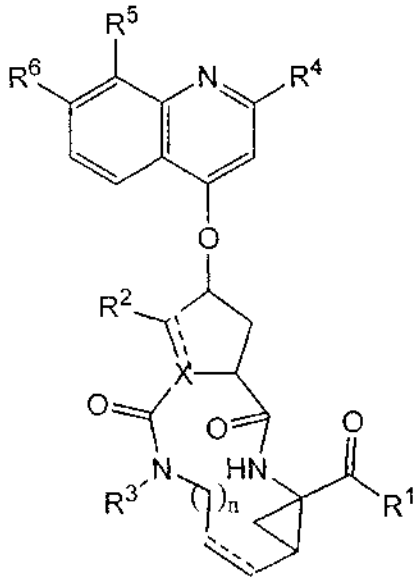
We Claim:

1. A compound having the formula



(I)

an *N*-oxide, salt, or stereoisomer thereof, wherein

each dashed line (represented by - - - - -) represents an optional double bond;

X is N, CH and where X bears a double bond it is C;

$\mathbf{R^1}$ is $-OR^7$, $-NH-SO_2R^8$;

$\mathbf{R^2}$ is hydrogen, and where **X** is C or CH, $\mathbf{R^2}$ may also be C_{1-6}alkyl;

$\mathbf{R^3}$ is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{3-7}cycloalkyl;

$\mathbf{R^4}$ is aryl or Het;

n is 3, 4, 5, or 6;

$\mathbf{R^5}$ represents halo, C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, polyhaloC_{1-6}alkyl, phenyl, or Het;

$\mathbf{R^6}$ represents C_{1-6}alkoxy, or dimethylamino;

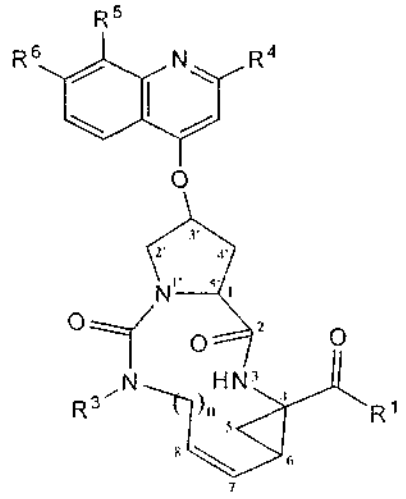
$\mathbf{R^7}$ is hydrogen; aryl; Het; C_{3-7}cycloalkyl optionally substituted with C_{1-6}alkyl; or C_{1-6}alkyl optionally substituted with C_{3-7}cycloalkyl, aryl or with Het;

$\mathbf{R^8}$ is aryl; Het; C_{3-7}cycloalkyl optionally substituted with C_{1-6}alkyl; or C_{1-6}alkyl optionally substituted with C_{3-7}cycloalkyl, aryl or with Het;

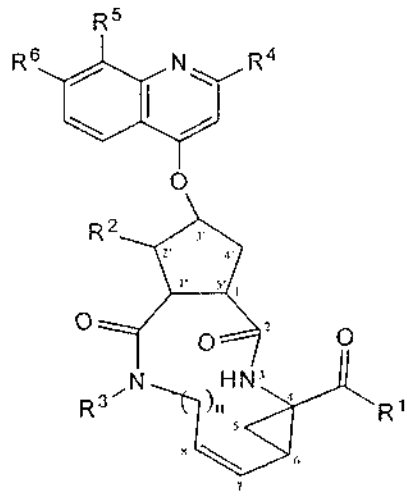
aryl as a group or part of a group is phenyl optionally substituted with one, two or three substituents selected from halo, hydroxy, nitro, cyano, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl, amino, mono- or di-C_{1-6}alkylamino, azido, mercapto, polyhaloC_{1-6}alkyl, polyhaloC_{1-6}alkoxy, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonylpiperazinyl, and morpholinyl; wherein the morpholinyl and piperidinyl groups may be optionally substituted with one or with two C_{1-6}alkyl radicals;

Het as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, said heterocyclic ring being optionally condensed with a benzene ring; and wherein said Het as a whole is optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl, amino, mono- or di-C_{1-6}alkylamino, azido, mercapto, polyhaloC_{1-6}alkyl, polyhaloC_{1-6}alkoxy, C_{3-7}cycloalkyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonylpiperazinyl, and morpholinyl; wherein the morpholinyl and piperidinyl groups may be optionally substituted with one or with two C_{1-6}alkyl radicals.

