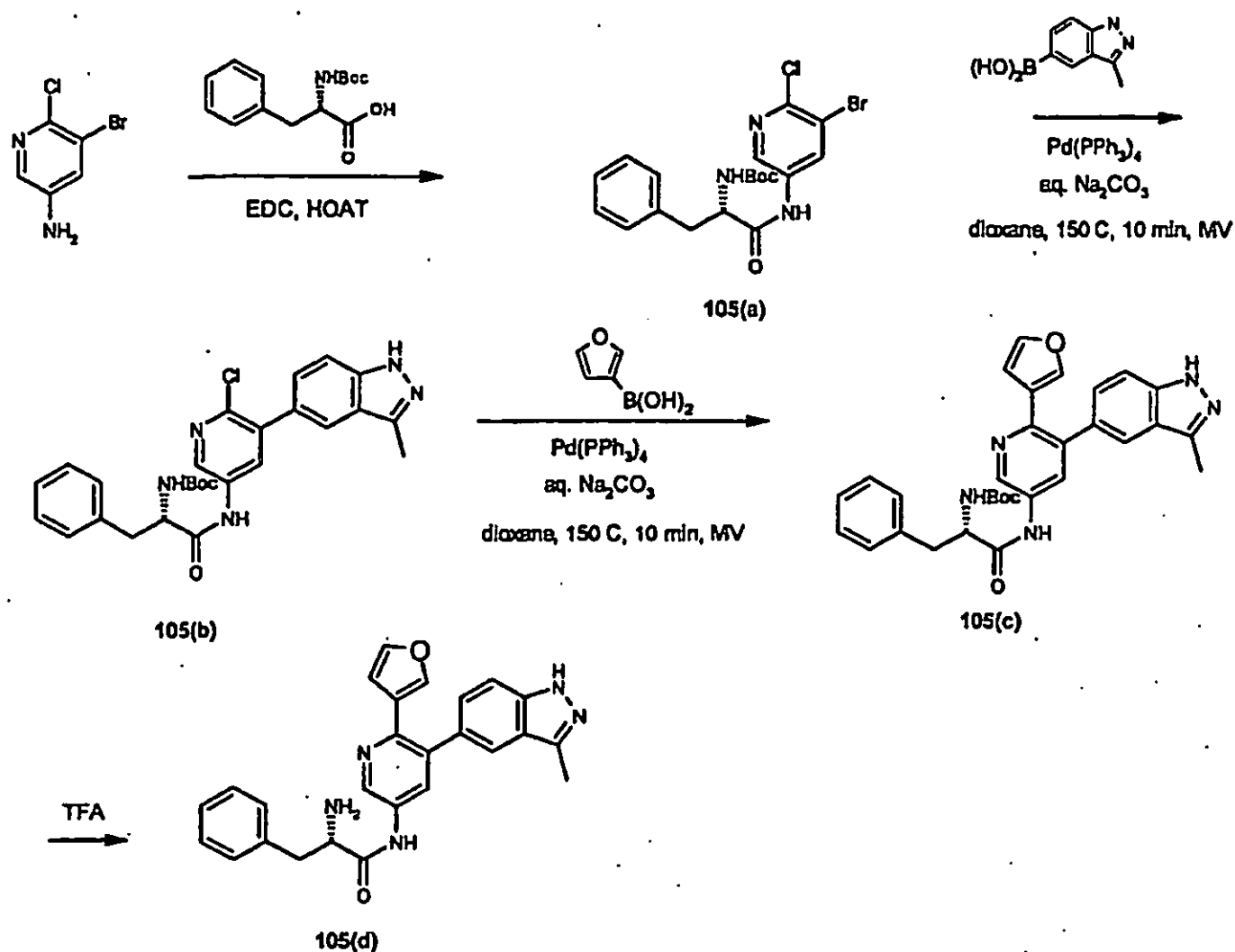


- Amides such as 105(d) can be prepared by amide forming coupling reactions between carboxylic acids and amines such as 2-chloro-3-bromo-5-amino-pyridine using a coupling reagent such as EDC (1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) /HOAT (1-Hydroxy-7-azabenzotriazole), DCC (1,3-Dicyclohexylcarbodiimide), DIC (1,3-Diisopropylcarbodiimide), HBTU (O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate), HATU (O-7-Azabenzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate), etc. (Scheme 14).
- 15
- 20

Scheme 14

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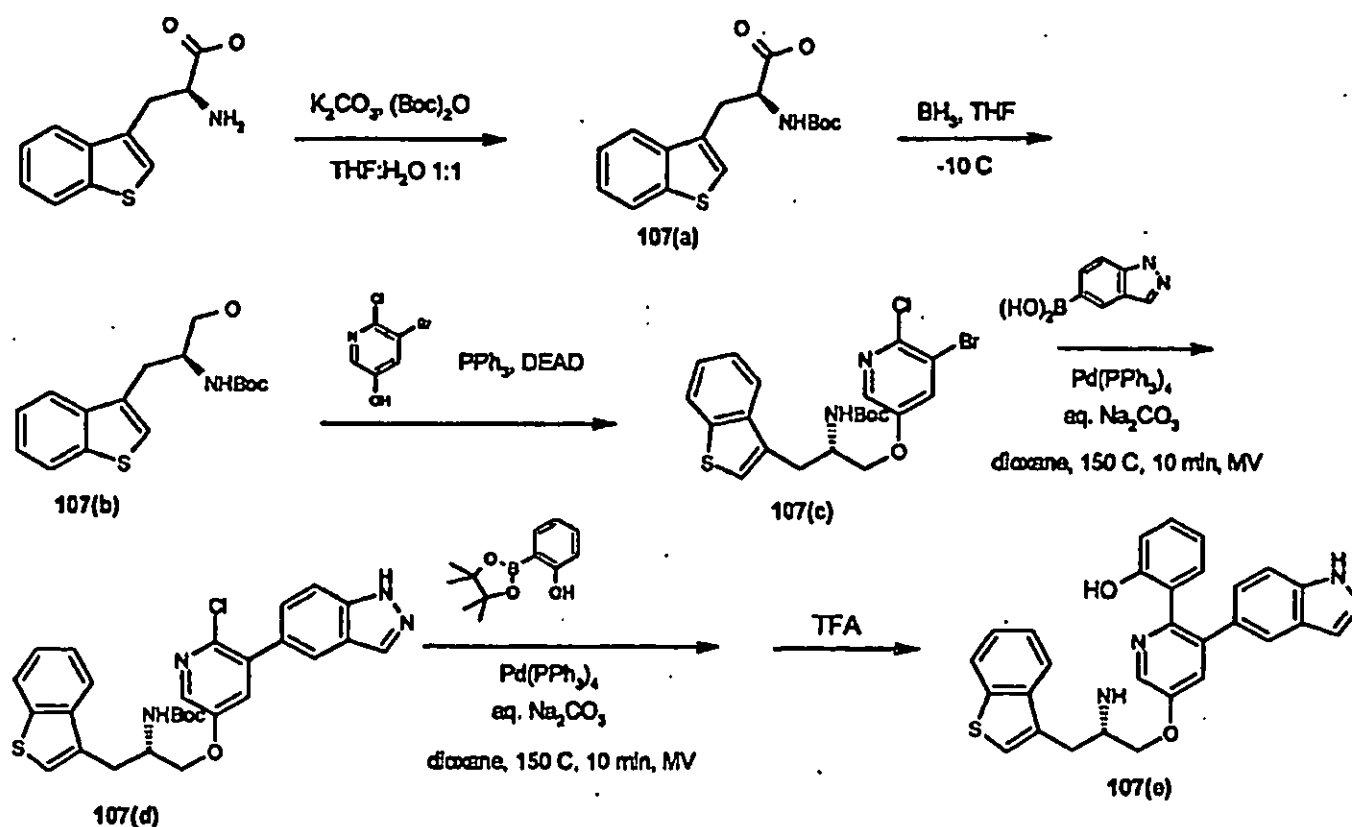


- Ethers such as 107(b) can be prepared by Mitsunobu coupling with hydroxy-pyridines such as 2-chloro-3-bromo-5-hydroxy-pyridine and alcohols such as Boc-(2S)-2-amino-3-(3-thiophene)-1-propanol (Scheme 15). Then, using the methods
- 5 described in Scheme 1, the desired compounds can be prepared.

Scheme 15

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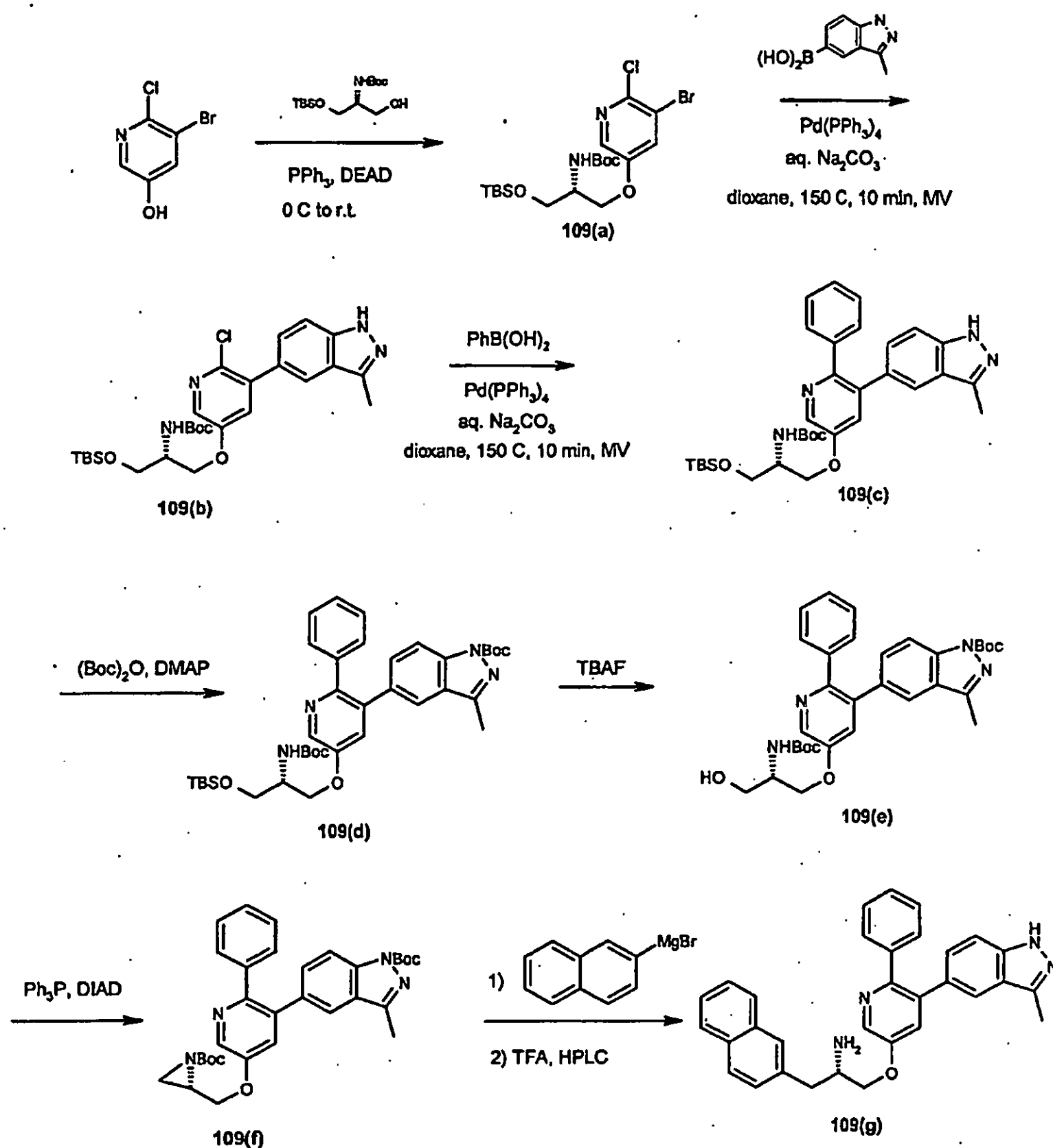
- Ethers such as 109(b) can be prepared by Mitsunobu coupling with hydroxy-pyridines such as 2-chloro-3-bromo-5-hydroxy-pyridine and alcohols such as Boc-
- 5 (2S)-2-amino-3-(t-butyl-dimethylsilyloxy)-1-propanol (Scheme 16). Then, using the Pd-mediated cross coupling reactions, the pyridine can be substituted.
- Deprotection of the silyl ether protecting group with a fluoride such as tetrabutylammonium fluoride and Mitsunobu cyclization reaction forms the
- 10 Intermediate Boc-aziridine 109(f). The aziridine then reacts with Grignard reagents such as 2-naphthyl magnesium bromide to form the 3-aryl substituted-2-Boc-amino-propyl ethers, which are then deprotected to provide desired compounds such as as 109(g).

Scheme 16

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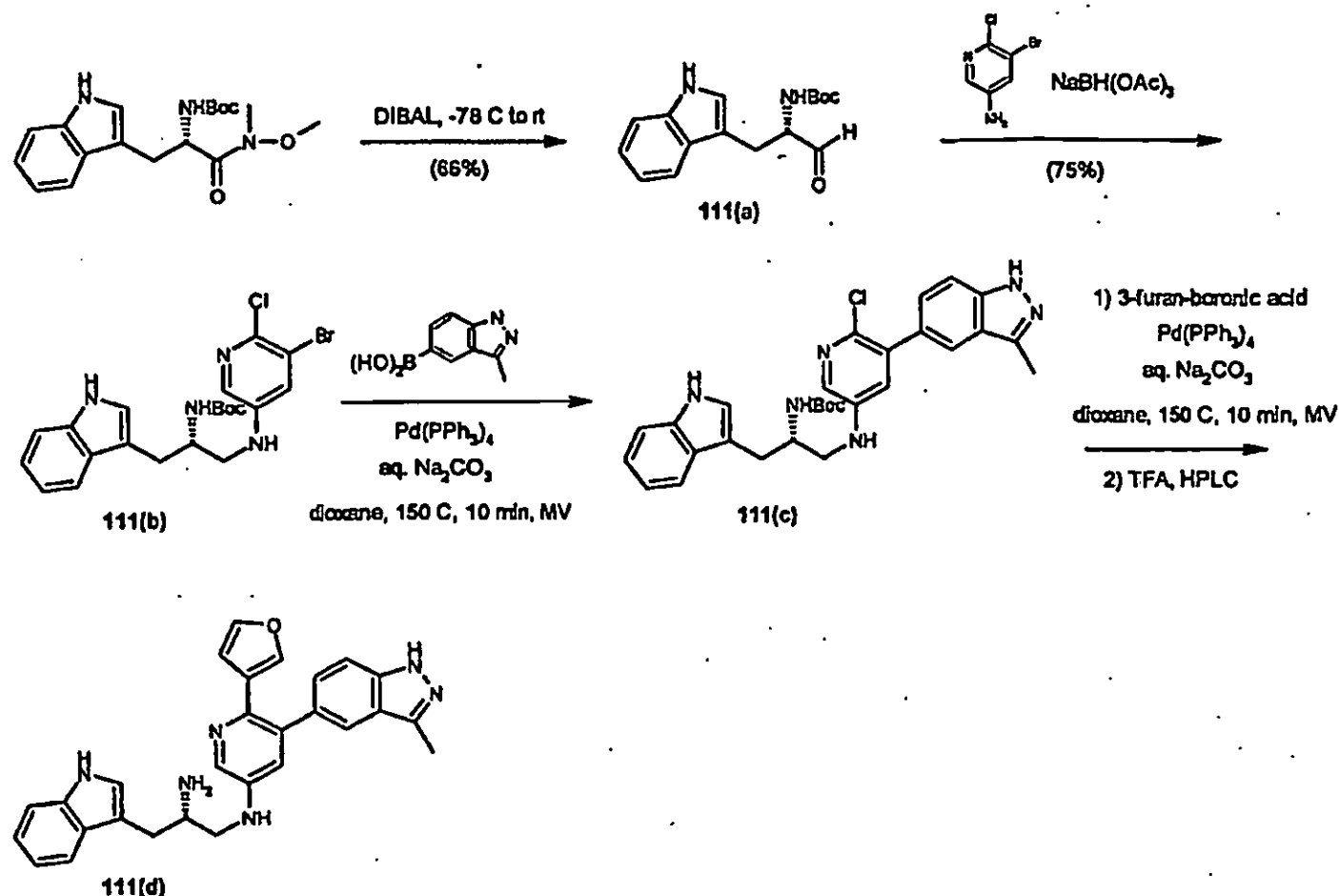
Amines such as 111(b) can be prepared by reductive amination using aldehydes such as Boc-(2S)-2-amino-3-(3-indole)-1-propanal and a reducing agent such as triacetoxyborohydride (Scheme 17). Then, Pd-mediated cross coupling reactions and standard deprotection steps provide the desired compounds such as 111(d).

Scheme 17

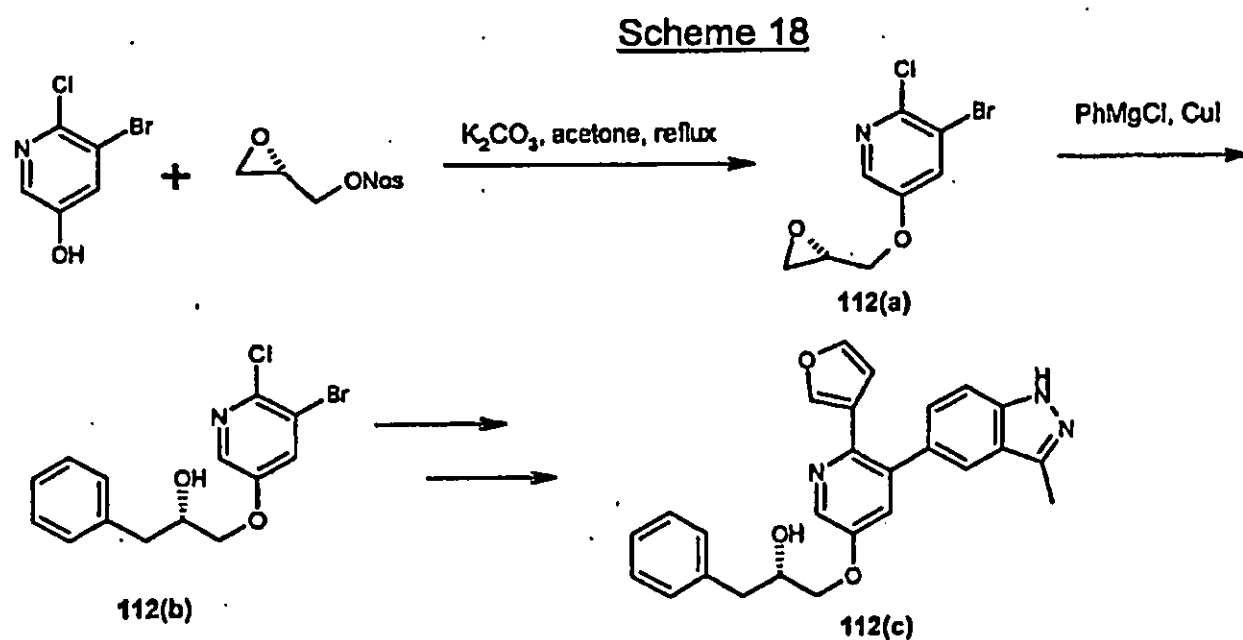
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- Ethers such as 112(a) can also be prepared by alkylation with (2S)-oxiranylmethyl 2-nitrobenzenesulfonate (Scheme 18). The epoxide can then be opened by Grignard reagents such as phenyl magnesium chloride to provide alcohol intermediates such as 112(b). Pd-mediated cross-coupling reactions and deprotection steps provide the desired compounds such as 112(c).



10

1H-thieno[3,2-c]pyrazole intermediates 121(c) and (d) can be prepared by cyclization of Boc-protected hydrazone 121(b) (Scheme 19). Stannylation and Pd-mediated cross coupling to halogenated pyridine intermediate 69(a), followed by a

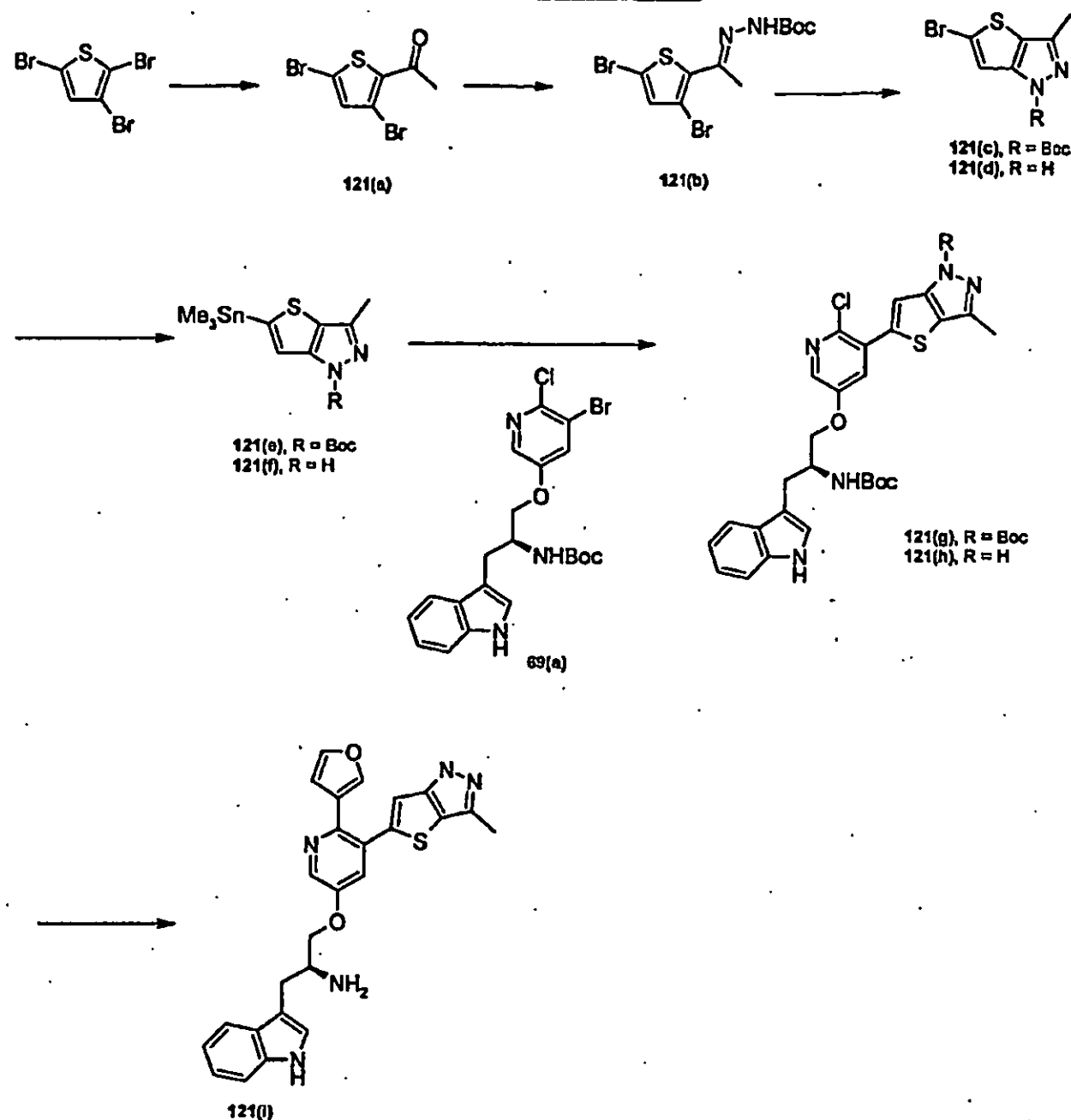
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second Pd-mediated cross coupling step and deprotection steps provide the desired compounds such as 121(i).

Scheme 19



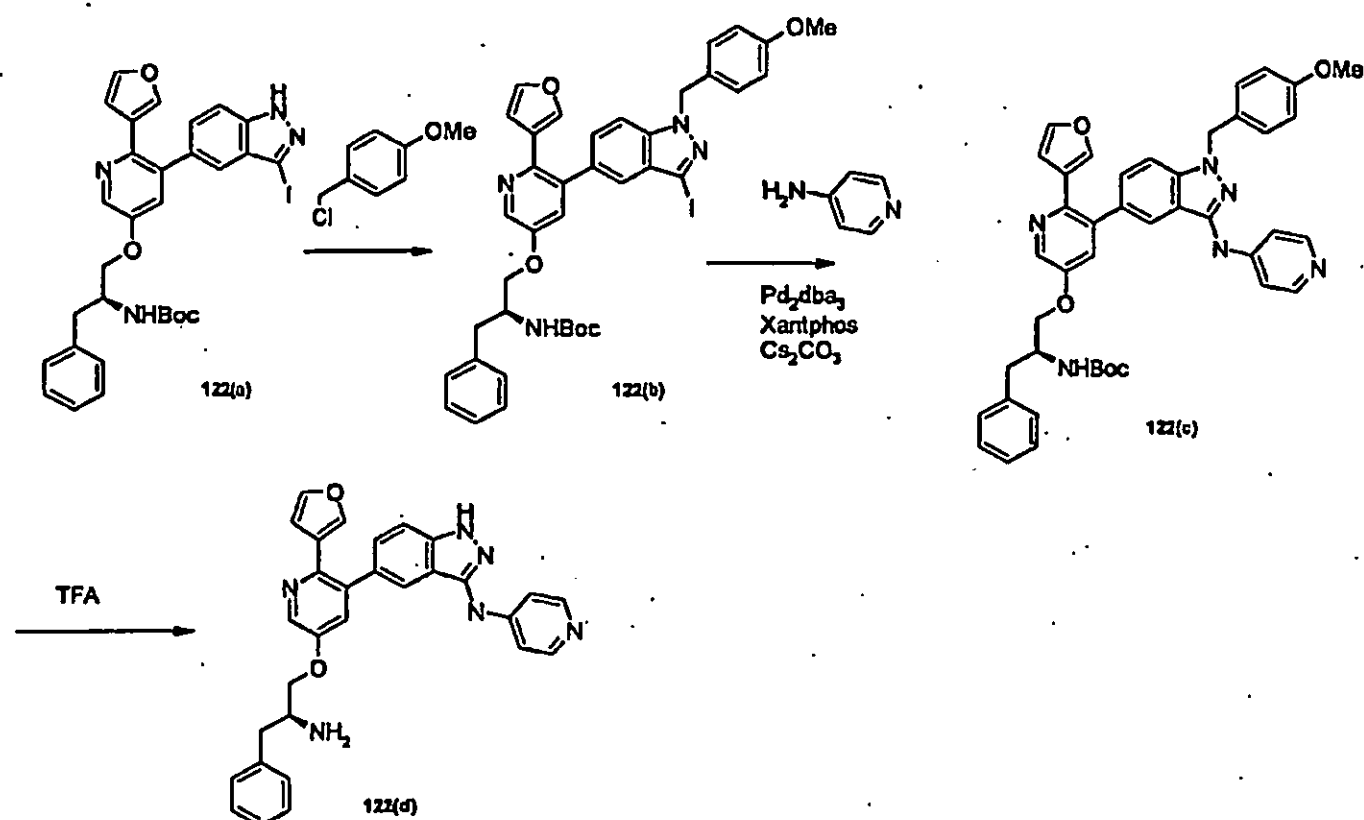
- 5 Palladium-mediated Buchwald/ Hartwig reactions can be used to functional the 3-position of indazoles such as 122(b) to introduce substituted amines such as 4-amino-pyridine (Schemes 20) or amides such as benzamide (Scheme 21, JOC, 2004, 69(17), 5578-5587). Following deprotection steps, desired compounds such as 122(d) or 123(b) can be prepared.

10

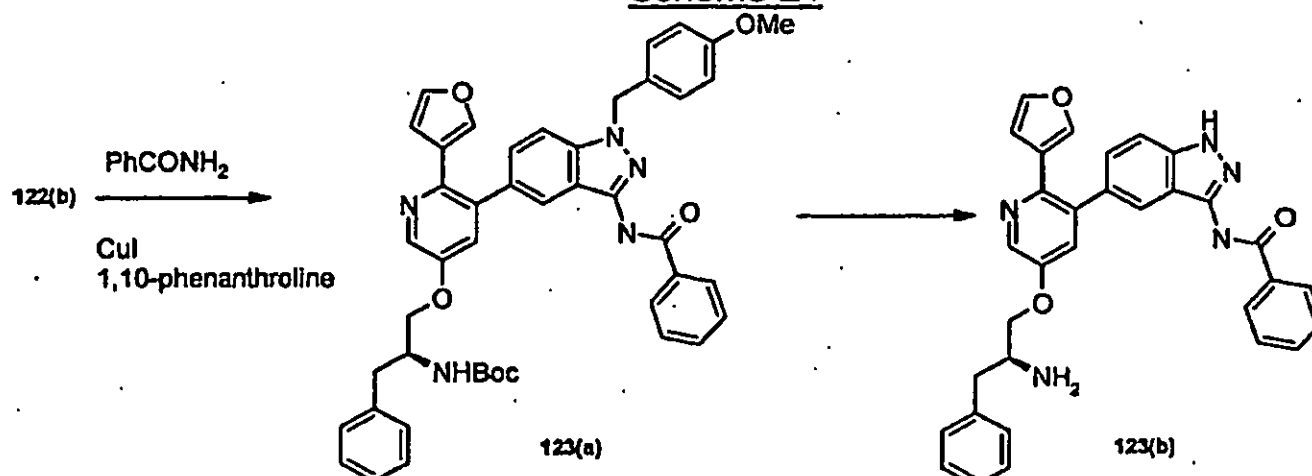
Scheme 20

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Scheme 21



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3-Ethyl-indazole intermediate 133(d) can be prepared by addition of ethyl magnesium bromide to 5-bromo-2-fluoro-benzaldehyde to form alcohol intermediate 133(a), followed by oxidation with an oxidant such as Dess-Martin periodinane to produce ketone 133(b), hydrazone formation, and cyclization (Scheme 22).

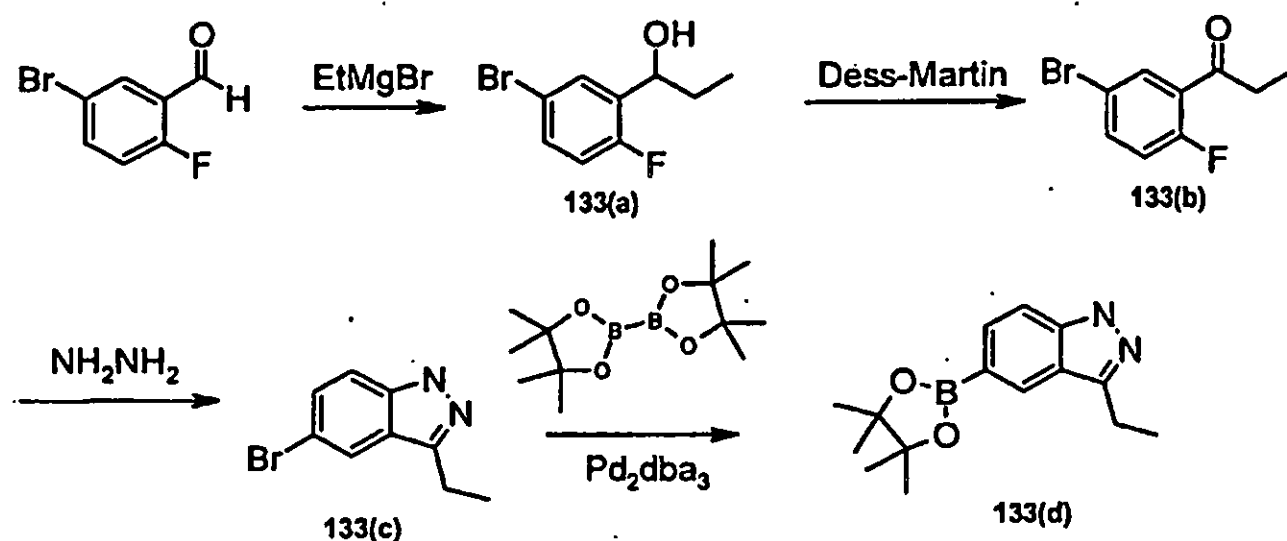
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Scheme 22

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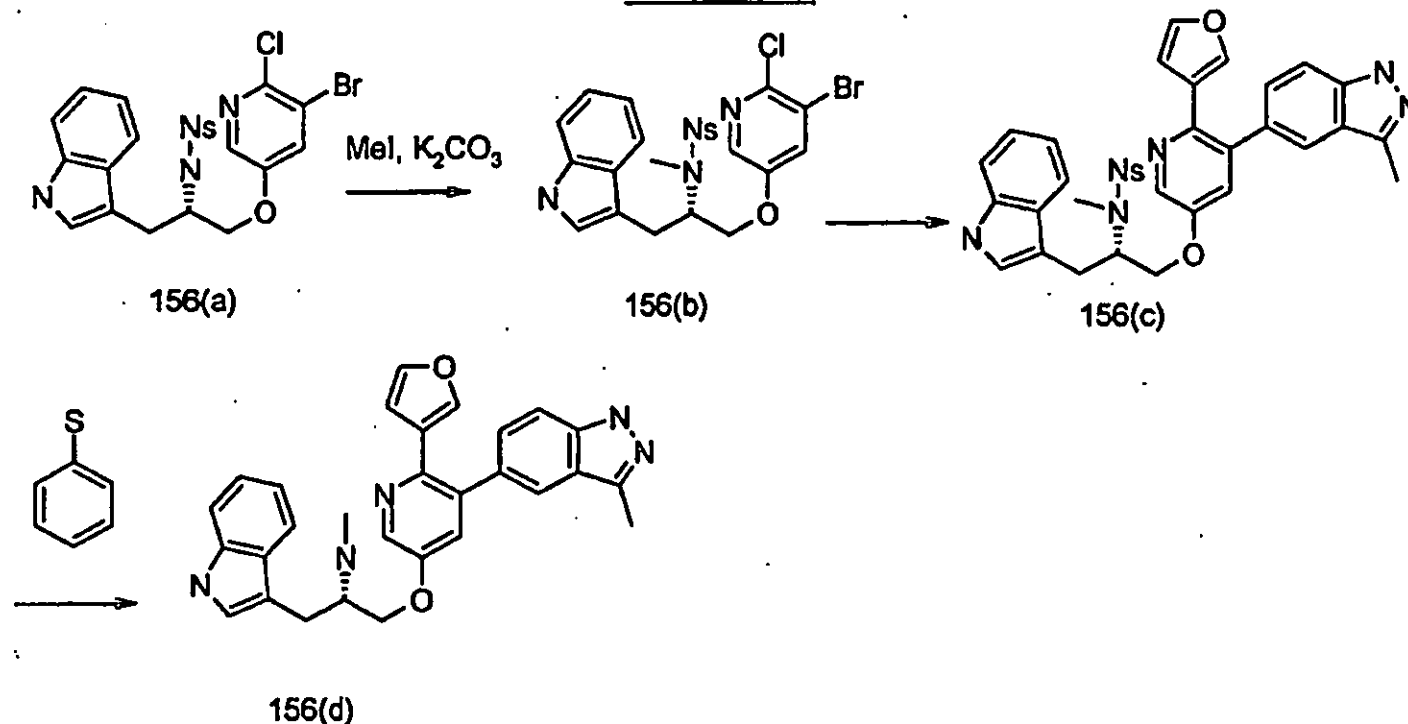
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- 5 Methylation of the nitrogen can be conducted by alkylation of nosyl-protected amine 156(a) using methyl iodide and base (Scheme 23). Pd-mediated cross-coupling reactions followed by deprotection of the nosyl group with a mercaptan such as phenyl mercaptan provides the desired compounds such as 156(d).

Scheme 23



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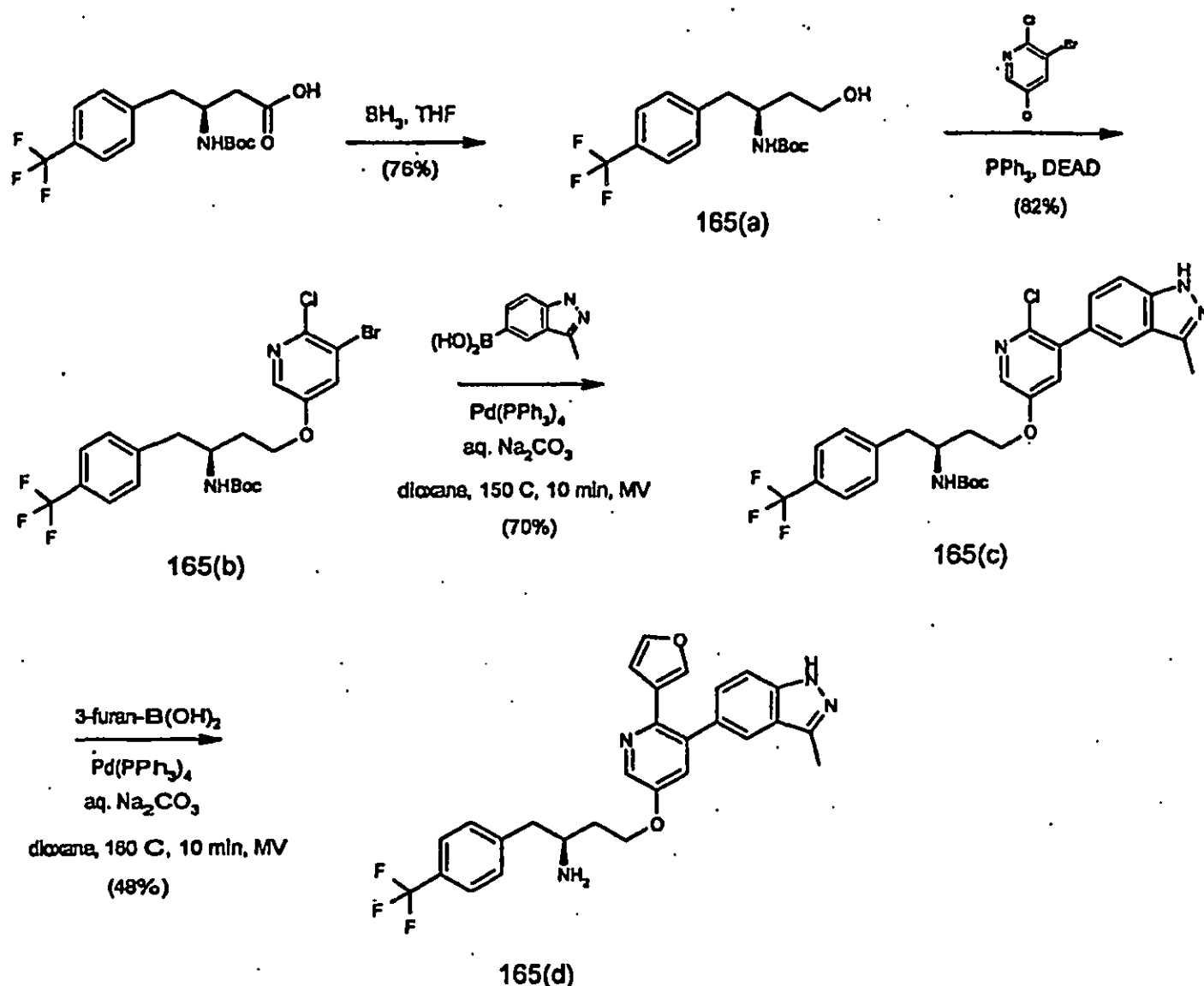
- 15 Ethers such as 165(b) can be prepared by Mitsunobu coupling with hydroxy-pyridines such as 2-chloro-3-bromo-5-hydroxy-pyridine and alcohols such as Boc-(2S)-3-amino-4-(4-trifluoromethylphenyl)-1-butanol (Scheme 24). Then, using Pd-mediated cross coupling methods and deprotection steps, desired compounds such as 165(d) can be prepared.

Scheme 24

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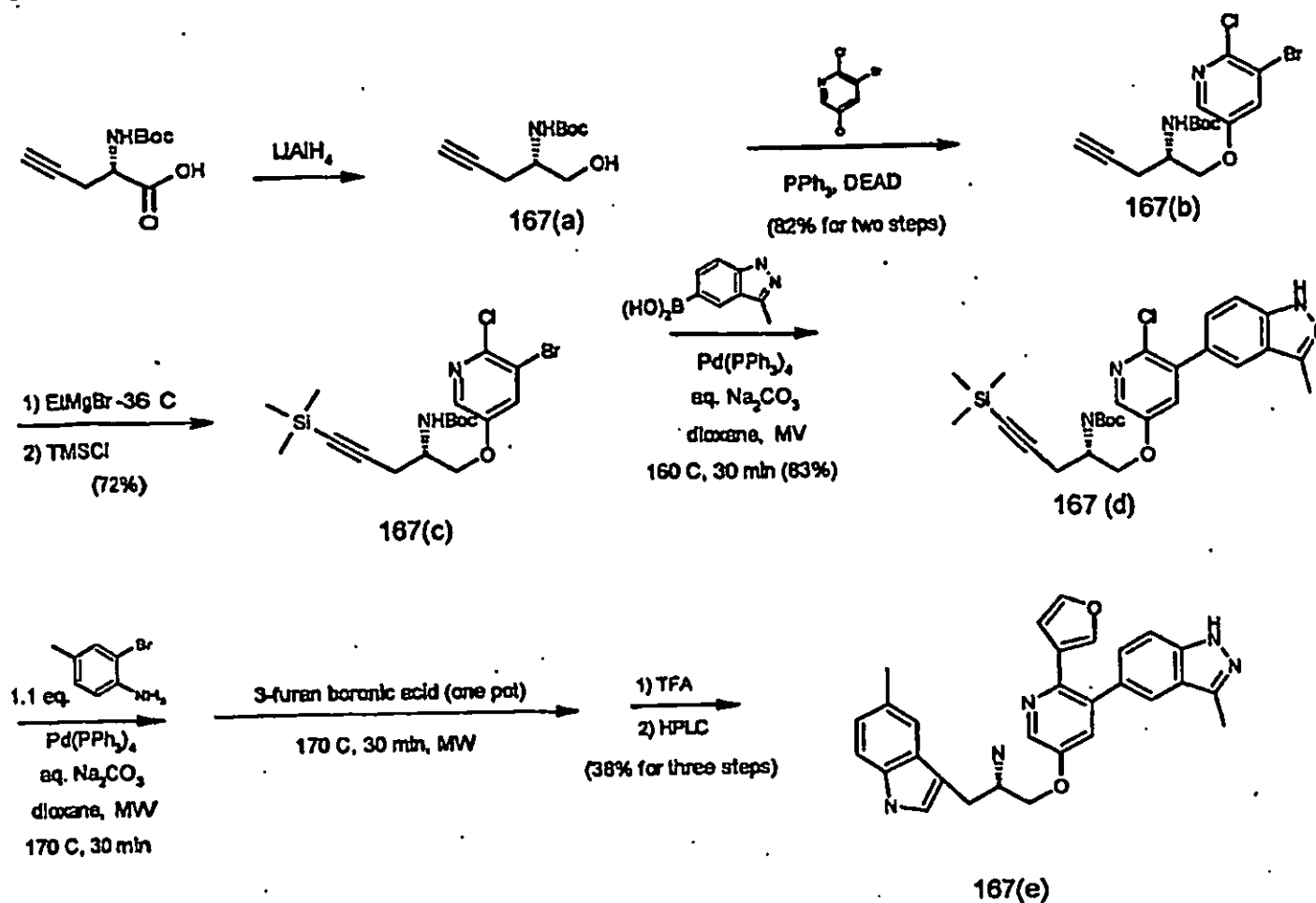


5 Ether intermediate 167(b) can be prepared by Mitsunobu coupling with hydroxy-pyridines such as 2-chloro-3-bromo-5-hydroxy-pyridine and alcohols such as Boc-(2S)-2-amino-pent-4-yn-1-ol (Scheme 25 and Scheme 26). Silylation of the alkyne followed by a Pd-mediated cross coupling reaction provides intermediate 167(d), which is then subjected to the indole formation reaction of R. Larock (JOC 1998, 63(22); 7652-7662), followed by a second Pd-mediated cross coupling reaction, and deprotection steps to provide desired compounds such as 167(e).

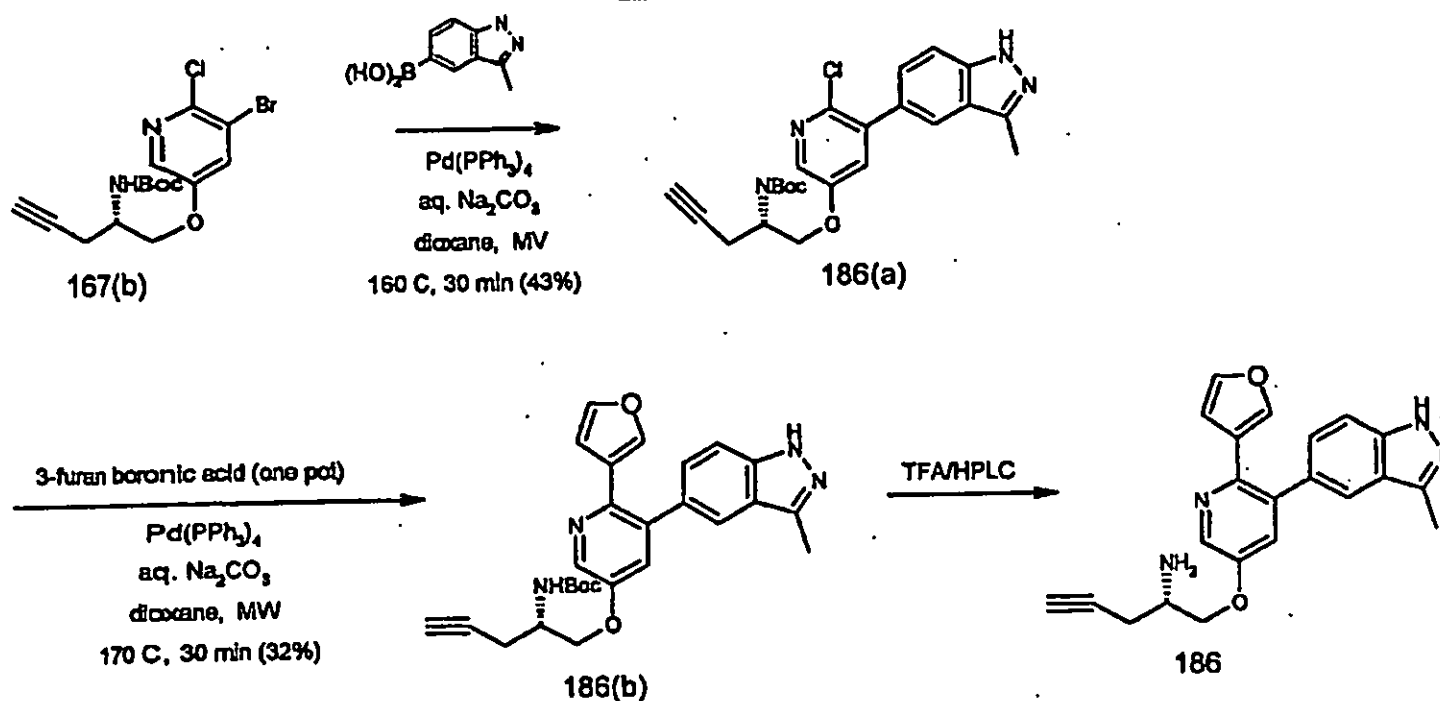
Scheme 25

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Scheme 26



5

The 4-aza-indazole intermediate 169(b) is prepared by cyclization of hydrazone generated from 1-(3-fluoro-2-pyridinyl)ethanone (Scheme 27). N-oxidation of the pyridine followed by treatment with phosphorus oxychloride provides chloro-4-aza-indazole intermediate 169(e).

