(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 June 2014 (26.06.2014)

(10) International Publication Number
WO 2014/095920 A1

(51) International Patent Classification:
A61K 47/48 (2006.01) ***C07D 453/02*** (2006.01)
A61P 11/08 (2006.01) ***C07D 235/24*** (2006.01)
A61K 31/13 (2006.01) ***C07C 15/50*** (2006.01)
A61K 31/439 (2006.01) ***C07C 271/38*** (2006.01)
A61K 31/4184 (2006.01)

(21) International Application Number:
PCT/EP2013/076973

(22) International Filing Date:
17 December 2013 (17.12.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
12382513.5 18 December 2012 (18.12.2012) EP
61/750,959 1 October 2013 (01.10.2013) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(54) Title: NEW CYCLOHEXYL AND QUINUCLIDINYL CARBAMATE DERIVATIVES HAVING BETA2 ADRENERGIC AGONIST AND M3 MUSCARINIC ANTAGONIST ACTIVITY

(57) Abstract: The present invention relates to novel compounds having β2 adrenergic agonist and M3 muscarinic antagonist dual activity, to pharmaceutical compositions containing them, to the process for their preparation and to their use in respiratory therapies.

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CYCLOHEXYL AND QUINUCLIDINYL CARBAMATE DERIVATIVES HAVING SS2 ADRENERGIC AGONIST AND M3 MUSCARINIC ANTAGONIST ACTIVITIES

FIELD OF THE INVENTION.

The present invention relates to novel compounds having β2 adrenergic agonist and M3 muscarinic antagonist dual activity. This invention also relates to pharmaceutical compositions containing them, process for their preparation and their use in respiratory therapies.

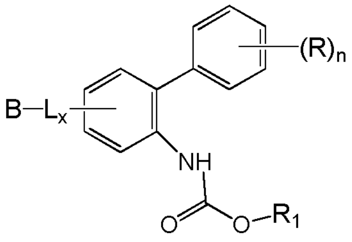
BACKGROUND OF THE INVENTION.

Bronchodilator agents play an outstanding role in the treatment of respiratory disorders such as COPD and asthma. Beta-adrenergic agonists and cholinergic muscarinic antagonists are well established bronchodilator agents in widespread clinical use. Beta-adrenergic agonists currently used by the inhaled route include short-acting agents such as salbutamol (qid) or terbutaline (tid) and long-acting agents as salmeterol and formoterol (bid). These agents produce bronchodilation through stimulation of adrenergic receptors on airway smooth muscle, reversing the bronchoconstrictor responses to a variety of mediators, such as acetylcholine. Inhaled muscarinic antagonists currently used include the short-acting ipratropium bromide or oxitropium bromide (qid) and the long-acting tiotropium (qd). These agents produce bronchodilation by reducing vagal cholinergic tone of airway smooth muscle. In addition to improve lung function these agents also improve quality of life and reduce exacerbations. There are in the clinical literature a number of studies strongly demonstrating that the administration of a combination of a beta-2 agonist and a M3 antagonist is more efficacious for the treatment of COPD than either of the components alone (for example, van Noord, J.A., et al., Eur.Respir.J., 2005, 26, 214-222). Pharmaceutical compositions containing a combination of both types of bronchodilator agents are also known in the art for use in respiratory therapy. As an example, WO2009013244 discloses a medical composition containing salmeterol as beta-adrenergic agonist agent and tiotropium as antimuscarinic agent.

A single molecule possessing dual activity at muscarinic M3 and adrenergic β2 receptors (MABA) would be desirable both in terms of efficacy and side-effects in the treatment of COPD. It would show also a relevant advantage in terms of formulation compared with the two-component combination. It would be also easier to co-formulate with other therapeutic agents such as inhaled anti-inflammatories to create triple therapy combinations. Thus there is a need for new compounds having both beta2 receptor agonist and muscarinic activity and being suitable for the treatment of respiratory diseases, such as asthma and COPD.

SUMMARY OF THE INVENTION.

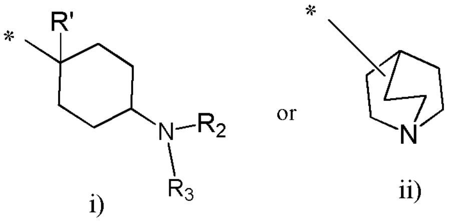
The invention provides novel compounds that possess both β2 adrenergic receptor agonist and muscarinic receptor antagonist activities. Accordingly, there is provided a compound of formula (A), and pharmaceutically acceptable salts, and deuterated derivates thereof.



Formula (A)

wherein

- R is selected from the group consisting of a hydrogen atom, a halogen atom, a hydroxyl group, a linear or branched C_{1-4} alkyl group, a linear or branched C_{1-4} hydroxyalkyl group and a linear or branched C_{1-4} alkoxy group,
- n has a value of 1 or 2,
- R_1 represents a group of formula:

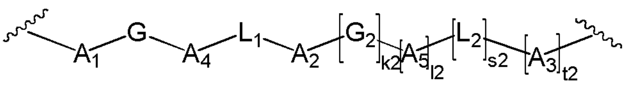


wherein:

  - R_2 and R_3 independently represent a hydrogen atom, a linear or branched C_{1-6} alkyl group, preferably a linear or branched C_{1-4} alkyl group, a (C_{5-6} aryl)-(C_{1-4})alkyl group or a linear or branched C_{1-4} alkoxy group,
  - R' represents a hydrogen atom or a lineal or branched C_{1-4} alkyl group,
  - * represents the point of attachment of R_1 to the remainder of the molecule of formula (A),
- L_x is a suitable covalent linker, and
- B is a moiety having a beta2-adrenergic binding activity.

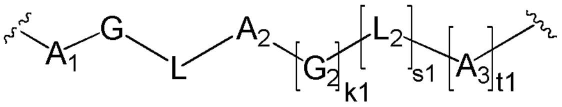
L_x is a linker defined as a covalent bond between the beta2-agonist moiety B and the biphenyl moiety of formula (A).

In one embodiment of the present invention, the linker L_x has the following formula:



Formula (La)

or



Formula (Lb)

wherein k1, k2, s1, s2, l2, t1 and t2 independently have a value of 0 or 1;

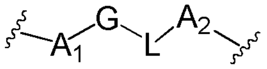
- A_1, A_2, A_3, A_4 and A_5 each independently are selected from the group consisting of a direct bond, a C_{1-10} alkylene group, a C_{2-10} alkenylene group and a C_{2-10} alkynylene group, wherein said groups are optionally substituted with one or more substituents selected from a halogen atom, a hydroxy group, a linear or branched C_{1-4} alkyl group, a linear or branched C_{1-4} alkoxy group, a C_{5-6} aryl group and a C_{3-7} cycloalkyl group,

- L, L_1 and L_2 independently are selected from a direct bond, -O-, $-NR^c-$, -S-, -S(O)-, $-SO_2-$, $-NR^c(CO)-$, $-(CO)NR^c-$, $–NR^c(CO)(CH_2)_qO-$, $–O(CH_2)_q(CO)NR^c-$, $-NR^c(CO)(CH_2)_qNR^c(CO)-$, $–O(CH_2)_qNR^c-$, $–NR^c(CH_2)_qO-$, $–NR^c(CO)NR^d-$, -C(O)-, -C(O)O-, -OC(O)-, $-S(O)_2NR^c-$, $-NR^cS(O)_2-$, $-NR^cS(O)_2NR^d-$, $–C(O)NR^cS(O)_2-$ and $–S(O)_2NR^cC(O)-$, wherein R^c and R^d are independently selected from a hydrogen atom and a linear or branched C_{1-4} alkyl group and q has a value of 0, 1, 2, 3 or 4.

- G and G_2 independently are selected from the group consisting of a direct bond, a C_{3-10} mono- or bicyclic cycloalkyl group, a C_5-C_{14} mono- or bicyclic aryl group, a 3 to 14-membered saturated or unsaturated mono- or bicyclic heterocyclyl group having one or more heteroatoms selected from N, S and O, a 5- to 14-membered mono- or bicyclic heteroaryl group having one or more heteroatoms selected from N, S and O and a bicyclic ring system comprising two monocyclic ring systems which are linked between each other by a covalent bond or by a –O- or –NH- group, wherein said monocyclic ring systems are independently selected from a C_{3-8} cycloalkyl group, a C_{5-6} aryl group, a 3- to 8-membered saturated or unsaturated heterocyclyl group having one or more heteroatoms selected from N, S and O and a 5- to 6-membered heteroaryl group having one or more heteroatoms selected from N, S and O, wherein the cyclic groups independently are optionally substituted with one or more substituents selected from a halogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a carboxy group, a cyano group, a nitro group, a hydroxy group, an oxo group, a trifluoromethyl group and a trifluoromethoxy group.

In a preferred embodiment, all of k1, k2, s1, s2, l2, t1 and t2 have a value of 0

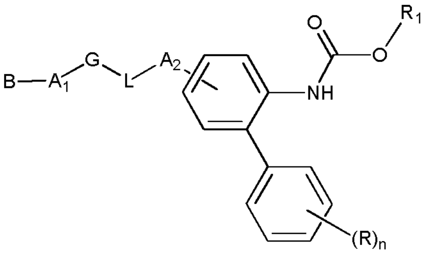
In a still preferred embodiment the linker L has the following formula (Lb1):



Formula (Lb1)

wherein A_1, A_2, L_1 and G are as defined above.

In a preferred embodiment, compounds of the present invention have the following formula (B):



Formula(B)

Wherein A_1, A_2, B, L, G, n, R and R_1 are as defined above.

The invention also provides synthetic processes and intermediates described herein, which are useful for preparing compounds of the invention.

The invention further provides a pharmaceutical composition comprising at least a compound of the invention and a pharmaceutically-acceptable carrier.

The invention also provides a compound of the invention as described herein for use in the treatment of human or animal body by therapy.

The invention is also directed to the compounds as described herein, for use in the treatment of a pathological condition or disease associated with dual β2 adrenergic receptor and muscarinic receptor activities in particular wherein the pathological condition or disease is selected from a pulmonary disease, such as asthma or chronic obstructive pulmonary disease, pre-term labor, glaucoma, a neurological disorder, a cardiac disorder, inflammation, urological disorders such as urinary incontinence and gastrointestinal disorders such as irritable bowel syndrome or spastic colitis, preferably asthma and chronic obstructive pulmonary disease.

The invention also provides the use of the compounds of the invention as described herein, for the manufacture of a medicament for the treatment of a pathological condition or disease associated with dual β2 adrenergic receptor and muscarinic receptor activities, in particular wherein the pathological condition or disease is selected from a pulmonary disease, such as asthma or chronic obstructive pulmonary disease, pre-term labor, glaucoma, a neurological disorder, a cardiac disorder, inflammation, urological disorders such as urinary incontinence and gastrointestinal disorders such as irritable bowel syndrome or spastic colitis, preferably asthma and chronic obstructive pulmonary disease.

The invention is also directed to a method of treatment of a pathological condition or disease associated with dual β2 adrenergic receptor and muscarinic receptor activities, in particular wherein the pathological condition or disease is selected from a pulmonary disease, such as asthma or chronic obstructive pulmonary disease, pre-term labor, glaucoma, a neurological disorder, a cardiac disorder, inflammation, urological disorders such as urinary incontinence and gastrointestinal disorders such as irritable bowel syndrome or spastic colitis, preferably asthma and chronic obstructive pulmonary disease, comprising administering a therapeutically effective amount of the compounds of the invention or a pharmaceutical composition of the invention to a subject in need of such treatment.

The invention also provides a combination product comprising (i) at least a compound of the invention as described herein; and (ii) one or more active ingredients selected from the group consisting of a corticosteroid and/or a PDE4 inhibitor, for simultaneous, separate or sequential use in the treatment of the human or animal body.

DETAILED DESCRIPTION OF THE INVENTION

When describing the compounds, compositions and methods of the invention, the following terms have the following meanings, unless otherwise indicated.

As used herein the term C_{1-6} alkyl embraces linear or branched radicals having 1 to 6, preferably 1 to 4 carbon atoms. Examples include methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

As used herein, the term C_1-C_{10} alkylene embraces divalent alkyl moieties typically having from 1 to 10 carbon atoms, preferably from 1 to 6 carbon atoms, more preferably from 1 to 4 carbons atoms. Examples of C_1-C_{10} alkylene radicals include methylene, ethylene, propylene, butylene, pentylene and hexylene radicals.

As used herein, the term C_2-C_{10} alkenylene embraces divalent alkenyl moieties typically having from 2 to 10 carbon atoms, preferably from 2 to 6 carbon atoms, more preferably from 2 to 4 carbons atoms. Examples of C_2-C_{10} alkenylene radicals include vinylene, propenylene, butenylene, pentenylene, hexenylene, heptenylene, octenylenyl radicals.

As used herein, the term C_2-C_{10} alkynylene embraces divalent alkynyl moieties having 2 to 10 carbon atoms, preferably from 2 to 6 carbon atoms, more preferably from 2 to 4 carbons atoms. Examples include propynylene, butynylene, heptynylene, octynylene.

As used herein, the term C_{1-4} alkoxy (or alkyloxy) embraces optionally substituted, linear or branched oxy-containing radicals each having alkyl portions of 1 to 4 carbon atoms. Preferred alkoxy radicals include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, sec-butoxy and t-butoxy.

As used herein, the term C_{4-6} cycloalkyl group embraces saturated carbocyclic radicals monocyclic or polycyclic ring having from 4 to 6 carbon atoms, preferably from 3 to 5 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. It is preferably cyclopropyl, cyclobutyl and cyclopentyl.

As used herein, the term C_5-C_{14} aryl radical embraces typically a C_5-C_{14}, preferably a C_6-C_{14}, more preferably a C_6-C_{10} monocyclic or polycyclic aryl radical. Examples of aryl radicals include phenyl, naphthyl, naphthalenyl, anthranyl and phenanthryl.

As used herein, the term 5- to 14- membered heteroaryl radical embraces typically a 5- to 14- membered ring system comprising at least one heteroaromatic ring and containing at least one heteroatom selected from O, S and N. A 5- to 14- membered heteroaryl radical may be a single ring or two or more fused rings wherein at least one ring contains a heteroatom.

Examples include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, furyl, benzofuranyl, oxadiazolyl, oxazolyl, isoxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, thiadiazolyl, thienyl, pyrrolyl, benzothiazolyl, indolyl, indazolyl, purinyl, quinolyl, isoquinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, quinolizinyl, cinnolinyl, triazolyl, indolizinyl, indolinyl, isoindolinyl, isoindolyl, imidazolidinyl, pteridinyl, thianthrenyl, pyrazolyl, 2H-pyrazolo[3,4-d]pyrimidinyl, 1H-pyrazolo[3,4-d]pyrimidinyl, thieno[2,3-d] pyrimidinyl and the various pyrrolopyridyl radicals.

As used herein, the term 3- to 14-membered heterocyclyl radical embraces typically a non-aromatic, saturated or unsaturated C_3-C_{14} carbocyclic ring system in which one or more, for example 1, 2, 3 or 4 of the carbon atoms preferably 1 or 2 of the carbon atoms are replaced by a heteroatom selected from N, O and S. A heterocyclic radical may be a single ring or two or more fused rings wherein at least one ring contains a heteroatom, and may have one or more double bonds

Examples of 3 to 14-membered heterocyclic radicals include piperidyl, pyrrolidyl, pyrrolinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, pyrazolinyl, pirazolidinyl, quinuclidinyl, triazolyl, pyrazolyl, tetrazolyl, imidazolidinyl, imidazolyl, oxiranyl, thiaranyl, aziridinyl, oxetanyl, thiatanyl, azetidinyl, 4,5-dihydro-oxazolyl, 2-benzofuran-1(3H)-one, 1,3-dioxol-2-one, tetrahydrofuranyl, 3-aza-tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,4-azathianyl, oxepanyl, thiephanyl, azepanyl, 1,4-dioxepanyl, 1,4-oxathiepanyl, 1,4-oxaazepanyl, 1,4-dithiepanyl, 1,4-thiezepanyl, 1,4-diazepanyl, tropanyl, (1S,5R)-3-aza-bicyclo[3.1.0]hexyl, 3,4-dihydro-2H-pyranyl, 5,6-dihydro-2H-pyranyl, 2H-pyranyl, 2,3-hydrobenzofuranyl, 1,2,3,4-tetrahydropyridinyl, 1,2,5,6-tetrahydropyridinyl, isoindolinyl and indolinyl.