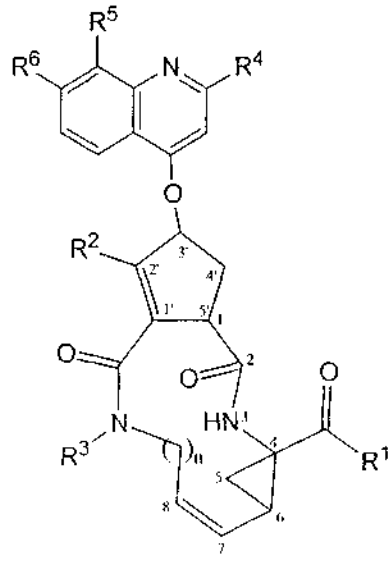
2. A compound as claimed in claim 1, wherein the compound has the formula (I-c), (I-d), or (I-e):



(I-c)

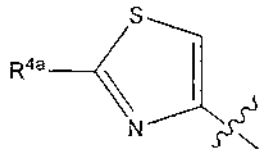
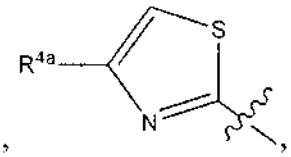
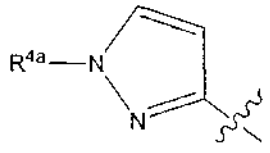
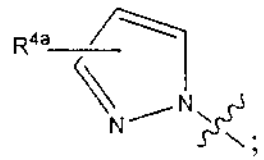


(I-d)



(I-e)

3. A compound as claimed in any one of claims 1-2, wherein R^4 is selected from the group consisting of phenyl, pyridin-4-yl,

wherein R^{4a} is, each independently, hydrogen, halo, C_{1-6}alkyl, amino, or mono- or di-C_{1-6}alkylamino.

4. A compound as claimed in any one of claims 1-3, wherein R^5 is methyl, ethyl, isopropyl, *tert*-butyl, fluoro, chloro, or bromo; and R^6 is methoxy.

5. A compound as claimed in any one of claims 1-4, wherein
   (a) R^1 is $-OR^7$, wherein R^7 is C_{1-6}alkyl or hydrogen;
   (b) R^1 is $-NHS(=O)_2R^8$, wherein R^8 is methyl, cyclopropyl, or phenyl; or
   (c) R^1 is $-NHS(=O)_2R^8$, wherein R^8 is cyclopropyl substituted with methyl.

6. A compound as claimed in claim 5, wherein R^1 is $-NHS(=O)_2R^8$, wherein R^8 is methyl, cyclopropyl, or phenyl.

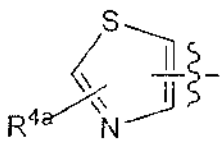
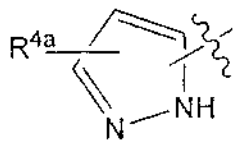
7. A compound as claimed in any one of claims 1-6, wherein n is 4 or 5.

8. A compound as claimed in any one of claims 1-7, wherein n is 4.

9. A compound as claimed in any one of claims 1-8, wherein R^3 is hydrogen or C_{1-6}alkyl.

10. A compound as claimed in claim 9, wherein R^3 is hydrogen or methyl.

11. A compound as claimed in any one of claims 1-2, wherein R^4 is a radical


(q)

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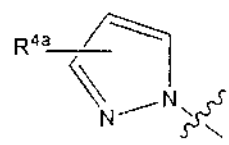
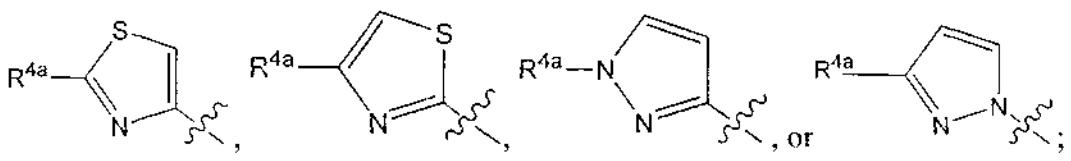

(q'-1)

wherein, where possible a nitrogen may bear an R^{4a} substituent or a link to the remainder of the molecule; each R^{4a} in any of the R^4 substituents may be selected from those mentioned as possible substituents on Het, as specified in claim 1.