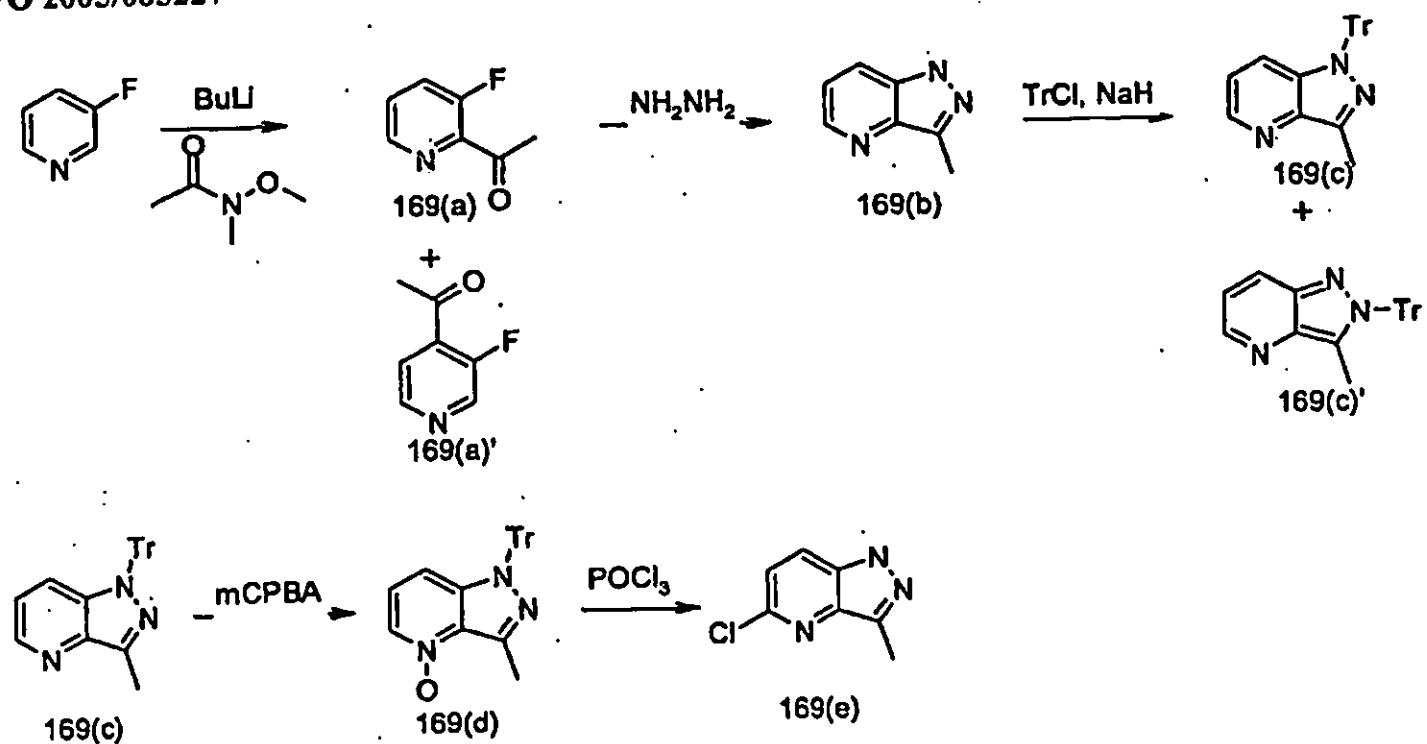
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Scheme 27

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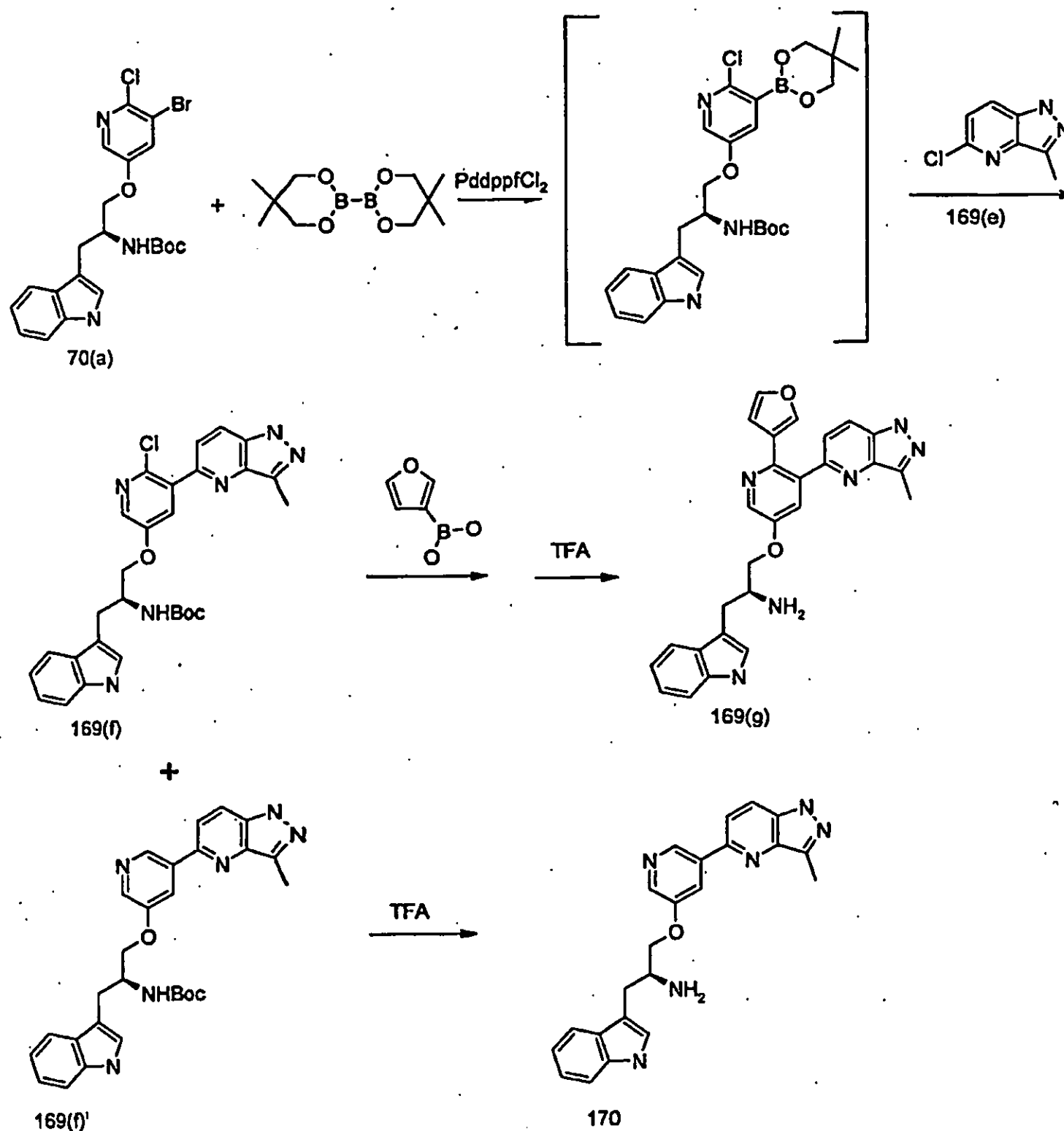


- 5 Halogenated pyridine intermediate 70(a) is selectively borylated and coupled to 169(e) to produce the 3-substituted pyridine intermediate 169(f) (Scheme 28). A second Pd-mediated cross coupling reaction, and deprotection step provide desired compounds such as 170.

Scheme 28

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Zinc cyanide addition to 3-iodo-indazole intermediate 122(b), followed by treatment with trifluoroacetic acid provides 3-nitrile 171(b) and 3-amide 172

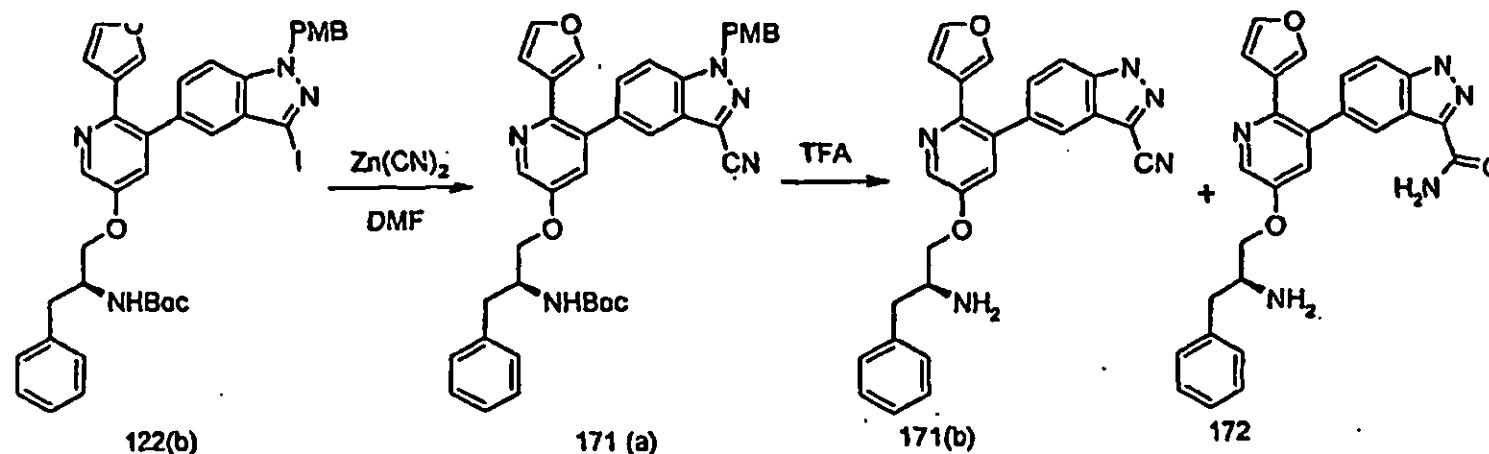
5 (Scheme 29).

Scheme 29

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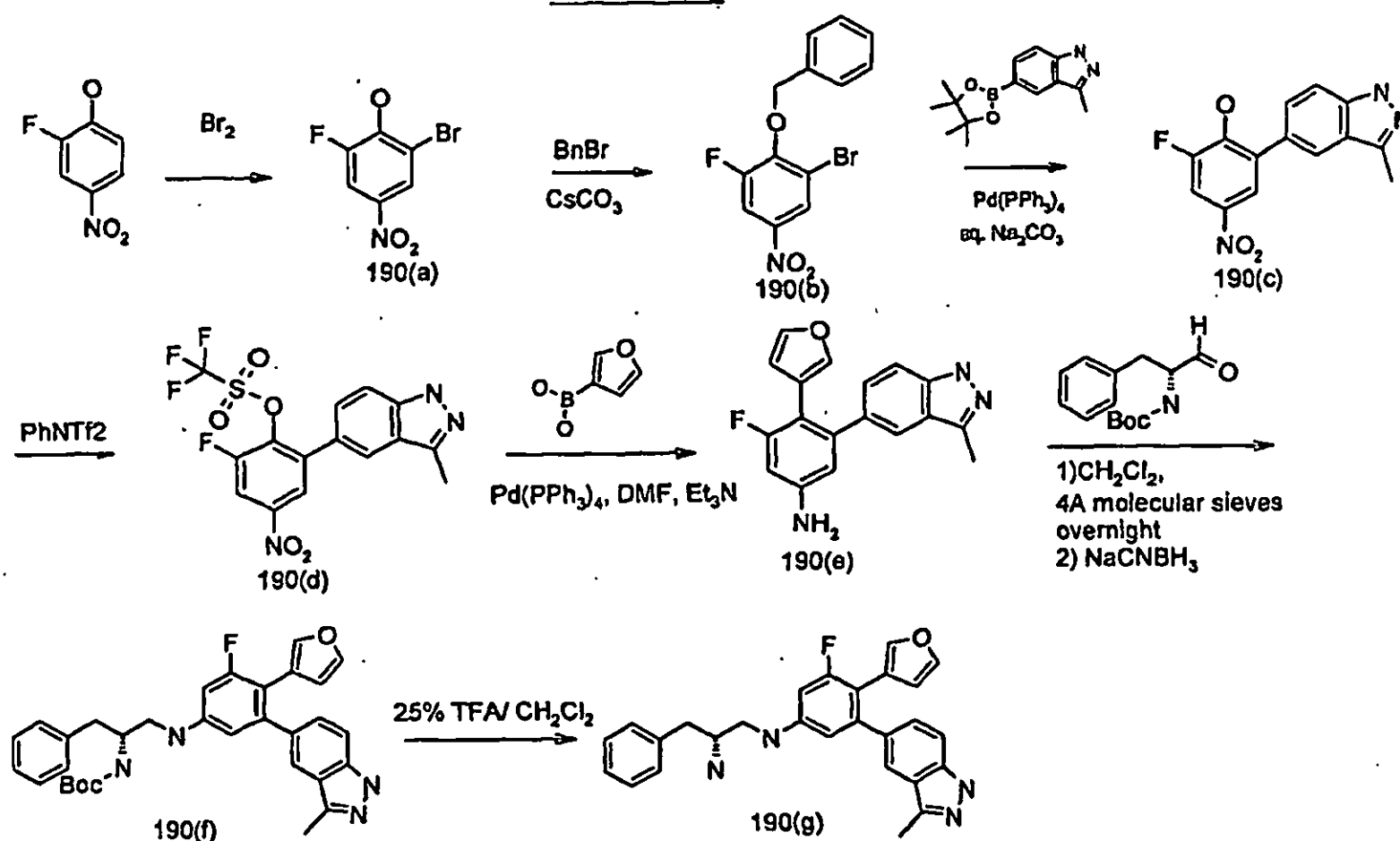
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- Nitro phenol intermediate 190(a) can be prepared by selective bromination of 2-fluoro-4-nitro-phenol. Protection of the phenol as a benzyl ether followed by Pd-mediated cross coupling reaction provides intermediate 190(c). The benzyl group is removed under the Suzuki reaction conditions. Triflate formation with N-phenyltriflimide followed by a second Pd-mediated cross-coupling reaction provides aniline intermediate 190(e). Reduction of the nitro group occurs under the Suzuki reaction conditions. Reductive amination and final deprotection provides desired compounds such as 190(g).

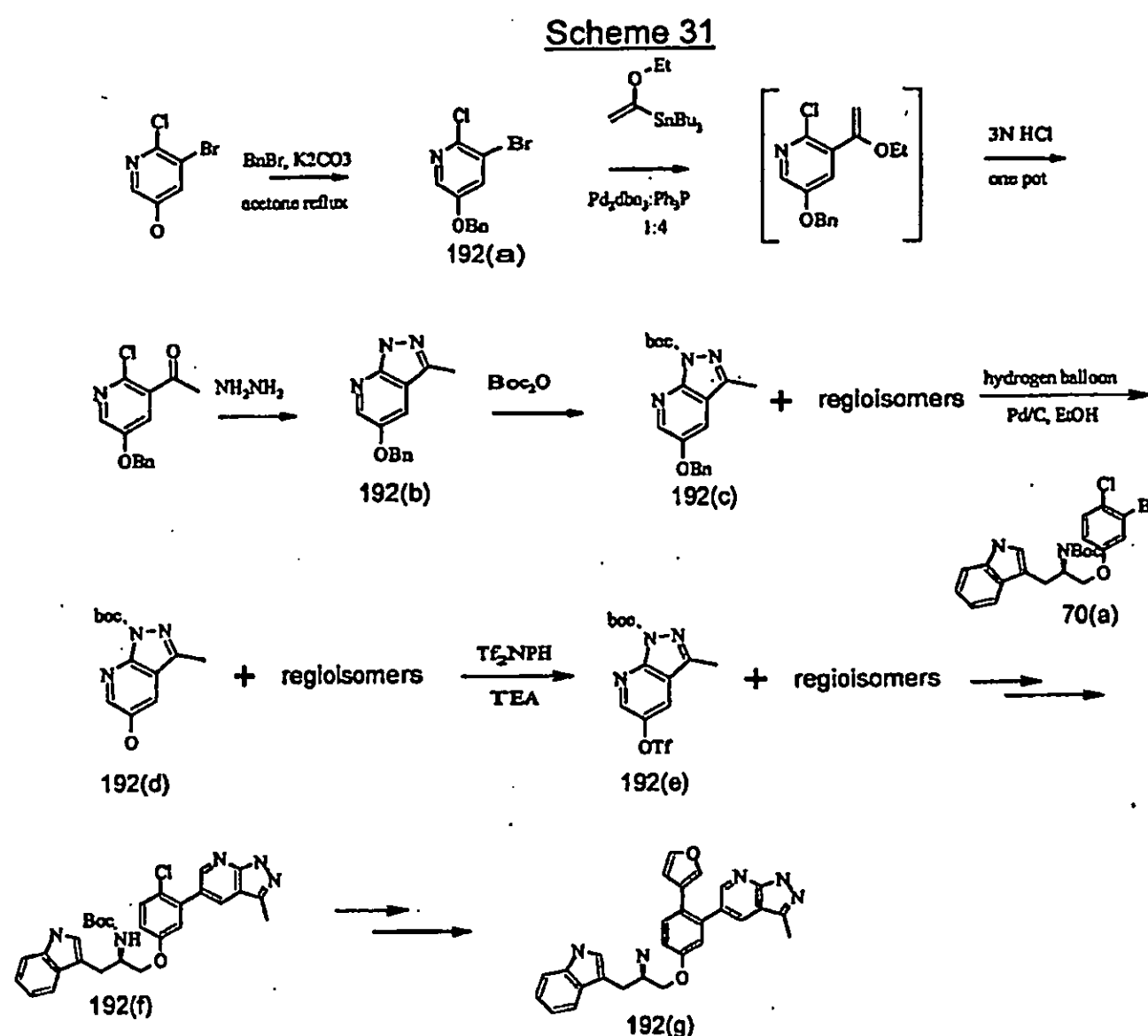
Scheme 30



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Stille coupling with [1-(ethoxy)ethenyl](triethyl)stannane and halogenated pyridine intermediate 192(a), followed by treatment to dilute acid, then hydrazine provides 7-aza-indazole intermediate 192(b). Deprotection of the phenol, triflate formation, and boronic acid formation, followed by Pd-mediated cross coupling reactions to the halogenated pyridine intermediate 70(a) and deprotection steps provide desired compounds such as 192(g).



10

By the term "co-administering" and derivatives thereof as used herein is meant either simultaneous administration or any manner of separate sequential administration of an AKT inhibiting compound, as described herein, and a further active ingredient or ingredients, known to be useful in the treatment of cancer, including chemotherapy and radiation treatment, or to be useful in the treatment of arthritis. The term further active ingredient or ingredients, as used herein, includes any compound or therapeutic agent known to or that demonstrates advantageous properties when administered to a patient in need of treatment for cancer or arthritis. Preferably, if the administration is not simultaneous, the compounds are

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but not limited to, intravenous, intramuscular, oral, subcutaneous, intradermal, and parenteral.

The pharmaceutically active compounds of the present invention are incorporated into convenient dosage forms such as capsules, tablets, or injectable preparations. Solid or liquid pharmaceutical carriers are employed. Solid carriers include, starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid;. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but, preferably, will be from about 25 mg to about 1 g per dosage unit. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampoule, or an aqueous or nonaqueous liquid suspension.

The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral or parenteral products.

Doses of the presently invented pharmaceutically active compounds in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity preferably selected from the range of 0.001 - 100 mg/kg of active compound, preferably 0.001 - 50 mg/kg. When treating a human patient in need of an Akt inhibitor, the selected dose is administered preferably from 1-6 times daily, orally or parenterally. Preferred forms of parenteral administration include topically, rectally, transdermally, by injection and continuously by infusion. Oral dosage units for human administration preferably contain from 0.05 to 3500 mg of active compound. Oral administration, which uses lower dosages is preferred. Parenteral administration, at high dosages, however, also can be used when safe and convenient for the patient.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular Akt inhibitor in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular patient being treated will result in a need to adjust dosages, including patient age, weight, diet, and time of administration.

The method of this invention of inducing Akt inhibitory activity in mammals, including humans, comprises administering to a subject in need of such activity an

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effective Akt inhibiting amount of a pharmaceutically active compound of the present invention.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use as an Akt inhibitor.

5 The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in therapy.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in treating cancer.

10 The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in treating arthritis.

The invention also provides for a pharmaceutical composition for use as an Akt inhibitor which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

15 The invention also provides for a pharmaceutical composition for use in the treatment of cancer which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

The invention also provides for a pharmaceutical composition for use in treating arthritis which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

20 No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

In addition, the pharmaceutically active compounds of the present invention can be co-administered with further active ingredients, such as other compounds known to treat cancer or arthritis, or compounds known to have utility when used in
25 combination with an Akt inhibitor.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative and
30 not a limitation of the scope of the present invention in any way.

Experimental Details

The compounds of Examples 1 to 222 are readily made according to
35 Schemes 1 to 31 or by analogous methods.

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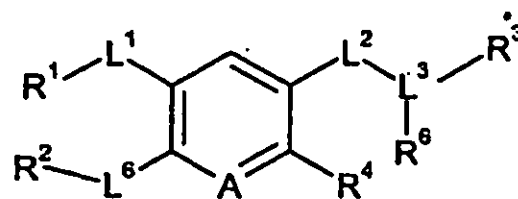
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What is claimed is:

1. A compound of Formula (I):

5



(I)

wherein:

- 10 A is selected from: nitrogen, -C-halogen and -CH;

L¹ is selected from the group consisting of a bond, -O-, -N(R⁵)-, -S-, -S(O)-, -S(O₂)-, alkyl, and -N(R⁵)C(O)-;

- 15 L² is selected from the group consisting of a bond, -O-, heterocycle, -N(R⁵)-, -N(R⁵)C(O)-, -S-, -S(O)-, -S(O₂)-, and -C(O)N(R⁵)-;

- 20 L³ is alkyl, wherein the alkyl is optionally substituted with one or two substituents independently selected from the group consisting of amino, methylamino, dimethylamino, oxo, and hydroxy;

L⁶ is selected from the group consisting of a bond, -O-, -N(R⁵)-, -S-, -S(O)-, -S(O₂)-, alkyl, and -N(R⁵)C(O)-;

- 25 R¹ is selected from the group consisting of aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocycle and substituted heterocycle;

- 30 R² is selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, and a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally containing one or more heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one

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or more substituents selected from the group consisting of: alkyl, substituted alkyl, trifluoroalkoxy, C₁-C₁₂aryl, aryloxy, -O(CH₂)_qR³¹, -NHC(O)-NHR⁴¹, -C(O)R⁴³, substituted cycloalkyl, substituted C₁-C₁₂aryl, heterocycle, substituted heterocycle, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen, -C(O)OR⁷, -C(O)NR⁸R⁹, -S(O)₂NR⁸R⁹, and -S(O)_nR⁷,
 5 where n is 0-2, q is 1-6,
 R⁷ is hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl,
 R³¹ is C₁-C₁₂aryl, cycloalkyl and heterocycle, each of which is optionally
 10 substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, acyloxy, amino, methylamino, dimethylamino, N-acylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl,
 R⁴¹ is selected from hydrogen, C₁-C₁₂aryl, cycloalkyl and heterocycle, wherein C₁-C₁₂aryl, cycloalkyl and heterocycle are optionally substituted
 15 with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, amino, methylamino, dimethylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl,
 R⁴³ is selected from C₁-C₁₂aryl, cycloalkyl and heterocycle, each of which is optionally substituted with from 1 to 4 substituents selected from:
 20 halogen, hydroxyalkyl, alkoxy, amino, methylamino, dimethylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl, and
 R⁸ and R⁹ are independently hydrogen, cycloalkyl, C₁-C₁₂aryl, substituted cycloalkyl, substituted C₁-C₁₂aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of:
 25 alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, -C(O)OR¹⁰, -S(O)_nR¹⁰, -C(O)NR¹⁰R¹¹, -S(O)₂NR¹⁰R¹¹, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, and substituted aryl,
 or R⁸ and R⁹ taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other
 30 heteroatom selected from oxygen and nitrogen, where the ring is optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,
 where R¹⁰ and R¹¹ are independently hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted cycloalkyl and substituted
 35 C₁-C₁₂aryl, and n is 0-2,
 and when L⁶ is a bond, R² can additionally be halogen;

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R³ and R⁶ are independently selected from the group consisting of hydrogen, amino, methylamino, dimethylamino, aryl, substituted aryl, heterocycle, substituted heterocycle, cycloalkyl, substituted cycloalkyl, -S-C₁-C₁₂aryl, -O-C₁-C₁₂aryl, -OalkylC₁-C₁₂aryl, aryloxy, substituted aryloxy and arylalkoxy; and

5

R⁴ is selected from the group consisting of hydrogen and halogen;

where R⁵ is selected from the group consisting of hydrogen, -S(O)₂CH₃, -S(O)₂H and alkyl;

10

provided that when,

R¹ is azaindazole, substituted azaindazole, 1H-thienopyrazole, substituted 1H-thienopyrazole, benzamide, substituted benzamide, phenylethanone, substituted phenylethanone, thiophene, substituted thiophene, furan or substituted

15

furan, R² may additionally be hydrogen;

further provided that when

R¹ is isoquinoline,

20

R² is not furyl or alkyl.

2. A pharmaceutically acceptable salt, hydrate, solvate or pro-drug of a compound of Formula (I), as described in claim 1,

25

3. The compound of Formula (I), as claimed in claim 1, wherein

A is selected from: nitrogen, -C-halogen and -CH;

30

L¹ is selected from the group consisting of a bond, -O-, -N(R⁵)-, -S-, -S(O)-, -S(O₂)-, alkyl, and -N(R⁵)C(O)-;

L² is selected from the group consisting of a bond, -O-, heterocycle, -N(R⁵)-, -N(R⁵)C(O)-, -S-, -S(O)-, -S(O₂)-, and -C(O)N(R⁵)-;

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L³ is alkyl, wherein the alkyl is optionally substituted with one or two substituents independently selected from the group consisting of amino, methylamino, dimethylamino, oxo, and hydroxy;

5 L⁶ is a bond;

R¹ is selected from the group consisting of C₁-C₁₂aryl and substituted C₁-C₁₂aryl;

10 R² is selected from alkyl, substituted alkyl, halogen, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, and C₁-C₁₂aryl optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, trifluoroalkoxy, C₁-C₁₂aryl, aryloxy, -O(CH₂)_qR³¹, -NHC(O)-NHR⁴¹, -C(O)R⁴³, hydroxy, alkoxy, cycloalkyl, N-acylamino, nitro and
15 halogen,

where q is 1-6,

R³¹ is C₁-C₁₂aryl, cycloalkyl and heterocycle, each of which is optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, acyloxy, amino, methylamino, dimethylamino, N-acylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl,
20

R⁴¹ is selected from hydrogen, C₁-C₁₂aryl, cycloalkyl and heterocycle, wherein C₁-C₁₂aryl, cycloalkyl and heterocycle are optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, amino, methylamino, dimethylamino, hydroxy, nitro, tetrazole, cyano, oxo and trifluoromethyl,
25

R⁴³ is selected from C₁-C₁₂aryl, cycloalkyl and heterocycle, each of which is optionally substituted with from 1 to 4 substituents selected from: halogen, hydroxyalkyl, alkoxy, amino, methylamino, dimethylamino, hydroxyl, nitro, tetrazole, cyano, oxo and trifluoromethyl,
30

R³ and R⁶ are independently selected from the group consisting of hydrogen, amino, methylamino, dimethylamino, aryl, substituted aryl, heterocycle, substituted heterocycle, cycloalkyl, substituted cycloalkyl, -S-C₁-C₁₂aryl, aryloxy and arylalkoxy; and
35

R⁴ is selected from the group consisting of hydrogen and halogen;

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where R^5 is selected from the group consisting of hydrogen, $-S(O)_2CH_3$, $-S(O)_2H$ and alkyl;

provided that when,

5 R^1 is azaindazole, substituted azaindazole, 1H-thienopyrazole, substituted 1H-thienopyrazole, benzamide, substituted benzamide, phenylethanone, substituted phenylethanone, thiophene, substituted thiophene, furan or substituted furan,

R^2 may additionally be hydrogen;

10

further provided that when

R^1 is Isoquinoline,

R^2 is not furyl or alkyl.

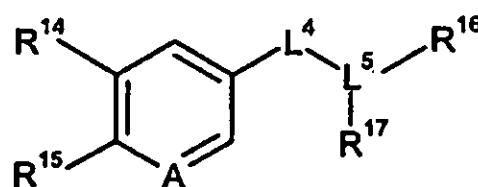
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4. A pharmaceutically acceptable salt, hydrate, solvate or pro-drug of a compound of Formula (I), as described in claim 3.

5. A compound of Claim 1 represented by the following Formula

(II):

20



(II)

wherein:

A is selected from nitrogen, $-CF$ and $-CH$;

25

L^4 is selected from the group consisting of a bond, heterocycle, $-O-$, and $-NH-$;

L^5 is alkyl, wherein the alkyl is optionally substituted with one or two substituents independently selected from the group consisting of amino, oxo, and hydroxy;

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R¹⁴ is selected from the group consisting of C₁-C₁₂aryl, and substituted C₁-C₁₂aryl;

5 R¹⁵ is selected from alkyl, substituted alkyl, halogen, cycloalkyl, substituted cycloalkyl, heterocycle, substituted heterocycle, C₁-C₁₂aryl and C₁-C₁₂aryl optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, trifluoroalkoxy, aryloxy, -O(CH₂)_qR³¹, -NHC(O)-NHR⁴¹, -C(O)R⁴³, hydroxy, alkoxy, acyloxy, amino, cycloalkyl, N-acylamino, nitro, cyano and halogen,
10 where q is 1-6,
R³¹ is C₁-C₁₂aryl optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl, alkoxy, and hydroxy,
R⁴¹ is selected from hydrogen and C₁-C₁₂aryl optionally substituted with from 1 to 4 substituents selected from: halogen, alkyl, hydroxyalkyl,
15 alkoxy, and hydroxy,
R⁴³ is C₁-C₁₂aryl substituted with from 1 to 4 substituents selected from: halogen, hydroxyalkyl, alkoxy, and hydroxy, and

20 R¹⁶ and R¹⁷ are independently selected from the group consisting of hydrogen, C₁-C₁₂aryl, substituted C₁-C₁₂aryl, heterocycle, cycloalkyl, -S-C₁-C₁₂aryl, and C₁-C₁₂arylalkoxy;

provided that when,

25 R¹⁴ is azaindazole, substituted azaindazole, 1H-thienopyrazole, substituted 1H-thienopyrazole, benzamide, substituted benzamide, phenylethanone, substituted phenylethanone, 2-pyridinecarboxamide, substituted 2-pyridinecarboxamide, (methylsulfonyl)benzene, substituted (methylsulfonyl)benzene, thiophene, substituted thiophene, furan or substituted furan,

30 R¹⁵ may additionally be hydrogen;

further provided that when

R¹⁴ is isoquinoline,

R¹⁵ is not furyl or alkyl.

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6. A pharmaceutically acceptable salt, hydrate, solvate or pro-drug of a compound of Formula (II), as described in claim 5.

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7. A compound of Formula (II), as described in claim 5:

wherein

5 A is selected from nitrogen, -CF and -CH;

L⁴ is selected from the group consisting of a bond, -O-, and -NH-;

10 L⁵ is alkyl, wherein the alkyl is substituted with one or two substituents independently selected from the group consisting of amino, oxo, and hydroxy;

15 R¹⁴ is selected from phenyl, pyridine, indazole, 7-azaindole, quinoline, isoquinoline, substituted phenyl, substituted pyridine, substituted indazole, substituted 7-azaindole, substituted quinoline and substituted isoquinoline;

20 R¹⁵ is selected from cycloalkyl, substituted cycloalkyl, phenyl, pyridine, thiophene, furan, pyrrole, indazole, quinoline, isoquinoline, 7-azaindole, substituted phenyl, substituted pyridine, substituted thiophene, substituted furan, substituted indazole, substituted quinoline, substituted 7-azaindole and substituted isoquinoline; and

25 R¹⁶ and R¹⁷ are independently selected from the group consisting of hydrogen, indole, substituted indole, azaindole, substituted azaindole, naphthalene, substituted naphthalene, benzofuran, substituted benzofuran, phenyl, pyridine, thiophene, furan, pyrrole, substituted phenyl, substituted pyridine, substituted thiophene, substituted furan, and substituted pyrrole;

30 provided that when,

35 R¹⁴ is 7-azaindazole, 4-azaindazole, 1H-thieno[3,2-c]pyrazole, benzamide, 1-phenylethanone, 2-furancarboxamide, 1-(2-furanyl)ethanone, 2-thienylcarboxamide, 1-(2-thienyl)ethanone, substituted 7-azaindazole, substituted 4-azaindazole, substituted 1H-thieno[3,2-c]pyrazole, substituted benzamide, substituted 1-phenylethanone, substituted 2-furancarboxamide, substituted 1-(2-furanyl)ethanone, substituted 2-thienylcarboxamide or substituted 1-(2-

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thienyl)ethanone, 2-pyridinecarboxamide, substituted 2-pyridinecarboxamide,
 (methylsulfonyl)benzene, substituted (methylsulfonyl)benzene,
 R^{15} may additionally be hydrogen;

- 5 further provided that when
 R^{14} is isoquinoline,
 R^{15} is not furyl or alkyl.

8. A pharmaceutically acceptable salt, hydrate, solvate or pro-
 10 drug of a compound of Formula (II), as described in claim 7.

9. A compound of claim 1 selected from:

- 15 (S)-1-Benzyl-2-[5-(3-methyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-furan-2-yl-5-(3-methyl-1H-indazol-5-yl)-pyridin-3-yloxy]-
 ethylamine;

- 20 (S)-1-Benzyl-2-[5,6-bis-(3-methyl-1H-indazol-5-yl)-pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-thiophen-2-yl-5-(3-methyl-1H-indazol-5-yl)-pyridin-3-yloxy]-
 ethylamine;

- 25 (S)-1-Benzyl-2-[6-(4-chlorophenyl)-5-(3-methyl-1H-indazol-5-yl)-pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-(3-chlorophenyl)-5-(3-methyl-1H-indazol-5-yl)-pyridin-3-yloxy]-
 ethylamine;

- 30 (S)-1-Benzyl-2-[6-benzyl-5-(3-methyl-1H-indazol-5-yl)-pyridin-3-yloxy]-ethylamine;

(S)-1-Benzyl-2-[6-cyclopent-1-enyl-5-(3-methyl-1H-indazol-5-yl)-pyridin-3-yloxy]-
 ethylamine;

- 35 (S)-1-Benzyl-2-[6-cyclopentyl-5-(3-methyl-1H-indazol-5-yl)-pyridin-3-yloxy]-ethylamine;

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- (S)-1-Benzyl-2-[6-cyclohex-1-enyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;
- 5 (S)-1-Benzyl-2-[6-cyclohexyl-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;
- 3-Methyl-5-[2-phenyl-5-(piperidin-4-ylmethoxy)-pyridin-3-yl]-1H-indazole;
- 10 3-[5-(3-Methyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-propylamine;
- (S)-1-Benzyl-2-[5- (3-methyl-1H-indazol-5-yl) -6-(5-methyl-thiophen-2-yl)-pyridin-3-yloxy]-ethylamine;
- 15 (S)-1-Benzyl-2-[5- (3-methyl-1H-indazol-5-yl) -6-(5-methyl-furan-2-yl)-pyridin-3-yloxy]-ethylamine;
- 3-Methyl-5-[2-phenyl-5-(4-pyridin-3-yl-methyl-piperazin-1-yl)-pyridin-3-yl]-1H-indazole;
- 20 3-Methyl-5-[2-phenyl-5-(4-pyridin-4-ylmethyl-piperazin-1-yl)-pyridin-3-yl]-1H-indazole;
- [(1S)-2-[[6-(3-furanyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- 25 [(1S)-2-[[5-(3-methyl-1H-indazol-5-yl)-6-(5-chloro-2-thienyl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- [(1S)-2-[[6-(3-aminophenyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- 30 (S)-1-Benzyl-2-[5-(1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine;
- (S)-1-Benzyl-2-[6-[3-(3-fluoro-benzyloxy)phenyl]-5- (3-methyl-1H-indazol-5-yl) -pyridin-3-yloxy]-ethylamine;
- 35 (S)-1-Benzyl-2-[5-(3-phenyl-1H-indazol-5-yl)-6-phenyl-pyridin-3-yloxy]-ethylamine;

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- [(1S)-2-[[5-(3-methyl-1H-indazol-5-yl)-6-(1H-pyrrol-2-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- 5 N-{3-[5-[[[(2S)-2-amino-3-phenylpropyl]oxy]-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]phenyl]benzamide;
- N-{3-[5-[[[(2S)-2-amino-3-phenylpropyl]oxy]-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]phenyl}-2,6-difluorobenzamide;
- 10 N-{3-[5-[[[(2S)-2-amino-3-phenylpropyl]oxy]-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]phenyl}cyclohexanecarboxamide;
- [(1S)-2-[[5-[3-(2-furanyl)-1H-indazol-5-yl]-6-phenyl-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- 15 {[(1S)-2-phenyl-1-[[[6-phenyl-5-[3-(2-thienyl)-1H-indazol-5-yl]-3-pyridinyl]oxy)methyl]ethyl}amine;
- 20 [(1S)-2-[[5-[3-(3-furanyl)-1H-indazol-5-yl]-6-phenyl-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- [(1S)-2-[[5-[3-(3-thienyl)-1H-indazol-5-yl]-6-phenyl-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- 25 3-[5-[[[(2S)-2-amino-3-phenylpropyl]oxy]-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]phenol;
- [(1S)-2-[[5-(2,3-dimethyl-2H-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- 30 [(1S)-2-[[5-(3-cyclopropyl-1H-indazol-5-yl)-6-(3-furanyl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- 35 [(1S)-2-[[5-(3-methyl-1H-indazol-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;

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[(1S)-2-[[6-{1-[(3-fluorophenyl)methyl]-1H-pyrazol-4-yl}-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;

5 ((1S)-2-phenyl-1-[[6-phenyl-5-{3-[5-(1-piperazinylmethyl)-2-furanyl]-1H-indazol-5-yl}-3-pyridinyl]oxy]methyl)ethyl]amine;

[(1S)-2-((6-(3-furanyl)-5-[3-(2-furanyl)-1H-indazol-5-yl]-3-pyridinyl)oxy)-1-(phenylmethyl)ethyl]amine;

10 [(1S)-2-((5-(3-methyl-1H-indazol-5-yl)-6-[3-(phenyloxy)phenyl]-3-pyridinyl)oxy)-1-(phenylmethyl)ethyl]amine;

15 3-[[5-[5-(5-[(2S)-2-amino-3-phenylpropyl]oxy)-2-phenyl-3-pyridinyl]-1H-indazol-3-yl]-2-furanyl]methyl)amino]propanenitrile ;

[(1S)-2-((6-(2-furanyl)-5-[3-(2-furanyl)-1H-indazol-5-yl]-3-pyridinyl)oxy)-1-(phenylmethyl)ethyl]amine;

20 {5-[5-[(2S)-2-amino-3-phenylpropyl]oxy]-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]-2-thienyl}methanol;

{(1S)-2-phenyl-1-[[6-phenyl-5-[3-(phenylmethyl)-1H-indazol-5-yl]-3-pyridinyl]oxy]methyl}ethyl]amine;

25 [(1S)-2-[[5-(3-methyl-1H-indazol-5-yl)-6-(1-methyl-1H-pyrrol-2-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;

5-(5-[(2S)-2-amino-3-phenylpropyl]oxy)-2-phenyl-3-pyridinyl-1H-indazol-3-amine;

30 [(1S)-2-((5-[3-(1-methylethenyl)-1H-indazol-5-yl]-6-phenyl-3-pyridinyl)oxy)-1-(phenylmethyl)ethyl]amine;

35 [(1S)-2-[[5-(3-methyl-1H-indazol-5-yl)-6-(1H-pyrazol-4-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;

(2S)-N,N-dimethyl-1-[[5-(3-methyl-1H-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy]-3-phenyl-2-propanamine;

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- [(1S)-2-[[3-(3-methyl-1H-indazol-5-yl)-2,4'-bipyridin-5-yl]oxy]-1-(phenylmethyl)ethyl]amine;
- 5 [(1S)-2-[[3-(3-methyl-1H-indazol-5-yl)-2,3'-bipyridin-5-yl]oxy]-1-(phenylmethyl)ethyl]amine;
- [(1S)-2-[[5-(3-iodo-1H-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- 10 [(1S)-2-[[5-(3-methyl-1H-indazol-5-yl)-6-{3-[(trifluoromethyl)oxy]phenyl}-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- [(1S)-2-[[6-(3,5-dimethyl-4-isoxazolyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- 15 4-[5-[[[(2S)-2-amino-3-phenylpropyl]oxy]-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]phenol];
- 20 2-[5-[[[(2S)-2-amino-3-phenylpropyl]oxy]-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]phenol];
- [(1S)-2-[[6-[3-(ethyloxy)phenyl]-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- 25 [(1S)-2-[[5-(3-methyl-1H-indazol-5-yl)-6-[3-(methyloxy)phenyl]-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- {3-[5-[[[(2S)-2-amino-3-phenylpropyl]oxy]-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]phenyl}(phenyl)methanone;
- 30 [(1S)-2-[[6-[3-[(1-methylethyl)oxy]phenyl]-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- 35 [(1S)-2-[[5-[3-(2-furanyl)-1H-indazol-5-yl]-6-(1H-pyrrol-2-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;

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- [(1S)-2-[[6-(2-[[3-fluorophenyl)methyl]oxy]phenyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- 5 [(1S)-2-[[6-(4-[[3-fluorophenyl)methyl]oxy]phenyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- [(1S)-2-[[5-[3-(5-chloro-2-thienyl)-1H-indazol-5-yl]-6-phenyl-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- 10 [(1S)-2-[[5-[3-(4-methyl-2-thienyl)-1H-indazol-5-yl]-6-phenyl-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- [(1S)-2-[[5-[3-(5-methyl-2-furanyl)-1H-indazol-5-yl]-6-phenyl-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- 15 [(1S)-2-[[5-[3-(5-methyl-2-thienyl)-1H-indazol-5-yl]-6-phenyl-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- [(1S)-2-[[6-ethenyl-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- 20 [(1S)-2-phenyl-1-[[[6-phenyl-5-[3-(1H-pyrrol-2-yl)-1H-indazol-5-yl]-3-pyridinyl]oxy)methyl]ethyl]amine;
- 25 [(1S)-2-(1H-indol-3-yl)-1-[[[5-(3-methyl-1H-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy)methyl]ethyl]amine;
- 5-(3-methyl-1H-indazol-5-yl)-6-phenyl-N-(3-phenylpropyl)-3-pyridinamine;
- 30 5-(3-methyl-1H-indazol-5-yl)-6-phenyl-N-(3-phenylbutyl)-3-pyridinamine;
- [(2S)-2-amino-3-phenylpropyl][5-(3-methyl-1H-indazol-5-yl)-6-phenyl-3-pyridinyl]amine;
- 35 [(2S)-2-amino-3-phenylpropyl][6-(3-furanyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]amine;

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((1S)-2-[[6-(3-furanyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-
 {[(phenylmethyl)oxy]methyl}ethyl)amine;

5 N-[(2S)-2-amino-3-phenylpropyl]-N-[5-(3-methyl-1H-indazol-5-yl)-6-phenyl-3-
 pyridinyl]methanesulfonamide;

5-(3-methyl-1H-indazol-5-yl)-N-[2-methyl-2-(phenylthio)propyl]-6-phenyl-3-
 pyridinamine;

10 [(1S)-2-[[6-(3-furanyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(1H-indol-3-
 ylmethyl)ethyl]amine;

((1S)-2-[[5-(3-methyl-1H-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy]-1-
 {[(phenylmethyl)oxy]methyl}ethyl)amine;

15 (2S)-2-amino-3-[[5-(3-methyl-1H-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy]-1-propanol;

5-(3-methyl-1H-indazol-5-yl)-6-phenyl-N-[(2S)-2-pyrrolidinylmethyl]-3-pyridinamine;

20 ((2S)-2-amino-3-{4-[(phenylmethyl)oxy]phenyl}propyl)[5-(3-methyl-1H-indazol-5-yl)-
 6-phenyl-3-pyridinyl]amine;

[(2S)-2-amino-3-phenylpropyl][5-(1H-indazol-5-yl)-6-phenyl-3-pyridinyl]amine;

25 [(2S)-2-amino-3-phenylpropyl][6-(3-furanyl)-5-(1H-indazol-5-yl)-3-pyridinyl]amine;

[(2S)-2-amino-3-phenylpropyl][5-(1H-indazol-5-yl)-6-(3-thienyl)-3-pyridinyl]amine;

2-[5-(((2S)-2-amino-3-phenylpropyl)amino)-3-(1H-indazol-5-yl)-2-pyridinyl]phenol;

