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November 17, 2021

The Controller of Patents,
Indian Patent Office,
Intellectual Property Office Building,
Plot No 32, Sector -14, Dwarka
New Delhi

Re: PRE-GRANT OPPOSITION AGAINST INDIAN PATENT APPLICATION NO.
201717032083 FILED ON: 11.09.2017 U/S 25(1) FILED BY THE DELHI
NETWORK OF POSITIVE PEOPLE (DNP+)

Applicant: 1) GLAXOSMITHKLINE INTELLECTUAL PROPERTY (NO. 2)
LIMITED; 2) ANACOR PHARMACEUTICALS INC.

Title: BENZOXABOROLE COMPOUNDS AND USES THEREOF

Respected Sir,

We are filing this Pre-Grant Representation/Opposition U/S 25 (1) of the Patents Act, 1970 and Rule 55 of the Patent Rules, 2003 in Form 7A.

The Learned Controller is requested to take the documents on record and proceed further in the matter and keep the Petitioner advised of each and every step taken in the matter.

We crave the leave of the Learned Controller to submit additional documents or evidence or if necessary to support any of the averments in the representation as may be necessitated in the proceeding.

Lastly, we request the Learned Controller to grant an opportunity of being heard before the above representation is finally decided.

Yours Sincerely,

RAJESHWARI H. IN/PA-358
AGENT FOR THE OPPONENT
OF RAJESHWARI & ASSOCIATES

Encl.: As stated

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Also at: A - 202, First Floor, Shivalik Enclave, Malviya Nagar, New Delhi-110017

**BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE,
NEW DELHI**

In the matter of Section 25(1) of The Patents Act, 1970 as amended by The Patents (Amendment) Act 2005;

AND

In the matter of Rule 55 of The Patents Rules 2003 as amended by the Patent (Amendment) Rules, 2006

AND

IN THE MATTER of Indian Patent Application 201717032083 filed on 11/09/2017 in the name of 1) GLAXOSMITHKLINE INTELLECTUAL PROPERTY (NO.2) LIMITED 2) ANACOR PHARMACEUTICALS INC.

REPRESENTATION BY:

THE DELHI NETWORK OF POSITIVE PEOPLE

.....OPPONENT

VS.

**1.) GLAXOSMITHKLINE INTELLECTUAL PROPERTY (NO.2) LIMITED;
2.) ANACOR PHARMACEUTICALS INC.**

.....APPLICANT

REPRESENTATION BY WAY OF OPPOSITION U/S 25(1)

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5.	Annexure – 3: Copy of US2013165411	310-356

6.	Power of Attorney	Will follow
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Dated this day 17th of November, 2021



RAJESHWARI H IN/PA - 0358
AGENT FOR THE OPPONENT
OF RAJESHWARI AND ASSOCIATES

TO,
THE CONTROLLER OF PATENTS
THE PATENT OFFICE, DELHI

FORM 7A
THE PATENTS ACT,
1970 (39 OF 1970)
AND
THE PATENTS RULES, 2003
REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT
[See Rule 55]

We, **THE DELHI NETWORK OF POSITIVE PEOPLE**, having address at A1-5, House No. 141 Gali No. 3, IGNOU Main Road, Neb Saral, New Delhi - 110068; India hereby give representation by way of opposition to the grant of patent in respect of application No: **201717032083** filed on **11/09/2017** made by **1) GLAXOSMITHKLINE INTELLECTUAL PROPERTY (NO.2) LIMITED 2) ANACOR PHARMACEUTICALS INC.** on the grounds:

- i. Section 25(1)(b)(i)- invention so far as claimed in any claim of the complete specification has been published
- ii. Section 25(1)(e) – the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step
- iii. Section 25(1)(f) - Subject of any claim of the complete specification is not an invention
- iv. Section 25(1)(h) - Non disclosure of information required u/s 8.

(Detailed grounds are set out in the Opposition as attached)

My address in India is:

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Dated, this 17th day of November, 2021



RAJESHWARI H IN/PA - 0358
 AGENT FOR THE OPPONENT
 OF RAJESHWARI AND ASSOCIATES

TO
 THE CONTROLLER OF PATENTS,
 THE PATENT OFFICE, DELHI

BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE,
NEW DELHI

In the matter of Section 25(1) of The Patents Act, 1970 as amended by The Patents (Amendment) Act 2005;

AND

In the matter of Rule 55 of The Patents Rules 2003 as amended by the Patent (Amendment) Rules, 2006

AND

IN THE MATTER of Indian Patent Application 201717032083 filed on 11/09/2017 in the name of 1) GLAXOSMITHKLINE INTELLECTUAL PROPERTY (NO.2) LIMITED 2) ANACOR PHARMACEUTICALS INC.

REPRESENTATION BY:

THE DELHI NETWORK OF POSITIVE PEOPLE

.....OPPONENT

VS.

1.) GLAXOSMITHKLINE INTELLECTUAL PROPERTY (NO.2) LIMITED;

2.) ANACOR PHARMACEUTICALS INC.

.....APPLICANT

REPRESENTATION BY WAY OF PRE-GRANT OPPOSITION UNDER SECTION
25(1) OF THE PATENTS ACT, 1970

OPPONENT'S BACKGROUND

1. The Opponent, THE DELHI NETWORK OF POSITIVE PEOPLE is a community based non-profit organisation representing the needs of people living with HIV/AIDS ("PLHAs") and Hepatitis C (HCV), and having registered address at A1-5, House No. 141 Gali No. 3, IGNOU Main Road, Neb Saral, New Delhi - 110068; India.

2. The Opponent is a PLHIV (People Living with HIV) network working extensively in the area of access to medicines. The Opponent's work includes but is not limited to service delivery, treatment literacy and community empowerment. The main focus and emphasis is advocating for access to medicines as they believe every individual should get treatment and no one should suffer and die due to lack of medicines. Of main concern to the Opponent, is the impact of product patent protection on access to effective and affordable tuberculosis medicines for people in India and across the developing world.

GENERAL BACKGROUND ON TUBERCULOSIS AND MULTI-DRUG RESISTANT TUBERCULOSIS TREATMENT

3. The bacterium Mycobacterium Tuberculosis (MTB) causes Tuberculosis (TB). This is an infectious disease. Tuberculosis generally affects the lungs, but can also affect other parts of the body. When infections do not show symptoms, it is termed as latent tuberculosis. The Government of India has a Tuberculosis division at the Central Government level and for the year 2020, India had a total 18,05,670 notified cases¹ of tuberculosis. The WHO estimates that India had an estimated incidence of 26.4 lakh cases in 2019. WHO's 'Global tuberculosis report 2020' available at the WHO site gives detailed data and estimates on Tuberculosis patient numbers, prevalence etc. As of 2018, one quarter of the world's population is thought to have latent infection with TB and within this population, India accounts for slightly more than 25% of the total number of infected populace.
4. TB is the leading killer of People Living with HIV (PLHIV) with one-third of HIV related deaths occurring due to TB co-infection in 2015. The risk of developing TB is estimated to be between 26 and 31 times greater in PLHIV than among those without HIV infection. TB and HIV co-infection leads to synergy of the disease with rapid progression of TB and re-activation of latent TB risk being 12 and 20 times greater in PLHIV. Similarly, TB also accelerates the disease progression of HIV.
5. As Tuberculosis is a disease emanating from a bacterium, the treatment regime comprises administering anti-bacterial medicines, over a period of time. If patients are found to have

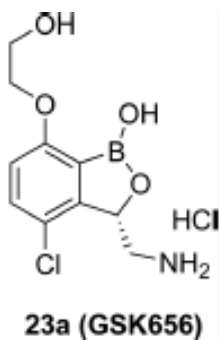
¹ Page 17, at < <https://tbcindia.gov.in/showfile.php?lid=3587>>

developed resistance to existing treatment regime, the case is termed as multi-drug resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB). The resistance can either be primary i.e. resistance developed before the initiation of treatment or secondary resistance developed after the initiation of anti-tuberculosis treatment in patients. Active tuberculosis (i.e. Patients with active symptoms), requires several drugs (involving multiple antibiotics) to be co-administered in a regime for a period of minimum 6 months or more.

6. In 2018, the Indian Ministry of Health released the “Report of the First National Anti-Tuberculosis Drug Resistance Survey” which indicated an almost 22% resistance to fluoroquinolones in India. Therefore, there is a pressing need to ensure better availability of newer TB drugs to treat growing resistant strains of TB infections in patients. The need of the hour is affordable TB drugs which addresses the problem of both MDR, XDR and TDR (total drug resistant) TB infections which will enable effective and faster recovery of the patients, one such drug is GSK 3036656. This has been claimed in the Present Application and it is submitted that the honourable Patent Controller should scrutinise the Present Application with strict scrutiny. Its decision will have far reaching impact on the availability of affordable access to lifesaving treatment to TB patients not only in India but across the world.

GSK656/ GSK3036656 / GSK070

7. GSK070/ GSK 3036656 is a protein synthesis target for tuberculosis and belongs to benzoxaborole class of drugs. In a later phase 2b study carried out in South Africa, it was shown that it has in vivo antitubercular activity with efficacy in the standard acute and chronic murine assays, and when it was administered in combination with new antitubercular drugs, it is more active than present standard of care. The Applicant has designated this compound as GSK070/ GSK656/ GSK 3036656 (each term used interchangeably, hereafter) in its public literature.
8. The present Opponent is particularly interested in the following compound:



PRESENT APPLICATION & LOCUS STANDI

9. The Opponent has reviewed the file available at the IPASS system of the Indian Patent Office in respect of present Application and notes that this Indian application was filed at the Patent Office, New Delhi. According to the information and documents available therein, following are the relevant details:

APPLICATION NUMBER	201717032083
DATE OF FILING	11/09/2017
APPLICANT NAME	1. GLAXOSMITHKLINE INTELLECTUAL PROPERTY (NO.2) LIMITED 2. ANACOR PHARMACEUTICALS INC.
TITLE OF INVENTION	BENZOXABOROLE COMPOUNDS AND USES THEREOF
PRIORITY DATE	12/02/2015
PCT DETAILS	WO2016128949 from PCT/IB2016/050776
PCT INTERNATIONAL FILING DATE	12/02/2016
REQUEST FOR EXAMINATION DATE	Not yet filed
PUBLICATION DATE (U/S 11A)	01/12/2017

FIRST EXAMINATION REPORT DATE	N.A.
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10. As per S.25(1), a pre-grant opposition can be instituted by any person as long as an Application is still under prosecution. The present Application has not matured into a patent as of the date of filing of this pre-grant representation. Hence, the present pre-grant opposition being filed by opponent, working for improving access to medicines, is validly filed and is not time barred. A copy of the complete specification with claims and downloaded from IPASS is attached as **Annexure 1**.

11. The Opponent submits that as a foundation point, the present Application should be considered ‘abandoned’ u/s S.11B(4) read along with R. 24B.

S.11B(4) of the Act states:

‘11B. Request for examination—

1) No application for a patent shall be examined unless the applicant or any other interested person makes a request in the prescribed manner for such examination within the prescribed period.

...

4) In case the applicant or any other interested person does not make a request for examination of the application for a patent within the period as specified under sub-section (1) or sub-section (3), the application shall be treated as withdrawn by the applicant:’

12. Rule 24B of the Patents Rules specifies the prescribed ‘manner’ and ‘period’ noted above. This Rule states as under:

‘Rule 24B

Examination of Application

(1)(i) A request for examination under section 11B shall be made in Form 18 within forty-eight months from the date of priority of the application or from the date of filing of the application, whichever is earlier;

(ii) The period within which the request for examination under sub-section (3) of section 11B to be made shall be forty-eight months from the date of priority if applicable, or forty-eight months from the date of filing of the application;

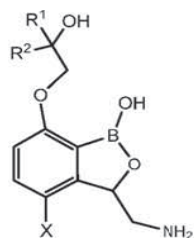
(iii) The request for examination under sub-section (4) of section 11B shall be made within forty-eight months from the date of priority or from the date of filing of the application, or within six months from the date of revocation of the secrecy direction, whichever is later;'

13. The priority date for the present Application is 12/Feb/2015. The filing date (deemed, by virtue of PCT designation) is 12/Feb/2016. The National Phase entry date in India is 11/Sep/2017. Thus, Applicant was required to file a Request for Examination by 12/Feb/2019, i.e. within 48 months from priority. 48 months have also elapsed from the deemed filing date as well as the Indian entry date. With no 'Request for Examination' filed in time, S. 11B (4) now requires the Patent Office declare the present Application 'withdrawn' due to inaction by Applicant.

PRESENT SPECIFICATION & CLAIMS

14. The present Specification runs into 150 pages and was filed with 45 claims. At the time of national phase entry, Applicant voluntarily deleted claims 46 through 53 from the PCT version. These claims are divided amongst following groups:

- i) Current claim 1 is an independent claim that covers a compound of Formula III, wherein X (i.e. 4th position is substituted with a halogen) and R1 and R2 can be H, CH₃etc

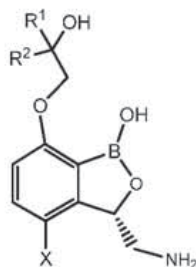


Formula III

- ii) Claim 2 to 7 are dependent on claim 1, in particular claim 2 covers either chlorine or bromine halogen at 4th position of the compound of formula III. Claim 6 and 7 cover the

compound with structure of formula III which is having either bromo or chloro at 4th position.

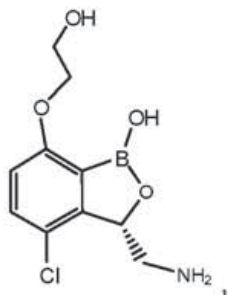
- iii) Claim 8 is an independent claim covering formula IIIa of the compound with possible substituents at position 3 and 7 of the compound.



Formula IIIa

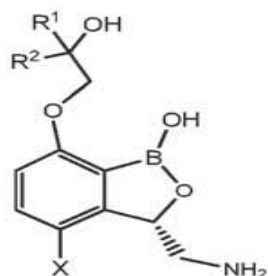
- iv) Claims 9 is dependent on claim 8 and cover the pharmaceutically acceptable salt and structure of compound with Formula IIIa with possible substitutions at position 4.
- v) Claim 10 to 15 are dependent on claim 9 (thus in turn, dependent on independent claim 8) which covers the claimed compound with formula IIIa. Claim 11 to 13 covers the compound with structure of formula IIIa which is having either bromo at 4th position or chloro at 4th position.

Claim 14 covers the compound with formula IIIa with chlorine as substitution at 4th position and its pharmaceutically acceptable salt thereof.



Claim 15 (dependent on claim 9) covers the compound with formula IIIa with bromine as substitution at 4th position and its pharmaceutically acceptable salt thereof with an excipient – thus making it a composition claim.

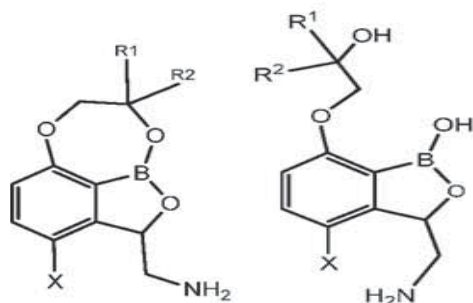
- vi) Claim 16 is an independent claim covering the formula IIIa and its substitutes at X, R1 and R2 and its salt or hydrate thereof.



Formula IIIa

- vii) Claim 17 to 19 are also composition claims and dependent on claim 16. They include the substitution of **bromine** at 4th position i.e. X and at position 7 i.e. R1 and R2 and its pharmaceutically acceptable salt thereof.

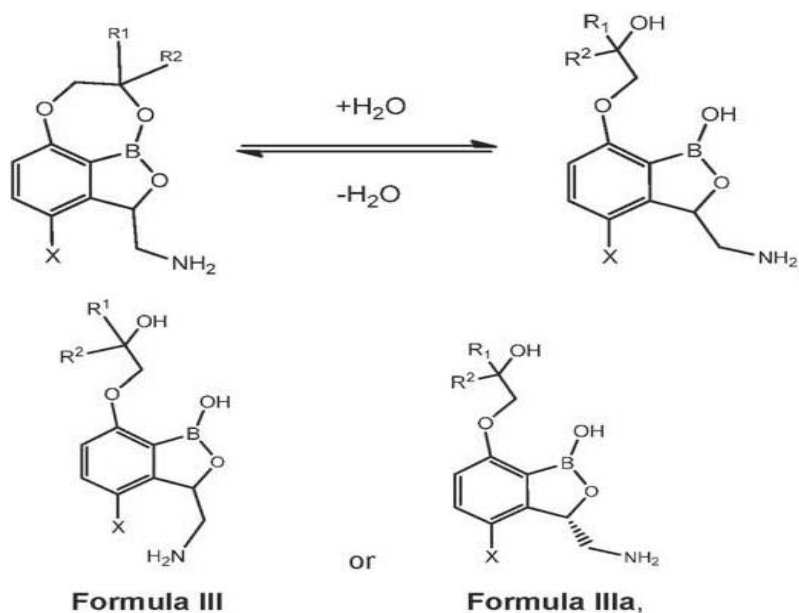
- viii) Claim 20 is an independent claim covering the compound and its pharmaceutically acceptable salt present in equilibrium state in presence of water in a closed form with formula II and an open form with formula III. It also enlists the substituents of the claimed compound at X, R1 and R2 in the open and closed form of the compound.



Formula II,

Formula III

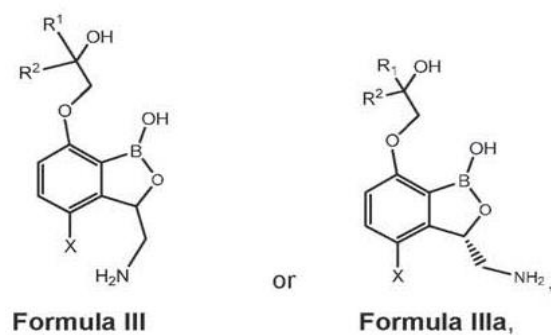
- ix) Claim 21 is an independent claim of the compound or its pharmaceutically acceptable salt present in equilibrium in presence of water between a compound having the formula III and formula IIIa with substituents at X with chloro or bromo and R1 is H and R2 is CH₃.



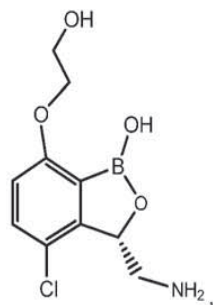
x) Claim 22 is an independent claim for compound with an X-ray crystal structure as shown in Figure 5.

xi) Claim 23 is an independent claim of the compound with an XPRD pattern as shown in Figure 6 and its pharmaceutically acceptable salt thereof with a pharmaceutically acceptable excipient- **thus making it a composition claim.**

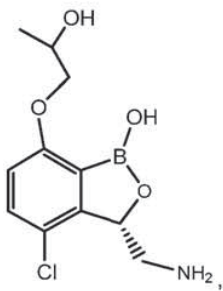
xii) Claim 24 is an independent claim of the compound or its pharmaceutically acceptable salt in presence of water having the structure of formula III or IIIa.



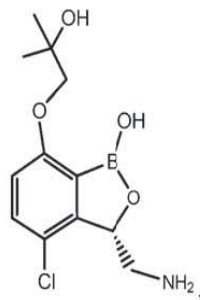
xiii) Claim 25 to 30 covers compound with following formula and their pharmaceutically acceptable salts thereof.



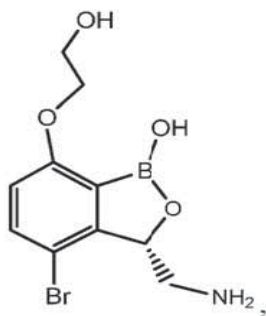
Claim 25



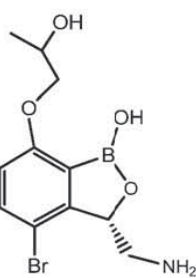
Claim 26



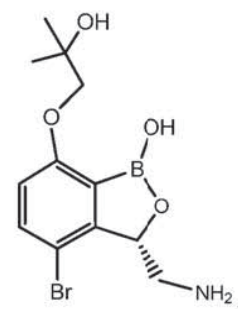
Claim 27



Claim 28

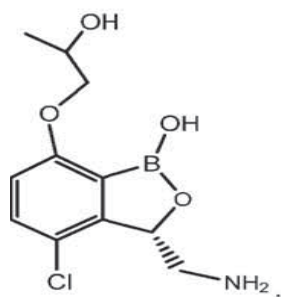


Claim 29

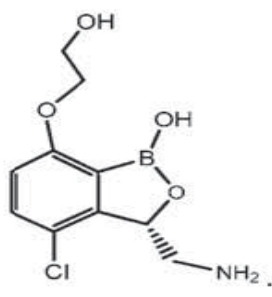


Claim 30

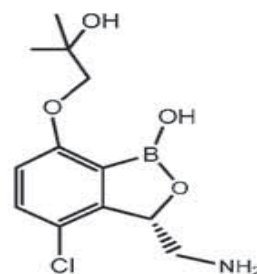
xiv) Claim 31 to 33 are dependent on claim 8 and are **composition claims** for compound(s) of the following structure:



Claim 31

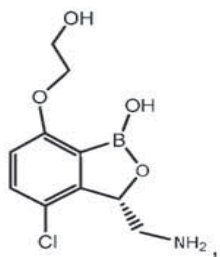


Claim 32

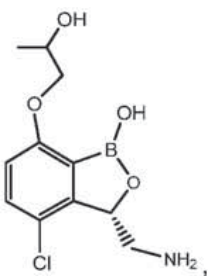


Claim 33

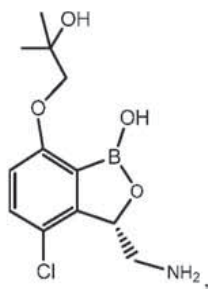
xv) Claim 34 is an independent claim, covering a **pharmaceutical composition comprising compound: (S)-(3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocdazulen-2-yl)methanamine hydrochloride** together with pharmaceutically acceptable salt and excipients with the following structure.



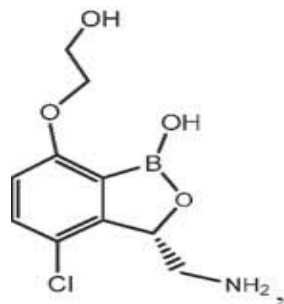
xvi) Claim 35 is an independent claim, covering **pharmaceutical composition comprising a compound (3S)-S-(3-chloro-8-methyl-7,8, dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine hydrochloride** together with pharmaceutically acceptable salt and excipients with the following structure.



xvii) Claim 36 is an independent claim, covering **pharmaceutical composition comprising a compound (S)-S-(3-chloro-8, 8-dimethyl-7,8, dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine hydrochloride** together with pharmaceutically acceptable salt and excipients with the following structure.



xviii) Claim 37 is an independent claim covering the pharmaceutically acceptable salt of a compound wherein the salt is a hydrochloride (HCl) or a dihydrogen sulfate (H₂SO₄).



xix) Claim 38 to 41 covers the compound according to preceding claims and their pharmaceutically acceptable salts. Claim 41 narrows down the salt to be either hydrochloride (HCl) or a dihydrogen sulfate (H₂SO₄).

xx) Claim 42 to 45 are method claims covering the killing of mycobacteria tuberculosis causing the disease tuberculosis in humans.

15. Opponent believes that GSK656 (structure noted earlier) is apparently covered in at least the following claims of present Application: independent claim 1, 8 (formula IIIa), dependent claims 9/ 14/ 24 (formula III and IIIa)/ 25, dependent pharmaceutical composition claims 32 (on claim 8)/ 34 and 37 covering the salt form of the compound HCl or H₂SO₄.

SUMMARY OF GROUNDS CONSIDERED FOR OPPOSITION

16. The Opponent brings this representation under the following grounds, each of which are without prejudice to one another and stand on an independent footing:

i) S.25(1)(b)(i):

'that the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim—

(i) *in any specification filed in pursuance of an application for a patent made in India on or after the 1st day of January, 1912'*

ii) S.25(1)(e):

'(e) that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter

published as mentioned in clause (b) or having regard to what was used in India before the priority date of the applicant's claim;'

iii) S.25(1)(f):

'(f) that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act;'

[S.3(d), 3(e), 3(i) and not filing of RFE in time]

iv) S.25(1)(g):

'(g) that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed;'

v) S.25(1)(g):

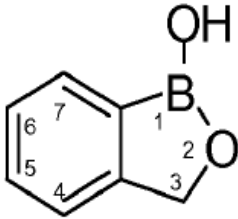
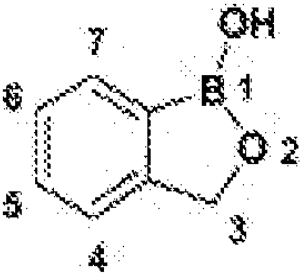
'(h) That the Applicant did not disclose information required by Section 8.

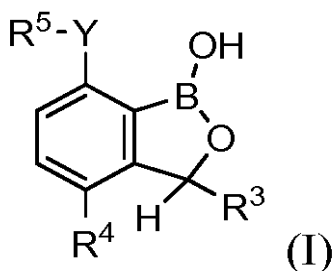
DISCUSSION OF RELEVANT PRIOR ART:

17. The Opponent will be using the following prior art documents and numbering scheme throughout its submissions:
18. **D1:** WO2012033858 {later filed in India as 602/KOLNP/2013} bearing publication date of 15 March 2012 discloses certain 1-hydroxy-1,3, -dihydro-benzo[c][1,2]oxaboroles as effective antibacterial compounds. D1 further discusses that some compounds from this class as being tested for their effectiveness against M.Tuberculosis. D1 covers within its claims, benzoxaborole compounds that have substitution at 4th position for a halogen atom (as annexed herewith **Annexure – 2**).
19. **D2:** US2013165411 bearing publication date of 27 June 2013 has been mentioned in present Specification. Applicant admits that D2 discloses the benzoxaborole compounds to be used as antimicrobial agents. The only difference cited by the applicant is halogen substitution on the benzoxaborole ring, refer para no.0014 at page no. 4 and 5 of the present specification. **D2** document includes the possibility of substitution with halogen in the tricyclic boron compounds (as annexed herewith **Annexure – 3**).

DETAILED GROUNDS**I. THAT CLAIMS OF THE PRESENT APPLICATION MUST BE REJECTED AS THE CLAIMED INVENTION WAS PUBLISHED BEFORE THE PRIORITY DATE OF PRESENT CLAIMS**

20. **D1** i.e. WO2012033858 was published on 15/Mar/2012- i.e. much before the priority date of present '083 filing. **D1** entered India as 602/KOLNP/2013 and the Specification in Markush form covers huge number of molecules including possible halogen substitution at 4th position. **D1**'s Specification section does not disclose the specific GSK656 structure however, it goes on to specifically claim GSK656 in its claims. Before we look at those claims, the general discussion in **D1** Specification is relevant to understand how it connects to GSK656. Details are illustrated in the below table:

WO2012/033858 (D1)	Present application
<p data-bbox="240 968 641 999">Same Markush: refer page no.1</p>  <p data-bbox="240 1524 662 1556">Refer page no.15, para no.[0061]</p>	<p data-bbox="912 968 1304 999">Same markush refer page no.4</p> 



Further the C* carbon atom stereo center is in the S configuration, refer para no. [0064]

When the above compound (I) is substituted with the listed substituents a compound similar to Formula III of the present application is disclosed. Refer para no. [0090] at page no. 22

The R4 substituent is narrowed down to one of the halogen, refer page no. 60 para no.[0195-0197].

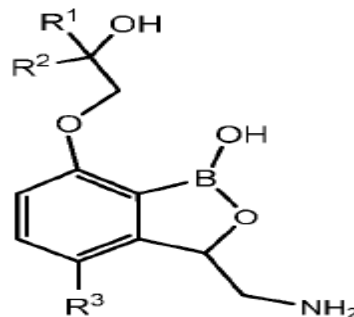
From above, it is evident that halogen substitution including chlorine at position 4 is already covered in D1.

Para no. [0206] at page no.61 enlists the substituents of R5 which includes methyl, ethyl, propyl, isopropyl, isobutyl etc

Para no. [0213] at page no. 62 lists the substituents

R3 – unsubstituted aminoalkyl(NH₂)

R4 – halogen (chlorine)



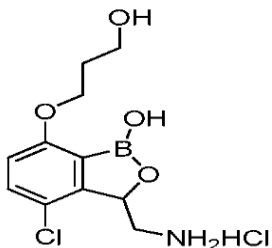
Formula III

Compound I in prior art document substitution leads to above formula III.

Y – O

R5 – unsubstituted alkyl (hydroxyethoxy)

Para no.253 at page no. 71.

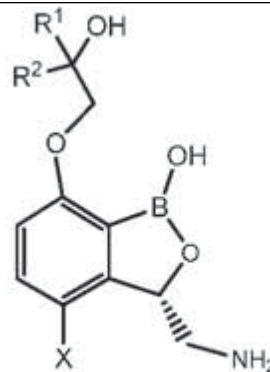


3-Aminomethyl-4-chloro-7-(3-hydroxy-propoxy)-
3H-benzo[c][1,2]oxaborol-1-ol hydrogen chloride

Example K and L in the D1 patent discloses the presence of ethoxy in position 7 substitution in the enantiomer form B and A, refer page no. 91 in para no. [0296], [0298] and [0299].

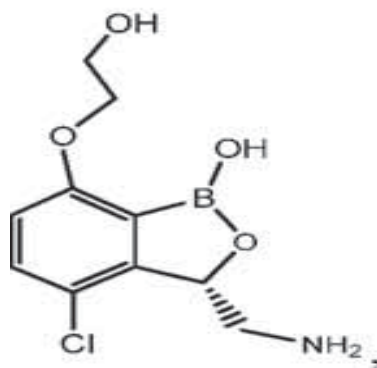
K: (R)-3-(Aminomethyl)-4-chloro- 7-ethoxybenzo[c][1,2] oxaborol-1(3H)-ol hydrochloride

L: (S)-3-(Aminomethyl)-4-chloro- 7-ethoxybenzo[c][1,2] oxaborol-1(3H)-ol hydrochloride

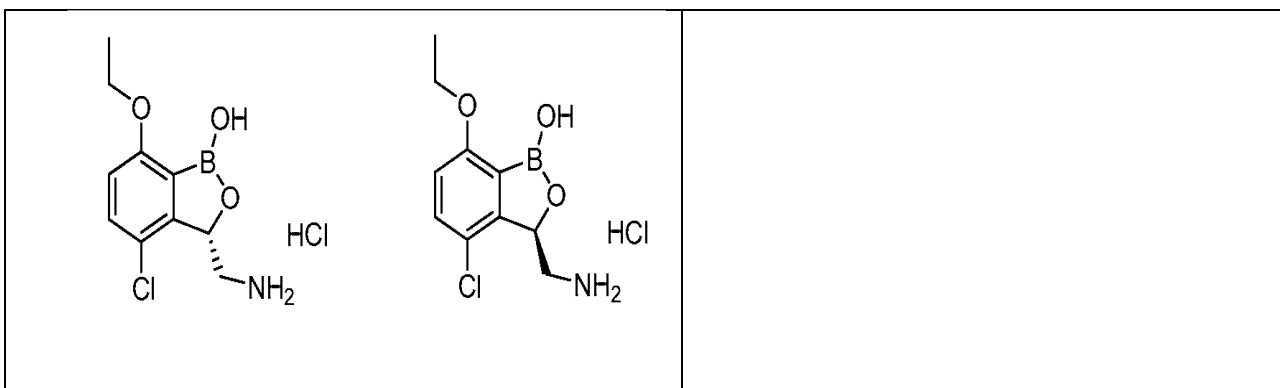


Formula IIIa

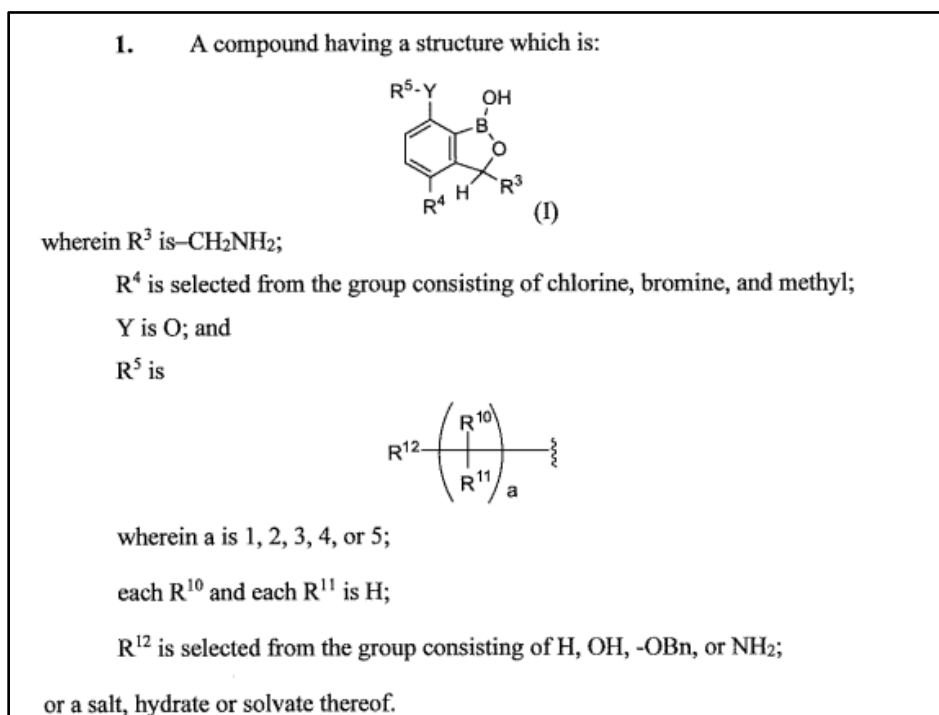
When the structure included in the prior art (refer para no.253 of D1) is compared with the below structure claimed in the present application the structure is overlapping, the only difference seen is in the side chain at position 7.



(S)-3-(Aminomethyl)-4-chloro-7-(2-hydroxyethoxy)benzo[c][1,2]oxaborol-1(3H)-ol hydrochloride. (Claim 14)



21. The Specification section of **D1** did not disclose the exact structure of GSK656, however, the same Applicant (Anacor/ Glaxo) apparently claimed GSK656 within the claim section of **D1**. Claims 1/ 6/ 13 of D1 specifically claim a compound having halogen substitution at R4 as well composition for such compound(s). Specifically, claim 6 of D1 covers R4 selected from fluorine, chlorine, bromine, and iodine.
22. Likewise, when we look at current claims of 602/KOLNP/2013 (specifically, claims 1 and 10 from Aug 2021 amendments), we see that present Applicant already seeks to claim GSK656 in these claims. Whether Applicant is entitled to secure an Indian patent on Application 602/KOLNP/2013 covering GSK656 by claiming GSK656 therein - which he has not disclosed in '602 Specification - is a matter beyond the present submission.



...

7. A pharmaceutical formulation comprising:
- a) the compound as claimed in claim 1, or a pharmaceutically acceptable salt thereof; and
 - b) a pharmaceutically acceptable excipient.

...

10. The compound as claimed in claim 1, or a salt, hydrate or solvate thereof, wherein R⁴ is chlorine; and Y is O.

23. Claims section of **D1** / present IN claims 1/7/10 of IN602, by virtue of being published prior to present Application specifically destroys novelty for the core structure (where R₄ = halogen) and consequently destroys novelty for GSK656 compound and compositions containing the same. The Applicant is caught in a Catch-22 situation. His '602 filing does not enable GSK656 and hence '602 Application cannot be rightfully used to claim GSK656 therein. Applicant then files present '083 Application where he discloses GSK656. However, Applicant's own claims text in **D1**/'602 destroy novelty for GSK656 as the substitutions in those claims cover GSK656. So, even present '083 claims cannot stand on their own. Objectively, due to Applicant's own actions, Applicant cannot get a claim covering GSK656 in either Application. The present application ('083) is nothing but an ill-founded attempt at extending the monopoly on GSK656 and formulations thereof from Sep'31 through to Sep '37.

24. The Hon'ble Supreme Court of India too in *Novartis AG v. Union of India*, [(2013) 6 SCC 1] has also discussed the issue of evergreening of patents. The Patents Act should be interpreted by the Hon'ble Patent Controller in light of all the relevant circumstances surrounding the Amending Act. The Hon'ble Madras High Court, in *Novartis AG v. Union of India and Others*, (2007) 4 MLJ 1153, while upholding Section 3(d) against a constitutional challenge, stated:

"We have borne in mind the object which the Amending Act wanted to achieve namely, *to prevent evergreening; to provide easy access to the citizens of this country to life*

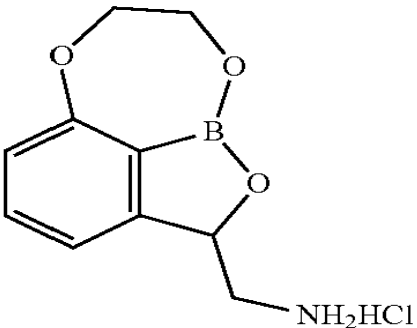
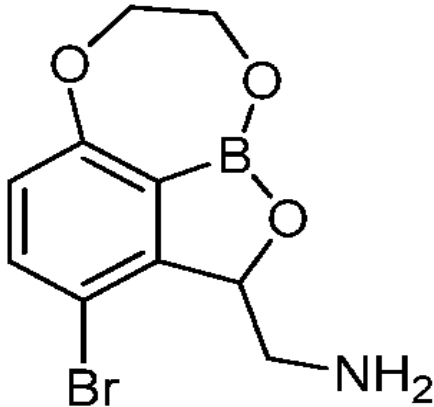
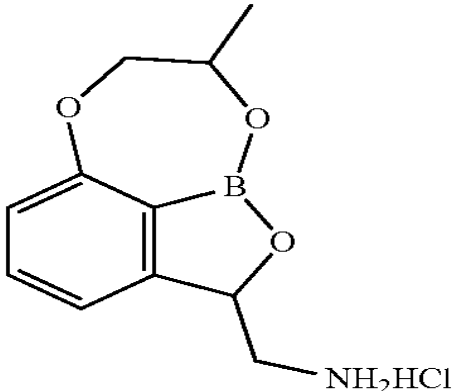
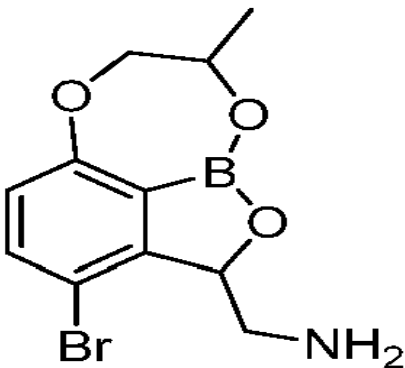
saving drugs and to discharge their Constitutional obligation of providing good health care to its citizens.” [see para 19] (emphasis added).

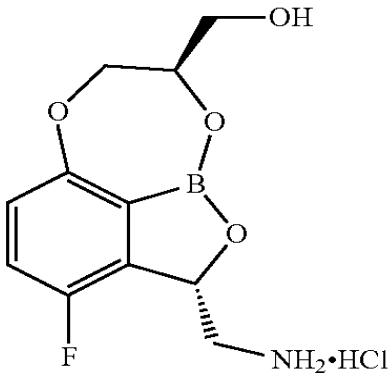
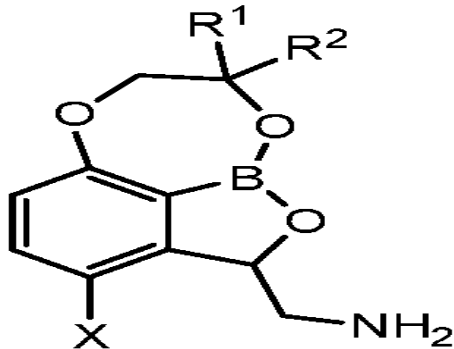
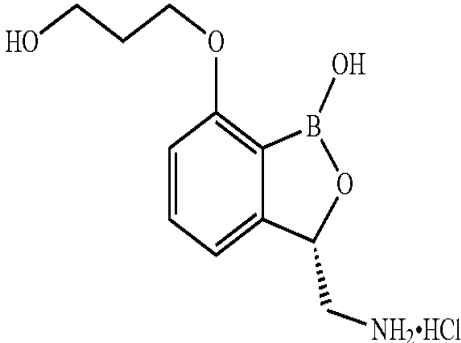
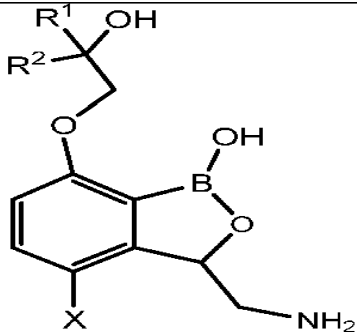
25. In particular, D1 document discloses and claims the compound of claim 14 with same formula. Accordingly, as claims section of D1 clearly destroys novelty of all claims of present ‘083 and hence all claims of present ‘083 are liable to be rejected in totality.

II. CLAIMS OF THE PRESENT APPLICATION ARE CHALLENGED UNDER SECTION 25(1)(e) OF THE PATENTS ACT, ON GROUND OF LACKING INVENTIVE STEP AS DEFINED UNDER SECTIONS 2(1)(ja) OF THE PATENTS ACT

26. Section 2(1)(j), requires that an invention be either a new product or process involving an inventive step and capable of industrial application. ‘Inventive step’ is further defined in Section 2(1)(ja) as ‘a feature of an invention that involves technical step as compared to existing knowledge ..’.
27. Independent of the Opponent’s anticipation argument from claims section of D1, the Opponent now submits, that D1, in combination with D2 renders the present claims as non-patentable as the claims are found obvious and lacking an inventive step.
28. We have already seen the general disclosure of D1. We now move to **D2**. US2013165411 bearing a publication date of 27/June/2013 is mentioned in the present Specification. According to applicant’s own admission, **D2** discloses benzoxaborole compounds to be used as antimicrobial agents. The only difference over **D2** vis-à-vis present Specification is the halogen substitution on the benzoxaborole ring [refer para no.0014 at page no. 4 and 5 of the present Specification].
29. Opponent submits that **D2** document includes the possibility of such substitution with halogen in the tricyclic boron compounds - refer para no.0008 and 0029 at page no. 2 and 3. Further, **D2** also covers the ring-opened form of tricyclic boron compounds including hydrated forms, refer para no.0041 at page no.4.

30. Example 19 of the compound structure [refer para no.0174, at page number 30] is similar to compound formula II or IIa of the present Application. Further example 9 and 24 discloses the closed forms of the claimed compound. The below table provides a comparison of the overlapping structure of the compounds as claimed in the present Application.

US2013/165411 (D2)	Present Application
 <p>Example 24</p>	 <p>Refer para no.00163 at page no.42</p>
 <p>Example 9</p>	 <p>Refer para no.00163 at page no.42</p>

 <p>Example 19 (discloses halogen substitution at position 4)</p>	 <p>Formula II</p>
 <p>Example 25 (except for the absence of substitution at position 4, the structure overlaps with formula III of the impugned application)</p>	 <p>Formula III</p>

31. It is further emphasized that most of the above prior art documents are from Anacor/ Glaxo, thereby establishing the fact that Applicant already is aware of the know-how around Benzoxaborole class of compounds including the present compounds of '083 claims. The markush structure of the lead compound remains the same since the disclosure was made starting from **D1**, in several patent documents from the Applicant itself. The Applicant has been making minor tweaks to a core structure and filing sequential patents. The substitutions made to the markush structure in **D1** cover all the possible embodiments and multiple compounds can be obtained for the appropriate therapeutic effect. The Applicant continues to

file multiple patent applications for same class of drugs with various substitutions to obtain multiple patent monopolies over iterations of the core markush.

32. Based on a combined reading of **D1** and **D2**, it is clear that the benzoxaborole class of compounds, their use as anti-bacterial agents and the key substitutions possible in the markush structure to reach a compound effective against tuberculosis are clearly expressed to a person skilled in art. Further combining D2 with the disclosure of overlapping structure of benzoxaborole in **D1**, key compounds and specific substitutions in claim 10 of **D1**, render present claims as lacking an inventive step and making them obvious to a person skilled in the art.
33. The IPO has to examine the inventive step for GSK656 and formulations containing the same after examining the documents **D1** and **D2**, the state of art as of filing of present '083. In a similar case, the Opponent submits that the Controller, while determining inventive step, has held that mere "replacement of alkyl and/or other group" to a known structure cannot be considered as technical advancement under S. 2(1) (ja) (See order dated 21.02.2020 of the Assistant Controller of Patents and Designs in the matter of patent application 478/MUMNP/2015).
34. An inventive step requires a 'technical advance as compared to existing knowledge'. It is this 'technical advance' which is the inventor's hard work and for which he gets the monopoly. As of the filing date of present '083 Specification, as much as it pertains to GSK656 and formulations containing them, the Applicant had not made any 'technical advance' in the present '083 Specification over disclosure in **D1** and **D2**, and so there is no case of having an 'inventive step' present in Specification.
35. The present '083 application claims same set of compounds which is both structurally and functionally disclosed in D1 and for use in the treatment of Tuberculosis as disclosed in the prior art documents, therefore claims are found to be obvious and lacks inventive step. Thus, based on the disclosure of the **D1** and **D2**, a person skilled in the art can work on the substitutions to very well reach the GSK656 compound with reasonable expectation that such compounds would work for treating tuberculosis. A POSITA who is equipped with the state

of art disclosed in **D1** and **D2** would look at the multiple Anacor/ Glaxo filings and would be motivated to adopt and experiment on the same lines to arrive at various compounds for treating tuberculosis and compositions containing them.

36. The Opponent has clearly shown how the compound claims as well as the formulation claims are not inventive over prior art and lack an inventive step. Accordingly, the present Opponent submits that the entire set of present claims (compound and formulation) are obvious for a POSITA and lacking an inventive step thereby failing to fulfill the requirement under Section 2(1)(j) and 2(1)(ja) of the Patents Act, 1970, based on documents cited above, thus claims of present '083 Application are liable to be rejected in totality.

III. CLAIMS OF THE PRESENT APPLICATION ARE CHALLENGED UNDER SECTION 25(1)(f) OF THE PATENTS ACT, ON GROUND OF NOT BEING PATENTABLE ON ACCOUNT OF SECTION Ss. 3(d), 3(e) 3(i)& 11B AND THEREFORE ARE OBJECTED TO UNDER SECTION 25(1)(f)

37. Section 25(1)(f) of the Patents Act allows opposition to grant of patent on the ground of the claimed invention not being an invention within the meaning of the Patents Act, 1970. Section 25(1)(f) reads as follows:

“(1) Where an application for a patent has been published but a patent has not been granted, any person may, in writing, represent by way of opposition to the Controller against the grant of patent on the ground—

.. (f) that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act.”

38. The Opponent submits that the subject matter of present claims is not patentable under the Act on following independent counts:

- A. Violation of S.11B;
- B. 3(d)
- C. 3(e)
- D. 3(i)

A: VIOLATION OF S.11B(4) - Not filing the Request for Examination within allotted time

39. Applicant has not filed the Request for Examination within 48 months from priority. Consequently, the Application must be treated as ‘*withdrawn by applicant*’ u/s 11B. Once an application is withdrawn post publication by applicant, the claims of such application become public property and no longer constitute an ‘invention’.
40. The Patent Office has consistently maintained that non-filing of the request for examination renders the application as withdrawn as per S.11B. Opponent craves leave to refer to IPO decision dated 30/Jan/2012 in App. No. 3775/DELNP/2010. Opponent also would like to submit 2 decisions emanating from the High Court of Delhi in context of. S.11:
1. Nippon Steel Corporation² v/s Union of India [dated 08/Feb/2011] &
 2. Sphaera Pharma Pte. Ltd.³ v/s Union of India [dated 16/Feb/2018].
41. The act of withdrawal renders the entire subject matter of the application, not patentable under the Act. Based on these facts and above cases, this Application (and every claim therein) no longer survives and this Application is liable to be rejected u/s 25(1)(f).

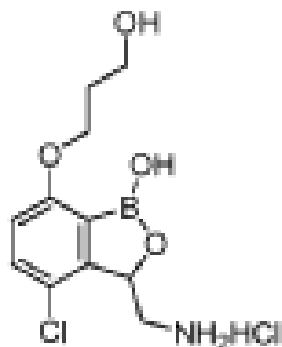
B: S.3(d) Mere discovery of a new form of a known substance which does not result in the enhancement of known efficacy

42. That present 083 Specification fails on disclosing ‘technical advance as compared to existing knowledge’- which is a requirement of Section 2(1)(ja)- that forms foundation for a rejection under Section 25(1)(e); and
- a) S.3(d) applies since presently claimed GSK656 compound is structurally very similar to compound covered in Example B from D1 and enhanced efficacy data for GSK656 versus Example B of D1 is not given.
 - b) S.3(e) applies to formulation claims 15, 17, 19, 23 and 31-36 – as they seek to cover a mere admixture with excipients.
 - c) S.3(i) applies to claims 42-45 as they seek to cover a method of use of the compound.

² <https://indiankanoon.org/doc/75686456/>

³ <https://indiankanoon.org/doc/100231956/>

43. As noted earlier, **D1** Specification generally discloses the subject matter of present claims. Importantly, **D1** also discloses the compound with following structure at example B:



44. Present Specification includes in-vitro assays wherein the MIC of the compounds is measured against *M. tuberculosis* clinical strains. These assay inform that zeroed down compounds G4-Cl of example 4 and G4-Br of example 2 have better MIC value of less than 0.1 μ M in comparison to strains resistant Isoniazide, Rifampicin, Ethionamide, Sterptomycin, Ethambutol, Pyrazinamide etc and *M. tuberculosis* sensitive strains. Further table 3 enlists MIC values of all the compounds claimed in the present specification against other bacteria such as *E. coli*, *A. baumannii* ATCC etc. The compounds of '083 Specification are than tested for anti-bacterial activity against *Mycobacterium tuberculosis* and SI index by comparing them with both benzoxaborole and non-benzoxaborole comparator compounds. It is thereafter concluded that G4-Cl of example 4 and G4-Br of example 2 exhibit better SI index when compared with non-benzoxaborole comparator compounds, refer para number 00439, 00440.
45. Opponent notes that the examples and data given in present '083 Specification do not establish the efficacy of the claimed compounds over the already known benzoxaborole compound B as disclosed in **D1**, which Opponent submits, is the closest 'known substance' for examination u/s 3(d). The data in '083 Specification does not establish the therapeutic efficacy of the claimed compound(s) over this known compound. Opponent submits that S.3(d) applies since presently claimed GSK656 is very similar to/ derivative of / new form of above compound from D1 and enhanced efficacy data for presently claimed GSK656 versus this compound from prior art needs to be given. Unless, Applicant can show enhanced efficacy against the right set of structurally similar compounds (in this case, above compound

from example B of **D1**), it cannot pass the threshold of Section 3(d) and the compound claims will be liable to be rejected u/s 3(d).

46. The Opponent submits that the Applicant via D1s' Indian filing 602/KOLNP/2013, is already seeking a *Markush* patent encompassing GSK656. This D1/ 602 application, if granted an Indian patent, shall expire on 07/Sep/2031. Thus, the present application ('083) now attempts at extending the monopoly on GSK656 compound from Sep 2031 through to Feb 2036. This attempt at evergreening of patents is not allowed in our statute or jurisprudence. This is expressly prohibited by S.3(d) and hence claims 1-41 are not patentable.

C: S. 3(e) – substance obtained by mere admixture resulting in aggregating of properties of components thereof

47. It is submitted that claims 15, 17, 19, 23 and 31-36 of the Present Application are composition claims (even if all of these do not use the word 'composition') as they claim some combination of a molecule and excipients. Each of these composition claims are liable to be rejected as the claimed composition(s) is nothing more than a simple statement of a mere admixture of the molecule with an excipient.
48. It may be noted that while determining the question of a claim passing the test of Section 3(e), Asst. Controller of Patents and Designs had remarked that, "*The question of efficacy and or synergism are matters of scientific facts which are required to be embodied in the specification so that the said characteristics are apparent from the specification.*" (See order of the Asst. Controller of Patents & Designs in patent application 314/MUM/2008, at lines 3-5 at internal page 7).
49. There is not a single working example for any specific composition or a formula for composition with specific excipients— in terms of a working composition anywhere in the Specification. The Specification does not explain any quantitative details or details pertaining to scaling a composition to pharmaceutical manufacturing levels. Further the burden is on the Applicant to show synergism by supportive experimental data or comparative examples for a preferred composition versus other compositions. It is submitted that compositions claimed in the Present Application are a mere admixture. The resulting compositions will only have mere

aggregation of properties of the individual components. Further, the Applicant has failed to disclose any synergistic effect of the claimed composition in the complete specification.

50. Section 3(e) excludes patentability of a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance. With the failure to fulfill its obligation to provide working examples and experimental or comparative data to show synergy of the claimed composition, the composition claims 15, 17, 19, 23 and 31-36 fails Section 3(e) and must be rejected.

D: S. 3(i) Method of treatment

51. S.3(i) holds that treatment of human beings to render them free of disease is ‘not an invention’. Claims 42-45 are method of treatment claims for treatment of humans for tuberculosis and hence hit by S.3(i) and therefore liable to be rejected.

IV. CLAIMS OF THE PRESENT APPLICATION ARE CHALLENGED UNDER SECTION 25(1)(g) OF THE PATENTS ACT, ON GROUND THAT THE SPECIFICATION DOES NOT SUFFICIENTLY / CLEARLY DESCRIBE THE INVENTION OR THE METHOD FOR ITS PERFORMANCE.

52. This section has two alternative grounds –

1. the specification does not sufficiently and clearly describe the invention itself (i.e. obfuscation or hiding the ‘core invention’)

or

- b. the specification does not sufficiently and clearly describe the manner in which it is to be performed (i.e. hiding the manner of performing the invention).

53. The Specification does not sufficiently/ clearly describe the manner in which a composition is to be performed. The lack of any example/ process for making a composition has already been noted in earlier paragraphs. Hence Composition claims 15, 17, 19, 23 and 31-36 fail the patentability exam under S.25(1)(g).

54. Similarly, present claims 20 through 24 are unclear on what is open form/ closed form. The Applicant, vide these 5 claims, is trying to claim something that has been, at best discussed only vaguely in its Specification.
55. Applicant's scientists (most of whom are inventors for either D1 or present '083) in their Article: J. Med. Chem. 2017, 60, 19, 8011–8026⁴ in which GSK656 is disclosed as compound 23a { According to table 1 of the Article, 23a has a CL substituted at position 4 and 24a has a Br] }, stated that:

“It is interesting to note that 23a or 24a is present as a seven-membered tricyclic ring form based on ¹H NMR in deuterated DMSO (Figure 3), suggesting that an equilibrium exists between open and close forms depending on solvent and environment. This dynamic equilibrium between open and closed forms of the benzoxaborole pharmacophore and its six- and seven-membered analogues has been studied by Hall and his group.

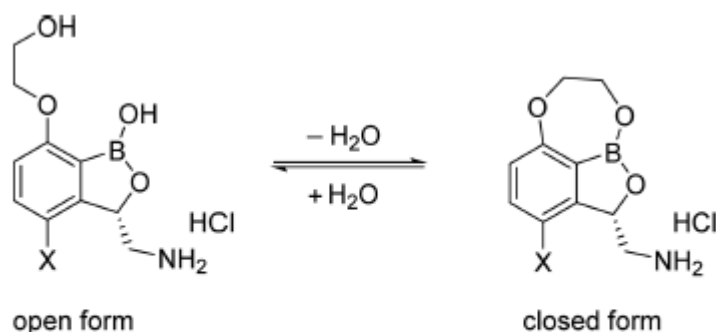


Figure 3. 3-Aminomethyl 4-halogen benzoxaborole inhibitors 23a and 24a.

56. This Article was published in Sep 2017 (after priority of present '083) and even then, the Applicant was not completely sure of how GSK656 exists. '083 Specification does not sufficiently and clearly describe what is open form/ closed form and the so-called equilibrium nor gives clarity on what is the actual invention since a later person would not know whether any GSK656 that he makes/ formulates into a composition is in open form or has transformed into open/ closed form, post manufacture. The Opponent believes that

⁴<https://pubs.acs.org/doi/10.1021/acs.jmedchem.7b00631>

pharmacologically, the open and closed form are different compounds. Opponent has tried to check regulatory databases and believes that Applicant has conducted clinical trial on the open form of GSK656.

57. In absence of adequate disclosure on what is open form/ closed form and / when they exist and how are these different from the compounds in **D1/D2**, these 5 claims are liable to be rejected u/s S.25(1)(g).

S.25(1)(h) – Non disclosure of information required u/s 8:

S.25(1)(h) states that an application can be opposed on the ground that

‘the Applicant has failed to disclose to the Controller the information required by section 8 or has furnished the information which in any material particular was false to his knowledge.’

58. An objection under Section 25(1)(h) is raised herein without prejudice to the grounds raised above. It is submitted that the Applicant has failed to comply with the mandatory requirements of Section 8 of the Patents Act. In the context of fulfilment of the applicant’s duty under Section 8, the Opponent submits two important rulings from the Hon’ble High Court of Delhi.

a. Suresh Behl vs. Koninklijke Philips Electronics [MANU/DE/2785/2014] (while adjudicating a matter on revocation) had noted: *“For the aforesaid reasons, we are of the view that the power to revoke a patent under Section 64(1) is discretionary and consequently it is necessary for the Court to consider the question as to whether the omission on the part of the plaintiff was intentional or whether it was a mere clerical and bonafide error.”*

b. Chemtura Corporation vs. Union of India (UOI) and Ors. [2009 (41) PTC260(Del)]

59. The Applicant has filed Form 3, thrice– once initially and then twice in 2018. For sake of brevity, Opponent will focus on the last Form 3 filed on 23rd Aug 2018. We note that the Applicant has intentionally not given relevant and sensitive information (especially the case of refusals from multiple patent offices) with the Indian Patent Office and hence the present Application has to be refused in entirety.

BR	BR112017017213-5	Shown as Pending. Actual status: Application discontinued
CA	CA2976308	Status shown as pending; Current status: Abandoned
China	CN107548398	Mentioned in Form 3 as ‘Published’. Current status: ??
Egypt	PCT 1367/2017	Mentioned in Form 3 as ‘Published’. Current status: ??
EP	Application no. EP16706003.7	Published as EP3256480. ‘Deemed withdrawn’ as of 10/May/2019.
Malaysia	PI2017702942	Mentioned in Form 3 as ‘Published’. Current status: ‘Withdrawn’
Philippines	PH 1/2017/501427	Mentioned in Form 3 as ‘Pending’. Current status: INACTIVE/FORFEITED FOR NON- REVIVAL ON WITHDRAWAL ON RSE
US	US20180037595	Abandoned – not shown at all in Form 3.

60. The Applicant has intentionally not filed the above abandonments or the negative Examination reports associated therewith. Applicant has wilfully not submitted the above documents as they are negative / extremely prejudicial to its claims at the Indian Patent Office. This is a clear and *mala-fide* violation of Applicant’s obligations u/s 8 and thus renders the entire Application ripe for refusal.

PRAYER FOR RELIEF

61. In view of the above said references Opponent prays as follows:

- a) To declare the present Application ‘abandoned’ by virtue of S.11, read along with R. 24B;
- b) To reject the claims of Application No. 201717032083 *in toto*;
- c) To be heard and be allowed to lead evidence (documentary and oral) before any order is passed;

- d) that the Opponent may be granted an opportunity of being heard in the matter before any final orders are passed;
- e) To allow the Opponent to file further submissions, documents as evidence if necessary to support the averments or in case the Applicant amends the claims;
- d) For costs in this matter;
- e) For any further and other relief in the facts and circumstances that may be granted in favour of the Opponent in the interest of justice.

Dated this 17th day of November, 2021



RAJESHWARI H. IN/PA – 0358
AGENT FOR THE OPPONENT
OF RAJESHWARI AND ASSOCIATES

To
THE CONTROLLER OF PATENTS
PATENT OFFICE, NEW DELHI

Annexure - 1

FORM-2

**THE PATENT ACT, 1970
(39 OF 1970)
AND
THE PATENT RULES, 2003
(As Amended)**

**COMPLETE SPECIFICATION
(See section 10; rule 13)**

"BENZOXABOROLE COMPOUNDS AND USES THEREOF"

GLAXOSMITHKLINE INTELLECTUAL PROPERTY (NO.2) LIMITED, a corporation organized and existing under the laws of United Kingdom of 980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom. ; and

ANACOR PHARMACEUTICALS, INC., a corporation organized and existing under the laws of USA of 1020 East Meadow Circle, Palo Alto, California 94303, USA.

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

BENZOXABOROLE COMPOUNDS AND USES THEREOF

FIELD OF THE INVENTION

[0001] This invention relates to compounds, compositions containing them, their use in therapy, including their use as anti-mycobacterials, for example in the treatment of tuberculosis, and methods for the preparation of such compounds.

BACKGROUND OF THE INVENTION

[0002] Mycobacterium is a genus in the class of bacteria called *Actinobacteria* with its own distinct family known as *Mycobacteriaceae*. Mycobacterium contains various obligate and opportunistic pathogens of animals, which may also be transmitted to humans and cause disease in humans, thus exhibiting a considerable zoonotic potential. During the past few decades, members of the *Mycobacterium avium-intracellulare* complex (MAIC) emerged as pathogens of human diseases, including lymphadenitis in children, pulmonary tuberculosis-like disease, and disseminated infections (occurring predominantly in immunocompromised persons, particularly AIDS patients). Similarly, important animal diseases result from infections in an animal by members of this group, e.g., avian tuberculosis and paratuberculosis in ruminants. MAIC includes *M. intracellulare* and 4 subspecies of *M. avium*, namely, *M. avium subsp. avium*, *M. avium subsp. hominissuis*, *M. avium subsp. silvaticum*, and *M. avium subsp. paratuberculosis*. Whereas members of the *M. tuberculosis* complex are transmitted by direct host contact, MAIC species are acquired predominantly from environmental sources, including soil, water, dust, and feed.

[0003] *Mycobacterium tuberculosis* (MTB) is a small aerobic non-motile high-GC bacillus with an "outer-membrane" that is unusually thick, "waxy," hydrophobic, rich in mycolic acids, and extremely impermeable, making mycobacterium infections difficult to treat. One third of the world's population is thought to be infected (including latent MTB), but this number increases to upwards of 80% of the population in many Asian and African countries. If untreated, the death rate from active MTB infections is more than 50%. In addition, the combination of HIV and MTB is deadly and increasing numbers of MTB strains are becoming resistant to standard of care drugs; approximately 300,000 new cases of multidrug resistant (MDR) *M. tuberculosis* are reported each year. Multidrug resistant (MDR) *M. tuberculosis* are resistant to isoniazid and rifampicin, and extensive drug resistant (XDR) *M. tuberculosis* are also resistant to at least one quinolone and one aminoglycoside. As can be seen in Figure 1, XDR *M. tuberculosis* has been reported across much of the globe.

[0004] Add to these issues the ease of transmission, as shown in Figure 2, the globalization of travel, and the ongoing relocation and emigration of many segments of the world's population and it is apparent that MTB is becoming a global crisis.

[0005] Synthetic drugs for treating tuberculosis (TB) have been available for over half a century, but incidences of the disease continue to rise world-wide. More than 2 billion people are currently infected with *M. tuberculosis*, most being latent cases, and it is estimated that over 9 million new cases occur each year, worldwide, resulting in from 1.7 to nearly 2 million deaths per year. In 2004 alone approximately 24,500 new infections and close to 5,500 deaths were recorded, each day. See Zignol, Met al., M. Surveillance of anti-tuberculosis drug resistance in the world: an updated analysis, 2007-2010. Bull. World Health Organ 2012, 90 (2), 111-119D) Co-infection with HIV is driving the increase in incidence (Williams, B. G.; Dye, C. *Science*, **2003**, 301, 1535) and the cause of death in 31 % of AIDS patients in Africa can be attributed to TB. See Corbett, E. Let al.,. *Arch. Intl. Med.*, **2003**, 163, 1009, Septkowitz, Aet al., *Clin. Microbiol. Rev.* **1995**, 8, 180).

[0006] The limitations of tuberculosis therapy and prevention are well known. The current available vaccine, BCG was introduced in 1921 and fails to protect most people past childhood. According to a 2006 report - "International Standards for Tuberculosis Care", a document developed by the Tuberculosis Coalition for Technical Assistance (TBCTA) which partners include Centers for Disease Control, American Thoracic Society, Tuberculosis Foundation, KNCV, the World Health Organization and the International Union Against Tuberculosis and Lung Disease - patients who do become infected with active disease currently endure two months of combination therapy with medicines introduced between 50 and 60 years ago – isoniazid (1952), rifampin (1963), pyrazinamide (1954) and ethambutol (1961) – followed by another 4 months of isoniazid and rifampin (also known as rifampicin). Alternatively the continuation phase could include Isoniazid and ethambutol for six months when adherence cannot be assessed, but according to this report, a longer continuation phase is associated with a higher rate of failure and relapse, especially in patients with HIV infection. Moreover, as detailed in this report, the doses of antituberculosis drugs used should conform to international recommendation and fixed-dose combinations of two (isoniazid and rifampicin), three (isoniazid, rifampicin, and pyrazinamide), and four (isoniazid, rifampicin, pyrazinamide, and ethambutol) drugs are highly recommended, especially when it is not possible to monitor the patient to ensure the treatment is ingested.

[0007] Daily dosing is required in these treatment phases and poor compliance drives the emergence and spread of multi-drug-resistant strains, which are challenging to treat. Shorter courses of more active agents which can be taken less frequently and which

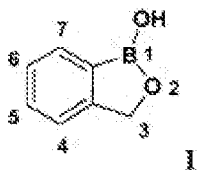
present a high barrier to the emergence of resistance, i.e. agents which are effective against multi-drug resistant strains of TB (MDR-TB), are urgently required. A March 2013 report (<http://www.aidsmap.com/Once-weekly-continuation-phase-TB-treatment-equals-standard-of-care/page/2589498/>) suggests that a two-drug combination of rifapentine (a long-acting derivative of rifampicin) with moxifloxacin (a fluoroquinolone antibiotic that has not been used previously in TB treatment) can allow tuberculosis (TB) treatment to be taken once-weekly during the four-month continuation phase and achieves the same standard of care as the traditional continuation treatment of daily treatment with isoniazid and rifampin. Such a treatment phase would allow treatment supervision to extend throughout the continuation phase, increasing adherence. However, moxifloxacin is not yet approved for treatment of TB, and the once-weekly treatment protocol is not yet endorsed or approved as an alternative standard of care treatment - guideline panels at international and national levels will need to review the published evidence to determine if this alternative continuation treatment protocol should be recommended and adopted. In addition, rifapentine is expensive, and interactions between rifapentine and antiretroviral drugs in the non-nucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor classes may prevent its use in TB patients who are also HIV positive and taking antiretroviral medicines. Thus, at present, the costs/benefits analysis of a continuation treatment with weekly rifapentine versus daily rifampicin is yet to be fully assessed.

[0008] The tuberculosis drug Sirturo™ (bedaquiline) was approved in the United States in late December 2012, and another, delamanid, is attempting to gain regulatory approval in the EU. However, both are reserved for drug-resistant tuberculosis, which accounts for just 5% of new cases. A 2007 Editorial and News Focus in *Nature Medicine* discusses many aspects of TB such as pathogenesis, epidemiology, drug discovery and vaccine development to date (*Nature Medicine*, 2007, *Focus on Tuberculosis*, Vol **13**(3), pages 263-312), noting that 125 years after the anniversary of the discovery of *Mycobacterium tuberculosis*, more than one-third of people in the world are infected with *M. tuberculosis*, and of these, more than 1 in 10 will develop the disease known as tuberculosis, formerly known as consumption, in their lifetime.

[0009] When coupled with the emergence of multi-drug resistant strains of *Mycobacterium tuberculosis* (MDR-TB), the scale of the problem is amplified. The global rise of bacteria and other microorganisms resistant to antibiotics and antimicrobials in general, poses a major threat. Deployment of massive quantities of antimicrobial agents into the ecosphere during the past 60 years has introduced a powerful selective pressure for the emergence and spread of antimicrobial-resistant pathogens. There is therefore a need to

discover and develop new chemical entities to treat TB (recent leads are reviewed in: Grosset JH, Singer TG, Bishai WR. New Drugs for the Treatment of Tuberculosis: Hope and Reality. *Int J Tuberc Lung Dis*. 2012 Aug;16(8):1005-14).

[0010] The present invention relates to substituted benzoxaboroles and certain benzoxaborole compounds that show unexpected selectivity for inhibiting replication of *Mycobacterium tuberculosis* (*M. tuberculosis*) versus inhibition (toxicity) of human cells compared to other benzoxaborole compounds, and exhibit sub-micromolar MIC values against mycobacterium species, particularly *Mycobacterium tuberculosis* and *Mycobacterium tuberculosis* complex (MTC), *Mycobacterium avium* and *Mycobacterium avium* complex (MAC) and *Mycobacterium avium intracellulare* complex (MAIC). Generally speaking, a benzoxaborole has the following structure and substituent numbering system:



[0011] Boron-containing molecules such as benzoxaboroles that are useful as antimicrobials have been described previously, see e.g. "Benzoxaboroles – Old compounds with new applications" Adamczyk-Woźniak, A. et al., *Journal of Organometallic Chemistry* Volume 694, Issue 22, 15 October 2009, Pages 3533–3541, and U.S. Pat. Pubs. US20060234981, US20070155699, WO2012033858, and US2013165411.

[0012] Certain benzoxaboroles which are substituted at position 7 may form a benzoxaborole compound (see US20090227541, US2013165411 and WO/KR2015/016558) and may also exist as an equilibrium mixture of a tricyclic form and an open form. When the resulting 7-substituted benzoxaborole is additionally substituted with a halogen substituent at position 4 and an aminomethyl substituent at position 3, such compounds are surprisingly selective towards and effective against mycobacteria including *M. tuberculosis*. The selectivity observed is assessed by comparing MIC values for such compounds relative to inhibition (toxicity) of these compounds to human cells, compared to other benzoxaborole compounds.

[0013] Applicants have surprisingly found that certain substituted benzoxaboroles substituted at the 7 position, as numbered in formula I above, exist in an equilibrium mixture of open form and closed form in the presence of water, such as in solution where water is present, and exist in the open form in the solid state.

[0014] US20090227541 discloses a multitude of compounds, including two benzoxaborole compounds with differing antibacterial activity against a panel of Gram

negative bacteria (See e.g. Tables 1 and 2), but does not disclose benzoxaborole compounds with halogen substitution on the benzoxaborole ring. WO2012033858 discloses benzoxaborole compounds with activity against *Mycobacterium tuberculosis*, including certain benzoxaborole compounds (see e.g. Examples 1.A through 1.V), but again, no benzoxaborole compounds are disclosed with halogen substitution on the benzoxaborole ring. US2013165411 discloses benzoxaborole compounds showing activity against *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Klebsiella pneumoniae* (see Table 1), but notes specifically that the halogen-substituted tricyclic compounds investigated (Examples 17, 18 and 19) lack activity against *A. baumannii*, with MIC values $\geq 16 \mu\text{g}/\mu\text{L}$ antibacterial activity (see para. [0218] discussing the structures in Figure 1B (lower box) of US2013165411).

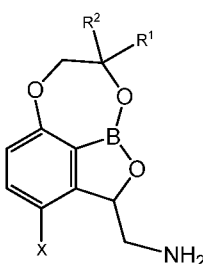
SUMMARY OF THE INVENTION

[0015] The inventors have surprisingly found that benzoxaborole compounds and certain substituted benzoxaboroles as described herein show unexpected selectivity for inhibiting replication of *Mycobacterium tuberculosis* (*M. tuberculosis*) versus inhibition (toxicity) of human cells compared to other benzoxaborole compounds. These substituted benzoxaborole compounds exhibit sub-micromolar MIC values against *M. tuberculosis*, which is comparable to or better than the MIC values for current therapies available for inhibiting *M. tuberculosis*. Further, in other embodiments, the substituted and benzoxaborole compounds as described herein are envisioned for use in combination with current anti-tubercular compounds and are envisioned to achieve greater efficacy in treating animals, including humans, infected with *M. tuberculosis*.

[0016] Resistance remains an issue in the treatment of tuberculosis (TB) and one clinical strategy is to focus on early combination with other TB drugs and to expedite early assessment of the compound's efficacy in patients. Compounds whose structure comprises Formula III or Formula IIIa offer a unique opportunity to address the serious issues which arise during the treatment of TB, such as multi-drug resistance, extensive-drug resistance, reactivity and/or adverse interaction between therapeutic agents in a multi-drug combination, and treatment length, thereby addressing potential patient needs.

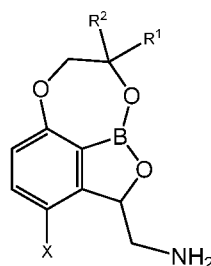
[0017] In certain embodiments of the present invention there is featured combinations of anti-tuberculosis agents and certain benzoxaboroles, and combinations of antituberculosis agents and substituted benzoxaboroles, for use in the treatment of *Mycobacterium tuberculosis* infections in animals, including humans. In particular

[0019] In particular embodiments, the benzoxaborole is a compound or a salt thereof, including a pharmaceutically acceptable salt thereof, whose structure comprises Formula II:

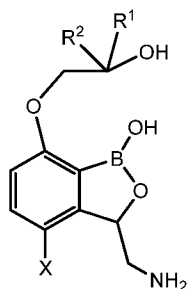


wherein X is selected from chloro, fluoro, bromo and iodo; R¹ and R² are each independently selected from H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, and -CH(CH₃)₂.

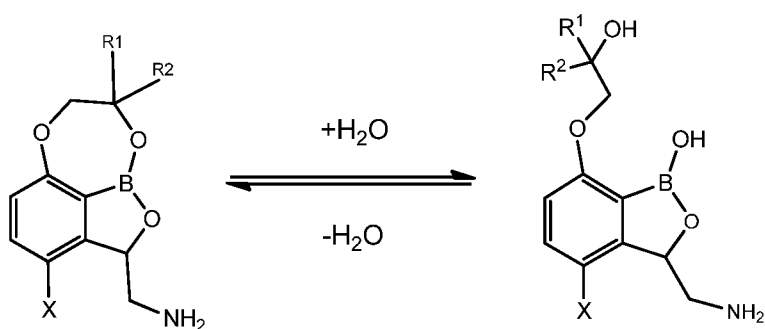
[0020] In particular embodiments, the substituted benzoxaborole is a compound or a salt thereof, including a pharmaceutically acceptable salt thereof, whose closed form comprises Formula II:



and whose open form structure comprises Formula III,

**Formula III ,**

[0021] wherein X is selected from chloro, fluoro, bromo and iodo; R¹ and R² are each independently selected from H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, and -CH(CH₃)₂. In particular embodiments, the substituted benzoxaborole may exist in equilibrium, as indicated below, between a closed form (Formula II) and an open form (Formula III), in certain environments and/or solvents.

**Formula II****Closed Form****Formula III****Open Form**

[0022] wherein X is selected from chloro, fluoro, bromo and iodo; R¹ and R² are each independently selected from H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, and -CH(CH₃)₂. In particular environments, the substituted benzoxaborole may exist in the open form of Formula III in the solid state.

[0023] In particular embodiments there is provided a compound whose structure comprises Formula II or Formula III or a salt thereof, wherein X is chloro or bromo; R¹ and R² are each independently selected from H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, and -CH(CH₃)₂.

[0024] In particular embodiments there is provided a compound whose structure comprises Formula II or Formula III or a salt thereof, wherein X is fluoro, R¹ and R² are as described herein.

[0025] In particular embodiments there is provided a compound whose structure comprises Formula II or Formula III or a salt thereof, wherein X is chloro, R¹ and R² are as described herein.

[0026] In particular embodiments there is provided a compound whose structure
5 comprises Formula II or Formula III or a salt thereof, wherein X is bromo, R¹ and R² are as described herein.

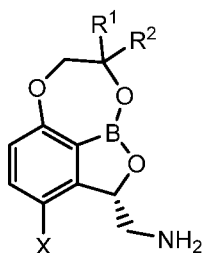
[0027] In particular embodiments there is provided a compound whose structure comprises Formula II or Formula III or a salt thereof, wherein X is iodo, R¹ and R² are as described herein.

10 [0028] In particular embodiments there is provided a compound whose structure comprises Formula II or Formula III or a salt thereof, wherein X is chloro or bromo, R¹ and R² are each independently selected from H, -CH₃, and -CH₂CH₃.

[0029] In particular embodiments there is provided a compound whose structure comprises Formula II or Formula III or a salt thereof, wherein X is chloro or bromo, R¹ and R²
15 are each independently selected from H and -CH₃.

[0030] In particular embodiments there is provided a compound whose structure comprises Formula II or Formula III or a salt thereof, wherein X is fluoro or iodo, R¹ and R² are each independently selected from H and -CH₃.

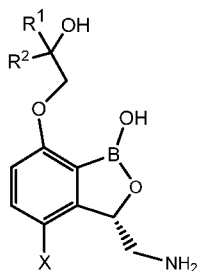
[0031] In particular embodiments there is provided a compound comprising a
20 structure of Formula IIa:



Formula IIa

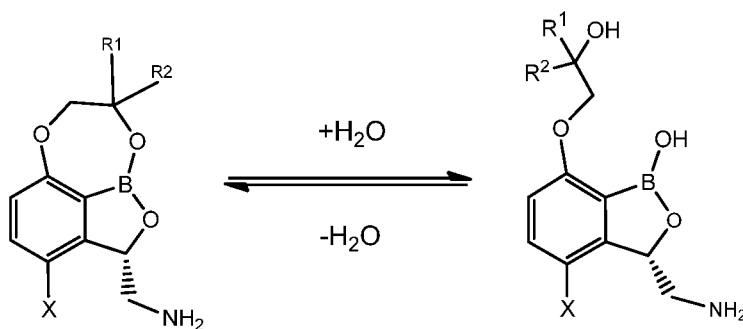
wherein X is fluoro, chloro, bromo or iodo, and R¹ and R² are each independently selected from H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, and -CH(CH₃)₂, or a salt thereof, including a
25 pharmaceutically acceptable salt thereof.

[0032] In particular embodiments there is provided a compound comprising a structure of Formula IIIa

**Formula IIIa**

wherein X is fluoro, chloro, bromo or iodo, and R^1 and R^2 are each independently selected from H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, and $-CH(CH_3)_2$, or a salt thereof, including a pharmaceutically acceptable salt thereof.

[0033] In particular embodiments, the compound of Formula IIa may exist in equilibrium, as indicated below, between a closed form (Formula IIa) and an open form (Formula IIIa), in certain environments and/or solvents.



Formula IIa
Closed Form

Formula IIIa
Open Form

[0034] In particular embodiments, the compound of Formula IIIa may exist in the open form of Formula IIIa in the solid state.

[0035] In particular embodiments there is provided a compound whose structure comprises Formula IIa or Formula IIIa wherein X is fluoro, chloro, bromo or iodo and R^1 and R^2 are each independently selected from H, $-CH_3$, and $-CH_2CH_3$, or a salt thereof, including a pharmaceutically acceptable salt thereof.

[0036] In particular embodiments there is provided a compound whose structure comprises Formula IIa or Formula IIIa wherein X is fluoro, chloro, bromo or iodo and R^1 and R^2 are each independently selected from H and $-CH_3$, or a salt thereof, including a pharmaceutically acceptable salt thereof.

[0037] In particular embodiments there is provided a compound whose structure comprises Formula IIa or Formula IIIa or a salt thereof, wherein X is fluoro, and R¹ and R² are as described herein.

[0038] In particular embodiments there is provided a compound whose structure
5 comprises Formula IIa or Formula IIIa or a salt thereof, wherein X is chloro, and R¹ and R² are as described herein.

[0039] In particular embodiments there is provided a compound whose structure comprises Formula IIa or Formula IIIa or a salt thereof, wherein X is bromo, and R¹ and R² are as described herein.

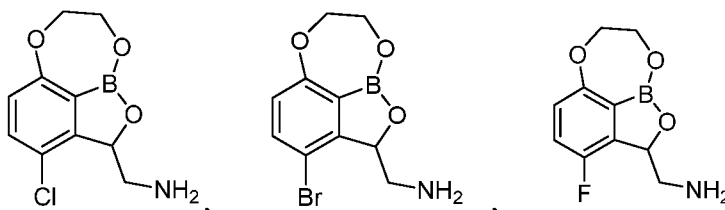
10 [0040] In particular embodiments there is provided a compound whose structure comprises Formula IIa or Formula IIIa or a salt thereof, wherein X is iodo, and R¹ and R² are as described herein.

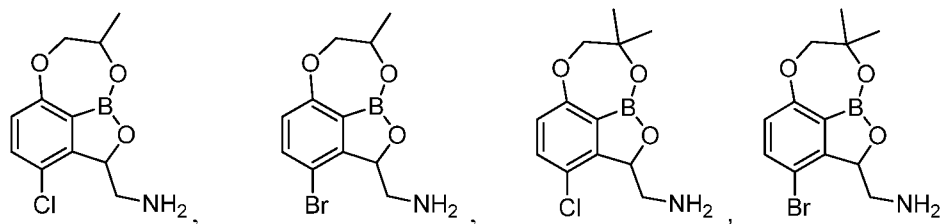
[0041] In particular embodiments there is provided a compound whose structure comprises Formula IIa or Formula IIIa wherein X is chloro or bromo and R¹ and R² are each
15 independently selected from H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, and -CH(CH₃)₂, or a salt thereof, including a pharmaceutically acceptable salt thereof.

[0042] In particular embodiments there is provided a compound whose structure comprises Formula IIa or Formula IIIa wherein X is chloro or bromo, and R¹ and R² are each
20 independently selected from H, -CH₃, and -CH₂CH₃, or a salt thereof, including a pharmaceutically acceptable salt thereof.

[0043] In particular embodiments there is provided a compound whose structure comprises Formula IIa or Formula IIIa wherein X is chloro or bromo, and R¹ and R² are each
independently selected from H and -CH₃, or a salt thereof, including a pharmaceutically acceptable salt thereof.

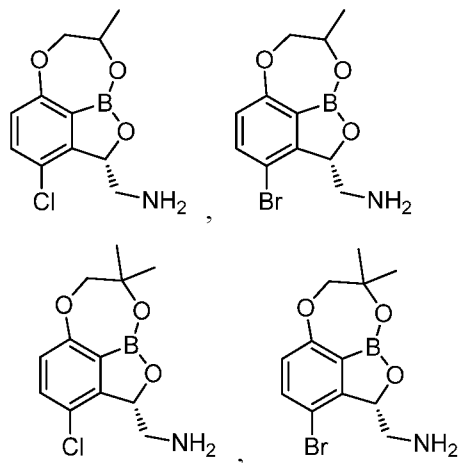
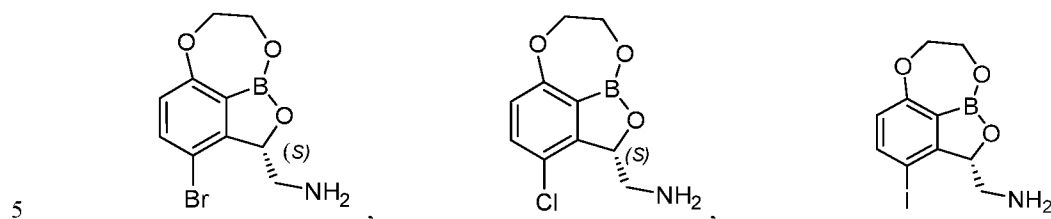
25 [0044] In particular embodiments, the benzoxaborole is a compound whose structure comprises Formula II as indicated below:





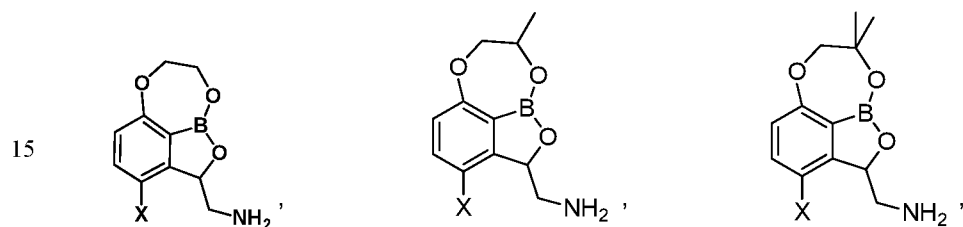
or a pharmaceutically acceptable salt thereof.

[0045] In particular embodiments, the benzoxaborole is a compound whose structure comprises Formula IIa as indicated below:



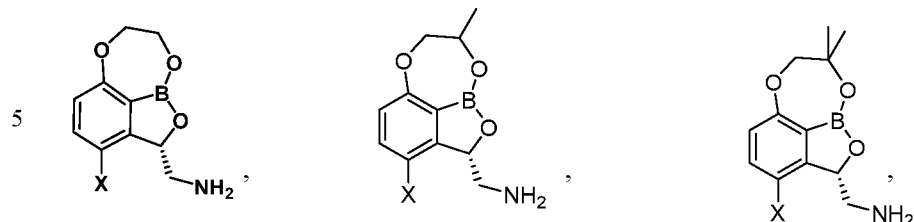
or a pharmaceutically acceptable salt thereof.

10 [0046] In other embodiments, the benzoxaborole is a compound whose structure comprises Formula II as indicated below:



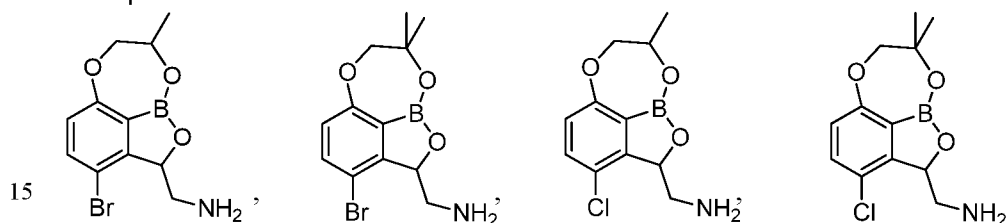
wherein X is as defined herein, or a pharmaceutically acceptable salt thereof.

[0047] In other embodiments, the benzoxaborole is a compound whose structure comprises Formula IIa as indicated below:



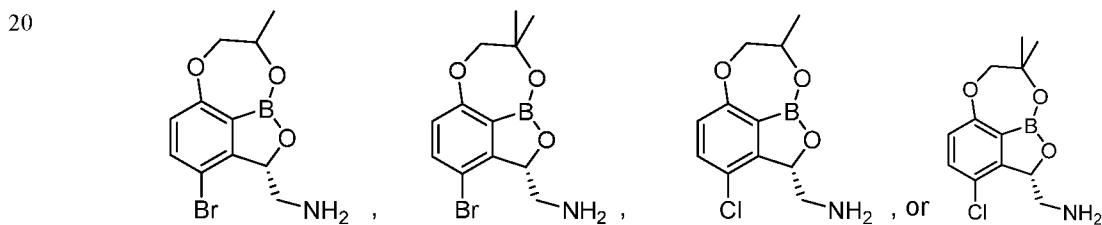
wherein X is as defined herein, or a pharmaceutically acceptable salt thereof.

10 [0048] In still other embodiments, the benzoxaborole is a compound whose structure comprises Formula II as indicated below:



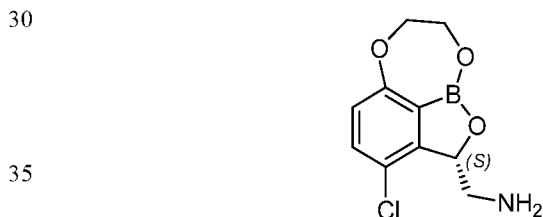
and a pharmaceutically acceptable salt thereof.

[0049] In still other embodiments, the benzoxaborole is a compound whose structure comprises Formula IIa as indicated below:

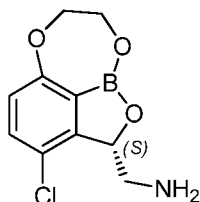


[0050] or a pharmaceutically acceptable salt thereof.

[0051] In another embodiment there is provided a compound, (S)-(3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine, comprising a structure as indicated below:

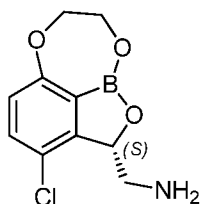


[0052] In another embodiment there is provided a compound, (S)-(3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methanamine, comprising a structure as indicated below:

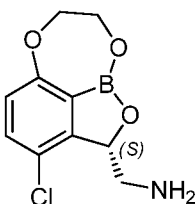


or a pharmaceutically acceptable salt thereof.

[0053] In another embodiment there is provided a pharmaceutically acceptable salt of a compound, (S)-(3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methanamine, comprising a structure as indicated below:

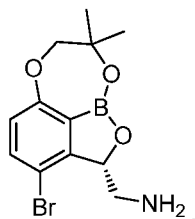


[0054] Another embodiment provides a pharmaceutical composition comprising a compound, (S)-(3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methanamine, comprising a structure as indicated below:

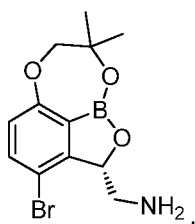


together with at least one pharmaceutically acceptable excipient.

[0055] In yet another embodiment there is provided a compound, (S)-(3-bromo-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methanamine, comprising a structure as indicated below:

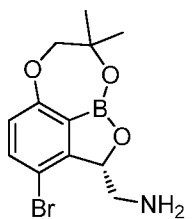


[0056] Still another embodiment provides a compound, (S)-(3-bromo-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine, comprising a structure as indicated below:

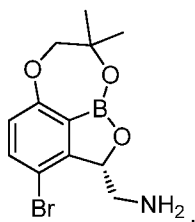


or a pharmaceutically acceptable salt thereof.

[0057] Another embodiment provides a pharmaceutically acceptable salt of a compound, (S)-(3-bromo-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine, comprising a structure as indicated below:



[0058] Another embodiment provides a pharmaceutical composition comprising a compound, (S)-(3-bromo-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine, comprising a structure as indicated below:

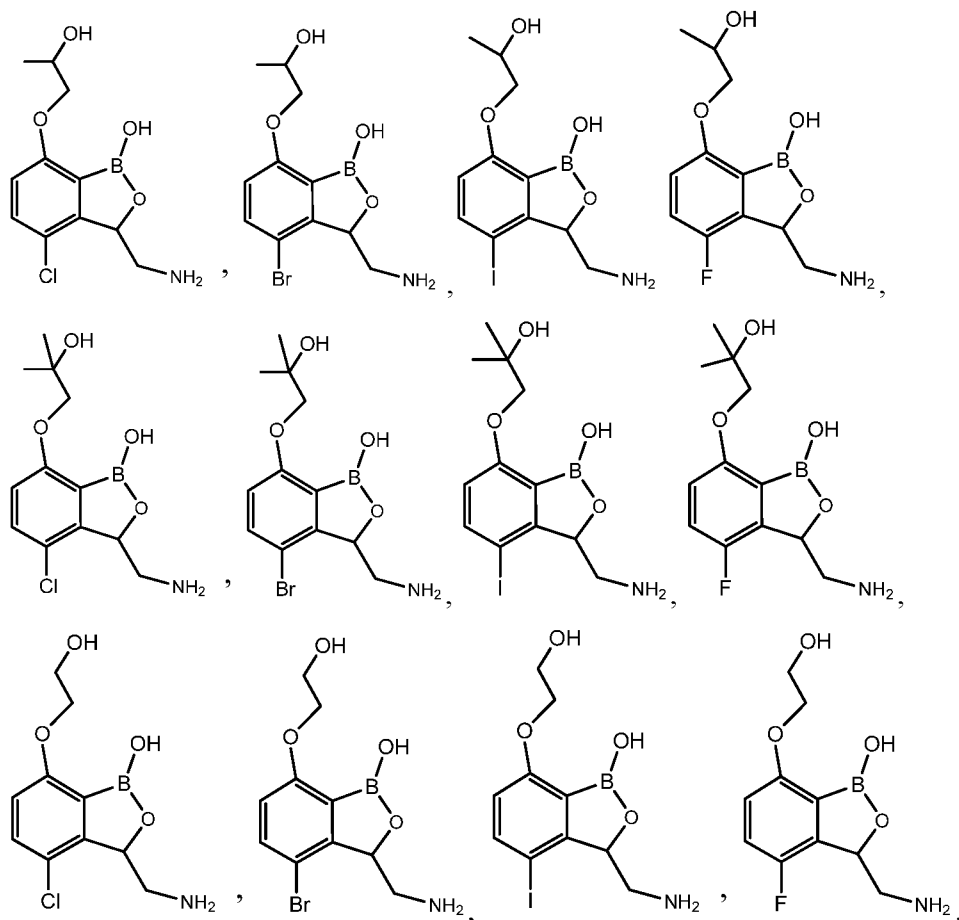


together with at least one pharmaceutically acceptable excipient.

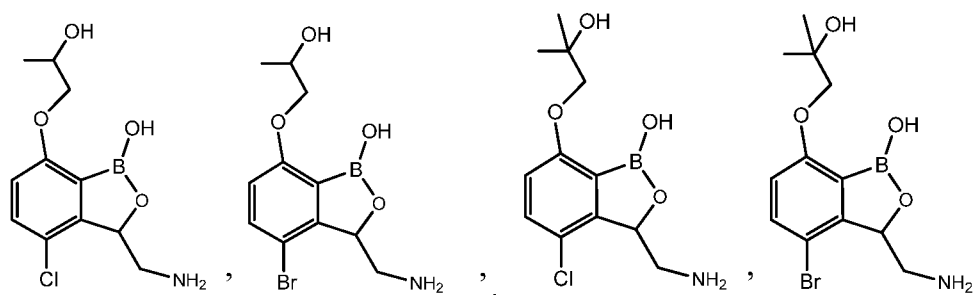
[0059] One embodiment provides a compound whose structure comprises Formula II or Formula IIa or a salt thereof, which is:

- (3-bromo-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine;
- (S)-(3-bromo-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine;
- 5 (3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine;
- (S)-(3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine;
- (3-chloro-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine;
- (3-bromo-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine;
- 10 (3-bromo-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine;
- (S)-(3-bromo-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine;
- 15 (3-chloro-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine;
- (S)-(3-chloro-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine;
- (3-fluoro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine; or
- 20 (S)-(3-iodo-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine.

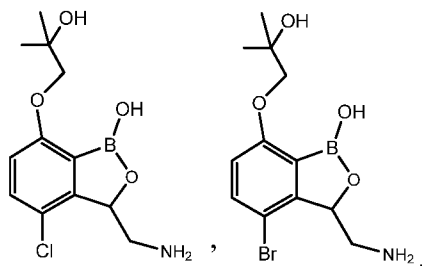
[0060] In particular embodiments, the substituted benzoxaborole is a compound in the open form, or a pharmaceutically acceptable salt thereof, comprising a structure of Formula III as indicated below:



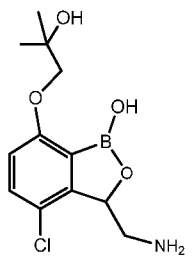
- 5 **[0061]** In other embodiments, the substituted benzoxaborole is a compound in the open form, or a pharmaceutically acceptable salt thereof, comprising a structure of Formula III as indicated below:



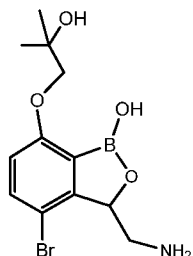
- 10 **[0062]** In other embodiments, the substituted benzoxaborole is a compound in the open form, or a pharmaceutically acceptable salt thereof, comprising a structure of Formula III as indicated below:



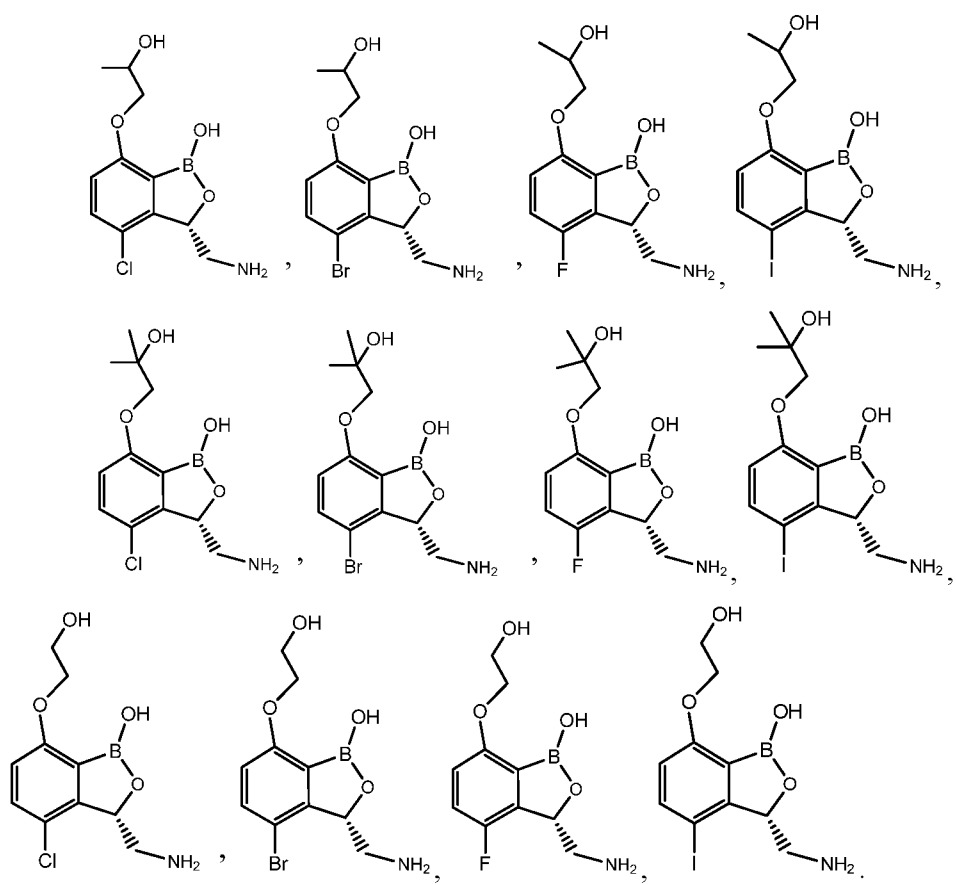
[0063] In other embodiments, the substituted benzoxaborole is a compound in the open form, or a pharmaceutically acceptable salt thereof, comprising a structure of Formula
 5 III as indicated below:



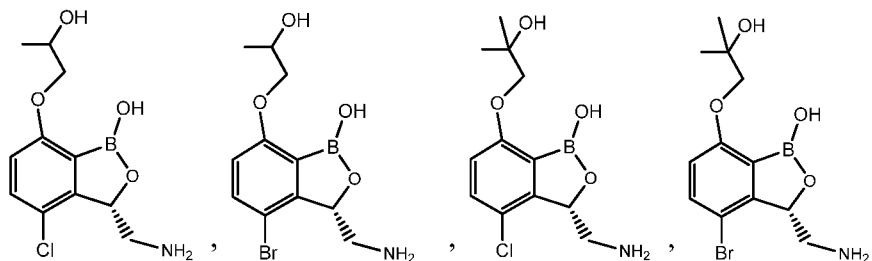
[0064] In other embodiments, the substituted benzoxaborole is a compound in the open form, or a pharmaceutically acceptable salt thereof, comprising a structure of Formula
 10 III as indicated below:



[0065] In particular embodiments, the substituted benzoxaborole is a compound in the open form, or a pharmaceutically acceptable salt thereof, comprising a structure of Formula IIIa as indicated below:

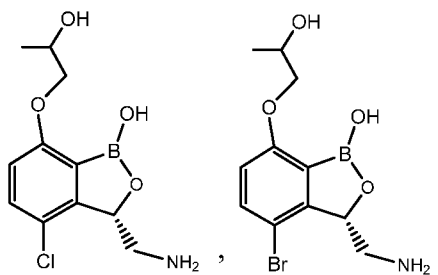


[0066] In other embodiments, the substituted benzoxaborole is a compound in the open form, or a pharmaceutically acceptable salt thereof, comprising a structure of Formula IIIa as indicated below:



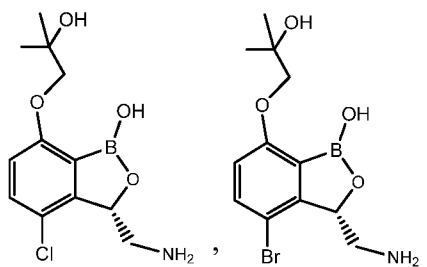
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[0067] In other embodiments, the substituted benzoxaborole is a compound in the open form, or a pharmaceutically acceptable salt thereof, comprising a structure of Formula IIIa as indicated below:



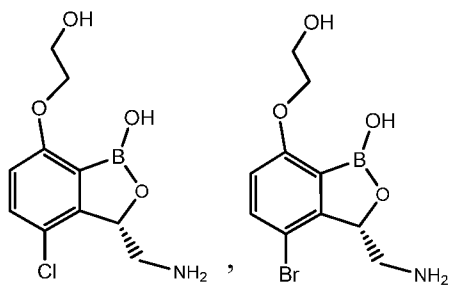
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[0068] In other embodiments, the substituted benzoxaborole is a compound in the open form, or a pharmaceutically acceptable salt thereof, comprising a structure of Formula IIIa as indicated below:

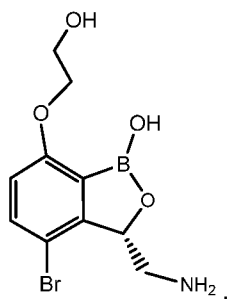


15

[0069] In other embodiments, the substituted benzoxaborole is a compound in the open form, or a pharmaceutically acceptable salt thereof, comprising a structure of Formula IIIa as indicated below:



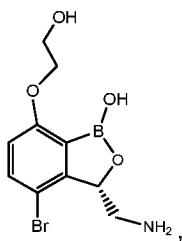
[0070] A compound, (S)-(3-bromo-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine, having an open form structure comprising:



5

or a pharmaceutically acceptable salt thereof.

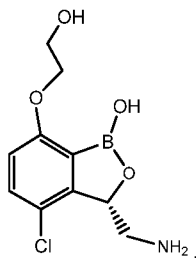
[0071] A pharmaceutical composition comprising a compound, (S)-(3-bromo-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine, having an open form structure comprising:



10

or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable excipient.

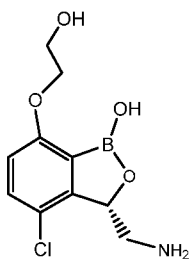
[0072] A compound, (S)-(3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methanamine, having an open form structure comprising:



5 or a pharmaceutically acceptable salt thereof.

[0073] A pharmaceutical composition comprising a compound, (S)-(3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methanamine, having an open form structure comprising:

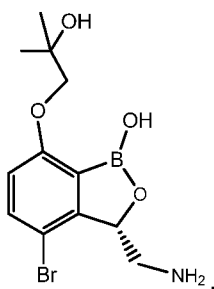
10



or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable excipient.

[0074] A compound, (S)-(3-bromo-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methanamine, having an open form structure comprising:

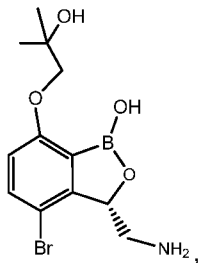
15



or a pharmaceutically acceptable salt thereof.

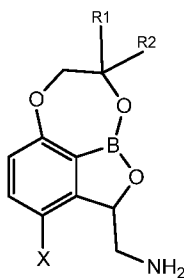
[0075] A pharmaceutical composition comprising a compound, (S)-(3-bromo-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methanamine, having an

open form structure comprising:



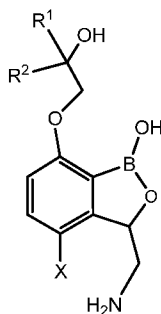
or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable excipient.

[0076] In particular embodiments the substituted benzoxaborole is a compound, or a pharmaceutically acceptable salt thereof, in equilibrium between a closed form comprising the structure of Formula II:



Formula II

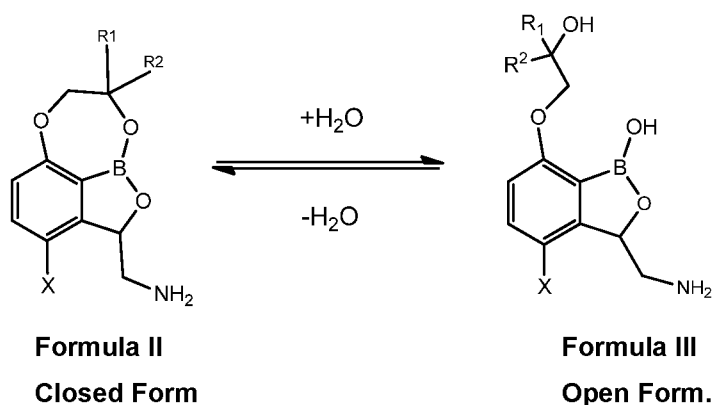
and an open form comprising the structure of Formula III:



Formula III

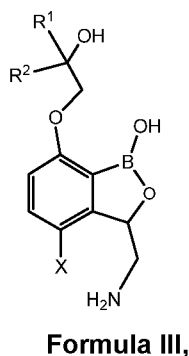
wherein X is selected from chloro, fluoro, bromo and iodo; R¹ and R² are each independently selected from H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, and -CH(CH₃)₂.

[0077] In certain embodiments, the substituted benzoxaborole in the presence of water is a compound in equilibrium comprising the structure of Formula II and the structure of Formula III:



5

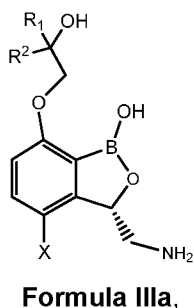
[0078] In other embodiments the substituted benzoxaborole is a compound or a pharmaceutically acceptable salt thereof having a structure of Formula III:



10

wherein X, R¹ and R² are as defined herein.

[0079] In other embodiments the substituted benzoxaborole is a compound or a pharmaceutically acceptable salt thereof having a structure of Formula IIIa:



15

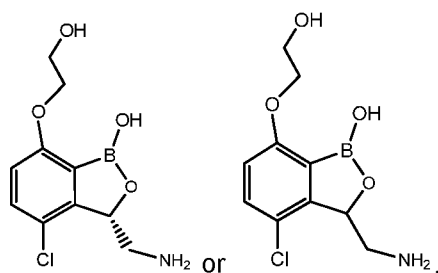
[0080] wherein X, R¹ and R² are as defined herein.

[0081] In particular embodiments the substituted benzoxaboroles having a structure of Formula III and the substituted benzoxaboroles having a structure of Formula IIIa are in the solid state.

5 [0082] In particular embodiments, substituted benzoxaboroles as described herein exist in an open form structure as described by Formula III or Formula IIIa, in the presence of water.

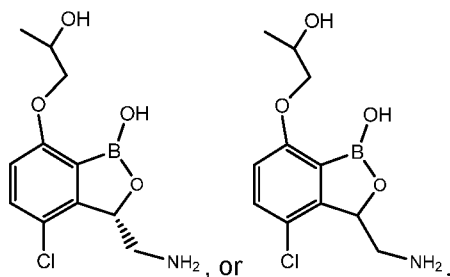
[0083] In particular embodiments, substituted benzoxaboroles as described herein exist in equilibrium between a closed form as described by Formula II or Formula IIa, and an
10 open form as defined by Formula III or Formula IIIa, in certain environments, such as in aqueous solvents.

[0084] In another embodiment there is provided a compound in an open form as shown below:



15 or a pharmaceutically acceptable salt thereof.

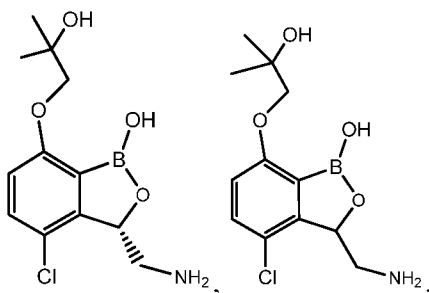
[0085] In another embodiment there is provided a compound in an open form as shown below:



or a pharmaceutically acceptable salt thereof.

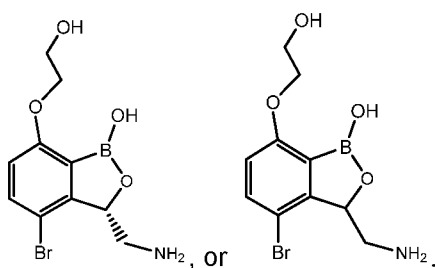
20

[0086] In another embodiment there is provided a compound in an open form as shown below:



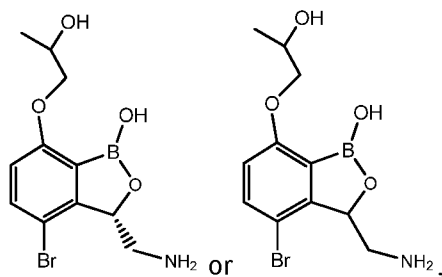
or a pharmaceutically acceptable salt thereof.

[0087] In another embodiment there is provided a compound in an open form as
5 shown below:



or a pharmaceutically acceptable salt thereof.

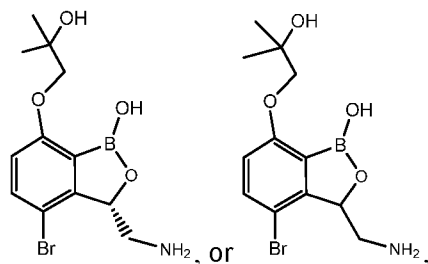
[0088] In another embodiment there is provided a compound in an open form as
shown below:



10

or a pharmaceutically acceptable salt thereof.

[0089] In another embodiment there is provided a compound in an open form as
shown below:



or a pharmaceutically acceptable salt thereof.

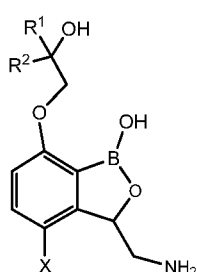
[0090] In another embodiment there is provided a compound having a single X-ray crystal structure as shown in Figure 5, together with a pharmaceutically acceptable salt thereof.

[0091] Another embodiment provides a compound having an XRPD pattern substantially as shown in Figure 6, or a pharmaceutically acceptable salt thereof.

[0092] Still another embodiment provides a compound whose crystal structure has an XRPD pattern with the peaks substantially as present in Figure 6.

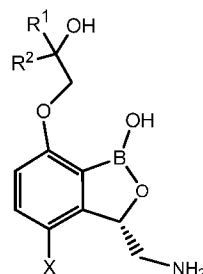
[0093] Another embodiment provides a compound whose crystal structure has an XRPD pattern having the peaks substantially as present in Figure 6, wherein the crystal for the XRPD pattern was prepared by slow evaporation from water or an aqueous solvent.

[0094] A compound in the presence of water comprising the structure of Formula III or Formula IIIa:



Formula III

or



Formula IIIa,

wherein X, R¹ and R² are as defined herein.

[0095] In a related embodiment, the pharmaceutically acceptable salt is selected from hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like. In other related embodiments, the pharmaceutically acceptable salt is derived from organic acids including acetic acid, propionic acid, isobutyric acid, maleic acid, malonic acid, benzoic acid, succinic acid, suberic acid, fumaric acid, glucaronic acid, galacturonic acid, lactic acid, mandelic acid, phthalic acid, benzenesulfonic

acid, p-tolylsulfonic acid, citric acid, tartaric acid, methanesulfonic acid, and the like. Still other related embodiments the pharmaceutically acceptable salt includes salts of amino acids such as arginate, lysinate and the like.

