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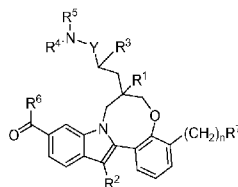
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(54) **Title:** MACROCYCLIC AND 7-AMINOALKYL-SUBSTITUTED BENZOXAZOCINES FOR TREATMENT OF HEPATITIS C INFECTIONS



(I)

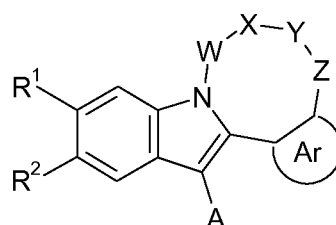
(57) **Abstract:** The present invention provides a compound of formula (I), wherein R^1 is selected from hydrogen, hydroxyl, fluoro or a C_{1-4} alkoxy group or R^1 is linked to R^3 to form a 4, 5 or 6-membered aliphatic ring optionally containing one N or O atom; R^2 is selected from cyclopentyl or cyclohexyl optionally substituted by a fluoro; R^3 is hydrogen or is linked to R^1 as hereinbefore defined; R^4 is hydrogen, a C_{1-4} alkyl group optionally substituted by a group NR^8R^9 in which R^8 and R^9 are each hydrogen or a C_{1-4} alkyl group or R^4 is linked to R^6 to form a $(CH_2)_mNR^{10}SO_2N$ group wherein m is an integer selected from 2 or 3 and R^{10} is a C_{1-4} alkyl group; R^5 is hydrogen or a C_{1-4} alkyl group; R^6 is hydroxyl or is linked to R^4 as hereinbefore defined; R^7 is hydrogen or an aliphatic ring of 4-7 ring atoms containing one or two heteroatoms selected from O, N or S or a group $S(O)$, $S(O)_2NH$ or NC_{1-4} alkyl and optionally substituted by fluoro or R^7 is a 5- 10-membered heteroaromatic ring system containing 1 to 4 heteroatoms independently selected from N, O and S, which ring is optionally substituted by one or two halo atoms or C_{1-4} alkyl or C_{1-4} alkoxy groups; Y is a single bond or a CH_2 group; when R^4 is linked to R^6 and m is 3 then Y is a single bond; when R^4 is linked to R^6 and m is 2 then Y is a CH_2 group; n is an integer from zero to four, with the proviso that when R^1 is hydrogen, n is not zero; or a pharmaceutically acceptable salt thereof, pharmaceutical formulations containing it and its use in medicine, particularly for the treatment of HCV infections. Hepatitis C (HCV) is a cause of viral infections. Methods of preparing compounds of the formula (I) are also disclosed.

MACROCYCLIC AND 7-AMINOALKYL-SUBSTITUTED BENZOXAZOCINES FOR TREATMENT OF HEPATITIS C INFECTIONS

The present invention relates to macrocyclic indole compounds, to pharmaceutical compositions containing them, to their use in the prevention and treatment of hepatitis C infections and to methods of preparation of such compounds and compositions.

Hepatitis C (HCV) is a cause of viral infections. There is as yet no adequate treatment for HCV infection but it is believed that inhibition of its RNA polymerase in mammals, particularly humans, would be of benefit.

Published International applications WO2006/046030 and WO2006/046039 (both Istituto Di Ricerche Di Biologia Molecolare P. Angeletti SpA) disclose certain tetracyclic indole derivatives of the formula (A):



(A)

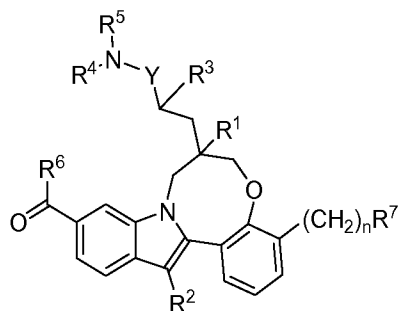
wherein R¹, R², A, Ar, W, X, Y, and Z are defined therein, useful for the treatment or prevention of infection by hepatitis C virus. Published International applications WO2007/029029 and WO2007/054741 (both Istituto Di Ricerche Di Biologia Molecolare P. Angeletti SpA) disclose structurally related tetracyclic indole derivatives, useful for the treatment or prevention of infection by hepatitis C virus.

Published International application WO2007/129119 (Istituto Di Ricerche Di Biologia Molecolare P. Angeletti SpA) specifically discloses compounds of the formula (A) wherein R¹ is carboxy and R² is hydrogen, A is cyclohexyl, Z is oxygen, W and Y are both CH₂ and X is a spiro-azetidine ring optionally substituted on the ring nitrogen atom.

We have now discovered a further class of macrocyclic indole derivatives useful for the treatment or prevention of infection by hepatitis C virus.

Thus, the present invention provides the compound of the formula (I):

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(I)

wherein R^1 is selected from hydrogen, hydroxyl, fluoro or a C_{1-4} alkoxy group or R^1 is linked to R^3 to form a 4, 5 or 6-membered aliphatic ring optionally containing one N or O atom;

5 R^2 is selected from cyclopentyl or cyclohexyl optionally substituted by a fluoro;

R^3 is hydrogen or is linked to R^1 as hereinbefore defined;

R^4 is hydrogen, a C_{1-4} alkyl group optionally substituted by a group NR^8R^9 , in which R^8 and R^9 are each hydrogen or a C_{1-4} alkyl group or R^4 is linked to R^6 to form a $(CH_2)_mNR^{10}SO_2N$ group wherein m is an integer selected from 2 or 3 and R^{10} is a C_{1-4} alkyl group;

10 R^5 is hydrogen or a C_{1-4} alkyl group;

R^6 is hydroxyl or is linked to R^4 as hereinbefore defined;

R^7 is hydrogen or an aliphatic ring of 4-7 ring atoms containing one or two heteroatoms selected from O, N or S or a group $S(O)$, $S(O)_2$, NH or NC_{1-4} alkyl and optionally substituted by fluoro or R^7 is a 5-10-membered heteroaromatic ring system containing 1 to 4 heteroatoms independently selected from N, O and S, which ring is optionally substituted by one or two halo atoms or C_{1-4} alkyl or C_{1-4} alkoxy groups;

Y is a single bond or a CH_2 group; when R^4 is linked to R^6 and m is 3 then Y is a single bond; when R^4 is linked to R^6 and m is 2 then Y is a CH_2 group;

n is an integer from zero to four;

20 with the proviso that when R^1 is hydrogen, n is not zero;

and pharmaceutically acceptable salts thereof.

Suitably, R^1 is selected from hydrogen, hydroxyl, fluoro or a methoxy group or R^1 is linked to R^3 to form a 5 or 6-membered aliphatic ring optionally containing one N or O atom such as a furan ring.

25 Suitably, R^2 is selected from cyclohexyl or cyclohexyl optionally substituted by a fluoro and preferably R^2 is cyclohexyl.

Suitably R^3 is hydrogen or linked to R^1 to form a 5 or 6-membered aliphatic ring optionally containing one N or O atom such as a furan ring. Preferably R^3 is hydrogen when R^4 is linked to R^6 .

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Suitably R^4 is a C_{1-4} alkyl group optionally substituted by a group NR^8R^9 or is linked to R^6 as hereinbefore defined and R^{10} is a methyl group.

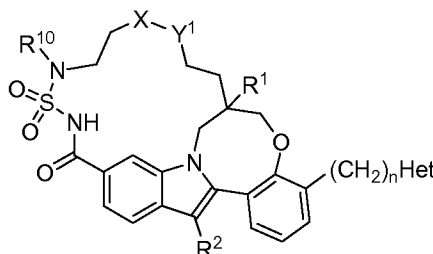
In one embodiment of the present invention, R^7 is a five- or six-membered aliphatic ring optionally containing 1 or 2 heteroatoms independently selected from N and O and S, and which ring is optionally substituted by one or two fluoro. Suitably, in this case, R^7 is 1-piperidino, 1-morpholino or 1-pyrrolidino optionally substituted by one or two fluoro.

In a further embodiment of the present invention, R^7 is a 5-10-membered heteroaromatic ring system containing 1, 2 or 3 heteroatoms independently selected from N, O and S and which ring is optionally substituted by one or two fluoro atoms or a methyl, ethyl or methoxy group.

In a further embodiment of the present invention, R^7 is hydrogen.

Suitably n is zero or one or three and preferably n is one to three.

In a preferred embodiment, the present invention provides the compound of the formula (II):



(II)

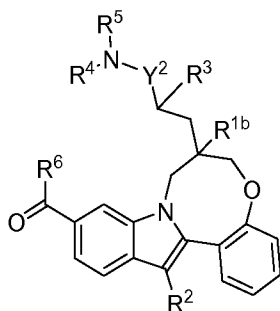
wherein n , R^1 , R^2 and R^{10} are as hereinbefore defined, XY^1 is a group CH_2NR^5 or NR^5CH_2 wherein R^5 is as hereinbefore defined, and Het is an aliphatic ring of 4-7 ring atoms containing one or two heteroatoms selected from O, N or S or a group $S(O)$, $S(O)_2$, NH or NC_{1-4} alkyl, Het being optionally substituted by 1-3 fluoro or Het is a 5-10-membered heteroaromatic ring system containing 1 to 4 heteroatoms independently selected from N, O and S, which ring is optionally substituted by one or two halo atoms or C_{1-4} alkyl or C_{1-4} alkoxy groups, and pharmaceutically acceptable salts thereof.

Suitably R^1 is hydrogen, hydroxyl or fluoro, and preferably hydrogen.

Suitably Het is a 5- or 6-membered aliphatic ring system containing 1 or 2 heteroatoms independently selected from N, and O which ring is optionally substituted by one or two halo atoms, suitably fluoro, or a C_{1-4} alkyl or C_{1-4} alkoxy group,, and pharmaceutically acceptable salts thereof. Preferably Het is 1-piperidino, 1-morpholino or 1-pyrrolidino optionally substituted by one or two fluoro.

In a further preferred embodiment, the present invention provides the compound of the formula (III):

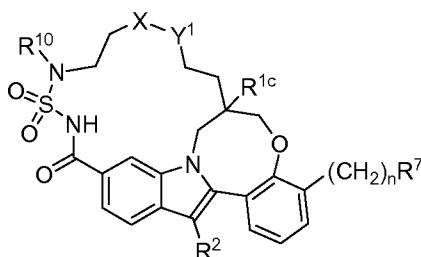
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(III)

wherein R^2 to R^6 are as hereinbefore defined and Y^2 is a single bond or a CH_2 group and R^{1b} is linked to R^3 to form a 4, 5 or 6-membered aliphatic ring optionally containing one N or O atom, and pharmaceutically acceptable salts thereof. Suitably, R^{1b} is linked to R^3 to form a 5 or 6-membered aliphatic ring optionally containing one N or O atom such as a furan ring.

In a further preferred embodiment, the present invention provides the compound of the formula (IV):



(IV)

wherein n , X , Y^1 , R^2 , R^7 and R^{10} are as hereinbefore defined and R^{1c} is fluoro or hydroxyl, and pharmaceutically acceptable salts thereof.

When any variable occurs more than one time in formula (I) or in any substituent, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "alkyl" as a group or part of a group means that the group is straight or branched. Examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkenyl groups include vinyl and allyl.

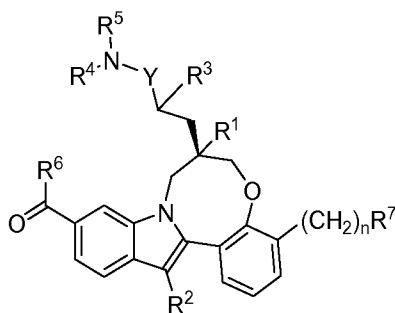
When used herein, the term aliphatic ring as a group or part of a group means a ring system which contains 4 to 7 ring atoms and single or double bonds which do not impart aromaticity to the ring. The ring may optionally contain 1 or 2 heteroatoms independently selected from N and O and S or a group $S(O)$, $S(O)_2$, NH or $NC_{1-4}alkyl$. Particular examples of such groups include pyrrolino, morpholino, and piperidino.

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When used herein, the term “heteroaryl” as a group or part of a group means a 5-10 membered heteroaromatic ring system containing 1 to 4 heteroatoms selected from N, O and S. Particular examples of such groups include pyrrolyl, furanyl, thienyl, pyridyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazolyl, oxadiazolyl, thiadiazolyl, triazinyl, tetrazolyl, indolyl, benzothienyl, benzimidazolyl, benzofuryl, quinoliny and isoquinoliny.

Where a compound or group is described as “optionally substituted” none, one or more substituents may be present. Furthermore, optional substituents may be attached to the compounds or groups which they substitute in a variety of ways, either directly or through a connecting group of which the following are examples: amine, amide, ester, ether, thioether, sulfonamide, sulfamide, sulfoxide, urea, thiourea and urethane. As appropriate an optional substituent may itself be substituted by another substituent, the latter being connected directly to the former or through a connecting group such as those exemplified above.

When R¹ is hydrogen the preferred stereochemistry of the compounds of the formula (I) is as shown below:



Specific compounds within the scope of this invention include:

(7*R*)-14-cyclohexyl-18,21-dimethyl-4-(piperidin-1-ylmethyl)-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide,
 (7*R*)-14-cyclohexyl-4-[(3,3-difluoropyrrolidin-1-yl)methyl]-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide,
 (7*R*)-14-cyclohexyl-18,21-dimethyl-4-(pyrrolidin-1-ylmethyl)-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide,
 (7*R*)-14-cyclohexyl-18,21-dimethyl-4-(morpholin-4-ylmethyl)-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide,

- 14-cyclohexyl-7-hydroxy-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5] benzoxazocin-15-one 17,17-dioxide,
- 14-cyclohexyl-7-fluoro-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5] benzoxazocin-15-one 17,17-dioxide,
- 5 14-cyclohexyl-7-hydroxy-4,18,22-trimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminiothioiminomethano)indolo[1,2-*e*][1,5] benzoxazocin-15-one 17,17-dioxide,
- 10 (2*S*,4*R*) and (2*R*,4*S*)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
- (2*S*,4*R*) or (2*R*,4*S*)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
- (2*R*,4*S*) or (2*S*,4*R*)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
- 15 (2*R*,4*R*) and (2*S*,4*S*)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
- (2*R*,4*R*) or (2*S*,4*S*)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
- 20 (2*S*,4*S*) or (2*R*,4*R*)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
- (2*S*,4*S*) and (2*R*,4*R*)-14'-cyclohexyl-4-[(dimethylamino)methyl]-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
- (2*S*,4*S*) or (2*R*,4*R*)-14'-cyclohexyl-4-[(dimethylamino)methyl]-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
- 25 (2*R*,4*R*) or (2*S*,4*S*)-14'-cyclohexyl-4-[(dimethylamino)methyl]-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
- (2*R*,4*S*) and (2*S*,4*R*)-14'-cyclohexyl-4-[(dimethylamino)methyl]-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
- 30 (2*R*,4*S*) or (2*S*,4*R*)-14'-cyclohexyl-4-[(dimethylamino)methyl]-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
- (2*S*,4*R*) or (2*R*,4*S*)-14'-cyclohexyl-4-[(dimethylamino)methyl]-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
- (2*S*,4*S*) and (2*R*,4*R*)-14'-cyclohexyl-4-{[isopropyl(methyl)amino]methyl}-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
- 35 (2*R*,4*S*) and (2*S*,4*R*)-14'-cyclohexyl-4-{[isopropyl(methyl)amino]methyl}-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,

(2S,4S) and (2R,4R)-14'-cyclohexyl-4-(morpholin-4-ylmethyl)-4,5-dihydro-3H-spiro[furan-2,7'-indolo[1,2-e][1,5]benzoxazocine]-11'-carboxylic acid,

(2R,4S) and (2S,4R)-14'-cyclohexyl-4-(morpholin-4-ylmethyl)-4,5-dihydro-3H-spiro[furan-2,7'-indolo[1,2-e][1,5]benzoxazocine]-11'-carboxylic acid,

5 and pharmaceutically acceptable salts thereof.

For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid
10 addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, fumaric acid, *p*-toluenesulfonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or sulfuric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a
15 suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, *e.g.* sodium or potassium salts; and alkaline earth metal salts, *e.g.* calcium or magnesium salts.

The salts may be formed by conventional means, such as by reacting the free base form
20 of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

The present invention includes within its scope prodrugs of the compounds of formula (I)
25 above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible *in vivo* into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

A prodrug may be a pharmacologically inactive derivative of a biologically active
30 substance (the "parent drug" or "parent molecule") that requires transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. The transformation *in vivo* may be, for example, as the result of some metabolic process, such as chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulfate ester, or reduction or oxidation of a susceptible functionality.

35 The present invention includes within its scope solvates of the compounds of formula (I) and salts thereof, for example, hydrates.

The present invention also includes within its scope any enantiomers, diastereomers, geometric isomers and tautomers of the compounds of formula (I). It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the invention.

5 The present invention further provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in therapy.

The present invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for treatment or prevention of infection by hepatitis C virus in a human or animal.

10 In another aspect, the invention provides the use of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treatment or prevention of infection by hepatitis C virus in a human or animal.

A further aspect of the invention provides a pharmaceutical composition comprising a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier. The composition may be in any suitable form, depending on the intended method of administration. It may for example be in the form of a tablet, capsule or liquid for oral administration, or of a solution or suspension for administration parenterally.

20 The pharmaceutical compositions optionally also include one or more other agents for the treatment of viral infections such as an antiviral agent, or an immunomodulatory agent such as α -, β - or γ -interferon.

In a further aspect, the invention provides a method of inhibiting hepatitis C virus polymerase and/or of treating or preventing an illness due to hepatitis C virus, the method involving administering to a human or animal (preferably mammalian) subject suffering from the condition a therapeutically or prophylactically effective amount of the pharmaceutical composition described above or of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof. "Effective amount" means an amount sufficient to cause a benefit to the subject or at least to cause a change in the subject's condition.

30 The dosage rate at which the compound is administered will depend on a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age of the patient, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition and the host undergoing therapy. Suitable dosage levels may be of the order of 0.02 to 5 or 10 g per day, with oral dosages two to five times higher. For instance, administration of from 1 to 50 mg of the compound per kg of body weight from one to three times per day may be in order. Appropriate values are selectable by routine testing.

35 An additional aspect of the invention provides a method of preparation of a pharmaceutical composition, involving admixing at least one compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically

acceptable adjuvants, diluents or carriers and/or with one or more other therapeutically or prophylactically active agents.

The present invention also provides a process for the preparation of compounds of formula (I). For the purposes of inhibiting HCV NS5B polymerase, treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection and inhibiting HCV viral replication and/or HCV viral production, the compounds of the present invention, optionally in the form of a salt, can be administered by any means that produces contact of the active agent with the agent's site of action. They can be administered by one or more conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but typically are administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. The compounds of the invention can, for example, be administered by one or more of the following: orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation (such as in a spray form), or rectally, in the form of a unit dosage of a pharmaceutical composition containing an effective amount of the compound and conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. Liquid preparations suitable for oral administration (e.g., suspensions, syrups, elixirs and the like) can be prepared according to techniques known in the art and can employ any of the usual media such as water, glycols, oils, alcohols and the like. Solid preparations suitable for oral administration (e.g., powders, pills, capsules and tablets) can be prepared according to techniques known in the art and can employ such solid excipients as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like. Parenteral compositions can be prepared according to techniques known in the art and typically employ sterile water as a carrier and optionally other ingredients, such as solubility aids. Injectable solutions can be prepared according to methods known in the art wherein the carrier comprises a saline solution, a glucose solution or a solution containing a mixture of saline and glucose. Further description of methods suitable for use in preparing pharmaceutical compositions of the present invention and of ingredients suitable for use in said compositions is provided in Remington's Pharmaceutical Sciences, 18th edition (ed. A. R. Gennaro, Mack Publishing Co., 1990).