As used herein, the term halogen atom embraces chlorine, fluorine, bromine or iodine atoms typically a fluorine, chlorine or bromine atom. The term halo when used as a prefix has the same meaning.

Also included within the scope of the invention are the isomers, polymorphs, pharmaceutically acceptable salts, N-oxides, isotopes, solvates and prodrugs of the compounds of formula (I). Any reference to a compound of formula (I) throughout the present specification includes a reference to any isomer, polymorph, pharmaceutically acceptable salt, N-oxide, isotope, solvate or prodrug of such compound of formula (I).

Isomers

Compounds containing one or more chiral centre may be used in enantiomerically or diastereoisomerically pure form, in the form of racemic mixtures and in the form of mixtures enriched in one or more stereoisomer. The compounds of the present invention as described and claimed encompass the racemic forms of the compounds as well as the individual enantiomers, diastereomers, and stereoisomer-enriched mixtures.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate using, for example, chiral high pressure liquid chromatography (HPLC). Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomehc mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to one skilled in the art. Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% isopropanol, typically from 2 to 20%, and from 0 to 5% of an alkylamine, typically 0.1 % diethylamine. Concentration of the eluate affords the enriched mixture. Stereoisomer conglomerates may be separated by conventional techniques known to those skilled in the art. See, e.g. "Stereochemistry of Organic Compounds" by Ernest L. Eliel (Wiley, New York, 1994).

The compounds of Formula (I) may exhibit the phenomena of tautomerism and structural isomerism. Tautomers exist as mixtures of a tautomeric set in solution. In solid form, usually one tautomer predominates. Even though one tautomer may be described, the present invention includes all tautomers of the compounds of Formula (I).

Polymorphs

The compounds of the present invention may exist in different physical forms, i.e. amorphous and crystalline forms.
Moreover, the compounds of the invention may have the ability to crystallize in more than one form, a characteristic which is known as polymorphism. Polymorphs can be distinguished by various physical properties well known in the art such as X-ray diffraction pattern, melting point or solubility. All physical forms of the compounds of the present invention, including all polymorphic forms ("polymorphs") thereof, are included within the scope of the invention.

Salts

As used herein, the term pharmaceutically acceptable salt refers to a salt prepared from a base or acid which is acceptable for administration to a patient, such as a mammal. Such salts can be derived from pharmaceutically-acceptable inorganic or organic bases and from pharmaceutically-acceptable inorganic or organic acids.

As used herein, the term pharmaceutically acceptable salt embraces salts with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids, for example hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic, hydroiodic and nitric acid; and organic acids, for example citric, fumaric, gluconic, glutamic, lactic, maleic, malic, mandelic, mucic, ascorbic, oxalic, pantothenic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic, p-toluenesulphonic acid, xinafoic (1-hydroxy-2-naphthoic acid), napadisilic (1,5-naphthalenedisulfonic acid) and the like. Particularly preferred are salts derived from fumaric, hydrobromic, hydrochloric, acetic, sulfuric, methanesulfonic, xinafoic, and tartaric acids.

Salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Particularly preferred are ammonium, calcium, magnesium, potassium and sodium salts.

Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including alkyl amines, arylalkyl amines, heterocyclyl amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-

diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

Other preferred salts according to the invention are quaternary ammonium compounds wherein an equivalent of an anion (X^-) is associated with the positive charge of the N atom. X^- may be an anion of various mineral acids such as, for example, chloride, bromide, iodide, sulphate, nitrate, phosphate, or an anion of an organic acid such as, for example, acetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, trifluoroacetate, methanesulphonate and *p*-toluenesulphonate. X^- is preferably an anion selected from chloride, bromide, iodide, sulphate, nitrate, acetate, maleate, oxalate, succinate or trifluoroacetate. More preferably X^- is chloride, bromide, trifluoroacetate or methanesulphonate.

N-oxides

As used herein, an N-oxide is formed from the tertiary basic amines or imines present in the molecule, using a convenient oxidising agent.

Isotopes

The invention also includes isotopically-labeled compounds of the invention, wherein one or more atoms is replaced by an atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulfur, such as ^{35}S. Certain isotopically-labeled compounds of the invention, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, ^{3}H, and carbon-14, ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with heavier isotopes such as deuterium, ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

Preferred isotopically-labeled compounds include deuterated derivatives of the compounds of the invention. As used herein, the term deuterated derivative embraces compounds of the invention where in a particular position at least one hydrogen atom is replaced by deuterium. Deuterium (D or ^{2}H) is present at a natural abundance of 0.015 molar %.

Solvates

The compounds of the invention may exist in both unsolvated and solvated forms. The term solvate is used herein to describe a molecular complex comprising a compound of the invention and an amount of one or more pharmaceutically acceptable solvent molecules. The term hydrate is employed when said solvent is water. Examples of solvate forms include, but are not limited to, compounds of the invention in association with water, acetone, dichloromethane, 2-propanol, ethanol, methanol, dimethylsulfoxide (DMSO), ethyl acetate, acetic acid, ethanolamine, or mixtures thereof. It is specifically contemplated that in the present invention one solvent molecule can be associated with one molecule of the compounds of the present invention, such as a hydrate.

Furthermore, it is specifically contemplated that in the present invention, more than one solvent molecule may be associated with one molecule of the compounds of the present invention, such as a dihydrate. Additionally, it is specifically contemplated that in the present invention less than one solvent molecule may be associated with one molecule of the compounds of the present invention, such as a hemihydrate. Furthermore, solvates of the present invention are contemplated as solvates of compounds of the present invention that retain the biological effectiveness of the non-solvate form of the compounds.

Prodrugs

Prodrugs of the compounds described herein are also within the scope of the invention. Thus certain derivatives of the compounds of the present invention, which derivatives may have little or no pharmacological activity themselves, when administered into or onto the body may be converted into compounds of the present invention having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T. Higuchi and W. Stella) and Bioreversible Carriers in Drug Design, Pergamon Press, 1987 (ed. E. B. Roche, American Pharmaceutical Association).

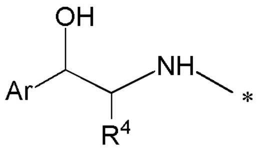
Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of the present invention with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in Design of Prodrugs by H. Bundgaard (Elsevier, 1985).

Typically B is a moiety having a beta2-adrenergic binding activity such that the IC_{50} of the compound is 1mM or less, preferably 100 µM or less, more preferably 10 µM or less, more preferably 1µM or less, more preferably 500 nM or less, most preferably 250 nM or less, as measured in a beta2-adrenergic binding assay.

Typically said beta2-adrenergic binding assay comprises:

a) providing a membrane suspension comprising Sf9 cells in an assay buffer
b) incubating with 3H-CGP12177 in plates previously treated with assay buffer containing a coating agent
c) measuring binding of test compound in the presence of propanolol
d) maintaining incubation
e) terminating the binding reactions
f) determining the affinity of the test compound for the receptor by repeating steps a) to e) using multiple different test compound concentrations.
g) calculating an IC_{50} using the four parameters-log equation.

Typically B represents a group of formula (IB):



Formula (IB)

wherein:

- R^4 is selected from the group consisting of a hydrogen atom, a linear or branched C_{1-4} alkyl group and a linear or branched C_{1-4} alkoxy group,
- Ar is selected from the group consisting of a C_{3-10} saturated or unsaturated, mono- or bicyclic cycloalkyl group, a C_5-C_{14} mono- or bicyclic aryl group, a 3 to 14-membered saturated or unsaturated mono- or bicyclic heterocyclyl group having one or more heteroatoms selected from N, S and O, a 5- to 14-membered mono- or bicyclic heteroaryl group having one or more heteroatoms selected from N, S and O and wherein the cyclic groups independently are optionally substituted with one or more substituents selected from a halogen atom, a cyano group, a nitro group, an oxo group, a carboxy group, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, $-CF_3$, $–OCF_3$, $-NR^eR^f$, $-(CH_2)_p$-OH, $-NR^e(CO)R^f$, $-NR^e$-SO_2-R^g, $-SO_2NR^eR^f$, $-OC(O)R^h$ and $–NR^e(CH_2)_{(0-2)}$-R^i, wherein p has a value of 0, 1 or 2 and wherein:

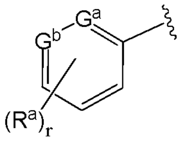
  R^e and R^f independently represent a hydrogen atom or a linear or branched C_{1-4} alkyl group,

  R^g is selected from the group consisting of a linear or branched C_{1-4} alkyl group, a C_{5-6}aryl group, a saturated or unsaturated C_{3-8} cycloalkyl, wherein the cyclic groups independently are optionally substituted with one or more substituents selected from a halogen atom, a C_{1-4} alkyl group and a C_{1-4} alkoxy group,

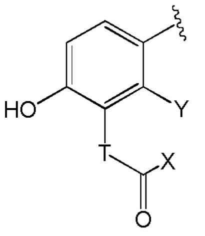
  R^h is selected from a hydrogen atom,$-NR^eR^f$ and a C_{5-6} aryl group which is optionally substituted with one or more substituents selected from a C_{1-4} alkyl group and a C_{1-4} alkoxy group,

  R^i is selected from the group consisting of a C_{5-6} aryl group, a C_{3-8} cycloalkyl group and a 3 to 8 membered saturated or unsaturated heterocyclyl group, which groups independently are optionally substituted with one or more substituents selected from a halogen atom, a C_{1-4} alkyl group and a C_{1-4} alkoxy group.

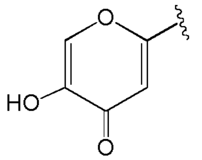
Preferably, Ar represents a group of formula:



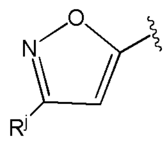
(a)



(b)



(c)

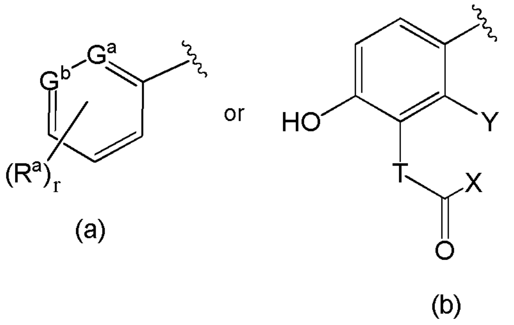


(d)

wherein

- G^a and G^b independently are selected from a nitrogen atom and a carbon atom,
- r has a value of 0, 1, 2 or 3 and
- R^a is seleted from the group consisting of a halogen atom, an amino group, a cyano group, a nitro group, an oxo group, a carboxy group, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, $-CF_3$, $–OCF_3$, $-(CH_2)_p-OH$, -NH(CO)H, $-NH-SO_2-R^g$, $-SO_2NH_2$, -OC(O)H, –O(CO)-(4-methyl)phenyl, $–O(CO)-N(CH_3)_2$, $-OC(O)NH_2$ and $–NH(CH_2)_{(1-2)}-R^i$, group, wherein p is as defined above and R^g and R^i independently are selected from a phenyl group optionally substituted with a one substituent selected from a methyl group or a methoxy group,
- R^j represents a halogen atom,
- T is selected from the group consisting of $–CH_2-$ and –NH-,
- Both X and Y represent a hydrogen atom or X together with Y form the group $–CH_2-CH_2-$, -CH=CH-, $-CH_2-O-$ or –S-, wherein in the case of $-CH_2-O-$ the methylene group is bound to the carbonyl group holding X and the oxygen atom is bound to the carbon atom in the phenyl ring holding Y,

Preferably, Ar represents a compound of formula (a) or (b) wherein:



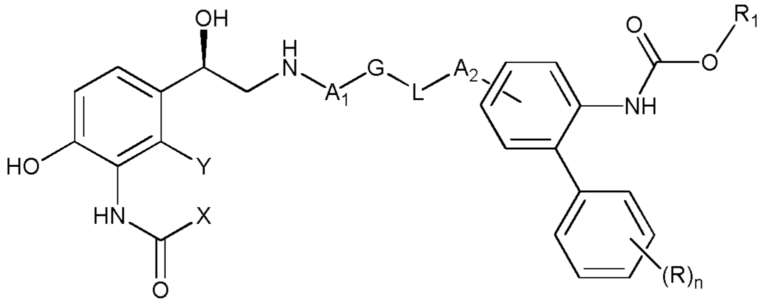
- Both G^a and G^b represent a carbon atom,
- R^a is seleted from the group consisting of halogen atom, amino group, cyano group, nitro group, $-(CH_2)_p-OH$, -NH(CO)H, $-NH-SO_2-CH_3$, $-SO_2NH_2$, -OC(O)H, –O(CO)-(4-methyl)phenyl, $–O(CO)-N(CH_3)_2$, $-OC(O)NH_2$ and $-CF_3$ group, wherein p has a value of 0, 1 or 2,
- T represents –NH- group,
- Both X and Y represent a hydrogen atom or X together with Y form the group –CH=CH-, $-CH_2-CH_2-$, $-CH_2-O-$ or –S-, wherein in the case of $-CH_2-O-$ the methylene group is bound to the carbon atom in the amido substituent holding X and the oxygen atom is bound to the carbon atom in the phenyl ring holding Y

In a still prefered embodiment Ar is selected from the group consisting of 3-bromoisoxazol-5-yl, 3,4-dihydroxyphenyl, 4-hydroxy-3-(methylsulfonamido)phenyl, 3,4-

bis(4-methylbenzoyloxy)phenyl, 3,5-bis(dimethylcarbamoyloxy)phenyl, (5-hydroxy-6-hydroxymethyl)pyrid-2-yl, (4-amino-3,5-dichloro)phenyl, 4-hydroxyphenyl, 4-hydroxy-3-(2-hydroxyethyl)phenyl, 4-hydroxy-3-(hydroxymethyl)phenyl, [4-amino-3-chloro-5-(trifluoromethyl)]phenyl, (3-formamido-4-hydroxy)phenyl, 8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl, 8-hydroxy-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl, 5-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-8-yl, 4-hydroxy-2-oxo-2,3-dihydrobenzo[d]thiazol-7-yl. Preferably Ar is selected from the group consisting of 4-hydroxy-3-(hydroxymethyl)phenyl, (3-formamido-4-hydroxy)phenyl, 8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl, 8-hydroxy-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl and 5-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-8-yl.

In another embodiment Ar represents a compound of formula (b) wherein X and Y are as defined above and T represents a –NH- group.