[0096] In particular aspects of the invention, the compound comprising Formula II or
 5 Formula IIa, or the compound comprising Formula III or Formula IIIa, is a mixture of diastereomers. In other particular aspects of the invention, the compound of Formula II or Formula IIa and the compound of Formula III or Formula IIIa is a diastereomer. In other particular aspects of the invention, the compound of Formula II and the compound of Formula III is a racemic mixture of enantiomers. In still other particular aspects of the
 10 invention, the compound of Formula II is a specific enantiomer. In particular aspects of the invention when R¹ and R² are both H or CH₃, the compound of Formula II or Formula IIa and the compound of Formula III or Formula IIIa has (S) stereochemistry at the chiral center. One embodiment provides a combination comprising: a first therapeutic agent wherein the first therapeutic agent is a compound as described herein, or a pharmaceutically acceptable
 15 salt thereof; optionally a second therapeutic agent; optionally a third therapeutic agent; optionally a fourth therapeutic agent; optionally a fifth therapeutic agent; and optionally a sixth therapeutic agent.

[0097] A related embodiment provides a combination as described wherein the optional second, third, fourth, fifth and sixth therapeutic agent is independently selected from
 20 isoniazid, rifampin, pyrazinamide, ethambutol, moxifloxacin, rifapentine, clofazimine, bedaquiline (TMC207), nitroimidazo-oxazine PA-824, delamanid (OPC-67683), an oxazolidinone such as linezolid, tedizolid, radezolid, sutezolid (PNU-100480), or posizolid (AZD-5847), EMB analogue SQ109, a benzothiazinone, a dinitrobenzamide or an antiviral agent including an antiretroviral agent.

[0098] A related embodiment provides a combination as described wherein the
 25 antiretroviral agents is zidovudine, didanosine, lamivudine, zalcitabine, abacavir, stavudine, adefovir, adefovir dipivoxil, fozivudine, todoxil, emtricitabine, alovudine, amdoxovir, elvucitabine, nevirapine, delavirdine, efavirenz, loviride, immunocal, oltipraz, capravirine, lersivirine, GSK2248761, TMC-278, TMC-125, etravirine, saquinavir, ritonavir, indinavir,
 30 nelfinavir, amprenavir, fosamprenavir, brecanavir, darunavir, atazanavir, tipranavir, palinavir, lasinavir, enfuvirtide, T-20, T-1249, PRO-542, PRO-140, TNX-355, BMS-806, BMS-663068 and BMS-626529, 5-Helix, raltegravir, elvitegravir, GSK1349572, GSK1265744, vicriviroc (Sch-C), Sch-D, TAK779, maraviroc, TAK449, didanosine, tenofovir, lopinavir, or darunavir.

[0099] Another embodiment of the invention provides a combination as described wherein the second, third, fourth, fifth and sixth therapeutic agent is selected from a therapeutic agent approved or recommended for the treatment of tuberculosis.

[00100] One embodiment of the present invention provides a pharmaceutical
5 formulation comprising a first therapeutic agent, said first therapeutic agent being a therapeutically effective amount of a compound whose structure comprises Formula II or Formula IIa or whose structure comprises Formula III or Formula IIIa according to any of the embodiments described herein or a pharmaceutically acceptable salt thereof. A related
10 embodiment provides a combination as described herein and a pharmaceutically acceptable excipient, adjuvant or diluent. In another embodiment, the pharmaceutical formulation may further comprise a second therapeutic agent.

[00101] Another embodiment provides a method of killing mycobacteria and/or inhibiting replication of mycobacteria that causes disease in an animal, comprising contacting the mycobacteria with an effective amount of a compound whose structure
15 comprises Formula II or Formula IIa or whose structure comprises Formula III or Formula IIIa as described herein or a pharmaceutically acceptable salt thereof, so as to kill the mycobacteria and/or prevent the replication of the mycobacteria.

[00102] Another embodiment of the invention provides a method of treating a mycobacterium infection in an animal comprising: administering to the animal any one of: (i)
20 a therapeutically effective amount of a compound whose structure comprises Formula II or Formula IIa or whose structure comprises Formula III or Formula IIIa as described herein or a pharmaceutically acceptable salt thereof; (ii) a therapeutically effective amount of a combination comprising a compound whose structure comprises Formula II or Formula IIa or whose structure comprises Formula III or Formula IIIa as described herein or a
25 pharmaceutically acceptable salt thereof; or (iii) a therapeutically effective amount of a pharmaceutical formulation comprising a compound whose structure comprises Formula II or Formula IIa or whose structure comprises Formula III or Formula IIIa as described herein or a pharmaceutically acceptable salt thereof, so as to treat the mycobacterium infection in the animal.

[00103] In a further aspect, the invention provides a method of killing
30 mycobacteria and/or inhibiting replication of mycobacteria or a method of treating a mycobacterial infection in an animal such as livestock and pets, including cattle sheep, goats, dogs and cats, or a human, including an immune-suppressed human said method comprising: contacting the mycobacteria with an effective amount of a compound whose

structure comprises Formula II or Formula IIa or a compound whose structure comprises Formula III or Formula IIIa as described herein, thereby killing the mycobacteria and/or inhibiting replication of the mycobacteria, or said method comprising administering to the animal with the mycobacterial infection a therapeutically effective amount of a compound
 5 whose structure comprises Formula II or Formula IIa or whose structure comprises Formula III or Formula IIIa as described herein, or a pharmaceutically acceptable salt thereof. In an exemplary embodiment, the compound of Formula II or compound of Formula IIa is part of a pharmaceutical formulation described herein. In another exemplary embodiment the compound of Formula III or compound of Formula IIIa is part of a pharmaceutical formulation
 10 described herein. In another exemplary embodiment, the contacting occurs under conditions which permit entry of the combination into the mycobacterium.

[00104] Another embodiment of the invention provides a method as described herein, wherein the mycobacteria is selected from *Mycobacterium tuberculosis*, *Mycobacterium avium* including subspecies (subsp.) *Mycobacterium avium subsp. avium*,
 15 *Mycobacterium avium subsp. hominissuis*, *Mycobacterium avium subsp. silvaticum*, and *Mycobacterium avium subsp. paratuberculosis*; *Mycobacterium kansasii*, *Mycobacterium malmoeense*, *Mycobacterium simiae*, *Mycobacterium szulgai*, *Mycobacterium xenopi*, *Mycobacterium scrofulaceum*, *Mycobacterium abscessus*, *Mycobacterium chelonae*, *Mycobacterium haemophilum*, *Mycobacterium leprae*, *Mycobacterium marinum*,
 20 *Mycobacterium fortuitum*, *Mycobacterium parafortuitum*, *Mycobacterium gordonae*, *Mycobacterium vaccae*, *Mycobacterium bovis*, *Mycobacterium bovis BCG*, *Mycobacterium africanum*, *Mycobacterium canetti*, *Mycobacterium caprae*, *Mycobacterium microti*, *Mycobacterium pinnipedi*, *Mycobacterium leprae*, *Mycobacterium ulcerans*, *Mycobacterium intracellulare*, *Mycobacterium tuberculosis* complex. (MTC), *Mycobacterium avium* complex (MAC),
 25 *Mycobacterium avian-intracellulare* complex (MAIC), *Mycobacterium gordonae* clade; *Mycobacterium kansasii* clade; *Mycobacterium chelonae* clade; *Mycobacterium fortuitum* clade; *Mycobacterium parafortuitum* clade; and *Mycobacterium vaccae* clade.

[00105] Another embodiment provides a method of treating a mycobacterium infection in an animal comprising: administering to the animal any one of: (i) a therapeutically
 30 effective amount of a compound whose structure comprises Formula II or Formula IIa or whose structure comprises Formula III or Formula IIIa as described herein or a pharmaceutically acceptable salt thereof; (ii) a therapeutically effective amount of a combination comprising a compound whose structure comprises Formula II or Formula IIa or whose structure comprises Formula III or Formula IIIa as described herein or a

pharmaceutically acceptable salt thereof; or (iii) a therapeutically effective amount of a pharmaceutical formulation comprising a compound whose structure comprises Formula II or Formula IIa or whose structure comprises Formula III or Formula IIIa as described herein or a pharmaceutically acceptable salt thereof, so as to treat the mycobacterium infection in the animal, wherein the mycobacterium infection is a *M. tuberculosis* infection.

[00106] .Another embodiment provides a compound whose structure comprises Formula II or Formula IIa or whose structure comprises Formula III or Formula IIIa as described herein or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease resulting from a mycobacterial infection in an animal, including a human. Another embodiment provides a compound as described herein, wherein the disease is selected from tuberculosis, leprosy, Johne's disease, Buruli or Bairnsdale ulcer, Crohn's disease, pulmonary disease or pulmonary infection. pneumonia, bursa, synovial, tendon sheaths, localized abscess, lymphadenitis, skin and soft tissue infections Lady Windermere syndrome, MAC lung disease, disseminated *Mycobacterium avium* complex (DMAC), disseminated *Mycobacterium avium* intracellulare complex (DMAIC), hot-tub lung, MAC mastitis, MAC pyomyositis, *Mycobacterium avum* paratuberculosis, or granuloma, disease.

[00107] One embodiment provides the use of a compound whose structure comprises Formula II or Formula IIa or whose structure comprises Formula III or Formula IIIa as described herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of mycobacterial infection in an animal.

[00108] Another embodiment provides a method of treating a disease resulting from a mycobacterial infection in an animal, particularly in a mammal, more particularly in a human, which method comprises administering to the animal in need of such treatment an effective amount of a compound Formula II or an effective amount of a compound of Formula III as described herein or a pharmaceutically acceptable salt thereof. Another embodiment provides a method as described, wherein the disease is selected from tuberculosis, leprosy, Johne's disease, Buruli or Bairnsdale ulcer, Crohn's disease, pulmonary disease or pulmonary infection. pneumonia, bursa, synovial, tendon sheaths, localized abscess, lymphadenitis, skin and soft tissue infections Lady Windermere syndrome, MAC lung disease, disseminated *Mycobacterium avium* complex (DMAC), disseminated *Mycobacterium avium* intracellulare complex (DMAIC), hot-tub lung, MAC mastitis, MAC pyomyositis, *Mycobacterium avum* paratuberculosis, or granuloma disease.

[00109] Another embodiment provides a method of treating a mycobacterial infection in an animal, particularly in a mammal, which method comprises administering to

the animal in need of such treatment a therapeutically effective amount of a compound described herein, or pharmaceutically acceptable salt thereof. Another embodiment provides a method of treating a mycobacterial infection in an animal, particularly a mammal, wherein the mycobacterial infection is *Mycobacterium tuberculosis*.

5 **[00110]** In one embodiment there is provided a pharmaceutical formulation comprising a first therapeutic agent, said first therapeutic agent being a therapeutically effective amount of a compound described herein or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, adjuvant or diluent.

[00111] More particularly, a pharmaceutical formulation is provided comprising
 10 a first therapeutic agent that is a compound whose structure comprises Formula II or Formula IIa or whose structure comprises Formula III or Formula IIIa, said first therapeutic agent being a therapeutically effective amount of a compound as described herein or pharmaceutically acceptable salt thereof, in any embodiment as described herein; a pharmaceutically acceptable excipient, adjuvant or diluent; and a second therapeutic agent
 15 that is not a compound whose structure comprises Formula II or Formula IIa or whose structure comprises Formula III or Formula IIIa. In related aspects, the pharmaceutical formulation comprises a first therapeutic agent that is a compound whose structure comprises Formula II or Formula IIa or whose structure comprises Formula III or Formula IIIa as described herein, or a pharmaceutically acceptable salt thereof, and optionally
 20 comprises a second therapeutic agent that is not a compound whose structure comprises Formula II or Formula IIa or whose structure comprises Formula III or Formula IIIa, and optionally comprises a third therapeutic agent, and optionally comprises a fourth therapeutic agent, and optionally comprises a fifth therapeutic agent, and optionally comprises a sixth therapeutic agent. In related aspects, the second, third, fourth, fifth and sixth therapeutic agent is an anti-mycobacterial agent other than a compound whose structure comprises
 25 Formula II or Formula IIa or whose structure comprises Formula III or Formula IIIa. In related aspects, the second, third, fourth, fifth and sixth therapeutic agent is selected from isoniazid, rifampin, pyrazinamide, ethambutol, moxifloxacin, rifapentine, clofazimine, bedaquiline (TMC207), nitroimidazo-oxazine PA-824, delamanid (OPC-67683),
 30 oxazolidinone such as linezolid, tedizolid, radezolid, sutezolid (PNU-100480), and posizolid (AZD-5847), EMB analogue SQ109, a benzothiazinone, a dinitrobenzamide and an antiviral agent including an antiretroviral agent. In related aspects, the second, third, fourth, fifth and sixth therapeutic agent is a therapeutic agent approved and/or recommended for the treatment of tuberculosis.

[00112] A related embodiment provides a pharmaceutical formulation comprising a compound whose structure comprises Formula II or Formula IIa or whose structure comprises Formula III or Formula IIIa, or a salt thereof, and optionally comprises a second, third, fourth, fifth or sixth therapeutic agent, wherein the optional first, second, third, fourth, fifth or sixth therapeutic agent is an antiretroviral agent selected from of zidovudine, didanosine, lamivudine, zalcitabine, abacavir, stavudine, adefovir, adefovir dipivoxil, fozivudine, todoxil, emtricitabine, alovudine, amdoxovir, elvucitabine, nevirapine, delavirdine, efavirenz, loviride, immunocal, oltipraz, capravirine, lersivirine, GSK2248761, TMC-278, TMC-125, etravirine, saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, fosamprenavir, brecanavir, darunavir, atazanavir, tipranavir, palinavir, lasinavir, enfuvirtide, T-20, T-1249, PRO-542, PRO-140, TNX-355, BMS-806, BMS-663068 and BMS-626529, 5-Helix, raltegravir, elvitegravir, GSK1349572, GSK1265744, vicriviroc (Sch-C), Sch-D, TAK779, maraviroc, TAK449, didanosine, tenofovir, lopinavir, or darunavir.

[00113] As described herein, embodiments of the invention include coadministering, whether simultaneously, sequentially or in combination, a first therapeutic agent that is a substituted benzoxaborole or salt thereof as described herein, preferably a substituted benzoxaborole of Formula II or Formula IIa or a substituted benzoxaborole of Formula III or Formula IIIa as described herein, or a pharmaceutically acceptable salt thereof, optionally in combination with a second therapeutic agent, optionally in combination with a third therapeutic agent, optionally in combination with a fourth therapeutic agent, optionally in combination with a fifth and/or a sixth therapeutic agent, to a subject exposed to or infected with a mycobacterium species, including a *Mycobacterium tuberculosis* species. In certain embodiments, the first therapeutic agent is a benzoxaborole compound of Formula II or Formula IIa as described herein or a pharmaceutically acceptable salt thereof, and the second and/or third and/or fourth therapeutic agent is an anti-tubercular agent. In certain embodiments, the mycobacterium species is a drug-resistant variant; in certain embodiments the mycobacterium species is a multi-drug resistant variant.

[00114] In other particular embodiments there is provided a method for killing mycobacteria comprising contacting the mycobacteria or an animal, including a human, exposed to or infected with a mycobacterium with a first therapeutic agent that is a compound whose structure comprises Formula II or Formula IIa or whose structure comprises Formula III or Formula IIIa as described herein, or a pharmaceutically acceptable salt thereof, optionally contacting the cells or subject with a second therapeutic agent, optionally contacting the cells or subject with a third therapeutic agent, optionally contacting the cells or subject with a fourth therapeutic agent, optionally contacting the cells or subject

with a fifth and/or a sixth therapeutic agent, such that contacting kills mycobacteria cells. In particular embodiments, the first therapeutic agent is a substituted benzoxaborole that is a compound whose structure comprises Formula II or Formula IIa or whose structure comprises Formula III or Formula IIIa as described herein, or a pharmaceutically acceptable salt thereof and the optional second, third, fourth, fifth and/or sixth therapeutic agent is an anti-tubercular agent or a salt thereof. In other particular embodiments, the subject was exposed to or is infected with *Mycobacterium tuberculosis*.

[00115] Still other particular embodiments provide a method for inhibiting the replication of mycobacterial cells, the method comprising contacting the mycobacterial cells or an animal, including a human exposed to or infected with a mycobacterial cells with a first therapeutic agent that is a compound as described herein or a salt thereof, optionally contacting the mycobacterial cells or animal with a second therapeutic agent, optionally contacting the mycobacterial cells or animal with a third therapeutic agent, optionally contacting the mycobacterial cells or animal with a fourth therapeutic agent, optionally contacting the mycobacterial cells or animal with a fifth and/or a sixth therapeutic agent, such that contacting inhibits the replication of the mycobacterial cells. In particular embodiments, the first therapeutic agent is a substituted benzoxaborole that is a compound as described herein or a salt thereof and the optional second, third, fourth, fifth and/or sixth therapeutic agent is an anti-tubercular agent or a salt thereof. In other particular embodiments, the subject was exposed to or is infected with *Mycobacterium tuberculosis*.

BRIEF DESCRIPTIONS OF THE DRAWINGS

[00116] **Figure 1** is a world map indicating where, geographically, XDR-TB has been documented.

[00117] **Figure 2** shows transmission of tuberculosis.

[00118] **Figure 3** is a graph of MIC values (from Tables 1A and 1B) for **Example 4** G4-Cl against clinical isolates of *M. tuberculosis*.

[00119] **Figure 4** is a graph of MIC values (from Tables 2A, 2B, 2C and 2D) for **Example 2** and **Example 4** (G2-Br and G4-Cl, respectively) against clinical isolates of *M. tuberculosis*.

[00120] **Figure 5** shows a view of a cation and anion from the G4-Cl crystal structure. Anisotropic atomic displacement ellipsoids for the non-hydrogen atoms are shown

at the 50% probability level. Hydrogen atoms are displayed with an arbitrarily small radius. A second disorder component for the anion is not shown.

[00121] **Figure 6** shows a simulated XRPD pattern (2-40° 2θ, CuKα) for the G4-Cl crystal structure measured at 290K (blue, vertical offset = 0, scale factor = 1) compared to an experimental pattern for lot 142384053 (black, vertical offset = 2000, scale factor = 5).

[00122] **Figure 7** shows a view of a hydrate crystal structure of G4-Cl. Anisotropic atomic displacement ellipsoids for the non-hydrogen atoms are shown at the 50% probability level. Hydrogen atoms are displayed with an arbitrarily small radius.

[00123] **Table A** shows crystal data and data collection and refinement summary for the G4-Cl X-ray diffraction study.

[00124] **Tables 1A and 1B** provide MIC values for **Example 4** G4-Cl tested against *M. tuberculosis* Clinical Isolates: Sensitive (A) and Resistant (B) **Table 1A** is MIC results for **Example 4** against *M. tuberculosis* strains sensitive to known TB agents and **Table 1B** is MIC results for **Example 4** against *M. tuberculosis* strains resistant to one or more known TB agents. The resistance pattern of clinical isolates is indicated by the following abbreviations H: Isoniazide, R: Rifampicin, T: Ethionamide, S: Streptomycin, E: Ethambutol, Z: Pyrazinamide, K: Kanamycin, A: Amikacin and CP: Capreomycin.

[00125] **Tables 2A and 2B** provide MIC values for **Example 4** G4-Cl tested against various strains of *M. tuberculosis* Clinical Isolates: Sensitive (A) and Resistant (B). **Table 2A** is MIC results for **Example 4** against *M. tuberculosis* strains sensitive to known TB agents, and **Table 2B** is MIC results for **Example 4** against *M. tuberculosis* strains resistant to one or more known TB agents.

[00126] **Tables 2C and 2D** provide MIC values for **Example 2** G2-Br tested against 40 strains of *M. tuberculosis* Clinical Isolates: Sensitive (C) and Resistant (D). **Table 2C** is MIC results for **Example 2** against *M. tuberculosis* strains sensitive to known TB agent and **Table 2D** is MIC results for **Example 2** against *M. tuberculosis* strains resistant to one or more known TB agents. The resistance pattern of clinical isolates is indicated by the following abbreviations H: Isoniazide, R: Rifampicin, T: Ethionamide, S: Streptomycin, E: Ethambutol, Z: Pyrazinamide, K: Kanamycin, A: Amikacin and CP: Capreomycin.

[00127] **Table 3** provides MIC values against non-Mycobacterial strains for compounds of Formula II or Formula IIa.

[00128] Table 4A provides LeuRS inhibition IC50 values, MIC values against the *M. tuberculosis* standard strain Mtb H37Rv, toxicity values against human HepG2 cells, and selectivity values for Certain Comparator Benzoxaborole Compounds.

[00129] Table 4B provides the data classifications listed in Table 4A for
5 Compounds of Formula II or Formula IIa.

DETAILED DESCRIPTION OF SPECIFIC EMBODIMENTS

[00130] "Animal" as used herein means any of a kingdom (Animalia) of living things including many-celled organisms, including livestock and pets, including cattle, sheep, goats, dogs and cats, or a human, including an immune-suppressed human.

10 [00131] "Combination of the invention," as used herein refers to the combinations of compounds discussed herein, salts (e.g. pharmaceutically acceptable salts), prodrugs, solvates and hydrates of these compounds.

[00132] "Diastereomer" as used herein refers to one of a pair of stereoisomers that is not mirror images of the other stereoisomer.

15 [00133] "Enantiomer" as used herein refers to one of a pair of non-superimposable racemic compounds (racemates) that is a mirror image of the other enantiomer. Enantiomers have the property of rotating the plane of polarized light in one direction or another when in pure form but as a racemic mixture, the mixture does not rotate the plane of polarized light.

20 [00134] "Effective" amount of a compound, combination thereof or formulation thereof, means an amount of a compound that is the active agent, including a combination of formulation thereof, such that the amount is sufficient to provide the desired local or systemic effect. A "therapeutically effective" or "pharmaceutically effective" amount refers to the amount of compound, including a combination or formulation thereof, sufficient to achieve a
25 desired therapeutic or pharmaceutical result.

[00135] The term "pharmaceutically acceptable salt" is meant to include a salt of a compound described herein which is prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds as described herein contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount
30 of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino (such as choline or diethylamine or amino acids such as d-arginine, l-arginine, d-

lysine or L-lysine), or magnesium salt, or a similar salt. When compounds as described herein contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al., "Pharmaceutical Salts", Journal of Pharmaceutical Science 66: 1-19 (1977)). Certain specific compounds as described herein contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[00136] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compounds in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

[00137] In addition to salt forms, the invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein readily undergo chemical changes under physiological conditions to provide the compounds as described herein. Additionally, prodrugs can be converted to the compounds as described herein by chemical or biochemical methods in an ex vivo environment.

[00138] Certain of the compounds of Formula II and Formula IIa and certain of the compounds of Formula III and Formula IIIa may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

[00139] Certain of the substituted benzoxaboroles of Formula II and Formula IIa described herein may exist in equilibrium between a closed form as shown in Formula II and Formula IIa and an open form, as shown in Formula III and Formula IIIa, in certain solvent environments. In addition, certain of the substituted benzoxaboroles described herein, when dissolved in organic solvents, for example DMSO- d_6 and CD_3OD , exist in the closed form, as indicated by the 1H NMR data in the synthesis Examples below. In contrast,

single crystal X-ray, X-ray powder diffraction (XRPD) and solid state NMR indicate that certain of the substituted benzoxaboroles described herein exist in the open forms of Formula III and Formula IIIa in the solid state. Throughout the application, substituted benzoxaboroles described herein may be shown either in the closed forms of Formula II and Formula IIa, or in the open forms of Formula III and Formula IIIa. It is also understood that in certain solvent conditions, such as organic solvents, the substituted benzoxaboroles as described herein may exist the closed forms of Formula II and Formula IIa, whereas in other solvent conditions, e.g. when any water is present, the substituted benzoxaboroles described herein may exist in equilibrium between the closed forms of Formula II and Formula IIa and the open forms of Formulas III and Formula IIIa. It has also been shown that certain of the substituted benzoxaboroles described herein may exist in the open forms of Formula III and Formula IIIa in the solid state. XRPD has also shown that compounds of Formula II and Formula IIa may exist as a hydrate under certain conditions.

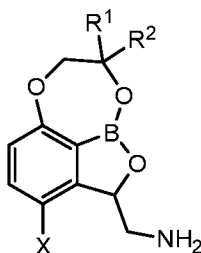
[00140] The compounds of Formula II and Formula IIa and the compounds of Formula III and Formula IIIa may be prepared in crystalline or non-crystalline form and, if crystalline, may optionally be solvated, e.g. as the hydrate. This invention includes within its scope stoichiometric solvates (e.g. hydrates) as well as compounds containing variable amounts of solvent (e.g. water). The subject invention also includes isotopically-labeled compounds which are identical to those recited in Formula II and Formula IIa or identical to those recited in Formula III and Formula IIIa but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature. Examples of isotopes that can be incorporated into compounds as described herein include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine, iodine and chlorine such as ^3H , ^{11}C , ^{14}C , ^{18}F , ^{123}I or ^{125}I .

[00141] Compounds of the present invention and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as ^3H or ^{14}C have been incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, ie. ^3H , and carbon-14, ie. ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. ^{11}C and ^{18}F isotopes are particularly useful in PET (positron emission tomography).

[00142] Because the compounds of Formula II and Formula IIa and the compounds of Formula III and Formula IIIa as described herein are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in

substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions.

- 5 **[00143]** One embodiment provides a benzoxaborole compound or a salt thereof having a structure comprising Formula II:



Formula II

- wherein X is selected from chloro, fluoro, bromo and iodo; R¹ and R² are each
10 independently H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, and -CH(CH₃)₂.

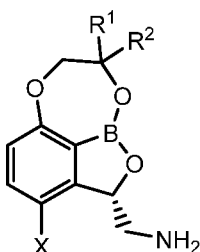
[00144] One embodiment provides a compound whose structure comprises Formula II wherein X is chloro or bromo and R¹ and R² are independently selected from H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, and -CH(CH₃)₂.

- [00145]** One embodiment provides a compound whose structure comprises
15 Formula II or a salt thereof, wherein X is chloro or bromo; R¹ and R² are independently H, -CH₃, or -CH₂CH₃.

[00146] One embodiment provides a compound whose structure comprises Formula II or a salt thereof, wherein X is chloro or bromo; R¹ and R² are independently selected from H and -CH₃.

- 20 **[00147]** One embodiment provides a compound whose structure comprises Formula II or a salt thereof, wherein X is fluoro or iodo; R¹ and R² are independently selected from H and -CH₃.

[00148] Another embodiment provides a compound whose structure comprises Formula IIa

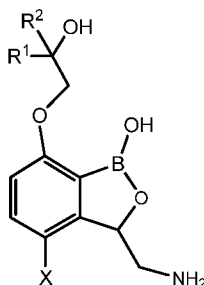


25

Formula IIa

wherein X is fluoro, chloro, bromo or iodo, and R¹ and R² are independently H or -CH₃, or a pharmaceutically acceptable salt thereof.

[00149] One embodiment provides a benzoxaborole compound or a salt thereof having a structure comprising Formula III:

**Formula III**

wherein X is selected from chloro, fluoro, bromo and iodo; R¹ and R² are each independently H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, and -CH(CH₃)₂.

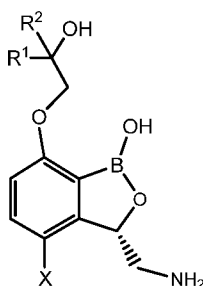
10 [00150] One embodiment provides a compound whose structure comprises Formula III wherein X is chloro or bromo and R¹ and R² are independently selected from H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, and -CH(CH₃)₂.

[00151] One embodiment provides a compound whose structure comprises Formula III or a salt thereof, wherein X is chloro or bromo; R¹ and R² are independently H, -CH₃, or -CH₂CH₃.

15 [00152] One embodiment provides a compound whose structure comprises Formula III or a salt thereof, wherein X is chloro or bromo; R¹ and R² are independently selected from H and -CH₃;

[00153] One embodiment provides a compound whose structure comprises Formula III or a salt thereof, wherein X is fluoro or iodo; R¹ and R² are independently selected from H and -CH₃.

[00154] Another embodiment provides a compound whose structure
5 comprises Formula IIIa



Formula IIIa

wherein X is fluoro, chloro, bromo or iodo, and R¹ and R² are independently H or -CH₃, or a pharmaceutically acceptable salt thereof.

10 [00155] In one aspect the invention provides a pharmaceutical composition comprising a compound whose structure comprises Formula II or whose structure comprises Formula III, or a pharmaceutically acceptable salt or solvate thereof, and one or more pharmaceutically acceptable carriers, excipients or diluents.

[00156] Another aspect of the invention further provides a method of treatment of a
15 mycobacterial infection in a mammal, particularly in a human, which method comprises administering to a mammal in need of such treatment an effective amount of a first therapeutic agent that is a compound whose structure comprises Formula II or a compound whose structure comprises Formula IIa, or a compound whose structure comprises Formula III or a compound whose structure comprises Formula IIIa, or a pharmaceutically acceptable
20 salt or solvate thereof. Related embodiments further comprise administering to a mammal in need of such treatment an effective amount of a first therapeutic agent that is a compound whose structure comprises Formula II or a compound whose structure comprises Formula IIa, or a pharmaceutically acceptable salt thereof, optionally administering in combination with an effective amount of a second therapeutic agent, optionally administering in
25 combination with an effective amount of a third therapeutic agent, optionally administering in combination with an effective amount of a fourth therapeutic agent, optionally administering in combination with an effective amount of a fifth therapeutic agent, optionally administering in combination with an effective amount of a sixth therapeutic agent.

[00157] Related embodiments further comprise administering to a mammal in need of such treatment an effective amount of a first therapeutic agent that is a compound whose structure comprises Formula III or a compound whose structure comprises Formula IIIa, or a pharmaceutically acceptable salt thereof, optionally administering in combination with an effective amount of a second therapeutic agent, optionally administering in combination with an effective amount of a third therapeutic agent, optionally administering in combination with an effective amount of a fourth therapeutic agent, optionally administering in combination with an effective amount of a fifth therapeutic agent, optionally administering in combination with an effective amount of a sixth therapeutic agent.

[00158] In related aspects of the embodiment the optional second, third, fourth, fifth and sixth therapeutic agent is an anti-mycobacterial agent. In related aspects, administering the first therapeutic agent and optionally administering the second, third, fourth, fifth and sixth therapeutic agent occurs concurrently, or administering the first therapeutic agent and optionally administering the second, third, fourth, fifth and sixth therapeutic agent occurs sequentially. In other related aspects of the invention, any one of the second, third, fourth, fifth or sixth therapeutic agent is selected from an antimicrobial agent, an antiviral agent, an anti-infective agent, an analgesic, a vitamin, a nutritional supplement, an anti-inflammatory agent, an analgesic, and an steroid.

[00159] The invention yet further provides a compound whose structure comprises Formula II, or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment of a mycobacterial infection in a mammal, particularly in a human. In related aspects, the mammal is a human wherein the mycobacterial infection is a *Mycobacterium tuberculosis* infection. In other aspects, the human with a *Mycobacterium tuberculosis* infection is also infected with a retrovirus, including a human immunodeficiency virus.

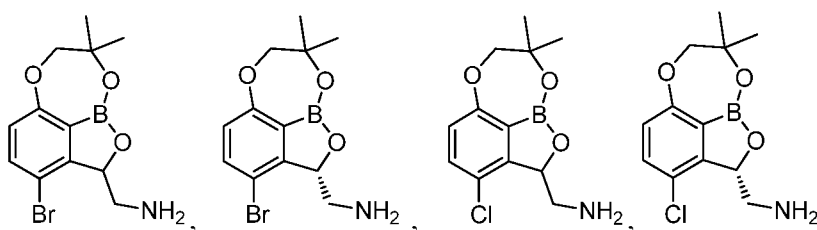
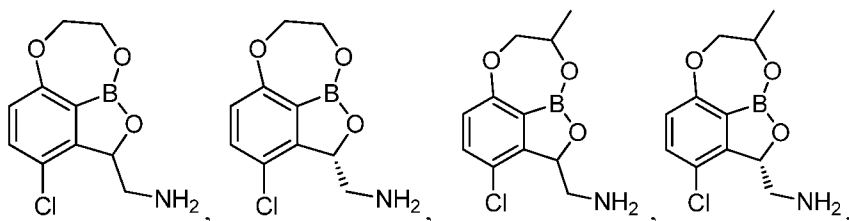
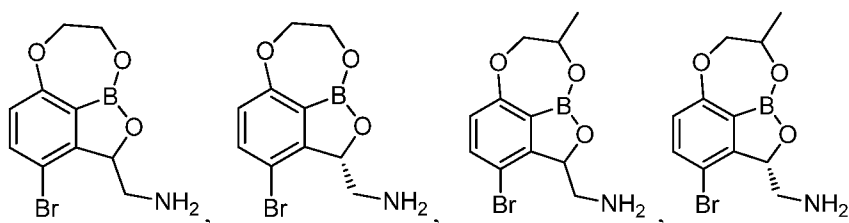
[00160] The invention still further provides the use of a compound whose structure comprises Formula II or Formula IIa, or a pharmaceutically acceptable salt or solvate thereof or a compound whose structure comprises Formula III or Formula IIIa, in the manufacture of a medicament for use in the treatment of a mycobacterial infection in a mammal, particularly in a human.

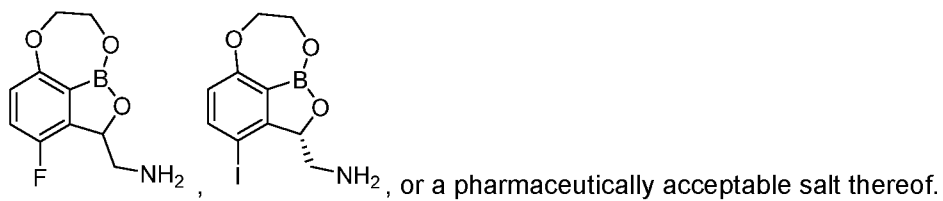
[00161] The invention also provides a pharmaceutical composition comprising a compound whose structure comprises Formula II or Formula IIa or a compound whose structure comprises Formula II or Formula IIa, or a pharmaceutically acceptable salt, or solvate thereof, and one or more pharmaceutically acceptable carriers, excipients or

diluents, for use in the treatment of a mycobacterial infection in a mammal, particularly in a human.

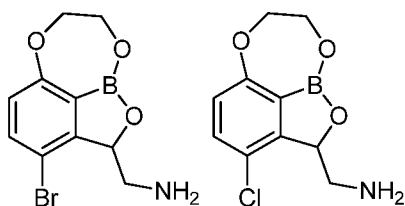
[00162] The invention also provides a pharmaceutical composition comprising a compound whose structure comprises Formula II or Formula IIa or a compound whose structure comprises Formula II or Formula IIa, or a pharmaceutically acceptable salt, or solvate thereof, and one or more pharmaceutically acceptable carriers, excipients or diluents, for use in the treatment of mycobacterial infections in a mammal, particularly in a human.

[00163] In another particular embodiment the substituted benzoxaborole in the combination has a structure as indicated below:





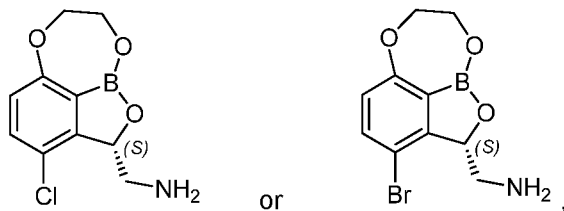
[00164] In one particular embodiment, the compound comprises a structure as indicated below:



5

or a pharmaceutically acceptable salt thereof.

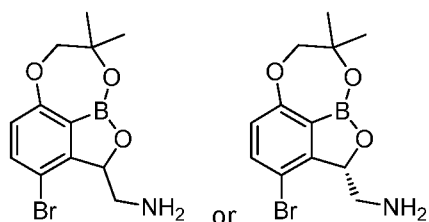
[00165] In one particular embodiment, the compound comprises a structure as indicated below:



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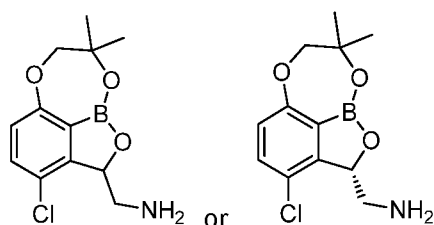
or a pharmaceutically acceptable salt thereof.

[00166] In one particular embodiment, the compound comprises a structure as indicated below:



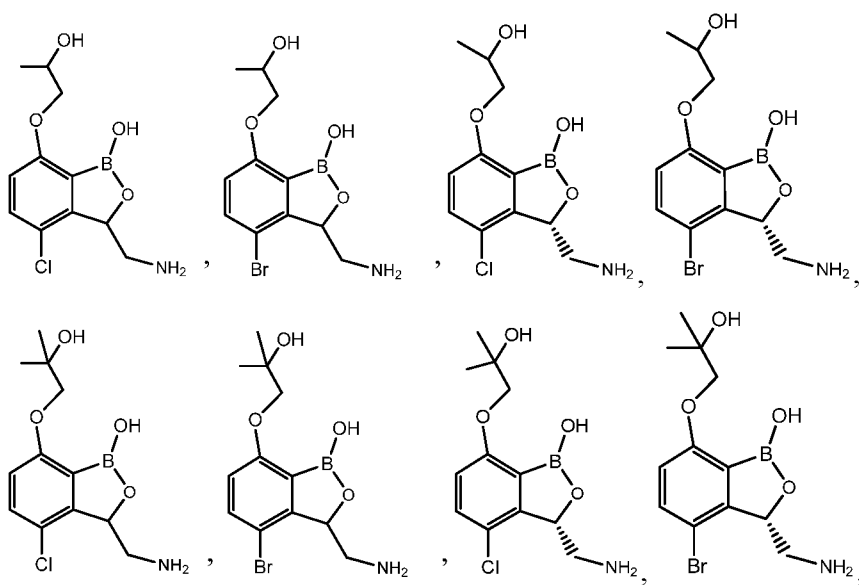
or a pharmaceutically acceptable salt thereof.

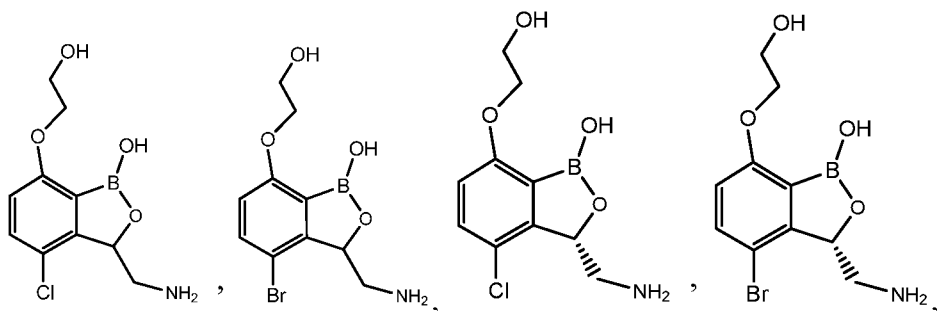
5 [00167] In one particular embodiment, the compound comprises a structure as indicated below:



10 [00168] or a pharmaceutically acceptable salt thereof.

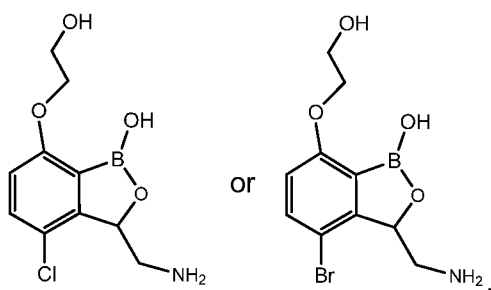
[00169] In another particular embodiment the substituted benzoxaborole in the combination has a structure indicated below:





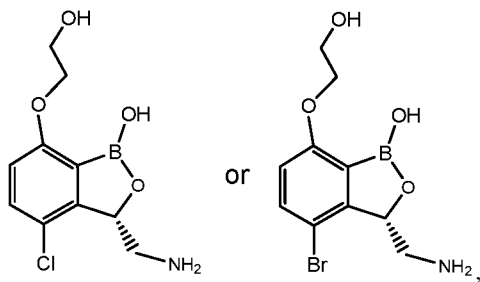
, or a pharmaceutically acceptable salt thereof.

[00170] In one particular embodiment, the compound comprises a structure as indicated below:



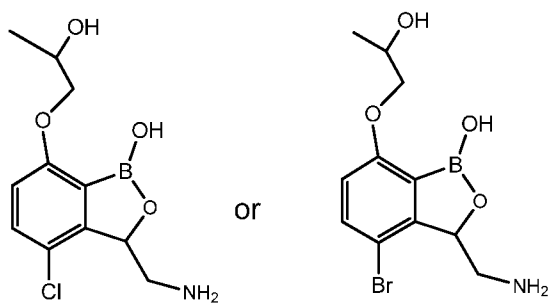
or a pharmaceutically acceptable salt thereof.

[00171] In one particular embodiment, the compound comprises a structure as indicated below:



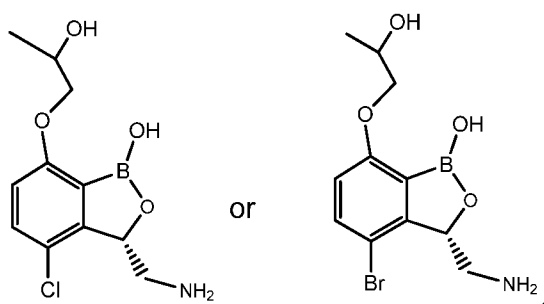
or a pharmaceutically acceptable salt thereof.

[00172] In one particular embodiment, the compound comprises a structure as indicated below:



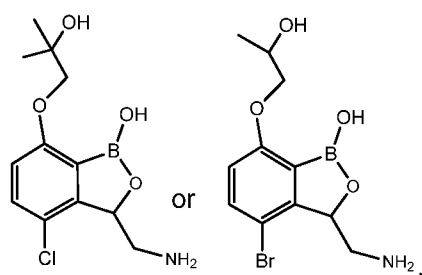
or a pharmaceutically acceptable salt thereof.

5 [00173] In one particular embodiment, the compound comprises a structure as indicated below:



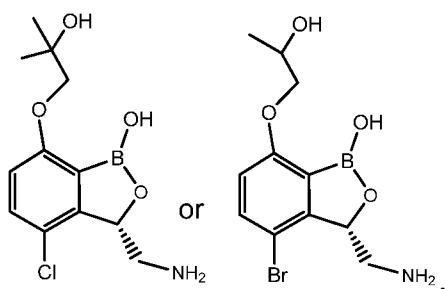
or a pharmaceutically acceptable salt thereof.

10 [00174] In one particular embodiment, the compound comprises a structure as indicated below:



or a pharmaceutically acceptable salt thereof.

[00175] In one particular embodiment, the compound comprises a structure as indicated below:



or a pharmaceutically acceptable salt thereof.

[00176] An embodiment of the invention provides a compound which is:

- 5 (3-bromo-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine;
- (S)-(3-bromo-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine;
- (3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine;
- (S)-(3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine;
- 10 (3-chloro-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine;
- (3-bromo-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine;
- (3-bromo-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine;
- 15 (S)-(3-bromo-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine;
- (3-chloro-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine;
- (S)-(3-chloro-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine;
- 20 (3-fluoro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine;
- (S)-(3-iodo-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine;

or a pharmaceutically acceptable salt thereof.

[00177] In another particular embodiment, the treatment of a mycobacterial infection or condition occurs through inhibition of an editing domain of an aminoacyl tRNA synthetase by means of binding to the editing active site. In another exemplary embodiment, the treatment of a mycobacterial infection or condition occurs through blocking
5 of an editing domain of an aminoacyl tRNA synthetase.

[00178] In a particular embodiment, the mycobacterial infection and/or disease is treated through oral administration of the combination of the invention. In an exemplary embodiment, the mycobacterial infection and/or disease is treated through intravenous administration of the combination of the invention.

10 **Pharmaceutical Formulations**

[00179] In another aspect, the invention is a pharmaceutical formulation which includes: (a) a pharmaceutically acceptable excipient; (b) a combination of the invention. In another aspect, the pharmaceutical formulation includes: (a) a pharmaceutically acceptable excipient; and (b) a combination described herein. In another aspect, the pharmaceutical
15 formulation includes: (a) a pharmaceutically acceptable excipient; and (b) a combination described herein, or a salt, prodrug, hydrate or solvate thereof. In another aspect, the pharmaceutical formulation includes: (a) a pharmaceutically acceptable excipient; and (b) a combination described herein, or a salt, hydrate or solvate thereof. In another aspect, the pharmaceutical formulation includes: (a) a pharmaceutically acceptable excipient; and (b) a
20 combination described herein, or a salt, hydrate or solvate thereof. In another aspect, the pharmaceutical formulation includes: (a) a pharmaceutically acceptable excipient; and (b) a salt of a combination described herein. In an exemplary embodiment, the salt is a pharmaceutically acceptable salt. In another aspect, the pharmaceutical formulation includes: (a) a pharmaceutically acceptable excipient; and (b) a prodrug of a combination
25 described herein. In another aspect, the pharmaceutical formulation includes: (a) a pharmaceutically acceptable excipient; and (b) a combination described herein. In an exemplary embodiment, the pharmaceutical formulation is a unit dosage form. In an exemplary embodiment, the pharmaceutical formulation is a single unit dosage form.

[00180] In an exemplary embodiment, the pharmaceutical formulation is a unit
30 dosage form. In an exemplary embodiment, the pharmaceutical formulation is a single unit dosage form. In an exemplary embodiment, the pharmaceutical formulation is a two unit dosage form. In an exemplary embodiment, the pharmaceutical formulation is a three unit dosage form. In an exemplary embodiment, the pharmaceutical formulation is a four unit dosage form. In an exemplary embodiment, the pharmaceutical formulation is a five unit
35 dosage form. In an exemplary embodiment, the pharmaceutical formulation is a six unit

dosage form. In an exemplary embodiment, the pharmaceutical formulation is a one, two, three, four, five, six or seven unit dosage form comprising a first unit dosage form and a second, third, fourth, fifth and/or sixth unit dosage form, wherein the first unit dosage form includes a) a therapeutically effective amount of a compound as described herein and b) a first pharmaceutically acceptable excipient; and the second, third, fourth, fifth, and/or sixth unit dosage form includes c) a therapeutically acceptable amount of an additional therapeutic agent that is an anti-mycobacterial agent and d) a second pharmaceutically acceptable excipient.

[00181] Information regarding excipients of use in the formulations of the invention can be found in Remington: The Science and Practice of Pharmacy, 21st Ed., Pharmaceutical Press (2011) which is incorporated herein by reference.

Combinations

[00182] In an exemplary embodiment, the invention provides a) a first therapeutic agent that is a benzoxaborole compound or salt thereof as described herein; b) a second therapeutic activity. In certain embodiments, the second therapeutic agent is an antibacterial agent, more specifically an anti-tubercular agent, more specifically an anti-*M. tuberculosis* agent.

[00183] In an exemplary embodiment, the combination is part of a pharmaceutical formulation described herein. Such conditions are known to one skilled in the art and specific conditions are set forth in the Examples appended hereto.

Dosage forms of the Combination

[00184] The individual components of the combinations of the invention, for example, a combination described herein, may be administered either simultaneously or sequentially in a unit dosage form. The unit dosage form may be a single or multiple unit dosage form. In an exemplary embodiment, the invention provides a combination in a single unit dosage form. An example of a single unit dosage form is a capsule wherein both the benzoxaborole compound and additional therapeutic agent are contained within the same capsule. In an exemplary embodiment, the invention provides a combination in a two unit dosage form. An example of a two unit dosage form is a first capsule which contains the benzoxaborole compound and a second capsule which contains the additional therapeutic agent. Thus the term 'single unit' or 'two unit' or 'multiple unit' refers to the object which the patient ingests, not to the interior components of the object. Appropriate doses of benzoxaborole compound will be readily appreciated by those skilled in the art. Appropriate

doses of an additional therapeutic agent that is not a compound whose structure comprises Formula II or Formula IIa or appropriate doses of an additional therapeutic agent that is not a compound whose structure comprises Formula III or Formula IIIa will be readily appreciated by those skilled in the art. In one particular embodiment, the benzoxaborole compound is present in the combination in a therapeutically effective amount. In one particular embodiment, the additional therapeutic agent that is not a compound whose structure comprises Formula II or Formula IIa is present in the combination in an amount sufficient to kill or reduce the presence, amount or growth rate of mycobacteria exposed to the substituted benzoxaborole, including *M. tuberculosis*. In one particular embodiment, the additional therapeutic agent that is not a compound whose structure comprises Formula III or Formula IIIa is present in the combination in an amount sufficient to kill or reduce the presence, amount or growth rate of mycobacteria exposed to the substituted benzoxaborole, including *M. tuberculosis*.

Additional therapeutic agent(s) in the Combination

[00185] The combinations of the invention, for example, a combination described herein, may also include an additional therapeutic agent or therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a benzoxaborole compound described herein or a pharmaceutically acceptable salt thereof, and at least one additional therapeutic agent. The invention thus provides, in a further aspect, a combination comprising a benzoxaborole compound described herein or a pharmaceutically acceptable salt thereof, and at least one additional therapeutic agent. In an exemplary embodiment, the additional therapeutic agent is an antimycobacterial agent. In one aspect, the invention comprises: a) a combination of the invention; and b) at least one additional therapeutic agent. In another exemplary embodiment, the invention comprises: a) a combination of the invention; b) a first additional therapeutic agent; and c) a second additional therapeutic agent. In another exemplary embodiment, the invention comprises: a) a combination of the invention; b) a first additional therapeutic agent; c) a second additional therapeutic agent; and d) a third additional therapeutic agent. The first additional therapeutic agent or second additional therapeutic agent or third additional therapeutic agent may be selected from the additional therapeutic agents described herein.

[00186] The combinations may conveniently be presented for use in the form of a pharmaceutical formulation. In a further aspect of the present invention there is provided a pharmaceutical combination comprising a compound whose structure comprises Formula II, or a pharmaceutically acceptable salt or solvate thereof, together with one or more additional

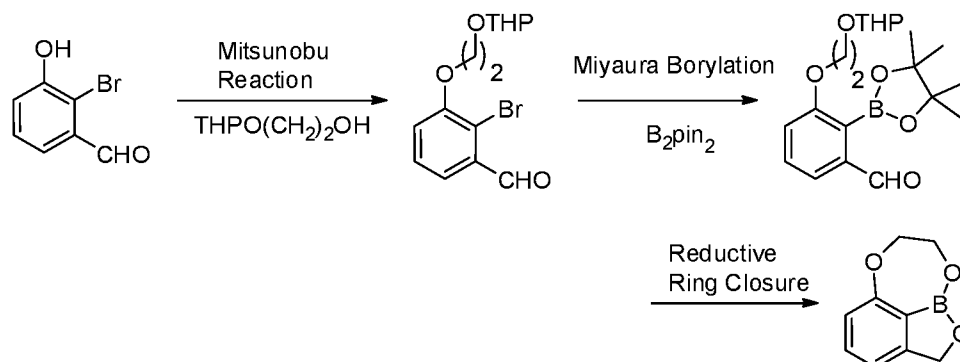
therapeutic agents, and one or more pharmaceutically acceptable carriers, excipients or diluents. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical Formulations by any convenient route.

5 **[00187]** When an additional therapeutic agent is used with a combination as described herein against the same disease state, the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art. It will be appreciated that the amount of a compound as described herein required for use in treatment will vary with the nature of the condition being treated
10 and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian.

Preparation of Boron-Containing Compounds

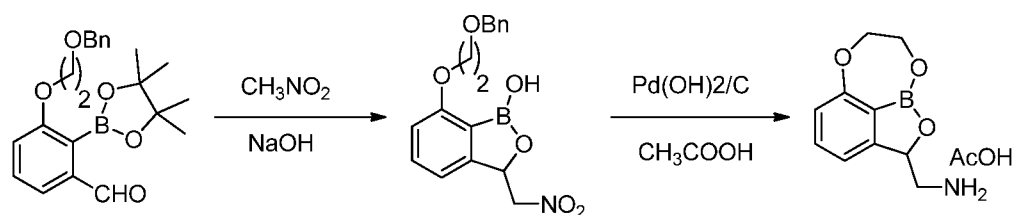
[00188] Compounds of use in the invention can be prepared using commercially available starting materials, known intermediates, or by using the synthetic
15 methods described herein, or published in references described and incorporated by reference herein, such as US Patent Nos. 7,816,344, 8,461,364, US8,703,742, 9,243,003 and continuation and divisional applications thereof; US publication numbers US20100292504, US20140315860 and applications claiming priority therefrom; and PCT published application numbers WO2008/157726, WO2010080558, WO2011127143,
20 WO2012/033858 and WO2015/021396 and applications claiming priority therefrom. The general procedures used to synthesize the compounds of Formula III and Formula IIIa, are described in the reaction Schemes below and are illustrated in the Examples.

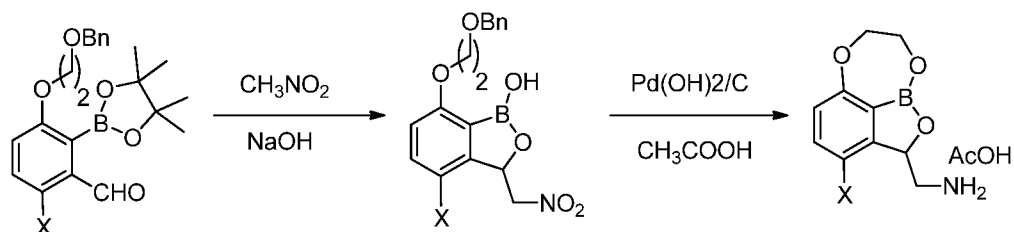
[00189] Certain benzoxaborole compounds may be prepared by a Mitsunobu reaction to convert the hydroxyl substituent of 2-bromo-3-hydroxy-benzaldehyde into the
25 tetrahydropyranyloxyethoxy ether with tetrahydropyranyloxyethanol in triphenylphosphine (PPh₃), tetrahydrofuran (THF) and diisopropyl azodicarboxylate (DIAD), followed by Miyaura borylation of the bromine substituent using bis(pinacolato)diboron (B₂pin₂) with a palladium catalyst (PdCl₂) and potassium acetate (KOAc), and then reductive ring closure to form the tricyclic compound using sodium borohydride (NaBH₄) in anhydrous methanol
30 (MeOH), as outlined in Scheme 1.

[00190] **Scheme 1**

[00191] THP-protected alkyl bromide may also be used to attach a substituent to hydroxybenzaldehyde via a $\text{S}_{\text{N}}2$ reaction to prepare benzoxaborole compounds. Examples of the use of a $\text{S}_{\text{N}}2$ reaction for preparing benzoxaborole compounds can be seen in the Examples described below, such as in Example 1, step (b) and Example 4, Method B, step (c).

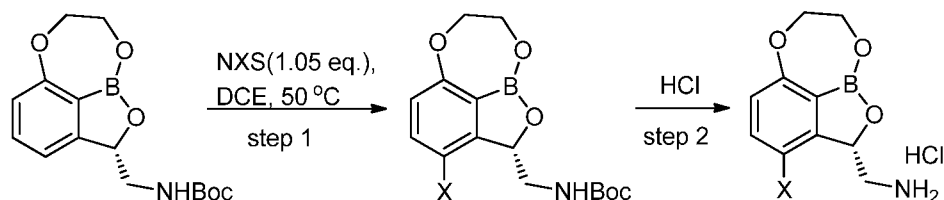
[00192] Other benzoxaborole compounds as described herein may be prepared as outlined in Schemes 2 and 3, wherein a nitro-aldol reaction is performed on the aldehyde substituent of, for example, 3-(2-benzyloxy-ethoxy)-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde using nitromethane (MeNO_2) with base (NaOH) to prepare the nitro-substituted benzyl-protected benzoxaborole compound, followed by ring-closure to and reduction of the nitro substituent to the amine with $\text{Pd}(\text{OH})_2/\text{C}$ in glacial acetic acid to form the desired benzoxaborole compound.

[00193] **Scheme 2**

[00194] **Scheme 3**

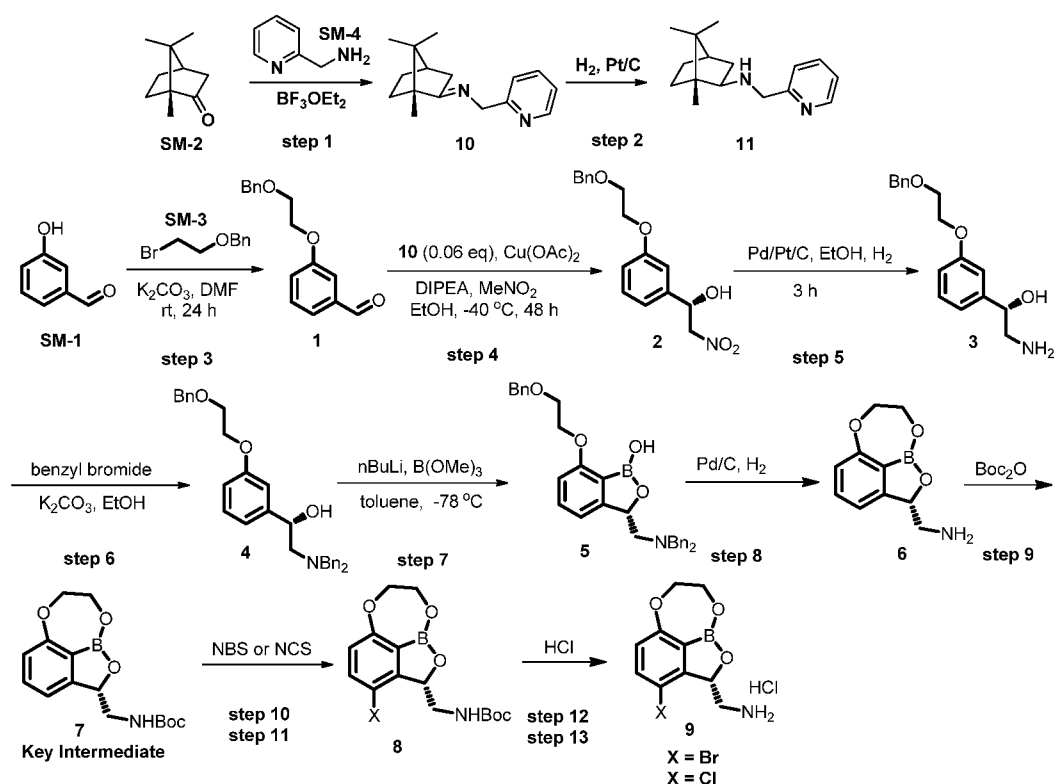
[00195] Other benzoxaborole compounds as described herein may be prepared as outlined in Scheme 4.

5

[00196] **Scheme 4**

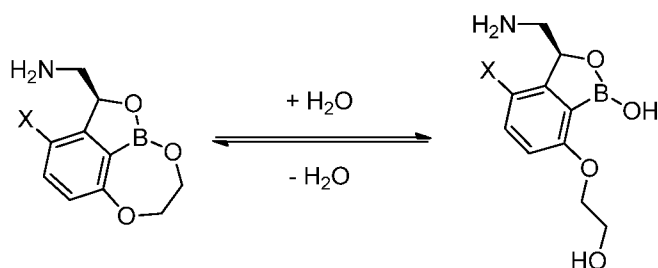
[00197] Other benzoxaborole compounds as described herein may be prepared as outlined in Scheme 5.

[00198]

Scheme 5

[00199]

Although not expressly shown, compounds 6, 7, 8 and 9 of Scheme 5 can exist in equilibrium with the corresponding open depending on the environment. Such an equilibrium is shown by example below:

**Closed Form****Open Form**

[00200]

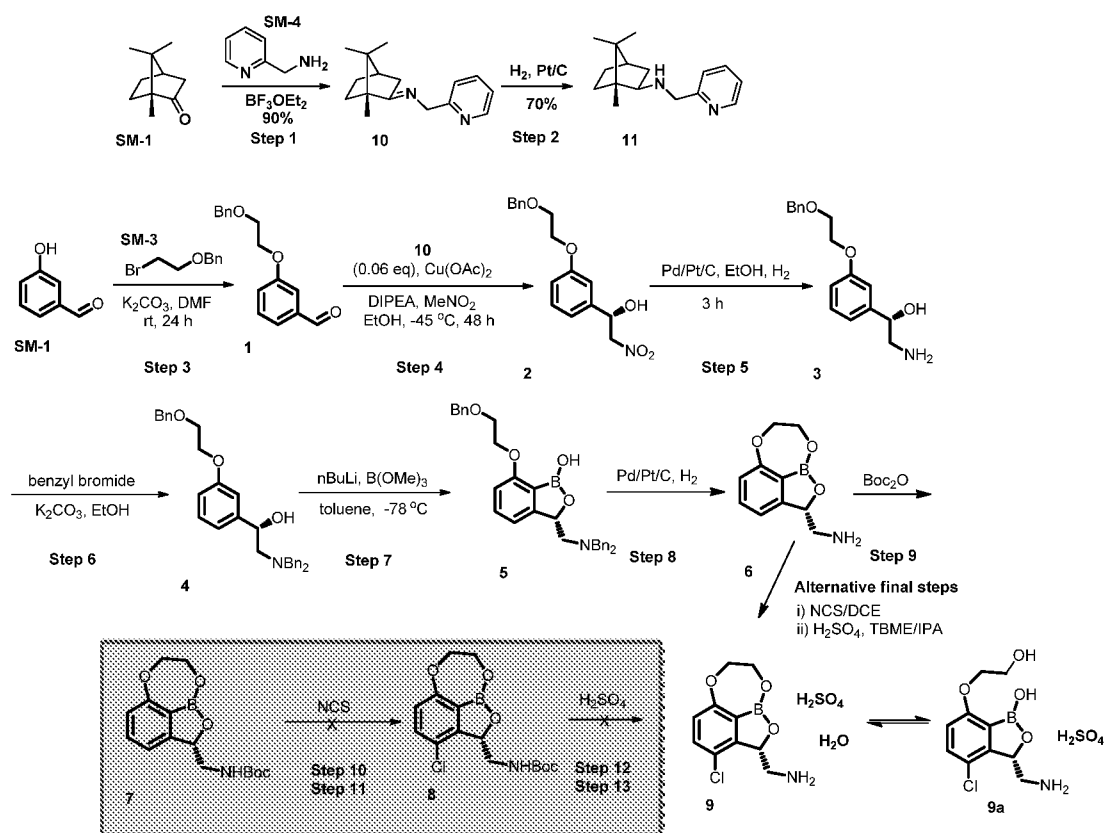
In addition, certain substituted benzoxaboroles disclosed herein have been found to exist in the open form when present in the solid state. A combination of single crystal X-ray, X-ray powder diffraction (XRPD) and solid state NMR analysis confirms that certain substituted benzoxaboroles disclosed herein exist in the open form in the solid state.

Solution state NMR studies also show that when dissolved in solution, certain substituted benzoxaborole compounds disclosed herein exist in equilibrium between the open and closed form, and that the balance of the equilibrium is affected by the solvent used and the presence of H₂O.

5 [00201] It is understood that the substituted benzoxaboroles disclosed herein, whether shown in the closed form or the open form, may exist in the closed form in organic solvents such as DMSO and CH₃OH, may exist in an equilibrium between the closed form and open form in an aqueous solvent environment, and may exist in the open form in the solid state.

10 [00202] Alternatively, certain benzoxaborole compounds may be prepared as outlined in **Scheme 6**. A mixture of (S)-*tert*-butyl ((7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methyl)carbamate (13.25 kg) and NCS (8.75 kg) in dichloroethane (132.5 L) was heated at 70 °C until the reaction judged complete by HPLC. The mixture was concentrated under reduced pressure, cooled to 25 °C and acetone (106 L) added. The
15 slurry was filtered, washing with acetone (26.5 L). The wet cake was slurried in water (13.25 L) and 1,4-dioxane (66.25 L), heated to 50 °C for 20-30 minutes, cooled to 15 °C, filtered and the cake washed with 1,4-dioxane (26.5 L). The wet cake was dissolved in methanol (68.9 L), filtered and the filtrate concentrated under reduced pressure. Methyl tertiary butyl
20 ether (66.25 L) was added to the residue and the mixture concentrated under reduced pressure. Methyl tertiary butyl ether (78.7 L), isopropanol (8.7 L) and sulphuric acid (4.6 L) were added, the mixture heated to 50 °C and stirred until the sulphate content was 24.32-29.72%. The mixture was cooled to 25 °C, stirred for 1 hour, filtered, the cake washed with methyl tertiary butyl ether (17.5 L) and dried to give the desired product (42%).

[00203] **Scheme 6**



[00204] As can be seen in **Scheme 6**, in this route the final steps 10/11 and 12/13 are replaced with alternative final steps, eliminating the protection/deprotection steps.

5 [00205] It is also noted that compounds 6, 7, 8 and 9 can exist in equilibrium with the corresponding open depending on the environment, as illustrated for compound 9.

Composition and Formulations

[00206] The compounds as described herein may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with formulation of anti-mycobacterial agents, or formulation of other anti-tubercular agents.

[00207] The compounds described herein will normally, but not necessarily, be formulated into pharmaceutical compositions prior to administration to a patient. In one aspect, the invention is directed to a pharmaceutical composition comprising a compound whose structure comprises Formula II or compound of Formula IIa, or a pharmaceutically acceptable salt. In another aspect the invention is directed to a pharmaceutical composition comprising a compound whose structure comprises Formula II or a compound whose

structure comprises Formula IIa, or a pharmaceutically acceptable salt, and one or more pharmaceutically acceptable carriers, excipients or diluents. The carrier, excipient or diluent must be "acceptable" in the sense of being compatible with the other ingredients of the Formulation and not deleterious to the recipient thereof.

5 **[00208]** The compounds described herein will normally, but not necessarily, be formulated into pharmaceutical compositions prior to administration to a patient. In one aspect, the invention is directed to a pharmaceutical composition comprising a compound whose structure comprises Formula III or Formula IIIa, or a pharmaceutically acceptable salt. In another aspect the invention is directed to a pharmaceutical composition comprising a
10 compound whose structure comprises Formula III or a compound whose structure comprises Formula IIIa, or a pharmaceutically acceptable salt, and one or more pharmaceutically acceptable carriers, excipients or diluents. The carrier, excipient or diluent must be "acceptable" in the sense of being compatible with the other ingredients of the Formulation and not deleterious to the recipient thereof.

15 **[00209]** The pharmaceutical compositions described herein include those in a form adapted for oral, or parenteral use and may be used for the treatment of a mycobacterial infection in a mammal including a human.

[00210] The pharmaceutical compositions described herein include those in a form adapted for oral, topical or parenteral use and may be used for the treatment of
20 mycobacterial infections in a mammal including a human.

[00211] The composition may be formulated for administration by any convenient route. For the treatment of tuberculosis, the compositions may be in the form of tablets, capsules, powders, granules, lozenges, aerosols or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

25 **[00212]** Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants,
30 for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations

may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example
5 almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

[00213] Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

10 [00214] For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

15 [00215] In one aspect of the invention, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are
20 prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

25 [00216] The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 20-1000 mg of the active ingredient. The dosage as employed for adult human treatment will typically range from 50 to 300 mg per day, for instance 150 to 200 mg per day depending on the
30 route and frequency of administration. Such a dosage corresponds to 0.5 to 5 mg/kg per day. Preferably the dosage is from 0.5 to 2 mg/kg per day and more preferably the dose is less than 1 mg/kg per day.

[00217] The compound whose structure comprises Formula II or Formula IIa, or a pharmaceutically acceptable pharmaceutically acceptable salt or solvate thereof, may

be the sole therapeutic agent in the compositions described herein, or it may be present in the Formulation in combination with one or more additional therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound whose structure comprises Formula II, or a pharmaceutically acceptable salt, solvate thereof
5 together with one or more additional therapeutic agents.

[00218] The compound whose structure comprises Formula III or Formula IIIa, or a pharmaceutically acceptable pharmaceutically acceptable salt or solvate thereof, may be the sole therapeutic agent in the compositions described herein, or it may be present in the formulation in combination with one or more additional therapeutic agents. The
10 invention thus provides, in a further aspect, a combination comprising a compound whose structure comprises Formula III or a compound whose structure comprises Formula IIIa, or a pharmaceutically acceptable salt, solvate thereof together with one or more additional therapeutic agents.

[00219] The one or more additional therapeutic agent is, for example, an agent
15 useful for the treatment of tuberculosis in a mammal. Examples of such therapeutic agents include, rifampin, pyrazinamide, ethambutol, moxifloxacin, rifapentine, clofazimine, bedaquiline (TMC207), nitroimidazo-oxazine PA-824, delamanid (OPC-67683), oxazolidinone such as linezolid, tedizolid, radezolid, sutezolid (PNU-100480), and posizolid (AZD-5847), EMB analogue SQ109, a benzothiazinone, a dinitrobenzamide and an antiviral
20 agent including an antiretroviral agent, or any TB agent being developed for the treatment of TB with a positive response in Phase IIa EBA trials, or any TB agent under development by the Global Alliance for Tuberculosis.

[00220] When a compound whose structure comprises Formula II or Formula IIa or a compound whose structure comprises Formula III or Formula IIIa, or a
25 pharmaceutically acceptable salt or solvate thereof, is used in combination with one or more additional therapeutic agents, the dose of the compound or agent may differ from that when the compound or agent is used alone. Appropriate doses will be readily appreciated by those skilled in the art. It will be appreciated that the amount of a compound described herein and the one or more additional therapeutic agents required for use in treatment will
30 vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian.

[00221] The combinations may conveniently be presented for use in the form of a pharmaceutical Formulation. In a further aspect of the present invention there is provided a pharmaceutical combination comprising a compound whose structure comprises
35 Formula II, or a pharmaceutically acceptable salt or solvate thereof, together with one or

more additional therapeutic agents, and one or more pharmaceutically acceptable carriers, excipients or diluents. In a further aspect of the present invention there is provided a pharmaceutical combination comprising a compound whose structure comprises Formula III or Formula IIIa, or a pharmaceutically acceptable salt or solvate thereof, together with one or more additional therapeutic agents, and one or more pharmaceutically acceptable carriers, excipients or diluents. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical Formulations by any convenient route.

[00222] When administration is sequential, either the compound of the present invention or one or more additional therapeutic agent may be administered first. When administration is simultaneous, the combination may be administered either in the same or different pharmaceutical composition. When combined in the same formulation it will be appreciated that the compound and agents must be stable and compatible with each other and the other components of the formulation. When formulated separately they may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art.

Methods of Inhibiting Bacterial Growth or Killing Bacteria

[00223] The compounds exemplified and described herein, and combinations of described compounds, are expected to exhibit potency against mycobacteria and therefore have the potential to kill mycobacteria and/or inhibit the replication of mycobacteria. The combinations as described herein are expected to exhibit potency against mycobacteria possessing resistance to standard-of-care anti-mycobacterial agents, and thus have the potential to kill mycobacteria and/or inhibit the replication of such "resistant" mycobacteria. In aspects of the invention, compounds as described herein possess a remarkable activity against a selection of drug sensitive mycobacterial isolates, including, MDR-TB (multidrug resistant TB) and XDR-TB (extensively-drug resistant TB) clinical isolates, exhibiting MIC values of $<0.32 \mu\text{M}$ and the majority have MIC values at between $0.04 - 0.08 \mu\text{M}$ in 96 isolates investigated.

[00224] A compound as described herein may be used for inhibiting or killing mycobacteria. In a further aspect, the invention provides a method of killing mycobacteria and/or inhibiting replication of mycobacteria or a method of treating a mycobacterial infection in an animal such as livestock and pets, including cattle, sheep, goats, dogs and cats, or a human, including an immune-suppressed human said method comprising: contacting the mycobacteria with an effective amount of a compound as described herein, thereby killing the

mycobacteria and/or inhibiting replication of the mycobacteria, or said method comprising administering to the animal with the mycobacterial infection a therapeutically effective amount of a pharmaceutical composition of the invention, wherein the pharmaceutical composition comprises a compound whose structure comprises Formula III or a compound
 5 whose structure comprises Formula IIIa, or a pharmaceutically acceptable salt thereof. In an exemplary embodiment, the combination is part of a pharmaceutical formulation described herein. In another exemplary embodiment, the contacting occurs under conditions which permit entry of the combination into the mycobacterium.

[00225] In a further aspect, the invention provides a method of killing
 10 mycobacteria and/or inhibiting replication of mycobacteria or a method of treating a mycobacterial infection in an animal such as livestock and pets, including cattle, sheep, goats, dogs and cats, or a human, including an immune-suppressed human said method comprising: contacting the mycobacteria with an effective amount of a compound or combination as described herein, thereby killing the mycobacteria and/or inhibiting
 15 replication of the mycobacteria, or said method comprising administering to the animal with the mycobacterial infection a therapeutically effective amount of a pharmaceutical composition of compound or a combination as described herein, wherein the pharmaceutical composition comprises a compound whose structure comprises Formula III or a compound whose structure comprises Formula IIIa, or a pharmaceutically acceptable salt thereof. In
 20 an exemplary embodiment, the combination is part of a pharmaceutical formulation described herein. In another exemplary embodiment, the contacting occurs under conditions which permit entry of the combination into the mycobacterium.

[00226] In an exemplary embodiment, the mycobacteria is killed or its replication is inhibited, or the mycobacterial infection is treated, through oral administration of
 25 a combination as described herein. In an exemplary embodiment, the mycobacteria is killed or its replication is inhibited, or the mycobacterial infection is treated, through intravenous administration of a compound or combination thereof as described herein. In an exemplary embodiment, the mycobacterium is killed or its replication is inhibited, or the mycobacterial infection is treated, through subcutaneous administration of a combination as described
 30 herein, wherein the combination comprises a compound whose structure comprises Formula II or a compound whose structure comprises Formula IIa, or wherein the combination comprises a compound whose structure comprises Formula III or a compound whose structure comprises Formula IIIa, or a pharmaceutically acceptable salt thereof.

[00227] In exemplary embodiments, the mycobacteria is contacted or the
 35 mycobacterial infection is treated with a combination as described herein comprising a first

therapeutic agent that is a compound whose structure comprises Formula II or a compound whose structure comprises Formula IIa or a salt thereof, or the mycobacterial infection is treated with a combination whose structure comprises Formula III or a compound whose structure comprises Formula IIIa or salt thereof, and optionally comprising a second, third, fourth, fifth and sixth therapeutic agent in a population of mycobacteria comprising a resistant mycobacterium with a mutation conferring resistance to any one or more of the optional second, third, fourth, fifth and sixth therapeutic agent. In related embodiments, the optional second, third, fourth, fifth and sixth therapeutic agent, or a salt thereof, is an anti-mycobacterial agent, particularly a known anti-mycobacterial agent, more preferably a standard-of-care anti-mycobacterial agent.

[00228] In another exemplary embodiment, there is provided a method of killing and/or inhibiting replication of mycobacteria that causes or is associated with a disease in an animal, or a method of treating a mycobacterial infection in an animal, the method comprising contacting the mycobacteria with an effective amount of a compound whose structure comprises Formula II or Formula IIa or a salt thereof, or contacting the mycobacteria with an effective amount of a compound whose structure comprises Formula III or Formula IIIa or salt thereof, so as to kill and/or prevent replication of the mycobacterium, or administering to the animal a therapeutically effective amount of a compound whose structure comprises Formula II or Formula IIa or a salt thereof, wherein the mycobacteria is selected from *Mycobacterium tuberculosis*, *Mycobacterium avium* including subspecies (subsp.) *Mycobacterium avium subsp. avium*, *Mycobacterium avium subsp. hominissuis*, *Mycobacterium avium subsp. silvaticum*, and *Mycobacterium avium subsp. paratuberculosis*; *Mycobacterium balnei*, *Mycobacterium sherrisii*, *Mycobacterium africanum*, *Mycobacterium microti*, *Mycobacterium silvaticum*, *Mycobacterium colombiense*, *Mycobacterium indicus pranii*, *Mycobacterium gastri*, *Mycobacterium gordonae*, *Mycobacterium hiberniae*, *Mycobacterium nonchromogenicum*, *Mycobacterium terrae*, *Mycobacterium trivial*, *Mycobacterium kansasii*, *Mycobacterium malmoeense*, *Mycobacterium simiae*, *Mycobacterium triplex*, *Mycobacterium genavense*, *Mycobacterium florentinum*, *Mycobacterium lentiflavum*, *Mycobacterium palustre*, *Mycobacterium kubicae*, *Mycobacterium parascrofulaceum*, *Mycobacterium heidelbergense*, *Mycobacterium interjectum*, *Mycobacterium szulgai*, *Mycobacterium branderi*, *Mycobacterium cookie*, *Mycobacterium celatum*, *Mycobacterium bohemicum*, *Mycobacterium haemophilum*, *Mycobacterium lepraemurium*, *Mycobacterium lepromatosis*, *Mycobacterium botniense*, *Mycobacterium chimaera*, *Mycobacterium conspicuum*, *Mycobacterium doricum*, *Mycobacterium forcinogenes*, *Mycobacterium heckeshornense*, *Mycobacterium lacus*,

Mycobacterium monacense, *Mycobacterium montefiorensense*, *Mycobacterium murale*,
Mycobacterium nebraskense, *Mycobacterium saskatchewanense*, *Mycobacterium*
scrofulaceum, *Mycobacterium shimoidel*, *Mycobacterium tusciae*, *Mycobacterium xenopi*,
5 *Mycobacterium fortuitum* subsp. *acetamidolyticum*, *Mycobacterium boenickei*,
Mycobacterium perigrinum, *Mycobacterium porcinum*, *Mycobacterium senegalense*,
Mycobacterium septicum, *Mycobacterium neworleansense*, *Mycobacterium houstonense*,
Mycobacterium mucogenicum, *Mycobacterium mageritense*, *Mycobacterium brisbanense*,
Mycobacterium cosmeticum, *Mycobacterium parafortuitum*, *Mycobacterium austroafricanum*,
10 *Mycobacterium diernhoferi*, *Mycobacterium hodieri*, *Mycobacterium neoaurum*,
Mycobacterium prederkisbergense, *Mycobacterium aurum*, *Mycobacterium vaccae*,
Mycobacterium chitae, *Mycobacterium fallax*, *Mycobacterium confluentis*, *Mycobacterium*
flavescens, *Mycobacterium madagascariense*, *Mycobacterium phlei*, *Mycobacterium*
smegmatis, *Mycobacterium goodii*, *Mycobacterium colinskii*, *Mycobacterium*
15 *thermoresistibile*, *Mycobacterium gadium*, *Mycobacterium kormossense*, *Mycobacterium*
obuense, *Mycobacterium sphagni*, *Mycobacterium agri*, *Mycobacterium aichiense*,
Mycobacterium alvei, *Mycobacterium arupense*, *Mycobacterium brumae*, *Mycobacterium*
canariense, *Mycobacterium chubuense*, *Mycobacterium conceptionense*, *Mycobacterium*
duvalii, *Mycobacterium elephantis*, *Mycobacterium gilvum*, *Mycobacterium hassiacum*,
20 *Mycobacterium holsaticum*, *Mycobacterium immunogenum*, *Mycobacterium massiliense*,
Mycobacterium moriokaense, *Mycobacterium psychrotolerans*, *Mycobacterium*
pyrenivorans, *Mycobacterium vanbaalenii*, *Mycobacterium pulveris*, *Mycobacterium*
arosiense, *Mycobacterium aubagnense*, *Mycobacterium caprae*, *Mycobacterium*
chlorophenolicum, *Mycobacterium fluoroanthenvivorans*, *Mycobacterium kumamotoense*,
25 *Mycobacterium novocastrense*, *Mycobacterium parmense*, *Mycobacterium phocaicum*,
Mycobacterium poriferae, *Mycobacterium rhodesiae*, *Mycobacterium seolense*,
Mycobacterium tokalense, *Mycobacterium xenopi*; *Mycobacterium scrofulaceum*;
Mycobacterium abscessus; *Mycobacterium chelonae*; *Mycobacterium haemophilum*;
Mycobacterium leprae; *Mycobacterium marinum*; *Mycobacterium fortuitum*; *Mycobacterium*
30 *bovis*; *Mycobacterium ulcerans*; *Mycobacterium pseudoshottsii*, *Mycobacterium shottsii*,
Mycobacterium intracellulare; *Mycobacterium tuberculosis* complex (MTC); *Mycobacterium*
avian-intracellulare complex (MAIC) member and *Mycobacterium avium* complex (MAC)
member.

[00229] In related aspects, the mycobacterium is *Mycobacterium tuberculosis*.
35 In other aspects, the mycobacterium is *Mycobacterium avium*, *Mycobacterium kansasii*,

Mycobacterium malmoeense, *Mycobacterium simiae*, *Mycobacterium szulgai*, *Mycobacterium xenopi*, *Mycobacterium scrofulaceum*, *Mycobacterium abscessus*, *Mycobacterium chelonae*, *Mycobacterium haemophilum*, *Mycobacterium leprae*, *Mycobacterium marinum*, *M. fortuitum*, *Mycobacterium bovis*, *M. bovis BCG*, *M. africanum*, *M. canetti*, *M. caprae*, *M. microti*, *M. pinnipedi*, *M. leprae* or *Mycobacterium ulcerans*. In related embodiments, the mycobacterium is a subspecies (subsp.) of *Mycobacterium avium*, including *Mycobacterium avium subsp. avium*, *Mycobacterium avium subsp. hominissuis*, *Mycobacterium avium subsp. silvaticum*, and *Mycobacterium avium subsp. paratuberculosis*. In another related embodiment, the mycobacterium is *Mycobacterium intracellulare*. In further related
 10 embodiments, the mycobacterium is a member of the *Mycobacterium tuberculosis* complex. (MTC) the *Mycobacterium avium* complex (MAC) or the *Mycobacterium avian-intracellulare* complex (MAIC). In related embodiments, the mycobacterium is a non-tuberculosis complex or clade, including: *Mycobacterium avium* complex; *Mycobacterium gordonae* clade; *Mycobacterium kansasii* clade; *Mycobacterium chelonae* clade; *Mycobacterium fortuitum*
 15 clade; *Mycobacterium parafortuitum* clade; and *Mycobacterium vaccae* clade.

[00230] In an exemplary embodiment, the mycobacteria in the methods described herein comprises a resistant mycobacterium. In an exemplary embodiment, the resistant mycobacterium is a mutation of a mycobacteria described herein.

Methods of Treating and/or Preventing Disease

20 [00231] The combinations of the present invention exhibit potency against mycobacteria, and therefore have the potential to achieve therapeutic efficacy in animals, including humans.

[00232] In another aspect, the invention provides a method of treating and/or preventing a disease. The method includes administering to the animal a therapeutically
 25 effective amount of a compound as described herein, or a combination thereof, sufficient to treat and/or prevent the disease. In an exemplary embodiment, the compound or the combination described herein can be used in human or veterinary medical therapy, particularly in the treatment or prophylaxis of mycobacterial-associated disease. In an exemplary embodiment, the combination is described herein.

30 [00233] In another exemplary embodiment, the animal is as defined herein. In another exemplary embodiment, the disease is a systemic disease or a cutaneous disease. In another exemplary embodiment, the disease is a respiratory disease.

Abbreviations

[00234] In describing the invention, chemical elements are identified in accordance with the Periodic Table of the Elements. Abbreviations and symbols utilized herein are in accordance with the common usage of such abbreviations and symbols by those skilled in the chemical arts. The following abbreviations are used herein:

	AcOH	acetic acid
	Ac ₂ O	acetic anhydride
	AIBN	2-2'-Azobisisobutyronitrile
10	BOC	N-tert-butoxycarbonyl
	BOC anhydride	di- <i>tert</i> -butyl dicarbonate
	B ₂ pin ₂	bis(pinacolato)diboron diboron, also known as
		4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane
15	Celite®	a filter aid composed of acid-washed diatomaceous silica, (a trademark of Manville Corp., Denver, Colorado)
	CD ₃ OD	deuterated methanol
	CTAB	cetyltrimethylammonium bromide
	DCM	dichloromethane
	DIAD	diisopropyl azodicarboxylate
20	DIBAL-H	diisobutyl aluminium hydride
	DME	dimethoxyethane
	DCE	dichloroethane
	DMF	dimethylformamide
	DMSO-d ₆	deuterated dimethylsulfoxide
25	DMSO	dimethylsulfoxide
	ESI	Electrospray ionization
	ES MS	Electrospray mass spectrometry
	Et ₂ O	diethyl ether
	EtOH	ethanol
30	EtOAc, EA	ethyl acetate
	h	hours
	HPLC	high performance liquid chromatography
	KOAc	potassium acetate
	LCMS	Liquid chromatography mass spectroscopy
35	mCPBA	meta-chloro perbenzoic acid
	MeNO ₂	nitromethane
	MeOH	methanol
	NBS	N-bromosuccinimide
	NCS	N-chlorosuccinimide
40	NIS	N-iodosuccinimide

	NXS	N-halosuccinimide
	NaBH(OAc) ₃	sodium triacetoxyborohydride
	NMR	Nuclear Magnetic Resonance spectroscopy
	PE	petroleum ether
5	PPh ₃	triphenylphosphine
	rt or r.t.	room temperature
	RT	retention time
	SFC	supercritical fluid chromatography
	t-BuOMe	methyl t-butyl ether
10	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	uv	ultraviolet

15 EXAMPLES

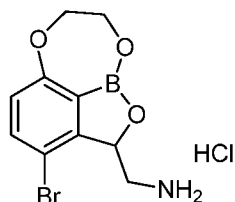
[00235] The following examples illustrate the invention. These Examples are not intended to limit the scope of the invention, but rather to provide guidance to the skilled artisan to prepare and use the compounds, compositions, and methods of the invention. While particular embodiments of the invention are described, the skilled artisan will appreciate that various changes and modifications can be made. References to preparations carried out in a similar manner to, or by the general method of, other preparations, may encompass variations in routine parameters such as time, temperature, workup conditions, minor changes in reagent amounts etc.

[00236] Proton nuclear magnetic resonance (¹H NMR) spectra were recorded, and chemical shifts are reported in parts per million (δ) downfield from the internal standard tetramethylsilane (TMS). Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. Mass spectra were obtained using electrospray (ES) ionization techniques. All temperatures are reported in degrees centigrade.

[00237] Reactions involving metal hydrides including lithium hydride, lithium aluminium hydride, di-isobutylaluminium hydride, sodium hydride, sodium borohydride and sodium triacetoxyborohydride are carried out under argon unless otherwise specified.

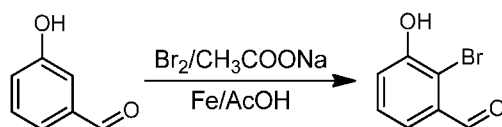
SYNTHESIS

[00238] **Example 1 3-bromo-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methanamine hydrochloride (G1-Br)**



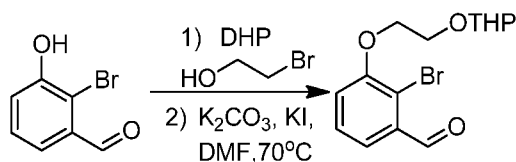
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[00239] **(a) 2-bromo-3-hydroxybenzaldehyde**



[00240] A suspension of 3-hydroxybenzaldehyde (5 g, 40 mmol), iron powder (172 mg, 3 mmol) and sodium acetate (6.72 g, 80 mmol) in acetic acid (40 mL) was warmed until a clear solution was obtained and then cooled to room temperature. To this mixture was added dropwise a solution of bromine (7.2 g, 45 mmol) in glacial acetic acid (10 mL) over 15 min. After the addition, the reaction mixture was stirred for 2 h and then poured into ice-water. The resulting mixture was extracted with dichloromethane (3×50 mL). The combined extracts were dried over anhydrous Na₂SO₄ and concentrated. The residue was re-crystallized from dichloromethane to afford the product (2.3 g, 28%). ¹H NMR (300 MHz, DMSO-*d*₆): δ 10.75 (s, 1H), 10.26 (s, 1H), 7.38-7.24 (m, 3H).

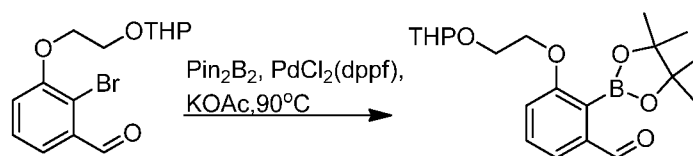
[00241] **(b) 2-bromo-3-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)benzaldehyde**



[00242] Dihydropyran (1.26 g, 15 mmol) was added dropwise at 0°C to 2-bromoethanol (1.875 g, 15 mmol). The mixture was stirred 30 min at 0°C and then 2h at rt. 2-bromo-3-hydroxy benzaldehyde (2 g, 10 mmol) was added to this mixture, followed by potassium carbonate (1.518 g, 11 mmol), potassium iodide (332 mg, 2 mmol) and dry DMF

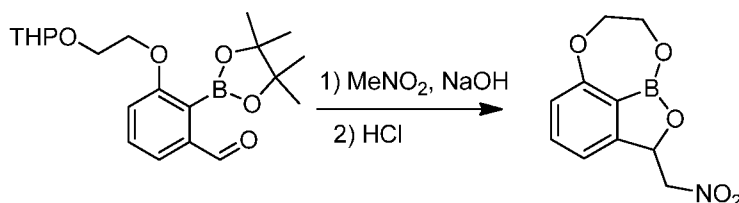
(20 mL). The reaction was stirred at 70°C overnight. The solution was cooled to rt and diluted with diethyl ether (100 mL). The inorganic salts were removed by filtration and the filtrate was diluted with hexanes (100 mL). The organic layer was washed with water (50 mL×3), and then concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate and petroleum ether as eluents to give the target compound (3 g, 92%) as a yellow oil. MS (ESI) m/z =351 $[M+23]^+$, Rf=0.7 (PE:EA=3). 1H NMR (300 MHz, DMSO- d_6): δ 10.29 (s, 1H), 7.50-7.41 (m, 3H), 4.75 (s, 1H), 4.31-4.28 (m, 2H), 4.00-3.94 (m, 1H), 3.82-3.75 (m, 2H), 3.47-3.43 (m, 1H), 1.73-1.50 (m, 6H).

10 [00243] (c) 3-((2-(tetrahydro-2H-pyran-2-yl)oxy)ethoxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde



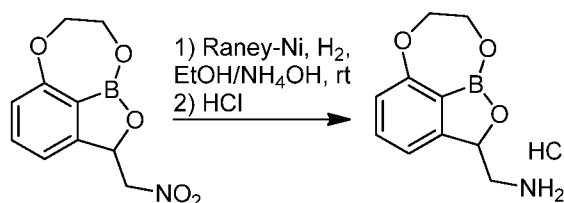
15 [00244] A solution of 2-bromo-3-(2-(tetrahydro-2H-pyran-2-yloxy)ethoxy)benzaldehyde (160 g, 0.49 mol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (249 g, 0.98 mol), Pd(dppf)Cl₂ (20 g, 24.5 mmol) and KOAc (144 g, 1.47 mol) in DMF (2.0 L) was stirred at 90°C overnight. Then the reaction mixture was treated with water (4 L) and then extracted with EtOAc (3×1.5 L). The combined organic layers were washed with brine (250 mL), dried over anhydrous Na₂SO₄ and concentrated to dryness in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether: ethyl acetate =10:1 to 2:1) to give the target compound as a yellow oil (88 g, yield 48%). MS (ESI) m/z =317 $[M+H]^+$, Rf=0.4 (PE:EA=3). 1H NMR (300 MHz, DMSO- d_6): δ 9.88 (s, 1H), 7.60-7.51 (m, 2H), 7.31-7.28 (d, 1H), 4.64-4.63 (m, 1H), 4.16-4.13 (m, 2H), 4.00-3.94 (m, 1H), 3.82-3.75 (m, 2H), 3.47-3.43 (m, 1H), 1.73-1.50 (m, 6H), 1.29 (m, 12H).

25 [00245] (d) 2-(nitromethyl)-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulene



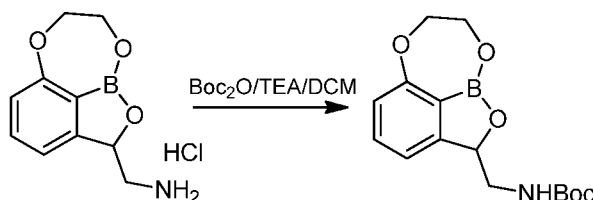
[00246] To a solution of NaOH (4.8 g, 0.12 mol) in water (100 mL) was added nitromethane (18.3 g, 0.3 mol) at 5-10 °C. After stirring for 15 min at 5-10 °C, cetyltrimethylammonium bromide (CTAB) (2.2 g, 6 mmol) was added to the reaction mixture and followed by the addition of 3-(2-(tetrahydro-2H-pyran-2-yloxy)ethoxy)- 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (45 g, 0.12 mol) at 5-10 °C. The reaction mixture was stirred at rt for 5 h. The reaction mixture was acidified to pH=1 using diluted hydrochloric acid and stirred at rt overnight. The reaction mixture was filtered to give the target compound (14.5 g, 51%) as a white solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.50-7.45 (t, 1H), 7.16-7.13 (d, 1H), 6.91-6.88 (d, 1H), 5.91-5.88 (m, 1H), 5.37-5.31 (m, 1H), 4.69-4.61 (m, 2H), 4.41-4.14 (m, 3H).

[00247] (e) (7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methanamine hydrochloride



[00248] A solution of 2-(nitromethyl)-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulene (1.5 g, 6.4 mmol), Raney Ni (200 mg) and 2 M NH₃ in EtOH (5 mL) in ethanol (40 mL) was shaken under an atmosphere of H₂ for 2 h at rt. The mixture was filtered through a bed of Celite and the filtrate was concentrated in vacuo. The crude amine was dissolved in EtOH (20 mL) and a saturated solution of HCl (gas) in Et₂O (30 mL) was added immediately. After 1 h, the suspension was filtered and the resulting solid was washed with acetonitrile/hexanes (2:1, 2×20 mL) to give the compound as a white solid (700 mg, 45%). MS (ESI) *m/z* = 206/224 [M+H]⁺.

[00249] (f) *tert*-butyl ((7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate

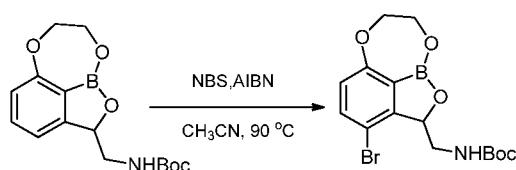


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[00250] To a mixture of (7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methanamine hydrochloride (700 mg, 2.9 mmol) and triethylamine (878.7 mg, 8.7 mmol)

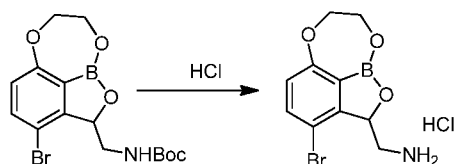
in dichloromethane (10 mL) at 0°C was added di-*tert*-butyl dicarbonate (948 mg, 4.35 mmol) and the mixture was stirred for 2 h at room temperature. The reaction was quenched with sat. NaHCO₃ (15 mL) and the resulting mixture was extracted with EtOAc (3×20 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by flash-column chromatography using ethyl acetate and petroleum ether as eluents to give the desired product (500 mg, 56%). MS (ESI) m/z = 250 [M-56]⁺.

[00251] (g) *tert*-butyl ((3-bromo-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methyl)carbamate



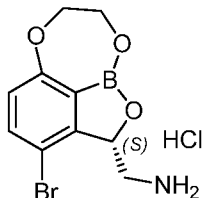
[00252] To a solution of *tert*-butyl ((7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methyl)carbamate (0.5 mg, 1.64 mmol) and NBS (354 mg, 2.0 mmol) in acetonitrile (15 mL) was added AIBN (27 mg) and the mixture was stirred for 1 h at 90°C. The reaction mixture was then concentrated under vacuum and the residue was purified by preparatory-HPLC to give the desired product (300 mg, 50%). MS (ESI) m/z = 328/330 [M -56]⁺.

[00253] (h) Title compound



[00254] A mixture of *tert*-butyl ((3-bromo-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methyl)carbamate (0.2 g, 0.522 mmol) in saturated HCl (gas) in Et₂O (10 mL) was stirred at rt for 1 h and concentrated to dryness (water bath temperature < 30°C). The residue was triturated with acetonitrile (2×5 mL) and the white solid was dried under high vacuum to give the product (140 mg, 83%) as a white solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.36 (s, 3H), 7.64-7.61 (d, 1H), 6.93-6.90 (d, 1H), 5.51-5.49 (d, 1H), 4.69 (m, 1H), 4.36-4.23 (m, 3H), 3.62 (m, 1H), 3.05-3.01 (m, 1H). MS (ESI) m/z = 284/286 [M + H]⁺.

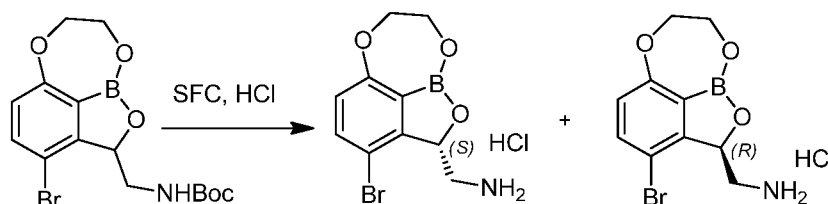
[00255] **Example 2 (S)-(3-bromo-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methanamine hydrochloride (G2-Br)**



Method A

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[00256] **(a) Title compound**



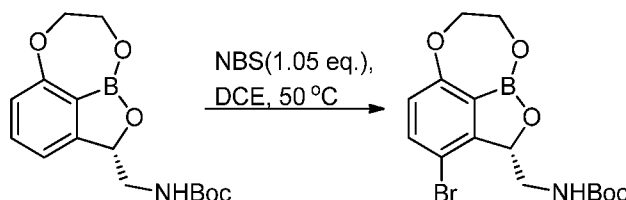
[00257] The racemic compound *tert*-butyl((3-bromo-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methyl)carbamate (Example 1, (g)) was separated via
 10 supercritical fluid chromatography (SFC) (chiral column CHIRALCEL OJ-H, eluted with MeOH (15%) and CO₂ (85%) and two chiral compounds (S)-*tert*-butyl ((3-bromo-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methyl)carbamate (second eluting isomer, RT= 3.8 min) and (R)-isomer *tert*-butyl ((3-bromo-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methyl)carbamate (first eluting isomer, RT=3.3 min) were
 15 obtained. Each of the chiral compounds (1.2 g, 3.13 mmol) in saturated HCl (gas) in Et₂O (20 mL) was stirred at room temperature for 1 h and concentrated to dryness (water bath < 30°C). The residue was washed with acetonitrile (2×5 mL) and the white solid was dried under high vacuum to give the product (900 mg, 90%) as a white solid. MS (ESI) *m/z* = 284/286 [M + H]⁺.

20 **(S)-(3-bromo-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methanamine hydrochloride:** ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.40 (s, 3H), 7.63-7.61 (d, 1H), 6.92-6.89 (d, 1H), 5.50-5.48 (d, 1H), 4.68 (m, 1H), 4.35-4.22 (m, 3H), 3.60 (m, 1H), 3.00 (m, 1H).

(R)-(3-bromo-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methanamine hydrochloride: ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.30 (s, 3H), 7.64-7.61 (d, 1H), 6.93-6.90
 25 (d, 1H), 5.51-5.49 (d, 1H), 4.68 (m, 1H), 4.36-4.23 (m, 3H), 3.61 (m, 1H), 3.05-3.01 (m, 1H).

Method B

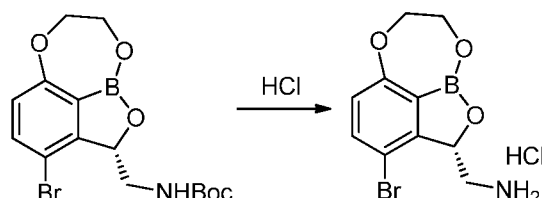
[00258] (a) (S)-*tert*-butyl ((3-bromo-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate



5

[00259] A mixture of (S)-*tert*-butyl ((7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate (110.0 g, 360.50 mmol) (Example 4, Method B, (h)) and NBS (67.4 g, 378.53 mmol) in DCE (1.1 L) was heated at 50°C for 6 h. The solution was washed with hot water (1 L) three times and the organic solution was concentrated under vacuum to obtain the desired product (132.0 g, crude) as a yellow gum (used in next step without purification). ¹H NMR (400 MHz, DMSO-*d*₆): 7.57-7.55 (d, J=8 Hz, 1H), 6.96 (s, 1H), 6.85-6.83 (d, J=8 Hz, 1H), 5.25 (m, 1H), 4.71-4.69 (m, 1H), 4.34-4.07 (m, 3H), 3.76-3.69 (m, 1H), 3.17-3.16(m, 1H), 1.33 (s, 9H). LC-MS: [M-55] = 327.8.

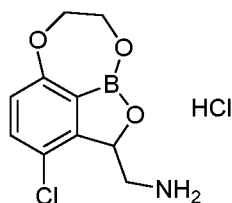
15 [00260] (b) Title compound



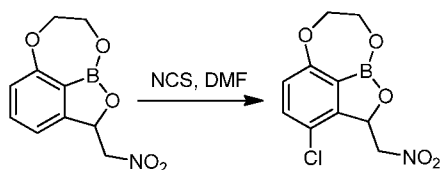
[00261] A solution of (S)-*tert*-butyl ((3-bromo-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate (130.0 g, crude) and conc. HCl (100 mL) in 1,4-dioxane (500 mL) was stirred at r.t. for 8 h, during which time colorless solids were precipitated and filtered and washed with 2-propanol (200 mL). The solid was dried under vacuum at 50°C for 6 h to obtain the hydrochloride salt of desired product (60.0 g, 51.9% total yield over two steps) as a colorless solid. ¹H NMR (400 MHz, DMSO-*d*₆): 8.45 (s, 3H), 7.64-7.62 (d, J=8, 1H), 6.92-6.90 (d, J=8, 1H), 5.52 (m, 1H), 4.69 (m, 1H), 4.37-4.15 (m, 3H), 3.74-3.50 (m, 1H), 3.05-2.95 (m, 1H). ¹³C NMR (400 MHz, DMSO-*d*₆): 161.80, 151.28, 137.57, 118.64, 107.18, 80.04, 73.86, 69.18, 41.88. LC-MS: [M+1]⁺ = 283.9.

25

[00262] Example 3 3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methanamine hydrochloride (G3-Cl)



(a) 3-chloro-2-(nitromethyl)-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocdazulene

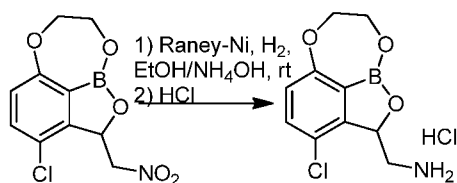


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[00263] To a solution of 2-(nitromethyl)-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocdazulene (29 g, 123.4 mmol) (Example 1, (d)) in DMF (250 mL) at 80°C was added a solution of NCS (16.5 g, 123.4 mmol) in DMF (100 mL). The mixture was stirred for 30 min at 80°C. The reaction mixture was poured into ice-water and extracted with EtOAc (200 mL×3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by re-crystallization from petroleum ether/ethyl acetate (10:1) to give 24 g of crude product. MS (ESI) m/z = 270 [M + H]⁺. ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.52-7.49 (d, 1H), 6.99-6.96 (d, 1H), 5.96-5.93 (m, 1H), 5.42-5.30 (m, 1H), 4.80-4.61 (m, 2H), 4.43-4.17 (m, 3H).

15

[00264] (b) Title compound

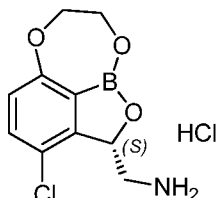


[00265] A solution of 3-chloro-2-(nitromethyl)-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocdazulene (24 g, 89.22 mmol), Raney Ni (4.0 g) and 7 M NH₃ in MeOH (20 mL) in methanol (300 mL) was shaken under an atmosphere of H₂ for 2 h at rt. The mixture was filtered through a bed of Celite and the filtrate was concentrated under vacuum. The crude amine was dissolved in MeOH (20 mL) and concentrated HCl (5 mL) was added. The resulting mixture was stirred at rt for 1 h and then concentrated under reduced pressure. The resulting solid was washed with acetonitrile/hexanes (2:1, 2×200 mL) to give the desired product (12 g, 50%) as a white solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.19 (s, 3H), 7.51-

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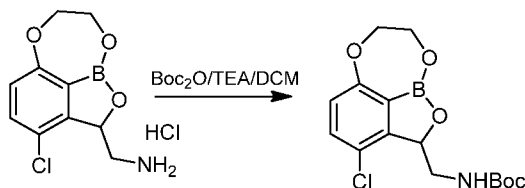
7.48 (d, 1H), 6.99-6.96 (d, 1H), 5.56-5.54 (d, 1H), 4.69 (m, 1H), 4.36-4.23 (m, 3H), 3.58 (m, 1H), 3.05-3.01 (m, 1H). MS (ESI) m/z = 240 $[M + H]^+$.

[00266] Example 4-I (S)-(3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methanamine hydrochloride (G4-Cl)



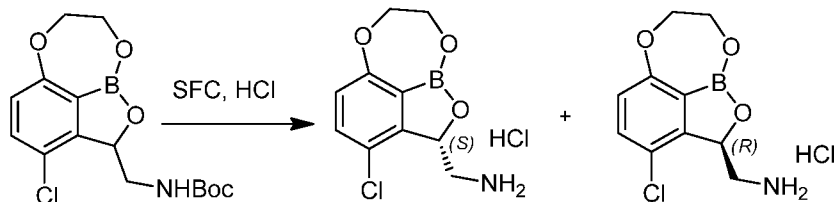
Method A

[00267] (a) *tert*-butyl ((3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate



[00268] To a mixture of (3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methanamine hydrochloride (8.0 g, 33.7 mmol) (Example 3,(b)) and triethylamine (10.2 g, 101.2 mmol) in dichloromethane (250 mL) at 0°C was added di-*tert*-butyl dicarbonate (11 g, 50.6 mmol) and the mixture was stirred for 2 h at rt. The reaction was quenched with sat. NaHCO₃ (150 mL) and the resulting mixture was extracted with EtOAc (2×200 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified by preparative-HPLC using Daisogel 10μ C18 column (250 x 50 mm) and eluted with gradient water/acetonitrile (0.05% TFA) to give the desired product (4.6 g, 47%). MS (ESI) m/z = 284 $[M-56]^+$.

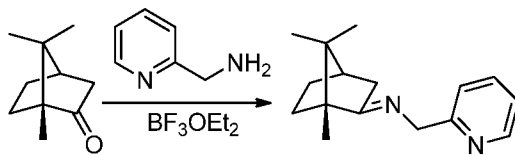
[00269] (b) Title compound



- [00270] The racemic compound *tert*-butyl ((3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methyl)carbamate was separated via SFC (chiral column CHIRALCEL OJ-H) eluted with EtOH (15%) and CO₂ (85%) and the two chiral compounds (S)-*tert*-butyl ((3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methyl)carbamate (second eluting isomer, RT = 2.9 min) and (R)-*tert*-butyl((3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methyl)carbamate (first eluting isomer, RT = 2.6 min) were obtained. Each of the chiral compounds (4.6 g, 13.6 mmol) was stirred at rt in 80 mL of saturated HCl (gas) in Et₂O for 1 h and concentrated to dryness (water bath temperature < 30°C). The residue was triturated with acetonitrile (2×5 mL) and the white solid was dried under high vacuum to give the two products (S)-(3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methanamine hydrochloride (1.2 g) and (R)-(3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methanamine hydrochloride (2.3 g) respectively as white solids. MS (ESI) *m/z* = 240 [M + H]⁺.
- 15 (S)-(3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methanamine hydrochloride: ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.30 (s, 3H), 7.51-7.48 (d, 1H), 6.99-6.96 (d, 1H), 5.59-5.57 (d, 1H), 4.68 (m, 1H), 4.36-4.23 (m, 3H), 3.58 (s, 1H), 3.03-2.99 (m, 1H).
- G4-Cl-(R) (R)-(3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methanamine hydrochloride: ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.28 (s, 3H), 7.51-7.48 (d, 1H), 6.99-6.96 (d, 1H), 5.58-5.56 (d, 1H), 4.69 (m, 1H), 4.36-4.23 (m, 3H), 3.59 (m, 1H), 3.05-3.01 (m, 1H).
- 20

Method B

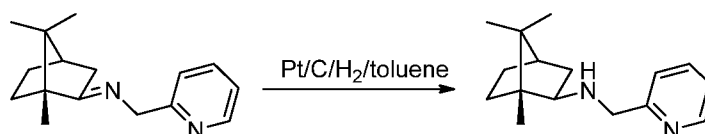
- [00271] (a) (Z)-1-(pyridin-2-yl)-N-((1R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)methanamine
- 25



- [00272] A mixture of (+)-camphor (371 g, 2.44 mol), pyridin-2-ylmethanamine (277 g, 2.56 mol) and BF₃·Et₂O (17 g, 0.12 mol) in toluene (3.7 L) was charged into a 5 L round bottom flask equipped with a Dean Stark trap, reflux condenser, thermometer and nitrogen inlet. The mixture was heated to reflux with azeotropic removal of water for 20 h. The mixture was cooled to 15 °C and quenched with 5% aqueous sodium bicarbonate (2.5
- 30

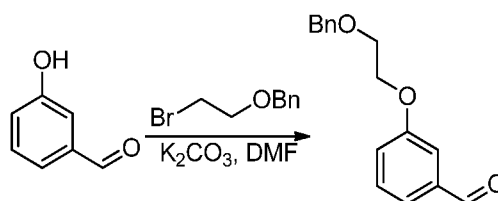
L), the organic phase was separated and washed with water (1.25 L \times 2), then the mixture was concentrated down to 2 L under vacuum. The residue was used in next step without purification. ^1H NMR (400 MHz, $\text{DMSO-}d_6$): 8.47-8.48 (d, J = 4.4 Hz, 1H), 8.77-8.74 (t, J = 7.6 Hz, 1H), 7.43-7.41 (d, J = 8.0 Hz, 1H), 7.25-7.22 (dd, J = 4.8 Hz, 1H), 4.49-4.38 (dd, J = 16.4 Hz, 2H), 2.46-2.42 (m, 1H), 1.97-1.93 (m, 2H), 1.84-1.79 (m, 1H), 1.71-1.64 (m, 1H), 1.33-1.22 (m, 2H), 0.93 (s, 3H), 0.92 (s, 3H), 0.73 (s, 3H). LCMS: $[\text{M}+\text{H}]^+ = 243$.

[00273] (b) (1*R*)-1,7,7-trimethyl-N-(pyridin-2-ylmethyl)bicyclo[2.2.1]heptan-2-amine



[00274] 5% Pt/C (40 g) was charged into a 5 L pressure vessel, followed by a solution of (Z)-1-(pyridin-2-yl)-N-((1*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)methanamine (2.44 mol) in toluene (2 L). The vessel was pressurized with 100 psi hydrogen for a period of 12 h. The solid was filtered through Celite[®] and the cake was washed with toluene (1 L). The filtrate was concentrated under vacuum to obtain the desired product (435 g obtained, total yield: 73%, over two steps) as a pale yellow oil. ^1H NMR (400 MHz, $\text{DMSO-}d_6$): 8.49-8.48 (d, J = 4.8 Hz, 1H), 7.75-7.71 (t, J = 7.6 Hz, 1H), 7.40-7.38 (d, J = 7.6 Hz, 1H), 7.24-7.21 (dd, J = 5.2 Hz, 1H), 3.79-3.64 (dd, J = 14.4 Hz, 2H), 2.53-2.49 (m, 1H), 1.99 (s, 1H), 1.68-1.42 (m, 5H), 1.05 (s, 3H), 0.87 (s, 3H), 0.78 (s, 3H). LCMS: $[\text{M}+\text{H}]^+ = 245$.