30

2-[5-(((2S)-2-amino-3-phenylpropyl)amino)-3-(3-methyl-1H-indazol-5-yl)-2-
 pyridinyl]phenol;

35 [(2S)-2-amino-3-phenylpropyl][5-(3-methyl-1H-indazol-5-yl)-6-(1H-pyrrol-2-yl)-3-
 pyridinyl]amine;

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[(2S)-2-amino-3-phenylpropyl][5-(3-methyl-1H-indazol-5-yl)-6-(5-methyl-2-thienyl)-3-pyridinyl]amine;

5 [(2R)-2-amino-3-phenylpropyl][5-(1H-indazol-5-yl)-6-(3-thienyl)-3-pyridinyl]amine;
2-[5-[[[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy]-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]phenol];

10 [(1S)-2-(1H-indol-3-yl)-1-([5-(3-methyl-1H-indazol-5-yl)-6-(1H-pyrrol-2-yl)-3-pyridinyl]oxy)methyl]ethylamine;

[(1S)-2-(1H-indol-3-yl)-1-([5-(3-methyl-1H-indazol-5-yl)-6-(5-methyl-2-thienyl)-3-pyridinyl]oxy)methyl]ethylamine;

15 [(1S)-2-[[6-ethyl-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;

20 [(1S)-2-[[6-(3-furanyl)-5-(1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;

[(1S)-2-[[5-(3-ethenyl-1H-indazol-5-yl)-6-(3-furanyl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;

25 [(1S)-2-[[5-(3-ethyl-1H-indazol-5-yl)-6-(3-furanyl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;

[(1S)-2-([6-(3-furanyl)-5-[3-(3-pyridinyl)-1H-indazol-5-yl]-3-pyridinyl]oxy)-1-(phenylmethyl)ethyl]amine;

30 [(1S)-2-[[6-methyl-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;

[(1S)-2-([5-(3-methyl-1H-indazol-5-yl)-6-[2-(methyloxy)phenyl]-3-pyridinyl]oxy)-1-(phenylmethyl)ethyl]amine;

35 [(1S)-2-[[6-[2-(ethyloxy)phenyl]-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;

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- [(1S)-2-[[6-[5-chloro-2-(methyloxy)phenyl]-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- 5 [(1S)-2-[[6-[5-fluoro-2-(propyloxy)phenyl]-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- [(1S)-2-[[5-[3-(1-methylethyl)-1H-indazol-5-yl]-6-phenyl-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- 10 [(1S)-2-[[5-(6-fluoro-3-methyl-1H-indazol-5-yl)-6-(3-furanyl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- N-[6-(3-furanyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]-L-phenylalaninamide;
- 15 N-[6-(2-hydroxyphenyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]-L-phenylalaninamide;
- 2-[5-[[[(2S)-2-amino-3-(1-benzothien-3-yl)propyl]oxy]-3-(1H-indazol-5-yl)-2-pyridinyl]phenol];
- 20 [(1S)-2-(1-benzothien-3-yl)-1-[[6-(2-furanyl)-5-(1H-indazol-5-yl)-3-pyridinyl]oxy)methyl]ethyl]amine;
- 25 [(1S)-2-[[5-(3-methyl-1H-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy]-1-(2-naphthalenylmethyl)ethyl]amine;
- N-[5-(3-methyl-1H-indazol-5-yl)-6-(1H-pyrrol-2-yl)-3-pyridinyl]-L-phenylalaninamide;
- 30 [(2S)-2-amino-3-(1H-indol-3-yl)propyl][6-(3-furanyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]amine;
- (2S)-1-[[6-(3-furanyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-3-phenyl-2-propanol;
- 35 1-[3-[5-[[[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy]-2-(3-furanyl)-3-pyridinyl]phenyl]ethanone;

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- [(1S)-2-[[6-cyclopentyl-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(1H-indol-3-ylmethyl)ethyl]amine;
- 5 [(1S)-2-(1-benzothien-3-yl)-1-[[5-(1H-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy)methyl]ethyl]amine;
- [(1S)-2-(1-benzothien-3-yl)-1-[[6-(3-furanyl)-5-(1H-indazol-5-yl)-3-pyridinyl]oxy)methyl]ethyl]amine;
- 10 [(1S)-2-(1-benzothien-3-yl)-1-[[5-(1H-indazol-5-yl)-6-(3-thienyl)-3-pyridinyl]oxy)methyl]ethyl]amine;
- [(1S)-2-(1-benzothien-3-yl)-1-[[5-(1H-indazol-5-yl)-6-(1H-pyrrol-2-yl)-3-pyridinyl]oxy)methyl]ethyl]amine;
- 15 [(1S)-2-[[5-(1H-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy]-1-(1H-pyrazol-1-ylmethyl)ethyl]amine;
- [(1S)-2-(1-benzothien-3-yl)-1-[[5-(1H-indazol-5-yl)-6-(5-methyl-2-thienyl)-3-pyridinyl]oxy)methyl]ethyl]amine;
- 20 [(1S)-2-[[6-(3-furanyl)-5-(3-methyl-1H-thieno[3,2-c]pyrazol-5-yl)-3-pyridinyl]oxy]-1-(1H-indol-3-ylmethyl)ethyl]amine;
- 25 5-[5-[[[(2S)-2-amino-3-phenylpropyl]oxy]-2-(3-furanyl)-3-pyridinyl]-N-4-pyridinyl-1H-indazol-3-amine;
- N-[5-[5-[[[(2S)-2-amino-3-phenylpropyl]oxy]-2-(3-furanyl)-3-pyridinyl]-1H-indazol-3-yl]benzamide;
- 30 (1E)-1-[3-[5-[[[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy]-2-(3-furanyl)-3-pyridinyl]phenyl]ethanone oxime;
- 35 [(1S)-2-[[6-(3-furanyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)propyl]amine;

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(2S)-N-methyl-1-[[5-(3-methyl-1H-indazol-5-yl)-6-phenyl-3-pyridinyl]oxy]-3-phenyl-2-propanamine;

5 [(1S)-2-[[6-[5-fluoro-2-(methyloxy)phenyl]-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;

[(1S)-2-[[6-[3,5-difluoro-2-(methyloxy)phenyl]-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;

10 [(1S)-2-([6-(3-furanyl)-5-[3-(4-pyridinyl)-1H-indazol-5-yl]-3-pyridinyl]oxy)-1-(phenylmethyl)ethyl]amine;

2-[5-[[[(2S)-2-amino-3-phenylpropyl]oxy]-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]-4-fluorophenol;

15 2-[5-[[[(2S)-2-amino-3-phenylpropyl]oxy]-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]-4,6-difluorophenol;

20 2-[5-[[[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy]-3-(6-fluoro-3-methyl-1H-indazol-5-yl)-2-pyridinyl]phenol;

2-[5-[[[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy]-3-(3-ethyl-1H-indazol-5-yl)-2-pyridinyl]phenol;

25 [(1S)-2-[[5-(3-ethyl-1H-indazol-5-yl)-6-(3-furanyl)-3-pyridinyl]oxy]-1-(1H-indol-3-ylmethyl)ethyl]amine;

[(1S)-2-[[5-(3-ethyl-1H-indazol-5-yl)-6-(2-furanyl)-3-pyridinyl]oxy]-1-(1H-indol-3-ylmethyl)ethyl]amine;

30 [(1S)-2-[[5-(3-ethyl-1H-indazol-5-yl)-6-(1H-pyrrol-2-yl)-3-pyridinyl]oxy]-1-(1H-indol-3-ylmethyl)ethyl]amine;

35 [(1S)-2-([6-(3-furanyl)-5-[3-(1-methyl-1H-pyrazol-4-yl)-1H-indazol-5-yl]-3-pyridinyl]oxy)-1-(phenylmethyl)ethyl]amine;

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- [(1S)-2-({6-(3-furanyl)-5-[3-(1H-pyrrol-2-yl)-1H-indazol-5-yl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;
- 5 [(1S)-2-({6-(3-furanyl)-5-[3-(1H-pyrazol-4-yl)-1H-indazol-5-yl]-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;
- [(1S)-2-({5-(6-fluoro-3-methyl-1H-indazol-5-yl)-6-(2-furanyl)-3-pyridinyl}oxy)-1-(1H-indol-3-ylmethyl)ethyl]amine;
- 10 [(1S)-2-({5-(6-fluoro-3-methyl-1H-indazol-5-yl)-6-(1H-pyrrol-2-yl)-3-pyridinyl}oxy)-1-(1H-indol-3-ylmethyl)ethyl]amine;
- [(1S)-2-({5-(6-fluoro-3-methyl-1H-indazol-5-yl)-6-(3-furanyl)-3-pyridinyl}oxy)-1-(1H-indol-3-ylmethyl)ethyl]amine;
- 15 [(1S)-2-({6-(1-benzothien-2-yl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;
- [(1S)-2-({6-(1-benzofuran-2-yl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl}oxy)-1-(phenylmethyl)ethyl]amine;
- 20 [(1S)-2-({6-(3-furanyl)-5-[3-(methylsulfonyl)phenyl]-3-pyridinyl}oxy)-1-(1H-indol-3-ylmethyl)ethyl]amine;
- 25 5-[5-({[(2S)-2-(1-azetidiny)-3-(1H-indol-3-yl)propyl]oxy}-2-(3-furanyl)-3-pyridinyl)-3-methyl-1H-indazole;
- [(1S)-2-({6-(3-furanyl)-5-[3-(1H-pyrazol-4-yl)-1H-indazol-5-yl]-3-pyridinyl}oxy)-1-(1H-indol-3-ylmethyl)ethyl]amine;
- 30 3-[5-({[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy}-2-(3-furyl)pyridin-3-yl]benzamide;
- 4-[5-({[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy}-2-(3-furyl)pyridin-3-yl]benzamide;
- 35 5-(5-({[(2S)-3-(1H-indol-3-yl)-2-(1-piperidinyl)propyl]oxy}-2-phenyl-3-pyridinyl)-3-methyl-1H-indazole;

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- 5-(2-(3-furanyl)-5-(((2S)-3-(1H-indol-3-yl)-2-(4-morpholinyl)propyl)oxy)-3-pyridinyl)-3-methyl-1H-indazole;
- 5 [(1S)-2-((6-(3-furanyl)-5-[3-(1H-pyrazol-4-yl)-1H-indazol-5-yl]-3-pyridinyl)oxy)-1-(1H-indol-3-yl)methyl)ethyl]amine;
- [(1S)-2-((6-(3-furanyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl)oxy)-1-(1H-indol-3-yl)methyl)ethyl]dimethylamine;
- 10 (3S)-3-(((6-(3-furanyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl)oxy)methyl)-2-methyl-2,3,4,9-tetrahydro-1H-carboline;
- 1-{5-[5-(((2S)-2-amino-3-(1H-indol-3-yl)propyl)oxy)-2-(3-furanyl)-3-pyridinyl]-2-thienyl}ethanone;
- 15 (2S)-1-((6-(3-furanyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl)oxy)-3-(1H-indol-3-yl)-N-methyl-2-propanamine;
- 5-[5-(((2S)-2-amino-3-(1H-indol-3-yl)propyl)oxy)-2-(3-furanyl)-3-pyridinyl]-N,N-dimethyl-2-furancarboxamide;
- 20 5-[5-(((2S)-2-amino-3-(1H-indol-3-yl)propyl)oxy)-2-(3-furanyl)-3-pyridinyl]-N-methyl-2-furancarboxamide;
- 25 5-[5-(((2S)-2-amino-3-(1H-indol-3-yl)propyl)oxy)-2-(3-furanyl)-3-pyridinyl]-2-furancarboxamide;
- [(2S)-2-amino-3-phenylpropyl]((6-(3-furanyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl)methylamine);
- 30 [(1S)-2-(3,4-dichlorophenyl)-1-(((5-(3-methyl-1H-indazol-5-yl)-6-phenyl-3-pyridinyl)oxy)methyl)ethyl]amine;
- N-[5-(3-methyl-1H-indazol-5-yl)-6-phenyl-3-pyridinyl]-L-phenylalaninamide;
- 35 N-[5-(3-methyl-1H-indazol-5-yl)-6-phenyl-3-pyridinyl]-L-phenylalaninamide;

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2-[5-[[[(2S)-2-amino-3-(1H-indol-3-yl)propyl]amino]-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]-4-fluorophenol;

5 ((1S)-3-{[6-(3-furanyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy}-1-{4-(trifluoromethyl)phenyl]methyl}propyl)amine;

[(1S)-3-{[6-(3-furanyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy}-1-(1H-indol-3-ylmethyl)propyl]amine;

10 {(1S)-2-{[6-(3-furanyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy}-1-[(5-methyl-1H-indol-3-yl)methyl]ethyl)amine;

[(1S)-2-(1H-indol-3-yl)-1-[[5-(3-methyl-1H-indazol-5-yl)-6-(1H-pyrrol-3-yl)pyridin-3-yl]oxy]methyl]ethyl)amine;

15 [(1S)-2-{[6-(3-furanyl)-5-(3-methyl-1H-pyrazolo[4,3-b]pyridin-5-yl)-3-pyridinyl]oxy}-1-(1H-indol-3-ylmethyl)ethyl)amine;

20 [(1S)-2-(1H-indol-3-yl)-1-[[5-(3-methyl-1H-pyrazolo[4,3-b]pyridin-5-yl)-3-pyridinyl]oxy]methyl]ethyl)amine;

5-[5-[[[(2S)-2-amino-3-phenylpropyl]oxy]-2-(3-furanyl)-3-pyridinyl]-1H-indazole-3-carboxamide;

25 5-[5-[[[(2S)-2-amino-3-phenylpropyl]oxy]-2-(3-furanyl)-3-pyridinyl]-1H-indazole-3-carbonitrile;

(2S)-1-{[6-(2-furanyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy}-3-(1H-indol-3-yl)-2-propanamine;

30 2-[5-[[[(2S)-2-amino-3-(1-benzothien-3-yl)-3-propyl]oxy]-3-(1H-indazol-5-yl)-2-pyridinyl]-4-fluorophenol;

35 2-[5-[[[(2S)-2-amino-3-(1-benzothien-3-yl)-3-propyl]oxy]-3-(1H-indazol-5-yl)-2-pyridinyl]-4,6-difluorophenol;

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- [(1S)-2-(1-benzothien-3-yl)-1-([5,6-bis(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy)methyl)ethyl]amine;
- 5 [(1S)-2-(1-benzothien-3-yl)-1-([4-(3-furanyl)-3-(3-methyl-1H-indazol-5-yl)phenyl]oxy)methyl)ethyl]amine;
- 4'-{[(2S)-2-amino-3-(1-benzothien-3-yl)propyl]oxy}-3,5-difluoro-2'-(3-methyl-1H-indazol-5-yl)-2-biphenylol;
- 10 4'-{[(2S)-2-amino-3-(1-benzothien-3-yl)propyl]oxy}-5-fluoro-2'-(3-methyl-1H-indazol-5-yl)-2-biphenylol;
- 2-[5-{[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy}-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]-4,6-difluorophenol;
- 15 [(2S)-2-amino-3-(1H-indol-3-yl)propyl][5-(3-methyl-1H-indazol-5-yl)-6-(1H-pyrrol-2-yl)-3-pyridinyl]amine;
- [(2S)-2-amino-3-(1H-indol-3-yl)propyl][6-[5-fluoro-2-(methyloxy)phenyl]-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]amine;
- 20 2-[5-{[(2S)-2-amino-3-(1H-indol-3-yl)propyl]amino}-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]phenol;
- 25 2-[5-{[(2S)-2-amino-3-(1H-indol-3-yl)propyl]amino}-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]phenol;
- [(2S)-2-amino-3-(5-fluoro-1H-indol-3-yl)propyl][6-(3-furanyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]amine;
- 30 [(2S)-2-amino-4-pentyn-1-yl][6-(3-furanyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]amine;
- [(2S)-2-amino-3-(5,6,7-trifluoro-1H-indol-3-yl)propyl][6-(3-furanyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]amine;
- 35

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- [(2S)-2-amino-3-(5,7-difluoro-1H-indol-3-yl)propyl][6-(3-furanyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]amine;
- 5 [(1S)-2-[[6-(3-furanyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(1H-pyrrolo[2,3-b]pyridin-2-ylmethyl)ethyl]amine;
- [(2R)-2-amino-3-phenylpropyl][3-fluoro-4-(3-furanyl)-5-(3-methyl-1H-indazol-5-yl)phenyl]amine;
- 10 [(2R)-2-amino-3-(1H-indol-3-yl)propyl][3-fluoro-4-(3-furanyl)-5-(3-methyl-1H-indazol-5-yl)phenyl]amine;
- [(1S)-2-[[6-(3-furanyl)-5-(3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-3-pyridinyl]oxy]-1-(1H-indol-3-ylmethyl)ethyl]amine;
- 15 [(1S)-2-(1H-indol-3-yl)-1-(((6-(2-methyl-3-furanyl)-5-(3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-3-pyridinyl]oxy)methyl)ethyl]amine;
- [(1S)-2-(1H-indol-3-yl)-1-(((5-(3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-6-phenyl-3-pyridinyl]oxy)methyl)ethyl]amine;
- 20 [(1S)-2-[[6-(3-furanyl)-5-(3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-3-pyridinyl]oxy]-1-(1H-indol-3-ylmethyl)ethyl]methanamine;
- 25 2-[5-(((2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy)-3-(3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-2-pyridinyl]phenol;
- 2-[5-(((2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy)-3-(3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-2-pyridinyl]-6-fluorophenol;
- 30 [(1S)-2-[[5-[3-(3,5-dimethyl-4-isoxazolyl)-1H-indazol-5-yl]-6-(3-furanyl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- [(1S)-2-[[6-(3-furanyl)-5-[3-(2-pyridinyl)-1H-indazol-5-yl]-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
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- [(1S)-2-[[6-(2-chlorophenyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- 5 [(1S)-2-[[5-(3-methyl-1H-indazol-5-yl)-6-(2-methylphenyl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- [(1S)-2-[[6-(2-fluorophenyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- 10 2-[5-[[[(2S)-2-amino-3-phenylpropyl]oxy]-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]-4-chlorophenol;
- [(1S)-2-[[6-(1-benzothien-3-yl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- 15 3-[5-[[[(2S)-2-amino-3-phenylpropyl]oxy]-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]benzamide;
- 3-[5-[[[(2S)-2-amino-3-phenylpropyl]oxy]-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]benzonitrile;
- 20 [(1S)-2-[[5-(3-methyl-1H-indazol-5-yl)-6-(3-nitrophenyl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- 25 [(1S)-2-[[5-(3-methyl-1H-indazol-5-yl)-6-(4-methyl-2-thienyl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- N-{3-[5-[[[(2S)-2-amino-3-phenylpropyl]oxy]-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]phenyl}-N'-phenylurea;
- 30 [(1S)-2-[[5-(3-methyl-1H-indazol-5-yl)-6-(2-thienyl)-3-pyridinyl]oxy]-1-(phenylmethyl)ethyl]amine;
- [(1S)-2-(1H-indol-3-yl)-1-[[6-(2-methyl-3-furanyl)-5-(3-methyl-1H-indazol-5-yl)-3-pyridinyl]oxy]methyl]ethyl]amine;
- 35

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- {2-[5-[[[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy}-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]phenyl]amine;
- 5 2-[5-[[[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy}-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]-6-fluorophenol;
- 2-[5-[[[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy}-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]-4-chlorophenol;
- 10 2-[5-[[[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy}-3-(3-methyl-1H-indazol-5-yl)-2-pyridinyl]-4-fluorophenol;
- [(1S)-2-[[[6-[3,5-difluoro-2-(methyloxy)phenyl]-5-(3-methyl-1H-thieno[3,2-c]pyrazol-5-yl)-3-pyridinyl]oxy]-1-(1H-indol-3-ylmethyl)ethyl]amine;
- 15 2-[5-[[[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy}-3-(3-methyl-1H-thieno[3,2-c]pyrazol-5-yl)-2-pyridinyl]-4,6-difluorophenol;
- 2-[5-[[[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy}-3-(3-methyl-1H-thieno[3,2-c]pyrazol-5-yl)-2-pyridinyl]phenol;
- 20 2-[5-[[[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy}-3-(3-methyl-1H-thieno[3,2-c]pyrazol-5-yl)-2-pyridinyl]-4-chlorophenol;
- 25 3-[5-[[[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy}-3-pyridinyl]benzamide;
- 1-[3-[5-[[[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy}-3-pyridinyl]phenyl]ethanone; and
- 5-[[[(2S)-2-amino-3-(1H-indol-3-yl)propyl]oxy]-2-(3-furanyl)-3,4'-bipyridine-2'-carboxamide.
- 30

10. A pharmaceutically acceptable salt, hydrate, solvate or pro-drug of a compound of Formula (II), as described in claim 9.

35 11. A pharmaceutical composition comprising a compound according to claim 1, and/or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof and a pharmaceutically acceptable carrier.

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(54) Title: **HEDGEHOG PATHWAY ANTAGONISTS**

(57) Abstract: Aromatic compounds for treating various diseases and pathologies are disclosed. The methods use of such compounds are also provided. Accordingly, the present invention makes available methods and compositions for inhibiting aberrant growth states resulting from *hedgehog* gain-of-function, *ptc* loss-of-function or *smoothened* gain-of-function.

HEDGEHOG PATHWAY ANTAGONISTS**CROSS REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit of priority under 35 U.S.C. § 119(e) of U.S. Serial No. 60/507,164, filed September 29, 2003, the entire content of which is incorporated herein by reference.

BACKGROUND OF THE INVENTION**FIELD OF THE INVENTION**

[0002] The present invention relates generally to the use of compounds to treat a variety of disorders, diseases and pathologic conditions and more specifically to the use of various aromatic compounds for inhibiting signaling pathways.

BACKGROUND INFORMATION

[0003] Pattern formation is the activity by which embryonic cells form ordered spatial arrangements of differentiated tissues. Speculation on the mechanisms underlying these patterning effects usually centers on the secretion of a signaling molecule that elicits an appropriate response from the tissues being patterned. More recent work aimed at the identification of such signaling molecules implicates secreted proteins encoded by individual members of a small number of gene families.

[0004] Members of the Hedgehog family of signaling molecules mediate many important short- and long-range patterning processes during invertebrate and vertebrate development. Exemplary hedgehog genes and proteins are described in PCT publications WO 95/18856 and WO 96/17924. The vertebrate family of hedgehog genes includes at least four members, three of which, herein referred to as Desert hedgehog (Dhh), Sonic hedgehog (Shh) and Indian hedgehog (Ihh), apparently exist in all vertebrates, including fish, birds, and mammals. A fourth member, herein referred to as tiggie-winkle hedgehog (Thh), appears specific to fish. Desert hedgehog (Dhh) is expressed principally in the testes, both in mouse embryonic development and in the adult rodent and human; Indian

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hedgehog (Ihh) is involved in bone development during embryogenesis and in bone formation in the adult; and, Shh is primarily involved in morphogenic and neuroinductive activities. Given the critical inductive roles of hedgehog polypeptides in the development and maintenance of vertebrate organs, the identification of hedgehog interacting proteins and their role in the regulation of gene families known to be involved in cell signaling and intercellular communication provides a possible mechanism of tumor suppression.

[0005] The ability to modulate one or more genes that are part of the hedgehog signaling cascade thus represents a possible therapeutic approach to several clinically significant cancers. A need therefore exists for methods and compounds that inhibit signal transduction activity by modulating activation of a *hedgehog*, *patched*, or *smoothened*-mediated signal transduction pathway, such as the Hedgehog signaling pathway, to reverse or control aberrant growth.

SUMMARY OF THE INVENTION

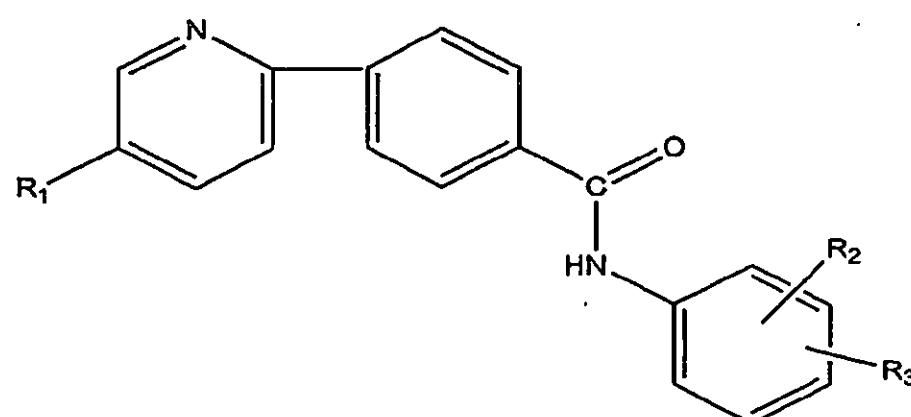
[0006] The present invention provides various methods and compounds for inhibiting activation of signaling pathways, such as the Hedgehog pathway e.g., to inhibit aberrant growth states resulting from phenotypes such as *ptc* loss-of-function, *hedgehog* gain-of-function, or *smoothened* gain-of-function.

[0007] The present invention makes available methods and reagents, comprising contacting the cell with an agent, such as an aromatic compound, in a sufficient amount to agonize a normal *ptc* activity, antagonize a normal hedgehog activity, or antagonize *smoothened* activity, e.g., to reverse or control the aberrant growth state.

[0008] According to one embodiment of the invention, compounds having the structure (I) are provided, or a pharmaceutically acceptable salt thereof:

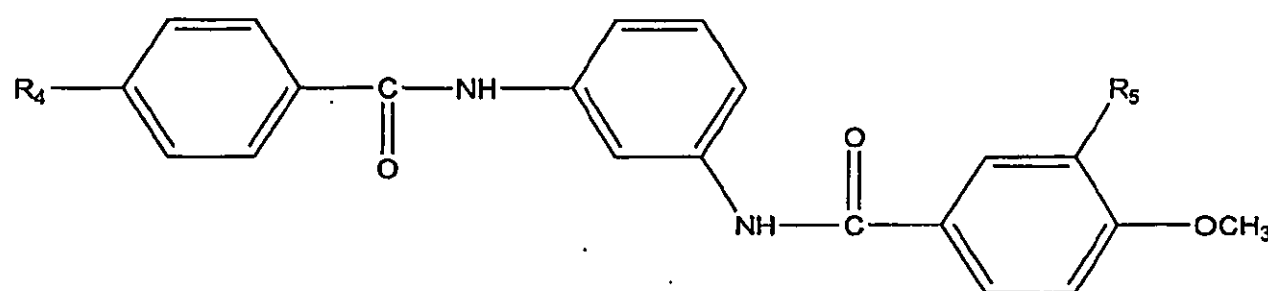
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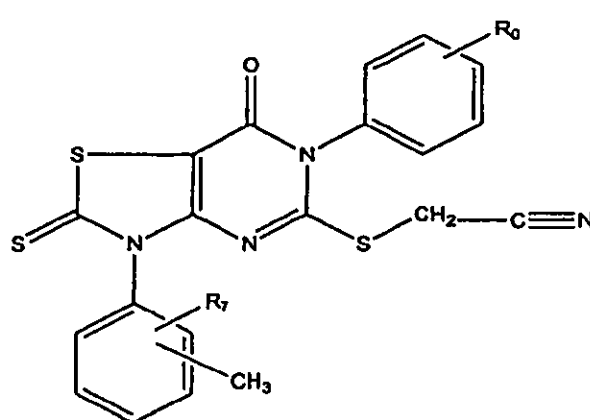
(I)

[0009] According to one embodiment of the invention, compounds having the structure (II) are provided, or a pharmaceutically acceptable salt thereof:



(II)

[0010] According to one embodiment of the invention, compounds having the structure (III) are provided, or a pharmaceutically acceptable salt thereof:



(III)

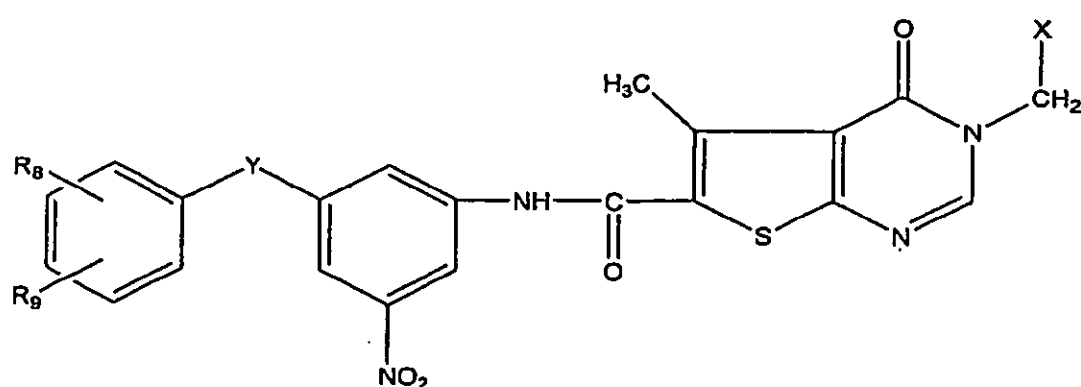
[0011] According to one embodiment of the invention, compounds having the structure (IV) are provided, or a pharmaceutically acceptable salt thereof:

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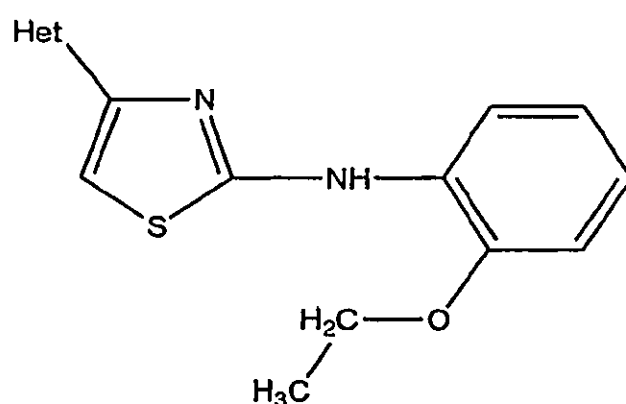
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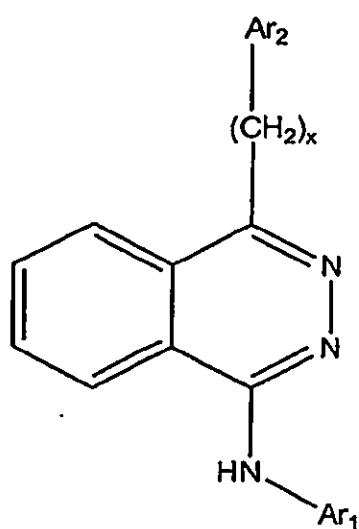
(IV)

[0012] According to one embodiment of the invention, compounds having the structure (V) are provided, or a pharmaceutically acceptable salt thereof:



(V)

[0013] According to one embodiment of the invention, compounds having the structure (VI) are provided, or a pharmaceutically acceptable salt thereof:



(VI)

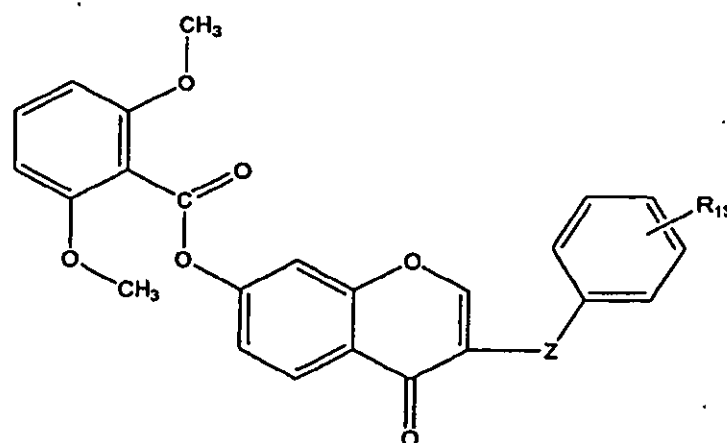
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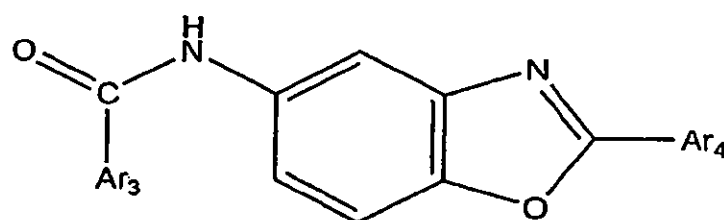
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[0014] According to one embodiment of the invention, compounds having the structure (VII) are provided, or a pharmaceutically acceptable salt thereof:



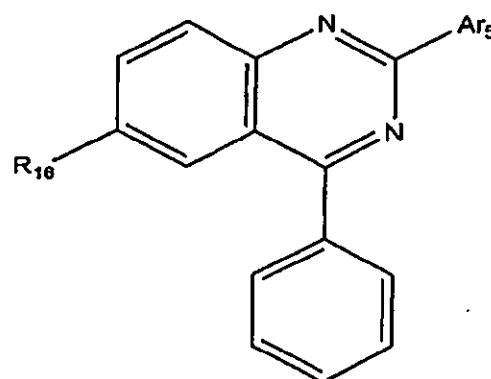
(VII)

[0015] According to one embodiment of the invention, compounds having the structure (VIII) are provided, or a pharmaceutically acceptable salt thereof:



(VIII)

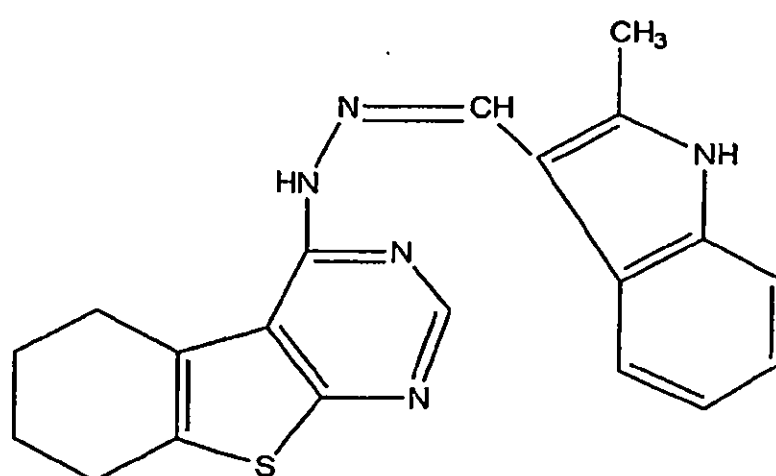
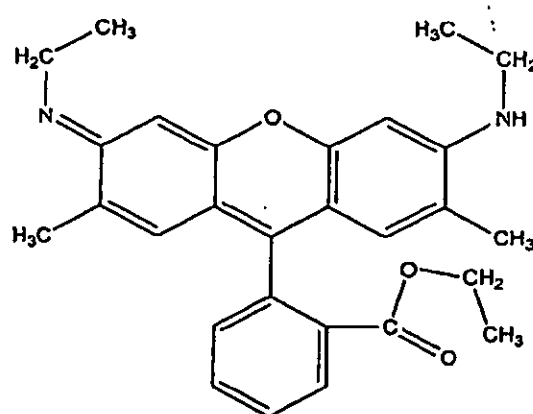
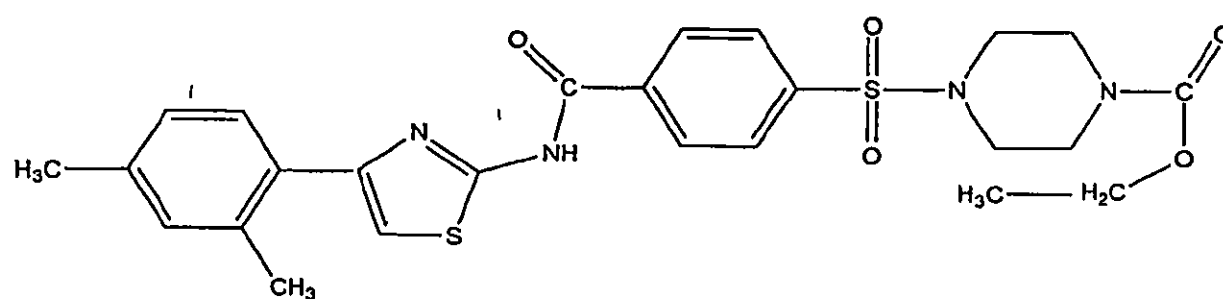
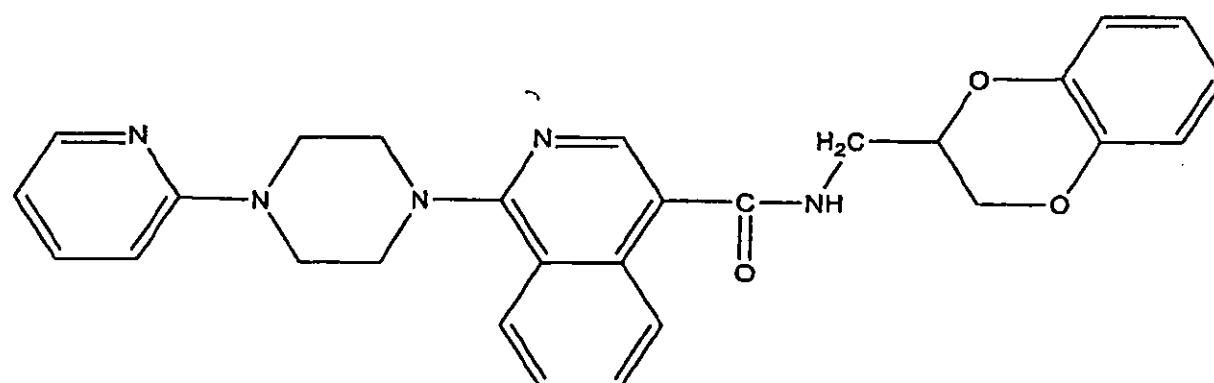
[0016] According to one embodiment of the invention, compounds having the structure (IX) are provided, or a pharmaceutically acceptable salt thereof:



(IX)

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molecules having a molecular weight less than 2500 amu, more preferably less than 1500 amu, and even more preferably less than 750 amu, and are capable of inhibiting at least some of the biological activities of hedgehog, e.g. Hh, Shh, Ihh, Dhh, specifically in target cells.

[0043] Thus, the methods of the present invention include the use of compounds, such as aromatic compounds, which antagonize activity of the hedgehog pathway resulting in the regulation of repair and/or functional performance of a wide range of cells, tissues, and organs having the phenotype of *ptc* loss-of-function, *hedgehog* gain-of-function, or *smoothened* gain-of-function. In an alternative embodiment, the present invention provides compounds, such as aromatic compounds, which agonize activity of the hedgehog pathway, resulting in the regulation of repair and/or functional performance of a wide range of cells, tissues, and organs having the phenotype of *ptc* gain-of-function, *hedgehog* loss-of-function, or *smoothened* loss-of-function. For instance, the subject methods have therapeutic and cosmetic applications ranging from regulation of neural tissues, bone and cartilage formation and repair, regulation of spermatogenesis, regulation of smooth muscle, regulation of lung, liver and other organs arising from the primitive gut, regulation of hematopoietic function, regulation of skin and hair growth, etc. Moreover, the subject methods can be performed on cells which are provided in culture (*in vitro*), or on cells in a whole animal (*in vivo*). See, for example, PCT publications WO 95/18856 and WO 96/17924 (the specifications of which are expressly incorporated by reference herein).

[0044] In an embodiment, the subject method can be to treat epithelial cells having a phenotype of *ptc* loss-of-function, *hedgehog* gain-of-function, or *smoothened* gain-of-function employing a compound, such as an aromatic compound, which antagonizes hedgehog function, e.g., by agonizing *hedgehog*, *patched*, or *smoothened* activity. For instance, the subject method can be used in treating or preventing basal cell carcinoma or other hedgehog pathway-related disorders. In an alternative embodiment, the subject method can be to treat epithelial cells having a phenotype of *ptc* gain-of-function, *hedgehog* loss-of-function, or *smoothened* loss-of-function employing an agent which

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agonizes hedgehog function, e.g., by antagonizing *hedgehog*, *patched*, or *smoothened* activity.

[0045] In another embodiment, the subject method can be used as part of a treatment regimen for cancer. Such cancers include malignant medulloblastoma and other primary CNS malignant neuroectodermal tumors, rhabdomyosarcoma, lung cancer, and in particular small cell lung cancer, gut-derived tumors, including but not limited to cancer of the esophagus, stomach, pancreas, and biliary duct system, or prostatic and bladder cancers.

[0046] In another aspect, the present invention provides pharmaceutical preparations comprising, an aromatic compound such as described herein, formulated in an amount sufficient to regulate, *in vivo*, the hedgehog pathway, e.g., proliferation or other biological consequences of mis-expression of *ptc*, *hedgehog*, or *smoothened*.

[0047] The subject treatments using the subject compounds can be effective for both human and animal subjects. Animal subjects to which the invention is applicable extend to both domestic animals and livestock, raised either as pets or for commercial purposes. Examples are dogs, cats, cattle, horses, sheep, hogs, and goats.

[0048] The following terminology and definitions apply as used in the present application. The chemical terms are generally used in conformity with the terminology recommended by the International Union of Pure and Applied Chemistry (IUPAC).

[0049] The phrase "aberrant modification or mutation" of a gene refers to such genetic lesions as, for example, deletions, substitution or addition of nucleotides to a gene, as well as gross chromosomal rearrangements of the gene and/or abnormal methylation of the gene. Likewise, "mis-expression" of a gene refers to aberrant levels of transcription of the gene relative to those levels in a normal cell under similar conditions, as well as non-wild-type splicing of mRNA transcribed from the gene.

[0050] "Basal cell carcinomas" exist in a variety of clinical and histological forms such as nodular-ulcerative, superficial, pigmented, morphealike, fibroepithelioma and nevoid syndrome. Basal cell carcinomas are the most common cutaneous neoplasms

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found in humans. The majority of new cases of nonmelanoma skin cancers fall into this category.

[0051] The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate surrounding tissues and to give rise to metastases. Exemplary carcinomas include: "basal cell carcinoma", which is an epithelial tumor of the skin that, while seldom metastasizing, has potentialities for local invasion and destruction; "squamous cell carcinoma", which refers to carcinomas arising from squamous epithelium and having cuboid cells; "carcinosarcoma", which include malignant tumors composed of carcinomatous and sarcomatous tissues; "adenocystic carcinoma", carcinoma marked by cylinders or bands of hyaline or mucinous stroma separated or surrounded by nests or cords of small epithelial cells, occurring in the mammary and salivary glands, and mucous glands of the respiratory tract; "epidermoid carcinoma", which refers to cancerous cells which tend to differentiate in the same way as those of the epidermis; i.e., they tend to form prickle cells and undergo cornification; "nasopharyngeal carcinoma", which refers to a malignant tumor arising in the epithelial lining of the space behind the nose; and "renal cell carcinoma", which pertains to carcinoma of the renal parenchyma composed of tubular cells in varying arrangements. Other carcinomatous epithelial growths are "papillomas", which refers to benign tumors derived from epithelium and having a papillomavirus as a causative agent; and "epidermoidomas", which refers to a cerebral or meningeal tumor formed by inclusion of ectodermal elements at the time of closure of the neural groove.

[0052] The "corium" or "dermis" refers to the layer of the skin deep to the epidermis, consisting of a dense bed of vascular connective tissue, and containing the nerves and terminal organs of sensation. The hair roots, and sebaceous and sweat glands are structures of the epidermis which are deeply embedded in the dermis.

[0053] "Dental tissue" refers to tissue in the mouth which is similar to epithelial tissue, for example gum tissue. The method of the present invention is useful for treating periodontal disease.

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[0054] "Dermal skin ulcers" refer to lesions on the skin caused by superficial loss of tissue, usually with inflammation. Dermal skin ulcers which can be treated by the method of the present invention include decubitus ulcers, diabetic ulcers, venous stasis ulcers and arterial ulcers. Decubitus wounds refer to chronic ulcers that result from pressure applied to areas of the skin for extended periods of time. Wounds of this type are often called bedsores or pressure sores. Venous stasis ulcers result from the stagnation of blood or other fluids from defective veins. Arterial ulcers refer to necrotic skin in the area around arteries having poor blood flow.

[0055] The term "ED₅₀" means the dose of a drug which produces 50% of its maximum response or effect.

[0056] The terms "epithelia", "epithelial" and "epithelium" refer to the cellular covering of internal and external body surfaces (cutaneous, mucous and serous), including the glands and other structures derived therefrom, e.g., corneal, esophageal, epidermal, and hair follicle epithelial cells. Other exemplary epithelial tissue includes: olfactory epithelium, which is the pseudostratified epithelium lining the olfactory region of the nasal cavity, and containing the receptors for the sense of smell; glandular epithelium, which refers to epithelium composed of secreting cells; squamous epithelium, which refers to epithelium composed of flattened plate-like cells. The term epithelium can also refer to transitional epithelium, like that which is characteristically found lining hollow organs that are subject to great mechanical change due to contraction and distention, e.g., tissue which represents a transition between stratified squamous and columnar epithelium.

[0057] The term "epithelialization" refers to healing by the growth of epithelial tissue over a denuded surface.

[0058] The term "epidermal gland" refers to an aggregation of cells associated with the epidermis and specialized to secrete or excrete materials not related to their ordinary metabolic needs. For example, "sebaceous glands" are holocrine glands in the corium that secrete an oily substance and sebum. The term "sweat glands" refers to glands that secrete

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sweat, situated in the corium or subcutaneous tissue, opening by a duct on the body surface.

[0059] The term "epidermis" refers to the outermost and nonvascular layer of the skin, derived from the embryonic ectoderm, varying in thickness from 0.07-1.4 mm. On the palmar and plantar surfaces it comprises, from within outward, five layers: basal layer composed of columnar cells arranged perpendicularly; prickle-cell or spinous layer composed of flattened polyhedral cells with short processes or spines; granular layer composed of flattened granular cells; clear layer composed of several layers of clear, transparent cells in which the nuclei are indistinct or absent; and horny layer composed of flattened, cornified non-nucleated cells. In the epidermis of the general body surface, the clear layer is usually absent.

[0060] The "growth state" of a cell refers to the rate of proliferation of the cell and/or the state of differentiation of the cell. An "altered growth state" is a growth state characterized by an abnormal rate of proliferation, e.g., a cell exhibiting an increased or decreased rate of proliferation relative to a normal cell.