Still in another embodiment of the present invention, compounds of the present invention have the following formula (I):



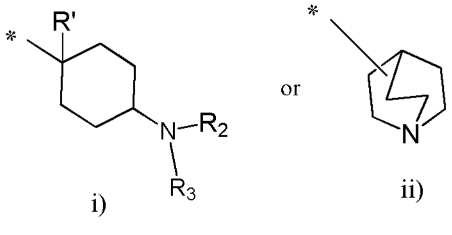
Formula (I)

Wherein:

- R is selected from the group consisting of a hydrogen atom, a halogen atom, a hydroxyl group, a linear or branched C_{1-4} alkyl group, a linear or branched C_{1-4} hydroxyalkyl group and a linear or branched C_{1-4} alkoxy group,
- n has a value of 1 or 2,
- X and Y are both hydrogen atoms or X together with Y form the group –CH=CH-, -CH_2-O- or –S-, wherein in the case of -CH_2-O- the methylene group is bound to the carbon atom in the amido substituent holding X and the oxygen atom is bound to the carbon atom in the phenyl ring holding Y,
- A_1 and A_2 independently are selected from the group consisting of a direct bond, a C_{1-10} alkylene group, a C_{2-10} alkenylene group and a C_{2-10} alkynylene group, wherein said groups are optionally substituted with one or more substituents selected from a

halogen atom, a hydroxy group, a linear or branched C_{1-4} alkyl group, a linear or branched a C_{1-4} alkoxy group, a C_{5-6} aryl group and a C_{3-7} cycloalkyl group,

- G is selected from the group consisting of a direct bond, a C_{3-10} mono- or bicyclic cycloalkyl group, a C_{5-14} mono- or bicyclic aryl group, a 3- to 14-membered saturated or unsaturated mono- or bicyclic heterocyclyl group having one or more heteroatoms selected from N, S and O, a 5- to 14-membered mono- or bicyclic heteroaryl group having one or more heteroatoms selected from N, S and O and a bicyclic ring system consisting of two monocyclic ring systems which are linked between each other by a covalent bond or by a –O- group, wherein said monocyclic ring systems are independently selected from a C_{3-8} cycloalkyl group, a C_{5-6} aryl group, a 3- to 8-membered saturated or unsaturated heterocyclyl group having one or more heteroatoms selected from N, S and O and a 5- to 6-membered heteroaryl group having one or more heteroatoms selected from N, S and O, wherein the cyclic groups independently are optionally substituted with one or more substituents selected from a halogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a carboxy, group, a cyano group, a nitro group, a hydroxy group, an oxo group, a trifluoromethyl group and a trifluoromethoxy group.
- L is selected from a direct bond, -O-, $-NR^c-$, -S-, -S(O)-, $-SO_2-$, $-NR^c(CO)-$, $-(CO)NR^c-$, $–NR^c(CO)(CH_2)_qO-$, $–O(CH_2)_q(CO)NR^c-$, $-NR^c(CO)(CH_2)_qNR^c(CO)-$, $–O(CH_2)_qNR^c-$, $–NR^c(CH_2)_qO-$, $–NR^c(CO)NR^d-$, -C(O)-, -C(O)O-, -OC(O)-, $-S(O)_2NR^c-$, $-NR^cS(O)_2-$, $-NR^cS(O)_2NR^d-$, $–C(O)NR^cS(O)_2-$ and $–S(O)_2NR^cC(O)-$, wherein R^c and R^d are independently selected from a hydrogen atom and a linear or branched C_{1-4} alkyl group and q has a value of 0, 1, 2, 3 or 4.
- R_1 represents a group of formula:



wherein R_2 and R_3 independently represent a hydrogen atom, a linear or branched C_{1-4} alkyl group or a (C_{5-6} aryl)-(C_{1-4})alkyl group, and R' represents a hydrogen atom or a linear or branched C_{1-4} alkyl group.

Typically, A_1 and A_2 independently are selected from the group consisting of C_{1-6} alkylene group, C_{1-6} alkenylene group and C_{1-6} alkynylene group, wherein said groups are optionally substituted with one or more substituents selected from a halogen atom, a hydroxy group, a C_{1-2} alkyl group, a C_{1-2} alkoxy group, a C_{5-6} aryl group and a C_{3-6} cycloalkyl group.

Preferably, A_1 and A_2 independently represent a C_{1-6} alkylene group optionally substituted with one or more substituents selected from a C_{1-2} alkyl group, a C_{1-2} alkoxy group and a phenyl group, preferably A_1 and A_2 independently represent a C_{1-4} alkylene group optionally substituted with one or two substituents selected from a methyl group and a methoxy group, more preferably substituted with one or two methyl groups.

Typically, X together with Y form the group -CH=CH- or $-CH_2$-O-. Preferably, X together with Y form the group –CH=CH-.

Typically, L is selected from the group consisting a direct bond, -O-, -NR^c-, -S-, -S(O)-, -SO_2-, -NR^c(CO)-, -(CO)NR^c-, –NR^c(CO)$(CH_2)_q$O-, –O$(CH_2)_q$(CO)NR^c-, -NR^c(CO)$(CH_2)_q$$NR^c$(CO)-, –O$(CH_2)_q$$NR^c$-, –$NR^c$$(CH_2)_q$O-, –$NR^c(CO)NR^d$-, -C(O)-, -C(O)O-, -OC(O)-, -$S(O)_2$$NR^c$-, -$NR^c$$S(O)_2$-, -$NR^c$$S(O)_2$$NR^d$-, –C(O)$NR^c$$S(O)_2$- and –$S(O)_2$$NR^c$C(O)-, wherein R^c and R^d are independently selected from a hydrogen atom and a linear or branched C_{1-4} alkyl group and q has a value of 0, 1, 2, 3 or 4.

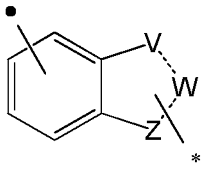
Preferably, L is selected from the group consisting of direct bond, -O-, -NR^c-, -NR^c(CO)-, -(CO)NR^c-, –NR^c(CO)$(CH_2)_q$O-, –O$(CH_2)_q$(CO)NR^c-, -NR^c(CO)$(CH_2)_q$$NR^c$(CO)-, –O$(CH_2)_q$$NR^c$-, –$NR^c$$(CH_2)_q$O-, –$NR^c(CO)NR^d$-, -C(O)-, -C(O)O-, -OC(O)- wherein R^c and R^d independently are selected from a hydrogen atom and a methyl group.

Preferably L is selected from a direct bond, -O-, -NR^c(CO)-, -(CO)NR^c-, –NR^c(CO)$(CH_2)_q$O-, –O$(CH_2)_q$(CO)NR^c- and -C(O)-, wherein R^c and R^d independently are selected from a hydrogen atom and a methyl group. More preferably L is selected from a direct bond, -NR^c(CO)-, -(CO)NR^c-,–O$(CH_2)_q$(CO)NR^c- and -C(O)-, being most preferably a direct bond, -NR^c(CO)- and -(CO)NR^c-, wherein R^c represents a hydrogen atom or a methyl group.

Typically G is selected from the group consisting of a direct bond, a C_{3-7} cycloalkyl group, a C_{5-14} mono- or bicyclic aryl group, a 3- to 14-membered saturated or unsaturated mono- or bicyclic heterocyclyl group having one or more heteroatoms selected from N, S and O, a 5- to 14-membered mono- or bicyclic heteroaryl group having one or more heteroatoms selected from N, S and O and a bicyclic ring system comprising two monocyclic ring systems which are linked between each other by a covalent bond or by a –O- group, wherein said monocyclic ring system is independently selected from the group consisting of a C_{3-8} cycloalkyl group and a C_{5-6} aryl group,wherein the cyclic groups independently are optionally substituted with one or more substituents selected from a halogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a carboxy, group, a cyano group, a nitro group, a hydroxy group, an oxo group, a trifluoromethyl group and a trifluoromethoxy group.

Preferably G is selected from the group consisting of a direct bond, a C_{3-7} cycloalkyl group, a C_5-C_6 aryl group, a 8- to 10-membered saturated or unsaturated bicyclic heterocyclyl group having one or more heteroatoms selected from N, S and O, a 8- to 10-membered bicyclic heteroaryl group having one or more heteroatoms selected from N, S and O, wherein the cyclic groups independently are optionally substituted with one or more substituents selected from a halogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a cyano group, a nitro group, a hydroxy group and an oxo group.

More preferably G is selected from the group consisting of a C_{3-7} cycloalkyl group, a C_5-C_6 aryl group, or a group of formula



Formula (Iwa)

wherein

- V, W and Z are independently selected from a –N-, -NH, -C-, -CH-, -S-, -O- and –C(O)-,

wherein the cyclic groups independently are optionally substituted with one or more substituents selected from a halogen atom, a C_{1-4} alkyl group and a C_{1-4} alkoxy group.,

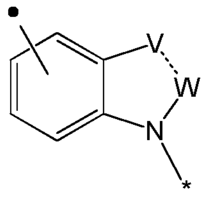
The dashed lines in formula (Iwa) represents a single bond or double bond depending on the nature of V, W and Z.

Typically W represents a –N-, -NH- or –C(O)- group, preferably W represents a –C(O)- group.

Typically, V represents a –N-, -NH-, -S- or -O- group, preferably V is a –N-, -NH- or –O- group..

In a preferred embodiment V represents a –N-, -NH-, or –O- group while W represents a –C(O)- group and Z is a –N- or –NH- group..

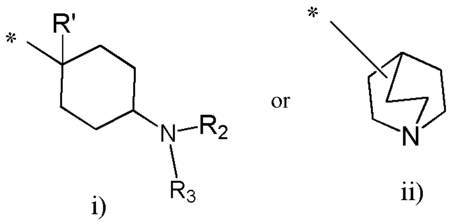
In a still preferred embodiment, G represents a phenylene group or a cylohexyl group or a group of formula



Formula (Iwb)

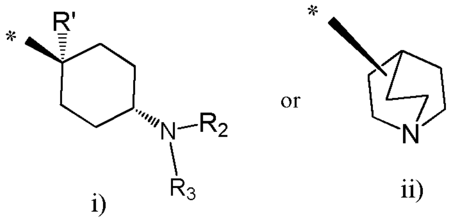
Wherein V represents a –N-, -NH- or –O- group and W represents a -C(O)- group, and wherein the cyclic groups are independently optionally substituted with one or two substituents selected from a chlorine atom, methyl group and methoxy group.

Typically, R_1 represents a group of formula:



wherein R', R_2 and R_3 independently represent a hydrogen atom or a C_{1-2} alkyl group..

Preferably R_1 represents a group of formula:



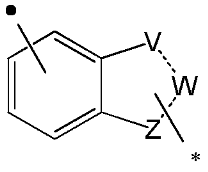
wherein R', R_2 and R_3 independently represent a hydrogen atom or a C_{1-2} alkyl group, preferably R', R_2 and R_3 independently represent a hydrogen atom or a methyl group, more preferably both R_2 and R_3 represent a hydrogen atom and R' represents a hydrogen atom or a methyl group.

More preferably, when R_1 represents the azabicyclo group of formula ii), the asymmetric carbon atom of said azabicyclo group to which the rest of the molecule is bounded, has the (R) configuration.

Typically R is selected from the group consisting of a hydrogen atom, a halogen atom or a hydroxy group, preferably R represents a hydrogen atom or a hydroxy group, more preferably R represents a hydrogen.

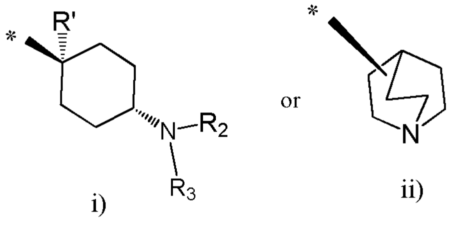
Typically n has a value of 1 or 2, preferably 1.

In one embodiment of the present invention A_1 and A_2 independently represent a direct bond, a C_{1-6} alkylene group optionally substituted with a methyl group, X together with Y form the group –CH=CH-, L is selected from the group consisting of a direct bond, --O-, -NR^c(CO)-, -NR^c(CO)O-, -O(CO)NR^c-, -NR^c(CO)-$(CH_2)_4NR^c$(CO)-, -NR^c(CO)-, and -(CO)NR^c-, wherein R^c represents a hydrogen atom or a methyl group, G represents a phenylene group or a cylohexyl group or a group of formula:



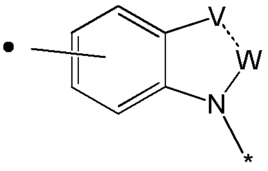
Formula (Iwa)

Wherein V and Z independently are selected from the group consisting of –N-, -NH-, -O- and –S-, and W represents a -N-, -NH-, -O-, or a –C(O)- group, and wherein the cyclic groups are independently optionally substituted with one or two substituents selected from a chlorine atom, methyl group and methoxy group, R^1 represents a group of formula:



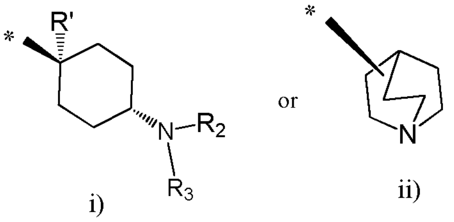
wherein both R_2 and R_3 are indenpendently selected from a hydrogen atom, a methyl group and a propyl group substituted with a phenyl group, R' represents a hydrogen atom or a methyl group, R represents a hydrogen atom and n has a value of 1.

In a still preferred embodiment, A_1 and A_2 independently represent a C_{1-4} alkylene group optionally substituted with one or two methyl groups, X together with Y form the group –CH=CH-, L is selected from the group consisting of a direct bond, -NR^c(CO)- and -(CO)NR^c-, wherein R^c represents a hydrogen atom or a methyl group, G represents a phenylene group or a cylohexyl group or a group of formula



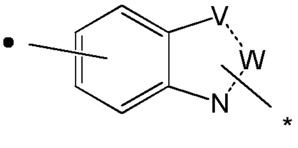
Formula (Iwb)

Wherein V represents a –N-, -NH- or -O- group and W represents a –C(O)- group, and wherein the cyclic groups are independently optionally substituted with one or two substituents selected from a chlorine atom, methyl group and methoxy group, R^1 represents a group of formula:



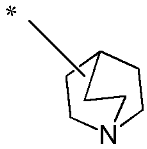
wherein preferably both R_2 and R_3 represent a hydrogen atom, R' represents a hydrogen atom or a methyl group, R represents a hydrogen atom and n has a value of 1.

In a still preferred embodiment, the present invention provides compounds of formula (I), wherein R represents a hydrogen atom and n has a value of 1, A_1 and A_2 independently represent a C_{1-5} alkylene group optionally substituted with one or two methyl groups, X together with Y form the group –CH=CH-, L is selected from the group consisting of a direct bond, -O-, -NR^c(CO)O-, -NR^c(CO)-, -(CO)NR^c-, -O(CH_2)(CO)NR^c-, wherein R^c represents a hydrogen atom or a methyl group, G represents a phenylene group or a pyridyl group or a group of formula



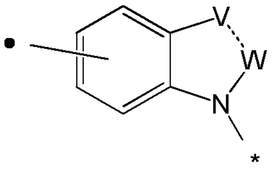
Formula (Iwc)

Wherein V represents a –CH-, –N-, -NH-, -S-, or -O- group and W represents a –CH-, –N=, -NH-, –C(O)- group, and wherein the cyclic groups are independently optionally substituted with one or two substituents selected from a chlorine atom, methyl group and methoxy group, R^1 represents a group of formula:



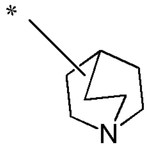
ii)

More preferably, in compounds of formula (I), R represents a hydrogen atom and n has a value of 1, A_1 and A_2 independently represent a C_{1-4} alkylene group optionally substituted with one or two methyl groups, X together with Y form the group –CH=CH-, L is selected from the group consisting of a direct bond, -NR^c(CO)- and -(CO)NR^c-, wherein R^c represents a hydrogen atom or a methyl group, G represents a phenylene group or a group of formula



Formula (Iwb)

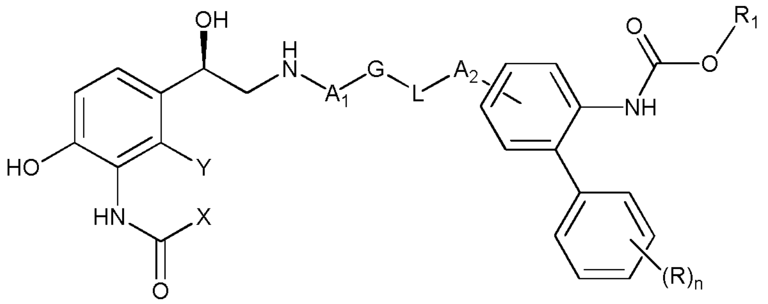
Wherein V represents a –N-, -NH-, or -O- group and W represents a –C(O)- group, and wherein the cyclic groups are independently optionally substituted with one or two substituents selected from a chlorine atom, methyl group and methoxy group, R^1 represents a group of formula:



ii)

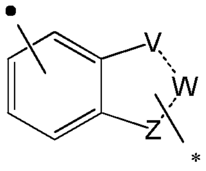
wherein preferably the the moiety attached to R^1 is in the 3- or the 4-position with respect to the quinuclidinyl radical.