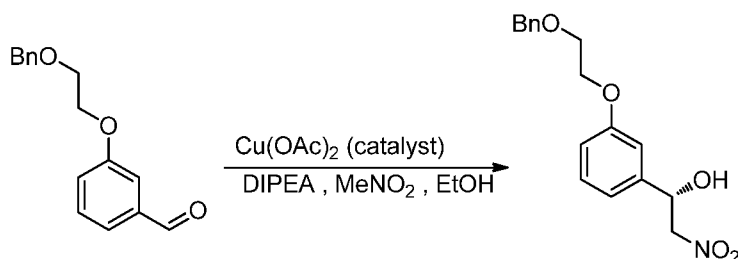
[00275] (c) 3-(2-(benzyloxy)ethoxy)benzaldehyde



[00276] To a solution of 3-hydroxybenzaldehyde (2.90 kg, 23.75 mol), and ((2-bromoethoxy)methyl)benzene (4.26 kg, 19.79 mol) in DMF (9.3 L) was added K_2CO_3 (3.83 kg, 27.70 mol). The reaction mixture was stirred at r.t. for 24 h. Water (15 L) and tert-butyl methyl ether (23 L) were added to the reaction mixture. The organic phase was separated and washed with 1N NaOH (2X15 L) and water (15 L) sequentially, and then concentrated to a minimum. Ethanol (23 L) was added and the solution was concentrated under vacuum to

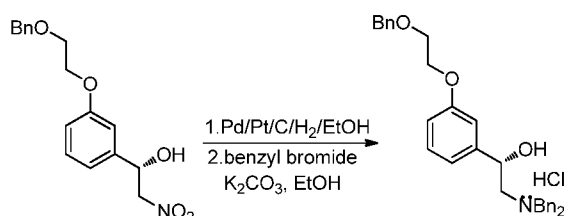
afford the desired product (4.7 kg, 93%) as a colourless oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): 9.98 (s, 1H), 7.55-7.52 (m, 2H), 7.46 (s, 1H), 7.36-7.34 (m, 4H), 7.32-7.26 (m, 2H), 4.57 (s, 2H), 4.25-4.22 (t, $J = 4.4$ Hz, 2H), 3.80-3.78 (t, $J = 4.4$ Hz, 2H). LCMS: $[\text{M}+\text{Na}]^+ = 279$.

5 [00277] (d) (S)-1-(3-(2-(benzyloxy)ethoxy)phenyl)-2-nitroethanol



[00278] A mixture of copper (II) acetate (167 g, 0.92 mol), (1*R*)-1,7,7-trimethyl-N-(pyridin-2-ylmethyl)bicyclo[2.2.1]heptan-2-amine (269 g, 1.10 mol) in ethanol (19 L) was stirred at r.t. for 1 h, then a solution of 3-(2-(benzyloxy)ethoxy)benzaldehyde (4.70 kg, 18.34 mol) in ethanol (5 L) was added. The reaction mixture was cooled to a temperature range between -30 °C and -40 °C, and then nitromethane (9.9 L, 183.40 mol) was added dropwise, keeping the temperature below -30 °C, followed by the addition of diisopropylethylamine (285 g, 2.20 mol). The reaction was stirred at -30 °C for 24 h, and then quenched with trifluoroacetic acid (314 g, 2.75 mol). 1 N HCl (24 L) and TBME (47 L) were added to the resulting solution. The separated organic phase was washed with water (24 L) and then concentrated under vacuum. The residue was added to a mixture of petroleum ether/ethyl acetate=5:1 (10 L). Then the yellow solid was precipitated, and collected by filtration with Buchner funnel and dried under vacuum at 40°C for 6 h to afford the desired product (5.00 kg, 86%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): 7.38-7.25 (m, 6H), 7.03 (s, 1H), 7.01-6.99 (d, $J = 7.6$ Hz, 1H), 6.90-6.87 (dd, $J = 8.0$ Hz, 1H), 6.09-6.08 (d, $J = 5.2$ Hz, 1H), 5.26-5.22 (m, 1H), 4.86-4.82 (dd, $J = 12.4$ Hz, 1H), 4.57-4.51 (m, 3H), 4.15-4.13 (m, 2H), 3.78-3.76 (t, $J = 4.8$ Hz, 2H). LC-MS: $[\text{M}+\text{Na}]^+ = 340$.

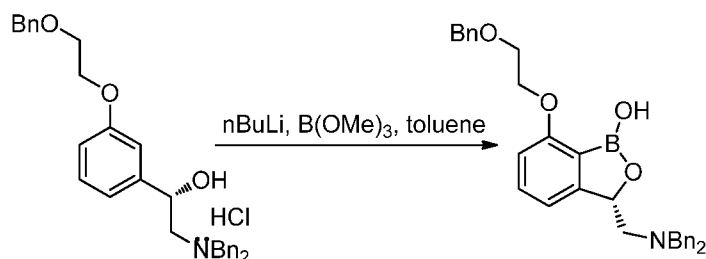
15 [00279] (e) (S)-1-(3-(2-(benzyloxy)ethoxy)phenyl)-2-(dibenzylamino)ethanol hydrochloride



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[00280] 10% Pd/C (800 g) and 10% Pt/C (200 g) were charged to a pressure vessel, followed by a solution of (S)-1-(3-(2-(benzyloxy)ethoxy)phenyl)-2-nitroethanol (5.00 kg, 15.76 mol) in ethanol (50 L). The vessel was pressurized with 100 psi hydrogen for 12 h at r.t.. The solid was filtered through Celite® and the cake was washed with ethanol (5 L). To the filtrate, K₂CO₃ (4.80 kg, 34.67 mol) and benzyl bromide (5.93 kg, 34.67 mol) were added sequentially. The reaction mixture was stirred at r.t. for 24 h. The solid was filtered and washed with ethanol (1 L). The filtrate was diluted with water (20 L) and then heated to 50°C. The solution was stirred at 50°C for 30 min and then conc. HCl (1.5 L) was added dropwise over 1 h. The mixture was cooled to 0°C and held at 0°C for additional 30 min. The product was filtered and washed with 20% aqueous ethanol (1 L) to afford the hydrochloric salt of desired product (5.00 kg, 63% over two steps) as a colourless solid. ¹H NMR (400 MHz, DMSO-*d*₆): 10.67 (s, 1H), 7.72-7.68 (m, 4H), 7.47-7.45 (m, 6H), 7.38-7.26 (m, 5H), 7.25-7.21 (t, *J* = 7.6 Hz, 1H), 6.86-6.84 (d, *J* = 8.0 Hz, 1H), 6.77 (s, 1H), 6.77-6.75 (d, *J* = 7.2 Hz, 1H), 6.36 (s, 1H), 5.04-5.02 (d, *J* = 9.2 Hz, 1H), 4.58 (s, 2H), 4.51-4.38 (m, 4H), 4.09-4.07 (t, *J* = 4.0 Hz, 2H), 3.77-3.75 (t, *J* = 3.2 Hz, 2H), 3.13-2.96 (m, 2H). LC-MS: [M+H]⁺ = 468.

[00281] (f) (S)-7-(2-(benzyloxy)ethoxy)-3-((dibenzylamino)methyl)benzo[c][1,2]oxaborol-1(3H)-ol



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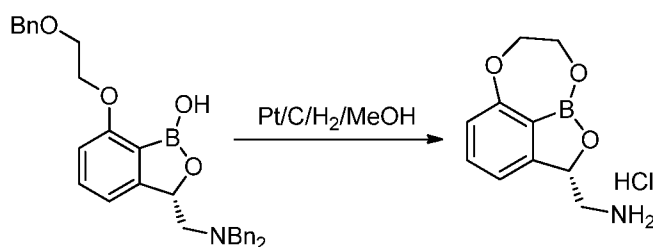
[00282] To a -30 °C solution of (S)-1-(3-(2-(benzyloxy)ethoxy)phenyl)-2-(dibenzylamino)ethanol hydrochloride (3.85 kg, 7.64 mol) in dry toluene (39 L) under N₂ atmosphere was added *n*-BuLi (15.3 L, 38.20 mol) dropwise over 6 h. After addition, the mixture was stirred at -30 °C for another 1 h, and then cooled to -70°C; trimethyl borate (3.97 kg, 38.20 mol) was added dropwise keeping the temperature below -60 °C. After addition, the reaction mixture was allowed to warm to r.t. and stirred overnight. The reaction was quenched with 5% aqueous NaHCO₃ (20 L) and stirred vigorously for 15 min, the resulting suspension was filtered and the filtrate was separated. The organic layer was washed with water (20 L × 3) and concentrated under vacuum and the residue was purified by gel chromatography eluting with petroleum ether/ethyl acetate=5:1 to afford desired product

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(1.80 kg, 48 %) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): 8.81 (s, 1H), 7.39-7.22 (m, 16H), 6.82-6.80 (d, $J = 7.6$ Hz, 1H), 6.72-6.70 (d, $J = 7.6$ Hz, 1H), 5.34-5.31 (dd, $J = 7.6$ Hz, 1H), 4.60 (s, 2H), 4.22-4.19 (t, $J = 4.4$ Hz, 2H), 3.80-3.72 (m, 6H), 2.88-2.84 (dd, $J = 13.6$ Hz, 1H), 2.47-2.45 (dd, $J = 10$ Hz, 1H). LC-MS: $[\text{M}+\text{H}]^+ = 494$.

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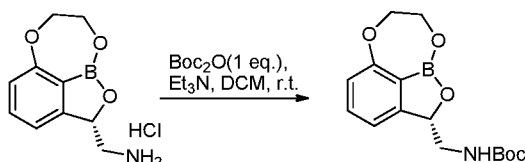
[00283] (g) (S)-(7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methanamine hydrochloride



[00284] 10 % Pd/C (180 g) was charged to a pressure vessel, followed by a solution of (S)-7-(2-(benzyloxy)ethoxy)-3-((dibenzylamino)methyl)benzo[c][1,2]oxaborol-1(3H)-ol (1.80 kg, 3.65 mol) in methanol (18 L), toluene (3.6 L) and 1 N HCl (4 L). The vessel was pressurized with 100 psi hydrogen for a period of 12 h at 50°C. The solid was filtered through Celite and the cake was washed with methanol (1 L). The filtrate was concentrated under vacuum and the residue was treated with 2-propanol (3.6 L), stirred at r.t. for 30 min. The resulting solid was collected by filtration and washed with 2-propanol (500 mL), dried under vacuum at 50°C for 6 h to afford the desired product (680 g, 77%) as a pale yellow powder. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): 8.38 (s, 3H), 7.52-7.48 (t, $J = 8.0$ Hz, 1H), 7.17-7.15 (d, $J = 7.6$ Hz, 1H), 6.92-6.90 (d, $J = 7.6$ Hz, 1H), 5.55 (m, 1H), 4.71-4.68 (m, 1H), 4.38-4.22 (m, 3H), 3.53-3.50 (m, 1H), 2.91-2.86 (m, 1H). LC-MS: $[\text{M}+\text{H}]^+ = 206$.

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[00285] (h) (S)-tert-butyl ((7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate



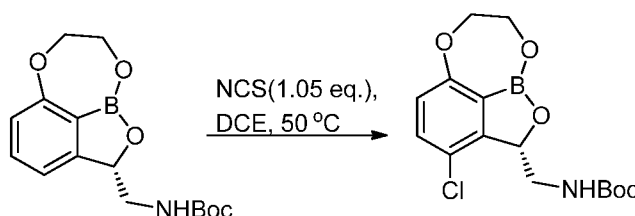
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[00286] To a solution of (S)-(7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methanamine hydrochloride (390 g, 1.62 mol) and Et_3N (163.4 g,

4.85 mol) in DCM (4.6 L) was added (Boc)₂O (353.0 g 1.62 mol) dropwise over 2 h at r.t.. After addition, the reaction mixture was stirred at r.t. for another 3 h. The reaction was quenched with 1N HCl (4 L) and the organic phase was separated and washed with water (4 L), concentrated under vacuum to obtain desired product (460 g, 93%) as a pale white solid.

¹H NMR (400 MHz, DMSO-*d*₆): 7.46-7.42 (t, *J* = 7.6 Hz, 1H), 7.07 (s, 1H), 7.02-7.00 (d, *J* = 7.2 Hz, 1H), 6.87-6.85 (d, *J* = 8.0 Hz, 1H), 5.27 (m, 1H), 4.68-4.65 (m, 1H), 4.34-4.18 (m, 3H), 3.41(s, 1H), 3.14-3.08 (m, 1H), 1.38 (s, 9H). LC-MS: [M-55] = 250.

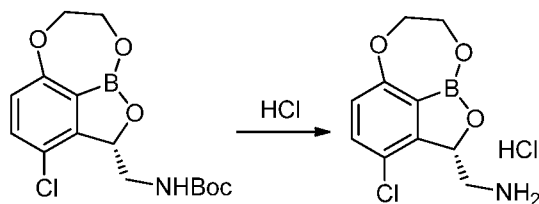
[00287] (i) (S)-*tert*-butyl ((3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methyl)carbamate



[00288] A mixture of (S)-*tert*-butyl ((7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methyl)carbamate (315.0 g, 1.03 mol) and NCS (144.5 g, 1.08 mol) in dichloroethane (3.5 L) was heated at 50°C for 24 h. The solution was washed with hot water (50°C, 4 L × 3) and the organic phase was concentrated under vacuum to obtain desired product (400.0 g, crude) as a yellow solid, which was used in the next step without further purification.

¹H NMR (400 MHz, DMSO-*d*₆): 7.44-7.42 (d, *J* = 8.4 Hz, 1H), 6.99 (s, 1H), 6.91-6.89 (d, *J* = 8.4 Hz, 1H), 5.33 (m, 1H), 4.72-4.69 (m, 1H), 4.35-4.19 (m, 3H), 3.73-3.71 (m, 1H), 3.17-3.15 (m, 1H), 1.33 (s, 9H). LC-MS: [M-55] = 284.

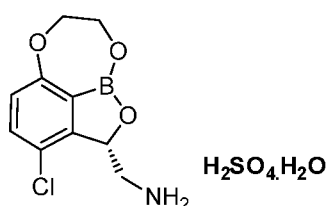
[00289] (j) Title compound



[00290] A solution of (S)-*tert*-butyl ((3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methyl)carbamate (400.0 g, crude) and conc. HCl (500 mL) in 1,4-dioxane (2 L) was stirred at r.t. for 8 h, during which time colourless solids were precipitated,

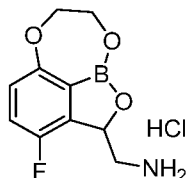
collected and washed with 2-propanol (200 mL). The solid was recrystallized from H₂O and dioxane (400 mL/2000 mL) to obtain the hydrochloride salt of desired product (110.0 g, 39%, over two steps). ¹H NMR (400 MHz, DMSO-*d*₆): 8.48-8.35 (br, 3H), 7.52-7.50 (d, J = 8.8 Hz, 1H), 7.00-6.97 (d, J = 8.4 Hz, 1H), 5.60 (m, 1H), 4.71 (m, 1H), 4.38-4.21 (m, 3H), 3.64-3.55 (m, 1H), 3.04-2.99 (m, 1H). ¹³C NMR (400 MHz, DMSO-*d*₆): 161.22, 149.15, 134.61, 119.35, 118.31, 79.14, 73.92, 69.22, 41.88. LC-MS: [M+H]⁺ = 240.

[00291] Example 4-II (S)-(3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methanamine dihydrogensulfate•H₂O (G4-Cl)

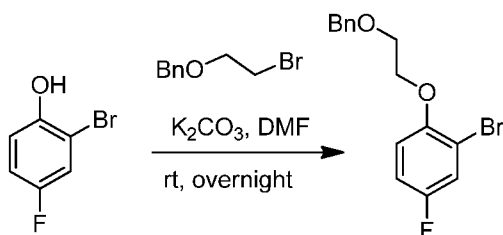


[00292] A mixture of (S)-*tert*-butyl ((7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methyl)carbamate (13.25 kg) and NCS (8.75 kg) in dichloroethane (132.5 L) was heated at 70 °C until the reaction judged complete by HPLC. The mixture was concentrated under reduced pressure, cooled to 25 °C and acetone (106 L) added. The slurry was filtered, washing with acetone (26.5 L). The wet cake was slurried in water (13.25 L) and 1,4-dioxane (66.25 L), heated to 50 °C for 20-30 minutes, cooled to 15 °C, filtered and the cake washed with 1,4-dioxane (26.5 L). The wet cake was dissolved in methanol (68.9 L), filtered and the filtrate concentrated under reduced pressure. Methyl tertiary butyl ether (66.25 L) was added to the residue and the mixture concentrated under reduced pressure. Methyl tertiary butyl ether (78.7 L), isopropanol (8.7 L) and sulphuric acid (4.6 L) were added, the mixture heated to 50 °C and stirred until the sulphate content was 24.32-29.72%. The mixture was cooled to 25 °C, stirred for 1 hour, filtered, the cake washed with methyl tertiary butyl ether (17.5 L) and dried to give the desired product (42%).

[00293] **Example 5 (3-fluoro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methanamine hydrochloride (G5-F)**



[00294] **(a) 1-(2-(benzyloxy)ethoxy)-2-bromo-4-fluorobenzene**

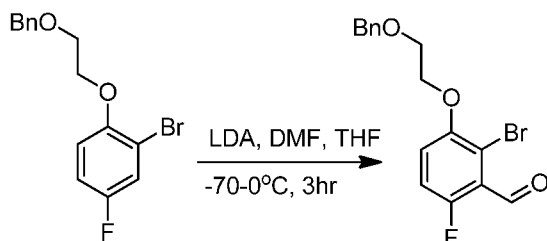


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[00295] A solution of 2-bromo-4-fluorophenol (1.91 g, 10 mmol), ((2-bromoethoxy)methyl)benzene (2.6 g, 12 mmol) and K_2CO_3 (2.76 g, 20 mmol) in 40 mL of DMF was stirred at 25 °C for 16 h. Then the mixture was poured into 300 mL of water, extracted with ethyl acetate (200 mL), washed with water (200 mL) and brine (100 mL), and dried over anhydrous sodium sulfate. The solvent was evaporated at 40 °C under reduced pressure and the residue was purified by silica gel chromatography eluting with ethyl acetate and petroleum ether (1:5) to afford the product (3.1 g, 95%) as a colorless oil. 1H NMR (300 MHz, DMSO- d_6): δ 7.55 (dd, 1H), 7.36-7.15 (m, 7H), 4.60 (s, 2H), 4.22-4.19 (m, 2H), 3.80-3.77 (m, 2H).

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[00296] **(b) 3-(2-(benzyloxy)ethoxy)-2-bromo-6-fluorobenzaldehyde**

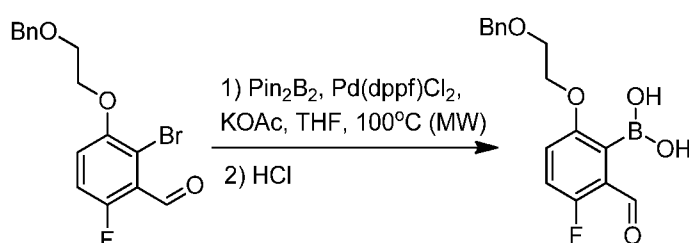


[00297] A solution of 1-(2-(benzyloxy)ethoxy)-2-bromo-4-fluorobenzene (1.6 g, 4.9 mmol) in 30 mL of THF was cooled to -70 °C, and LDA (2.0 M in THF, 3.5 mL, 7 mmol) was added dropwise. The resulting mixture was kept stirring for 2 h at low temperature

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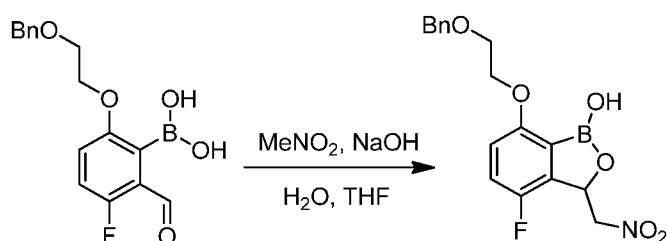
before a solution of DMF (1.1g, 15 mmol) in THF (3 mL) was added. The mixture was stirred for 1 h and then allowed to warm to 0 °C. It was quenched by saturated aq. NH₄Cl and the mixture was extracted with ethyl acetate (100 mL). The organic layer was washed with water (50 mL) and brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography eluting with ethyl acetate and petroleum ether (1:3) to afford the product (1.2 g, 69%) as a colorless oil. ¹H NMR (300 MHz, DMSO-d₆): δ 10.22 (s, 1H), 7.48-7.27 (m, 7H), 4.60 (s, 2H), 4.29-4.26 (m, 2H), 3.82-3.79 (m, 2H).

[00298] (c) 6-(2-(benzyloxy)ethoxy)-3-fluoro-2-formylphenylboronic acid



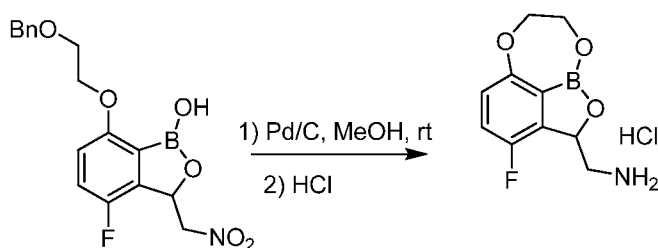
[00299] A solution of 3-(2-(benzyloxy)ethoxy)-2-bromo-6-fluorobenzaldehyde (1 g, 2.8 mmol), Pin₂B₂ (1 g, 4 mmol), KOAc (0.56 g, 6 mmol) and Pd(dppf)Cl₂ (0.05 g) in 30 mL of THF was degassed with N₂ for six times. Then the mixture was heated at 100 °C (microwave irradiated) for 4 h. The reaction mixture was cooled to room temperature, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate and petroleum ether (1:5). The fractions were combined and concentrated under reduced pressure. The residue was dissolved in THF (20mL) and 6N HCl (4 mL) and the resulting mixture was stirred at room temperature for 1h. After it was extracted with ethyl acetate (20ml x 3), the combined organic layer was concentrated under reduced pressure to afford the crude product (0.5 g, 56%). It was used directly in the next step without further purification. LC-MS: 336.0 [M+H₂O]⁺.

[00300] (d) 7-(2-(benzyloxy)ethoxy)-4-fluoro-3-(nitromethyl)benzo[c][1,2]oxaborol-1(3H)-ol



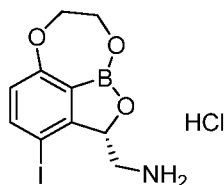
[00301] To a stirred solution of 6-(2-(benzyloxy)ethoxy)-3-fluoro-2-formylphenylboronic acid (0.5 g, 1.6 mmol) and CH_3NO_2 (0.2 g, 3.5 mmol) in 10 mL of THF was added a solution of NaOH (0.028 g, 0.7 mmol) in 3 mL of water at room temperature. Then the mixture was stirred at room temperature for 16 h and acidified with conc. HCl to pH=1 at 0°C. The mixture was extracted with ethyl acetate (20 mL) and the organic layer was washed with water (10 mL) and brine (10 mL) then dried over anhydrous sodium sulphate. After the solvent was removed under reduced pressure, the residue was purified by silica gel chromatography eluting with ethyl acetate and petroleum ether (1:10) to afford the crude product (0.5 g, 88%) as a colourless oil. LC-MS: 379.0 $[\text{M}+\text{H}_2\text{O}]^+$.

10 [00302] (e) Title compound

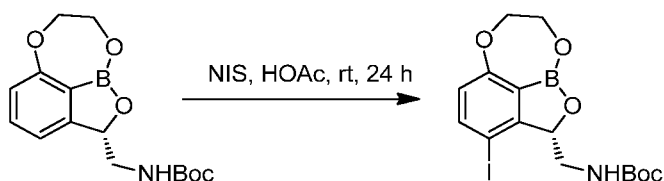


[00303] A solution of 7-(2-(benzyloxy)ethoxy)-4-fluoro-3-(nitromethyl)benzo[c][1,2]oxaborol-1(3H)-ol (0.5 g, 1.4 mmol) and Pd/C (10%, 0.1 g) in 20 mL of methanol was hydrogenated under 1 atm of H_2 at room temperature for 48 h. Then it was filtered through a bed of Celite and the filtrate was concentrated under reduced pressure to give an oil. The crude product was purified by preparative-HPLC using Daisogel 10 μ C18 column (250 x 50 mm) and eluted with a gradient of water/acetonitrile (0.05% TFA). The collected fraction was concentrated under reduced pressure. The residue was dissolved in ether (5 mL) and 2N HCl (0.2 mL) was added. The resulting mixture was stirred at room temperature for 1 h. The solid was collected by filtration and washed with ether (10 mL) to give the title compound (0.035 g, 10%) as a white solid. LC-MS: 223.9 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.22 (brs, 3H), 7.33 (t, 1H), 6.97 (dd, 1H), 5.68 (d, 1H), 4.69 (brs, 1H), 4.37-4.23 (m, 3H), 3.43-3.40 (m, 1H), 3.03 (t, 1H).

[00304] **Example 6 (S)-(3-iodo-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methanamine hydrochloride (G6-I)**

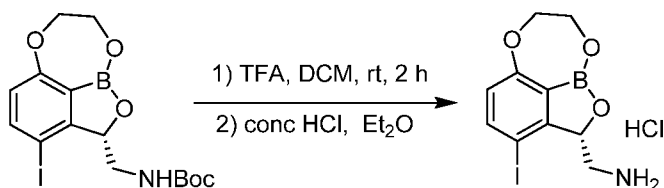


5 [00305] **(a) (S)-tert-butyl ((3-iodo-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate**



[00306] A solution of (S)-tert-butyl ((7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate (300 mg, 0.98 mmol) (Example 4, Method B, (h)) and NIS (265 mg, 1.18 mmol) in 6 mL of AcOH was stirred at room temperature for 24 h. The solvent was evaporated at 40 °C under reduced pressure. The residue was purified by preparative-HPLC using Daisogel 10 μ C18 column (250 x 50 mm) and eluted with a gradient of water/acetonitrile (0.05% TFA) to afford the product (200 mg, 47%) as light yellow oil. LC-MS: 432 [M+H]⁺.

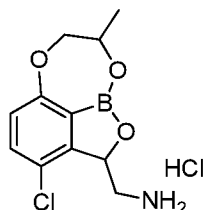
15 [00307] **(b) Title compound**



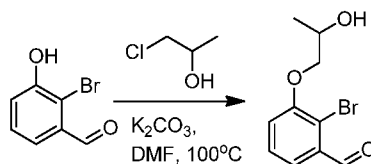
[00308] A solution of (S)-tert-butyl ((3-iodo-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate (140 mg, 0.32 mmol) and TFA (0.5 ml) in 5 mL of DCM was stirred at room temperature for 2 h. The solvent was evaporated at 40 °C under reduced pressure. The residue was dissolved in ether (5 mL) and 2N HCl in water (0.2 mL) was added. The resulting mixture was stirred at room temperature for 15 min. The solid was collected by filtration and washed with ether (10 mL) to give the title compound (90 mg, 75%)

as a white solid. LC-MS: 332.0 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6): δ 8.47 (brs, 3H), 7.80 (d, 1H), 6.78 (d, 1H), 5.37 (m, 1H), 4.72-4.53 (m, 1H), 4.4⁹-4.08 (m, 3H), 3.78-3.5₇ (m, 1H), 3.06-2.78 (m, 1H).

[00309] **Example 7 (3-chloro-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methanamine hydrochloride (G7-Cl)**



[00310] **(a) 2-bromo-3-(2-hydroxypropoxy)benzaldehyde**

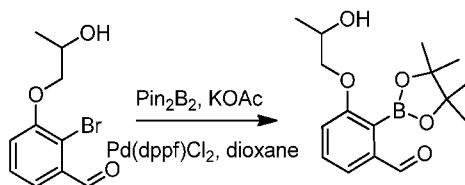


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[00311] A solution of 2-bromo-3-hydroxybenzaldehyde (6.0 g, 29.85 mmol), 1-chloropropan-2-ol (8.46 g, 89.55 mmol) and K_2CO_3 (8.24, 59.7 mmol) in DMF (100 mL) was stirred at 100°C overnight. Then the reaction mixture was quenched by adding water (4 L) and then extracted with EtOAc (3x1.5 L). The combined organic layers were washed with brine (250 mL), dried over anhydrous Na_2SO_4 and concentrated to dryness in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether: ethyl acetate =5:1 to 2:1) to give the target crude compound (8.77 g). MS (ESI) m/z =259/261 $[M+H]^+$.

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[00312] **(b) 3-(2-hydroxypropoxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde**



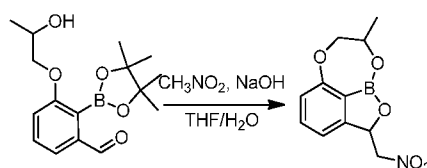
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[00313] A solution of 2-bromo-3-(2-hydroxypropoxy)benzaldehyde (8.77 g, 34 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (17.27 g, 68 mmol), $Pd(dppf)Cl_2$ (2.49 g, 3.4 mmol) and KOAc (9.99 g, 102 mmol) in dioxane (200 mL) was stirred at 100°C overnight. Then the reaction mixture was quenched by adding water (200

mL) and then extracted with EtOAc (3x200 mL). The combined organic layers were washed with brine (250 mL), dried over anhydrous Na₂SO₄ and concentrated to dryness in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether: ethyl acetate =5:1 to 1:1) to give the target crude compound (6 g). MS (ESI) *m/z* =307 [M +H]⁺.

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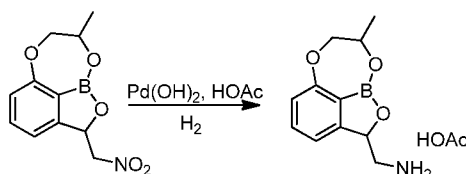
[00314] (c) 8-methyl-2-(nitromethyl)-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulene



[00315] To a solution of NaOH (261.4 mg, 6.54 mmol) in water (8 mL) was added nitromethane (1.2 g, 19.6 mmol) at 5-10°C. After stirring for 15 min at 5-10°C, CTAB (0.19 g, 0.52 mmol) was added to the reaction mixture and followed by the addition of 3-(2-hydroxypropoxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (2.0 g, 6.54 mmol) at 5-10°C. The reaction mixture was stirred at rt for 5 h. The reaction mixture was acidified to pH=1 using diluted hydrochloric acid and stirred at rt overnight. The reaction mixture was filtered to give the target compound (541 mg, 33%).

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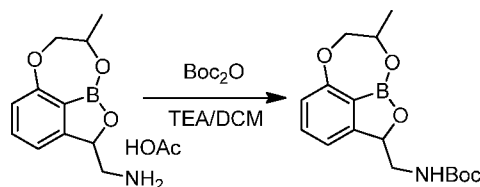
[00316] (d) (8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methanamine acetate



[00317] A solution of 8-methyl-2-(nitromethyl)-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulene (541 mg, 2.173 mmol) and palladium hydroxide (300 mg) in acetic acid (10 mL) was shaken under an atmosphere of H₂ overnight at room temperature. The mixture was filtered through a bed of Celite and the filtrate was concentrated in vacuo to give the crude compound (350 mg). MS (ESI) *m/z* = 220 [M +H]⁺.

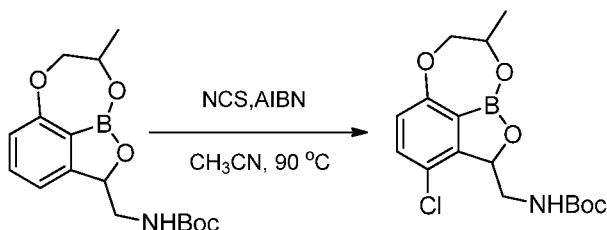
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[00318] (e) *tert*-butyl ((8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate



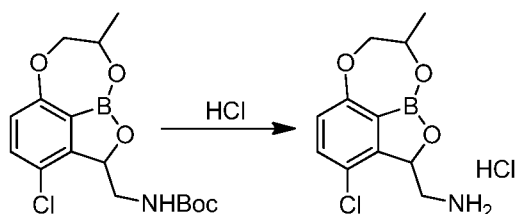
[00319] To the mixture of crude compound (8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methanamine acetate (3.0 g, 10.75 mmol) and triethylamine (6.5 g, 64.5 mmol) in dichloromethane (100 mL) at 0°C was added di-*tert*-butyl dicarbonate (3.5 g, 16.13 mmol) and the mixture was stirred for 2 h at room temperature. The reaction was quenched with sat. NaHCO₃ (15 mL) and the resulting mixture was extracted with EtOAc (3x80 mL), the combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by preparative-HPLC using a Daisogel 10μ C18 column (250 x 50 mm), eluted with gradient water/acetonitrile (0.05% TFA) to give the product (700 mg). MS (ESI) *m/z* = 264 [M-56]⁺. ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.44-7.39 (m, 1H), 7.01-6.98 (m, 2H), 6.88-6.85 (m, 1H), 5.24 (m, 1H), 4.52-4.44 (m, 2H), 4.18-4.00 (m, 1H), 3.39-3.36 (m, 1H), 3.15-3.06 (m, 1H), 1.42-1.09 (m, 15H).

[00320] (f) *tert*-butyl ((3-chloro-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate



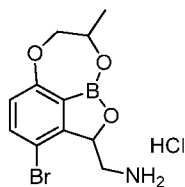
[00321] To a solution of *tert*-butyl ((8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate (300 mg, 0.94 mmol) and 1-chloropyrrolidine-2,5-dione (151.4 mg, 1.13 mmol) in CH₃CN (20 mL) was added 2,2'-Azobis(2-methylpropionitrile) (15.4 mg, 0.094 mmol) and the mixture was stirred for 2 h at 90°C. The reaction mixture was then concentrated under high vacuum and the residue was purified by preparative-HPLC using a Gemini® 5μ C18 column (150 x 21.2 mm) and eluted with gradient water/acetonitrile (0.05% TFA) to give the desired product (150 mg, 45%). MS (ESI) *m/z* = 298 [M-56]⁺.

[00322] (g) Title compound

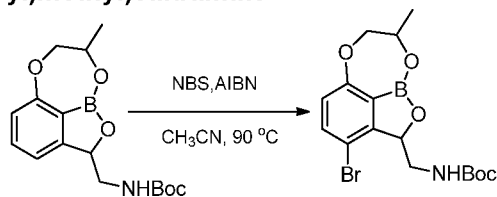


[00323] *tert*-butyl ((3-chloro-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methyl)carbamate (150 mg, 0.425mmol) in Et₂O/HCl and Et₂O (10 mL) was stirred at room temperature for 2 h and concentrated to dryness (water bath < 30 °C). The residue was washed with acetonitrile (2×5 mL) and the white solid was dried in high vacuo to give the product (120 mg, 97%) as a white solid. ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.28 (s, 3H), 7.51-7.48 (d, 1H), 7.02-6.99 (d, 1H), 5.58-5.56 (d, 1H), 4.57 (m, 2H), 4.33-4.17 (m, 1H), 3.72-3.56 (m, 1H), 3.05-3.01 (m, 1H), 1.30-1.23 (m, 3H). MS (ESI) *m/z* = 254 [M + H]⁺.

[00324] **Example 8 (3-bromo-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methanamine hydrochloride (G8-Br)**



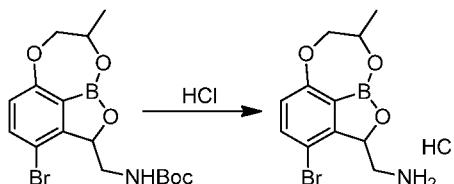
[00325] (a) *tert*-butyl ((8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methyl)carbamate



[00326] To a solution of *tert*-butyl ((8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methyl)carbamate (180 mg, 0.564 mmol) (Example 5, (e)) and 1-bromopyrrolidine-2,5-dione (120 mg, 0.677 mmol) in CH₃CN (20 mL) was added 2,2'-Azobis(2-methylpropionitrile) (9.2 mg, 0.056 mmol) and the mixture was stirred for 2 h at 90 °C. The reaction mixture was then concentrated in high vacuo and the residue was purified

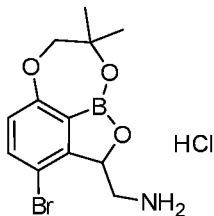
by preparative-HPLC using a Gemini® 5u C18 column (150 × 21.2 mm) eluted with gradient water/acetonitrile (0.05% TFA) to give the product (60 mg). MS (ESI) m/z = 342/344 [M - 56]⁺.

[00327] (b) Title compound



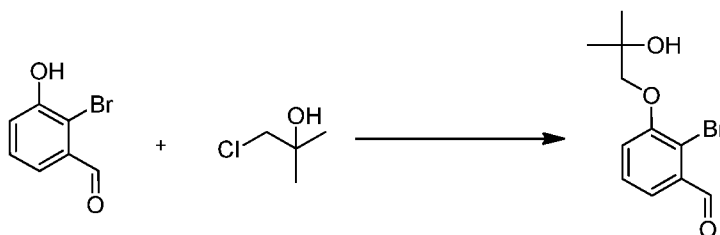
5 [00328] *tert*-butyl ((3-bromo-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methyl)carbamate (60 mg, 0.15 mmol) in saturated HCl (gas) in Et₂O (10 mL) was stirred at rt for 2 h and concentrated to dryness (water bath temperature < 30 °C). The residue purified by preparative-HPLC using a Gemini® 5u C18 column (150 × 21.2 mm) eluted with gradient water/acetonitrile (0.05% TFA) to give the product (20 mg) as
10 a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.12 (br, 3H), 7.65 (m, 1H), 6.96 (m, 1H), 5.45 (m, 1H), 4.58 (m, 2H), 4.29-4.16 (m, 1H), 3.77-3.59 (m, 1H), 3.04 (m, 1H), 1.29-1.21 (d, 3H). MS (ESI) m/z = 298/300 [M + H]⁺.

[00329] Example 9 (3-bromo-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methanamine hydrochloride (G9-Br)



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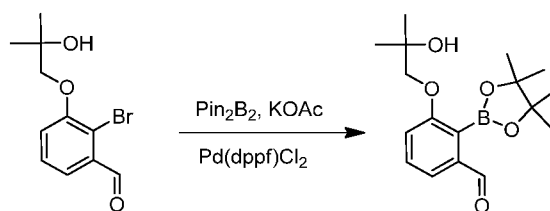
[00330] (a) 2-bromo-3-(2-hydroxy-2-methylpropoxy)benzaldehyde



[00331] A solution of 2-bromo-3-hydroxybenzaldehyde (7.5 g, 37.3 mmol), 1-chloro-2-methylpropan-2-ol (9.4 g, 85.6 mmol) and Na₂CO₃ (6.7 g, 63.2 mmol) in 70 mL of
20 DMSO was stirred at 140 °C for 3 hours. Then the mixture was cooled to room temperature, poured into 300 mL of water, extracted with ethyl acetate (600 mL), washed with water (300

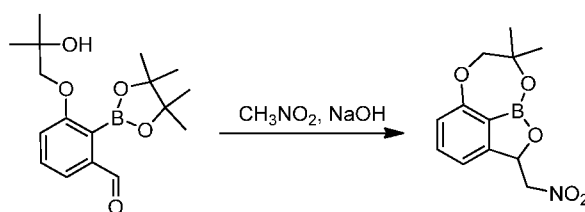
mL), brine (50 mL), dried over anhydrous sodium sulfate. The solvent was evaporated at 40 °C under reduced pressure and the residue was purified by silica gel chromatography, eluting with a mixture of ethyl acetate and petroleum ether (1:3) to give the title compound (9.2 g, 90.3%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 10.43 (s, 1H), 7.54 (dd, 1H, J1=3.0, J2=7.5), 7.40~7.34 (m, 1H), 7.54 (dd, 1H, J1=3, J2=7.5), 3.90 (s, 2H), 1.42 (s, 6H).

[00332] (b) 3-(2-hydroxy-2-methylpropoxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde



[00333] A solution of 2-bromo-3-(2-hydroxy-2-methylpropoxy)benzaldehyde (9.2 g, 33.7 mmol), Pin₂B₂ (17.1 g, 67.4 mmol), KOAc (9.9 g, 101.1 mmol) and Pd(dppf)Cl₂ (2.5 g) in 240 mL of 1,4-dioxane was degassed with N₂ for six times. Then the reaction was stirred at 99 °C under nitrogen for 16 hours. The reaction was cooled, filtered, then evaporated at 40 °C under reduced pressure and the residue was purified by silica gel chromatography, eluting with a mixture of ethyl acetate and petroleum ether (1:5) to give the title compound (10 g, crude) including de-Br by-product (used directly in the next step without further purification).

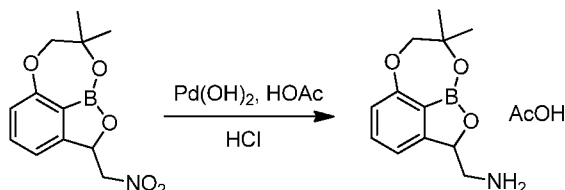
[00334] (c) 8,8-dimethyl-2-(nitromethyl)-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulene



[00335] To a stirred solution of 3-(2-hydroxy-2-methylpropoxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (10 g, 31.3 mmol) and CH₃NO₂ (5.7 g, 93.8 mmol) in 100 mL of THF was added a solution of NaOH (1.25 g, 31.3 mmol) in 60 mL of water at room temperature. Then the reaction was stirred at room temperature for 16 hours. Then the reaction was acidified by conc. HCl to pH=1 at 0 °C and stirred at room temperature for 1 hour. The mixture was extracted with ethyl acetate (100 mL), washed with water (30 mL), then brine (30 mL), dried over anhydrous sodium sulphate. The solvent was

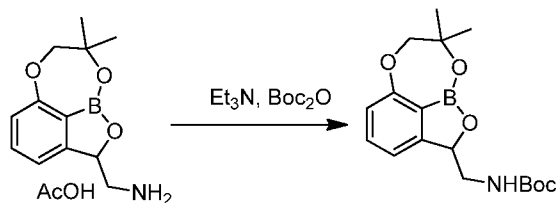
evaporated at 40 °C under reduced pressure and the residue was purified by silica gel chromatography eluting with a mixture of ethyl acetate and petroleum ether (1:10) to give the title compound (3 g, 36.5%) as a colourless oil.

5 [00336] (d) (8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methanamine acetate



10 [00337] A solution of 8,8-dimethyl-2-(nitromethyl)-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulene (1 g, 3.8 mmol) and Pd(OH)₂ (10%, 0.2 g) in 20 mL of acetic acid was hydrogenated at 1 atm of H₂ at rt for 16 hours. Then the mixture was filtered and the solvent was evaporated at 40°C under reduced pressure to give the title compound (0.9 g, crude) as an oil (acetate salt). LC-MS: 234.1 [M+H]⁺.

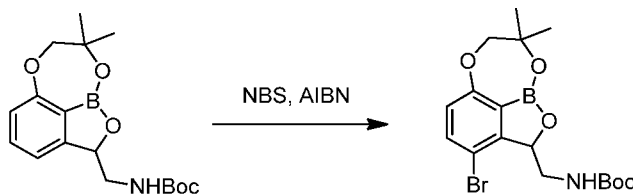
 [00338] (e) *tert*-butyl ((8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methyl)carbamate



15 [00339] To a stirred solution of (8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methanamine acetate (0.7 g, 2.39 mmol) in 70 mL of CH₂Cl₂ cooled to 0°C was added Et₃N (0.61 g, 6.0 mmol). Then Boc₂O (0.98 g, 4.5 mmol) was added in one portion, and the reaction was stirred at room temperature for 16 hours. The mixture was washed with 0.3 N HCl (30 mL), water (30 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated at 40°C at reduced pressure and the residue was purified by silica gel chromatography eluting with a mixture of ethyl acetate and petroleum ether (1:4) to give the title compound (0.63 g, 79%) as an oil. LC-MS: 234.1 [M+H-100]⁺.

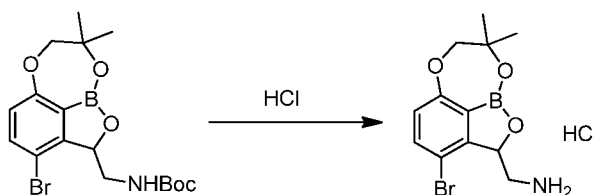
20

[00340] (f) *tert*-butyl ((3-bromo-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate



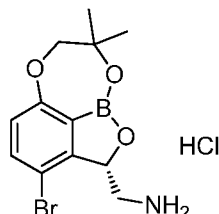
5 [00341] A solution of *tert*-butyl ((8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate (232 g, 0.70 mmol), NBS (143 mg, 0.80 mmol) and AIBN (20 mg) in 30 mL of acetonitrile was stirred at reflux for 1 hour. The solvent was evaporated at 40°C at reduced pressure and the residue was purified by silica gel chromatography eluting with a mixture of ethyl acetate and petroleum ether (1:4) to give the
10 title compound (260 mg, 88.6%) as a solid. LC-MS: 312.0/314.0 [M+H-100]⁺.

[00342] (g) Title compound

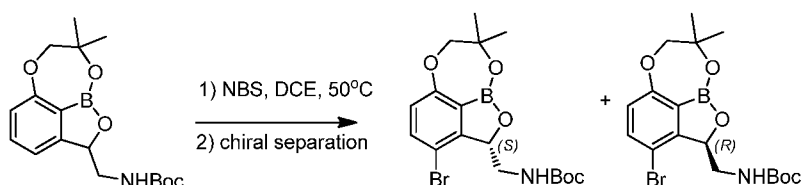


[00343] A solution of *tert*-butyl ((3-bromo-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate (260 mg, 0.63 mmol) in a saturated
15 HCl solution in 1,4-dioxane (20 mL) was stirred at room temperature for 3 hours. The solvent was evaporated at 40°C under reduced pressure and the residue was purified by preparative-HPLC using a Gemini[®] 5u C18 column (150 × 21.2 mm) eluted with gradient water/acetonitrile (0.05% TFA) treating with 0.1 mL of concentrated HCl to give the desired product (20 mg, 9.1%) as a white solid. LC-MS: 311.9 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD):
20 δ 7.63 (d, 1H, J=8), 6.95 (d, 1H, J=8), 5.52~5.45 (m, 1H), 4.41 (d, 1H, J=12), 4.17 (d, 1H, J=16), 4.09~3.85 (m, 1H), 3.13~2.98 (m, 1H), 1.37~1.30 (m, 6H).

[00344] **Example 10** (S)-(3-bromo-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methanamine hydrochloride (**G10-Br**):

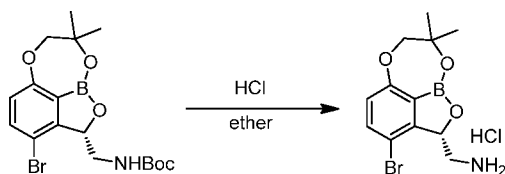


[00345] **(a)** (S)-*tert*-butyl ((3-bromo-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate



[00346] A solution of *tert*-butyl ((8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate (5.5g, 16.5 mmol) (Example 9, (e)) and NBS (3.2 g, 18.2 mmol) in 100 mL of dichloroethane was stirred at 50°C for 18 hours. The solvent was evaporated at 40°C under reduced pressure and the residue was purified by silica gel chromatography eluting with a mixture of ethyl acetate and petroleum ether (1:10) to give the title compound (5.9 g, 86.5%) as an oil. The racemic compound separated via SFC (chiral column CHIRALPAK AD-H, eluted with EtOH (20%) and CO₂ (80%)) to give 2.2g of (S)-isomer (first eluting isomer, RT = 3.0 min) and 2.2 g of (R)-isomer (second eluting isomer, RT = 4.1 min). LC-MS: 312.0/314.0 [M+H-100]⁺.

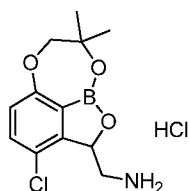
[00347] **(b) Title compound**



[00348] Dry HCl was bubbled through a solution of (S)-*tert*-butyl ((3-bromo-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate (2.2 g, 5.34 mmol) in diethyl ether (150 mL) at room temperature for 3 hours and then stirred for 18 hours. The solvent was filtered and the filter cake was dried in vacuo to give the (S)-isomer (1.4 g, 76%) as a white solid. LC-MS: 311.9 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.23 (brs, 3H), 7.64 (d, 1H, J=8), 6.96 (d, 1H, J=8), 5.48~5.46 (m, 1H), 4.43~4.40 (m, 1H),

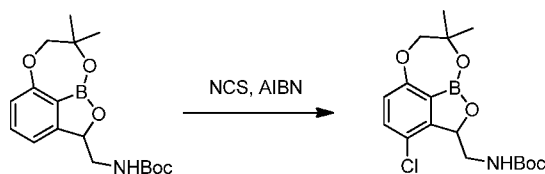
4.21~4.10 (m, 1H), 3.75~3.55 (m, 1H), 3.05~2.95 (m, 1H), 1.36~1.27 (ds, 6H). Similarly, the acid treatment of (R)-*tert*-butyl ((3-bromo-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate gave the corresponding (R)-isomer as a white solid (1.4 g, 76%). LC-MS: 312.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.29 (brs, 3H), 7.65 (d, 1H, J=8), 6.96 (d, 1H, J=8), 5.48~5.46 (m, 1H), 4.42~4.39 (m, 1H), 4.22~4.10 (m, 1H), 3.75~3.50 (m, 1H), 3.03~2.93 (m, 1H), 1.36~1.27 (ds, 6H).

[00349] **Example 11 (3-chloro-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methanamine hydrochloride (G11-Cl)**



10

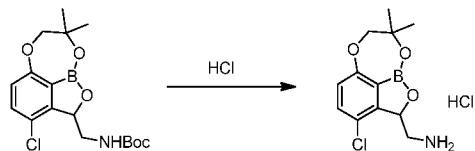
[00350] **(a) *tert*-butyl ((3-chloro-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate**



[00351] A solution of *tert*-butyl ((8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate (519 mg, 1.56 mmol) (Example 9, (e)), NCS (250 mg, 1.87 mmol) and AIBN (30 mg) in 50 mL of acetonitrile was stirred at reflux for 1 hour. The solvent was evaporated at 40 °C under reduced pressure and the residue was purified by silica gel chromatography eluting with a mixture of ethyl acetate and petroleum ether (1:5) to afford the desired product (300 mg, 52.4%, containing 6-Cl isomer) as a solid. LC-MS: 268.1 [M+H-100]⁺.

20

[00352] **(b) Title compound**

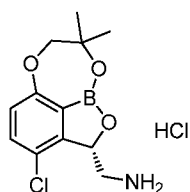


[00353] A solution of *tert*-butyl ((3-chloro-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate (300mg, 0.82 mmol) in a saturated

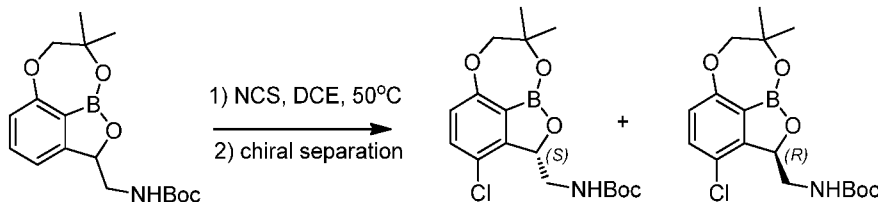
25

HCl solution in 1,4-dioxane (30 mL) was stirred at room temperature for 3 hours. The solvent was evaporated at 40 °C under reduced pressure and the residue was purified by preparative-HPLC using a Gemini® 5u C18 column (150 × 21.2 mm) eluted with gradient water/acetonitrile (0.05% TFA) followed by treating with 0.1 mL of conc. HCl to give the
 5 desired product (94 mg, 37.9%) as a white solid. LC-MS: 268.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.40 (brs, 3H), 7.52 (d, 1H, J=8), 7.02 (d, 1H, J=8), 5.60~5.58 (m, 1H), 4.42~4.38 (m, 1H), 4.23~4.07 (m, 1H), 3.67~3.57 (m, 1H), 3.02~2.92 (m, 1H), 1.36~1.27 (m, 6H).

10 [00354] **Example 12 (S)-(3-chloro-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methanamine hydrochloride (G12-Cl)**



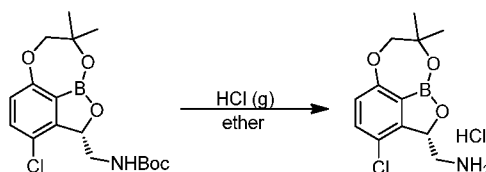
[00355] (a) **(S)-tert-butyl ((3-chloro-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methyl)carbamate**



15

[00356] A solution of tert-butyl ((8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[*cd*]azulen-2-yl)methyl)carbamate (4.1g, 12.3 mmol) (Example 9, (e)) and NCS (1.73 g, 13 mmol) in 100 mL of dichloroethane was stirred at 50°C for 5 hours. The solvent was evaporated at 40°C under reduced pressure and the residue was purified by silica gel chromatography eluting with a mixture of ethyl acetate and petroleum ether (1:10) to give the
 20 title compound (2.6 g, 58%) as an oil. The racemic compound was separated via SFC (chiral column CHIRALPAK AD-H, eluted with EtOH (20%) and CO₂ (80%)) to give 1.2 g of (S)-isomer (first eluting isomer, RT = 2.6 min) and 1.2 g of (R)-isomer (second eluting isomer, RT = 3.5 min. LC-MS: 268.0 [M+H-100]⁺.

[00357] (b) Title compound

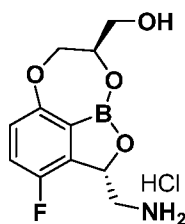


[00358] Dry HCl was bubbled through a solution of (S)-tert-butyl ((3-chloro-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate (1.2 g, 3.27 mmol) in diethyl ether (150 mL) at room temperature for 3 hours and then stirred for 18 hours. The solvent was filtered and the filter cake was dried in vacuo to give the (S)-isomer (0.8 g, 80%) as a white solid. LC-MS: 268 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.34 (brs, 3H), 7.52 (d, 1H, J=8), 7.02 (d, 1H, J=8), 5.58~5.56 (m, 1H), 4.42~4.39 (m, 1H), 4.22~4.07 (m, 1H), 3.67~3.53 (m, 1H), 3.03~2.95 (m, 1H), 1.36~1.27 (ds, 6H).

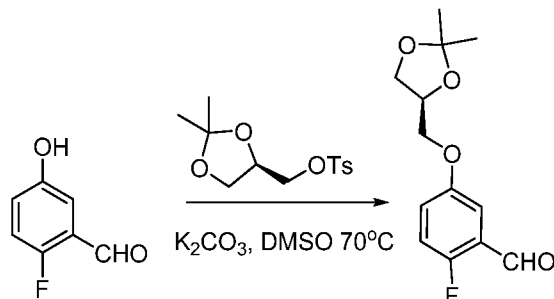
[00359] Similarly, the acid treatment of (R)-tert-butyl ((3-chloro-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-2-yl)methyl)carbamate gave the corresponding (R)-isomer (G25-Cl(R)) as a white solid (1.2 g, 80%). LC-MS: 268 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.33 (bs, 3H), 7.52 (d, 1H, J=8), 7.02 (d, 1H, J=8), 5.58 (m, 1H), 4.42~4.39 (m, 1H), 4.21~4.07 (m, 1H), 3.67~3.54 (m, 1H), 3.03~2.95 (m, 1H), 1.36~1.27 (ds, 6H).

[00360] **Example 13 ((2S,8R)-2-(aminomethyl)-3-fluoro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-8-yl)methanol hydrochloride (C15-F)**

[00361]

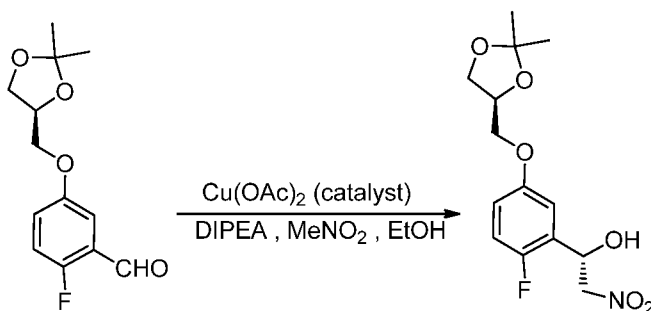


[00362] (a) (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-2-fluorobenzaldehyde



[00363] A solution of 2-fluoro-5-hydroxybenzaldehyde (1.9 g, 13.6 mmol), (R)-
 5 (2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methylbenzenesulfonate (4.3 g, 15 mmol) and K_2CO_3 (2.37 g, 17.2 mmol) in 40 mL of DMSO was stirred at $70^\circ C$ for 16 h. Then the mixture was poured into 300 mL of water, extracted with ethyl acetate (200 mL), washed with water (200 mL) and brine (100 mL), and dried over anhydrous sodium sulfate. The solvent was evaporated at $40^\circ C$ under reduced pressure and the residue was purified by silica gel
 10 chromatography eluting with ethyl acetate and petroleum ether (1:5) to afford the product (2.9 g, 84%) as a colorless oil. LC-MS: 255.1 $[M+H]^+$. 1H NMR (300 MHz, CD_3OD): δ 10.30 (s, 1H), 7.31-7.28 (m, 1H), 7.16-7.05 (m, 2H), 4.49-4.45 (m, 1H), 4.18-3.85 (m, 4H), 1.45-1.40 (d, 6H).

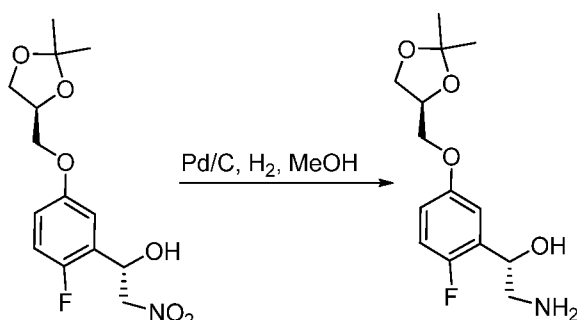
15 [00364] (b) (S)-1-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-2-fluorophenyl)-2-nitroethanol



[00365] A mixture of copper (II) acetate (0.2 g, 1.1 mmol), (1R)-1,7,7-trimethyl-N-(pyridin-2-ylmethyl)bicyclo[2.2.1]heptan-2-amine (0.3 g, 1.23 mmol) (Example 4, Method
 20 B, (b)) in ethanol (30 mL) was stirred at r.t. for 1 h, then a solution of (S)-5-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-2-fluorobenzaldehyde (2.9 g, 11.4 mmol) in ethanol (50 mL) was added. The reaction mixture was cooled to $-35^\circ C$ to $-40^\circ C$, and then nitromethane (7 g, 115 mmol) was added dropwise, maintaining the temperature below $-35^\circ C$, followed by the

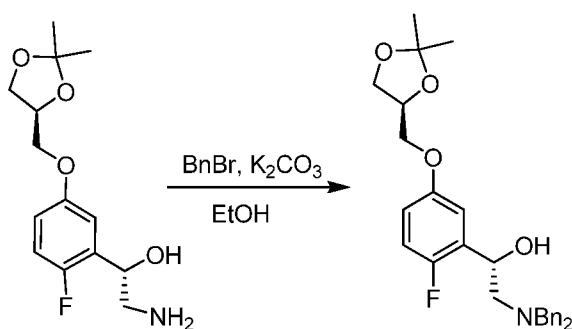
addition of diisopropylethylamine (0.32 g, 2.50 mmol). The reaction was stirred at -35 °C for 24 h, and then quenched with trifluoroacetic acid (0.29 g, 2.5 mmol). EtOAc (200 mL) was added to the resulting solution. The separated organic phase was washed with water (200 mL) and then concentrated under vacuum. The residue was purified by silica gel chromatography eluting with ethyl acetate and petroleum ether (1:10) to afford the product (3.3 g, 92%) as a colourless oil. LC-MS: 316.1 [M+H]⁺.

[00366] (c) (S)-2-amino-1-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-2-fluorophenyl)ethanol



[00367] A solution of (S)-1-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-2-fluorophenyl)-2-nitroethanol (3.2 g, 10.2 mmol) and Pd/C (10%, 0.5 g) in 70 mL of methanol was hydrogenated under 1 atm of H₂ at room temperature for 48 h. Then it was filtered through a bed of Celite and the filtrate was concentrated under reduced pressure to afford the crude product (2.9 g, 100%) as a colourless oil. It was used directly in the next step without further purification. LC-MS: 286.2 [M+H]⁺.

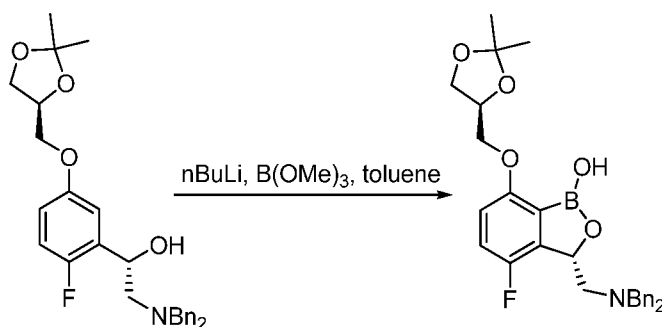
[00368] (d) (S)-2-(dibenzylamino)-1-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-2-fluorophenyl)ethanol



[00369] To a stirred solution of (S)-2-amino-1-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-2-fluorophenyl)ethanol (2.9 g, 10.2 mmol) in 50 mL of EtOH were added K₂CO₃ (2.8 g, 20.3 mmol) and BnBr (3.6 g, 21 mmol). The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure

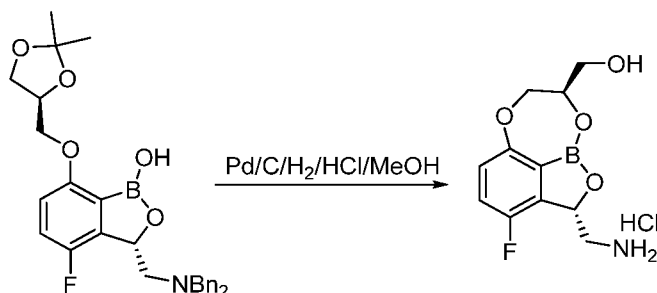
and the residue was purified by silica gel chromatography eluting with ethyl acetate and petroleum ether (1:10) to afford the product (3.8 g, 80%) as a colourless oil. LC-MS: 466.2 [M+H]⁺

[00370] (e) (S)-3-((dibenzylamino)methyl)-7-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-4-fluorobenzo[c][1,2]oxaborol-1(3H)-ol



[00371] To a solution of (S)-2-((dibenzylamino)methyl)-1-(5-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-2-fluorophenyl)ethanol (3.3 g, 7.1 mmol) in dry toluene (40 mL) at -30 °C under N₂ atmosphere was added n-BuLi (2.5 M in hexane, 20 mL, 50 mmol) dropwise over 30 minutes. After addition, the mixture was stirred at 0 °C for another 2 h, and then cooled to -70 °C; trimethyl borate (5.2 g, 50 mmol) was added dropwise keeping the temperature below -50 °C. After addition, the reaction mixture was allowed to warm to -40 °C for 3 h and then warmed to r.t. and stirred overnight. The reaction was quenched with 5% aqueous NaHCO₃ (20 mL) and stirred vigorously for 15 min, the resulting suspension was filtered and the filtrate was separated. The organic layer was washed with water (20 mL x 3) and concentrated in vacuum to afford the crude product (3 g, 86%) as a yellow oil. LC-MS: 492.2 [M+1]⁺

[00372] (f) Title compound

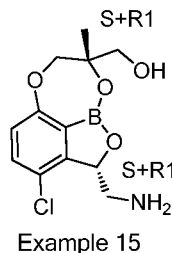
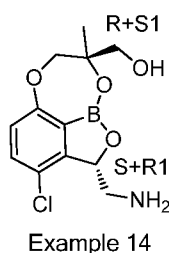


[00373] A solution of (S)-3-((dibenzylamino)methyl)-7-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-4-fluorobenzo[c][1,2]oxaborol-1(3H)-ol (3 g, 6.1 mmol) and Pd/C (10%, 0.7 g) in 50 mL of methanol with 2 mL of conc HCl was hydrogenated under 1 atm of

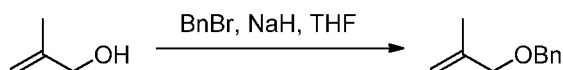
H₂ at room temperature for 48 h. Then it was filtered through a bed of Celite and the filtrate was concentrated at reduced pressure to give an oil. The crude product was purified by preparative-HPLC using Daisogel 10 μ C18 column (250 x 50 mm) and eluted with a gradient of water/acetonitrile (0.05% TFA). The collected fraction was concentrated under reduced pressure. The residue was dissolved in ether (30 mL) and sat. HCl (g) in ether (30 mL) and the mixture was stirred at room temperature for 1 h. The solid was collected by filtration and washed with ether to give the title compound (0.4 g, 23%) as a white solid. LC-MS: 254.2 [M+H]⁺. ¹H NMR (400 MHz, D₂O): δ 7.20-7.16 (m, 1H), 6.94-6.91 (m, 1H), 5.55-5.53 (m, 1H), 4.17-4.04 (m, 3H), 3.70-3.62 (m, 3H), 3.19-3.14 (m, 1H).

[00374] **Example 14 ((2S, 8R or 2R, 8S)-2-(aminomethyl)-3-chloro-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-8-yl)methanol (C16-Cl)**

[00375] **Example 15 ((2S, 8S, or 2R, 8R)-2-(aminomethyl)-3-chloro-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-8-yl)methanol (G17-Cl)**

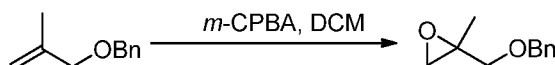


[00376] (a) **((2-methylallyloxy)methyl)benzene**



[00377] A solution of methallyl alcohol (80 g, 1.1 mol) in THF (100 mL) was added dropwise to a suspension of NaH (66 g, 1.65 mol) in THF (800 mL) at 25 °C under argon. After 1 h, a solution of benzyl bromide (207 g, 1.2 mol) in THF (100 mL) was added slowly and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with saturated NH₄Cl solution (200 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over Na₂SO₄. The solvent was removed under reduced pressure. The residue was distilled to afford the desired product (134 g, 74%) as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.40 – 7.29 (m, 5H), 5.05 (s, 1H), 4.97 (s, 1H), 4.54 (s, 2H), 3.98 (s, 2H), 1.82 (s, 3H).

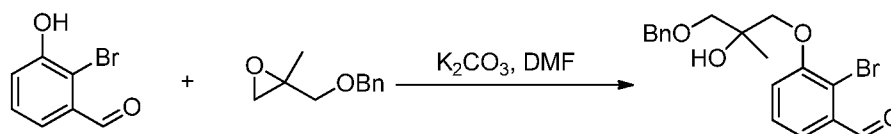
[00378] **(2-(benzyloxymethyl)-2-methyloxirane)**



[00379] ((2-methylallyloxy)methyl)benzene (41.5 g, 256 mmol) was dissolved

in DCM (1200 mL) and cooled to 0 °C. *m*-CPBA (69.7 g, 384 mmol) was added and the
 5 mixture was stirred overnight at room temperature for 12 h. After the white precipitate was
 filtered off, the filtrate was washed with saturated Na₂CO₃ solution (200 mL), H₂O (200 mL),
 and brine. After the solvent was removed under reduced pressure, the crude residue was
 purified by silica gel chromatography eluting with ethyl acetate and petroleum ether (1:20) to
 afford the pure product (20 g, 44%) as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.40 –
 10 7.29 (m, 5H), 4.60 (q, *J* = 12.0 Hz, 2H), 3.61 (d, *J* = 11.0 Hz, 1H), 3.48 (d, *J* = 11.0 Hz, 1H),
 2.78 (d, *J* = 4.9 Hz, 1H), 2.66 (d, *J* = 4.9 Hz, 1H), 1.43 (s, 3H).

[00380] 3-(3-(benzyloxy)-2-hydroxy-2-methylpropoxy)-2-bromobenzaldehyde



[00381] To a solution of 2-(benzyloxymethyl)-2-methyloxirane (26 g, 145.9

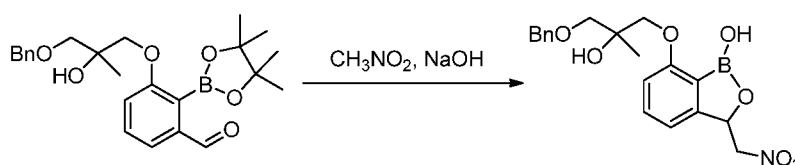
mmol) in DMF (700 mL) was added K₂CO₃ (42 g, 304.3 mmol), followed by 2-bromo-3-
 20 hydroxybenzaldehyde (30 g, 149.3 mmol). The suspension was stirred at 90 °C for 6 h. The
 mixture was cooled down to room temperature, diluted with brine and extracted with ethyl
 acetate (200 mL x 3). The organic solvent was removed under vacuum and the residue was
 purified by silica gel chromatography eluting with ethyl acetate and petroleum ether (1:20) to
 afford the pure product (27 g, 49%) as light yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆): δ
 25 10.29 (s, 1H), 7.512 – 7.41 (m, 3H), 7.31 – 7.23 (m, 5H), 4.91 (s, 1H), 4.53 (dd, *J*₁ = 12.4 Hz,
*J*₂ = 17.2 Hz, 2H), 4.06 (d, *J* = 9.2 Hz, 1H), 3.91 (d, *J* = 9.2 Hz, 1H), 3.54 (d, *J* = 9.3 Hz, 1H),
 3.47 (d, *J* = 9.3 Hz, 1H), 1.27 (s, 3H).

[00382] 3-(3-(benzyloxy)-2-hydroxy-2-methylpropoxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde



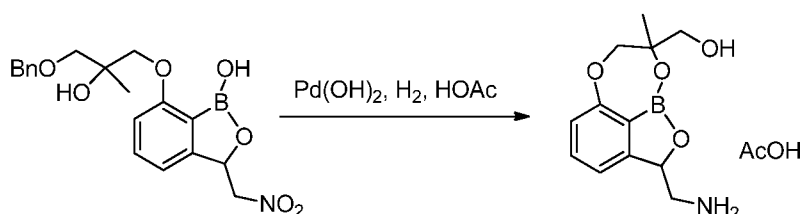
[00383] A solution of 3-(3-(benzyloxy)-2-hydroxy-2-methylpropoxy)-2-bromobenzaldehyde (21.3 g, 56.2 mmol), Pin₂B₂ (28.6 g, 112.4 mmol), KOAc (6.1 g, 61.9 mmol), PdCl₂(dppf) · DCM (1.23 g, 1.7 mmol) in DMF (150 mL) was degassed for 3 times with nitrogen. The mixture was heated at 90°C for 16 h. After the reaction was worked up with ethyl acetate and brine, the residue was purified by silica gel chromatography eluting with ethyl acetate and petroleum ether (1:20) to afford the desired product (15.3 g, 64%) as light yellow oil. LC-MS: 367.1 [344+Na]⁺

[00384] **3-(3-(benzyloxy)-2-hydroxy-2-methylpropoxy)-3-(nitromethyl)benzo[c][1,2]oxaborol-1(3H)-ol**



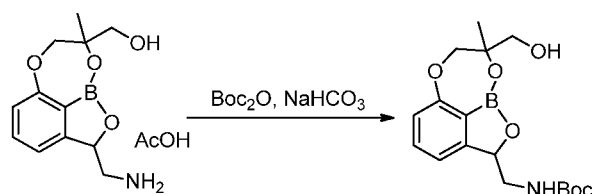
[00385] To an ice-cold solution of 3-(3-(benzyloxy)-2-hydroxy-2-methylpropoxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (18.8 g, 44.1 mmol) in THF was added a solution of NaOH (1.76 g, 44.1 mmol) in water (100 mL). After stirring for 15 min, CH₃NO₂ (3.3 g, 53 mmol) was added and the mixture was stirred at room temperature for 15 h. The reaction solution was acidified with AcOH to pH 3-5. The suspension was extracted with ethyl acetate (50 mL x 3). The combined organic layer was evaporated under vacuum, and the residue was purified by silica gel chromatography eluting with ethyl acetate and petroleum ether (1:10) to afford the pure product (6.8 g, 40%) as colorless oil. LC-MS: 386.0 [M-1]⁻

[00386] **2-(aminomethyl)-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[d]azulen-8-yl)methanol acetate**



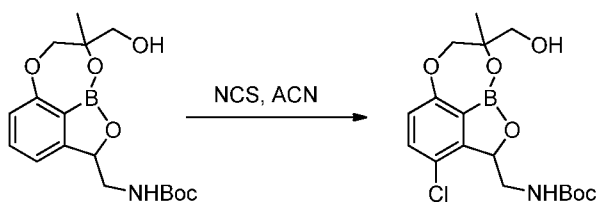
[00387] Pd(OH)₂/C (200 mg) was added to a solution of 7-(3-(benzyloxy)-2-hydroxy-2-methylpropoxy)-3-(nitromethyl)benzo[c][1,2]oxaborol-1(3H)-ol (1 g, crude) in AcOH (20 mL). The solution was degassed 3 times with H₂, and stirred at room temperature for 12 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated under vacuum to afford the crude product (1 g, crude) as yellow solid.

[00388] tert-butyl ((8-(hydroxymethyl)-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methyl)carbamate



[00389] NaHCO₃ (437 mg, 5.2 mmol) was added to a solution of (2-(aminomethyl)-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-8-yl)methanol acetate (650 mg, 2.1 mmol) in t-BuOH (10 mL) and H₂O (10 mL) at room temperature. After stirring for 15 min, (Boc)₂O (854 mg, 3.9 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. The mixture was acidified with AcOH to pH 6-7 and extracted with DCM (30 mL x 3). Combined organic layers were evaporated under vacuum, and the residue was purified by silica gel chromatography eluting with ethyl acetate and petroleum ether (1:3) to afford the desired product (400 mg, 55%) as colorless oil. LC-MS: 294.1 [M-55]⁺

[00390] tert-butyl ((3-chloro-8-(hydroxymethyl)-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methyl)carbamate

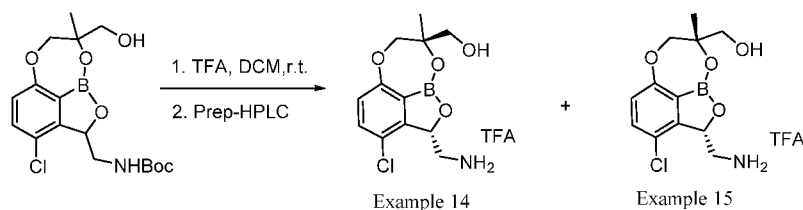


[00391] To a solution of tert-butyl ((8-(hydroxymethyl)-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methyl)carbamate (200 mg, 0.57 mmol) in ACN (10 mL) was added NCS (77 mg, 0.57 mmol), and the solution was stirred at 90°C for 16 h. The reaction was quenched with NH₄Cl solution, extracted with ethyl acetate (20 mL x 3). The organic layer was washed with brine, dried over Na₂SO₄, concentrated in vacuum. The

crude residue was purified by silica gel chromatography eluting with ethyl acetate and petroleum ether (1:3) to afford the crude product (240 mg, crude) as yellow oil. LC-MS: 284.1 [283+H]⁺

[00392] Title compounds

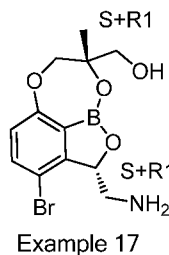
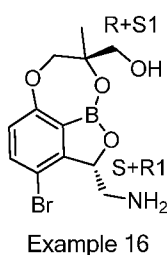
5



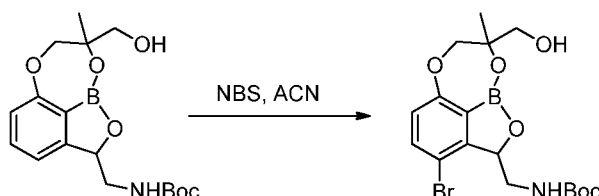
[00393] tert-butyl ((3-chloro-8-(hydroxymethyl)-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocdazulen-2-yl)methyl)carbamate (240 mg, crude) was dissolved in a solution of TFA (1 mL) in DCM (10 mL). The solution was stirred at room temperature for 1 h, and then was concentrated in vacuum. The crude product was purified by preparative-HPLC using Daisogel 10 μ C18 column (250 x 50 mm) and eluted with a gradient of water/acetonitrile (0.05% TFA). The collected fraction was concentrated under reduced pressure to afford the title compounds. ((2S, 8R or 2R, 8S)-2-(aminomethyl)-3-chloro-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocdazulen-8-yl)methanol LC-MS: 284.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.23 (s, 3H), 7.52 (d, *J* = 8.6 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 5.56 (dd, *J* = 8.5, 2.1 Hz, 1H), 4.55 (s, 1H), 4.15 (s, 1H), 3.59 (s, 1H), 3.45 (s, 2H), 3.04 (s, 1H), 1.21 (s, 3H). ((2S, 8S, or 2R, 8R)-2-(aminomethyl)-3-chloro-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocdazulen-8-yl)methanol LC-MS: 284.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.12 (s, 2H), 7.51 (s, 1H), 7.02 (s, 1H), 5.55 (s, 1H), 4.54 (s, 1H), 4.24 – 3.92 (m, 1H), 3.78 – 3.29 (m, 3H), 3.02 (s, 1H), 1.25 (s, 3H).

[00394] Example 16 ((2S, 8R, or 2R, 8S)-2-(aminomethyl)-3-bromo-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocdazulen-8-yl)methanol (C18-Br)
[00395] Example 17 ((2S, 8S, or 2R, 8R)-2-(aminomethyl)-3-bromo-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocdazulen-8-yl)methanol (G19-Br)

25



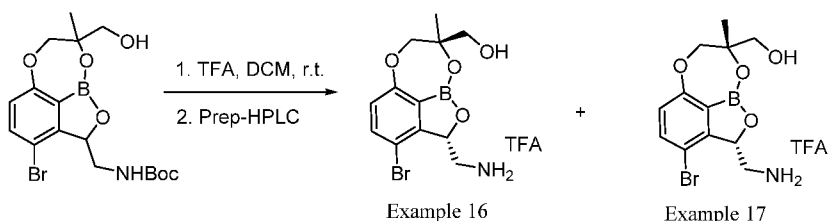
[00396] tert-butyl ((3-bromo-8-(hydroxymethyl)-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methyl)carbamate



5

[00397] To a solution of tert-butyl ((8-(hydroxymethyl)-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methyl)carbamate (200 mg, 0.57 mmol) in ACN (10 mL) was added NBS (102 mg, 0.57 mmol), and the solution was stirred at 90°C for 1 h. The reaction was quenched with NH₄Cl solution, extracted with ethyl acetate (20 mL x 3).
 10 The organic layer was washed with brine, dried over Na₂SO₄, concentrated in vacuum. The crude residue was purified by silica gel chromatography eluting with ethyl acetate and petroleum ether (1:3) to afford the product (230 mg, crude) as pale solid. LC-MS: 328.1 [M-Boc+H]⁺.

[00398] Title compounds



15

[00399] tert-butyl ((3-bromo-8-(hydroxymethyl)-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methyl)carbamate (230 mg, crude) was dissolved in a solution of TFA (1 mL) in DCM (10 mL). The solution was stirred at room temperature for 1 h, and then was concentrated in vacuum. The crude product was purified by preparative-HPLC using Daisogel 10μ C18 column (250 x 50 mm) and eluted with a gradient of water/acetonitrile (0.05% TFA). The collected fraction was concentrated under reduced pressure to afford the title compounds. ((2S, 8R, or 2R, 8S)-2-(aminomethyl)-3-bromo-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-8-yl)methanol LC-MS: 328.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.10 (s, 3H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.07 – 6.88 (m, 1H), 5.56 – 5.39 (m, 1H), 5.36 – 5.17 (m, 1H), 4.61-4.52 (m, 1H), 4.19-4.07 (m, 1H), 3.62 (d, *J* = 11.9 Hz, 1H), 3.51 – 3.39 (m, 2H), 3.04 (s, 1H), 1.18 (s, 3H). ((2S, 8S, or 2R, 8R)-2-(aminomethyl)-3-bromo-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-8-yl)methanol LC-MS: 328.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.10 (s, 3H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.07 – 6.88 (m, 1H), 5.56 – 5.39 (m, 1H), 5.36 – 5.17 (m, 1H), 4.61-4.52 (m, 1H), 4.19-4.07 (m, 1H), 3.62 (d, *J* = 11.9 Hz, 1H), 3.51 – 3.39 (m, 2H), 3.04 (s, 1H), 1.18 (s, 3H).
 25 ((2S, 8S, or 2R, 8R)-2-(aminomethyl)-3-bromo-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-8-yl)methanol LC-MS: 328.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.10 (s, 3H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.07 – 6.88 (m, 1H), 5.56 – 5.39 (m, 1H), 5.36 – 5.17 (m, 1H), 4.61-4.52 (m, 1H), 4.19-4.07 (m, 1H), 3.62 (d, *J* = 11.9 Hz, 1H), 3.51 – 3.39 (m, 2H), 3.04 (s, 1H), 1.18 (s, 3H).

yl)methanol LC-MS: 328.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.13 (s, 2H), 7.65 (s, 1H), 6.98 (s, 1H), 5.47 (s, 1H), 5.26 – 5.06 (m, 1H), 4.53 (s, 1H), 4.19 – 3.97 (m, 1H), 3.83 – 3.56 (m, 1H), 3.51 – 3.26 (m, 2H), 3.01-2.93 (m, 1H), 1.25 (s, 3H).

5 Single Crystal X-Ray Diffraction Study and X-ray Powder Diffraction Pattern Simulation

[00400] *Single Crystal X-Ray Diffraction Study of a salt of G4-Cl*

[00401] Single crystals were prepared by the slow evaporation of an aqueous solution of G4-Cl. The molecular structure of G4-Cl was determined at 290K from three-dimensional X-ray diffraction data and is shown in Figure 5. The study (details summarised
10 in Table A) confirmed the atomic connectivity of G4-Cl, with derived bond distances and angles being fully consistent with the proposed structure. The structure determination also allowed the unambiguous assignment of the absolute configuration.

[00403] *Single Crystal X-Ray Diffraction Study of the free base of G4-Cl*

[00404] Single crystals were prepared by the slow evaporation of an ethanol
15 solution of the free base of G4-Cl. The molecular structure of the free base of G4-Cl was determined at 290K from three-dimensional X-ray diffraction data and is shown in Figure 7. The study confirmed the atomic connectivity of the free base of G4-Cl, with derived bond distances and angles being fully consistent with the proposed structure.

Table A. Crystal data and data collection and refinement summary for the G4-Cl X-ray Diffraction study

Moiety formula	$C_{10}H_{14}BCINO_4^+ \cdot HO_4S^-$	
Formula weight	355.55	
Temperature	290(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	$a = 4.57555(15)$ Å	$\alpha = 90^\circ$
	$b = 14.7514(5)$ Å	$\beta = 94.475(3)^\circ$
	$c = 21.4719(7)$ Å	$\gamma = 90^\circ$
Volume	$1444.84(8)$ Å ³	
Z	4	
Density (calculated)	1.635 Mg/m ³	
Theta range for data collection	3.35 to 28.18°	
Index ranges	$-6 \leq h \leq 5$ $-19 \leq k \leq 19$ $-27 \leq l \leq 28$	
Reflections collected	56556	
Independent reflections	6492 [R(int) = 0.0589]	
Coverage of independent reflections	99.7 %	
Data / restraints / parameters	6492 / 261 / 501	
Goodness-of-fit on F^2	1.092	
Δ/σ_{\max}	0.001	
Final R indices		
4472 data; $I > 2\sigma(I)$ all data	$R1 = 0.0445$, $wR2 = 0.0914$ $R1 = 0.0769$, $wR2 = 0.1028$	
Absolute structure parameter	0.00(5)	
Largest diff. peak and hole	0.300 and -0.280 eÅ ⁻³	

[00406] X-Ray Powder Diffraction (XRPD) Simulation

[00407] Having successfully solved and refined the single crystal structure of G4-Cl, the unit cell dimensions and atomic co-ordinates were used to simulate an XRPD pattern. This was found to be concordant with an experimental pattern for lot 142384053
5 (Figure 6) showing that the single crystal result is representative of a bulk sample of G4-Cl.

[00408] The single crystal structure (Figure 5 and Table A) combined with the simulated XRPD pattern (Figure 6) confirm that G4-Cl is in the open form in the solid state.

[00409] A single crystal grown of the free base of G4-Cl was grown from ethanol and used to obtain a crystal structure of the free base of G4-Cl (Figure 7). When
10 this crystal structure was combined with a simulated XRPD pattern these studies confirm that the free base of G4-Cl exists as a hydrate under certain conditions.

In Vitro Assays**Example 18****MIC determination against mycobacteria**

[00410] The measurement of the Minimum Inhibitory Concentration (MIC) against *M. tuberculosis* strains for each tested compound was performed in 96-well flat-bottom, polystyrene microtiter plates in a final volume of 100uL. Ten two-fold drug dilutions in neat DMSO starting at 50mM were performed. Drug solutions were added to Middlebrook 7H9 medium (Difco) and isoniazid (INH) (Sigma Aldrich) was used as a positive control with 2-fold dilutions of INH starting at 160ug/mL. The inoculum was standardized to approximately 1x10⁷ cfu/ml and diluted 1 in 100 in Middlebrook 7H9 broth (Difco). This inoculum (100uL) was added to the entire plate but G-12 and H-12 wells were used as blank controls. All plates were placed in a sealed box to prevent drying out of the peripheral wells and incubated at 37°C without shaking for six days. A Resazurin solution was prepared by dissolving one tablet of Resazurin (Resazurin Tablets for Milk Testing; Ref 330884Y' VWR International Ltd) in 30mL of sterile PBS (phosphate buffered saline). Of this solution, 25uL were added to each well. Fluorescence was measured (Spectramax M5 Molecular Devices, Excitation 530nm, Emission 590nm) after 48 hours to determine the MIC value.

[00411] **Example 19**

MIC against Clinical strains

[00412] The BACTEC MGIT 960 System (Becton Dickinson) was used to carry out MIC determination in clinical isolates (Institute Carlos III) following the manufacturer instructions. The resistance pattern of clinical isolates is indicated by the following abbreviations H: Isoniazide, R: Rifampicin, T: Ethionamide, S: Streptomycin, E: Ethambutol, Z: Pyrazinamide, K: Kanamycin, A: Amikacin and CP: Capreomycin. Results for compound **EXAMPLE 4** G4-CI are shown in Tables 1A, 1B, 2A and 2B, and Figures 3 and 4. Results for **EXAMPLE 2** G2-Br are shown in Tables 2C and 2D, and Figure 4.

[00413] **Table 1 provides MIC values for EXAMPLE 4 G4-CI tested against *M. tuberculosis* Sensitive (A) and Resistant (B) Clinical Isolates**

A

Strain	362	457	3	356	357	370	137	169	192	199	206	207	208	223
MIC (μM)	0.04	0.04	0.04	0.04	0.04	0.04	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08
Strain	231	237	247	248	249	250	253	255	256	257	261	265	269	281

MIC (μ M)	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08
Strain	292	296	311	314	316	317	322	323	324	326	327	328	329	332
MIC (μ M)	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08
Strain	333	337	358	361	371	385	391	424	440	442	460	481	716	729
MIC (μ M)	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08
Strain	730	731	733	734	736	737	52	267	374	274	325	705	161	
MIC (μ M)	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.16	0.16	0.16	0.31	

B

Strain	1819	670	330	198	242	409	141	415	330
Resistance	HSRZ	HRZ	RSR	H	H	HR	HRT	HRT	HS
MIC (μ M)	≤ 0.02	0.04	0.04	0.08	0.08	0.08	0.08	0.08	0.08
Strain	175	709	732	201	202	277	605	123	106
Resistance	S	S	S	HRE	S	H	HSERZ ACp	HSERZ KTACp	HR
MIC (μ M)	0.08	0.08	0.08	0.08	0.08	0.08	0.16	0.16	0.16
Strain	562	139	514	1672	167	254	297	192	CR
Resistance	HSERZ KTA	HSERZK TACp	HSRT	HSRZ	HSRZ	H	HSR	HS	HSERZ
MIC (μ M)	0.08	0.08	0.08	0.08	0.08	0.16	0.16	0.31	0.31

[00414] Figure 3 provides a graphical representation of the MIC data in
 5 Tables 1A and 1B for EXAMPLE 4 G4-CI, plotted as number of strains with a particular
 MIC value (y) versus the particular MIC value obtained (x) in μ M. As can be seen in
 Figure 3, G4-CI (Example 4) exhibited a MIC value of less than 0.1 μ M against 85 of the 96
 clinical isolate strains tested (sensitive and resistant), indicating the very good activity of this
 compound against a significant number of *M. tuberculosis* clinical isolate strains. The
 10 breakdown is a measured MIC of ≤ 0.2 μ M for 1 strain; a measured MIC of 0.04 μ M for 8
 strains; a measured MIC of 0.08 μ M for 76 strains; a measured MIC of 0.16 μ M for 8 strains;
 and a measured MIC of 0.31 μ M for 3 strains.

[00415] Tables 2A and 2B provide MIC values for EXAMPLE 4 G4-CI
 tested against *M. tuberculosis* Sensitive (A) and Resistant (B) Clinical Isolates

15 A

Strain	137	169	192	199	206	207	208	223	231	237	247	248
MIC (μ M)	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08
Strain	249	255	261	265	269	281	292	314	316	317	322	323
MIC (μ M)	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08
Strain	324	326	327	328	329	332	333	358				

MIC (μM)	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08
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B

Strain	175	198	242	330	141
Resistance	S	H	H	HSR	HRT
MIC (μM)	0.08	0.08	0.08	0.08	0.08
Strain	1819	1672	167	139	123
Resistance	HSRZ	HSRZ	HSRZ	HSERZKTACp	HSERZKTACp
MIC (μM)	0.02	0.08	0.08	0.08	0.16

[00416] Tables 2C and 2D provide MIC values for EXAMPLE 2 G2-Br tested against the same *M. tuberculosis* Sensitive (A) and Resistant (B) Clinical Isolates tested in 2A and 2B with G4-CI

C

Strain	137	169	192	199	206	207	208	223	231	237	247	248
MIC (μM)	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08
Strain	249	255	261	265	269	281	292	314	316	317	322	323
MIC (μM)	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08
Strain	324	326	327	328	329	332	333	358				
MIC (μM)	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08				

D

Strain	175	198	242	330	141
Resistance	S	H	H	HSR	HRT
MIC (μM)	0.08	0.08	0.08	0.08	0.08
Strain	1819	1672	167	139	123
Resistance	HSRZ	HSRZ	HSRZ	HSERZKTACp	HSERZKTACp
MIC (μM)	0.04	0.08	0.08	0.08	0.08

10

[00417] Figure 4 provides a graphical representation of the MIC data in Tables 2A through 2D for G2-Br (Example 2 – light bar) and G4-CI (Example 4 – dark bar), plotted as number of strains with a particular MIC value (y) versus the particular MIC value obtained (x), in μM. As can be seen in Figure 4, G4-CI (Example 4) and G2-Br (Example 2) exhibited a MIC value of less than 0.1 μM for nearly all of the *M. tuberculosis* clinical isolate strains tested in this experiment. The breakdown is a measured MIC of ≤0.2 μM for 1 strain G4-CI (Example 4); a measured MIC of 0.04 μM for 1 strain (G2-Br (Example

15

2)); a measured MIC of 0.08 μ M for 40 strains (G2-Br (Example 2) and G4-Cl (Example 4)); a measured MIC of 0.16 μ M for 1 strain (G2-Br (Example 2) and G4-Cl (Example 4)); and no measured MIC of 0.31 μ M for G2-Br (Example 2) or G4-Cl (Example 4) for any strain.

Example 20

5 General antimicrobial activity assay

[00418] Whole-cell antimicrobial activity was determined by broth microdilution using the Clinical and Laboratory Standards Institute (CLSI) recommended procedure, Document M7-A7, "Methods for Dilution Susceptibility Tests for Bacteria that Grow Aerobically".

10 [00419] Table 3 provides MIC values against bacterial strains K12; *E. coli* K12 tolC/Tn10; *A. baumannii* ATCC 17978; and *P. aeruginosa* PA01 for compounds disclosed in the Examples. As can be seen, the Example compounds do not generally possess significant activity across several pathogenic Gram negative bacteria, as well as an efflux pump deficient *E. coli*. But as shown in Table 4 below, the compounds disclosed in the

15 Examples do possess significant activity against *M. tuberculosis*. Moreover, as can be seen, tricyclic comparator benzoxaboroles lacking a 4-halogen (eg C2-H, C5-H and C12-H) have greater activity against these bacterial strains whereas benzoxaborole compounds with the third ring being a seven-membered ring between the 1 and 7 positions of the benzoxaborole, additionally having 4-halo, 3-aminomethyl substitution with (S) stereochemistry at the 3

20 position (eg G2-Br and G4-Cl) have very poor activity against these bacteria. This is in marked contrast to their respective activities against *M. tuberculosis*, where the 4-halo compounds generally display very good activity but the benzoxaboroles without a 4-halogen are poorer (compare the *M. tuberculosis* MIC values for the same set of compounds in Tables 4A and 4B).

[00420] Table 3 provides MIC values against bacterial strains K12; *E. coli* K12 tolC/Tn10; *A. baumannii* ATCC 17978; and *P. aeruginosa* PA01 for compounds disclosed in the Examples.

Compound	MIC: <i>E. coli</i> K12 [ug/mL]	MIC: <i>E. coli</i> K12 tolC::Tn10 [ug/mL]	MIC: <i>A. baumannii</i> ATCC 17978 [ug/mL]	MIC: <i>P. aeruginosa</i> PA01 [ug/mL]
Example 1 G1-Br	>64	>64	>64	>64
Example 2 G2-Br	64	64	64	64
Example 3 G3-Cl	>64	>64	>64	>64
Example 4 G4-Cl	64	64	64	64
Example 5 G5-F	32	64	>64	4
Example 6 G6-I	-	-	-	-
Example 7 G7-Cl	>64	>64	>64	>64
Example 8 G8-Br	>64	>64	>64	>64
Example 9 G9-Br	>64	>64	>64	>64
Example 10 G10-Br	>64	>64	>64	>64
Example 11 G11-Cl	>64	>64	>64	>64
Example 12 G12-Cl	>64	>64	>64	>64
C1-H	-	-	-	-
C2-H	2	4	2	2
C3-H	-	-	-	-
C4-Br	64	64	64	64
C5-H	-	-	-	-
C6-Cl	64	64	64	64
C7-Cl2	-	-	-	-
C8-Cl	-	-	-	-
C9-Cl	-	-	-	-
C10-H	-	-	-	-
C11-H	2	2	4	2
C12-H	4	2	4	16
C13-Cl	-	-	-	-
C14-Cl2	-	-	-	-
C15-F	-	-	-	-

Compound	MIC: <i>E. coli</i> K12 [ug/mL]	MIC: <i>E. coli</i> K12 tolC::Tn10 [ug/mL]	MIC: <i>A. baumannii</i> ATCC 17978 [ug/mL]	MIC: <i>P. aeruginosa</i> PA01 [ug/mL]
C16-Cl	-	-	-	-
C17-Cl	-	-	-	-
C18-Br	-	-	-	-
C19-Br	-	-	-	-

[00421] Example 21

LeuRS Expression and Purification

[00422] For biochemical analyses an N-terminal six histidine-tagged LeuRS was over-expressed in *Escherichia coli* which were *E. coli* codon-optimised (GenScript, Piscataway NJ, USA), from human mitochondria and cytoplasm, and *M. tuberculosis*. N-terminal six histidine-tagged LeuRS proteins were over-expressed and purified according to Novagen (Madison, WI, USA) using an *E. coli* BL21(DE3) T7 RNA polymerase over-expression strain.

[00423] Example 22

Aminoacylation assay

[00424] Experiments were performed in 96-well microtiter plates, using 80 µL reaction mixtures containing 50 mM HEPES-KOH (pH 8.0), 30 mM MgCl₂ 30 mM KCl, 13 µM L-[¹⁴C]leucine (306 mCi/mmol, Perkin-Elmer), 15 uM total *E. coli* tRNA (Roche, Switzerland), 0.02% (w/v) BSA, 1 mM DTT, 0.2 pM LeuRS and 4 mM ATP at 30 °C. Reactions were started by the addition of 4 mM ATP. After 7 minutes, reactions were quenched and tRNA was precipitated by the addition of 50 µL of 10% (w/v) TCA and transferred to 96-well nitrocellulose membrane filter plates (Millipore Multiscreen HTS, MSHAN4B50). Each well was then washed three times with 100 µL of 5% TCA. Filter plates were then dried under a heat lamp and the precipitated L-[¹⁴C]leucine tRNA_{Leu} were quantified by liquid scintillation counting using a Wallac MicroBeta Trilux model 1450 liquid scintillation counter

(PerkinElmer, Waltham, MA, USA). The only difference was with the human cytoplasmic LeuRS when we used tRNA isolated from Brewer's Yeast (Roche Diagnostics GmbH).

[00425] Example 23

IC₅₀ determination

5 **[00426]** To determine the inhibitor concentration, which reduces enzyme activity by 50% (IC₅₀), increasing concentrations of compound (Anacor Pharmaceuticals Inc., Palo Alto, CA, USA) were incubated with LeuRS enzyme, tRNA and L-leucine 20 minutes. Reactions were initiated by the addition of 4 mM ATP. Reactions were stopped after 7 minutes then precipitated and counted to quantify radioactivity. IC₅₀ values were
10 determined using the Graphpad Prism software package (Graphpad Software Inc. (La Jolla, CA, USA).

[00427] Example 24

HepG2 cytotoxicity assay

[00428] HepG2 cells (HB-8065) were fed fresh medium (Essential Minimum
15 Eagle Medium, EMEM, supplemented with 5% fetal calf serum and 2mM L-glutamine) the day before subculturing the plates. On the day of plate seeding, a cell suspension of 100,000 cells/mL in culture medium was prepared. Cell suspension (100uL) was added in each well of a black 96-well microplate with clear bottom, collagen coated, (Becton Dickinson) except in column 11, that was dispensed only 100uL of culture medium. The plates were incubated
20 for 24h. It was made up a range of 10 doses of test substances by preparing serial dilutions 1:2 from the stock solution in 100% DMSO and made a dilution of 1:200 of each dose in medium, to achieve a final concentration of 0.5% of DMSO. After 24h, culture medium was removed from the plate and 150uL of test compound dilutions were added in two replicates and 150uL of 0.5% DMSO in culture medium to columns 11 and 12 (blank control). Plates
25 were incubated for 48 and at 37°C, 5% CO₂, 95% relative humidity. The medium was then removed and 200uL of fresh culture medium was added and 50uL of Resazurin solution to each well and incubated for 1 h and a half. Plates were removed from incubator to allow the fluorescence to stabilise at room temperature protected from light for 15 min. For read out of viability of cells we used Resazurine (BDH). Resazurin is used as an oxidation-reduction
30 indicator that yields a colorimetric change and a fluorescent signal in response to metabolic activity. As cell grows, metabolic activity results in a chemical reduction of Resazurin indicated by a change from non-fluorescent blue to the reduced fluorescent pink form. The

degree of Resazurin fluorescence is therefore, an indicator of the number of viable cells in the culture system. Fluorescence was measured at an excitation wavelength of 515nm and an emission wavelength of 590nm in a Microplate reader1420 Multilabel HTS counter, Victor 2, (Wallac).

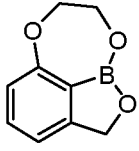
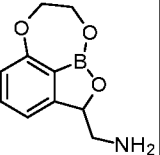
5 **[00429]** The fluorescence value of each well is corrected by subtracting the background value (average of column 11) from the absolute value. The percentages of inhibition are calculated relatively to the DMSO control wells (average of column 12). For each compound, the average value of the duplicate samples is calculated and the curve is fitted to Sigmoidal dose-response (variable slope) nonlinear regression curve adjustment
10 (GraphPad) in order to calculate the IC₅₀ (Tox50).

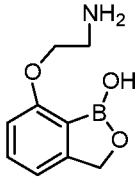
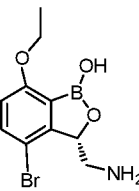
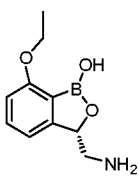
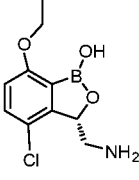
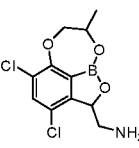
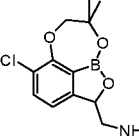
[00430] Example 25

The Effect of Compounds Described Herein Against *Mycobacterium tuberculosis*

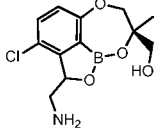
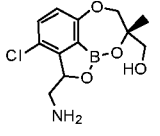
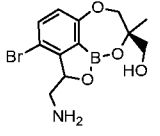
15 **[00431]** Compounds of the present invention were tested for antibacterial activity against a *Mycobacterium tuberculosis* species and also tested for human liver cell toxicity using HepG2 cells. Exemplary compounds as described herein were compared to comparator compounds C1-H through C19-Br, as shown in Tables 4A and 4B.

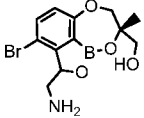
[00432] **Table 4A** provides LeuRS inhibition IC₅₀ values, MIC values against the *M. tuberculosis* standard strain Mtb H37Rv, toxicity values against human HepG2 cells, and selectivity values for Certain Comparator Benzoxaborole Compounds

Compound Designation	Compound Structure	Mtb LeuRS IC ₅₀ (uM)	Human cyto LeuRS IC ₅₀ (uM)	Human mito LeuRS IC ₅₀ (uM)	Mtb H37Rv MIC (uM) (B)	HepG2 cell 48h Tox50 (uM) (A)	Selectivity Index (A/B)
C1-H		12.2	101	-	31	-	-
C2-H (racemic)		0.506	272	>300	1.88	>50	>26

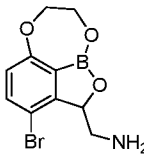
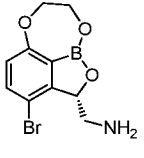
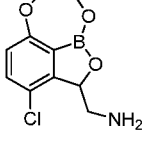
Compound Designation	Compound Structure	Mtb LeuR S IC ₅₀ (uM)	Human cyto LeuRS IC ₅₀ (μM)	Human mito LeuRS IC ₅₀ (μM)	Mtb H37Rv MIC (μM) (B)	HepG2 cell 48h Tox50 (μM) (A)	Selectivity Index (A/B)
C3-H		17.6	35.7	-	62	>50	>0.8
C4-Br		0.07	31, (73, 67)	>300	0.1	32	320
C5-H		0.111	25.6	>300	0.6	1.8	3
C6-Cl		0.05	38.8	>300	0.1	36.3	363
C7-Cl ₂		7.97	-	-	2.5	>50	>20
C8-Cl		6.05	-	-	>5.0	>50	10

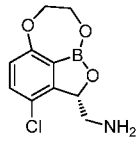
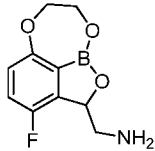
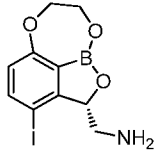
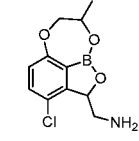
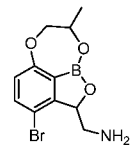
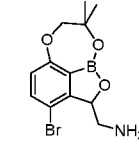
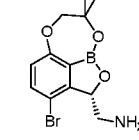
Compound Designation	Compound Structure	Mtb LeuR S IC ₅₀ (uM)	Human cyto LeuRS IC ₅₀ (μM)	Human mito LeuRS IC ₅₀ (μM)	Mtb H37Rv MIC (μM) (B)	HepG2 cell 48h Tox50 (μM) (A)	Selectivity Index (A/B)
C9-Cl		37.59	-	-	5.0	>50	>10
C10-H		>300	-	-	>5.0	>50	10
C11-H		0.51	-	-	1.56	>50 (40%)	>32
C12-H		1.33	-	-	>5.0	24.5	>4.9
C13-Cl		2.16	-	-	5.0	>50	>10
C14-Cl ₂		4.67	-	-	>5.0	>50	>10
EXAMPLE 13 C15-F ((2 <i>S</i> ,8 <i>R</i>)-2-(aminomethyl)-3-fluoro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-8-yl)methanol		0.48	-	-	0.55	>50	>10

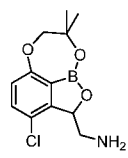
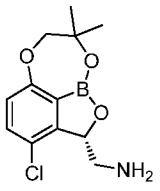
Compound Designation	Compound Structure	Mtb LeuR S IC ₅₀ (uM)	Human cyto LeuRS IC ₅₀ (μM)	Human mito LeuRS IC ₅₀ (μM)	Mtb H37Rv MIC (μM) (B)	HepG2 cell 48h Tox50 (μM) (A)	Selectivity Index (A/B)
EXAMPLE 14 C16-Cl ((8R)-2-(aminomethyl)-3-chloro-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-8-yl)methanol		4.17	-	-	1.25	>50	>4
EXAMPLE 15 C17-Cl ((8S)-2-(aminomethyl)-3-chloro-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-8-yl)methanol		3.13	-	-	0.93	>50	>50
EXAMPLE 16 C18-Br ((8R)-2-(aminomethyl)-3-bromo-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-8-yl)methanol		2.69	-	-	1.25	>50	>40

Compound Designation	Compound Structure	Mtb LeuRS IC ₅₀ (uM)	Human cyto LeuRS IC ₅₀ (μM)	Human mito LeuRS IC ₅₀ (μM)	Mtb H37Rv MIC (μM) (B)	HepG2 cell 48h Tox50 (μM) (A)	Selectivity Index (A/B)
EXAMPLE 17 C19-Br ((8S)-2-(aminomethyl)-3-bromo-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-8-yl)methanol		1.97	-	-	0.925	>50	>50

[00433] **Table 4B** provides LeuRS inhibition IC₅₀ values, MIC values against the *M. tuberculosis* standard strain Mtb H37Rv, toxicity values against human HepG2 cells, and selectivity values for compounds of the Examples set forth below.

Compound Designation	Compound Structure From ¹ NMR in Examples	Mtb LeuRS IC ₅₀ (uM)	Human cyto LeuRS IC ₅₀ (μM)	Human mito LeuRS IC ₅₀ (μM)	Mtb H37Rv MIC (μM) (B)	HepG2 cell 48 h Tox50 (μM) (A)	Selectivity Index (A/B)
EXAMPLE 1 G1-Br		0.154			0.18	>50	>277
EXAMPLE 2 G2-Br		0.115	118	>300	0.07	292.4	4177
EXAMPLE 3 G3-Br		0.244			0.47	> 50	>106

Compound Designation	Compound Structure From ¹ NMR in Examples	Mtb LeuRS IC ₅₀ (uM)	Human cyto LeuRS IC ₅₀ (uM)	Human mito LeuRS IC ₅₀ (uM)	Mtb H37Rv MIC (uM) (B)	HepG2 cell 48 h Tox50 (uM) (A)	Selectivity Index (A/B)
EXAMPLE 4 G4-Cl		0.148	94.7	>300	0.08	>1000	>12500
EXAMPLE 5 G5-F		0.46			0.6	49.1	164
EXAMPLE 6 G6-I		0.33			0.3	36.4	121
EXAMPLE 7 G7-Cl		1.08	>300	-	0.20	>50	>250
EXAMPLE 8 G8-Br		1.43	>300	-	0.30	>50	>167
EXAMPLE 9 G9-Br		1.25	>300	-	0.30	>50	>167
EXAMPLE 10 G10-Br		1.13	>300		0.16	460	2875

Compound Designation	Compound Structure From ¹ NMR in Examples	Mtb LeuRS IC ₅₀ (uM)	Human cyto LeuRS IC ₅₀ (uM)	Human mito LeuRS IC ₅₀ (uM)	Mtb H37Rv MIC (uM) (B)	HepG2 cell 48 h Tox50 (uM) (A)	Selectivity Index (A/B)
EXAMPLE 11 G11-Cl		0.68	>300	-	0.27	>50	>185
EXAMPLE 12 G25-Cl		0.78	>300		0.08	322	4025

[00434] As can be seen in Table 4B, for Examples 2, 4, 10 and 12 (G2-Br, G4-Cl, G10-Br and G12-Cl) there appears to be increased selectivity for inhibiting growth of *M. tuberculosis* versus toxicity for human HepG2 cells for a benzoxaborole compound with the third ring being a seven-membered ring between the 1 and 7 positions of the benzoxaborole, additionally having 4-halo, 3-aminomethyl substitution with (S) stereochemistry at the 3 position.

[00435] Tables 4A and 4B show a comparison of certain benzoxaborole compounds with and without halogen substitution, certain benzoxaborole compounds with and without halogen substitution at position 4 of the benzoxaborole ring structure, and certain bicyclic compounds. From the Mtb H37Rv MIC values (B), and the HepG2 cell 48 h Tox₅₀ values (A), it is possible to determine selectivity for inhibition of *M. tuberculosis* versus inhibition (toxicity) of human cells for these compounds (see far right column of Tables 4A and 4B).

[00436] Compounds **Example 2** G2-Br and **Example 4** G4-Cl were found to have selectivity indices against *M. tuberculosis* of 4177 and >12,500, respectively (see Table 4B). Further, as seen in Table 4B the IC₅₀ values for these compounds against *M. tuberculosis* were found to be sub-micromolar, at 0.13 and 0.1, respectively. As can be seen, the selectivity index (SI) of **Example 2** G2-Br and **Example 4** G4-Cl against *M. tuberculosis* is unexpectedly improved over other benzoxaborole compounds. **Example 2** G2-Br and **Example 4** G4-Cl, which are benzoxaborole compounds having a halogen

substituent at the C-4 position of the benzoxaborole ring and an aminomethyl substituent at position C3 of the benzoxaborole ring having "(S)" relative stereochemistry at that stereocenter, are surprisingly more selective for activity against *M. tuberculosis* than other benzoxaborole compounds lacking some of these features versus inhibition (toxicity) of human cells for these compounds. In addition, the MIC values against *M. tuberculosis* H37Rv strain for **Example 2** G2-Br and **Example 4** G4-Cl are both <0.1 µM in contrast to other benzoxaborole compounds in this study.

[00437] Thus, as seen in Table 4B, compounds **Example 2** G2-Br and **Example 4** G4-Cl were found to have a SI against *Mycobacterium tuberculosis* of 4177 (**Example 2** G2-Br) and >12,500 (**Example 4** G4-Cl), respectively. These SI values are surprisingly better than any of the comparator compounds tested to date.