12. A compound as claimed in any one of claims 1-2, wherein R^4 is selected from the group consisting of:



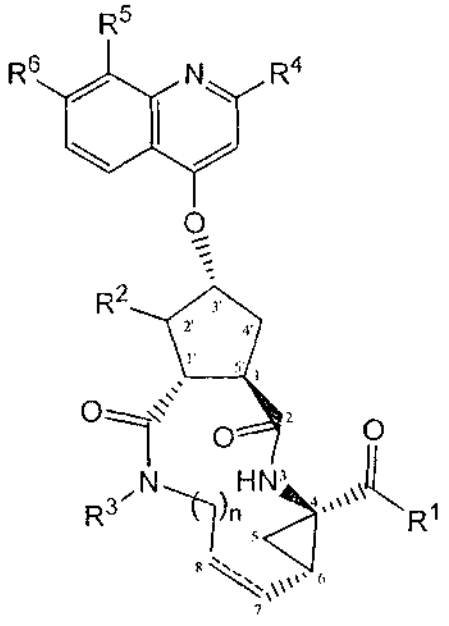
(q-1) (q-2) (q-3) (q-4)

wherein each R^{4a} is hydrogen, halo, C_{1-6}alkyl, amino, or mono- or di-C_{1-6}alkylamino, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl; and wherein the morpholinyl and piperidinyl groups may optionally substituted with one or two C_{1-6}alkyl radicals.

13. A compound as claimed in claim 12, wherein in radicals (q-1), (q-2), (q-3), or (q-4) each R^{4a} is, each independently, hydrogen, halo, C_{1-6}alkyl, amino, or mono- or di-C_{1-6}alkylamino.

14. A compound as claimed in any one of claims 1-13, wherein R^6 is methoxy.

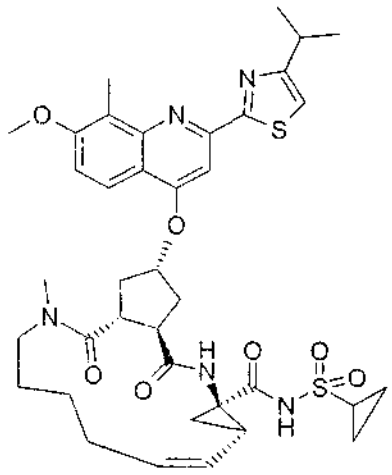
15. A compound as claimed in claim 1, wherein the compound has the structure:



(I-b)

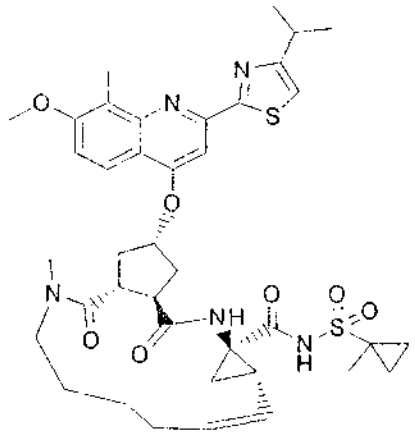
16. A compound as claimed in claim 15 wherein R^2 is hydrogen and a double bond is present between carbon atoms 7 and 8.

17. A compound as claimed in claim 1 wherein the compound of formula (I) is:

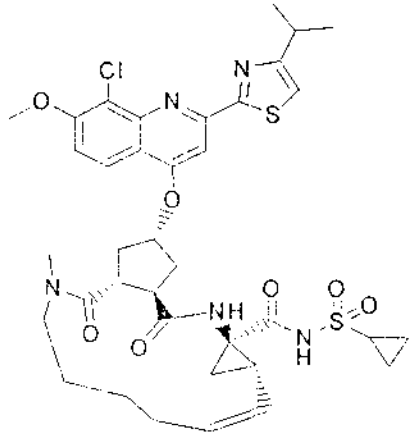


18. A compound as claimed in claim 17, wherein the compound is a white solid.

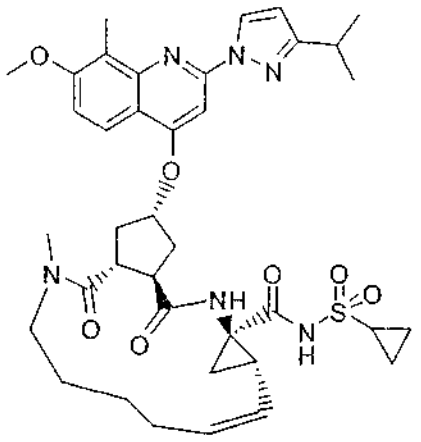
19. A compound as claimed in claim 1 wherein the compound of formula (I) is:



20. A compound as claimed in claim 1 wherein the compound of formula (I) is:



21. A compound as claimed in claim 1 wherein the compound of formula (I) is:



22. A compound as claimed in any of claims 1-21 other than an N-oxide, or salt.

23. A compound as claimed in any of claims 1-21 other than an N-oxide.

24. A combination comprising
    (a) a compound as defined in any one of claims 1 to 23 or a pharmaceutically acceptable salt thereof; and
    (b) ritonavir, or a pharmaceutically acceptable salt thereof.