[0061] The term "agonist" refers to an agent or analog that binds productively to a receptor and mimics its biological activity. The term "antagonist" refers to an agent that binds to receptors but does not provoke the normal biological response. Thus, an antagonist potentiates or recapitulates, for example, the bioactivity of *patched*, such as to repress transcription of target genes. The antagonists can be used to overcome a *ptc* loss-of-function and/or a *smoothened* gain-of-function, the latter also being referred to as 'smoothened antagonists'. The term 'hedgehog antagonist' as used herein refers not only to any agent that may act by directly inhibiting the normal function of the hedgehog protein, but also to any agent that inhibits the hedgehog signaling pathway, and thus recapitulates the function of *ptc*. The term 'hedgehog agonist' likewise refers to an agent which antagonizes or blocks the bioactivity of *patched*, such as to increase transcription of target genes. The hedgehog antagonists can be used to overcome a *ptc* gain-of-function and/or a *smoothened* loss-of-function, the latter also being referred to as 'smoothened agonists'.

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[0062] The term "*hedgehog* gain-of-function" refers to an aberrant modification or mutation of a *ptc* gene, *hedgehog* gene, or *smoothed* gene, or a decrease (or loss) in the level of expression of such a gene, which results in a phenotype which resembles contacting a cell with a hedgehog protein, e.g., aberrant activation of a hedgehog pathway. The "gain-of-function" may include a loss of the ability of the *ptc* gene product to regulate the level of expression of Ci genes, e.g., Gli1, Gli2, and Gli3. The term '*hedgehog* gain-of-function' is also used herein to refer to any similar cellular phenotype (e.g., exhibiting excess proliferation) which occurs due to an alteration anywhere in the hedgehog signal transduction pathway, including, but not limited to, a modification or mutation of hedgehog itself. For example, a tumor cell with an abnormally high proliferation rate due to activation of the hedgehog signaling pathway would have a '*hedgehog* gain-of-function' phenotype, even if hedgehog is not mutated in that cell. '*Hedgehog* loss-of-function' refers to the direct opposite of a *hedgehog* gain-of-function, e.g., an aberrant modification or mutation that results in a phenotype which resembles contacting a cell with an agent which blocks hedgehog function.

[0063] As used herein, "immortalized cells" refers to cells which have been altered via chemical and/or recombinant means such that the cells have the ability to grow through an indefinite number of divisions in culture.

[0064] "Internal epithelial tissue" refers to tissue inside the body which has characteristics similar to the epidermal layer in the skin. Examples include the lining of the intestine. The method of the present invention is useful for promoting the healing of certain internal wounds, for example wounds resulting from surgery.

[0065] The term "keratosis" refers to proliferative skin disorder characterized by hyperplasia of the horny layer of the epidermis. Exemplary keratotic disorders include keratosis follicularis, keratosis palmaris et plantaris, keratosis pharyngea, keratosis pilaris, and actinic keratosis.

[0066] The term "LD₅₀" means the dose of a drug which is lethal in 50% of test subjects.

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[0067] The term "*patched* loss-of-function" refers to an aberrant modification or mutation of a *ptc* gene, or a decreased level of expression of the gene, which results in a phenotype which resembles contacting a cell with a hedgehog protein, e.g., aberrant activation of a hedgehog pathway. The 'gain-of-function' may include a loss of the ability of the *ptc* gene product to regulate the level of expression of Ci genes, e.g., Gli1, Gli2 and Gli3.

[0068] A "patient" or "subject" to be treated by the subject method can mean either a human or non-human animal.

[0069] The term "prodrug" is intended to encompass compounds which, under physiological conditions, are converted into the therapeutically active agents of the present invention. A common method for making a prodrug is to include selected moieties which are hydrolyzed under physiological conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal.

[0070] As used herein, "proliferating" and "proliferation" refer to cells undergoing mitosis.

[0071] The term "proliferative skin disorder" refers to any disease/disorder of the skin marked by unwanted or aberrant proliferation of cutaneous tissue. These conditions are typically characterized by epidermal cell proliferation or incomplete cell differentiation, and include, for example, X-linked ichthyosis, psoriasis, atopic dermatitis, allergic contact dermatitis, epidermolytic hyperkeratosis, and seborrheic dermatitis. For example, epidermodysplasia is a form of faulty development of the epidermis. Another example is "epidermolysis", which refers to a loosened state of the epidermis with formation of blebs and bullae either spontaneously or at the site of trauma.

[0072] The term "psoriasis" refers to a hyperproliferative skin disorder which alters the skin's regulatory mechanisms. In particular, lesions are formed which involve primary and secondary alterations in epidermal proliferation, inflammatory responses of the skin, and an expression of regulatory molecules such as lymphokines and inflammatory factors.

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Psoriatic skin is morphologically characterized by an increased turnover of epidermal cells, thickened epidermis, abnormal keratinization, inflammatory cell infiltrates into the dermis layer and polymorphonuclear leukocyte infiltration into the epidermis layer resulting in an increase in the basal cell cycle. Additionally, hyperkeratotic and parakeratotic cells are present.

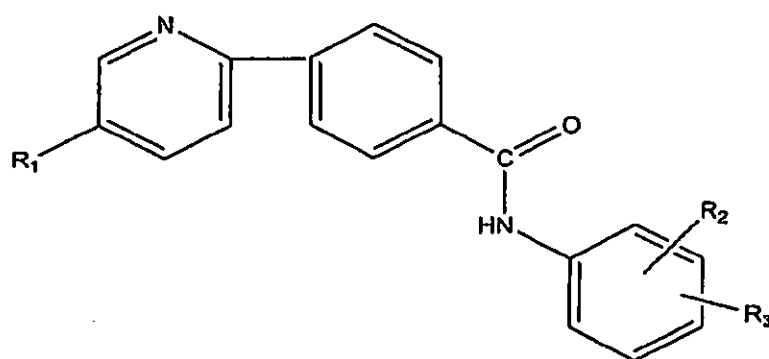
[0073] The term “*smoothened* gain-of-function” refers to an aberrant modification or mutation of a *smo* gene, or an increased level of expression of the gene, which results in a phenotype which resembles contacting a cell with a hedgehog protein, e.g., aberrant activation of a hedgehog pathway. While not wishing to be bound by any particular theory, it is noted that *ptc* may not signal directly into the cell, but rather interact with *smoothened*, another membrane-bound protein located downstream of *ptc* in hedgehog signaling (Marigo et al., *Nature* 384: 177-179 (1996)). The *smo* gene is a segment-polarity gene required for the correct patterning of every segment in *Drosophila* (Alcedo et al., *Cell* 86: 221-232(1996)). Human homologs of *smo* have been identified. See, for example, Stone et al., *Nature* 384:129-134(1996), and GenBank accession no. U84401. The *smoothened* gene encodes an integral membrane protein with characteristics of heterotrimeric G-protein-coupled receptors; i.e., 7-transmembrane regions. This protein shows homology to the *Drosophila* Frizzled (Fz) protein, a member of the wingless pathway. It was originally thought that *smo* encodes a receptor of the Hh signal. However, this suggestion was subsequently disproved, as evidence for *ptc* being the Hh receptor was obtained. Cells that express Smo fail to bind Hh, indicating that *smo* does not interact directly with Hh (Nusse, *Nature* 384: 119-120 (1996)). Rather, the binding of Sonic hedgehog (SHH) to its receptor, PTCH, is thought to prevent normal inhibition by PTCH of *smoothened* (SMO), a seven-span transmembrane protein.

[0074] The term “transformed cells” refers to cells which have spontaneously converted to a state of unrestrained growth, i.e., they have acquired the ability to grow through an indefinite number of divisions in culture. Transformed cells may be characterized by such terms as neoplastic, anaplastic and/or hyperplastic, with respect to their loss of growth control.

[0118] As described in further detail below, it is contemplated that the subject methods can be carried out using a variety of different aromatic compounds, which can be readily identified, e.g., by such drug screening assays as described herein.

[0119] According to an embodiment of the invention, a first type of compound is provided for treatment of various diseases, disorders, and pathologies. The compounds of the first type can include an alkylpyridyl moiety bridged to a benzamide moiety, where the benzamide moiety can include a first substituent attached to the benzamide moiety via the nitrogen atom of the benzamide moiety. The first substituent can comprise an aryl structure which can include at least one second substituent, where the second substituent can be an unsubstituted or substituted alkyl, a halogen, an alkoxy, acetyl, or nitro.

[0120] Compounds of the first type can be described as compounds having the general structure (I), or a pharmaceutically acceptable salt thereof:



(I)

[0121] In structure (I), R_1 can be an alkyl, for example, ethyl, *n*-propyl or *n*-amyl; R_2 can be hydrogen, an alkyl (e.g., methyl), halogen (e.g., chlorine), or an alkoxy group (e.g., methoxy); and R_3 can be an unsubstituted or substituted alkyl group (e.g., methyl or trifluoromethyl), halogen (e.g., chlorine or iodine), an alkoxy group (e.g., methoxy), acetyl group, or nitro group.

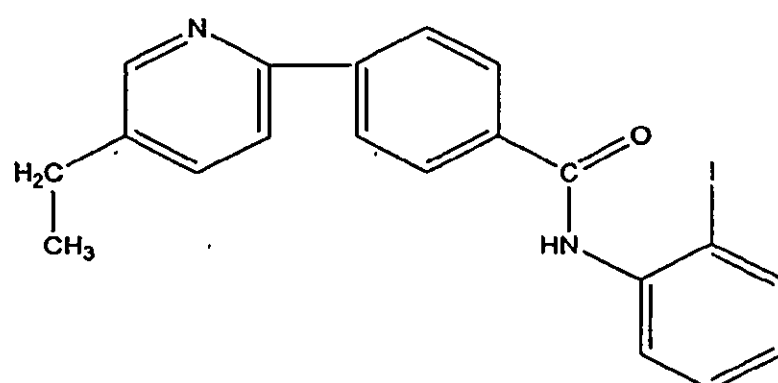
[0122] Some examples of particular compounds described by the general structure (I) include compounds having the formulae (1)-(7):

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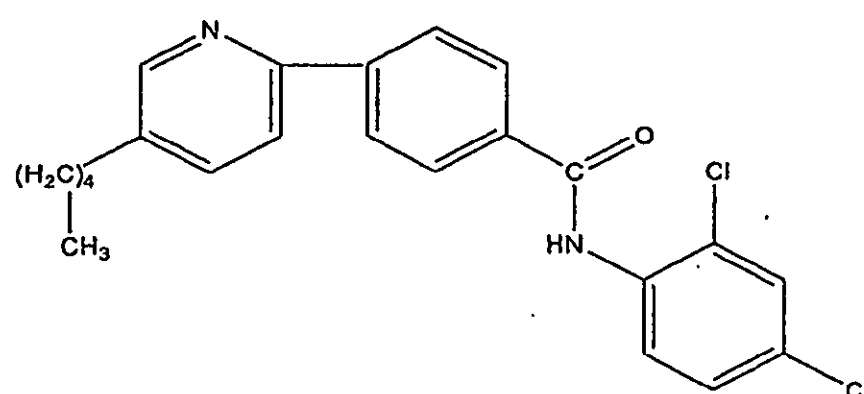
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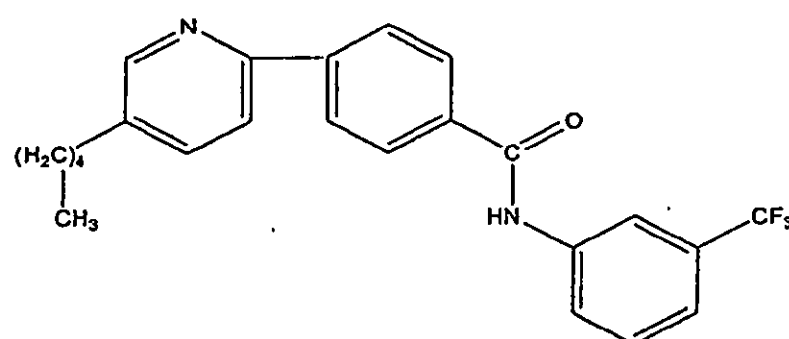
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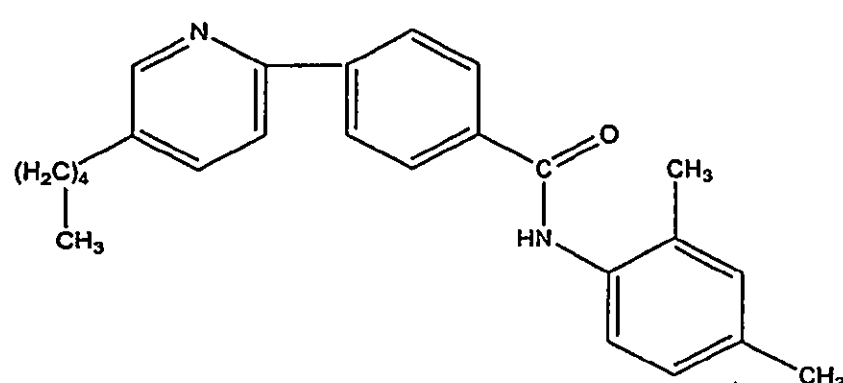
(1)



(2)



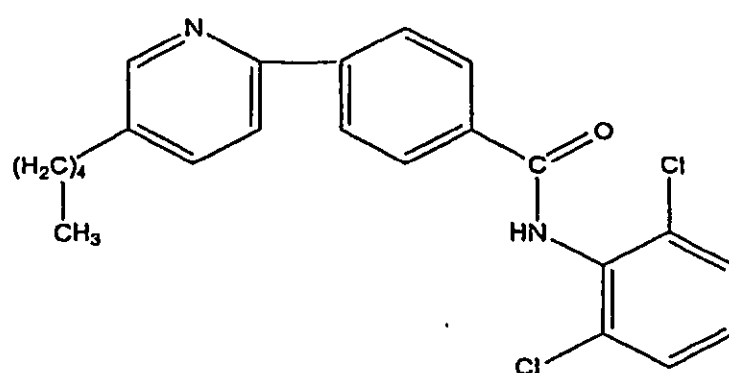
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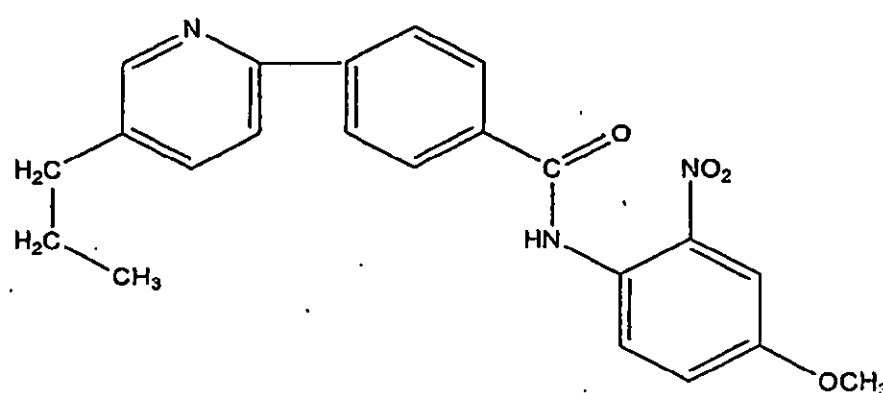
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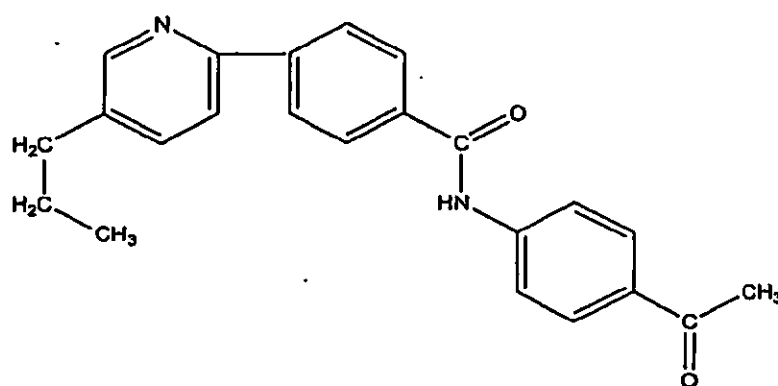
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(5)



(6)



(7)

[0123] According to an embodiment of the invention, a second type of compounds is provided for treatment of various diseases, disorders, and pathologies. The compounds of the second type can include two benzamide moieties connected with a phenylene bridge, for example, the 1,3-phenylene bridge. The benzamide moieties can include a substituent, such as *tert*-butyl, chlorine, bromine, or nitro.

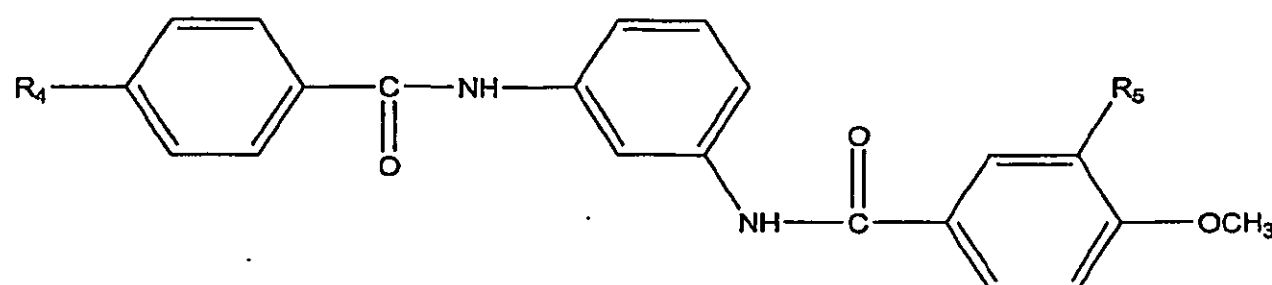
[0124] Compounds of the second type can be described as compounds having the general structure (II), or a pharmaceutically acceptable salt thereof:

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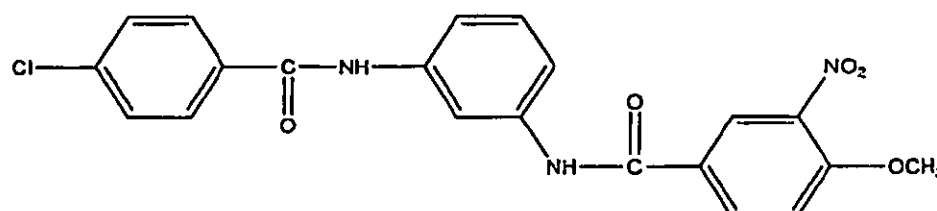
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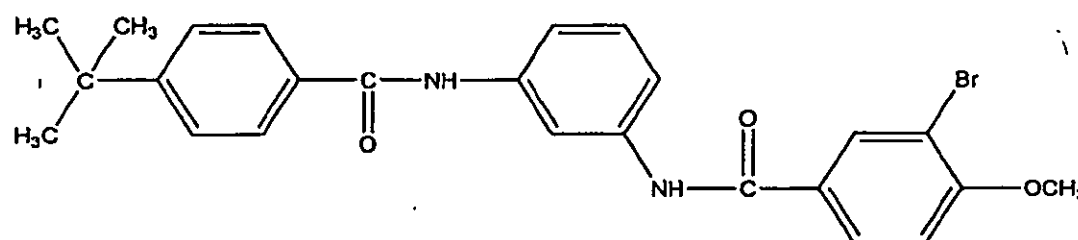
(II)

[0125] In structure (II), R_4 can be *tert*-butyl or chlorine, and R_5 can be nitro group or bromine.

[0126] Some examples of particular compounds described by the general structure (II) include compounds having the formulae (8) or (9):



(8)



(9)

[0127] According to an embodiment of the invention, a third type of compounds is provided for treatment of various diseases, disorders, and pathologies. The compounds of the third type can include a first heterocyclic ring fused with a second heterocyclic ring, where the first ring can be 1,3-diazine-6-one, and the second ring can be N-substituted thiazole-2-thione or a substituted thiophene.

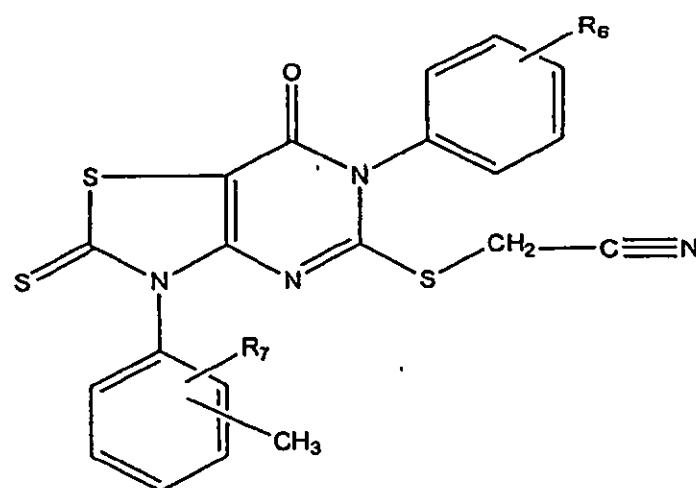
[0128] Compounds of the third type can be described as compounds having either the general structure (III), or the general structure (IV), or a pharmaceutically acceptable salt thereof:

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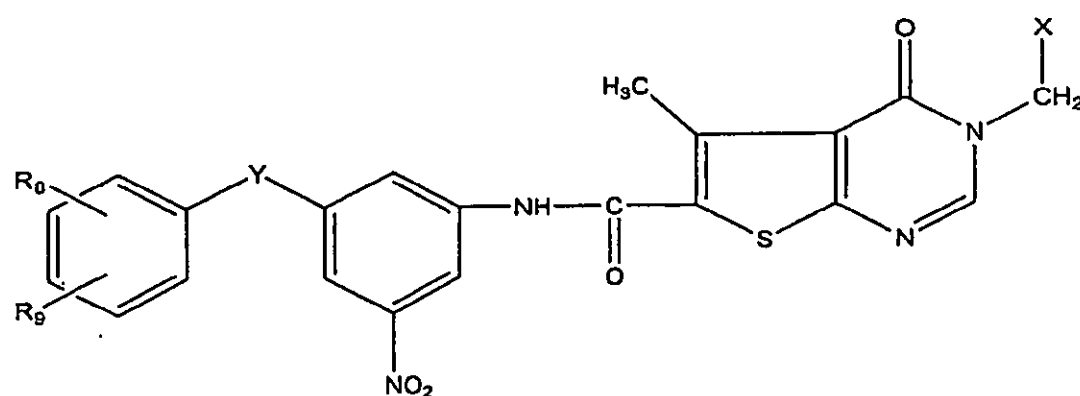
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(III)



(IV)

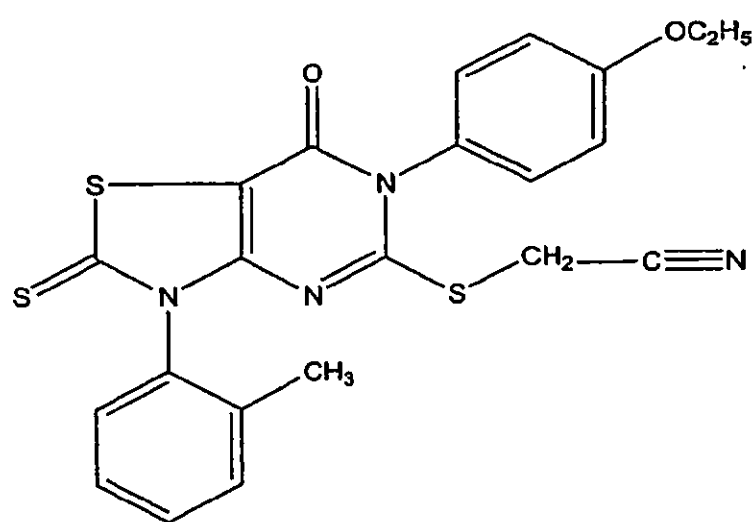
[0129] In structure (III), R_6 can be methyl or ethoxy group, and R_7 can be hydrogen or methyl. In structure (IV), R_8 can be hydrogen or methyl, R_9 can be hydrogen, chlorine or fluorine, X can be ethyl or fluorophenyl, and Y can be an atom of oxygen or sulfur. Some examples of particular compounds described by the general structure (III) include compounds having the formulae (10) and (11), and some examples of particular compounds described by the general structure (IV) include compounds having the formulae having the formulae (12)-(15):

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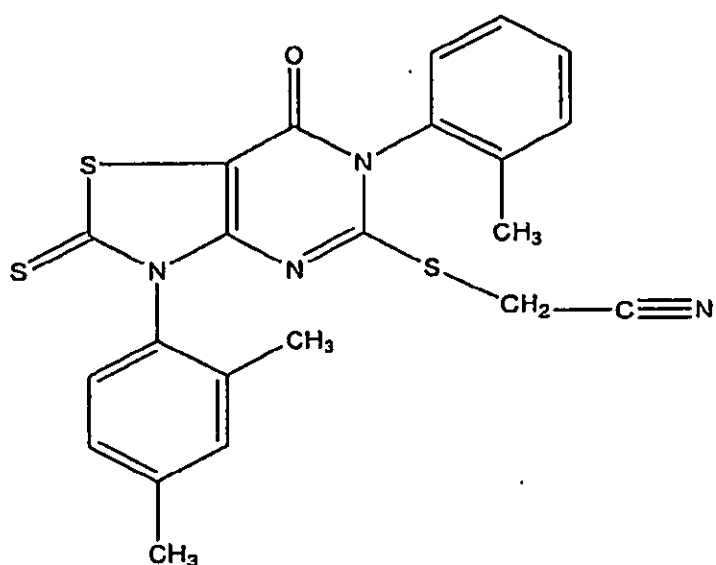
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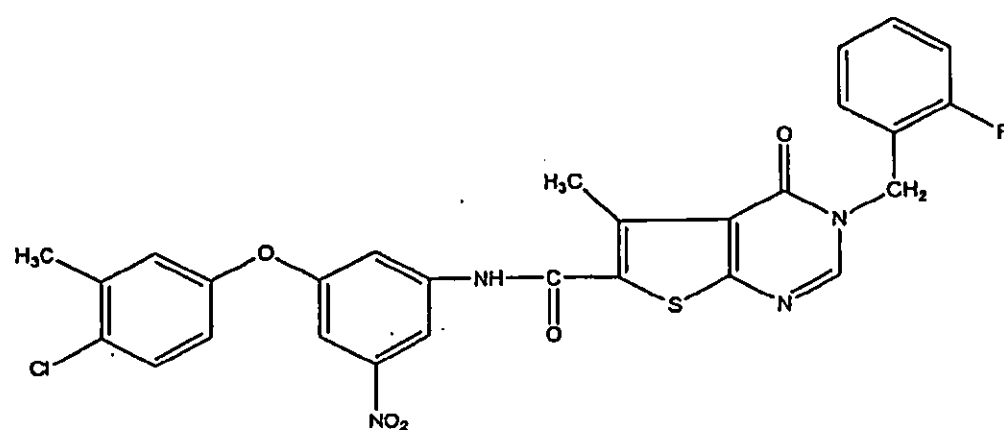
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(10)



(11)



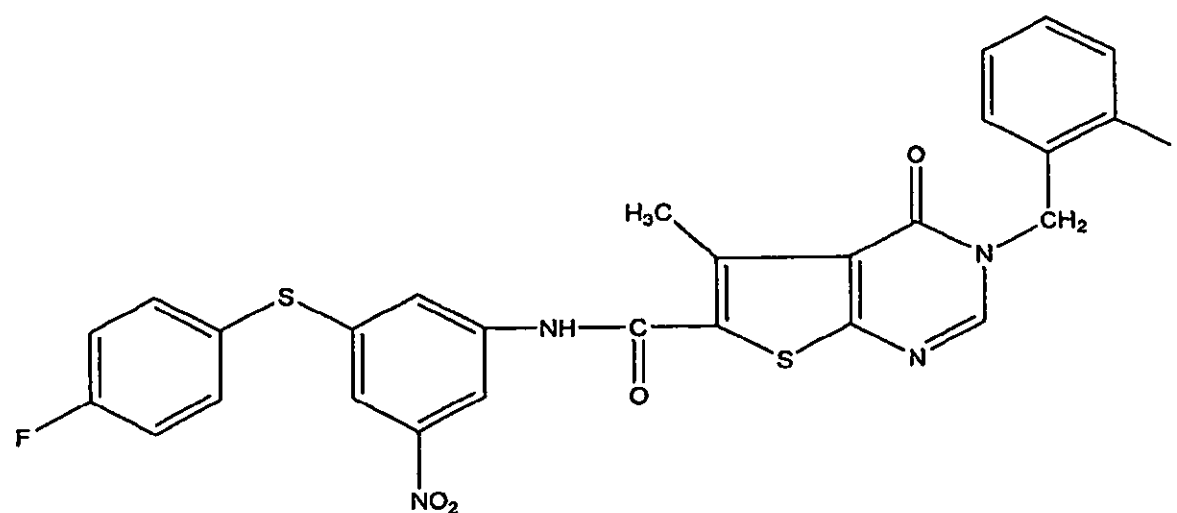
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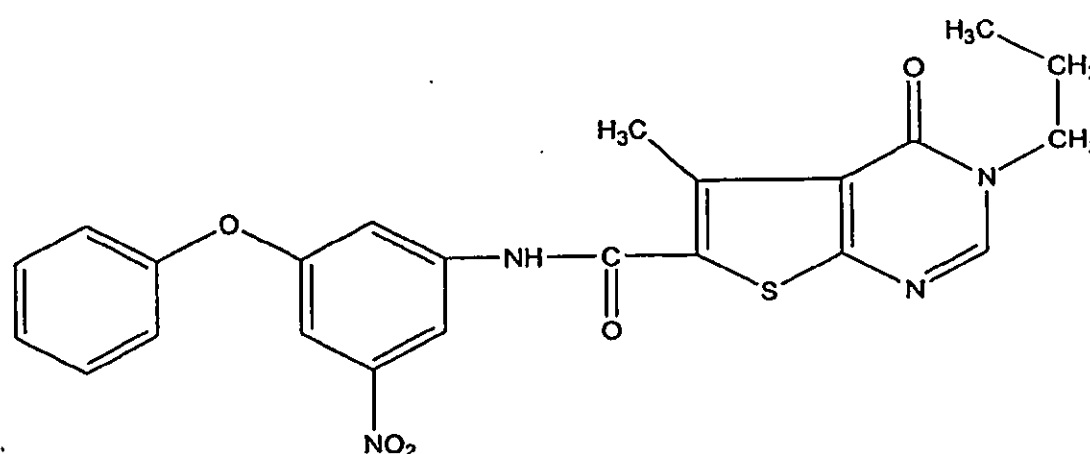
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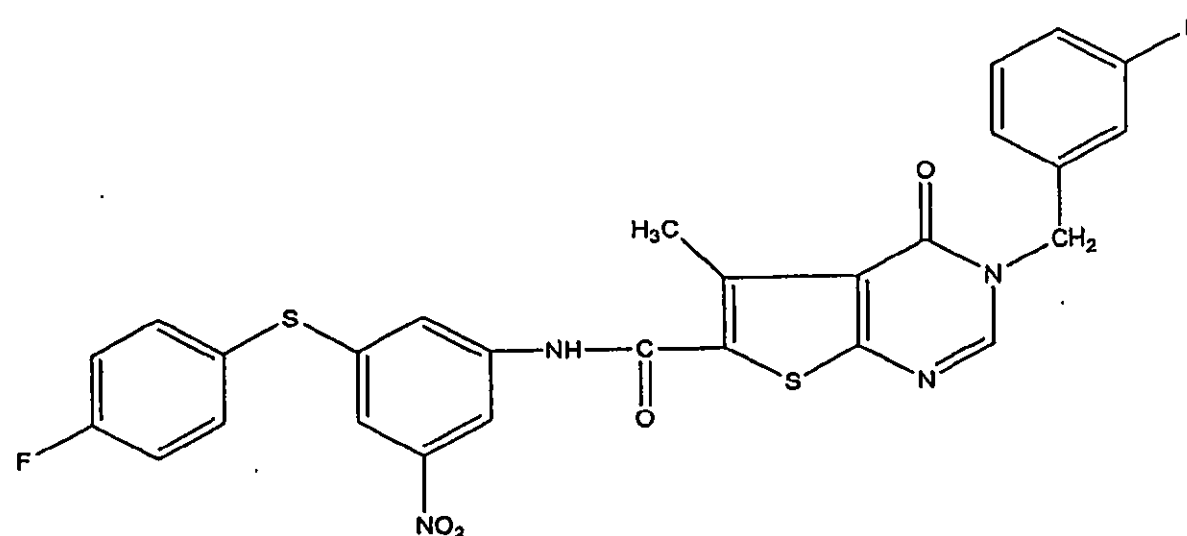
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(13)



(14)



(15)

[0130] According to an embodiment of the invention, a fourth type of compounds is provided for treatment of various diseases, disorders, and pathologies. The compounds of the fourth type can include a thiazole moiety carrying a heterocyclic substituent and a

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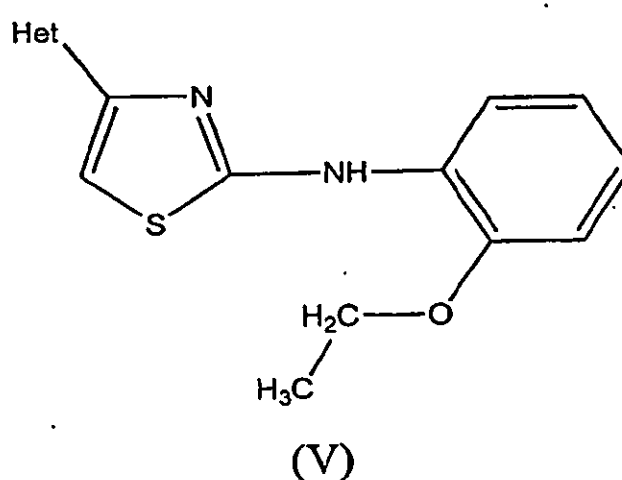
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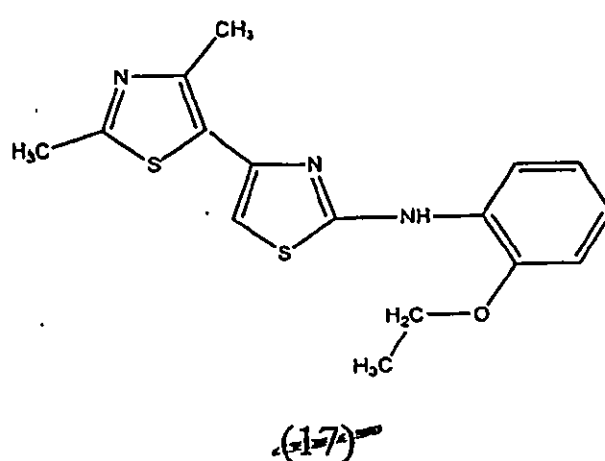
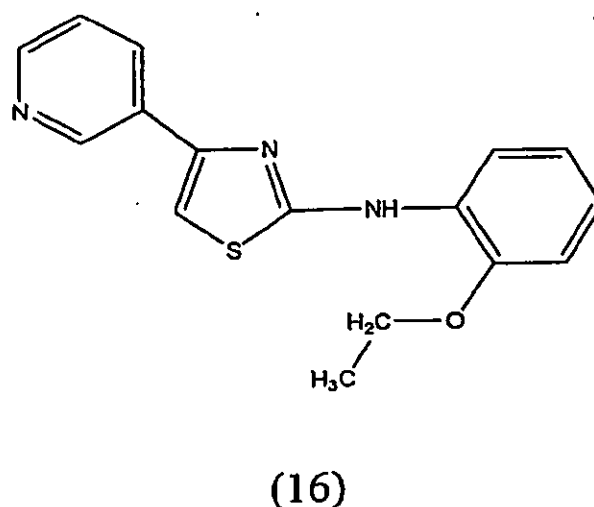
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secondary amino substituent, where the heterocyclic substituent can be thiazolyl or pyridyl, and the secondary amino substituent can be ethoxyphenylene group.

[0131] Compounds of the fourth type can be described as compounds having the general structure (V), or a pharmaceutically acceptable salt thereof:



[0132] In structure (V), Het is a heterocyclic radical, for example, pyridyl or thiazolyl. Some examples of particular compounds described by the general structure (V) include compounds having the formulae having the formulae (16) or (17):



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[0152] In certain embodiments, the subject aromatic compounds can be chosen on the basis of their selectivity for the ptc/smoothened pathway(s). This selectivity can be for the ptc/smoothened pathway(s) versus other steroid-mediated pathways (such as testosterone or estrogen mediated activities), as well as selectivity for particular ptc/smoothened pathways, e.g., which isotype specific for ptc (e.g., ptc-1, ptc-2). For instance, the subject method may employ aromatic compounds that do not substantially interfere with the biological activity of such steroids as aldosterone, androstane, androstene, androstenedione, androsterone, cholecalciferol, cholestane, cholic acid, corticosterone, cortisol, cortisol acetate, cortisone, cortisone acetate, deoxycorticosterone, digitoxigenin, ergocalciferol, ergosterol, estradiol-17- α , estradiol-17- β , estriol, estrane, estrone, hydrocortisone, lanosterol, lithocholic acid, mestranol, β -methasone, prednisone, pregnane, pregnenolone, progesterone, spironolactone, testosterone, triamcinolone and their derivatives, at least so far as those activities are unrelated to ptc-related signaling.

[0153] In one embodiment, the subject aromatic compounds for use in the present methods have a k_d for members of the nuclear hormone receptor superfamily of greater than 1 μ M, and more specifically greater than 1 mM, e.g., it does not bind estrogen, testosterone receptors or the like. In one embodiment, the subject compounds have no estrogenic activity at physiological concentrations (e.g., in the range of 1 ng - 1 mg/kg).

[0154] Thus, in one embodiment, untoward side effects that may be associated with certain members of the aromatic compounds can be reduced by, for example, using the drug screening assays described herein. The application of combinatorial and medicinal chemistry techniques to the aromatic compounds provides a means for reducing such unwanted negative side effects including personality changes, shortened life spans, cardiovascular diseases and vascular occlusion, organ toxicity, hyperglycemia and diabetes, Cushnoid features, "wasting" syndrome, steroidal glaucoma, hypertension, peptic ulcers, and increased susceptibility to infections. For certain embodiments, it will be beneficial to reduce the teratogenic activity relative to jervine, as for example, in the use of the subject method to selectively inhibit spermatogenesis.

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[0155] Another aspect of the present invention relates to a method of modulating a differentiated state, survival, and/or proliferation of a cell having a *ptc* loss-of-function, *hedgehog* gain-of-function, or *smoothened* gain-of-function, by contacting the cells with an aromatic compound as set forth above according to the subject method and as the circumstances may warrant.

[0156] For instance, it is contemplated by the invention that, in light of the findings of an apparently broad involvement of *hedgehog*, *ptc*, and *smoothened* in the formation of ordered spatial arrangements of differentiated tissues in vertebrates, the subject method could be used as part of a process for generating and/or maintaining an array of different vertebrate tissue both *in vitro* and *in vivo*. The aromatic compound, whether inductive or anti-inductive with respect proliferation or differentiation of a given tissue, can be, as appropriate, any of the preparations described above.

[0157] For example, the present method of using subject aromatic compounds is applicable to cell culture techniques wherein, whether for genetic or biochemical reasons, the cells have a *ptc* loss-of-function, *hedgehog* gain-of-function, or *smoothened* gain-of-function phenotype. Alternatively, a subject aromatic compound may be employed in a related method directed towards cells which have a *ptc* loss-of-function, *hedgehog* gain-of-function, or *smoothened* gain-of-function phenotype. *In vitro* neuronal culture systems have proven to be fundamental and indispensable tools for the study of neural development, as well as the identification of neurotrophic factors such as nerve growth factor (NGF), ciliary trophic factors (CNTF), and brain derived neurotrophic factor (BDNF). One use of the present method may be in cultures of neuronal stem cells, such as in the use of such cultures for the generation of new neurons and glia. In such embodiments of the subject method, the cultured cells can be contacted with an aromatic compound of the present invention in order to alter the rate of proliferation of neuronal stem cells in the culture and/or alter the rate of differentiation, or to maintain the integrity of a culture of certain terminally differentiated neuronal cells. In an exemplary embodiment, the subject method can be used to culture, for example, sensory neurons or, alternatively, motoneurons. Such neuronal cultures can be used as convenient assay systems as well as sources of implantable cells for therapeutic treatments.

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[0158] In another embodiment, the subject method can be used in the treatment of neoplastic or hyperplastic transformations such as may occur in the central nervous system. For instance, the subject compounds can be utilized to cause such transformed cells to become either post-mitotic or apoptotic. The present method may, therefore, be used as part of a treatment for, e.g., malignant gliomas, meningiomas, medulloblastomas, neuroectodermal tumors, and ependymomas. In another embodiment, the subject method can be used as part of a treatment regimen for malignant medulloblastoma and other primary CNS malignant neuroectodermal tumors.

[0159] In certain embodiments, the subject method is used as part of treatment program for medulloblastoma. Medulloblastoma, a primary brain tumor, is the most common brain tumor in children. A medulloblastoma is a primitive neuroectodermal tumor arising in the posterior fossa. They account for approximately 25% of all pediatric brain tumors (Miller). Histologically, they are small round cell tumors commonly arranged in true rosettes, but may display some differentiation to astrocytes, ependymal cells or neurons (Rorke; Kleihues). PNET's may arise in other areas of the brain including the pineal gland (pineoblastoma) and cerebrum. Those arising in the supratentorial region generally fare worse than their PF counterparts.

[0160] Medulloblastoma/PNET's are known to recur anywhere in the CNS after resection, and can even metastasize to bone. Pretreatment evaluation should therefore include an examination of the spinal cord to exclude the possibility of "dropped metastases". Gadolinium-enhanced MRI has largely replaced myelography for this purpose, and CSF cytology is obtained postoperatively as a routine procedure.

[0161] In other embodiments, the subject method is used as part of treatment program for ependymomas. Ependymomas account for approximately 10% of the pediatric brain tumors in children. Grossly, they are tumors that arise from the ependymal lining of the ventricles and microscopically form rosettes, canals, and perivascular rosettes. In the CHOP series of 51 children reported with ependymomas, 3/4 were histologically benign. Approximately 2/3 arose from the region of the 4th ventricle. One third presented in the supratentorial region. Age at presentation peaks between birth and 4 years, as

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as part of a treatment of lung carcinoma and adenocarcinomas, and other proliferative disorders involving the lung epithelia.

[0174] Many other tumors may, based on evidence such as involvement of the hedgehog pathway in these tumors, or detected expression of hedgehog, or their receptors in these tissues during development, be affected by treatment with the subject aromatic compounds. Such tumors include, but are by no means limited to, tumors related to Gorlin's syndrome (e.g., basal cell carcinoma, medulloblastoma, meningioma, etc.), tumors evidenced in ptc knock-out mice (e.g., hemangioma, rhabdomyosarcoma, etc.), tumors resulting from gli-1 amplification (e.g., glioblastoma, sarcoma, etc.), tumors connected with TRC8, a ptc homolog (e.g., renal carcinoma, thyroid carcinoma, etc.), Ext-1-related tumors (e.g., bone cancer, etc.), Shh-induced tumors (e.g., lung cancer, chondrosarcomas, etc.), and other tumors (e.g., breast cancer, urogenital cancer (e.g., kidney, bladder, ureter, prostate, etc.), adrenal cancer, gastrointestinal cancer (e.g., stomach, intestine, etc.), etc.).

[0175] In still another embodiment of the present invention, compositions comprising one or more of the subject compounds can be used in the *in vitro* generation of skeletal tissue, such as from skeletogenic stem cells, as well as the *in vivo* treatment of skeletal tissue deficiencies. The present invention particularly contemplates the use of subject compounds to regulate the rate of chondrogenesis and/or osteogenesis. By "skeletal tissue deficiency", it is meant a deficiency in bone or other skeletal connective tissue at any site where it is desired to restore the bone or connective tissue, no matter how the deficiency originated, e.g. whether as a result of surgical intervention, removal of tumor, ulceration, implant, fracture, or other traumatic or degenerative conditions.

[0176] For instance, the methods of the present invention can be used as part of a regimen for restoring cartilage function to a connective tissue. Such methods are useful in, for example, the repair of defects or lesions in cartilage tissue which is the result of degenerative wear such as that which results in arthritis, as well as other mechanical derangements which may be caused by trauma to the tissue, such as a displacement of torn meniscus tissue, meniscectomy, a laxation of a joint by a torn ligament, malignment

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276:817-21 (1997); Xie et al., *Genes Chromosomes Cancer* 18:305-9 (1997); Stone et al., *Nature* 384:129-34 (1996); and Johnson et al., *Science* 272:1668-71 (1996).

[0210] The subject method can also be used to treatment patients with BCNS, e.g., to prevent BCC or other effects of the disease which may be the result of *ptc* loss-of-function, *hedgehog* gain-of-function, or *smoothed* gain-of-function. Basal cell nevus syndrome is a rare autosomal dominant disorder characterized by multiple BCCs that appear at a young age. BCNS patients are very susceptible to the development of these tumors; in the second decade of life, large numbers appear, mainly on sun-exposed areas of the skin. This disease also causes a number of developmental abnormalities, including rib, head and face alterations, and sometimes polydactyly, syndactyly, and spina bifida. They also develop a number of tumor types in addition to BCCs: fibromas of the ovaries and heart, cysts of the skin and jaws, and in the central nervous system, medulloblastomas and meningiomas. The subject methods can be used to prevent or treat such tumor types in BCNS and non-BCNS patients. Studies of BCNS patients show that they have both genomic and sporadic mutations in the *ptc* gene, suggesting that these mutations are the ultimate cause of this disease.

[0211] In another aspect, the present invention provides pharmaceutical preparations and methods for controlling the formation of megakaryocyte-derived cells and/or controlling the functional performance of megakaryocyte-derived cells. For instance, certain of the compositions disclosed herein may be applied to the treatment or prevention of a variety hyperplastic or neoplastic conditions affecting platelets.

[0212] It will be apparent to one of ordinary skill that certain instances described above may respond favorably to administration of a hedgehog agonist or antagonist, depending on the particular effect on the hedgehog pathway desired. For example, although a hedgehog agonist may be useful in maintaining a culture of undifferentiated stem cells, a hedgehog antagonist may be employed to maintain a differentiation state in a culture of differentiated cells. Such methods are considered to fall within the scope of the present invention.