[00438] Addition of a chloro or bromo substituent at C4 of the benzoxaborole ring confers an unexpected increase in the selectivity index. C2-H (racemic; no halogen substituent at C4 of the benzoxaborole ring) has a selectivity index of >26 whereas **Example 1** G1-Br (racemic; bromo substituent at C-4 of the benzoxaborole ring) has an SI of >277. Similarly, **Example 3** G3-Cl (racemic; chloro substituent at C-4 of the benzoxaborole ring) has an SI of >106 compared to C2-H with an SI of >26.

[00439] Formation of a third ring involving the 1 and 7 positions of the benzoxaborole ring confers an unexpected increase in the selectivity index. C4-Br, the (S) enantiomer of a non-benzoxaborole comparator compound with a Br at the C4 position of the benzoxaborole ring, has an SI of 320, whereas **Example 2** G2-Br, the (S) enantiomer of a benzoxaborole with a Br at the C-4 position, has an SI of 4177. Similarly, C6-Cl, the (S) enantiomer of a non-benzoxaborole comparator compound with a Cl at the C4 position of the benzoxaborole ring, has an SI of 363, whereas **Example 4** G4-Cl, the (S) enantiomer of a benzoxaborole with a Cl at the C-4 position, has an SI of >12,500.

[00440] If one compares the SI of **Example 2** G2-Br and **Example 4** G4-Cl to the SI of C5-H, the (S) enantiomer of a non-benzoxaborole comparator compound with a H at the C4 position of the benzoxaborole ring, one can see the SI of such a compound without a halogen substituent at C4 is only 3, indicating such a compound has very little selectivity for inhibiting *M. tuberculosis* compared to killing human cells.

[00441] Certain substitutions of the 7-membered tricyclic ring confer an unexpected increase in the selectivity index. Table 4B shows **Example 9** G9-Br and **Example 11** G11-Cl with SI indices of >167 and >185, respectively, whereas comparator compounds C9-Cl (a benzoxaborole with a chloro substituent at C4 and -CH₃ substitution at

R³ and R⁴ of the 7-membered ring) and C10-H (a benzoxaborole with a hydrogen at C4 and -CH₃ substitution at R³ and R⁴ of the 7-membered ring) have SI indices of 10. This arguably indicates that substitution at the R³ and R⁴ positions is not favored for selectivity for *M. tuberculosis* versus inhibition (toxicity) of human cells for these compounds. It also suggests
5 that the presence of a halogen at position C4 of the benzoxaborole ring (see C9-Cl) is not sufficient to overcome the negative effect of methyl substitution at both R³ and R⁴ of the 7-membered tricyclic ring at the R³/R⁴ position.

[00442] In other respects **Example 2** G2-Br and **Example 4** G4-Cl also have SI values unexpectedly higher than related open ring benzoxaboroles (substituted
10 benzoxaboroles) lacking a halogen substituent at the C4 position of the benzoxaborole ring. Compare the SI for C5-H (5) to the SIs for **Example 2** G2-Br and **Example 4** G4-Cl. Benzoxaboroles that are not benzoxaboroles but which have a halogen at the C4 position of the benzoxaborole ring show improved SIs relative to no halogen, but still exhibit SI values significantly lower than the SIs for **Example 2** G2-Br and **Example 4** G4-Cl (compare C5-H
15 to C3-Br and C6-Cl; but then compare all three C5-H, C3-Br and C6-Cl to the SI values of **Example 2** G2-Br and **Example 4** G4-Cl).

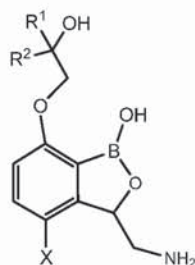
[00443] Thus, the benzoxaboroles of the invention, particularly **Example 2** G2-Br and **Example 4** G4-Cl, show surprisingly higher SIs relative to the SIs of related
20 benzoxaboroles for *M. tuberculosis* versus human cells.

[00444] It is to be understood that the invention covers all combinations of aspects with all other suitable aspects and/or exemplary embodiments described herein. It is to be understood that the invention also covers all combinations of exemplary
25 embodiments with all other suitable aspects and/or exemplary embodiments described herein.

[00445] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and
30 patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

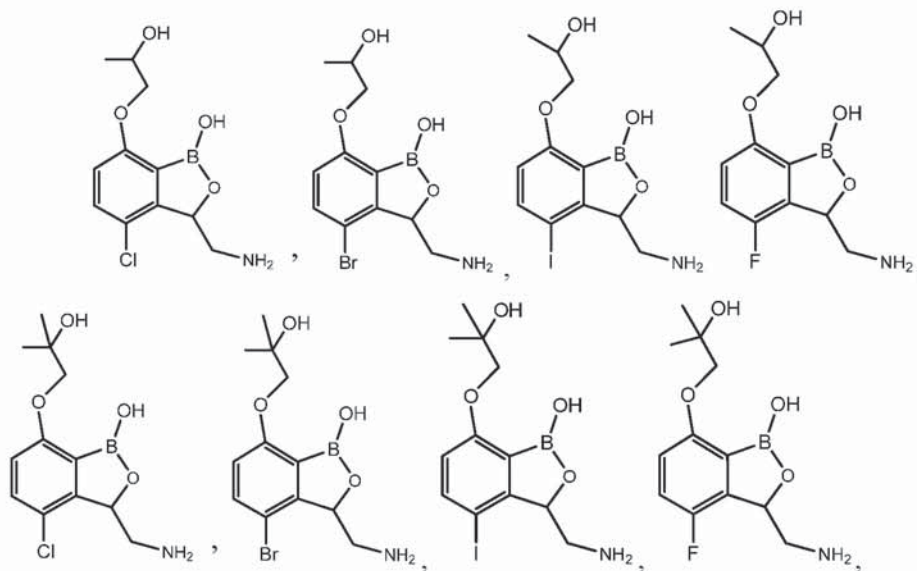
WHAT IS CLAIMED IS:

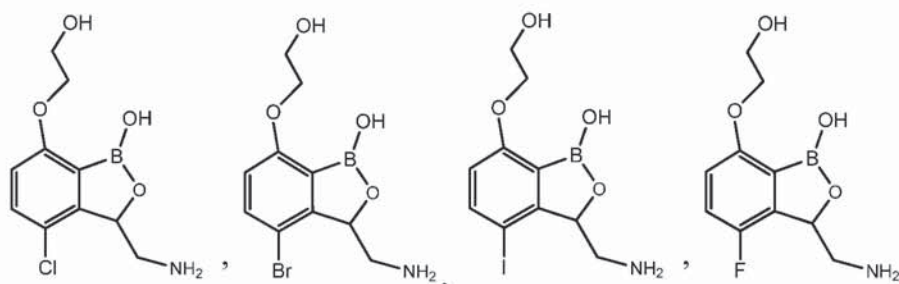
1. A compound comprising the structure of Formula III:

**Formula III**

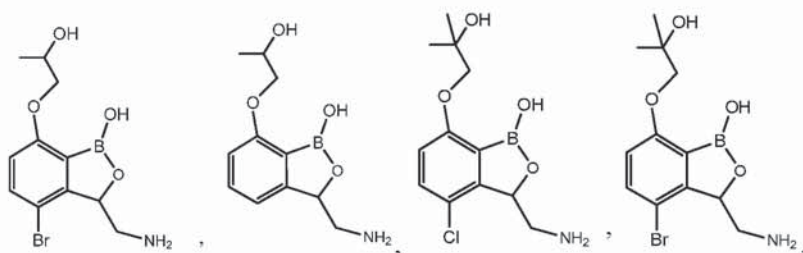
wherein X is selected from fluoro, chloro, bromo or iodo and R^1 and R^2 are each independently selected from H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, and $-CH(CH_3)_2$; or a salt or hydrate thereof.

2. A compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein X is chloro or bromo.
3. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, comprising the structure of Formula III as indicated below:

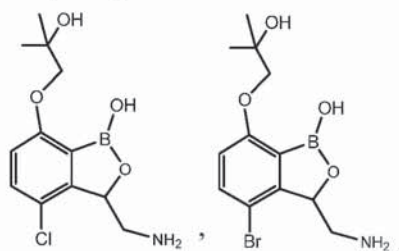




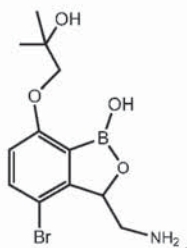
4. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, comprising the structure of Formula III as indicated below:



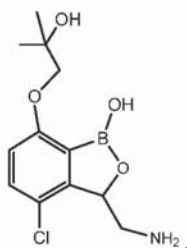
5. A compound according to claim 1 or a pharmaceutically acceptable salt thereof, comprising the structure of Formula III as indicated below:



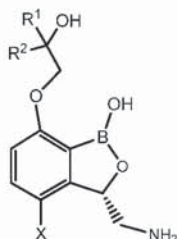
6. A compound according to claim 1 or a pharmaceutically acceptable salt thereof, comprising the structure of Formula III as indicated below:



7. A compound according to claim 1 or a pharmaceutically acceptable salt thereof, comprising the structure of Formula III as indicated below:



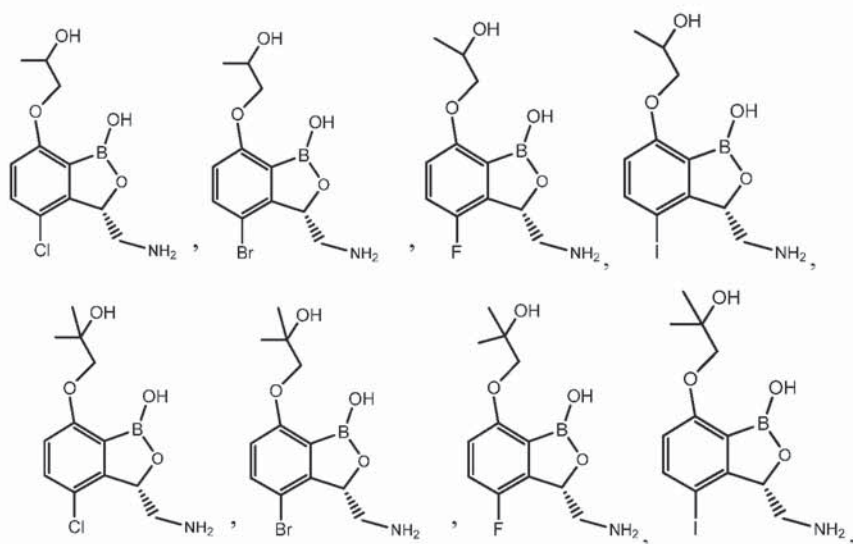
8. A compound comprising the structure of Formula IIIa:

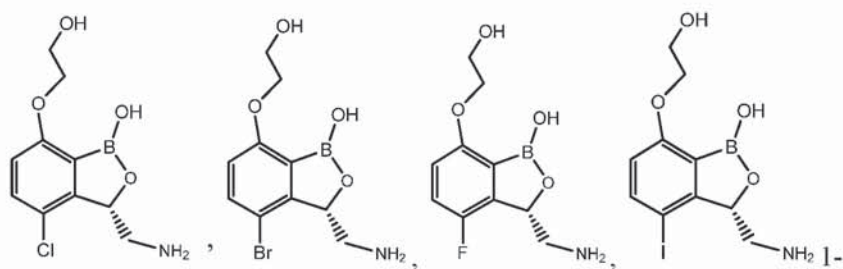


Formula IIIa

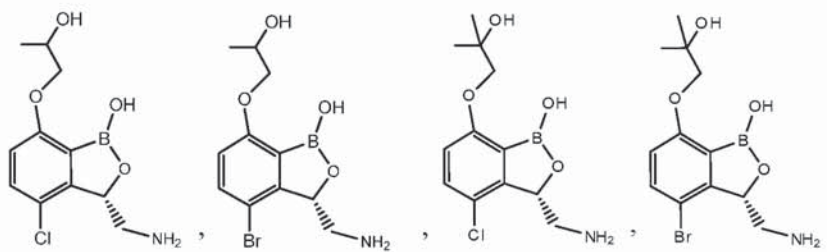
wherein X is fluoro, chloro, bromo or iodo, and R¹ and R² are each independently selected from H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, and -CH(CH₃)₂, or a salt or hydrate thereof.

9. A compound according to claim 8 or a pharmaceutically acceptable salt thereof, comprising a structure of Formula IIIa as indicated below:

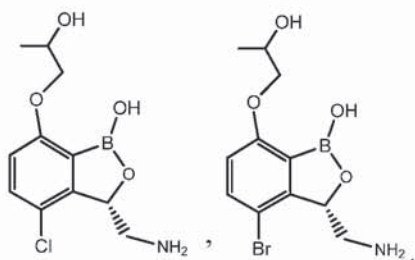




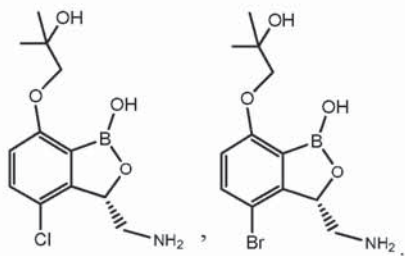
10. A compound according to claim 9 or a pharmaceutically acceptable salt thereof, comprising a structure of Formula IIIa as indicated below:



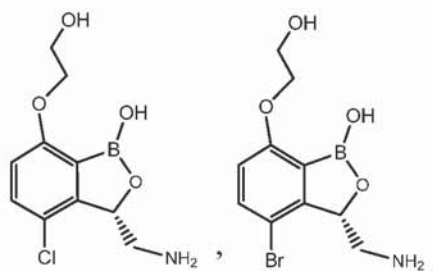
11. A compound according to claim 9 or a pharmaceutically acceptable salt thereof, comprising a structure of Formula IIIa as indicated below:



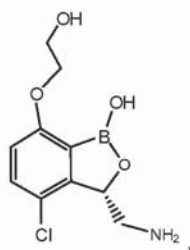
12. A compound according to claim 9 or a pharmaceutically acceptable salt thereof, comprising a structure of Formula IIIa as indicated below:



13. A compound according to claim 9 or a pharmaceutically acceptable salt thereof, comprising the structure of Formula IIIa as indicated below:

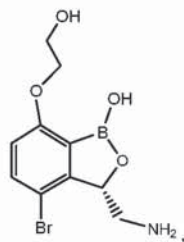


14. A compound according to claim 9 or a pharmaceutically acceptable salt thereof, comprising the structure of Formula IIIa as indicated below:



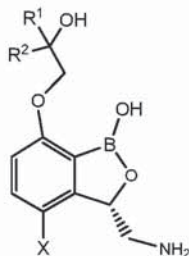
or a pharmaceutically acceptable salt thereof.

15. A compound according to claim 9, or a pharmaceutically acceptable salt thereof, comprising the structure of Formula IIIa as indicated below:



or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable excipient.

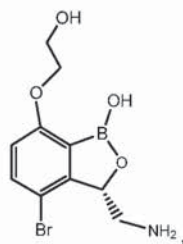
16. A compound comprising the structure of Formula IIIa:



Formula IIIa

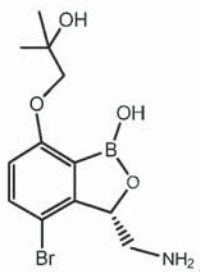
wherein X is fluoro, chloro, bromo or iodo, and R^1 and R^2 are each independently selected from H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, and $-CH(CH_3)_2$, or a salt or hydrate thereof.

17. A compound according to claim 16 consisting of the structure of Formula IIIa as indicated below:



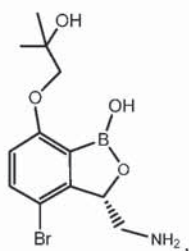
or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable excipient.

18. A compound according to claim 16 consisting of the structure of Formula IIIa as indicated below:



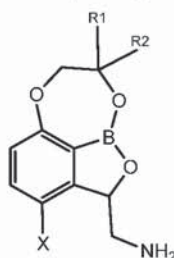
or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable excipient.

19. A compound according to claim 16 consisting of the structure of Formula IIIa as indicated below:



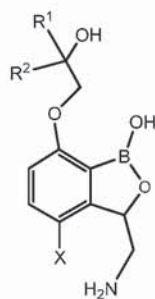
or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable excipient.

20. A compound, or a pharmaceutically acceptable salt thereof, in equilibrium in the presence of water between a closed form comprising the structure of Formula II:



Formula II,

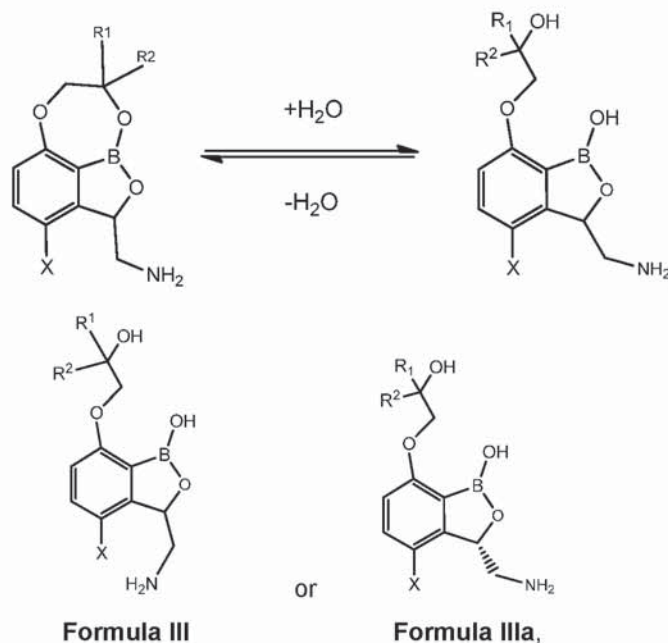
and an open form comprising the structure of Formula III,



Formula III

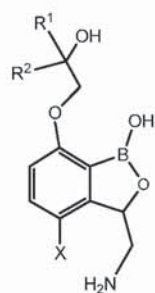
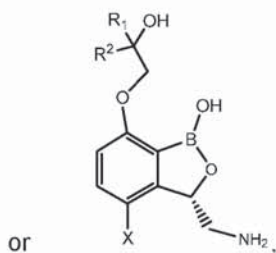
wherein X is selected from chloro, fluoro, bromo and iodo; R¹ and R² are each independently selected from H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, and -CH(CH₃)₂.

21. A compound or a pharmaceutically acceptable salt thereof, in equilibrium in the presence of water between a compound having the structure of Formula III below and a compound have the structure of Formula IIIa below:



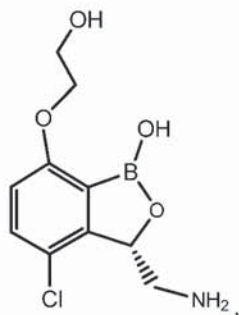
wherein X is chloro or bromo and R^1 and R^2 are independently selected from H and CH_3 .

22. A compound having a single X-ray crystal structure as shown in Figure 5, together with a pharmaceutically acceptable salt thereof.
23. A compound having an XRPD pattern substantially as shown in Figure 6, or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable excipient..
24. A compound or a pharmaceutically acceptable salt thereof, in the presence of water comprising the structure of Formula III or Formula IIIa:

**Formula III****Formula IIIa,**

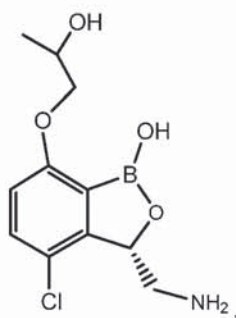
wherein X is chloro or bromo and R¹ and R² are independently selected from H and CH₃.

25. A compound consisting of the structure as shown below:



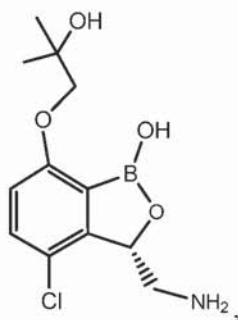
or a pharmaceutically acceptable salt thereof.

26. A compound consisting of the structure as shown below:



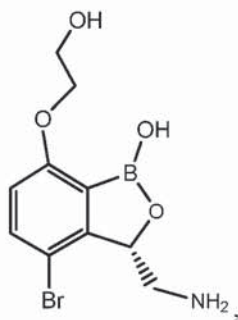
or a pharmaceutically acceptable salt thereof.

27. A compound consisting of the structure as shown below:



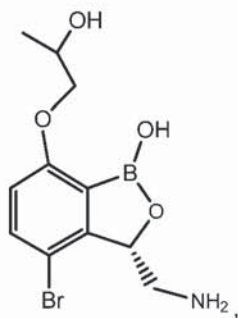
or a pharmaceutically acceptable salt thereof.

28. A compound consisting of the structure as shown below:



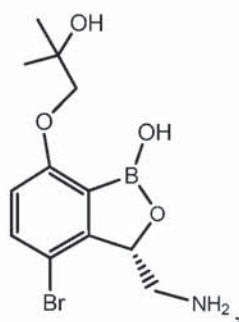
or a pharmaceutically acceptable salt thereof.

29. A compound consisting of the structure as shown below:



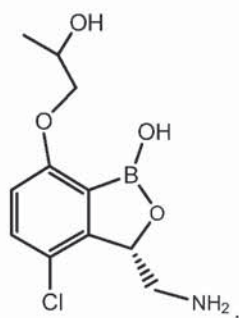
or a pharmaceutically acceptable salt thereof.

30. A compound consisting of the structure as shown below:

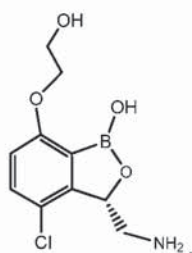


or a pharmaceutically acceptable salt thereof.

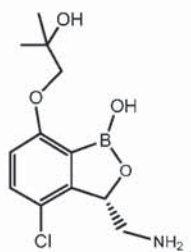
31. A composition comprising a compound according to claim 8 or a pharmaceutically acceptable salt thereof, whose structure is:



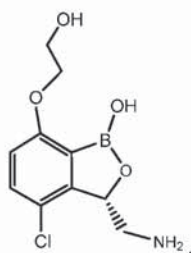
32. A composition comprising a compound according to claim 8 or a pharmaceutically acceptable salt thereof, whose structure is:



33. A composition comprising a compound according to claim 8 or a pharmaceutically acceptable salt thereof, whose structure is:

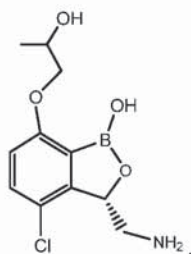


34. A pharmaceutical composition comprising a compound, (S)-(3-chloro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine hydrochloride, whose structure comprises:



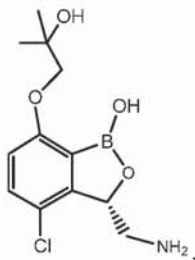
together with a pharmaceutically acceptable salt and a pharmaceutically acceptable excipient.

35. A pharmaceutical composition comprising a compound, (3S)-S-(3-chloro-8-methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine hydrochloride, having a structure:



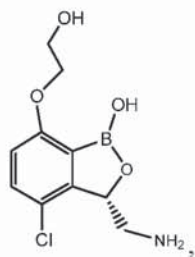
together with pharmaceutically acceptable salt and a pharmaceutically acceptable excipient.

36. A pharmaceutical composition comprising a compound, (S)-(3-chloro-8,8-dimethyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methanamine hydrochloride, whose structure is:



together with a pharmaceutically acceptable salt and a pharmaceutically acceptable excipient.

37. A pharmaceutically acceptable salt of a compound whose structure is:



wherein the pharmaceutically acceptable salt is a hydrochloride salt (HCl) or a dihydrogen sulfate (H₂SO₄) salt.

38. A compound according to any preceding claim wherein the pharmaceutically acceptable salt is selected from a hydrochloride, a hydrobromide, a hydriodide, a nitride, a carbonate, a monohydrogencarbonate, a phosphate, a monohydrogenphosphate, a dihydrogenphosphate, a sulfate, a monohydrogensulfate, a dihydrogensulfate, or a phosphonate salt.

39. A compound according to any preceding claim wherein the pharmaceutically acceptable salt is an acetate, a propionate, an isobutyrate, a maleate, a malonate, a benzoate, a succinate, a suberate, a fumarate, a glucuronate, a galacturonate, a lactate, a mandelate, a phthalate, a benzenesulfonate, a p-tolylsulfonate, a citrate, a tartrate, or a methanesulfonate salt.

40. A compound according to any of claims any preceding claim wherein the pharmaceutically acceptable salt is a salt of an amino acid including an arginate or a lysinate salt.

41. A compound according to claim any preceding claim wherein the pharmaceutically acceptable salt is a hydrochloride salt or a dihydrogensulfate salt.
42. A method of killing a mycobacteria and/or inhibiting the replication of mycobacteria that cause disease in an animal, comprising contacting the mycobacteria or the animal infected with the mycobacteria with a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof according to any of claims 1-41, so as to kill the mycobacteria and/or prevent the replication of the mycobacteria.
43. A method according to claim 23, wherein the mycobacteria is *Mycobacterium tuberculosis*.
44. A method according to claim 42, wherein the disease is tuberculosis.
45. A method according to claim 42, wherein the animal is a human.
- ~~46. A compound whose structure comprises Formula III or Formula IIIa according to any of claims 1-42, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease resulting from a mycobacterial infection in an animal. **(Deleted)**~~
47. A compound according to claim 46, wherein the mycobacterial infection is a *Mycobacterium tuberculosis* infection. **(Deleted)**
48. A compound according to claim 46, wherein the disease is selected from tuberculosis, leprosy, Johne's disease, Buruli or Bairnsdale ulcer, Crohn's disease, pulmonary disease or pulmonary infection, pneumonia, bursa, synovial, tendon sheaths, localized abscess, lymphadenitis, skin and soft tissue infections Lady Windermere syndrome, MAC lung disease, disseminated *Mycobacterium avium* complex (DMAC), disseminated *Mycobacterium avium intracellulare* complex (DMAIC), hot-tub lung, MAC mastitis, MAC pyomyositis, *Mycobacterium avium* paratuberculosis, or granuloma disease.
- ~~49. A compound according to claim 48, wherein the disease is tuberculosis. **(Deleted)**~~
- ~~50. A compound according to claim 48, wherein the animal is a human. **(Deleted)**~~
- ~~51. A use of a compound whose structure comprises Formula III or Formula IIIa according to any of claims 1-41, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a mycobacterial infection in an animal.~~

~~52. The use of claim 51, wherein the mycobacterial infection is a *Mycobacterium tuberculosis* infection. (Deleted)~~

~~53. The use of claim 52 wherein the animal is a human. (Deleted)~~

Dated this 11th day of September 2017



**Archana Shanker
Of Anand and Anand Advocates
Agents for the Applicants**

Abstract

COMPOSÉS BENZOXABOROLE ET LEURS UTILISATIONS

Compounds whose structure comprises Formula II, or a compound whose structure comprises Formula III wherein X is selected from chloro, fluoro, bromo and iodo, R1 and R2 are each independently selected from H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, or -CH(CH₃)₂, compositions containing them, their use in therapy, including their use as anti-mycobacterial agents, for example in the treatment of a mycobacterial infection in a mammal, and methods for the preparation of such compounds, are provided.

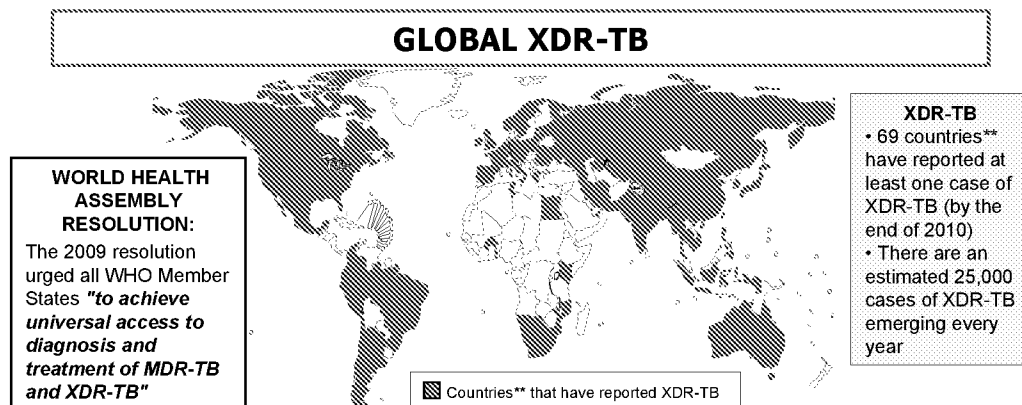


FIGURE 1

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Transmission of *M. tuberculosis*

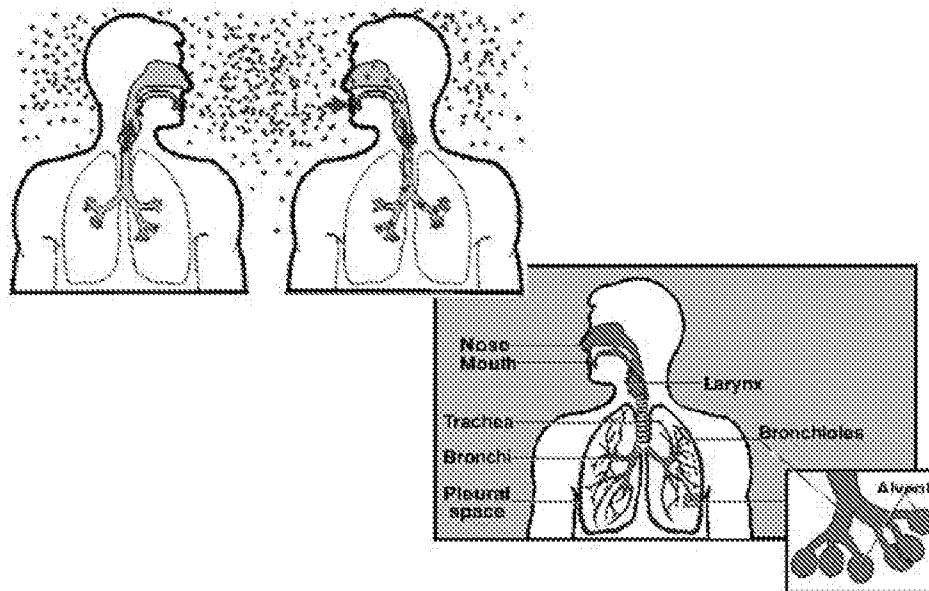


FIGURE 2

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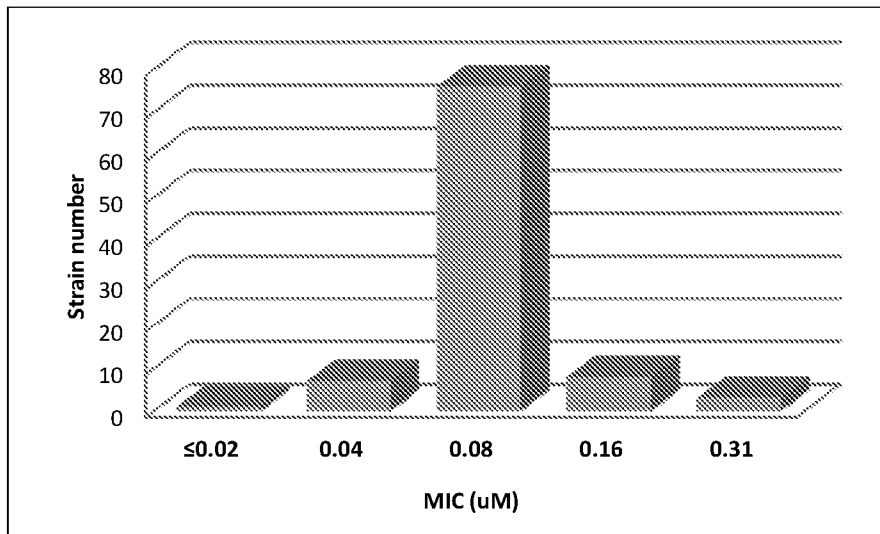


FIGURE 3

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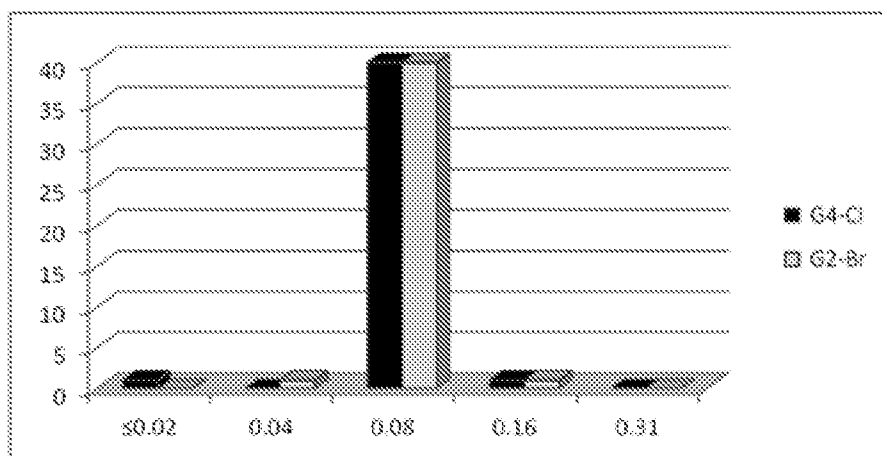


FIGURE 4

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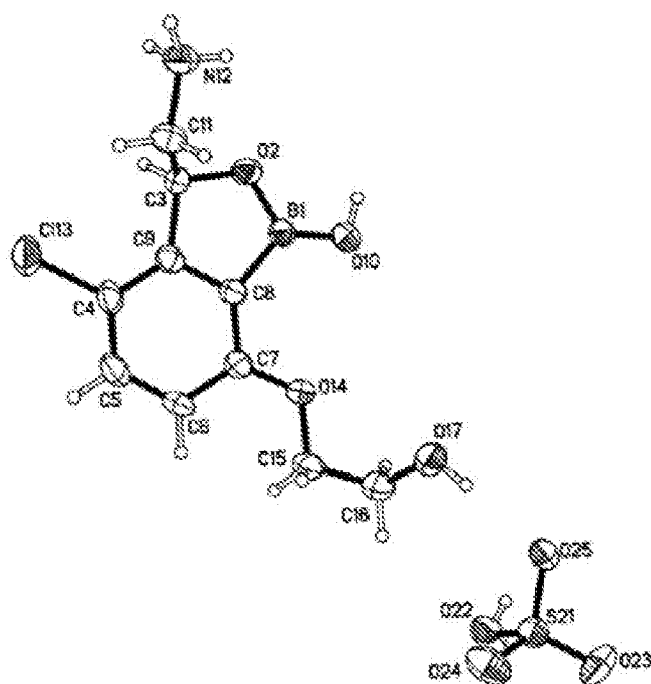


FIGURE 5

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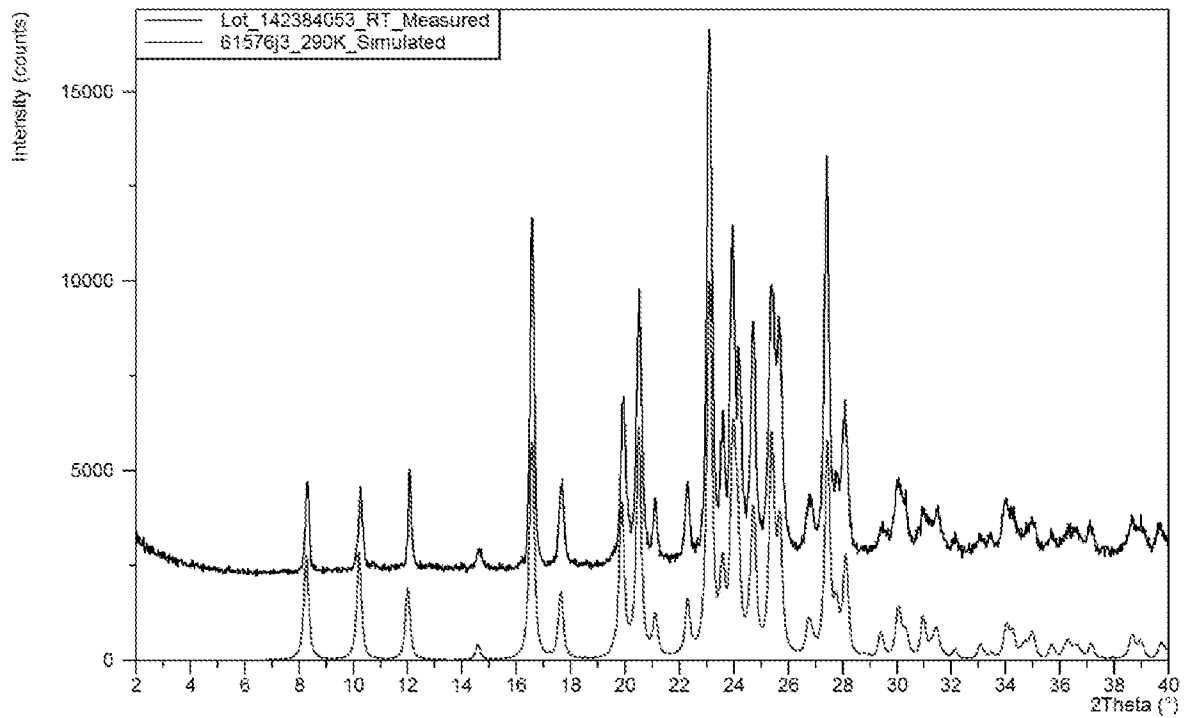


FIGURE 6

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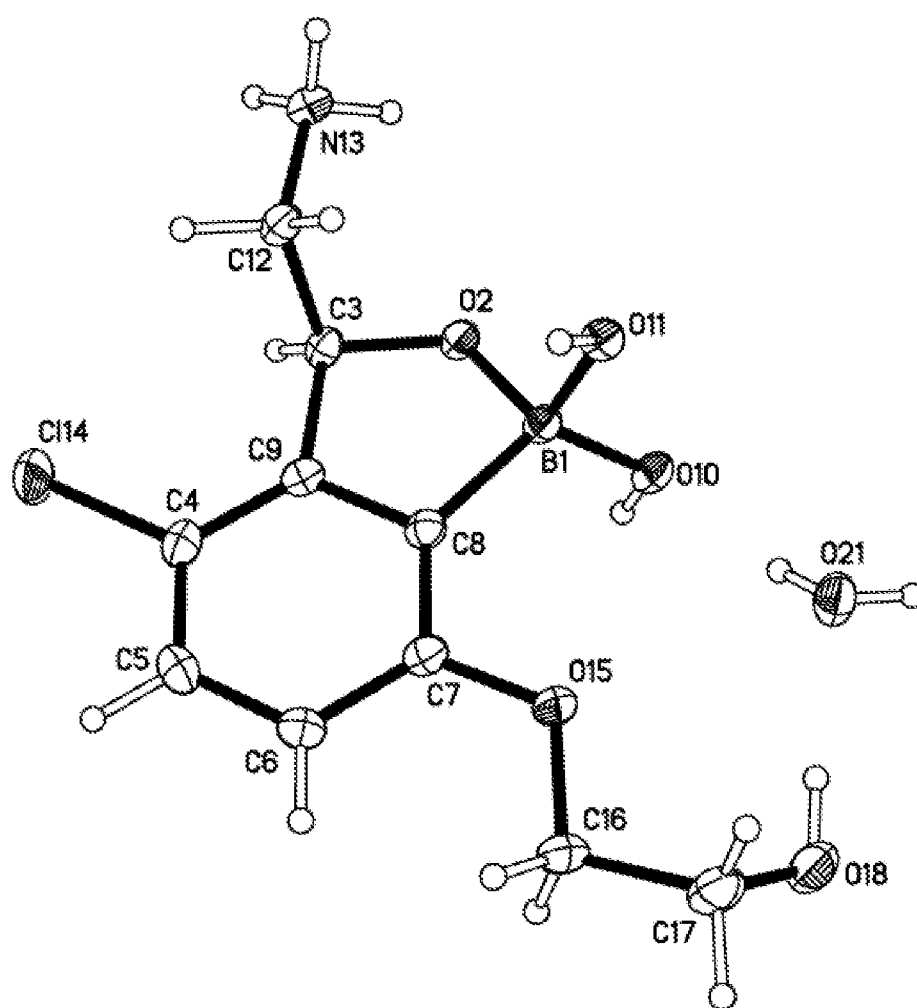


FIGURE 7

Archana

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C07F 5/02 (2006.01)(71) Applicant (for all designated States except US): **ANACOR PHARMACEUTICALS, INC.** [US/US]; 1020 East Meadow Circle, Palo Alto, CA 94303 (US).

(21) International Application Number:

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(72) Inventors; and

(22) International Filing Date:

7 September 2011 (07.09.2011)

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[Continued on next page]

(54) Title: BORON-CONTAINING SMALL MOLECULES

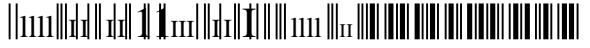
Figure 1

Compound #	A. baumannii ATCC 17978 MIC	B. subtilis ATCC 29229 MIC	H. influenzae ATCC 39766 MIC	K. pneumoniae ATCC 13883 MIC	P. aeruginosa ATCC 27853 MIC	M. luteus MIC	L. monocytogenes MIC	M. tuberculosis H37Rv MIC	M. tuberculosis H37Rv MIC
A	16	6	3	6	20	0.37	>64	0.97	
B	>64	>64	2	>64	>64	<0.025	>64	0.13	
C	8	4	1	4	>64	0.04	0.52	0.13	
D	>64	>64	0.5	>64	>64	<0.02	0.07	0.09	
E	>64	>64	1	>64	>64	0.05	0.70	0.07	
F	>64	>64	NT	>64	>64	<0.2	26.20	0.2	
G	8	16	NT	8	>64	<0.2	31.90	0.31	
H	>64	>64	NT	>64	>64	16.80	48.46	27.6	
I	>64	>64	NT	>64	>64	0.30	<0.391	0.04	
J	>64	>64	NT	>64	>64	0.59	0.69	0.03	
K	>64	>64	>64	>64	>64	>64	NT	NT	
L	>64	64	<0.12	32	>64	<0.004	<0.039	0.02	
M	>64	>64	NT	>64	>64	NT	NT	21.02	
N	1.5	0.5	NT	1	3	NT	NT	0.09	
O	32	0.74	8	8	64	0.28	>64	0.91	
P	32	NT	4	8	32	1.91	>64	0.896	
Q	32	1.1	16	8	64	3.73	>64	0.878	
R	>64	1.6	16	8	64	1.01	>64	0.892	
S	>64	1.1	8	8	64	0.88	>50	0.61	
T	16	1.345292	16	8	16	NT	NT	0.895	
U	16	1.231968	4	8	>64	0.33	5.91	NT	
V	>64	>64	32	64	>64	NT	NT	0.114	

(57) Abstract: This invention relates to, among other items, benzoxaborole compounds and their use for treating bacterial infections.

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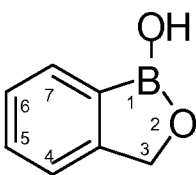
BORON-CONTAINING SMALL MOLECULES**CROSS-REFERENCE TO RELATED APPLICATION**

[0001] This application claims the benefit of U.S. Provisional Pat. App. No. 61/380,596, filed September 7, 2010, which is incorporated by reference in its entirety
5 for all purposes.

BACKGROUND OF THE INVENTION

[0002] The global rise of bacteria and other microorganisms resistant to antibiotics and antimicrobials in general, poses a major threat. Deployment of massive quantities of antimicrobial agents into the ecosphere during the past 60 years has introduced a
10 powerful selective pressure for the emergence and spread of antimicrobial-resistant pathogens. Thus, there is a need to discover new broad spectrum antimicrobials, such as antibiotics, useful in combating microorganisms, especially those with multidrug-resistance.

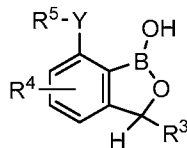
[0003] Boron-containing molecules, such as 1-hydroxy-1,3-dihydro-benzo[c][1,2]
15 oxaborole (also sometimes known as 1-hydroxy-benzo[c][1,2]oxaborole or oxaboroles or cyclic boronic esters), useful as antimicrobials have been described previously, such as in U.S. Pat. Apps. 12/142,692; 11/505,591 and 11/357,687. Generally speaking, a 1-hydroxy-1,3-dihydro-benzo[c][1,2]oxaborole has the following structure and substituent numbering system:



20 Surprisingly, it has now been discovered that certain classes of 1-hydroxy-1,3-dihydro-benzo[c][1,2]oxaboroles are effective antibacterials. This, and other uses of these 1-hydroxy-1,3-dihydro-benzo[c][1,2]oxaboroles are described herein.

SUMMARY OF THE INVENTION

[0004] In a first aspect, the invention provides a compound having a structure according to the formula:



5 wherein R³ is substituted or unsubstituted nitroalkyl or substituted or unsubstituted aminoalkyl; R⁴ is selected from the group consisting of halogen, unsubstituted alkyl and unsubstituted phenyl; Y is O or S; R⁵ is selected from the group consisting of substituted or unsubstituted alkyl and substituted or unsubstituted heteroalkyl, or a salt, hydrate or solvate thereof.

10 [0005] In a second aspect, the invention provides a combination comprising: a) a compound of the invention, or a pharmaceutically acceptable salt thereof; and b) a therapeutically active agent.

[0006] In a third aspect, the invention provides a pharmaceutical formulation comprising: a) a compound of the invention, or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable excipient.

15

[0007] In a fourth aspect, the invention provides a method of killing or inhibiting the growth of a bacteria, said method comprising: contacting said bacteria with an effective amount of a compound of the invention or a combination of the invention, or a pharmaceutically acceptable salt thereof, thereby killing or inhibiting the growth of the bacteria.

20

[0008] In a fifth aspect, the invention provides a method of treating a bacterial infection comprising: administering to an animal suffering from said infection an effective amount of a compound of the invention, or a pharmaceutically-acceptable salt thereof, thereby treating the bacterial infection.

25 [0009] In a sixth aspect, the invention provides a method of inhibiting the editing domain of a t-RNA synthetase, comprising: contacting the synthetase with an effective amount of a compound of the invention, or a pharmaceutically-acceptable salt thereof, thereby inhibiting the synthetase.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] FIG. 1 displays biological data for exemplary compounds of the invention.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions and Abbreviations

5 [0011] As used herein, the singular forms "a," "an", and "the" include plural references unless the context clearly dictates otherwise. For example, reference to "an active agent" includes a single active agent as well as two or more different active agents in combination. It is to be understood that present teaching is not limited to the specific dosage forms, carriers, or the like, disclosed herein and as such may vary.

10 [0012] The abbreviations used herein generally have their conventional meaning within the chemical and biological arts.

[0013] The following abbreviations have been used: Ac is acetyl; AcOH is acetic acid; ACTBr is cetyltrimethylammonium bromide; AIBN is azobisisobutyronitrile or 2,2 azobisisobutyronitrile; aq. is aqueous; Ar is aryl; B₂pin₂ is bis(pinacolato)diboron; Bn is, in general, benzyl [see Cbz for one example of an exception]; (BnS)₂ is benzyl disulfide; BnSH is benzyl thiol or benzyl mercaptan; BnBr is benzyl bromide; Boc is tert-butoxy carbonyl; Boc₂O is di-*tert*-butyl dicarbonate; Bz is, in general, benzoyl; BzOOH is benzoyl peroxide; Cbz or Z is benzyloxycarbonyl or carboxybenzyl; Cs₂CO₃ is cesium carbonate; CSA is camphor sulfonic acid; CTAB is
 15 cetyltrimethylammonium bromide; Cy is cyclohexyl; DABCO is 1,4-diazabicyclo[2.2.2]octane; DCM is dichloromethane or methylene chloride; DHP is dihydropyran; DIAD is diisopropyl azodicarboxylate; DIEA or DIPEA is *N,N*-diisopropylethylamine; DMAP is 4-(dimethylamino)pyridine; DME is 1,2-dimethoxyethane; DMF is *N,N*-dimethylformamide; DMSO is dimethylsulfoxide;
 20 equiv or eq. is equivalent; EtOAc is ethyl acetate; EtOH is ethanol; Et₂O is diethyl ether; EDCI is \wedge -(*S*-dimethylaminopropyl)- \wedge -*N*'-ethylcarbodiimide hydrochloride; ELS is evaporative light scattering; equiv or eq is equivalent; h is hours; HATU is 0-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate; HOBt is *N*-hydroxybenzotriazole; HCl is hydrochloric acid; HPLC is high pressure liquid
 25 chromatography; ISCO Companion is automated flash chromatography equipment with fraction analysis by UV absorption available from Presearch; KOAc or AcOK is potassium acetate; K₂CO₃ is potassium carbonate; LiAlH₄ or LAH is lithium

- aluminum hydride; LDA is lithium diisopropylamide; LHMDs is lithium bis(trimethylsilyl) amide; KHMDS is potassium bis(trimethylsilyl) amide; LiOH is lithium hydroxide; m-CPBA is 3-chloroperoxybenzoic acid; MeCN or ACN is methyl cyanide or cyanomethane or ethanenitrile or acetonitrile which are all names for the
- 5 same compound; MeOH is methanol; MgSO_4 is magnesium sulfate; mins or min is minutes; Mp or MP is melting point; NaCNBH_3 is sodium cyanoborohydride; NaOH is sodium hydroxide; Na_2SO_4 is sodium sulfate; NBS is N-bromosuccinimide; NH_4Cl is ammonium chloride; NIS is N-iodosuccinimide; N_2 is nitrogen; NMM is N-methylmorpholine; n-BuLi is n-butyllithium; overnight is O/N; $\text{PdCl}_2(\text{pddf})$ is I, Γ -
- 10 Bis(diphenylphosphino) ferrocene]dichloropalladium(II); Pd/C is the catalyst known as palladium on carbon; $\text{Pd}_2(\text{dba})_3$ is an organometallic catalyst known as tris(dibenzylideneacetone) dipalladium(O); Ra Ni or Raney Ni is Raney nickel; Ph is phenyl; PMB is *p*-methoxybenzyl; PrOH is 1-propanol; iPrOH is 2-propanol; POCl_3 is phosphorus chloride oxide; PTSA is *para*-toluene sulfonic acid; Pyr. or Pyr or Py as
- 15 used herein means pyridine; RT or rt or r.t. is room temperature; sat. is saturated; Si-amine or Si-NH₂ is amino-functionalized silica, available from SiliCycle; Si-pyr is pyridyl-functionalized silica, available from SiliCycle; TEA or Et₃N is triethylamine; TFA is trifluoroacetic acid; Tf₂O is trifluoromethanesulfonic anhydride; THF is tetrahydrofuran; TFAA is trifluoroacetic anhydride; THP is tetrahydropyran; TMSI
- 20 is trimethylsilyl iodide; H₂O is water; diNO₂-PhSO₂Cl is dinitrophenyl sulfonyl chloride; 3-F-4-NO₂-PhSO₂Cl is 3-fluoro-4-nitrophenylsulfonyl chloride; 2-MeO-4-NO₂-PhSO₂Cl is 2-methoxy-4-nitrophenylsulfonyl chloride; and (EtO)₂POCH₂COOEt is a triethylester of phosphonoacetic acid known as triethyl phosphonoacetate.
- 25 **[0014]** "Compound of the invention," as used herein refers to the compounds discussed herein, salts (e.g. pharmaceutically acceptable salts), prodrugs, solvates and hydrates of these compounds.
- [0015]** The term "poly" as used herein means at least 2. For example, a polyvalent metal ion is a metal ion having a valency of at least 2.
- 30 **[0016]** "Moiety" refers to a radical of a molecule that is attached to the remainder of the molecule.

[0017] The symbol $\sim \wedge \cap$, whether utilized as a bond or displayed perpendicular to a bond, indicates the point at which the displayed moiety is attached to the remainder of the molecule.

[0018] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (*i.e.* Ci-Cio means one to ten carbons). In some embodiments, the term "alkyl" means a straight or branched chain, or combinations thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers.

[0019] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified, but not limited, by $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

[0020] The term "alkenylene" by itself or as part of another substituent means a divalent radical derived from an alkene.

[0021] The term "cycloalkylene" by itself or as part of another substituent means a divalent radical derived from a cycloalkyl.

[0022] The term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from an heteroalkane.

[0023] The term "heterocycloalkylene" by itself or as part of another substituent means a divalent radical derived from an heterocycloalkane.

[0024] The term "arylene" by itself or as part of another substituent means a divalent radical derived from an aryl.

5 [0025] The term "heteroarylene" by itself or as part of another substituent means a divalent radical derived from heteroaryl.

[0026] The terms "alkoxy," "alkylamino" and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively.

10 [0027] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and at least one heteroatom. In some embodiments, the term "heteroalkyl," by itself or in combination with another term, means a stable straight or
 15 branched chain, or combinations thereof, consisting of the stated number of carbon atoms and at least one heteroatom. In an exemplary embodiment, the heteroatoms can be selected from the group consisting of B, O, N and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) B, O, N and S may be placed at any interior
 20 position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to, -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂-S(0)-CH₃, -CH₂-CH₂-S(0)₂-CH₃, -CH=CH-O-CH₃, -CH₂-CH=N-OCH₃, and -CH=CH-N(CH₃)-CH₃. Up to two heteroatoms may be consecutive, such as, for
 25 example, -CH₂-NH-OCH₃. Similarly, the term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified, but not limited by, -CH₂-CH₂-S-CH₂-CH₂- and -CH₂-S-CH₂-CH₂-NH-CH₂-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (*e.g.*, alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the
 30 like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group

is written. For example, the formula - C(0)₂R'- represents both - C(0)₂R'- and - R'C(0)₂.

[0028] The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

[0029] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C₁₋₄)alkyl" is meant to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0030] The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, substituent that can be a single ring or multiple rings (preferably from 1 or 2 or 3 rings), which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four heteroatoms. In an exemplary embodiment, the heteroatom is selected from B, N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalyl, 5-quinoxalyl, 3-quinolyl, and 6-quinolyl.

Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below.

[0031] For brevity, the term "aryl" when used in combination with other terms (*e.g.*, aryloxy, arylthioxy, arylalkyl) includes those radicals in which an aryl group is attached through the next moiety to the rest of the molecule. Thus, the term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (*e.g.*, benzyl, 1-(3-nitrophenyl)ethyl and the like). A substituent such as benzyl or 1-(3-nitrophenyl)ethyl can also be represented by 'substituted alkyl' wherein the ethyl radical is substituted with a 3-nitrophenyl moiety. The term "aryloxy" is meant to include those radicals in which an aryl group is attached to an oxygen atom. The term "aryloxyalkyl" is meant to include those radicals in which an aryl group is attached to an oxygen atom which is then attached to an alkyl group (*e.g.*, phenoxymethyl, 3-(1-naphthyloxy)propyl, and the like).

[0032] For brevity, the term "heteroaryl" when used in combination with other terms (*e.g.*, heteroaryloxy, heteroarylthioxy, heteroarylalkyl) includes those radicals in which a heteroaryl group is attached through the next moiety to the rest of the molecule. Thus, the term "heteroarylalkyl" is meant to include those radicals in which a heteroaryl group is attached to an alkyl group (*e.g.*, pyridylmethyl and the like). The term "heteroaryloxy" is meant to include those radicals in which a heteroaryl group is attached to an oxygen atom. The term "heteroaryloxyalkyl" is meant to include those radicals in which an aryl group is attached to an oxygen atom which is then attached to an alkyl group. (*e.g.*, 2-pyridyloxymethyl and the like).

[0033] Each of the above terms (*e.g.*, "alkyl," "heteroalkyl," "aryl" and "heteroaryl") are meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0034] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) are generically referred to as "alkyl group substituents," and they can be one or more of a variety of groups selected from, but not limited to: -R', -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -C(O)₂R', -CONR'R'', -OC(O)NR'R'', -NR'C(O)R', -NR'-C(O)NR''R''', -NR''C(O)₂R', -NR''''-C(NR'R''R''')=NR''''',

-NR^{'''}-C(NR^{R''})=NR^{'''}, -S(0)R', -S(0)₂R', -S(0)₂NR^{R''}, -NR^{''}S(0)₂R', -CN, -N(0)₂, -N₃, -CH(Ph)₂, fluoro(Ci-C₄)alkoxy, and fluoro(Ci-C₄)alkyl, in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical.

R', R'', R''', R^{'''} and R^{'''} each preferably independently refer to hydrogen,

- 5 substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, *e.g.*, aryl substituted with 1 or 2 or 3 halogens, substituted or unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''', R^{'''} and R^{'''} groups when more than one of these groups is
- 10 present. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6-, or 7-membered ring. For example, -NR'R'' is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups
- 15 other than hydrogen groups, such as haloalkyl (*e.g.*, -CF₃ and -CH₂CF₃) and acyl (*e.g.*, -C(0)CH₃, -C(0)CF₃, -C(0)CH₂OCH₃, and the like).

[0035] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are generically referred to as "aryl group substituents."

- The substituents are selected from, for example: -R', -OR', =O, =NR', =N-OR', -
- 20 NR^{R''}, -SR', -halogen, -SiR'R''R''', -OC(0)R', -C(0)R\ -C(0)₂R', -CONR^{R''}, -OC(0)NR^{R''}, -NR^{''}C(0)R', -NR'-C(0)NR^{R''}, -NR^{''}C(0)₂R', -NR^{'''}-C(NR^{R''}R''')=NR^{'''}, -NR^{'''}-C(NR^{R''})=NR^{'''}, -S(0)R', -S(0)₂R', -S(0)₂NR^{R''}, -NR^{''}S(0)₂R', -CN, -N(0)₂, -N₃, -CH(Ph)₂, fluoro(Ci-C₄)alkoxy, and fluoro(Ci-C₄)alkyl, in a number ranging from zero to the total number of open valences on the aromatic
- 25 ring system; and where R', R'', R''', R^{'''} and R^{'''} are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R',
- 30 R'', R''', R^{'''} and R^{'''} groups when more than one of these groups is present.

[0036] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(0)-(CRR')_q-U-, wherein T and U are independently -NR-, -O-, -CRR'- or a single bond, and q is an

integer from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CRR'-, -O-, -NR'-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'- or a single bond, and r is an integer from 1 or 2 or 3 or 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula - (CRR')_s-X-(CR''R''')_d-, where s and d are independently integers from 0 or 1 or 2 or 3, and X is -O-, -NR'-, -S-, -S(O)-, -S(O)₂-, or -S(O)₂NR'-. The substituents R, R', R'' and R''' are preferably independently selected from hydrogen or substituted or unsubstituted (C₁ or C₂ or C₃ or C₄ or C₅ or C₆)alkyl.

[0037] "Ring" as used herein, means a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. A ring includes fused ring moieties. The number of atoms in a ring is typically defined by the number of members in the ring. For example, a "5- to 7-membered ring" means there are 5 or 6 or 7 atoms in the encircling arrangement. Unless otherwise specified, the ring optionally includes a heteroatom. Thus, the term "5- to 7-membered ring" includes, for example phenyl, pyridinyl and piperidinyl. The term "5- to 7-membered heterocycloalkyl ring", on the other hand, would include pyridinyl and piperidinyl, but not phenyl. The term "ring" further includes a ring system comprising more than one "ring", wherein each "ring" is independently defined as above.

[0038] As used herein, the term "heteroatom" includes atoms other than carbon (C) and hydrogen (H). Examples include oxygen (O), nitrogen (N) sulfur (S), silicon (Si), and boron (B).

[0039] The term "leaving group" means a functional group or atom which can be displaced by another functional group or atom in a substitution reaction, such as a nucleophilic substitution reaction. By way of example, representative leaving groups include triflate, chloro, bromo and iodo groups; sulfonic ester groups, such as mesylate, tosylate, brosylate, nosylate and the like; and acyloxy groups, such as acetoxy, trifluoroacetoxy and the like.

[0040] The symbol "R" is a general abbreviation that represents a substituent group that is selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl and substituted or unsubstituted heterocycloalkyl groups.

[0041] By "effective" amount of a drug, formulation, or permeant is meant a sufficient amount of an active agent to provide the desired local or systemic effect. A "Topically effective," "pharmaceutically effective," or "therapeutically effective" amount refers to the amount of drug needed to effect the desired result.

10 [0042] The term "pharmaceutically acceptable salt" is meant to include a salt of a compound of the invention which is prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with
15 a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino (such as choline or diethylamine or amino acids such as d-arginine, l-arginine, d-lysine or l-lysine), or magnesium salt, or a similar salt. When compounds of the invention contain relatively basic
20 functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric,
25 dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate
30 and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al., "Pharmaceutical Salts", Journal of Pharmaceutical Science 66: 1-19 (1977)). Certain specific compounds of the invention contain both

basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0043] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compounds in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0044] In addition to salt forms, the invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein readily undergo chemical changes under physiological conditions to provide the compounds of the invention. Additionally, prodrugs can be converted to the compounds of the invention by chemical or biochemical methods in an *ex vivo* environment.

[0045] Certain compounds of the invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the invention. Certain compounds of the invention may exist in multiple crystalline or amorphous forms.

[0046] Certain compounds of the invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are encompassed within the scope of the invention. The graphic representations of racemic, ambiscalemic and scalemic or enantiomerically pure compounds used herein are taken from Maehr, *J. Chem. Ed.* 1985, 62: 114-120. Solid and broken wedges are used to denote the absolute configuration of a stereocenter unless otherwise noted. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are included.

[0047] Compounds of the invention can exist in particular geometric or stereoisomeric forms. The invention contemplates all such compounds, including *cis*- and *trans*-isomers, (-)- and (+)-enantiomers, (R)- and (S)-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, such as enantiomerically or diastereomerically enriched mixtures, as falling within the scope of the invention. Additional asymmetric carbon atoms can be present in a

substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

[0048] Optically active (*R*)- and (*S*)-isomers and *d* and *l* isomers can be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques.

5 If, for instance, a particular enantiomer of a compound of the invention is desired, it can be prepared by asymmetric synthesis, or by derivatization with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as an amino group, or an acidic functional
10 group, such as a carboxyl group, diastereomeric salts can be formed with an appropriate optically active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means known in the art, and subsequent recovery of the pure enantiomers. In addition, separation of enantiomers and diastereomers is frequently accomplished using chromatography
15 employing chiral, stationary phases, optionally in combination with chemical derivatization (e.g., formation of carbamates from amines).

[0049] The compounds of the invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for
20 example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the invention, whether radioactive or not, are intended to be encompassed within the scope of the invention.

[0050] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable vehicle" refers to any formulation or carrier medium that provides the
25 appropriate delivery of an effective amount of an active agent as defined herein, does not interfere with the effectiveness of the biological activity of the active agent, and that is sufficiently non-toxic to the host or patient. Representative carriers include water, oils, both vegetable and mineral, cream bases, lotion bases, ointment bases and the like. These bases include suspending agents, thickeners, penetration enhancers,
30 and the like. Their formulation is well known to those in the art of cosmetics and topical pharmaceuticals. Additional information concerning carriers can be found in

Remington: The Science and Practice of Pharmacy, 21st Ed., Lippincott, Williams & Wilkins (2005) which is incorporated herein by reference.

[0051] The term "excipients" is conventionally known to mean carriers, diluents and/or vehicles used in formulating drug compositions effective for the desired use.

5 [0052] The term "microbial infection" or "infection by a microorganism" refers to any infection of a host tissue by an infectious agent including, but not limited to, bacteria or protozoa (see, e.g., Harrison's Principles of Internal Medicine, pp. 93-98 (Wilson et al, eds., 12th ed. 1991); Williams et al, J. of Medicinal Chem. **42**:1481-1485 (1999), herein each incorporated by reference in their entirety).

10 [0053] "Biological medium," as used herein refers to both in vitro and in vivo biological milieus. Exemplary in vitro "biological media" include, but are not limited to, cell culture, tissue culture, homogenates, plasma and blood. In vivo applications are generally performed in mammals, preferably humans.

[0054] "Inhibiting" and "blocking," are used interchangeably herein to refer to the
15 partial or full blockade of enzyme. In an exemplary embodiment, the enzyme is an editing domain of a tRNA synthetase.

[0055] Boron is able to form additional covalent or dative bonds with oxygen, sulfur or nitrogen under some circumstances in this invention.

[0056] Embodiments of the invention also encompass compounds that are poly-
20 or multi-valent species, including, for example, species such as dimers, trimers, tetramers and higher homologs of the compounds of use in the invention or reactive analogues thereof.

[0057] "Salt counterion", as used herein, refers to positively charged ions that associate with a compound of the invention when the boron is fully negatively or
25 partially negatively charged. Examples of salt counterions include H^+ , H_3O^+ , ammonium, potassium, calcium, magnesium (such as choline or diethylamine or amino acids such as d-arginine, 1-arginine, d-lysine or 1-lysine) and sodium.

[0058] The compounds comprising a boron bonded to a carbon and three heteroatoms (such as three oxygens described in this section) can optionally contain a
30 fully negatively charged boron or partially negatively charged boron. Due to the

negative charge, a positively charged counterion may associate with this compound, thus forming a salt. Examples of salt counterions include H^+ , H_3O^+ , ammonium, potassium, calcium, magnesium (such as choline or diethylamine or amino acids such as d-arginine, 1-arginine, d-lysine or 1-lysine) and sodium. The salts of the compounds are implicitly contained in descriptions of these compounds.

I7. Introduction

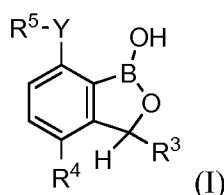
[0059] The invention provides novel boron compounds and methods for the preparation of these molecules. The invention further provides methods of treating bacterial infections, killing or inhibiting the growth of bacteria in part or wholly through the use of the compounds described herein. In another aspect, the invention is a combination of a compound of the invention and an antibiotic. In another aspect, the invention is a pharmaceutical formulation comprising a pharmaceutically acceptable excipient and a compound of the invention. In another aspect, the invention is a pharmaceutical formulation comprising a compound of the invention, an antibiotic, and a pharmaceutically acceptable excipient.

III. Composition of Matter

III. a.) Compounds

[0060] In one aspect the invention provides a compound of the invention. In an exemplary embodiment, the invention provides a compound described herein, or a salt thereof. In an exemplary embodiment, the salt of a compound described herein is a pharmaceutically acceptable salt. In an exemplary embodiment, the invention provides a compound described herein, or a pharmaceutically acceptable salt thereof. In an exemplary embodiment, the invention provides a compound described in a formula provided herein. In an exemplary embodiment, the invention provides a compound described herein.

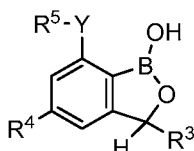
[0061] In an aspect, the invention provides a compound having a structure which is:



wherein R^3 is substituted or unsubstituted nitroalkyl or substituted or unsubstituted aminoalkyl; R^4 is selected from the group consisting of halogen, unsubstituted alkyl

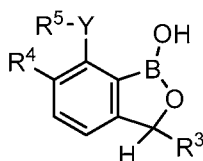
unsubstituted alkoxy and unsubstituted phenyl; Y is O or S; R⁵ is selected from the group consisting of substituted or unsubstituted alkyl and substituted or unsubstituted heteroalkyl; or a salt, hydrate or solvate thereof.

[0062] In an aspect, the invention provides a compound having a structure which is:



wherein R³ is substituted or unsubstituted nitroalkyl or substituted or unsubstituted aminoalkyl; R⁴ is selected from the group consisting of halogen, unsubstituted alkyl, unsubstituted alkoxy, and unsubstituted phenyl; Y is O or S; R⁵ is selected from the group consisting of substituted or unsubstituted alkyl and substituted or unsubstituted heteroalkyl; or a salt, hydrate or solvate thereof.

[0063] In an aspect, the invention provides a compound having a structure which is:



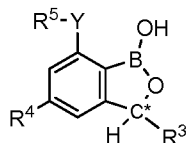
wherein R³ is substituted or unsubstituted nitroalkyl or substituted or unsubstituted aminoalkyl; R⁴ is selected from the group consisting of halogen, unsubstituted alkyl, unsubstituted alkoxy, and unsubstituted phenyl; Y is O or S; R⁵ is selected from the group consisting of substituted or unsubstituted alkyl and substituted or unsubstituted heteroalkyl; or a salt, hydrate or solvate thereof.

[0064] In an exemplary embodiment, there is provided a compound having a structure according to the following formula:



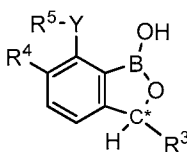
wherein C* is a carbon atom stereocenter which has a configuration which is (R) or (S). In an exemplary embodiment, the C* stereocenter is in the (S) configuration.

[0065] In an exemplary embodiment, there is provided a compound having a structure according to the following formula:



wherein C* is a carbon atom stereocenter which has a configuration which is (R) or (S). In an exemplary embodiment, the C* stereocenter is in the (S) configuration.

[0066] In an exemplary embodiment, there is provided a compound having a structure according to the following formula:



wherein C* is a carbon atom stereocenter which has a configuration which is (R) or (S). In an exemplary embodiment, the C* stereocenter is in the (S) configuration.

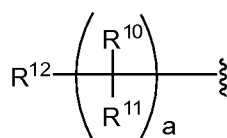
[0067] In an exemplary embodiment, Y, R⁵ and R⁴ are as described herein, R³ is-(CR²⁰R²¹)_nNR²²R²³ in which n is an integer selected from 1 to 10; each R²⁰ and each R²¹ is independently selected from the group consisting of H, R²⁶, OR²⁶, NR²⁶R²⁷, SR²⁶, -S(O)R²⁶, -S(O)₂R²⁶, -S(O)₂NR²⁶R²⁷, -C(O)R²⁷, -C(O)OR²⁷, -C(O)NR²⁶R²⁷; R²² and R²³ are independently selected from the group consisting of H, -S(O)R²⁸, -S(O)₂R²⁸, -S(O)₂NR²⁸R²⁹, -C(O)R²⁸, -C(O)OR²⁸, -C(O)NR²⁸R²⁹, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein each R²⁶, each R²⁷, each R²⁸ and each R²⁹ is independently selected from the group consisting of H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0068] In an exemplary embodiment, Y, R⁵ and R⁴ are as described herein, and R³ is -CH₂NH₂ or -CH₂NH₂. In an exemplary embodiment, Y, R⁵ and R⁴ are as described herein, and R³ is -CH₂NH₂. In an exemplary embodiment, Y, R⁵ and R⁴ are as described herein, R³ is -CH₂NH₂, and C* has a configuration which is (S).

[0069] In an exemplary embodiment, Y, R⁵ and R³ are as described herein, and R⁴ is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and *sec*-butyl. In an exemplary embodiment, Y, R⁵ and R³ are as described herein, and R⁴ is selected from the group consisting of fluorine, chlorine, bromine, and iodine. In an exemplary embodiment, Y, R⁵ and R³ are as described herein, and R⁴ is chlorine or bromine. In an exemplary embodiment, Y, R⁵ and R³ are as described herein, and R⁴ is chlorine.

[0070] In an exemplary embodiment, Y, R⁵ and R³ are as described herein, and R⁴ is selected from the group consisting of methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, and *sec*-butoxy. In an exemplary embodiment, Y, R⁵ and R³ are as described herein, and R⁴ is methoxy or ethoxy. In an exemplary embodiment, Y, R⁵ and R³ are as described herein, and R⁴ is methoxy.

[0071] In an exemplary embodiment, Y, R⁴ and R³ are as described herein, and R⁵ is:



wherein a is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; each R¹⁰ and each R¹¹ is independently selected from the group consisting of H, substituted or unsubstituted alkyl, OH and NH₂; R¹² is selected from the group consisting of H, R⁷, halogen, cyano, amidino, OR⁷, NR⁷R⁸, SR⁷, -N(R⁷)S(O)₂R⁸, -C(O)R⁷, -C(O)OR⁷, -C(O)NR⁷R⁸ wherein each R⁷ and each R⁸ is independently selected from the group consisting of H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. In an exemplary embodiment, Y, R⁴, R³, R¹⁰, R¹¹, and R¹² are as described herein, and a is 1, 2, 3, 4, or 5. In an exemplary embodiment, Y, R⁴, R³, R¹⁰, R¹¹, and R¹² are as described herein, and a is 2, 3, or 4. In an exemplary embodiment, Y, R⁴, R³, R¹⁰, R¹¹, and R¹² are as described herein, and a is 3. In an exemplary embodiment, Y, R⁴, R³, a, and R¹² are as described herein, and each R¹⁰ and each R¹¹ is independently selected from the group consisting of H, substituted or unsubstituted alkyl, OH, and NH₂. In an exemplary embodiment, Y, R⁴, R³, a, and R¹² are as described herein, and each R¹⁰ and each R¹¹ is H. In an exemplary embodiment, Y, R⁴, R³, R¹⁰, R¹¹, and a are as

described herein, and R^{12} is selected from the group consisting of H, OH, NH_2 , methyl, ethyl, $-NHS(0)_2CH_3$, cyano, $-NHC(0)CH_3$, $-NHC(0)NHCH_2CH_3$, $-C(0)NH_2$, $-C(0)OH$, 4-(methoxy)phenyl, benzyl, benzoxy, $-NHC(0)OCH_2Ph$, $-C(0)NHCH_2CH_2OH$ and $-C(NH_2)(NH)$.

5 **[0072]** In an exemplary embodiment, R^4 , R^3 , and R^5 are as described herein, and Y is O. In an exemplary embodiment, R^4 , R^3 , and Y are as described herein, and R^5 is unsubstituted alkyl. In an exemplary embodiment, R^4 , R^3 , and Y are as described herein, and R^5 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, and sec-butyl.

10 **[0073]** In an exemplary embodiment, R^4 is halogen, R^3 is $-CH_2NH_2$; Y is O; and R^5 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, and sec-butyl. In an exemplary embodiment, R^4 is halogen, R^3 is $-CH_2NH_2$; Y is O; and R^5 is selected from the group consisting of methyl, ethyl, propyl, and isopropyl. In an exemplary embodiment, R^4 is halogen, R^3 is $-CH_2NH_2$; Y is O; and R^5 is selected from the group consisting of butyl, isobutyl, t-butyl, and sec-butyl.

15 **[0074]** In an exemplary embodiment, R^4 is chlorine, R^3 is $-CH_2NH_2$; Y is O; and R^5 is selected from the group consisting of methyl, ethyl, propyl, and isopropyl. In an exemplary embodiment, R^4 is chlorine, R^3 is $-CH_2NH_2$; Y is O; and R^5 is selected from the group consisting of butyl, isobutyl, t-butyl, and sec-butyl.

20 **[0075]** In an exemplary embodiment, R^4 is fluorine, R^3 is $-CH_2NH_2$; Y is O; and R^5 is selected from the group consisting of methyl, ethyl, propyl, and isopropyl. In an exemplary embodiment, R^4 is fluorine, R^3 is $-CH_2NH_2$; Y is O; and R^5 is selected from the group consisting of butyl, isobutyl, t-butyl, and sec-butyl.

25 **[0076]** In an exemplary embodiment, R^4 is bromine, R^3 is $-CH_2NH_2$; Y is O; and R^5 is selected from the group consisting of methyl, ethyl, propyl, and isopropyl. In an exemplary embodiment, R^4 is bromine, R^3 is $-CH_2NH_2$; Y is O; and R^5 is selected from the group consisting of butyl, isobutyl, t-butyl, and sec-butyl.

30 **[0077]** In an exemplary embodiment, R^4 is halogen, R^3 is $-CH_2NH_2$; Y is O; and R^5 is methyl. In an exemplary embodiment, R^4 is fluorine, R^3 is $-CH_2NH_2$; Y is O; and R^5 is methyl. In an exemplary embodiment, R^4 is chlorine, R^3 is $-CH_2NH_2$; Y is

O; and R⁵ is methyl. In an exemplary embodiment, R⁴ is bromine, R³ is-CH₂NH₂; Y is O; and R⁵ is methyl.

[0078] In an exemplary embodiment, R⁴ is halogen, R³ is-CH₂NH₂; Y is O; and R⁵ is ethyl. In an exemplary embodiment, R⁴ is fluorine, R³ is-CH₂NH₂; Y is O; and
5 R⁵ is ethyl. In an exemplary embodiment, R⁴ is chlorine, R³ is-CH₂NH₂; Y is O; and R⁵ is ethyl. In an exemplary embodiment, R⁴ is bromine, R³ is-CH₂NH₂; Y is O; and R⁵ is ethyl.

[0079] In an exemplary embodiment, R⁴ is halogen, R³ is-CH₂NH₂; Y is O; and R⁵ is propyl. In an exemplary embodiment, R⁴ is fluorine, R³ is-CH₂NH₂; Y is O;
10 and R⁵ is propyl. In an exemplary embodiment, R⁴ is chlorine, R³ is-CH₂NH₂; Y is O; and R⁵ is propyl. In an exemplary embodiment, R⁴ is bromine, R³ is-CH₂NH₂; Y is O; and R⁵ is propyl.

[0080] In an exemplary embodiment, R⁴ is halogen, R³ is-CH₂NH₂; Y is O; and R⁵ is isopropyl. In an exemplary embodiment, R⁴ is fluorine, R³ is-CH₂NH₂; Y is O;
15 and R⁵ is isopropyl. In an exemplary embodiment, R⁴ is chlorine, R³ is-CH₂NH₂; Y is O; and R⁵ is isopropyl. In an exemplary embodiment, R⁴ is bromine, R³ is-CH₂NH₂; Y is O; and R⁵ is isopropyl.

[0081] In an exemplary embodiment, R⁴ is halogen, R³ is-CH₂NH₂; Y is O; and R⁵ is unsubstituted C₄ alkyl. In an exemplary embodiment, R⁴ is fluorine, R³ is-
20 CH₂NH₂; Y is O; and R⁵ is unsubstituted C₄ alkyl. In an exemplary embodiment, R⁴ is chlorine, R³ is-CH₂NH₂; Y is O; and R⁵ is unsubstituted C₄ alkyl. In an exemplary embodiment, R⁴ is bromine, R³ is-CH₂NH₂; Y is O; and R⁵ is unsubstituted C₄ alkyl.

[0082] In an exemplary embodiment, R⁴ is halogen, R³ is-CH₂NH₂; Y is O; and R⁵ is unsubstituted C₅ alkyl. In an exemplary embodiment, R⁴ is fluorine, R³ is-
25 CH₂NH₂; Y is O; and R⁵ is unsubstituted C₅ alkyl. In an exemplary embodiment, R⁴ is chlorine, R³ is-CH₂NH₂; Y is O; and R⁵ is unsubstituted C₅ alkyl. In an exemplary embodiment, R⁴ is bromine, R³ is-CH₂NH₂; Y is O; and R⁵ is unsubstituted C₅ alkyl.

[0083] In an exemplary embodiment, R⁴ is halogen, R³ is-CH₂NH₂; Y is O; and R⁵ is unsubstituted C₆ alkyl. In an exemplary embodiment, R⁴ is fluorine, R³ is-
30 CH₂NH₂; Y is O; and R⁵ is unsubstituted C₆ alkyl. In an exemplary embodiment, R⁴

is chlorine, R^3 is $-CH_2NH_2$; Y is O; and R^5 is unsubstituted C_6 alkyl. In an exemplary embodiment, R^4 is bromine, R^3 is $-CH_2NH_2$; Y is O; and R^5 is unsubstituted C_6 alkyl.

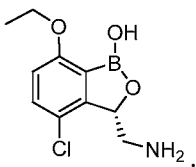
[0084] In an exemplary embodiment, R^4 is chlorine, R^3 is $-CH_2NH_2$; Y is O; and R^5 is selected from the group consisting of methyl, ethyl, propyl, and isopropyl. In an exemplary embodiment, R^4 is chlorine, R^3 is $-CH_2NH_2$; Y is O; and R^5 is selected from the group consisting of butyl, isobutyl, t-butyl, and sec-butyl.

[0085] In an exemplary embodiment, R^4 is fluorine, R^3 is $-CH_2NH_2$; Y is O; and R^5 is selected from the group consisting of methyl, ethyl, propyl, and isopropyl. In an exemplary embodiment, R^4 is fluorine, R^3 is $-CH_2NH_2$; Y is O; and R^5 is selected from the group consisting of butyl, isobutyl, t-butyl, and sec-butyl.

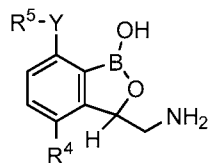
[0086] In an exemplary embodiment, R^4 is bromine, R^3 is $-CH_2NH_2$; Y is O; and R^5 is selected from the group consisting of methyl, ethyl, propyl, and isopropyl. In an exemplary embodiment, R^4 is bromine, R^3 is $-CH_2NH_2$; Y is O; and R^5 is selected from the group consisting of butyl, isobutyl, t-butyl, and sec-butyl.

[0087] In an exemplary embodiment, R^4 is as described herein, R^3 is $-CH_2NH_2$; Y is O; and R^5 is substituted or unsubstituted alkyl. In an exemplary embodiment, Y and R^5 are as described herein, R^3 is $-CH_2NH_2$; and R^4 is halogen. In an exemplary embodiment, Y is as described herein, R^4 is halogen; Y is O; and R^5 is unsubstituted alkyl. In an exemplary embodiment, R^3 is $-CH_2NH_2$; R^4 is chlorine; Y is O; and R^5 is substituted or unsubstituted alkyl. In an exemplary embodiment, R^4 is as described herein, R^3 is $-CH_2NH_2$; Y is O; and R^5 is ethyl.

[0088] In an exemplary embodiment, the compound has a structure which is

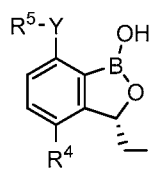


[0089] In an exemplary embodiment, the compound has a structure which is



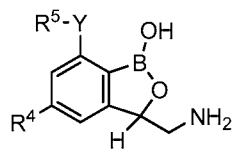
, wherein R^4 , Y and R^5 are as described herein.

[0090] In an exemplary embodiment, the compound has a structure which is



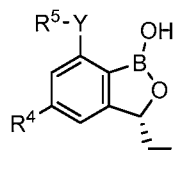
, wherein R^4 , Y and R^5 are as described herein. In an exemplary embodiment, Y is O, and R^4 and R^5 are as described herein. In an exemplary embodiment, Y is O, R^4 is halogen, and R^5 are as described herein. In an exemplary embodiment, Y is O, R^4 is halogen, and R^5 is unsubstituted alkyl. In an exemplary embodiment, Y is O, R^4 is halogen, and R^5 is methyl or ethyl or propyl or isopropyl. In an exemplary embodiment, Y is O, R^4 is halogen, and R^5 is butyl or isobutyl or neobutyl or t-butyl.

[0091] In an exemplary embodiment, the compound has a structure which is



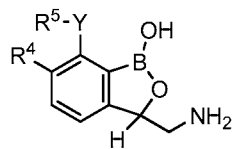
10 , wherein R^4 , Y and R^5 are as described herein.

[0092] In an exemplary embodiment, the compound has a structure which is



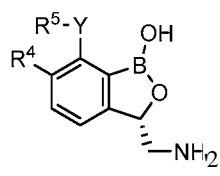
15 , wherein R^4 , Y and R^5 are as described herein. In an exemplary embodiment, Y is O, and R^4 and R^5 are as described herein. In an exemplary embodiment, Y is O, R^4 is halogen, and R^5 are as described herein. In an exemplary embodiment, Y is O, R^4 is halogen, and R^5 is unsubstituted alkyl. In an exemplary embodiment, Y is O, R^4 is halogen, and R^5 is methyl or ethyl or propyl or isopropyl. In an exemplary embodiment, Y is O, R^4 is halogen, and R^5 is butyl or isobutyl or neobutyl or t-butyl.

[0093] In an exemplary embodiment, the compound has a structure which is



20 , wherein R^4 , Y and R^5 are as described herein.

[0094] In an exemplary embodiment, the compound has a structure which is



, wherein R^4 , Y and R^5 are as described herein. In an exemplary embodiment, Y is O, and R^4 and R^5 are as described herein. In an exemplary embodiment, Y is O, R^4 is halogen, and R^5 are as described herein. In an exemplary embodiment, Y is O, R^4 is halogen, and R^5 is unsubstituted alkyl. In an exemplary embodiment, Y is O, R^4 is halogen, and R^5 is methyl or ethyl or propyl or isopropyl. In an exemplary embodiment, Y is O, R^4 is halogen, and R^5 is butyl or isobutyl or neobutyl or t-butyl.

[0095] In an exemplary embodiment, said alkyl is linear alkyl or branched alkyl,

10 In an exemplary embodiment, said heteroalkyl is linear heteroalkyl or branched heteroalkyl.

[0096] In an exemplary embodiment, the invention provides poly- or multi-valent species of the compounds of the invention, including a dimer or a trimer. Another exemplary embodiment of the invention provides an anhydride of the compounds of the invention. In another exemplary embodiment, the invention provides poly- or multi-valent species of the compounds of the invention. In an exemplary embodiment, the invention provides a dimer of the compounds described herein. In an exemplary embodiment, the invention provides a dimer of the compounds described herein.

20 [0097] In an exemplary embodiment, the invention provides an anhydride of the compounds described herein. In an exemplary embodiment, the invention provides an anhydride of the compounds described herein.

[0098] In an exemplary embodiment, the invention provides a trimer of the compounds described herein. In an exemplary embodiment, the invention provides a trimer of the compounds described herein.

[0099] The compounds of the invention can form a hydrate with water, solvates with alcohols such as methanol, ethanol, propanol, and the like; adducts with amino compounds, such as ammonia, methylamine, ethylamine, and the like; adducts with

acids, such as formic acid, acetic acid and the like; complexes with ethanolamine, quinoline, amino acids, and the like.

[0100] In an exemplary embodiment, the invention provides a compound described herein, or a salt, hydrate or solvate thereof, or a combination thereof. In an exemplary embodiment, the invention provides a compound described herein, or a salt, hydrate or solvate thereof. In an exemplary embodiment, the invention provides a compound described herein, or a salt thereof. In an exemplary embodiment, the salt is a pharmaceutically acceptable salt. In an exemplary embodiment, the invention provides a compound described herein, or a hydrate thereof. In an exemplary embodiment, the invention provides a compound described herein, or a solvate thereof. In an exemplary embodiment, the invention provides a compound described herein, or a prodrug thereof. In an exemplary embodiment, the invention provides a salt of a compound described herein. In an exemplary embodiment, the invention provides a pharmaceutically acceptable salt of a compound described herein. In an exemplary embodiment, the invention provides a hydrate of a compound described herein. In an exemplary embodiment, the invention provides a solvate of a compound described herein. In an exemplary embodiment, the invention provides a prodrug of a compound described herein. In an exemplary embodiment, the invention provides a compound as described in **FIG. 1**, or a salt thereof. In an exemplary embodiment, the invention provides a compound as described in **FIG. 1**, or a pharmaceutically acceptable salt thereof.

[0101] In an exemplary embodiment, alkyl is linear alkyl. In another exemplary embodiment, alkyl is branched alkyl.

[0102] In an exemplary embodiment, heteroalkyl is linear heteroalkyl. In another exemplary embodiment, heteroalkyl is branched heteroalkyl.

III. b) Combinations comprising additional therapeutic agents

[0103] The compounds of the invention may also be used in combination with additional therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of the invention together with at least one additional therapeutic agent, or a salt, prodrug, hydrate or solvate thereof. In an exemplary embodiment, the compound of the invention is a compound described herein, or a salt thereof. In an exemplary embodiment, the additional therapeutic

agent is a compound of the invention. In an exemplary embodiment, the additional therapeutic agent includes a boron atom. In an exemplary embodiment, the additional therapeutic agent does not contain a boron atom. In an exemplary embodiment, the additional therapeutic agent is a compound described in sections III a) or b).

- 5 **[0104]** When a compound of the invention is used in combination with a second therapeutic agent active against the same disease state, the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art. It will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature
10 of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian.

- [0105]** In an exemplary embodiment, the additional therapeutic agent is an antibacterial agent. In an exemplary embodiment, the additional therapeutic agent is an antituberculosis agent. In an exemplary embodiment, the additional therapeutic
15 agent is rifampicin. In an exemplary embodiment, the additional therapeutic agent is isoniazid. In an exemplary embodiment, the additional therapeutic agent is pyrazinamide. In an exemplary embodiment, the additional therapeutic agent is ethambutol. In an exemplary embodiment, the additional therapeutic agent is isoniazid. In an exemplary embodiment, the additional therapeutic agent is
20 streptomycin. In an exemplary embodiment, the additional therapeutic agent is an aminoglycoside. In an exemplary embodiment, the additional therapeutic agent is amikacin or kanamycin. In an exemplary embodiment, the additional therapeutic agent is a polypeptide. In an exemplary embodiment, the additional therapeutic agent is selected from the group consisting of capreomycin, viomycin, and enviomycin. In
25 an exemplary embodiment, the additional therapeutic agent is a fluoroquinolone. In an exemplary embodiment, the additional therapeutic agent is selected from the group consisting of ciprofloxacin, levofloxacin, and moxifloxacin. In an exemplary embodiment, the additional therapeutic agent is a thioamide. In an exemplary embodiment, the additional therapeutic agent is ethionamide or prothionamide. In an
30 exemplary embodiment, the additional therapeutic agent is cycloserine. In an exemplary embodiment, the additional therapeutic agent is p-aminosalicylic acid. In an exemplary embodiment, the additional therapeutic agent is selected from the group consisting of rifabutin, linezolid, thioacetazone, thioridazine, arginine, vitamin D, and

R207910. In an exemplary embodiment, the additional therapeutic agent is a macrolide.

[0106] The individual components of such combinations may be administered either simultaneously or sequentially in a unit dosage form. The unit dosage form may be a single or multiple unit dosage forms. In an exemplary embodiment, the invention provides a combination in a single unit dosage form. An example of a single unit dosage form is a capsule wherein both the compound of the invention and the additional therapeutic agent are contained within the same capsule. In an exemplary embodiment, the invention provides a combination in a two unit dosage form. An example of a two unit dosage form is a first capsule which contains the compound of the invention and a second capsule which contains the additional therapeutic agent. Thus the term 'single unit' or 'two unit' or 'multiple unit' refers to the object which the animal (for example, a human) ingests, not to the interior components of the object. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

[0107] The combinations referred to herein may conveniently be presented for use in the form of a pharmaceutical formulation. Thus, an exemplary embodiment of the invention is a pharmaceutical formulation comprising a) a compound of the invention; b) an additional therapeutic agent and c) a pharmaceutically acceptable excipient. In an exemplary embodiment, the pharmaceutical formulation is a unit dosage form. In an exemplary embodiment, the pharmaceutical formulation is a single unit dosage form. In an exemplary embodiment, the pharmaceutical formulation is a single unit dosage form which includes a compound of the invention; an antibiotic and a pharmaceutically acceptable excipient. In an exemplary embodiment, the pharmaceutical formulation is a single unit dosage form which includes a compound of the invention; an antibiotic and at least one pharmaceutically acceptable excipient. In an exemplary embodiment, the pharmaceutical formulation is a two unit dosage form. In an exemplary embodiment, the pharmaceutical formulation is a two unit dosage form comprising a first unit dosage form and a second unit dosage form, wherein the first unit dosage form includes a) a compound of the invention and b) a first pharmaceutically acceptable excipient; and the second unit dosage form includes c) an additional therapeutic agent and d) a second pharmaceutically acceptable excipient. In an exemplary embodiment, the pharmaceutical formulation is a two unit

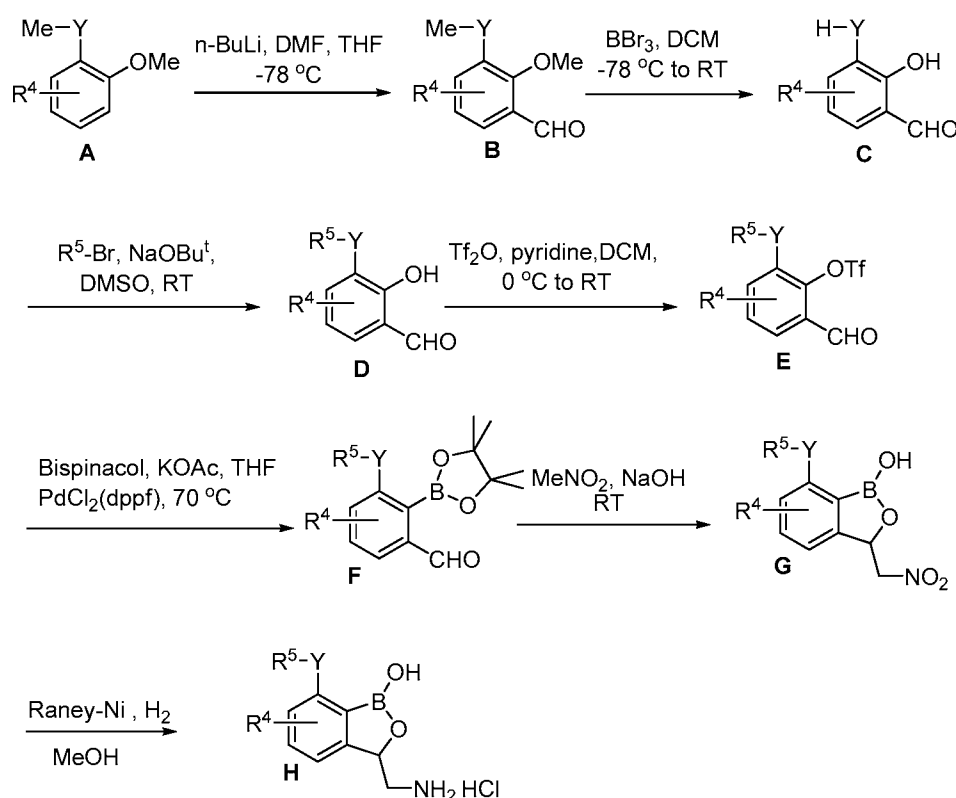
dosage form comprising a first unit dosage form and a second unit dosage form, wherein the first unit dosage form includes a) a compound of the invention and b) a first pharmaceutically acceptable excipient; and the second unit dosage form includes c) an antibiotic and d) a second pharmaceutically acceptable excipient.

5 **III. c) Preparation of Boron-Containing Compounds**

[0108] Compounds of use in the invention can be prepared using commercially available starting materials, known intermediates, or by using the synthetic methods published in references described and incorporated by reference herein, such as U.S. Pat. Apps. 12/142,692 and U.S. Pat. Pubs. US20060234981, US20070155699 and
10 US20070293457.

[0109] The following general procedures were used as indicated in generating the examples and can be applied, using the knowledge of one of skill in the art, to other appropriate compounds to obtain additional analogues.

General reaction scheme 1



[0110] Scheme 1 describes a synthesis for compounds of (I), wherein R^4 is fluorine or chlorine and Y and R^5 are as described herein. The fluoro or chloro compound of formula A, which may be prepared or maybe available commercially from Sigma-Aldrich, is reacted with a strong base (such as $n-BuLi$, $sec-BuLi$, or $t-BuLi$, 2 equiv)

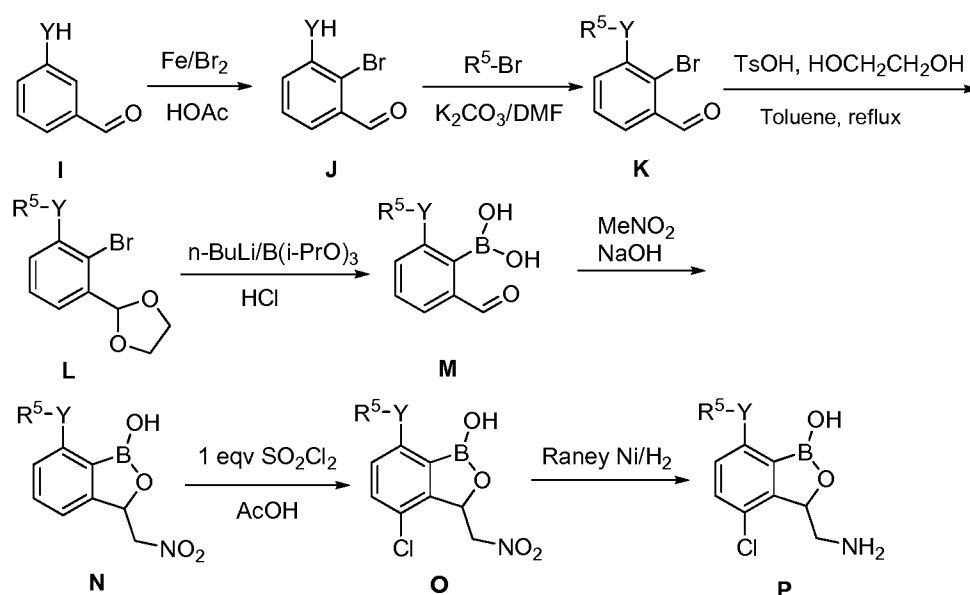
followed by quenching with a formylating agent (such as DMF, dimethylformamide, formanilide, N-formylmorpholine, large excess) to give the compound of formula B. Treatment of compound B with a demethylating agent (typically BBr_3 , 2 equiv) in a suitable solvent (dichloromethane, THF) gives the phenol of formula C. Compound C

5 can react with a corresponding bromide or mesylate (1-1.5 equiv) in the presence of a base (such as KOtBu , K_2CO_3 , or Cs_2CO_3 , 1.5-2 equiv) in an aprotic solvent such as DMF or DMSO to afford the compound of formula D. Compound D may be converted to triflate E by the reaction with 1.2 equiv of trifluoromethanesulfonic anhydride and pyridine in dichloromethane. The conversion of triflate E to boronate F

10 can be achieved by the reaction with bis(pinacolato)diborane (2 equiv), KOAc (3 equiv) and catalytic amount of $\text{PdCl}_2(\text{dppf})$ (4-8 mol%). The reaction of compound F with nitromethane (3 equiv) in the presence of sodium hydroxide (3 equiv) in water or THF gives the nitro compound of formula G. The compound G can be converted to the final product of formula H by the Raney-Ni reduction (Raney Ni, 2 equiv w/w, 2.0

15 M NH_3 in EtOH, absolute EtOH).

General reaction scheme 2



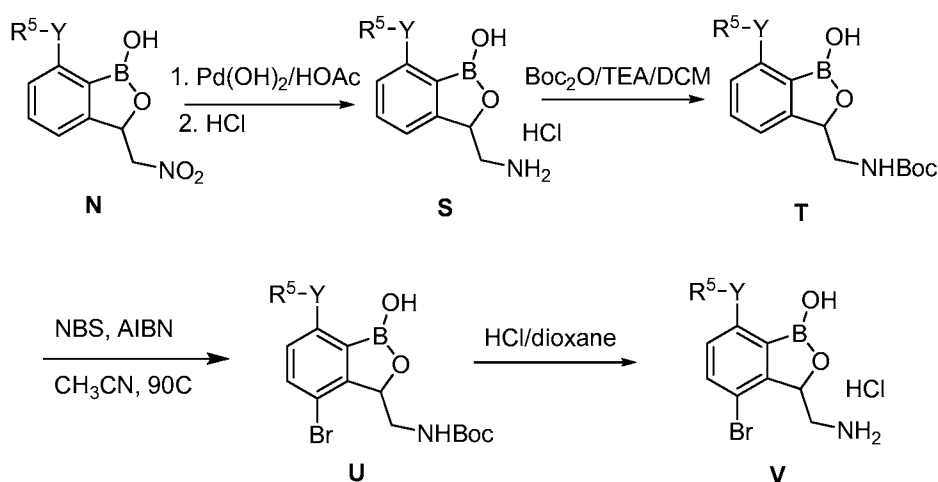
[0111] Scheme 2 describes a synthesis for compounds of (I), wherein R^4 is chlorine, Y and R^5 are as described herein. The phenol or thiophenol of formula I,

20 which may be prepared or maybe available commercially from Sigma-Aldrich, react with a solution of bromine and catalytic amount of iron powder in glacial acetic acid to give the bromo substituted compound of formula J. The alkylation of J can be achieved by reacting with a bromide in the presence of a base such as potassium

carbonate in solvents like DMF or acetonitrile. The protection of aldehyde K may be achieved by refluxing with ethylene glycol in toluene, in the presence of catalytic amount of *p*-toluenesulfonic acid. The reaction of the compound L with BuLi and triisopropyl borate, followed by treating with hydrochloric acid yields boronic acid M.

- 5 The reaction of compound M with nitromethane in the presence of sodium hydroxide gives the nitro compound of formula N. The treatment of N with 1 equivalent of sulfonyl chloride affords the chloro substituted compound O. The Raney-Ni reduction of compound O in MeOH gives the final product of formula P.

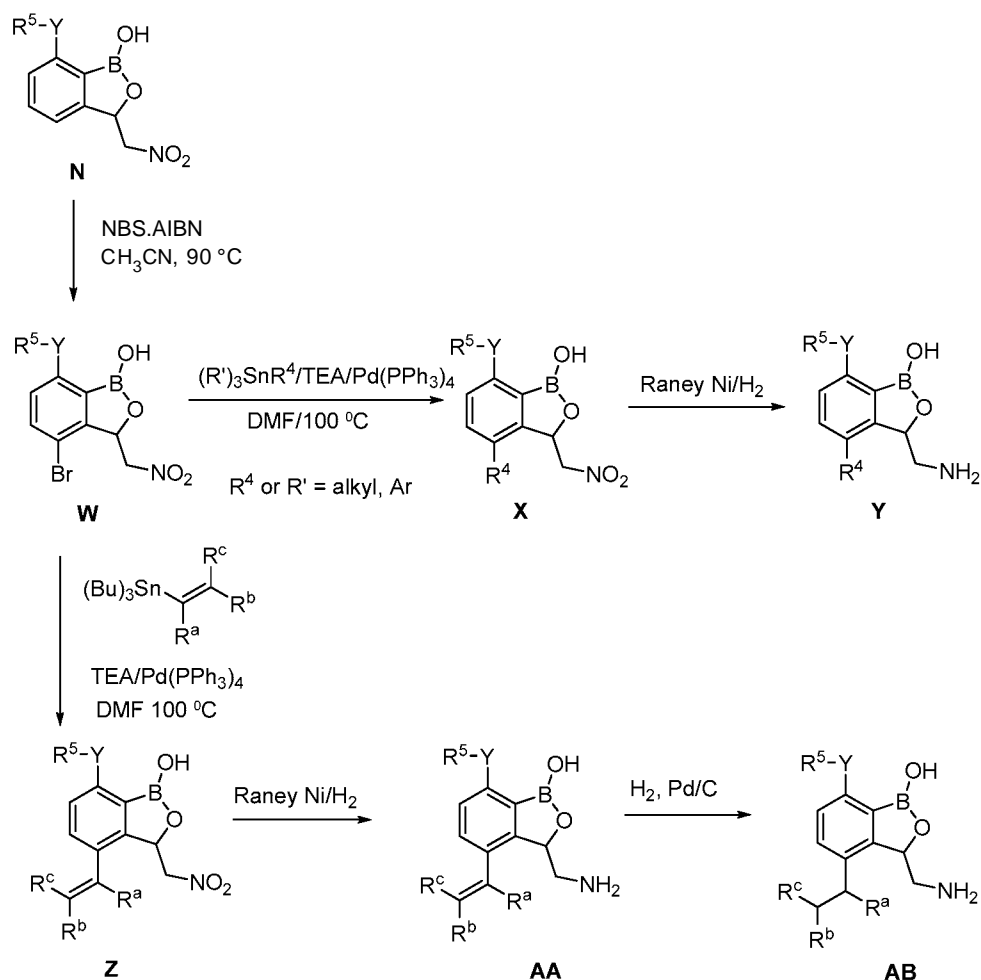
General reaction scheme 3



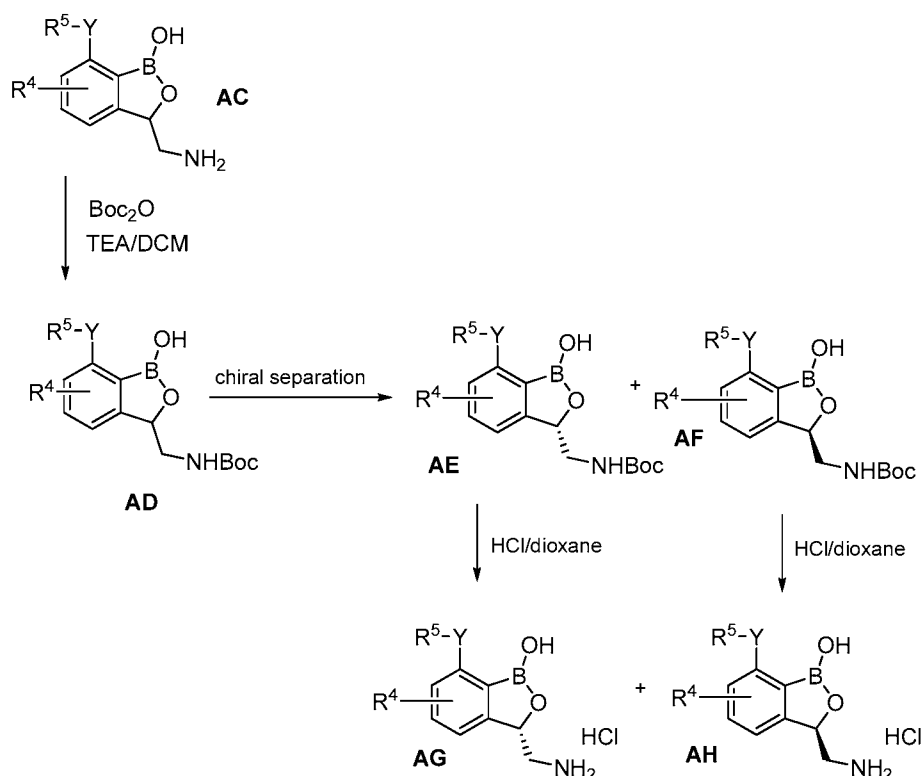
10

[0112] Scheme 3 describes a synthesis for compounds of (I), wherein R⁴ is bromine, Y and R⁵ are as described herein. The compound of formula N, which may be prepared according to Scheme 2, can be reduced to the amine of formula S, by hydrogenation in the presence of palladium hydroxide or Raney-Ni reduction as described above. The amine of formula S reacts with an N-Protecting reagent such as Boc anhydride in the presence of base like triethylamine in dichloromethane to give Boc-protected compound of formula T. The treatment of T with N-bromosuccinimide and catalytic amount of AIBN in acetonitrile gives the bromo substituted compound of formula U. Deprotection of compound U in the presence of acid such as HCl in dioxane will afford the final compound of formula U.

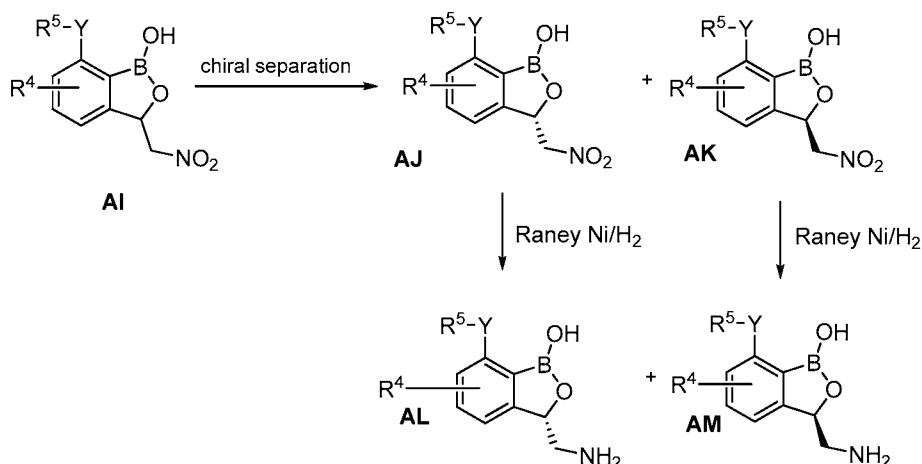
20

General reaction scheme 4

- [0113] Scheme 4 describes a synthesis for compounds of (I), wherein R⁴ is an alkyl or aryl group, Y and R⁵ are as described herein. The compound of formula N, which may be prepared according to Scheme 2, can be brominated with N-bromosuccinimide and catalytic amount of AIBN in a solvent such as acetonitrile to give the bromide of formula W. Stille coupling of W with an organotin compound such as tetramethylstannane or tributyl-phenyl-stannane in the presence of catalytic Pd(Ph₃P)₄ in DMF affords the compound of formula X. Compound X can be reduced to the final compound of formula Y by hydrogenation in the presence of palladium on carbon or Raney-Ni reduction as described above. Alternatively, Stille reaction of W with an organotin compound such as vinyltributyltin in the presence of catalytic amount of Pd(Ph₃P)₄ in DMF affords the compound of formula Z. After Raney-Ni reduction of compound Z, further hydrogenation in the presence of palladium on carbon as described above will afford the final compound of formula AB.

General reaction scheme 5: Chiral separation

- [0114] Scheme 5 describes a method to separate compounds (I) into their enantiomeric isomers, wherein R^4 , Y , and R^5 are as described herein. The compound of formula AC, which may be prepared according to Scheme 1 or Scheme 2 or Scheme 3 or Scheme 4, can be converted to the Boc-protected compound AD by the reaction with an N-Protecting reagent such as Boc anhydride in the presence of base like triethylamine in dichloromethane. Racemic compound AD can be resolved via chiral HPLC using a chiral column such as ChiralPak AD-H and SF C0₂/methanol as eluent. Two compounds collected are enantiomer AE and enantiomer AF. Analysis of the enantiomeric purity of each isomer can be achieved using a chiral column such as ChiralPak AD column. The Boc-protected compounds AE and AF can be converted to the final chiral compounds AG and AH, by deprotection using acid such as HCl in dioxane.

General reaction scheme 6: Chiral separation

[0115] Scheme 6 describes an alternative method to separate chiral compounds **AI** into their enantiomeric isomers, wherein R^4 , Y , and R^5 are as described herein. The compound of formula **AI** may be prepared according to Scheme 1 or Scheme 2 or Scheme 3 or Scheme 4. The separation of the two enantiomers was achieved by dissolving the racemic material **AI** in a suitable solvent and applying to an appropriate chiral column and eluent system. The collected separated enantiomer samples were then concentrated and used in the next step without further purification. Using this technique, it is possible to achieve a range of enantiomeric excesses of the separated enantiomers. The nitro compound **AJ** and **AK** can be converted to the final chiral compounds **AL** and **AM**, respectively, by Raney-Ni reduction (Raney Ni, 2 equiv w/w, 2.0 M NH₃ in EtOH, absolute EtOH).

IV. Assays

[0116] Art-recognized techniques of genetics and molecular biology are of use to identify compounds that bind to and/or inhibit an enzyme, such as a tRNA synthetase. Moreover, these techniques are of use to distinguish whether a compound binds to and/or inhibits a particular domain of the enzyme. For example, for leucyl tRNA synthetase (LeuRS), these techniques can distinguish whether a compound binds to and/or inhibits the synthetic domain, the editing domain, or both the editing and synthetic domains. The *Mycobacterium tuberculosis leuS* gene was synthesized by Genscript (Piscataway, NJ) using *E. coli* optimized codons and protein was made using standard T7 RNA polymerase over-expression protocols and standard purification protocols.

IV. a) *LeuRS*

[0117] In an exemplary assay, activity of a representative compound against the editing domain was confirmed. To identify the target of a novel boron-containing antibacterial compound, mutants in *E.coli* showing resistance to the compound were isolated. Characterization of mutants showed that they have an 32-256 fold increase in resistance to the compound over wildtype. The mutants were furthermore shown to be sensitive to various antibacterial agents with known modes of action, suggesting that the cellular target of the compound is distinct from the target of the other antibacterial agents. The *leuS* gene from the mutants was cloned onto a plasmid and their resistance was confirmed by MIC. The editing domain from these mutants were sequenced and the mutations were all located in the editing domain of this enzyme.