25. A combination comprising
    (a) a compound as defined in any one of claims 1 to 23 or a pharmaceutically acceptable salt thereof; and
    (b) interferon α, pegylated interferon α and/or ribavirin.

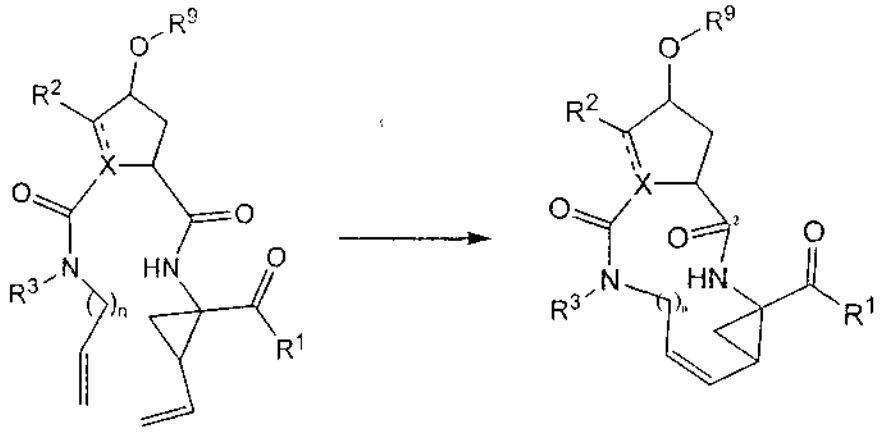
26. A pharmaceutical composition comprising a carrier, and as active ingredient an anti-virally effective amount of a compound as claimed in any one of claims 1-23 or a combination as claimed in any one of claims 24-25.

27. A compound according to any of claims 1-23 or a combination according to any one of claims 24-25, for use as a medicament.

28. A compound as claimed in any of claims 1-23 or a combination according to any one of claims 24-25, for inhibiting HCV replication.

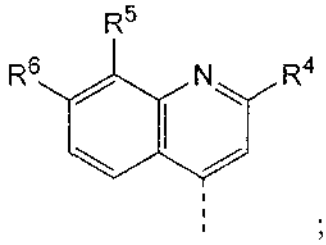
29. A process for preparing a compound as claimed in any of claims 1 - 23, wherein said process comprises:

(a) preparing a compound of formula (I) wherein the bond between C_7 and C_8 is a double bond, which is a compound of formula (I-i), by forming a double bond between C_7 and C_8, in particular via an olefin metathesis reaction, with concomitant cyclization to the macrocycle as outlined in the following reaction scheme:



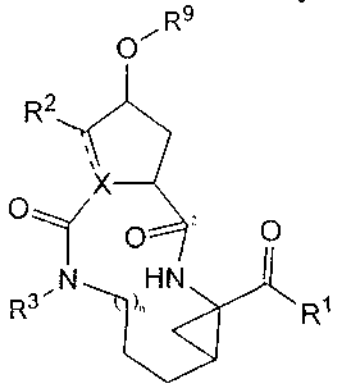
(1a) (I-i)

wherein in the above and following reaction schemes R^9 represents a radical



;

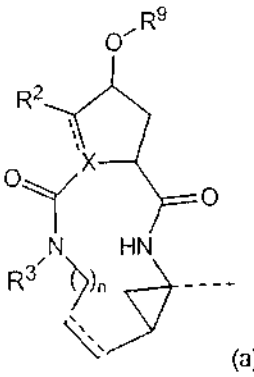
(b) converting a compound of formula (I-i) to a compound of formula (I) wherein the link between C7 and C8 in the macrocycle is a single bond, i.e. a compound of formula (I-j):



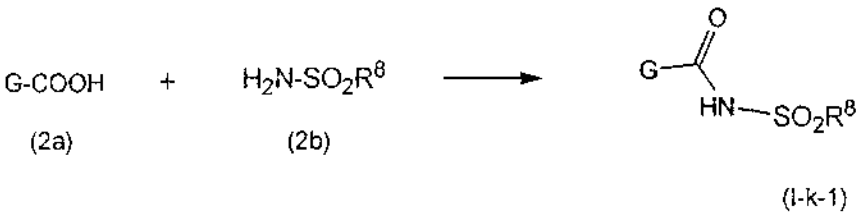
(I-j)

by a reduction of the C7-C8 double bond in the compounds of formula (I-j);