As noted above, the present invention also relates to a method of inhibiting HCV NS5B activity, inhibiting HCV viral replication and/or HCV viral production, treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection with a compound of the present invention in combination with one or more therapeutic agents and a pharmaceutical composition comprising a compound of the present invention and one or more therapeutic agents selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent. Such therapeutic agents active against HCV include, but are not limited to, ribavirin, levovirin, viramidine, thymosin alpha-1, R7025 (an

enhanced interferon (Roche)), interferon- β , interferon- α , pegylated interferon- α (peginterferon- α), a combination of interferon- α and ribavirin, a combination of peginterferon- α and ribavirin, a combination of interferon- α and levovirin, and a combination of peginterferon- α and levovirin. The combination of pegylated-interferon and ribavirin represents the current Standard of Care for HCV treatment. The combination of one or more compounds of the present invention with the Standard of Care for HCV treatment, pegylated-interferon and ribavirin is specifically contemplated as being encompassed by the present invention. Interferon- α includes, but is not limited to, recombinant interferon- α 2a (such as ROFERON interferon available from Hoffmann-LaRoche, Nutley, NJ), pegylated interferon- α 2a (PEGASYS), interferon- α 2b (such as INTRON-A interferon available from Schering Corp., Kenilworth, NJ), pegylated interferon- α 2b (PEGINTRON), a recombinant consensus interferon (such as interferon alfacon-1), albuferon (interferon- α bound to human serum albumin (Human Genome Sciences)), and a purified interferon- α product. Amgen's recombinant consensus interferon has the brand name INFERGEN. Levovirin is the L-enantiomer of ribavirin which has shown immunomodulatory activity similar to ribavirin. Viramidine represents an analog of ribavirin disclosed in International Patent Application Publication WO 01/60379. In accordance with the method of the present invention, the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms.

For the treatment of HCV infection, the compounds of the invention may also be administered in combination with the antiviral agent NS5B polymerase inhibitor R7128 (Roche). The compounds of the present invention also may be combined for the treatment of HCV infection with antiviral 2'-C-branched ribonucleosides disclosed in Rogers E. Harry-O'Kuru *et al.*, *A Short, Flexible Route toward 2'-C-Branched Ribonucleosides*, 62 J. ORG. CHEM. 1754-59 (1997); Michael S. Wolfe & Rogers E. Harry-O'Kuru, *A Concise Synthesis of 2'-C-Methylribonucleosides*, 36(42) TETRAHEDRON LETTERS 7611-14 (1995); U.S. Patent No. 3,480,613; and International Patent Application Publications WO 01/90121, WO 01/92282, WO 02/32920, WO 04/002999, WO 04/003000 and WO 04/002422; the entire contents of each of which are incorporated by reference. Such 2'-C-branched ribonucleosides include, but are not limited to, 2'-C-methyl-cytidine, 2'-C-methyl-uridine, 2'-C-methyl-adenosine, 2'-C-methyl-guanosine, and 9-(2-C-methyl- β -D-ribofuranosyl)-2,6-diaminopurine, and the corresponding amino acid ester of the ribose C-2', C-3', and C-5' hydroxyls and the corresponding optionally substituted cyclic 1,3-propanediol esters of the 5'-phosphate derivatives.

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with an agent that is an inhibitor of HCV NS3 serine protease. HCV NS3 serine protease is an essential viral enzyme and has been described to be an excellent target for inhibition of HCV replication. Exemplary substrate and non-substrate based inhibitors of HCV NS3 protease inhibitors are disclosed in International Patent Application Publications WO 98/22496, WO 98/46630, WO 99/07733, WO 99/07734, WO 99/38888,

WO 99/50230, WO 99/64442, WO 00/09543, WO 00/59929, WO 02/48116, WO 02/48172, WO 2008/057208 and WO 2008/057209, in British Patent No. GB 2 337 262, and in U.S. Patent Nos. 6,323,180 and 7,470,664.

5 The compounds of the present invention may also be combined for the treatment of HCV infection with nucleosides having anti-HCV properties, such as those disclosed in International Patent Application Publications WO 02/51425, WO 01/79246, WO 02/32920, WO 02/48165 and WO 2005/003147 (including R1656, (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine, shown as compounds 3-6 on page 77); WO 01/68663; WO 99/43691; WO 02/18404 and WO 2006/021341, and U.S. Patent Application Publication
10 US 2005/0038240, including 4'-azido nucleosides such as R1626, 4'-azidocytidine; U.S. Patent Application Publications US 2002/0019363, US 2003/0236216, US 2004/0006007, US 2004/0063658 and US 2004/0110717; U.S. Patent Nos. 7,105,499, 7,125,855, 7,202,224; and International Patent Application Publications WO 02/100415, WO 03/026589, WO 03/026675, WO 03/093290, WO 04/011478, WO 04/013300 and WO 04/028481; the content of each is
15 incorporated herein by reference in its entirety.

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with an agent that is an inhibitor of HCV NS5B polymerase. Such HCV NS5B polymerase inhibitors that may be used as combination therapy include, but are not limited to, those disclosed in International Patent Application Publications
20 WO 02/057287, WO 02/057425, WO 03/068244, WO 2004/000858, WO 04/003138 and WO 2004/007512; U.S. Patent Nos. 6,777,392, 7,105,499, 7,125,855, 7,202,224 and U.S. Patent Application Publications US 2004/0067901 and US 2004/0110717; the content of each is incorporated herein by reference in its entirety. Other such HCV polymerase inhibitors include, but are not limited to, valopicitabine (NM-283; Idenix) and 2'-F-2'-beta-methylcytidine (*see also*
25 WO 2005/003147).

In one embodiment, additional nucleoside HCV NS5B polymerase inhibitors that are used in combination with the present HCV NS5B inhibitors are selected from the following compounds: 4-amino-7-(2-*C*-methyl- β -D-arabino furanosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(2-*C*-methyl- β -D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-methylamino-7-(2-*C*-methyl- β -D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-dimethylamino-7-(2-*C*-methyl- β -D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-cyclopropylamino-7-(2-*C*-methyl- β -D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(2-*C*-vinyl- β -D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(2-*C*-hydroxymethyl- β -D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(2-*C*-fluoromethyl- β -D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-5-methyl-7-(2-*C*-methyl- β -D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(2-*C*-methyl- β -D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxylic acid; 4-amino-5-bromo-7-(2-*C*-methyl- β -D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-5-chloro-7-(2-*C*-methyl- β -D-

ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-5-fluoro-7-(2-*C*-methyl-β-*D*-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 2,4-diamino-7-(2-*C*-methyl-β-*D*-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 2-amino-7-(2-*C*-methyl-β-*D*-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 2-amino-4-cyclopropylamino-7-(2-*C*-methyl-β-*D*-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 2-amino-7-(2-*C*-methyl-β-*D*-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one; 4-amino-7-(2-*C*-ethyl-β-*D*-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(2-*C*,2-*O*-dimethyl-β-*D*-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 7-(2-*C*-methyl-β-*D*-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one; 2-amino-5-methyl-7-(2-*C*, 2-*O*-dimethyl-β-*D*-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one; 4-amino-7-(3-deoxy-2-*C*-methyl-β-*D*-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(3-deoxy-2-*C*-methyl-β-*D*-arabino furanosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-2-fluoro-7-(2-*C*-methyl-β-*D*-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(3-*C*-methyl-β-*D*-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(3-*C*-methyl-β-*D*-xylofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(2,4-di-*C*-methyl-β-*D*-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(3-deoxy-3-fluoro-2-*C*-methyl-β-*D*-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; and the corresponding 5'-triphosphates; or a pharmaceutically acceptable salt thereof.

The compounds of the present invention may also be combined for the treatment of HCV infection with non-nucleoside inhibitors of HCV polymerase such as those disclosed in U.S. Patent Application Publications US 2006/0100262 and US 2009/0048239; International Patent Application Publications WO 01/77091, WO 01/47883, WO 02/04425, WO 02/06246, WO 02/20497, WO 2005/016927 (in particular JTK003), WO 2004/041201, WO 2006/066079, WO 2006/066080, WO 2008/075103, WO 2009/010783 and WO 2009/010785; the content of each is incorporated herein by reference in its entirety.

In one embodiment, additional non-nucleoside HCV NS5B polymerase inhibitors that are used in combination with the present HCV NS5B inhibitors are selected from the following compounds: 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(2-morpholin-4-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-3-methoxy-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; methyl ({[(14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocin-11-yl)carbonyl]amino}sulfonyl)acetate; ({[(14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocin-11-yl)carbonyl]amino}sulfonyl)acetic acid; 14-cyclohexyl-*N*-[(dimethylamino)sulfonyl]-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxamide; 3-chloro-14-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine 11-carboxylic acid; *N*-(11-carboxy-14-

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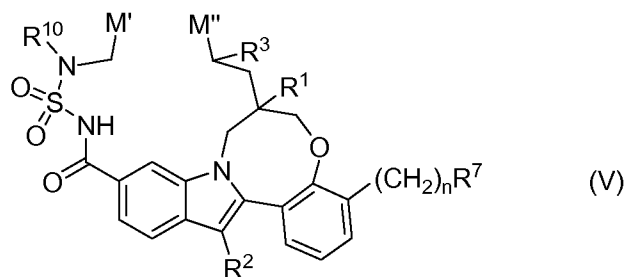
cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocin-7-yl)-*N,N*-dimethylethane-1,2-diaminium bis(trifluoroacetate); 14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylic acid; 14-cyclohexyl-6-methyl-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-3-methoxy-6-methyl-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-3-methoxy-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[3-(dimethylamino)propyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-7-oxo-6-(2-piperidin-1-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(2-morpholin-4-ylethyl)-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(diethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(1-methylpiperidin-4-yl)-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-*N*-[(dimethylamino)sulfonyl]-7-oxo-6-(2-piperidin-1-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxamide; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-*N*-[(dimethylamino)sulfonyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxamide; 14-cyclopentyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 6-allyl-14-cyclohexyl-3-methoxy-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclopentyl-6-[2-(dimethylamino)ethyl]-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 13-cyclohexyl-5-methyl-4,5,6,7-tetrahydrofuro[3',2':6,7][1,4]diazocino[1,8-*a*]indole-10-carboxylic acid; 15-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-6,7,8,9-tetrahydro-5*H*-indolo[2,1-*a*][2,6]benzodiazonine-12-carboxylic acid; 15-cyclohexyl-8-oxo-6,7,8,9-tetrahydro-5*H*-indolo[2,1-*a*][2,5]benzodiazonine-12-carboxylic acid; 13-cyclohexyl-6-oxo-6,7-dihydro-5*H*-indolo[1,2-*d*][1,4]benzodiazepine-10-carboxylic acid; and pharmaceutically acceptable salts thereof.

In another embodiment, the present HCV NS5B polymerase inhibitors are used in combination with non-nucleoside HCV NS5A inhibitors and pharmaceutically acceptable salts thereof.

Compounds of formula (I) wherein R⁴ is linked to R⁶ may be prepared by:

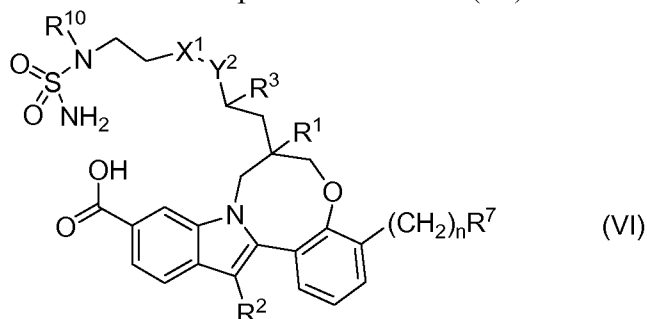
a) internal ring closure of the compound of formula (V):

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where R^1 , R^2 , R^3 , R^6 and R^7 are as defined in relation to formula (I), and M' and M'' have suitable precursor functionality to form group $X-Y^1$ as defined in relation to formula (II). For instance, when $X-Y^1$ is $N(CH_3)-CH_2$, M' can be CHO and M'' can be $HN(CH_3)-CH_2-$, where the reaction is carried out in the presence of a mild reducing agent, such as sodium cyanoborohydride, in a suitable solvent mixture, such as aqueous methanol, at pH 5-6.

b) internal ring closure of the compound of formula (VI):



where R^1 , R^2 , R^3 , R^6 and R^7 are as defined in relation to formula (I), and X^1 and Y^2 are either X and Y^1 as defined in formula (II) or suitable precursors. The reaction is conveniently carried out in the presence of a coupling reagent, such as EDC, and an additive, such as DMAP, in a suitable solvent such as DMF, DCM and mixtures thereof.

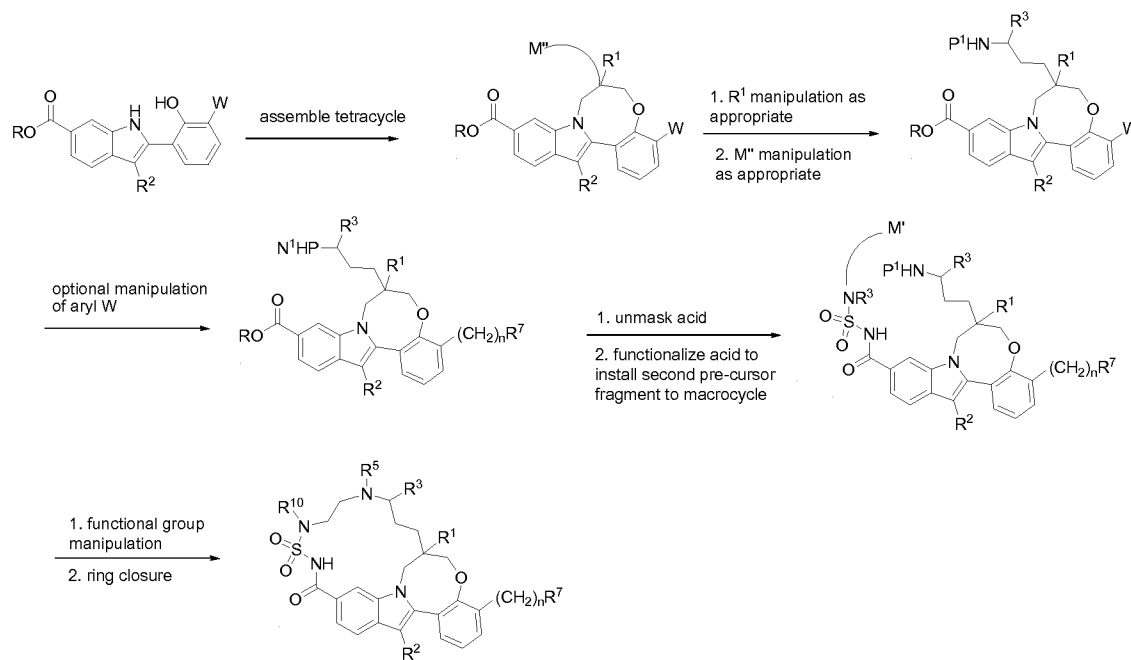
Compounds of formulae (V) and (VI) are either known in the art or may be prepared by conventional methodology well known to one of ordinary skill in the art using, for instance, procedures described in the accompanying Descriptions and Examples, or by alternative procedures which will be readily apparent.

Compounds of formula (I) can be converted into other compounds of formula (I) using synthetic methodology well known in the art. For instance, the compound of formula (I) where NR^5 and/or NR^{10} comprises an N-H group may be converted into the compound of formula (I) where NR^5 and/or NR^{10} comprises an N- CH_3 group by methylation using formaldehyde followed by a mild reducing agent, such as sodium borohydride. By analogy, using similar conditions, the compound of formula (I) where NR^5 and/or NR^{10} comprises an N-H group may be converted into the compound of formula (I) where NR^5 and/or NR^{10} comprises an N- CH_2CH_3 or an N- $CH(CH_3)_2$ group by using acetaldehyde or acetone, respectively. Alternatively, alkylation of the N-H group may be carried out using a suitable alkyl halide and a base, such as potassium carbonate, in a suitable solvent, such as acetone, MeCN or DMF.

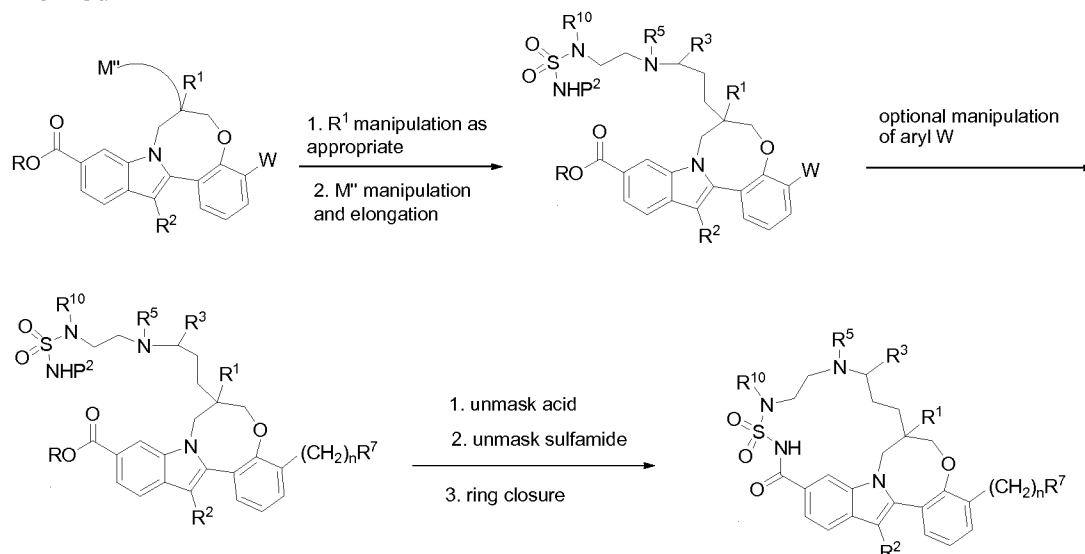
General Synthetic schemes

Three general strategies were employed for assembly of compounds from the macrocyclic class (**Methods A, B and C**); **Method C** can be regarded as an extension of **Methods A, and B**.

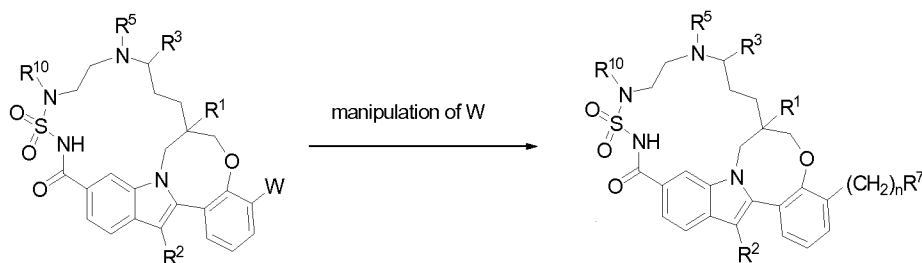
5 Method A



where W is a precursor of (CH₂)_nR⁷ and M' is a precursor of (CH₂)_m. In Method A, a suitably functionalized tether was assembled, bearing an R¹ (as appropriate) and a pre-cursor fragment to one section of the macrocycle. Following (where necessary) modification at R¹, functional group manipulation sets up the protected amine head-group in the macrocyclic linker. Based on the nature of the (CH₂)_nR⁷ group, modification of the pre-cursor functionality W can be performed at this juncture. Unmasking of the acid at C6 and functionalisation introduces a pre-cursor fragment to the remaining segment of the macrocycle. Functional group manipulation and macrocyclization (*eg, via* amide bond formation, alkylation or reductive amination) sets up the macrocycle. Functional groups on the macrocycle can then be manipulated post-closure, *eg, via* reductive amination, alkylation, amide reduction, amide formation *etc.*

Method B

The precursor assembled in Method A was modified at R^1 if appropriate, and then the M'' functionality was converted into the desired linker terminating in the protected sulfamide. Based on the nature of the $(CH_2)_n\text{Het}$ group, modification of the pre-cursor functionality W can be performed at this juncture, or can also be performed prior to manipulation of R^1 or M'' . Unmasking of the acid and sulfamide was followed by cyclization and optionally by further manipulation of the functional groups in the macrocycle.