[0118] Assays to determine whether, and how effectively, a particular compound binds to and/or inhibits the editing domain of a selected tRNA synthetase are also set forth herein, and additional assays are readily available to those of skill in the art.

Briefly, in an exemplary assay, an improperly charged tRNA and a tRNA synthetase that is capable of editing the improperly charged tRNA are combined. The resulting mixture is contacted with the putative inhibitor and the degree of editing inhibition is observed.

[0119] Another assay uses genetics to show that a drug works via the editing domain. In this assay, the compound is first tested against a strain of cells over-expressing copies of the tRNA synthetase gene. The compound's effect on the over-expressing strain is compared with a control strain to determine whether the compound is active against the synthetase. If the minimum inhibitory concentration (MIC) is 2-fold higher in the strain with extra copies of the synthetase gene than the MIC of the inhibitor against a wild type cell, a further genetic screen is conducted to determine whether the increased resistance is due to mutations in the editing domain. In this second screen, the control strain is challenged against a high concentration of the inhibitor. The colonies surviving the challenge are isolated and DNA from these cells is isolated. The editing domain is amplified using a proof-reading PCR enzyme and the appropriate primers. The PCR product can be purified using standard procedures. The sequence amplified mutant DNA is compared to wild-type. If the mutant DNA bears mutations in the editing domain, such results would suggest that

the compound binds to the editing domain and affects the editing function of the molecule through this domain.

[0120] Generally, the compounds to be tested are present in the assays in ranges from about 1 pM to about 100 mM, preferably from about 1 pM to about 1 μ M.

5 Other compounds range from about 1 nM to about 100 nM, preferably from about 1 nM to about 1 μ M.

[0121] The effects of the test compounds upon the function of the enzymes can also be measured by any suitable physiological change. When the functional consequences are determined using intact cells or animals, one can also measure a
10 variety of effects such as transmitter release, hormone release, transcriptional changes to both known and uncharacterized genetic markers, changes in cell metabolism such as cell growth or pH changes, and changes in intracellular second messengers such as Ca^{2+} , or cyclic nucleotides.

[0122] Utilizing the assays set forth herein and others readily available in the art,
15 those of skill in the art will be able to readily and routinely determine other compounds and classes of compounds that operate to bind to and/or inhibit the editing domain of tRNA synthetases.

[0123] In another aspect, the invention provides a method for identifying a compound which binds to an editing domain of a tRNA synthetase comprising:
20 a) contacting said editing domain with a test compound under conditions suitable for binding; and b) detecting binding of said test compound to said editing domain. In an exemplary embodiment, detecting binding of said compound comprises use of at least one detectable element, isotope, or chemical label attached to said compound. In an exemplary embodiment, the element, isotope or chemical label is detected by a
25 fluorescent, luminescent, radioactive, or absorbance readout. In an exemplary embodiment, the contacting of said test compound with said editing domain also includes further contacting said test compound and said editing domain with a member selected from AMP and a molecule with a terminal adenosine. In an exemplary embodiment, the tRNA synthetase is derived from leucyl tRNA synthetase.
30 In an exemplary embodiment, the tRNA synthetase is derived from a mutated tRNA synthetase, wherein said mutated tRNA synthetase comprises amino acid mutations in an editing domain. In another exemplary embodiment, wherein said editing domain

of a tRNA synthetase comprises the amino acid sequence of a peptide sequence described herein.

[0124] In another aspect, the invention provides a method for identifying a compound which binds to an editing domain of a tRNA synthetase, said assay comprising: a) contacting said editing domain of a tRNA synthetase with said compound under conditions suitable for binding of said compound with said editing domain of a tRNA synthetase; b) comparing a biological activity of said editing domain of a tRNA synthetase contacting said compound to said biological activity when not contacting said compound; and c) identifying said compound as binding to said editing domain of a tRNA synthetase if said biological activity of said editing domain of a tRNA synthetase is reduced when contacting said compound. In an exemplary embodiment, the biological activity is hydrolysis of noncognate amino acid. In another exemplary embodiment, the hydrolysis of said noncognate amino acid is detected through the use of one or more labels. In another exemplary embodiment, the labels include a radiolabel, a fluorescent marker, an antibody, or a combination thereof. In another exemplary embodiment, said labels can be detected using spectroscopy. In another exemplary embodiment, said editing domain of a tRNA synthetase is derived from leucyl tRNA synthetase.

[0125] In another aspect, the invention provides a method of generating a tRNA molecule with a noncognate amino acid comprising: a) creating or isolating a mutated tRNA synthetase with altered amino acid editing domains; and b) contacting a tRNA molecule with said mutated tRNA synthetase and a noncognate amino acid. In another exemplary embodiment, the mutated tRNA synthetase contains one or more amino acid mutations in an editing domain. In another exemplary embodiment, the mutated tRNA synthetase is unable to bind with a compound of the invention. In another exemplary embodiment, the mutated tRNA synthetase is unable to bind with a compound described herein, or a pharmaceutically acceptable salt thereof. In another exemplary embodiment, the mutated tRNA synthetase is unable to bind with a compound according to a formula described herein, or a pharmaceutically acceptable salt thereof.

[0126] In another aspect, the invention provides a composition that comprises one or more tRNA molecules attached to noncognate amino acids, wherein said tRNA

molecules are synthesized using one or more mutated tRNA synthetases isolated from a microorganism or a cell line derived from a microorganism. In an exemplary embodiment, the microorganism is a bacteria. In an exemplary embodiment, wherein said mutated tRNA synthetases contain amino acid mutations in their editing domains.

5 **V. Amino acid and nucleotide sequences used in assays**

[0127] Amino acid and nucleotide sequences of use in the invention are published in references described and incorporated by reference herein, such as U.S. Pat. Apps. 12/142,692 and U.S. Pat. Pubs. US20060234981, US20070155699 and US20070293457. The sequence for the codon optimized *M. tuberculosis leuS* gene is
10 as follows:

CATATGACCGAAAGCCCGACCGCAGGTCCGGGTGGTGTGCCGCGTGCGGA
TGATGCAGATAGCGATGTGCCGCGTTATCGTTATACCGCGGAACCTGGCGG
CGCGTCTGGAACGTACCTGGCAGGAAAACCTGGGCGCGTCTGGGCACCTTT
AACGTGCCGAACCCGGTGGGTAGCCTGGCACCGCCGGATGGTGCAGCAGT
15 GCCGGATGATAAACTGTTTGTGCAGGATATGTTTCCGTATCCGAGCGGCG
AAGGCCTGCATGTGGGCCATCCGCTGGGCTATATTGCGACCGATGTGTAT
GCGCGTTATTTTCGTATGGTGGGCCGTAACTGCTGCATGCGCTGGGCTTT
GATGCGTTTGGTCTGCCGGCGGAACAGTATGCGGTGCAGACCGGCACCCA
TCCGCGTACCCGTACCGAAGCGAACGTGGTGAACCTTTCGTCGTCAGCTGG
20 GCCGTCTGGGCTTTGGCCATGATAGCCGTCGTAGCTTTAGCACCAACCGATG
TGGATTTTTATCGTTGGACCCAGTGGATTTTTCTGCAGATTTATAACGCGT
GGTTTGATAACACCGCGAACAAGCGCGTCCGATTAGCGAACTGGTGGCG
GAATTTGAAAGCGGTGCACGTTGCCTGGATGGTGGTCGTGATTGGGCAAA
ACTGACCGCAGGTGAACGTGCGGATGTGATTGATGAATATCGTCTGGTGT
25 ATCGTGCGGATAGCCTGGTGAACCTGGTGCCCGGGTCTGGGTACCGTGCTG
GCAAACGAAGAAGTGACCGCAGATGGCCGTAGCGATCGTGGCAACTTTCC
GGTGTTCGTAAACGTCTGCGTCAGTGGATGATGCGTATTACCGCGTATGC
GGATCGTCTGCTGGATGATCTGGATGTGCTGGATTGGCCGGAACAGGTGA
AAACCATGCAGCGTAACTGGATTGGCCGTAGCACCGGCGCGGTGGCGCTG
30 TTTAGCGCGCGTGCGGCGAGCGATGATGGCTTTGAAGTGGATATTGAAGT
GTTTACCACCCGTCCGGATACCCTGTTTGGCGCGACCTATCTGGTGCTGGC
GCCGGAACATGATCTGGTGGATGAACCTGGTGGCGGCAAGCTGGCCGGCAG
GTGTGAACCCGCTGTGGACCTATGGCGGTGGTACCCCGGGTGAAGCAATT
GCAGCATATCGTCGTGCGATTGCGGCGAAAAGCGATCTGGAACGTCAGGA
35 AAGCCGTGAAAAAACCGGCGTGTTTCTGGGCAGCTATGCGATTAACCCGG
CGAACGGCGAACCGGTGCCGATTTTTATTGCGGATTATGTGCTGGCGGGC
TATGGCACCGGCGCGATTATGGCGGTGCCGGGCCATGATCAGCGTGATTG
GGATTTTTCGCGTGCCTTTGGCCTGCCGATTGTGGAAGTGATTGCAGGTGG
AAACATTAGCGAAAGCGCGTATACCGGCGATGGCATTCTGGTGAACAGCG
40 ATTATCTGAACGGCATGAGCGTGCCGGCAGCAAAACGTGCAATTGTGGAT
CGTCTGGAAAGCGCAGGTCGTGGTCGTGCACGTATTGAATTTAACTGCG
TGATTGGCTGTTTTCGCGTCAGCGTTATTGGGGCGAACCGTTTCCGATTGT
GTATGATAGCGATGGCCGTCCGCATGCGCTGGATGAAGCGGCGCTGCCGG
TGGAACCTGCCGGATGTGCCGGATTATAGCCCGGTGCTGTTTGATCCGGAT

GATGCGGATAGCGAACCGAGCCCGCCGCTGGCGAAAGCGACCGAATGGG
 TGCATGTGGATCTGGATCTGGGCGATGGCCTGAAACCGTATAGCCGTGAT
 ACCAACGTGATGCCGCAGTGGGCGGGCAGCAGCTGGTATGAACTGCGTTA
 TACCGATCCGCATAACAGCGAACGTTTTTGC GCGAAAGAAAACGAAGCGT
 5 ATTGGATGGGTCCGCGTCCGGCAGAACATGGTCCGGATGATCCGGGTGGT
 GTGGATCTGTATGTGGGCGGCGCGGAACATGCGGTGCTGCATCTGCTGTA
 TAGCCGTTTTTGGCATAAAGTGCTGTATGATCTGGGCCATGTGAGCAGCCG
 TGAACCGTATCGTCGTCTGGTGAACCAGGGCTATATTCAGGCGTATGCGT
 ATACCGATGCGCGTGGCAGCTATGTGCCGGCGGAACAAGTGATTGAACGT
 10 GGCGATCGTTTTGTGTATCCGGGCCCCGGATGGCGAAGTGGAAGTGTTTC A
 GGAATTTGGCAAAATTGGCAAAAGCCTGAAAAACAGCGTGAGCCCGGAT
 GAAATTTGCGATGCGTATGGCGCGGATACCCTGCGTGTGTATGAAATGAG
 CATGGGCCCCGCTGGAAGCGAGCCGTCCGTGGGCGACCAAAGATGTGGTGG
 GCGCGTATCGTTTTCTGCAGCGTGTGTGGCGTCTGGTGGTGGATGAACATA
 15 CCGGCGAAACCCGTGTGGCGGATGGCGTGGAACTGGATATTGATACCCTG
 CGTGCGCTGCATCGTACCATTGTGGGCGTGAGCGAAGATTTTGC GGGCGCT
 GCGTAACAACACCGCGACCGCGAAACTGATTGAATATACCAACCATCTGA
 CCAAAAAACATCGTGATGCAGTGCCGCGTGCGGCAGTGGAACCGCTGGTG
 CAGATGCTGGCACCGCTGGCACCGCATATTGCGGAAGAACTGTGGCTGCG
 20 TCTGGGCAACACCACCAGCCTGGCGCATGGCCCGTTTCCGAAAGCGGATG
 CGGCGTATCTGGTGGATGAAACCGTGGAATATCCGGTGCAGGTGAACGGC
 AAAGTGCGTGGTCTGTGGTGGTGGCGGCGGATACCGATGAAGAAACCCT
 GAAAGCGGCGGTGCTGACCGATGAAAAAGTGCAGGCGTTTCTGGCGGGC
 GCGACCCCGCGTAAAGTGATTGTGGTGGCGGGCCGTCTGGTGAACCTGGT
 25 GATTTAACCTCGAG

VI. Methods

[0128] In another aspect, the compounds of the invention can be utilized to inhibit an enzyme. In another aspect, the compounds of the invention and/or combinations of the invention exhibit potency against microorganisms, such as bacteria, and therefore have the potential to kill and/or inhibit the growth of microorganisms. In another aspect, the compounds of the invention and/or combinations of the invention exhibit potency against microorganisms, such as bacteria, and therefore have the potential to achieve therapeutic efficacy in the animals described herein.

VI. a) *LeuRS*

35 [0129] In an exemplary embodiment, the compounds of the invention exhibit the ability of inhibiting the editing domain of tRNA synthetases, such as leucyl tRNA synthetase, of microorganisms, such as bacteria, and therefore have the potential to be used as editing domain inhibitors of microorganism tRNA synthetases.

40 [0130] According to another aspect of the invention, a method for binding to and/or inhibiting the editing domain of a tRNA synthetase is provided which comprises contacting a tRNA synthetase with a compound of the invention that inhibits the

editing domain under conditions in which the tRNA synthetase interacts with its substrate to form an aminoacyl adenylate intermediate and, preferably, to form a charged tRNA. Such conditions are known to those skilled in the art. In an exemplary embodiment, the compound has a structure according to a formula

5 described herein. In an exemplary embodiment, the compound is described herein, or a salt, hydrate or solvate thereof, or a combination thereof. In an exemplary embodiment, the invention provides a compound described herein, or a salt, hydrate or solvate thereof. In an exemplary embodiment, the invention provides a compound described herein, or a salt thereof. In an exemplary embodiment, the invention

10 provides a compound described herein, or a salt thereof. The tRNA synthetase is contacted with an amount of compound of the invention sufficient to result in a detectable amount of tRNA synthetase inhibition. This method can be performed on a tRNA synthetase that is contained within an organism or which is outside an organism. In an exemplary embodiment, the method is performed on a tRNA

15 synthetase that is contained within a microorganism or a microbial cell that is in, or on the surface of, an animal. In an exemplary embodiment, the animal is a human. The method results in a decrease in the amount of charged tRNA produced by the tRNA synthetase that has an inhibited editing domain. In an exemplary embodiment, the inhibition takes place in a cell, such as a microorganism cell. In another exemplary

20 embodiment, the microorganism cell is a bacteria. In another exemplary embodiment, the tRNA synthetase is leucyl tRNA synthetase.

[0131] In an exemplary embodiment, the invention provides a method of inhibiting conversion of a tRNA molecule into a charged tRNA molecule. The method involves contacting a tRNA synthetase with a compound of the invention effective to inhibit

25 activity of an editing domain of said tRNA synthetase, under conditions sufficient to inhibit said activity, thereby inhibiting said conversion. In an exemplary embodiment, the compound of the invention is a compound described herein, or a pharmaceutically acceptable salt thereof. In an exemplary embodiment, the inhibition occurs within a cell, and the cell is a microorganism cell. In another exemplary embodiment, the

30 microorganism cell is a bacteria. In another exemplary embodiment, the microorganism cell is a bacteria which is described herein. In another exemplary embodiment, the enzyme is a leucyl tRNA synthetase of a bacteria described herein. In another exemplary embodiment, the tRNA synthetase is leucyl tRNA synthetase.

In another exemplary embodiment, the compound has a $K_{D, \text{synthesis}}$ of greater than 100 μM against a synthetic domain of said tRNA synthetase.

[0132] In certain embodiments, the mechanism of action of a compound of the invention is to inhibit the conversion of a tRNA molecule into a charged tRNA

5 molecule by binding to and/or inhibiting at least the editing domain of the synthetase.

The compounds of use in this method may also inhibit or otherwise interact with the synthetic domain (e.g., the active site of the synthetic domain). In a presently

preferred embodiment, the editing domain is inhibited selectively in the presence of the synthetic domain. In a preferred embodiment, the synthetic domain is essentially

10 uninhibited, while the editing domain is inhibited at least 50%, preferably at least

60%, more preferably at least 70%, still more preferably, at least 80% and even still

more preferably at least 90% of the activity of the tRNA synthetase. In another

preferred embodiment, the synthetic domain is inhibited by at most 50%, preferably at

most 30%, preferably at most 20%, 10%, preferably at most 8%, more preferably at

15 most 5%, still more preferably, at most 3% and even still more preferably at most 1%.

Inhibition of the editing domain produces a decrease in the amount of the properly charged tRNA which results in retardation or cessation of cell growth and division.

[0133] In another exemplary embodiment, the ratio of a minimum concentration of said compound inhibiting said editing domain to a minimum concentration of said

20 compound inhibiting said synthetic domain of said tRNA synthetase, represented as

$K_{D, \text{edit}}/K_{D, \text{synthesis}}$, is less than one. In another exemplary embodiment, the $K_{D, \text{edit}}/K_{D, \text{synthesis}}$ of the compound is a member selected from less than 0.5, less than 0.1 and less than 0.05.

VI. b) *Inhibiting Microorganism Growth or Killing Microorganisms*

25 [0134] The compounds of the invention and/or combinations of the invention exhibit potency against microorganisms, such as bacteria, and therefore have the potential to treat, and/or prevent a microorganism infection, or kill and/or inhibit the growth of microorganisms.

[0135] In a further aspect, the invention provides a method of treating and/or

30 preventing a microorganism infection, or a method of killing and/or inhibiting the growth of a microorganism, said method comprising: contacting said microorganism with an effective amount of a compound of the invention, thereby killing and/or

inhibiting the growth of the microorganism. In a further aspect, the invention provides a method of treating and/or preventing a microorganism infection, or a method of killing and/or inhibiting the growth of a microorganism, said method comprising: contacting said microorganism with an effective amount of a combination of the invention, thereby killing and/or inhibiting the growth of the microorganism.

[0136] In a further aspect, the invention provides a method of treating a bacterial infection comprising administering to an animal suffering from the infection an effective amount of a compound of the invention or a combination of the invention, or a pharmaceutically acceptable salt thereof, thereby treating the bacterial infection. In an exemplary embodiment, the invention provides a method of treating a bacterial infection comprising administering to an animal suffering from the infection an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an effective amount of an antibiotic, or a pharmaceutically acceptable salt thereof, thereby treating the bacterial infection.

[0137] In a further aspect, the invention provides a method of preventing a bacterial infection comprising administering to an animal a prophylactic amount of a compound of the invention or a combination of the invention, or a pharmaceutically acceptable salt thereof, thereby treating the bacterial infection. In an exemplary embodiment, the invention provides a method of preventing a bacterial infection comprising administering to an animal a prophylactic amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

[0138] In an exemplary embodiment, the microorganism is a bacteria. In an exemplary embodiment, the compound or combination is described herein, or a salt, prodrug, hydrate or solvate thereof, or a combination thereof. In an exemplary embodiment, the invention provides a compound or combination described herein, or a salt, hydrate or solvate thereof. In an exemplary embodiment, the invention provides a compound or combination described herein, or a prodrug thereof. In an exemplary embodiment, the invention provides a compound or combination described herein, or a salt thereof. In another exemplary embodiment, the compound or combination of the invention is a compound or combination described herein, or a pharmaceutically acceptable salt thereof. In another exemplary embodiment, the compound or compound of the combination is described by a formula listed herein, or

a pharmaceutically acceptable salt thereof. In an exemplary embodiment, the compound is part of a combination described herein. In an exemplary embodiment, the compound is part of a pharmaceutical formulation described herein. In another exemplary embodiment, the contacting occurs under conditions which permit entry of the compound into the organism. Such conditions are known to one skilled in the art and are described herein.

[0139] In another aspect, the microorganism is inside, or on the surface of an animal. In another exemplary embodiment, the animal is described herein. In another exemplary embodiment, the animal is a human.

[0140] In an exemplary embodiment, the microorganism infection is treated and/or prevented, or the microorganism is killed or its growth is inhibited, through oral administration of the compound of the invention and/or the combination of the invention. In an exemplary embodiment, the microorganism infection is treated and/or prevented, or the microorganism is killed or its growth is inhibited through intravenous administration of the compound of the invention and/or the combination of the invention.

[0141] In an exemplary embodiment, the microorganism is a bacterium. In an exemplary embodiment, an infection is caused by and/or associated with a microorganism, particularly a bacterium. In an exemplary embodiment, the bacterium is a gram-positive bacteria. In another exemplary embodiment, the gram-positive bacterium is selected from the group consisting of *Staphylococcus* species, *Streptococcus* species, *Bacillus* species, *Mycobacterium* species, *Corynebacterium* species (*Propionibacterium* species), *Clostridium* species, *Actinomyces* species, *Enterococcus* species and *Streptomyces* species. In another exemplary embodiment, the gram-positive bacterium is selected from the group consisting of *Propionibacterium acnes*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Staphylococcus haemolyticus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Actinomyces israelii*, *Bacillus anthracis*, *Corynebacterium diphtheria*, *Clostridium perfringens*, *Clostridium botulinum*, *Clostridium tetani*, and *Clostridium difficile*. In another exemplary embodiment, the gram-positive bacterium is selected from the group consisting of *Staphylococcus*

aureus, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Enterococcus faecalis*, *Enterococcus faecium*, *Clostridium difficile* and *Propionibacter acnes*. In another exemplary embodiment, the bacterium is a gram-negative bacterium. In another exemplary embodiment, the gram-negative bacterium

5 is selected from the group consisting of *Acinetobacter* species, *Neisseria* species, *Pseudomonas* species, *Brucella* species, *Agrobacterium* species, *Bordetella* species, *Escherichia* species, *Shigella* species, *Yersinia* species, *Salmonella* species, *Klebsiella* species, *Enterobacter* species, *Haemophilus* species, *Pasteurella* species, *Streptobacillus* species, spirochetal species, *Campylobacter* species, *Vibrio* species,

10 *Helicobacter* species, *Bacteroides* species, *Citrobacter* species, *Proteus* species, *Providencia* species, *Serratia* species, *Stenotrophomonas* species and *Burkholderia* species. In another exemplary embodiment, the gram-negative bacterium is selected from the group consisting of *Acinetobacter* species, *Pseudomonas* species, *Escherichia* species, *Klebsiella* species, *Enterobacter* species, *Bacteroides* species,

15 *Citrobacter* species, *Proteus* species, *Providencia* species, *Serratia* species, *Stenotrophomonas* species and *Burkholderia* species. In another exemplary embodiment, the gram-negative bacterium is selected from the group consisting of *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Pseudomonas aeruginosa*, *Legionella pneumophila*, *Escherichia coli*, *Yersinia pestis*, *Haemophilus influenzae*, *Helicobacter*

20 *pylori*, *Campylobacter fetus*, *Campylobacter jejuni*, *Vibrio cholerae*, *Vibrio parahaemolyticus*, *Treponema pallidum*, *Rickettsia prowazekii*, *Rickettsia rickettsii*, *Chlamydia trachomatis*, *Chlamydia psittaci*, *Brucella abortus*, *Agrobacterium tumefaciens*, *Francisella tularensis*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Acinetobacter baumannii*, *Bacteroides fragilis*, *Citrobacter freundii*, *Proteus*

25 *mirabilis*, *Providencia stuartii*, *Serratia marcescens*, *Stenotrophomonas maltophilia* and *Burkholderia cepacia*. In another exemplary embodiment, the gram-negative bacterium is selected from the group consisting of *Pseudomonas aeruginosa*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Acinetobacter baumannii*, *Bacteroides fragilis*, *Citrobacter freundii*, *Proteus*

30 *mirabilis*, *Providencia stuartii*, *Serratia marcescens*, *Stenotrophomonas maltophilia* and *Burkholderia cepacia*. In another exemplary embodiment, the gram-negative bacterium is selected from the group consisting of *Enterobacter aerogenes*, *Enterobacter cloacae*, *Enterobacter sakazakii*, *Escherichia coli*, *Klebsiella*

pneumoniae, *Proteus mirabilis*, *Serratia marcescens* and *Citrobacterfreundii*. In another exemplary embodiment, the gram-negative bacterium is a *Providencia* spp..

[0142] In an exemplary embodiment, the microorganism is an acid-fast bacteria.

In another exemplary embodiment, the bacterium is a *Mycobacterium* spp.. In

5 another exemplary embodiment, the bacterium is *Mycobacterium avium*. In another exemplary embodiment, the bacterium is *Mycobacterium avium-intracellulare*. In another exemplary embodiment, the bacterium is *Mycobacterium kansasii*. In another exemplary embodiment, the bacterium is *Mycobacterium leprae*. In another exemplary embodiment, the bacterium is *Mycobacterium lepromatosis*. In another
10 exemplary embodiment, the bacterium is *Mycobacterium africanum*. In another exemplary embodiment, the bacterium is *Mycobacterium canetti*. In another exemplary embodiment, the bacterium is *Mycobacterium microti*. In another exemplary embodiment, the bacterium is *Mycobacterium tuberculosis*. In another exemplary embodiment, the bacterium is *Mycobacterium tuberculosis* which is multi-
15 drug resistant. In another exemplary embodiment, the bacterium is *Mycobacterium tuberculosis* which is extensively drug resistant. In another exemplary embodiment, the bacterium is *Mycobacterium tuberculosis* which is resistant to rifampicin. In another exemplary embodiment, the bacterium is *Mycobacterium tuberculosis* which is resistant to isoniazid. In another exemplary embodiment, the bacterium is
20 *Mycobacterium tuberculosis* which is resistant to kanamycin. In another exemplary embodiment, the bacterium is *Mycobacterium tuberculosis* which is resistant to capreomycin. In another exemplary embodiment, the bacterium is *Mycobacterium tuberculosis* which is resistant to amikacin.

[0143] In another exemplary embodiment, the bacterium is a *Pseudomonas*

25 species. In another exemplary embodiment, the bacterium is *Pseudomonas aeruginosa*. In another exemplary embodiment, the bacterium is selected from the group consisting of *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia* and *Burkholderia cepacia*. In another exemplary embodiment, the bacterium is *Acinetobacter baumannii*. In another exemplary
30 embodiment, the bacterium is *Stenotrophomonas maltophilia*. In another exemplary embodiment, the bacterium is *Burkholderia cepacia*. In another exemplary embodiment, the bacterium is *Acinetobacter* species. In another exemplary embodiment, the bacterium is *Acinetobacter anitratus*. In another exemplary

embodiment, the bacterium is selected from the group consisting of *Enterobacter aerogenes*, *Enterobacter cloacae*, *Enterobacter sakazakii*, *E. coli*, *K. pneumoniae*, *P. mirabilis*, *Serratia marcescens*, *Citrobacterfreundii* and *Providencia spp.* In another exemplary embodiment, the bacterium is selected from the group consisting of

5 *Enterobacter aerogenes*, *Enterobacter cloacae*, *Enterobacter sakazakii*, *E. coli*, *K. pneumoniae*, *P. mirabilis*, *Serratia marcescens*, *Citrobacterfreundii*, *Providencia spp.*, *S. aureus*, *S. pneumonia*, *S. pyogenes*, *E. faecalis*, and *E. faecium*. In another exemplary embodiment, the bacterium is selected from the group consisting of

10 *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*. In another exemplary embodiment, the bacterium is selected from the group consisting of *S. aureus*, *S. pneumonia*, *S. pyogenes*, *E. faecalis*, and *E. faecium*. In another exemplary embodiment, the bacterium is selected from the group consisting of Viridans group *Strep.*. In another exemplary embodiment, the bacterium is selected from the group consisting of *Strep. mitis*, *Strep. mutans*, *Strep. oralis*,

15 *Strep. sanguis*, *Strep. sobrinus* and *Strep. millari*. In another exemplary embodiment, the bacterium is *S. pneumonia*. In another exemplary embodiment, the bacterium is *H. influenzae*. In another exemplary embodiment, the bacterium is *S. aureus*. In another exemplary embodiment, the bacterium is *M. catarrhalis*. In another exemplary embodiment, the bacterium is *M. pneumoniae*. In another exemplary

20 embodiment, the bacterium is *L. pneumoniae*. In another exemplary embodiment, the bacterium is *C. pneumoniae*. In another exemplary embodiment, the bacterium is *S. pyogenes*. In another exemplary embodiment, the bacterium is an anaerobe. In another exemplary embodiment, the bacterium is an *Alcaligenes* species. In another exemplary embodiment, the bacterium is a *B. cepacia*. In another exemplary

25 embodiment, the bacterium is selected from the group consisting of *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Providencia stuartii*, *Serratia marcescens*, and *Citrobacterfreundii*. In another exemplary embodiment, the bacterium is resistant to methicillin. In another exemplary embodiment, the bacterium is methicillin-resistant *Staphylococcus aureus*. In another

30 exemplary embodiment, the bacterium is selected from the group consisting of *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Mycobacterium catarrhalis*, *Mycobacterium pneumoniae*, *Legionella pneumophila* and *Chlamydia pneumoniae*. In another exemplary embodiment, the bacterium is selected from the group consisting of *Enterobacter cloacae*, *Escherichia coli*,

Klebsiella pneumoniae, *Proteus mirabilis*, *Serratia marcescens*, *Citrobacterfreundii*,
Providencia stuartii, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*,
Stenotrophomonas maltophilia, *Burkholderia cepacia*, *Staphylococcus aureus*,
Streptococcus pneumoniae, *Streptococcus pyogenes*, *Enterococcus faecalis*, and
5 *Enterococcus faecium*. In another exemplary embodiment, the bacterium is selected
from the group consisting of *Staphylococcus aureus*, *Staphylococcus epidermidis*,
Staphylococcus haemolyticus, *Streptococcus pyogenes*, *Streptococcus agalactiae* and
Streptococcus pneumoniae.

[0144] In an exemplary embodiment, the microorganism is a bacterium, which is
10 selected from the group consisting of bacilli, including *Bacillus* species,
Corynebacterium species (also Propionibacterium) and *Clostridium* species;
filamentous bacteria, including *Actinomyces* species and *Streptomyces* species; bacilli,
such as *Pseudomonas* species, *Brucella* species, *Agrobacterium* species, *Bordetella*
species, *Escherichia* species, *Shigella* species, *Yersinia* species, *Salmonella* species,
15 *Klebsiella* species, *Enterobacter* species, *Haemophilus* species, *Pasteurella* species,
and *Streptobacillus* species; spirochetal species, *Campylobacter* species, *Vibrio*
species; and intracellular bacteria including *Rickettsiae* species and *Chlamydia*
species.

VI. b) Microorganism Infection

20 [0145] The compounds of the invention and/or combinations of the invention
exhibit potency against microorganisms, such as bacteria, and therefore have the
potential to be used to treat and/or prevent a microorganism infection, such as a
bacterial infection.

[0146] In a further aspect, the invention provides a method of treating a bacterial
25 infection comprising administering to an animal suffering from the infection an
effective amount of a compound of the invention, or a pharmaceutically acceptable salt
thereof, thereby treating the bacterial infection. In an exemplary embodiment, the
invention provides a method of treating a bacterial infection comprising administering
to an animal suffering from the infection an effective amount of a compound of the
30 invention, or a pharmaceutically acceptable salt thereof, and an effective amount of an
antibiotic, or a pharmaceutically acceptable salt thereof, thereby treating the bacterial
infection.

[0147] In a further aspect, the invention provides a method of preventing a bacterial infection comprising administering to an animal a prophylactic amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, thereby treating the bacterial infection. In an exemplary embodiment, the invention provides a method of preventing a bacterial infection comprising administering to an animal a prophylactic amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an effective amount of an antibiotic, or a pharmaceutically acceptable salt thereof, thereby treating the bacterial infection.

VI. c) Diseases

[0148] The compounds of the invention and/or combinations of the invention exhibit potency against microorganisms, such as bacteria, and therefore have the potential to achieve therapeutic efficacy in the animals described herein.

[0149] In another aspect, the invention provides a method of treating and/or preventing a disease. In an exemplary embodiment, the method includes administering to the animal a therapeutically effective amount of a compound of the invention, thereby treating and/or preventing the disease. In an exemplary embodiment, the method includes administering to the animal a therapeutically effective amount of a combination of the invention, thereby treating and/or preventing the disease. In an exemplary embodiment, the compound of the invention or the combination of the invention can be used in human or veterinary medical therapy, particularly in the treatment or prophylaxis of bacterial-associated disease. In an exemplary embodiment, the compound is described herein, or a salt, prodrug, hydrate or solvate thereof, or a combination thereof. In an exemplary embodiment, the invention provides a compound described herein, or a prodrug thereof. In an exemplary embodiment, the invention provides a compound described herein, or a salt, hydrate or solvate thereof. In an exemplary embodiment, the invention provides a compound described herein, or a salt thereof. In another exemplary embodiment, the compound of the invention is a compound described herein, or a pharmaceutically acceptable salt thereof. In an exemplary embodiment, the compound is a compound described herein, or a pharmaceutically acceptable salt thereof. In an exemplary embodiment, the compound is according to a formula described herein, or a pharmaceutically acceptable salt thereof. In an exemplary embodiment, the compound is part of a combination described herein. In an exemplary embodiment,

the compound is part of a pharmaceutical formulation described herein. In another exemplary embodiment, the disease is a systemic disease. In another exemplary embodiment, the disease is a topical disease. In an exemplary embodiment, the animal being administered the compound is not otherwise in need of treatment with the compound.

[0150] In an exemplary embodiment, the disease is treated through oral administration of a compound of the invention and/or a combination of the invention. In an exemplary embodiment, the disease is treated through intravenous administration of a compound of the invention and/or a combination of the invention. In an exemplary embodiment, the disease is treated through subcutaneous administration of a compound of the invention and/or a combination of the invention.

Systemic Diseases

[0151] In another aspect, the invention provides a method of treating a systemic disease. The method involves contacting an animal with a compound of the invention and/or a combination of the invention.

[0152] In another exemplary embodiment, the disease is associated with a bacteria described herein. In another exemplary embodiment, the disease is associated with infection by a Gram-positive bacteria. In an exemplary embodiment, the disease is associated with a *Staphylococcus* species. In another exemplary embodiment, the disease is selected from the group consisting of pneumonia, gastroenteritis, toxic shock syndrome, community acquired pneumonia (CAP), meningitis, septic arthritis, urinary tract infection, bacteremia, endocarditis, osteomyelitis, skin and skin-structure infection. In an exemplary embodiment, the disease is associated with a *Streptococcus* species. In another exemplary embodiment, the disease is selected from the group consisting of strep throat, skin infections, necrotizing fasciitis, toxic shock syndrome, pneumonia, otitis media and sinusitis. In an exemplary embodiment, the disease is associated with an *Actinomyces* species. In another exemplary embodiment, the disease is actinomycosis. In an exemplary embodiment, the disease is associated with a *Nocardia* species. In another exemplary embodiment, the disease is pneumonia. In an exemplary embodiment, the disease is associated with a *Corynebacterium* species. In another exemplary embodiment, the disease is diphtheria. In an exemplary embodiment, the disease is associated with a

Listeria species. In another exemplary embodiment, the disease is meningitis. In an exemplary embodiment, the disease is associated with a *Bacillus* species. In another exemplary embodiment, the disease is anthrax or food poisoning. In an exemplary embodiment, the disease is associated with a *Clostridium* species. In another
 5 exemplary embodiment, the disease is selected from the group consisting of botulism, tetanus, gas gangrene and diarrhea.

[0153] In an exemplary embodiment, the disease is associated with a *Mycobacterium* species. In an exemplary embodiment, the disease is associated with *Mycobacterium tuberculosis*. In an exemplary embodiment, the disease is associated
 10 with *Mycobacterium kansasii*. In an exemplary embodiment, the disease is associated with *Mycobacterium avium-intracellulare*. In another exemplary embodiment, the disease is leprosy. In another exemplary embodiment, the disease is tuberculosis. In another exemplary embodiment, the disease is pulmonary tuberculosis. In another exemplary embodiment, the disease is extrapulmonary tuberculosis. In another
 15 exemplary embodiment, the disease is associated with multi-drug resistant tuberculosis. In another exemplary embodiment, the disease is associated with extensively drug resistant tuberculosis.

[0154] In another exemplary embodiment, the disease is associated with infection by a Gram-negative bacteria. In an exemplary embodiment, the disease is associated
 20 with a *Neisseria* species. In another exemplary embodiment, the disease is selected from the group consisting of meningitis, gonorrhea, otitis externa and folliculitis. In an exemplary embodiment, the disease is associated with an *Escherichia* species. In another exemplary embodiment, the disease is selected from the group consisting of diarrhea, urinary tract infections, meningitis, sepsis and HAP. In an exemplary
 25 embodiment, the disease is associated with a *Shigella* species. In another exemplary embodiment, the disease is selected from the group consisting of diarrhea, bacteremia, endocarditis, meningitis and gastroenteritis. In an exemplary embodiment, the disease is associated with a *Salmonella* species. In another exemplary embodiment, the disease is selected from the group consisting of Typhoid fever, sepsis, gastroenteritis,
 30 endocarditis, sinusitis and meningitis. In an exemplary embodiment, the disease is associated with a *Yersinia* species. In another exemplary embodiment, the disease is selected from the group consisting of Typhoid fever, bubonic plague, enteric fever and gastroenteritis. In an exemplary embodiment, the disease is associated with a

Klebsiella species. In another exemplary embodiment, the disease is sepsis or urinary tract infection. In an exemplary embodiment, the disease is associated with a *Proteus* species. In another exemplary embodiment, the disease is an urinary tract infection. In an exemplary embodiment, the disease is associated with an *Enterobacter* species.

5 In another exemplary embodiment, the disease is a hospital-acquired infection. In an exemplary embodiment, the disease is associated with a *Serratia* species. In another exemplary embodiment, the disease is selected from the group consisting of a urinary tract infection, skin and skin-structure infection and pneumonia. In an exemplary embodiment, the disease is associated with a *Vibrio* species. In another exemplary

10 embodiment, the disease is cholera or gastroenteritis. In an exemplary embodiment, the disease is associated with a *Campylobacter* species. In another exemplary embodiment, the disease is gastroenteritis. In an exemplary embodiment, the disease is associated with a *Helicobacter* species. In another exemplary embodiment, the disease is chronic gastritis. In an exemplary embodiment, the disease is associated

15 with a *Pseudomonas* species. In another exemplary embodiment, the disease is selected from the group consisting of pneumonia, osteomyelitis, burn-wound infections, sepsis, UTIs, endocarditis, otitis and corneal infections. In an exemplary embodiment, the disease is associated with a *Bacteroides* species. In another exemplary embodiment, the disease is periodontal disease or aspiration pneumonia.

20 In an exemplary embodiment, the disease is associated with a *Haemophilus* species. In another exemplary embodiment, the disease is selected from the group consisting of meningitis, epiglottitis, septic arthritis, sepsis, chancroid and vaginitis. In an exemplary embodiment, the disease is associated with a *Bordetella* species. In another exemplary embodiment, the disease is Whooping cough. In an exemplary

25 embodiment, the disease is associated with a *Legionella* species. In another exemplary embodiment, the disease is pneumonia or pontiac fever. In an exemplary embodiment, the disease is associated with a *Francisella* species. In another exemplary embodiment, the disease is tularemia. In an exemplary embodiment, the disease is associated with a *Brucella* species. In another exemplary embodiment, the

30 disease is brucellosis. In an exemplary embodiment, the disease is associated with a *Pasteurella* species. In another exemplary embodiment, the disease is a skin infection. In an exemplary embodiment, the disease is associated with a *Gardnerella* species. In another exemplary embodiment, the disease is vaginitis. In an exemplary embodiment, the disease is associated with a *Spirochetes* species. In another

exemplary embodiment, the disease is syphilis or Lyme disease. In an exemplary embodiment, the disease is associated with a *Chlamydia* species. In another exemplary embodiment, the disease is chlamydia. In an exemplary embodiment, the disease is associated with a *Rickettsiae* species. In another exemplary embodiment, the disease is Rocky Mountain spotted fever or typhus.

[0155] In an exemplary embodiment, the disease is associated with *Mycoplasma pneumoniae*. In another exemplary embodiment, the disease is tracheobronchitis or walking pneumonia. In an exemplary embodiment, the disease is associated with *Ureaplasma urealyticum*. In another exemplary embodiment, the disease is urethritis.

In another exemplary embodiment, the disease is pyelonephritis. In another exemplary embodiment, the disease is an intra-abdominal infection. In another exemplary embodiment, the disease is febrile neutropenia. In another exemplary embodiment, the disease is a pelvic infection. In another exemplary embodiment, the disease is bacteraemia. In another exemplary embodiment, the disease is septicaemia.

[0156] In an exemplary embodiment, the disease is an acute exacerbation of chronic obstructive pulmonary disease. In an exemplary embodiment, the disease is chronic obstructive pulmonary disease. In an exemplary embodiment, the disease is pharyngitis. In an exemplary embodiment, the disease is tonsillitis. In an exemplary embodiment, the disease is Acute Exacerbation of Chronic Bronchitis (AECB). In an exemplary embodiment, the disease is cervicitis. In an exemplary embodiment, the disease is genital ulcer disease.

[0157] In an exemplary embodiment, for any of the methods described herein, the animal is selected from the group consisting of human, cattle, deer, reindeer, goat, honey bee, pig, sheep, horse, cow, bull, dog, guinea pig, gerbil, rabbit, cat, camel, yak, elephant, ostrich, otter, chicken, duck, goose, guinea fowl, pigeon, swan, and turkey. In another exemplary embodiment, for any of the methods described herein, the animal is selected from the group consisting of a human, cattle, goat, pig, sheep, horse, cow, bull, dog, guinea pig, gerbil, rabbit, cat, chicken and turkey. In another exemplary embodiment, for any of the methods described herein, the animal is a human.

[0158] In an exemplary embodiment, for any of the methods described herein, a compound of the invention, a combination of the invention, a compound described

herein or a pharmaceutically acceptable salt thereof, or combination described herein, and/or a pharmaceutical formulation described herein can be used.

VII. Pharmaceutical Formulation

[0159] In another aspect, the invention provides a pharmaceutical formulation comprising: a) a compound of the invention; and b) a pharmaceutically acceptable excipient. In another aspect, the invention provides a pharmaceutical formulation comprising: a) a combination of the invention; and b) a pharmaceutically acceptable excipient. In an exemplary embodiment, the compound is according to a formula described herein. In an exemplary embodiment, the compound is according to an example described herein. In an exemplary embodiment, the compound of the invention or combination of the invention is a compound described herein or combination described herein, or a pharmaceutically acceptable salt thereof. In an exemplary embodiment, the compound of the invention is a compound described herein.

[0160] In an exemplary embodiment, the compound of the invention is present in the pharmaceutical formulation in an amount of between about 0.0001% to about 60% (w/w). In an exemplary embodiment, the amount is between about 0.01% to about 10% (w/w). In an exemplary embodiment, the amount is between about 0.1% to about 10% (w/w). In an exemplary embodiment, the amount is between about 0.25% to about 6% (w/w). In an exemplary embodiment, the amount is between about 0.5% to about 5% (w/w). In an exemplary embodiment, the amount is between about 0.1% and about 1.0% (w/w). In an exemplary embodiment, the amount is between about 1.0% and about 2.0% (w/w). In an exemplary embodiment, the amount is between about 2.0% and about 3.0% (w/w). In an exemplary embodiment, the amount is between about 3.0% and about 4.0% (w/w). In an exemplary embodiment, the amount is between about **4.0%** and about **5.0%** (w/w).

[0161] The pharmaceutical formulations of the invention can take a variety of forms adapted to the chosen route of administration. Those skilled in the art will recognize various synthetic methodologies that may be employed to prepare non-toxic pharmaceutical formulations incorporating the compounds described herein. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable solvents that may be used to prepare solvates of the compounds of the

invention, such as water, ethanol, propylene glycol, mineral oil, vegetable oil and dimethylsulfoxide (DMSO).

[0162] The compositions of the invention may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. It is further understood that the best method of administration may be a combination of methods. Oral administration in the form of a pill, capsule, elixir, syrup, lozenge, troche, or the like is particularly preferred. The term parenteral as used herein includes subcutaneous injections, intradermal, intravascular (e.g., intravenous), intramuscular, spinal, intrathecal injection or like injection or infusion techniques.

[0163] The pharmaceutical formulations containing compounds of the invention are preferably in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

[0164] Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical formulations, 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 may contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that 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; lubricating agents, for example magnesium stearate, stearic acid or talc; and extenders and bulking agents, such as microcrystalline cellulose. 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.

[0165] 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.

[0166] 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, polyvinylpyrrolidone, gum tragacanth and gum acacia; and dispersing or wetting agents, which 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. 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.

[0167] Oily suspensions may be formulated by suspending the active ingredients 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 palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0168] 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, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Other dispersing agents include hydrophilic polymers, electrolytes, Tween™ 60 or 80, PEG, polyvinylpyrrolidone (PVP; commercially known as

PlasdoneTM), and the carbohydrate-based dispersing agents such as, for example, hydroxypropylcellulose and hydroxypropylcellulose ethers (e.g., HPC, HPC-SL, and HPC-L), hydroxypropylmethylcellulose and hydroxypropylmethylcellulose ethers (e.g. HPMC K100, HPMC K4M, HPMC K15M, and HPMC K100M),

5 carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate stearate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), polyvinylpyrrolidone/vinyl acetate copolymer (PlasdoneTM, e.g., S-630), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and

10 formaldehyde (also known as tyloxapol), poloxamers (e.g., Pluronic F68TM, F88TM, and F108TM, which are block copolymers of ethylene oxide and propylene oxide); and poloxamines (e.g., Tetronic 9080, also known as Poloxamine 9080, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Corporation, Parsippany, N.J.)).

15 Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0169] Pharmaceutical formulations of the invention may also be in the form of oil-in-water emulsions and water-in-oil emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or

20 mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth; naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol; anhydrides, for example sorbitan monooleate; and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan

25 monooleate. The emulsions may also contain sweetening and flavoring agents.

[0170] 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. The pharmaceutical formulations may be in the form of a sterile injectable aqueous or oleaginous

30 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 non-toxic parenterally acceptable diluent or solvent, for

example as a solution in 1,3-butanediol. 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 medium. For this purpose any bland fixed oil may be employed including
5 synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0171] The composition of the invention may also be administered in the form of suppositories, e.g., for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at
10 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.

[0172] Alternatively, the compositions can be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can
15 either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

[0173] For administration to non-human animals, the composition containing the therapeutic compound may be added to the animal's feed or drinking water. Also, it will be convenient to formulate animal feed and drinking water products so that the
20 animal takes in an appropriate quantity of the compound in its diet. It will further be convenient to present the compound in a composition as a premix for addition to the feed or drinking water. The composition can also added as a food or drink supplement for humans.

[0174] Dosage levels of the order of from about 5 mg to about 250 mg per
25 kilogram of body weight per day and more preferably from about 25 mg to about 150 mg per kilogram of body weight per day, are useful in the treatment of the above-indicated conditions. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the condition being treated and the particular mode of administration. Dosage unit forms
30 will generally contain between from about 1 mg to about 500 mg of an active ingredient.

[0175] Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most disorders, a dosage regimen of 4 times daily or less is preferred. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

[0176] Preferred compounds of the invention will have desirable pharmacological properties that include, but are not limited to, oral bioavailability, low toxicity, low serum protein binding and desirable in vitro and in vivo half-lives. Penetration of the blood brain barrier for compounds used to treat CNS disorders is necessary, while low brain levels of compounds used to treat peripheral disorders are often preferred.

[0177] The amount of the composition required for use in treatment will vary not only with the particular compound selected but also with 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 clinician.

[0178] In an exemplary embodiment, the pharmaceutical composition described herein includes an additional active ingredient. In another exemplary embodiment, the additional active ingredient is a compound that has been approved for human use by the United States Food and Drug Administration. In another exemplary embodiment, the additional active ingredient is an immunosuppressive agent. In still another exemplary embodiment, the additional active ingredient is selected from the group consisting of corticosteroids, aminosalicylates, azathioprine (6-mercaptopurine), methotrexate and cyclosporine, etanercept, infliximab, adalimumab, alefacept, efalizumab and anakinra.

[0179] In still another exemplary embodiment, the additional active ingredient is selected from the group consisting of betamethasone, tacrolimus and pimecrolimus. In still another exemplary embodiment, the additional active ingredient is selected from the group consisting of an activated vitamin D analog and an arotinoid (an aromatic retinoic acid analog). In still another exemplary embodiment, the additional active ingredient is carboxipotriol, such as Tazorac (tazarotene).

VII. a) Topical formulations

[0180] In a preferred embodiment, the methods of the invention can be employed through the topical application of the compounds described herein. Topical administration includes for example, transmucosal, transdermal, ungual and transungual routes of administration. The topical compositions useful in the subject invention can be made into a wide variety of product types. These include, but are not limited to, lotions, creams, gels, sticks, sprays, ointments, pastes, foams, mousses, masks, eye ointments, eye or ear drops, impregnated dressings, wipes, cleansers including soaps, body washes and shampoos, and make-up products, such as bases, blushes, lipsticks, and eye shadows, among others. These product types can comprise several types of carrier systems including, but not limited to particles, nanoparticles, and liposomes. If desired, disintegrating agents can be added, such as the cross-linked polyvinyl pyrrolidone, agar or alginic acid or a salt thereof such as sodium alginate. Techniques for formulation and administration can be found in Remington: The Science and Practice of Pharmacy, supra. The formulation can be selected to maximize delivery to a desired target site in the body. The formulations can also include various conventional colorants, fragrances, thickeners, preservatives, humectants, emollients, demulcents, solubilizing excipients, dispersants, penetration enhancers, plasticizing agents, preservatives, stabilizers, demulsifiers, wetting agents, sunscreens, emulsifiers, moisturizers, astringents, deodorants, and the like, which can be added to provide additional benefits such as, for example, improving the feel and/or appearance of the topical preparation.

[0181] Lotions, which are preparations that are to be applied to the skin, nail, hair, claw or hoof surface without friction, are typically liquid or semi-liquid preparations in which finely divided solid, waxy, or liquid are dispersed. Lotions will typically contain suspending agents to produce better dispersions as well as compounds useful for localizing and holding the active agent in contact with the skin, nail, hair, claw or hoof, e.g., methylcellulose, sodium carboxymethyl-cellulose, or the like.

[0182] Creams containing the active agent for delivery according to the invention are viscous liquid or semisolid emulsions, either oil-in-water or water-in-oil. Cream bases are water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase is generally comprised of petrolatum or a fatty alcohol, such as cetyl- or stearyl alcohol; the aqueous phase usually, although not necessarily, exceeds

the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation, as explained in Remington: The Science and Practice of Pharmacy, supra, is generally a nonionic, anionic, cationic or amphoteric surfactant.

[0183] Ointments, which are semisolid preparations, are typically based on petrolatum or other petroleum derivatives. As will be appreciated by the ordinarily skilled artisan, the specific ointment base to be used is one that provides for optimum delivery for the active agent chosen for a given formulation, and, preferably, provides for other desired characteristics as well, e.g., emolliency or the like. As with other carriers or vehicles, an ointment base should be inert, stable, nonirritating and non-sensitizing. As explained in Remington: The Science and Practice of Pharmacy, 19th Ed. (Easton, Pa.: Mack Publishing Co., 1995), at pages 1399-1404, ointment bases may be grouped in four classes: oleaginous bases; emulsifiable bases; emulsion bases; and water-soluble bases. Oleaginous ointment bases include, for example, vegetable oils, fats obtained from animals, and semisolid hydrocarbons obtained from petroleum. Preferred water-soluble ointment bases are prepared from polyethylene glycols of varying molecular weight; again, reference may be had to Remington: The Science and Practice of Pharmacy, supra, for further information.

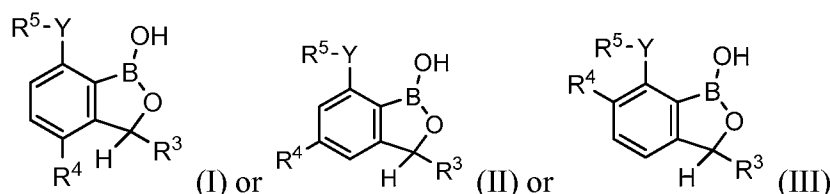
[0184] Useful formulations of the invention also encompass sprays and aerosols. Sprays generally provide the active agent in an aqueous and/or alcoholic solution which can be misted onto the skin, nail, hair, claw or hoof for delivery. Such sprays include those formulated to provide for concentration of the active agent solution at the site of administration following delivery, e.g., the spray solution can be primarily composed of alcohol or other like volatile liquid in which the drug or active agent can be dissolved. Upon delivery to the skin, nail, hair, claw or hoof, the carrier evaporates, leaving concentrated active agent at the site of administration. Examples of aerosol technology are disclosed in US Patents 6,682,716; 6,716,415; 6,716,417; 6,783,753; 7,029,658; and 7,033,575.

[0185] Examples of solubilizing excipients include polyethoxylated fatty acids, PEG-fatty acid diesters, PEG-fatty acid mono-ester and di-ester mixtures, polyethylene glycol glycerol fatty acid esters, alcohol-oil transesterification products, polyglycerized fatty acids, propylene glycol fatty acid esters, mixtures of propylene glycol esters-glycerol esters, mono- and diglycerides, sterol and sterol derivatives,

polyethylene glycol sorbitan fatty acid esters, polyethylene glycol alkyl ethers, sugar esters, polyethylene glycol alkyl phenols, polyoxyethylene-polyoxypropylene block copolymers, sorbitan fatty acid esters, lower alcohol fatty acid esters, ionic surfactants, tocopherol esters, and sterol esters.

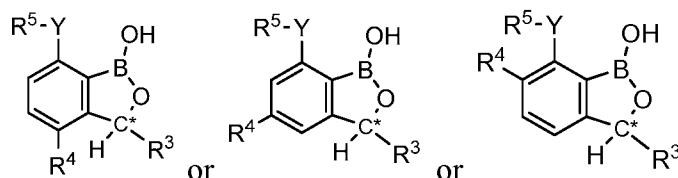
5 [0186] Exemplary embodiments are summarized herein below.

[0187] In an exemplary embodiment, the invention provides a compound having a structure according to a formula which is:



10 wherein R^3 is substituted or unsubstituted nitroalkyl or substituted or unsubstituted aminoalkyl; R^4 is selected from the group consisting of halogen, unsubstituted alkyl, unsubstituted alkoxy, and unsubstituted phenyl; Y is O or S; and R^5 is selected from the group consisting of substituted or unsubstituted alkyl and substituted or unsubstituted heteroalkyl; or a salt, hydrate or solvate thereof.

15 [0188] In an exemplary embodiment, according to the above paragraph, having a structure which is



wherein C^* is a carbon atom stereocenter which has a configuration which is (R) or (S).

20 [0189] In an exemplary embodiment, according to any of the above paragraphs, wherein C^* stereocenter is in a (S) configuration.

[0190] In an exemplary embodiment, according to any of the above paragraphs, wherein R^3 is $-(CR^{20}R^{21})_nNR^{22}R^{23}$ in which n is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; each R^{20} and each R^{21} is independently selected from the group consisting of H, R^{26} , OR^{26} , $NR^{26}R^{27}$, SR^{26} , $-S(O)R^{26}$, $-S(O)_2R^{26}$, $-S(O)_2NR^{26}R^{27}$, $-C(O)R^{27}$, $-C(O)OR^{27}$,
25 and $-C(O)NR^{26}R^{27}$

R^{22} and R^{23} are independently selected from the group consisting of H, $-S(O)R^{28}$, $-S(O)_2R^{28}$, $-S(O)_2NR^{28}R^{29}$, $-C(O)R^{28}$, $-C(O)OR^{28}$, $-C(O)NR^{28}R^{29}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl; wherein each R^{26} , each R^{27} , each R^{28} and each R^{29} is independently selected from the group consisting of H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0191] In an exemplary embodiment, according to any of the above paragraphs, R^3 is $-CH_2NH_2$.

[0192] In an exemplary embodiment, according to any of the above paragraphs, R^3 is $-CH_2NH_2$, and C^* has a configuration which is (S).

[0193] In an exemplary embodiment, according to any of the above paragraphs, R^4 is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and *sec*-butyl.

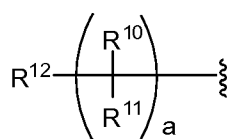
[0194] In an exemplary embodiment, according to any of the above paragraphs, R^4 is selected from the group consisting of fluorine, chlorine, bromine, and iodine.

[0195] In an exemplary embodiment, according to any of the above paragraphs, R^4 is fluorine.

[0196] In an exemplary embodiment, according to any of the above paragraphs, R^4 is chlorine.

[0197] In an exemplary embodiment, according to any of the above paragraphs, R^4 is bromine.

[0198] In an exemplary embodiment, according to any of the above paragraphs, R^5 is:



wherein a is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; each R¹⁰ and each R¹¹ is independently selected from the group consisting of H, substituted or unsubstituted alkyl, OH and NH₂;

R¹² is selected from the group consisting of H, R⁷, halogen, cyano, amidino, OR⁷,
 5 NR⁷R⁸, SR⁷, -N(R⁷)S(O)₂R⁸, -C(O)R⁷, -C(O)OR⁷, -C(O)NR⁷R⁸ wherein each R⁷ and each R⁸ is independently selected from the group consisting of H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

10 [0199] In an exemplary embodiment, according to any of the above paragraphs, a is 1, 2, 3, 4, or 5.

[0200] In an exemplary embodiment, according to any of the above paragraphs, a is 2, 3, or 4.

[0201] In an exemplary embodiment, according to any of the above paragraphs,
 15 each R¹⁰ and each R¹¹ is independently selected from the group consisting of H, substituted or unsubstituted alkyl, OH, and NH₂.

[0202] In an exemplary embodiment, according to any of the above paragraphs, each R¹⁰ and each R¹¹ is H.

[0203] In an exemplary embodiment, according to any of the above paragraphs,
 20 R¹² is selected from the group consisting of H, OH, NH₂, methyl, ethyl, -NHS(O)₂CH₃, cyano, -NHC(O)CH₃, -NHC(O)NHCH₂CH₃, -C(O)NH₂, -C(O)OH, 4-(methoxy)phenyl, benzyl, benzoxy, -NHC(O)OCH₂Ph, -C(O)NHCH₂CH₂OH and -C(NH₂)(NH).

[0204] In an exemplary embodiment, according to any of the above paragraphs, Y
 25 is O.

[0205] In an exemplary embodiment, according to any of the above paragraphs, R⁵ is unsubstituted alkyl.

[0206] In an exemplary embodiment, according to any of the above paragraphs, R⁵ is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl,
 30 isobutyl, t-butyl, and sec-butyl.

[0207] In an exemplary embodiment, according to any of the above paragraphs, R^3 is $-\text{CH}_2\text{NH}_2$; and Y is O; and R^5 is substituted or unsubstituted alkyl.

[0208] In an exemplary embodiment, according to any of the above paragraphs, R^3 is $-\text{CH}_2\text{NH}_2$; and R^4 is halogen.

5 [0209] In an exemplary embodiment, according to any of the above paragraphs, R^4 is halogen; Y is O; and R^5 is unsubstituted alkyl.

[0210] In an exemplary embodiment, according to any of the above paragraphs, R^3 is $-\text{CH}_2\text{NH}_2$, and C^* has a configuration which is (S) and R^4 is halogen.

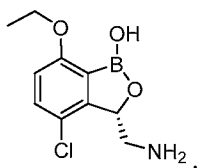
10 [0211] In an exemplary embodiment, according to any of the above paragraphs, R^3 is $-\text{CH}_2\text{NH}_2$, and C^* has a configuration which is (S), R^5 is unsubstituted alkyl and R^4 is halogen.

[0212] In an exemplary embodiment, according to any of the above paragraphs, Y is O, R^3 is $-\text{CH}_2\text{NH}_2$, and C^* has a configuration which is (S), R^5 is unsubstituted C_1 or C_2 or C_3 or C_4 alkyl and R^4 is halogen.

15 [0213] In an exemplary embodiment, according to any of the above paragraphs, R^3 is $-\text{CH}_2\text{NH}_2$; R^4 is chlorine; Y is O; and R^5 is substituted or unsubstituted alkyl.

[0214] In an exemplary embodiment, according to any of the above paragraphs, R^3 is $-\text{CH}_2\text{NH}_2$; Y is O; and R^5 is ethyl.

20 [0215] In an exemplary embodiment, according to any of the above paragraphs, the compound has a structure which is



[0216] In an exemplary embodiment, the invention provides a composition comprising: (a) a first stereoisomer of the compound according to any of the above paragraphs; b) at least one additional stereoisomer of the first stereoisomer; wherein
25 the first stereoisomer is present in an enantiomeric excess of at least 80% relative to said at least one additional stereoisomer.

[0217] In an exemplary embodiment, according to any of the above paragraphs, wherein said enantiomeric excess is at least 92%.

[0218] In an exemplary embodiment, according to any of the above paragraphs, wherein the C* stereocenter of the first stereoisomer is in a (S) configuration.

[0219] In an exemplary embodiment, according to any of the above paragraphs, wherein R³ is -CH₂NH₂.

5 [0220] In an exemplary embodiment, the invention provides a composition according to any of the above paragraphs, wherein the C* stereocenter is in a (S) configuration, and said composition is substantially free of the (R) enantiomer of the compound.

[0221] In an exemplary embodiment, the invention provides a combination
10 comprising the compound according to any of the above paragraphs, or a pharmaceutically acceptable salt thereof, together with at least one other therapeutically active agent.

[0222] In an exemplary embodiment, the invention provides a pharmaceutical formulation comprising: (a) a compound according to any of the above paragraphs, or
15 a pharmaceutically acceptable salt thereof; and (b) a pharmaceutically acceptable excipient.

[0223] In an exemplary embodiment, according to any of the above paragraphs, the formulation is in a unit dosage form.

[0224] In an exemplary embodiment, according to any of the above paragraphs,
20 the formulation is for oral or topical use.

[0225] In an exemplary embodiment, the invention provides a method of inhibiting an enzyme, comprising: contacting the enzyme with the compound according to any of the above paragraphs, thereby inhibiting the enzyme.

[0226] In an exemplary embodiment, according to any of the above paragraphs,
25 the enzyme is a t-RNA synthetase which comprises an editing domain.

[0227] In an exemplary embodiment, according to any of the above paragraphs, the enzyme is a leucyl t-RNA synthetase.

[0228] In an exemplary embodiment, the invention provides a method of killing and/or preventing the growth of a microorganism, comprising: contacting
30 microorganism with an effective amount of a compound according to any of the

above paragraphs, or a pharmaceutically acceptable salt thereof, thereby killing and/or preventing the growth of the microorganism.

[0229] In an exemplary embodiment, according to any of the above paragraphs, the microorganism is a bacterium.

5 [0230] In an exemplary embodiment, according to any of the above paragraphs, the microorganism is *Mycobacterium tuberculosis*.

[0231] In an exemplary embodiment, the invention provides a method of treating and/or preventing a disease in an animal, comprising: administering to the animal a therapeutically effective amount of compound according to any of the above
10 paragraphs, or a pharmaceutically-acceptable salt thereof, thereby treating and/or preventing the disease.

[0232] In an exemplary embodiment, according to any of the above paragraphs, the disease is tuberculosis.

[0233] In an exemplary embodiment, according to any of the above paragraphs,
15 the animal is a human.

[0234] In an exemplary embodiment, the invention provides a method of inhibiting the editing domain of a t-RNA synthetase, comprising: contacting the synthetase with an effective amount of a compound according to any of the above paragraphs, or a pharmaceutically-acceptable salt thereof, thereby inhibiting the
20 synthetase.

[0235] In an exemplary embodiment, according to any of the above paragraphs, the synthetase is a leucyl t-RNA synthetase.

[0236] In an exemplary embodiment, according to any of the above paragraphs, the synthetase is a *Mycobacterium tuberculosis* leucyl t-RNA synthetase.

25 [0237] In an exemplary embodiment, the invention provides the use of a compound according to any of the above paragraphs or a combination according to any of the above paragraphs or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment and/or prophylaxis of bacterial infection.

[0238] It is to be understood that the present invention covers all combinations of aspects and/or embodiments, as well as suitable, convenient and preferred groups described herein.

[0239] The invention is further illustrated by the Examples that follow. The
5 Examples are not intended to define or limit the scope of the invention.

EXAMPLES

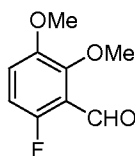
[0240] Proton NMR are recorded on Varian AS 300 spectrometer and chemical shifts are reported as δ (ppm) down field from tetramethylsilane. Mass spectra are determined on Micromass Quattro II.

10 [0241] The *M. tuberculosis* LeuRS gene (DNA sequence listed herein) was prepared by GenScript and cloned into the T7 expression vector pET28a(+) at the NdeI-XhoI sites. Over-expression of *M. tuberculosis* LeuRS from this construct generated a version of *M. tuberculosis* LeuRS with an N-terminal his-tag, which will use the standard procedures for purification of his-tagged proteins.

15 EXAMPLE 1

A. 3-Aminomethyl-4-fluoro -7-(3-hydroxy-propoxy)-3H-benzofcJfl,2Joxaborol-1-ol; bis trifluoroacetic salt

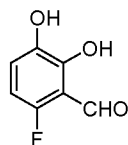
6-Fluoro-2,3-dimethoxy-benzaldehyde



20 [0242] To a solution of 4-fluoro-1,2-dimethoxy-benzene (20.0 g, 128.07 mmol) in anhydrous THF (200 mL) under nitrogen at -78 °C was added dropwise a 2.5M solution in hexane of n-BuLi (102.4 mL, 256.14 mmol) for duration 30 min and the reaction mixture was further stirred at the same temperature for 3 h. The reaction mixture was quenched carefully with DMF (100 mL) at -65 °C to -40 °C and left
25 overnight. 2N HCl (300 mL) was added dropwise at -60 °C and the mixture stirred for 30 min. The two layers were separated and the aqueous layer extracted with EtOAc. The combined organic layers were washed with water and brine, dried over MgSC⁺, filtered and concentrated in vacuo. Purification was completed by flash column chromatography (20% EtOAc / hexane). Yield 18.0 g (85%). ¹H NMR (400 MHz, CHLOROFORM -d) δ ppm 10.39 (s, 1 H), 7.09 (dd, *J*=9.4, 5.1 Hz, 1 H), 6.84 (t, *J*=9.6
30

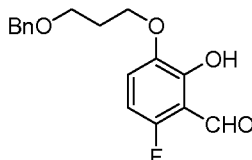
Hz, 1 H), 3.98 (s, 3 H), 3.88 (s, 3 H). ^{19}F NMR (376 MHz, CHLOROFORM- d): -126 ppm.

6-Fluoro-2,3-dihydroxy-benzaldehyde



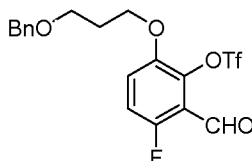
- 5 [0243] To a solution of 6-fluoro-2,3-dimethoxy-benzaldehyde (18.0 g, 97.74 mmol) in anhydrous dichloromethane (100 mL) under nitrogen at -60 °C was added dropwise $\text{BBr}_3 \cdot \text{OEt}_2$ (195 mL, 195.48 mmol) over 30 min and the solution was allowed to warm up to r.t and stirred for 4h. The reaction mixture was cooled to -60 °C and 2N HCl (250 mL) was carefully added drop wise. The mixture was stirred at
- 10 r.t overnight. The two layers were separated and the aqueous layer extracted with DCM. The combined organic layers were washed with water, sat. NaHCO_3 solution, water and brine and dried over MgSO_4 . The solvent was removed in vacuo to provide the title compound which was used in the next step without further purification. Yield 11.15 g (74%). ^1H NMR (400 MHz, CHLOROFORM- d) δ ppm 11.53 (s, 1 H), 10.23 (s, 1 H), 7.11 (dd, $J=8.8, 5.3$ Hz, 1 H), 6.57 (t, $J=9.6$ Hz, 1 H), 5.48 (s, 1 H). ^{19}F NMR (376 MHz, CHLOROFORM- d): -132 ppm.
- 15

3-(3-Benzyloxy-propoxy)-6-fluoro-2-hydroxy-benzaldehyde



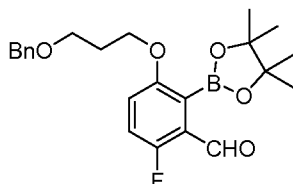
- [0244] To a solution of 6-fluoro-2,3-dihydroxy-benzaldehyde (11.15 g, 71.42 mmol) in anhydrous DMSO (88 mL) under nitrogen were added sequentially sodium *t*-butoxide (13.72 g, 142.84 mmol) and benzyl-3-bromopropyl ether (17.29 g, 78.56 mmol) and the reaction mixture stirred at rt for 18 h. The mixture was diluted with water (400 mL) and extracted with EtOAc (4x100 mL). The combined organic layer was washed with water and brine, dried over MgSO_4 , filtered and concentrated in
- 25 vacuo. Purification was completed by flash chromatography (20% EtOAc / hexane). Yield 11.5 g (77 %). ^1H NMR (400 MHz, CHLOROFORM- d) δ ppm 11.62 (s, 1 H), 10.23 (s, 1 H), 7.42 - 7.16 (m, 5 H), 7.05 (dd, $J=8.8, 5.3$ Hz, 1 H), 6.54 (t, $J=9.6$ Hz, 1 H), 4.52 (s, 2 H), 4.13 (t, $J=6.3$ Hz, 2 H), 3.68 (t, $J=6.1$ Hz, 2 H), 2.12 (quin, $J=6.2$ Hz, 2 H). ^{19}F NMR (376 MHz, CHLOROFORM- d): -132 ppm.

Trifluoro-methanesulfonic acid 6-(3-benzyloxy-propoxy)-3-fluoro-2-formyl-phenyl ester



[0245] Trifluoromethanesulfonic anhydride (1.11 g, 3.94 mmol) was added dropwise to a solution of pyridine (389 mg, 4.92 mmol) and 3-(3-benzyloxy-propoxy)-6-fluoro-2-hydroxy-benzaldehyde (1 g, 3.28 mmol) in CH_2Cl_2 (5 mL) at 0 °C (bath temp). The reaction mixture was then allowed to warm to rt and was stirred until complete consumption of starting material (as determined by TLC). Et_2O and 2 N HCl were then added. The organic layer was separated and washed with sat. NaHCO₃ then brine. The organic layer was dried (Na_2SO_4) and filtered through a short silica gel plug, washing with Et_2O . The filtrate was concentrated in vacuo to give 1.10 g of the desired triflate (yield 76%) that was used directly without further purification. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 10.32 (s, 1 H), 7.44 - 7.21 (m, 7 H), 4.51 (s, 2 H), 4.18 (t, *J*=6.1 Hz, 2 H), 3.68 (t, *J*=5.7 Hz, 2 H), 2.14 (quin, *J*=5.8 Hz, 2 H).

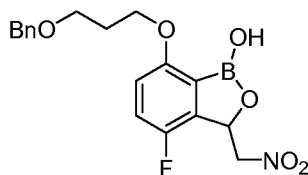
3-(3-Benzyloxy-propoxy)-6-fluoro-2-(4,4,5,5-tetramethyl-1,3,2]dioxaborolan-2-yl)-benzaldehyde



[0246] A solution of trifluoro-methanesulfonic acid 6-(3-benzyloxy-propoxy)-3-fluoro-2-formyl-phenyl ester (1.092 g, 2.50 mmol) in anhydrous 1,4-dioxane (10 mL) was added bis(pinacolato)diborane (953 mg, 3.75 mmol) and KOAc (736 mg, 7.50 mmol) at rt, then degassed with N_2 for 20 min. $\text{PdCl}_2(\text{dppf})$ (46 mg, 8 mol %) was added and the resulting solution was stirred at 100 °C until the reaction was complete. The solution was cooled to rt, filtered through Celite® or silica gel and concentrated in vacuo. The residue was taken up in EtOAc. The organic layer was then washed with H_2O then brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The product was purified by flash chromatography (20% EtOAc / hexane) to give 0.5 g of the title compound along with detriflated by product ratio ~ 1:1 by ¹H NMR spectrum. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 10.33 (s, 1 H), 7.41 - 7.23 (m, 6 H), 7.19 (d, *J*=9.4 Hz, 1 H), 4.57 - 4.42 (m, 2 H), 4.06 (t, *J*=6.3 Hz, 2 H), 3.69 - 3.64 (m, 2 H),

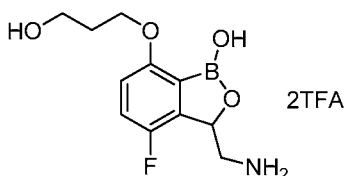
2.20 - 2.00 (m, 2 H), 1.44 (s, 12 H); ^{19}F NMR (376 MHz, CHLOROFORM- d) δ ppm -73.72.

7-(3-Benzyloxy-propoxy)-4-fluoro-3-nitromethyl-3H-benzo[C] [1,2]oxaborol-1-ol



- 5 [0247] NaOH (48 mg, 1.20 mmol) was added to 3-(3-benzyloxy-propoxy)-6-fluoro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde (500 mg, 1.2 mmol) in H_2O (3 mL) at rt, and the reaction mixture was stirred at rt for 5 min. MeNO_2 (219 mg, 3.6 mmol) was added dropwise and the mixture was stirred at rt for 16 h. The reaction mixture was acidified with 2 N HCl and extracted with EtOAc.
- 10 The organic fraction was washed with H_2O then brine, dried (MgSO_4), and concentrated in vacuo. Purification was accomplished by flash chromatography (10-40% EtOAc / hexane) to give 120 mg of the title compound by ^1H NMR spectrum. ^1H NMR (400 MHz, CHLOROFORM- d) δ ppm 7.40-7.22 (m, 5 H), 7.11 (t, $J=8.8$ Hz, 1 H), 6.81 (t, $J=8.6$ Hz, 1 H), 5.93 (dd, $J=9.0, 2.3$ Hz, 1 H), 4.99 (dd, $J=13.1, 2.5$ Hz, 1 H), 4.62 - 4.53 (m, 2 H), 4.43 (dd, $J=12.9, 9.0$ Hz, 1 H), 4.19-4.01 (m, 2 H), 3.66 (dt, $J=15.9, 5.7$ Hz, 2 H), 2.18 - 1.94 (m, 2 H); ^{19}F NMR (376 MHz, CHLOROFORM- d) δ ppm -72.81 (s, 1 F); MS (ESI) m/z = 374 ($M - 1$, negative).

3-Aminomethyl-4-fluoro-7-(3-hydroxy-propoxy)-3H-benzo[c][1,2]oxaborol-1-ol; bis-trifluoroacetic acid salt

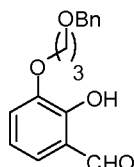


- 20 [0248] A mixture of 7-(3-benzyloxy-propoxy)-4-fluoro-3-nitromethyl-3H-benzo[C][1,2]oxaborol-1-ol (120 mg, 0.32 mmol) and 20% $\text{Pd}(\text{OH})_2$ (120 mg, 1:1 w/w substrate to catalyst) in AcOH (10 mL) was shaken under an atmosphere of H_2 (45-50 psi) in a Parr shaker. Once the reaction was complete, the mixture was filtered
- 25 through Celite[®]. The filtrate was concentrated in vacuo to give a gummy material. Remaining AcOH was removed by co-evaporation with toluene (3 x) to give the amine. Purification by preparative HPLC (0.1% aq $\text{CF}_3\text{CO}_2\text{H}$ / CH_3CN) produced 12 mg of the title compound as a white solid (yield 8.4%). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 9.14 (br. s., 1 H), 8.02 (br. s., 3 H), 7.25 (d, $J=7.8$ Hz, 1 H), 6.93 (d, $J=7.4$

Hz, 1 H), 5.43 (br. s., 1 H), 4.55 (br. s., 1 H), 4.07 (br. s., 2 H), 3.56 (br. s., 2 H), 3.42 - 3.37 (m, 1 H), 2.95 (br. s., 1 H), 1.86 (br. s., 2 H); ^{19}F NMR (376 MHz, DMSO- d_6) δ ppm -73.90 (s, 6 F), -131.51 (s, 1 F); MS (ESI) m/z = 256 ($M + 1$, positive); HPLC purity: 95.65% (MaxPlot 200 - 400 nm), 96.63% (220 nm).

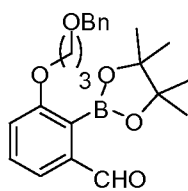
5 B. **3-(Aminomethyl)-4-chloro-7-(3-hydroxypropoxy)benzofcJfl,2Joxaborol-l(3H)-ol hydrochloride**

3-(3-Benzyloxy-propoxy)-2-hydroxy-benzaldehyde



[0249] NaH (2.95 g, 72.4 mmol) was added to an ice-cold solution of 2,3-
 10 dihydroxybenzaldehyde (5.0 g, 36 mmol) in anhydrous DMSO (45 mL). Benzyl-3-bromopropyl ether (6.45 mL, 36.2 mmol) was then added and the mixture was stirred at rt for 12 h. The mixture was neutralized using 1 N HCl and then extracted with EtOAc. The organic fraction was washed with H₂O and concentrated in vacuo. The residue was purified by flash chromatography (8:2 hexane/EtOAc) to give the title
 15 compound as a brown oil: yield 8.40 g (81%). ^1H NMR (400 MHz, CDCl_3) δ (ppm): 9.93 (s, 1H), 7.36-7.23 (m, 6H), 7.20-7.16 (m, 2H), 6.98-6.91 (m, 1H), 4.53 (s, 2H), 4.19 (t, J = 6.2 Hz, 2H), 3.70 (t, J = 6.1 Hz, 2H), 2.19-2.16 (m, 2H).

3-(3-Benzyloxy-propoxy)-2-(4,4,5,5-tetramethyl-f1,3,2]dioxaborolan-2-yl)-benzaldehyde

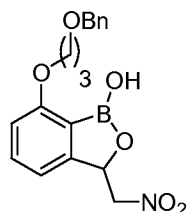


20 [0250] Trifluoromethanesulfonic anhydride (4.60 mL, 27.9 mmol) was added dropwise to a solution of pyridine (3.42 mL, 42.5 mmol) and 3-(3-benzyloxy-propoxy)-2-hydroxy-benzaldehyde (7.6 g, 26 mmol) in CH_2Cl_2 (200 mL) at 0 °C (bath temp). The reaction mixture was then allowed to warm to rt and was stirred
 25 until complete consumption of starting material (as determined by TLC). Et₂O and 2 N HCl were then added. The organic layer was separated and washed with sat. NaHCO₃ then brine. The organic layer was dried (Na_2SO_4) and filtered through a short silica gel plug, washing with Et₂O. The filtrate was concentrated in vacuo to give 8.60 g of the desired triflate (yield 77%>) that was used directly without further

purification. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 10.23 (s, 1H), 7.54-7.47 (m, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.36-7.22 (m, 6H), 4.52 (s, 2H), 4.23 (t, *J* = 6.3 Hz, 2H), 3.71 (t, *J* = 6.1 Hz, 2H), 2.21-2.17 (m, 2H).

[0251] A solution of trifluoro-methanesulfonic acid 2-(3-benzyloxy-propoxy)-6-formyl-phenyl ester (8.0 g, 19 mmol) in anhydrous 1,4-dioxane (160 mL) was added
 5 bis(pinacolato)diborane (9.71 g, 38.2 mmol) and KOAc (5.71 g, 57.4 mmol) at rt, then degassed with N₂ for 20 min. PdCl₂(dppf) (1.39 g, 1.89 mmol) was added and the resulting solution was stirred at 100 °C until the reaction was complete. The solution was cooled to rt, filtered through Celite® or silica gel and concentrated in vacuo. The
 10 residue was taken up in EtOAc. The organic layer was then washed with H₂O then brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The product was purified by flash chromatography (9:1 hexane/EtOAc) to give 4.80 g of the title compound (yield 43%) along with some pinacol contamination and was used without further purification. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 9.93 (s, 1H), 7.46 (t, *J* = 7.8 Hz,
 15 1H), 7.41-7.36 (m, 1H), 7.35-7.24 (m, 5H), 7.08 (d, *J* = 7.8 Hz, 1H), 4.50 (s, 2H), 4.10 (t, *J* = 6.3 Hz, 2H), 3.67 (t, *J* = 6.3 Hz, 2H), 2.11 (quin, *J* = 6.2 Hz, 2H), 1.43 (s, 12H).

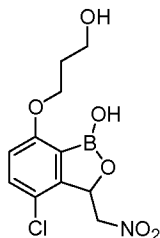
7-(3-Benzyloxy-propoxy)-3-nitromethyl-3H-benzo[c][1,2]oxaborol-1-ol



[0252] NaOH aq. (NaOH (3.64 g, 83 mmol) was added to 3-(3-benzyloxy-propoxy)-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde (36 g, 91
 20 mmol) in H₂O (180 mL), and THF (50 mL) at rt, and the reaction mixture was stirred at rt for 5 min. MeNO₂ (16.6 g, 273 mmol) was added dropwise and the mixture was stirred at rt for 16 h. The reaction mixture was acidified with 2 N HCl and extracted
 25 with EtOAc. The organic fraction was washed with H₂O then brine, dried (MgSO₄), and concentrated in vacuo. Purification was accomplished by flash chromatography (1:1 hexane/EtOAc) to give 15.9 g of the title compound as a light yellow oil (yield 50%). ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 9.05 (s, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.35-7.20 (m, 5H), 7.06 (d, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 5.70 (dd, *J* =
 30 9.4, 2.3 Hz, 1H), 5.29 (dd, *J* = 13.7, 2.7 Hz, 1H), 4.53 (dd, *J* = 13.3, 9.4 Hz, 1H), 4.45

(s, 2H), 4.11 (t, $J = 6.1$ Hz, 2H), 3.60 (t, $J = 6.3$ Hz, 2H), 2.04-1.91 (m, 2H); MS (ESI): $m/z = 356$ (M-1, negative); HPLC purity: 99.35% (MaxPlot 200-400 nm), 97.32% (220 nm).

4-Chloro-7-(3-hydroxy-propoxy)-3-nitromethyl-3H-benzo[c][1,2]oxaborol-1-ol



5

[0253] To 7-(3-benzyloxy-propoxy)-3-nitromethyl-3H-benzo[c][1,2]oxaborol-1-ol (1.1 g, 3.0 mmol) in glacial AcOH (10 mL) in cold water bath was added SO_2Cl_2 (0.7 mL, 9.07 mmol) dropwise over 5 minutes period. The resulting solution was stirred for 30 minutes at the same temperature then 1.5 h at room temperature. The

10

solution was quenched with crushed ice and then diluted with EtOAc (100 mL). The organic layer was washed with water, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. To the crude residue in MeOH (20 mL) was added $\text{Pd}(\text{OH})_2$ (10% w/w on carbon, 0.7 g), cone HCl was added until pH was 1, and the reaction vessel was pressurized to 40 psi with hydrogen for 30 minutes at room temperature.

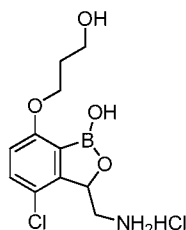
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The resulting mixture was filtered through a pad of Celite® and washed with EtOAc. The filtrate was concentrated in vacuo, then the residue was purified by silica gel column chromatography (EtOAc:Hex, 1:1) providing the title compound (0.2 g, 24% in 2 steps). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 9.31 (br. s., 1 H), 7.49 (d, $J=8.2$ Hz, 1 H), 6.98 (d, $J=8.6$ Hz, 1 H), 5.76 (dd, $J=8.2, 2.7$ Hz, 1 H), 5.33 (dd, $J=13.2, 2.3$

20

Hz, 1 H), 4.70 (dd, $J=13.0, 8.4$ Hz, 1 H), 4.55 (br. s., 1 H), 4.15 - 4.05 (m, 2 H), 3.61 - 3.55 (m, 2 H), 1.95 - 1.77 (m, 2 H).

3-Aminomethyl-4-chloro-7-(3-hydroxy-propoxy)-3H-benzo[c][1,2]oxaborol-1-ol hydrogen chloride



25

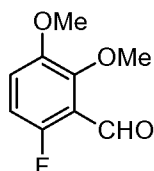
[0254] 4-Chloro-7-(3-hydroxy-propoxy)-3-nitromethyl-3H-benzo[c][1,2]oxaborol-1-ol (105 mg, 0.35 mmol) in methanolic ammonia solution (2 M, 20 mL) was added Ra/Ni (0.15 g, 2800 Nickel slurry in water) and the reaction

vessel was pressurized to 40 psi with hydrogen overnight at room temperature. The resultant mixture was filtered through a pad of Celite® and washed with EtOAc. The filtrate was concentrated in vacuo and the residue was added water (1 mL), followed by cone HCl to pH 1. The heterogeneous mixture was lyophilized provide the title

5 compound (130 mg, quantitative) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.14 (br. s., 1 H), 8.36 (br. s., 3 H), 7.49 (d, *J*=8.2 Hz, 1 H), 6.99 (d, *J*=8.2 Hz, 1 H), 5.40 (d, *J*=7.0 Hz, 1 H), 4.40 (br. s., 1 H), 4.10 (br. s., 2 H), 3.59 (br. s., 2 H), -3.30 (hidden, 1H), 2.89 (br. s., 1 H), 1.89 (br.s, 2 H); MS (ESI) *m/z* = 272 (M+1, positive); HPLC purity: 96.92% (MaxPlot 200 - 400 nm), 97.96% (220 nm).

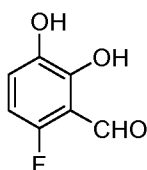
10 C. **3-Aminomethyl-7-ethoxy-4-fluoro-3H-benzofcJfl,2J-oxaborol-l-ol; hydrochloride**

6-Fluoro-2,3-dimethoxy-benzaldehyde



[0255] To a cold (-78 °C) solution of 4-fluoro-1,2-dimethoxybenzene (15.00 g, 96.05 mmol) in anhydrous THF (150 mL) was added n-BuLi (84.5 mL, 211.32 mmol, 2.5 M solution in hexanes) under nitrogen and stirred it for 3 h at -78 °C. Quenched the reaction with DMF (75 mL) at -65 °C, added 2N HCl (300 mL) dropwise and further stirred for 30 min. Two layers separation was observed. Aqueous layer was extracted with EtOAc. Combined organic layers were washed with water, brine and dried over MgSO₄. Filtered the ethyl acetate layer and concentrated it *in vacuo*. The title compound was purified by flash column chromatography using pure hexanes then 10 and 20% EtOAc in hexanes which provided 14.40 g (78.19 mmol, 82%) of the title compound as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.23 (s, 1 H), 7.36 (dd, *J*=9.0, 5.1 Hz, 1 H), 7.03 (t, *J*=9.6 Hz, 1 H), 3.87 (s, 3 H), 3.83 (s, 3 H); ¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm -131.68 - -131.66 (m, 1F).

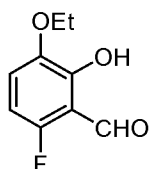
6-Fluoro-2,3-dihydroxy-benzaldehyde



[0256] To a cold (-78 °C) solution of 6-fluoro-2,3-dimethoxy-benzaldehyde (4.50 g, 24.43 mmol) in anhydrous dichloromethane (30 mL) was added BBr₃ (1M in DCM,

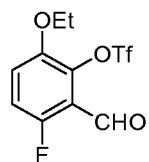
48.8 mL, 48.87 mmol) dropwise (duration 30 min). The reaction was warmed to room temperature and stirred for 4 h. Again cooled it to -78 °C and added 2N HCl (60 mL) to it dropwise. The reaction was stirred for overnight at room temperature and extracted with DCM. Combined organic layers were washed with water, sat. NaHCO₃ solution, brine and dried over MgSO₄. Filtration and removal of solvent provided 2.42 g (15.50 mmol, 64%) of the title compound as a yellow solid. This was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.22 (s, 1 H), 7.04 (dd, *J*=8.6, 5.5 Hz, 1 H), 6.61 (dd, *J*=10.4, 8.8 Hz, 1 H); ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -131.69- -131.65 (m, 1F).

10 *3-Ethoxy-6-fluoro-2-hydroxy-benzaldehyde*



[0257] To a solution of 6-fluoro-2,3-dihydroxy-benzaldehyde (1.00 g, 6.40 mmol) in dry DMSO (10 mL) was added NaOBu^t (1.23 g, 12.81 mmol) and ethyl bromide (0.77 g, 7.04 mmol) under N₂ and stirred at RT for 18 h. The resultant mixture was diluted with water, acidified to pH ~6 with 2N.HCl and extracted with EtOAc (4x25 mL). Combined organic layers were washed with water and brine and dried over MgSO₄. Filtration and removal of the solvent under reduced pressure provided 1.05 g (5.70 mmol, 89 %) of the title compound as yellow solid. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 10.24 (s, 1 H), 7.04 (dd, *J*=8.8, 5.3 Hz, 1 H), 6.61 - 6.50 (m, 1 H), 4.09 (q, *J*=7.0 Hz, 3 H), 1.46 (t, *J*=7.0 Hz, 3 H); ¹⁹F NMR (376 MHz, CHLOROFORM-*d*) δ ppm -132.19- -132.15 (m, 1F).

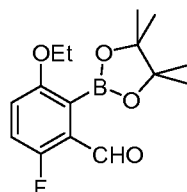
Trifluoro-methanesulfonic acid 6-ethoxy-3-fluoro-2-formyl-phenyl ester



[0258] To a cold (0 °C) solution of 3-ethoxy-6-fluoro-2-hydroxy-benzaldehyde (1.05 g, 5.70 mmol) in dry DCM (90 ml) was added pyridine (675 mg, 8.53 mmol) under nitrogen and stirred the reaction mixture at 0 °C for 10 min. Then added triflic anhydride (1.93 g, 6.84 mmol) slowly and continued stirring for 3 h at RT. Diluted the reaction with 1N.HCl (25 mL) and extracted with DCM (2x 100 mL). The organic layer was washed with water and brine and dried over MgSO₄. Filtered and

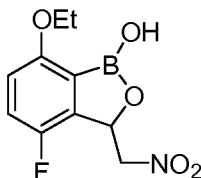
concentrated the filtrate. Purification of the residue by flash column chromatography with 5% ethyl acetate in hexanes gave 1.12 g, (3.54 mmol, 62%) of the title compound as a white solid. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 10.34 (s, 1 H), 7.31 - 7.13 (m, 2 H), 4.13 (q, *J*=7.0 Hz, 2 H), 1.48 (t, *J*=7.0 Hz, 3 H); ¹⁹F NMR (376 MHz, CHLOROFORM-*d*) δ ppm -128.15- -128.11 (m, 1F), -73.56 (s, 3F).

3-Ethoxy-6-fluoro-2-(4,4,5,5-tetramethyl-[1,3,2] dioxaborolan-2-yl)-benzaldehyde



- [0259] A solution of trifluoro-methanesulfonic acid 6-ethoxy-3-fluoro-2-formyl-phenyl ester (1.60 g, 5.05 mmol) in anhydrous THF (50 mL) was degassed for 40 min. Added bis(pinacolato)diborane (3.85 g, 15.17 mmol), KOAc (1.50 g, 15.17 mmol) and PdCl₂(dppf) (296 mg, 8 mol %) and stirred the reaction at 70 °C (bath temp) for 3 h. Another addition of bis(pinacolato)diborane (1.40 g, 5.51 mmol) and heating at 70 °C for 2h completed the reaction. The resultant mixture was cooled to room temperature and filtered through a pad of Celite®. Concentrated the filtrate.
- 15 Purification of the residue by flash column chromatography with hexanes and 5% EtOAc/hexanes yielded 1.65 g of title compound as white solid. ¹H NMR confirms presence of title compound but with some impurities. It was used in next step without further purification. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 10.29 (s, 1 H), 7.12 - 6.97 (m, 2 H), 4.00 (q, *J*=7.0 Hz, 2 H), 1.46 (s, 12 H), 1.41 (t, *J*=6.8 Hz, 3 H);
- 20 ¹⁹F NMR (376 MHz, CHLOROFORM-*d*) δ ppm -133.71- -133.67 (m, 1F).

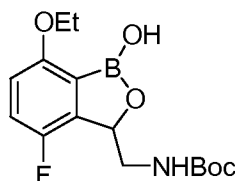
7-Ethoxy-4-fluoro-3-nitromethyl-3H-benzo[c][1,2]oxaborol-1-ol



- [0260] 3-Ethoxy-6-fluoro-2-(4,4,5,5-tetramethyl-[1,3,2] dioxaborolan-2-yl)-benzaldehyde (1.65 g, 5.61 mmol) was added to a solution of NaOH (225 mg, 5.60 mmol) in H₂O (10 mL) and stirred for 10 min at RT. Added nitromethane (1.03 g, 16.83 mmol) dropwise and stirred for 4 h at RT. The reaction mixture was acidified with 4N HCl and extracted with ethyl acetate. Organic layer was washed with water, brine and dried over MgSO₄, filtered and concentrated *in vacuo*. Purification of the

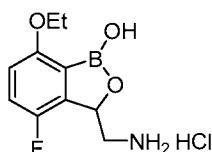
residue by flash column chromatography with 10 to 40% EtOAc/hexanes afforded 1.7 g of a mixture of compounds by ^1H NMR spectrum. This mixture was used in next step without further purification. ^1H NMR (400 MHz, CHCl_3) δ ppm 7.13 (t, $J=8.8$ Hz, 1 H), 6.79 (dd, $J=8.8, 2.5$ Hz, 1 H), 5.95 (d, $J=9.0$ Hz, 1 H), 5.14 (s, 1 H), 5.01 (dd, $J=13.3, 2.3$ Hz, 1 H), 4.44 (dd, $J=13.3, 9.0$ Hz, 1 H), 4.10 (q, $J=6.8$ Hz, 2 H), 1.45 (t, $J=6.8$ Hz, 3 H); ^{19}F NMR (376 MHz, CHCl_3) δ ppm -131.00- -130.97 (m, 1F).

7-Ethoxy-4-fluoro-1-hydroxy-1,3-dihydro-benzo[c][1,2]oxaborol-3-ylmethyl)-carbamic acid tert-butyl ester



[0261] To a cold (0 °C) solution of 7-ethoxy-4-fluoro-3-nitromethyl-3H-benzo[c][1,2]oxaborol-1-ol (500mg, 1.96 mmol) in dry MeOH (20 mL) was added $(\text{Boc})_2\text{O}$ (856 mg, 3.92 mmol) followed by $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (466 mg, 1.96 mmol) under nitrogen. Stirred the reaction mixture under nitrogen for 20 min and added NaBH_4 (445 mg, 11.76 mmol) in portions and left it for overnight at RT. Evaporated the solvent and diluted the reaction with 30 ml of ethyl acetate and filtered it through Celite. Filtrate was concentrated and residue was purified by flash column chromatography using 5% MeOH/DCM, but a mixture (950 mg) of products was obtained which was used in next step without further purification.

3-Aminomethyl-7-ethoxy-4-fluoro-3H-benzofcJ[1,2]oxaborol-1-ol; hydrochloride

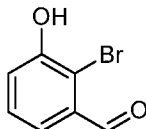


[0262] A solution of 7-ethoxy-4-fluoro-1-hydroxy-1,3-dihydro-benzo[c][1,2]oxaborol-3-ylmethyl)-carbamic acid tert-butyl ester (450 mg, 1.38 mmol) in 4M HCl (in 1,4-dioxane, 15 mL) was stirred at RT for overnight. The solvent was removed under reduced pressure. Recrystallization from EtOAc/hexanes provided 245 mg (0.93 mmol, 62%) of the title compound as white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 9.15 (br. s., 1 H), 8.20 (br. s., 3 H), 7.26 (t, $J=9.0$ Hz, 1 H), 6.95 - 6.85 (m, 1 H), 5.45 (d, $J=6.3$ Hz, 1 H), 3.30 (hidden, 1H), 4.05 (q, $J=6.9$ Hz, 2 H), 2.89 (br. s., 1 H), 1.30 (t, $J=6.8$ Hz, 3 H); ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ ppm -131.68- -

131.66 (m, IF); MS (ESI) m/z = 226 (M+1, positive); HPLC purity: 91.87 % (MaxPlot 200 - 400 nm), 90.33% (220 nm); Anal. Calcd for $\text{C}_{10}\text{H}_4\text{BClFNO}_3 \cdot 0.5 \text{H}_2\text{O}$: C 44.40%; H 5.59%; N 5.18%. Found: C 44.30%; H 5.42%; N 5.50%.

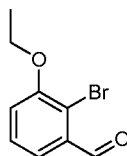
D. 3-(Aminomethyl)-4-chloro-7-ethoxybenzof[1,2]oxaborol-1(3H)-ol

5 **2-Bromo-3-hydroxybenzaldehyde**

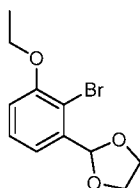


[0263] The suspension of 3-hydroxybenzaldehyde (5 g, 0.04 mol), iron powder (172 mg, 3 mmol) and sodium acetate (6.72 g, 0.08 mol) in acetic acid (40 mL) was warmed until a clear solution was obtained and then cooled to room temperature. To this mixture was dropwise added a solution of bromine in glacial acetic acid (10 mL) over 15 min. After the addition, the reaction mixture was stirred for 2 h and then poured into ice-water. The resulting mixture was extracted with dichloromethane (3x50 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated. The residue was re-crystallized from dichloromethane to afford the product (2.3 g, yield 28%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.30 (s, 1H), 7.54-7.51 (m, 1H), 7.39-7.35 (m, 1H), 7.31-7.27 (m, 1H), 5.90 (s, 1H).

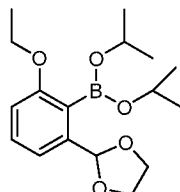
2-Bromo-3-ethoxybenzaldehyde



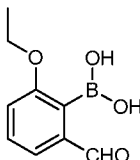
[0264] The suspension of 2-bromo-3-hydroxybenzaldehyde (120 g, 0.60 mol), K_2CO_3 (247 g, 1.79 mol) and bromoethane (135 mL, 1.79 mol) in DMF (700 mL) was stirred at 70 °C for 3 h. After the reaction was quenched with water (50 mL), the resulting mixture was extracted with EtOAc (3x60 mL). The combined organic layers were washed with water (50 mL) and aqueous LiCl solution (50 mL), dried over anhydrous Na_2SO_4 and concentrated to dryness in vacuo. The residue was purified by column chromatography on silica gel to give the target compound (128 g, yield 94%>). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.45 (s, 1H), 7.52-7.50 (d, 1H), 7.38-7.34 (t, 1H), 7.13-7.10 (d, 1H), 4.18-4.13 (m, 2H), 1.53-1.50 (m, 3H).

2-(2-Bromo-3-ethoxyphenyl)-1,3-dioxolane

[0265] To a solution of 2-bromo-3-ethoxybenzaldehyde (128 g, 0.56 mol) and glycol (253 mL, 4.49 mol) in toluene (600 mL) was added *p*-toluenesulfonic acid (10 g, 0.06 mol). The reaction flask had a Dean and Stark condenser attached and the reaction mixture was refluxed to remove the water for 4 h. The reaction mixture was then cooled to room temperature and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give the target compound (132 g, yield 86%).

10 *Diisopropyl 2-(1,3-dioxolan-2-yl)-6-ethoxyphenylboronate*

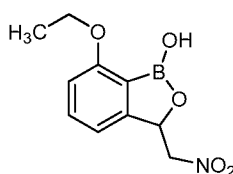
[0266] To the solution of 2-(2-bromo-3-ethoxyphenyl)-1,3-dioxolane (132 g, 0.48 mol) in anhydrous THF (500 mL) was dropwise added *n*-BuLi (2.5 M in THF, 386 mL, 0.97 mol) at -78 °C under nitrogen protection. The mixture was stirred at -78 °C for 2 h and then triisopropyl borate (227 mL, 0.97 mol) was dropwise added. The resulting mixture was stirred at this temperature for 4 h. After the reaction was quenched by adding saturated aqueous NH_4Cl solution (200 mL), the resulting mixture was extracted with EtOAc (3x300 mL). The combined organic layers were washed with water (200 mL) and brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography on silica gel to give the target compound (136 g, yield 87%).

2-Ethoxy-6-formylphenylboronic acid

[0267] To the mixture of diisopropyl 2-(1,3-dioxolan-2-yl)-6-ethoxyphenylboronate (136 g, 0.42 mol) in THF (500 mL) was added diluted HCl (2N, 200 mL) slowly at room temperature with stirring. After stirred for 1.5 h at room

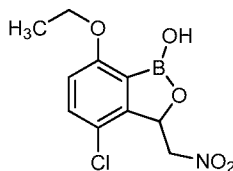
temperature, the reaction mixture was basified with 20% aqueous solution of NaOH to pH=12 and then washed with EtOAc (2x100 mL). The aqueous layer was acidified by using the diluted HCl (2N) to pH=2 and then extracted with EtOAc (3x100 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated to dryness. The residue was purified by column chromatography on silica gel to give the target compound as white solid (80 g, yield 83%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.93 (s, 1H), 7.92 (s, 2H), 7.45-7.48 (m, 2H), 7.23-7.28 (d, 1H), 4.01-4.06 (m, 2H), 1.69-1.20 (m, 3H).

7-Ethoxy-3-(nitromethyl)benzo[c][1,2]oxaborol-1 (3H)-ol



[0268] The mixture of 2-ethoxy-6-formylphenylboronic acid (80 g, 0.41 mol), NaOH (16.5 g, 0.41 mol) and CTAB (7.7 g, 20 mmol) in H₂O (100 mL) and THF (500 mL) was stirred for 0.5 h at room temperature. After dropwise addition of nitromethane (14 mL, 2.4 mol), the reaction mixture was stirred at room temperature for 3 h. Then the cyclization was afforded by adding the diluted HCl (2 N) to pH=2 and then extracted with EtOAc (3x300 mL). The combined organic layers were washed with brine (250 mL), dried over anhydrous Na₂SO₄ and concentrated to dryness in vacuo. The residue was purified by column chromatography on silica gel to give the target compound as white solid (92 g, yield 94%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.06 (s, 1H), 7.46-7.43 (t, 1H), 7.07-7.05 (d, 1H), 6.89-6.87 (d, 1H), 5.71-5.69 (m, 1H), 5.31-5.27 (m, 1H), 4.57-4.51 (m, 1H), 4.12-4.07 (m, 2H), 1.34-1.30 (t, 3H).

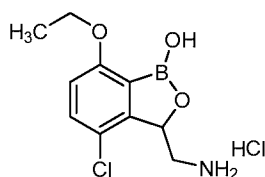
4-Chloro-7-ethoxy-3-(nitromethyl)benzo[c][1,2]oxaborol-1 (3H)-ol



[0269] To a solution of 7-ethoxy-3-(nitromethyl)benzo[c][1,2]oxaborol-1(3H)-ol (42 g, 0.18 mol) in DMF (200 mL) at 80 °C was added a solution of NCS (11.8 g, 0.18 mol) in DMF (50 mL) in 30 min. The reaction was quenched with an aqueous solution of LiCl solution (500 mL) and the resulting mixture was extracted by EtOAc

(3x250 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give the compound as white solid. (39.7 g, contaminated with 18% C6-C1 regioisomer). The mixture was then re-crystallized from Ether/PE (1/5) to give the pure compound (28 g, yield 46.3%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.32 (s, 1H), 7.50-7.48 (d, 1H), 6.98-6.96 (d, 1H), 5.77-5.74 (d, 1H), 5.35-5.31 (d, 1H), 4.73-4.67 (m, 1H), 4.12-4.07 (m, 2H), 1.34-1.28 (t, 3H).

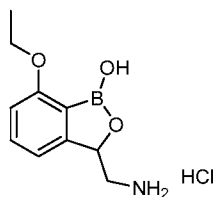
3-(Aminomethyl)-4-chloro-7-ethoxybenzo[c][1,2]oxaborol-1(3H)-ol hydrochloride



- 10 **[0270]** A mixture of 4-chloro-7-ethoxy-3-(nitromethyl)benzo[c][1,2]oxaborol-1(3H)-ol (47 g, 0.17 mol), Raney Ni (2 g) and 2 M NH_3 in EtOH (40 mL) in EtOH (200 mL) was stirred under an atmosphere of H_2 for 2 h and then filtrated. The filtrate was acidified by using 4.5 N HCl in EtOH (100 mL). After stirring for 30 min, the mixture was concentrated and the residue was washed with CH_3CN (2x50 mL) to give
- 15 the product as white solid (43 g, yield 89%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.13 (s, 1 H), 8.18 (s, 3H), 7.50-7.51 (d, 1H), 6.97-7.00 (d, 1H), 5.36-5.39 (m, 1H), 4.08-4.14 (m, 2H), 3.55-3.59 (m, 1H), 2.90-2.95 (m, 1H), 1.33-1.36 (m, 3H); MS (ESI) m/z = 242 $[\text{M} + \text{H}]^+$.

20 E. *3-(Aminomethyl)-4-bromo-7-ethoxybenzo[c][1,2]oxaborol-1(3H)-ol 2,2,2-trifluoroacetate salt*

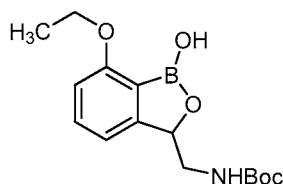
3-(Aminomethyl)-7-ethoxybenzo[c][1,2]oxaborol-1(3H)-ol hydrochloride salt



- [0271]** To the solution of 7-ethoxy-3-(nitromethyl)benzo[c][1,2]oxaborol-1(3H)-ol (2 g, 8.43 mmol), Raney Ni (200 mg) and 2 M NH_3 in EtOH (10 mL) in ethanol(35 mL) was shaken under an atmosphere of H_2 for 2 h at room temperature. The mixture was filtered through a bed of Celite and the filtrate was concentrated in vacuo. The crude amine was dissolved in EtOAc (10 mL) and HCl in Et_2O (30 mL) was added immediately. After 1 h, the suspension was filtered and the resulting solid was

washed with acetonitrile/hexanes (2:1, 2x20 mL) to give the compound as white solid (1 g, yield 57.2%). ¹H NMR (400 MHz, *O**MSO*-*d*₆) δ 8.89 (s, 1H), 8.22 (s, 3H), 7.48-7.44 (t, 1H), 7.06-7.04 (d, 1H), 6.90-6.88 (d, 1H), 5.31-5.29 (m, 1H), 4.13-4.08 (m, 2H), 3.45-3.39 (m, 1H), 2.80-2.78 (m, 1H), 1.36-1.33 (m, 3H); MS (ESI) *m/z* = 208 [M + H]⁺.

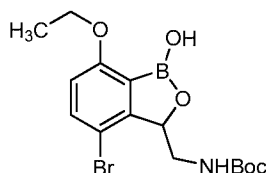
tert-Butyl (7-ethoxy-1-hydroxy-1,3-dihydrobenzo[*c*][1,2]oxaborol-3-yl)methyl-carbamate



[0272] To the mixture of 3-(aminomethyl)-7-ethoxybenzo[*c*][1,2]oxaborol-

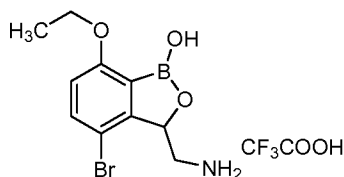
- 10 1(3H)-ol hydrochloride salt (300 mg, 1.23 mmol) and triethylamine (622 mg, 6.16 mmol) in dichloromethane (35 mL) at 0 °C was added di-*tert*-butyl dicarbonate (402.8 mg, 1.85 mmol) and the mixture was stirred for 2 h at room temperature. After the reaction was quenched with sat. NaHCO₃ (45 mL) and the resulting mixture was extracted with EtOAc (3x30 mL), the combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by flash-column chromatography to give the product (320 mg, yield 84.6%).

tert-Butyl (4-bromo-7-ethoxy-1-hydroxy-1,3-dihydrobenzo[*c*][1,2]oxaborol-3-yl)-methylcarbamate



- 20 [0273] To the solution of *tert*-butyl (7-ethoxy-1-hydroxy-1,3-dihydrobenzo[*c*][1,2]oxaborol-3-yl)methyl-carbamate (250 mg, 0.81 mmol) and 1-bromopyrrolidine-2,5-dione (173.9 mg, 0.98 mmol) in CH₃CN (50 mL) was added 2,2'-Azobis(2-methylpropionitrile) (10 mg) and the mixture was stirred for 1 h at 90 °C. The reaction mixture was then concentrated in high vacuo and the residue was purified by prep-HPLC to give the product (200 mg, yield 63.6%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.90 (s, 1H), 7.55-7.53 (d, 1H), 6.85-6.82 (d, 1H), 5.08-5.07 (d, 1H), 4.11-4.07 (m, 2H), 3.82-3.79 (d, 1H), 3.06-3.03 (m, 1H), 1.39 (s, 9H), 1.30 (t, 3H); MS (ESI) *m/z* = 387 [M + H]⁺.

3-(Aminomethyl)-4-bromo-7-ethoxybenzo[c][1,2]oxaborol-1 (3H)-ol 2,2,2-trifluoroacetate salt

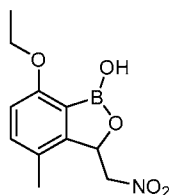


[0274] The mixture of *tert*-butyl (4-bromo-7-ethoxy- 1-hydroxy- 1,3-

5 dihydrobenzo[c][1,2]oxaborol-3-yl)-methylcarbamate (200 mg, 51.8 mmol) in 2,2,2-trifluoroacetic acid and dichloromethane (1:1, 20 mL) was stirred at room temperature for 1 h and concentrated to dryness (water bath < 30 °C). The residue was washed with acetonitrile (2x5 mL) and the white solid was dried in high vacuo to give the product (190 mg, yield 91.6%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.12 (s, 1H), 8.04 (s, 3H), 7.65-7.62 (d, 1H), 6.94-6.92 (d, 1H), 5.27-5.25 (m, 1H), 4.13-4.08 (m, 2H), 3.64-3.61 (m, 1H), 2.99-2.92 (m, 1H), 1.36-1.33 (t, 3H); MS (ESI) *m/z* = 287 [M + H]⁺.

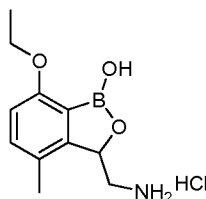
F. *3-(Aminomethyl)- 7-ethoxy-4-methylbenzo[c][1,2]oxaborol-1(3H)-ol hydrochloride salt*

15 *7-Ethoxy-4-methyl-3-(nitromethyl)benzo[c][1,2]oxaborol-1(3H)-ol*



[0275] A mixture of 4-bromo-7-ethoxy-3-(nitromethyl)benzo[c][1,2]oxaborol-1(3H)-ol (200 mg, 0.63 mmol), tetramethylstannane (341.7 mg, 1.90 mmol) and Pd(PPh₃)₄ (Cat. 20 mg) in DMF (35 mL) was stirred overnight at 90 °C under N₂ protection. The reaction was quenched by adding ice-water and the resulting mixture was extracted with ethyl acetate (3x30 mL). The combined extracts were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by prep-TLC to give the product (72 mg, yield 45.3%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.00 (s, 1H), 7.23-7.21 (d, 1H), 6.83-6.81 (d, 1H), 5.77-5.75 (m, 1H), 5.27-5.24 (m, 1H), 4.50-4.44 (m, 1H), 4.08-4.03 (m, 2H), 2.25 (s, 3H), 1.33-1.29 (t, 3H).