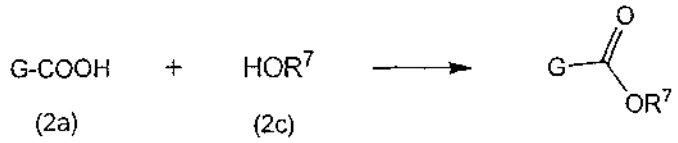
(c) preparing a compound of formula (I) wherein R^1 represents $-NHSO_2R^8$, said compounds being represented by formula (I-k-1), by forming an amide bond between a intermediate (2a) and an sulfonylamine (2b), or preparing a compound of formula (I) wherein R^1 represents $-OR^7$, i.e. a compound (I-k-2), by forming an ester bond between an intermediate (2a) and an alcohol (2c) as outlined in the following scheme wherein G represents a group:



(a),

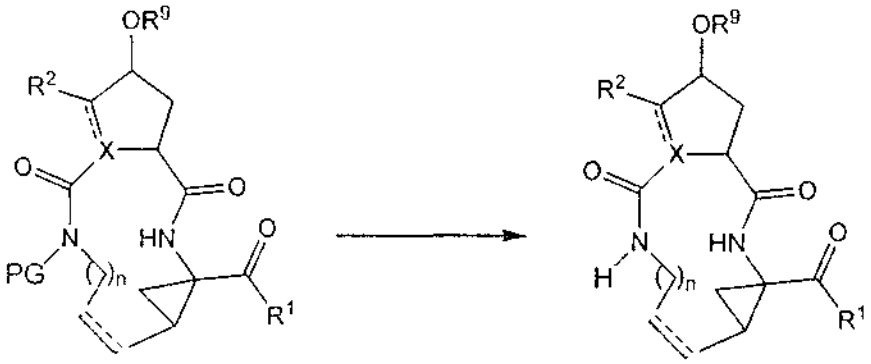


(2a) (2b) (I-k-1)



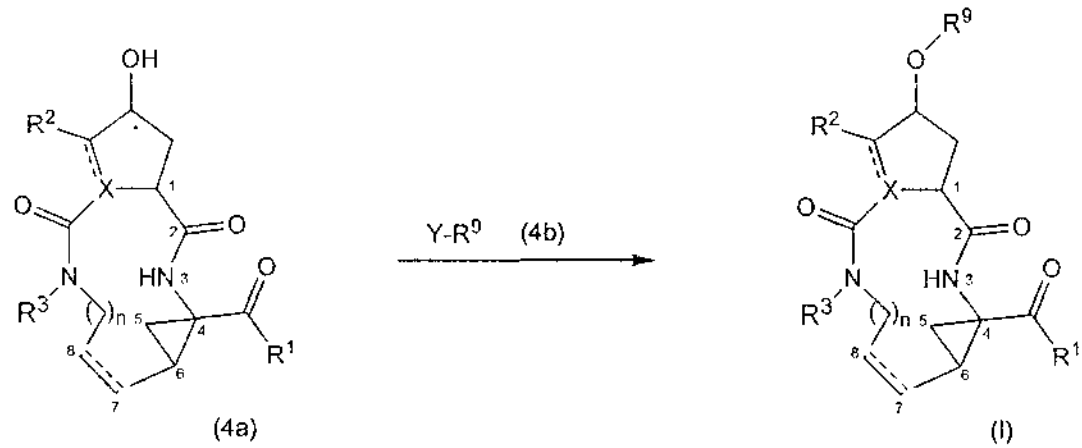
(2a) (2c) (I-k-2)

(d) preparing a compound of formula (I) wherein R^3 is hydrogen, said compound being represented by (I-l), from a corresponding nitrogen-protected intermediate (3a), wherein PG represents a nitrogen protecting group:



(3a) (I-l)

(e) reacting an intermediate (4a) with intermediate (4b) as outlined in the following reaction scheme:



wherein Y in (4b) represents hydroxy or a leaving group; and where Y represents hydroxy the reaction of (4a) with (4b) is a Mitsunobu reaction; and where Y represernts a leaving group the reaction of (4a) with (4b) is a substitution reaction;

(f) converting compounds of formula (I) into each other by a functional group transformation reaction; or

(g) preparing a salt form by reacting the free form of a compound of formula (I) with an acid or a base.

Dated this 28.12.207

Payal Kalra

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ATTORNEY FOR THE APPLICANT[S]