In one embodiment, the present invention provides compounds of formula(I)



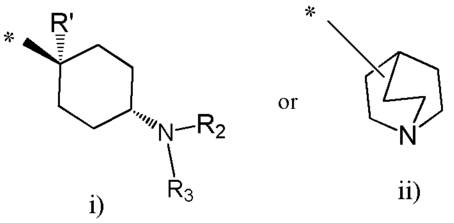
Formula (I)

Wherein, R represents a hydrogen atom and n has a value of 1, A_1 and A_2 independently represent a direct bond or a C_{1-6} alkylene group optionally substituted with a methyl group, X together with Y form the group –CH=CH- $-CH_2-CH_2-$ or $-CH_2-O-$, L is selected from the group consisting of a direct bond, -O-, $-NR^c(CO)O-$, $-O(CH_2)(CO)NR^c-$, $-NR^c(CO)-(CH_2)_4NR^c(CO)-$, $-(CH_2)_{(0-1)}NR^c(CO)-$, $-(CO)NR^c-$ and –NH(CO)NH-, wherein R^c represents a hydrogen atom or a methyl group, G represents a direct bond, a phenylene group, a pyridyl group, a cyclobutyl group, a cylohexyl group or a group of formula:



Formula (Iwa)

Wherein V and Z independently are selected from the group consisting of –N-, -NH-, -C-, -O- and –S-, and W represents a -N-, -NH-, -C-, or a –C(O)- group, and wherein the phenylene group, pyridyl group, cyclobutyl group, cylohexyl group and the group of formula (Iwa) are independently optionally substituted with one or two substituents selected from a chlorine atom, methyl group and methoxy group, R^1 represents a group of formula:



wherein R_2 and R_3 are indenpendently selected from a hydrogen atom, a methyl group, a hexyl group and a propyl group substituted with a phenyl group and R' represents a hydrogen atom or a methyl group.

Particular individual compounds of the invention include:

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]propyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[4-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]butyl}biphenyl-2-yl)carbamate
trans-4-(methylamino)cyclohexyl (4-{3-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]propyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]propyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]propyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-indol-1-yl]propyl}biphenyl-2-yl)carbamate,
(3*R*)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-({[(2*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2*H*)-yl]butyl}biphenyl-2-yl)carbamate,
trans-4-aminocyclohexyl (4-{3-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]propyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[3-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy]butyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy]butyl}biphenyl-2-yl)carbamate,
trans-4-aminocyclohexyl (4-{4-[4-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]butyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)ethyl]amino}methyl)-1,3-benzoxazol-2-yl]butyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[3-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]propyl}biphenyl-2-yl)carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[({[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino}carbonyl)oxy]-propyl}biphenyl-2-yl)carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-indol-1-yl]butyl}biphenyl-2-yl)carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzothiazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[4-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]propyl}biphenyl-2-yl)carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1,3-benzoxazol-2-yl]butyl}biphenyl-2-yl)carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2H-1,2,3-benzotriazol-2-yl]butyl}biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl (4-{4-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (5-{4-[4-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]butyl}biphenyl-2-yl)carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (5-{4-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl [4-(4-{[4-({[(2*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]propyl}biphenyl-2-yl)carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-({[(2R)-2-hydroxy-2-(5-hydroxy-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-8-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl (4-{3-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]propyl}biphenyl-2-yl)carbamate, trans-4-aminocyclohexyl (4-{4-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-indol-1-yl]butyl}biphenyl-2-yl)carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl (4-{5-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]pentyl}biphenyl-2-yl)carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[6-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]propyl}biphenyl-2-yl)carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{5-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]pentyl}biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl [4-(4-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl {4-[(6-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}hexyl)oxy]biphenyl-2-yl}carbamate,

trans-4-aminocyclohexyl (5-{4-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl (4-{4-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]butyl}biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl [5-(4-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl [4-(5-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-5-oxopentyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl [4-(4-{[4-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate, trans-4-aminocyclohexyl (4-{4-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxy-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate,

trans-4-[methyl(3-phenylpropyl)amino]cyclohexyl [4-(4-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl [4-(3-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-3-oxopropyl)biphenyl-2-yl]carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl [4-(4-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl (4-{4-[[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl](methyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl [4-(4-{[trans-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)cyclohexyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl [4-(4-{[4-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}propyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl (4-{4-[(5-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-5-oxopentyl)(methyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl (4-{3-[{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenoxy]acetyl}(methyl)amino]-propyl}biphenyl-2-yl)carbamate,

trans-4-amino-1-methylcyclohexyl [4-(3-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino} methyl)-5-methoxyphenyl]amino}-3-oxopropyl)biphenyl-2-yl]carbamate,

trans-4-amino-1-methylcyclohexyl [4-(3-{[trans-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)cyclohexyl]amino}-3-oxopropyl)biphenyl-2-yl]carbamate,

1-azabicyclo[2.2.2]oct-4-yl [4-(3-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino}-3-oxopropyl)biphenyl-2-yl]carbamate, trans-4-aminocyclohexyl (4-{2-[{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5methoxyphenoxy]acetyl}(methyl)amino]ethyl}biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl (4-{2-[({[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino}carbonyl)oxy]ethyl}biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl (4-{4-[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy]butyl}biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl [4-(4-{[trans-3-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)cyclobutyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl [4-(3-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxybenzoyl]amino}propyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl [4-(3-{4-[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy]phenyl}propyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl [4-(4-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)benzyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl [4-(4-{[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)pyridin-2-yl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

trans-4-[hexyl(methyl)amino]cyclohexyl [4-(4-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl [4-(4-{[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)pyridin-3-yl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

Trans-4-aminocyclohexyl (4-(3-(Trans-4-((((2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)cyclohexanecarboxamido)propyl)-biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl (4-{3-[({[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino} carbonyl)amino] propyl}biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl [4-(4-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxybenzoyl]amino}butyl)biphenyl-2-yl] carbamate,
1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]Carbamate,
trans-4-aminocyclohexyl (4-{3-[({[trans-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)cyclohexyl]oxy}acetyl)(methyl)amino] propyl}biphenyl-2-yl)carbamate,
1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate
trans-4-aminocyclohexyl (4-{4-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-benzimidazol-1-yl]butyl}biphenyl-2-yl)carbamate,
trans-4-amino-1-methylcyclohexyl [4-(4-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino} methyl)-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,
1-azabicyclo[2.2.2]oct-4-yl (4-{3-[{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenoxy]acetyl}(methyl)amino propyl}biphenyl-2-yl)carbamate,
1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxybenzoyl]amino}butyl)biphenyl-2-yl]carbamate and
1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)pyridin-3-yl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

and pharmaceutically acceptable salts and deuterated derivates thereof.

Of particular interest are the compounds:
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[4-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]butyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-indol-1-yl]propyl}biphenyl-2-yl)carbamate,

(3*R*)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-({[(2*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2*H*)-yl]butyl}biphenyl-2-yl)carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[3-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy]butyl}biphenyl-2-yl)carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy]butyl}biphenyl-2-yl)carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)ethyl]amino}methyl)-1,3-benzoxazol-2-yl]butyl}biphenyl-2-yl)carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[({[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino}carbonyl)oxy]-propyl}biphenyl-2-yl)carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-indol-1-yl]butyl}biphenyl-2-yl)carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[4-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]propyl}biphenyl-2-yl)carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2H-1,2,3-benzotriazol-2-yl]butyl}biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl (4-{4-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl [4-(4-{[4-({[(2*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-({[(2R)-2-hydroxy-2-(5-hydroxy-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-8-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{5-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]pentyl}biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl [4-(4-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl (4-{4-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]butyl}biphenyl-2-yl)carbamate,
trans-4-aminocyclohexyl (4-{4-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxy-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl [4-(4-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,
trans-4-aminocyclohexyl [4-(4-{[trans-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)cyclohexyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,
trans-4-aminocyclohexyl [4-(4-{[4-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}propyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,
trans-4-aminocyclohexyl (4-{3-[{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenoxy]acetyl}(methyl)amino]-propyl}biphenyl-2-yl)carbamate,
trans-4-aminocyclohexyl (4-{2-[({[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino}carbonyl)oxy]ethyl}biphenyl-2-yl)carbamate,
trans-4-aminocyclohexyl [4-(3-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxybenzoyl]amino}propyl)biphenyl-2-yl]carbamate,
trans-4-aminocyclohexyl [4-(4-{[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)pyridin-3-yl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,
Trans-4-aminocyclohexyl (4-(3-(trans-4-((((2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)cyclohexanecarboxamido)propyl)-biphenyl-2-yl)carbamate,
trans-4-aminocyclohexyl [4-(4-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxybenzoyl]amino}butyl)biphenyl-2-yl]carbamate,
1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

1-azabicyclo[2.2.2]oct-4-yl (4-{3-[{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenoxy]acetyl}(methyl)amino]propyl}biphenyl-2-yl)carbamate, and
1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxybenzoyl]amino}butyl)biphenyl-2-yl]carbamate,

and pharmaceutically acceptable salts and deuterated derivates thereof.

The invention is also directed to a compound of the invention as described herein for use in the treatment of the human or animal body by therapy.

According to another embodiment the present invention covers pharmaceutical compositions comprising at least a compound of the ivenntion, as hereinabove described, in admixture with pharmaceutically acceptable diluents or carriers.

In an embodiment of the present invention the pharmaceutical composition further comprises a therapeutically effective amount of one or more other therapeutic agents, in particular one or more drugs selected from the group consisting of corticosteroids, and PDE4 inhibitors.

It is also an embodiment of the present invention that the pharmaceutical composition is formulated for administration by inhalation.

The compounds of the present invention as hereinabove defined may also be combined with one or more other therapeutic agents, in particular one or more drugs selected from the group consisting of corticosteroids and PDE4 inhibitors, for simultaneous, separate or sequential use in the treatment of the human or animal body.

The invention is also directed to compounds of the present invention for use in the treatment of a pathological condition or disease associated with both β2 adrenergic receptor and muscarinic receptor activities such as a pulmonary disease. In particular the pulmonary disease is asthma or chronic obstructive pulmonary disease.

The pathological condition or disease can also be applied within the scope of the present invention to the treatment of a disease or condition selected from the group consisting of pre-term labor, glaucoma, neurological disorders, cardiac disorders, and inflammation, urological disorders such as urinary incontinence and gastrointestinal disorders such as irritable bowel syndrome or spastic colitis.

The invention is also directed to the use of compounds of the present invention for the manufacture of a medicament for the treatment of pathological condition or disease associated with one or both β2 adrenergic receptor and muscarinic receptor activities such as a pulmonary disease, in particular asthma or chronic obstructive pulmonary disease, pre-term labor, glaucoma, neurological disorders, cardiac disorders, inflammation, urological disorders and gastrointestinal disorders, preferably, asthma and chronic obstructive pulmonary disease.

The invention is also directed to a method of treating these diseases, which comprises administering a therapeutically effective amount of a pharmaceutical composition comprising a dual β2 adrenergic receptor agonists and muscarinic receptor antagonists according to the present invention. The method further comprises administering a therapeutically effective amount of one or more other therapeutic agent selected from the group consisting of a corticosteroid and a PDE4 inhibitor.

The invention is also directed to a method of modulating the activity of a β2 adrenergic and/or a M3 receptor, the method comprising stimulating a β2 adrenergic receptor and/or blocking a M3 receptor with a modulatory amount of compounds of the present invention.

The term "therapeutically effective amount" refers to an amount sufficient to effect treatment when administered to a patient in need of treatment.

The term "treatment" as used herein refers to the treatment of a disease or medical condition in a human patient which includes:

(a) preventing the disease or medical condition from occurring, i.e., prophylactic treatment of a patient;

(b) ameliorating the disease or medical condition, i.e., causing regression of the disease or medical condition in a patient;

(c) suppressing the disease or medical condition, i.e., slowing the development of the disease or medical condition in a patient; or

(d) alleviating the symptoms of the disease or medical condition in a patient.

The phrase "disease or condition associated with β2 adrenergic receptor and muscarinic activities" includes all disease states and/or conditions that are acknowledged now, or that are found in the future, to be associated with both β2 adrenergic receptor and muscarinic receptor activity. Such disease states include, but are not limited to, pulmonary diseases, such as asthma and chronic obstructive pulmonary disease (including chronic bronchitis and emphysema), as well as neurological disorders and cardiac disorders. β2 adrenergic receptor activity is also known to be associated with pre-term labor (see International Patent Application Publication Number WO 98/09632), glaucoma and some types of inflammation (see International Patent Application Publication Number WO 99/30703 and Patent Application Publication Number EP 1 078 629).

On the other hand M3 receptor activity is associated with gastrointestinal-tract disorders such as Irritable bowel syndrome (IBS) (see, for ex., US5397800), GI ulcers , spastic colitis (see, for ex., US 4556653); urinary-tract disorders such as urinary incontinence (see, for ex., J.Med.Chem., 2005, 48, 6597-6606), pollakiuria; motion sickness and vagally induced sinus bradycardia.

GENERAL SYNTHETIC PROCEDURES

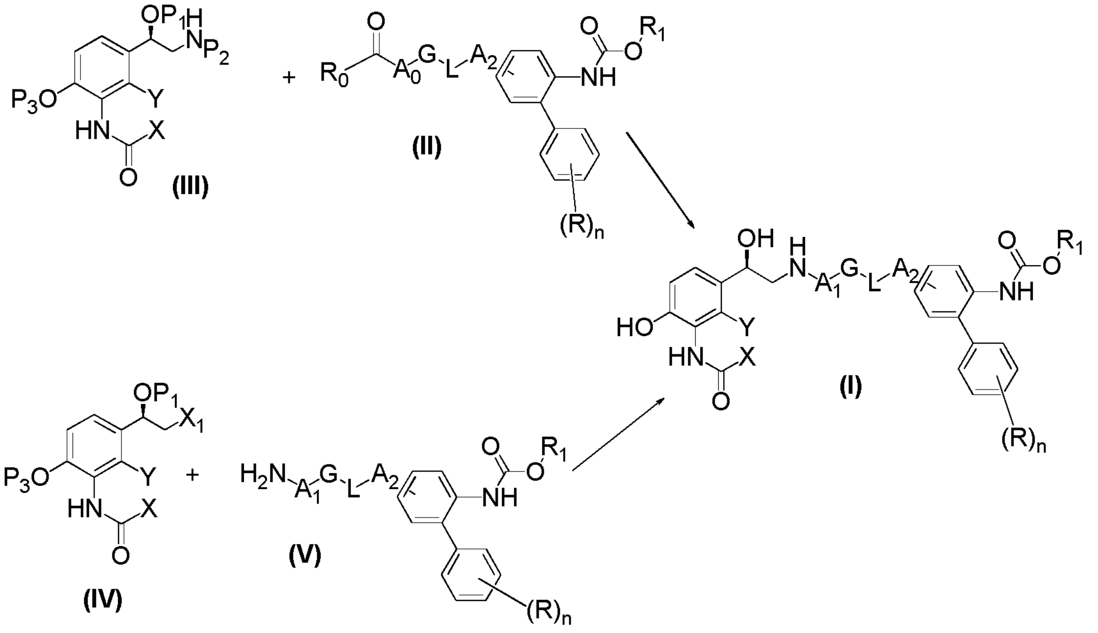
The compounds of the invention can be prepared using the methods and procedures described herein, or using similar methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given. Other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group, as well as suitable conditions for protection and deprotection, are well known in the art. For example, numerous protecting groups, and their introduction and removal are described in T. W. Greene and G. M. Wuts, Protecting Groups in Organic Synthesis, Third Edition, Wiley, New York, 1999, and references cited therein.

Processes for preparing compounds of the invention are provided as further embodiments of the invention and are illustrated by the procedures below.

One of the most convenient route for the preparation of compounds of formula (I) is depicted in Scheme 1.