3-(Aminomethyl)-7-ethoxy-4-methylbenzo[c][1,2]oxaborol-1 (3H)-ol hydrochloride salt

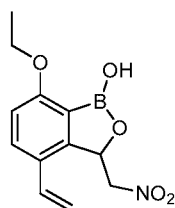


[0276] A mixture of 7-ethoxy-4-methyl-3-(nitromethyl)benzo[c][1,2]oxaborol-

1 l(3H)-ol (80 mg, 0.32 mmol), Raney Ni (50 mg) and NH_3/EtOH (2 mL) in EtOH (10 mL) was stirred under an atmosphere of H_2 for 2 h and then filtrated. The filtrate was acidified by using 4.5 N HCl in EtOH (15 mL). After stirring for 30 min, the mixture was concentrated in vacuo and the residue was washed with CH_3CN (2x3 mL) to give the product as white solid (39 mg, yield 47.5%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.80 (s, 1H), 8.15 (s, 3H), 7.24-7.22 (d, 1H), 6.83-6.81 (d, 1H), 5.37-5.35 (m, 1H), 4.08-4.03 (m, 2H), 3.36-3.28 (m, 1H), 2.73-2.70 (m, 1H), 2.23 (s, 3H), 1.34-1.30 (t, 3H); MS (ESI) m/z = 222 $[\text{M} + \text{H}]^+$.

G. 3-(Aminomethyl)-7-ethoxy-4-ethylbenzofcJfl,2Joxaborol-1(3H)-ol

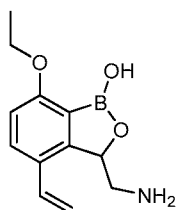
7-Ethoxy-3-(nitromethyl)-4-vinylbenzo[c][1,2]oxaborol-1(3H)-ol



[0277] A mixture of 4-bromo-7-ethoxy-3-(nitromethyl)benzo[c] [1,2]oxaborol-

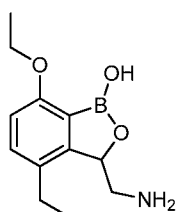
1 l(3H)-ol (900 mg, 2.85mmol), vinyltributyltin (5.2 g, 53 mmol) and $\text{Pd}(\text{Ph}_3\text{P})_4$ (230 mg, 0.2 mmol) in DMF (45 mL) was degassed for 15 min with N_2 and then stirred at 100 °C for 30 min in microwave reactor (Biotage). After the reaction was quenched with ice-water, the resulting mixture was extracted with EtOAc (3x30 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 and then concentrated to dryness in vacuo. The residue was purified by column chromatography on silica gel to give the compound (650 mg, yield 87%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.10 (s, 1H), 7.64-7.66 (d, 1H), 6.93-6.95 (d, 1H), 6.77-6.84 (m, 1H), 5.93-5.96 (d, 1H), 5.69-5.73 (d, 1H), 5.28-5.31 (d, 1H), 5.10-5.14 (d, 1H), 4.44-4.49 (m, 1H), 4.09-4.14 (m, 2H), 1.32-1.35 (m, 3H); MS (ESI) m/z = 264 $[\text{M} + \text{H}]^+$.

3-(Aminomethyl)-7-ethoxy-4-vinylbenzo[c][1,2]oxaborol-1(3H)-ol

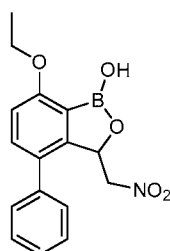


[0278] A mixture of 7-ethoxy-3-(nitromethyl)-4-vinylbenzo[c][1,2]oxaborol-1(3H)-ol (205 mg, 0.78 mmol), Raney-Ni (50 mg) and 2 M NH₃ in EtOH (5 mL) in EtOH (10 mL) was shaken under an atmosphere of H₂ for 2 h at room temperature. The mixture was filtered through a bed of Celite and the filtrate was concentrated in vacuo. The crude amine was dissolved in EtOAc (2 mL) and HCl in Et₂O (20 mL) was added immediately. After 1 h, the suspension was filtered and the resulting solid was used directly for the next step without further purification.

3-(Aminomethyl)-7-ethoxy-4-ethylbenzo[c][1,2]oxaborol-1(3H)-ol

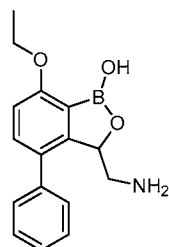


[0279] To a suspension of 3-(aminomethyl)-7-ethoxy-4-vinylbenzo[c][1,2]oxaborol-1(3H)-ol (175 mg, 0.75 mmol) with Pd/C (40 mg) in EtOH (5 mL) was shaken under an atmosphere of H₂ for 2 h at room temperature. The mixture was filtered through a bed of Celite and the filtrate was concentrated in vacuo. The crude amine was dissolved in EtOAc (2 mL) and HCl in Et₂O (15 mL) was added immediately. After 1 h, the suspension was filtered and the resulting solid was washed with hexanes to give the target compound (23 mg, yield 13%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.81 (s, 1H), 8.18 (s, 3H), 7.31-7.29 (d, 1H), 6.68-6.88 (d, 1H), 5.38-5.40 (d, 1H), 4.04-4.09 (d, 2H), 3.30-3.35 (m, 1H), 2.66-2.71 (m, 1H), 1.31-1.34 (m, 3H), 1.15-1.17 (m, 3H); MS (ESI) *m/z* = 236 [M + H]⁺.

H. 3-(Aminomethyl)-7-ethoxy-4-phenylbenzo[c][1,2]oxaborol-1(3H)-ol*7-Ethoxy-3-(nitromethyl)-4-phenylbenzo[c][1,2]oxaborol-1(3H)-ol***[0280]** A mixture of 4-bromo-7-ethoxy-3-(nitromethyl)benzo[c][1,2]oxaborol-

5 l(3H)-ol (315 mg, 1 mmol), tributyl-pfienyl-stannane (750 mg, 2 mmol) and Pd(Pli₃P)₄ (Cat.) in DMF (15 mL) was degassed for 15 min with N₂ and then stirred at 100 °C for 30 min in microwave reactor (Biotage). After the reaction was quenched with ice-water, the resulting mixture was extracted with EtOAc (3x40 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried

10 over anhydrous Na₂SO₄ and then concentrated to dryness. The residue was purified by column chromatography on silica gel to give the compound as white solid (60 mg, yield 20%). ¹HNMR (400 MHz, DMSO-*d*₆) δ 9.13 (s, 1 H), 7.46-7.49 (m, 5H), 7.34-7.48 (m, 2H), 6.17-6.20 (m, 1H), 4.88-4.92 (m, 1H), 4.21-4.25 (m, 1H), 4.05-4.16 (m, 2H), 1.34-1.37 (m, 3H).

15 *3-(Aminomethyl)-7-ethoxy-4-phenylbenzo[c][1,2]oxaborol-1(3H)-ol***[0281]** A mixture of 7-ethoxy-3-(nitromethyl)-4-phenylbenzo[c][1,2]oxaborol-1(3H)-ol (60 mg, 0.19 mmol), Raney-Ni (-25 mg) and 2 M NH₃ in EtOH (2 mL) in EtOH (10 mL) was shaken under an atmosphere of H₂ for 2 h at room temperature.

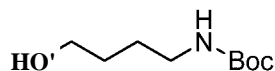
20 The mixture was filtered through a bed of Celite and the filtrate was concentrated in vacuo. The crude amine was dissolved in EtOAc (1 mL) and HCl in Et₂O (5 mL) was added immediately. After 1 h, the suspension was filtered and the resulting solid was washed with hexanes to give the compound as white solid (30 mg, yield 51%).

¹HNMR (400 MHz, DMSO-*d*₆) δ 8.89 (s, 1 H), 8.04 (s, 3H), 7.43-7.46 (d, 5H), 7.36-7.38 (d, 1H), 6.98-7.00 (d, 1H), 5.78-5.81 (d, 1H), 4.09-4.14 (m, 2H), 2.56-2.59 (m, 1H), 2.24-2.30 (m, 1H), 1.33-1.36 (m, 3H); MS (ESI) *m/z* = 284 [M + H]⁺.

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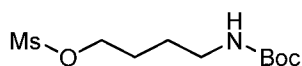
I. 7-(4-Aminobutoxy)-3-(aminomethyl)-4-chlorobenzofcJfl,2Joxaborol-l(3H)-ol dihydrochloride

tert-Butyl 4-hydroxybutylcarbamate



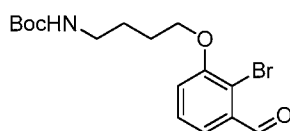
- 5 [0282] To a mixture of 4-aminobutan-1-ol (4.0 g, 45 mmol) and TEA (7.5 mL, 54 mmol) in DCM (200 mL) was added (Boc)₂O (10.2 g, 47.2 mmol). The reaction mixture was stirred for 2 h at room temperature and then washed with water (2x150 mL) and the solution of citric acid (100 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated to give the product as yellow oil 7.5 g. (yield 10 88%).

4-(tert-Butoxycarbonyl)butyl methanesulfonate



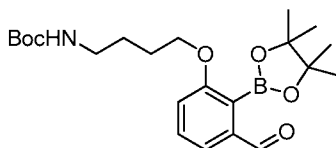
- [0283] To a mixture of *tert-butyl* 4-hydroxybutylcarbamate (7.5 g, 40 mmol) and TEA (3.6 mL, 48 mmol) in DCM (100 mL) at 0 °C was dropwise added MsCl (6.6 15 mL, 48 mmol). The mixture was stirred at room temperature for 1 h and then washed with water (2x100 mL) and the solution of citric acid (100 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated to give the product as yellow oil (10.0 g, yield 94%).

tert-Butyl 4-(2-bromo-3-formylphenoxy)butylcarbamate



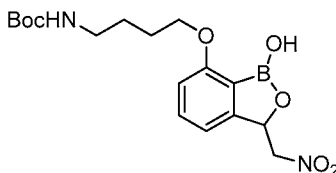
- 20 [0284] To a mixture of 2-bromo-3-hydroxybenzaldehyde (3.0 g, 15 mmol) and *tert*-butoxycarbonyl)butyl methanesulfonate (4.8 g, 18 mmol) in DMF (40 mL) was added K₂CO₃ (6.2 g, 45 mmol). The mixture was stirred at 80 °C for 45 min and quenched by addition of aqueous LiCl solution (80 mL). The mixture was extracted 25 with EtOAc (2x80 mL) and the combined organic layers were dried over anhydrous Na₂SO₄ and then concentrated to give the crude product as brown oil (6.0 g).

tert-Butyl 4-(3-formyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-butylcarbamate



[0285] A mixture of *tert*-butyl 4-(2-bromo-3-formylphenoxy)butylcarbamate (6.0 g, 16 mmol), KOAc (5.0 g, 48 mmol), (Pin)₂B₂ (7.7 g, 86 mmol) and Pb(dppf)Cl₂ (1.25 g, 1.6 mmol) in dioxane (100 mL) was degassed for 15 min with N₂ and refluxed for 2 h under N₂ protection. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel to give the product as yellow oil (3.5 g, yield 55%).

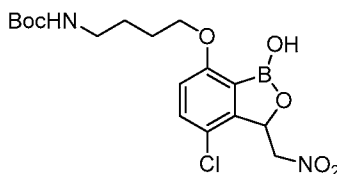
10 *tert*-Butyl-4-(1-hydroxy-3-(nitromethyl)-1,3-dihydrobenzof[c][1,2]oxa-borol-7-yloxy)butylcarbamate



[0286] To a solution of *tert*-butyl 4-(3-formyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenoxy)-butylcarbamate (3.5 g, 8.3 mmol) and CTAB (cat.) in THF (50 mL) was added MeNO₂ (2.8 mL, 49 mmol), followed by an aqueous solution of NaOH (0.36 g, 9.1 mmol) in H₂O (5 mL). The mixture was stirred at room temperature for 45 min. The cyclization was afforded by adding 2N HCl solution until pH=2 at 0 °C. The reaction mixture was extracted with EtOAc (3x50 mL) and the organic layers were dried over anhydrous Na₂SO₄, and then concentrated in vacuo.

20 The residue was purified by chromatography on silica gel (PE: EtOAc=3 :1) to give the product as yellow oil (1.7 g, yield 53.6%). ¹H NMR (400 MHz, OMSO-*d*₆) δ 9.05 (s, 1H), 7.44-7.47 (t, 1H), 7.06-7.08 (d, 1H), 6.88-6.90 (d, 1H), 9.86 (t, 1H), 5.70-5.72 (m, 1H), 5.29-5.33 (m, 1H), 4.53-4.59 (m, 1H), 4.02-4.06 (t, 2H), 2.95-2.30 (m, 2H), 1.67-1.72 (m, 2H), 1.52-1.57 (m, 2H), 1.38 (s, 9H).

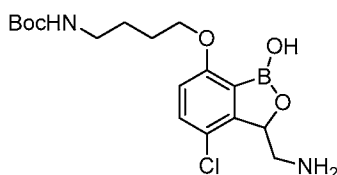
tert-Butyl-4-(4-chloro-1-hydroxy-3-(nitromethyl)-1,3-dihydrobenzo[c][1,2]oxaborol-7-yloxy)butylcarbamate



[0287] A mixture of *tert*-butyl 4-(1-hydroxy-3-(nitromethyl)-1,3-

5 dihydrobenzo[c][1,2]oxaborol-7-yloxy)-butylcarbamate (640 mg, 1.7 mmol) in DMF (20 mL) was added NCS (226 mg, 1.7 mmol) in DMF (5 mL). The mixture was heated to 80 °C for 2 h. After the reaction was quenched with an aqueous LiCl solution (100 mL), the resulting mixture was extracted with EtOAc (3x50 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in
10 vacuo. The residue was purified by prep-HPLC to give the product (280 mg, yield 67.5%). ¹H NMR (400 MHz, OMSO-*d*₆) δ 9.29 (s, 1H), 7.47-7.49 (d, 1H), 6.96-6.98 (d, 1H), 6.80 (s, 1H), 5.74-5.77 (m, 1H), 5.31-5.35 (m, 1H), 4.67-4.72 (m, 1H), 4.02-4.05 (m, 2H), 2.94-2.99 (m, 2H), 1.68-1.72 (m, 2H), 1.50-1.56 (m, 2H), 1.36 (s, 9H).

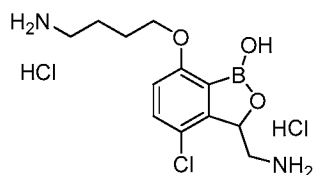
tert-Butyl 4-(3-(aminomethyl)-4-chloro-1-hydroxy-1,3-dihydro-benzo[c][1,2]oxaborol-7-yloxy)butylcarbamate



[0288] A mixture of *tert*-butyl 4-(1-hydroxy-3-(nitromethyl)-1,3-

dihydrobenzo[c][1,2]oxaborol-7-yl-oxy)-butylcarbamate (410 mg, 1 mmol), Raney-Ni (100 mg) and 2 N NH₃ in EtOH (3 mL) in EtOH (15 mL) was shaken under an
20 atmosphere of H₂ for 2 h at room temperature. The mixture was filtered through a bed of Celite and the filtrate was concentrated in vacuo. The resulting solid was used directly for the next step.

7-(4-Aminobutoxy)-3-(aminomethyl)-4-chlorobenzo[c][1,2]oxaborol-1(3H)-ol dihydrochloride



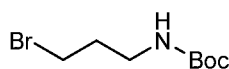
[0289] To a mixture of the crude *tert*-butyl-4-(3-(aminomethyl)-4-chloro-1-hydroxy-1,3-dihydrobenzo[c][1,2]-oxa-borol-7-yloxy)butylcarbamate in DCM (5

mL) was added CF₃COOH (2 mL) at room temperature. The reaction mixture was stirred for 1 h and concentrated in vacuo. The crude amine was dissolved in EtOAc (1 mL) and HCl in Et₂O (10 mL) was added immediately. After 1 h, the suspension was filtered and the resulting solid was washed with hexanes to give the target

5 compound as white solid (180 mg, yield: 42%). ¹H NMR (400 MHz, OMSO-*d*₆) δ 9.16 (s, 1H), 8.28 (s, 3H), 8.03 (d, 3H), 7.49-7.51 (d, 1H), 6.99-7.01 (d, 1H), 5.38-5.40 (m, 1H), 4.05-4.08 (m, 2H), 3.56-3.59 (d, 1H), 2.84-2.91 (m, 3H), 1.71-1.83 (m, 4H); MS (ESI) *m/z* = 285 [M + H]⁺.

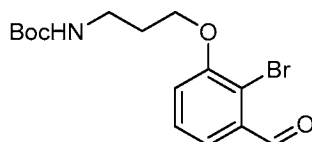
10 **J. 3-(Aminomethyl)-7-(3-aminopropoxy)-4-chlorobenzoic acid, 2loxaborol-1(3H)-ol**

tert-Butyl 3-bromopropylcarbamate



[0290] To a mixture of 3-bromopropan-1-amine (10.95 g, 50 mmol) and TEA (15.4 mL, 110 mmol) in DCM (100 mL) at 0 °C was added (Boc)₂O (11.4 g, 52.5 mmol). The reaction mixture was stirred at room temperature overnight and then washed with water (3x100 mL) and the solution of citric acid (100 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated to give the product as yellow oil (9.0 g, yield 76%).

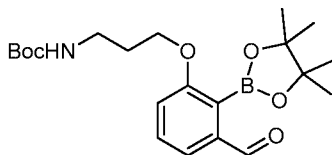
tert-Butyl 3-(2-bromo-3-formylphenoxy)propylcarbamate



20 [0291] A mixture of 2-bromo-3-hydroxybenzaldehyde (5 g, 24.9 mmol), 3-(*tert*-butoxy carbonylamino)-propyl methanesulfonate (7.55 g, 30 mmol) and Cs₂CO₃ (24 g, 75 mmol) in DMF (60 mL) was stirred at 50 °C for 3 h and quenched with water (600 mL). The resulting mixture was extracted with EtOAc (3x60 mL) and the combined organic layers were washed with brine (60 mL), dried over anhydrous Na₂SO₄ and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (PE/EtOAc=10/1) to give the product (7.2 g, yield 81%). ¹H NMR (400 MHz, CDCl₃) δ 10.43 (s, 1H), 7.53 (dd, *J*=7.8 Hz, 1.6 Hz, 1H), 7.37 (t, *J*=7.8 Hz, 1H), 7.12 (dd, *J*=8.2 Hz, 1.6 Hz, 1H), 5.16 (s, 1H), 4.15 (t, *J*=5.9 Hz, 2H), 3.42 (m, 2H), 2.10 (m, 2H), 1.44 (s, 9H); MS (ESI) *m/z* = 358 [M+H]⁺.

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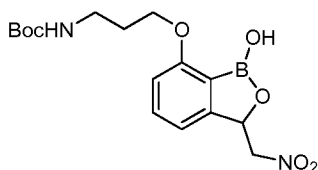
tert-Butyl 3-(3-formyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenoxy)propylcarbamate



[0292] A solution of *tert*-butyl 3-(2-bromo-3-formylphenoxy)propylcarbamate

- 5 (7.1 g, 20 mmol), B_2pin_2 (10 g, 40 mmol), $Pd(dppf)Cl_2$ (800 mg, 2 mmol) and KOAc (5.9 g, 60 mmol) in 1,4-dioxane (30 mL) was degassed with N_2 and stirred at 80 °C for 5 h. The mixture was cooled to room temperature and diluted with EtOAc (100 mL). The organic layer was washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 and then concentrated. The residue was purified by
- 10 chromatography on silica gel (PE/ EtOAc =5/1) to give the product (3.1 g, yield 38.3%). 1H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.48 (t, J =7.8 Hz, 1H), 7.40 (m, 1H), 7.09 (d, J =8.2 Hz, 1H), 4.76 (s, 1H), 4.05 (t, J =6.3 Hz, 2H), 3.32 (m, 2H), 2.00 (m, 2H), 1.45 (s, 12H), 1.43 (s, 9H); MS (ESI) m/z =406 $[M+H]^+$.

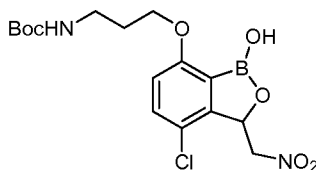
tert-Butyl 3-(1-hydroxy-3-(nitromethyl)-1,3-dihydrobenzo[*c*][1,2]oxaborol-7-yloxy)-propylcarbamate



[0293] A mixture of *tert*-butyl 3-(3-formyl-2-(4,4,5,5-tetramethyl-1,3,2-

- dioxaborolan-2-yl) phenoxy)propylcarbamate (3.1 g, 8.47 mmol), $MeNO_2$ (775 mg, 12.7 mmol), CTAB (310 mg, 0.85 mmol) and NaOH (407 mg, 10 mmol) in THF (35
- 20 mL) and H_2O (8 mL) was stirred at room temperature for 3 h. The mixture was adjusted to pH 2-3 using 2N HCl and then stirred for 30 min. The mixture was extracted with EtOAc (2x80 mL). The organic layer was washed with water (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 and then concentrated. The residue was purified by column chromatography on silica gel (PE/ EtOAc =5/1) to give the
- 25 product (2 g, yield 64.5%). 1H NMR (400 MHz, $OMSO-d_6$) δ 9.05 (s, 1H), 7.47 (t, J =7.8 Hz, 1H), 7.07 (d, J =7.4 Hz, 1H), 6.91 (m, 2H), 5.72 (dd, J =9.0, 2.7 Hz, 1H), 5.31 (dd, J =13.3, 2.7 Hz, 1H), 4.54 (dd, J =13.3, 9.4 Hz, 1H), 4.05 (t, J =6.3 Hz, 2H), 3.09 (m, 2H), 1.83 (m, 2H), 1.37 (s, 9H); MS (ESI) m/z =367 $[M+H]^+$.

tert-Butyl-4-(4-chloro-1-hydroxy-3-(nitromethyl)-1,3-dihydrobenzo[c][1,2]oxaborol-7-yloxy) propylcarbamate

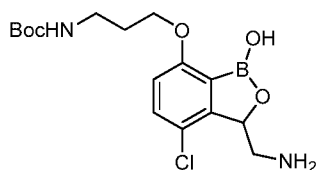


[0294] To a mixture of *tert*-butyl 4-(1-hydroxy-3-(nitromethyl)-1,3-

5 dihydrobenzo[c][1,2]oxaborol-7-yl-oxy)propylcarbamate (2.9 g, 8 mmol) in DMF (35 mL) was added NCS (1.0 g, 8 mmol) in DMF (15mL). The reaction mixture was heated to 80 °C for 2 h and then quenched with an aqueous LiCl solution (300 mL). The resulting mixture was extracted with EtOAc (3x100 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was
10 purified by prep-HPLC to give the product as white solid (480 mg, yield 15.2%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.28 (s, 1H), 7.49-7.51 (d, 1H), 6.96-6.98 (d, 1H), 6.85 (s, 1H), 5.74-5.77 (m, 1H), 5.31-5.35 (m, 1H), 4.67-4.72 (m, 1H), 4.03-4.06 (m, 2H), 3.07-3.11 (m, 2H), 1.82-1.86 (m, 2H), 1.37 (s, 9H); MS (ESI) *m/z* = 401 [M + H]⁺.

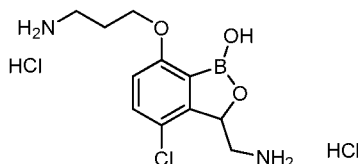
tert-Butyl 3-(3-(aminomethyl)-4-chloro-1-hydroxy-1,3-dihydro-benzo[c][1,2]oxaborol-7-yloxy)propylcarbamate

15



[0295] A mixture of *tert*-butyl 3-(4-chloro-1-hydroxy-3-(nitromethyl)-1,3-dihydrobenzo[c][1,2]oxaborol-7-yloxy)propylcarbamate (480 mg, 1.2 mmol), Raney-Ni (500 mg) and 2 M NH₃ in EtOH (3 mL) in EtOH (15 mL) was shaken under an
20 atmosphere of H₂ for 2 h at room temperature. The mixture was filtered through a bed of Celite and the filtrate was concentrated in vacuo. The resulting solid was used directly for the next step.

3-(Aminomethyl)-7-(3-aminopropoxy)-4-chlorobenzo[c][1,2]oxaborol-1(3H)-ol

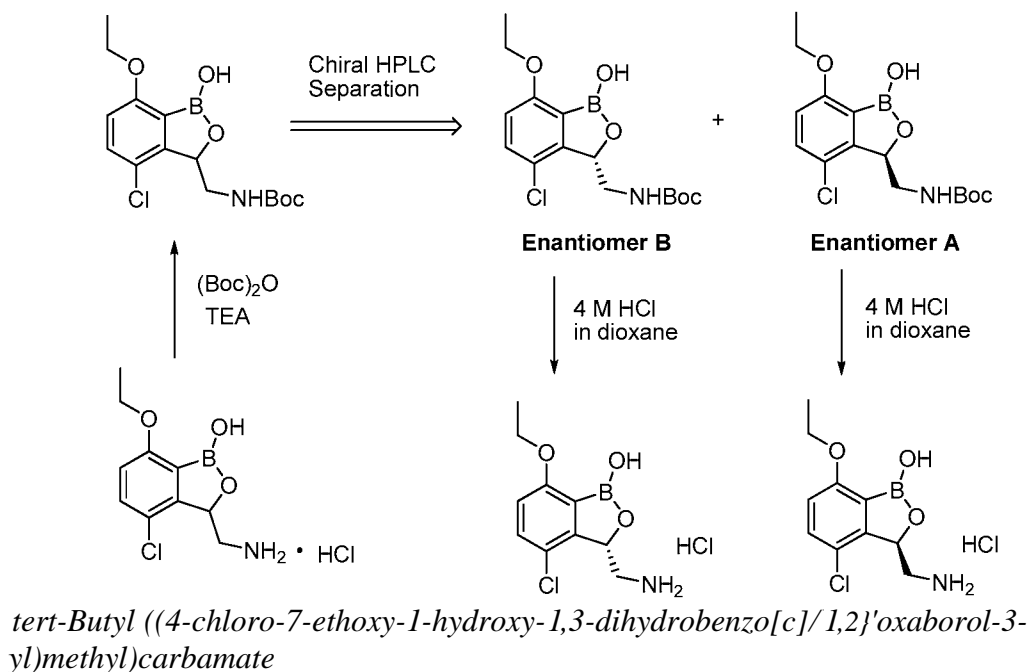


[0296] To a mixture of the crude *tert*-butyl 3-(3-(aminomethyl)-4-chloro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yloxy)propylcarbamate in DCM (10 mL) was added CF₃COOH (2.0 mL) at 0 °C. The reaction mixture was stirred for 1 h

and concentrated in vacuo. The crude amine was dissolved in EtOH (2 mL) and HCl in Et₂O (2 mL) was added immediately. After 1 h, the mixture was concentrated in vacuo. The residue was re-crystallized by EtOH/Et₂O to give the target compound (173.4 mg, yield 42%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.28 (s, 1H), 8.36 (s, 3H), 8.17 (s, 3H), 7.50-7.52 (d, 1H), 6.98-7.00 (d, 1H), 5.39-5.42 (m, 1H), 4.13-4.16 (m, 2H), 3.56-3.59 (d, 1H), 2.98-2.99 (m, 2H), 2.87 (s, 1H), 2.04-2.10 (m, 2H); MS (ESI) *m/z* = 271 [M + H]⁺.

K. *(R)*-3-(Aminomethyl)-4-chloro-7-ethoxybenzo[c][1,2]oxaborol-1(3H)-ol hydrochloride and

10 L. *(S)*-3-(Aminomethyl)-4-chloro-7-ethoxybenzo[c][1,2]oxaborol-1(3H)-ol hydrochloride



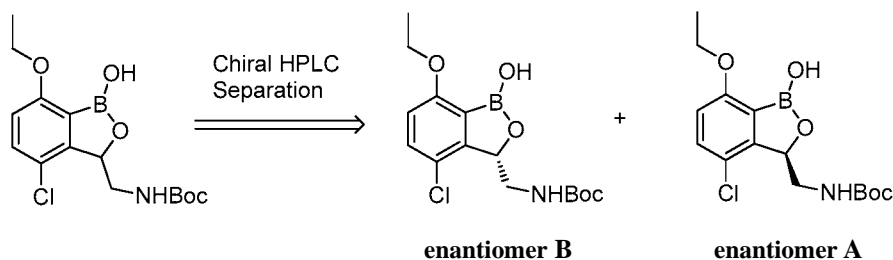
15

[0297] A solution of 3-(aminomethyl)-4-chloro-7-ethoxybenzo[*c*][1,2]oxaborol-1(3H)-ol hydrochloride (38.4 g, 0.16 mol) and Et₃N (47.8 g, 0.47 mol) in CH₂Cl₂ (350 mL) at 0 °C was added di-*tert*-butyl dicarbonate (172 g, 0.79 mol) and the reaction was stirred for 2 h at room temperature. After the reaction was quenched by addition of sat. NaHCO₃ (100 mL) and the resulting mixture was extracted with EtOAc (3x120 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give the

20

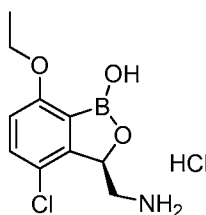
compound as white solid (27 g, yield 50%). ¹H NMR (400 MHz, *O**MSO*-*d*₆) δ 8.92 (s, 1 H), 7.40-7.42 (d, 1H), 6.88-6.90 (d, 1H), 6.77-6.79 (m, 1H), 5.15-5.16 (d, 1H), 4.06-4.13 (m, 2H), 3.75-3.78 (d, 1H), 3.03-3.08 (m, 1H), 1.31-1.34 (m, 12H); MS (ESI) *m/z* = 286 [M + H]⁺.

- 5 *(S)*-*tert*-Butyl ((4-chloro-7-ethoxy-1-hydroxy-1,3-dihydrobenzo[*c*][1,2]oxaborol-3-yl)methyl)carbamate and *(R)*-*tert*-butyl ((4-chloro-1'-ethoxy-1-hydroxy-1,3-dihydrobenzofc[1,2]oxaborol-3-yl)methyl)carbamate



- 10 **[0298]** 25.7 g of *tert*-butyl ((4-chloro-7-ethoxy-1-hydroxy-1,3-dihydrobenzo[*c*][1,2]oxaborol-3-yl)methyl)carbamate dissolved in acetonitrile (10 mg/ml) was resolved via chiral HPLC using ChiralPak AD-H (250×30 mm I.D.) and SF C0₂/methanol as eluent. Flow rate is 70mL/min. UV detection was monitored at 220 nm. Two peaks were collected and evaporated to give 10.65 g of enantiomer A (faster eluting isomer) and 10.15 g of enantiomer B (slower eluting isomer). Analysis
- 15 of the pooled fractions using a ChiralPak AD-3 (150x4.6 mm I.D.) and the same mobile phase showed enantiomer A with a retention time of 3.12 min and 98.7% e.e, and enantiomer B with a retention time of 3.44 min and 98.5% e.e.

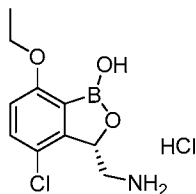
(R)-3-(Aminomethyl)-4-chloro-7-ethoxybenzo[*c*][1,2]oxaborol-1(3*H*)-ol hydrochloride



- 20 **[0299]** Enantiomer A (7.0 g, 20.5 mmol) was dissolved in 30 mL of dioxane and treated with 4M HCl (26.7 mL, 106.6 mmol) in dioxane. The reaction mixture was stirred at room temperature for overnight until the reaction was completed indicated by LC/MS. After dioxane was removed in vacuo and diethyl ether was added, an off-
- 25 white solid was collected and dried under high-vacuum. This material was re-dissolved in acetonitrile and water (1:1, v/v) and lyophilized to give 5.17 g of the title compound as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.11 (s, 1 H), 8.22

(s, 3H), 7.47 (d, 1H), 6.95 (d, 1H), 5.34-5.37 (m, 1H), 4.06-4.11 (m, 2H), 3.53-3.56 (m, 1H), 2.89 (m, 1H), 1.30-1.34 (m, 3H); MS (ESI) m/z = 242.0 $[M + H]^+$.

(S)-3-(Aminomethyl)-4-chloro-7-ethoxybenzof[1,2]oxaborol-1(3H)-ol hydrochloride



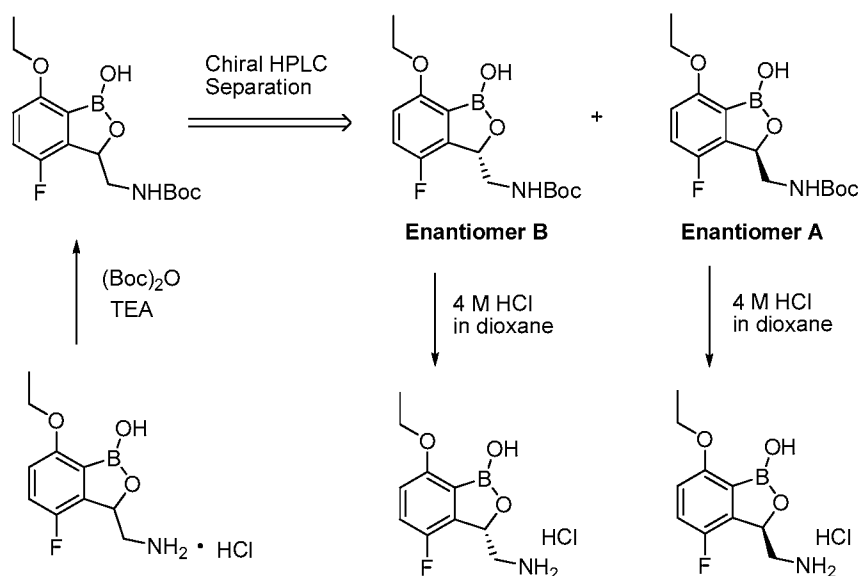
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[0300] Enantiomer B (7.0 g, 20.5 mmol) was dissolved in 30 mL of dioxane and treated with 4M HCl (26.7 mL, 106.6 mmol) in dioxane. The reaction mixture was stirred at room temperature for overnight until the reaction was completed indicated by LC/MS. After dioxane was removed in vacuo and diethyl ether was added, an off-white solid was collected and dried under high-vacuum. This material was re-dissolved in acetonitrile and water (1:1, v/v) and lyophilized to give 5.23 g of the title compound as an off-white solid. ¹H NMR (400 MHz, *OMSO-d*₆) δ 9.11 (s, 1H), 8.25 (s, 3H), 7.47 (d, 1H), 6.95 (d, 1H), 5.35-5.38 (m, 1H), 4.06-4.11 (m, 2H), 3.53-3.56 (m, 1H), 2.88 (m, 1H), 1.30-1.33 (m, 3H); MS (ESI) m/z = 242.0 $[M + H]^+$.

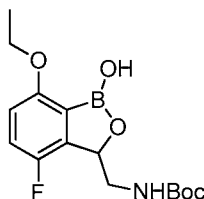
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15 M. *(R)*-3-(Aminomethyl)-4-fluoro-7-ethoxybenzof[1,2]oxaborol-1(3H)-ol hydrochloride and

N. *(S)*-3-(Aminomethyl)-4-fluoro-7-ethoxybenzof[1,2]oxaborol-1(3H)-ol hydrochloride

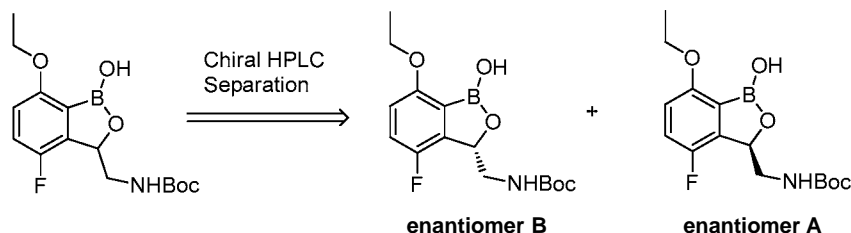


tert-Butyl ((4-fluoro-7-ethoxy-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)methyl)carbamate



[0301] This compound was prepared from 3-aminomethyl-7-ethoxy-4-fluoro-3H-benzo[c][1,2]-oxaborol-1-ol, hydrochloride, using the similar procedure as described above.

(*S*)-*tert*-Butyl ((4-fluoro-7-ethoxy-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)methyl)carbamate and (*R*)-*tert*-butyl ((4-fluoro-7-ethoxy-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)methyl)carbamate

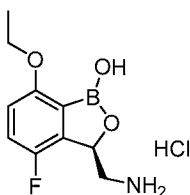


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[0302] 4.5 g of *tert*-butyl ((4-fluoro-7-ethoxy-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)methyl)carbamate dissolved in ethanol (100 mg/ml) was resolved via chiral HPLC using ChiralCel OZ-H column (250×30 mm I.D.) and SF C0₂/hexane: ethanol(1 :1) as eluent. Flow rate is 70mL/min. UV detection was monitored at 220 nm. Two peaks were collected and evaporated to give 2.1 g of enantiomer A (faster eluting isomer) and 2.2 g of enantiomer B (slower eluting isomer). Analysis of the pooled fractions using a ChiralCel OZ-H (150x4.6 mm I.D.) and SF C0₂/ethanol (0.05% DEA) as mobile phase showed enantiomer A with a retention time of 2.66 min and 99.5% e.e, and enantiomer B with a retention time of 3.31 min and 98.1% e.e.

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(*R*)-3-(Aminomethyl)-4-fluoro-7-ethoxybenzo[c][1,2]oxaborol-1(3H)-ol hydrochloride

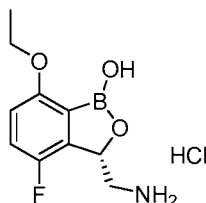


[0303] Enantiomer A (2.1 g) was treated with 200 mL of 1.6 N HCl in MeOH and stirred at room temperature for 5 hours until the reaction was completed indicated by LC/MS. After water (100 mL) was added, the residue was lyophilized overnight to

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give 1.40 g of the title compound as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.16 (br. s., 1H), 8.34 (br. s., 3H), 7.26 (t, 1H), 6.70 - 6.92 (m, 1H), 5.48 (d, 1H), 4.06 (q, 2 H), 3.35 (m, 1H), 2.88 (m, 1H), 1.30 (t, 3H); MS (ESI) *m/z* = 226.1 (M+1, positive).

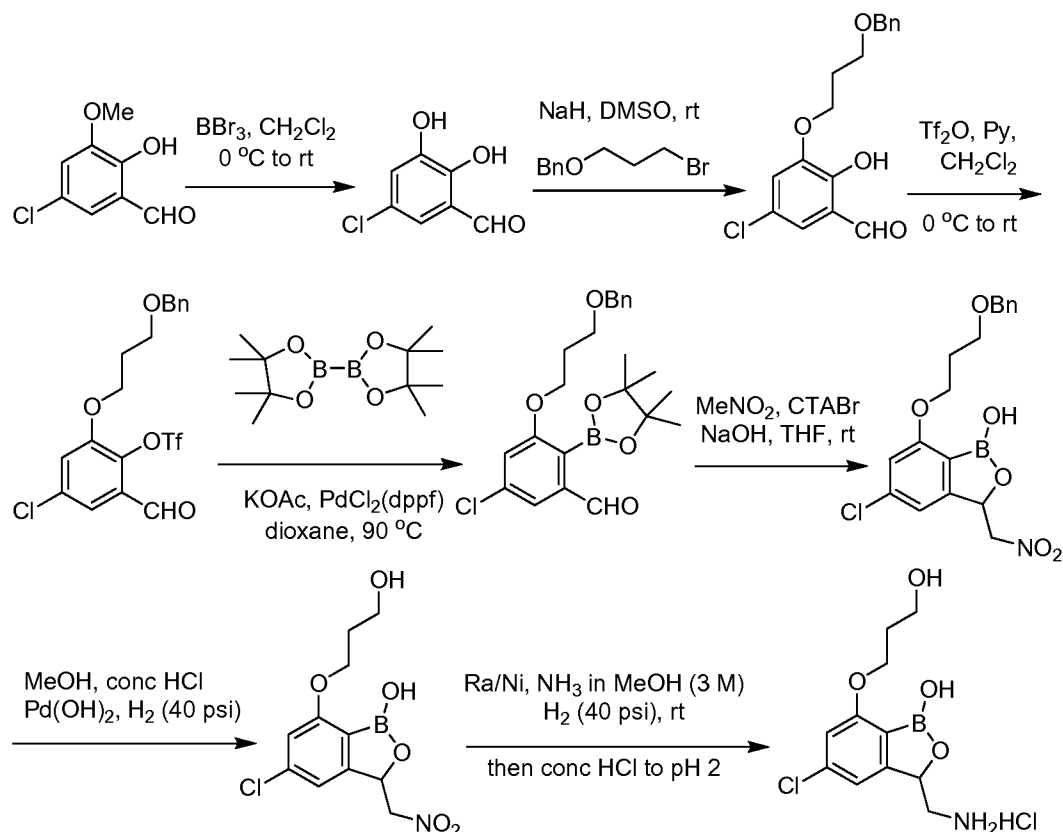
5 *(S)*-3-(Aminomethyl)-4-fluoro-7-ethoxybenzofcJfl,2]oxaborol-1 (3H)-ol hydrochloride



[0304] Enantiomer **B** (2.1 g) was treated with 200 mL of 1.6 N HCl in MeOH and stirred at room temperature for 5 hours until the reaction was completed indicated by LC/MS. After water (100 mL) was added, the residue was lyophilized overnight to

10 give 1.43 g of the title compound as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.16 (br. s., 1H), 8.31 (br. s., 3 H), 7.26 (t, 1H), 6.70 - 6.92 (m, 1 H), 5.48 (d, 1H), 4.06 (q, 2 H), 3.35 (m, 1H), 2.88 (m, 1 H), 1.31 (t, 3 H); MS (ESI) *m/z* = 226.1 (M+1, positive).

O. **3-Aminomethyl-5-chloro-7-(3-hydroxy-propoxy)-3H-benzofcJfl,2Joxaborol-
l-ol hydrochloride**



5-Chloro-2,3-dihydroxy-benzaldehyde

- 5 [0305] To a solution of 5-chloro-2-hydroxy-3-methoxy-benzaldehyde (7 g, 37.5 mmol) in anhydrous CH_2Cl_2 (200 mL) at 0 °C was added a solution of BBr_3 in CH_2Cl_2 (1 M, 93.7 mL, 93.7 mmol) and the reaction mixture was stirred overnight at room temperature. The solution was diluted with CH_2Cl_2 (200 mL), washed with water, brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure generating the title compound (6.2 g, 36.0 mmol, 96%) as a light yellow solid. ^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 11.02 (s, 1 H), 9.83 (s, 1 H), 7.18 (s, 1 H), 7.14 (d, $J=2.3$ Hz, 1 H), 5.71 (s, 1 H).

3-(3-Benzyloxy-propoxy)-5-chloro-2-hydroxy-benzaldehyde

- 15 [0306] To a solution of 5-chloro-2,3-dihydroxy-benzaldehyde (3.1 g, 17.7 mmol) in anhydrous DMSO (20 mL) was added NaH (60% in mineral oil, 1.50 g, 35.4 mmol) portion-wise and the mixture was stirred for 30 minutes. The solution was cooled to 0 °C and a solution of 3-benzyloxy-1-bromopropane (3.1 mL, 17.7 mmol) in DMSO (3 mL) was added dropwise over 10 minutes period. The ice bath was removed. After overnight, the solution was diluted with EtOAc (100 mL), washed

with water, brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The product was purified by silica gel column chromatography (2:1 hexanes-EtOAc mobile phase) generating the title compound (5.3 g, 16.6 mmol, 94%) as a light yellow oil. ^1H NMR (400 MHz, CHCl_3) δ ppm 10.81 (s, 1 H), 9.87 (s, 1 H), 7.42 - 7.28 (m, 5 H), 7.17 (s, 1 H), 7.08 (s, 1 H), 4.53 (s, 2 H), 4.17 (t, $J=6.2$ Hz, 2 H), 3.69 (t, $J=5.8$ Hz, 2 H), 2.15 (t, $J=6.2$ Hz, 2 H).

Trifluoro-methanesulfonic acid 2-(3-benzyloxy-propoxy)-4-chloro-6-formyl-phenyl ester

[0307] To a solution of 3-(3-benzyloxy-propoxy)-5-chloro-2-hydroxy-benzaldehyde (5.3 g, 16.6 mmol) and pyridine (3.4 mL, 41.5 mmol) in CH_2Cl_2 (70 mL) at 0 °C was added Tf_2O (3.1 mL, 18.3 mmol) drop-wise over 5 minutes period and the reaction mixture was stirred for 3 h at room temperature. The solution was diluted with CH_2Cl_2 (100 mL), washed with water, brine, dried over Na_2SO_4 , then concentrated under reduced pressure. The product was purified by silica gel column chromatography (2:1 hexanes-EtOAc mobile phase) generating the title compound (3.8 g, 8.5 mmol, 51%) as a light yellow oil. ^1H NMR (400 MHz, CHCl_3) δ ppm 10.18 (s, 1 H), 7.48 (d, $J=2.3$ Hz, 1 H), 7.37 - 7.29 (m, 6 H), 4.52 (s, 2 H), 4.23 (t, $J=6.2$ Hz, 2 H), 3.69 (t, $J=5.8$ Hz, 2 H), 2.16 (t, $J=6.0$ Hz, 2 H); ^{19}F NMR (376 MHz, CHCl_3) δ ppm -73.23 (s).

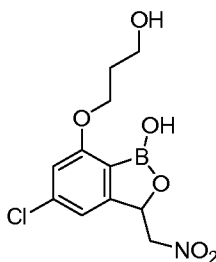
3-(3-Benzyloxy-propoxy)-5-chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-benzaldehyde

[0308] To a solution of trifluoro-methanesulfonic acid 2-(3-benzyloxy-propoxy)-4-chloro-6-formyl-phenyl ester (3.8 g, 8.4 mmol) in anhydrous 1,4-dioxane (50 mL) was added bis(pinacolato)diborane (4.3 g, 16.9 mmol) and KOAc (2.5 g, 25.4 mmol) successively and the resulting solution was degassed with N_2 for 20 minutes. $\text{PdCl}_2(\text{dppf})$ (0.5 g, 0.67 mmol) was added and the resulting mixture was stirred overnight at 90 °C. The solution was diluted with EtOAc (100 mL), washed with water, brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The product was purified by silica gel column chromatography (4:1 hexanes-EtOAc mobile phase) generating the title compound (3.4 g, 7.8 mmol, 92%+) as a colorless oil. ^1H NMR (400 MHz, CHCl_3) δ ppm 9.87 (s, 1 H), 7.40 - 7.28 (m, 6 H), 7.03 (br s, 1 H), 4.50 (s, 2 H), 4.09 (t, $J=6.4$ Hz, 2 H), 3.70 - 3.60 (m, 2 H), 2.10 (t, $J=6.2$ Hz, 2 H), 1.42 (s, 12 H).

7-(3-Benzoyloxy-propoxy)-5-chloro-3-nitromethyl-3H-benzo[c][l,2]oxaborol-1-ol

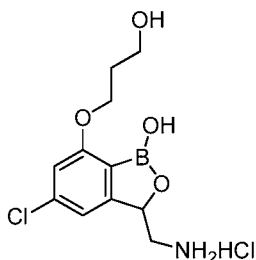
[0309] To a solution of 3-(3-benzyloxy-propoxy)-5-chloro-2-(4,4,5-trimethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde (3.4 g, 7.8 mmol) and nitromethane (1.7 mL, 31.3 mmol) in THF (20 mL) was added a solution of NaOH (0.025 M, 40 mL). After 12 h, 2 N HCl was added until pH was 1. The solution was diluted with EtOAc (150 mL), washed with water, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by silica gel column chromatography (4:1 hexanes-EtOAc mobile phase) to give the title compound product (1.7 g, 56%) as a colorless gel. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.39 - 7.28 (m, 5 H), 6.92 (s, 1 H), 6.83 (s, 1 H), 5.85 (br s, 1 H), 5.81 (dd, *J*=8.5, 3.9 Hz, 1 H), 4.70 (dd, *J*=13.2, 3.9 Hz, 1 H), 4.59 (s, 2 H), 4.47 (dd, *J*=13.0, 8.7 Hz, 1 H), 4.21 - 4.07 (m, 2 H), 3.71 - 3.60 (m, 2 H), 2.10 (quin, *J*=5.7 Hz, 2 H).

5-Chloro-7-(3-hydroxy-propoxy)-3-nitromethyl-3H-benzo[c][l,2]oxaborol-1-ol



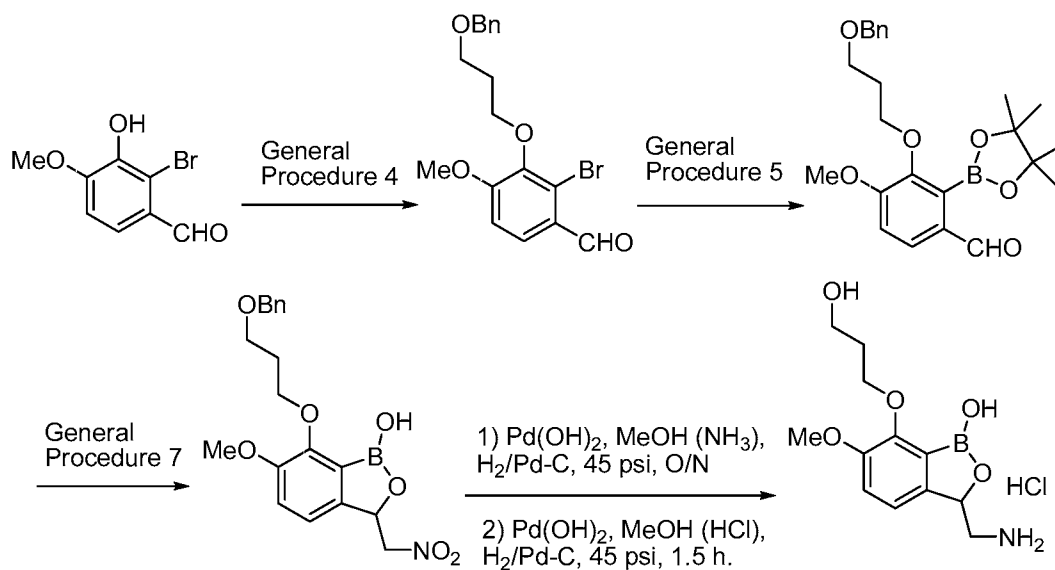
[0310] 7-(3-Benzoyloxy-propoxy)-5-chloro-3-nitromethyl-3H-benzo[c][l,2]oxaborol-1-ol (0.3 g, 0.91 mmol) in MeOH (30 mL) was added cone HCl (1 mL) and Pd(OH)₂ (10% w/w on carbon, 0.2 g) and the reaction vessel was pressurized to 40 psi with hydrogen for 30 minutes at room temperature. The mixture was filtered through a pad of Celite® and washed with EtOAc. The filtrate was concentrated in vacuo and the product was purified by prep. HPLC (C 18 column, using acetonitrile and 0.1% AcOH/water solution gradient) provided the title compound (80 mg, 33%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.19 (s, 1 H), 7.22 (s, 1 H), 6.97 (s, 1 H), 5.71 (dd, *J*=8.9, 2.3 Hz, 1 H), 5.32 (dd, *J*=13.2, 2.7 Hz, 1 H), 4.64 (dd, *J*=13.6, 8.9 Hz, 1 H), 4.53 (t, *J*=4.8 Hz, 1 H), 4.12 (t, *J*=6.0 Hz, 2 H), 3.57 (q, *J*=5.5 Hz, 2 H), 1.86 (t, *J*=6.2 Hz, 2 H).

3-Aminomethyl-5-chloro-7-(3-hydroxy-propoxy)-3H-benzo[c][1,2]oxaborol-1-ol hydrochloride



- [0311] To a 5-chloro-7-(3-hydroxy-propoxy)-3-nitromethyl-3H-benzo[c][1,2]oxaborol-1-ol (80 mg, 0.27 mmol) in methanolic ammonia solution (2 M, 20 mL) was added Ra/Ni (-0.1 g, 2800 Nickel slurry in water) and the reaction vessel was pressurized to 40 psi with hydrogen overnight at room temperature. The mixture was filtered through a pad of Celite® and washed with EtOAc. The filtrate was concentrated in vacuo and to the resulting residue was added water (1 mL), followed by cone HCl to pH 1. The heterogeneous mixture was lyophilized providing the title compound as a hygroscopic ivory solid (79 mg, quantitative). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.20 (s, 1 H), 6.99 (s, 1 H), 5.28 (dd, *J*=8.0, 2.5 Hz, 1 H), 4.13 (t, *J*=6.0 Hz, 2 H), 3.59 (t, *J*=6.0 Hz, 2 H), 3.47 (dd, *J*=13.0, 2.5 Hz, 1 H), 2.89 (dd, *J*=13.2, 8.6 Hz, 1 H), 1.89 (t, *J*=6.0 Hz, 2 H); MS (ESI) *m/z* = 272 (*M*+1, positive); HPLC purity: 96.83% (MaxPlot 200 - 400 nm), 95.40% (220 nm).

P. 3-Aminomethyl-7-(3-hydroxy-propoxy)-6-methoxy-3H-benzolc[1,2]oxaborol-1-ol hydrochloride



3-(3-Benzyloxy-propoxy)-2-bromo-4-methoxy-benzaldehyde

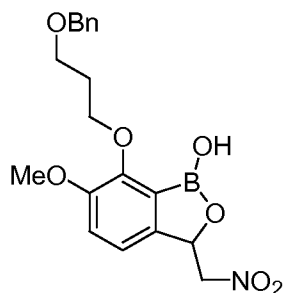
- [0312] Synthesized according to the methods of general procedure 4 in U.S. Pat. Pub. No. 20090227541 (U.S. Pat. App. No. 12/142,692) using the following reactants

and amounts: 2-bromo-3-hydroxy-4-methoxy-benzaldehyde (1.0 g, 4.32 mmol), (3-bromo-propoxymethyl)-benzene (0.76 mL, 4.32 mmol), cesium carbonate (2.11 g, 6.5 mmol), DMF (30 mL). Purification: flash chromatography (10% EtOAc/hexanes): yield 1.54 g (95%). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 10.26 (s, 1 H), 7.73 (d, *J*=8.6 Hz, 1 H), 7.46-7.18 (m, 5 H), 6.95 (d, *J*=8.6 Hz, 1 H), 4.56 (s, 2 H), 4.14 (t, *J*=6.1 Hz, 2 H), 3.92 (s, 3 H), 3.77 (t, *J*=6.2 Hz, 2 H), 2.15 (quin, *J*=6.5 Hz, 2 H); MS (ESI): *m/z* = 381 (M+1, positive).

3-(3-Benzyloxy-propoxy)-4-methoxy-2-(4,4,5,5-tetramethyl-1,3,2]dioxaborolan-2-yl)-benzaldehyde

- 10 [0313] Synthesized according to the methods of general procedure 5 in U.S. Pat. Pub. No. 20090227541 (U.S. Pat. App. No. 12/142,692) using the following reactants and amounts: 3-(3-benzyloxy-propoxy)-2-bromo-4-methoxy-benzaldehyde (14.82 g, 39 mmol), bis(pinacolato)diboran (14.86 g, 58.5 mmol), KOAc (11.46 g, 117 mmol), PdCl₂(dppf) (8.5 g, 11.7 mmol), dioxane (200 mL). Purification: flash column chromatography (15% EtOAc/hexanes): yield 3.42 g (22%). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 9.79 (s, 1 H), 7.53 (d, *J*=8.2 Hz, 1 H), 7.40-7.24 (m, 5 H), 6.98 (d, *J*=8.2 Hz, 1 H), 4.53 (s, 2 H), 4.12 (t, *J*=6.4 Hz, 2 H), 3.88 (s, 3 H), 3.69 (t, *J*=6.4 Hz, 2 H), 2.10 (quin, *J*=6.5 Hz, 2 H), 1.44 (s, 12 H).

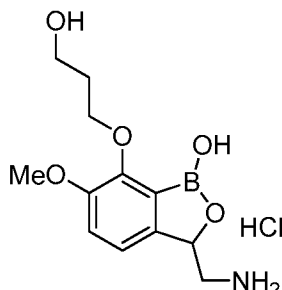
7-(3-Benzyloxy-propoxy)-6-methoxy-3-nitromethyl-3H-benzo[c][1,2]oxaborol-1-ol



- 20 [0314] Synthesized according to the methods of general procedure 8 in U.S. Pat. Pub. No. 20090227541 (U.S. Pat. App. No. 12/142,692) using the following reactants and amounts: 3-(3-benzyloxy-propoxy)-4-methoxy-2-(4,4,5,5-tetramethyl-1,3,2]dioxaborolan-2-yl)-benzaldehyde (3.36 g, 7.88 mmol), nitromethane (1.28 mL, 23.66 mmol), NaOH (0.22 g, 5.52 mmol), THF (6 mL), water (18 mL). Purification: flash column chromatography (30% EtOAc/hexanes): yield 1.2 g (41%). ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 9.36 (s, 1 H), 7.40-7.22 (m, 5 H), 7.22-7.04 (m, 2 H), 5.68 (dd, *J*=9.4, 2.7 Hz, 1 H), 5.29 (dd, *J*=13.4, 2.5 Hz, 1 H), 4.52 (dd, *J*=13.3, 9.4

Hz, 1 H), 4.45 (s, 2 H), 4.25 (t, $J=6.2$ Hz, 2 H), 3.75 (s, 3 H), 3.61 (t, $J=6.2$ Hz, 2 H), 1.92 (quin, $J=6.5$ Hz, 2 H).

3-Aminomethyl-7-(3-hydroxy-propoxy)-6-methoxy-3H-benzo[c][1,2]oxaborol-1-ol; hydrochloride



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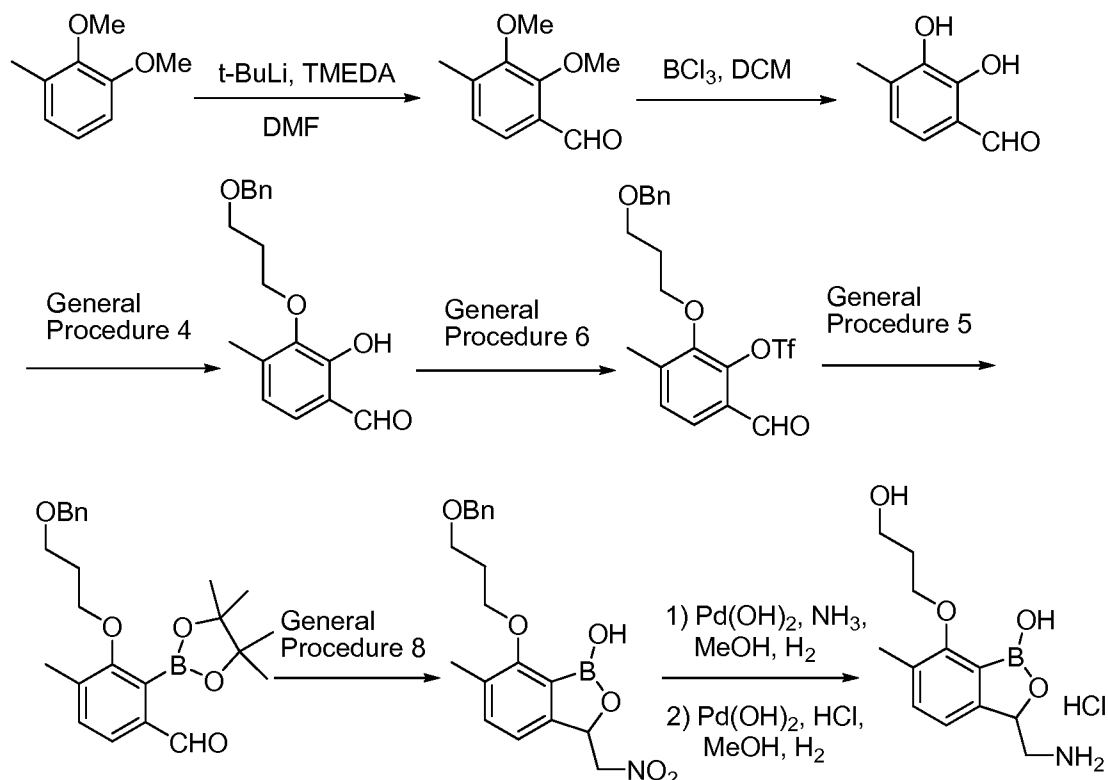
[0315] To a solution of 7-(3-benzyloxy-propoxy)-6-methoxy-3-nitromethyl-3H-benzo[c][1,2]oxaborol-1-ol (0.5 g, 1.29 mmol) in methanolic ammonia (10 mL) was added palladium hydroxide (0.25 g, 45 wt%) in a hydrogenation bottle and the flask was charged with hydrogen at 45 psi for 18 h. The catalyst was filtered off and the solvent was evaporated under reduced pressure. In order to assure all the ammonia has been stripped off, the compound was subjected to the high vacuum for 1 h. The crude (0.4 g) obtained was further dissolved in methanol (15 mL) and transferred to a hydrogenation bottle and concentrated HCl (5-6 drops) was added to make it to pH 2. To this solution palladium hydroxide (0.11 g, 25 wt%) was added and the flask was charged with hydrogen to 45 psi for 1.5 h. The catalyst was filtered off through a pad of Celite and the solvent evaporated. Purification was accomplished by preparative HPLC generating 0.16 g (41%) of the title compound as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.06 (br. s, 1 H), 7.17 (d, $J=8.2$ Hz, 1 H), 7.12 - 7.02 (m, 1 H), 5.32 (dd, $J=7.8, 2.3$ Hz, 1 H), 4.46 - 4.27 (m, 2 H), 4.14 (t, $J=4.5$ Hz, 2 H), 3.78 (s, 3 H), 3.44 (dd, $J=13.3, 2.7$ Hz, 1 H), 2.88 (dd, $J=13.3, 8.2$ Hz, 1 H), 2.08 - 1.94 (m, 2 H); MS (ESI): m/z = 268 (M+1, positive); HPLC purity: 95.35% (MaxPlot 200 - 400 nm), 97.48% (220 nm).

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Q. 3-Aminomethyl - 7-(3-hydroxy-propoxy)-6-methyl-3H-benzofcJfl,2Joxaborol-1-ol; hydrochloride



1,2-Dimethoxy-3-methyl-benzene

- 5 **[0316]** To a cooled (0 °C) solution of 1,2-dimethoxy-3-methylbenzene (2.05 g, 13.45 mmol) and TMEDA (2.8 mL, 18.83 mmol) in diethyl ether (100 mL) was added t-butyllithium (1.7 M in pentane, 9.5 mL, 16.14 mmol). The color of the solution changed to light yellow and after a few minutes a white precipitate was observed. The suspension was stirred at room temperature for 18 h, cooled to 0 °C and
- 10 dimethylformamide (2.08 mL, 26.90 mmol) was added dropwise. The precipitate disappeared and the color of the solution changed to light pink. After stirring for 0.5 h, ice was added followed by 1N HCl (30 mL), the compound was extracted into ethyl acetate, dried (Na₂SO₄) and the solvent was evaporated to obtain light brown oil. Purification by flash column chromatography (5% EtOAc/hexane) generated the title
- 15 compound: yield 1.4 g (58%). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 10.34 (s, 1 H), 7.49 (d, *J*=8.2 Hz, 1 H), 7.01 (d, *J*=7.8 Hz, 1 H), 4.00 (s, 3 H), 3.86 (s, 3 H), 2.33 (s, 3 H). MS (ESI): *m/z* = 181 (M+1, positive).

2,3-Dihydroxy-4-methyl-benzaldehyde

- [0317]** To a solution of 1,2-dimethoxy-3-methyl-benzene (13.8 g, 76.66 mmol) cooled to -30 °C (dry ice/ acetone) in dichloromethane (200 mL) was added boron

trichloride (230 mL, 230 mmol) dropwise and the mixture was left to stir overnight at room temperature. The solution was cooled to 0 °C and ice/ water was added carefully, and then extracted with excess of dichloromethane. The organic layer was washed with water, dried (Na₂SO₄) and the solvent was evaporated. Purification by silica gel column chromatography (10-20% EtOAc/hexane) gave the title compound as a crystalline solid: yield 9.2 g (80%). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 11.11 (s, 1 H), 9.82 (s, 1 H), 7.05 (d, *J*=8.2 Hz, 1 H), 6.81 (d, *J*=8.6 Hz, 1 H), 5.67 (s, 1 H), 2.33 (s, 3 H).

3-(3-Benzyloxy-propoxy)-2-hydroxy-4-methyl-benzaldehyde

- 10 [0318] Synthesized according to the methods of general procedure 4 in U.S. Pat. Pub. No. 20090227541 (U.S. Pat. App. No. 12/142,692) using the following reactants and amounts: 2,3-dihydroxy-4-methyl-benzaldehyde (9 g, 59.21 mmol), (3-bromopropoxymethyl)-benzene (11.5 mL, 65.13 mmol), sodium tert-butoxide (12.52 g, 130.26 mmol) and DMSO (100 mL). Purification: flash column chromatography (5-15 10% EtOAc/hexane): yield 15.1 g (85%). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 11.05 (s, 1 H), 9.84 (s, 1 H), 7.38-7.26 (m, 5 H), 7.20 (d, *J*=7.8 Hz, 1 H), 6.80 (d, *J*=8.2 Hz, 1 H), 4.55 (s, 2 H), 4.15 (t, *J*=6.2 Hz, 2 H), 3.73 (t, *J*=6.2 Hz, 2 H), 2.31 (s, 3 H), 2.19-2.00 (m, 2 H).

Trifluoro-methanesulfonic acid 2-(3-benzyloxy-propoxy)-6-formyl-3-methyl-phenyl ester

- 20 [0319] Synthesized according to the methods of general procedure 6 in U.S. Pat. Pub. No. 20090227541 (U.S. Pat. App. No. 12/142,692) using the following reactants and amounts: 3-(3-Benzyloxy-propoxy)-2-hydroxy-4-methyl-benzaldehyde (0.3 g, 1.0 mmol), trifluoromethanesulfonic acid (0.34 mL, 2.0 mmol), pyridine (0.25 mL, 3.1 mmol), dichloromethane (15 mL). Purification: flash column chromatography (10-25 15% EtOAc/hexane): yield 0.25 g (59%). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 10.14 (s, 1 H), 7.61 (d, *J*=7.8 Hz, 1 H), 7.42-7.29 (m, 6 H), 4.53 (s, 2 H), 4.07 (t, *J*=6.4 Hz, 2 H), 3.71 (t, *J*=6.1 Hz, 2 H), 2.40 (s, 3 H), 2.07 - 2.22 (m, 2 H). ¹⁹F NMR (400 MHz, CDCl₃) δ (ppm): -73.63 (s).

- 30 *3-(3-Benzyloxy-propoxy)-4-methyl-2-(4,4,5,5-tetramethyl-f1,3,2]dioxaborolan-2-yl)-benzaldehyde*

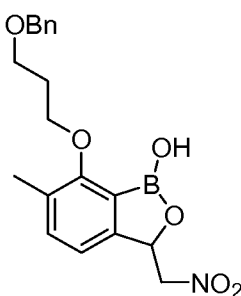
[0320] Synthesized according to the methods of general procedure 5 in U.S. Pat. Pub. No. 20090227541 (U.S. Pat. App. No. 12/142,692) using the following reactants

and amounts: trifluoro-methanesulfonic acid 2-(3-benzyloxy-propoxy)-6-formyl-3-methyl-phenyl ester (0.26 g, 0.6 mmol), bis(pinacolato)diboran (0.31 g, 1.2 mmol), KOAc (0.18 g, 1.8 mmol), PdCl₂(dppf) (0.13 g, 0.18 mmol), THF (10 mL).

Purification: flash column chromatography (15% EtOAc/hexane): yield 0.091 g

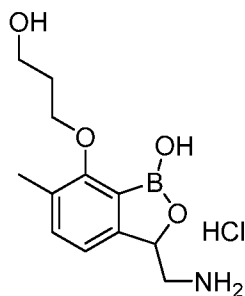
- 5 (36%). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 9.89 (s, 1 H), 7.47 (d, *J*=7.4 Hz, 1 H), 7.40-7.25 (m, 6 H), 4.52 (s, 2 H), 4.02 (t, *J*=6.4 Hz, 2 H), 3.70 (t, *J*=6.2 Hz, 2 H), 2.32 (s, 3 H), 2.20-2.08 (m, 2 H), 1.45 (s, 12 H).

7-(3-Benzyloxy-propoxy)-6-methyl-3-nitromethyl-3H-benzo[c][1,2]oxaborol-1-ol



- 10 **[0321]** Synthesized according to the methods of general procedure 8 in U.S. Pat. Pub. No. 20090227541 (U.S. Pat. App. No. 12/142,692) using the following reactants and amounts: 3-(3-benzyloxy-propoxy)-4-methyl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde (1.14 g, 2.78 mmol), nitromethane (0.45 mL, 8.34 mmol), NaOH (0.78 g, 1.95 mmol), THF (3 mL) and water (9 mL). Purification:
- 15 flash column chromatography (25% EtOAc/hexanes) : yield 0.42 g (41%). ¹H NMR (400 MHz, **DMSO-d₆**) δ (ppm): 9.41 (s, 1 H), 7.37-7.18 (m, 6 H), 7.03 (d, *J*=7.8 Hz, 1 H), 5.69 (dd, *J*=9.2, 2.5 Hz, 1 H), 5.28 (dd, *J*=13.7, 2.7 Hz, 1 H), 4.52 (dd, *J*=13.3, 9.4 Hz, 1 H), 4.46 (s, 2 H), 4.33 (t, *J*=6.1 Hz, 2 H), 3.58 (t, *j*= 6.1 Hz, 2 H), 2.12 (s, 3 H), 2.01-1.87 (m, 2 H). MS (ESI): *m/z* = 370 (M-1, negative).

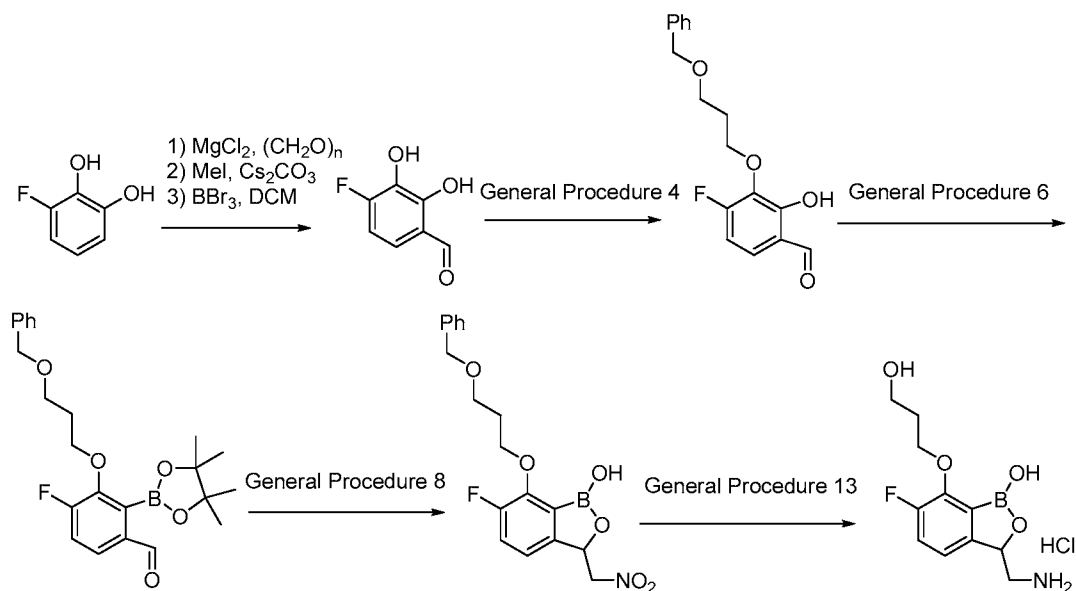
- 20 *3-Aminomethyl-7-(3-hydroxy-propoxy)-6-methyl-3Hbenzofc][1,2] oxaborol-1-ol hydrochloride*



[0322] To a solution of 7-(3-benzyloxy-propoxy)-6-methyl-3-nitromethyl-3H-benzo[c][1,2]oxaborol-1-ol (0.42 g, 1.13 mmol) in methanolic ammonia (15 mL) was

added palladium hydroxide (0.2 g, 45 wt%) in a hydrogenation bottle and the flask was charged with hydrogen at 45 psi for 18 h. The catalyst was filtered off and the solvent was evaporated under reduced pressure. In order to assure all the ammonia has been stripped off, the compound was subjected to the high vacuum for 1 h. The crude (0.38 g) obtained was further dissolved in methanol (15 mL) and transferred to a hydrogenation bottle and concentrated HCl (5-6 drops) was added to make it to pH 2. To this solution palladium hydroxide (0.1 g, 25 wt%) was added and the flask was charged with hydrogen at 45 psi for 1.5 h. The catalyst was filtered off through a pad of Celite and the solvent evaporated. Purification by preparative HPLC provided 0.12 g (39%) of the title compound as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.40 (s, 1 H), 7.12 (d, *J*=7.4 Hz, 1 H), 6.80 (d, *J*=7.4 Hz, 1 H), 5.08-4.91 (m, 1 H), 4.49-4.21 (m, 2 H), 3.64 (t, *J*=5.7 Hz, 2 H), 3.17 (dd, *J*=12.9, 3.1 Hz, 1 H), 2.66 (dd, *J*=12.7, 8.0 Hz, 1 H), 2.14 (s, 3 H), 1.81 (quin, *J*=5.7 Hz, 2 H). MS (ESI): *m/z* = 252 (*M*+1, positive); HPLC purity: 98.25% (MaxPlot 200 - 400 nm), 98.39% (220 nm).

R. 3-Aminomethyl-6-fluoro-7-(3-hydroxy-propoxy)-3H-benzofcJfl,2Joxaborol-1-ol; hydrochloride salt



4-Fluoro-2,3-dihydroxy-benzaldehyde

- [0323]** To a solution of 3-fluoro-benzene-1,2-diol (20 g, 156 mmol) in anhydrous acetonitrile (400 mL) was added magnesium chloride (37.1 g, 312 mmol), paraformaldehyde (31.6 g) and triethylamine (134 mL, 975 mmol). The reaction mixture was heated at 80 °C for 8 h. The reaction mixture was cooled to room temperature and the solid was collected by filtration. The solid was treated with cold

2 N HCl and the aqueous layer was extracted with EtOAc. The organic layer was concentrated in vacuo yielding 20.4 g of crude. After a second run 40.8 g of crude was dissolved in DMF (1 L), cooled to 0 °C, added to Cs₂CO₃ (340 g, 1.04 mol) portion-wise. Then methyl iodide (330 mL, 5.28 mol) was added. After warming to
 5 room temperature and stirring overnight the solution was filtered, ethyl acetate was added and the organic layer was washed with water (3 X). After concentration in vacuo the product was purified by Biotage silica gel chromatography (2% to 3% to 10% to 20% EtOAc/ hexanes) resulting in 14.8 g of dimethoxy compound. This material was dissolved in DCM and cooled to -30 °C and BC1₃ (1 M in DCM, 134
 10 mL, 0.1343 mol) was added to the solution at -30 °C. After overnight at room temperature, the solution was cooled to -70 °C and BBr₃ (1 M in DCM, 67.25 mL, 0.067 mol) was added. After overnight warming to room temperature, the solution was cooled in an ice bath and slowly ice water was added. The DCM layer was separated and the aqueous layer was extracted with DCM (2X). The combined
 15 organic layer was extracted with brine (2X), dried over Na₂SO₄, filtered and concentrated in vacuo. After triturating the residue obtained with hexanes/DCM (6:4) the 5.60 g (11% yield) of the title compound obtained was a brownish pink solid. This material was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 11.36 (s, 1H), 9.83 (s, 1H), 7.16 - 7.13 (m, 1H), 6.82 -
 20 6.78 (m, 1H), 5.48 (brs, 1H). ¹⁹F NMR (376 MHz, *OMSO-d*₆ with D₂O) δ (ppm): -119.03 - -119.08 (m, 1F).

3-(3-Benzyloxy-propoxy)-4-fluoro-2-hydroxy-benzaldehyde

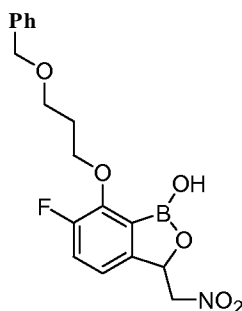
[0324] Synthesized according to the methods of general procedure 4 in U.S. Pat. Pub. No. 20090227541 (U.S. Pat. App. No. 12/142,692) using the following reactants
 25 and amounts: 4-fluoro-2,3-dihydroxy-benzaldehyde (5.15 g, 32.9 mmol), NaOtBu (6.95 g, 72.3 mmol), DMSO (200 mL), (3-bromo-propoxymethyl)-benzene (8.31 g, 36.3 mmol). Purification: Biotage silica gel chromatography (hexanes/ ethyl acetate gradient) generated 4.00 g of a mixture of the title compound and the dialkylated product. This material was used in the next step without further purification. ¹H
 30 NMR (400 MHz, *OMSO-d*₆) δ (ppm): 10.13 (s, 1H), 7.66 -7.54 (m, 5H), 7.53 - 7.33 (m, 1H), 6.92 - 6.90 (m, 1H), 4.53 (s, 2H), 4.52 - 4.44 (m, 2H), 3.71 - 3.62 (m, 2H), 2.18 - 2.13 (m, 2H). ¹⁹F NMR (376 MHz, *OMSO-d*₆ with D₂O) δ (ppm): -121.03 - -121.08 (m, 1F).

3-(3-Benzyloxy-propoxy)-4-fluoro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde

[0325] Synthesized according to the methods of general procedure 6 in U.S. Pat. Pub. No. 20090227541 (U.S. Pat. App. No. 12/142,692) using the following reactants and amounts: 3-(3-benzyloxy-propoxy)-4-fluoro-2-hydroxy-benzaldehyde (4.00 g, 13.1 mmol), pyridine (2.34 mL, 28.9 mmol), DCM (100 mL), triflate anhydride (2.21 mL, 13.5 mmol). Purification: Biotage silica gel chromatography (hexanes/ ethyl acetate gradient) generated 2.00 g of triflate that was used immediately according to general procedure 5 in U.S. Pat. Pub. No. 20090227541 (U.S. Pat. App. No. 12/142,692).

[0326] Synthesized according to the methods of general procedure 5 in U.S. Pat. Pub. No. 20090227541 (U.S. Pat. App. No. 12/142,692) using the following reactants and amounts: trifluoro-methanesulfonic acid 2-(3-benzyloxy-propoxy)-3-fluoro-6-formyl-phenyl ester (2.0 g, 4.57 mmol), THF (15 mL), B₂pin₂ (2.20 g, 8.66 mmol), KOAc (1.60 g, 16.3 mmol), PdCl₂(dppf)·DCM (0.40 g, 0.55 mmol). Purification: Biotage silica gel chromatography (hexanes/ ethyl acetate gradient) generated 0.50 g (26% yield) of the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 9.86 (s, 1H), 7.51 (dd, *J* = 8.2, 4.0 Hz, 1H), 7.34 - 7.31 (m, 5H), 7.21 (dd, *J* = 11.0, 8.2 Hz, 1H), 4.51 (s, 2H), 4.24 (td, *J* = 6.5, 2.0 Hz, 2H), 3.67 (t, *J* = 6.2 Hz, 2H), 2.11 - 2.07 (m, 2H); 1.33 (s, 12H); ¹⁹F NMR (376 MHz, DMSO-*d*₆ with D₂O) δ (ppm): -120.3 - -121.1 (m, 1F).

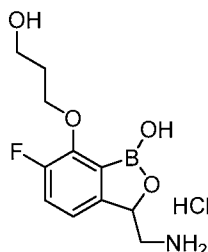
*7-(3-Benzyloxy-propoxy)-6-fluoro-3-nitromethyl-3H-benzo[*c*][1,2]oxaborol-1-ol*



[0327] Synthesized according to the methods of general procedure 8 in U.S. Pat. Pub. No. 20090227541 (U.S. Pat. App. No. 12/142,692) using the following reactants and amounts: 3-(3-benzyloxy-propoxy)-4-fluoro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde (0.40 g, 0.966 mmol), nitromethane (0.15 mL, 2.89 mmol), NaOH (0.038 g, 0.96 mmol), THF (10 mL), water (10 mL). This generated 0.34 g (94% yield) of the title compound. ¹H NMR (400 MHz, DMSO-*d*₆)

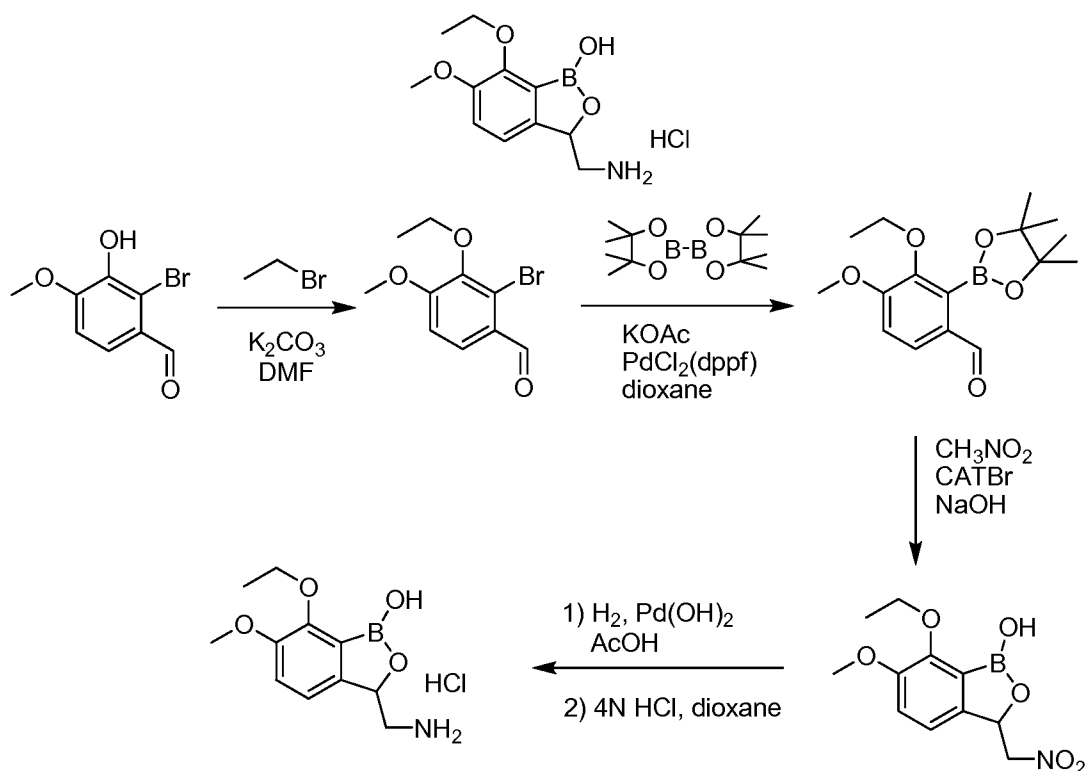
δ (ppm): 9.83 (s, 1H), 7.32 - 7.02 (m, 7H), 5.78 - 5.75 (m, 1H), 5.28 - 5.23 (m, 1H), 4.60 - 4.56 (m, 1H), 4.42 (s, 2H), 4.37 (brs, 2H), 3.57 (brs, 2H), 1.92 (brs, 2H). ^{19}F NMR (376 MHz, $\text{OMSO}-d_6$ with D_2O) δ (ppm): -132.3 (IF).

5 *3-Aminomethyl-6-fluoro-7-(3-hydroxy-propoxy)-3H-benzo[c][1,2]oxaborol-1-ol; hydrochloride salt*



[0328] To a mixture of 7-(3-benzyloxy-propoxy)-6-fluoro-3-nitromethyl-3H-benzo[c][1,2]oxaborol-1-ol (0.34 g, 0.906 mmol) and methanolic ammonia (2M, 20 mL) in a Parr apparatus was added $\text{Pd}(\text{OH})_2$ on carbon (0.30 g). The apparatus was charged with hydrogen (~ 40 psi) and was shaken overnight at rt. The suspension was filtered through Celite® with methanol washing and was concentrated in vacuo. The 310 mg of cream colored solid was dissolved in methanol (20 mL), transferred to Parr apparatus and the pH was adjusted to ~ 3 with a few drops of concentrated HCl. Then $\text{Pd}(\text{OH})_2$ on carbon (0.20 g) was added and the apparatus was charged with hydrogen (~ 40 psi). After 35 minutes, the suspension was filtered through Celite® with methanol washing and was concentrated in vacuo. Purification was accomplished by reverse phase preparative HPLC (acetonitrile/ water (0.1% AcOH) gradient) generating 100 mg (43% yield) of the title compound as a white solid. mp 265 - 267 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$ with D_2O) δ (ppm): 7.41 (dd, $J = 11.1, 8.2$ Hz, 1H), 7.07 (dd, $J = 7.9, 2.8$ Hz, 1H), 5.29 (d, $J = 7.0$ Hz, 1H), 4.36 (t, $J = 6.0$ Hz, 2H), 3.62 (br.s, 2H), 3.45 (d, $J = 12.9$ Hz, 1H), 2.92 - 2.86 (m, 1H), 1.93 - 1.83 (m, 2H); ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$ with D_2O) δ (ppm): -135.0 (IF); MS (ESI) $m/z = 256$ (M+1, positive); HPLC purity: 98.57% (MaxPlot 200-400 nm), 97.28% (220 nm).

S. **3-Aminomethyl-7-ethoxy-6-methoxy-3H-benzofcfl,2]oxaborol-1-ol;**
hydrochloric acid salt



5 **2-Bromo-3-ethoxy-4-methoxy-benzaldehyde**

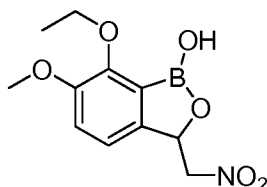
[0329] Ethyl bromide (2.88 g, 26.4 mmol) was added to a mixture of 2-bromo-3-hydroxy-4-methoxybenzaldehyde (5.08 g, 22 mmol) and potassium carbonate (4.56 g, 33 mmol) in anhydrous DMF (50 mL) at room temperature under nitrogen. The reaction mixture was stirred at 35 °C for 18 h, diluted with EtOAc (150 mL), washed with water (2x50 mL), brine, dried over Na₂SO₄ and concentrated to give crude product as a white solid. Purification by silica column chromatography (eluant : 30% EtOAc in Hexanes) to generate 5.65 g (99% yield) of the title compound as a white solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 10.26 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.95 (s, 3H), 1.46 (t, *J* = 7.0 Hz, 3H); MS (ESI) *m/z* = 261 (M+1, positive).

[3-Ethoxy-4-methoxy-2-(4,4,5,5-tetramethyl-f1,3,2]dioxaborolan-2-yl)-benzaldehyde

[0330] Synthesized according to the methods of general procedure 5 in U.S. Pat. Pub. No. 20090227541 (U.S. Pat. App. No. 12/142,692) using the following reactants and amounts: 2-bromo-3-ethoxy-4-methoxy-benzaldehyde (4 g, 15.43 mmol), KOAc (4.55 g, 46.29 mmol), bis(pinacolato)diboron (7.84 g, 30.86 mmol). PdCl₂(dppf) (0.91 g, 1.24 mmol) in dry dioxane (90 mL). The crude product was purified by silica gel column chromatography (eluant : EtOAc / hexanes 1:9 then 1:3) to afford the title

compound as a white solid (1.50 g, 32 % yield). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 9.71 (s, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 4.01 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 1.38 (s, 12H), 1.35 (t, *J* = 7.0 Hz, 3H).

7-Ethoxy-6-methoxy-3-nitromethyl-3H-benzo[c][1,2]oxaborol-1-ol



5

[0331] Synthesized according to the methods of general procedure 9 in U.S. Pat. Pub. No. 20090227541 (U.S. Pat. App. No. 12/142,692) using the following reactants and amounts: [3-ethoxy-4-methoxy-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde (1.47 g, 4.80 mmol), nitromethane (0.92 g, 14.4 mmol), CATBr (88 mg, 0.24 mmol) in dry THF (20 mL) and NaOH (0.025 M aqueous solution).

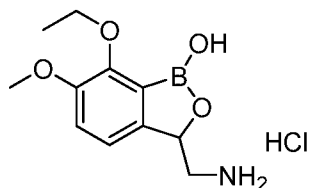
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Purification by silica gel column chromatography (eluant: 10% EtOAc/ hexane to 30% EtOAc/ hexane) to obtain the title compound as a yellow solid (0.75 g, 59 %>).

¹H NMR {400 MHz, DMSO-d₆ + D₂O (0.01 ml)} δ (ppm) 9.34 (s, 1H), 7.18 (d, *J* = 8.1 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 5.68 (dd, *J* = 9.2, 2.0 Hz, 1H), 5.29 (dd, *J* = 13.2, 2.8 Hz, 1H), 4.55-4.50 (m, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.77 (s, 3H), 1.27 (t, *J* = 7.0 Hz, 3H); MS (ESI) *m/z* = 261 (M-1, negative).

15

3-Aminomethyl-7-ethoxy-6-methoxy-3H-benzofcJfl,2Joxaborol-1-ol; hydrochloride salt



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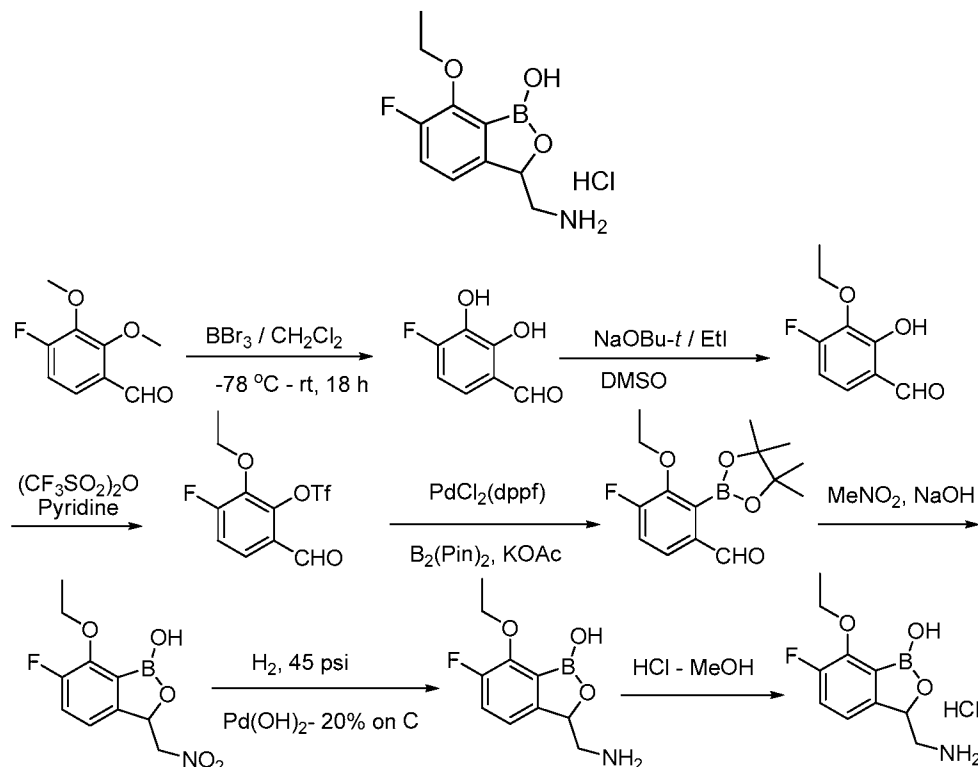
[0332] Synthesized according to the methods of general procedure 13 in U.S. Pat. Pub. No. 20090227541 (U.S. Pat. App. No. 12/142,692) using the following reactants and amounts: 7-Ethoxy-6-methoxy-3-nitromethyl-3H-benzo[c][1,2]oxaborol-1-ol (0.97 g, 3.63 mmol), glacial acetic acid (20 mL), Pd(OH)₂ on carbon (20%> metal content, 50%> weight- wet) (300 mg). Purification: preparative HPLC (CI 8 column, using acetonitrile and 0.1 % >AcOH/water solution) provided the title compound (0.28 g; 28% yield). m.p. 202-204 °C. ¹H NMR {400 MHz, CD₃OD} δ (ppm) 7.20 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 1H), 5.40 (dd, *J* = 8.4, 2.8 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.31 (s, 3H), 3.56 (dd, *J* = 13.6, 7.2 Hz, 1H), 2.92 (dd, *J* = 13.2, 7.2 Hz 1H),

25

1.33 (t, $J = 7$ Hz, 3H); MS (ESI) $m/z = 238$ (M+1, positive); HPLC purity: 98.79% (MaxPlot 200 - 400 nm) and 99.13% (220 nm).

**T. 3-Aminomethyl-7-ethoxy-6-fluoro-3H-benzofcJfl,2Joxaborol-1-ol;
hydrochloride salt**

5



4-Fluoro-2,3-dihydroxybenzaldehyde

[0333] To a solution at -78 °C of 2,3-dimethoxy-4-fluorobenzaldehyde (7.0 g, 38.0 mmol) in dry dichloromethane (150 mL) was added dropwise BBr₃ (23.8 g, 95.0 mmol) in dichloromethane (30 mL). Reaction mixture was allowed to attain room temperature and stirred for 18 h. Then reaction mixture was cooled to -78 °C, and quenched with a mixture of methanol (10 mL) and water (50 mL) and stirred at room temperature for 30 min. Precipitated solid was separated by filtration and washed with cold dichloromethane. Dichloromethane layer was concentrated to yield the title compound as a solid (5.2 g, 88%). ¹H NMR (400 MHz, CHLOROFORM- α) δ ppm: 11.38 (s, 1 H), 9.84 (s, 1 H), 7.15 (dd, $J=8.6, 5.5$ Hz, 1 H), 6.81 (t, $J=9.4$ Hz, 1 H), 5.47 (s, 1 H); MS (ESI) $m/z = 155$ (M-1, negative).

3-Ethoxy-4-fluoro-2-hydroxybenzaldehyde

[0334] To a solution of 2,3-dihydroxy-4-fluorobenzaldehyde (3.0 g, 19.23 mmol) in DMSO (100 mL), NaOBu-*t* (3.692 g, 38.46 mmol) was added in portions at room temperature and stirred for 15 min. Then iodoethane was added dropwise at room

temperature and stirred for 18 h. The reaction mixture was poured onto crushed ice (200 mL) and acidified with 2.5 M HCl to pH 3.0. The product was extracted with ethyl acetate (2 x 100 mL), concentrated and the product was chromatographed on a column of silica gel (Hex:EtOAc = 95:5) to give the title compound as a crystalline solid (2.3 g, 65%). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm: 11.36 (s, 1 H), 9.83 (s, 1 H), 7.39 - 7.19 (m, 1 H), 6.77 (t, *J*=9.2 Hz, 1 H), 4.22 (q, *J*=7.0 Hz, 2 H), 1.40 (t, *J*=7.0 Hz, 3 H); MS (ESI) *m/z* = 183 (*M*+1, positive).

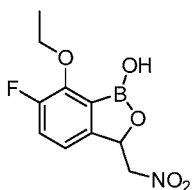
Trifluoromethanesulfonic acid 2-ethoxy-3-fluoro-6-formyl-phenyl ester

[0335] To a mixture of 3-ethoxy-4-fluoro-2-hydroxybenzaldehyde (2.208 g, 12.0 mmol) and pyridine (1.986 g, 24.0 mmol) in dichloromethane (30.0 mL) at 0 °C was added dropwise trifluoromethanesulfonic anhydride (4.060, 14.4 mmol) in dichloromethane (5.0 mL). The reaction mixture was stirred at 0 °C for 2 h and room temperature for 3 h. Then diluted with dichloromethane (40 mL), washed with 2M HCl, brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give the title compound as a light yellow liquid (3.3 g, 87%). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm: 10.15 (s, 1 H), 7.66 (dd, *J*=8.6, 5.5 Hz, 1 H), 7.28 - 7.22 (m, 1 H), 4.36 (q, *J*=6.9 Hz, 2 H), 1.47 (t, *J*=7.0 Hz, 3 H).

3-Ethoxy-4-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-benzaldehyde

[0336] To a solution of trifluoromethanesulfonic acid 2-ethoxy-3-fluoro-6-formyl-phenyl ester (2.2 g, 6.96 mmol) in dry THF (35.0 mL) bis(pinacolato)diboron (2.134 g, 8.4 mmol), PdCl₂(dppf) (367 mg, 0.5 mmol) and potassium acetate (1.372 g, 14.0 mmol) were added and purged with nitrogen for 15 min. The reaction mixture was heated under reflux for 24 h. Cooled to room temperature and diluted with ethyl acetate (40 mL) and filtered through Celite. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel (Hex:EtOAc = 9:1) to give the title compound as an off-white solid (850.0 mg, 42 %). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm: 9.87 (s, 1 H), 7.51 (dd, *J*=8.2, 4.3 Hz, 1 H), 7.22 (dd, *J*=10.9, 8.6 Hz, 1 H), 4.20 (q, *J*=7.0 Hz, 2 H), 1.46 (s, 12 H), 1.40 (t, *J*=7.0 Hz, 3 H); MS (ESI) *m/z* = 295 (*M*+1, positive).

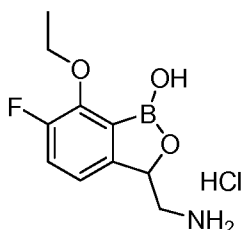
7-Ethoxy-6-fluoro-3-nitromethyl-3H-benzo[c][1,2]oxaborol-1-ol



[0337] To a cooled solution of sodium hydroxide (80 mg, 2.0 mmol) in water (3.0 mL), nitromethane (244.0 mg, 4.0 mmol) was added at 0 °C and stirred for 10 min.

- 5 Then 3-ethoxy-4-fluoro-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde (588.0 mg, 2.0 mmol) in THF (5.0 mL) was added. The reaction mixture was stirred at for 1 h at 0 °C and for 2 h at room temperature. The reaction mixture was acidified with 2.5 M HCl (1.0 mL) and the product was extracted with ethyl acetate (2 x 20 mL). The organic extracts were combined and washed with brine
- 10 and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and product was chromatographed on a column of silica gel(CH₂Cl₂ : MeOH = 95:5) to give the title compound as a solid (350 mg, 69%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 7.40 (dd, *J*=11.3, 8.2 Hz, 1 H), 7.16 (dd, *J*=8.0, 3.3 Hz, 1 H), 5.74 (d, *J*=9.0 Hz, 1 H), 5.30 (dd, *J*=13.5, 2.2 Hz, 1 H), 4.62 (dd, *J*=13.5, 9.2 Hz, 1 H),
- 15 4.35 (q, *J*=6.8 Hz, 2 H), 1.28 (t, *J*=6.8 Hz, 3 H); MS (ESI) *m/z* = 254 (M-1, negative).

3-Aminomethyl-7-ethoxy-6-fluoro-3H-benzo[c][1,2]oxaborol-1-ol; hydrochloride salt



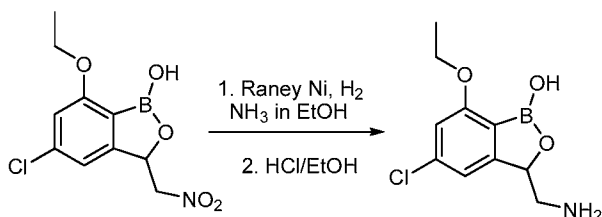
- [0338] To a solution of 7-ethoxy-6-fluoro-3-nitromethyl-3H-benzo[c][1,2]oxaborol-1-ol (320.0 mg, 1.25 mmol) in methanol (5.0 mL), 5.0 mL of
- 20 2M ammonia in methanol and 160 mg of Pd(OH)₂ on C were added and hydrogenated at 45 PSI for 18 h. Catalyst was removed by filtration and the filtrate was concentrated to generating an off-white solid (250 mg). This solid was dissolved in methanol (3 mL) and 3.0 mL of 1.2 M HCl in methanol was added and stirred at room temperature for 3 h. Excess HCl and solvent were removed under reduced pressure
- 25 and the product was triturated with ether to give the title compound as an off-white solid (140 mg, 43%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 9.43 (s, 1 H), 8.13 (br. s., 3 H), 7.40 (dd, *J*=11.5, 8.0 Hz, 1 H), 7.16 (dd, *J*=7.8, 3.1 Hz, 1 H), 5.32 (d, *J*=6.3

5-Chloro-3-ethoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde

[0341] A mixture of 4-chloro-2-ethoxy-6-formylphenyl trifluoromethanesulfonate (330 mg, 1 mmol), KOAc (350 mg, 2.0 mmol), bis(pinacolato)diborane (600 mg, 2.0 mmol) and PdCl₂(dppf)CH₂Cl₂ (65 mg, 0.08 mmol, 8 mol%) in dioxane (30 mL) was degassed for 15 min with N₂ and stirred at 100 °C for 3 h. After quenched with ice-water, the reaction mixture was extracted with EtOAc (3x30 mL). The combined organic layers were washed with sat. aqueous NaHCO₃ (20 mL) and brine (20 mL), dried over anhydrous Na₂SO₄ and then concentrated. The residue was purified by column chromatography on silica gel to give the compound (150 mg, yield: 43%).

5-Chloro-7-ethoxy-3-(nitromethyl)benzo[c][1,2]oxaborol-1(3H)-ol

[0342] The mixture of 5-chloro-3-ethoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (310 mg, 1 mmol), NaOH (40 mg, 1 mmol) and CTAB (5 mg, 0.05 mmol) in H₂O (2 mL) and THF (10 mL) was stirred for 0.5 h at room temperature. After dropwise addition of nitromethane (0.2 mL, 2 mmol), the reaction mixture was stirred at room temperature for 3 h. Then the cyclization was afforded by adding the diluted aqueous HCl solution (2 N) to pH=2 and then extracted with EtOAc (3x30 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na₂SO₄ and concentrated to dryness. The residue was purified by prep-HPLC to give the compound (100 mg, yield: 56%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.20 (s, 1 H), 7.22 (s, 1H), 6.96 (s, 1H), 5.69-5.72 (m, 1H), 5.30-5.34 (m, 1H), 4.61-4.67 (m, 1H), 4.10-4.15 (m, 2H), 1.31-1.34 (m, 3H);

3-(Aminomethyl)-5-chloro-7-ethoxybenzo[c][1,2]oxaborol-1(3H)-ol

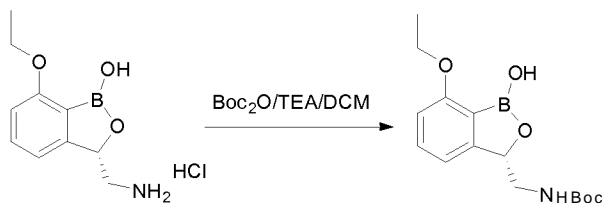
[0343] A mixture of 5-chloro-7-ethoxy-3-(nitromethyl)benzo[c][1,2]oxaborol-

1(3H)-ol (270 mg, 1.0 mmol), Raney-Ni (-125 mg) and 2 M NH₃ in EtOH (2 mL) in EtOH (10 mL) was shaken under an atmosphere of H₂ for 2 h at room temperature. The mixture was filtered through a bed of Celite and the filtrate was concentrated in vacuo. The crude amine was dissolved in EtOAc (2 mL) and HCl solution in Et₂O (20 mL) was added immediately. After 1 h, the suspension was filtered and the resulting solid was washed with hexanes to give compound the target compound (100

mg, yield: 43%). ^1H NMR (400 MHz, DMSO- d_6) δ 9.06 (s, 1H), 8.18 (s, 3H), 7.22 (s, 1H), 6.96 (s, 1H), 5.27-5.29 (m, 1H), 4.10-4.13 (m, 2H), 3.40-3.47 (m, 1H), 2.87-2.92 (m, 1H), 1.30-1.36 (m, 3H); MS (ESI) m/z = 242 $[\text{M} + \text{H}]^+$.

V. *(S)*-3-(aminomethyl)-4-bromo-7-ethoxybenzo[c][1,2]oxaborol-1(3H)-ol hydrochloride

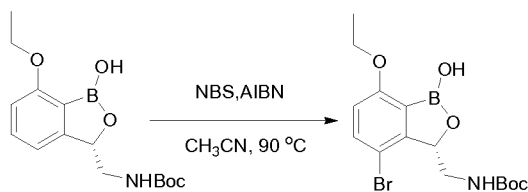
Step 1: *tert*-butyl (7-ethoxy-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)methyl-carbamate



[0344] To the mixture of 3-(aminomethyl)-7-ethoxybenzo[c][1,2]oxaborol-1(3H)-

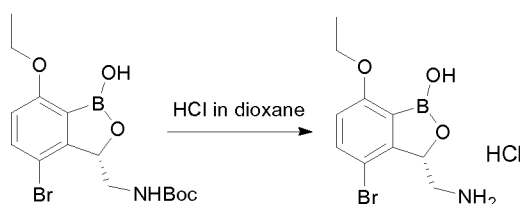
ol hydrochloride salt (5.0 g, 20.5 mmol) and triethylamine (10.4 g, 103.0 mmol) in dichloromethane (250 mL) at 0°C was added di-*tert*-butyl dicarbonate (6.7 g, 30.8 mmol). The mixture was stirred for 4 h at room temperature. After the reaction was quenched with sat. NaHCO_3 (500 mL), the resulting mixture was extracted with EtOAc (3x300 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacum. The residue was purified by flash-column chromatography (2.5 % to 5.0 % MeOH in DCM) to give the product (5.51 g, yield 87%).

Step 2: *tert*-butyl (4-bromo-7-ethoxy-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)-methylcarbamate



[0345] To the solution of *tert*-butyl (7-ethoxy-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-3-yl)methyl-carbamate (5.5 g, 17.9 mmol) and 1-bromopyrrolidine-2,5-dione (3.8 g, 21.5 mmol) in CH_3CN (1100 mL) was added 2,2'-Azobis(2-methylpropionitrile) (220 mg). The mixture was stirred for 1 h at 90 °C. The reaction mixture was then concentrated in high vacuum and the residue was purified by column chromatography (2.5 % to 5.0 % MeOH in DCM) to give the product (3.7 g, yield 54%). ^1H NMR (300 MHz, DMSO- d_6) δ 8.90 (s, 1H), 7.55-7.53 (d, 1H), 6.85-6.82 (d, 1H), 5.08-5.07 (d, 1H), 4.11-4.07 (m, 2H), 3.82-3.79 (bd, 1H), 3.06-3.03 (m, 1H), 1.39 (s, 9H), 1.30 (t, 3H); MS (ESI) m/z = 387 $[\text{M} + \text{H}]^+$.

Step 3: (*S*)-3-(aminomethyl)-4-bromo-7-ethoxybenzo[*c*][1,2]oxaborol-1(3*H*)-ol hydrochloride



[0346] The mixture of *tert*-butyl (4-bromo-7-ethoxy-1-hydroxy-1,3-

5 dihydrobenzo[*c*][1,2]oxaborol-3-yl)-methylcarbamate (3.7 g, 9.6 mmol) in 4N HCl in dioxane (12 ml, 48.0 mmol) was stirred at room temperature for 2 h and then concentrated to dryness (water bath < 30 °C). The residue was triturated with DCM/ether (1/10, 2x10 mL) and the white solid was dried in high vacuum to give the product (2.96 g, yield: 92%). ¹H NMR (300 MHz, *OMSO-d*₆) 9.11 (s, 1H), 8.1 (bs, 3H), 7.63-7.60 (d, 1H), 6.92-6.89 (d, 1H), 5.27-5.24 (m, 1H), 4.12-4.05 (m, 2H), 3.62-3.57 (m, 1H), 2.99-2.92 (m, 1H), 1.34-1.30 (t, 3H); MS (ESI) *m/z* = 287 [M + H]⁺.

EXAMPLE 2

LeuRSIC50 Testing

[0347] Experiments were performed in 96-well microtiter plates, using 80 μL reaction mixtures containing 50 mM HEPES-KOH (pH 8.0), 30 mM MgCl₂ and 30 mM KCl, 13 μM [¹⁴C]leucine (306 mCi/mmol, Perkin-Elmer), 15 uM total E.coli tRNA (Roche, Switzerland), 0.02% (w/v) BSA, 1 mM DTT, 0.2 pM LeuRS and 4 mM ATP at 30°C. Reactions were started by the addition of 4 mM ATP. After 7 minutes, reactions were quenched and tRNA was precipitated by the addition of 50 μL of 10% (w/v) TCA and transferred to 96-well nitrocellulose membrane filter plates (Millipore Multiscreen HTS, MSHAN4B50). Each well was then washed three times with 100 μL of 5% TCA. Filter plates were then dried under a heat lamp and the precipitated [¹⁴C]leucine tRNA^{Leu} was quantified by liquid scintillation counting using a Wallac MicroBeta Trilux model 1450 liquid scintillation counter (PerkinElmer, Waltham MA).

[0348] To determine the inhibitor concentration which reduces enzyme activity by 50% (IC₅₀), increasing concentrations of inhibitor were incubated with LeuRS enzyme, tRNA and leucine for 20 minutes. Reactions were initiated by the addition of 4 mM ATP and stopped after 7 minutes then precipitated and counted to quantify radioactivity.

[0349] Biochemical testing results for exemplary compounds of the invention are provided in **FIG. 1**.

EXAMPLE 3

Antibacterial MIC Testing

5 [0350] All MIC testing of bacteria followed the Clinical and Laboratory Standards Institute (CLSI) guidelines for antimicrobial testing of aerobic bacteria (Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard - Seventh Edition)(M07-A7) and anaerobic bacteria (Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard -
10 Seventh Edition) (M11-A7).

[0351] Antibacterial MIC testing results for exemplary compounds of the invention are provided in **FIG. 1**.

EXAMPLE 4

Microplate Alamar Blue Assay (MABA)

15 [0352] The microplate alamar blue assay (MABA) was essentially performed as described by Collins, L., *et al.*, *Antimicrob Agents Chemother* 41: 1004-1009 (1997). For example, black, clear-bottomed 96-well microplates (black view plates; Packard Instrument Company, Meriden, Conn.) with the outer perimeter wells filled with sterile water to prevent dehydration in experimental wells. Initial drug dilutions were
20 prepared in dimethyl sulfoxide and subsequent two fold dilutions were performed in 0.1 ml of 7H9GC (no Tween 80) in the microplates. Frozen inocula were initially diluted 1:20 in BACTEC 12B medium followed by a 1:50 dilution in 7H9GC. Addition of 100 μ L to wells resulted in final bacterial titers of between 2.0×10^5 and 5×10^4 CFU/mL for H37Rv and H37Ra, respectively. Wells containing drug only
25 were used to detect autofluorescence of compounds plus additional control wells consisted of bacteria only (B) and medium only (M). Plates were incubated at 37°C. Starting at day 4 of incubation, 20 μ L of IOx alamar Blue solution (Alamar Biosciences/ Accumed, Westlake, Ohio) and 12.5 μ L of 20% Tween 80 were added to one B well and one M well, and plates were reincubated at 37°C. Wells were
30 observed at 12 and 24 h for a color change from blue to pink and for a reading of greater than or equal to 50,000 fluorescence units (FU). Fluorescence was measured in a Cytofluor II microplate fluorometer (PerSeptive Biosystems, Framingham, Mass.)

in bottom-reading mode with excitation at 530 nm and emission at 590 nm. If the B wells became pink by 24 h, reagent was added to the entire plate. If the well remained blue or 50,000 FU was measured, additional M and B wells were tested daily until a color change occurred, at which time reagents were added to all remaining wells.