Method C

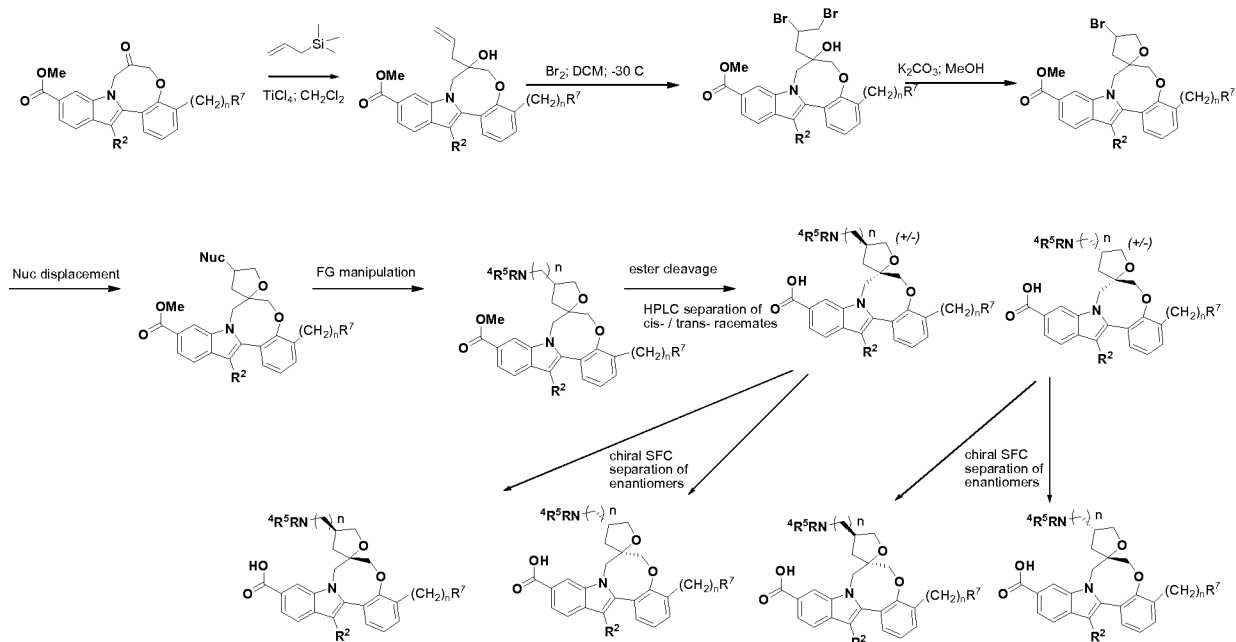
The modification of W was done after closure of the macrocyclic ring according to procedures A or B. Further manipulation of the functional groups NR⁵ and NR¹⁰ in the macrocycle can then follow. The order of these steps can also be reversed.

Two general strategies may be employed for assembly of spirocyclic compounds (**Methods D**, and **E**). **Method E** can be considered an extension of **D**.

Method D

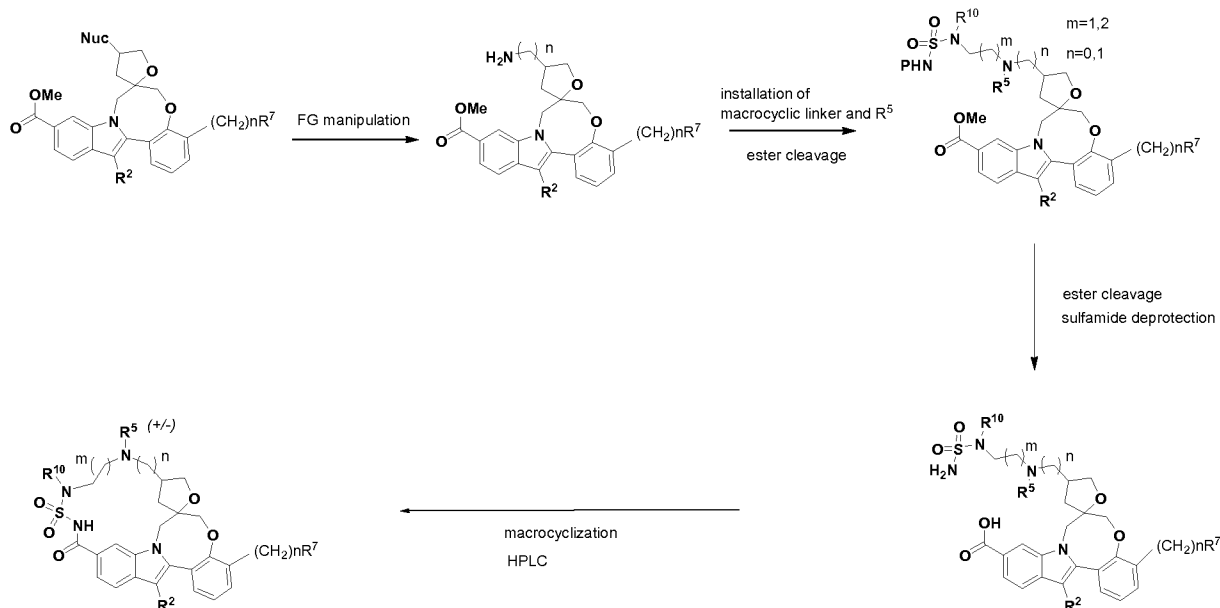
In Method D, a suitably functionalized keto-tether is assembled first (as described in **WO 2006/046030**). Allylation sets up the quaternary centre. Activation of the double bond with subsequent cyclization generates the spiro-system with a suitable handle for further functionalization. Nucleophilic displacement and functional group manipulation introduces the side chain. Following ester cleavage, preparative HPLC allows for separation of the relative cis- and trans- diastereoisomers on the dihydro-spirofuran ring, as their racemates. Separation of the enantiomers could be realized *via* chiral SFC.

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Method E

In Method E, functional group manipulation of the spirocyclic intermediate from method D afforded the primary amine. Installation of the macrocyclic linker and R^1 on the nitrogen (in analogous fashion to what is described in **WO 2009/010783** and **WO 2009/010785**), was followed by sequential ester deprotection and unmasking of the sulfamide. Macrocyclization under peptide coupling conditions afforded the desired targets.



During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by

means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 4th edition, 2007. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

5 The present invention is illustrated further by the following non-limiting examples.

The compounds of the invention were tested for inhibitory activity against the HCV RNA dependent RNA polymerase (NS5B) in an enzyme inhibition assay as described in example i). The compounds generally have IC₅₀'s below 100 nM in this assay.

10 The potential for compounds of the invention to inhibit HCV replication may be demonstrated using a cell based sub-genomic replication assay as described in example ii).

Compound names in the examples were generated using software from ACDLabs (version 8.0).

i) In-vitro HCV NS5B Enzyme Inhibition Assay

15 Published International patent application WO 96/37619 describes the production of recombinant HCV RdRp from insect cells infected with recombinant baculovirus encoding the enzyme. The purified enzyme was shown to possess *in vitro* RNA polymerase activity using RNA as template. The reference describes a polymerisation assay using poly(A) and oligo(U) as a primer or an heteropolymeric template. Incorporation of tritiated UTP or NTPs is quantified
20 by measuring acid-insoluble radioactivity. The present inventors have employed this assay to screen the various compounds described above as inhibitors of HCV RdRp.

Incorporation of radioactive UMP was measured as follows. The standard reaction (50 µl) was carried out in a buffer containing 20 mM tris/HCl pH 7.5, 5 mM MgCl₂, 1 mM DTT, 50 mM NaCl, 0.03% N-octylglucoside, 1 µCi [³H]-UTP (40 Ci/mmol, NEN), 10 µM UTP and 10
25 µg/ml poly(A) or 5µM NTPs and 5µg/ml heteropolymeric template. Oligo(U)₁₂ (1 µg/ml, Genset) was added as a primer in the assay working on Poly(A) template. The final NS5B enzyme concentration was 5 nM. The order of assembly was: 1) compound, 2) enzyme, 3) template/primer, 4) NTP. After 1 h incubation at 22 °C the reaction was stopped by adding 50 µl of 20% TCA and applying samples to DE81 filters. The filters were washed thoroughly with 5%
30 TCA containing 1M Na₂HPO₄/NaH₂PO₄, pH 7.0, rinsed with water and then ethanol, air dried, and the filter-bound radioactivity was measured in the scintillation counter. Carrying out this reaction in the presence of various concentrations of each compound set out above allowed determination of IC₅₀ values by utilising the formula:

35
$$\% \text{ Residual activity} = 100/(1+[I]/IC_{50})^s$$

where [I] is the inhibitor concentration and "s" is the slope of the inhibition curve.

ii) Cell based HCV Replication Assay

Cell clones that stably maintain subgenomic HCV replicon were obtained by transfecting Huh-7 cells with an RNA replicon identical to I₃₇₇neo/NS3-3'/wt described by Lohmann *et al.* (1999) (EMBL-genbank No. AJ242652), followed by selection with neomycin sulfate (G418).

- 5 Viral replication was monitored by measuring the expression of the NS3 protein by an ELISA assay performed directly on cells grown in 96 wells microtiter plates (Cell-ELISA) using the anti-NS3 monoclonal antibody 10E5/24 (as described in published International application WO 02/59321). Cells were seeded into 96 well plates at a density of 10⁴ cells per well in a final volume of 0.1 ml of DMEM/10% FCS. Two hours after plating, 50 µl of DMEM/10% FCS
- 10 containing a 3x concentration of inhibitor were added, cells were incubated for 96 hours and then fixed for 10 minutes with ice-cold isopropanol. Each condition was tested in duplicate and average absorbance values were used for calculations. The cells were washed twice with PBS, blocked with 5% non-fat dry milk in PBS + 0.1% Triton X100 + 0.02% SDS (PBSTS) and then incubated o/n at 4°C with the 10E5/24 mab diluted in Milk/PBSTS. After washing 5 times with
- 15 PBSTS, the cells were incubated for 3 hours at room temperature with Fc specific anti-mouse IgG conjugated to alkaline phosphatase (Sigma), diluted in Milk/PBSTS. After washing again as above, the reaction was developed with p-Nitrophenyl phosphate disodium substrate (Sigma) and the absorbance at 405/620 nm read at intervals. For calculations, we used data sets where samples incubated without inhibitors had absorbance values comprised between 1 and 1.5. The
- 20 inhibitor concentration that reduced by 50% the expression of NS3 (IC₅₀) was calculated by fitting the data to the Hill equation,

$$\text{Fraction inhibition} = 1 - (A_i - b) / (A_0 - b) = [I]^n / ([I]^n + IC_{50})$$

25 where:

- A_i = absorbance value of HBI10 cells supplemented with the indicated inhibitor concentration.
- A₀ = absorbance value of HBI10 cells incubated without inhibitor.
- b = absorbance value of Huh-7 cells plated at the same density in the same microtiter plates
- 30 and incubated without inhibitor.
- n = Hill coefficient.

Representative data for compounds of this invention are reported in Table A.

- 35 To determine the cellular toxicity of the compounds, a standard MTT assay as described by T. Mosmann (Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays; J Immunol Methods. 1983, 65, 55-63) was used. The assay is based on the capacity of mitochondrial dehydrogenase enzymes in living cells to convert the yellow water-

soluble substrate 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) into a dark blue formazan product, which is insoluble in water. The amount of formazan produced is directly proportional to the cell number in a range of cell line.

5 **iii) General Procedures**

All solvents were obtained from commercial sources (Fluka, puriss.) and were used without further purification. With the exception of routine deprotection and coupling steps, reactions were carried out under an atmosphere of nitrogen in oven dried (110 °C) glassware. Organic extracts were dried over sodium sulfate, and were concentrated (after filtration of the drying agent) on rotary evaporators operating under reduced pressure. Flash chromatography was carried out on silica gel following published procedure (W.C. Still *et al.*, J. Org. Chem. **1978**, *43*, 2923) or on commercial flash chromatography systems (Biotage corporation and Jones Flashmaster II) utilising pre-packed columns.

Reagents were usually obtained directly from commercial suppliers (and used as supplied) but a limited number of compounds from in-house corporate collections were utilised. In the latter case the reagents are readily accessible using routine synthetic steps that are either reported in the scientific literature or are known to those skilled in the art.

¹H NMR spectra were recorded on Bruker AM series spectrometers operating at (reported) frequencies between 300 and 600 MHz. Chemical shifts (δ) for signals corresponding to non-exchangeable protons (and exchangeable protons where visible) are recorded in parts per million (ppm) relative to tetramethylsilane and are measured using the residual solvent peak as reference. Signals are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad, and combinations thereof); coupling constant(s) in hertz (Hz); number of protons. Mass spectral (MS) data were obtained on a Perkin Elmer API 100, or Waters MicroMass ZQ, operating in negative (ES⁻) or positive (ES⁺) ionization mode and results are reported as the ratio of mass over charge (*m/z*) for the parent ion only. Preparative scale HPLC separations were carried out on a Waters Delta Prep 4000 separation module, equipped with a Waters 486 absorption detector or on an automated Waters Fraction Lynx or Gilson preparative system. In all cases compounds were eluted with linear gradients of water and MeCN both containing 0.1% TFA using flow rates between 15 and 40 mL/min.

The following abbreviations are used in the examples, the schemes and the tables:
Ac: acetyl; aq.: aqueous; Ar: aryl; atm: atmosphere; 9-BBN: 9-borabicyclo[3.3.1]nonane; cat.: catalytic; dioxan(e): 1,4-dioxane; dppf: (1,1'-bis(diphenylphosphino)ferrocene); DAST: diethylaminosulfur trifluoride; 1,2-DCE: 1,2-dichloroethane; DCM: dichloromethane; DIAD: diisopropylazodicarboxylate; DIC: 1,3-diisopropyl carbodiimide; DIPEA: diisopropylethyl amine; DMA: *N,N*-dimethylacetamide; DMAP: *N,N*-dimethylpyridin-4-amine; DME: dimethoxyethane; DMF: dimethylformamide; DMS: dimethylsulfide; DMSO: dimethylsulfoxide; DMP: Dess-Martin Periodinane; DPPA: diphenylphosphorylazide; EDC: 1-

ethyl-(3-dimethylaminopropyl)carbodiimide HCl salt; eq: equivalent(s); Et₃N: triethylamine; EtOAc: ethyl acetate; Et₂O: diethyl ether; EtOH: ethanol; Et₃SiH: triethylsilane; FC: Flash Chromatography; h: hour(s); HOAc: acetic acid; HATU: O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate; HOBt: 1 hydroxybenzotriazole; Me: methyl; MeCN: acetonitrile; MeOH: methanol; min: minute(s); Ms: methanesulfonyl; MS: mass spectrum; NBS: *N*-bromo succinimide; PE: petroleum ether; Ph: phenyl; quant.: quantitative; RP-HPLC: reversed phase high-pressure liquid chromatography; RT: room temperature; sat.: saturated; sec: second(s); SFC: Super-critical fluid chromatography; sat. aq.: saturated solution; TBAF: tetrabutyl ammonium fluoride; TBTU: O-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate; TFA: trifluoroacetic acid; THF: tetrahydrofuran; THP: tetrahydropyranyl; TMS: trimethylsilyl; Ts: *para*-toluene sulfonyl.

Compounds were assayed in the above described cell-based HCV replication assay (example ii) and results are reported as EC₅₀ activity ranges in Table 1.

Intermediate A: (2*R*)-4-azido-2-({*tert*-butyl(dimethyl)silyl}oxy)methyl)butyl methanesulfonate

Step 1: methyl 4-azidobutanoate

To a solution of methyl-4-bromobutyrate in DMSO (0.6 M) was added with stirring NaN₃ (1.5 eq). The suspension was heated (45-50 °C, oil bath) with stirring for 5 h. After cooling, H₂O was added and the mixture extracted with Et₂O. The organic extracts were washed with brine and dried over Na₂SO₄. The solvent was removed *in vacuo* and the crude oil used without further purification (99%).

Step 2: 4-azidobutanoic acid

Methyl 4-azidobutanoate was suspended in 1N NaOH (1.2 eq) and the minimum of MeOH was added to make the reaction mixture homogenous. After 1 h at RT temperature, MeOH was removed *in vacuo*. The aqueous solution was washed with Et₂O and acidified to pH = 0 with concentrated HCl and then extracted with Et₂O. The combined organic phases were dried over Na₂SO₄. The solvent was removed *in vacuo* and the crude oil obtained was used without further purification (quant.).

Step 3: (4*S*)-3-(4-azidobutanoyl)-4-benzyl-1,3-oxazolidin-2-one

Et₃N was added to a stirred mixture of 4-azidobutanoic acid in THF (0.3 M) cooled to -78 °C and stirring was continued at this temperature for 10 min. Pivaloyl chloride (1.3 eq) was added dropwise. The resulting mixture was warmed to 0 °C and stirred for 1 h before re-cooling to -78°C. In a separate flask, (4*S*)-4-benzyl-1,3-oxazolidin-2-one was dissolved in THF (0.8 M) and

cooled to -78°C before dropwise addition of *n*-BuLi (1.6M, 1.35 eq.) over 10 min. The mixture was stirred at -78°C for 1 h and then transferred into the -78°C solution of mixed anhydride using a syringe. The reaction was stirred at -78°C for 1 h, then at RT for a further 1h. The reaction was quenched by addition of sat. aq. NH_4Cl before partitioning between H_2O and EtOAc. The layers were separated and the aqueous phase re-extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by FC eluting with 10 to 30% EtOAc/PE to give the product as a colourless oil (74%). $(\text{ES}^+) m/z$ 289 $(\text{M}+\text{H})^+$.

Step 4: (4S)-3-[(2R)-4-azido-2-(hydroxymethyl)butanoyl]-4-benzyl-1,3-oxazolidin-2-one

The foregoing compound was dissolved in DCM (0.1 M) and cooled to -10°C . TiCl_4 (1.1 eq) was added dropwise to the mixture, such that the internal temperature did not rise above 0°C . The mixture was stirred an additional 30 min and then DIPEA (1.15 equiv.) was added dropwise, such that the internal temperature did not rise above 0°C . The deep red solution was stirred an additional 45 min at -10°C . *s*-Trioxane (1.2 eq) was added to the reaction mixture in one portion, followed by dropwise addition of TiCl_4 (1.1 eq). The reaction mixture was stirred for 2 h at -10°C and then quenched by dropwise addition of sat. aq. NaHCO_3 . The mixture was stirred for 30 min, poured into H_2O and extracted with DCM. The combined organic extracts were washed once with sat. aq. NH_4Cl , dried with Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by FC eluting with 30 to 70% EtOAc/PE to give the product as a colourless oil (61%). $(\text{ES}^+) m/z$ 319 $(\text{M}+\text{H})^+$; $[\alpha]_{\text{D}}^{20}$: $+42.9^{\circ}$ ($c = 1$, CHCl_3).

Step 5: (4S)-3-[(2R)-4-azido-2-({[tert-butyl(dimethyl)silyl]oxy}methyl)butanoyl]-4-benzyl-1,3-oxazolidin-2-one

The foregoing compound was dissolved in DCM (0.17 M) and treated with DMAP (0.1 eq) and Et_3N (1.8 eq). The solution was cooled to 0°C and *tert*-butyldimethylchlorosilane (1.5 eq) was added in one portion. The mixture was stirred at 0°C for 30 min, warmed to RT and stirred for an additional 18 h. The reaction mixture was poured into sat. aq. NaHCO_3 and extracted with DCM. The combined organic extracts were dried with Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by FC eluting with 10 to 20 % EtOAc/PE to give the product as a colourless oil (90%). $(\text{ES}^+) m/z$ 433 $(\text{M}+\text{H})^+$; $[\alpha]_{\text{D}}^{20}$: $+30.2^{\circ}$ ($c = 1$, CHCl_3).

Step 6: (2S)-4-azido-2-({[tert-butyl(dimethyl)silyl]oxy}methyl)butan-1-ol

The foregoing compound was dissolved in Et_2O (0.17 M), treated with MeOH (1.1 eq) and cooled to 0°C . LiBH_4 (1.1 eq) was added in one portion and the mixture was stirred for 30 min at 0°C . The mixture was warmed to RT and stirred for 1 h. The mixture was then cooled to 0°C and sat. aq. NaHCO_3 was carefully added over 30 min. The biphasic mixture was stirred vigorously for 1 h at 0°C and then poured into H_2O . The aqueous layer was extracted with

EtOAc and the combined organic extracts were dried with Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by FC eluting with 10 to 20% EtOAc/PE to give the product as a colourless oil (60%). ¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 0.03 (s, 6H), 0.87 (s, 9H), 1.52-1.57 (m, 2H), 1.58-1.64 (m, 1H), 3.34-3.39 (m, 4H), 3.51 (dd, *J* 10.0, 5.6, 1H), 3.58 (dd, *J* 10.0, 5.6, 1H), 4.43-4.45 (m, 1H); (ES⁺) *m/z* 260 (M+H)⁺; [α]_D²⁰ : -1.5° (*c* = 1, CHCl₃).