Scheme 1

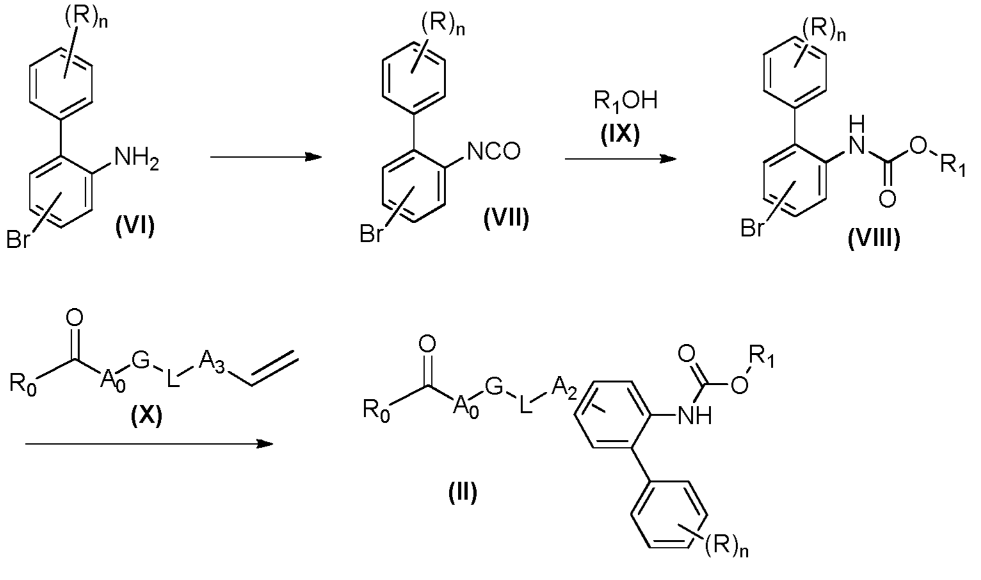


Compounds of formula **(I)** may be prepared by reacting intermediates of formula **(II)** wherein A_0 represents a group that together with the adjacent methylene newly formed affords the A_1 group, being R_0 hydrogen or lower alkyl group, with intermediates of formula **(III)** wherein X_1 represents a leaving group such as a halogen atom, P_1 and P_3 independently represent a hydrogen atom or a oxygen-protecting group such as a silyl or benzyl ether and P_2 represents a hydrogen atom or a nitrogen-protecting group such as for example a benzyl group. This reaction is best carried out in a solvent or mixture of solvents like THF, methanol, dichloromethane or DMSO at a temperature between 0°C and 60°C using a hydride like sodium borohydride or sodium triacetoxyborohydride as reducing agent.

Alternatively, compounds of formula **(I)** may also be prepared by reacting intermediates of formula **(V)** with intermediates of formula **(IV)** wherein X_1, P_1 and P_3 have the same meaning as disclosed above, following the same synthetic procedure; and subsequently removing whichever protecting group present in the intermediate to provide a compound of formula **(I)**. Such deprotection processes involve, for example, a desilylation process, by using triethylamine trihydrofluoride, TBAF, hydrogen chloride or other acidic reagents in an inert solvent like THF in a range of temperatures between 0°C and 50°C. The deprotection could also be carried out by a debenzylation process, for example, by hydrogenating the compound in the presence of a catalyst such as palladium on charcoal in an inert solvent like ethanol or THF or a mixture of solvents. This reaction is typically carried out at a hydrogen pressure between 10 and 60 psi and in a range of temperatures between room temperature and 50°C.

Intermediates of formula **(II)** may be prepared as depicted in Scheme 2, starting from known biphenylamine compounds **(VI)** trough subsequent conversion to isocyanates **(VII)** (using acylating agents like diphosgene) and carbamates **(VIII)** by treatment with an optionally protected amino alcohol **(IX)**. The bromocarbamates **(VIII)** are then coupled to an olefinic fragment **(X)** via, for ex., a Heck reaction, carried out in the presence of a palladium salt, a phosphine and a base, for ex., palladium acetate, tri-o-tolylphosphine and diisopropylethylamine in a solvent like acetonitrile or THF in a range of temperatures between room temperature and 120°C.

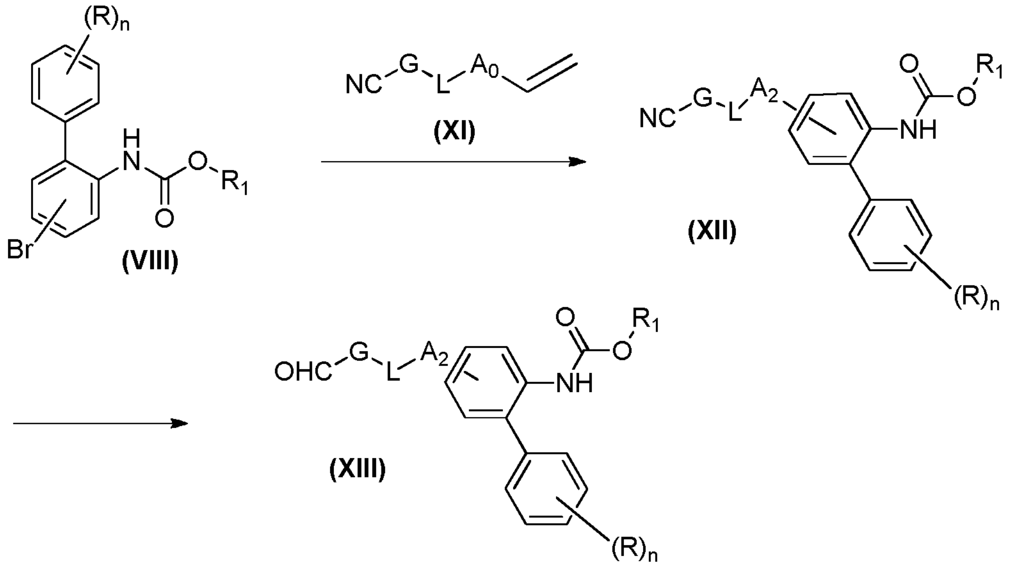
Scheme 2



In the particular case of R_0 being a hydrogen atom with A_1= $-CH_2-$ and G an aryl group, the corresponding intermediates **(XIII)** (having A_2 a number of methylene groups equal to that of A_3 plus 2) could also be prepared starting from the corresponding nitriles **(XII)** by coupling to the bromo derivatives **(VIII)** in a similar way as described previously and then converting the intermediates **(XII)** to the aldehydes **(XIII)** by reduction, for ex., with

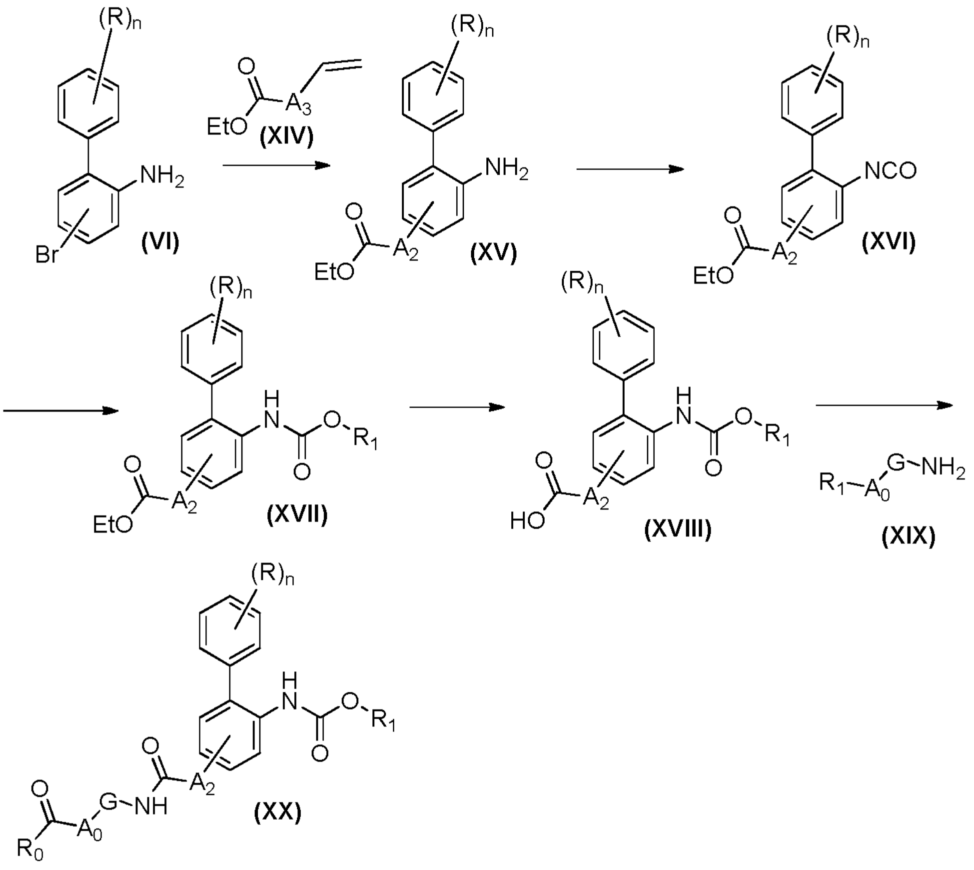
NiAl alloy in formic acid at a temperature between 50°C and 100°C, as shown in Scheme 3:

Scheme 3



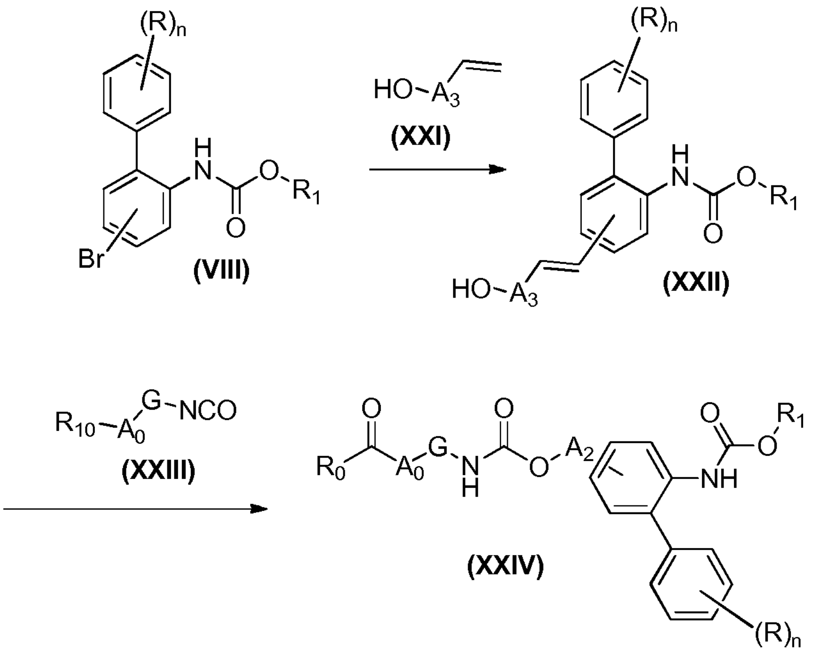
Still in other particular cases when G represents an aryl group and L the amide –NHCO- or carbamate –NHCOO- functionalities it is possible to prepare the intermediates (II) by building the G-L bond in the last step as disclosed in Schemes 4 and 5:

Scheme 4



By a similar coupling process as described above for compounds **(II)** followed by a hydrogenation of the carbon-carbon double bond –catalysed by palladium or palladium hydroxide- it is possible to access to intermediates **(XV)**, being A_2 and A_3 as defined earlier. The amines **(XV)** are then readily converted to the carbamates **(XVII)** through the isocyanates **(XVI)** according to the process described above for the preparation of intermediates **(VIII)**. After hydrolysis of the esters **(XVII)** to the carboxylic acids **(XVIII)**, carried out by the usual methods as treatment with aqueous alkali, a coupling step with an amine **(XIX)** follows to give intermediates **(XX)**. This process is catalysed by a coupling agent such as HATU and a tertiary amine as diisopropyl ethyl amine, in a solvent like THF or methylene chloride at a temperature between room temperature and the reflux temperature of the solvent. R_1 stands for the $-A_0$-CO-R_0 group or a rest that could revert to it through some simple transformation (for ex., a deprotection of a silylated alcohol plus an oxidation step to the carbonyl group).

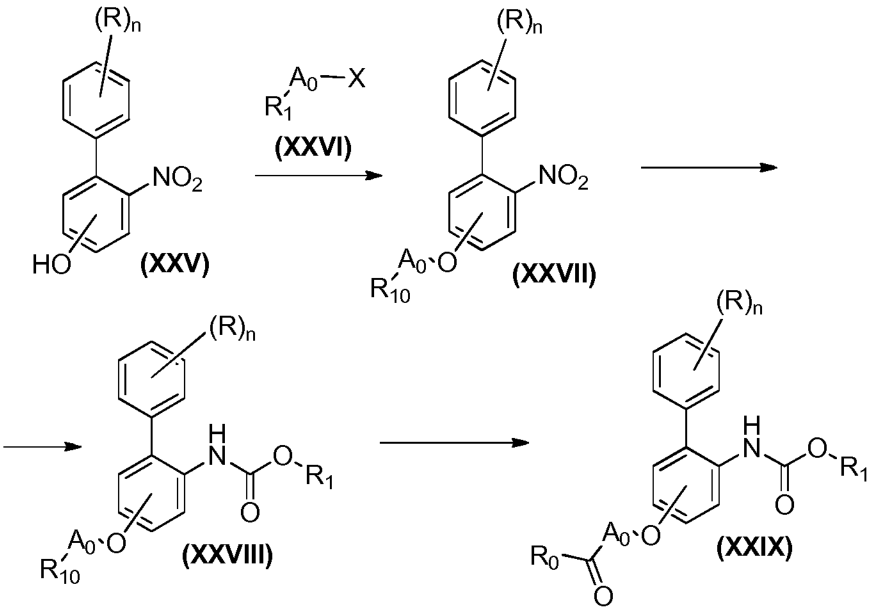
Scheme 5



Alcohols **(XXII)** are easily prepared from intermediates **(VIII)** via a coupling reaction Heck-type using the same conditions as described above for the synthesis of intermediates **(II)**. By reaction of **(XXII)** with isocyanates **(XXIII)** carbamates **(XXIV)** are obtained using a variety of inert solvents or with no solvent at all, in a range of temperatures from room temperature to 150°C. Here R_{10} has the same meaning as in intermediates **(XIX)** described above.

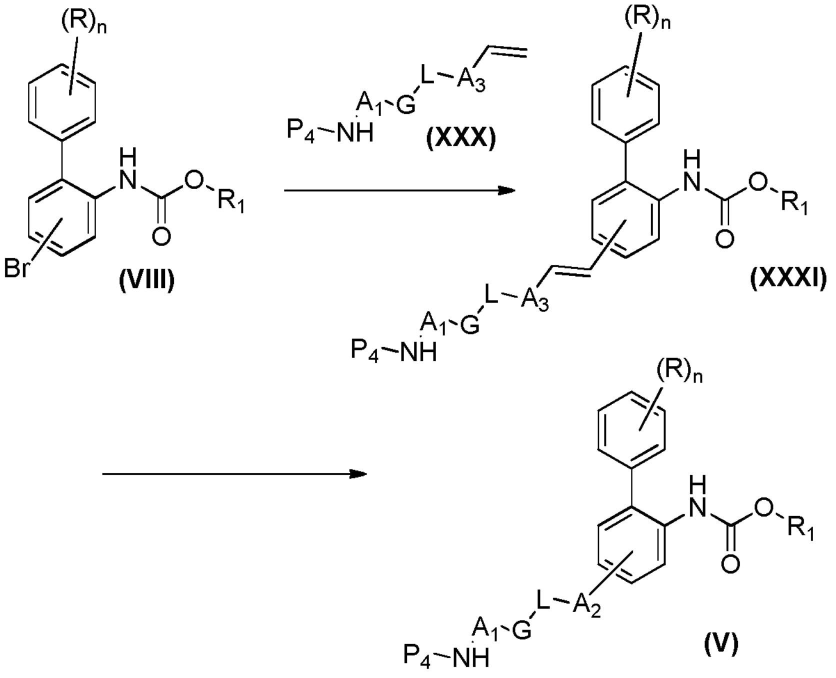
In the case of A_2 and G being direct bonds and L an oxygen atom it is possible to prepare the corresponding intermediates **(XXIX)** trough the process depicted in Scheme 6. By direct alkylation of the known phenols **(XXV)** with derivatives **(XXVI)** (being X a leaving group) in the presence of a base like an alkali carbonate or a tertiary amine intermediates **(XXVII)** are prepared (being R_1 as defined above). Compounds **(XXVII)** are in turn converted to carbamates **(XXVIII)** through subsequent reduction to anilines, conversion to isocyanates and reaction with alcohols as described in Scheme 2. After some deprotection and/or oxidation steps, intermediates **(XXIX)** are easily obtained.