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[0213] In another aspect, the present invention provides pharmaceutical preparations comprising the subject aromatic compounds. The aromatic compounds for use in the subject method may be conveniently formulated for administration with a pharmaceutically acceptable and/or sterile medium, such as water, buffered saline, polyol (for example, glycerol, propylene glycol, liquid polyethylene glycol and the like) or suitable mixtures thereof. The optimum concentration of the active ingredient(s) in the chosen medium can be determined empirically, according to procedures well known to medicinal chemists. As used herein, "biologically acceptable medium" includes any and all solvents, dispersion media, and the like which may be appropriate for the desired route of administration of the pharmaceutical preparation. The use of such media for pharmaceutically active substances is known in the art. Except insofar as any conventional media or agent is incompatible with the activity of the subject compounds, its use in the pharmaceutical preparation of the invention is contemplated. Suitable vehicles and their formulation inclusive of other proteins are described, for example, in the book Remington's Pharmaceutical Sciences (Remington's Pharmaceutical Sciences. Mack Publishing Company, Easton, Pa., USA 1985). These vehicles include injectable "deposit formulations".

[0214] Pharmaceutical formulations of the present invention can also include veterinary compositions, e.g., pharmaceutical preparations of the subject compounds suitable for veterinary uses, e.g., for the treatment of live stock or domestic animals, e.g., dogs.

[0215] Methods of introduction may also be provided by rechargeable or biodegradable devices. Various slow release polymeric devices have been developed and tested *in vivo* in recent years for the controlled delivery of drugs, including proteinacious biopharmaceuticals. A variety of biocompatible polymers (including hydrogels), including both biodegradable and non-degradable polymers, can be used to form an implant for the sustained release of a subject compound at a particular target site.

[0216] The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given by forms suitable for each administration

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route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, controlled release patch, etc. administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral and topical administrations are preferred.

[0217] The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

[0218] The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

[0219] These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

[0220] Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms such as described below or by other conventional methods known to those of skill in the art.

[0221] Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

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[0222] The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[0223] A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

[0224] In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, intravenous, intracerebroventricular and subcutaneous doses of the compounds of this invention for a patient will range from about 0.0001 to about 100 mg per kilogram of body weight per day.

[0225] If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

[0226] The term "treatment" is intended to encompass also prophylaxis, therapy and cure.

[0227] In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species can be treated.

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However, the method can also be practiced in other species, such as avian species (e.g., chickens).

[0228] The compound of the invention can be administered as such or in admixtures with pharmaceutically acceptable carriers and can also be administered in conjunction with other antimicrobial agents such as penicillins, cephalosporins, aminoglycosides and glycopeptides. Conjunctive therapy, thus includes sequential, simultaneous and separate administration of the active compound in a way that the therapeutical effects of the first administered one is not entirely disappeared when the subsequent is administered.

[0229] Embodiments of the present invention also provide articles of manufacture that can include a packaging material and a pharmaceutical composition contained within the packaging material. The packaging material can comprise a label which indicates that the pharmaceutical composition can be used for treatment of one or more disorders identified above.

[0230] The pharmaceutical composition can include a compound according to the present invention. In addition to a compound of the present invention, the pharmaceutical may also contain other therapeutic agents, and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques known in the art of pharmaceutical formulation.

[0231] Thus, in one embodiment, the invention provides a pharmaceutical composition including a therapeutic agent and a compound of the invention. The compound is present in a concentration effective to treat cancer.

[0232] The compounds of the invention may be formulated into therapeutic compositions as natural or salt forms. Pharmaceutically acceptable non-toxic salts include the base addition salts (formed with free carboxyl or other anionic groups) which may be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine,

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trimethylamine, 2-ethylamino-ethanol, histidine, procaine, and the like. Such salts may also be formed as acid addition salts with any free cationic groups and will generally be formed with inorganic acids such as, for example, hydrochloric, sulfuric, or phosphoric acids, or organic acids such as acetic, citric, p-toluenesulfonic, methanesulfonic acid, oxalic, tartaric, mandelic, and the like.

[0233] Salts of the invention can include amine salts formed by the protonation of an amino group with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like. Salts of the invention can also include amine salts formed by the protonation of an amino group with suitable organic acids, such as p-toluenesulfonic acid, acetic acid, methanesulfonic acid and the like. Additional excipients which are contemplated for use in the practice of the present invention are those available to those of ordinary skill in the art, for example, those found in the United States Pharmacopeia Vol. XXII and National Formulary Vol. XVII, U.S. Pharmacopeia Convention, Inc., Rockville, MD (1989), the relevant contents of which is incorporated herein by reference. In addition, polymorphs of the invention compounds are included in the present invention.

[0234] Pharmaceutical compositions of the invention may be administered by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, intrathecal, or intracisternal injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents. The present compounds may, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. The present compounds may also be administered liposomally.

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[0235] The pharmaceutical compositions for the administration of the compounds of this embodiment, either alone or in combination with other therapeutic agents, may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs.

[0236] Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated to form osmotic therapeutic tablets for control release.

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[0237] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[0238] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. Also useful as a solubilizer is polyethylene glycol, for example. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or *n*-propyl, *p*-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0239] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0240] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a

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dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0241] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

[0242] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a parenterally-acceptable diluent or solvent or cosolvent or complexing agent or dispersing agent or excipient or combination thereof, for example 1,3-butanediol, polyethylene glycols, polypropylene glycols, ethanol or other alcohols, povidones, various brands of TWEEN surfactant, sodium dodecyl sulfate, sodium deoxycholate, dimethylacetamide, polysorbates, poloxamers, cyclodextrins, lipids, and excipients such as inorganic salts (e.g., sodium chloride), buffering agents (e.g., sodium citrate, sodium phosphate), and sugars (e.g., saccharose and dextrose). Among the acceptable vehicles and solvents that may be employed are water, dextrose solutions, Ringer's solutions and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0243] Depending on the condition being treated, these pharmaceutical compositions may be formulated and administered systemically or locally. Techniques for formulation and administration may be found in the latest edition of "Remington's Pharmaceutical Sciences" (Mack Publishing Co, Easton Pa.). Suitable routes may, for example, include oral or transmucosal administration; as well as parenteral delivery, including intramuscular, subcutaneous, intramedullary, intrathecal, intraventricular, intravenous,

intraperitoneal, or intranasal administration. For injection, the pharmaceutical compositions of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiologically buffered saline. For tissue or cellular administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0244] The compounds of the present invention may also be administered in the form of suppositories for rectal, urethral, or vaginal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

[0245] For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention are employed. (For purposes of this application, topical application shall include mouthwashes and gargles).

[0246] In one embodiment, the invention compounds are administered in combination with an anti-inflammatory agent, antihistamines, chemotherapeutic agent, immunomodulator, therapeutic antibody or a protein kinase inhibitor, e.g., a tyrosine kinase inhibitor, to a subject in need of such treatment. While not wanting to be limiting, chemotherapeutic agents include antimetabolites, such as methotrexate, DNA cross-linking agents, such as cisplatin/carboplatin; alkylating agents, such as canbusil;

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topoisomerase I inhibitors such as dactinomycin; microtubule inhibitors such as taxol (paclitaxol), and the like. Other chemotherapeutic agents include, for example, a vinca alkaloid, mitomycin-type antibiotic, bleomycin-type antibiotic, antifolate, colchicine, demecolone, etoposide, taxane, anthracycline antibiotic, doxorubicin, daunorubicin, carminomycin, epirubicin, idarubicin, mithoxanthrone, 4-dimethoxy-daunomycin, 11-deoxydaunorubicin, 13-deoxydaunorubicin, adriamycin-14-benzoate, adriamycin-14-octanoate, adriamycin-14-naphthaleneacetate, amsacrine, carmustine, cyclophosphamide, cytarabine, etoposide, lovastatin, melphalan, topotecan, oxalaplatin, chlorambucil, methotrexate, lomustine, thioguanine, asparaginase, vinblastine, vindesine, tamoxifen, or mechlorethamine. While not wanting to be limiting, therapeutic antibodies include antibodies directed against the HER2 protein, such as trastuzumab; antibodies directed against growth factors or growth factor receptors, such as bevacizumab, which targets vascular endothelial growth factor, and OSI-774, which targets epidermal growth factor; antibodies targeting integrin receptors, such as Vitaxin (also known as MEDI-522), and the like. Classes of anticancer agents suitable for use in compositions and methods of the present invention include, but are not limited to: 1) alkaloids, including, microtubule inhibitors (e.g., Vincristine, Vinblastine, and Vindesine, etc.), microtubule stabilizers (e.g., Paclitaxel [Taxol], and Docetaxel, Taxotere, etc.), and chromatin function inhibitors, including, topoisomerase inhibitors, such as, epipodophyllotoxins (e.g., Etoposide [VP-16], and Teniposide [VM-26], etc.), and agents that target topoisomerase I (e.g., Camptothecin and Irinotecan [CPT-11], etc.); 2) covalent DNA-binding agents [alkylating agents], including, nitrogen mustards (e.g., Mechlorethamine, Chlorambucil, Cyclophosphamide, Ifosfamide, and Busulfan [Myleran], etc.), nitrosoureas (e.g., Carmustine, Lomustine, and Semustine, etc.), and other alkylating agents (e.g., Dacarbazine, Hydroxymethylmelamine, Thiotepa, and Mitocycin, etc.); 3) noncovalent DNA-binding agents [antitumor antibiotics], including, nucleic acid inhibitors (e.g., Dactinomycin [Actinomycin D], etc.), anthracyclines (e.g., Daunorubicin [Daunomycin, and Cerubidine], Doxorubicin [Adriamycin], and Idarubicin [Idamycin], etc.), anthracenediones (e.g., anthracycline analogues, such as, [Mitoxantrone], etc.), bleomycins (Blenoxane), etc., and plicamycin (Mithramycin), etc.; 4) antimetabolites, including, antifolates (e.g., Methotrexate, Folex, and Mexate, etc.), purine antimetabolites

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(e.g., 6-Mercaptopurine [6-MP, Purinethol], 6-Thioguanine [6-TG], Azathioprine, Acyclovir, Ganciclovir, Chlorodeoxyadenosine, 2-Chlorodeoxyadenosine [CdA], and 2'-Deoxycoformycin [Pentostatin], etc.), pyrimidine antagonists (e.g., fluoropyrimidines [e.g., 5-fluorouracil (Adrucil), 5-fluorodeoxyuridine (FdUrd) (Floxuridine)] etc.), and cytosine arabinosides (e.g., Cytosar [ara-C] and Fludarabine, etc.); 5) enzymes, including, L-asparaginase; 6) hormones, including, glucocorticoids, such as, antiestrogens (e.g., Tamoxifen, etc.), nonsteroidal antiandrogens (e.g., Flutamide, etc.), and aromatase inhibitors (e.g., anastrozole [Arimidex], etc.); 7) platinum compounds (e.g., Cisplatin and Carboplatin, etc.); 8) monoclonal antibodies conjugated with anticancer drugs, toxins, and/or radionuclides, etc.; 9) biological response modifiers (e.g., interferons [e.g., IFN- α , etc.] and interleukins [e.g., IL-2, etc.], etc.); 10) adoptive immunotherapy; 11) hematopoietic growth factors; 12) agents that induce tumor cell differentiation (e.g., all-trans-retinoic acid, etc.); 13) gene therapy techniques; 14) antisense therapy techniques; 15) tumor vaccines; 16) therapies directed against tumor metastases (e.g., Batimistat, etc.); and 17) inhibitors of angiogenesis.

[0247] The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions. Examples of other therapeutic agents include the following: cyclosporins (e.g., cyclosporin A), CTLA4-Ig, antibodies such as ICAM-3, anti-IL-2 receptor (Anti-Tac), anti-CD45RB, anti-CD2, anti-CD3 (OKT-3), anti-CD4, anti-CD80, anti-CD86, agents blocking the interaction between CD40 and gp39, such as antibodies specific for CD40 and/or gp39 (i.e., CD154), fusion proteins constructed from CD40 and gp39 (CD40Ig and CD8gp39), inhibitors, such as nuclear translocation inhibitors, of NF-kappa B function, such as deoxyspergualin (DSG), cholesterol biosynthesis inhibitors such as HMG CoA reductase inhibitors (lovastatin and simvastatin), non-steroidal antiinflammatory drugs (NSAIDs) such as ibuprofen and cyclooxygenase inhibitors such as rofecoxib, steroids such as prednisone or dexamethasone, gold compounds, antiproliferative agents such as methotrexate, FK506 (tacrolimus, Prograf), mycophenolate mofetil, cytotoxic drugs such as azathioprine and cyclophosphamide, TNF- α inhibitors such as tenidap, anti-TNF

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antibodies or soluble TNF receptor, and rapamycin (sirolimus or Rapamune) or derivatives thereof.

[0248] Other agents that may be administered in combination with invention compounds include protein therapeutic agents such as cytokines, immunomodulatory agents and antibodies. As used herein the term "cytokine" encompasses chemokines, interleukins, lymphokines, monokines, colony stimulating factors, and receptor associated proteins, and functional fragments thereof. As used herein, the term "functional fragment" refers to a polypeptide or peptide which possesses biological function or activity that is identified through a defined functional assay.

[0249] The cytokines include endothelial monocyte activating polypeptide II (EMAP-II), granulocyte-macrophage-CSF (GM-CSF), granulocyte-CSF (G-CSF), macrophage-CSF (M-CSF), IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-12, and IL-13, interferons, and the like and which is associated with a particular biologic, morphologic, or phenotypic alteration in a cell or cell mechanism.

[0250] When other therapeutic agents are employed in combination with the compounds of the present invention they may be used for example in amounts as noted in the Physician Desk Reference (PDR) or as otherwise determined by one having ordinary skill in the art.

[0251] In the treatment or prevention of conditions which involve cellular proliferation, an appropriate dosage level can generally be between about 0.01 and about 1000 mg per 1 kg of patient body weight per day which can be administered in single or multiple doses. For example, the dosage level can be between about 0.01 and about 250 mg/kg per day; more narrowly, between about 0.5 and about 100 mg/kg per day. A suitable dosage level can be between about 0.01 and about 250 mg/kg per day, between about 0.05 and about 100 mg/kg per day, or between about 0.1 and about 50 mg/kg per day, or about 1.0 mg/kg per day. For example, within this range the dosage can be between about 0.05 and about 0.5 mg/kg per day, or between about 0.5 and about 5 mg/kg per day, or between about 5 and about 50 mg/kg per day. For oral administration, the compositions can be provided in the form of tablets containing between about 1.0 and

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about 1,000 mg of the active ingredient, for example, about 1.0, about 5.0, about 10.0, about 15.0, about 20.0, about 25.0, about 50.0, about 75.0, about 100.0, about 150.0, about 200.0, about 250.0, about 300.0, about 400.0, about 500.0, about 600.0, about 750.0, about 800.0, about 900.0, and about 1,000.0 mg of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds can be administered on a regimen of 1 to 4 times per day, such as once or twice per day. There may be a period of no administration followed by another regimen of administration.

[0252] It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[0253] Compounds of the present invention can be used, alone or in combination with an effective amount of a therapeutic antibody (or therapeutic fragment thereof), a chemotherapeutic or an immunotoxic agent, for treatment of tumors. Illustrative examples of chemotherapeutic agents that can be used for this purpose include doxorubicin, docetaxel, or taxol. It should be further understood that the invention includes combination therapy including a compound of the invention, including but not limited to vasculostatic agents, such as tyrosine, serine or threonine kinase inhibitors, for example, Src-family inhibitors, and any chemotherapeutic agent or therapeutic antibody.

[0254] The subject aromatic compounds, and derivatives thereof, can be prepared readily by employing known synthetic methodology. As is well known in the art, these coupling reactions are carried out under relatively mild conditions and tolerate a wide range of "spectator" functionality. Additional compounds may be synthesized and tested in a combinatorial fashion, to facilitate the identification of additional compounds which may be employed in the subject method.

[0255] The aromatic compounds of the present invention, particularly libraries of variants having various representative classes of substituents, are amenable to

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combinatorial chemistry and other parallel synthesis schemes (see, for example, PCT WO 94/08051). The result is that large libraries of related compounds, e.g. a variegated library of compounds represented above, can be screened rapidly in high throughput assays in order to identify potential hedgehog regulator lead compounds, as well as to refine the specificity, toxicity, and/or cytotoxic-kinetic profile of a lead compound. For instance, *ptc*, *hedgehog*, and *smoothened* bioactivity assays, such as may be developed using cells with either a *ptc* loss-of-function, *hedgehog* gain-of-function, or *smoothened* gain-of-function, can be used to screen a library of the subject compounds for those having agonist activity toward *ptc* or antagonist activity towards *hedgehog* or *smoothened*. Alternatively, bioactivity assays using cells with either a *ptc* gain-of-function, *hedgehog* loss-of-function, or *smoothened* loss-of-function, can be used to screen a library of the subject compounds for those having antagonist activity toward *ptc* or agonist activity towards *hedgehog* or *smoothened*.

[0256] Simply for illustration, a combinatorial library for the purposes of the present invention is a mixture of chemically related compounds which may be screened together for a desired property. The preparation of many related compounds in a single reaction greatly reduces and simplifies the number of screening processes which need to be carried out. Screening for the appropriate physical properties can be done by conventional methods.

[0257] A variety of techniques are available in the art for generating combinatorial libraries of small organic molecules such as the subject aromatic compounds. See, for example, Blondelle et al., *Trends Anal. Chem.* 14:83 (1995); the Affymax U.S. Pat. Nos. 5,359,115 and 5,362,899; the Ellman U.S. Pat. No. 5,288,514; the Still et al. PCT publication WO 94/08051; the ArQule U.S. Pat. Nos. 5,736,412 and 5,712,171; Chen et al., *JACS* 116:2661 (1994); Kerr et al., *JACS* 115:252 (1993); PCT publications WO92/10092, WO93/09668 and WO91/07087; and the Lerner et al. PCT publication WO93/20242). Accordingly, a variety of libraries on the order of about 100 to 1,000,000 or more diversomers of the subject compounds can be synthesized and screened for particular activity or property.

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[0258] In an exemplary embodiment, a library of candidate compound diversomers can be synthesized utilizing a scheme adapted to the techniques described in the Still et al. PCT publication WO 94/08051, e.g., being linked to a polymer bead by a hydrolyzable or photolyzable group, optionally located at one of the positions of the candidate regulators or a substituent of a synthetic intermediate. According to the Still et al. technique, the library is synthesized on a set of beads, each bead including a set of tags identifying the particular diversomer on that bead. The bead library can then be "plated" with, for example, *ptc* loss-of-function, *hedgehog* gain-of-function, or *smoothened* gain-of-function cells for which a hedgehog agonist is sought. The diversomers can be released from the bead, e.g. by hydrolysis.

[0259] Many variations on the above and related pathways permit the synthesis of widely diverse libraries of compounds which may be tested as regulators of hedgehog function.

[0260] There are a variety of assays available for determining the ability of an aromatic compound such as a hedgehog antagonist to regulate *ptc*, *smoothened*, or *hedgehog* function, many of which can be disposed in high-throughput formats. In many drug screening programs which test libraries of compounds and natural extracts, high throughput assays are desirable in order to maximize the number of compounds surveyed in a given period of time. Thus, libraries of synthetic and natural products can be sampled for other compounds which are hedgehog antagonists.

[0261] In addition to cell-free assays, test compounds can also be tested in cell-based assays. In one embodiment, cells which have a *ptc* loss-of-function, *hedgehog* gain-of-function, or *smoothened* gain-of-function phenotype can be contacted with a test agent of interest, with the assay scoring for, e.g., inhibition of proliferation of the cell in the presence of the test agent.

[0262] In an exemplary embodiment, a library of candidate compounds obtained from ChemDiv, Inc. (San Diego, CA) was screened for Hh pathway modulators utilizing a scheme adapted to the techniques described in Chen et al., *PNAS* 99:14071-14076 (2002).

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Binding of the compounds to *patched* and *smoothened* was determined utilizing a scheme adapted to the techniques described in Chen et al., *Genes & Dev.* 16:2743-2748 (2002).

[0263] A number of gene products have been implicated in patched-mediated signal transduction, including patched, transcription factors of the cubitus interruptus (ci) family, the serine/threonine kinase fused (fu) and the gene products of costal-2, smoothened and suppressor of fused.

[0264] The induction of cells by hedgehog proteins sets in motion a cascade involving the activation and inhibition of downstream effectors, the ultimate consequence of which is, in some instances, a detectable change in the transcription or translation of a gene. Potential transcriptional targets of hedgehog-mediated signaling are the patched gene (Hidalgo and Ingham, *Development* 110, 291-301 (1990); Marigo et al., 1996) and the vertebrate homologs of the drosophila cubitus interruptus gene, the GLI genes (Hui et al., *Dev Biol* 162:402-413 (1994)). Patched gene expression has been shown to be induced in cells of the limb bud and the neural plate that are responsive to Shh. (Marigo et al. *PNAS* 93:9346-51 (1996); Marigo et al. *Development* 122:1225-1233 (1996)). The Gli genes encode putative transcription factors having zinc finger DNA binding domains (Orenic et al. *Genes & Dev* 4:1053-1067 (1990); Kinzler et al. *Mol Cell Biol* 10:634-642 (1990)). Transcription of the Gli gene has been reported to be upregulated in response to hedgehog in limb buds, while transcription of the Gli3 gene is downregulated in response to hedgehog induction Narigo et al. *Development* 122:1225-1233 (1996)). By selecting transcriptional regulatory sequences from such target genes, e.g., from patched or Gli genes, that are responsible for the up- or down-regulation of these genes in response to hedgehog signaling, and operatively linking such promoters to a reporter gene, one can derive a transcription based assay which is sensitive to the ability of a specific test compound to modify hedgehog-mediated signaling pathways. Expression of the reporter gene, thus, provides a valuable screening tool for the development of compounds that act as antagonists to hedgehog.

[0265] Reporter gene based assays of this invention measure the end stage of the above described cascade of events, e.g., transcriptional modulation. Accordingly, in

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practicing one embodiment of the assay, a reporter gene construct is inserted into the reagent cell in order to generate a detection signal dependent on *ptc* loss-of-function, *hedgehog* gain-of-function, *smoothened* gain-of-function, or stimulation by SHH themselves. The amount of transcription from the reporter gene may be measured using any method known to those of skill in the art to be suitable. For example, mRNA expression from the reporter gene may be detected using RNase protection or RNA-based PCR, or the protein product of the reporter gene may be identified by a characteristic stain or an intrinsic biological activity. The amount of expression from the reporter gene is then compared to the amount of expression in either the same cell in the absence of the test compound or it may be compared with the amount of transcription in a substantially identical cell that lacks the target receptor protein. Any statistically or otherwise significant decrease in the amount of transcription indicates that the test compound has in some manner agonized the normal *ptc* signal (or antagonized the gain-of-function *hedgehog* or *smoothened* signal), e.g., the test compound is a potential hedgehog antagonist.

[0266] A particular advantage to the screening assays of the invention finds application to the design of personalized medicine. For example, a plurality of test agents can be arranged in an array, which can be an addressable array, on a solid support such as a microchip, on a glass slide, on a bead, or in a well, and the cells of a subject (e.g., a biopsy sample) can be contacted with the different test agents to identify one or more agents having desirable characteristics, including, for example, in addition to the ability to modulate *ptc* loss-of-function, *hedgehog* gain-of-function, *smoothened* gain-of-function, minimal or no toxicity to the cell, desirable solubility characteristics, and the like. Consequently, a treatment regimen may be tailored specifically to the individual based upon the subject's levels of *ptc* loss-of-function, *hedgehog* gain-of-function, *smoothened* gain-of-function.

[0267] Once disease is established and a treatment protocol is initiated, screening assays of the invention may be repeated on a regular basis to evaluate whether any of the levels of *ptc* loss-of-function, *hedgehog* gain-of-function, *smoothened* gain-of-function in the patient begins to approximate that which is observed in a normal patient. The results

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obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months. Accordingly, the invention is also directed to methods for monitoring a therapeutic regimen for treating a subject having cancer. A comparison of any of the levels of *ptc* loss-of-function, *hedgehog* gain-of-function, *smoothened* gain-of-function prior to and during therapy indicates the efficacy of the therapy. Therefore, one skilled in the art will be able to recognize and adjust the therapeutic approach as needed.

[0268] As used herein, a "corresponding normal sample" is any sample taken from a subject of similar species that is considered healthy or otherwise not suffering from a cancer disease being treated. As such, a normal/standard levels of *ptc* loss-of-function, *hedgehog* gain-of-function, *smoothened* gain-of-function denotes the level of *ptc* loss-of-function, *hedgehog* gain-of-function, *smoothened* gain-of-function present in a sample from the normal sample. A normal level of *ptc* loss-of-function, *hedgehog* gain-of-function, *smoothened* gain-of-function can be established by combining body fluids or cell extracts taken from normal healthy subjects, preferably human, with antibody to the proteins of interest under conditions suitable for *ptc* loss-of-function, *hedgehog* gain-of-function, *smoothened* gain-of-function. Levels of *ptc* loss-of-function, *hedgehog* gain-of-function, *smoothened* gain-of-function in subject, control, and disease samples from biopsied tissues can be compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing and treating disease. A normal level of *ptc* loss-of-function, *hedgehog* gain-of-function, *smoothened* gain-of-function also can be determined as an average value taken from a population of subjects that is considered to be healthy, or is at least free of cancer. A variety of protocols including ELISA, RIA, and FACS are useful for measuring levels of *ptc* loss-of-function, *hedgehog* gain-of-function, *smoothened* gain-of-function, and provide a basis for diagnosing altered or abnormal levels *ptc* loss-of-function, *hedgehog* gain-of-function, *smoothened* gain-of-function.

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[0269] Although the invention has been described with reference to the above examples, it will be understood that modifications and variations are encompassed within the spirit and scope of the invention. Accordingly, the invention is limited only by the following claims.

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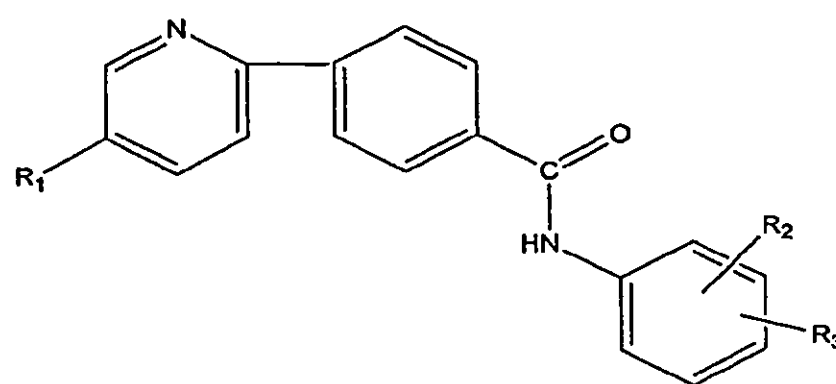
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WHAT IS CLAIMED IS:

1. A compound having the structure (I):



(I)

wherein:

R_1 is an alkyl;

R_2 is a substituent selected from a group consisting of hydrogen, an alkyl, halogen, and an alkoxy group; and

R_3 is a substituent selected from a group consisting of an unsubstituted or substituted alkyl group, halogen, an alkoxy group, acetyl group, and nitro group, or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein:

R_1 is selected from a group consisting of ethyl, *n*-propyl and *n*-amyl;

R_2 is selected from a group consisting of hydrogen, chlorine, methyl, and methoxy;

R_3 is selected from a group consisting of methyl, chlorine, iodine, trifluoromethyl, and methoxy.

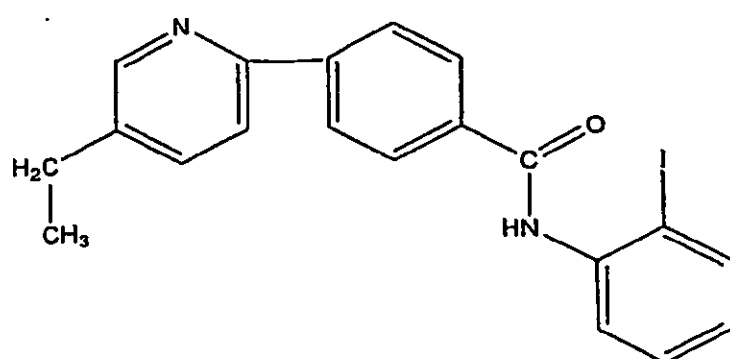
3. The compound of claim 1, wherein the compound having the structure (I) is selected from the group of compounds having the formulae (1)-(7):

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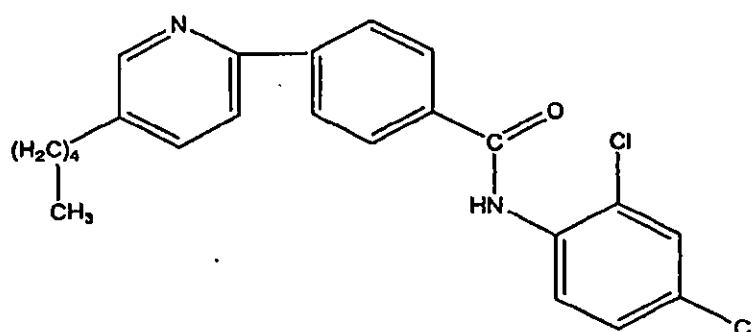
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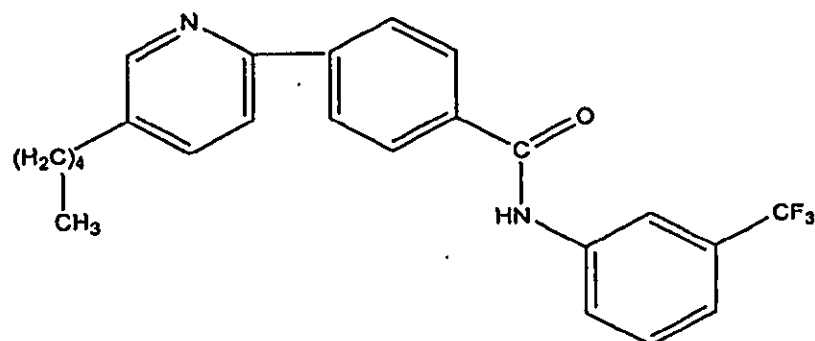
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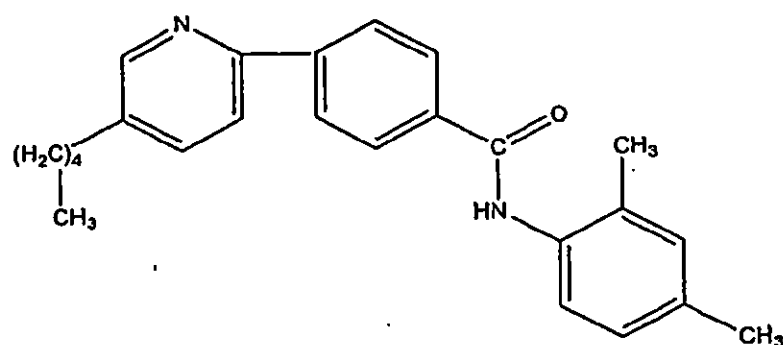
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(3)



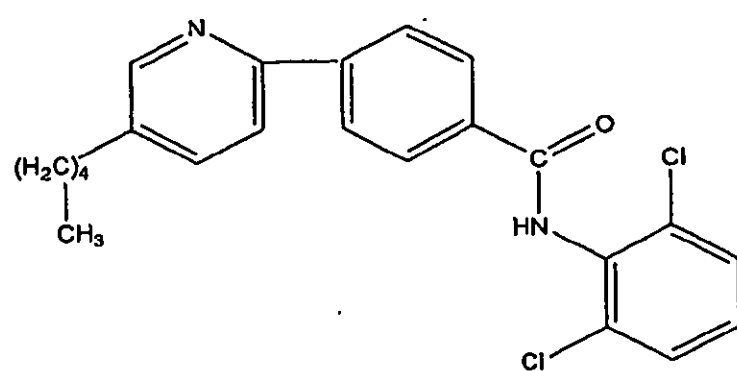
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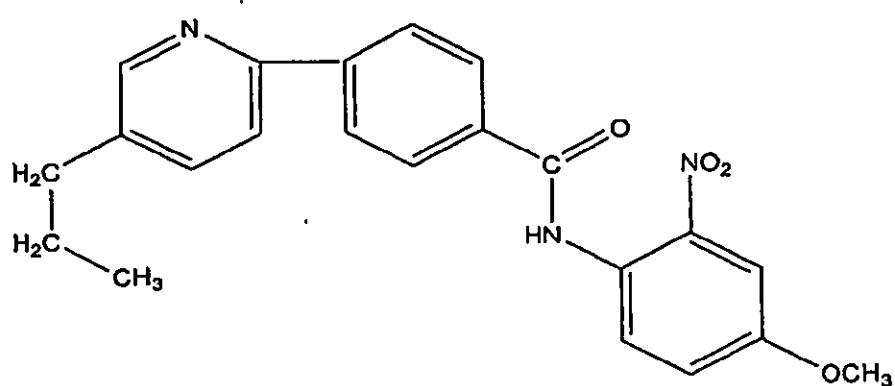
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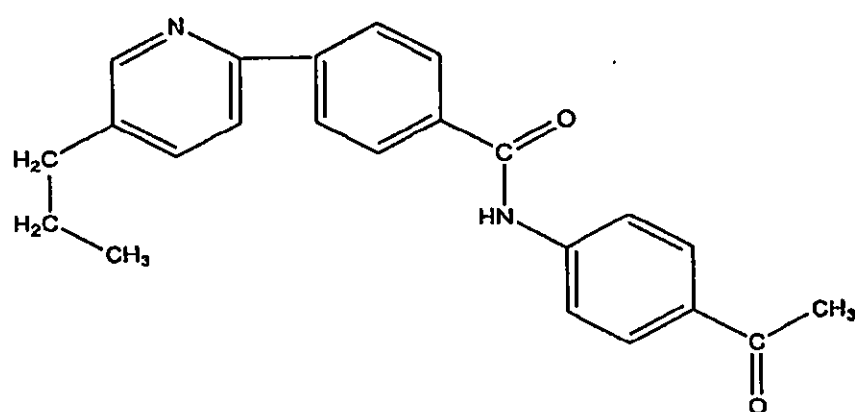
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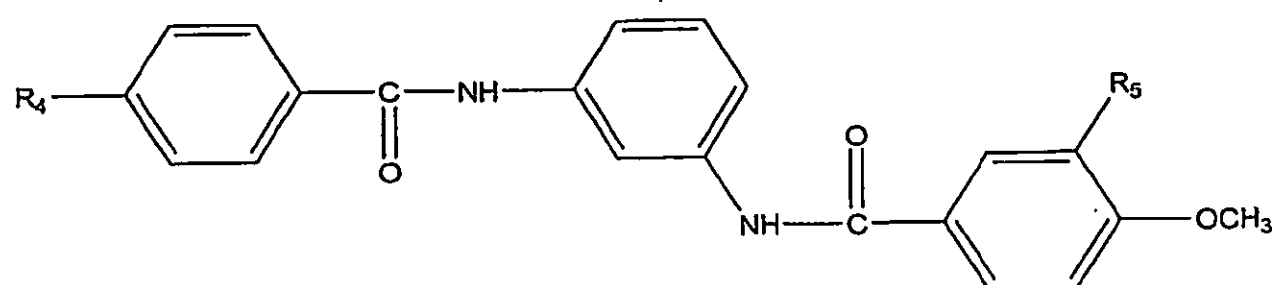


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(7)

4. A compound having structure (II):



(II)

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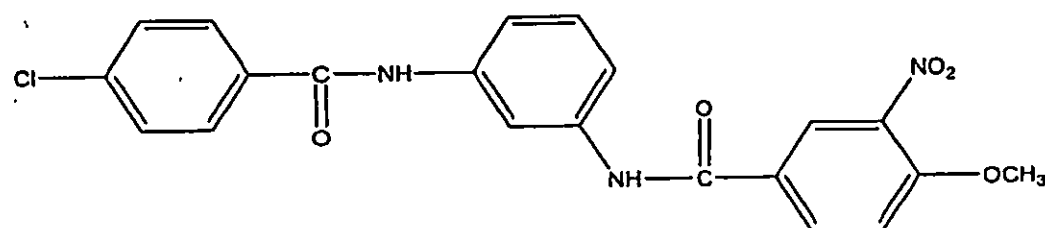
wherein:

R₄ is selected from a group consisting of *tert*-butyl and chlorine; and

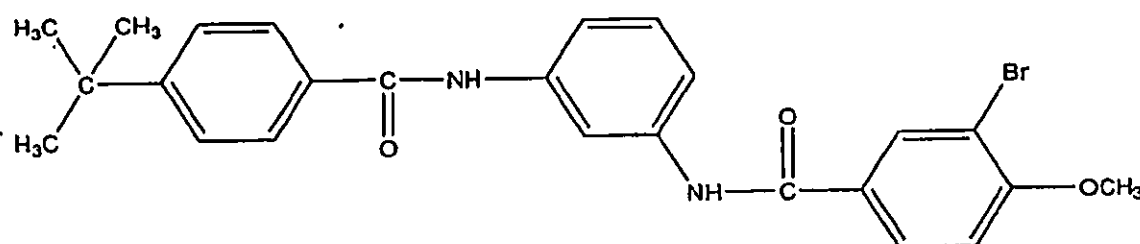
R₅ is selected from a group consisting of nitro group and bromine,

or a pharmaceutically acceptable salt thereof.

5. The compound of claim 4, wherein the compound having structure (II) is selected from a group consisting of compounds having the formulae (8) and (9):

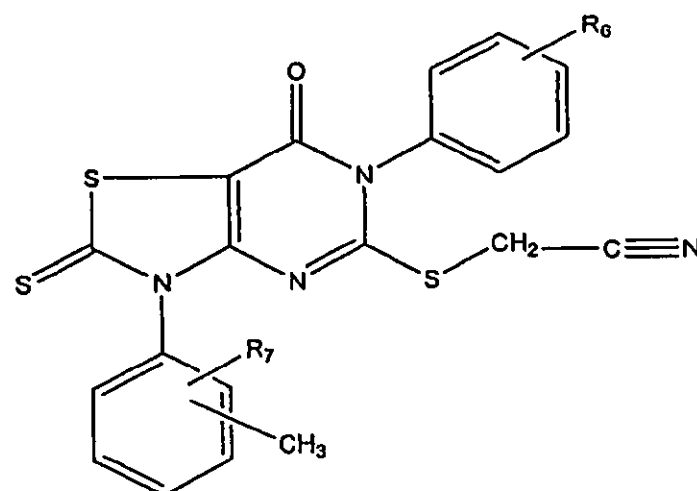


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(9)

6. A compound having the structure (III):



(III)

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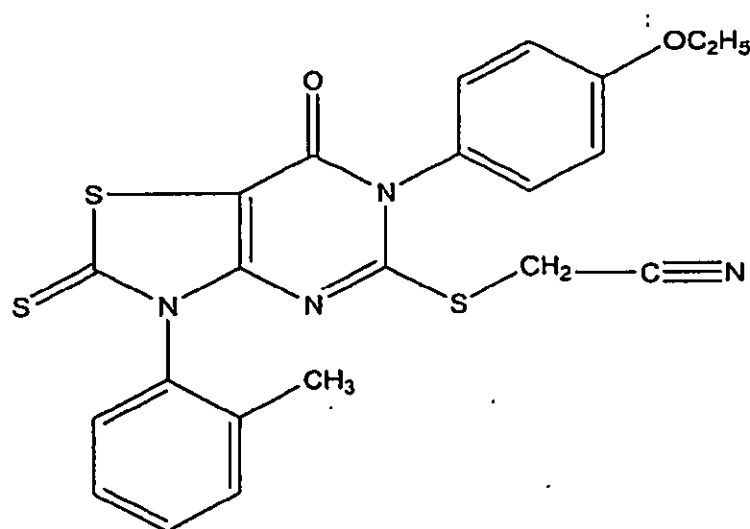
wherein:

R₆ is selected from a group consisting of methyl and ethoxy group; and

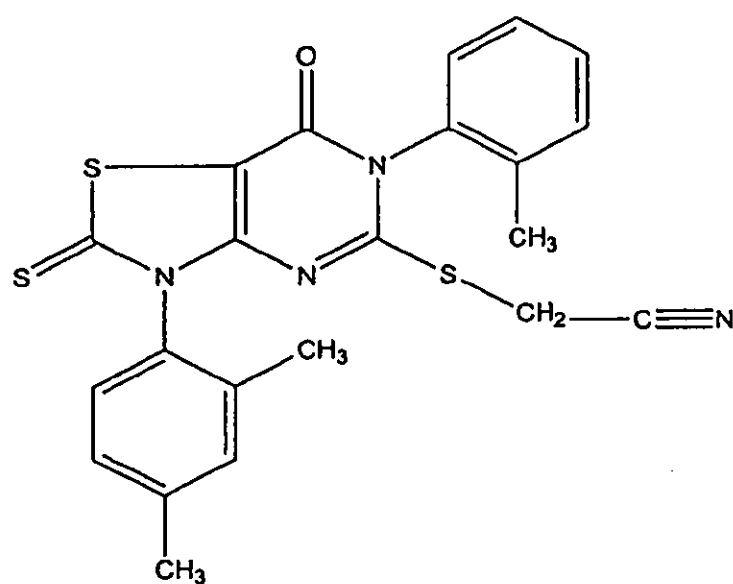
R₇ is selected from a group consisting of hydrogen and methyl,

or a pharmaceutically acceptable salt thereof.

7. The compound of claim 6, wherein the compound having the structure (III) is selected from the group of compounds having the formulae (10) and (11):



(10)



(11)

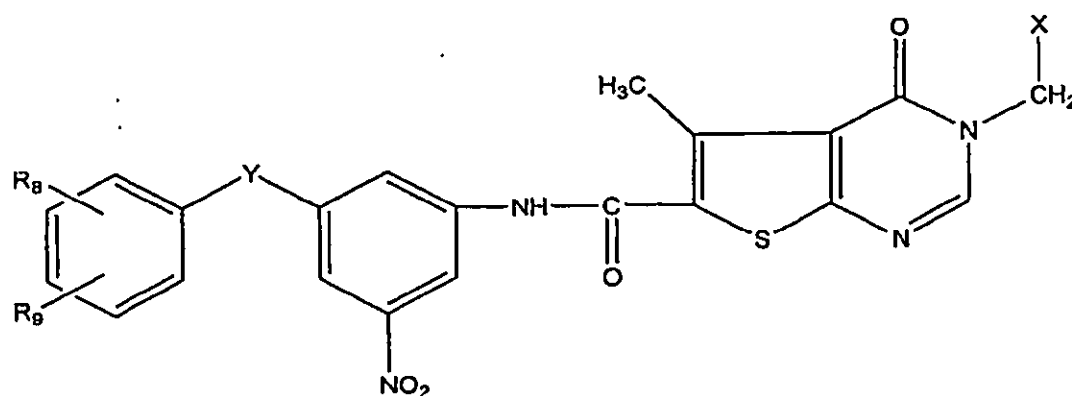
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8. A compound having the structure (IV):



(IV)

wherein:

R₈ is selected from a group consisting of hydrogen and methyl;

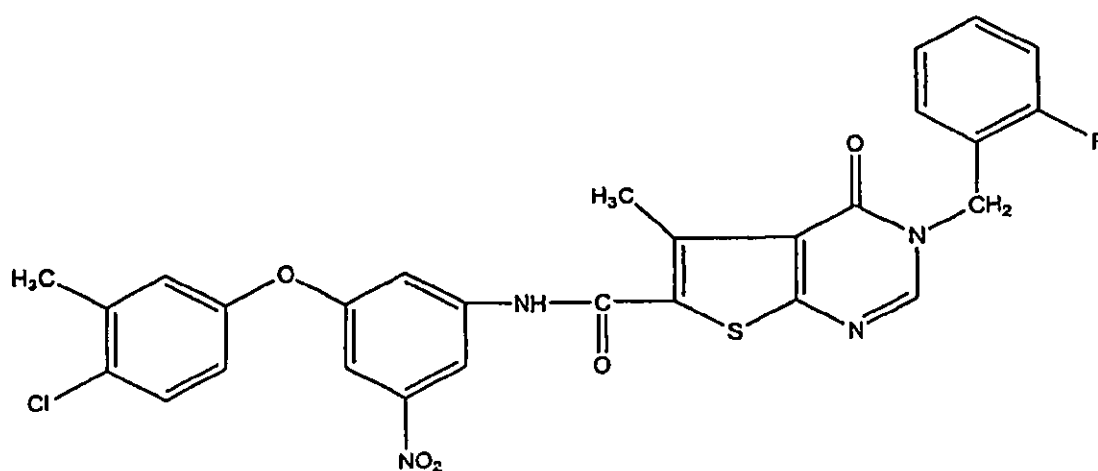
R₉ is selected from a group consisting of hydrogen, chlorine and fluorine;

X is selected from a group consisting of ethyl and fluorophenyl; and

Y is selected from a group consisting of oxygen and sulfur,

or a pharmaceutically acceptable salt thereof.