Step 7: (2*R*)-4-azido-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)butyl methanesulfonate

The foregoing compound was dissolved in DCM (0.13 M), DIPEA (2 eq) was added and the mixture was cooled to 0 °C. MsCl (1.1 eq) was added dropwise and the mixture was stirred for 15 min at 0 °C, then warmed to RT and stirred for an additional 15 min. The reaction mixture was then poured into 1N HCl and extracted with DCM. The combined organic extracts were washed once with sat. aq. NaHCO₃ and brine, dried with Na₂SO₄, filtered and concentrated *in vacuo*. The residue was used without further purification (95%). ¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 0.05 (s, 6H), 0.87 (s, 9H), 1.54-1.62 (m, 2H), 1.90-1.98 (m, 1H), 3.17 (s, 3H), 3.41-3.46 (m, 2H), 3.53-3.64 (m, 2H), 4.18 (d, *J* 5.4, 2H).

Intermediate B: (2*R*)-4-azido-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)pentyl methanesulfonate

Step 1: (2*S*)-5-azido-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)pentan-1-ol

The title compound was prepared from methyl 5-bromopentanoate, in analogous fashion to that described for methyl 4-bromobutanoate for the synthesis of intermediate A, steps 1-6. Purification by flash chromatography (9:1 to 7:3 PE:EtOAc) afforded the product as a colourless oil (38 %). ¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 0.03 (s, 6H), 0.87 (s, 9H), 1.28-1.33 (m, 2H), 1.48-1.53 (m, 1H), 1.53-1.61 (m, 2H), 3.28-3.31 (m, 2H), 3.32-3.36 (m, 2H), 3.50 (dd, *J* 10.0, 5.6, 1H), 3.57 (dd, *J* 10.0, 5.6, 1H), 4.34-4.36 (m, 1H); [α]_D²⁰ = -6.5° (*c* = 2.2, CHCl₃).

Step 2: (2*R*)-5-azido-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)pentyl methanesulfonate

(2*S*)-5-Azido-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)pentan-1-ol was treated in analogous fashion to the synthesis of intermediate A, step 7, to afford the title compound. ¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 0.05 (s, 6H), 0.87 (s, 9H), 1.28-1.43 (m, 2H), 1.56-1.63 (m, 2H), 1.82-1.88 (m, 1H), 3.16 (s, 3H), 3.31-3.35 (m, 2H), 3.52-3.62 (m, 2H), 4.16 (d, *J* 5.6, 2H).

Intermediate C: *N*-(2,2-dimethoxyethyl)-*N*-methylsulfuric diamide

Step 1: *N*-(2,2-dimethoxyethyl)-*N*-methylsulfuric diamide

Sulfamide (5 eq) was added to a solution of 2,2-dimethoxy-*N*-methylethanamine in dioxane (0.12 M). The reaction was stirred at reflux overnight. The solvent was removed *in vacuo*, the

residue taken up in EtOAc and washed with H₂O, brine, before being dried (Na₂SO₄), filtered and concentrated *in vacuo* to give the crude material. DCM was added and a precipitate formed, that was collected by filtration. Further trituration of the filtered solid with DCM afforded clean product (67 %). ¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 2.67 (s, 3H), 2.98 (d, *J* 5.3, 2H), 3.28 (s, 6H), 4.48 (t, *J* 5.3, 1H), 6.7 (s, 2H).

Intermediate D: [2-(methoxymethoxy)-3-methylphenyl]boronic acid

Step 1: 1-(methoxymethoxy)-2-methylbenzene

To a suspension of NaH (60% dispersion in mineral oil; 1.2 eq) in Et₂O/DMF (5:1, 0.2M) a solution of *o*-cresol in Et₂O (1 eq, 2M) was added dropwise over 15 min. A solution of MOMCl in Et₂O (1.1 eq, 2M) was added and the mixture was stirred for 30 min then poured into H₂O and extracted with Et₂O. The combined organic extracts were washed with 1N NaOH, H₂O and brine, dried over Na₂SO₄, filtered and evaporated *in vacuo* to give the title compound. The product was used in the next step without further purification.

Step 2: [2-(methoxymethoxy)-3-methylphenyl]boronic acid

To a solution of 1-(methoxymethoxy)-2-methylbenzene in diethyl ether (0.3M) cooled at -60 °C *t*BuLi in pentane (1.7M, 1.4 eq) was added dropwise and the mixture was stirred for 1 h while warming gradually to 0 °C then for a further 2 h at 0 °C. The mixture was cooled to -78 °C and a solution of B(OMe)₃ in THF (3 eq, 3.0M) was added dropwise and the mixture was allowed to reach RT and stirred overnight. The mixture was cooled to 0 °C and 1N HCl was added, then the reaction mixture was stirred for 2 h. All volatiles were removed under reduced pressure and the residue was extracted with EtOAc. The combined extracts were washed with H₂O and brine, dried over Na₂SO₄, filtered and evaporated *in vacuo* to give a yellow solid which was triturated with PE to give a white solid which was used without further purification. ¹H NMR (400 MHz, DMSO-*d*₆, 300 K) δ 2.24 (s, 3H), 3.45 (s, 3H), 4.99 (s, 2H), 7.00 (dd, *J* 7.2, 1H), 7.21 (d, *J* 7.2, 1H), 7.30 (d, *J* 7.2, 1H), 7.95 (s, 2H).

Intermediate E: *tert*-butyl methyl[3-(methylamino)propyl]carbamate

A solution of Boc₂O in THF (1.0 M) was added to a solution of *N,N*-dimethylpropane-1,3-diamine (4 eq) in THF (0.4 M) at 0 °C. The solution was warmed to RT over 72 h after which all volatiles were removed *in vacuo*. The residue was dissolved in EtOAc and washed with brine, dried over Na₂SO₄, filtered and evaporated to dryness. ¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 1.39 (s, 9H), 1.54-1.58 (m, 2H), 2.24 (s, 3H), 2.37-2.42 (m, 2H), 2.75 (s, 3H), 3.15-3.19 (m, 2H).

Example 1: (7R)-14-cyclohexyl-18,21-dimethyl-4-(piperidin-1-ylmethyl)-7,8-dihydro-6H-7,11-(propanoiminoethanoiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

5 Step 1: methyl 3-cyclohexyl-2-(3-formyl-2-methoxyphenyl)-1H-indole-6-carboxylate

Methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (prepared as in International patent application WO 2004/087714), (3-formyl-2-methoxyphenyl) boronic acid (1.5 eq) and Pd(PPh₃)₂Cl₂ (0.1 eq) were dissolved in dioxane (0.08M). The solution was degassed and flushed with Ar. An aq. solution of Na₂CO₃ solution (2 M, 1 eq) was added and the mixture was
10 heated to 110 °C for 2 h. All volatiles were evaporated *in vacuo* and the residual material was dissolved in EtOAc, filtered over Celite and evaporated *in vacuo*. The residual material was filtered over a plug of silica gel eluting with (PE/EtOAc 1:1). After evaporation of the fractions containing product and trituration with Et₂O the title compound was obtained as an off-white solid (77%). (ES⁺) *m/z* 392 (M+H)⁺.

15 Step 2: methyl 3-cyclohexyl-2-(3-formyl-2-hydroxyphenyl)-1H-indole-6-carboxylate
The foregoing compound was dissolved in dry DCM (0.1M) and treated dropwise with BBr₃ (1 M in DCM, 2 eq). After stirring for 1 h at RT, an excess of MeOH was added dropwise and stirring continued for 20 min. The volatiles were evaporated and the mixture partitioned between
20 EtOAc and 1N HCl. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Methyl 3-cyclohexyl-2-(3-formyl-2-hydroxyphenyl)-1H-indole-6-carboxylate (75%) was obtained pure after trituration with Et₂O. (ES⁺) *m/z* 378 (M+H)⁺.

Step 3: methyl 2-(2-({[(2R)-5-azido-2-({tert-butyl(dimethyl)silyl}oxy)methyl]pentyl}oxy}-3-formylphenyl)-3-cyclohexyl-1H-indole-6-carboxylate

25 A solution of the compound obtained in step 2 in DMA (0.1 M) was treated with Cs₂CO₃ (1.0 eq) at 90 °C and stirred for 30 min. Intermediate B (1.2 eq.) was added in one portion as a solution in DMA (1 M) and the mixture was stirred for 20 h at 90 °C, when an additional portion of intermediate B (0.2 eq.) as a solution in DMA (1 M) was added, followed by stirring for a total of 40 h at 90 °C. After cooling to RT the solution was diluted with EtOAc and washed with
30 H₂O (x3) and brine. The organic layer was dried with Na₂SO₄, filtered and evaporated to dryness. The residue was purified by FC eluting with 5 to 20% EtOAc/PE to give the product as a colourless solid (80%). (ES⁺) *m/z* 633 (M+H)⁺.

35 Step 4: methyl 2-(2-({[(2R)-5-azido-2-(hydroxymethyl)pentyl]oxy}-3-formylphenyl)-3-cyclohexyl-1H-indole-6-carboxylate

A solution of the foregoing compound in THF (0.1 M) was treated with TBAF (1.5 eq, 1.0 M in THF) at RT and stirred for 2 h. The reaction mixture was poured into 1N HCl and extracted with DCM. The combined organic extracts were washed once with water and brine, dried with

Na₂SO₄, filtered and concentrated *in vacuo*. The residue was used without further purification (quant.). (ES⁺) *m/z* 519 (M+H)⁺.

Step 5 : methyl 2-(2-((2*R*)-5-azido-2-((methylsulfonyl)oxy)methyl)pentyl)oxy-3-formylphenyl)-3-cyclohexyl-1*H*-indole-6-carboxylate

To a solution of the foregoing compound in DCM (0.18 M) was added DIPEA (2.2 eq) followed by methanesulfonyl chloride (1.2 eq) at 0 °C. The reaction was stirred at that temperature for 15 min, warmed to rt and stirred for an additional hour. The reaction mixture was poured into 1N HCl and extracted with DCM. The combined organic extracts were washed once with saturated NaHCO₃ solution, water and brine, dried with Na₂SO₄, filtered and concentrated *in vacuo*. The title compound was obtained as a colourless oil (99%). (ES⁺) *m/z* 597 (M+H)⁺.

Step 6 : methyl (7*R*)-7-(3-azidopropyl)-14-cyclohexyl-4-formyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

A solution of the foregoing compound in DMA (0.5 M) was added dropwise over 30 minutes to a suspension of Cs₂CO₃ (2.0 eq) in DMA (final concentration 0.050 M) heated at 60 °C. 4 hours after completion of the addition, the mixture was cooled to RT, diluted with EtOAc and washed with H₂O (2x) and brine (2x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by FC eluting with 5 to 20% EtOAc/PE to give the product as a colourless solid (64%). (ES⁺) *m/z* 501 (M+H)⁺; [α]_D²⁰ : +17.9° (*c* = 0.5, CHCl₃).

Step 7: methyl (7*R*)-7-(3-azidopropyl)-14-cyclohexyl-4-(piperidin-1-ylmethyl)-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

A solution of the foregoing compound in DCE (0.02 M) was treated with piperidine (1.5 eq) and acetic acid (1.0 eq). After 1 hour sodium triacetoxymethylborohydride (1.5 eq) was added and the reaction stirred at RT for 12 hours, diluted with EtOAc and washed with aq. sat. NaHCO₃, aq. sat. NH₄Cl and brine. The combined organic extracts were dried with Na₂SO₄, filtered and concentrated *in vacuo* to give the product as a colourless solid (quant.). (ES⁺) *m/z* 570 (M+H)⁺.

Step 8: methyl (7*R*)-7-((3-((tert-butoxycarbonyl)amino)propyl)-14-cyclohexyl-4-(piperidin-1-ylmethyl)-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

A solution of the foregoing compound in EtOAc/MeOH (3/1, 0.025 M) was treated with Boc₂O (1.5 eq) and 10 wt % palladium on carbon (0.1 eq). The reaction mixture was stirred under H₂(g) at RT for 12 hours. Then the catalyst was filtered off and the organic layer was concentrated *in vacuo* to give a residue that was purified by FC eluting with 30 to 70% EtOAc/PE to give the product as a colourless solid (34%). (ES⁺) *m/z* 644 (M+H)⁺.

Step 9: (7R)-7-{3-[(tert-butoxycarbonyl)amino]propyl}-14-cyclohexyl-4-(piperidin-1-ylmethyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid

A solution of the foregoing compound in MeOH (0.05 M) was treated with 2M aq. KOH (6.0 eq, 0.05M) and stirred at 60°C for 9 hours. The solvent was concentrated *in vacuo* then the reaction mixture was diluted with water and EtOAc, cooled to 0°C and treated dropwise with 1N HCl (aq.) to adjust the pH to 6. The phases were separated and the aq. phase extracted with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the product as a colourless solid (quant). (ES⁺) *m/z* 630 (M+H)⁺.

Step 10: tert-butyl {3-[(7R)-14-cyclohexyl-11-{[(2,2-dimethoxyethyl)(methyl)sulfamoyl]carbamoyl}-4-(piperidin-1-ylmethyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocin-7-yl]propyl} carbamate

A solution of the foregoing compound in DCM (0.04 M) was treated with EDC (1.5 eq), DMAP (3.0 eq) and *N*-(2,2-dimethoxyethyl)-*N*-methylsulfuric diamide (Intermediate C, 1.2 eq). The reaction was stirred at 40°C for 4 hours, diluted with EtOAc and washed with aqueous NaHCO₃ (sat), aqueous NH₄Cl (sat) and brine (x2). The combined organic extracts were dried with Na₂SO₄, filtered and concentrated *in vacuo* to give a residue that was purified by FC eluting with 2 to 8% MeOH/DCM + 0.1% TEA to give the product as a colourless solid (45%). (ES⁺) *m/z* 810 (M+H)⁺.

Step 11: (7R)-14-cyclohexyl-18,21-dimethyl-4-(piperidin-1-ylmethyl)-7,8-dihydro-6H-7,11-(propanoiminoethanoiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

A solution of the foregoing compound in THF (0.02 M) was treated with aqueous 3N HCl (10.0 eq) and stirred at 60°C for 3 hours. After completion of the reaction the mixture was cooled to 0°C and aqueous NaOH 2N was added to bring the pH to 6. The resulting mixture was diluted with MeOH (final concentration 8.0 mM) and sodium cyanoborohydride (3.0 eq) was added at RT. After 30 minutes formaldehyde (5.0 eq) was added, followed by sodium cyanoborohydride (2.0 eq). The resulting reaction was stirred for 12 hours then concentrated *in vacuo* to give a residue that was purified by RP-HPLC, eluting with MeCN/H₂O buffered with 0.1% TFA gradient. Fractions containing the product were combined and freeze dried to afford the product as a white powder (42%). ¹H NMR (pyridine-*d*₅), δ: 8.30 (d, *J* = 9.4 Hz, 1H), 8.19-8.06 (m, 2H), 7.91 (dd, *J* = 2.0 Hz, *J* = 7.2 Hz, 1H), 7.47-7.22 (m, 2H), 4.62-4.51 (m, 1H), 4.50-4.39 (m, 1H), 4.34-3.96 (m, 3H), 3.91-3.75 (m, 2H), 3.71-3.59 (m, 1H), 3.34-3.21 (m, 1H), 3.17-3.08 (m, 1H), 3.03 (s, 3H), 2.99-2.82 (m, 2H), 2.72-2.62 (m, 2H), 2.54-2.43 (m, 1H), 2.14 (s, 3H), 2.27-1.87 (m, 8H), 1.85-1.72 (m, 1H), 1.72-1.50 (m, 7H), 1.42-1.19 (m, 5H), 1.15-0.88 (m, 2H); NH-Proton not visible due to use of Pyridine; (ES⁺) *m/z* 662 (M+H)⁺.

Example 2: (7R)-14-cyclohexyl-18,21-dimethyl-4-[3-(pyrrolidin-1-yl)propyl]-7,8-dihydro-6H-7,11-(propanoiminoethanoiminiothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

5 Step 1: methyl (7R)-7-(3-azidopropyl)-14-cyclohexyl-4-[(1E)-3-methoxy-3-oxoprop-1-en-1-yl]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

To a suspension of anhydrous MeCN (0.11 M) containing LiCl (1.2 eq), methyl diethylphosphonoacetate (1.2 eq) and DIPEA (1.2 eq) was added methyl methyl (7R)-7-(3-azidopropyl)-14-cyclohexyl-4-formyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (Example 1, Step 6) and the reaction stirred for 16 hours at RT. After this time an additional LiCl (0.1 eq), methyl diethylphosphonoacetate (0.1 eq) and DIPEA (0.1 eq) were added. Two hours after the final addition, the reaction was poured into EtOAc and washed subsequently with water and brine. The crude was purified by FC (95:5; PE:EtOAc to 8:2), to obtain the title compound as a colourless oil (91 %). (ES⁺) m/z 557 (M+H)⁺.

15 Step 2: methyl (7R)-7-(3-aminopropyl)-14-cyclohexyl-4-(3-methoxy-3-oxopropyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

To a solution of the foregoing compound in isopropyl-acetate/isopropanol (10:1; 0.033 M) was added 1N HCl (0.1 eq) and Palladium on Carbon (10%; 0.15 eq). The resulting suspension was stirred under a hydrogen atmosphere (1 bar) for a total of 21 hr. The reaction was filtered and all volatiles removed *in vacuo* to obtain the title compound (99%). (ES⁺) m/z 533 (M+H)⁺.

25 Step 3: methyl (7R)-14-cyclohexyl-4-(3-hydroxypropyl)-7-[3-(methylamino)propyl]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

The foregoing compound was dissolved in THF (0.08M) and 2,2,2 trifluoroethyl acetate (2.0 eq) was added and the reaction was stirred for 1 hr. All volatiles were then removed *in vacuo*. The resulting crude was dissolved in THF (0.08M) and borane-methylsulfide complex (5.0 eq) was added at rt. After three hours the reaction was carefully quenched by the addition of a solution of HCl in MeOH (1.25 N, 20 eq) and heated to 80 °C for 1 hour. After evaporation of all volatiles the title compound was obtained and used as such (99%). (ES⁺) m/z 519 (M+H)⁺.

30 Step 4: methyl (7R)-7-{3-[(tert-butoxycarbonyl)(methyl)amino]propyl}-14-cyclohexyl-4-(3-hydroxypropyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

The foregoing compound was diluted with DCM (0.05M) and Et₃N (2.9 eq) and DMAP (0.1 eq) followed by Boc₂O were added. The reaction was stirred for 14 h, then diluted with DCM and washed sequentially with 0.5N HCl, sat. aq. NaHCO₃ solution and brine. After drying over sodium sulfate and removal of the solvent *in vacuo*, the residues was purified by FC (9:1; PE:EtOAc to 6:4), to obtain the title compound as a white solid (57 %). (ES⁺) m/z 641 (M+Na)⁺.

Step 5: methyl (7R)-7-{3-[(tert-butoxycarbonyl)(methyl)amino]propyl}-14-cyclohexyl-4-[3-(pyrrolidin-1-yl)propyl]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

5 The foregoing compound was dissolved in DCM/DMSO (10:1; 0.06M) and triethylamine (5.6 eq) followed by sulphur trioxide complex (10.0 eq) was added. After two hours the reaction was diluted with EtOAc and extracted with 1N HCl, NaHCO₃ and brine. After evaporation of all volatiles the resulting oil was diluted with DCE (0.1 M) and pyrrolidine (3.0 eq) and acetic acid (3.0 eq) were added. After 1 hour additional DCE was added to bring the concentration to
10 0.05M, before sodium triacetoxyborohydride (3.0 eq) was added and the reaction stirred for 15 hours. The reaction was diluted with EtOAc and washed with 0.5N HCl, NaHCO₃ and brine to obtain the title compound as white solid (99%) after evaporation of all volatiles. (ES⁺) *m/z* 673 (M+H)⁺.

15 Step 6: tert-butyl (3-{(7R)-14-cyclohexyl-11-{[(2,2-dimethoxyethyl)(methyl)sulfamoyl]carbamoyl}-4-[3-(pyrrolidin-1-yl)propyl]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocin-7-yl}propyl)methylcarbamate

The title compound was prepared in analogy to Example 1, Step 9 and Step 10 from methyl (7R)-7-{3-[(tert-butoxycarbonyl)(methyl)amino]propyl}-14-cyclohexyl-4-[3-(pyrrolidin-1-yl)propyl]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (prepared as
20 described in Example 2, Step 5). The compound was used after purification by FC eluting with 2 to 8% MeOH/DCM containing 0.1% TEA to give the product as a colourless solid (21%). (ES⁺) *m/z* 839 (M+H)⁺.