- 5 Plates were then incubated at 37°C, and results were recorded at 24 h post-reagent addition. Visual MICs were defined as the lowest concentration of drug that prevented a color change. For fluorometric MICs, a background subtraction was performed on all wells with a mean of triplicate M wells. Percent inhibition was defined as $1 - (\text{test well FU} / \text{mean FU of triplicate B wells}) \times 100$. The lowest drug
10 concentration effecting an inhibition of 90% was considered the MIC.

[0353] Biochemical testing results for exemplary compounds of the invention are provided in **FIG. 1**.

EXAMPLE 5

Low Oxygen Recovery Assay (LORA)

- 15 [0354] The low-oxygen recovery assay (LORA) was essentially performed as described by Cho *et al. Antimicrob Agents Chemother* 51: 1380-1385 (2007). A recombinant *M. tuberculosis* H₃₇R_v bearing luxAB on a plasmid, pFCA-luxAB, was used in all the LORA experiments. Frozen aliquots from a low oxygen adapted culture were thawed, diluted in Middlebrook 7H12 broth (Middlebrook 7H9 broth
20 containing 1 mg/mL Casitone, 5.6 µg/mL palmitic acid, 5 mg/mL bovine serum albumin, and 4 µg/ml filter-sterilized catalase), and sonicated for 15s. The cultures were diluted to obtain an A₅₇₀ of 0.03 to 0.05 and 3,000 to 7,000 RLUs per 100 µL. This corresponds to 5 x 10⁵ to 2 x 10⁶ CFU/mL. Twofold serial dilutions were prepared in a volume 100 µL in black 96-well microtiter plates, and 100 µL of the cell
25 suspension was added. For LORA, the microplate cultures were placed under anaerobic conditions (oxygen concentration, less than 0.16%) by using an Anoxomat model WS-8080 (MART Microbiology) and three cycles of evacuation and filling with a mixture of 10% H₂, 5% CO₂, and 85% N₂. An anaerobic indicator strip was placed inside the chamber to visually confirm the removal of oxygen. The plates were
30 incubated at 37°C for 10 days and then transferred to an ambient gaseous condition (5% CO₂-enriched air) incubator for a 28-h "recovery." On day 11 (after the 28-h aerobic recovery), 100 µL culture was transferred to white 96-well microtiter plates

for determination of luminescence. A 10% solution of n-decanal aldehyde (Sigma) in ethanol was freshly diluted 10-fold in PBS, and 100 μ l was added to each well with an autoinjector. Luminescence was measured in a Victor2 multilabel reader (Perkin-Elmer Life Sciences) by using a reading time of 1 s. The MIC was defined as the lowest drug concentration effecting growth inhibition of 90% relative to the growth for the drug-free controls.

[0355] Biochemical testing results for exemplary compounds of the invention are provided in FIG. 1.

EXAMPLE 6

10 Tuberculosis in vivo efficacy experiments

[0356] The TB *in vivo* efficacy experiments were essentially performed as described in Lenaerts *et al. Antimicrob Agents Chemother* 47: 783-785 (2003) with a few modifications. A highly susceptible gamma interferon specific pathogen-free C57BL/6-Ihgtmlts (GKO) mice (Jackson Laboratories, Bar Harbor, Maine) were exposed to a low-dose aerosol infection with *M. tuberculosis* strain Erdman in a Glas-Col inhalation exposure system as previously described in Kelly *et al. Antimicrob Agents Chemother* 40: 2809-2812 (1996). Every treatment group consisted of five mice for every following time point. Treatment was started 10 days after infection. One control group of infected mice was sacrificed at the start of treatment. A second group of infected but untreated mice was sacrificed after the cessation of treatment at 24 days. C and L were formulated in saline and E was formulated in 50% water/35% PEG400/5% PG, while rifampicin was formulated in 20% cyclodextrin. All compounds were administered by oral gavage. Rifampicin was dosed at 10 mg/kg QD PO. C was dosed at 100 mg/kg BID PO. E was dosed at 100 mg/kg BID PO. L was dosed at 100 mg/kg QD PO. After completion of therapy, the mice were sacrificed by carbon dioxide inhalation. Lungs were aseptically removed and disrupted in a tissue homogenizer. The number of viable organisms was determined by serial dilution of the homogenates on nutrient Middlebrook 7H1 1 agar plates (GIBCO BRL, Gaithersburg, Md.). The plates were incubated at 37°C in ambient air for 4 weeks prior to the counting of viable *M. tuberculosis* colonies (CFU).

30 [0357] On day 3, the control group had a mean log₁₀ CFU/lung of 2.83 (0.40). On day 10, the control group had a log₁₀ CFU/lung of 4.81 (0.08). On day 24, the control group had a log₁₀ CFU/lung of 8.96 (0.14). On day 24, the group treated with rifampicin had a log₁₀ CFU/lung of 6.16 (0.10). On day 24, the group treated with C

had a log₁₀ CFU/lung of 5.06 (0.26). On day 24, the group treated with E had a log₁₀ CFU/lung of 2.73 (0.05). On day 24, the group treated with L had a log₁₀ CFU/lung of 3.08 (0.06).

EXAMPLE 7

5 **Tuberculosis in vivo efficacy experiments**

[0358] The TB *in vivo* efficacy experiments were essentially performed as described in Lenaerts *et al. Antimicrob Agents Chemother* 47: 783-785 (2003) with a few modifications. A highly susceptible gamma interferon specific pathogen-free C57BL/6-Ifngtm^{lts} (GKO) mice (Jackson Laboratories, Bar Harbor, Maine) were exposed to a low-dose aerosol infection with *M. tuberculosis* strain Erdman in a Glas-Col inhalation exposure system as previously described in Kelly *et al. Antimicrob Agents Chemother* 40: 2809-2812 (1996). Every treatment group consisted of five mice for every following time point. Treatment was started 13 days after infection. One control group of infected mice was sacrificed at the start of treatment. A second group of infected but untreated mice was sacrificed after the cessation of treatment at 22 days. N was formulated in saline and E was formulated in 50% water/35% PEG400/5% PG, while Isoniazid (INH) was formulated in distilled water. All compounds were administered by oral gavage. INH was dosed at 25 mg/kg QD PO. E was dosed at 100 mg/kg QD PO. N was dosed at 100 mg/kg BID PO. After completion of therapy, the mice were sacrificed by carbon dioxide inhalation. Spleens and lungs were aseptically removed and disrupted in a tissue homogenizer. The number of viable organisms was determined by serial dilution of the homogenates on nutrient Middlebrook 7H11 agar plates (GIBCO BRL, Gaithersburg, Md.). The plates were incubated at 37°C in ambient air for 4 weeks prior to the counting of viable *M. tuberculosis* colonies (CFU).

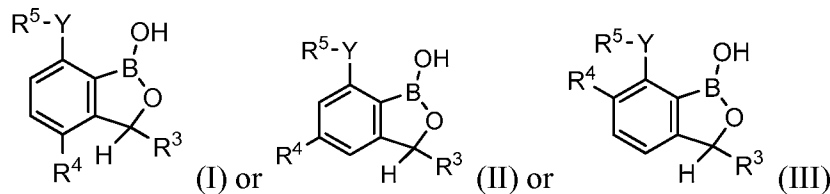
[0359] On day 13, the control group had a mean log₁₀ CFU of 7.02 (0.08) for lungs and mean log₁₀ CFU for spleens of 3.99 (0.21). On day 22, the control group had a log₁₀ CFU for lungs of 7.82 (0.11) and spleens of 6.69 (0.08). On day 22, the group treated with INH had a log₁₀ CFU for lungs of 5.29 (0.13) and for spleens of 4.27 (0.25). On day 22, the group treated with E had a log₁₀ CFU for lungs of 5.27 (0.12) and for spleens of 4.27 (0.25). On day 22, the group treated with N had a log₁₀ CFU for lungs of 5.51 (0.09) and spleens of 2.42 (0.48).

[0360] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light

thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

WHAT IS CLAIMED IS:

1 **1.** A compound having a structure which is:



3 wherein R^3 is substituted or unsubstituted nitroalkyl or substituted or unsubstituted
4 aminoalkyl;

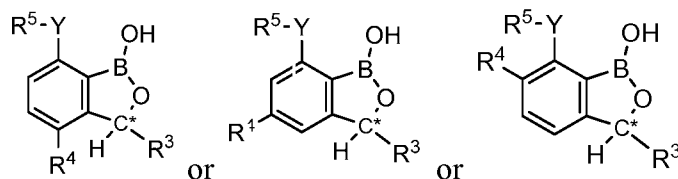
5 R^4 is selected from the group consisting of halogen, unsubstituted alkyl,
6 unsubstituted alkoxy, and unsubstituted phenyl;

7 Y is O or S; and

8 R^5 is selected from the group consisting of substituted or unsubstituted alkyl
9 and substituted or unsubstituted heteroalkyl;

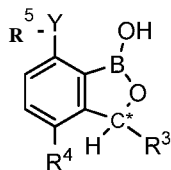
10 or a salt, hydrate or solvate thereof.

1 **2.** The compound of claim 1, having a structure which is:



3 wherein C^* is a carbon atom stereocenter which has a configuration which is (R) or
4 (S).

1 **3.** The compound of claim 1, having a structure which is



2 wherein the C^* is a carbon atom stereocenter which has a configuration which is (R)
3 or (S).

1 **4.** The compound of claim 2, wherein the C^* stereocenter is in a
2 (S) configuration.

1 **5.** The compound of claim 1, wherein R^3 is $-CH_2NH_2$.

- 1 **6.** The compound of claim **1**, wherein R^4 is selected from the
2 group consisting of fluorine, chlorine, bromine, and iodine.
- 1 **7.** The compound of claim **1**, wherein Y is O.
- 1 **8.** The compound of claim **1**, wherein R^5 is selected from the
2 group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, and sec-
3 butyl.
- 1 **9.** The compound of claim **1**, wherein R^3 is $-CH_2NH_2$; and R^4 is
2 halogen.
- 1 **10.** The compound of claim **1**, wherein R^3 is $-CH_2NH_2$; R^4 is
2 chlorine; Y is O; and R^5 is substituted or unsubstituted alkyl.
- 1 **11.** A composition comprising:
2 a) a first stereoisomer of the compound of claim **2**;
3 b) at least one additional stereoisomer of the first stereoisomer;
4 wherein the first stereoisomer is present in an enantiomeric excess of at least
5 80% relative to said at least one additional stereoisomer.
- 1 **12.** A combination comprising the compound of claim **1**, or a
2 pharmaceutically acceptable salt thereof, together with at least one other
3 therapeutically active agent.
- 1 **13.** A pharmaceutical formulation comprising:
2 a) the compound of claim **1**, or a pharmaceutically acceptable salt thereof; and
3 b) a pharmaceutically acceptable excipient.
- 1 **14.** A method of inhibiting an enzyme, comprising: contacting the
2 enzyme with the compound of claim **1**, thereby inhibiting the enzyme.
- 1 **15.** A method of killing and/or preventing the growth of a
2 microorganism, comprising: contacting the microorganism with an effective amount

3 of the compound of claim 1, thereby killing and/or preventing the growth of the
4 microorganism.

1 **16.** A method of treating and/or preventing a disease in an animal,
2 comprising: administering to the animal a therapeutically effective amount of the
3 compound of claim 1, or a pharmaceutically-acceptable salt thereof, thereby treating
4 and/or preventing the disease.

1 **17.** The method of claim 16, wherein the disease is tuberculosis.

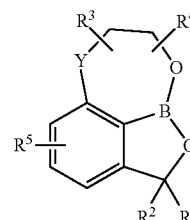
1 **18.** The method of claim 16, wherein the animal is a human.

1 **19.** A method of inhibiting the editing domain of a t-RNA
2 synthetase, comprising: contacting the synthetase with an effective amount of a
3 compound of claim 1, or a pharmaceutically-acceptable salt thereof, thereby inhibiting
4 the synthetase.

1 **20.** The use of a compound of claim 1 or a combination of claim 12
2 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for
3 the treatment and/or prophylaxis of bacterial infection

Figure 1

Compound #	A. baumannii ATCC 17978 MIC	E. coli ATCC 25922 MIC	H. influenzae ATCC 49766 MIC	K. pneumoniae ATCC 13883 MIC	P. aeruginosa ATCC 27853 MIC	MABA M. tuberculosis H37Rv MIC	LORA M. tuberculosis H37Rv MIC	M. tuberculosis LeuRS IC50 (uM)
A	16	6	3	6	20	0.37	>64	0.97
B	>64	>64	2	>64	>64	<0.025	>64	0.13
C	8	4	1	4	>64	0.04	0.52	0.13
D	>64	>64	0.5	>64	>64	<0.02	0.07	0.09
E	>64	>64	1	>64	>64	0.05	0.70	0.07
F	>64	>64	NT	>64	>64	<0.2	26.20	0.2
G	8	16	NT	8	>64	<0.2	31.90	0.31
H	>64	>64	NT	>64	>64	16.80	48.46	27.6
I	>64	>64	NT	>64	>64	0.30	<0.391	0.04
J	>64	>64	NT	>64	>64	0.59	0.69	0.03
K	>64	>64	>64	>64	>64	>64	NT	NT
L	>64	64	<0.12	32	>64	<0.004	<0.039	0.02
M	>64	>64	NT	>64	>64	NT	NT	21.02
N	1.5	0.5	NT	1	3	NT	NT	0.09
O	32	0.74	8	8	64	0.28	>64	0.91
P	32	NT	4	8	32	1.91	>64	0.896
Q	32	1.1	16	8	64	3.73	>64	0.878
R	>64	1.6	16	8	64	1.01	>64	0.892
S	>64	1.1	8	8	64	0.88	>50	0.61
T	16	1.345292	16	8	16	NT	NT	0.895
U	16	1.231968	4	8	>64	0.33	5.91	NT
V	>64	>64	32	64	>64	NT	NT	0.114

(19) **United States**(12) **Patent Application Publication**
GORDEEV et al.(10) **Pub. No.: US 2013/0165411 A1**(43) **Pub. Date: Jun. 27, 2013**(54) **TRICYCLIC BORON COMPOUNDS FOR
ANTIMICROBIAL THERAPY**(71) Applicant: **MICURX PHARMACEUTICALS,
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INC.**, George Town (KY)(21) Appl. No.: **13/722,912**(22) Filed: **Dec. 20, 2012****Related U.S. Application Data**(60) Provisional application No. 61/579,271, filed on Dec.
22, 2011.**Publication Classification**(51) **Int. Cl.**
C07F 5/02 (2006.01)(52) **U.S. Cl.**CPC **C07F 5/025** (2013.01)USPC **514/64; 558/290**(57) **ABSTRACT**Provided herein are antimicrobial tricyclic boron compounds
of the following formula I:

I

or pharmaceutically acceptable salts, complexes, or tau-
tomers thereof that are antibacterial agents, pharmaceutical
compositions containing them, methods for their use, and
methods for preparing these compounds.

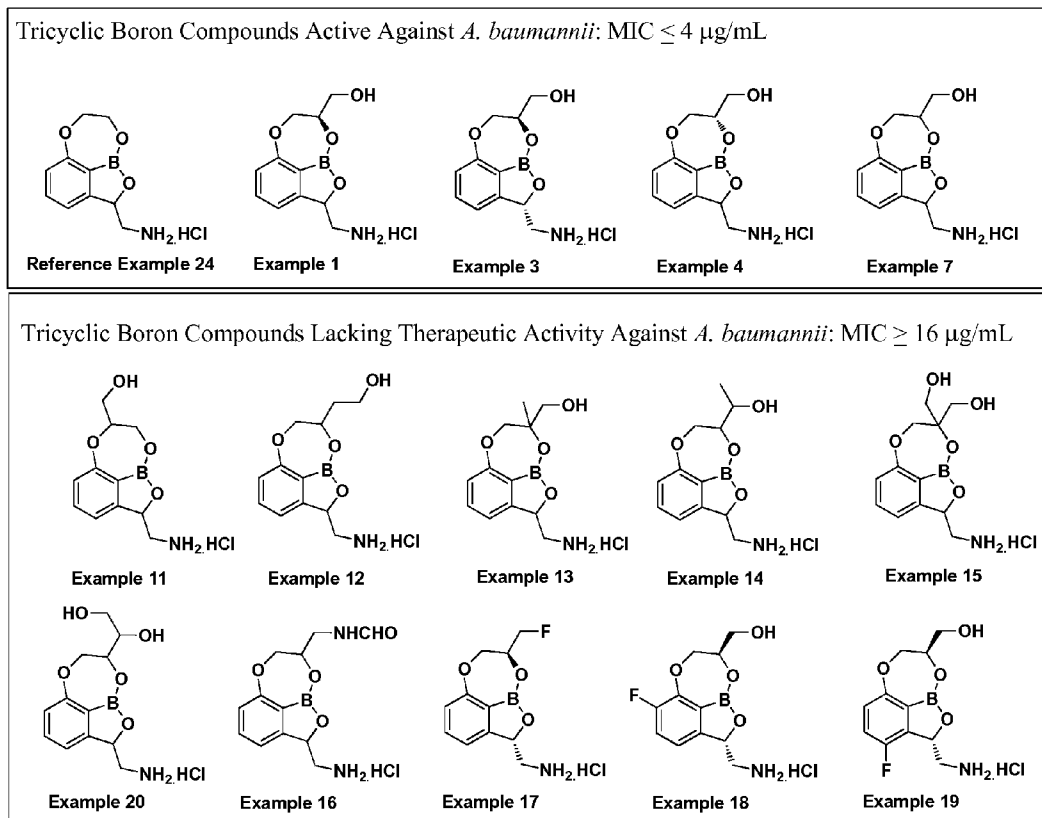


Figure 1

US 2013/0165411 A1

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TRICYCLIC BORON COMPOUNDS FOR ANTIMICROBIAL THERAPY

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit under 35 U.S.C. §119 of, and priority to, provisional application No. 61/579,271 entitled "Novel Tricyclic Boron Compounds for Antimicrobial Therapy", filed Dec. 22, 2011, the content of which is hereby incorporated by reference in its entirety.

FIELD

[0002] Provided herein are antimicrobial boron-organic compounds, pharmaceutical compositions thereof, methods for their use, and methods for preparing of the same. The compounds provided herein possess useful activity against bacterial species.

BACKGROUND

[0003] Owing to an increasing bacterial resistance, novel classes of antibacterial compounds are needed for the treatment of microbial infections. Agents acting via a new mechanism of action are desired to avoid undesired cross-resistance with existing drugs. Said agents are required to possess useful activity against key mammalian pathogens, including Gram-negative bacteria, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Escherichia coli*, and *Klebsiella pneumoniae*, as well as key Gram-positive bacteria such as multidrug-resistant staphylococci and streptococci, certain anaerobe pathogens such as *bacteroides* and *clostridia* species, such as *Clostridium difficile*, and acid-fast microorganisms, including *Mycobacterium tuberculosis* and *Mycobacterium avium*. These agents are also needed for treatment of serious parasitic infections, such as Trypanosomiasis.

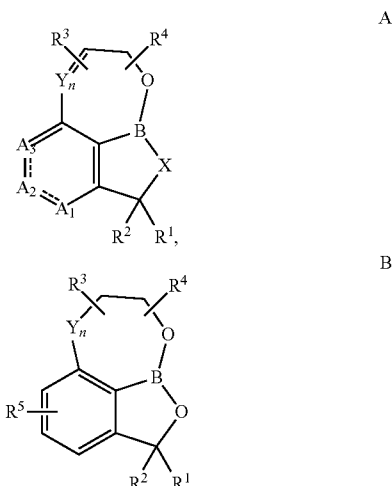
[0004] Several antibacterial boron-organic compounds have been previously described in the publications PCT WO 2005/013892, PCT WO 2007/131072, PCT WO 2008/157726, US 2009/0227541, US 2009/0239824, WO 2009/140309, PCT WO 2010/080558, PCT WO 2011/017125, and PCT WO 2012/033858. To date, no compound of this class has been approved for anti-infective therapy in human.

[0005] None of the aforementioned specifically contemplates any compound provided herein, its combination therapy, and/or its composition.

SUMMARY

[0006] Provided herein are pharmaceutical compounds with high antibacterial activity, including activity against Gram-negative and Gram-positive microorganisms, as well as against mycobacteria. These compounds are particularly active against Gram-negative bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Escherichia coli*, and *Klebsiella pneumoniae*. Said compounds are also active against yeast and fungi microorganism, such as *Candida albicans* or *Cryptococcus neoformans*. Certain compounds provided herein are also active against parasitic protozoan pathogens, such as *Trypanosoma brucei gambiense* or *Trypanosoma brucei rhodesiensis*.

[0007] Provided herein are compounds of the following formula A or B:



or a pharmaceutically acceptable salt, complex, or tautomer thereof, wherein:

R¹ and R² are independently H, F, C₁₋₆alkyl, C₁₋₆heteroalkyl, C₃₋₆cycloalkyl, C₁₋₆(amino)alkyl, aminomethyl, hydroxymethyl, C₁₋₆alkylNH₂, C₁₋₆alkylOH, C₁₋₆alkylNR₂, OC₁₋₆alkylNH₂, C₁₋₆alkylCH=NOR, C₁₋₆alkyl(imidazole), C₁₋₆alkyl(guanidine), C₁₋₆alkylC(=NH)NH₂, C₁₋₆alkylC(=NOH)NH₂; and wherein R is H, C₁₋₆alkyl, C₁₋₆heteroalkyl, C₁₋₆alkoxy, C₁₋₆alkylS(O)_m; wherein m is 0, 1, or 2; and wherein X is O, S, or NR', wherein R' is C(=O)C₁₋₆alkyl, C(=O)OC₁₋₆alkyl, C(=O)OC₁₋₆(hydroxyl)alkyl, C(=O)NH₂, C(=O)NHC₁₋₆alkyl, SO₂Ar, or SO₂C₁₋₆alkyl; and wherein

R³ and R⁴ are independently a single substituent or multiple substituents independently selected from H, halo, CN, C₁₋₆alkyl, C₁₋₆alkylamino, C₁₋₆alkoxy, C₂₋₆alkenyl, C₁₋₆heteroalkyl, C₁₋₆haloalkyl, C₁₋₆(hydroxy)alkyl, C₁₋₆(hydroxy)alkenyl, C₁₋₆(amino)alkyl, OC(=O)NH₂, OC(=O)NHC₁₋₆alkyl; or R³ and R⁴ taken together form C₃₋₆cycloalkyl group; and wherein

R⁵ is H, halo, CN, OH, NH₂, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkylamino, C₁₋₆(hydroxy)alkyl, C₁₋₆(amino)alkyl, C(=O)NHC₁₋₆alkyl, C(=O)NH-aryl; or NHC(=O)OC₁₋₆alkyl group; and wherein

Y is O, CH, CH₂, CF, CHF, CF₂, or S(O)_m; wherein m is 0, 1, or 2; and wherein A₁, A₂, and A₃ are independently N, O, S, NH, N—C₁₋₆alkyl, N—(CO)C₁₋₆alkoxy, N—SO₂C₁₋₆alkyl, or C—R⁵; wherein R⁵ for each of A₁-A₃ is independently selected from H, halo, CN, OH, NH₂, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkylamino, C₂₋₆alkenyl, C₁₋₆heteroalkyl, C₁₋₆(hydroxy)alkyl, C₁₋₆(amino)alkyl, C₁₋₆alkylCH=NOR, C₁₋₆alkylCH=NOH, C₁₋₆alkylC(=NOH)NH₂, C₁₋₆alkylC(=NH)NH₂, or C₁₋₆alkyl(guanidine), C(=O)NH₂, C(=O)NHC₁₋₆alkyl, C(=O)NH-aryl; NHC(=O)OC₁₋₆alkyl, pyridyl, triazolyl, oxazolyl, pyrazolyl, imidazolyl, or aryl group; and wherein

each bond with a dotted line is independently either a single bond or a double bond; and wherein

n is 0 or 1.

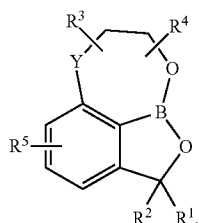
[0008] The alkyl, alkenyl, or cycloalkyl groups at each occurrence above independently are optionally substituted

with one, two, or three substituents selected from the group consisting of halo, aryl, Het¹, and Het². Het¹ at each occurrence is independently a C-linked 5- or 6-membered heterocyclic ring having 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur within the ring. Het² at each occurrence is independently a N-linked 5 or 6 membered heterocyclic ring having 1 to 4 nitrogen and optionally having one oxygen or sulfur within the ring.

[0009] In one embodiment, provided is a compound of formula A or B excluding generally class-related specific examples described in publications PCT WO 2008/157726, US 2009/0227541, and PCT WO 2009/140309.

[0010] In another embodiment, provided are compounds of formula A or B and with a proviso that when X is O; and wherein R¹, R³, and R⁴ are all H; and wherein R² is CH₂NH₂; and wherein A₁, A₂, and A₃ are all CH; and wherein bonds with dotted lines connecting A₁-A₃ comprise a benzene aromatic system; and wherein the bond with a dotted line connected to the group Y is a single bond; and wherein n is 1; then Y is other than O.

[0011] Also provided herein are compounds of the following formula I:



or a pharmaceutically acceptable salt, complex, or tautomer thereof, wherein:

R¹ and R² are independently H, F, C₁₋₆alkyl, C₁₋₆(amino)alkyl, aminomethyl, or C₁₋₆alkylNH₂; and wherein

R³ and R⁴ are independently a single substituent or multiple substituents independently selected from H, halo, CN, C₁₋₆alkyl, C₁₋₆(hydroxy)alkyl, C₁₋₆alkylamino, C₁₋₆alkoxy, C₁₋₆heteroalkyl, C₁₋₆haloalkyl, or C₁₋₆(amino)alkyl; and wherein

Y is O, S, CH₂, CHF, or CF₂; and wherein

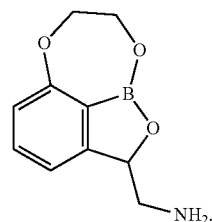
R⁵ is H, halo, CN, OH, or NH₂.

[0012] In one preferred embodiment, R¹ in a compound of formula I is H, and the chiral group CHR² has (S)-configuration of the chiral center.

[0013] In one aspect, provided is a compound of formula I and with a proviso that when R¹, R³, R⁴, and R⁵ are all H; and wherein R² is CH₂NH₂; then Y is other than O. Further provided herein are compounds of formula I wherein R¹, R³, R⁴, and R⁵ are all H; wherein R² is CH₂NH₂; and wherein Y is S, CH₂, CHF, or CF₂. Further provided herein are compounds of formula I wherein R¹, R³, R⁴, and R⁵ are all H; wherein R² is CH₂NH₂; wherein Y is O; and wherein at least one of R³ and R⁴ is other than H.

[0014] In a preferred aspect, provided is a compound of formula I and excluding generally related specific example(s) described in publications 2008/157726, US 2009/0227541,

and PCT WO 2009/140309. In certain embodiments, provided herein are compounds of formula I other than the following:



[0015] In additional preferred aspect, provided herein are compounds of formula I wherein R¹ is H; and wherein the chiral group CR¹R² has (S)-configuration.

[0016] In one preferred aspect, provided is a compound of formula I wherein R¹, R³, and R⁵ are all H; R² is CH₂NH₂, and R⁴ is CH₂OH group attached to the carbon atom of the ring fragment CH—O—B.

[0017] In yet another preferred aspect, provided is a compound of formula I wherein R¹, R³, and R⁵ are all H; R² is CH₂NH₂, and R⁴ is CH₂OH group attached to the carbon atom of the ring fragment CH—O—B, and wherein the resulted chiral group CHR⁴ has (R)-configuration. It is understood that any salts, solvates and coordination compounds, complexes, tautomers, ring-opened forms, and prodrugs of said compounds of formula I are also within the scope of the compounds provided herein.

[0018] In another aspect, provided herein are pharmaceutical compositions comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0019] In an additional aspect, provided herein are methods for treating Gram-negative or Gram-positive microbial infections in humans or other warm-blooded animals by administering to the subject in need a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof. The compound of formula I may be administered orally, parenterally, transdermally, topically, rectally, or intranasally in a pharmaceutical composition.

[0020] In another aspect, provided herein are compositions and methods for the treatment of microbial infections caused by microorganisms selected from *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Escherichia coli*, or *Klebsiella pneumoniae*.

[0021] In additional aspect, provided herein is a method for the treatment of a skin, soft tissue, respiratory, or an eye infection.

[0022] In yet another aspect, provided herein are intermediates and processes for preparing compounds of formula I.

BRIEF DESCRIPTION OF THE FIGURE

[0023] FIG. 1. Tricyclic boron compounds possessing and lacking therapeutic activity (potency expressed in MIC) against Gram-negative bacterial pathogen *A. baumannii*.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0024] Unless otherwise stated, the following terms used in the specification and Claims have the meanings given below:

[0025] The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_{i-j} indicates a moiety of the integer “i” to the integer “j” carbon atoms, inclusive. Thus, for example, C_{1-7} alkyl refers to alkyl of one to seven carbon atoms, inclusive.

[0026] The terms alkyl, alkenyl, etc. refer to both straight and branched groups, but reference to an individual radical such as “propyl” embraces only the straight chain radical, a branched chain isomer such as “isopropyl” being specifically referred to. The alkyl, alkenyl, etc. group may be optionally substituted with one, two, or three substituents selected from the group consisting of halo, aryl, Het¹, or Het². Representative examples include, but are not limited to, difluoromethyl, 2-fluoroethyl, trifluoroethyl, —CHCH-aryl, —CHCH-Het¹, —CH₂-phenyl, and the like.

[0027] The term “cycloalkyl” means a cyclic saturated monovalent hydrocarbon group of three to six carbon atoms, e.g., cyclopropyl, cyclohexyl, and the like. The cycloalkyl group may be optionally substituted with one, two, or three substituents selected from the group consisting of halo, aryl, Het¹, or Het².

[0028] The term “heteroalkyl” means an alkyl or cycloalkyl group, as defined above, having a substituent containing a heteroatom selected from N, O, or S(O)_n, where n is an integer from 0 to 2, including, hydroxy (OH), C_{1-4} alkoxy, amino, thio (—SH), and the like. Representative substituents include —NR_aR_b, —OR_a, or —S(O)_nR_c, wherein R_a is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, optionally substituted aryl, optionally substituted heterocyclic, or —COR (where R is C_{1-4} alkyl); R_b is hydrogen, C_{1-4} alkyl, —SO₂R (where R is C_{1-4} alkyl or C_{1-4} hydroxyalkyl), —SO₂NRR' (where R and R' are independently of each other hydrogen or C_{1-4} alkyl), —CONRR' (where R' and R are independently of each other hydrogen or C_{1-4} alkyl); n is an integer from 0 to 2; and R_c is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, optionally substituted aryl, or NR_aR_b where R_a and R_b are as defined above. Representative examples include, but are not limited to 2-methoxyethyl (—CH₂CH₂OCH₃), 2-hydroxyethyl (—CH₂CH₂OH), hydroxymethyl (—CH₂OH), 2-aminoethyl (—CH₂CH₂NH₂), 2-dimethylaminoethyl (—CH₂CH₂NHCH₃), benzyloxymethyl, thiophen-2-ylthiomethyl, and the like.

[0029] The term “halo” refers to fluoro (F), chloro (Cl), bromo (Br), or iodo (I).

[0030] The term aryl refers to phenyl, biphenyl, or naphthyl, optionally substituted with 1 to 3 substituents independently selected from halo, — C_{1-4} alkyl, —OH, —OC C_{1-4} alkyl, —S(O)_n C_{1-4} alkyl wherein n is 0, 1, or 2, — C_{1-4} alkylNH₂, —NHC C_{1-4} alkyl, —C(O)H, or —CN—OR_a wherein R_a is hydrogen or — C_{1-4} alkyl.

[0031] “Optional” or “optionally” means that the subsequently described event or circumstance may, but need not, occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, “aryl group optionally mono- or di-substituted with an alkyl group” means that the alkyl may but need not be present, and the description includes situations where the aryl group is mono- or disubstituted with an alkyl group and situations where the aryl group is not substituted with the alkyl group.

[0032] Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms

or the arrangement of their atoms in space are termed “isomers”. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers”.

[0033] Stereoisomers that are not mirror images of one another are termed “diastereomers” and those that are non-superimposable mirror images of each other are termed “enantiomers”. When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (–)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a “racemic mixture”.

[0034] The compounds may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)-stereoisomers or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and Claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of *Advanced Organic Chemistry*, 4th edition J. March, John Wiley and Sons, New York, 1992).

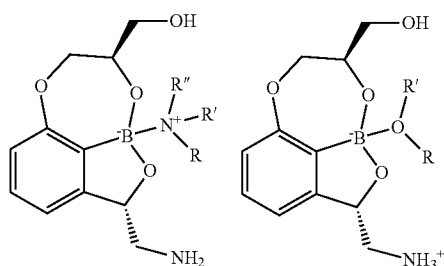
[0035] A “pharmaceutically acceptable carrier” means a carrier that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier that is acceptable for veterinary use as well as human pharmaceutical use. “A pharmaceutically acceptable carrier” as used in the specification and Claims includes both one and more than one such carrier.

[0036] A “pharmaceutically acceptable salt” of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include:

[0037] (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or

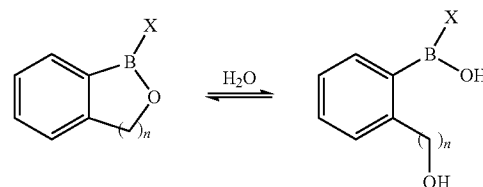
[0038] (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

[0039] A “complex” means a composition comprising a compound provided herein and an additional other ingredient (s) that may be bound or coordinated to said compound in a way of a solvate (such as a hydrate formed with water), and/or by forming at least one coordination or ionic bond between the compound and the complexing ingredient(s). Thus, the boron atom can change its coordination number (or valency) from three (in a non-complexed compound) to four (in its complex) by accepting additional electron density from a donor atom of the complexing ingredient, as observed for trigonal (tri-valent) boron compounds often existing in a complexed tetragonal form (as described by Hall in *Boronic Acids: Preparation, Applications in Organic Syntheses and Medicine*. Ed. Dennis G. Hall, Wiley-VCH Verlag GmbH & Co., 2005, pp. 1-26). Two examples of such complex compounds that may be formed by an exemplary compound provided herein and a nitrogen (amine) or oxygen (water, alcohol or ether) compound is illustrated below.



[0040] The complexing ingredients (such as ingredients $R(R')NR''$ or ROR' in exemplary structures above) may be used to improve certain useful physico-chemical and/or biological properties of the compounds provided herein, including but not limited to solubility, stability, pharmacokinetics, or antimicrobial activity and antibacterial spectrum. For example, a complex of the compound provided herein with an amine-type antimicrobial agent such as aminoglycoside, colistin, and/or polymyxin may be used to improve the therapeutic effect in the resulted complex, such as antibacterial effect on resistant pathogens not sufficiently eradicated by each of the complexed component alone.

[0041] The term “tautomers” means two or more forms or isomers of an organic compound that could be interconverted into each other via a common chemical reaction called tautomerization, generally analogous to that described by Smith et al., in *Advanced Organic Chemistry*. 2001, 5th Ed. NY: Wiley Interscience, pp. 1218-1223. The concept of tautomerizations is called tautomerism. The tautomerism may be accompanied by a change from a ring structure to an open structure, as observed, for example, for interconversion between the cyclic pyran form and the open chain form of glucose via formation and breaking of a C—O bond. The degree of tautomerism is often affected by a solvent effect, such as a hydration with water, and the media acidity. A related process concerning cyclic boron compounds may involve formation and breaking of a B—O bond as exemplified below:



Any ring-opened forms of the tricyclic boron compounds provided herein, including any hydrated (water-added) forms are treated herein as “tautomers” and are within the scope of this application. In general, a material comprised of tautomers is commonly treated as a single chemical entity, such as acetone that exists in two interchangeable forms due to keto-enol tautomerization.

[0042] “Treating” or “treatment” of a disease includes:

[0043] (1) preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease,

[0044] (2) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms, or

[0045] (3) relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

[0046] A “therapeutically effective amount” means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The “therapeutically effective amount” will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

[0047] “Leaving group” has the meaning conventionally associated with it in synthetic organic chemistry, i.e., an atom or group capable of being displaced by a nucleophile and includes halogen, C_{1-4} alkylsulfonyloxy, ester, or amino such as chloro, bromo, iodo, mesyloxy, tosyloxy, trifluorosulfonyloxy, methoxy, N,O-dimethylhydroxyl-amino, and the like.

[0048] “Prodrug” means any compound which releases an active parent drug according to a compound provided herein in vivo when such prodrug is administered to a mammalian subject. Prodrugs of a compound provided herein are prepared by modifying functional groups present in a compound provided herein in such a way that the modifications may be cleaved in vivo to release the parent compound. Prodrugs include compounds provided herein wherein a hydroxy, sulfhydryl, amido or amino group in the compound is bonded to any group that may be cleaved in vivo to regenerate the free hydroxyl, amido, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to esters (e.g., acetate, propionate, butyrate, formate, benzoate, phosphate or phosphonate derivatives), carbamates (e.g., N,N-dimethylaminocarbonyl) of hydroxy functional groups in compounds provided herein, and the like. It is understood that prodrugs could be utilized, for example, to improve oral bioavailability of a drug, direct the drug to a particular target organ, enhance stability for a particular administration route (e.g., aerosol), or improve its solubility, as reviewed, for example, by Ettmayer et al. in *J. Med. Chem.* 2004, vol. 47, pp 2393-2404.

[0049] The term “mammal” refers to all mammals including humans, livestock, and companion animals.

[0050] The compounds provided herein are generally named according to the IUPAC or CAS nomenclature system. Abbreviations which are well known to one of ordinary skill

in the art may be used (e.g. "Ar" for aryl, "Ph" for phenyl, "Me" for methyl, "Et" for ethyl, "h" for hour or hours and "rt" or "r.t." for room temperature).

Illustrative Embodiments

[0051] Within the broadest definition provided herein, certain compounds of the compounds of formula I may be preferred. Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

[0052] In some preferred compounds provided herein C_{1-4} alkyl can be methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and isomeric forms thereof.

[0053] In some preferred compounds provided herein C_{2-4} alkenyl can be vinyl, propenyl, allyl, butenyl, and isomeric forms thereof (including cis and trans isomers).

[0054] In some preferred compounds provided herein, R^1 is H, and the chiral group CHR^2 has (S)-configuration.

[0055] In some preferred compounds, R^1 is H, and the chiral group CR^1R^2 has (S)-configuration.

[0056] In some preferred compounds provided herein, R^1 , R^3 , and R^5 are all H, R^2 is CH_2NH_2 , and R^4 is CH_2OH group attached to the carbon atom of the ring fragment $CH-O-B$.

[0057] In other preferred compounds provided herein, R^1 , R^3 , and R^5 are all H; R^2 is CH_2NH_2 , and R^4 is CH_2OH group attached to the carbon atom of the ring fragment $CH-O-B$, and the resulted chiral group CHR^4 has (R)-configuration.

[0058] In some preferred compounds provided herein C_{3-6} cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and isomeric forms thereof.

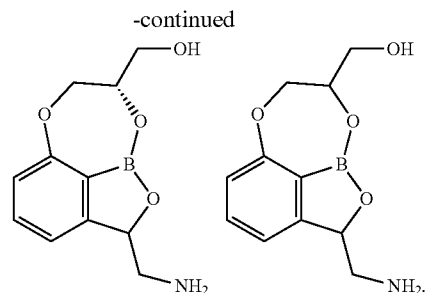
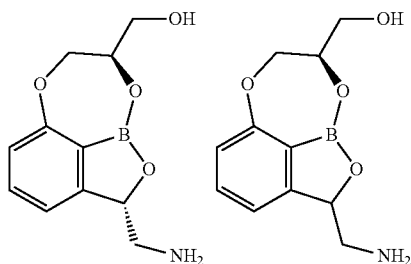
[0059] In some preferred compounds provided herein C_{1-4} heteroalkyl can be hydroxymethyl, hydroxyethyl, and 2-methoxyethyl.

[0060] In some preferred compounds provided herein halo can be fluoro (F) or chloro (Cl).

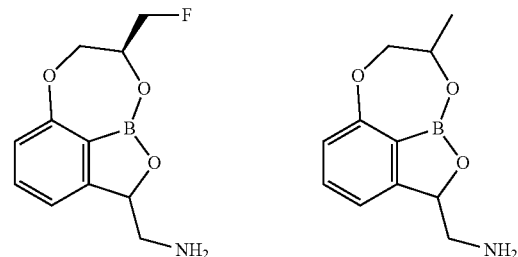
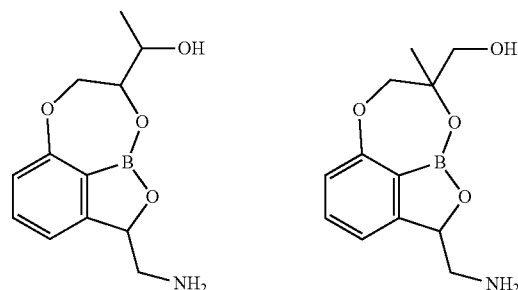
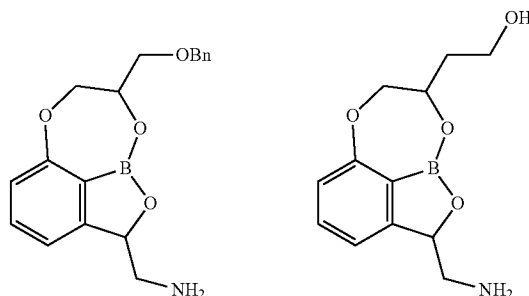
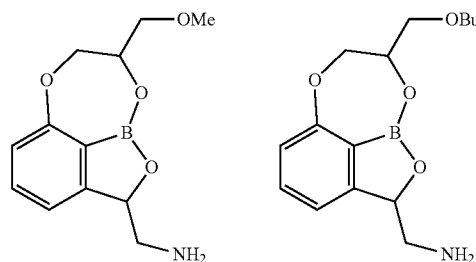
[0061] In some preferred compounds provided herein R^1 is H, and R^2 is CH_2NH_2 .

[0062] In some preferred embodiments, group R^3 is H, and R^4 is CH_2OH .

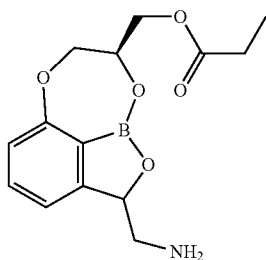
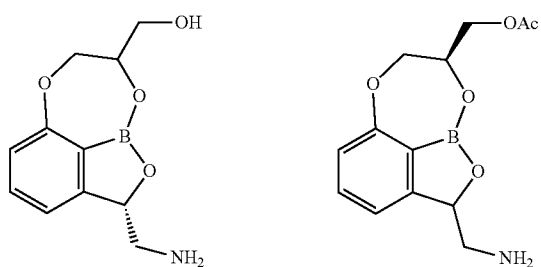
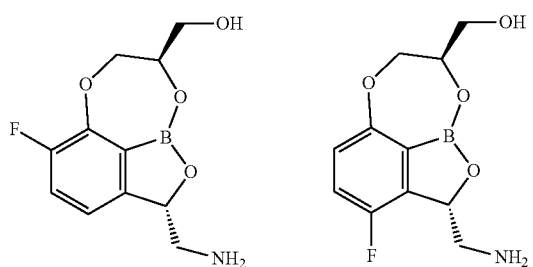
[0063] One preferred group of compounds provided herein is illustrated below.



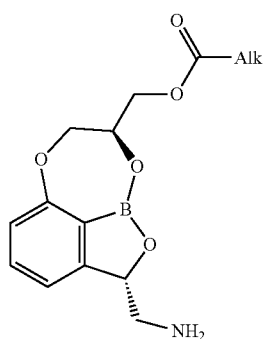
[0064] Additional group of compounds provided herein is illustrated below.



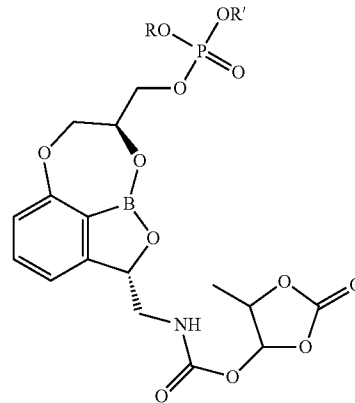
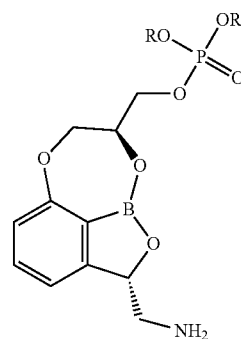
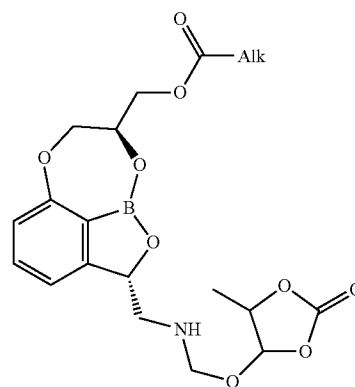
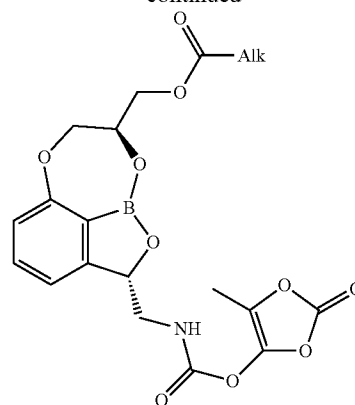
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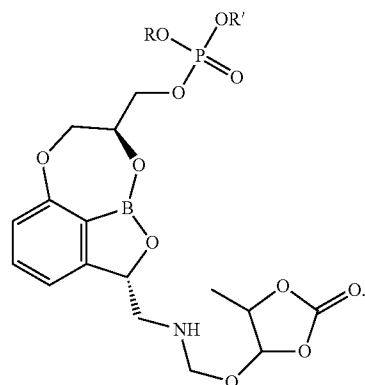
[0065] Another preferred group of prodrugs of compounds provided herein is illustrated below.



-continued



-continued



General Synthetic Methods

[0066] The compounds provided herein can be prepared in accordance with one or more of Schemes discussed below. Multitude of well-established methods for preparing boron compounds has been reviewed in a comprehensive monograph *Boronic Acids: Preparation, Applications in Organic Syntheses and Medicine*. Ed. Dennis G. Hall, Wiley-VCH Verlag GmbH & Co., 2005, pp. 1-549. These methods can be used either directly or with obvious variations to a trained chemist to prepare key intermediates and certain compounds provided herein.

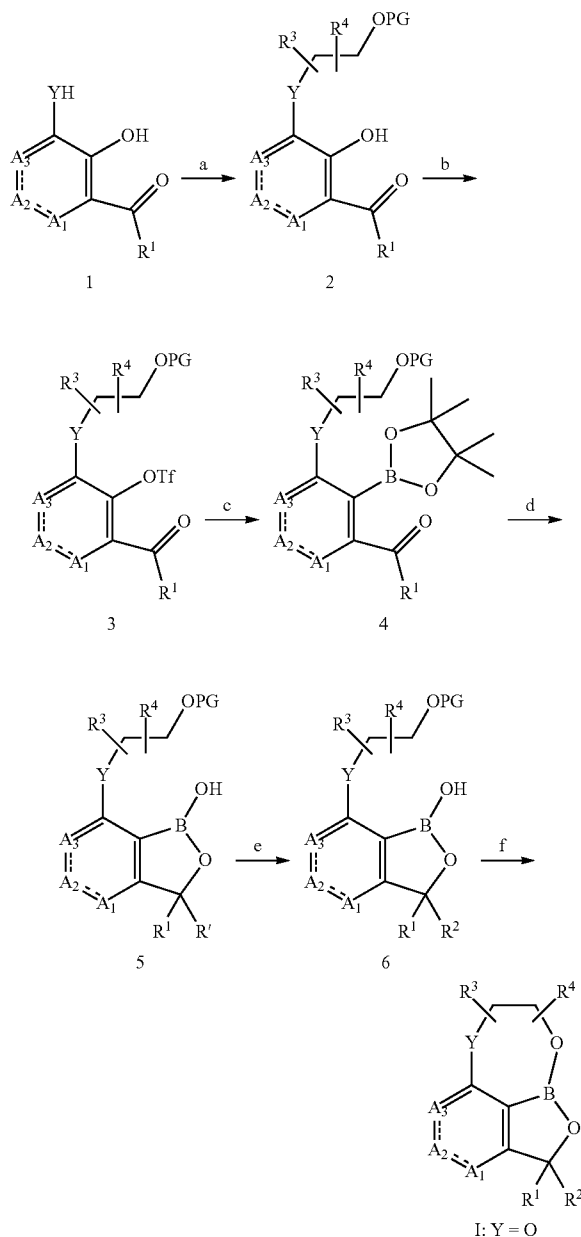
[0067] Additional general methods for preparation of some bicyclic boron compounds have been described, for example, in publications WO 2010/080558 and US 2009/0227541.

[0068] It is also understood that, if so required, any racemic compound(s) or intermediate(s) provided herein can be separated into asymmetric chiral materials of a desired optically active isomers using conventional means, including but not limited to chiral liquid chromatography or co-crystallization with a chiral auxiliary reagent, such as a conventional commercial chiral acid or amine.

[0069] Suitable synthetic sequences are readily selected per specific structures provided herein, but within the art known to individuals practicing organic synthesis, such as methods summarized in available chemistry data bases, such as in CAS Scifinder and Elsevier Reaxys. Based on these general methods, the enablement for making the compounds provided herein is straightforward and can be practiced within a common professional knowledge. Some general synthetic methods to prepare the compounds provided herein are illustrated below in Schemes 1-6 (non-limiting, for illustration only).

[0070] One general approach to the compounds provided herein is illustrated in general Scheme 1.

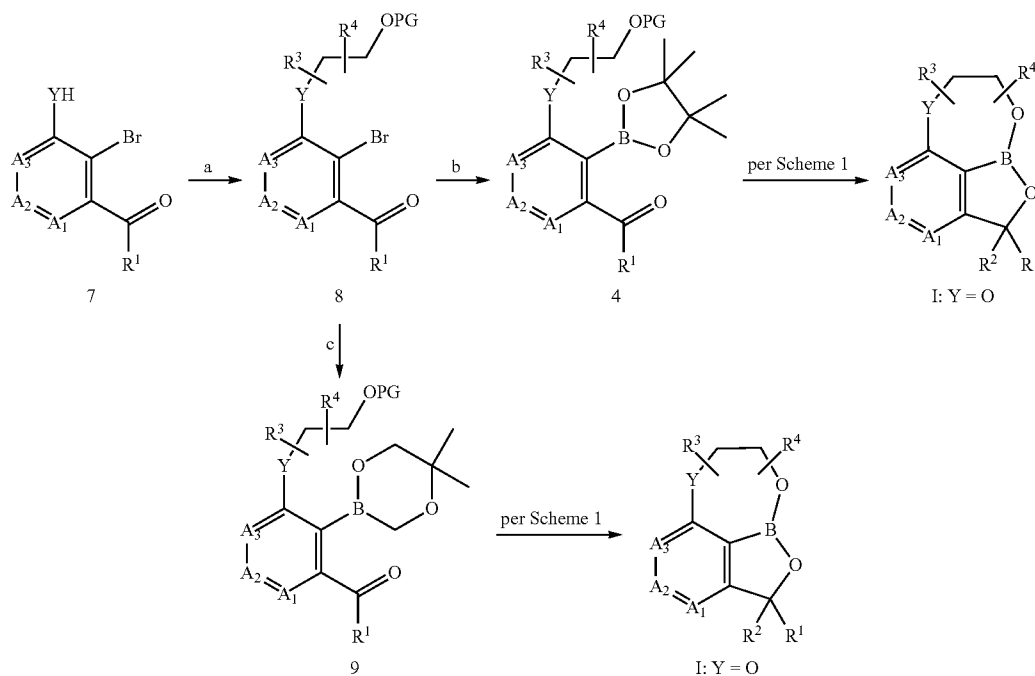
Scheme 1. General synthesis of tricyclic dioxaboron compounds from aromatic or heteroaromatic alcohols.



a) Alkylating agent such as halide, mesylate, or alike; base: K_2CO_3 , LiOH, TEA, DBU, or alike; Mitsunobu reaction for alkylating with an alcohol reagent; b) triflating reagent: Tf_2O , 2- Tf_2N -5-Cl-pyridine, or alike; base: K_2CO_3 , TEA, DBU, or alike; c) Pd catalyst: $Pd(dppf)_2Cl_2$ DCM, $Pd(OAc)_2$, or alike; bis(pinacolato)diboron; base: KOAc, Na_2CO_3 , or alike; d) methylene-active reagent Me—R': e.g. $MeNO_2$, MeCN, or alike; base: K_2CO_3 , NaOH, TEA, DBU, or alike; e) R^2 -unmasking method, e.g. reduction for $R' = NO_2$: such as Raney-Ni/ H_2 , $Pd/C/H_2$, $NiCl_2/NaBH_4$, and alike; f) protective group (PG) deprotection method, e.g. $Pd/C/H_2$ for PG = Bn; $Bu_4N^+F^-$ or LiF for PG = TBS; trifluoroacetic acid (TFA) for PG = trityl, and alike.

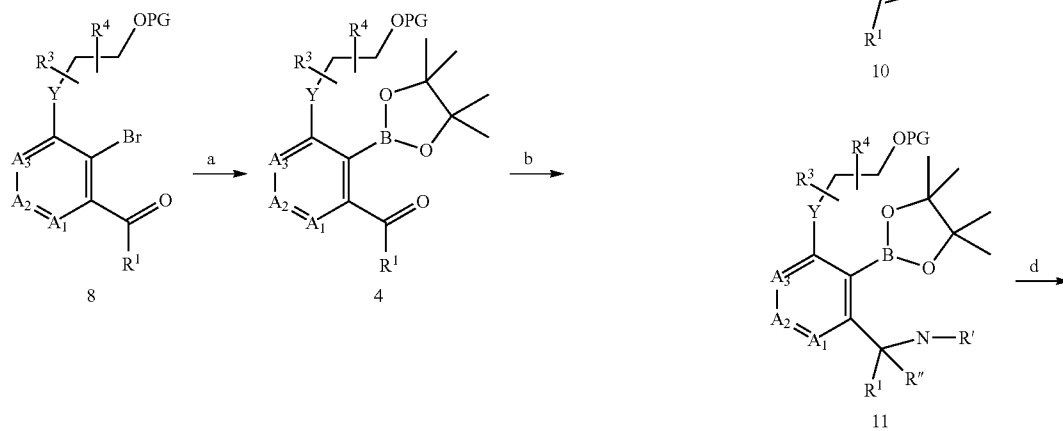
[0071] Another general synthesis of the compounds provided herein is illustrated in Scheme 2. A multitude of the requisite aromatic and heteroaromatic bromides of the type 7 is commercially available or can be readily prepared using literature methods.

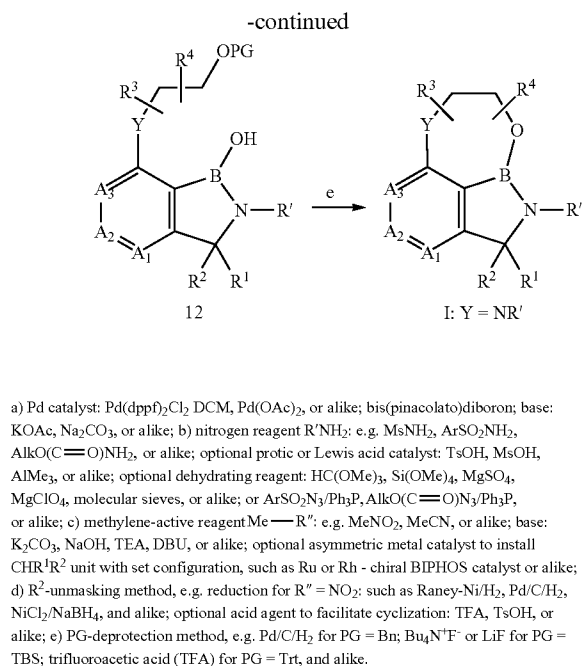
Scheme 2. General synthesis of tricyclic dioxaboron compounds from aromatic or heteroaromatic halides (exemplified for halide = bromide).



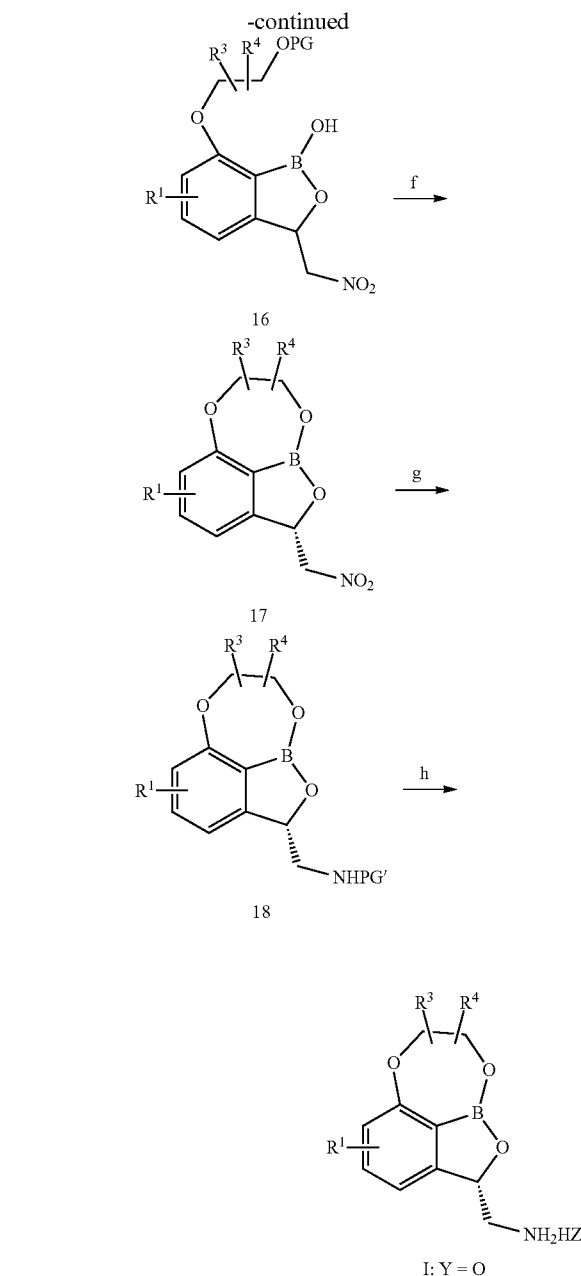
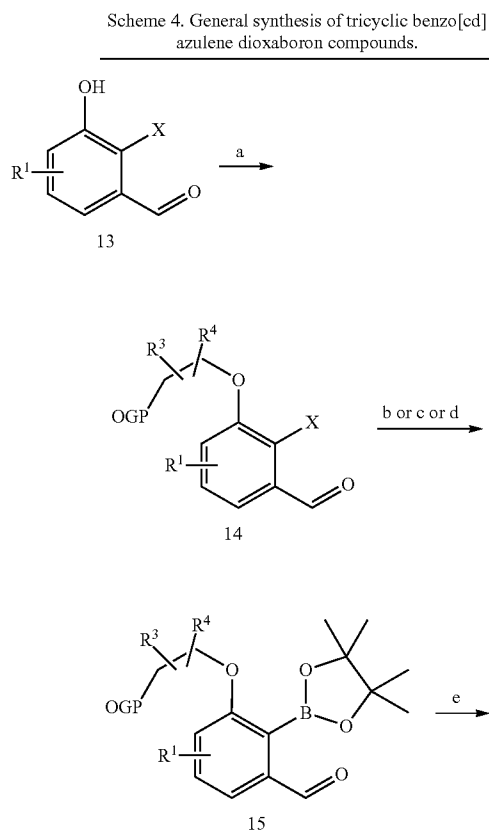
[0072] Additional general methods for synthesis of compounds provided herein are exemplified by general Scheme 3.

Scheme 3. General synthesis of tricyclic oxazaboron compounds from aromatic or heteroaromatic halides (exemplified for halide = bromide).





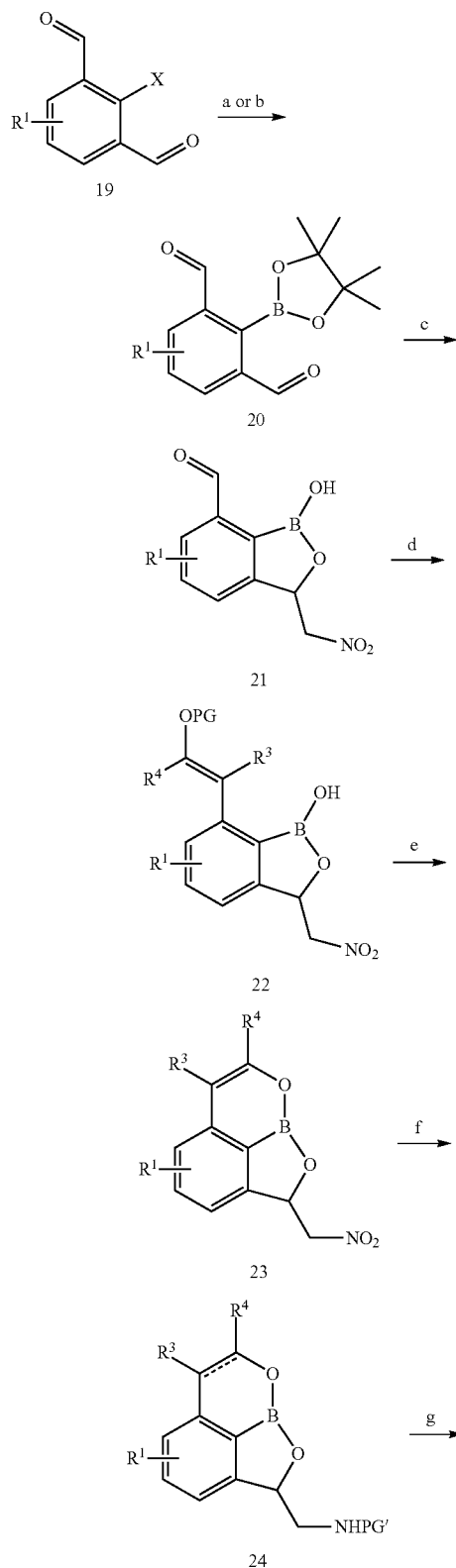
[0073] Another general approach to the compounds provided herein is illustrated in general Scheme 4.



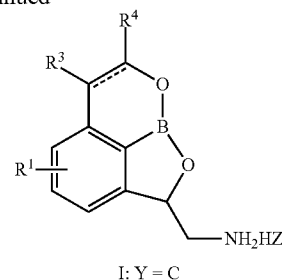
a) Alkylating agent such as halide mesylate, or alike; base: K₂CO₃, LiOH, TEA, DBU, or alike; Mitsunobu reaction for alkylating with an alcohol reagent; b) for X = halide (such as bromide): Pd catalyst: Pd(dppf)₂Cl₂ DCM, Pd(OAc)₂, or alike; bis(pinacolato)diboron; base: KOAc, Na₂CO₃, or alike; c) for X = H: lithiation reagent such BuLi, LDA, or alike; trialkyl borate; d) for X = OH: triflating reagent: Tf₂O, 2-Tf₂N-5-Cl-pyridine, or alike; base: K₂CO₃, TEA, DBU, or alike; then same as in method (b); e) nitromethane or equivalent thereof; with or without base such as NaOH, K₂CO₃, and alike; f) PG-deprotection method, e.g. Pd/C/H₂ for PG = Bn; Bu₄N⁺F⁻ or LiF for PG TBS; trifluoroacetic acid (TFA) for PG = Trt, aq. LiOH for ester, and alike; g) reducing agent(s) and an amine protecting agent: H₂/Pd/C, NaBH₄, SnCl₂, or alike, then with Boc₂O, or CbzCl, or aromatic aldehyde; h) primary amine protection group PG' removal reagent(s): acid for trityl, or Boc; H₂/Pd/C for benzyl or Cbz; aqueous base for amide, sulfonamide or carbamate, then salt-forming acid, such as aq. HCl, MsOH, or alike.

[0074] Yet another general synthesis of compounds provided herein is illustrated by Scheme 5.

Scheme 5. General synthesis of tricyclic dioxaborepine compounds.



-continued



a) For X = halide (such as bromide): Pd catalyst: Pd(dppf)₂Cl₂, DCM, Pd(OAc)₂, or alike; bis(pinacolato)diboron; base: KOAc, Na₂CO₃, or alike; b) for X = H: lithiation reagent such n-BuLi, LDA, or alike; trialkyl borate; c) nitromethane or equivalent thereof; with or without base such as NaOH, K₂CO₃, and alike; d) PG-deprotection method, e.g. Pd/C/H₂ for PG = Bn; Bu₄N⁺F⁻ or LiF for PG TBS; trifluoroacetic acid (TFA) for PG = Trt, aq. LiOH for ester, and alike; e) reducing agent(s) and an amine protecting agent: H₂/Pd/C, NaBH₄, SnCl₂, or alike, then with Boc₂O, or CbzCl, or aromatic aldehyde; h) primary amine protection group PG' removal reagent(s): acid for trityl, or Boc; H₂/Pd/C for benzyl or Cbz; aqueous base for amide, sulfonamide or carbamate, then salt-forming acid, such as aq. HCl, MeOH, or alike.

[0075] If needed, the general illustrative methods of Schemes 1-5 can be combined or modified based on the known to a trained chemist art, to employ for the preparation of a specific compound provided herein.

[0076] Further, prodrug derivatives of the compounds provided herein could be produced, for example, by conventional acylation of available alcohol or amine side chains, or by phosphorylation of available alcohol groups, and utilizing routine protection/deprotection sequence as needed.

[0077] Additional detailed synthetic schemes for the syntheses of specific compounds provided herein are illustrated by methods described for Examples below.

EXAMPLES

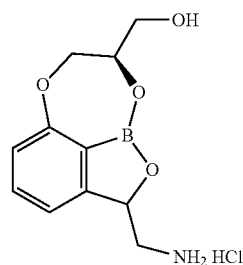
[0078] Embodiments provided herein are described in the following examples, which are meant to illustrate and not limit the scope of any invention provided herein. Common abbreviations well known to those with ordinary skills in the synthetic art used throughout. ¹H NMR spectra (δ, ppm) are recorded on 300 MHz or 400 MHz instrument in DMSO-d₆ unless specified otherwise. Mass-spectroscopy data for a positive ionization method are provided. Chromatography means silica gel chromatography unless specified otherwise. TLC means thin-layer chromatography. HPLC means reverse-phase HPLC. Unless specified otherwise, all reagents were either from commercial sources, or made by conventional methods described in available literature.

Example 1

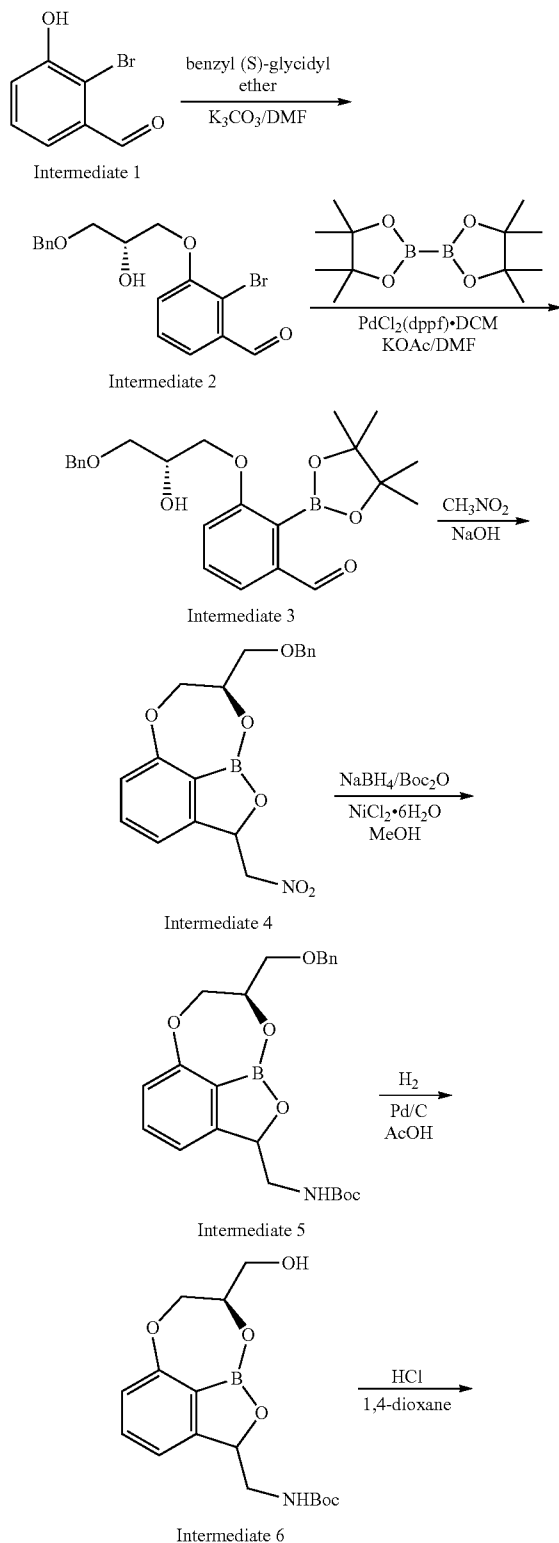
((8R)-2-(Aminomethyl)-7,8-dihydro-2H-1,6,9-tri-oxa-9a-borabenzoc[cd]azulen-8-yl)methanol hydrochloride

[0079]

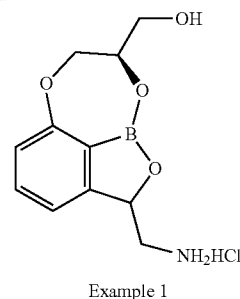
Example 1



[0080] Scheme for preparation of the compound of Example 1:



-continued



Intermediate 2.

[0081] K₂CO₃ (1.0 g) was added to 2-bromo-3-hydroxybenzaldehyde (1.5 g) in DMF (8 mL), followed by benzyl (S)-glycidyl ether (1.2 mL). The suspension was stirred at about 120° C. for about 1.5 h. After the starting bromide was consumed, the mixture was cooled down to r.t., diluted with brine and extracted with EtOAc. EtOAc was removed under vacuum and the residue was purified by silica gel column chromatography (eluent: 20-40% EtOAc/hexane) to afford the Intermediate 2 as an off-white oil (2.36 g). MS (m/z): 364.9, 366.9 [M+H].

Intermediate 3.

[0082] Intermediate 2 (2.16 g) was mixed with bis(pinacolato) diboron (3.0 g) and dissolved in DMF (12 mL). The solution was degassed, and KOAc (1.74 g) was added, followed by PdCl₂(dppf)₂·DCM (0.24 g). The suspension was again degassed three times with nitrogen, and then heated at about 90° C. for about 14 h. The reaction was worked up with EtOAc/brine/H₂O, and the product was purified by silica gel column chromatography (eluent: 10-40% EtOAc/hexane). Fractions containing the product were collected and evaporated under vacuum to afford the Intermediate 3. MS (m/z): 353.0 [Boronic acid+Na].

Intermediate 4.

[0083] The total of the Intermediate 3 from preceding step was dissolved in THF (6 mL) and water (18 mL). The biphasic solution was cooled down with ice/water, and nitromethane (0.95 mL) was added, followed by a solution of 10% aq. NaOH (about 2.4 mL). The reaction was stirred at r.t. o.n. and then acidified with AcOH to pH ca. 3-5. The suspension was extracted with EtOAc. The combined organic layers were evaporated under vacuum, and the residue was purified by silica gel column chromatography (eluent: 2-6% MeOH/DCM) to afford the Intermediate 4. MS (m/z): 356.0 [M+H].

Intermediate 5.

[0084] NiCl₂·6H₂O (0.34 g) was added to Intermediate 4 (0.5 g) in MeOH (6 mL), followed by Boc₂O (0.62 g). The solution was cooled down with ice/water, and then NaBH₄ (0.65 g) was added portionwise with stirring. The mixture

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was stirred at r.t. o.n. and then acidified with AcOH to pH ca. 3-5. Most of volatiles were removed under vacuum, and the residue was re-dissolved in EtOAc/H₂O, filtered through Celite, and then extracted with EtOAc (3×). The combined organic layers were concentrated in vacuo, and the residue was purified by silica gel column chromatography (eluent: 2-6% MeOH/DCM) to afford the Intermediate 5. MS (m/z): 326.0 [M-Boc+H].

Intermediate 6.

[0085] Intermediate 5 (0.26 g) in AcOH (5 mL) was hydrogenated at r.t. with 10% Pd/C (about 100 mg) for 2 h. The mixture was filtered through Celite and the solvent was removed under vacuum. The residue was purified on a silica gel column (eluent: 0.5-2% MeOH/DCM) to afford the Intermediate 6. MS (m/z): 236.1 [M-Boc+H].

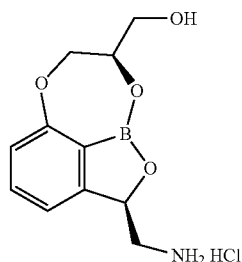
Compound of Example 1

[0086] Intermediate 6 (0.12 g, 0.36 mmol) was dissolved in 4N HCl in 1,4-dioxane (5 mL), and the solution was stirred at r.t. for about 2 h. The volatiles were removed under vacuum, and the residue was dissolved in water (about 3 mL) and filtered through 0.45 μm membrane filter. The aq. solution was lyophilized to afford the compound of Example 1. ¹H NMR: 8.12 (br s, 3H), 7.49 (t, J=7.80 Hz, 1H), 7.13 (d, J=7.50 Hz, 1H), 6.91 (d, J=9.10 Hz, 1H), 5.48 (d, J=7.50 Hz, 1H), 5.15 (m, 1H), 4.70 (m, 1H), 4.32 (m, 1H), 4.05 (m, 1H), 3.49 (m, 3H), 2.90 (m, 1H). MS (m/z): 235.9 [M+H].

Example 2

((2R,8R)-2-(Aminomethyl)-7,8-dihydro-2H-1,6,9-trioxo-9a-borabenz[cd]azulen-8-yl)methanol hydrochloride

[0087]



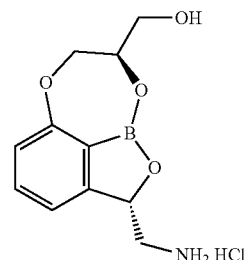
Compound of Example 2

[0088] The compound of Example 1 comprising a mixture of two diastereomers is subjected to HPLC separation (eluent: 0.1% trifluoroacetic acid in water/MeCN gradients) and the fractions containing the product are collected and lyophilized with addition of aq. HCl to afford the compound of Example 2.

Example 3

((2S,8R)-2-(Aminomethyl)-7,8-dihydro-2H-1,6,9-trioxo-9a-borabenz[cd]azulen-8-yl)methanol hydrochloride

[0089]



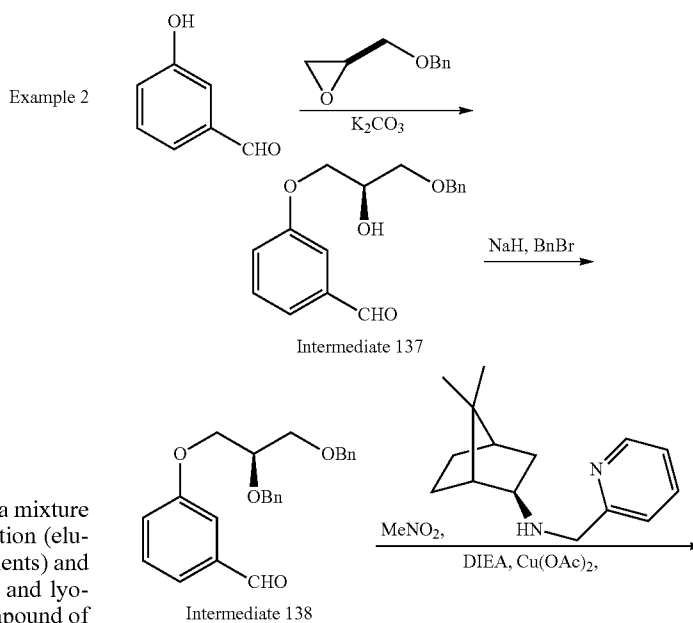
Compound of Example 3

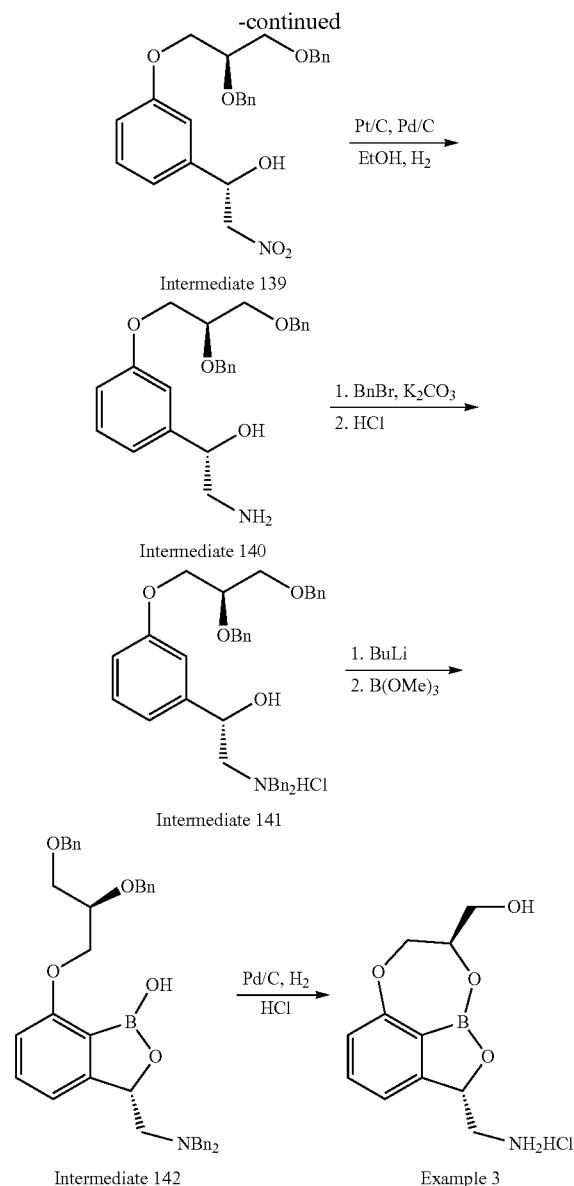
Method A.

[0090] The compound of Example 1 comprising a mixture of two diastereomers is subjected to HPLC separation (eluent: 0.1% trifluoroacetic acid (TFA) in water/MeCN gradient) and the fractions containing the product are collected and lyophilized with addition of aq. HCl to afford the compound of Example 3.

Method B

[0091] Scheme for preparation of the compound of Example 3 using Method B:





Intermediate 137.

Method I.

[0092] K_2CO_3 (12.6 g) was added to 3-hydroxybenzaldehyde (7.43 g) and (S)-2-((benzyloxy)methyl)oxirane (10.0 g) in DMF (45 mL), and the mixture was stirred at 90° C. for 5 h. Upon cooling to r.t., EtOAc (150 mL) and water (150 mL) were added, and the aqueous layer was extracted with EtOAc (2×150 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Solvent was evaporated under vacuum to afford the crude product that was purified by column chromatography (EtOAc/PE (petroleum ether) 1:4) to afford the Intermediate 137 as yellow oil.

Method II.

[0093] Performed as described above for Method I, except with the procedure scaled-up to 100 g of starting 3-hydroxy-

benzaldehyde, and using the resulted reaction solution directly at the next step, without isolation of the Intermediate 137.

Intermediate 138.

[0094] 60% NaH in oil (38 g) was added portionwise to the solution of the Intermediate 137 from the preceding step of Method II at 0° C. under N_2 , and the resulting solution was stirred for 1 h. BnBr (114 mL) was added dropwise with stirring at 0° C., the reaction mixture was allowed to warm up to r.t. and stirred until no Intermediate 137 was left per LCMS analysis. The reaction mixture was quenched with ice-cold water, and the product was extracted with EtOAc. Resulted organic layer was dried (Na_2SO_4), and solvent was evaporated under vacuum. The crude product was purified by column chromatography (gradient EtOAc/PE from 1:12 to 1:10) to afford the Intermediate 138.

Intermediate 139.

[0095] Copper (II) acetate (0.48 g) and (1S,2S,4R)-1,7,7-trimethyl-N-(pyridin-2-ylmethyl)bicyclo[2.2.1]heptan-2-amine (0.36 g) were dissolved in EtOH (12 mL) and THF (18 mL). The solution was stirred at r.t. for 1 h, then a solution of the Intermediate 138 (30 g) in EtOH (108 mL) and THF (162 mL) was added. The mixture was cooled at ca. -30 to -40° C., and nitromethane (43 mL) was added slowly with stirring while maintaining the temperature below -30° C. DIEA (13.9 mL) was added, and the reaction mixture was stirred at -30° C. until the Intermediate 138 was consumed (ca. 24-56 h) by LCMS. TFA (1.2 g) was added, and the reaction was stirred for ca. 10 min. Volatiles were removed under vacuum, and the residue was dissolves in MTBE, washed with 1N HCl, water and then filtered through Celite pad. The filtrate was dried (Na_2SO_4), and the solvent was removed under vacuum. The crude material was purified by column chromatography (EtOAc/PE 1:5) to afford the product as yellow oil.

Intermediate 140.

[0096] Intermediate 139 (8.0 g) was dissolved in EtOH (90 mL), and then 5% Pt/C (1.45 g) and 10% Pd/C (2.62 g) were added. The reaction mixture was stirred under H_2 for ca. 1.5 h at r.t., then filtered, and the resulting solution of the Intermediate 140 was used at the next step without further purification. MS (m/z): 408.0 [M+H].

Intermediate 141.

[0097] BnBr (13.65 g, 2.1 eq.) and K_2CO_3 (13.14 g, 2.5 eq.) were added to the solution of the Intermediate 140 obtained at the preceding step. The mixture was stirred o.n. and filtered aiding with EtOH. The filtrate was concentrated under vacuum to a volume of about 100 mL. This solution was diluted with water (65 mL) and stirred at 50° C. Conc. aq. HCl (4 mL) was added, and the mixture was stirred at 50° C. for ca. 30 min, then stirred at ca. 0° C. for 30 min. The product was filtered off and washed with cold 20% aqueous ethanol (80 mL). Solvent was removed under vacuum to afford the Intermediate 141 as a white solid. MS (m/z): 570.3 [M-HCl-H₂O+H].

Intermediate 142.

[0098] 2.6 M BuLi in hexanes (8.8 mL) was added dropwise with stirring over ca. 10 min to a solution of the Inter-

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mediate 141 (5 g) in toluene (32 mL) under nitrogen. The reaction mixture was stirred at r.t. for ca. 1 h, and cooled to ca. -30 to -40°C . Extra BuLi solution (3.1 mL) was added slowly, followed by extra BuLi solution (8.9 mL) at -25 to -30°C . The mixture was stirred for at this temperature for ca. 2-3 h, and then B(OMe)_3 (4.5 mL) was added, followed by dry THF (3.6 mL). The mixture was allowed to warm up to ca. 15 - 25°C . over ca. 30-60 min. 5% Aq. NaHCO_3 (50 mL) was added, and the mixture was stirred for about 15 min. The resulting suspension was filtered aiding with MTBE (ca. 20 mL). The filtrate was washed with water (4×20 mL) and dried (Na_2SO_4). Solvent was removed under vacuum, and the crude material purified by column chromatography to afford the Intermediate 142 as yellow oil. MS (m/z): 614.2 [M+H].

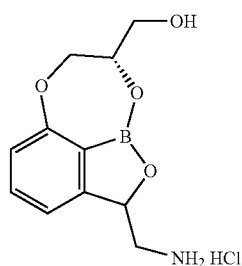
Compound of Example 3

[0099] Intermediate 142 (14 g) was dissolved in MeOH (120 mL) with 1N aq. HCl (25 mL). Pd/C (10%) was added, and the mixture was stirred under H_2 at 50°C . until the reaction was completed by LCMS. The mixture was filtered aiding with MeOH, and volatiles were removed under vacuum. The crude material was recrystallized from 2-propanol to afford the compound of Example 4 as a white solid. ^1H NMR: 8.21 (br s, 3H), 7.50 (t, $J=8.00$ Hz, 1H), 7.15 (d, $J=7.20$ Hz, 1H), 6.92 (d, $J=8.00$ Hz, 1H), 5.51 (m, 1H), 5.18 (m, 1H), 4.72 (m, 1H), 4.32 (m, 1H), 4.03 (m, 1H), 3.60-3.42 (m, 3H), 2.92 (m, 1H). MS (m/z): 235.6.

Example 4

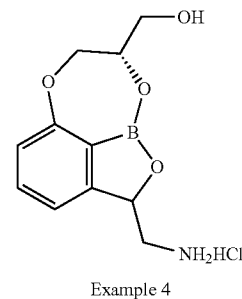
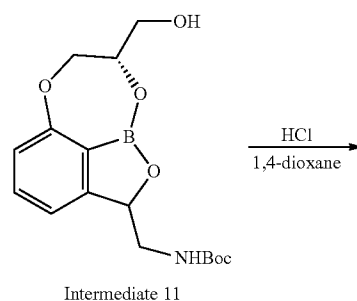
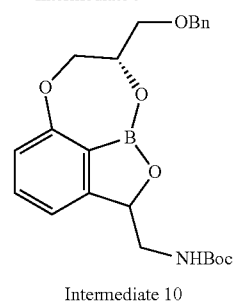
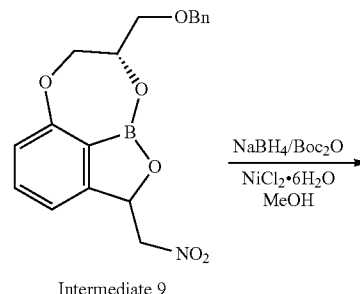
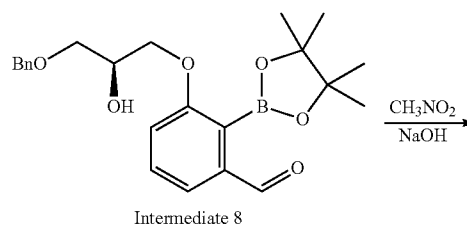
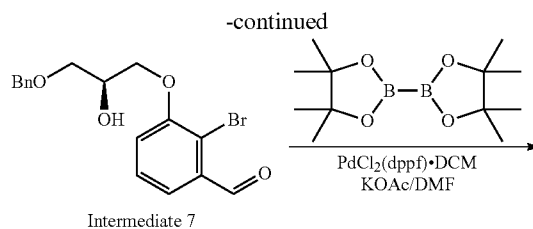
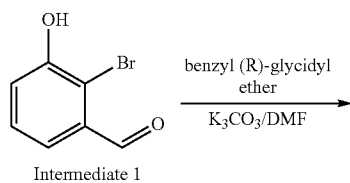
((8S)-2-(Aminomethyl)-7,8-dihydro-2H-1,6,9-tri-oxa-9a-borabenzoc[cd]azulen-8-yl)methanol hydrochloride

[0100]



Example 4

[0101] Scheme for preparation of the compound of Example 4:



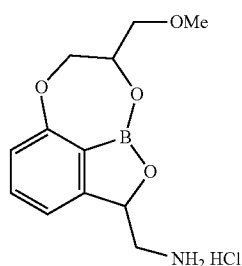
Compound of Example 4

[0102] The compound of Example 4 was prepared analogously to the procedures for preparation of the compound of Example 1, except using benzyl (R)-glycidyl ether instead of benzyl (S)-glycidyl ether to prepare the Intermediate 7, and then employing respective Intermediates 8-11 in procedures described above for methods with analogous Intermediates 3-6 (employed above to prepare the compound of Example 1). ¹H NMR: 8.25 (br s, 3H), 7.48 (t, J=7.20 Hz, 1H), 7.13 (d, J=7.50 Hz, 1H), 6.90 (d, J=7.80, 1H), 5.51 (d, J=5.10 Hz, 1H), 4.70 (m, 1H), 4.60 (m, 1H), 4.20 (m, 1H), 3.50-3.20 (m, overlapped with water signal), 2.92 (m, 1H). MS (m/z): 235.9 [M+H].

Example 5

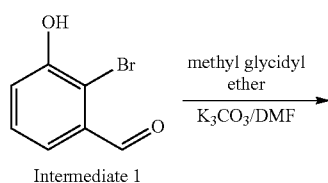
(8-(Methoxymethyl)-7,8-dihydro-2H-1,6,9-trioxo-9a-borabenz[cd]azulen-2-yl)methanamine hydrochloride

[0103]

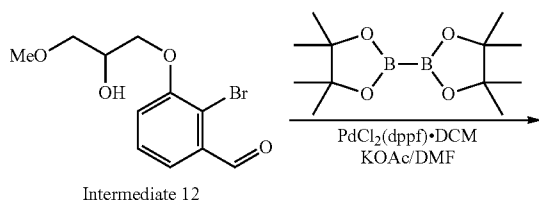


Example 5

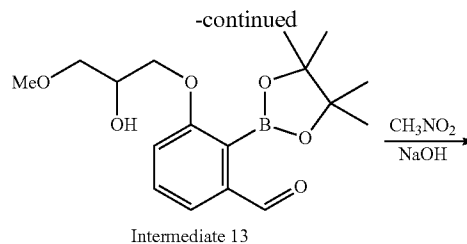
[0104] Scheme for preparation of the compound of Example 5:



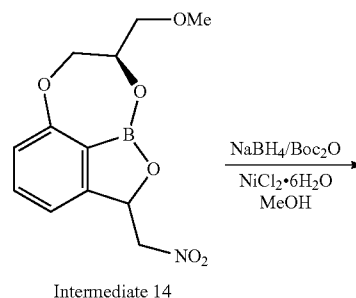
Intermediate 1



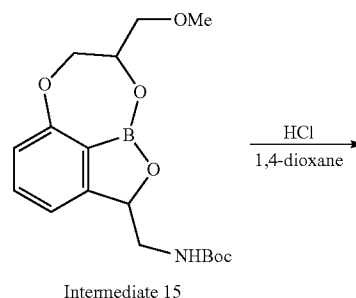
Intermediate 12



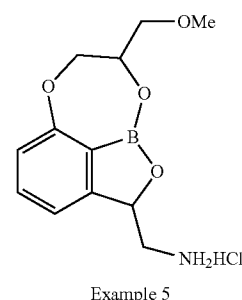
Intermediate 13



Intermediate 14



Intermediate 15



Example 5

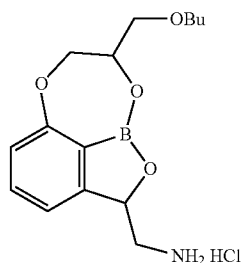
Compound of Example 5

[0105] The compound of Example 5 was prepared analogously to the procedures for preparation of the compound of Example 1, except using methyl-glycidyl ether instead of benzyl (S)-glycidyl ether to prepare the Intermediate 12, and then employing respective Intermediates 13-15 in procedures described above for methods with analogous Intermediates 3-5 (employed above to prepare the compound of Example 1). ¹H NMR: 8.19 (br s, 3H), 7.48 (t, J=7.20 Hz, 1H), 7.15 (d, J=7.45 Hz, 1H), 6.90 (m, 1H), 5.50 (m, 1H), 4.60 (m, 2H), 4.22 (m, 1H), 3.43 (m, overlapped with water signal), 2.90 (m, 1H). MS (m/z): 250.1 [M+H].

Example 6

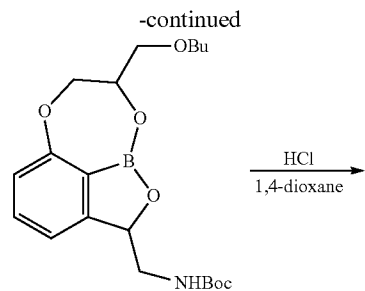
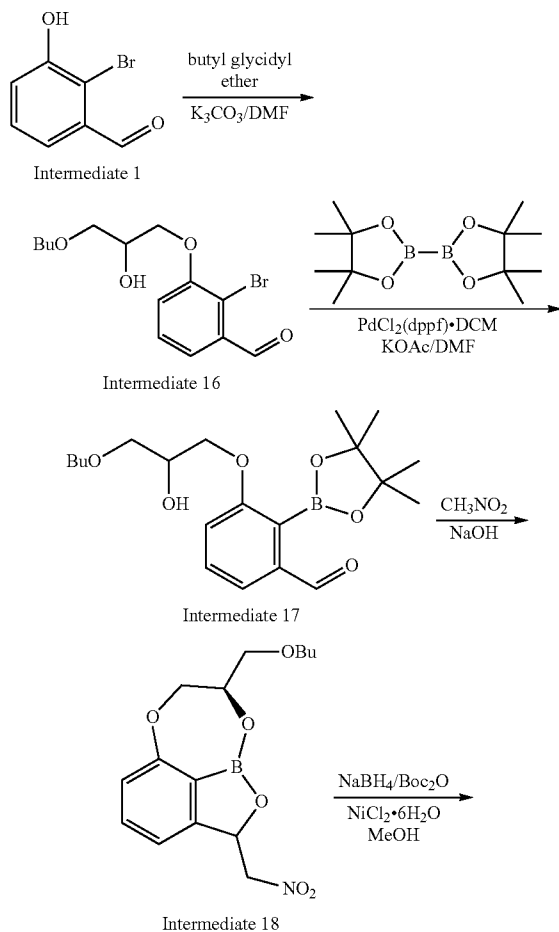
(8-(Butoxymethyl)-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methanamine hydrochloride

[0106]

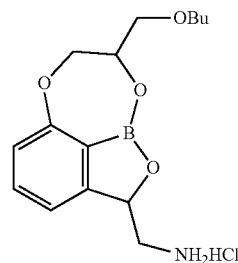


Example 6

[0107] Scheme for preparation of the compound of Example 6:



Intermediate 19



Example 6

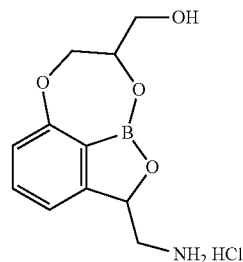
Compound of Example 6

[0108] The compound of Example 6 was prepared analogously to the procedures for preparation of the compound of Example 1, except using butyl glycidyl ether instead of benzyl (S)-glycidyl ether to prepare the Intermediate 16, and then employing respective Intermediates 17-19 in procedures described above for methods with analogous Intermediates 3-5 (employed to prepare the Compound of Example 1). ¹H NMR: 8.22 (br s, 3H), 7.54 (t, J=7.21 Hz, 1H), 7.18 (d, J=7.40 Hz, 1H), 6.94 (d, 1H), 5.50 (m, 1H), 4.68 (m, 1H), 4.52 (br, 1H), 4.21 (m, 1H), 4.05 (m, 1H), 3.58 (m, overlaps with water signal), 2.90 (m, 1H), 1.60-1.42 (m, 2H), 1.38-1.20 (m, 2H), 0.96-0.80 (m, 3H). MS (m/z): 292.0 [M+H].

Example 7

2-(Aminomethyl)-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-8-yl)methanol hydrochloride

[0109]



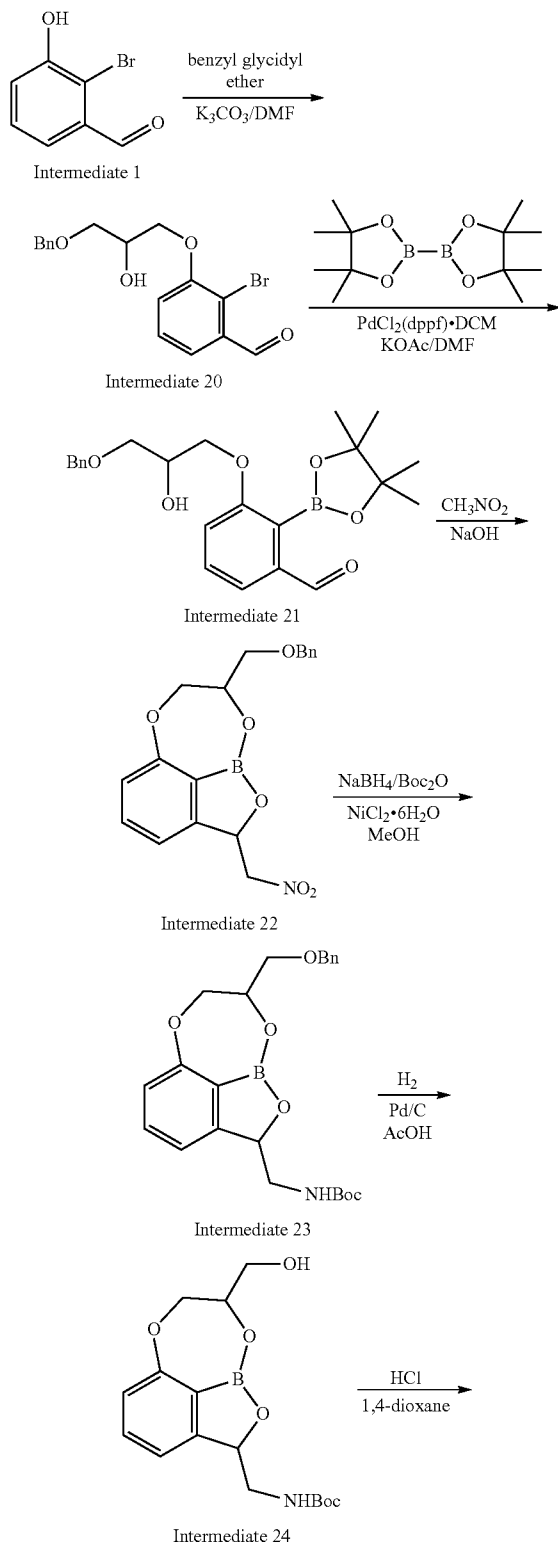
Example 7

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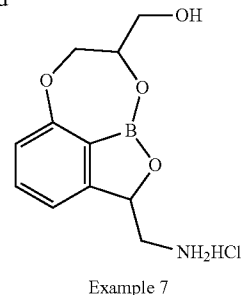
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[0110] Scheme for preparation of the compound of Example 7:



-continued



Compound of Example 7

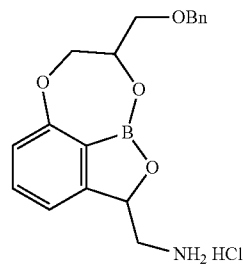
[0111] The compound of Example 4 was prepared analogously to the procedures for preparation of the compound of Example 1, except using benzyl glycidyl ether instead of benzyl (S)-glycidyl ether to prepare the Intermediate 20, and then employing respective Intermediates 21-24 in procedures described above for methods with analogous Intermediates 3-6 (employed to prepare the Compound of Example 1). ¹H NMR (CD₃OD): 7.49 (t, J=7.20 Hz, 1H), 7.08 (d, J=7.20 Hz, 1H), 6.93 (d, J=7.80 Hz, 1H), 5.54 (m, 1H), 4.40 (m, 1H), 4.21 (m, 1H), 4.05 (m, 1H), 3.80-3.52 (m, 4H), 3.01 (m, 1H). MS (m/z): 235.9 [M+H].

Example 8

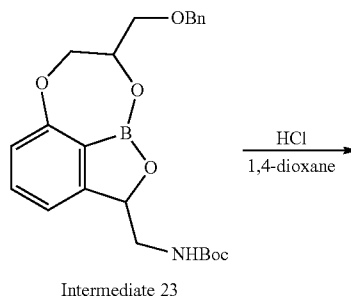
(8-((Benzyloxy)methyl)-7,8-dihydro-2H-1,6,9-trioxo-9a-borabenzoc[cd]azulen-2-yl)methanamine hydrochloride

[0112]

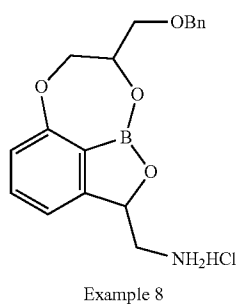
Example 8



[0113] Scheme for preparation of the compound of Example 8:



-continued



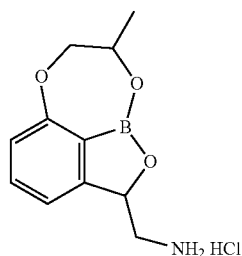
Compound of Example 8

[0114] Intermediate 23 (20 mg) was dissolved in 4N HCl in 1,4-dioxane (0.5 mL), and the solution was stirred at r.t. for 1 h. The volatiles were removed under vacuum, and the residue was dissolved in water (about 2 mL) and filtered. The aqueous solution lyophilized to afford the compound of Example 8. ¹H NMR (CD₃OD): 7.49 (t, J=7.80 Hz, 1H), 7.38-7.20 (m, 5H), 7.07 (d, J=6.90 Hz, 1H), 6.92 (dd, J 7.80 and 1.20 Hz, 1H), 5.48 (m, 1H), 4.57 (m, 2H), 4.40-4.02 (m, 2H), 3.80-3.50 (m, 4H), 3.00 (m, 1H). MS (m/z): 326.1.0 [M+1].

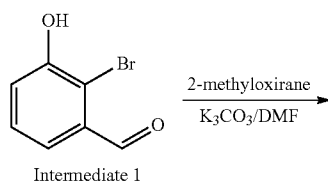
Example 9

(8-Methyl-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzocd]azulen-2-yl)methanamine hydrochloride

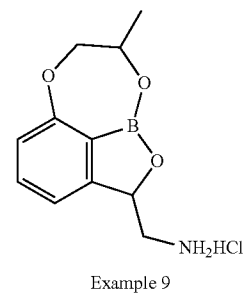
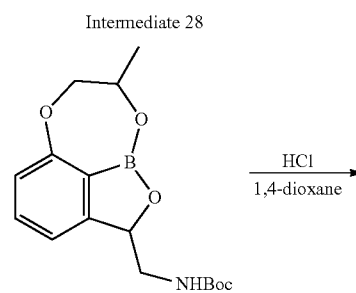
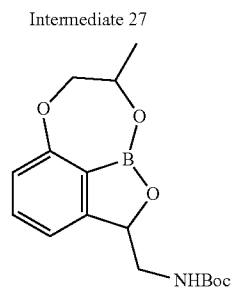
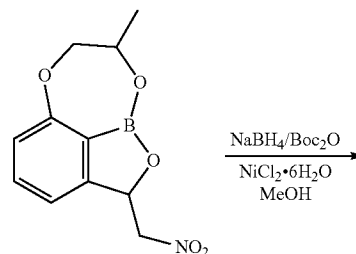
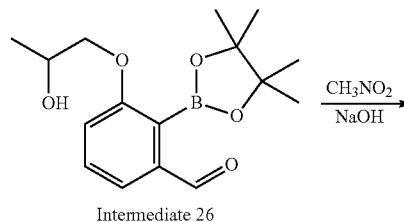
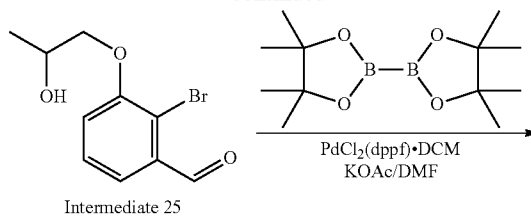
[0115]



[0116] Scheme for preparation of the compound of Example 9:



-continued



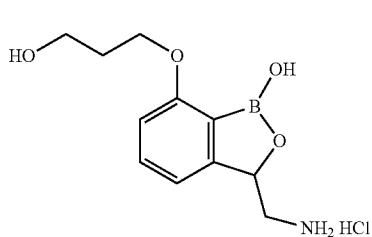
Compound of Example 9

[0117] The compound of Example 9 was prepared analogously to the procedures for preparation of the compound of Example 1, except using methyl oxirane instead of benzyl (S)-glycidyl ether to prepare the Intermediate 25, and then employing respective Intermediates 26-29 in procedures described above for methods with analogous Intermediates 3-6 (employed to prepare the compound of Example 1). ¹H NMR: 8.19 (br. s, 3H), 7.48 (t, J=7.50 Hz, 1H), 7.13 (d, J=7.20 Hz, 1H), 6.91 (m, 1H), 5.50 (m, 1H), 4.58-4.50 (m, 2H), 4.22-4.15 (m, 1H), 3.70-3.60 (m, 1H), 2.89 (m, 1H), 1.39-1.21 (m, 3H). MS (m/z): 220.1 [M+1].

Reference Example 10

3-(Aminomethyl)-7-(3-hydroxypropoxy)benzo[c][1,2]oxaborol-1(3H)-ol hydrochloride

[0118]



Reference Example 10

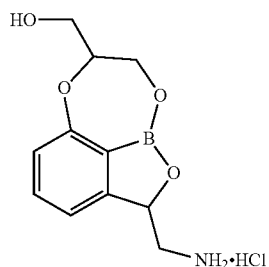
Reference Compound of Example 10

[0119] The reference Compound of Example 10 was prepared analogously to the procedures described in a publication US 2009/0227541. MS (m/z): 238.0 [M+H].

Example 11

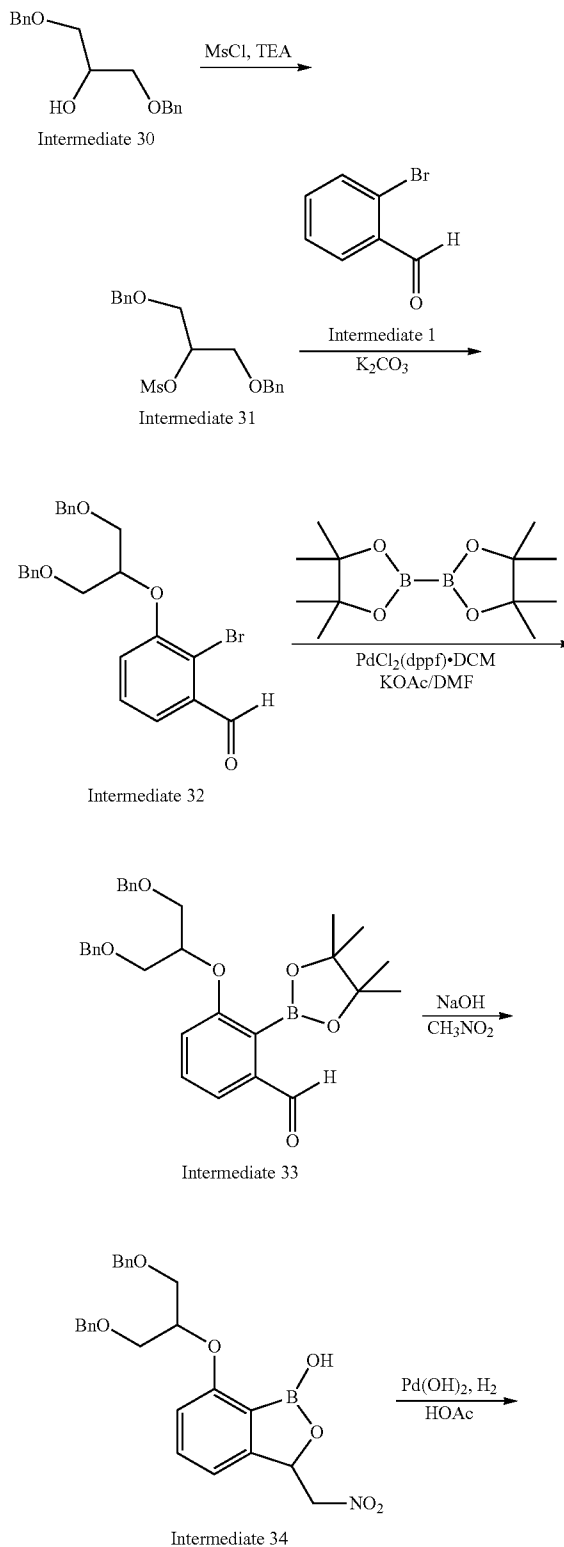
(2-(Aminomethyl)-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-7-yl)methanol hydrochloride

[0120]



Example 11

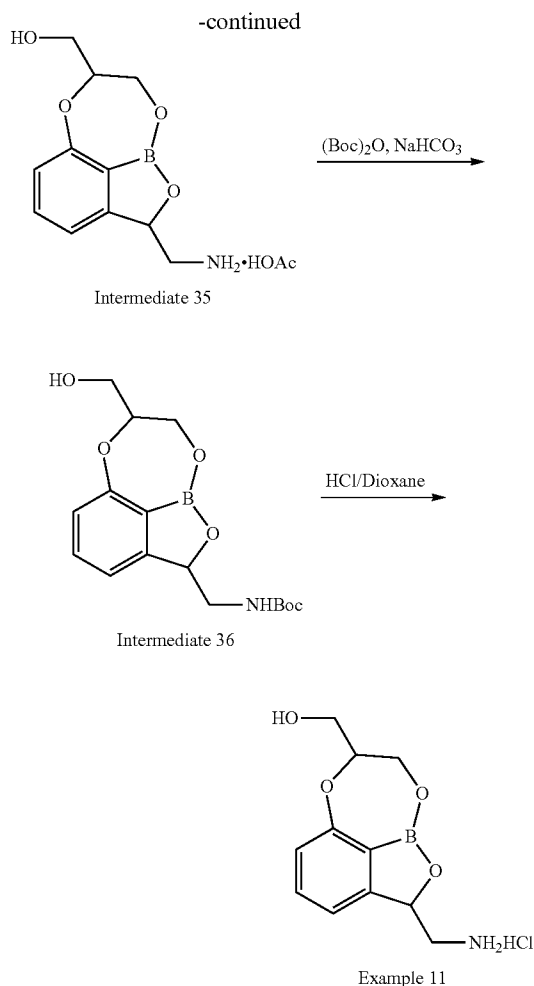
[0121] Scheme for preparation of the compound of Example 11:



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Intermediate 31.

[0122] MsCl (2.35 ml, 30.40 mmol) was added to a solution of Intermediate 30 (6.9 g, 25.33 mmol), TEA (7.06 ml, 50.66 mmol) in DCM (30 ml) at 0° C. and stirred for 30 min. The mixture was washed with water, and the organic layers were evaporated under vacuum. The crude was taken directly into next step.

Intermediate 32.

[0123] K₂CO₃ (7 g, 50.66 mmol) was added to a solution Intermediate 31 (9.52 g, 25.33 mmol) and Intermediate 1 (7.64 g, 38 mmol) in DMF (50 ml). The suspension was stirred at 90° C. for 24 h. After the starting bromide was consumed, the mixture was cooled down to r.t., diluted with brine and extracted with EtOAc. EtOAc was removed under vacuum and the residue was purified by silica gel column chromatography (eluent: EtOAc/PE (petroleum ether) 1:20 to 1:15) to afford the Intermediate 32 as a colorless oil.

Intermediate 33.

[0124] Intermediate 32 (7.46 g, 16.38 mmol) was mixed with bis(pinacolato)diboron (8.32 g, 32.77 mmol), KOAc

(1.74 g, 17.72 mmol), (4.85 g, 49.15 mmol), PdCl₂(dppf) DCM (0.365 g, 0.5 mmol), and dissolved in DMF (50 ml). The solution was degassed three times with nitrogen, and then heated at about 90° C. for about 14 h. The reaction was worked up with EtOAc/brine/H₂O, and the product was purified by silica gel column chromatography (eluent: EtOAc/PE 1:20 to 1:10) to afford the Intermediate 33 as a brown oil.

Intermediate 34.