9. The compound of claim 8, wherein the compound having the structure (IV) is selected from the group of compounds having the formulae (12)-(15):



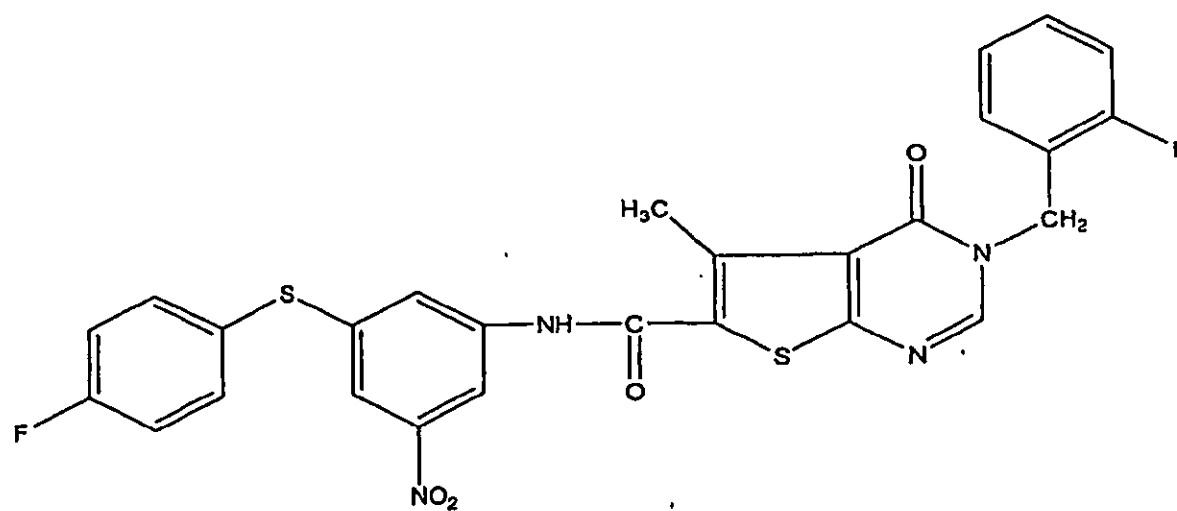
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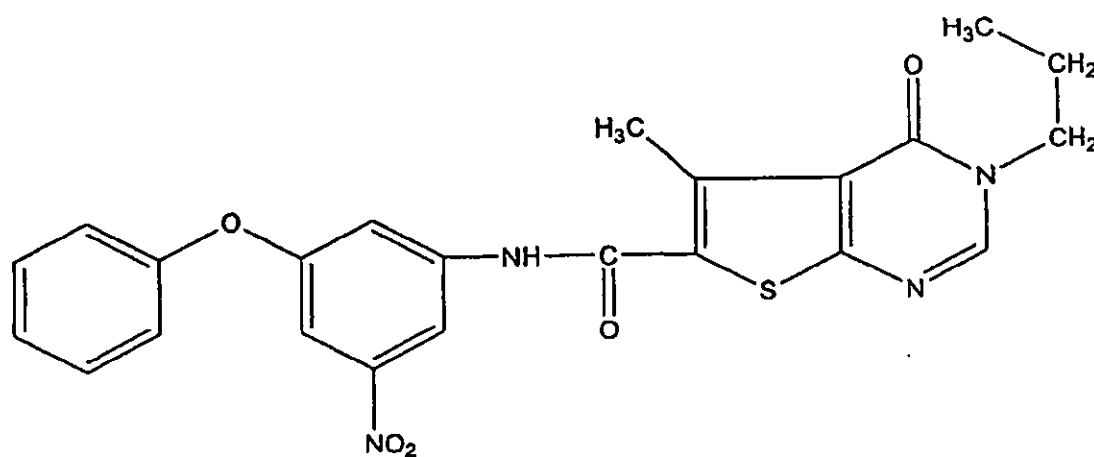
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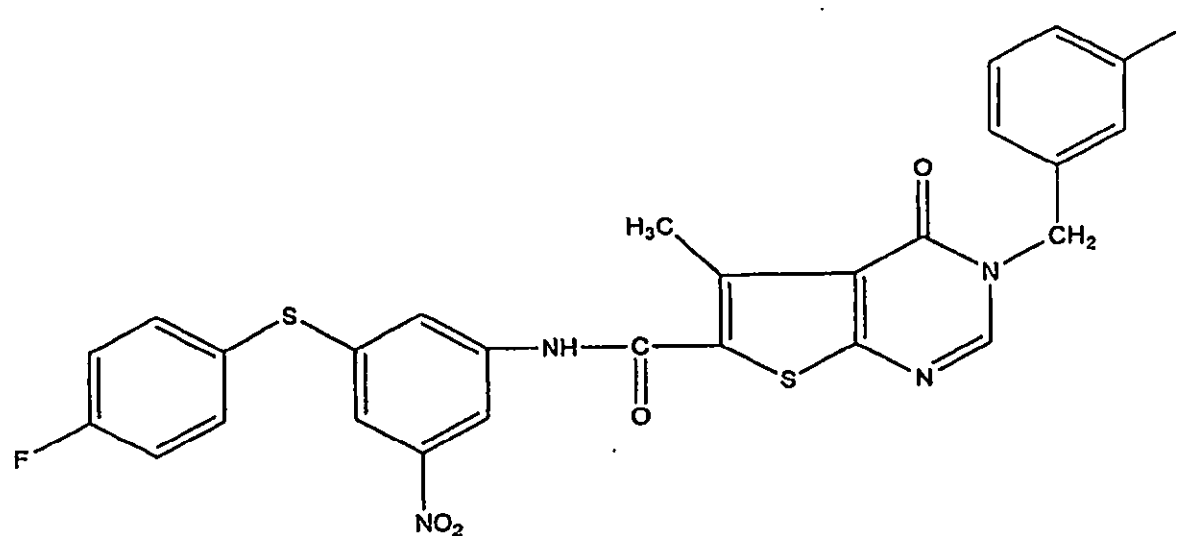
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(14)



(15)

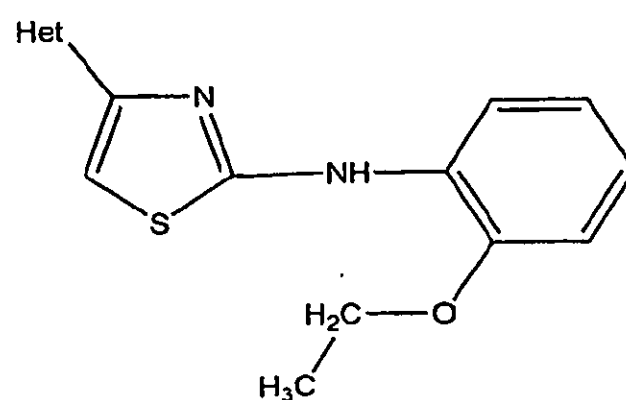
10. A compound having the structure (V):

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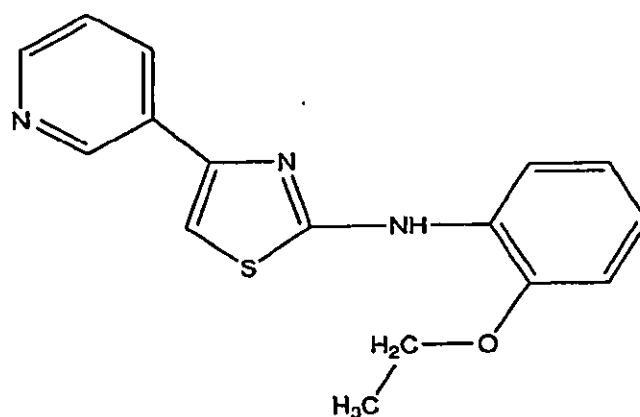


(V)

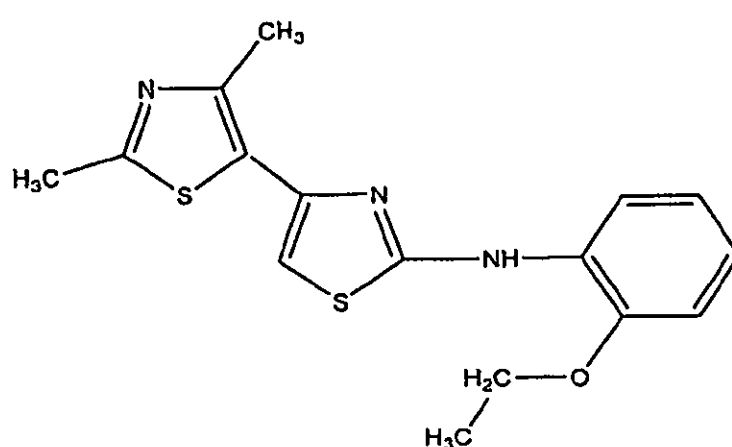
wherein Het is a heterocyclic radical.

11. The compound of claim 10, wherein the heterocyclic radical is selected from a group consisting of pyridyl and thiazolyl.

12. The compound of claim 10, wherein the compound having the structure (V) is selected from the group of compounds having the formulae (16) and (17):



(16)



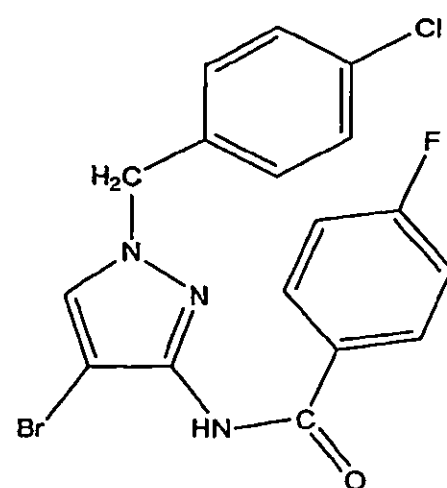
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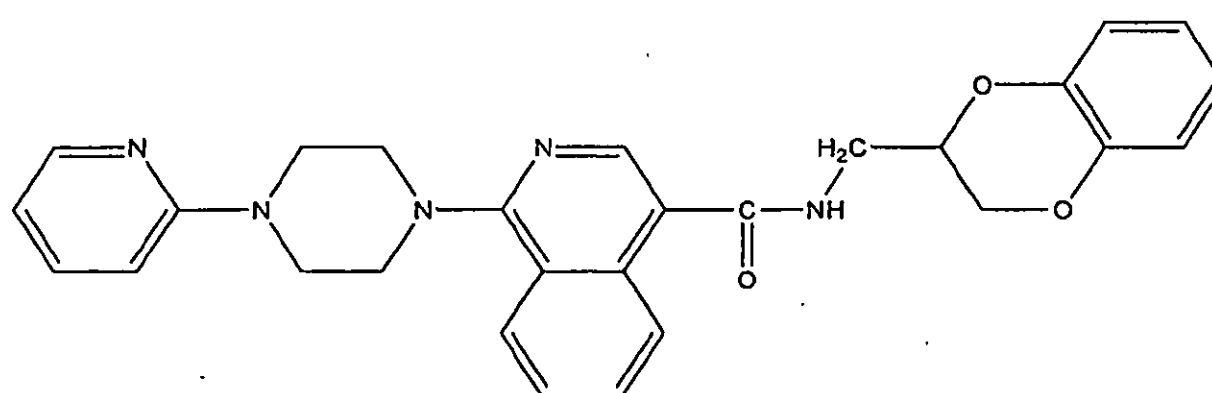
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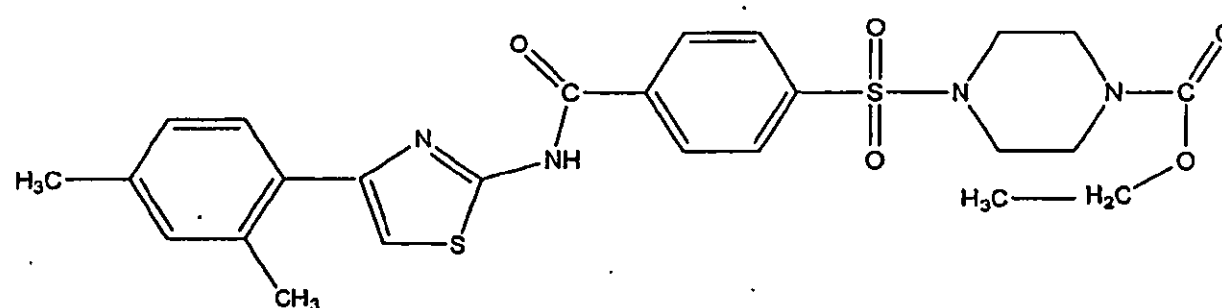
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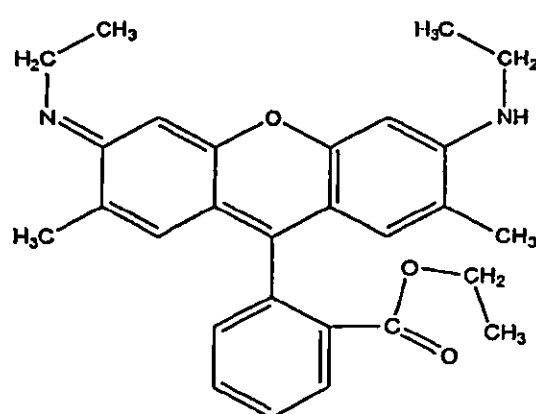
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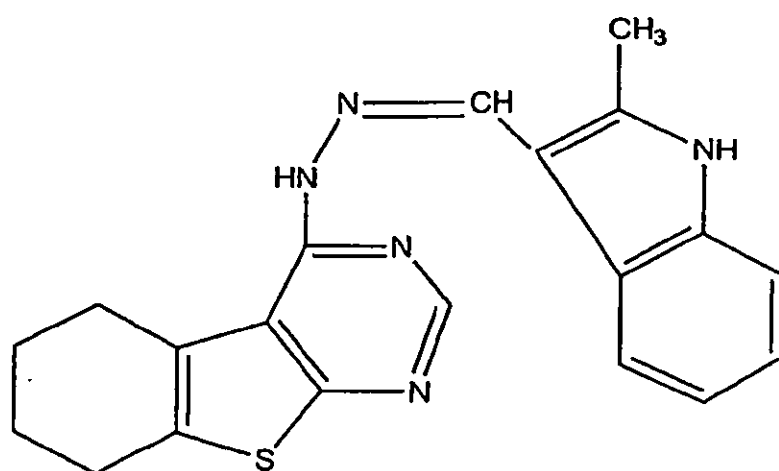
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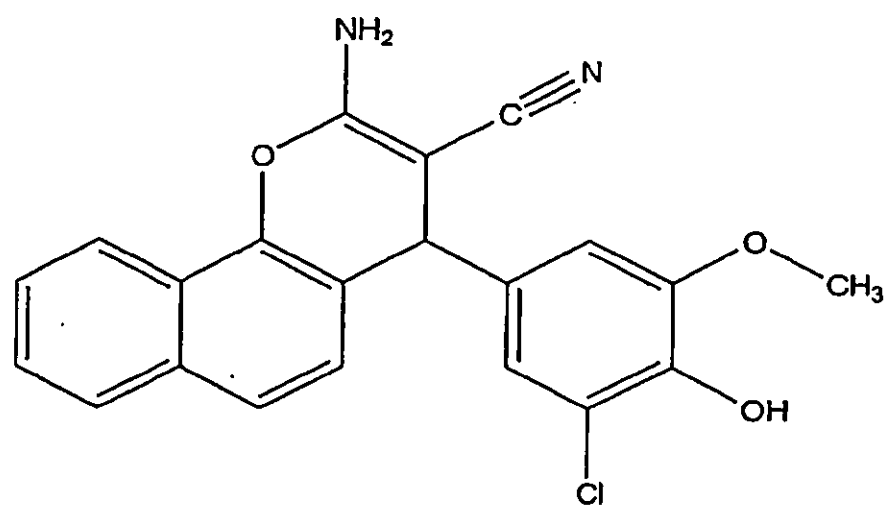
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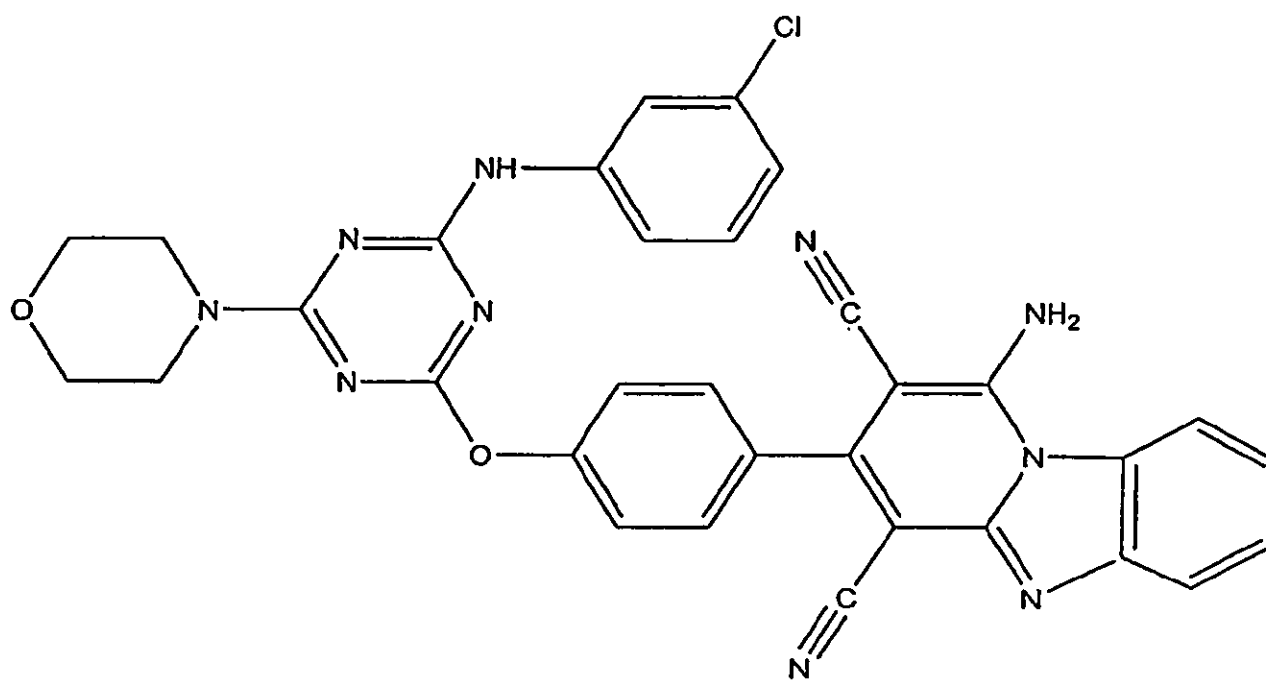
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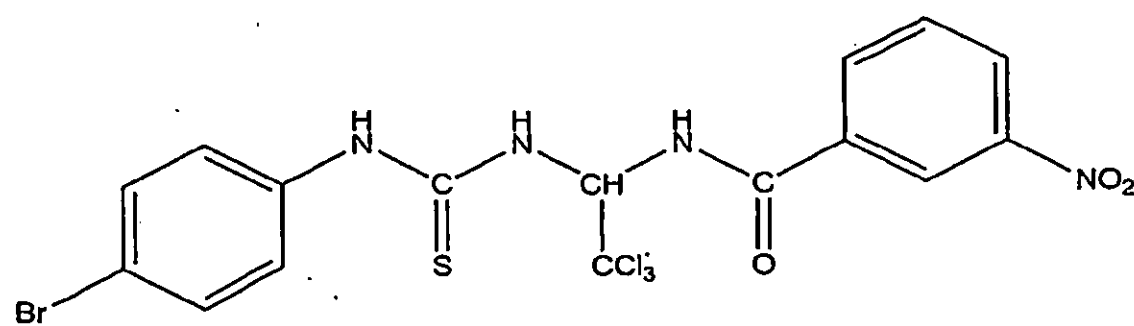
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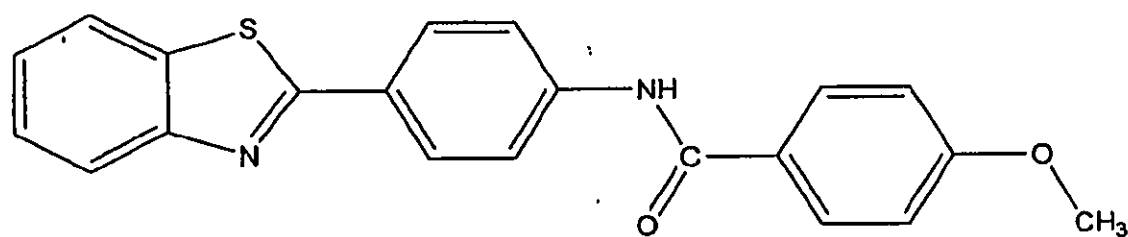
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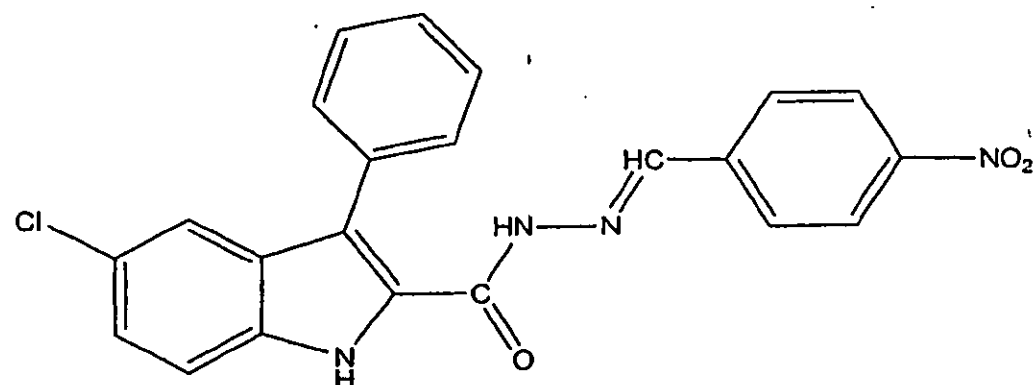
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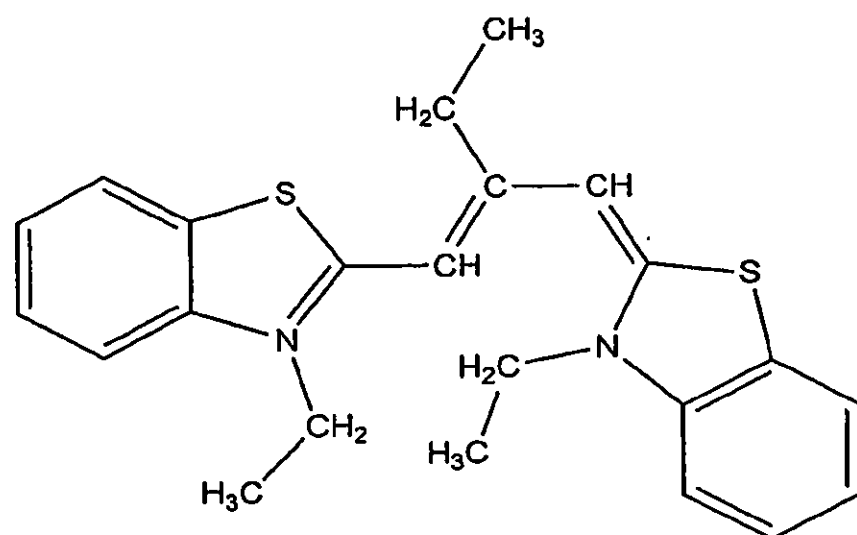
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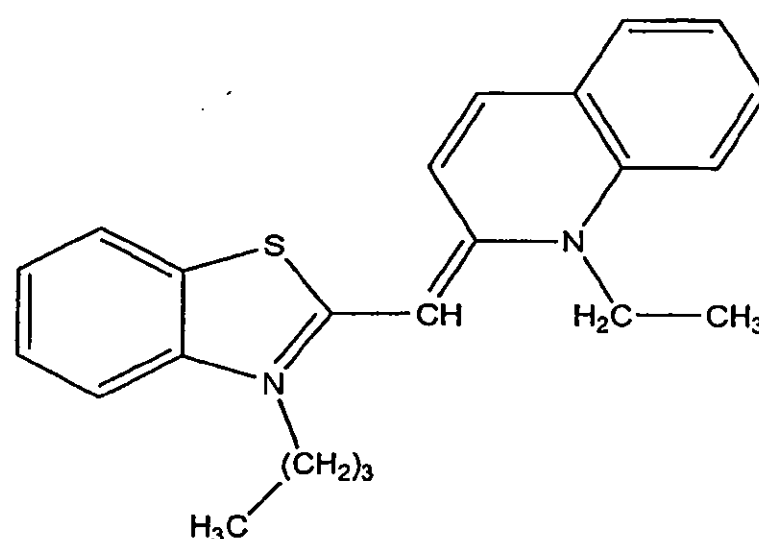
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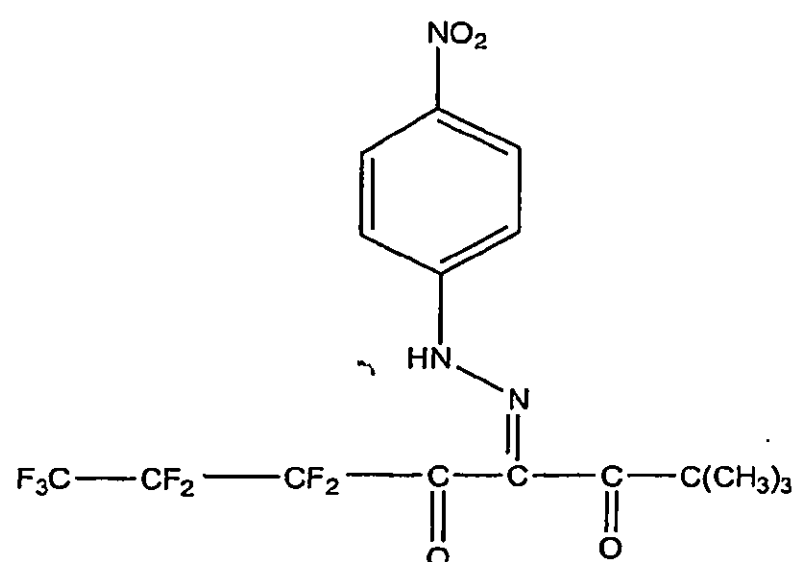
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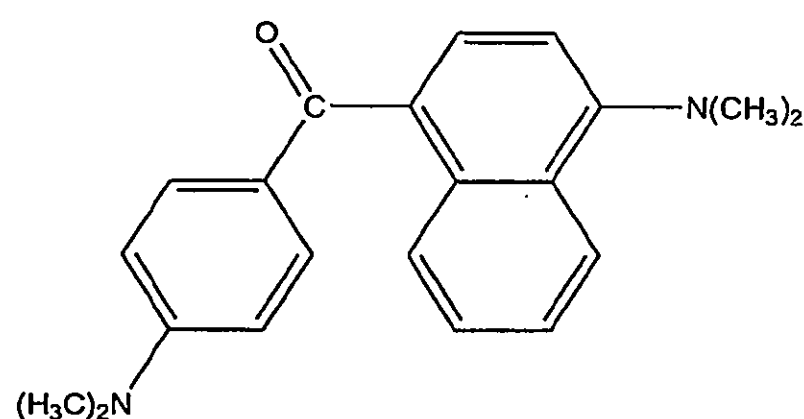
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(60)

24. A compound, comprising an alkylpyridyl moiety bridged to a benzamide moiety, wherein the benzamide moiety includes a first substituent attached to the benzamide moiety via the nitrogen atom of the benzamide moiety.

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25. The compound of claim 24, wherein the first substituent comprises an aryl structure which includes at least one second substituent, wherein the second substituent is selected from a group consisting of an unsubstituted or unsubstituted alkyl, a halogen, an alkoxy, acetyl, and nitro.

26. A compound, comprising two benzamide moieties connected with a phenylene bridge.

27. The compound of claim 26, wherein the phenylene bridge is 1,3-phenylene group.

28. The compound of claim 26, wherein each of the benzamide moieties includes a substituent, wherein the substituent is selected from a group consisting of *tert*-butyl, chlorine, bromine, and nitro.

29. A compound, comprising a first heterocyclic ring fused with a second heterocyclic ring, wherein:

(a) the first ring is a substituted 1,3-diazine-6-one; and

(b) the second ring is selected from an N-substituted thiazole-2-thione and a substituted thiophene.

30. A compound, comprising a thiazole moiety carrying a heterocyclic substituent and a secondary amino substituent, wherein:

(a) the heterocyclic substituent is elected from thiazolyl and pyridyl; and

(b) the secondary amino substituent is ethoxyphenylene group.

31. A compound, comprising a phtalazine moiety carrying at least two substituents, wherein:

(a) the first substituent includes a substituted phenyl or benzyl group; and

(b) the second substituent includes a secondary aromatic amino group.

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32. A compound, comprising a substituted chromone moiety carrying at least two substituents, wherein:

- (a) the first substituent includes a substituted phenyl or phenoxy group; and
- (b) the second substituent includes an aromatic ester group.

33. A compound, comprising a substituted benzoxazole moiety carrying at least two substituents, wherein:

- (a) the first substituent is selected from a substituted phenyl group and a substituted benzamido group; and
- (b) the second substituent is selected from a substituted phenyl group and a substituted furylamido group.

34. A compound, comprising a phenylquinazoline moiety and further including a substituent, wherein the substituent is selected from a secondary aromatic amino group and an anyline moiety.

35. A compound, comprising a thiazole moiety bridged to a substituted pyrrole-pyridine moiety.

36. The compound of claim 35, wherein the thiazole moiety further includes a secondary aromatic amino group.

37. A method for treating a cell proliferative disorder in a subject, said method comprising administering an effective amount of any compound of claims 1-36, or any combination thereof, or pharmaceutically acceptable salts, hydrates, solvates, crystal forms and individual diastereomers thereof, to a subject in need of such treatment.

38. The method of claim 37, wherein the cell proliferative disorder is basal cell carcinoma, medulloblastoma or meningioma.

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39. The method of claim 37, wherein the subject is a human or another mammal.

40. The method of claim 37, further including administering the compound in combination with a therapeutic agent, immunomodulatory agent, therapeutic antibody or an enzyme inhibitor.

41. The method of claim 40, wherein the therapeutic agent is methotrexate, cisplatin/carboplatin, canbusil, dactinomycin, taxol (paclitaxel), antifolate, colchicine, demecoline, etoposide, taxane/taxol, docetaxel, doxorubicin, anthracycline antibiotic, doxorubicin, daunorubicin, carminomycin, epirubicin, idarubicin, mithoxanthrone, 4-dimethoxy-daunomycin, 11-deoxydaunorubicin, 13-deoxydaunorubicin, adriamycin-14-benzoate, adriamycin-14-octanoate or adriamycin-14-naphthaleneacetate, irinotecan, topotecan, gemcitabine, 5-fluorouracil, leucovorin carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib, anthracyclines, rituximab, trastuzumab, bevacizumab, OSI-774, or Vitaxin.

42. A pharmaceutical composition comprising any compound of claims 1-36, or any combination thereof, in a pharmaceutically acceptable carrier.

43. An article of manufacture comprising packaging material and a pharmaceutical composition contained within the packaging material, wherein the packaging material comprises a label which indicates that the pharmaceutical composition can be used for treatment of disorders and wherein said pharmaceutical composition comprises any compound of claims 1-36, or any combination thereof.

44. A process for making a pharmaceutical composition comprising combining any compound of claims 1-36, or any combination thereof, or its pharmaceutically acceptable salts, hydrates, solvates, crystal forms salts and individual diastereomers thereof, and a pharmaceutically acceptable carrier.

45. A method of inhibiting an altered growth state of a cell having a *ptc* loss-of-function phenotype, a *hedgehog* gain-of-function phenotype or a *smoothened* gain-of-

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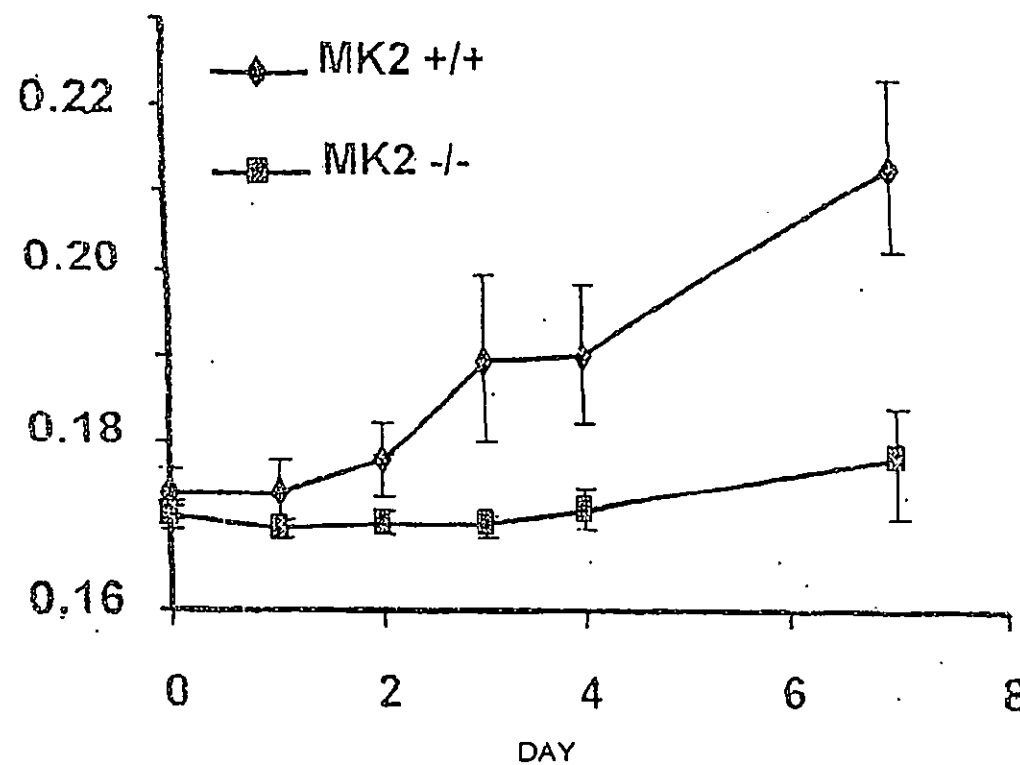
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[Continued on next page]

(54) Title: **ACYCLIC PYRAZOLE COMPOUNDS FOR THE INHIBITION OF MITOGEN ACTIVATED PROTEIN KINASE-ACTIVATED PROTEIN KINASE-2**



(57) Abstract: Compounds are described which inhibit mitogen activated protein kinase-activated protein kinase-2 (MK-2). Methods of making such compounds are described, as well as a method of using them for the inhibition of MK-2, and for the prevention or treatment of a disease or disorder that is mediated by $\text{TNF}\alpha$, where the method involves administering to the subject an MK-2 inhibiting compound of the present invention. Pharmaceutical compositions and kits which contain the present MK-2 inhibiting compounds are also described.

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**ACYCLIC PYRAZOLE COMPOUNDS FOR THE INHIBITION OF
MITOGEN ACTIVATED PROTEIN KINASE-ACTIVATED PROTEIN
KINASE-2**

**CROSS REFERENCE TO RELATED PATENTS AND PATENT
APPLICATIONS**

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[0001] This application is related to and claims the benefit of U.S. Provisional Patent Application Serial No. 60/434,962, filed December 20, 2002, which is incorporated by reference herein in its entirety.

BACKGROUND OF THE INVENTION

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(1) Field of the Invention:

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[0002] The present invention relates to certain cyclic and heterocyclic compounds which inhibit mitogen-activated protein kinase-activated protein kinase-2 (MAPKAP kinase-2, or MK-2), and also to methods of using such compounds to inhibit MK-2 and for the prevention and treatment of TNF α mediated diseases or disorders in subjects that are in need of such prevention and/or treatment.

(2) Description of the Related Art:

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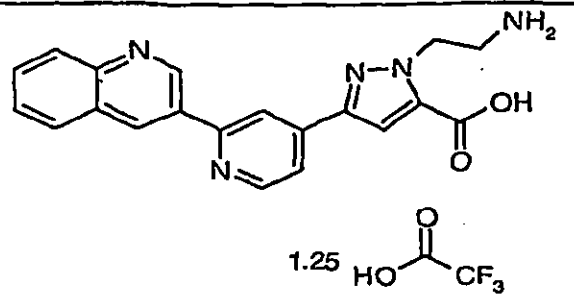
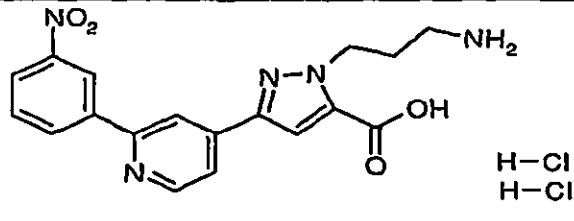
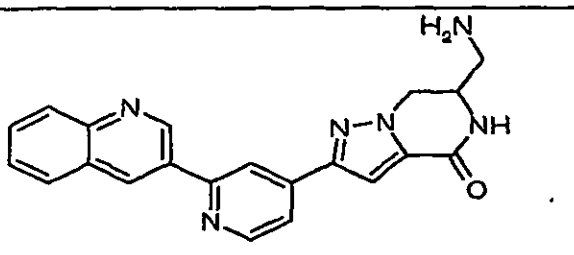
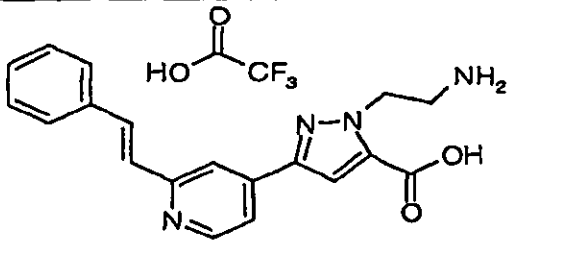
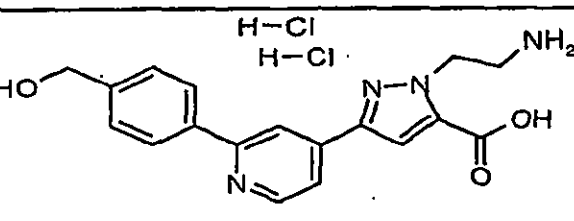
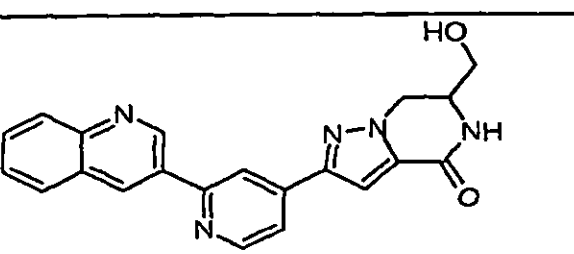
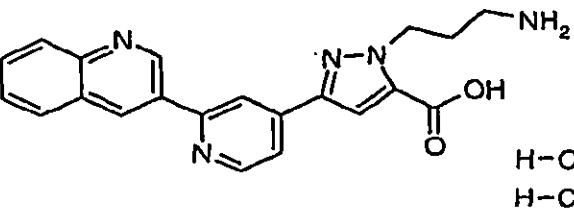
[0003] Mitogen-activated protein kinases (MAPKs) are members of conserved signal transduction pathways that activate transcription factors, translation factors and other target molecules in response to a variety of extracellular signals. MAPKs are activated by phosphorylation at a dual phosphorylation motif with the sequence Thr-X-Tyr by mitogen-activated protein kinase kinases (MAPKKs). In higher eukaryotes, the physiological role of MAPK signaling has been correlated with cellular events such as proliferation, oncogenesis, development and differentiation. Accordingly, the ability to regulate signal transduction via these pathways could lead to the development of treatments and preventive therapies for human diseases associated with MAPK signaling, such as inflammatory diseases, autoimmune diseases and cancer.

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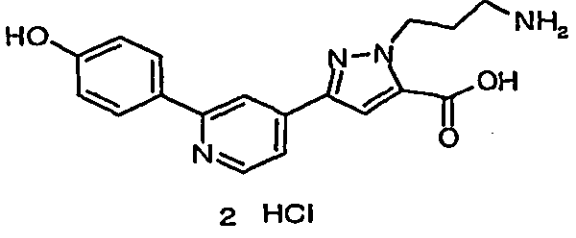
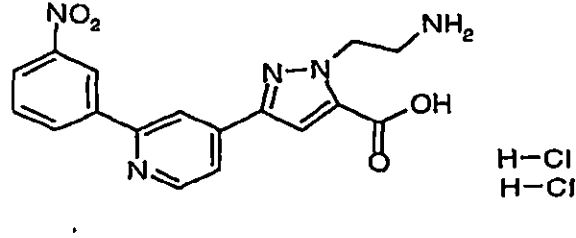
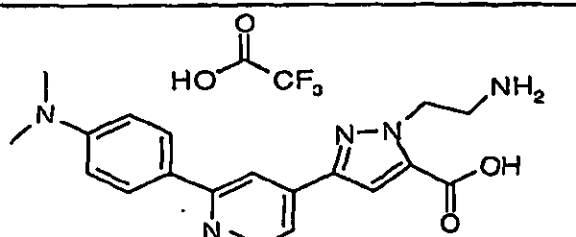
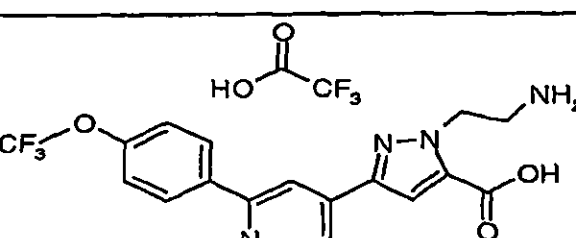
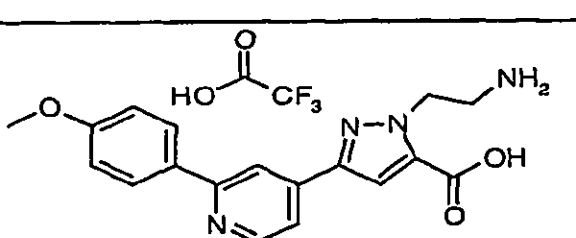
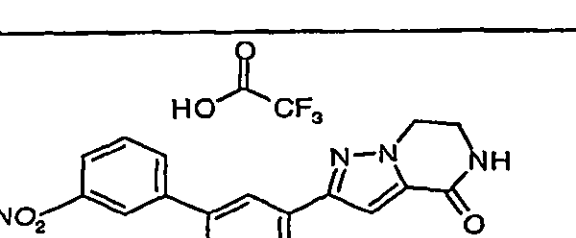
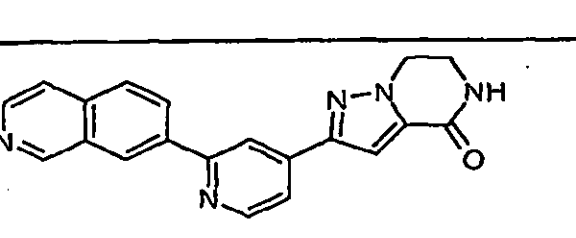
[0004] In mammalian cells, three parallel MAPK pathways have been described. The best characterized pathway leads to the activation of the extracellular-signal-regulated kinase (ERK). Less well understood are the

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Table I: MK-2 Inhibiting Compounds			
No.	Structure ^a	Compound Name(s) ^b	MK-2 Avg. IC ₅₀ (uM)
1	 1.25 HO-C(=O)-CF ₃	1-(2-aminoethyl)-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylic acid trifluoroacetate	0.0269
2	 H-Cl H-Cl	1-(3-aminopropyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid dihydrochloride	0.0397
3		6-(aminomethyl)-2-(2-quinolin-3-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.0477
4	 HO-C(=O)-CF ₃	1-(2-aminoethyl)-3-[2-[(E)-2-phenylethenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylic acid trifluoroacetate	0.0505
5	 H-Cl H-Cl	1-(2-aminoethyl)-3-[2-[4-(hydroxymethyl)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylic acid dihydrochloride	0.0533
6		6-(hydroxymethyl)-2-(2-quinolin-3-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.0615
7	 H-Cl H-Cl	1-(3-aminopropyl)-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylic acid dihydrochloride	0.0686

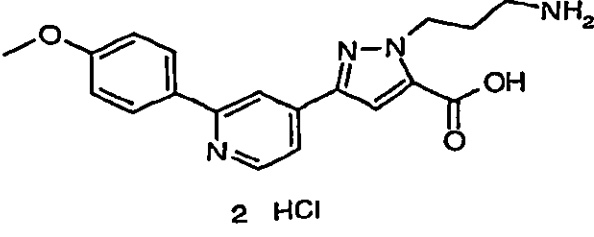
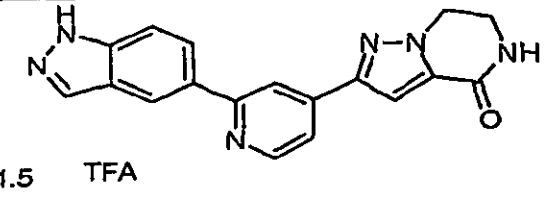
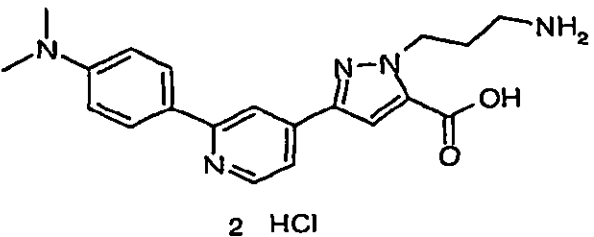
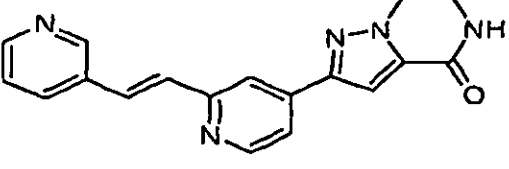
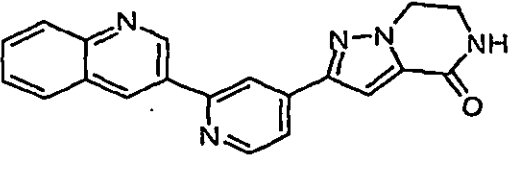
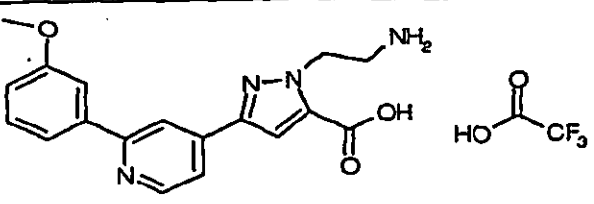
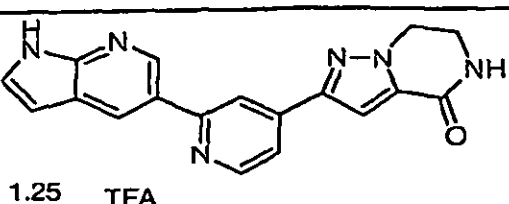
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8	 2 HCl	1-(3-aminopropyl)-3-[2-(4-hydroxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid hydrochloride	0.102
9	 H-Cl H-Cl	1-(2-aminoethyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid dihydrochloride	0.109
10	 HO-CF ₃	1-(2-aminoethyl)-3-[2-[4-(dimethylamino)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylic acid trifluoroacetate	0.117
11	 HO-CF ₃	1-(2-aminoethyl)-3-[2-[4-(trifluoromethoxy)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylic acid trifluoroacetate	0.161
12	 HO-CF ₃	1-(2-aminoethyl)-3-[2-(4-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid trifluoroacetate	0.168
13	 HO-CF ₃	2-[2-(3-nitrophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	0.171
14		2-(2-isoquinolin-7-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.194