25 Step 7: (7S)-14-cyclohexyl-18,21-dimethyl-4-[3-(pyrrolidin-1-yl)propyl]-7,8-dihydro-6H-7,11-(propanoiminoethanoiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

The title compound was prepared in analogy to Example 1, Step 11 starting from the foregoing compound. After purification by RP-HPLC, eluting with MeCN/H₂O buffered with 0.1% TFA
30 gradient, the fractions containing the product were combined and freeze-dried to afford the product as a white powder (33%). ¹H NMR (DMSO-*d*₆), δ : 9.65 (bs, 1H), 8.03 (s, 1H), 7.88 (d, *J* = 8.9 Hz, 1H), 7.50-7.46 (m, 2H), 7.28 (t, *J* = 7.7 Hz, 1H), 7.23 (dd, *J* = 1.9 Hz, 7.7 Hz, 1H), 4.46-4.38 (m, 2H), 3.97-3.76 (m, 2H), 3.70-3.47 (m, 6H), 3.42-3.35 (m, 2H), 3.24-3.12 (m, 4H), 3.09 (s, 3H), 3.06-2.99 (m, 3H), 2.86 (s, 3H), 2.84-2.79 (m, 3H), 2.75-2.58 (m, 2H), 2.09-1.81
35 (m, 8H), 1.73-1.66 (m, 4H), 1.48-1.29 (m, 2H), 1.15-1.05 (m, 2H); (ES⁺) *m/z* 676 (M+H)⁺.

Example 3: (7R, 7S)-14-cyclohexyl-7-hydroxy-4,18,22-trimethyl-7,8-dihydro-6H-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

Step 1: methyl 3-cyclohexyl-2-[2-(methoxymethoxy)-3-methylphenyl]-1H-indole-6-carboxylate

Methyl 2-bromo-3-cyclohexyl-1H-indole-6-carboxylate (prepared as described in International patent application WO 2004/087714), [2-(methoxymethoxy)-3-methylphenyl]boronic acid (Intermediate D; 1 eq) and bis(triphenylphosphine)palladium(II) chloride (0.1 eq) were dissolved in dioxane (0.1M). The solution was degassed and flushed with argon. A 2M aqueous solution of Na₂CO₃ (6 eq) was added and the mixture was heated to 100 °C. After 2 h the mixture was cooled and diluted with EtOAc. The solution was washed with 1N aqueous HCl then brine. After drying over Na₂SO₄ and filtering, all volatiles were evaporated *in vacuo*. The residual material was subjected to FC (15 % EtOAc/PE). After evaporation of the product fractions the product was obtained as a pale yellow oil (95 %). (ES⁺) *m/z* 408 (M+H)⁺.

Step 2: methyl 3-cyclohexyl-2-(2-hydroxy-3-methylphenyl)-1H-indole-6-carboxylate

A solution of the foregoing compound in MeOH (0.08 M) was treated with aqueous 3N HCl (3 eq) and the mixture was warmed to 80 °C for 1.5 h. The mixture was cooled and all volatiles were evaporated *in vacuo*. The residual material was dissolved in EtOAc and the solution washed with sat. aq. NaHCO₃ and brine. After drying over Na₂SO₄ and filtering, all volatiles were evaporated *in vacuo* leaving a beige amorphous solid (quant). (ES⁺) *m/z* 364 (M+H)⁺.

Step 3: (S)-methyl 3-cyclohexyl-2-[3-methyl-2-(oxiran-2-ylmethoxy)phenyl]-1H-indole-6-carboxylate

A solution of the foregoing compound in DMF (0.18 M) was treated with CsF (3 eq). After 10 mins (S)-(+)-glycidyl tosylate (1.2 eq) was added and the mixture stirred at RT overnight. The mixture was diluted with EtOAc and washed with 1N aqueous HCl, sat. aq. NaHCO₃ and brine. After drying over Na₂SO₄ and filtering, all volatiles were evaporated *in vacuo*. A brown residue was obtained (99%). (ES⁺) *m/z* 420 (M+H)⁺.

Step 4: methyl (7S)-14-cyclohexyl-7-hydroxy-4-methyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

A solution of the foregoing compound in DMA (0.09 M) was added slowly to a suspension of Cs₂CO₃ (1 eq) in DMA (0.28 M) at 70 °C. After 4 h the mixture was cooled and diluted with EtOAc. The solution was extracted with 1N aq. HCl, sat. aq. NaHCO₃ and brine. After drying over Na₂SO₄ and filtering, all volatiles were evaporated *in vacuo*. The product was purified by FC (20-40 % EtOAc/PE). The product was obtained as a yellow amorphous solid (90 %). (ES⁺) *m/z* 420 (M+H)⁺.

Step 5: methyl 14-cyclohexyl-4-methyl-7-oxo-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

5 A solution of the foregoing compound in DCM (0.1 M) was treated with DMP (1.3 eq). After stirring for 2 h at RT, sat. aq. NaHCO₃ was added and the reaction extracted into EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, filtered and evaporated to dryness. The residue was used directly in the next step. (ES⁺) *m/z* 418 (M+H)⁺.

10 Step 6: methyl 14-cyclohexyl-7-hydroxy-4-methyl-7-(prop-2-en-1-yl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

A solution of the foregoing compound in DCM (0.1 M) was treated with titanium tetrachloride (1.5 eq) and stirred at RT for 5 mins before cooling to 0 °C. Allyl trimethylsilane (1.1 eq) was added dropwise and the mixture stirred for 2 h before diluting with EtOAc. The mixture was washed with H₂O then brine, dried over Na₂SO₄, filtered and evaporated to dryness. The residue
15 was purified by FC eluting with 10 to 30% EtOAc/PE to give the product as a yellow solid (39 % over 2 steps). (ES⁺) *m/z* 460 (M+H)⁺.

Step 7: methyl 14-cyclohexyl-7-hydroxy-4-methyl-7-(2-oxoethyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

20 A solution of the foregoing compound in THF/H₂O (2:1, 0.08 M) was treated with osmium tetroxide (0.02 eq) followed by sodium periodate (3.0 eq). The reaction was stirred at RT for 2 h, diluted with EtOAc and washed with H₂O (x 2) and brine. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated *in vacuo* to give a residue that was used directly in the next step. (ES⁺) *m/z* 462 (M+H)⁺.

25 Step 8: methyl 7-{2-[[3-[(tert-butoxycarbonyl)(methyl)amino]propyl](methyl)amino]ethyl}-14-cyclohexyl-7-hydroxy-4-methyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

A solution of the foregoing compound in MeOH (0.1 M) was treated with *tert*-butyl methyl[3-(methylamino)propyl]carbamate (Intermediate E) (1.5 eq) and acetic acid (1.0 eq). After 10 min
30 sodium cyanoborohydride (2 eq) was added and the reaction stirred at RT for 12 hours, diluted with EtOAc and washed with sat. aq. NaHCO₃ and brine. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated *in vacuo* to give a brown oil which was taken on without further purification. (ES⁺) *m/z* 648 (M+H)⁺.

Step 9: methyl 14-cyclohexyl-7-hydroxy-4-methyl-7-(2-{methyl[3-(methylamino)propyl]amino}ethyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

A solution of the foregoing compound in DCM (0.1 M) was treated with TFA (65 eq) at RT and stirred for 2 h. All volatiles were removed *in vacuo* to give a residue that was purified by RP-HPLC (Waters Xterra column; MeCN/H₂O/0.1 % TFA gradient), eluting with MeCN/H₂O buffered with 0.1% TFA gradient. Fractions containing the product were combined and freeze dried to afford the product as a white powder (15% over 3 steps). (ES⁺) *m/z* 548 (M+H)⁺.

Step 10: methyl 7-{2-[(3-{[(tert-butoxycarbonyl)sulfamoyl](methyl)amino}propyl)(methyl)amino]ethyl}-14-cyclohexyl-7-hydroxy-4-methyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

A solution of the foregoing compound in THF (0.05 M) was treated with (tert-butoxycarbonyl){[4-(dimethyliminio)pyridin-1(4H)-yl]sulfonyl}azanide (prepared as described in *Org. Lett.* **2001**, 3, 2241-2243) (1.2 eq) and triethylamine (2.5 eq) and stirred at RT for 4 h. The reaction was diluted with EtOAc and washed with 1N aq. HCl, brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was taken on to the next step without further purification. (ES⁺) *m/z* 727 (M+H)⁺.

Step 11: 7-{2-[(3-{[(tert-butoxycarbonyl)sulfamoyl](methyl)amino}propyl)(methyl)amino]ethyl}-14-cyclohexyl-7-hydroxy-4-methyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid

A solution of the foregoing compound in MeOH/THF (1:1, 0.02 M) was treated with 2N aq. NaOH (20 eq.) and the reaction stirred at 70 °C for 2 h. The reaction was cooled to RT before diluting with EtOAc and acidifying the aqueous layer with 3 N aq. HCl. The aqueous layer was extracted again with EtOAc and the combined organic layers washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The material was taken on without further purification. (ES⁺) *m/z* 713 (M+H)⁺.

Step 12: 14-cyclohexyl-7-hydroxy-4-methyl-7-[2-(methyl{3-[methyl(sulfamoyl)amino]propyl}amino)ethyl]-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid

A solution of the foregoing compound in DCM (0.04 M) was treated with TFA (40 eq) and the resulting mixture stirred at RT for 2 h. All volatiles were removed *in vacuo* and the residue dissolved in EtOAc. The mixture was washed with 3 N aq. HCl, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The material was taken on without further purification. (ES⁺) *m/z* 613 (M+H)⁺.

Step 13: (7R, 7S)-14-cyclohexyl-7-hydroxy-4,18,22-trimethyl-7,8-dihydro-6H-7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

A solution of the foregoing compound in DCM (0.02 M) was treated with EDC (2 eq), DMAP (3.5 eq) and Et₃N (2 eq) and the resulting mixture was stirred at RT for 72 h. The mixture was diluted with EtOAc, washed with 3 N aq. HCl and concentrated *in vacuo*. The residue was purified by RP-HPLC (Waters Xterra column; MeCN/H₂O/0.1 % TFA gradient). Fractions containing the pure compound were combined and lyophilized to afford the product as a white powder (13 %). This material was identified an approximately 1:1* mixture of diastereomers (due to chiral nitrogen on protonation) by ¹H NMR. ¹H NMR (400 MHz, DMSO-*d*₆ + TFA, 300 K) δ 1.11-1.53 (m, 5H), 1.69-1.97 (m, 9H), 2.32 and 2.33* (s, 3H), 2.63-2.68 (m, 1H), 2.76 and 2.88* (d, *J* 4.4, 3H), 2.96 and 3.06* (s, 3H), 3.08-3.26 (m, 1H), 3.58-3.64 (m, 3H), 3.66-3.82 (m, 3H), 3.88-3.92 and 4.33-4.36* (m, 1H), 4.14-4.18 (m, 1H), 4.45-4.53 (m, 1H), 7.07-7.09 and 7.18-7.20* (m, 1H), 7.15-7.17 and 7.23-7.27* (m, 1H), 7.38-7.43* and 7.56-7.58 (m, 2H), 7.85-7.87 and 7.91-7.93* (m, 1H), 8.00 and 8.55* (s, 1H), 8.07 and 8.94* (br s, 1H); (ES⁺) *m/z* 595 (M+H)⁺.

Example 4: (7R or 7S)-14-cyclohexyl-7-hydroxy-18,21-dimethyl-7,8-dihydro-6H-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-e][1,5]benzoxazocin-15-one 17,17-dioxide

Step 1: methyl 14-cyclohexyl-7-oxo-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

To a solution of methyl (7S)-14-cyclohexyl-7-hydroxy-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (prepared as described in International patent application WO2006/046030) in dry DCM (0.075M) DMP (1.5 eq) was added in one portion at 0 °C and the suspension was stirred at room temperature for 2 h. The suspension was diluted with EtOAc and washed with sat. aq. NaHCO₃/Na₂S₂O₃ solution (1:1 v/v), brine, dried over Na₂SO₄, filtered and evaporated *in vacuo* to leave a residue which after trituration with Et₂O gave the title compound as a creamy solid (76%). (ES⁺) *m/z* 404 (M+H)⁺.

Step 2: methyl 7-allyl-14-cyclohexyl-7-hydroxy-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

Methyl 14-cyclohexyl-7-oxo-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate was dissolved in dry DCM (0.065M) and treated dropwise with TiCl₄ (1.5 eq). After stirring the dark solution at room temperature for 5 minutes neat allyltrimethylsilane (1.1 eq) was added at 0 °C and stirring was continued at this temperature for 1 h. The reaction was quenched with cold water and the aqueous phase extracted with EtOAc. The organic phase was then washed with

water, brine, dried over Na₂SO₄, filtered and evaporated *in vacuo* to give the title compound as a pale yellow powder (98%) which was used as such in the next step. (ES⁺) *m/z* 446 (M+H)⁺.

Step 3: methyl 14-cyclohexyl-7-hydroxy-7-(3-hydroxypropyl)-7,8-dihydro-6H-indolo[1,2-
e][1,5]benzoxazocine-11-carboxylate

To a solution of methyl 7-allyl-14-cyclohexyl-7-hydroxy-7,8-dihydro-6H-indolo[1,2-
e][1,5]benzoxazocine-11-carboxylate in dry THF (0.1M), BH₃·DMS complex (2.0 eq) was added
at 0 °C and the solution was stirred at room temperature for 1 h. H₂O₂ (35% v/v in water) and 2N
NaOH (aq) were added at 0 °C and the solution was stirred at room temperature overnight. Sat.
aq. NaHCO₃ was added and the solution was diluted with EtOAc and washed with water, brine,
dried over Na₂SO₄, filtered and evaporated *in vacuo* to give a residue which was used as such
(97%). (ES⁺) *m/z* 464 (M+H)⁺.

Step 4: methyl 14-cyclohexyl-7-hydroxy-7-(3-oxopropyl)-7,8-dihydro-6H-indolo[1,2-
e][1,5]benzoxazocine-11-carboxylate

To a solution of methyl 14-cyclohexyl-7-hydroxy-7-(3-hydroxypropyl)-7,8-dihydro-6H-
indolo[1,2-e][1,5]benzoxazocine-11-carboxylate in dry DCM (0.075M), DMP (1.5 eq) was
added in one portion at 0 °C and the solution was stirred at room temperature for 2 h. The
solution was diluted with EtOAc and washed with sat. aq. NaHCO₃/Na₂S₂O₃ solution (1:1 v/v),
brine, dried over Na₂SO₄, filtered and evaporated *in vacuo* to leave a residue which was used as
such (100%). (ES⁺) *m/z* 462 (M+H)⁺.

Step 5 : (-) and (+) methyl 7-{3-[{2-[(tert-
butoxycarbonyl)(methyl)amino]ethyl}{(methyl)amino]propyl}-14-cyclohexyl-7-hydroxy-7,8-
dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

To a solution of methyl 14-cyclohexyl-7-hydroxy-7-(3-oxopropyl)-7,8-dihydro-6H-indolo[1,2-
e][1,5]benzoxazocine-11-carboxylate in MeOH (0.1M) *tert*-butyl methyl[2-
(methylamino)ethyl]carbamate (prepared as described in European patent application
EPO296811) (1.15 eq) and acetic acid (3.0 eq) followed by sodium cyanoborohydride (2.0 eq)
were added and the solution was stirred at room temperature overnight. Water was added to the
solution and MeOH removed *in vacuo* to get a residue which was diluted with EtOAc and
washed with sat. aq. NaHCO₃, brine, dried over Na₂SO₄ filtered and evaporated *in vacuo* to give
a residue that was purified by automated RP-HPLC, eluting with MeCN/H₂O buffered with 0.1%
TFA gradient. Fractions containing the product were combined and freeze dried to afford the
product as a white powder. The isomers at the quaternary centre were separated by chiral SFC,
eluting with MeOH/Et₂NH as modifier, to afford (-)-methyl 7-{3-[{2-[(*tert*-
butoxycarbonyl)(methyl)amino]ethyl}{(methyl)amino]propyl}-14-cyclohexyl-7-hydroxy-7,8-
dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (1st eluting enantiomer, ee>99% by

analytical SFC, $[\alpha]_D^{20}$: -23.2° (14%) (ES^+) m/z 634 ($M+H$)⁺ and (+)-methyl 7-{3-[2-[(*tert*-butoxycarbonyl)(methyl)amino]ethyl}(methyl)amino]propyl}-14-cyclohexyl-7-hydroxy-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate (2nd eluting enantiomer, ee>99% by analytical SFC, $[\alpha]_D^{20}$: +20.6° (12%) (ES^+) m/z 634 ($M+H$)⁺.

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Step 6 : methyl (7*R* or 7*S*)-14-cyclohexyl-7-hydroxy-7-(3-{methyl[2-(methylamino)ethyl]amino}propyl)-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

A solution of (+)-methyl 7-{3-[2-[(*tert*-butoxycarbonyl)(methyl)amino]ethyl}(methyl)amino]propyl}-14-cyclohexyl-7-hydroxy-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate in DCM/TFA (4/1) (0.02M) was stirred at room temperature for 2 h. Solvent was removed *in vacuo* and the residue was dissolved in EtOAc and washed with sat. aq. NaHCO₃, brine, dried over Na₂SO₄ filtered and evaporated *in vacuo* to give the title compound as a pale yellow powder (78%). (ES^+) m/z 534 ($M+H$)⁺.

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Step 7: methyl (7*R* or 7*S*)-7-{3-[2-{[(*tert*-butoxycarbonyl)amino]sulfonyl}(methyl)amino]ethyl}(methyl)amino]propyl}-14-cyclohexyl-7-hydroxy-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

To a solution of the foregoing compound in dry THF (0.07M), (*tert*-butoxycarbonyl){[4-(dimethyliminio)pyridin-1(4*H*)-yl]sulfonyl}azanide (prepared as described in *Org. Lett.* **2001**, 3, 2241-2243) (1.5 eq) was added and the suspension was stirred at room temperature overnight and at 45 °C for 3 h. After cooling the solution was diluted with EtOAc and washed with 1N HCl (aq), sat. aq. NaHCO₃, brine, dried over Na₂SO₄ filtered and evaporated *in vacuo* to give the title compound as a pale yellow powder which was used as such (100%). (ES^+) m/z 713 ($M+H$)⁺.

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Step 8: (7*R* or 7*S*)-7-{3-[2-{[(*tert*-butoxycarbonyl)amino]sulfonyl}(methyl)amino]ethyl}(methyl)amino]propyl}-14-cyclohexyl-7-hydroxy-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylic acid

A solution of the foregoing compound in dioxane (0.05M) was treated with 1N KOH (aq) (5 eq) and heated at 70 °C for 1.5 h. After cooling 6N HCl (aq) was added to neutralize the mixture and the solvent was removed *in vacuo*. The residue was dissolved in EtOAc and washed with water, brine, dried over Na₂SO₄ filtered and evaporated *in vacuo* to leave the title compound as a yellow powder which was used as such (100%). (ES^+) m/z 699 ($M+H$)⁺.

Step 9: (7*R* or 7*S*)-7-{3-[2-{(aminosulfonyl)(methyl)amino]ethyl}(methyl)amino]propyl}-14-cyclohexyl-7-hydroxy-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylic acid

A solution of the foregoing compound in DCM/TFA (4/1) (0.05 M) was stirred at room temperature for 3 h. Volatiles were removed *in vacuo* and the residue dissolved in EtOAc and

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washed with sat. aq. NaHCO₃, brine, dried over Na₂SO₄ filtered and evaporated *in vacuo* to give the title compound as a yellow glass (60%). (ES⁺) *m/z* 599 (M+H)⁺.