Scheme 6



Finally, intermediates **(V)** from Scheme 2 can be prepared, *inter alia*, as depicted in Scheme 7, by coupling of shown intermediates **(VIII)** with compounds **(XXX)** in a Heck-type mode as described earlier to give protected amines **(XXXI)**, being A_3 as defined previously and P_4 an amino-protecting group. By subsequent deprotection (ex., hydrolysis of a BOC group in acidic medium) compounds **(V)** are thus synthesized.

Scheme 7



EXAMPLES

General. Reagents, starting materials, and solvents were purchased from commercial suppliers and used as received. Concentration refers to evaporation under vacuum using a Büchi rotatory evaporator. Reaction products were purified, when necessary, by flash chromatography on silica gel (40-63 μm) with the solvent system indicated or using preparative HPLC conditions (see bellow description of two systems used). Spectroscopic data were recorded on a Varian Gemini 300 spectrometer. HPLC-MS were performed on a Gilson instrument equipped with a Gilson piston pump 321, a Gilson 864 vacuum degasser, a Gilson liquid handler 215, a Gilson 189 injection module, a Gilson Valvemate 7000, a 1/1000 splitter, a Gilson 307 make-up pump, a Gilson 170 diode array detector, and a Thermoquest Finnigan aQa detector.

HPLC system 1:

C-18 reverse phase column silica from MERK, water/acetonitrile (without buffer) as eluents using a gradient from 0% to 100%.

Intermediate 1.

3-allyl-2-oxo-2,3-dihydro-1,3-benzoxazole-6-carbonitrile

To a solution of 2-oxo-2,3-dihydrobenzo[d]oxazole-6-carbonitrile (210mg, 1.31mmol, that product was synthesized by a mixture of 6-bromo-1,3-benzoxazol-2(3H)-one (2 g; 9.34 mmol) and copper (I) cyanide (1.42 g; 15.86 mmol) in 6 ml DMF, heated at 150°C under nitrogen atmosphere for 22 hr. After cooling to room temperature, a solution of 1.55 g (31.6 mmol) of sodium cyanide in 32 ml water is added followed by 1 hr stirring. The system is extracted thoroughly with ethyl acetate, washed with brine, dried and concentrated in vacuum) in acetonitrile (4mL) was added potassium carbonate (362mg, 2.62mmol) and potassium iodide (43mg, 0.26mmol) in a sealed tub. Then 3-bromoprop-1-ene (0.9mL, 10.4mmol) was added to the reaction. The mixture was stirred overnight at 70°C. The solid residue was filtrated through Celite. The solvent of the filtrate was removed under reduced pressure and the crude obtained was treated with ether giving a solid (150mg, 57% yield), which was used in the next step without further purification.

LRMS (m/z): 201 (M+1)+.

Intermediate 2

3-allyl-2-oxo-2,3-dihydro-1,3-benzoxazole-6-carbaldehyde

To a solution of 3-allyl-2-oxo-2,3-dihydro-1,3-benzoxazole-6-carbonitrile (Intermediate 1; 150mg, 0.75mmol) in 1.64mL of a solution of Formic Acid 75% was added Niquel-

Aluminium (121.9mg, 1.42mmol). The mixture was stirred overnight at 75°C. The solids were removed by filtration through Celite and the solvent was removed under reduced pressure. The crude obtained was treated with ether giving a solid (140mg; 92% yield), which was used in the next step without further purification.

LRMS (m/z): 204 (M+1)+.

Intermediate 3.

(4-bromobiphenyl-2-yl)amine

To a solution of 5-bromo-2-iodoaniline (500mg, 2.01mmol) in dioxane (20mL) was added potassium carbonate 4M (1.68mL). The mixture was purged into nitrogen. Phenylboronic acid (250mg, 2.01mmol) and norbornylphosphino Pd II (50mg) were added and the reaction was stirred for 3 hours at 110°C. The solvent was removed under reduced pressure and the crude was purified by column chromatography with silica gel, eluting with a mixture of hexane/ether to give the title compound as a solid (220mg, 53%).

LRMS (m/z): 249 (M+1)+.

Intermediate 4.

4-bromo-2-isocyanatobiphenyl

To a solution of triphosgene (143.4mg; 0.48mmol) in 1mL of toluene was added drop wise at 0°C a solution of (4-bromobiphenyl-2-yl)amine (Intermediate 3; 300mg, 1.21mmol) in 10mL of toluene. Once the addition is finished triethylamine (0.325mL, 2.42mmol) was added drop wise. The reaction mixture was stirred for 2 hours at room temperature. Cold pentane was added into the reaction mixture. The mixture was filtrated and the pentane of the filtrate was reduced under reduced pressure giving the title compound in solution of toluene, which was used in the next step without further manipulation.

LRMS (m/z): 289 (M+16)+; (aliquot in MeOH and detection of methylic ester).

Intermediate 5.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-bromobiphenyl-2-yl)carbamate

To a solution of Sodium (R)-quinuclidin-3-ol (3.61g, 24.1mmol), previously formed reflux-ing sodium with (R)-quinuclidin-3-ol at 125°C for 4 hours, in 10mL of toluene was added 4-bromo-2-isocyanatobiphenyl (6.63g, 21.1mmol). The mixture was stirred 2 hours at 120°C. The solvent was removed under reduced pressure and the crude was partitioned between ethyl acetate and hydrogen chloride 2N. The aqueous phase was neutralized and extracted with chloroform twice. The organic phase was dried, filtered and evaporated, giving the title compound as a solid (4.7g, 48%), which was used in the next step without further purification.

LRMS (m/z): 402;403 (M+1/M+2)+

Intermediate 6.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-3-(6-formyl-2-oxo-1,3-benzoxazol-3(2H)-yl)prop-1-en-1-yl]biphenyl-2-yl}carbamate

To a mixture of (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-bromobiphenyl-2-yl)carbamate (Intermediate 5; 400mg, 1mmol) and 3-allyl-2-oxo-2,3-dihydro-1,3-benzoxazole-6-carbaldehyde (Intermediate 2; 203mg, 1mmol) in acetonitrile (3 mL) in a sealed tub were added tri-o-tolylphosphine (304mg, 1mmol) and N,N-Diisopropylethylamine (0.34mL, 2mmol). The mixture was degassed under Argon during 5 minutes. Then palladium acetate (112mg, 0.5mmol) was added and the reaction mixture was stirred at 90°C for 6 hours. The crude was filtrated and the filtrate was evaporated to dryness. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2) to give the title compound as an oil (258mg, 49%).

LRMS (m/z): 524 (M+1)+

Intermediate 7.

(3R)-1-azabicyclo[2.2.2]oct-3-yl(4-{(1E)-3-[6-({[(2R)-2-{[tert-butyl(dimethyl) silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]prop-1-en-1-yl}biphenyl-2-yl)carbamate

To a mixture of (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-3-(6-formyl-2-oxo-1,3-benzoxazol-3(2H)-yl)prop-1-en-1-yl]biphenyl-2-yl}carbamate (258mg, 0.44mmol) and 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (175mg, 0.44mmol) (prepared according to preparation 8 from US20060035931) in 10mL of methanol was added DIEA (0.116mL, 0.97mmol) and sodium triacetoxyborohydride (282mg, 1.33mmol). The mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the crude obtained was suspended in chloroform, the solid was filtrated and the solvent was evaporated. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2) to give the title compound as a solid (255mg, 60%).

LRMS (m/z): 843 (M+1)+

Intermediate 8.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]propyl}biphenyl-2-yl)carbamate

To a solution of (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-3-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]prop-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 7; 79mg, 0.06mmol) in methanol (2mL) was added ammonium formate (77mg, 1.22mmol) and palladium hydroxide (8mg, 0.06mmol). The reaction mixture was stirred for 2hours at 80°C. The crude was filtrated and the solvent removed under reduced pressure. The crude obtained was partitioned between ethyl acetate and sodium bicarbonate. The organic phase was washed with water, dried, filtrated and the solvent was removed under reduced pressure, giving the title compound as a solid (10mg, 13%), which was used in the final step without further purification.

LRMS (m/z): 845 (M+1)+

EXAMPLE 1.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]propyl} biphenyl-2-yl)carbamate dihydrofluoride

To a solution of (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}-methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]propyl}biphenyl-2-yl)carbamate (10mg, 0.01mmol) in tetrahydrofurane (2 mL) was added triethylamine trihydrofluoride (18µL, 0.11mmol). The mixture was stirred overnight at room temperature. The solvent was removed and the residue was treated with acetonitrile giving a white solid as a title compound (8mg, 58%).

LRMS (m/z): 730 (M+1)+

1H NMR (300 MHz, dmso) δ 8.75 (s, 1H), 8.18 (d, 10.0 Hz, 1H), 7.56 – 7.01 (m, 10H), 6.93 (s, 1H), 6.49 (d, J = 10.0 Hz, 1H), 5.20 (bs, 1H), 4.60 (bs, 1H), 3.91 (m, 4H), 3.03 – 2.64 (m, 8H), 1.97 (m,, 3H), 1.67 (s, 4H), 1.12 (m, 3H).

Intermediate 9.

tert-butyl {2-[4-(but-3-en-1-yloxy)phenyl]ethyl}carbamate

To a solution of tert-butyl [2-(4-hydroxyphenyl)ethyl]carbamate (Intermediate 20 described in the patent WO2009/068177 A1; 1.7g, 7.29mmol) in dimethylformamide (15 mL) was added 4-bromobut-1-ene (0.88mL, 8.67mmol) and potassium carbonate

(1.21g, 8.75mmol). The mixture was stirred at 60°C overnight. The solvent was removed under reduced pressure and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane: ether to give the title compound as an oil (680mg, 16%).

LRMS (m/z): 292 (M+1)+

Intermediate 10.

(3R)-1-azabicyclo[2.2.2]oct-3-yl{4-[(1E)-4-(4-{2-[(tert-butoxycarbonyl)amino]ethyl}-phenoxy)but-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a solid (26mg, 39%) from tert-butyl {2-[4-(but-3-en-1-yloxy)phenyl]-ethyl}carbamate (27mg, 0.09mmol), (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-bromobiphenyl-2-yl)carbamate (Intermediate 5; 37mg, 0.09mmol), tri-o-tolylphosphine (40mg, 0.13mmol), N,N-Diisopropylethylamine (25μL, 0.14mmol) and palladium acetate (16mg, 0.07mmol) following the experimental procedure as described for Intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 612 (M+1)+

Intermediate 11.

(3R)-1-azabicyclo[2.2.2]oct-3-yl{4-[4-(4-{2-[(tert-butoxycarbonyl)amino]ethyl}-phenoxy)butyl]biphenyl-2-yl}carbamate

Obtained as a solid (367mg, 71%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-4-(4-{2-[(tert-butoxycarbonyl)amino]ethyl}phenoxy)but-1-en-1-yl]biphenyl-2-yl}carbamate (Inter-mediate 10; 490mg, 0.8mmol), ammonium formate (404mg, 6.41mmol) and palladium hydroxide (112mg, 0.8mmol) following the experimental procedure as described for Inter-mediate 8, the crude obtained was used without further purification.

LRMS (m/z): 614 (M+1)+

Intermediate 12.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[4-(2-aminoethyl)phenoxy]butyl}biphenyl-2-yl)carbamate

(3R)-1-azabicyclo[2.2.2]oct-3-yl{4-[4-(4-{2-[(tert-butoxycarbonyl)amino]ethyl}phenoxy) butyl]biphenyl-2-yl}carbamate (Intermediate 11; 367mg, 0.6mmol) was dissolved in 6mL of hydrogen chloride 4M in dioxane. The mixture was stirred for 2 hours at room temperature. The solvent was removed under reduced pressure and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:8:1) to give the title compound as a solid (255mg, 83%).

LRMS (m/z): 514 (M+1)+

Intermediate 13.

(3R)-1-azabicyclo[2.2.2]oct-3-yl{4-[4-(4-{2-[((2R)-2-[8-(benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl]-2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)amino]ethyl}-phenoxy)-butyl]biphenyl-2-yl}carbamate

To a solution of (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[4-(2-aminoethyl)phenoxy]butyl}-biphenyl-2-yl)carbamate (Intermediate 12; 255mg, 0.43mmol) in dimethylacetamide (4mL) was added 8-(benzyloxy)-5-((1R)-2-bromo-1-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-quinolin-2(1H)-one (US20040059116) (212mg, 0.43mmol), sodium bicarbonate (109mg, 1.3mmol) and sodium iodine (98mg, 0.65mmol). The mixture was stirred at 80°C for 24 hours. Water was poured into the reaction mixture and the solid was collected by filtration. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2) to give the title compound as a solid (132mg, 33%).

LRMS (m/z): 922 (M+1)+

Intermediate 14.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[4-(2-{[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]butyl}-biphenyl-2-yl)carbamate

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[4-(4-{2-[((2R)-2-[8-(benzyloxy)-2-oxo-1,2-dihydro-quinolin-5-yl]-2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)amino]ethyl}phenoxy) butyl]biphenyl-2-yl} carbamate (17mg, 0.02mmol) was dissolved in acetic acid (2mL) and submitted to an H-Cube® Continuous-flow Hydrogenation Reactor. Conditions used: Pressure: Full H2, Flow 1mL/min, T^a 40°C.

The solvent was removed under reduced pressure obtaining the diacetate salt of the title compound (10mg, 62%).

LRMS (m/z): 832 (M+1)+

EXAMPLE 2.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[4-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]butyl}biphenyl-2-yl)-carbamate di-hydrofluoride

Obtained as a white solid dihydrofluoride salt (24mg, 56%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[4-(2-{[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]butyl}biphenyl-2-yl)carbamate (45mg, 0.05mmol) and triethylamine trihydrofluoride (44µL, 0.27mmol) following the ex-perimental procedure as described for Example 1.

LRMS (m/z): 716 (M+1)+

1H NMR (300 MHz, dmso) δ 8.68 (s, 1H), 8.20 (d, J = 9.7 Hz, 1H), 7.45 – 7.27 (m, 4H), 7.22 (d, J = 3.5 Hz, 2H), 7.17 – 7.03 (m, 3H), 6.93 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.4 Hz, 2H), 6.52 (d, J = 9.7 Hz, 1H), 5.17 (s, 1H), 4.50 (s, 1H), 3.96 (s, 1H), 2.86 (bs, 3H), 2.67 (s, 7H), 2.46 – 2.33 (m, 2H), 1.82 (bs, 1H), 1.74 (bs, 3H), 1.58 (bs, 2H), 1.47 (bs, 2H), 1.29 (bs, 2H).

Intermediate 15.

trans-4-(methyltert-butylamino)cyclohexyl (4-bromobiphenyl-2-yl)carbamate

To a solution of 4-bromo-2-isocyanatobiphenyl (Intermediate 4; 227mg 0.91mmol) in 3mL of anhydridous toluene was added a solution of tert-butyl (trans-4-hydroxycyclohexyl)methylcarbamate methyl hidroxi (di-2-thienyl)acetate (Intermediate 3 from WO2011/141180A1; 278mg, 1.21mmol) in 5mL of anhydrous toluene. The reaction mixture was stirred at 75°C for 36 hours. The solvent was removed under reduced pressure and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane: Ether to give the title compound as a white solid (305mg, 66%).

LRMS (m/z): 504 (M+1)+

Intermediate 16.

4-(allylamino)-3-nitrobenzonitrile

To a solution of 4-amino-3-nitrobenzonitrile (5g, 0.03mol) in 12mL of dimethylacetamide was added 3-bromoprop-1-ene (2.67mL, 0.03mol) and potassium carbonate (21.1g, 0.153mol). The reaction mixture was stirred for 4 hours at 75°C. Water was added and the organic phase was extracted twice with ether. The organic phase was dried, filtered and the solvent was removed under reduced pressure. The crude obtained was crystallized with petroleum ether giving the title compound as an oil (5.8g, 93%).