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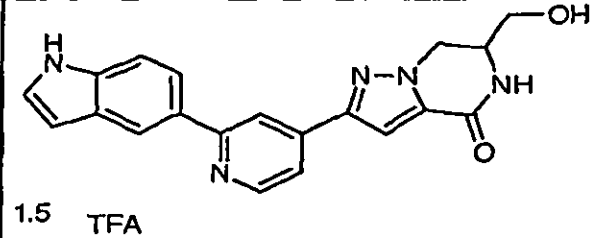
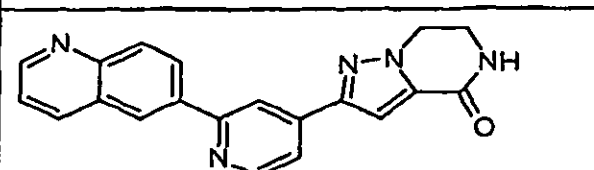
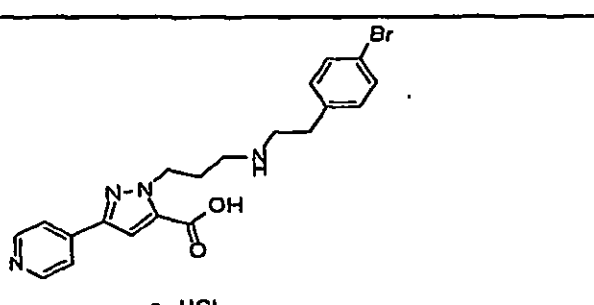
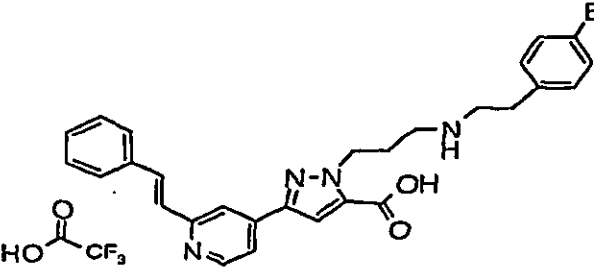
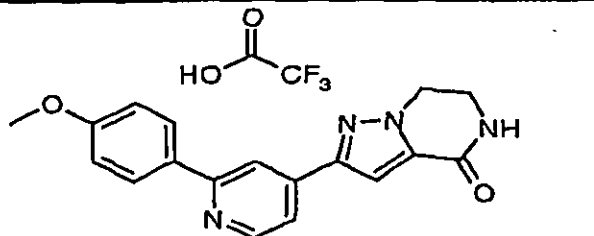
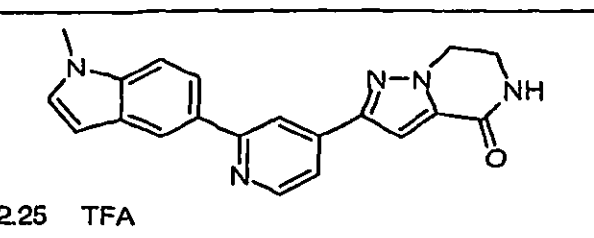
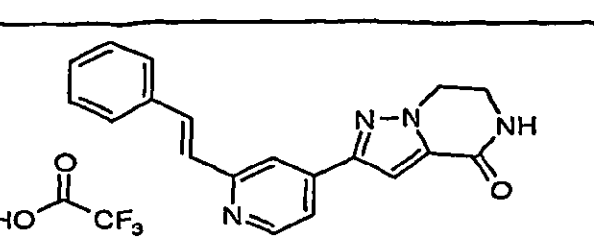
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15	 2 HCl	1-(3-aminopropyl)-3-[2-(4-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid hydrochloride	0.196
16	 1.5 TFA	2-[2-(1H-indazol-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	0.199
17	 2 HCl	1-(3-aminopropyl)-3-[2-(4-(dimethylamino)phenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid hydrochloride	0.203
18		2-[2-[(E)-2-pyridin-3-ylethenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.212
19		2-[2-(2-quinolin-3-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.216
20	 HO-C(=O)-CF ₃	1-(2-aminoethyl)-3-[2-(3-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylic acid trifluoroacetate	0.217
21	 1.25 TFA	2-[2-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	0.228

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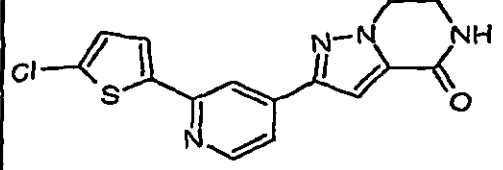
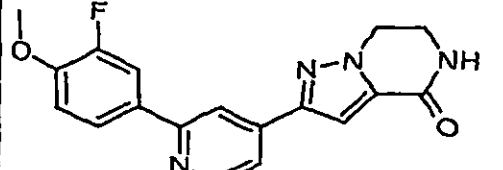
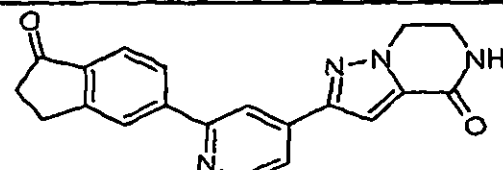
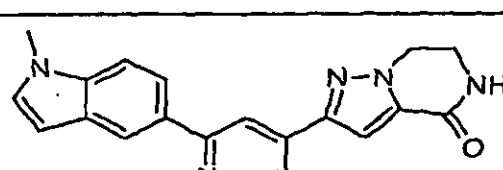
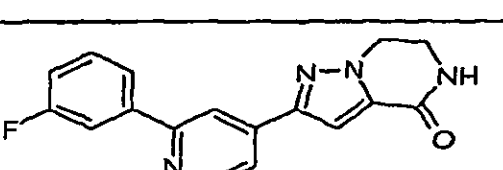
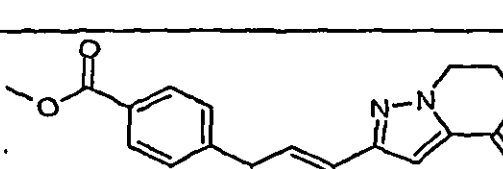
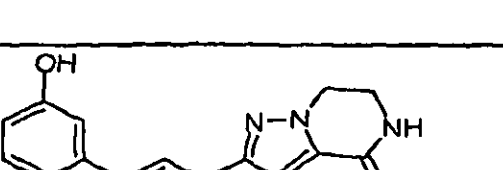
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22	 1.5 TFA	6-(hydroxymethyl)-2-[2-(1H-indol-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	0.25
23		2-(2-quinolin-6-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.298
24	 2 HCl	1-(3-[[2-(4-bromophenyl)ethyl]amino]propyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylic acid hydrochloride	0.3
25	 HO-CF ₃	1-(3-[[2-(4-bromophenyl)ethyl]amino]propyl)-3-[2-[(E)-2-phenylethenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylic acid trifluoroacetate	0.315
26	 HO-CF ₃	2-[2-(4-methoxyphenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	0.318
27	 2.25 TFA	2-[2-(1-methyl-1H-indol-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	0.322
28	 HO-CF ₃	2-[2-[(E)-2-phenylvinyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	0.371

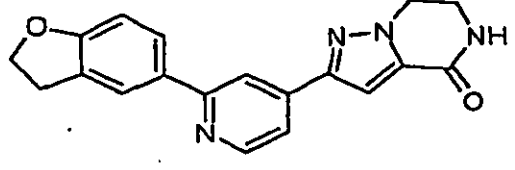
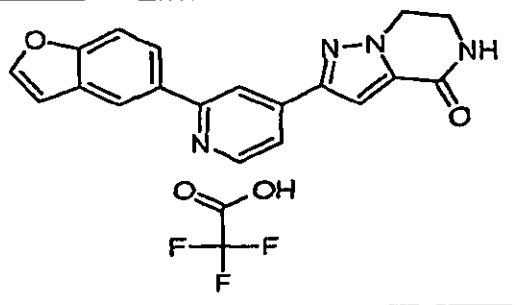
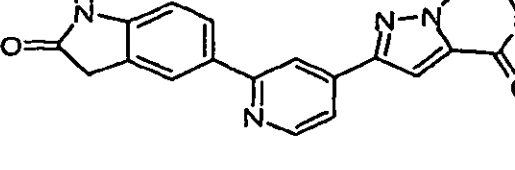
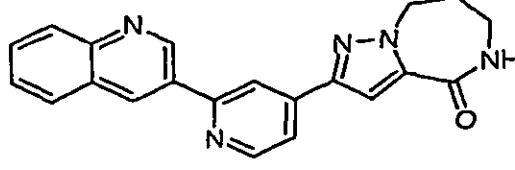
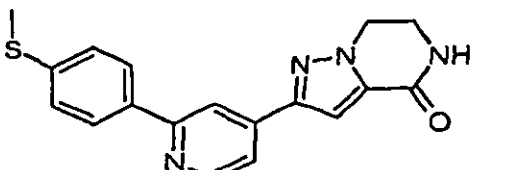
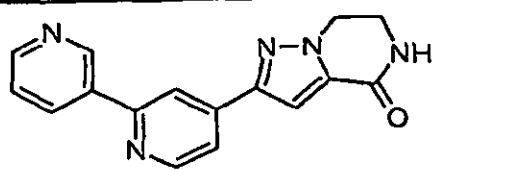
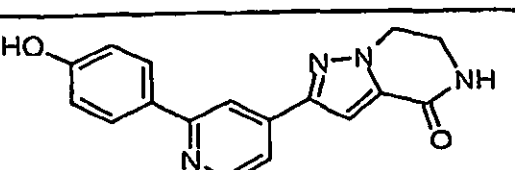
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29		2-[2-(5-chlorothiophen-2-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.444
30		2-[2-(3-fluoro-4-methoxyphenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.471
31		2-[2-(1-oxo-2,3-dihydro-1H-inden-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.478
32		2-[2-(1-methyl-1H-indol-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.479
33		2-[2-(3-fluorophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.505
34		methyl 4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyridin-2-yl]benzoate	0.511
35		2-[2-(3-hydroxyphenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.52

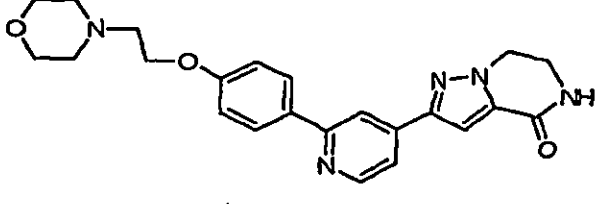
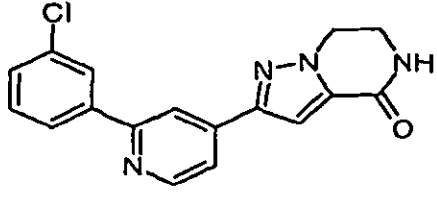
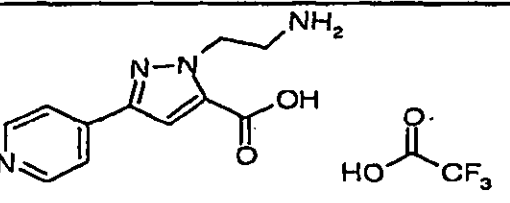
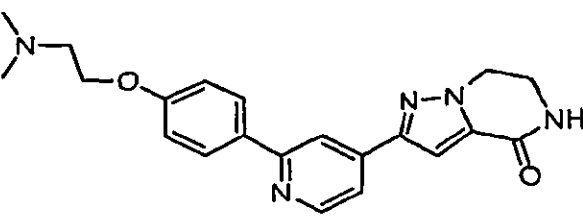
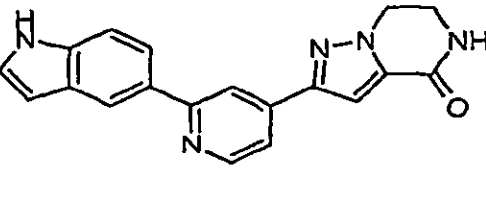
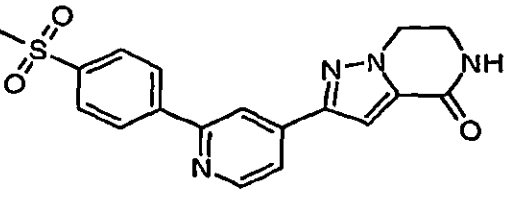
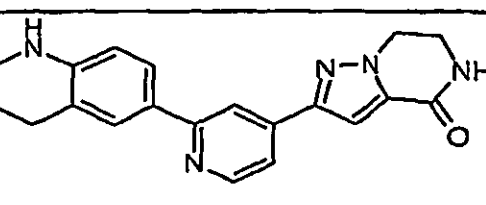
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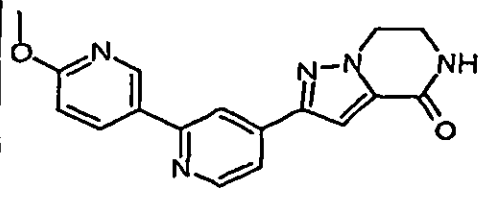
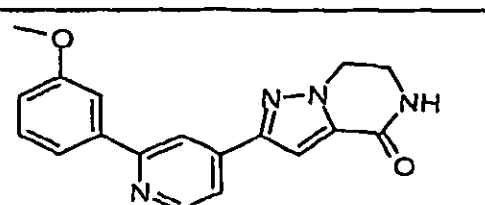
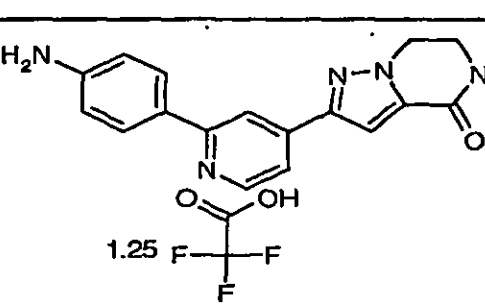
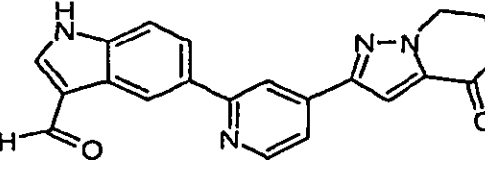
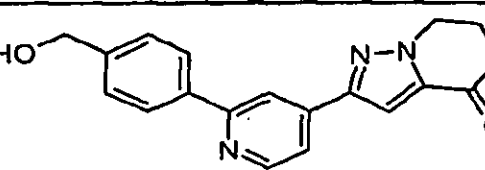
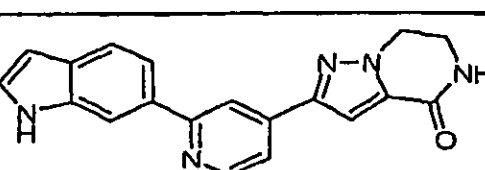
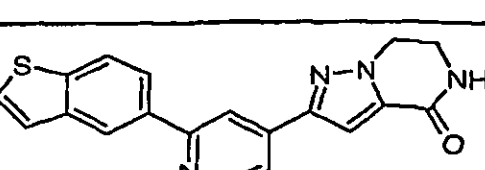
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36		2-[2-(2,3-dihydro-1-benzofuran-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.521
37		2-[2-(1-benzofuran-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	0.543
38		2-[2-(2-oxo-2,3-dihydro-1H-indol-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.554
39		2-(2-quinolin-3-ylpyridin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one	0.577
40		2-[2-[4-(methylthio)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.581
41		2-(2,3'-bipyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.586
42		2-[2-(4-hydroxyphenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.611

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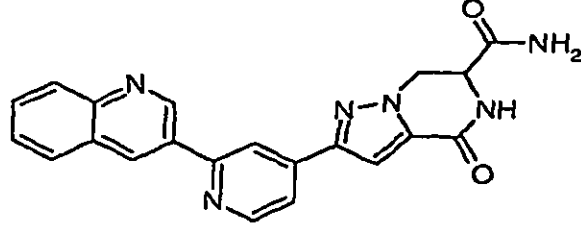
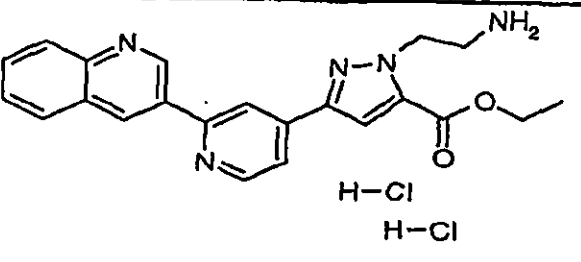
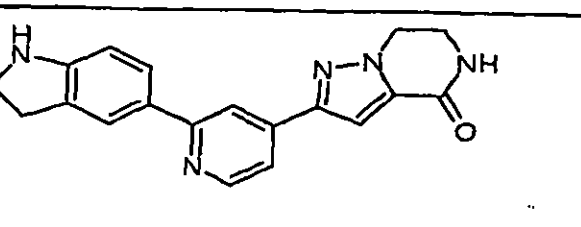
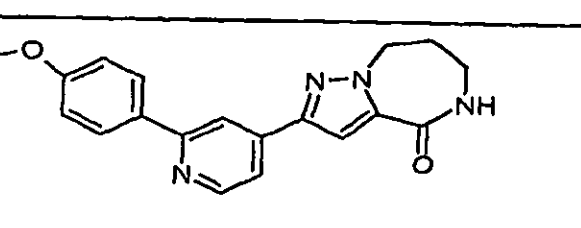
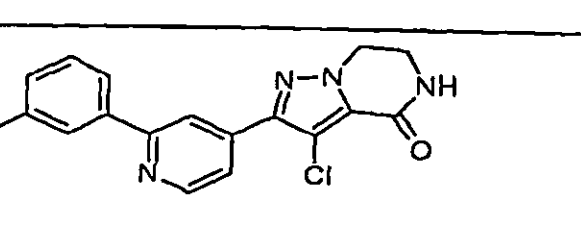
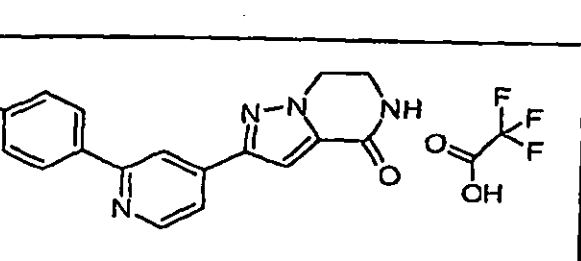
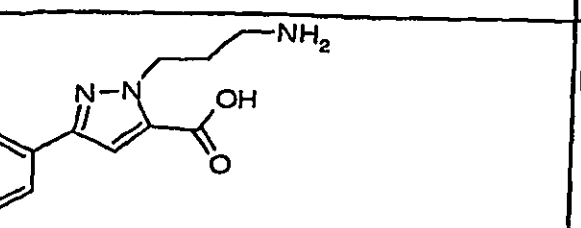
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43		2-[2-[4-(2-morpholin-4-ylethoxy)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.63
44		2-[2-(3-chlorophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.638
45		1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylic acid trifluoroacetate	0.735
46		2-[2-[4-[2-(dimethylamino)ethoxy]phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.766
47		2-[2-(1H-indol-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.808
48		2-[2-[4-(methylsulfonyl)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.821
49		2-[2-(1,2,3,4-tetrahydroquinolin-6-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.835

50		2-(6'-methoxy-2,3'-bipyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.866
51		2-[2-(3-methoxyphenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.906
52		2-[2-(4-aminophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	0.914
53		5-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyridin-2-yl]-1H-indole-3-carbaldehyde	0.923
54		2-[2-[4-(hydroxymethyl)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.929
55		2-[2-(1H-indol-6-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.93
56		2-[2-(1-benzothien-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	0.965

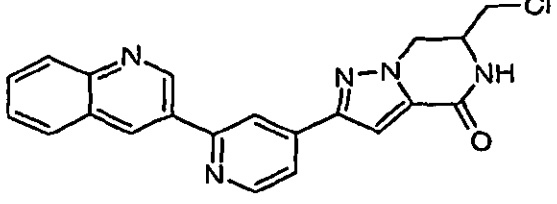
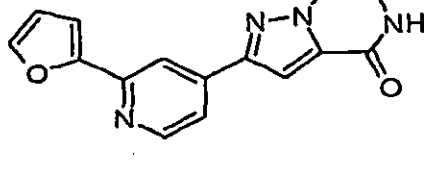
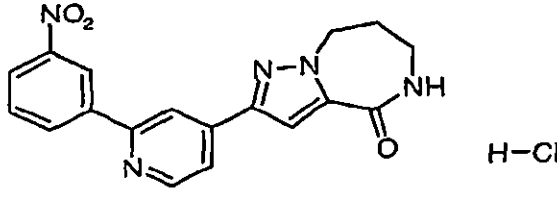
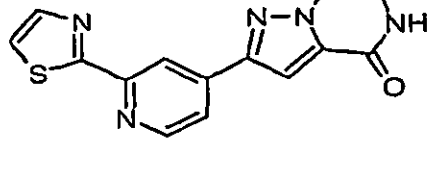
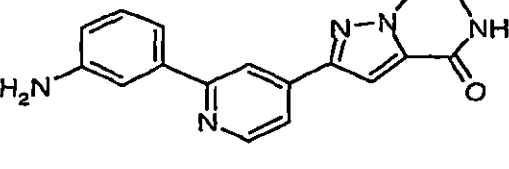
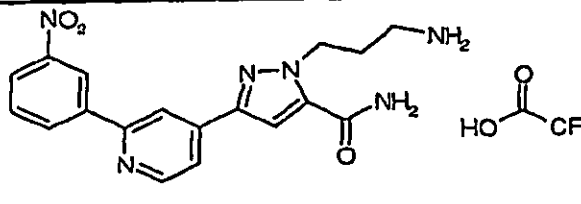
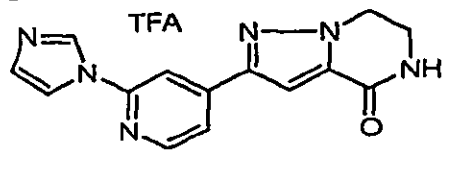
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57		4-oxo-2-(2-quinolin-3-ylpyridin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-6-carboxamide	1.01
58		ethyl 1-(2-aminoethyl)-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylate dihydrochloride	1.03
59		2-[2-(2,3-dihydro-1H-indol-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.07
60		2-[2-(4-methoxyphenyl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one	1.09
61		3-chloro-2-[2-(3-chlorophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.13
62		4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyridin-2-yl]benzaldehyde trifluoroacetate	1.15
63		1-(3-aminopropyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylic acid	1.16

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64		13012 or 6-(chloromethyl)-2-(2-quinolin-3-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.17
65		2-[2-(2-furyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.2
66		2-[2-(3-nitrophenyl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride	1.26
67		2-[2-(1,3-thiazol-2-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.29
68		2-[2-(3-aminophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.3
69		1-(3-aminopropyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxamide trifluoroacetate	1.32
70		2-[2-(1H-imidazol-1-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	1.36

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335

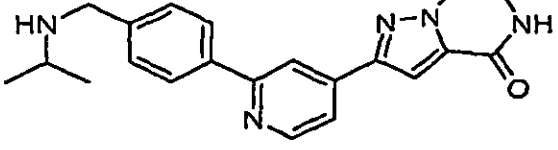
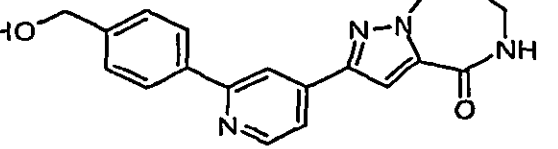
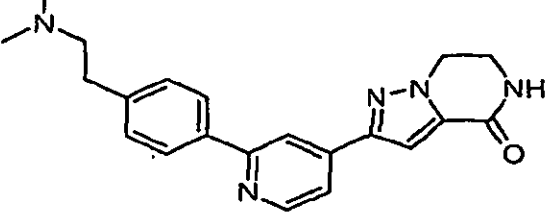
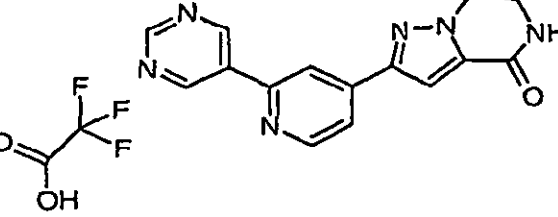
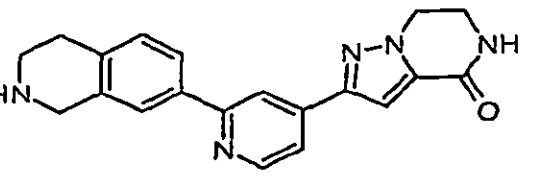
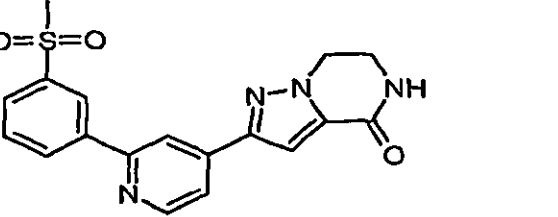
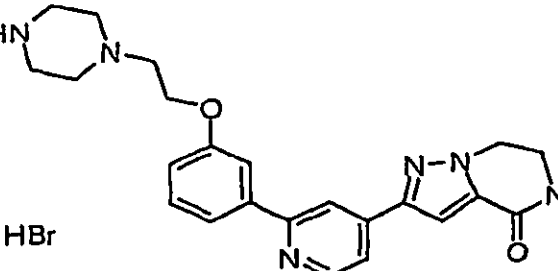
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71		2-[2-(4-hydroxyphenyl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate	1.37
72		3-bromo-2-[2-(3-chlorophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.39
73		2-[2-(3-furyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.46
74		2-[2-[4-(dimethylamino)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	1.53
75		2-(2-thien-3-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.55
76		2-[2-(2,3-dihydro-1,4-benzodioxin-6-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.56
77		2-(5'-methoxy-2,3'-bipyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.69

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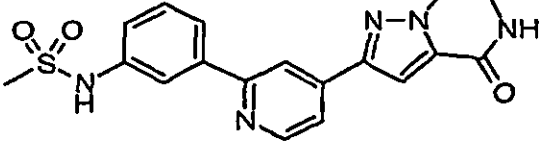
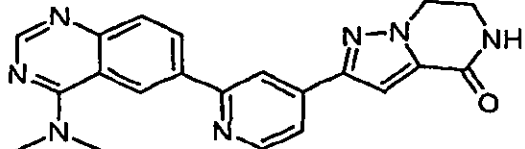
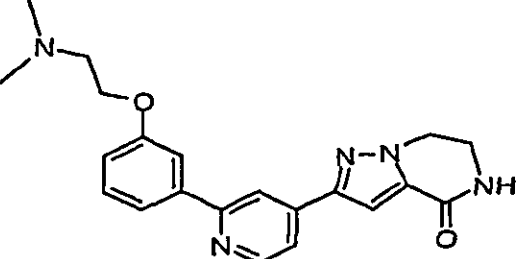
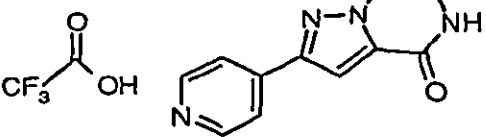
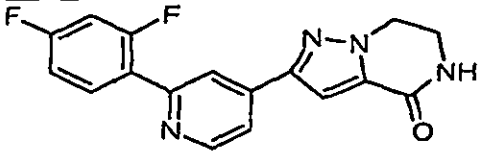
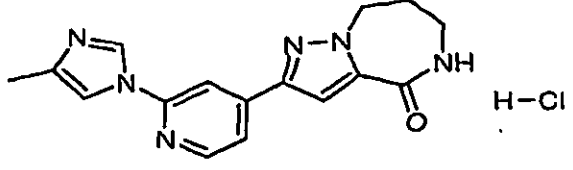
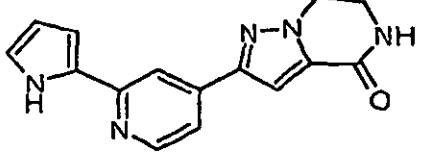
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78		2-(2-[4-((isopropylamino)methyl)phenyl]pyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.73
79		2-(2-[4-(hydroxymethyl)phenyl]pyridin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one	1.75
80		2-(2-[4-(2-(dimethylamino)ethyl)phenyl]pyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	1.98
81		2-(2-pyrimidin-5-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	1.99
82		2-[2-(1,2,3,4-tetrahydroisoquinolin-7-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	2.08
83		2-[2-[3-(methylsulfonyl)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	2.1
84		2-[2-[3-(2-piperazin-1-ylethoxy)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one hydrobromide	2.13

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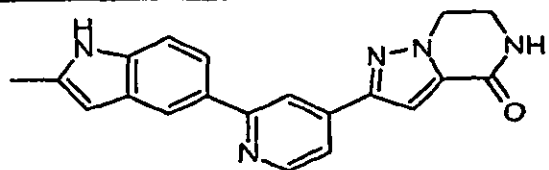
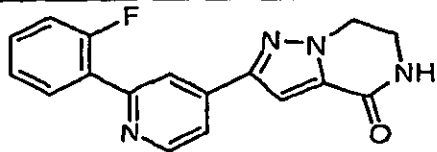
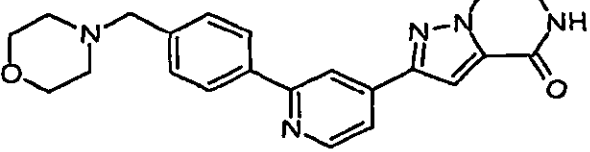
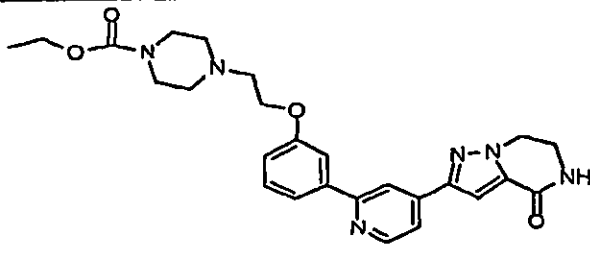
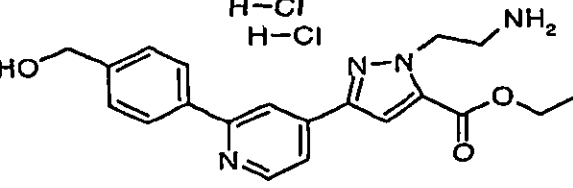
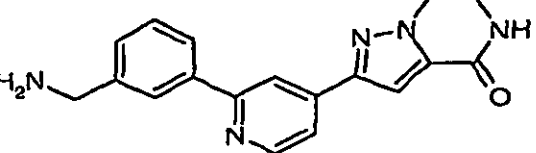
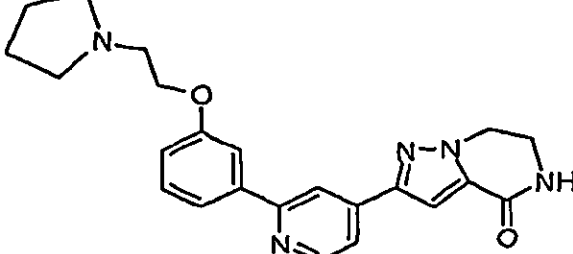
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85		N-[3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyridin-2-yl]phenyl]methanesulfonamide	2.29
86		2-[2-[4-(dimethylamino)quinazolin-6-yl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	2.4
87		2-[2-[3-[2-(dimethylamino)ethoxy]phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	2.4
88		2-pyridin-4-yl-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	2.6
89		2-[2-(2,4-difluorophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	2.62
90		2-[2-(4-methyl-1H-imidazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride	2.76
91		2-[2-(1H-pyrrol-2-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	2.79

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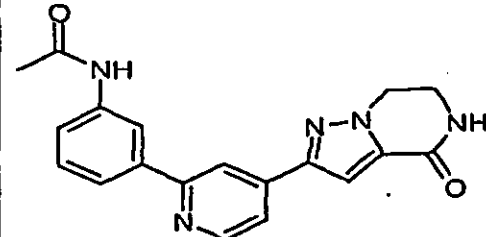
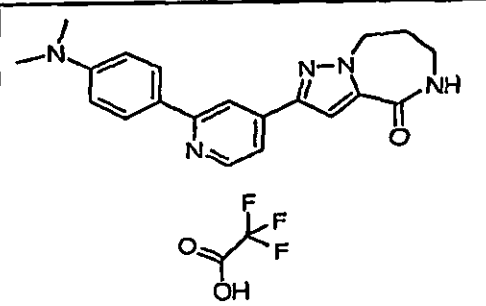
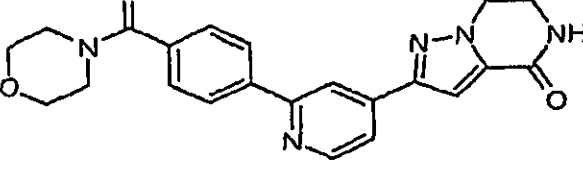
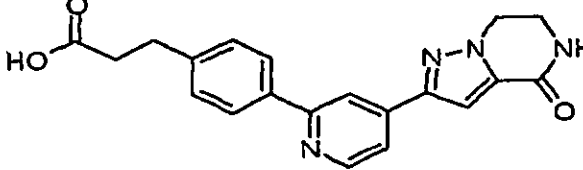
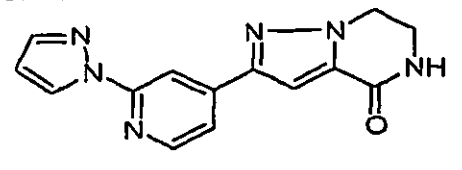
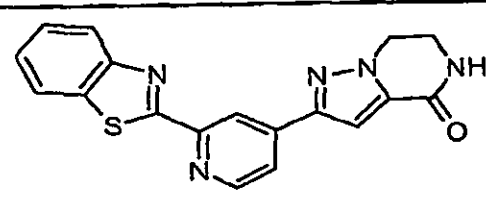
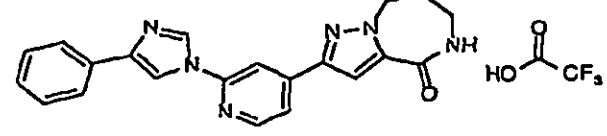
92		2-[2-(2-methyl-1H-indol-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	2.83
93		2-[2-(2-fluorophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	2.95
94		2-[2-[4-(morpholin-4-ylmethyl)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	2.99
95		ethyl 4-(2-{3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyridin-2-yl]phenoxy}ethyl)piperazine-1-carboxylate	3.02
96		ethyl 1-(2-aminoethyl)-3-[2-[4-(hydroxymethyl)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride	3.25
97		2-[2-[3-(aminomethyl)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	3.25
98		2-[2-[3-(2-pyrrolidin-1-ylethoxy)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	3.27

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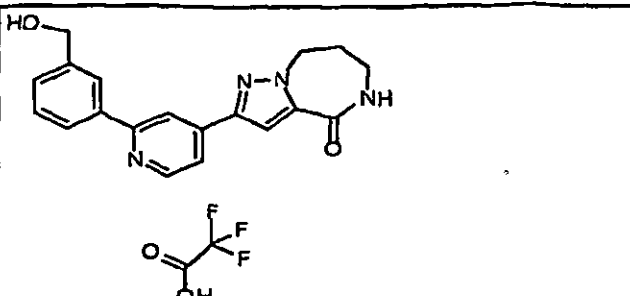
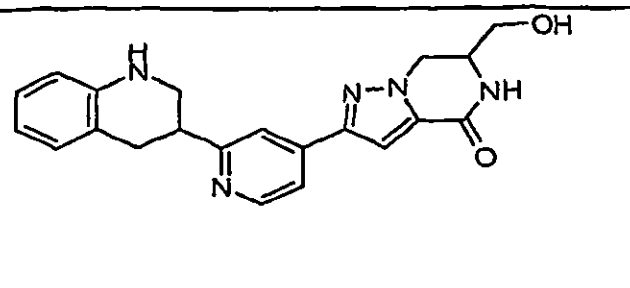
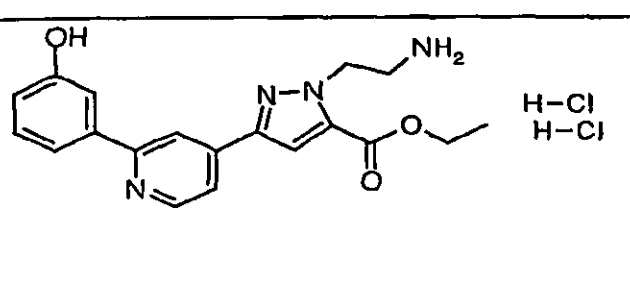
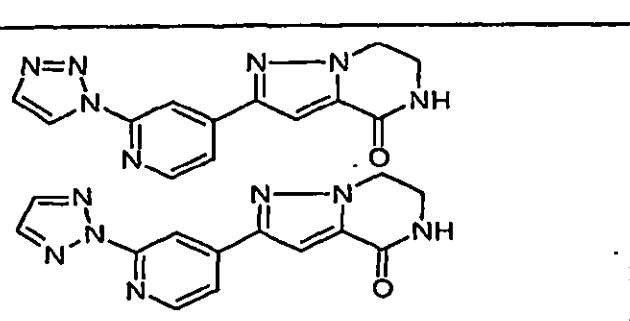
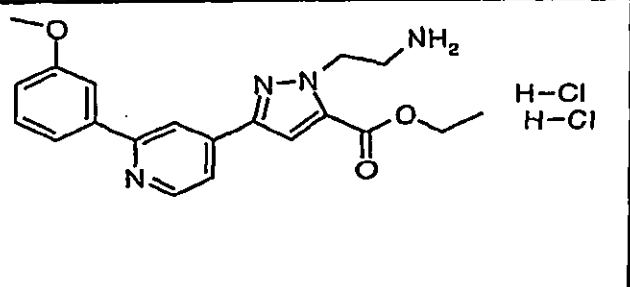
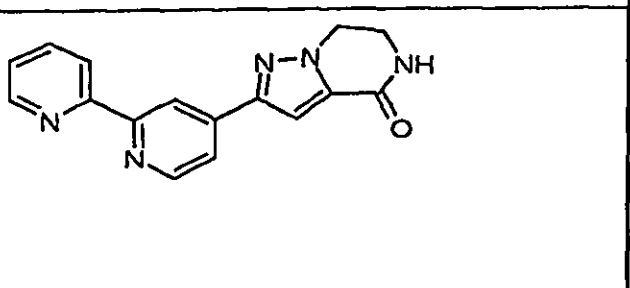
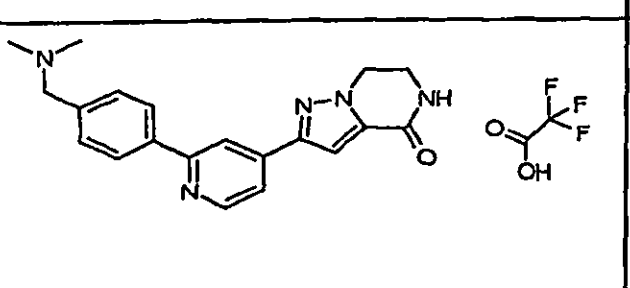
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99		N-[3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyridin-2-yl]phenyl]acetamide	3.31
100		2-[2-[4-(dimethylamino)phenyl]pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate	3.44
101		2-[2-[4-(morpholin-4-ylcarbonyl)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	3.65
102		3-[4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyridin-2-yl]phenyl]propanoic acid	4.19
103		2-[2-(1H-pyrazol-1-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	4.2
104		2-[2-(1,3-benzothiazol-2-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	4.27
105		2-[2-(4-phenyl-1H-imidazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate	4.31

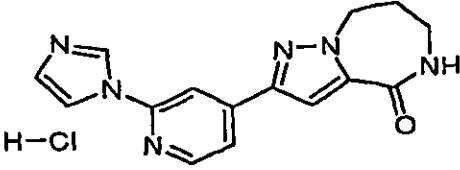
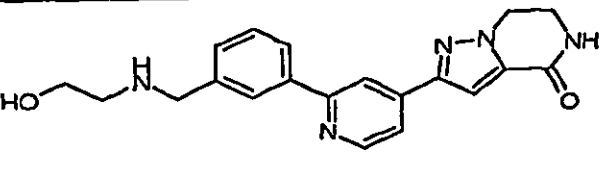
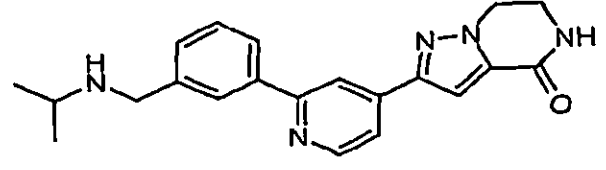
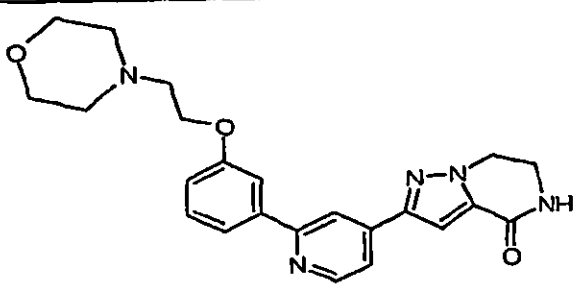
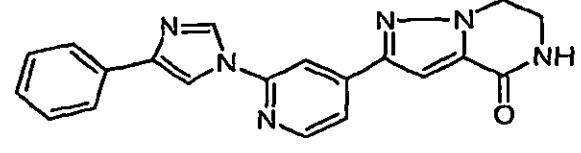
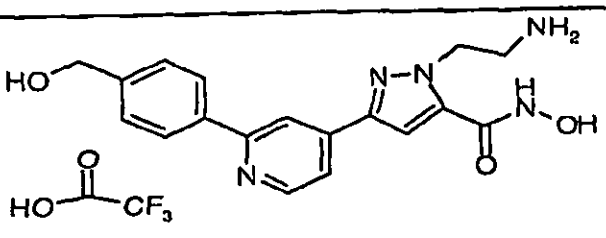
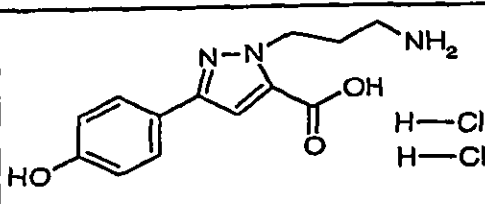
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106		2-[2-[3-(hydroxymethyl)phenyl]pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate	4.54
107		6-(hydroxymethyl)-2-[2-(1,2,3,4-tetrahydroquinolin-3-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	4.9
108		ethyl 1-(2-aminoethyl)-3-[2-(3-hydroxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride	4.98
109		2-[2-(2H-1,2,3-triazol-2-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one compound with 2-[2-(1H-1,2,3-triazol-1-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one (1:1)	5.21
110		ethyl 1-(2-aminoethyl)-3-[2-(3-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride	5.23
111		2-(2,2'-bipyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	5.34
112		2-[2-[4-(dimethylamino)methyl]phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	5.35

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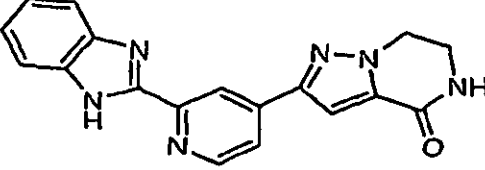
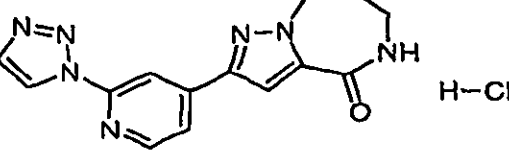
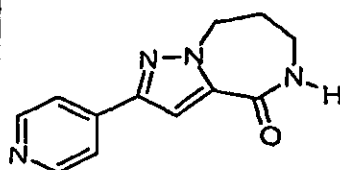
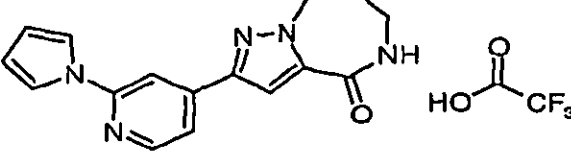
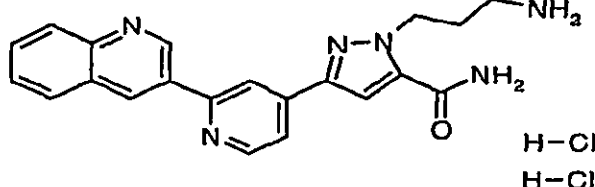
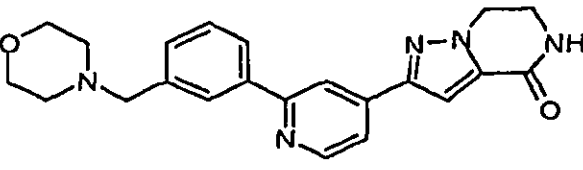
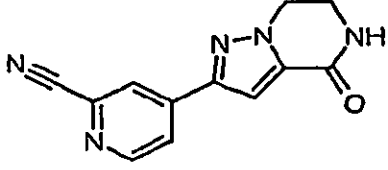
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113		2-[2-(1H-imidazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride	5.66
114		2-[2-(3-((2-hydroxyethyl)amino)methyl)phenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	5.78
115		2-[2-(3-((isopropylamino)methyl)phenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	6.27
116		2-[2-(3-(2-morpholin-4-ylethoxy)phenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	6.73
117		2-[2-(4-phenyl-1H-imidazol-1-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	7.04
118		1-(2-aminoethyl)-N-hydroxy-3-[2-(4-(hydroxymethyl)phenyl)pyridin-4-yl]-1H-pyrazole-5-carboxamide trifluoroacetate	7.91
119		1-(3-aminopropyl)-3-(4-hydroxyphenyl)-1H-pyrazole-5-carboxylic acid dihydrochloride	8.11