Step 10: (7R or 7S)-14-cyclohexyl-7-hydroxy-18,21-dimethyl-7,8-dihydro-6H-7,11-

5 (propanoiminoethanoiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide

A solution of the foregoing compound in DCM (0.02 M) was treated with EDC (2.0 eq) and DMAP (3.0 eq). The reaction was stirred at room temperature overnight, concentrated *in vacuo* to give a residue that was purified by automated RP-HPLC, eluting with MeCN/H₂O buffered
10 with 0.1% TFA gradient. Fractions containing the product were combined and freeze dried to afford the product as a white powder (20%). ¹H NMR (300 MHz, pyridine-*d*₅, 300 K) δ 1.08-2.41 (m, 10H), 2.43 (s, 3H), 2.42-3.21 (m, 9H), 3.27 (s, 3H), 3.62-3.71 (m, 1H), 3.80-3.98 (m, 1H), 4.04-4.19 (m, 1H), 4.33-4.37 (m, 1H), 4.45-4.65 (m, 1H), 5.00-5.05 (m, 1H), 7.35-7.65 (m, 4H), 7.98-8.05 (m, 1H), 8.22-8.37 (m, 1H), 8.72 (s, 1H); NH-Proton and OH-Proton not visible
15 due to use of Pyridine; (ES⁺) *m/z* 581 (M+H)⁺.

Example 5: (7S or 7R)-14-cyclohexyl-7-hydroxy-18,21-dimethyl-7,8-dihydro-6H-7,11-(propanoiminoethanoiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide

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Step 1: (7S or 7R)-14-cyclohexyl-7-hydroxy-18,21-dimethyl-7,8-dihydro-6H-7,11-

(propanoiminoethanoiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide

(-)-Methyl 7-{3-[{2-[(*tert*-butoxycarbonyl)(methyl)amino]ethyl}(methyl)amino]propyl}-14-cyclohexyl-7-hydroxy-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate (1st
25 eluting enantiomer from example 4 step 5, ee>99% by analytical SFC, [α]_D²⁰: -23.2°), was taken through the analogous sequence to example 4 steps 6-10 to afford the title compound as a white powder (13%). ¹H NMR (300 MHz, pyridine-*d*₅, 300 K) δ 1.08-2.41 (m, 10H), 2.43 (s, 3H), 2.42-3.21 (m, 9H), 3.27 (s, 3H), 3.62-3.71 (m, 1H), 3.80-3.98 (m, 1H), 4.04-4.19 (m, 1H), 4.33-
30 4.37 (m, 1H), 4.45-4.65 (m, 1H), 5.00-5.05 (m, 1H), 7.35-7.65 (m, 4H), 7.98-8.05 (m, 1H), 8.22-8.37 (m, 1H), 8.72 (s, 1H); NH-Proton and OH-Proton not visible due to use of Pyridine; (ES⁺) *m/z* 581 (M+H)⁺.

Example 6: 14-cyclohexyl-7-fluoro-18,21-dimethyl-7,8-dihydro-6H-7,11-

35 **(propanoiminoethanoiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide**

Step 1: methyl 7-allyl-14-cyclohexyl-7-fluoro-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

To a solution of methyl 7-allyl-14-cyclohexyl-7-hydroxy-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate (prepared as described in example 4 step 2) in DCM (0.1M), DAST (2.0 eq) was added dropwise at -78 °C and the mixture was stirred at this temperature for 1h. The reaction was put in an ice bath and neutralized with sat. aq. NaHCO₃ at 0 °C and then diluted with EtOAc. The organic phase was washed with brine, dried over Na₂SO₄ filtered and evaporated *in vacuo* to leave a residue that was purified by FC eluting with 20% EtOAc/PE to give the product as a pale yellow powder (59%). (ES⁺) *m/z* 448 (M+H)⁺.

Step 2: methyl 14-cyclohexyl-7-fluoro-7-(3-hydroxypropyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

To a solution of methyl 7-allyl-14-cyclohexyl-7-fluoro-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate in dry THF (0.1M), 9-BBN (4 eq) was added at 0 °C and the solution was stirred at room temperature for 1 h. H₂O₂ (35% v/v in water) and 2N NaOH (aq) were added at 0 °C and the solution was stirred at room temperature overnight. Sat. aq. NaHCO₃ was added and the solution was diluted with EtOAc and washed with water, brine, dried over Na₂SO₄ filtered and evaporated *in vacuo* to give a residue which was used as such (96%). (ES⁺) *m/z* 466 (M+H)⁺.

Step 3: methyl 14-cyclohexyl-7-fluoro-7-(3-oxopropyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

To a solution of methyl 14-cyclohexyl-7-fluoro-7-(3-hydroxypropyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate in dry DCM (0.07M), DMP (1.5 eq) was added in one portion at 0 °C and the solution was stirred at room temperature for 2 h. The solution was diluted with EtOAc and washed with sat. aq. NaHCO₃/Na₂S₂O₃ solution (1:1 v/v), brine, dried over Na₂SO₄ filtered and evaporated *in vacuo* to leave a residue which was used as such (100%). (ES⁺) *m/z* 464 (M+H)⁺.

Step 4 : methyl 7-{3-[(2-[(tert-butoxycarbonyl)(methyl)amino]ethyl){(methyl)amino}propyl]}-14-cyclohexyl-7-fluoro-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate

To a solution of methyl 14-cyclohexyl-7-fluoro-7-(3-oxopropyl)-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylate in MeOH (0.1M) *tert*-butyl methyl[2-(methylamino)ethyl]carbamate (prepared as described in European patent application EPO296811) (1.15 eq) and acetic acid (3 eq) followed by sodium cyanoborohydride (2 eq) were added and the solution was stirred at room temperature overnight. Water was added to the solution and MeOH removed *in vacuo* to get a residue which was diluted with EtOAc and

washed with sat. aq. NaHCO₃, brine, dried over Na₂SO₄ filtered and evaporated *in vacuo* to give a residue which was used as such (100%). (ES⁺) *m/z* 636 (M+H)⁺.

Step 5 : methyl 14-cyclohexyl-7-fluoro-7-(3-{methyl[2-(methylamino)ethyl]amino}propyl)-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

A solution of methyl 7-{3-[2-[(*tert*-butoxycarbonyl)(methylamino)ethyl](methylamino)propyl]-14-cyclohexyl-7-fluoro-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate in DCM/TFA (4/1) (0.05M) was stirred at room temperature for 2 h. Solvent was removed *in vacuo* and the residue was dissolved in EtOAc and washed with sat. aq. NaHCO₃, brine, dried over Na₂SO₄ filtered and evaporated *in vacuo* to give the title compound as a pale yellow powder (100%). (ES⁺) *m/z* 536 (M+H)⁺.

Step 6: methyl 7-{3-[2-[(*tert*-butoxycarbonyl)amino)sulfonyl](methylamino)ethyl}(methylamino)propyl}-14-cyclohexyl-7-fluoro-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

To a solution of methyl 14-cyclohexyl-7-fluoro-7-(3-{methyl[2-(methylamino)ethyl]amino}propyl)-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate in dry THF (0.08M), (*tert*-butoxycarbonyl){[4-(dimethyliminio)pyridin-1(4H)-yl)sulfonyl}azanide (prepared as described in *Org. Lett.* **2001**, 3, 2241-2243) (1.5 eq) was added and the suspension was stirred at room temperature overnight and at 45 °C for 3 h. After cooling the solution was diluted with EtOAc and washed with 1N HCl (aq), sat. aq. NaHCO₃, brine, dried over Na₂SO₄ filtered and evaporated *in vacuo* to give the title compound as a pale yellow powder which was used as such (100%). (ES⁺) *m/z* 715 (M+H)⁺.

Step 7: 7-{3-[2-[(*tert*-butoxycarbonyl)amino)sulfonyl](methylamino)ethyl}(methylamino)propyl}-14-cyclohexyl-7-fluoro-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylic acid

A solution of methyl 7-{3-[2-[(*tert*-butoxycarbonyl)amino)sulfonyl](methylamino)ethyl}(methylamino)propyl}-14-cyclohexyl-7-fluoro-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate in dioxane (0.1M) was treated with 1N KOH (aq) (5 eq) and heated at 70 °C for 1.5 h. After cooling HCl (6N) was added to neutralize the mixture and the solvent was removed *in vacuo*. The residue was dissolved in EtOAc and washed with water, brine, dried over Na₂SO₄ filtered and evaporated *in vacuo* to leave the title compound as a yellow powder which was used as such (88%). (ES⁺) *m/z* 701 (M+H)⁺.

Step 8: 7-{3-[2-[(aminosulfonyl)(methylamino)ethyl}(methylamino)propyl]-14-cyclohexyl-7-fluoro-7,8-dihydro-6H-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylic acid

A solution of 7-{3-[{2-[(*tert*-butoxycarbonyl)amino)sulfonyl}(methyl)amino]ethyl}(methyl)amino]propyl}-14-cyclohexyl-7-fluoro-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylic acid in DCM/TFA (4/1) (0.05 M) was stirred at room temperature for 3 h. Solvent was removed *in vacuo* and the residue dissolved in EtOAc and washed with sat. aq. NaHCO₃, brine, dried over Na₂SO₄ filtered and evaporated *in vacuo* to give the title compound as a yellow glass (75%). (ES⁺) *m/z* 601 (M+H)⁺.

Step 9: 14-cyclohexyl-7-fluoro-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocine-15-one 17,17-dioxide

A solution of 7-{3-[{2-[(aminosulfonyl)(methyl)amino]ethyl}(methyl)amino]propyl}-14-cyclohexyl-7-fluoro-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylic acid in DCM (0.02 M) was treated with EDC (2.0 eq) and DMAP (3.0 eq). The reaction was stirred at room temperature overnight, concentrated *in vacuo* to give a residue that was purified by automated RP-HPLC, eluting with MeCN/H₂O buffered with 0.1% TFA gradient. Fractions containing the product were combined and freeze dried to afford the product as a white powder (7%). ¹H NMR (300 MHz, DMSO-*d*₆, 300 K) δ 1.02-2.21 (m, 10H), 2.60-2.94 (m, 8H), 3.06-3.20 (m, 6H), 3.70-4.14 (m, 5H), 4.36-4.41 (m, 1H), 4.65-4.82 (m, 1H), 7.20-7.65 (m, 5H), 7.80-8.01 (m, 2H), 9.92 (s, 1H), 11.70 (s, 1H); (ES⁺) *m/z* 583 (M+H)⁺.

Example 7: (2*S*,4*R*) and (2*R*,4*S*)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid

Step 1: methyl 14-cyclohexyl-7-(2,3-dibromopropyl)-7-hydroxy-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate

Bromine (1.1 eq) was added dropwise to a stirred solution of methyl 7-allyl-14-cyclohexyl-7-hydroxy-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocine-11-carboxylate (prepared as described in example 4, step 2) (0.1 M) in DCM at – 30 °C under N₂, until the bromine colour persisted in solution. The reaction was stirred at – 30 °C for 2 h before being quenched at that temperature by the addition of a 1:1 v/v mixture of Na₂S₂O₃ (aq) and NaHCO₃ (aq). The phases were separated and the organics washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford the product as a pale yellow foam that was taken on without further purification. (ES⁺) *m/z* 604, 606, 608 (M+H)⁺; bromine isotopes.

Step 2: methyl 4-bromo-14'-cyclohexyl-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylate

K₂CO₃ (s) (2.5 eq) was added to a stirred solution of the foregoing compound (0.025 M) in MeOH. The reaction was stirred vigorously for 1 h before partitioning between EtOAc and 1*N*

HCl (aq). The organics were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford the product that was taken on without further purification. (ES⁺) m/z 524, 526 (M+H)⁺; bromine isotopes.

5 Step 3: methyl 4-azido-14'-cyclohexyl-4,5-dihydro-3H-spiro[furan-2,7'-indolo[1,2-e][1,5]benzoxazocine]-11'-carboxylate

Sodium azide (2.5 eq) was added to a stirred solution of the foregoing compound (0.04 M) in DMSO at RT under N₂ and the mixture left to stir overnight. A further 1 equivalent of sodium azide was introduced and the reaction left to stir for 5 days before partitioning between EtOAc and water. The organics were washed well with brine (2x), dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford the product that was taken on without further purification. (ES⁺) m/z 487 (M+H)⁺.

15 Step 4: methyl 4-amino-14'-cyclohexyl-4,5-dihydro-3H-spiro[furan-2,7'-indolo[1,2-e][1,5]benzoxazocine]-11'-carboxylate

Pd/C (10 wt %) was added as a slurry in EtOAc under N₂ to a solution of the forementioned compound (0.025 M) in EtOAc/MeOH (3/1) with 1.25 M methanolic HCl added (2.7 eq). The atmosphere in the reaction vessel was evacuated and re-charged with H₂. The reaction was stirred vigorously under H₂ (1 atm) overnight before purging the reaction vessel with N₂ and filtering the reaction mixture through a solkafloc pad under N₂ to remove catalyst. The filtered liquor was diluted with EtOAc and washed with sat. aq. NaHCO₃, ensuring that the aqueous layer is basic. The organics were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford the product that was taken on without further purification. (ES⁺) m/z 461 (M+H)⁺.

25 Step 5: methyl 14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3H-spiro[furan-2,7'-indolo[1,2-e][1,5]benzoxazocine]-11'-carboxylate

Aqueous formaldehyde solution (37 wt %; 6 eq) was added to a solution in methanol (0.07 M) of the preceding compound. The pH of the reaction medium was adjusted to circa pH 5 – 6 by the dropwise addition of acetic acid. Sodium cyanoborohydride (6 eq) was introduced and the reaction mixture left to stir at RT overnight. The reaction mixture was partitioned between EtOAc and sat. aq. NaHCO₃. The organics were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford the product as a clear glass that was taken on without further purification. (ES⁺) m/z 489 (M+H)⁺.

35 Step 6: 14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3H-spiro[furan-2,7'-indolo[1,2-e][1,5]benzoxazocine]-11'-carboxylic acid

2M NaOH (aq) (20 eq) was added to a solution of the foregoing compound (0.01 M) in a 2/1 mixture of THF/methanol. The reaction was stirred with heating at 60 °C for 2 hours before being allowed to cool to RT and partitioned between EtOAc and 1N HCl (aq), ensuring that the aqueous phase was acidic. The organics were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by automated RP-HPLC (Waters Sunfire column; C18; 10 µm; 19 x 250 mm; eluting with a MeCN/H₂O/0.1 % TFA gradient), permitting separation of the relative *cis*- and *trans*- stereochemistry isomers (with respect to the spiro junction and the dimethylamino moiety) as their racemic mixtures. Fractions containing the pure product isomers were lyophilized to afford the products as white powders (32 % combined yield; overall for steps 1-6). Relative stereochemistry supported by nOe studies.

First eluting (hplc-A): racemic mixture; (2*S*,4*R*) and (2*R*,4*S*)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid)

¹H NMR (600 MHz, DMSO-*d*₆, 294 K) δ 1.12-1.20 (m, 1H), 1.26-1.41 (m, 2H), 1.53-1.58 (m, 1H), 1.67-1.75 (m, 2H), 1.82-1.87 (m, 1H), 1.92-2.03 (m, 3H), 2.04-2.12 (m, 1H), 2.35-2.42 (m, 1H), 2.64-2.70 (m, 1H), 2.75-2.86 (m, 6H), 3.77 (d, *J* = 16.0 Hz, 1H), 3.89-3.94 (m, 2H), 4.08 (d, *J* = 12.6 Hz, 1H), 4.21-4.34 (m, 2H), 4.68 (d, *J* = 16.0 Hz, 1H), 7.17-7.26 (m, 3H), 7.47-7.51 (m, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 8.12 (s, 1H), 9.91 (b s, 1H), 12.60 (b s, 1H); diagnostic nOe's: C10'H to Me₂NC4H, C10'H to Me₂NC4HC5HaHbO-, Me₂NC4H to C5HaHb stronger than to C5HaHb; (ES⁺) *m/z* 475 (M+H)⁺.

Example 7a: (2*S*,4*R*) or (2*R*,4*S*)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid

And

Example 7b: (2*R*,4*S*) or (2*S*,4*R*)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid

The first eluting racemate (**hplc-A** from example 7 step 6) was further separated into its respective enantiomers by chiral SFC (flow 10ml/min; column chiralpack AD-H; isocratic 30 % MeOH/0.2% diethylamine) to afford with 39 % recovery the first eluting enantiomer SFC-1 (retention time 5.13 min; example 7a) and second eluting enantiomer SFC-2 (retention time 7.05 min; example 7b). ¹H nmr and MS data as for example 7.

Example 8: (2*S*,4*S*) and (2*R*,4*R*)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid

The procedure given for example 7, steps 1-6 afforded 2 racemic mixtures upon hplc purification. The second eluting racemate from hplc was prepared as described in example 7.

Second eluting (hplc-B): racemic mixture; (2*S*,4*S*) and (2*R*,4*R*)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid)

¹H NMR (600 MHz, DMSO-*d*₆, 300 K) δ 1.12-1.20 (m, 1H), 1.26-1.41 (m, 2H), 1.55-1.60 (m, 1H), 1.67-1.76 (m, 2H), 1.82-1.87 (m, 1H), 1.91-2.05 (m, 3H), 2.14-2.19 (m, 1H), 2.42-2.47 (m, 1H), 2.64-2.71 (m, 1H), 2.81-2.93 (m, 6H), 3.77 (d, *J* = 13.1 Hz, 1H), 3.88-3.92 (m, 2H), 3.98-4.02 (m, 1H), 4.05-4.10 (m, 2H), 4.73 (d, *J* = 15.7 Hz, 1H), 7.14-7.24 (m, 3H), 7.46-7.49 (m, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 8.14 (s, 1H), 10.10 (b s, 1H), 12.59 (b s, 1H); diagnostic nOe's: C10'H to Me₂NC4HC5HaHbO-, Me₂NC4H to C5HaHb stronger than to C5HaHb; (ES⁺) *m/z* 475 (M+H)⁺.

Example 8a: (2*S*,4*S*) or (2*R*,4*R*)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid

And

Example 8b: (2*R*,4*R*) or (2*S*,4*S*)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid

The second eluting racemate (**hplc-B**; example 8) was further separated into its respective enantiomers by chiral SFC (flow 10 ml/min; column chiralpack AD-H; isocratic 35 % MeOH/0.2% diethylamine for 6 mins, then 50 % MeOH/0.2% diethylamine) to afford with 36 % and 33 % recovery respectively the first eluting enantiomer SFC-1 (retention time 3.63 min; example 2a) and second eluting enantiomer SFC-2 (retention time 9.40 min; example 2b). ¹H nmr and MS data as for example 8.

Example 9:

Step 1: methyl 14'-cyclohexyl-4-(methylamino)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylate

2,2,2-trifluoroethyl formate (2.45 eq) was added to a solution (0.1 M) of methyl 4-amino-14'-cyclohexyl-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylate (prepared as described in example 7, step 4) in dry THF. The reaction was stirred at RT for 3 h, at which point *N*-formylation was complete. Volatiles were then removed *in vacuo*, and the resultant yellow foam re-solvated in THF to give a 0.05 M solution. Borane DMS complex (2M solution in THF; 6.3 eq) was added and the reaction was stirred at RT for 1 h before cautious quenching (*NB* – vigorous effervescence) with methanolic HCl (1.25 M). The now acidic reaction mixture was left to stir at RT overnight. Volatiles were removed *in vacuo* and the residue partitioned between EtOAc and sat. aq. NaHCO₃. The organics were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford the product. (ES⁺) *m/z* 475 (M+H)⁺.

Step 2: methyl 4-[[N-(tert-butoxycarbonyl)-N-methyl-beta-alanyl](methyl)amino]-14'-cyclohexyl-4,5-dihydro-3H-spiro[furan-2,7'-indolo[1,2-e][1,5]benzoxazocine]-11'-carboxylate
 N-(tert-butoxycarbonyl)-N-methyl-β-alanine (1.1 eq) was added to a solution of the foregoing compound (0.03 M) in dry DCM under N₂. DIPEA (2.5 eq) and then HATU (1.3 eq) were then introduced and the reaction left to stir overnight at RT before being concentrated *in vacuo*. The residue was taken up in EtOAc and washed with 1N HCl (aq) and brine, before being dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude was purified by flash chromatography (40 % EtOAc/PE) to afford the product (96 % over steps 1-2). (ES⁺) *m/z* 660 (M+H)⁺.