LRMS (m/z): 204 (M+1)+

Intermediate 17.

4-(allylamino)-3-aminobenzonitrile

To a solution of 4-(allylamino)-3-nitrobenzonitrile (Intermediate 16; 140mg, 0.69mmol) in ethanol (8mL) was added Tin(II)chloride (777mg, 3.44mmol). The reaction mixture was stirred for 12h at 90°C. The solution was basified by sodium hydroxide 8N and the solu-tion obtained was filtrated through Celite. The filtrate was extracted twice with ethyl ace-tate, the organic layer was dried, filtered and the solvent was removed under reduced pressure. The title compound was obtained as a solid (94mg, 79%).

LRMS (m/z): 174 (M+1)+

Intermediate 18.

1-allyl-1H-1,2,3-benzotriazole-5-carbonitrile

To a suspension of 4-(allylamino)-3-aminobenzonitrile (Intermediate 17, 1.5g, 0.008mol) in hydrogen chloride (14.7mL, 4N) was added at 0°C and drop wise a solution of sodium nitrite (0.9g, 0.012mol) in water (7mL). The reaction mixture was stirred overnight at room temperature. Water was added into the mixture and the organics were extracted with dichloromethane. The organic layer was dried, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Dichloromethane: Ethanol (9:1) to give the title compound as a solid (1.2g, 75%).

LRMS (m/z): 185 (M+1)+

Intermediate 19.

trans-4-(methytert-butylamino)cyclohexyl {4-[(1E)-3-(5-cyano-1H-1,2,3-benzo-triazol-1-yl)prop-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a solid (132mg, 84%) from trans-4-(methyltert-butylamino)cyclohexyl (4-bromobiphenyl-2-yl)carbamate (Intermediate 15; 250mg, 0.5mmol), 1-allyl-1H-1,2,3-benzotriazole-5-carbonitrile (Intermediate 18; 91mg, 0.49mmol), tri-o-tolylphosphine (151mg, 0.5mmol), palladium acetate (55mg, 0.24mmol) and N,N-Diisopropylethylamine (0.17mL, 0.99mmol) following the experimental procedure as described for Intermediate 6 and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane: Ether.

LRMS (m/z): 607 (M+1)+

Intermediate 20.

trans-4-(methyltert-butylamino)cyclohexyl {4-[3-(5-cyano-1H-1,2,3-benzotriazol-1-yl)propyl]biphenyl-2-yl}carbamate

Obtained as a white solid (110mg, 81%) from trans-4-(methytert-butylamino)cyclohexyl {4-[(1E)-3-(5-cyano-1H-1,2,3-benzotriazol-1-yl)prop-1-en-1-yl]biphenyl-2-yl}carbamate (In-termediate 19; 132mg, 0.22mmol), palladium hydroxide (7mg, 0.05 mmol) and ammonium formate (109mg, 1.73 mmol) following the experimental procedure as described for Inter-mediate 8. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane: Ether.

LRMS (m/z): 609 (M+1)+

Intermediate 21.

trans-4-(methylamino)cyclohexyl {4-[3-(5-cyano-1H-1,2,3-benzotriazol-1-yl)propyl]biphenyl-2-yl}carbamate

A solution of trans-4-(methyltert-butylamino)cyclohexyl {4-[3-(5-cyano-1H-1,2,3-benzotriazol-1-yl)propyl]biphenyl-2-yl}carbamate (Intermediate 20; 35mg, 0.06mmol) in 3mL of hydrogen chloride (4N in dioxane) was stirred for 2 hours at room temperature. The solvent was removed under reduced pressure and the crude obtained was treated with ether giving a white solid as the title compound (29mg, 90%), which was used in the next step without further purification.

LRMS (m/z): 509 (M+1)+

Intermediate 22.

trans-4-(methylamino)cyclohexyl {4-[3-(5-formyl-1H-1,2,3-benzotriazol-1-yl)propyl]biphenyl-2-yl}carbamate

Obtained as a solid (110mg whit 60% of purity by HPLC, 73%) from trans-4-(methylamino)cyclohexyl {4-[3-(5-cyano-1H-1,2,3-benzotriazol-1-yl)propyl]biphenyl-2-yl}carbamate (Intermediate 21; 96mg, 0.17mmol), Formic Acid 75% and Niquel-Aluminium (15mg, 0.17mmol) following the experimental procedure as described for In-termediate 2. The crude obtained was used in the next step without further manipulation.

LRMS (m/z): 512 (M+1)+

Intermediate 23.

trans-4-(methylamino)cyclohexyl (4-{3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]propyl}biphenyl-2-yl)carbamate

Obtained as a solid (20mg, 24%) from trans-4-(methylamino)cyclohexyl {4-[3-(5-formyl-1H-1,2,3-benzotriazol-1-yl)propyl]biphenyl-2-yl}carbamate (90mg, 0.1mmol), -((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate

(39mg, 0.1mmol) (prepared according to preparation 8 from US20060035931), DIEA (26µ, 0.15mmol) and sodium triacetoxyborohydride (63mg, 0.3mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography in reverse phase using as eluents water and acetonitrile.

LRMS (m/z): 831 (M+1)+

EXAMPLE 3.

trans-4-(methylamino)cyclohexyl (4-{3-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]propyl} biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a white solid (3mg, 37%) from trans-4-(methylamino)cyclohexyl (4-{3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]propyl}biphenyl-2-yl)carbamate (Inter-mediate 23; 10mg, 0.01mmol) and triethylamine trihydrofluoride (10µL, 0.06mmol) follow-ing the experimental procedure as described for Example 1.

LRMS (m/z):716 (M+1)+

1H NMR (300 MHz, cd3od) δ 8.30 (d, J = 9.8 Hz, 1H), 8.12 (s, 1H), 7.90 (s, 1H), 7.83 (d, J = 8.7 Hz, 1H), 7.69 (s, 1H), 7.46 – 7.29 (m, 2H), 7.24 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 7.9 Hz, 1H), 7.09 (bs, 1H), 6.99 (d, J = 8.3 Hz, 1H), 6.59 (d, J = 9.5 Hz, 1H), 5.38 (bs, 1H), 4.61 (s, 2H), 4.56 – 4.41 (m, 1H), 4.34 (s, 1H), 3.56 – 3.41 (m, 2H), 3.26 – 3.04 (m, 3H), 2.68 (bs, 2H), 2.41 (s, 2H), 2.07 (m, 3H), 1.41 (s, 2H).

Intermediate 24.

1-allyl-1H-1,2,3-benzotriazole-5-carbaldehyde

Obtained as a solid (0.45g, 35%) from 1-allyl-1H-1,2,3-benzotriazole-5-carbonitrile (Inter-mediate 18; 1g, 0.005mol), Formic Acid 75 and Niquel-Aluminium (0.72g, 0.008mol) fol-lowing the experimental procedure as described for Intermediate 2. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane: Ether.

LRMS (m/z): 188 (M+1)+

Intermediate 25.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-3-(5-formyl-1H-1,2,3-benzotriazol-1-yl)prop-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a solid (165mg, 58%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-bromobiphenyl-2-yl)carbamate (Intermediate 5; 200mg, 0.39mmol), 1-allyl-1H-1,2,3-benzotriazole-5-carbaldehyde (Intermediate 24; 180mg, 0.48mmol), tri-o-tolylphosphine (120mg, 0.39mmol), N,N-Diisopropylethylamine (0.13mL, 0.79mmol) and palladium ace-tate (65mg, 0.20mmol) following the experimental procedure as described for Intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:8:1)

LRMS (m/z): 508 (M+1)+

Intermediate 26.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]-oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]prop-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a foam (113mg, 51%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-3-(5-formyl-1H-1,2,3-benzotriazol-1-yl)prop-1-en-1-yl]biphenyl-2-yl}carbamate (Intermediate 25; 165mg, 0.23mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (76mg, 0.23mmol) (prepared according to preparation 8 from US20060035931), DIEA (60µL, 0.34mmol) and sodium triacetoxyborohydride (144mg, 0.38mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:8:1)

LRMS (m/z): 827 (M+1)+

Intermediate 27.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]propyl}biphenyl-2-yl)carbamate

Obtained as a yellow solid (85mg, 85%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]prop-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 26; 113mg, 0.12mmol), ammonium formate (143mg, 2.32mmol) and palla-dium hydroxide (14mg, 0.1mmol) following the experimental procedure as described for Intermediate 8. The crude obtained was used in the next step without further purification.

LRMS (m/z): 829 (M+1)+

EXAMPLE 4.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]propyl}biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a white solid (57mg, 88%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]propyl}biphenyl-2-yl)carbamate (85mg, 0.08mmol) and triethylamine trihydrofluoride (83µL, 0.51mmol) following the experimental procedure as described for Example 1.

LRMS (m/z):754 (M+1)+

1H NMR (300 MHz, dmso) δ 8.70 (s, 1H), 8.13 (d, J = 9.8 Hz, 1H), 7.99 (s, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.39 (bs, 3H), 7.22 (s, 1H), 7.10 (bs, 2H), 6.90 (d, J = 8.1 Hz, 1H), 6.43 (d, J = 9.5 Hz, 1H), 5.13 (s, 1H), 4.74 (s, 1H), 4.52 (s, 1H), 3.98 (s, 2H), 2.68 (bs, 6H), 2.25 (s, 3H), 1.84 (s, 2H), 1.59 (s, 4H), 1.32 (s, 2H).

Intermediate 28.

1-allyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carbonitrile

To a solution of 4-(allylamino)-3-aminobenzonitrile (Intermediate 17; 97mg, 0.54mmol) in dichloromethane (10mL) was added triphosgene (80mg, 0.27mmol) and triethylamine (0.113mL, 0.81mmol). The reaction mixture was stirred at room temperature overnight. The organic layer was washed with water and bicarbonate, dried, filtered and the solvent was removed under reduced pressure. The title compound was obtained as a gum (90mg, 66%), and it was used in the next step without further manipulation.

LRMS (m/z): 201 (M+1)+

Intermediate 29.

1-allyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carbaldehyde

Obtained as a solid (280mg, 25%) from 1-allyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carbonitrile (Intermediate 28; 600mg, 0.003mol), formic acid 75% and niquel aluminium (283mg, 0.003mol) following the experimental procedure as described for Intermediate 2. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane: ethanol

LRMS (m/z): 203 (M+1)+

Intermediate 30.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-3-(5-formyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)prop-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a solid (590mg, 65%) from 1-allyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carbaldehyde (Intermediate 29; 280mg, 1.38mmol), (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-bromobiphenyl-2-yl)carbamate (Intermediate 5; 650mg, 1.62mmol), tri-o-tolylphosphine (120mg, 0.39mmol), N,N-Diisopropylethylamine (0.13mL, 0.79mmol) and palladium ace-tate (65mg, 0.20mmol) following the experimental procedure as described for Intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:8:1).

LRMS (m/z): 523 (M+1)+

Intermediate 31.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]-oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]prop-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a solid (416mg, 52%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-3-(5-formyl-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)prop-1-en-1-yl]biphenyl-2-yl}carbamate (Intermediate 30, 590mg, 0.9mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (400mg, 1.01mmol) (prepared according to preparation 8 from US20060035931), DIEA (0.137mL, 0.26mmol) and sodium triacetoxyborohydride (700mg, 3.3mmol) following the experimental procedure as de-scribed for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:8:1)

LRMS (m/z): 842 (M+1)+

Intermediate 32.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]propyl}biphenyl-2-yl)carbamate

Obtained as a solid (194mg, 49%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]prop-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 31; 415mg, 0.417mmol), ammonium formate (570mg, 9.04mmol) and palladium hydroxide (45mg, 0.32mmol) following the experimental proce-dure as described for Intermediate 8. The crude obtained was used in the next step with-out further purification.

LRMS (m/z): 844 (M+1)+

EXAMPLE 5.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]propyl}biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a white solid (123mg, 62%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]propyl}biphenyl-2-yl)carbamate (198mg, 0.23mmol) and triethylamine trihydrofluoride (187µL, 1.17mmol) following the experimental procedure as described for Example 1.

LRMS (m/z):769 (M+1)+

1H NMR (300 MHz, dmso) δ 10.88 (s, 1H), 8.67 (s, 1H), 8.10 (d, J = 10.0 Hz, 1H), 7.36 (bs, 4H), 7.27 – 6.80 (m, 8H), 6.47 (d, J = 9.8 Hz, 1H), 5.11 (bs, 1H), 4.50 (bs, 1H), 3.60 (s, 2H), 3.04 (s, 2H), 2.80 – 2.55 (m, 7H), 2.42 (s, 2H), 1.95 (s, 2H), 1.78 (bs, 2H), 1.56 (s, 2H), 1.46 (s, 2H), 1.30 (s, 1H).

Intermediate 33.

1-allyl-1H-indole-5-carbaldehyde

To a solution of 1H-indole-5-carbaldehyde (200mg, 1.38mmol) in dimethylformamide (2mL) was added at 0°C sodium hydride (61mg, 2.54mmol) and the mixture was allowed to stirred for 30 minutes at 0°C. Then 3-bromoprop-1-ene (0.180mL, 2.08mmol) was added into the reaction mixture. The reaction was stirred overnight at room temperature. Water was added and the organics were extracted with hexane. The organic layer was dried, filtered and the solvent was removed under reduced pressure giving the title com-pound as an oil (251mg, 92%), which was used in the next step without further purifica-tion.

LRMS (m/z):186 (M+1)+

Intermediate 34.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-3-(5-formyl-1H-indol-1-yl)prop-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a solid (278mg, 78%) from 1-allyl-1H-indole-5-carbaldehyde (Intermediate 33; 110mg, 0.59mmol), (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-bromobiphenyl-2-yl)carbamate (Intermediate 5; 300mg, 0.59mmol), tri-o-tolylphosphine (180mg, 0.59mmol), N,N-Diisopropylethylamine (0.2mL, 1.15mmol) and palladium acetate

(65mg, 0.20mmol) fol-lowing the experimental procedure as described for Intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloro-form:methanol:ammonium (40:8:1).

LRMS (m/z): 506 (M+1)+

Intermediate 35.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]-oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-indol-1-yl]prop-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a solid (164mg, 38%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-3-(5-formyl-1H-indol-1-yl)prop-1-en-1-yl]biphenyl-2-yl}carbamate (275mg, 0.47mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (188mg, 0.48mmol) (prepared according to preparation 8 from US20060035931), DIEA (0.13mL, 0.75mmol) and sodium triacetoxyborohydride (300mg, 1.42mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloro-form:methanol:ammonium (40:4:0.2)

LRMS (m/z): 825 (M+1)+

Intermediate 36.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-indol-1-yl]propyl}biphenyl-2-yl)carbamate

Obtained as a solid (123mg, 47%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-indol-1-yl]prop-1-en-1-yl}biphenyl-2-yl)carbamate (287mg, 0.31mmol), ammonium formate (197mg, 3.12mmol) and palladium hydroxide (23mg, 0.16mmol) following the experimental procedure as described for Intermediate 8. The crude obtained was purified by column chromatography with silica gel, eluting with a mix-ture of chloroform:methanol:ammonium (40:4:0.2)

LRMS (m/z): 827 (M+1)+

EXAMPLE 6.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-indol-1-yl]propyl}biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a solid (56mg, 52%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]-amino}methyl)-1H-indol-1-yl]propyl}biphenyl-2-yl)carbamate (123mg, 0.15mmol) and triethylamine trihydrofluoride (187µL, 1.17mmol) following the experimental procedure as described for Example 1.