[0125] To an ice-cold solution of NaOH (0.333 g, 8.32 mmol) in water (10 ml) was added Intermediate 33 (4.18 g, 8.32 mmol) in THF (10 ml). After stirring for 15 min, nitromethane (0.537 ml, 9.98 mmol) was added dropwise, and the mixture was stirred at r.t. for 15 h. The mixture was acidified with AcOH to pH ca. 3-5. The suspension was extracted with EtOAc (3×). The combined organic layer were evaporated under vacuum, and the residue was purified by silica gel column chromatography (eluent: EtOAc/PE 1:4 to 1:1) to afford the Intermediate 34 as a brown oil.

Intermediate 35.

[0126] 20% Pd(OH)₂/C (50% water, 1 g) was added to a solution of Intermediate 34 (1.10 g, 2.37 mmol) in HOAc (8.5 ml). The solution was degassed three times with H₂, and stirred at r.t. for overnight. After filtering through celite pad, the filtrate was concentrated under vacuum with toluene to afford the Intermediate 35 as yellow solid. MS (m/z): 236.0 [M+H].

Intermediate 36.

[0127] NaHCO₃ (298.6 mg, 3.56 mmol) was added to a solution of Intermediate 35 (1.01 g, 2.37 mmol) t-BuOH (3 mL) and H₂O (3 mL) at r.t. After stirring at r.t. for 15 min. (Boc)₂O (516.7 mg, 2.37 mmol) was added and stirred at r.t. for 1.5 h. The mixture was acidified with AcOH to pH ca. 6-7 and extracted with DCM. Combined organic layers were evaporated under vacuum, and the residue purified by silica gel column chromatography (eluant: DCM/MeOH 20:1) to afford the Intermediate 36 as yellow oil. MS (m/z): 336.0 [M+H].

Compound of Example 11

[0128] Intermediate 36 (90.5 mg, 0.27 mmol) was dissolved in 4N HCl in 1,4-dioxane (2 mL), and the solution was stirred at r.t. for about 2 h. The volatiles were removed under vacuum, and the residue was dissolved in water ca. 3 mL) and filtered through 0.45 μm membrane filter. The aq. solution was lyophilized to afford the compound of Example 11. ¹H NMR: 8.16 (d, J=16.8 Hz, 2H), 7.51 (t, J=7.6 Hz, 1H), 7.15 (dd, J 7.6, 3.6 Hz, 1H), 6.92 (dd, J 8.0, 1.6 Hz, 1H), 5.50 (t, J=9.2 Hz, 1H), 4.46 (d, J=12.4 Hz, 1H), 4.24-4.18 (m, 2H), 3.76 (dd, J 11.6, 4.4 Hz, 1H), 3.62 (dd, J 10.0, 4.8 Hz, 1H), 3.50 (d, J=12.4 Hz, 1H), 3.00-2.88 (m, 1H). MS (m/z): 236.0 [M+H].

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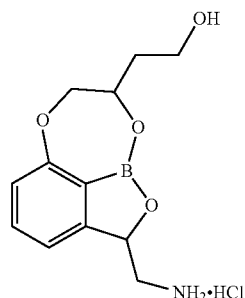
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Example 12

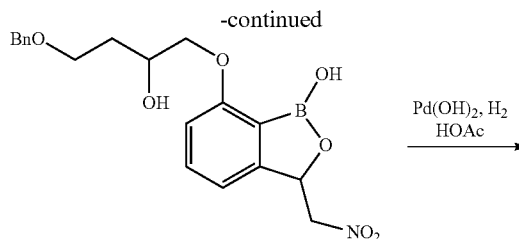
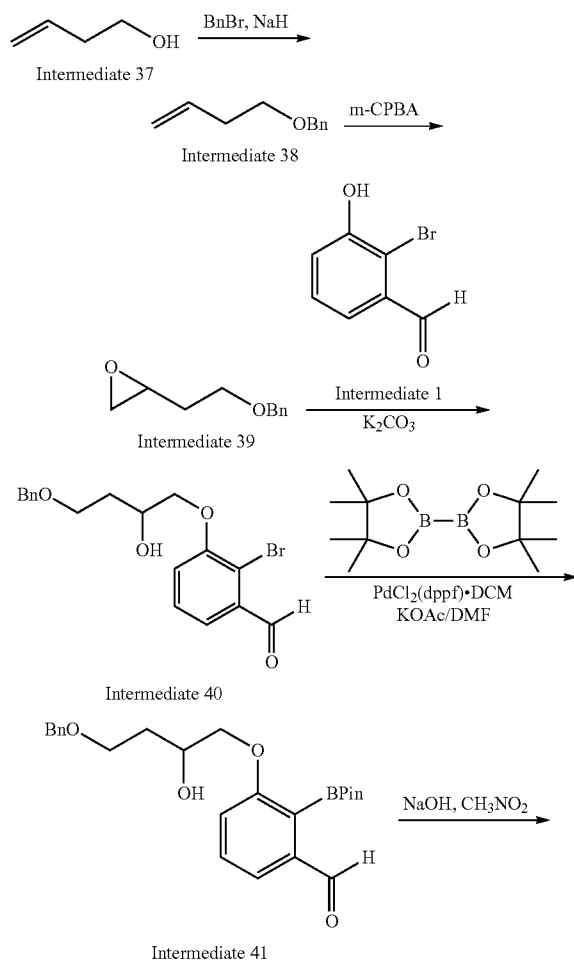
2-(2-(Aminomethyl)-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-8-yl)ethanol hydrochloride

[0129]

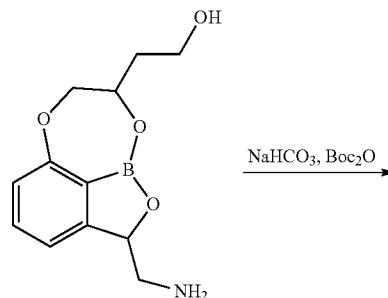


Example 12

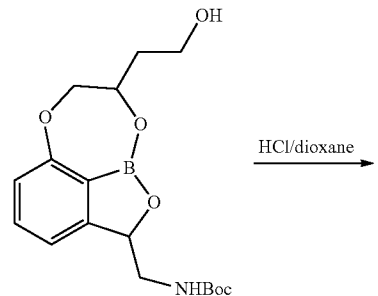
[0130] Scheme for preparation of the compound of Example 12:



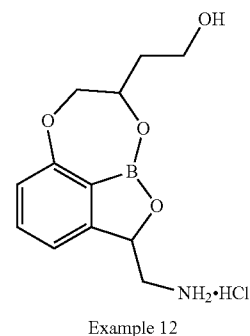
Intermediate 42



Intermediate 43



Intermediate 44



Example 12

Intermediate 38.

[0131] NaH (50% in oil, 2.88 g, 0.06 mol) was slowly added to a solution of Intermediate 37 (3 g, 0.041 mol) in 30 mL anhydrous DMF in ice-bath. After stirring for 0.5 h, BnBr (5.38 mL, 0.045 mol) was added to the reaction solution and stirred at r.t. for overnight. The mixture was poured into 80 mL H₂O at 0° C., extracted with EtOAc. The combined organic phase was washed with aq. NH₄Cl, brine and dried over Na₂SO₄. After concentration, the residue was dissolved in PE (petroleum ether), and filtered through a pad of silica gel. The filtrate was concentrated to afford the Intermediate 38 as colorless oil.

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Intermediate 39.

[0132] m-Chloroperoxybenzoic acid (m-CPBA, 6.4 g, 0.037 mol) was added to a DCM solution (50 mL) of Intermediate 38 (4 g, 0.025 mol) in portions. The mixture was stirred at r.t. for overnight. The white precipitate was filtered off, and the filtrate was washed with aq Na₂CO₃, H₂O, brine and dried (Na₂SO₄). After concentration, the residue was purified by silica gel column chromatography (eluent: PE/EtOAc 75:1) to afford the Intermediate 39 as yellow oil.

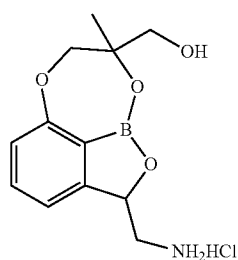
Compound of Example 12

[0133] The compound of Example 12 was prepared analogously to the procedures for preparation of the compound of Example 11, except using Intermediate 39 instead of the Intermediate 31 to prepare the Intermediate 40, and then employing respective Intermediates 41-44 in procedures described above for methods with analogous Intermediates 33-36 (employed to prepare the compound of Example 11). ¹H NMR (D₂O): 7.46 (t, J=7.6 Hz, 1H), 6.98 (d, J=7.2 Hz, 1H), 6.89 (d, J=8.0, 1H), 5.42-5.39 (m, 1H), 4.31-3.81 (m, 3H), 3.53 (m, 2H), 3.55-3.52 (m, 1H), 3.08-3.03 (m, 1H), 1.80-1.70 (m, 2H). MS (m/z): 250.1 [M+H].

Example 13

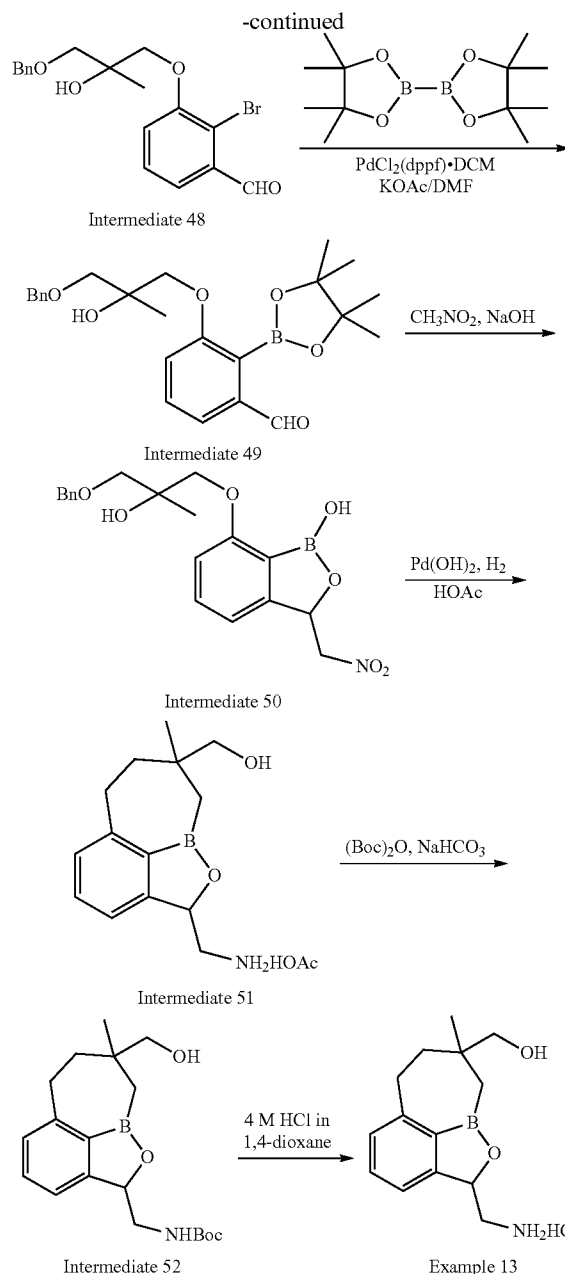
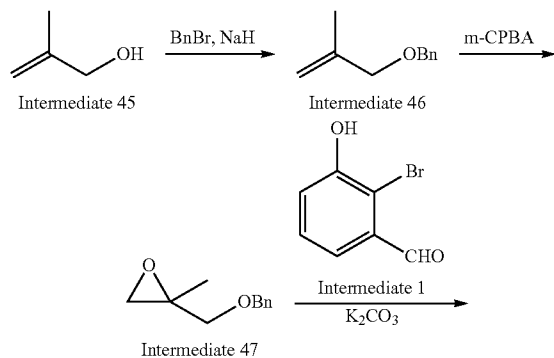
(2-(Aminomethyl)-8-methyl-7,8-dihydro-2H-1,6,9-trioxo-9a-borabenz[cd]azulen-8-yl)methanol hydrochloride

[0134]



Example 13

[0135] Scheme for preparation of the compound of Example 13:



Compound of Example 13

[0136] The compound of Example 13 was prepared analogously to the procedures for preparation of the compound of Example 12, except using Intermediate 45 instead of the Intermediate 37 to prepare the Intermediate 46, and then employing respective Intermediates 47-52 in procedures described above for methods with analogous Intermediates 39-44 (employed to prepare the compound of Example 12). ¹H NMR (D₂O): 7.48 (t, J=8.0 Hz, 1H), 7.01 (d, J=7.6 Hz, 1H), 6.91 (d, J=8.0 Hz, 1H), 5.41 (s, 1H), 3.65 (s, 2H), 3.60-3.54 (m, 3H), 3.06 (dd, J=13.6, 6.8 Hz, 1H), 1.20 (s, 3H). MS (m/z): 250.0 [M+H].

US 2013/0165411 A1

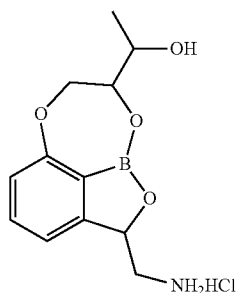
Jun. 27, 2013

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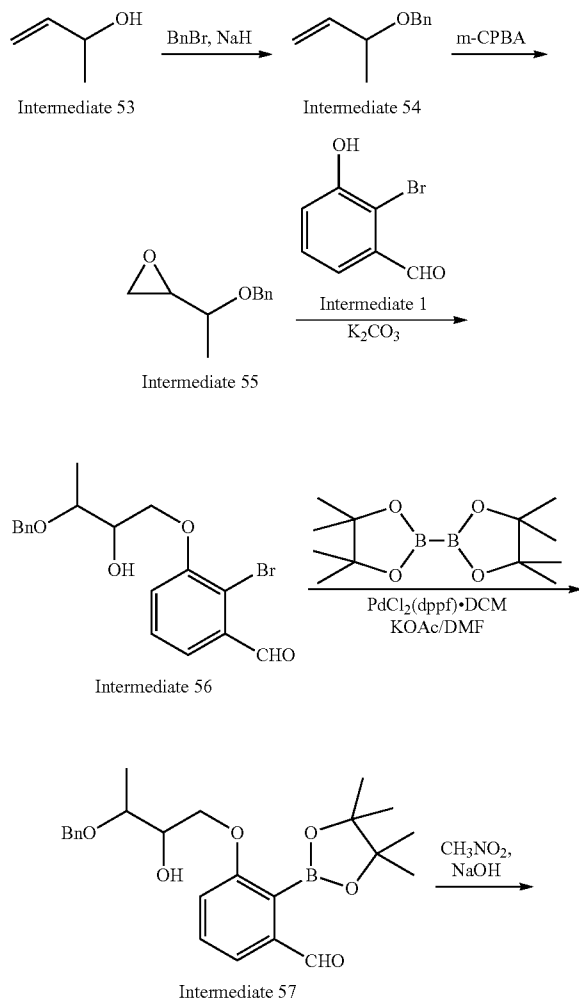
Example 14

[0137] 1-(2-(Aminomethyl)-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulen-8-yl)ethanol hydrochloride

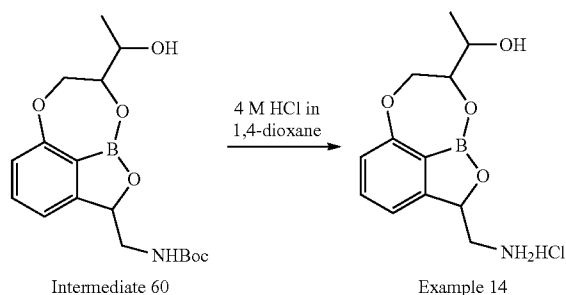
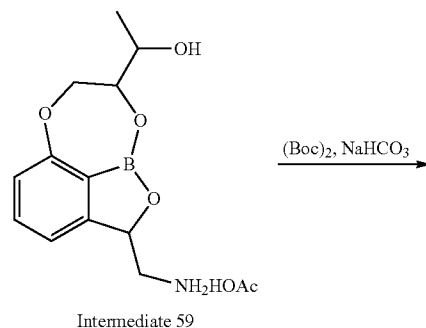
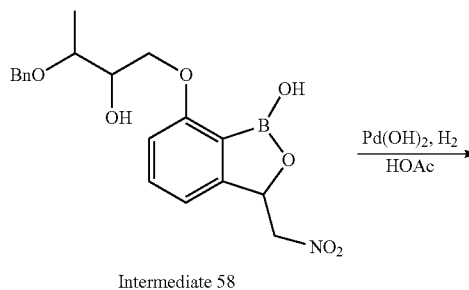
Example 14



[0138] Scheme for preparation of the compound of Example 14:



-continued



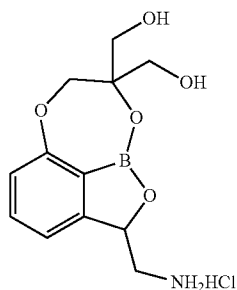
Compound of Example 14

[0139] The compound of Example 14 was prepared analogously to the procedures for preparation of the compound of Example 12, except using Intermediate 53 instead of the Intermediate 37 to prepare the Intermediate 54, and then employing respective Intermediates 55-60 in procedures described above for methods with analogous Intermediates 39-44 (employed to prepare the compound of Example 12). ¹H NMR (D₂O): 7.47 (t, J=8.0 Hz, 1H), 7.00-6.98 (m, 1H), 6.91-6.81 (m, 1H), 5.40 (s, 1H), 4.20-3.88 (m, 4H), 3.65-3.43 (m, 1H), 3.09-3.04 (m, 1H), 1.17-1.06 (m, 3H). MS (m/z): 250.0 [M+H].

Example 15

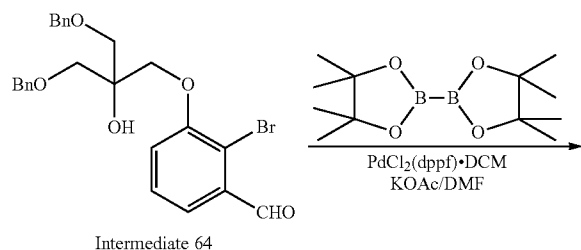
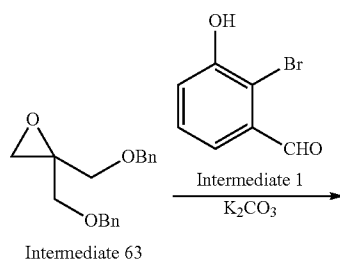
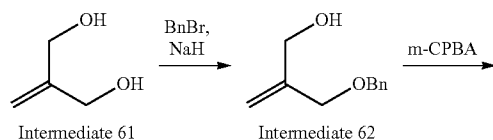
(2-(Aminomethyl)-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenzoc[cd]azulene-8,8-diyl)dimethanol hydrochloride

[0140]

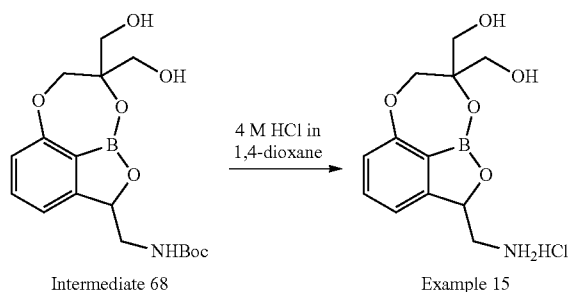
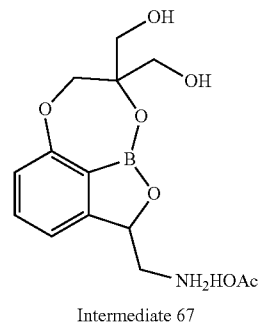
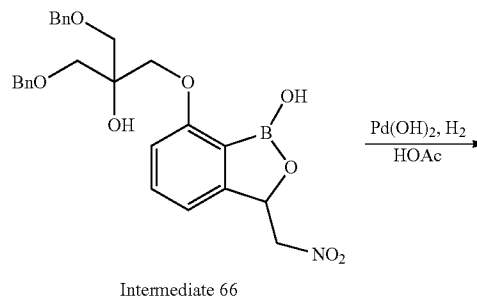
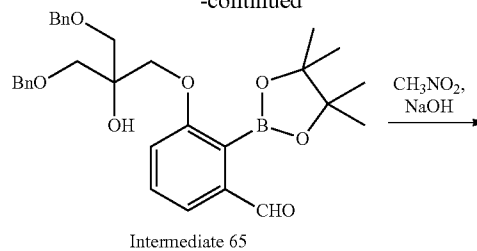


Example 15

[0141] Scheme for preparation of the compound of Example 15:



-continued



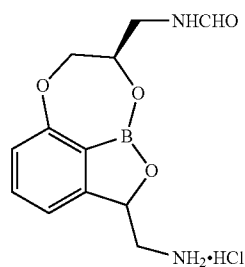
Compound of Example 15

[0142] The compound of Example 15 was prepared analogously to the procedures for preparation of the compound of Example 12, except using Intermediate 61 instead of Intermediate 37 to prepare the Intermediate 62, and then employing respective Intermediates 63-68 in procedures described above for methods with analogous Intermediates 39-44 (employed to prepare the compound of Example 12). ¹H NMR (D₂O): 7.43 (t, J=8.0 Hz, 1H), 6.96 (d, J=7.6 Hz, 1H), 6.86 (d, J=8.0 Hz, 1H), 5.37 (m, 1H), 4.08-4.10 (s, 2H), 3.60 (s, 4H), 3.51-3.55 (m, 1H), 3.00-3.06 (m, 1H). MS (m/z): 265.1 [M+H].

Example 16

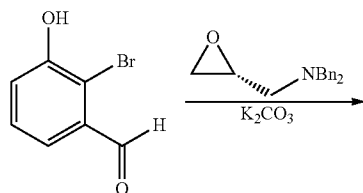
N-(((8R)-2-(aminomethyl)-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-8-yl)methyl)formamide hydrochloride

[0143]

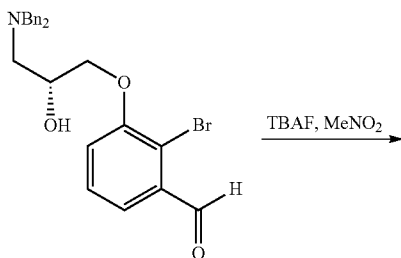


Example 16

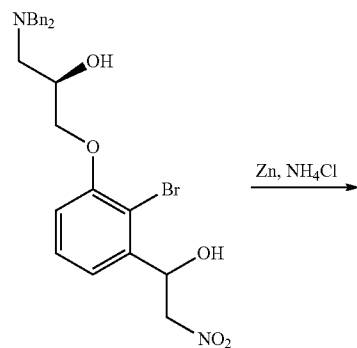
[0144] Scheme for preparation of the compound of Example 16:



Intermediate 69

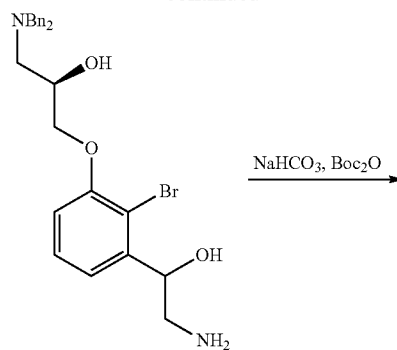


Intermediate 70

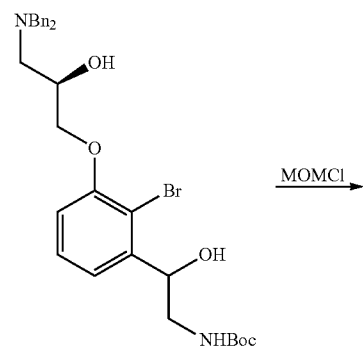


Intermediate 71

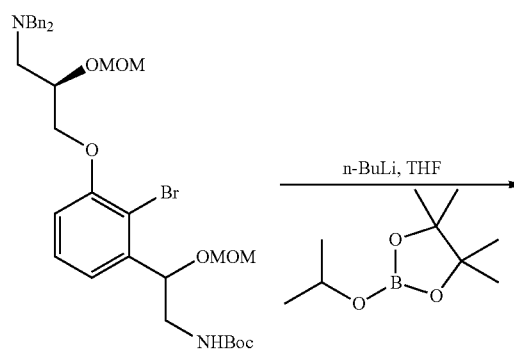
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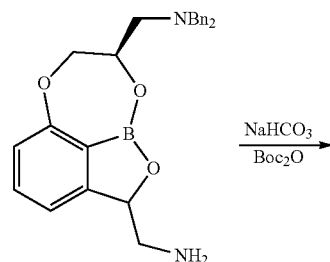
Intermediate 72



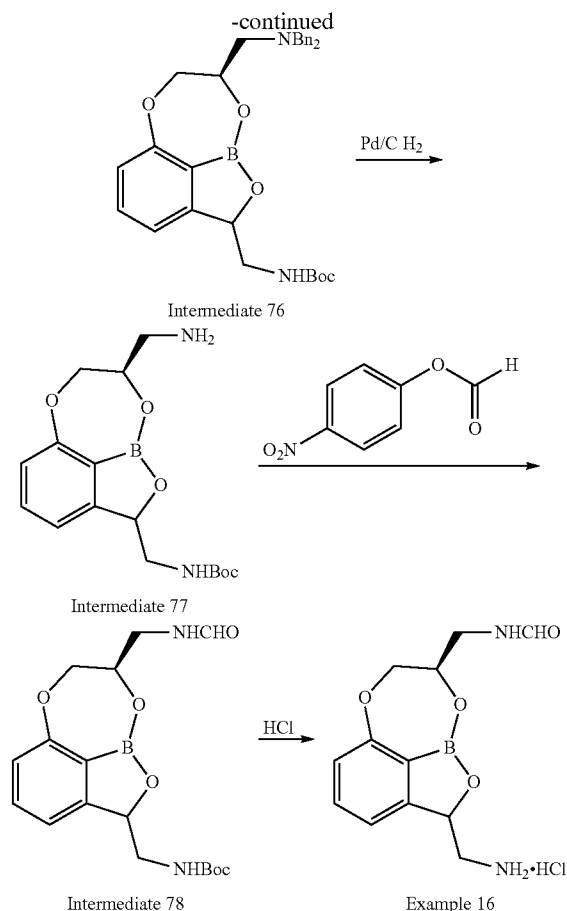
Intermediate 73



Intermediate 74



Intermediate 75



Intermediate 70.

[0145] K₂CO₃ (4.1 g) was added to a solution of Intermediate 69 (4.0 g) and (R)—N,N-dibenzyl-1-(oxiran-2-yl) methanamine (5.0 g; prepared as detailed in the ref. *J. Chem. Soc., Perkin Trans. 1*, 2001, 1086-1090) in DMF (20 mL). The suspension was stirred at 120° C. for 36 h. The mixture was cooled down to r.t., diluted with brine and extracted with EtOAc. EtOAc was removed under vacuum and the residue was taken directly into the next step. MS (m/z): 455.4 [M+H].

Intermediate 71.

[0146] 1M TBAF in THF (20 mL) was added dropwise to a solution of Intermediate 70 (9.5 g) and MeNO₂ (5.6 mL) in THF (100 mL) at 0° C. The mixture was stirred at same temperature for 3 h. The mixture was poured into ice-water (80 mL), extracted with EtOAc. The combined organic phase was washed with brine and concentrated under vacuum. The residue was purified by silica gel column chromatography to afford the Intermediate 71. MS (m/z): 516.4 [M+H].

Intermediate 72.

[0147] Zn (6.3 g) was added to a solution of Intermediate 71 (5.0 g) and NH₄Cl (5.2 g) in MeOH (80 mL). The suspension was stirred at r.t. for 2 h. After filtration, the filtrate was evaporated under vacuum to afford the Intermediate 72 used at next step without purification. MS (m/z): 486.5 [M+H].

Intermediate 73.

[0148] The total amount of Intermediate 72 was dissolved in MeOH (60 mL) and water (20 mL). NaHCO₃ (1.3 g) was added, followed by Boc₂O (3.3 g). The mixture was stirred at r.t. o.n. The solvent was removed under vacuum, the residue was re-dissolved in water and EtOAc. The organic layer was washed with brine, concentrated under vacuum to afford the Intermediate 73. MS (m/z): 586.5 [M+H].

Intermediate 74.

[0149] Methoxymethyl chloride (MOMCl, 5.5 mL) was added dropwise to a solution of Intermediate 73 (5.3 g) and DIEA (11.9 mL) in DCM (50 mL) at 0° C. The mixture was stirred at r.t. o.n. The mixture was washed with H₂O and extracted with DCM. The combined organic layer dried and concentrated. The residue was purified by silica gel column chromatography to afford the Intermediate 74. MS (m/z): 674.6 [M+H].

Intermediate 75.

[0150] 2.5M BuLi in hexanes (0.6 mL) was added dropwise to a solution of Intermediate 74 (202 mg) in THF (1 mL) under Ar at -78° C. After stirring at same temperature for 3 h, 1-isopropoxy-3,3,4,4-tetramethylborolane (468 mg) was added. The mixture was slowly warmed to r.t. and stirred for another 1 h. 8M HCl (1 mL) was added, and the mixture was stirred at r.t. o.n. Volatiles were removed by lyophilization to afford the Intermediate 75. MS (m/z): 415.3 [M+H].

Intermediate 76.

[0151] The total amount of the Intermediate 75 from preceding step was dissolved in MeOH (3 mL) and water (2 mL). NaHCO₃ (84 mg) was added, followed by Boc₂O (131 mg). The mixture was stirred at r.t. o.n. The solvent was removed under vacuum, the residue was re-dissolved in water and EtOAc. The organic larger was washed with brine, concentrated under vacuum. The residue was purified by HPLC to afford the Intermediate 76. MS (m/z): 515.3 [M+H].

Intermediate 77.

[0152] A suspension of Intermediate 76 (20 mg) and Pd/C (2 mg) in MeOH (1 mL) was degassed with H₂ for three times. The mixture was stirred under H₂ at r.t. for 3 h. After filtration, the filtrate was concentrated under vacuum to afford the Intermediate 77. MS (m/z): 334.2 [M+H].

Intermediate 78.

[0153] The total of the Intermediate 77 was dissolved in MeOH (1 mL). 4-Nitrophenyl formate (8 mg) was added, and the mixture was stirred r.t. for 6 h. The solvent was removed under vacuum to afford the Intermediate 78. MS (m/z): 362.2 [M+H].

Compound of Example 16

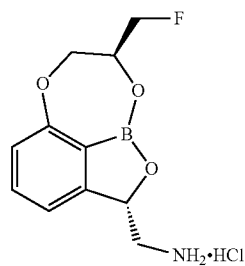
[0154] The total amount of Intermediate 78 from preceding step was added to 4M HCl in dioxane (1 mL). The mixture was stirred at r.t. for 2 h. Volatiles were removed under vacuum. The residue was dissolved in water (5 mL) and washed with EtOAc and Et₂O. The aqueous phase was lyophilized to afford the compound of Example 16. ¹H NMR (D₂O): 7.99 (s, 1H), 7.47 (dd, J 10.0, 6.0 Hz, 1H), 6.99 (d,

J=7.2 Hz, 1H), 6.87 (d, J=8.4 Hz, 1H), 5.39 (s, 1H), 4.12-4.19 (m, 2H), 4.35 (d, J=17.2 Hz, 1H), 3.33-4.48 (m, 2H), 3.20-3.25 (m, 1H), 3.04-3.13 (m, 1H). MS (m/z): 262.2 [M+H].

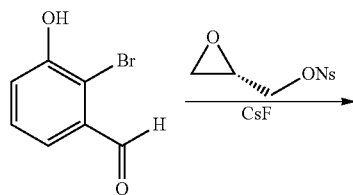
Example 17

((2S,8S)-8-(Fluoromethyl)-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methanamine hydrochloride

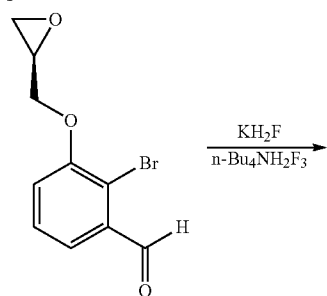
[0155]



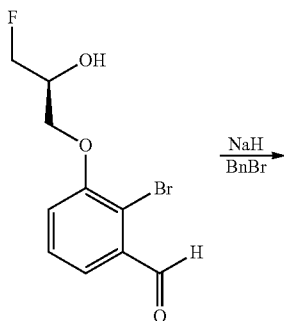
[0156] Scheme for preparation of the compound of Example 17:



Intermediate 1

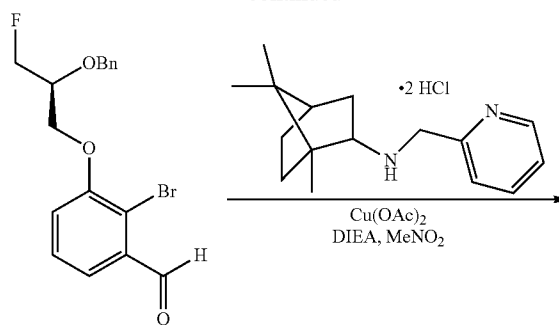


Intermediate 79

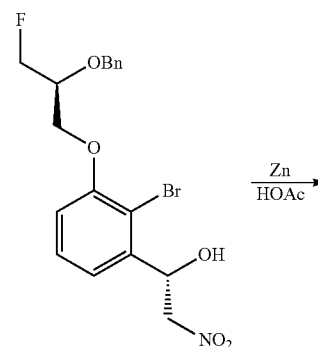


Intermediate 80

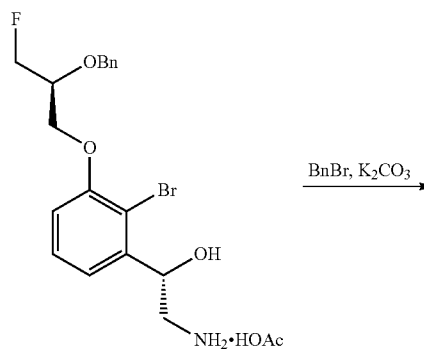
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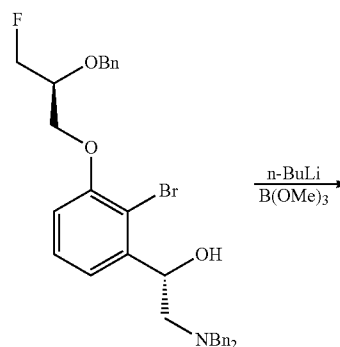
Intermediate 81



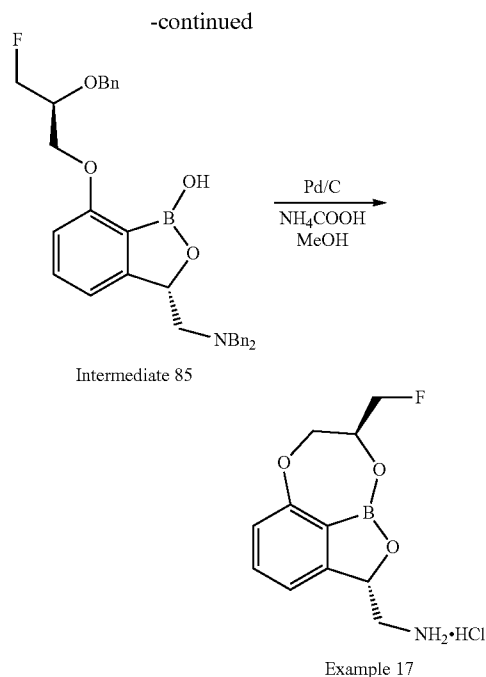
Intermediate 82



Intermediate 83



Intermediate 84



Intermediate 79.

[0157] CsF (27 g) was added to a solution of Intermediate 1 (9.0 g) and (S)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (23 g) in DMF (150 mL). The mixture was stirred at 80° C. for 40 h. The mixture was poured into ice-H₂O and extracted with EtOAc. The combined organic layers were washed with brine, dried and concentrated under vacuum. The residue was purified by silica gel column chromatography (eluent: PE/EtOAc 6:1) to afford the Intermediate 79.

Intermediate 80.

[0158] n-Bu₄NH₂F₃ (1.1 g) was added to a solution of Intermediate 79 (3.0 g) in chlorobenzene (6 mL), followed by KHF₂ (2.7 g). The mixture was stirred at 135° C. o.n. After cooling to r.t., the mixture was poured into ice-water and extracted with EtOAc. The combined organic layer was dried and concentrated under vacuum. The residue was purified by silica gel column chromatography (eluent: PE/EtOAc 5:2) to afford the Intermediate 80.

Intermediate 81.

[0159] NaH (0.38 g) was added to a solution of Intermediate 80 in DMF (20 mL) at 0° C. After stirring for 0.5 h, BnBr (1.03 mL) was added, and the mixture was stirred at r.t. o.n. The mixture was poured into ice-water, extracted with EtOAc. The organic layer was dried and evaporated under vacuum. The residue was purified by silica gel column chromatography (eluent: PE/EtOAc 10:1) to afford the Intermediate 81.

Intermediate 82.

[0160] A mixture of Cu(OAc)₂ (17.3 mg) and N-((1S,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)pyridin-2-amine dihydrochloride (36.3 mg) in EtOH (6 mL) was stirred at r.t. for 1 h, at which time Intermediate 81 (1.5 g) was added. The reaction mixture was cooled to -40° C. and nitromethane (2.2 mL) was added while maintaining the temperature below -30° C., followed by DIEA (0.7 mL). The mixture was stirred at -30° C. for 48 h. TFA (0.05 mL) was added, followed by water H₂O (50 mL), and EtOAc (50 mL). The aqueous layer was extracted with EtOAc. The organic layer was dried and concentrated under vacuum. The residue was purified by silica gel column chromatography (eluent: PE/EtOAc 8:1) to afford the Intermediate 82.

Intermediate 83.

[0161] Zn (1.44 g) was added to a solution of Intermediate 82 (630 mg) in HOAc (7 mL). The suspension was stirred at r.t. for 3 h. After filtration, the filtrate was evaporated to afford the Intermediate 83. MS (m/z): 399.3 [M+H].

Intermediate 84.

[0162] The total amount of Intermediate 83 was dissolved in EtOH (10 mL). K₂CO₃ (455 mg) was added, followed by BnBr (0.590 mL). The mixture was stirred at r.t. for 24 h. The mixture was diluted with water, extracted with EtOAc. The combined organic layer was dried and concentrated under vacuum. The residue was purified by silica gel column chromatography (eluent: PE/EtOAc 10:1) to afford the Intermediate 84. MS (m/z): 579.5 [M+H].

Intermediate 85.

[0163] 2.5M BuLi in hexanes (2.6 mL) was added dropwise to a solution of Intermediate 84 (762 mg) in THF (8 mL) under Ar at -78° C. After stirring at same temperature for 3 h, B(OMe)₃ (2.1 g) was added. The mixture was allowed to warm up to r.t. and stirred for another 1 h. The mixture was poured into ice-water, extracted with EtOAc. The combined organic layer was dried and concentrated under vacuum to afford the Intermediate 85. MS (m/z): 526.4 [M+H].

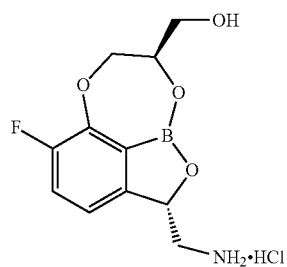
Compound of Example 17

[0164] To a suspension of Intermediate 85 (1.0 g) and Pd/C (250 mg) in MeOH (15 mL) stirred at 50° C. was added NH₄COOH (2.5 g). The mixture was stirred for 2 h. After filtration, the solvent was removed under vacuum. The residue was purified by HPLC to afford the compound of Example 17. ¹H NMR (D₂O): 7.49 (t, J=8.0 Hz, 1H), 7.00 (d, J=8.0 Hz, 1H), 6.91 (d, J=8.0 Hz, 1H), 5.39-5.40 (m, 1H), 4.58-4.70 (m, 1H), 4.47-4.54 (m, 1H), 4.11-4.33 (m, 3H), 3.54 (dd, J 13.2, 2.8 Hz, 1H), 3.07 (dd, J 13.2, 2.8 Hz, 1H). MS (m/z): 237.0 [M+H].

Example 18

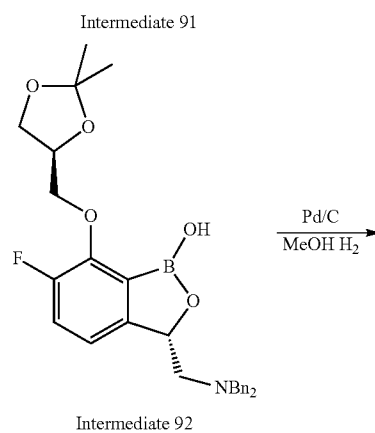
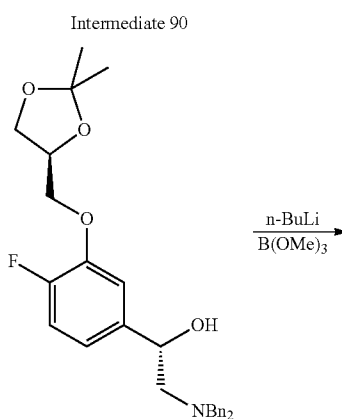
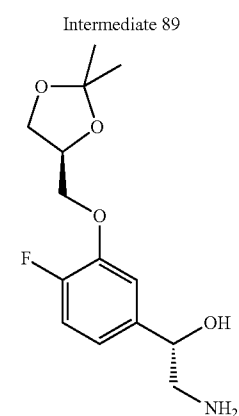
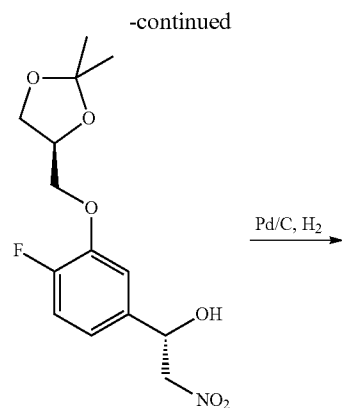
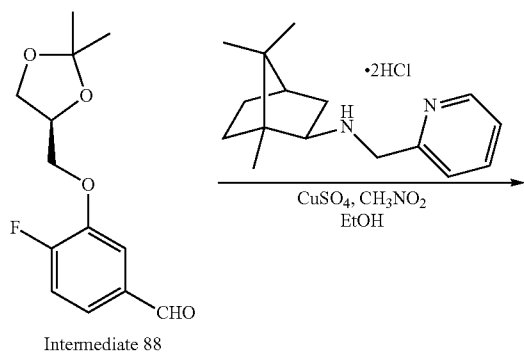
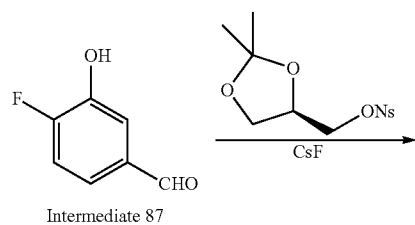
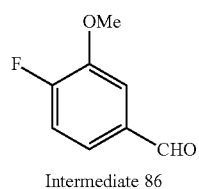
((2S,8R)-2-(Aminomethyl)-5-fluoro-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-8-yl)methanol hydrochloride

[0165]

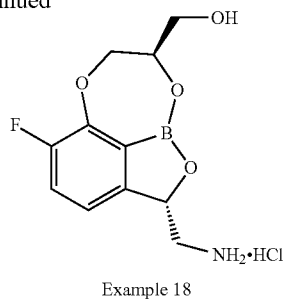


Example 18

[0166] Scheme for preparation of the Compound of Example 18:



-continued



Intermediate 87.

[0167] BBr_3 (32.6 g) was added dropwise to a mixture of Intermediate 86 (10 g) in anhydrous DCM at -78°C . The mixture was slowly warmed to r.t. and stirred for 4 h. The mixture was cooled to -78°C ., quenched with 2N HCl and then stirred at r.t. o.n. Water (40 mL) was added, and the mixture was extracted with DCM. The combined organic layer was dried and evaporated under vacuum. The residue was purified by silica gel column chromatography (eluent: PE/EtOAc 3:1) to afford the Intermediate 87 as yellow oil.

Intermediate 88.

[0168] CsF (20.0 g) was added to a solution of Intermediate 87 (3.7 g) and (R)-(2,2-dimethyl-1,3-dioxolan-4-yl)methyl 3-nitrobenzenesulfonate (9.64 g) in DMF (50 mL). The mixture was stirred at 80°C . for overnight. Water (40 mL) was added and extracted with EtOAc. The combined organic layer was washed, dried and concentrated under vacuum. The residue was purified by silica gel column chromatography (eluent: PE/EtOAc 3:1) to afford the Intermediate 88. MS (m/z): 579.5 [M+H].

Intermediate 89.

[0169] Intermediate 89 was synthesized analogously to the procedure for preparation of the Intermediate 82, except starting from Intermediate 88 instead of Intermediate 81. The residue was purified by silica gel column chromatography (eluent: PE/EtOAc 5:1) to afford the Intermediate 89 as yellow oil.

Intermediate 90.

[0170] A suspension of Intermediate 89 (1.0 g) and Pd/C in MeOH (2 mL) was stirred under H_2 atmosphere overnight. After filtration, the filtrate was concentrated under vacuum to afford the Intermediate 90. MS (m/z): 286.3 [M+H].

Intermediate 91.

[0171] K_2CO_3 (242 mg) was added to a solution of Intermediate 90 (250 mg) in EtOH, followed by BnBr (450 mg). The mixture was stirred at r.t. o.n. Water (40 mL) was added and the mixture was extracted with EtOAc. The combined organic layer was dried and concentrated under vacuum. The residue was purified by silica gel column chromatography (eluent: PE/EtOAc 1:1) to afford the Intermediate 91 as yellow oil. MS (m/z): 466.6 [M+H].

Intermediate 92.

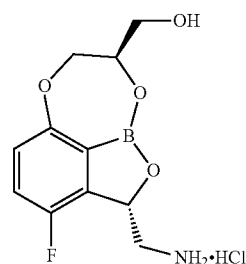
[0172] 2.5M BuLi (0.36) was added dropwise to a solution of Intermediate 91 (52 mg) in anhydrous toluene at -70°C . The mixture was slowly warmed up to 0°C . and stirred for 2 h. The mixture was cooled to -70°C ., then B(OMe)_3 (58.1 mg, 0.56 mmol) was added, and the mixture was stirred at 0°C . for 1 h. Water (10 mL) was added and the mixture was extracted with EtOAc. The combined organic layer was dried and concentrated under vacuum. The residue was purified by HPLC to afford the Intermediate 92 as yellow oil. MS (m/z): 492.4 [M+H].

Compound of Example 18

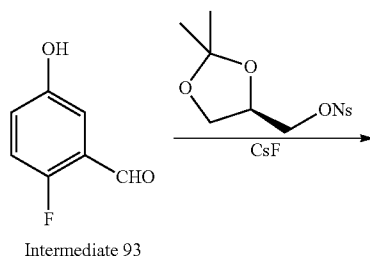
[0173] Concentrated HCl (1 mL) was added to a suspension of Intermediate 92 (35 mg) and Pd/C in MeOH. The mixture was stirred under H_2 for 2 h. The mixture was filtered and the solvent removed under vacuum. The residue was dissolved in MeOH and was purified by HPLC to afford the compound of Example 18 as a white solid. ^1H NMR (D_2O): 7.30-7.25 (m, 1H), 7.02-6.99 (m, 1H), 5.47-5.46 (m, 1H), 4.44-4.33 (m, 3H), 3.74-3.53 (m, 3H), 3.13-3.08 (m, 1H). MS (m/z): 254.0 [M+H].

Example 19

((2S,8R)-2-(Aminomethyl)-3-fluoro-7,8-dihydro-2H-1,6,9-trioxo-9a-borabenzoc[d]azulen-8-yl)methanol hydrochloride

[0174]

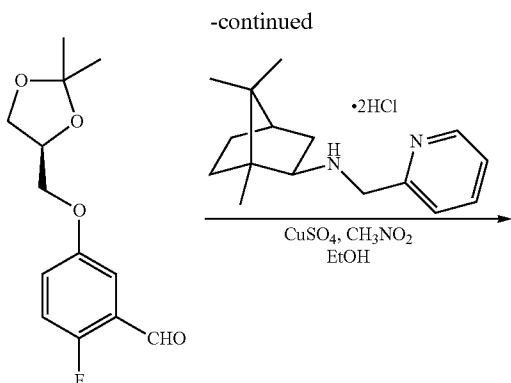
[0175] Scheme for preparation of the compound of Example 19:



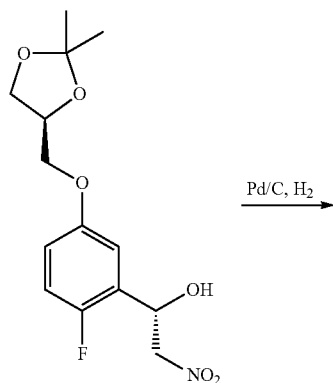
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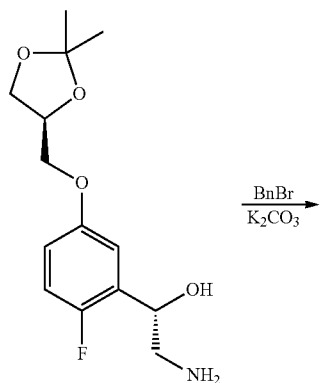
31



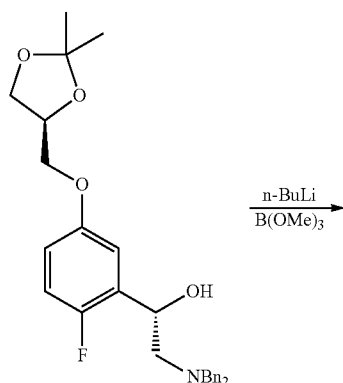
Intermediate 94



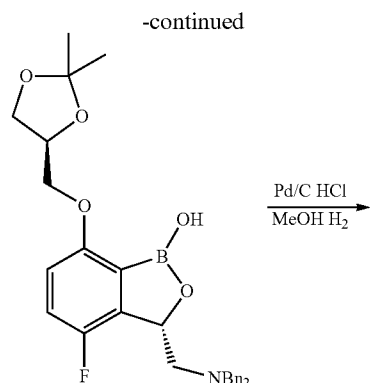
Intermediate 95



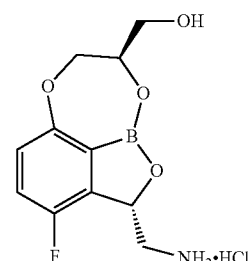
Intermediate 96



Intermediate 97



Intermediate 98



Example 19

Compound of Example 19

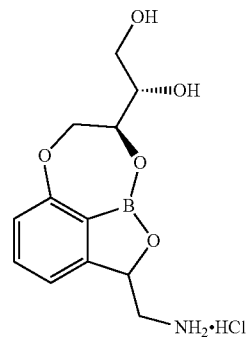
[0176] The compound of Example 19 was prepared analogously to the procedures for preparation of the compound of Example 18, except using Intermediate 93 instead of the Intermediate 87 to prepare the Intermediate 94, and then employing respective Intermediates 95-98 in procedures described above for methods with analogous Intermediates 89-92 (employed to prepare the compound of Example 18). ¹H NMR (D₂O): 7.10-7.08 (m, 1H), 6.87-6.86 (m, 1H), 5.48-5.47 (m, 1H), 5.15-5.06 (m, 3H), 3.67-3.53 (m, 3H), 3.17-3.12 (m, 1H). MS (m/z): 254.1 [M+H].

Example 20

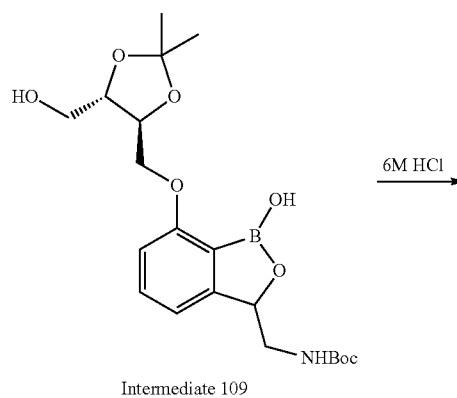
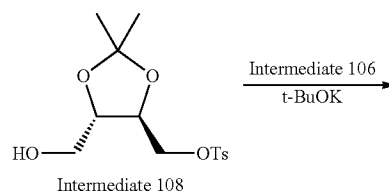
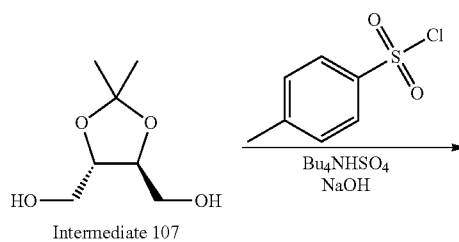
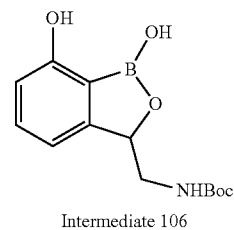
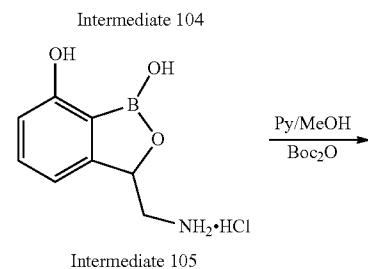
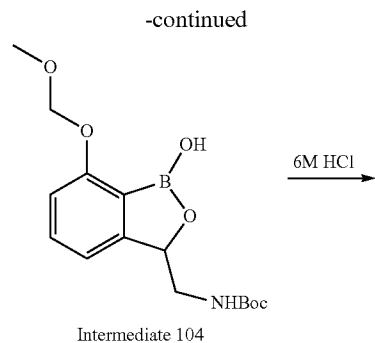
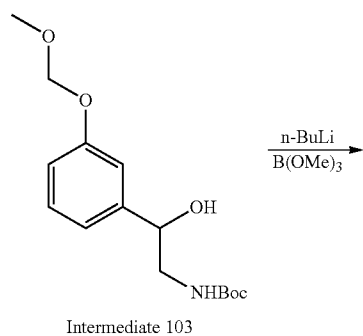
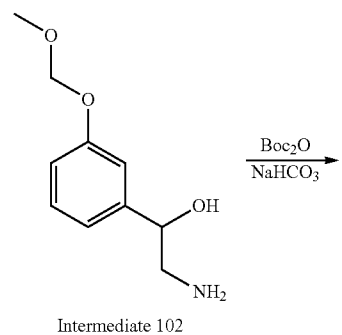
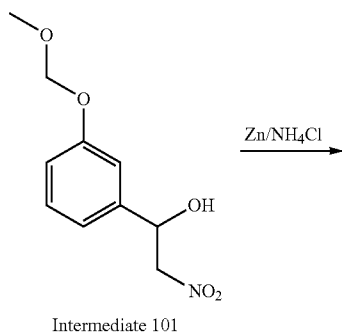
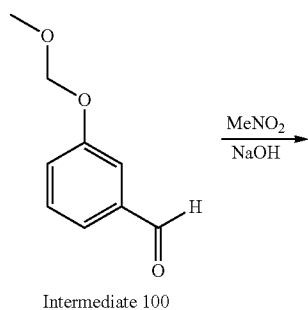
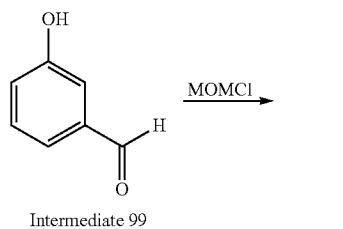
(1S)-1-((8S)-2-(Aminomethyl)-7,8-dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-8-yl)ethane-1,2-diol hydrochloride

[0177]

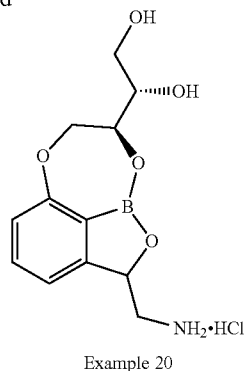
Example 20



[0178] Scheme for preparation of the compound of Example 20:



-continued



Intermediate 100.

[0179] Methoxymethyl chloride (MOMCl, 18.7 mL) was added to a solution of Intermediate 99 (10.0 g) and DIEA (41 mL) in DCM (100 mL). The resulting mixture was stirred at r.t. o.n. Water (50 mL) was added, and the mixture was extracted with DCM. The combined organic layer was washed with 1M NaOH, brine, dried (Na₂SO₄) and evaporated under vacuum to give the Intermediate 100.

Intermediate 101.

[0180] NaOH (3.1 g) in water (7 mL) was added to a solution of Intermediate 100 (13.0 g) and MeNO₂ (16.8 mL) in THF (100 mL) stirred at 0° C. The resulting mixture was stirred at r.t. for 4 days. Water was added, and the mixture was extracted with EtOAc. The organic layer was dried and evaporated under vacuum to give the Intermediate 101.

Intermediate 102.

[0181] Zn (6.5 g) was added to a suspension of Intermediate 101 (2.27 g) and NH₄Cl (5.3 g) in MeOH (30 mL). The resulting mixture was stirred at r.t. for 3 h. After filtration, the filtrate was evaporated under vacuum to afford the Intermediate 102. MS (m/z): 198.2 [M+H].

Intermediate 103.

[0182] A mixture of Intermediate 102 (5.3 g), Boc₂O (2.6 g) and NaHCO₃ (1.0 g) in MeOH (20 mL) was stirred at r.t. for overnight. Water was added, and the mixture was acted with EtOAc. The organic layer was dried (Na sulfate) and evaporated under vacuum. The residue was purified by silica gel column chromatography (eluent: PE/EtOAc) to afford the Intermediate 103. MS (m/z): 298.3 [M+H].

Intermediate 104.

[0183] 2.5M BuLi in hexanes (11.3 mL) was added dropwise to a solution of Intermediate 103 (2.1 g) in anhydrous toluene (30 mL) at -70° C. The mixture was slowly warmed to 0° C. and stirred for 2 h. The mixture was cooled to -70° C., and then B(OMe)₃ (4.4 g) was added, and the mixture was stirred at 0° C. for 2 h. Water was added, and the mixture was extracted with EtOAc. The organic layer was dried (Na sulfate) and evaporated under vacuum. The residue was purified by silica gel column chromatography to afford the Intermediate 104 as yellow oil. MS (m/z): 324.1 [M+H].

Intermediate 105.

[0184] 6M HCl (1 mL) was added to a solution of Intermediate 104 (38 mg) in MeOH (1 mL). The resulting mixture was stirred at r.t. for 2 h. Volatiles were removed under vacuum to afford the Intermediate 105. MS (m/z): 180.0 [M+H].

Intermediate 106.

[0185] A mixture of Intermediate 105 (40 mg), Boc₂O (44 mg) and pyridine (0.3 mL) in MeOH (2 mL) was stirred at r.t. for overnight. The solvent was removed under vacuum. The residue was treated with water and EtOAc. The organic layer was dried (Na sulfate) and evaporated under vacuum. The residue was purified by preparative TLC to afford the Intermediate 106. MS (m/z): 280.1 [M+H].

Intermediate 108.

[0186] Tosyl chloride (259 mg) was added to a solution of Intermediate 107 (200 mg), Bu₄NHSO₄ (42 mg, 0.123 mmol) and 15% aqueous NaOH (1.35 mmol). The resulting solution was stirred at r.t. for 2 h. Water was added and the mixture was extracted with DCM. The combined organic layers were dried and concentrated. The residue was purified by silica gel column chromatography (eluent: PE/EtOAc 2:1) to afford the Intermediate 109 as yellow oil.

Intermediate 109.

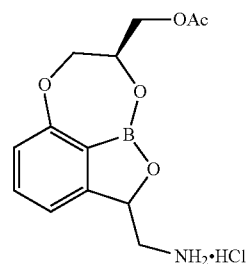
[0187] t-BuOK (45 mg) was added to a solution of Intermediate 106 (100 mg) in DMSO (1 mL) at 0° C., followed by addition of the Intermediate 108 (125 mg). The resulting mixture was stirred for 3 h, then filtered and evaporated under vacuum. Resulted crude product was purified by HPLC to afford the Intermediate 109 as a white solid. MS (m/z): 424.3 [M+H].

Compound of Example 20

[0188] A solution of Intermediate 109 (13 mg) in 4M HCl in dioxane (1 mL) was stirred for 2 h. Volatiles were removed by lyophilization to afford the compound of Example 20 as a white solid. ¹H NMR (D₂O): 7.41 (s, 1H), 6.95-6.85 (m, 2H), 5.36-5.35 (m, 1H), 4.17-4.05 (m, 3H), 3.58-3.44 (m, 4H), 3.04-3.03 (m, 1H). MS (m/z): 266.1 [M+H].

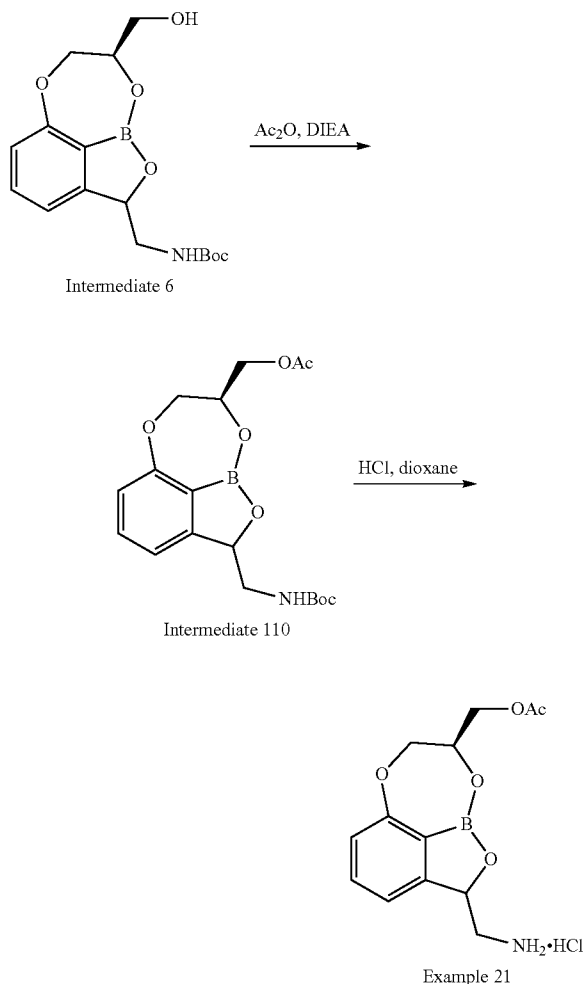
Example 21

((8S)-2-(Aminomethyl)-7,8-dihydro-2H-1,6,9-trioxo-9a-borabenzoc[cd]azulen-8-yl)methyl acetate hydrochloride

[0189]

Example 21

[0190] Scheme for preparation of the compound of Example 21:



Intermediate 110.

[0191] Acetic anhydride (32 μ L) was added to a solution of the Intermediate 6 (60 mg) and pyridine (31 μ L) in DCM (2 mL) at 0° C. The resulting mixture was stirred at r.t. for 2 h. The solvent was removed under vacuum and the residue purified by HPLC to afford the Intermediate 10. MS (m/z): 378.2 [M+H].

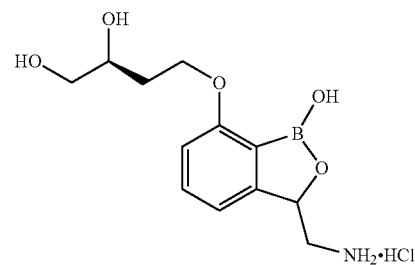
Compound of Example 21

[0192] The total amount of Intermediate 110 from preceding step was dissolved in 4M HCl in dioxane (1 mL). The mixture was stirred at r.t. for 1 h. Volatiles were removed by lyophilization to afford the compound of Example 21 as a light-yellow solid. ¹H NMR (D₂O): 7.48 (t, J=8.0 Hz, 1H), 7.00 (d, J=7.6 Hz, 1H), 6.90 (d, J=8.4 Hz, 1H), 5.40 (s, 1H), 4.30-4.12 (m, 5H), 3.73-3.53 (m, 3H), 3.09-3.04 (m, 1H), 1.99 (s, 3H). MS (m/z): 278.1 [M+H].

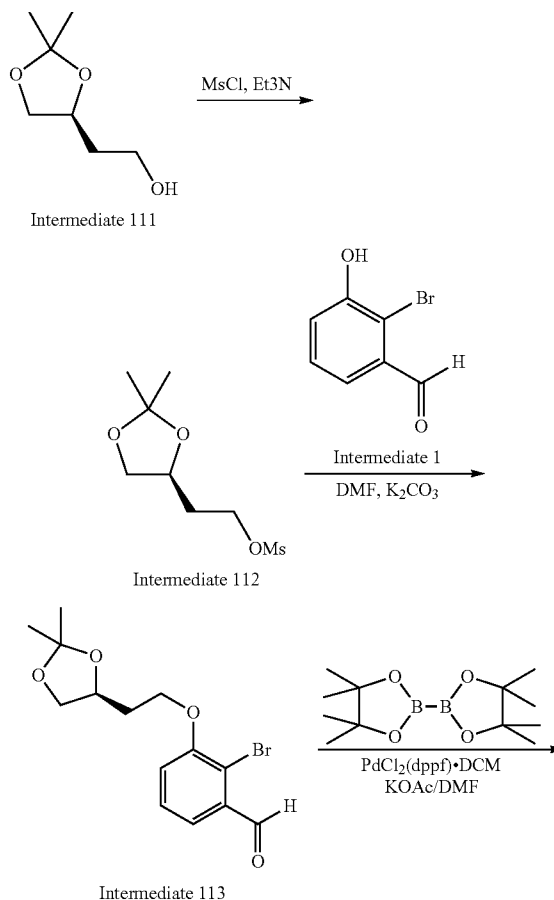
Example 22

(2S)-4-((3-(Aminomethyl)-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)oxy)butane-1,2-diol hydrochloride

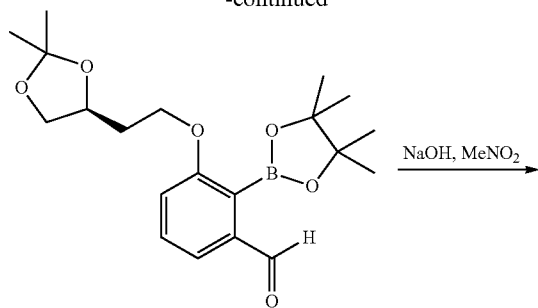
[0193]



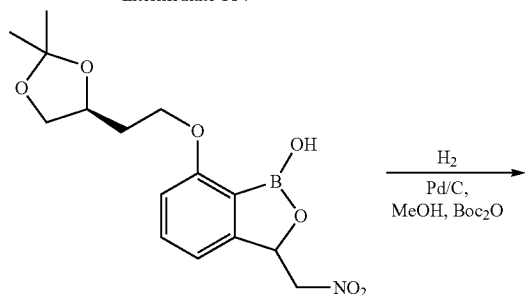
[0194] Scheme for preparation of the reference compound of Example 22:



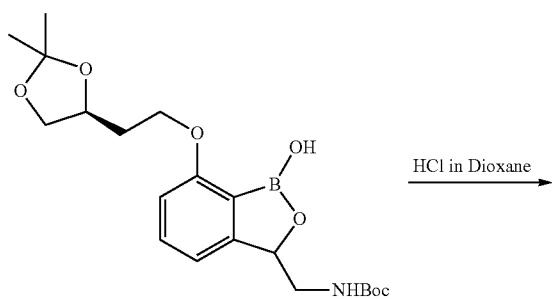
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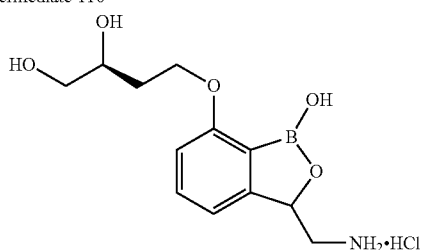
Intermediate 114



Intermediate 115



Intermediate 116



Example 22

Intermediate 115.

[0195] The Intermediate 115 was prepared analogously to the procedures for preparation of the compound of Example 11, except using Intermediate 111 instead of Intermediate 30 to prepare the Intermediate 112, and then employing respective Intermediates 113-115 in procedures described above for methods with analogous Intermediates 32-34 (employed to prepare the compound of Example 11).

Intermediate 116.

[0196] A mixture of Intermediate 115 (1.4 g), Boc_2O (0.5 g) and Pd/C (0.2 g) in MeOH (15 mL) was stirred under H_2 at

r.t. o.n. After filtration, the solvent was removed under vacuum. The residue was purified by HPLC to afford the Intermediate 116. MS (m/z): 408.3 [M+H].

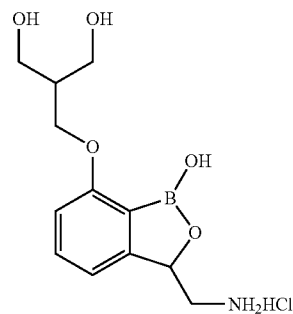
Compound of Example 22

[0197] Intermediate 116 (100 mg) was dissolved in 4M HCl in dioxane (1 mL). The mixture was stirred at r.t. for 1 h. Volatiles were removed by lyophilization to afford the reference compound of Example 22 as light-yellow solid. ^1H NMR (D_2O): 7.39 (t, $J=8.0$ Hz, 1H); 6.88 (d, $J=7.6$ Hz, 1H); 6.82 (d, $J=8.4$ Hz, 1H); 5.37 (d, $J=9.2$ Hz, 1H); 4.08 (s, 2H); 3.7-3.82 (m, 2H); 3.38-3.59 (m, 2H), 3.38-3.59 (m, 1H), 1.17-1.91 (m, 2H). MS (m/z): 268.1 [M+H].

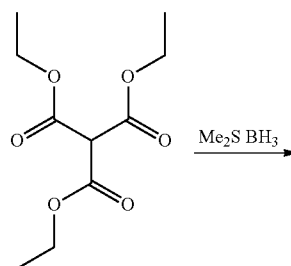
Example 23

[0198] 2-(((3-(Aminomethyl)-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)oxy)methyl)propane-1,3-diol hydrochloride

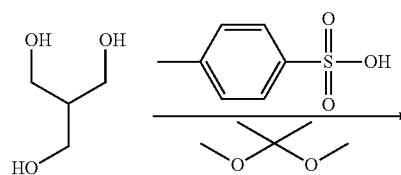
Example 23



[0199] Scheme for preparation of the reference compound of Example 23:



Intermediate 117

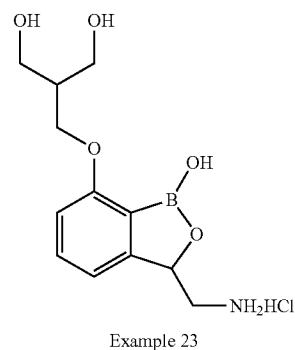
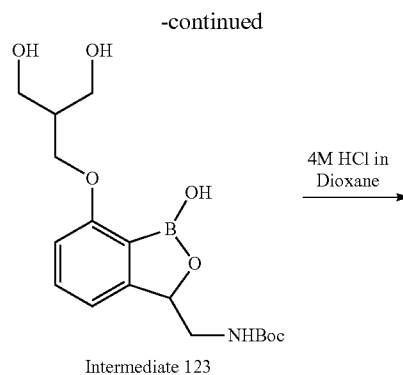
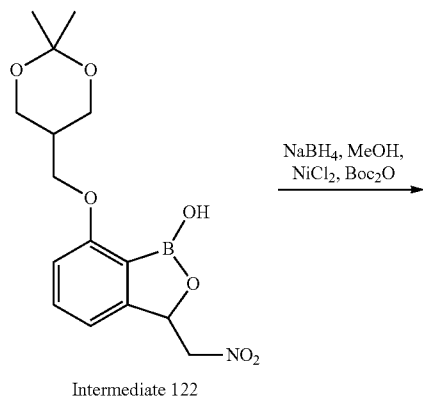
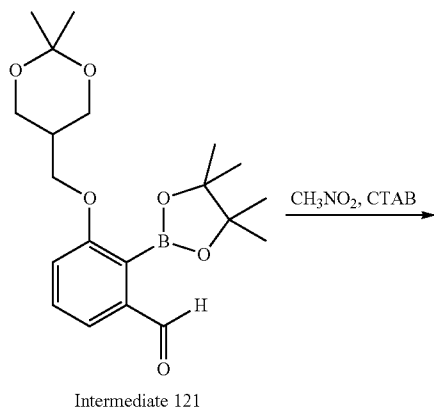
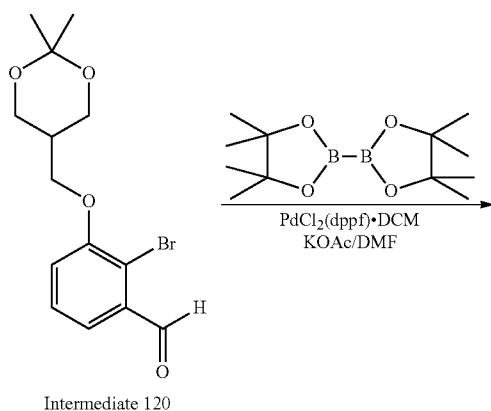
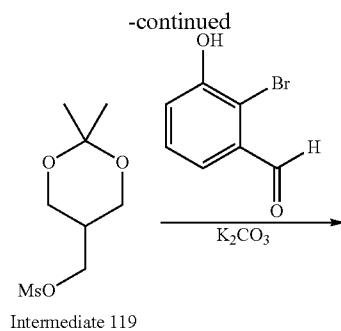


Intermediate 118

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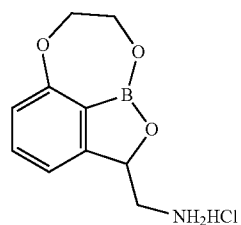


Compound of Example 23

[0200] The reference compound of Example 23 was prepared analogously to the procedures described in the PCT WO2008/157726. 1H NMR (D_2O): 8.33 (m, 1H), 7.39 (t, $J=7.2$ Hz, 1H), 6.90 (dd, J 13.6, 7.6 Hz, 2H), 5.26 (s, 1H), 4.11 (d, $J=6.0$ Hz, 2H), 3.65 (dd, J 5.6, 2.8 Hz, 4H), 3.45 (d, $J=13.6$ Hz, 1H), 3.23 (s, 1H), 3.05 (dd, J 13.2, 6.4 Hz, 1H), 2.13-2.17 (m, 1H). MS (m/z): 268.1 [$M+H$].

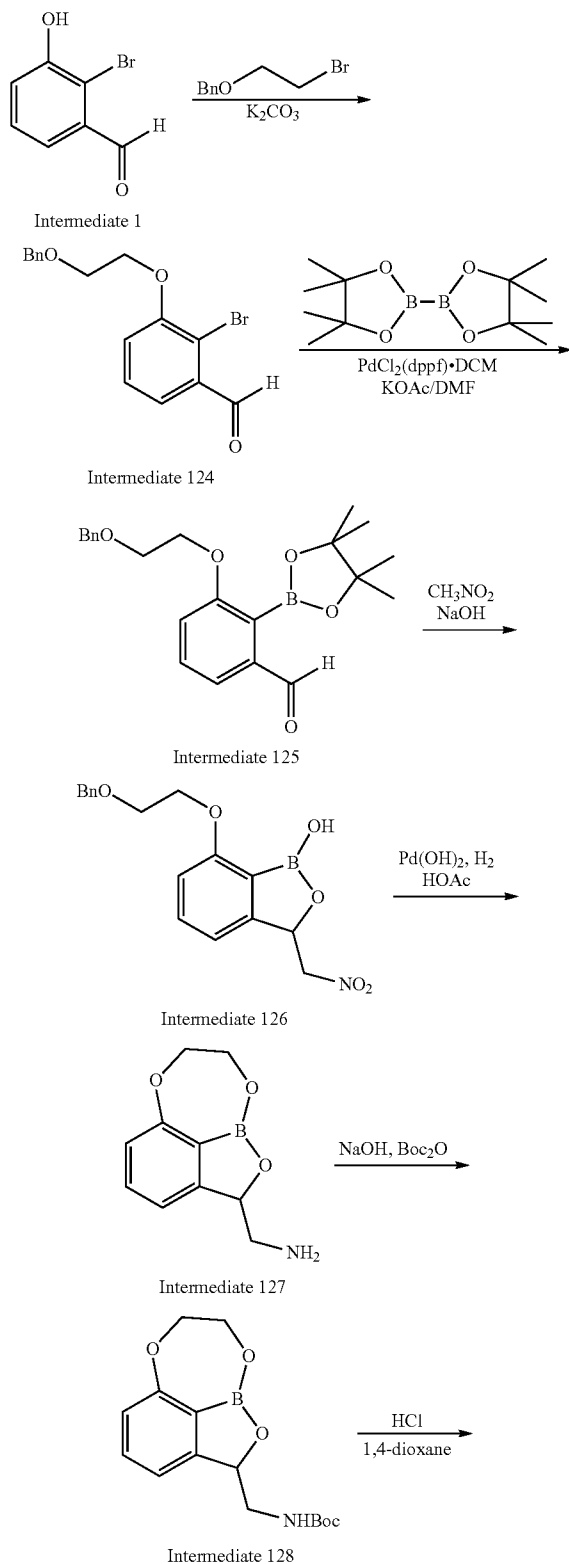
Example 24

(7,8-Dihydro-2H-1,6,9-trioxa-9a-borabenz[cd]azulen-2-yl)methanamine hydrochloride

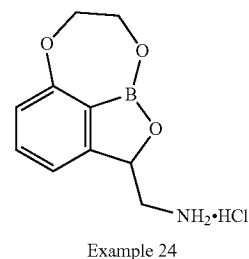
[0201]

Example 24

[0202] Scheme for preparation of the reference compound of Example 24:



-continued



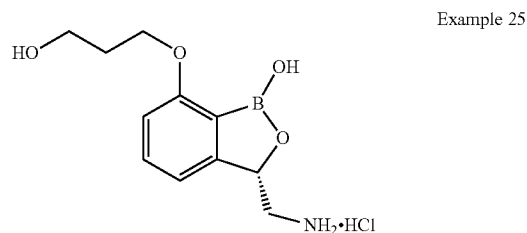
Compound of Example 24

[0203] The reference compound of Example 24 was prepared analogously to the procedures described in the PCT WO 2008/157726. ¹H NMR: 8.39 (s, 3H), 7.50 (t, J=7.8 Hz, 1H), 7.15 (d, J=7.2 Hz, 1H), 6.91 (d, J=8.4 Hz, 1H), 5.55-5.48 (m, 1H), 4.73-4.68 (m, 1H), 4.50-4.18 (m, 3H), 3.57-3.51 (m, 1H), 2.94-2.84 (m, 1H). MS (m/z): 206.0 [M+H].

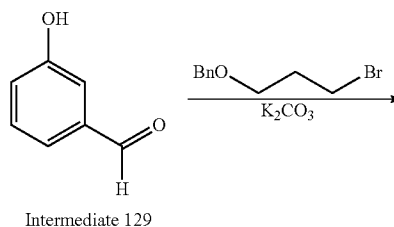
Example 25

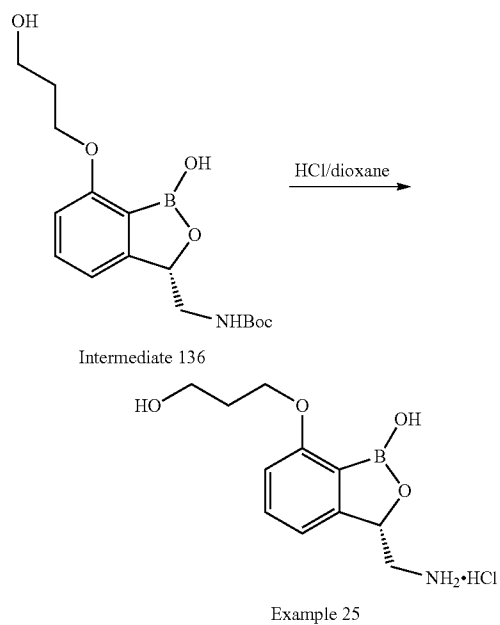
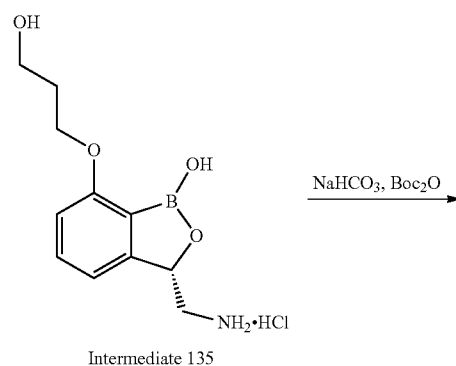
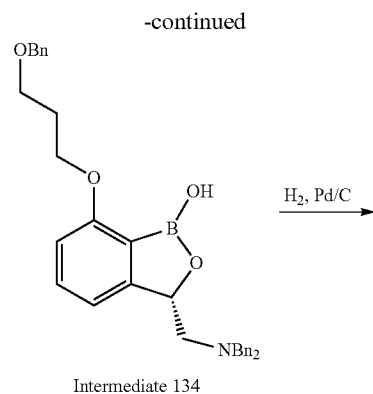
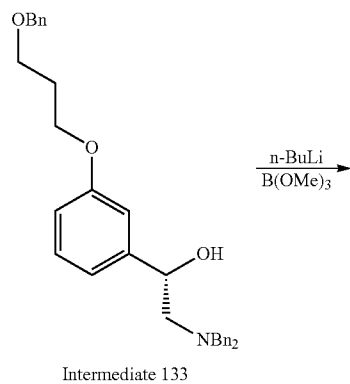
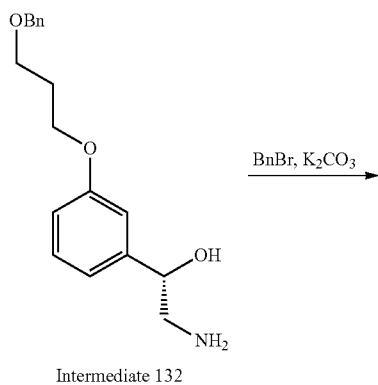
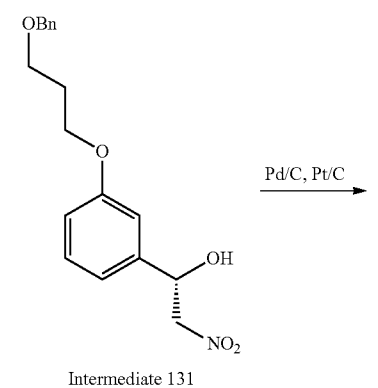
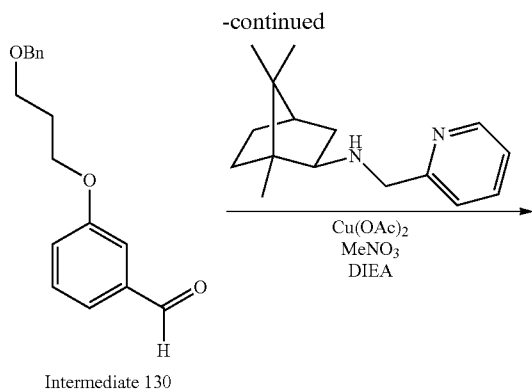
(S)-3-(Aminomethyl)-7-(3-hydroxypropoxy)benzo[c][1,2]oxaborol-1(3H)-ol hydrochloride

[0204]



[0205] Scheme for preparation of the compound of Example 25:





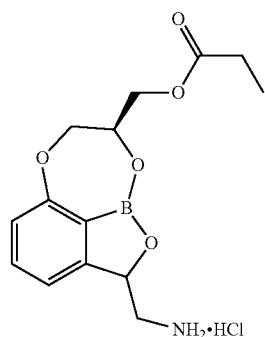
Compound of Example 25

[0206] The reference compound of Example 25 was prepared analogously to the procedures described in the PCT WO 2011/127143. ¹H NMR (D₂O): 7.53 (t, J=8.0 Hz, 1H), 7.01 (d, J=8.0 Hz, 2H), 5.39 (d, J=6.8 Hz, 1H), 4.18-4.21 (m, 2H), 3.74 (t, J=6.0 Hz, 2H), 3.57 (dd, J 13.2, 2.8 Hz, 1H), 3.08-3.12 (m, 1H), 1.97-2.03 (m, 2H). MS (m/z): 238.1 [M+H].

Example 26

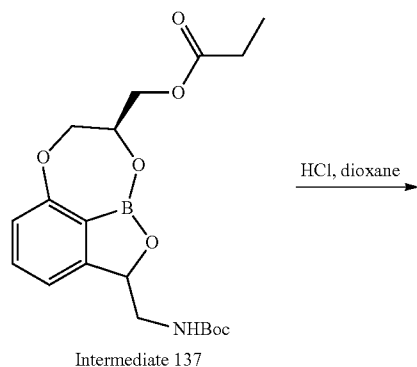
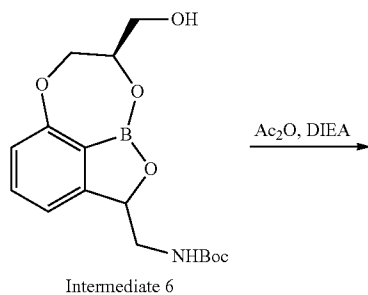
((8S)-2-(Aminomethyl)-7,8-dihydro-2H-1,6,9-tri-oxa-9a-borabenz[cd]azulen-8-yl)methyl propionate hydrochloride

[0207]

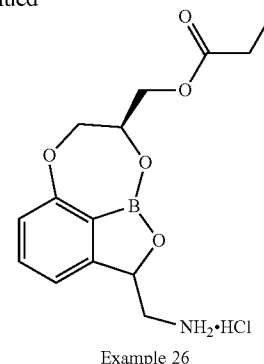


Example 26

[0208] Scheme for preparation of the Compound of Example 26:



-continued



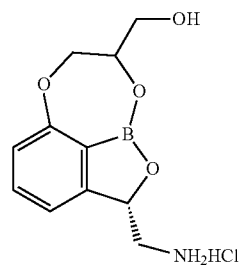
Compound of Example 26

[0209] The compound of Example 26 was prepared analogously to the procedures described for preparation of the compound of Example 21, except using propionic anhydride instead of acetic anhydride to prepare respective Intermediate 137. Light-yellow solid. ¹H NMR (D₂O): 7.41 (d, J=8.0 Hz, 1H); 6.96-6.84 (m, 2H); 5.32 (s, 1H); 4.27-4.09 (m, 5H); 3.51-3.48 (m, 1H); 3.09-3.04 (m, 1H); 2.30-2.29 (m, 2H); 0.98-0.95 (m, 3H). MS (m/z): 292 [M+H].

Example 27

((2S)-2-(Aminomethyl)-7,8-dihydro-2H-1,6,9-tri-oxa-9a-borabenz[cd]azulen-8-yl)methanol hydrochloride

[0210]



Example 27

Compound of Example 27

[0211] The compound of Example 24 is made using procedures described above for the preparation of the compound of Example 3 except using benzyl glycidyl ether instead of benzyl (R)-glycidyl ether.

Utility and Testing

[0212] The compounds provided herein exhibit potent activities against a variety of microorganisms, including Gram-positive and Gram-negative microorganisms. Accordingly, the compounds provided herein have broad antibacterial activity. Thus, the compounds provided herein are useful antimicrobial agents and may be effective against a number of human and veterinary pathogens, including Gram-positive

aerobic bacteria such as multiply-resistant staphylococci and streptococci, select Gram-negative microorganisms such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *E. coli*, *Klebsiella pneumoniae*, *H. influenzae* and *M. catarrhalis*, as well as anaerobic microorganisms such as *bacteroides* and clostridia species, and acid-fast microorganisms such as *Mycobacterium tuberculosis* and *Mycobacterium avium*.

[0213] The in vitro activity of compounds provided herein may be assessed by standard testing procedures such as the determination of minimum inhibitory concentration (MIC) as described in *Approved Standard. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*, 3rd ed., 1993, published by the National Committee for Clinical Laboratory standards, Villanova, Pa., USA. Low MIC values indicate high antibacterial activity, while high MIC values reveal a reduced antibacterial activity (with higher drug concentration required for pathogen eradication in the latter instance). Generally, MIC values of about ≤ 4 -8 $\mu\text{g/mL}$ against a particular pathogen indicate a therapeutic (i.e. suitable for therapy) potency for antibacterial drugs, while MIC values of ≥ 16 $\mu\text{g/mL}$ would reveal a lack of therapeutically useful activity for a test compound against this pathogen.

[0214] The useful in vitro activity (potency) of representative compounds provided herein against Gram-negative pathogens *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Escherichia coli*, or *Klebsiella pneumoniae* is illustrated by the MIC data of Table 1 below.

[0215] As evident from the data of Table 1, representative compounds provided herein are highly active against Gram-negative pathogens. In particular, tricyclic compounds of Examples 1, 3, 4, and 7 possess a remarkably enhanced potency against *P. aeruginosa* (MICs of 2-4 $\mu\text{g/mL}$), with about 2-4-fold higher improvement in the activity against this pathogen over the bicyclic reference compound of Example 10 (MIC of 8 $\mu\text{g/mL}$). The tricyclic compounds provided herein display potency similar to that for the bicyclic reference compound of Example 25 of a generally related oxaborole class from the PCT WO 2008/157726. This reference compound is the first antibacterial investigational drug of the new class, as reported, for example, by Zane et al. in a poster *Safety, tolerability, and pharmacokinetics of a novel Gram-negative antimicrobial, GSK2251052, in healthy subjects*, 21st European Congress of Clinical Microbiology and Infectious Diseases, 2011, Milan, Italy.

TABLE 1

Antibacterial activity against Gram-negative pathogens in vitro.				
EXAMPLES	<i>P. aeruginosa</i> PAE 1001 mg/mL	<i>E. coli</i> ECO 1003 mg/mL	<i>A. baumannii</i> ABA 4001 mg/mL	<i>K. pneumoniae</i> KPN 4027 mg/mL
Reference	4	2	4	4
Example 24 ^a				
Reference	32	64	64	64
Example 23 ^a				
Reference	4	2	4	1
Example 25 ^a				
Reference	8	4	8	4
Example 10 ^a				
Example 1	4	4	4	4
Example 3	2	2	4	2
Example 4	4	4	4 ^b	2 ^c
Example 7	4	8	4 ^b	4 ^c
Example 11	16	16	16	8

TABLE 1-continued

Antibacterial activity against Gram-negative pathogens in vitro.				
EXAMPLES	<i>P. aeruginosa</i> PAE 1001 mg/mL	<i>E. coli</i> ECO 1003 mg/mL	<i>A. baumannii</i> ABA 4001 mg/mL	<i>K. pneumoniae</i> KPN 4027 mg/mL
Example 12	16	8	>32	8
Example 13	8	8	16	8
Example 14	8	4	16	4
Example 15	64	>64	>64	>64
Example 16	32	>32	>32	>32
Example 17	8	2	>32	2
Example 18	32	>32	>32	32
Example 19	>32	>32	>32	>32
Example 20	>32	>32	>32	>32
Reference	>64	32	32	32
Example 22 ^d				

Notes:

^aReference compounds from the publication WO 2008/157726.

^bStrain *A. baumannii* MABA0001.

^cStrain *K. pneumoniae* KPN1004.

^dReference compound from the genus of the publication WO 2008/157726.

[0216] It is also remarkable that these tricyclic compounds generally related to the tricyclic compound of the reference compound of Example 24 possess similar or even improved antibacterial potency (MIC) vs. said compound, the sole prior tricyclic boron compound described in the PCT publication WO 2008/157726. For example, the compound of Example 3 exhibits 2-fold improved activity against representative strains of *P. aeruginosa*, *E. coli*, and *K. pneumoniae* as compared to the reference compound of Example 24 compound. This is quite striking in face of the highly restrictive structure-activity relationships (SAR) within this class of tricyclic boron compounds.

[0217] The severe SAR limitation is illustrated by a dramatic drop in the antibacterial activity resulted from simple isosteric substitutions or minimal structural variations. While being generally acceptable for many classes of bioactive compounds (as reviewed, e.g., by Meanwell in *J. Med. Chem.*, 2011, vol. 54, pp. 2529-2591), these are generally disfavored within the class of compounds provided herein. For example, a minor one-carbon shift of the hydroxymethyl side chain in the compound of Example 7 to result in its isomeric compound of Example 11 leads to 4-fold reduced potency vs. *P. aeruginosa* and *A. baumannii* for the latter analog. Likewise, a minimal extension (homologation) of the hydroxymethyl side chain of compound of Example 7 to produce respective 2-hydroxyethyl compound of Example 12 leads to a 4-fold loss of activity vs. *P. aeruginosa*, and total loss of activity vs. *A. baumannii* for the latter compound (see Table 1). An introduction of a sole methyl group either into the hydroxymethyl side chain of the compound of Example 7 (to produce 1-hydroxyethyl compound of Example 14), or into the endocyclic CH group attached to same hydroxymethyl group (to produce the compound of Example 13) leads to about 4-fold loss of activity vs. *A. baumannii* for both compounds of Example 13 and Example 14, as compared to the compound of Example 7. Likewise, introduction of an extra hydroxymethyl group at same endocyclic CH of the Example 7 to produce bis-hydroxymethyl compound of Example 15 leads to nearly complete loss of antibacterial potency (see Table 1). In a striking contrast with established principles of bioisosterism, even simple replacement of a hydrogen atom in benzene ring of the structure of compound of Example 3 for fluorine leads to reduced activity in compounds of Example 17 and 18. This

highly prohibitive SAR for tricyclic boron compounds may account for the fact that only the mono-substituted tricyclic compound (the reference compound of Example 24 herein) of this class was described in the PCT publication WO 2008/157726.

[0218] The restrictive SAR for the class of compounds provided herein is further summarized in the FIG. 1 below. As stated above, even minor structural modifications in the potent compounds (FIG. 1, top box structures) lead to a dramatic loss of the activity against *A. baumannii* in resulted closely related compounds (FIG. 1, lower box structures). This contrasts to isosteric modifications that are allowed by SAR for many other classes of bioactive agents (as reviewed by Meanwell in *J. Med. Chem.*, 2011, vol. 54, pp. 2529-2591) but disfavored for the class of tricyclic boron antibacterials provided herein.

[0219] Based on this SAR, one would expect only poor or no antibacterial potency for the tricyclic boron compounds of Examples 1, 3, 4, and 7. Thus, the antibacterial potency (MIC) data reveal the unique nature of the composition provided herein, such as compounds of Examples 1, 3, 4, and 7. The compounds provided herein are remarkably active, in face of the highly restrictive SAR that renders vast majority of other tricyclic boron compounds poorly active or entirely inactive, and thus unsuitable for therapy of Gram-negative infections in mammals.

[0220] Generally restrictive SAR for antibacterial boron compounds is further illustrated in Table 1 by a striking contrast of the potency data for the active reference compound of Example 25 vs. structurally close but essentially inactive reference compounds of Example 22 and Example 23 that incorporate two alcohol groups instead of one such group in the compound of Example 25. Aforementioned reference boron compounds incorporate a bicyclic rather than tricyclic oxaborole structure. Notably, both inactive compounds of Examples 22 and 23 would be generally related to theoretically feasible ring-opened bis-alcohol forms of compounds of Examples 1, 3, 4, and 7, which would be likewise expected to be inactive. Instead, the latter tricyclic compounds provided herein display a remarkably high activity against Gram-negative pathogens.

[0221] In addition to in vitro activity (potency determined as MIC), in vivo efficacy or ability to eradicate bacterial pathogens to the effect of survival of mammals under therapy is critical. It is well established that compounds with similar antibacterial potency in vitro (MIC) may display a dramatically different activity in vivo, resulting in a desired therapeutic effect for some efficacious compounds, or lack of any useful anti-infective effect for others, non-efficacious compounds. This critical for the actual therapy outcome is determined by multiple factors affecting the compound behavior in vivo, such as its absorption, distribution, metabolism, and excretion.

[0222] To establish the efficacy of the compounds provided herein in vivo, testing in a *P. aeruginosa* neutropenic mouse thigh infection model was performed with subcutaneous administration of test compounds analogously to the method described by Andes et al. in *Antimicrobial Agents and Chemotherapy*, 2002, 46(11), 3484-3489. In this model, a greater reduction in the bacterial colony-forming units (CFU) indicates more beneficial therapeutic effect (more bacterial eradication), while a lower CFU reduction indicates a lower effect (less bacterial eradication). The in vivo antibacterial effect is

also referred to as efficacy, in contrast to the term potency commonly used for in vitro activity (expressed as MIC).

[0223] Remarkably, the compound of Example 3 displays a strikingly improved activity in the animal model of infection as compared to the tricyclic reference compound of Example 24 (with both agents administered at the identical dosing of 30 mg/kg). Thus, in the *P. aeruginosa* mouse thigh infection model, the compound of Example 3 has effected about 3.6 log(i.e., about 3981-fold) reduction in the bacterial colony-forming units (CFU), while in a side-by-side test the reference compound of Example 24 has caused only about 1.7 log(i.e., about 50-fold) CFU reduction in the bacterial infestation. Thus, the compound of Example 3 effectively causes about a dramatic over 80-fold higher degree of the desired pathogen reduction when compared to the reference compound of Example 24. This beneficial therapeutic effect is quite remarkable, since one might anticipate, at best, only a similar efficacy for these two compounds, based on generally similar in vitro activity against *P. aeruginosa* for both agents (as illustrated in Table 1 above).

[0224] Likewise, when compared to the bicyclic reference compound of Example 25 (the first investigational oxaborole antibacterial) in another *P. aeruginosa* mouse thigh infection model test, the tricyclic compound of Example 3 has effected about 3.44 log(i.e., about 2754-fold) reduction in the bacterial colony-forming units (CFU), while the reference compound of Example 25 has caused only about 2.37 log CFU reduction (i.e., about 234-fold reduction), in a side-by-side test and using identical 30 mg/kg dosing for both agents. Thus, the tricyclic boron compound of Example 3 is about 12-fold more efficient in the *P. aeruginosa* thigh infection model as compared to the reference boron compound of Example 25 described in the PCT publication WO 2008/157726.

[0225] This dramatic improvement of therapeutic activity in vivo (efficacy) for the compound of Example 3 is remarkable as no prior data directing one skilled in art to expect this beneficial effect exist anywhere. Additional related compounds provided herein display alike surprisingly improved in vivo efficacy. Thus, in the aforementioned animal infection model, the tricyclic compound of Example 1 has effected about 3.2 log (i.e., about 1584-fold) CFU reduction, while in a side-by-side test of the bicyclic reference compound of Example 10 has caused only about 1.3 log(about 20-fold) CFU reduction, revealing a dramatic 79-fold superiority in the bacterial reduction of the compound of Example 1 provided herein over generally related bicyclic boron compound of Example 10 described in the PCT publication WO 2008/157726.

[0226] To further elucidate therapeutic potential of drug compounds, pharmacokinetic (PK) data is used to establish the key parameters predictive of the therapy outcome, such as area under the curve (AUC) for a plot monitoring the change in the systemic drug concentration over time. Thus, a higher AUC value indicates a greater exposure to the drug, commonly associated with a greater therapeutic potential due to a higher amount of drug available to combat the infection in a mammal. In contrast, a lower AUC value indicates a reduced exposure to the drug under study, resulting in a reduced amount of antibiotic available to combat bacterial infestations. To that end, the compounds provided herein have been tested in the rat PK model of intravenous administration performed analogously to methods described in the monograph *Current Protocols in Pharmacology*, 2005, 7.1.1-7.1.26, John Wiley & Sons, Inc.

[0227] Quite remarkably, the pharmacokinetic data for the compound of Example 3 in a rat PK model of intravenous administration revealed a greatly improved systemic exposure for this compound over the comparator reference compound of Example 24, with the exposure (AUC) for the compounds of Example 3 and Example 24 determined as about 14100 and 5300 ng/mL*h, respectively, at identical dosing of 10 mg/kg. This remarkable result represents a striking 2.7-fold improvement in the exposure to the drug in vivo for the compound of Example 3 over the reference compound of Example 24 described in the PCT publication WO 2008/157726. This beneficial in vivo exposure effect is remarkable, since one skilled in art might anticipate, at best, only a similar exposure (AUC) for these two compounds, since both of these belong to a general class of tricyclic boron compounds (see structures in FIG. 1 above).

[0228] Likewise, the in vivo exposure for this tricyclic compound of Example 3 is greatly improved when compared to in vivo exposure for the bicyclic compound of Example 25 (the investigational oxaborole drug comparator): with AUC values of about 14100 and 6241 ng/mL*h, respectively, representing a dramatic—over 2-fold—improvement for the compound of Example 3 achieved at the identical with the reference compound of Example 25 dosing of 10 mg/kg.

[0229] This dramatic improvement of in vivo exposure (AUC) for the compound of Example 3 is remarkable, as no prior data directing one skilled in art to expect this beneficial effect exist anywhere. Additional related compounds provided herein also display alike remarkably improved in vivo exposure. Thus, pharmacokinetic data for the compound of Example 1 in a rat model of intravenous administration reveal a greatly improved systemic exposure for this compound over the comparator reference compound of Example 10, with the AUC for the compounds of Example 1 and Example 10 determined as about 11520 and 5367 ng/mL*h, respectively. This result represents more than 2-fold improvement in the exposure for the tricyclic compound of Example 1 as compared to the bicyclic reference compound of Example 10 described in the PCT publication WO 2008/157726.

[0230] In summary, above support data illustrate that the compounds provided herein (such as compounds of Examples 1, 3, 4, and 7) possess a remarkably high or improved in vitro antibacterial potency against key Gram-negative pathogens (such as *A. baumannii* and *P. aeruginosa*), contrasting a severely restricted SAR that would not lead one skilled in art to anticipate such activity. In addition, the compounds provided herein also exhibit a dramatic in vivo activity (efficacy) improvement in animal models of infection (such as *P. aeruginosa* thigh infection model). Finally, select compounds provided herein exhibit beneficial enhancement in the systemic exposure (as demonstrated in the intravenous pharmacokinetics rat model).

[0231] Above representative data taken in its entirety reveal a remarkably superior therapeutic potential for the compounds provided herein (such as the compounds of Example 1, 3, 4, and 7), with the beneficial advantages in areas of potency, efficacy, and exposure compared to other boron anti-infectives, including that of the PCT publication WO 2008/157726. The dramatic improvement in three distinctly different critical parameters for antibacterial compounds provided herein (such as compounds of Examples 1, 3, 4, and 7) offers marked potential benefits for human or mammal therapy, including but not limited to shorter therapy duration, a

reduced effective drug dose, reduced possible adverse effects, and/or more convenient dosing regimen.

Administration and Pharmaceutical Formulations

[0232] In general, the compounds provided herein will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. By way of example, the compounds provided herein may be administered orally, parenterally, transdermally, topically, rectally, or intranasally. The actual amount of the compound provided herein, i.e., the active ingredient, will depend on a number of factors, such as the severity of the disease, i.e., the infection, to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, and other factors, all of which are within the purview of the attending clinician.

[0233] The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method provided herein, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range which includes the IC₅₀ (i.e., the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

[0234] When employed as pharmaceuticals, the compounds provided herein are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, parenteral, transdermal, topical, rectal, and intranasal.

[0235] These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

[0236] Also provided herein are pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds provided herein above associated with pharmaceutically acceptable carriers. In making the compositions provided herein, the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

[0237] In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active

compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

[0238] Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions provided herein can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

[0239] The quantity of an active component, that is the compound provided herein, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application, the potency of the particular compound and the desired concentration.

[0240] The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Preferably, the compound provided herein above is employed at no more than about 20 weight percent of the pharmaceutical composition, more preferably no more than about 15 weight percent, with the balance being pharmaceutically inert carrier(s).

[0241] The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically or therapeutically effective amount. It, will be understood, however, that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the severity of the bacterial infection being treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[0242] In therapeutic use for treating, or combating, bacterial infections in warm-blooded animals, the compounds or pharmaceutical compositions thereof will be administered orally, topically, transdermally, and/or parenterally at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the animal undergoing treatment which will be antibacterially effective. Generally, such antibacterially or therapeutically effective amount of dosage of active component (i.e., an effective dosage) will be in the range of about 0.1 to about 100, more preferably about 1.0 to about 50 mg/kg of body weight/day.

[0243] For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound provided herein. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the com-

position may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient provided herein.

[0244] The tablets or pills provided herein may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer, which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

[0245] The liquid forms in which the compositions provided herein may be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as corn oil, cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

[0246] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a facemask tent, or intermittent positive pressure-breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

[0247] Another preferred formulation employed in the methods provided herein employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds provided herein in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Pat. No. 5,023,252, issued Jun. 11, 1991, herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[0248] Frequently, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system used for the transport of biological factors to specific anatomical regions of the body is described in U.S. Pat. No. 5,011,472 which is herein incorporated by reference.

[0249] Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and pri-

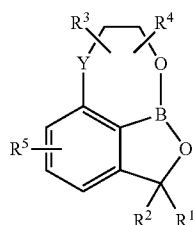
many amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions that can transiently open the blood-brain barrier.

[0250] Other suitable formulations can be found in *Remington's Pharmaceutical Sciences*, Mace Publishing Company, Philadelphia, Pa., 17th ed. (1985).

[0251] As noted above, the compounds described herein are suitable for use in a variety of drug delivery systems described above. Additionally, in order to enhance the in vivo serum half-life of the administered compound, the compounds may be encapsulated, introduced into the lumen of liposomes, prepared as a colloid, or other conventional techniques may be employed which provide an extended serum half-life of the compounds. A variety of methods are available for preparing liposomes, as described in, e.g., Szoka, et al., U.S. Pat. Nos. 4,235,871, 4,501,728 and 4,837,028 each of which is incorporated herein by reference.

[0252] As noted above, the compounds administered to a patient are in the form of pharmaceutical compositions described above. These compositions may be sterilized by conventional sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 and 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

1. A compound of the following formula I



I

or a pharmaceutically acceptable salt, complex, or tautomer thereof, wherein:

R¹ and R² are independently H, F, C₁₋₆alkyl, C₁₋₆(amino)alkyl, aminomethyl, or C₁₋₆alkylNH₂; and wherein

R³ and R⁴ are independently a single substituent or multiple substituents independently selected from H, halo, CN, C₁₋₆alkyl, C₁₋₆(hydroxy)alkyl, C₁₋₆alkylamino, C₁₋₆alkoxy, C₁₋₆heteroalkyl, C₁₋₆haloalkyl, or C₁₋₆(amino)alkyl; and wherein

Y is O, S, CH₂, CHF, or CF₂; and wherein

R⁵ is H, halo, CN, OH, or NH₂.

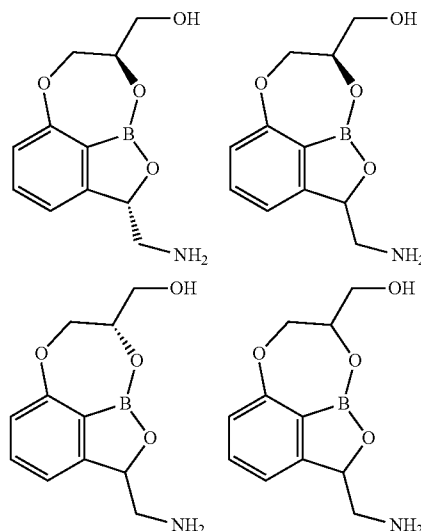
2. A compound of formula I of claim 1 and with a proviso that when R¹, R³, R⁴, R⁵ are all H; and wherein R² is CH₂NH₂; then Y is other than O.

3. A compound of claim 2 wherein R¹ is H; and wherein the chiral group CR¹R² has (S)-configuration.

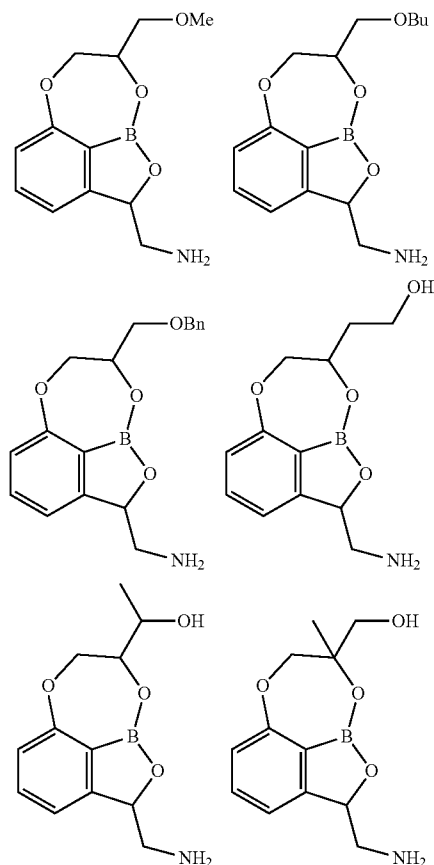
4. A compound of claim 3 wherein R¹, R³, and R⁵ are all H; R² is CH₂NH₂, and R⁴ is CH₂OH group attached to the carbon atom of the ring fragment CH—O—B.

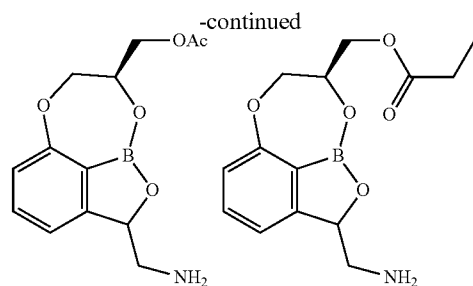
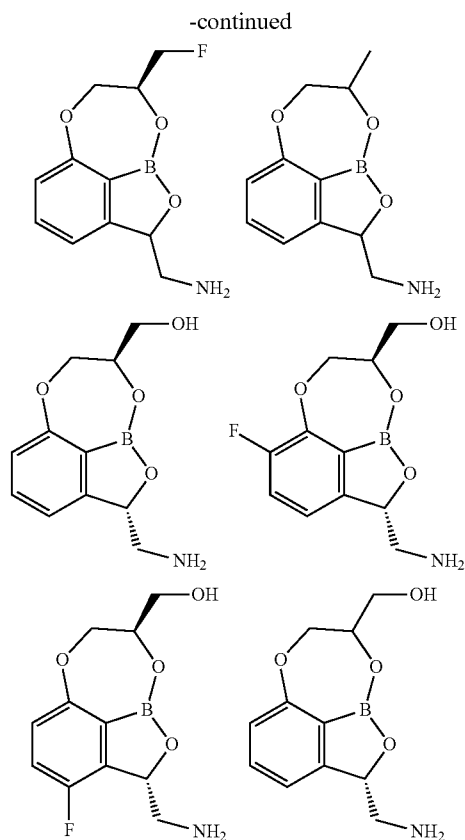
5. A compound of claim 4 wherein the chiral group CHR⁴ has (R)-configuration.

6. A compound of claim 5 selected from structures below.



7. A compound of claim 5 selected from structures below.





8. A method for the treatment of a microbial infection in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.

9. The method according to claim 8, wherein the compound is administered to the mammal orally, parenterally, transdermally, topically, rectally, or intranasally in a pharmaceutical composition.

10. A method according to claim 8 wherein the microbial infection is a Gram-negative, Gram-positive, or mycobacterial infection.

11. A method according to claim 8 wherein the microbial infection is caused by microorganisms selected from *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Escherichia coli*, or *Klebsiella pneumoniae*.

12. The method according to claim 8, wherein the infection is a skin, soft tissue, respiratory, or an eye infection.

13. A compound of claim 1 with a minimum inhibitory concentration against microorganisms *Pseudomonas aeruginosa* and *Acinetobacter baumannii* of less or equal to 4 $\mu\text{g/mL}$.

14. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

* * * * *