Step 3: methyl 14'-cyclohexyl-4-{methyl[3-(methylamino)propyl]amino}-4,5-dihydro-3H-spiro[furan-2,7'-indolo[1,2-e][1,5]benzoxazocine]-11'-carboxylate

Borane DMS complex (2M solution in THF; 20 eq) was added to a stirred solution of the foregoing compound (0.05 M) in dry THF at RT under N₂. The reaction was stirred at RT overnight before introducing a further 20 eq of borane DMS complex and stirring an additional 8 h. The reaction was cautiously quenched (*NB* – vigorous effervescence) with methanolic HCl (1.25 M). The now acidic reaction mixture was left to stir at RT for 48 h. Volatiles were removed *in vacuo* and the residue partitioned between EtOAc and sat. aq. NaHCO₃. The organics were washed with sat. aq. NaHCO₃, brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford the product. (ES⁺) *m/z* 546 (M+H)⁺.

Step 4: methyl 4-[[3-[[[tert-butoxycarbonyl]amino]sulfonyl](methyl)amino]propyl](methyl)amino]-14'-cyclohexyl-4,5-dihydro-3H-spiro[furan-2,7'-indolo[1,2-e][1,5]benzoxazocine]-11'-carboxylate

A solution of the foregoing compound in THF (0.03 M) was treated with (tert-butoxycarbonyl){[4-(dimethyliminio)pyridin-1(4*H*)-yl]sulfonyl}azanide (prepared as described in *Org. Lett.* **2001**, 3, 2241-2243) (1.1 eq) and the reaction heated at 40 °C for 2 h before being allowed to cool to RT. The reaction was diluted with EtOAc and washed with 1N aq. HCl, sat. aq NaHCO₃, water and brine before being dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was taken on to the next step without further purification. (ES⁺) *m/z* 725 (M+H)⁺.

Step 5: 4-[[3-[[[tert-butoxycarbonyl]amino]sulfonyl](methyl)amino]propyl](methyl)amino]-14'-cyclohexyl-4,5-dihydro-3H-spiro[furan-2,7'-indolo[1,2-e][1,5]benzoxazocine]-11'-carboxylic acid

2M NaOH (aq) (22 eq) was added to a solution of the foregoing compound (0.03 M) in a 2/1 mixture of MeOH/THF. The reaction was stirred with heating at 60 °C for 2 h before being allowed to cool to RT and the volatiles reduced *in vacuo*. The residue was partitioned between EtOAc and 1N HCl (aq), ensuring that the aqueous phase was acidic. The organics were washed

with water and brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. (ES⁺) *m/z* 711 (M+H)⁺.

Step 6: 4-[[3-[(aminosulfonyl)(methyl)amino]propyl](methyl)amino]-14'-cyclohexyl-4,5-dihydro-3H-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid

A solution of the foregoing compound in DCM (0.03 M) was treated with TFA (> 200 eq) and the resulting mixture stirred at 60 °C for 1 h before being allowed to cool to RT. All volatiles were removed *in vacuo* and the residue taken up in EtOAc and washed with 3 N HCl (aq), water and brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Trituration with Et₂O afforded the product as a tan coloured solid (62 % over steps 3-6). (ES⁺) *m/z* 611 (M+H)⁺.

Step 7:

A solution of the foregoing compound in DCM (0.006 M) was treated with DMAP (1.5 eq) and then EDAC.HCl (2 eq) and the resulting mixture was stirred at 40 °C for 1 h. A further 1.5 eq EDAC.HCl and 0.9 eq DMAP were then introduced and heating continued for 1.5 h before allowing the reaction to cool to RT and stir overnight. Volatiles were removed *in vacuo* and the residue taken up in DMSO, filtered and purified by RP-HPLC (Waters Sunfire column; C18; 10 μm; 19 x 250 mm; eluting with a MeCN/H₂O/0.1 % TFA gradient). Fractions containing the pure compound were combined and lyophilized to afford the product as a white powder (16 %).

¹H NMR (600 MHz, DMSO-*d*₆ + TFA, 300 K) δ 1.11-1.20 (m, 1H), 1.26-1.40 (m, 2H), 1.50-1.57 (m, 1H), 1.65-1.74 (m, 2H), 1.81-2.03 (m, 4H), 2.07-2.36 (m, 2H), 2.66-2.83 (m, 3H), 2.98-3.16 (m, 7H), 3.28-3.43 (m, 2H), 3.57-3.68 (m, 1H), 3.81-3.95 (m, 3H), 4.10-4.17 (m, 1H), 4.33-4.39 (m, 1H), 4.61-4.68 (m, 2H), 7.18-7.28 (m, 3H), 7.45-7.51 (m, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 8.38 (s, 1H); (ES⁺) *m/z* 593 (M+H)⁺.

Example 10: (2*S*,4*S*) and (2*R*,4*R*)-14'-cyclohexyl-4-[(dimethylamino)methyl]-4,5-dihydro-3H-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid

Step 1: methyl 4-cyano-14'-cyclohexyl-4,5-dihydro-3H-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylate

Sodium cyanide (2.6 eq) was added to a solution (0.15 M) of methyl 4-bromo-14'-cyclohexyl-4,5-dihydro-3H-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylate (prepared as described above in example 7, step 2) in dry DMSO under N₂. The reaction was stirred at RT for 4 days before partitioning between EtOAc and sat. aq. NaHCO₃. The organics were washed with water and then brine before being dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (10 – 30 % EtOAc/PE) to afford the product as a pale yellow foam (51 %). (ES⁺) *m/z* 471 (M+H)⁺.

Step 2: methyl 4-(aminomethyl)-14'-cyclohexyl-4,5-dihydro-3H-spiro[furan-2,7'-indolo[1,2-e][1,5]benzoxazocine]-11'-carboxylate

Borane DMS complex (2M solution in THF; 18 eq) was added to a stirred solution of the foregoing compound (0.05 M) in dry THF at RT under N₂. The reaction was stirred at RT for 1 h before cautious quenching (NB – vigorous effervescence) with methanolic HCl (1.25 M). Once all effervescence had subsided, the now acidic reaction mixture was heated at 60 °C for 2 h. Volatiles were removed *in vacuo* and the residue taken up in EtOAc and washed with sat. aq. NaHCO₃ (2x), brine (1x), dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford the product as a clear glass that was taken on without further purification. (ES⁺) *m/z* 475 (M+H)⁺.

Step 3: methyl 14'-cyclohexyl-4-[(dimethylamino)methyl]-4,5-dihydro-3H-spiro[furan-2,7'-indolo[1,2-e][1,5]benzoxazocine]-11'-carboxylate

Aqueous formaldehyde solution (37 wt %; 6 eq) was added to a solution in methanol (0.05 M) of the preceding compound. The pH of the reaction medium was adjusted to circa pH 5 – 6 by the dropwise addition of acetic acid. Sodium cyanoborohydride (6 eq) was introduced and the reaction mixture left to stir at RT for 30 min. The reaction mixture was partitioned between EtOAc and sat. aq. NaHCO₃. The organics were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford the product as a clear glass that was taken on without further purification. (ES⁺) *m/z* 503 (M+H)⁺.

Step 4: 14'-cyclohexyl-4-[(dimethylamino)methyl]-4,5-dihydro-3H-spiro[furan-2,7'-indolo[1,2-e][1,5]benzoxazocine]-11'-carboxylic acid

2M NaOH (aq) (20 eq) was added to a solution of the foregoing compound (0.025 M) in a 2/1 mixture of THF/methanol. The reaction was stirred with heating at 60 °C for 2 h before being allowed to cool to RT and partitioned between EtOAc and 1N HCl (aq), ensuring that the aqueous phase was acidic. The organics were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by automated RP-HPLC (Waters Sunfire column; C18; 10 µm; 19 x 250 mm; eluting with a MeCN/H₂O/0.1 % TFA gradient), permitting separation of the relative *cis*- and *trans*- stereochemistry isomers (with respect to the spiro junction and the dimethylaminomethyl moiety) as their racemic mixtures. Fractions containing the pure product isomers were lyophilized to afford the products as white powders (27 % combined yield; overall for steps 2 - 4). Relative stereochemistry confirmed by nOe studies.

First eluting (hplc-A): racemic mixture; (2*S*,4*S*) and (2*R*,4*R*)-14'-cyclohexyl-4-[(dimethylamino)methyl]-4,5-dihydro-3H-spiro[furan-2,7'-indolo[1,2-e][1,5]benzoxazocine]-11'-carboxylic acid

¹H NMR (600 MHz, DMSO-*d*₆, 300 K) δ 1.12-1.20 (m, 1H), 1.26-1.40 (m, 2H), 1.53-1.59 (m, 2H), 1.67-1.75 (m, 2H), 1.82-1.87 (m, 1H), 1.91-2.04 (m, 3H), 2.10-2.15 (m, 1H), 2.65-2.71 (m, 2H), 2.82-2.87 (m, 6H), 3.04-3.10 (m, 1H), 3.19-3.23 (m, 1H), 3.42-3.47 (m, 1H), 3.77 (d, *J* =

15.9 Hz, 1H), 3.87 (d, J = 12.9 Hz, 1H), 4.01-4.05 (m, 1H), 4.09 (d, J = 12.9 Hz, 1H), 4.55 (d, J = 15.9 Hz, 1H), 7.17-7.29 (m, 3H), 7.48-7.52 (m, 1H), 7.61 (dd, J = 8.4, 1.1 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 1.1 Hz, 1H), 9.37 (b s, 1H), 12.55 (b s, 1H); diagnostic nOe: C10'H to Me₂NCH₂C4H; (ES⁺) m/z 489 (M+H)⁺.

5

Example 10a: (2*S*,4*S*) or (2*R*,4*R*)-14'-cyclohexyl-4-[(dimethylamino)methyl]-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid

And

10 **Example 10b: (2*R*,4*R*) or (2*S*,4*S*)-14'-cyclohexyl-4-[(dimethylamino)methyl]-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid**

The first eluting racemate (**hplc-A** from example 10, step 4) was further separated into its respective enantiomers by chiral SFC (flow 10 ml/min; column chiralpack AD-H; isocratic 30 % EtOH/0.4% diethylamine) to afford the first eluting enantiomer SFC-1 (retention time 5.20 min; example 4a) and second eluting enantiomer SFC-2 (retention time 10.10 min; example 4b). ¹H
15 nmr and MS data as for example 10.

Example 11: (2*S*,4*R*) and (2*R*,4*S*)-14'-cyclohexyl-4-[(dimethylamino)methyl]-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid

The procedure given for example 10, steps 1-4 afforded 2 racemic mixtures upon hplc
20 purification. The second eluting racemate from hplc was prepared as described in example 10:
Second eluting (hplc-B): racemic mixture; (2*S*,4*R*) and (2*R*,4*S*)-14'-cyclohexyl-4-[(dimethylamino)methyl]-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid

¹H NMR (600 MHz, DMSO-*d*₆, 300 K) δ 1.12-1.21 (m, 1H), 1.26-1.41 (m, 2H), 1.54-1.60 (m, 1H), 1.65-1.76 (m, 3H), 1.82-1.88 (m, 1H), 1.92-2.06 (m, 3H), 2.24-2.29 (m, 1H), 2.65-2.72 (m, 2H), 2.82 (s, 6H), 3.23-3.38 (m, 2H – obscured by water peak), 3.63-3.67 (m, 1H), 3.73 (d, J = 12.1 Hz, 1H), 3.79 (d, J = 15.6 Hz, 1H), 3.80 (d, J = 12.1 Hz, 1H), 3.86-3.90 (m, 1H), 4.64 (d, J = 15.6 Hz, 1H), 7.10-7.22 (m, 3H), 7.43-7.46 (m, 1H), 7.6 (dd, J = 8.5, 1.3 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 8.13 (d, J = 1.3 Hz, 1H), 9.32 (b s, 1H), 12.55 (b s, 1H); diagnostic nOe: C10'H to Me₂NCH₂CH; (ES⁺) m/z 489 (M+H)⁺.
25
30

Example 11a: (2*S*,4*R*) or (2*R*,4*S*)-14'-cyclohexyl-4-[(dimethylamino)methyl]-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid

And

35 **Example 11b: (2*R*,4*S*) or (2*S*,4*R*)-14'-cyclohexyl-4-[(dimethylamino)methyl]-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid**

The second eluting racemate (**hplc-B**; example 11) was further separated into its respective enantiomers by chiral SFC (flow 10 ml/min; column chiralpack AD-H; isocratic 30 %

EtOH/0.4% diethylamine) to afford the first eluting enantiomer SFC-1 (retention time 7.30 min; example 5a) and second eluting enantiomer SFC-2 (retention time 10.80 min; example 5b). ¹H nmr and MS data as for example 11.

5 Example 12: (2*S*,4*S*) and (2*R*,4*R*)-14'-cyclohexyl-4-(morpholin-4-ylmethyl)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid

Step 1: ethyl 14'-cyclohexyl-4-(morpholin-4-ylmethyl)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylate

10 Methyl 4-(aminomethyl)-14'-cyclohexyl-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylate (prepared as described in example 10; step 2) was dissolved in dry ethanol (0.02 M). KI (0.2 eq), K₂CO₃ (4.2 eq) and 2,2-dichlorodiethyl ether (1.2 eq) were introduced and the reaction heated at reflux for 24 h. Further KI (0.2 eq), K₂CO₃ (6 eq) and 2,2-dichlorodiethyl ether (4 eq) were added and the reaction mixture submitted to 2 rounds
15 of heating in the microwave (Smith Creator; 150 °C for 1500 secs (normal power; no fixed hold time) each round). Volatiles were removed *in vacuo* and the residue was partitioned between water and EtOAc. The organics were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The product was taken on without further purification. (ES⁺) m/z 559 (M+H)⁺.

20 Step 2: 14'-cyclohexyl-4-(morpholin-4-ylmethyl)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid

2M NaOH (aq) (20 eq) was added to a solution of the foregoing compound (0.01 M) in a 2/1 mixture of THF/methanol. The reaction was stirred with heating at 60 °C for 1 h before being
25 allowed to cool to RT and the volatiles reduced *in vacuo*. The residue was partitioned between EtOAc and 1N HCl (aq), ensuring that the aqueous phase was acidic. The organics were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by automated RP-HPLC (Waters Sunfire column; C18; 10 μm; 19 x 250 mm; eluting with a MeCN/H₂O/0.1 % TFA gradient), permitting separation of the relative *cis*- and *trans*-
30 stereochemistry isomers (with respect to the spiro junction and the morpholinomethyl moiety) as their racemic mixtures. Fractions containing the pure product isomers were lyophilized to afford the products as white powders (21 % combined yield; overall for steps 1 - 2).

First eluting (hplc-A): racemic mixture; (2*S*,4*S*) and (2*R*,4*R*)-14'-cyclohexyl-4-(morpholin-4-ylmethyl)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid
35 ¹H NMR (400 MHz, DMSO-*d*₆ + TFA, 300 K) δ 1.11-1.25 (m, 1H), 1.27-1.41 (m, 2H), 1.52-1.63 (m, 2H), 1.66-1.77 (m, 2H), 1.81-1.89 (m, 1H), 1.90-2.07 (m, 3H), 2.13-2.21 (m, 1H), 2.65-2.72 (m, 1H), 3.07-3.18 (m, 3H), 3.25-3.32 (m, 2H), 3.41-3.54 (m, 3H), 3.65-3.78 (m, 2H), 3.79 (d, *J* = 15.4 Hz, 1H), 3.88 (d, *J* = 12.3 Hz, 1H), 3.95-4.09 (m, 3H), 4.11 (d, *J* = 12.3 Hz, 1H),

4.54 (d, $J = 15.4$ Hz, 1H), 7.15-7.29 (m, 3H), 7.44-7.52 (m, 1H), 7.62 (d, $J = 8.5$ Hz, 1H), 7.82 (d, $J = 8.5$ Hz, 1H), 8.10 (s, 1H); (ES⁺) m/z 531 (M+H)⁺.

Example 13: (2*R*,4*S*) and (2*S*,4*R*)-14'-cyclohexyl-4-(morpholin-4-ylmethyl)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid

The procedure given for example 12, steps 1-2 afforded 2 racemic mixtures upon hplc purification. The second eluting racemate from hplc was prepared as described in example 12.

Second eluting (hplc-B): racemic mixture; (2*R*,4*S*) and (2*S*,4*R*)-14'-cyclohexyl-4-(morpholin-4-ylmethyl)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid

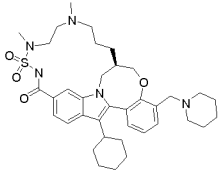
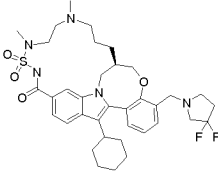
¹H NMR (400 MHz, DMSO-*d*₆ + TFA, 300 K) δ 1.12-1.24 (m, 1H), 1.28-1.41 (m, 2H), 1.53-1.62 (m, 1H), 1.66-1.78 (m, 3H), 1.82-1.88 (m, 1H), 1.90-2.07 (m, 3H), 2.27-2.35 (m, 1H), 2.65-2.74 (m, 1H), 2.75-2.84 (m, 1H), 3.05-3.17 (m, 2H), 3.31-3.38 (m, 2H), 3.47-3.56 (m, 2H), 3.66-3.75 (m, 4H), 3.77-3.84 (m, 2H), 3.88-3.93 (m, 1H), 3.95-4.05 (m, 2H), 4.66 (d, $J = 15.0$ Hz, 1H), 7.08-7.29 (m, 3H), 7.42-7.50 (m, 1H), 7.62 (d, $J = 8.6$ Hz, 1H), 7.84 (d, $J = 8.6$ Hz, 1H), 8.15 (s, 1H); (ES⁺) m/z 531 (M+H)⁺.

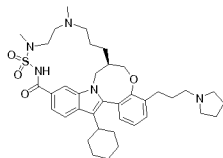
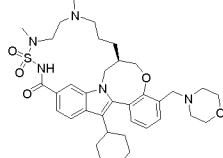
The exemplified compounds were assayed in the above described cell-based HCV replication assay (example ii)) and results are reported as IC₅₀ activity ranges in Tables 1 to 4.