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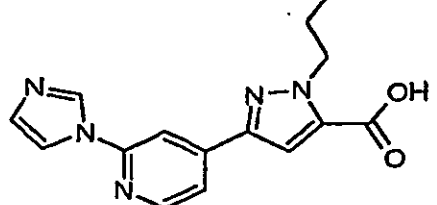
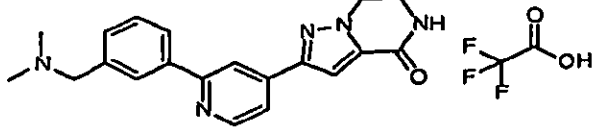
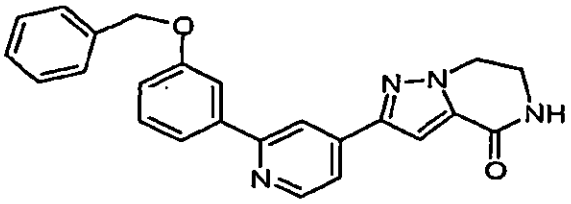
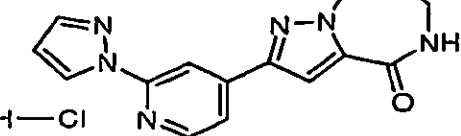
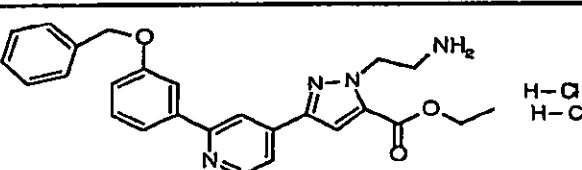
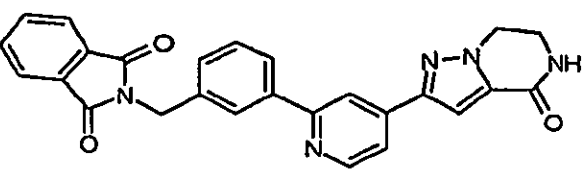
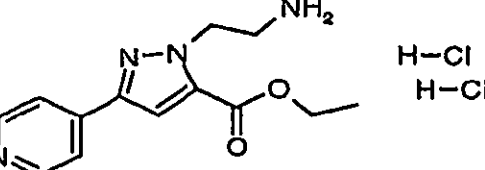
120		2-[2-(1H-benzimidazol-2-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	8.92
121	 H-Cl	2-[2-(1H-1,2,3-triazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride	9.05
122		2-pyridin-4-yl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one	10.1
123	 HO-CF ₃	2-[2-(1H-pyrrol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate	10.6
124	 H-Cl H-Cl	1-(3-aminopropyl)-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxamide dihydrochloride	10.7
125		2-[2-[3-(morpholin-4-ylmethyl)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	11.4
126		4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyridine-2-carbonitrile	13.8

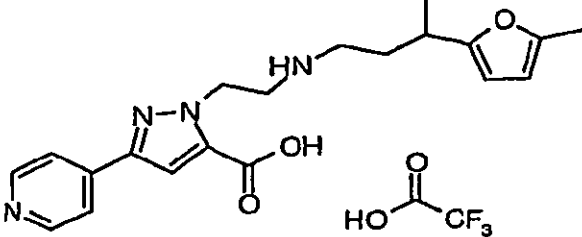
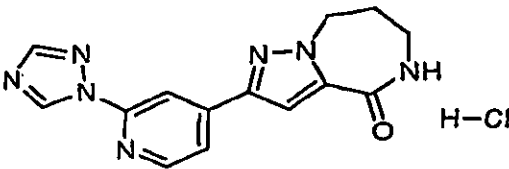
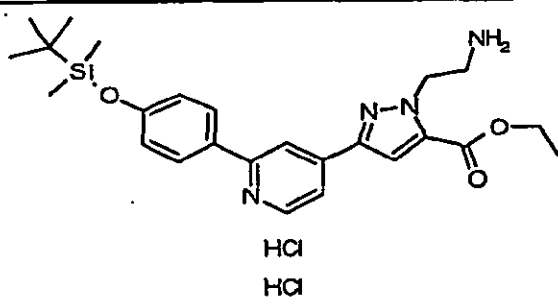
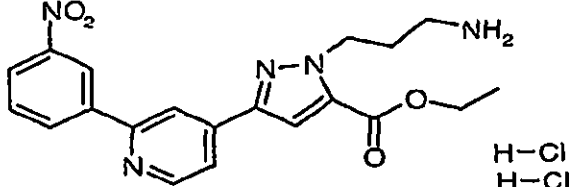
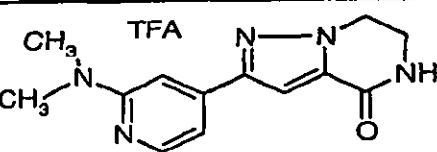
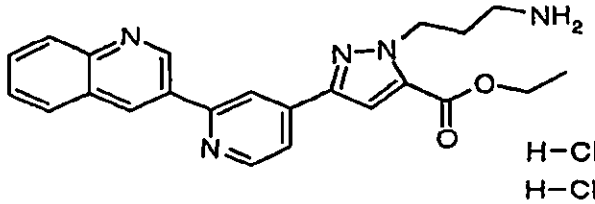
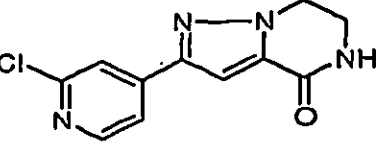
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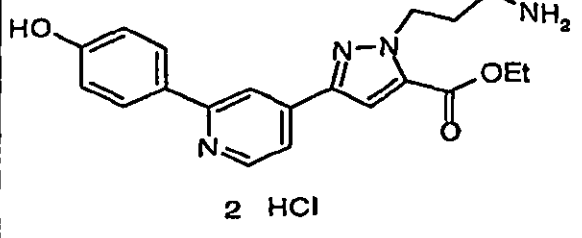
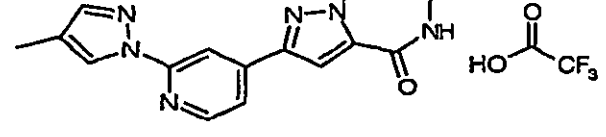
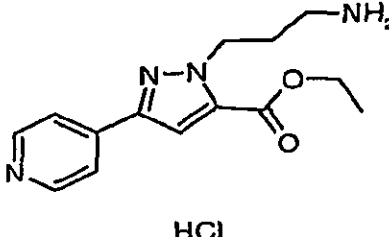
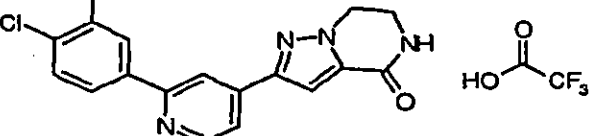
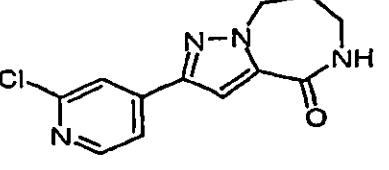
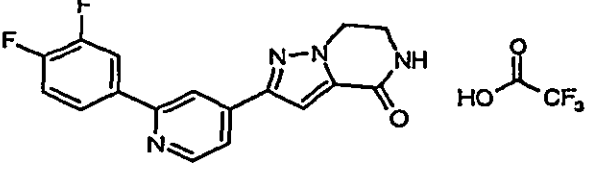
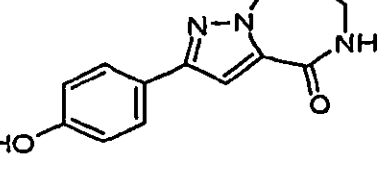
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127		3-[2-(1H-imidazol-1-yl)pyridin-4-yl]-1-propyl-1H-pyrazole-5-carboxylic acid	14.3
128		2-(2-{3-[(dimethylamino)methyl]phenyl}pyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	15.4
129		2-{2-[3-(benzyloxy)phenyl]pyridin-4-yl}-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	15.5
130		2-[2-(1H-pyrazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride	16.2
131		ethyl 1-(2-aminoethyl)-3-{2-[3-(benzyloxy)phenyl]pyridin-4-yl}-1H-pyrazole-5-carboxylate dihydrochloride	20
132		2-[3-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyridin-2-yl]benzyl]-1H-isoindole-1,3(2H)-dione	20
133		ethyl 1-(2-aminoethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylate dihydrochloride	24.5

134		1-(2-((3-(5-methyl-2-furyl)butyl)amino)ethyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylic acid trifluoroacetate	27.2
135		2-[2-(1H-1,2,4-triazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one hydrochloride	28.2
136		ethyl 1-(2-aminoethyl)-3-[2-(4-((tert-butyl(dimethyl)silyl)oxy)phenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride	28.3
137		ethyl 1-(3-aminopropyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride	31.6
138		2-[2-(dimethylamino)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	37.2
139		ethyl 1-(3-aminopropyl)-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylate dihydrochloride	38.6
140		2-(2-chloropyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	44.8

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141	 2 HCl	ethyl 1-(3-aminopropyl)-3-[2-(4-hydroxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate hydrochloride	47.5
142	 HO-C(=O)-CF ₃	2-[2-(4-methyl-1H-pyrazol-1-yl)pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one trifluoroacetate	53.4
143	 HCl	ethyl 1-(3-aminopropyl)-3-pyridin-4-yl-1H-pyrazole-5-carboxylate hydrochloride	60.8
144	 HO-C(=O)-CF ₃	2-[2-(3,4-dichlorophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	65.5
145		2-(2-chloropyridin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one	80.4
146	 HO-C(=O)-CF ₃	2-[2-(3,4-difluorophenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	88.9
147		2-(4-hydroxyphenyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one	118

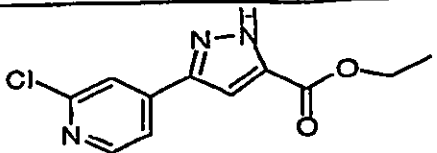
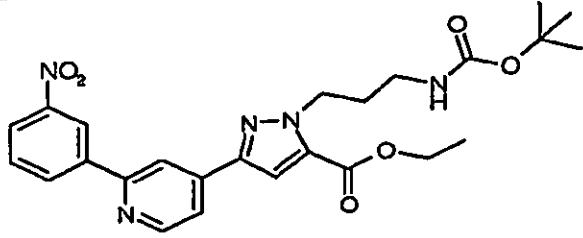
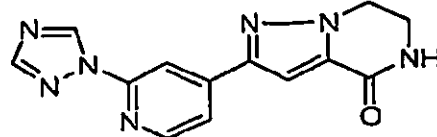
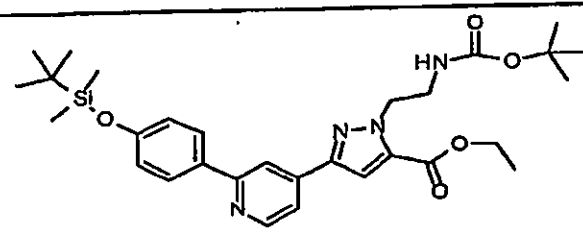
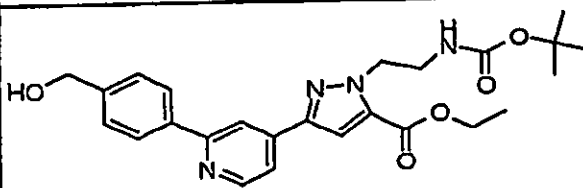
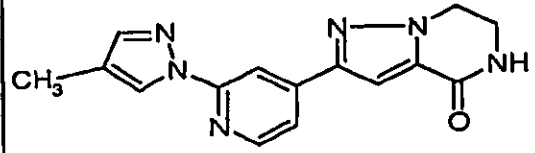
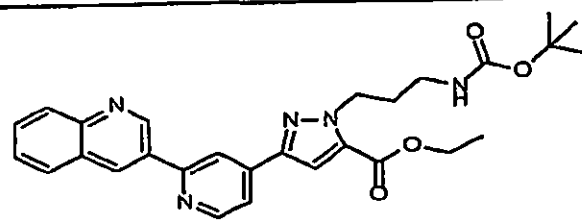
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148		2-[2-[4-(trifluoromethoxy)phenyl]pyridin-4-yl]-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one	124
149		2-[2-[4-(trifluoromethoxy)phenyl]pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	131
150		1-(3-aminopropyl)-3-(3-hydroxyphenyl)-1H-pyrazole-5-carboxylic acid trifluoroacetate	153
151		1-{3-[(tert-butoxycarbonyl)amino]propyl}-3-(4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid	155
152		ethyl 3-(1-oxidopyridin-4-yl)-1H-pyrazole-5-carboxylate	200
153		ethyl 1-(3-aminopropyl)-3-(4-methoxyphenyl)-1H-pyrazole-5-carboxylate hydrochloride	200
154		1-{3-[(tert-butoxycarbonyl)amino]propyl}-3-(3-methoxyphenyl)-1H-pyrazole-5-carboxylic acid	200

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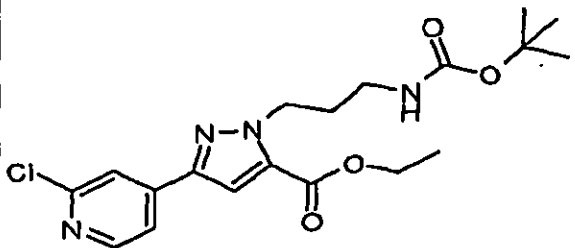
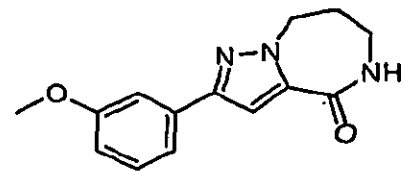
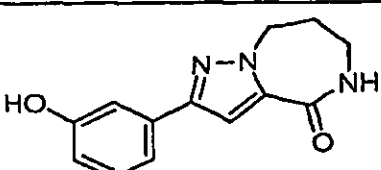
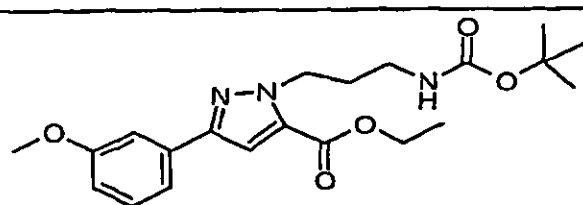
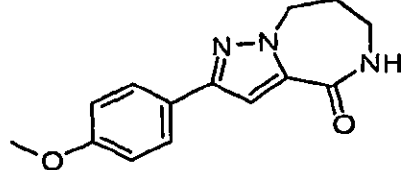
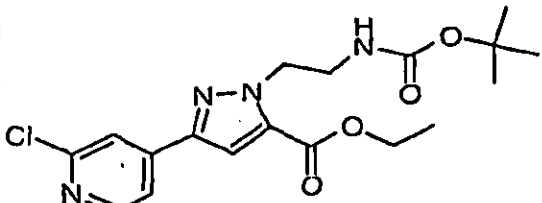
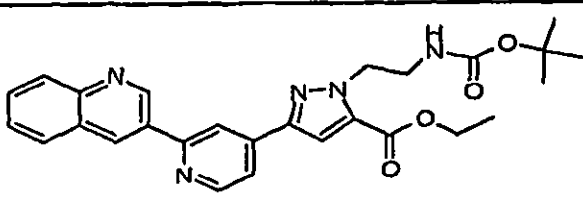
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155		ethyl 3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate	200
156		ethyl 1-{3-[(tert-butoxycarbonyl)amino]propyl}-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate	200
157		2-[2-(1H-1,2,4-triazol-1-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	200
158		ethyl 1-{2-[(tert-butoxycarbonyl)amino]ethyl}-3-[2-(4-[(tert-butyl(dimethyl)silyl]oxy)phenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate	200
159		ethyl 1-{2-[(tert-butoxycarbonyl)amino]ethyl}-3-[2-(4-(hydroxymethyl)phenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate	200
160		2-[2-(4-methyl-1H-pyrazol-1-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	200
161		2-[2-(4-(trifluoromethoxy)phenyl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one trifluoroacetate	200

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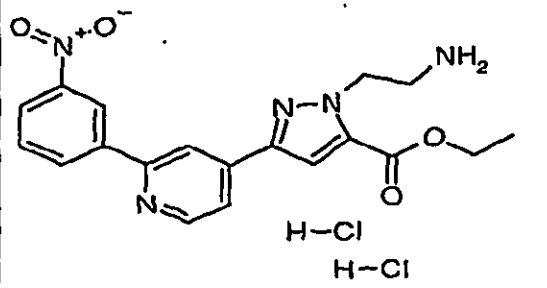
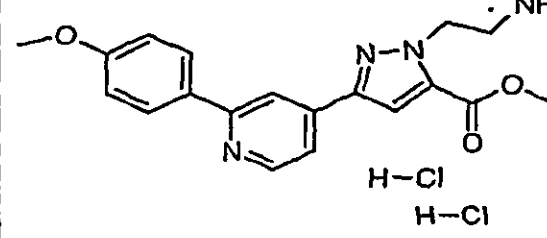
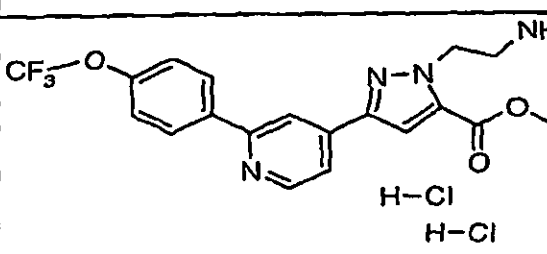
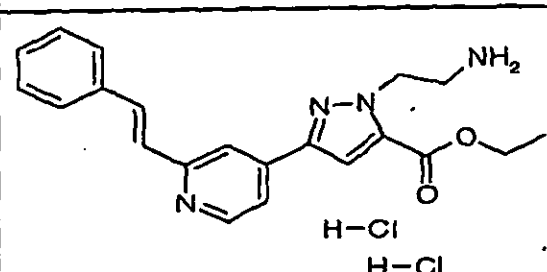
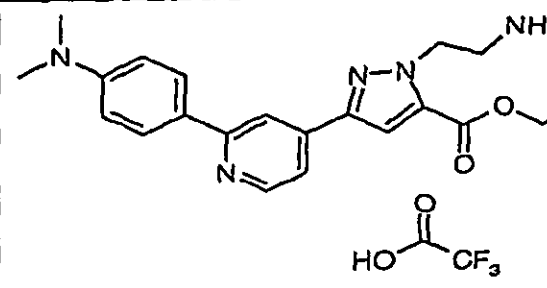
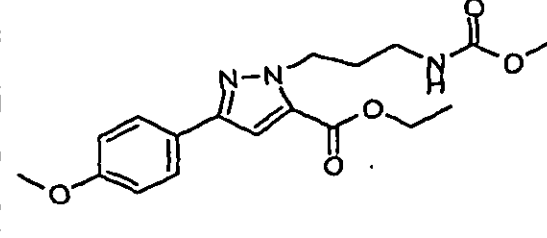
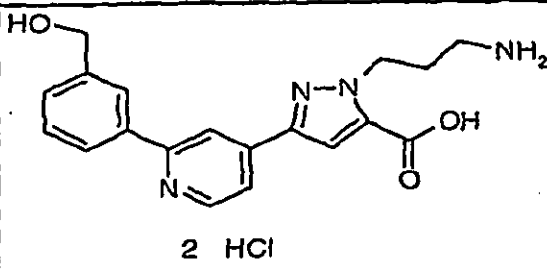
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162		ethyl 1-{3-[(tert-butoxycarbonyl)amino]propyl}-3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate	200
163		2-(3-methoxyphenyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one	200
164		2-(3-hydroxyphenyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one	200
165		ethyl 1-{3-[(tert-butoxycarbonyl)amino]propyl}-3-(3-methoxyphenyl)-1H-pyrazole-5-carboxylate	200
166		2-(4-methoxyphenyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-4-one	200
167		ethyl 1-{2-[(tert-butoxycarbonyl)amino]ethyl}-3-(2-chloropyridin-4-yl)-1H-pyrazole-5-carboxylate	
168		ethyl 1-{2-[(tert-butoxycarbonyl)amino]ethyl}-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylate	

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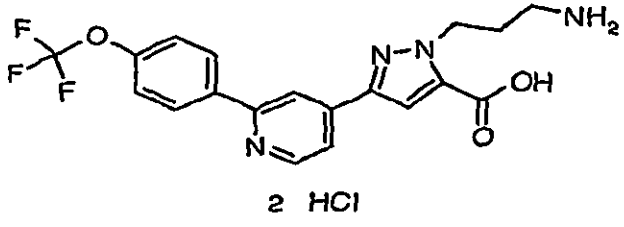
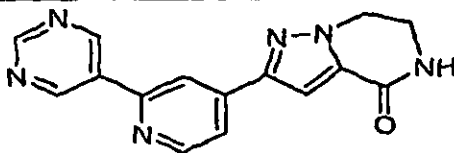
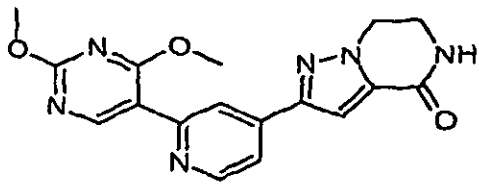
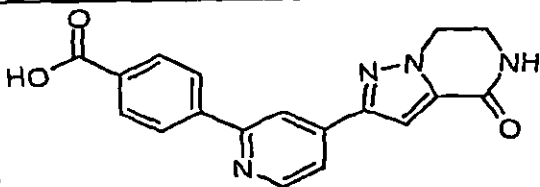
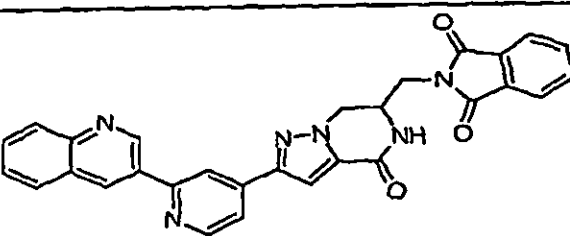
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169	 H-Cl H-Cl	ethyl 1-(2-aminoethyl)-3-[2-(3-nitrophenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride	
170	 H-Cl H-Cl	ethyl 1-(2-aminoethyl)-3-[2-(4-methoxyphenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride	
171	 H-Cl H-Cl	ethyl 1-(2-aminoethyl)-3-[2-(4-(trifluoromethoxy)phenyl)pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride	
172	 H-Cl H-Cl	ethyl 1-(2-aminoethyl)-3-[2-[(E)-2-phenylethenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylate dihydrochloride	
173	 HO-C(=O)-CF3	ethyl 1-(2-aminoethyl)-3-[2-[4-(dimethylamino)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylate trifluoroacetate	
174		ethyl 1-[3-[(tert-butoxycarbonyl)amino]propyl]-3-(4-methoxyphenyl)-1H-pyrazole-5-carboxylate	
175	 2 HCl	1-(3-aminopropyl)-3-[2-[3-(hydroxymethyl)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylic acid hydrochloride	

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176	 2 HCl	1-(3-aminopropyl)-3-[2-[4-(trifluoromethoxy)phenyl]pyridin-4-yl]-1H-pyrazole-5-carboxylic acid hydrochloride	
177		2-(2-pyrimidin-5-ylpyridin-4-yl)-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
178		2-[2-(2,4-dimethoxypyrimidin-5-yl)pyridin-4-yl]-6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one	
179		4-[4-(4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl)pyridin-2-yl]benzoic acid	
180		2-[[4-oxo-2-(2-quinolin-3-ylpyridin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-6-yl]methyl]-1H-isindole-1,3(2H)-dione	

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analogous circumstances. In determining the effective amount or dose, a number of factors are considered by the attending diagnostician, including but not limited to, the potency and duration of action of the compounds used, the nature and severity of the illness to be treated, as well as the sex, age, weight, general health and individual responsiveness of the patient to be treated, and other relevant circumstances.

[00076] The phrase "therapeutically-effective" indicates the capability of an agent to prevent, or improve the severity of, the disorder, while avoiding adverse side effects typically associated with alternative therapies. The phrase "therapeutically-effective" is to be understood to be equivalent to the phrase "effective for the treatment, prevention, or inhibition", and both are intended to qualify the amount of the MK-2 inhibitory compound for use in therapy which will achieve the goal of improvement in the severity of pain and inflammation and the frequency of incidence over treatment, while avoiding adverse side effects typically associated with alternative therapies.

[00077] Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711.

[00078] The frequency of dose will depend upon the half-life of the active components of the composition. If the active molecules have a short half life (e.g. from about 2 to 10 hours) it may be necessary to give one or more doses per day. Alternatively, if the active molecules have a long half-life (e.g. from about 2 to about 15 days) it may only be necessary to give a dosage once per day, per week, or even once every 1 or 2 months. A preferred dosage rate is to administer the dosage amounts described above to a subject once per day.

[00079] Daily dosages can vary within wide limits and will be adjusted to the individual requirements in each particular case. In general, for administration to adults, an appropriate daily dosage has been described above, although the limits that were identified as being preferred may be

exceeded if expedient. The daily dosage can be administered as a single dosage or in divided dosages.

5 [00080] For the purposes of calculating and expressing a dosage rate, all dosages that are expressed herein are calculated on an average amount-per-day basis irrespective of the dosage rate. For example, one 100 mg dosage of an MK-2 inhibitor taken once every two days would be expressed as a dosage rate of 50 mg/day. Similarly, the dosage rate of an ingredient where 50 mg is taken twice per day would be expressed as a dosage rate of 100 mg/day.

10 [00081] For purposes of calculation of dosage amounts, the weight of a normal adult human will be assumed to be 70 kg.

[00082] When the MK-2 inhibitor is supplied along with a pharmaceutically acceptable carrier, the pharmaceutical compositions that are described above can be formed. Pharmaceutically acceptable carriers include, but are not limited to, physiological saline, Ringer's, phosphate solution or buffer, buffered saline, and other carriers known in the art. Pharmaceutically acceptable carriers may also include stabilizers, anti-oxidants, colorants, and diluents. Pharmaceutically acceptable carriers and additives are chosen such that side effects from the pharmaceutical compound are minimized and the performance of the compound is not canceled or inhibited to such an extent that treatment is ineffective.

20 [00083] The term "pharmacologically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician. This amount can be a therapeutically effective amount.

25 [00084] The term "pharmaceutically acceptable" is used herein to mean that the modified noun is appropriate for use in a pharmaceutical product. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to, appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Exemplary ions include aluminum,

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calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, *N,N*-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (*N*-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include, without limitation, hydrochloric acid, hydroiodic acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid, oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

[00085] Also included in the compounds and compositions of the invention are the isomeric forms and tautomers and the pharmaceutically-acceptable salts of the present MK-2 inhibitors. Illustrative pharmaceutically acceptable salts are prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, *p*-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, β -hydroxybutyric, galactaric and galacturonic acids.

[00086] Suitable pharmaceutically-acceptable base addition salts of compounds of the present invention include metallic ion salts and organic ion salts. More preferred metallic ion salts include, but are not limited to, appropriate alkali metal (Group IA) salts, alkaline earth metal (Group IIA) salts and other physiological acceptable metal ions. Such salts can be made from the ions of aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines and quaternary ammonium salts, including in part, trifluoroacetate, trimethylamine, diethylamine, *N,N*-dibenzylethylenediamine,

chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of the above salts can be prepared by those skilled in the art by conventional means from the corresponding compound of the present invention.

5 [00087] The method of the present invention is useful for, but not limited to, the prevention and/or treatment of diseases and disorders that are mediated by TNF α and/or mediated by MK-2, including pain, inflammation and/or arthritis. For example, the compounds described herein would be useful for the treatment of any inflammation-related disorder described
10 below, such as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. The compounds described herein would also be useful for the treatment of an inflammation-related disorder in a subject suffering from such an inflammation-associated disorder.

[00088] As used herein, the terms "treating", "treatment", "treated", or
15 "to treat," mean to alleviate symptoms, eliminate the causation either on a temporary or permanent basis. The term "treatment" includes alleviation, elimination of causation of pain and/or inflammation associated with, but not limited to, any of the diseases or disorders described herein. The terms "prevent", "prevention", "prevented", or "to prevent," mean to prevent
20 or to slow the appearance of symptoms associated with, but not limited to, any of the diseases or disorders described herein.

[00089] In preferred embodiments, the methods and compositions of the present invention encompass the prevention and/or treatment of pain, inflammation and inflammation-related disorders.

25 [00090] In other preferred embodiments, the methods and compositions of the present invention encompass the treatment of any one or more of the disorders selected from the group consisting of connective tissue and joint disorders, neoplasia disorders, cardiovascular disorders, otic disorders, ophthalmic disorders, respiratory disorders, gastrointestinal
30 disorders, angiogenesis-related disorders, immunological disorders, allergic disorders, nutritional disorders, infectious diseases and disorders, endocrine disorders, metabolic disorders, neurological and

neurodegenerative disorders, psychiatric disorders, hepatic and biliary disorders, musculoskeletal disorders, genitourinary disorders, gynecologic and obstetric disorders, injury and trauma disorders, surgical disorders, dental and oral disorders, sexual dysfunction disorders, dermatologic disorders, hematological disorders, and poisoning disorders.

5 [00091] As used herein, the terms "neoplasia" and "neoplasia disorder", used interchangeably herein, refer to new cell growth that results from a loss of responsiveness to normal growth controls, e.g. to "neoplastic" cell growth. Neoplasia is also used interchangeably herein with the term
10 "cancer" and for purposes of the present invention; cancer is one subtype of neoplasia. As used herein, the term "neoplasia disorder" also encompasses other cellular abnormalities, such as hyperplasia, metaplasia and dysplasia. The terms neoplasia, metaplasia, dysplasia and hyperplasia can be used interchangeably herein and refer generally to
15 cells experiencing abnormal cell growth.

[00092] Both of the terms, "neoplasia" and "neoplasia disorder", refer to a "neoplasm" or tumor, which may be benign, premalignant, metastatic, or malignant. Also encompassed by the present invention are benign, premalignant, metastatic, or malignant neoplasias. Also encompassed by
20 the present invention are benign, premalignant, metastatic, or malignant tumors. Thus, all of benign, premalignant, metastatic, or malignant neoplasia or tumors are encompassed by the present invention and may be referred to interchangeably, as neoplasia, neoplasms or neoplasia-related disorders. Tumors are generally known in the art to be a mass of
25 neoplasia or "neoplastic" cells. Although, it is to be understood that even one neoplastic cell is considered, for purposes of the present invention to be a neoplasm or alternatively, neoplasia.

[00093] In still other preferred embodiments, the methods and compositions of the present invention encompass the prevention and
30 treatment of the connective tissue and joint disorders selected from the group consisting of arthritis, rheumatoid arthritis, spondyloarthropathies, gouty arthritis, lumbar spondylarthrosis, carpal tunnel syndrome, canine

hip dysplasia, systemic lupus erythematosus, juvenile arthritis, osteoarthritis, tendonitis and bursitis.

[00094] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the neoplasia disorders selected from the group consisting of acral lentiginous melanoma, actinic keratoses, adenocarcinoma, adenoid cystic carcinoma, adenomas, familial adenomatous polyposis, familial polyps, colon polyps, polyps, adenosarcoma, adenosquamous carcinoma, adrenocortical carcinoma, AIDS-related lymphoma, anal cancer, astrocytic tumors, bartholin gland carcinoma, basal cell carcinoma, bile duct cancer, bladder cancer, brain stem glioma, brain tumors, breast cancer, bronchial gland carcinomas, capillary carcinoma, carcinoids, carcinoma, carcinosarcoma, cavernous, central nervous system lymphoma, cerebral astrocytoma, cholangiocarcinoma, chondrosarcoma, choroid plexus papilloma/carcinoma, clear cell carcinoma, skin cancer, brain cancer, colon cancer, colorectal cancer, cutaneous T-cell lymphoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epithelioid, esophageal cancer, Ewing's sarcoma, extragonadal germ cell tumor, fibrolamellar, focal nodular hyperplasia, gallbladder cancer, gastrinoma, germ cell tumors, gestational trophoblastic tumor, glioblastoma, glioma, glucagonoma, hemangioblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, Hodgkin's lymphoma, hypopharyngeal cancer, hypothalamic and visual pathway glioma, insulinoma, intraepithelial neoplasia, interepithelial squamous cell neoplasia, intraocular melanoma, invasive squamous cell carcinoma, large cell carcinoma, islet cell carcinoma, Kaposi's sarcoma, kidney cancer, laryngeal cancer, leiomyosarcoma, lentigo maligna melanomas, leukemia-related disorders, lip and oral cavity cancer, liver cancer, lung cancer, lymphoma, malignant mesothelial tumors, malignant thymoma, medulloblastoma, medulloepithelioma, melanoma, meningeal, merkel cell

carcinoma, mesothelial, metastatic carcinoma, mucoepidermoid
 carcinoma, multiple myeloma/plasma cell neoplasm, mycosis fungoides,
 myelodysplastic syndrome, myeloproliferative disorders, nasal cavity and
 paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma,
 5 neuroepithelial adenocarcinoma nodular melanoma, non-Hodgkin's
 lymphoma, oat cell carcinoma, oligodendroglial, oral cancer,
 oropharyngeal cancer, osteosarcoma, pancreatic polypeptide, ovarian
 cancer, ovarian germ cell tumor, pancreatic cancer, papillary serous
 adenocarcinoma, pineal cell, pituitary tumors, plasmacytoma,
 10 pseudosarcoma, pulmonary blastoma, parathyroid cancer, penile cancer,
 pheochromocytoma, pineal and supratentorial primitive neuroectodermal
 tumors, pituitary tumor, plasma cell neoplasm, pleuropulmonary blastoma,
 prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma,
 rhabdomyosarcoma, sarcoma, serous carcinoma, small cell carcinoma,
 15 small intestine cancer, soft tissue carcinomas, somatostatin-secreting
 tumor, squamous carcinoma, squamous cell carcinoma, submesothelial,
 superficial spreading melanoma, supratentorial primitive neuroectodermal
 tumors, thyroid cancer, undifferentiated carcinoma, urethral cancer,
 uterine sarcoma, uveal melanoma, verrucous carcinoma, vaginal cancer,
 20 vipoma, vulvar cancer, Waldenstrom's macroglobulinemia, well
 differentiated carcinoma, and Wilm's tumor.

[00095] In other preferred embodiments, the methods and compositions
 of the present invention encompass the prevention and treatment of the
 cardiovascular disorders selected from the group consisting of myocardial
 25 ischemia, hypertension, hypotension, heart arrhythmias, pulmonary
 hypertension, hypokalemia, cardiac ischemia, myocardial infarction,
 cardiac remodeling, cardiac fibrosis, myocardial necrosis, aneurysm,
 arterial fibrosis, embolism, vascular plaque inflammation, vascular plaque
 rupture, bacterial-induced inflammation and viral induced inflammation,
 30 edema, swelling, fluid accumulation, cirrhosis of the liver, Bartter's
 syndrome, myocarditis, arteriosclerosis, atherosclerosis, calcification (such
 as vascular calcification and valvar calcification), coronary artery disease,

heart failure, congestive heart failure, shock, arrhythmia, left ventricular hypertrophy, angina, diabetic nephropathy, kidney failure, eye damage, vascular diseases, migraine headaches, aplastic anemia, cardiac damage, diabetic cardiac myopathy, renal insufficiency, renal injury, renal arteriopathy, peripheral vascular disease, left ventricular hypertrophy, cognitive dysfunction, stroke, and headache.

5
[00096] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the metabolic disorders selected from the group consisting of obesity, overweight, type I and type II diabetes, hypothyroidism, and hyperthyroidism.

10
[00097] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the respiratory disorders selected from the group consisting of asthma, bronchitis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, pulmonary edema, pulmonary embolism, pneumonia, pulmonary sarcoisosis, silicosis, pulmonary fibrosis, respiratory failure, acute respiratory distress syndrome and emphysema.

15
[00098] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the angiogenesis-related disorders selected from the group consisting of angiofibroma, neovascular glaucoma, arteriovenous malformations, arthritis, osler-weber syndrome, atherosclerotic plaques, psoriasis, corneal graft neovascularization, pyogenic granuloma, delayed wound healing, retrolental fibroplasias, diabetic retinopathy, scleroderma, granulations, solid tumors, hemangioma, trachoma, hemophilic joints, vascular adhesions, hypertrophic scars, age-related macular degeneration, coronary artery disease, stroke, cancer, AIDS complications, ulcers and infertility.

20
[00099] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the infectious diseases and disorders selected from the group consisting of

viral infections, bacterial infections, prion infections, spirochetes infections, mycobacterial infections, rickettsial infections, chlamydial infections, parasitic infections and fungal infections.

5 [000100] In still further embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the infectious diseases and disorders selected from the group consisting of hepatitis, HIV (AIDS), small pox, chicken pox, common cold, bacterial influenza, viral influenza, warts, oral herpes, genital herpes, herpes simplex infections, herpes zoster, bovine spongiform encephalopathy, 10 septicemia, streptococcus infections, staphylococcus infections, anthrax, severe acquired respiratory syndrome (SARS), malaria, African sleeping sickness, yellow fever, chlamydia, botulism, canine heartworm, rocky mountain spotted fever, lyme disease, cholera, syphilis, gonorrhea, encephalitis, pneumonia, conjunctivitis, yeast infections, rabies, dengue 15 fever, Ebola, measles, mumps, rubella, West Nile virus, meningitis, gastroenteritis, tuberculosis, hepatitis, and scarlet fever.

[000101] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the neurological and neurodegenerative disorders selected from the group 20 consisting of headaches, migraine headaches, Alzheimer's disease, Parkinson's disease, dementia, memory loss, senility, amyotrophy, ALS, amnesia, seizures, multiple sclerosis, muscular dystrophies, epilepsy, schizophrenia, depression, anxiety, attention deficit disorder, hyperactivity, bulimia, anorexia nervosa, anxiety, autism, phobias, spongiform 25 encephalopathies, Creutzfeldt-Jakob disease, Huntington's Chorea, ischemia, obsessive-compulsive disorder, manic depression, bipolar disorders, drug addiction, alcoholism and smoking addiction.

[000102] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the 30 dermatological disorders selected from the group consisting of acne, psoriasis, eczema, burns, poison ivy, poison oak and dermatitis.

5 [000103] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the surgical disorders selected from the group consisting of pain and swelling following surgery, infection following surgery and inflammation following surgery.

10 [000104] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the gastrointestinal disorders selected from the group consisting of inflammatory bowel disease, irritable bowel syndrome, Crohn's disease, gastritis, irritable bowel syndrome, diarrhea, constipation, dysentery, ulcerative colitis, gastric esophageal reflux, gastric ulcers, gastric varices, ulcers, and heartburn.

15 [000105] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the otic disorders selected from the group consisting of otic pain, inflammation, otorrhea, otalgia, fever, otic bleeding, Lermoyez's syndrome, Meniere's disease, vestibular neuronitis, benign paroxysmal positional vertigo, herpes zoster oticus, Ramsay Hunt's syndrome, viral neuronitis, ganglionitis, geniculate herpes, labyrinthitis, purulent labyrinthitis, viral
20 endolymphatic labyrinthitis, perilymph fistulas, noise-induced hearing loss, presbycusis, drug-induced ototoxicity, acoustic neuromas, aerotitis media, infectious myringitis, bullous myringitis, otitis media, otitis media with effusion, acute otitis media, secretory otitis media, serous otitis media, acute mastoiditis, chronic otitis media, otitis externa, otosclerosis,
25 squamous cell carcinoma, basal cell carcinoma, nonchromaffin paragangliomas, chemodectomas, globus jugulare tumors, globus tympanicum tumors, external otitis, perichondritis, aural eczematoid dermatitis, malignant external otitis, subperichondrial hematoma, ceruminomas, impacted cerumen, sebaceous cysts, osteomas, keloids,
30 otalgia, tinnitus, vertigo, tympanic membrane infection, typanitis, otic furuncles, otorrhea, acute mastoiditis, petrositis, conductive and sensorineural hearing loss, epidural abscess, lateral sinus thrombosis,

subdural empyema, otitic hydrocephalus, Dandy's syndrome, bullous myringitis, cerumen-impacted, diffuse external otitis, foreign bodies, keratosis obturans, otic neoplasm, otomycosis, trauma, acute barotitis media, acute eustachian tube obstruction, post-otic surgery, postsurgical
 5 otalgia, cholesteatoma, conductive and sensorineural hearing loss, epidural abscess, lateral sinus thrombosis, subdural empyema and otitic hydrocephalus.

[000106] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of the
 10 ophthalmic disorders selected from the group consisting of retinopathies, uveitis, ocular photophobia, acute injury to the eye tissue, conjunctivitis, age-related macular degeneration diabetic retinopathy, detached retina, glaucoma, vitelliform macular dystrophy type 2, gyrate atrophy of the choroid and retina, conjunctivitis, corneal infection, fuchs' dystrophy,
 15 iridocorneal endothelial syndrome, keratoconus, lattice dystrophy, map-dot-fingerprint dystrophy, ocular herpes, pterygium, myopia, hyperopia, and cataracts.

[000107] In other preferred embodiments, the methods and compositions of the present invention encompass the prevention and treatment of
 20 menstrual cramps, kidney stones, minor injuries, wound healing, vaginitis, candidiasis, sinus headaches, tension headaches, dental pain, periarteritis nodosa, thyroiditis, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Bahcet's syndrome, polymyositis, gingivitis, hypersensitivity, swelling occurring after injury, closed head injury, liver
 25 disease, and endometriosis.

[000108] As used herein, the terms "TNF α mediated disease or disorder" are meant to include, without limitation, each of the symptoms or diseases that are mentioned above.

[000109] The term "subject" for purposes of treatment includes any
 30 human or animal subject who is in need of the prevention of or treatment of any one of the TNF α mediated diseases or disorders. The subject is typically a mammal. "Mammal", as that term is used herein, refers to any

animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cattle, etc., Preferably, the mammal is a human.

5 [000110] For methods of prevention, the subject is any human or animal subject, and preferably is a subject that is in need of prevention and/or treatment of a TNF α mediated diseases or disorders. The subject may be a human subject who is at risk of obtaining a TNF α mediated disease or disorder, such as those described above. The subject may be at risk due to genetic predisposition, sedentary lifestyle, diet, exposure to disorder-
10 causing agents, exposure to pathogenic agents and the like.

[000111] The subject pharmaceutical compositions may be administered enterally and parenterally. Parenteral administration includes subcutaneous, intramuscular, intradermal, intramammary, intravenous, and other administrative methods known in the art. Enteral administration
15 includes solution, tablets, sustained release capsules, enteric coated capsules, and syrups. When administered, the pharmaceutical composition may be at or near body temperature.

[000112] In particular, the pharmaceutical compositions of the present invention can be administered orally, for example, as tablets, coated
20 tablets, dragees, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or
25 more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These
30 excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, maize starch, or alginic

acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

[000113] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredients are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients are present as such, or mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

[000114] Aqueous suspensions can be produced that contain the MK-2 inhibitors in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone gum tragacanth and gum acacia; dispersing or wetting agents may be naturally-occurring phosphatides, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate.

[000115] The aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, or one or more sweetening agents, such as sucrose or saccharin.

5 [000116] Oily suspensions may be formulated by suspending the active ingredients in an omega-3 fatty acid, a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol.

[000117] Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

10 [000118] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above.

15 Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

20 [000119] Syrups and elixirs containing the novel MK-2 inhibitory compounds may be formulated with sweetening agents, for example glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

25 [000120] The subject compositions can also be administered parenterally, either subcutaneously, or intravenously, or intramuscularly, or intrasternally, or by infusion techniques, in the form of sterile injectable aqueous or olagenous suspensions. Such suspensions may be formulated according to the known art using those suitable dispersing of wetting agents and suspending agents which have been mentioned above or other acceptable agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol.

30 Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending

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medium. For this purpose, any bland fixed oil may be employed including synthetic mono-, or di-, glycerides. In addition, n-3 polyunsaturated fatty acids may find use in the preparation of injectables.

5 [000121] The subject compositions can also be administered by inhalation, in the form of aerosols or solutions for nebulizers, or rectally, in the form of suppositories prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperature but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and poly-ethylene glycols.

10 [000122] The novel compositions can also be administered topically, in the form of creams, ointments, jellies, collyriums, solutions or suspensions.

[000123] Various delivery systems include capsules, tablets, and gelatin capsules, for example.

15 [000124] The following examples describe preferred embodiments of the invention. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the invention as disclosed herein. It is intended that the specification, together with the examples, be considered to be exemplary only, with the scope and spirit of the invention being indicated by the claims which follow the examples. In the examples all percentages are
20 given on a weight basis unless otherwise indicated.

GENERAL INFORMATION FOR PREPARATION METHODS:

[000125] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers.

25 [000126] NMR analysis:

[000127] Proton nuclear magnetic resonance spectra were obtained on a Varian Unity Innova 400, a Varian Unity Innova 300 a Varian Unity 300, a Bruker AMX 500 or a Bruker AV-300 spectrometer. Chemical shifts are given in ppm (δ) and coupling constants, J , are reported in Hertz.

30 Tetramethylsilane was used as an internal standard for proton spectra and the solvent peak was used as the reference peak for carbon spectra.

Mass spectra were obtained on a Perkin Elmer Sciex 100 atmospheric

24. The method according to claim 19, wherein the $\text{TNF}\alpha$ mediated disease or disorder is selected from the group consisting of: arthritis, rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, juvenile arthritis, asthma, bronchitis, menstrual cramps, tendinitis, bursitis, connective tissue injuries
 5 or disorders, skin related conditions, psoriasis, eczema, burns, dermatitis, gastrointestinal conditions, inflammatory bowel disease, gastric ulcer, gastric varices, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, cancer, colorectal cancer, herpes simplex infections, HIV,
 10 pulmonary edema, kidney stones, minor injuries, wound healing, vaginitis, candidiasis, lumbar spondylarthritis, lumbar spondylarthrosis, vascular diseases, migraine headaches, sinus headaches, tension headaches, dental pain, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, scleroderma, rheumatic fever, type I diabetes, myasthenia gravis,
 15 multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, swelling occurring after injury, myocardial ischemia, ophthalmic diseases, retinitis, retinopathies, conjunctivitis, uveitis, ocular photophobia, acute injury to the eye tissue, pulmonary inflammation, viral infections, cystic fibrosis, central nervous
 20 system disorders, cortical dementias, and Alzheimer's disease.

25. A method of preventing or treating a $\text{TNF}\alpha$ mediated disease or disorder in a subject, the method comprising administering to the subject at least one MK-2 inhibiting compound that is selected from the group consisting of the compounds described in claim 15.

26. A therapeutic composition comprising a compound having the structure described in claim 1.

27. A therapeutic composition comprising at least one MK-2 inhibitory compound that is described in claim 15.

28. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and at least one MK-2 inhibitory compound having the structure described in claim 1.

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29. The pharmaceutical composition according to claim 28, wherein the MK-2 inhibitory compound has an IC_{50} for MK-2 of not over 0.1 mM.

5 30. A kit comprising a dosage form that includes a therapeutically effective amount of at least one MK-2 inhibitory compound having a structure described in claim 1.

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