Activity ranges:

+++ : < 25 nM; ++ : 25 – 150 nM; + : 150 – 500 nM; * > 500 nM

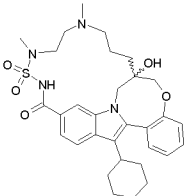
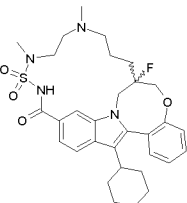
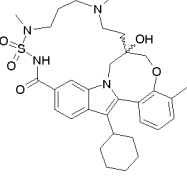
Table 1:

Ex No	Compound name	Structure	IC ₅₀ [*] (nM)	Proce- dure	m/z (ES ⁺)
1	(7 <i>R</i>)-14-cyclohexyl-18,21-dimethyl-4-(piperidin-1-ylmethyl)-7,8-dihydro-6 <i>H</i> -7,11-(propanoiminoethanoiminothioimino methano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide		+++	A	662
	(7 <i>R</i>)-14-cyclohexyl-4-[(3,3-difluoropyrrolidin-1-yl)methyl]-18,21-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(propanoiminoethanoiminothioimino methano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide		+++	A	684

2	(7 <i>R</i>)-14-cyclohexyl-18,21-dimethyl-4-(pyrrolidin-1-ylmethyl)-7,8-dihydro-6 <i>H</i> -7,11-(propanoiminoethanoiminothioimino methano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide		+++	A	676
	(7 <i>R</i>)-14-cyclohexyl-18,21-dimethyl-4-(morpholin-4-ylmethyl)-7,8-dihydro-6 <i>H</i> -7,11-(propanoiminoethanoiminothioimino methano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide		+++	A	664

* Inhibition of HCV subgenomic replication

Table 2:

Ex No	Compound name	Structure	IC ₅₀ [*] (nM)	Proce- dure	m/z (ES ⁺)
4	14-cyclohexyl-7-hydroxy-18,21-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide		++	B	581
6	14-cyclohexyl-7-fluoro-18,21-dimethyl-7,8-dihydro-6 <i>H</i> -7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide		+++	B	583
3	14-cyclohexyl-7-hydroxy-4,18,22-trimethyl-7,8-dihydro-6 <i>H</i> -7,11-(ethanoiminopropanoiminothioiminomethano)indolo[1,2- <i>e</i>][1,5]benzoxazocin-15-one 17,17-dioxide		+++	B	595

* Inhibition of HCV subgenomic replication

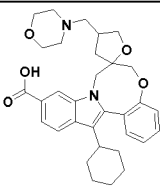
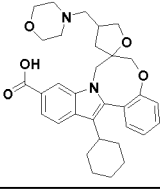
Table 3:

Ex No	Compound name	Structure	IC ₅₀ [*] (nM)	procedure	m/z (ES ⁺)
7	(2 <i>S</i> ,4 <i>R</i>) and (2 <i>R</i> ,4 <i>S</i>)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3 <i>H</i> -spiro[furan-2,7'-indolo[1,2- <i>e</i>][1,5]benzoxazocine]-11'-carboxylic acid		++	D	475
7a	(2 <i>S</i> ,4 <i>R</i>) or (2 <i>R</i> ,4 <i>S</i>)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3 <i>H</i> -spiro[furan-2,7'-indolo[1,2- <i>e</i>][1,5]benzoxazocine]-11'-carboxylic acid		*	D	475
7b	(2 <i>R</i> ,4 <i>S</i>) or (2 <i>S</i> ,4 <i>R</i>)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3 <i>H</i> -spiro[furan-2,7'-indolo[1,2- <i>e</i>][1,5]benzoxazocine]-11'-carboxylic acid		++	D	475
8	(2 <i>R</i> ,4 <i>R</i>) and (2 <i>S</i> ,4 <i>S</i>)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3 <i>H</i> -spiro[furan-2,7'-indolo[1,2- <i>e</i>][1,5]benzoxazocine]-11'-carboxylic acid		+	D	475
8a	(2 <i>R</i> ,4 <i>R</i>) or (2 <i>S</i> ,4 <i>S</i>)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3 <i>H</i> -spiro[furan-2,7'-indolo[1,2- <i>e</i>][1,5]benzoxazocine]-11'-carboxylic acid		*	D	475
8b	(2 <i>S</i> ,4 <i>S</i>) or (2 <i>R</i> ,4 <i>R</i>)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3 <i>H</i> -spiro[furan-2,7'-indolo[1,2- <i>e</i>][1,5]benzoxazocine]-11'-carboxylic acid		++	D	475
9			+++	F	593

Table 4:

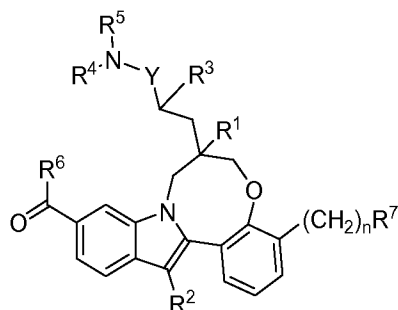
Ex no	Compound name	Structure	IC ₅₀ [*] (nM)	procedure	m/z (ES ⁺)
10	(2 <i>S</i> ,4 <i>S</i>) and (2 <i>R</i> ,4 <i>R</i>)-14'-cyclohexyl-4- [(dimethylamino)methyl]-4,5-dihydro-3 <i>H</i> - spiro[furan-2,7'-indolo[1,2- <i>e</i>][1,5]benzoxazocine]-11'-carboxylic acid		++	D	489
10a	(2 <i>S</i> ,4 <i>S</i>) or (2 <i>R</i> ,4 <i>R</i>)-14'-cyclohexyl-4- [(dimethylamino)methyl]-4,5-dihydro-3 <i>H</i> - spiro[furan-2,7'-indolo[1,2- <i>e</i>][1,5]benzoxazocine]-11'-carboxylic acid		*	D	489
10b	(2 <i>R</i> ,4 <i>R</i>) or (2 <i>S</i> ,4 <i>S</i>)-14'-cyclohexyl-4- [(dimethylamino)methyl]-4,5-dihydro-3 <i>H</i> - spiro[furan-2,7'-indolo[1,2- <i>e</i>][1,5]benzoxazocine]-11'-carboxylic acid		+++	D	489
11	(2 <i>R</i> ,4 <i>S</i>) and (2 <i>S</i> ,4 <i>R</i>)-14'-cyclohexyl-4- [(dimethylamino)methyl]-4,5-dihydro-3 <i>H</i> - spiro[furan-2,7'-indolo[1,2- <i>e</i>][1,5]benzoxazocine]-11'-carboxylic acid		++	D	489
11a	(2 <i>R</i> ,4 <i>S</i>) or (2 <i>S</i> ,4 <i>R</i>)-14'-cyclohexyl-4- [(dimethylamino)methyl]-4,5-dihydro-3 <i>H</i> - spiro[furan-2,7'-indolo[1,2- <i>e</i>][1,5]benzoxazocine]-11'-carboxylic acid		*	D	489
11b	(2 <i>S</i> ,4 <i>R</i>) or (2 <i>R</i> ,4 <i>S</i>)-14'-cyclohexyl-4- [(dimethylamino)methyl]-4,5-dihydro-3 <i>H</i> - spiro[furan-2,7'-indolo[1,2- <i>e</i>][1,5]benzoxazocine]-11'-carboxylic acid		++	D	489
	(2 <i>S</i> ,4 <i>S</i>) and (2 <i>R</i> ,4 <i>R</i>)-14'-cyclohexyl-4- {isopropyl(methyl)amino}methyl}-4,5- dihydro-3 <i>H</i> -spiro[furan-2,7'-indolo[1,2- <i>e</i>][1,5]benzoxazocine]-11'-carboxylic acid		++	D	517
	(2 <i>R</i> ,4 <i>S</i>) and (2 <i>S</i> ,4 <i>R</i>)-14'-cyclohexyl-4- {isopropyl(methyl)amino}methyl}-4,5- dihydro-3 <i>H</i> -spiro[furan-2,7'-indolo[1,2- <i>e</i>][1,5]benzoxazocine]-11'-carboxylic acid		++	D	517

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12	(2 <i>S</i> ,4 <i>S</i>) and (2 <i>R</i> ,4 <i>R</i>)-14'-cyclohexyl-4-(morpholin-4-ylmethyl)-4,5-dihydro-3 <i>H</i> -spiro[furan-2,7'-indolo[1,2- <i>e</i>][1,5]benzoxazocine]-11'-carboxylic acid		++	D	531
13	(2 <i>R</i> ,4 <i>S</i>) and (2 <i>S</i> ,4 <i>R</i>)-14'-cyclohexyl-4-(morpholin-4-ylmethyl)-4,5-dihydro-3 <i>H</i> -spiro[furan-2,7'-indolo[1,2- <i>e</i>][1,5]benzoxazocine]-11'-carboxylic acid		++	D	531

Claims

1. A compound of the formula (I):



(I)

wherein R^1 is selected from hydrogen, hydroxyl, fluoro or a C_{1-4} alkoxy group or R^1 is linked to R^3 to form a 4, 5 or 6-membered aliphatic ring optionally containing one N or O atom;

R^2 is selected from cyclopentyl or cyclohexyl optionally substituted by a fluoro;

R^3 is hydrogen or is linked to R^1 as hereinbeforedefined;

R^4 is hydrogen, a C_{1-4} alkyl group optionally substituted by a group NR^8R^9 , in which R^8 and R^9 are each hydrogen or a C_{1-4} alkyl group or R^4 is linked to R^6 to form a $(CH_2)_mNR^{10}SO_2N$ group wherein m is an integer selected from 2 or 3 and R^{10} is a C_{1-4} alkyl group;

R^5 is hydrogen or a C_{1-4} alkyl group;

R^6 is hydroxyl or is linked to R^4 as hereinbefore defined;

R^7 is hydrogen or an aliphatic ring of 4-7 ring atoms containing one or two heteroatoms selected from O, N or S or a group $S(O)$, $S(O)_2$, NH or NC_{1-4} alkyl and optionally substituted by fluoro or R^7 is a 5-10-membered heteroaromatic ring system containing 1 to 4 heteroatoms independently selected from N, O and S, which ring is optionally substituted by one or two halo atoms or C_{1-4} alkyl or C_{1-4} alkoxy groups;

Y is a single bond or a CH_2 group; when R^4 is linked to R^6 and m is 3 then Y is a single bond; when R^4 is linked to R^6 and m is 2 then Y is a CH_2 group;

n is an integer from zero to four;

with the proviso that when R^1 is hydrogen, n is not zero;
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 in which R^1 is selected from hydrogen, hydroxyl, fluoro or a methoxy group or R^1 is linked to R^3 to form a 5 or 6-membered aliphatic ring optionally containing one N or O atom such as a furan ring.

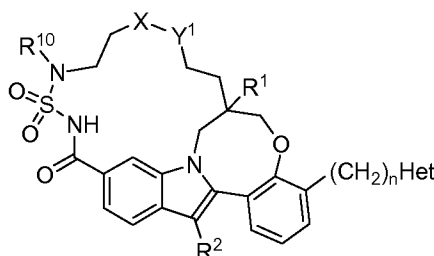
- 55 -

3. A compound according to either claim 1 or 2 in which R^2 is selected from cyclohexyl or cyclohexyl optionally substituted by a fluoro.

4. A compound according to any one of claims 1-3 in which R^3 is hydrogen or linked to R^1 to form a 5 or 6-membered aliphatic ring optionally containing one N or O atom.

5. A compound according to any one of claim 1-4 in which R^4 is a C_{1-4} alkyl group optionally substituted by a group NR^8R^9 or is linked to R^6 as hereinbefore defined and R^{10} is a methyl group.

6. A compound according to any one of claims 1-5 of the formula (II):



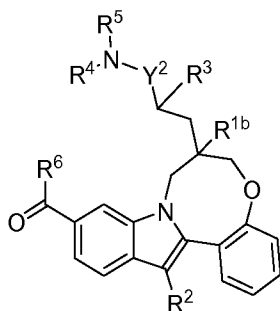
(II)

wherein n , R^1 , R^2 and R^{10} are as defined according to claims 1-5, XY^1 is a group CH_2NR^5 or NR^5CH_2 wherein R^5 is as defined according to claims 1-5, and Het is an aliphatic ring of 4-7 ring atoms containing one or two heteroatoms selected from O, N or S or a group $S(O)$, $S(O)_2$, NH or $NC_{1-4}alkyl$, Het being optionally substituted by 1-3 fluoro or Het is a 5-10-membered heteroaromatic ring system containing 1 to 4 heteroatoms independently selected from N, O and S, which ring is optionally substituted by one or two halo atoms or C_{1-4} alkyl or C_{1-4} alkoxy groups, or a pharmaceutically acceptable salt thereof.

7. A compound according to claim 7 in which Het is 1-piperidino, 1-morpholino or 1-pyrrolidino optionally substituted by one or two fluoro.

8. A compound according to any one of claims 1-5 of the formula (III):

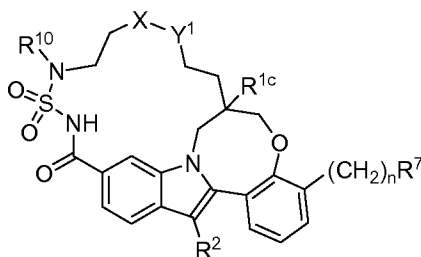
- 56 -



(III)

wherein R^2 to R^6 are as defined according to claims 1-5 and Y^2 is a single bond or a CH_2 group and R^{1b} is linked to R^3 to form a 4, 5 or 6-membered aliphatic ring optionally containing one N or O atom, or a pharmaceutically acceptable salt thereof.

9. A compound according to any one of claims 1-5 of the formula (IV):



(IV)

wherein n , X , Y^1 , R^2 , R^7 and R^{10} are as defined according to claims 1-5 and R^{1c} is fluoro or hydroxyl, or a pharmaceutically acceptable salt thereof.

10. A compound according to any one of claims 1-9 selected from:

(7*R*)-14-cyclohexyl-18,21-dimethyl-4-(piperidin-1-ylmethyl)-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide,
 (7*R*)-14-cyclohexyl-4-[(3,3-difluoropyrrolidin-1-yl)methyl]-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide,
 (7*R*)-14-cyclohexyl-18,21-dimethyl-4-(pyrrolidin-1-ylmethyl)-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide,

- (7*R*)-14-cyclohexyl-18,21-dimethyl-4-(morpholin-4-ylmethyl)-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide,
14-cyclohexyl-7-hydroxy-18,21-dimethyl-7,8-dihydro-6*H*-7,11-
- 5 (propanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5] benzoxazocin-15-one 17,17-dioxide,
14-cyclohexyl-7-fluoro-18,21-dimethyl-7,8-dihydro-6*H*-7,11-(propanoiminoethanoiminiothioiminomethano)indolo[1,2-*e*][1,5] benzoxazocin-15-one 17,17-dioxide,
- 10 14-cyclohexyl-7-hydroxy-4,18,22-trimethyl-7,8-dihydro-6*H*-7,11-(ethanoiminopropanoiminiothioiminomethano)indolo[1,2-*e*][1,5] benzoxazocin-15-one 17,17-dioxide,
(2*S*,4*R*) and (2*R*,4*S*)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
- 15 (2*S*,4*R*) or (2*R*,4*S*)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
(2*R*,4*S*) or (2*S*,4*R*)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
(2*R*,4*R*) and (2*S*,4*S*)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3*H*-spiro[furan-2,7'-
- 20 indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
(2*R*,4*R*) or (2*S*,4*S*)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
(2*S*,4*S*) or (2*R*,4*R*)-14'-cyclohexyl-4-(dimethylamino)-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
- 25 (2*S*,4*S*) and (2*R*,4*R*)-14'-cyclohexyl-4-[(dimethylamino)methyl]-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
(2*S*,4*S*) or (2*R*,4*R*)-14'-cyclohexyl-4-[(dimethylamino)methyl]-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
(2*R*,4*R*) or (2*S*,4*S*)-14'-cyclohexyl-4-[(dimethylamino)methyl]-4,5-dihydro-3*H*-spiro[furan-2,7'-
- 30 indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
(2*R*,4*S*) and (2*S*,4*R*)-14'-cyclohexyl-4-[(dimethylamino)methyl]-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
(2*R*,4*S*) or (2*S*,4*R*)-14'-cyclohexyl-4-[(dimethylamino)methyl]-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
- 35 (2*S*,4*R*) or (2*R*,4*S*)-14'-cyclohexyl-4-[(dimethylamino)methyl]-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,
(2*S*,4*S*) and (2*R*,4*R*)-14'-cyclohexyl-4-{[isopropyl(methyl)amino]methyl}-4,5-dihydro-3*H*-spiro[furan-2,7'-indolo[1,2-*e*][1,5]benzoxazocine]-11'-carboxylic acid,

(2R,4S) and (2S,4R)-14'-cyclohexyl-4- {[isopropyl(methyl)amino]methyl}-4,5-dihydro-3H-spiro[furan-2,7'-indolo[1,2-e][1,5]benzoxazocine]-11'-carboxylic acid,

(2S,4S) and (2R,4R)-14'-cyclohexyl-4-(morpholin-4-ylmethyl)-4,5-dihydro-3H-spiro[furan-2,7'-indolo[1,2-e][1,5]benzoxazocine]-11'-carboxylic acid,

- 5 (2R,4S) and (2S,4R)-14'-cyclohexyl-4-(morpholin-4-ylmethyl)-4,5-dihydro-3H-spiro[furan-2,7'-indolo[1,2-e][1,5]benzoxazocine]-11'-carboxylic acid,
and pharmaceutically acceptable salts thereof.

11. A pharmaceutical composition comprising a compound according to any one of claims 1-
10 or a pharmaceutically acceptable salt thereof in combination with a pharmaceutically
acceptable carrier.

12. A compound according to any one of claims 1-10 or a pharmaceutically acceptable salt
thereof for use in therapy.

13. A compound according to any one of claims 1-10 or a pharmaceutically acceptable salt
thereof for treatment or prevention of infection by hepatitis C virus in a human or animal.

14. The use of a compound according to any one of claims 1-10, or a pharmaceutically
acceptable salt thereof, for the manufacture of a medicament for treatment or prevention of
infection by hepatitis C virus in a human or animal.

15. A method of inhibiting hepatitis C virus polymerase and/or of treating or preventing an
illness due to hepatitis C virus, the method involving administering to a human or animal
(preferably mammalian) subject suffering from the condition a therapeutically or
prophylactically effective amount of the pharmaceutical composition described above or of a
compound of formula (I) according to any one of claims 1-10, or a pharmaceutically acceptable
salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2010/050045

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D498/20 C07D513/16 C07D513/20 A61K31/5517 A61P31/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/054741 A1 (ANGELETTI P IST RICHERCHE BIO [IT]; DI FILIPPO MARCELLO [IT]; HARPER S) 18 May 2007 (2007-05-18) page 47; table 3; compounds 316-329 General teaching of Markush formula (I) in:claim 1 For use in medications to treat hepatitis C infections:claim 17	1-5,8, 10-15
A	WO 2007/129119 A1 (ANGELETTI P IST RICHERCHE BIO [IT]; CAPITO ELENA [IT]; HABERMANN JOERG) 15 November 2007 (2007-11-15) page 38; example 9 page 40; example 11 ----- -/--	1-15

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

21 April 2010

Date of mailing of the international search report

08/06/2010

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Lange, Tim

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2010/050045

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/075103 A1 (ANGELETTI P IST RICHERCHE BIO [IT]; STANSFIELD IAN [IT]; KOCH UWE [IT]) 26 June 2008 (2008-06-26) page 33; example 5 use in therapy of hepatitic C infections:claim 20 Formula (Ia) in:claim 2 -----	1-7,9-15
X,P	WO 2009/010783 A1 (ANGELETTI P IST RICHERCHE BIO [IT]; CONTE IMMACOLATA [IT]; HABERMANN J) 22 January 2009 (2009-01-22) Page 19, lines 30-35 as well as:; page 106; examples 520, 521; table 5 page 55; example 14 page 72; example 25 Pharmaceutical compositions:claim 8 Use in therapy of Hepatitis C viral infections:claims 12-13 -----	1-7,9-15
X,P	WO 2009/010785 A1 (ANGELETTI P IST RICHERCHE BIO [IT]; CONTE IMMACOLATA [IT]; HABERMANN J) 22 January 2009 (2009-01-22) Compounds: (7R)-14-Cyclohexyl-4,18,21-trimethyl-7,8-d ihydro-6H-7,11-(propanoiminoethanoiminothi oiminoethano)indolo[1,2-e][1,5]benzoxazoci n-15-one-17,17dioxide and (7R)-14-Cyclohexyl-4,18,21-trimethyl-7,8-d ihydro-6H-7,11-(ethanoiminopropanoiminothi oiminoethano)indolo[1,2-e][1,5]benzoxazoci n-15-one-17,17dioxide:; page 24, line 19 - line 24 (7R)-14-[1R,2S)-2-Fluorocyclohexyl-4,18,2 1-trimethyl-7,8-dihydro-6H-7,11-(propanoim inoethanoiminothioiminoethano)indolo[1,2-e][1,5]benzoxazocin-15-one-17,17dioxide:; page 23, line 36 - line 38 Pharmaceutical compositions:claim 17 Use in therapy of hepatitis C viral infections:claims 19-20 -----	1-7,9-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2010/050045

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007054741 A1	18-05-2007	AU 2006313539 A1 CA 2628937 A1 CN 101305008 A EP 1948660 A1 JP 2009515865 T US 2009136449 A1	18-05-2007 18-05-2007 12-11-2008 30-07-2008 16-04-2009 28-05-2009
WO 2007129119 A1	15-11-2007	AU 2007246850 A1 CA 2651226 A1 CN 101437826 A EP 2027125 A1 JP 2009536189 T US 2010009959 A1	15-11-2007 15-11-2007 20-05-2009 25-02-2009 08-10-2009 14-01-2010
WO 2008075103 A1	26-06-2008	AU 2007335962 A1 CA 2672250 A1 EP 2121707 A1 US 2010076046 A1	26-06-2008 26-06-2008 25-11-2009 25-03-2010
WO 2009010783 A1	22-01-2009	AR 067542 A1 AU 2008277440 A1 AU 2008277442 A1 CA 2693533 A1 CA 2693537 A1 GB 2451184 A WO 2009010785 A1 PE 04782009 A1 US 2009048239 A1	14-10-2009 22-01-2009 22-01-2009 22-01-2009 22-01-2009 21-01-2009 22-01-2009 24-05-2009 19-02-2009
WO 2009010785 A1	22-01-2009	AR 067542 A1 AU 2008277440 A1 AU 2008277442 A1 CA 2693533 A1 CA 2693537 A1 GB 2451184 A WO 2009010783 A1 PE 04782009 A1 US 2009048239 A1	14-10-2009 22-01-2009 22-01-2009 22-01-2009 22-01-2009 21-01-2009 22-01-2009 24-05-2009 19-02-2009