LRMS (m/z):712 (M+1)+

1H NMR (300 MHz, dmso) δ 8.83 (s, 1H), 8.23 (d, J = 9.9 Hz, 1H), 7.67 (bs1H), 7.73 – 7.42 (m, 5H), 7.41 – 7.17 (m, 4H), 7.08 (bs, 2H), 6.62 – 6.47 (m, 2H), 6.45 (d, J=9.98Hz, 1H), 5.30 (bs, 1H), 4.65 (bs, 1H), 4.37-4.34 (m, 2H), 4.10 (bs, 2H), 3.20 (bs, 2H), 2.93 (s, 1H), 2.79 (bs, 3H), 2.57 – 2.28 (m, 2H), 1.98 (bs, 2H), 1.72 (bs, 4H), 1.43 (bs, 2H), 1.19 (bs, 2H).

Intermediate 37.

3-but-3-en-1-yl-2-oxo-2,3-dihydro-1,3-benzoxazole-6-carbonitrile

To a solution of 2-oxo-2,3-dihydrobenzo[d]oxazole-6-carbonitrile (see experimental in In-termediate 1;1.2g, 0.0075mol) in dimethylformamide (10mL) was added 4-bromobut-1-ene (1.21g, 0.009mol) and potassium carbonate (1.24g, 0.009mol). The reaction mixture was stirred at 60°C for 3 hours. The crude was filtered and the filtrate was evaporated. The crude obtained was treated with ether and hexane, giving a solid which was filtered. The solid obtained (1.02g, 63%) was the desired product and it was used in the next step without further purification.

LRMS (m/z):215 (M+1)+

Intermediate 38.

3-but-3-en-1-yl-2-oxo-2,3-dihydro-1,3-benzoxazole-6-carbaldehyde

Obtained as a solid (280mg, 22%) from 3-but-3-en-1-yl-2-oxo-2,3-dihydro-1,3-benzoxazole-6-carbonitrile (Intermediate 37; 1g, 0.004mol), Formic Acid 75% and Niquel-Aluminium (440mg, 0.005mol) following the experimental procedure as described for In-termediate 2. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane:dicloromethane.

LRMS (m/z): 218 (M+1)+

Intermediate 39.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-4-(6-formyl-2-oxo-1,3-benzoxazol-3(2H)-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a foam (650mg, 83%) from 3-but-3-en-1-yl-2-oxo-2,3-dihydro-1,3-benzoxazole-6-carbaldehyde (Intermediate 38; 270mg, 1mmol) (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-bromobiphenyl-2-yl)carbamate (Intermediate 5; 270mg, 1.25mmol), tri-o-tolylphosphine (303mg, 1mmol), N,N-Diisopropylethylamine (0.347mL, 2mmol) and palladium acetate (164mg, 0.5mmol) following the experimental procedure as described for Intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:8:1).

LRMS (m/z): 538 (M+1)+

Intermediate 40.

(3R)-1-azabicyclo[2.2.2]oct-3-yl(4-{(1E)-4-[6-({[(2R)-2-{[tert-butyl(dimethyl) silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a solid (200mg, 23%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-4-(6-formyl-2-oxo-1,3-benzoxazol-3(2H)-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate (Intermediate 39; 650mg, 1.21mmol, 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (331mg, 0.99mmol) (prepared according to prepara-tion 8 from US20060035931), DIEA (0.25mL, 1.49mmol) and sodium triacetoxyboro-hydride (630mg, 2.97mmol) following the experimental procedure as described for Inter-mediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2)

LRMS (m/z): 857 (M+1)+

Intermediate 41.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[6-({[(2R)-2-{[tert-butyl(dimethyl) silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a solid (200mg, 84%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 40; 200mg, 0.23mmol), ammonium formate (294mg, 4.67mmol) and palladium hydroxide (26mg, 0.19mmol) following the experimental proce-dure as described for Intermediate 8. The crude obtained was used in the next step with-out further purification.

LRMS (m/z): 859 (M+1)+

EXAMPLE 7.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl} biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a solid (95mg, 55%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 41; 200mg, 0.23mmol) and triethylamine trihydrofluoride (186µL, 1.17mmol) following the experimental procedure as described for Example 1.

LRMS (m/z): 744 (M+1)+

1H NMR (300 MHz, dmso) δ 8.64 (s, 1H), 8.14 (bs, 1H), 7.5-7.1 (m 11H), 6.90 (s, 1H), 6.47 (bs, 1H), 5.05 (bs, 1H), 4.47 (bs, 1H), 4..01-3.8 (m,, 5H), 3.15 – 2.86 (m, 2H), 2.63 (s, 4H), 2.41 – 2.21 (m, 1H), 2.07 (s, 2H), 1.67 (bs, 5H), 1.17 (bs, 4H).

Intermediate 42.

benzyl (trans-4-hydroxycyclohexyl)carbamate

Obtained as a white solid (5.27g, 84%) from trans-4-aminocyclohexanol (3.8g, 0.025mol), benzyl chloroformiate (3.9mL, 0.027mL) and sodium carbonate (5.8g, 0.054mol) following the experimental procedure as described in J.Med.Chem., 1987, 30,2,313. The crude ob-tained was used in the next step without further purification.

LRMS (m/z): 250 (M+1)+

Intermediate 43.

trans-4-benzyl-aminocyclohexyl (4-bromobiphenyl-2-yl)carbamate

To a solution of 4-bromo-2-isocyanatobiphenyl (1.88g, 0.007mol) in toluene (5mL) was added benzyl (trans-4-hydroxycyclohexyl)carbamate (Intermediate 42; 2.27g, 0.009mol) in toluene (20mL). The reaction mixture was stirred for 7 hours at 90°C. The solvent was removed under reduced pressure giving an oil, which was purified by column chromatog-raphy with silica gel, eluting with a mixture of Hexane:ether. The title compound was ob-tained as a white solid (1.7g, 47%)

LRMS (m/z): 524 (M+1)+

Intermediate 44.

trans-4-benzylaminocyclohexyl {4-[(1E)-3-(5-formyl-1H-1,2,3-benzotriazol-1-yl)prop-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a solid (500mg, 59%) from trans-4-tert-butylaminocyclohexyl (4-bromobiphenyl-2-yl)carbamate (Intermediate 43; 700mg, 1.34mmol), 1-allyl-1H-1,2,3-benzotriazole-5-carbaldehyde (Intermediate 24; 455mg, 1.34mmol), tri-o-tolylphosphine (407mg, 1.34mmol), N,N-Diisopropylethylamine (0.46mL, 2.67mmol) and palladium ace-tate (221mg, 0.67mmol) following the experimental procedure as described for Intermedi-ate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane:ether.

LRMS (m/z): 630 (M+1)+

Intermediate 45.

trans-4-benzylaminocyclohexyl (4-{(1E)-3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]-oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]prop-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a solid (150mg, 20%) from trans-4-tert-butylaminocyclohexyl {4-[(1E)-3-(5-formyl-1H-1,2,3-benzotriazol-1-yl)prop-1-en-1-yl]biphenyl-2-yl}carbamate (Intermediate 44; 500mg, 0.79mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (265mg, 0.79mmol) (prepared according to prepara-tion 8 from US20060035931), DIEA (0.2mL, 1.19mmol) and sodium triacetoxyborohydride (505mg, 2.38mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2)

LRMS (m/z): 949 (M+1)+

Intermediate 46.

trans-4-aminocyclohexyl (4-{3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]propyl}biphenyl-2-yl)carbamate

Obtained as a solid (150mg, 99%) from trans-4-benzylaminocyclohexyl (4-{(1E)-3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)-ethyl]-amino}methyl)-1H-1,2,3-benzotriazol-1-yl]prop-1-en-1-yl}biphenyl-2-yl)carbamate (150mg, 0.16mmol), ammonium formate (199mg, 3.16mmol) and palladium hydroxide (18mg, 0.13mmol) following the experimental procedure as described for Intermediate 8. The crude obtained was used in the next step without further purification.

LRMS (m/z): 817 (M+1)+

EXAMPLE 8.

trans-4-aminocyclohexyl (4-{3-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]propyl} biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a white solid (23mg, 17%) from trans-4-aminocyclohexyl (4-{3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}-methyl)-1H-1,2,3-benzotriazol-1-yl]propyl}biphenyl-2-yl)carbamate (150mg, 0.18mmol) and triethylamine trihydrofluoride (186μL, 1.17mmol) following the experimen-tal procedure as described for Example 1. The crude obtained was purified by reversed phase using as eluents Methanol and Water.

LRMS (m/z): 702 (M+1)+

1H NMR (300 MHz, cd3od) δ 8.28 (d, J = 9.8 Hz, 1H), 8.10 (s, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.7 Hz, 1H), 7.47 – 7.26 (m, 6H), 7.20 (dd, J = 20.7, 8.0 Hz, 2H), 7.03 (dd, J = 20.4, 7.8 Hz, 2H), 6.58 (d, J = 9.9 Hz, 1H), 5.36 (s, 1H), 4.79 (s, 2H), 4.49 (s, 1H), 4.31 (s, 2H), 3.34 (s, 2H), 3.10 (bs, 2H), 2.77 – 2.60 (m, 2H), 2.39 (s, 2H), 2.00 (bs, 2H), 1.55 – 1.22 (m, 4H).

Intermediate 47.

3-(but-3-en-1-yloxy)benzaldehyde

To a solution of 3-hydroxybenzaldehyde (2.5g, 0.02mol) in dimethylacetamide (20mL) was added 4-bromobut-1-ene (2.19mL, 0.022mol) and cesium carbonate (10g, 0.03mol). The mixture was stirred at 60°C for 48hours in a sealed tub. The precipitate was filtrated and washed with ethyl acetate. The organic layer was washed with water and the organic sol-vent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether, and the title com-pound was obtained as a solid (2.1g, 58%).

LRMS (m/z): 177 (M+1)+

Intermediate 48.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-4-(3-formylphenoxy)but-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a solid (207mg, 88%) from 3-(but-3-en-1-yloxy)benzaldehyde (Intermediate 47; 79mg, 0.45mmol), (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-bromobiphenyl-2-yl)carbamate (Intermediate 5; 225mg, 0.56mmol), tri-o-tolylphosphine (136mg, 0.45mmol), N,N-Diisopropylethylamine (156μL, 0.9mmol) and palladium acetate (74mg, 0.22mmol) following the experimental procedure as described for intermediate

6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 497 (M+1)+

Intermediate 49.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[3-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy]but-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a solid (160mg, 41%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-4-(3-formylphenoxy)but-1-en-1-yl]biphenyl-2-yl}carbamate (Intermediate 48; 207mg, 0.42mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (139mg, 0.42mmol) (prepared according to preparation 8 from US20060035931), DIEA (0.1mL, 0.63mmol) and sodium triacetoxyborohydride (265mg, 1.25mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mix-ture of chloroform:methanol:ammonium (40:4:0.2)

LRMS (m/z): 816 (M+1)+

Intermediate 50.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[3-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy] butyl}biphenyl-2-yl)carbamate

Obtained as a solid (53mg, 33%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[3-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy]but-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 49; 160mg, 0.2mmol), ammonium formate (217mg, 3.45mmol) and palladium hydroxide (19mg, 0.14mmol) following the experimental procedure as described for Intermediate 8. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2)

LRMS (m/z): 818 (M+1)+

EXAMPLE 9.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[3-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy]butyl}biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a yellow solid (31mg, 63%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[3-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

yl)ethyl]amino}methyl)phenoxy]butyl}biphenyl-2-yl)carbamate (Intermediate 50; 54mg, 0.07mmol) and triethylamine trihydrofluoride (53µL, 0.33mmol) following the experimental procedure as described for Example 1.

LRMS (m/z): 703 (M+1)+

1H NMR (300 MHz, dmso) δ 8.66 (s, 1H), 8.11 (d, J = 9.5 Hz, 1H), 7.38 (m, 5H), 7.20 (bs, 3H), 7.06 (d, J = 8.1 Hz, 2H), 6.90 (d, J = 9.3 Hz, 2H), 6.80 (s, 1H), 6.46 (d, J = 9.1 Hz, 1H), 5.08 (s, 1H), 4.50 (s, 1H), 3.96 (s, 2H), 3.74 (s, 2H), 3.12 – 2.95 (m, 2H), 2.67 (bs, 5H), 2.08 (bs, 1H), 1.75 (s, 3H), 1.57 (bs, 2H), 1.46 (s, 1H), 1.29 (s, 1H), 1.09 (s, 1H)

Intermediate 51.

4-(but-3-en-1-yloxy)benzaldehyde

To a solution of 4-hydroxybenzaldehyde (2g, 0.016mol) in dimethylformamide (14mL) was added 4-bromobut-1-ene (2.4mL, 0.024mol) and potassium carbonate (3.7g, 0.026mol). The reaction mixture was stirred for 20hours at 60°C. Water was added into the reaction and the crude was extracted with ethyl acetate. The organic layer was washed several times with water. The organics were dried, filtered and the solvent was removed under reduced pressure giving a solid (1.97g, 68%) as the title compound, which was used in the next step without further purification.

LRMS (m/z): 177 (M+1)+

Intermediate 52.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-4-(4-formylphenoxy)but-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as an oil (207mg, 65%) from 4-(but-3-en-1-yloxy)benzaldehyde (Intermediate 51; 99mg, 0.56mg), (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-bromobiphenyl-2-yl)carbamate (Intermediate 5; 225mg, 0.45mmol), tri-o-tolylphosphine (170mg, 0.56mmol), N,N-Diisopropylethylamine (195µL, 1.12mmol) and palladium acetate (63mg, 0.28mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 497 (M+1)+

Intermediate 53.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[4-({[(2R)-2-{[tert-butyl(dimethyl) silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino} methyl)phenoxy]but-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a solid (96mg, 24%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-4-(4-formylphenoxy)but-1-en-1-yl]biphenyl-2-yl}carbamate (Intermediate 52; 205mg, 0.41mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (207mg, 0.37mmol) (prepared according to preparation 8 from US20060035931), DIEA (0.1mL, 0.62mmol) and sodium triacetoxyborohydride (263mg, 1.24mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mix-ture of chloroform:methanol:ammonium (40:4:0.2)

LRMS (m/z): 816 (M+1)+

Intermediate 54.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy] butyl}biphenyl-2-yl)carbamate

Obtained as a solid (70mg, 48%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy]but-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 53; 96mg, 0.09mmol), ammonium formate (56mg, 0.89mmol) and palladium hydroxide (11mg, 0.08mmol) following the experimental procedure as described for Intermediate 8.

LRMS (m/z): 818 (M+1)+

EXAMPLE 10.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy]butyl}biphenyl-2-yl)carbamate

Obtained as a solid (8mg, 27%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy]butyl}biphenyl-2-yl)carbamate (Intermediate 54; 70mg, 0.04mmol) and triethylamine trihydrofluoride (35µL, 0.21mmol) following the experimental procedure as described for Example 1. The crude obtained was purified by column chro-matography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2)

LRMS (m/z): 703 (M+1)+

1H NMR (300 MHz, cd3od) δ 8.23 (d, J = 8.9 Hz, 1H), 7.31 (bs, 5H), 7.18-7.16 (m, 5H), 6.91-6.89 (m, 4H), 6.58 (d, J = 9.0 Hz, 1H), 5.19 (s, 1H), 4.64 (s, 1H), 3.98 (s, 2H), 3.75-3.71 (m, 6H), 3.60 (s, 1H), 3.12 (s, 1H), 2.73 (s, 6H), 2.56 (s, 1H), 1.63 – 1.04 (m, 5H).

Intermediate 55.

tert-butyl [2-(4-hydroxyphenyl)ethyl]carbamate

To a solution of 4-(2-aminoethyl)phenol (2g, 0.014mol) in a mixture of water and dioxane (30mL/15mL) was added potassium carbonate (2g, 0.014mol). The mixture was cooled to 0°C and a solution of di-tert-butyl dicarbonate (3.18g, 0.014mol) in dioxane (15mL) was added drop wise. The mixture was stirred for 1.5h at room temperature. The crude was partitioned between ethyl acetate and water, and the organic layer was washed with bi-carbonate and brine. The organics were dried, filtered and the solvent was removed under reduced pressure giving the title compound as a white solid (3.3g, 99%), which was used in the next step without further purification.

LRMS (m/z): 238 (M+1)+

Intermediate 56.

tert-butyl {2-[4-(but-3-en-1-yloxy)phenyl]ethyl}carbamate

Obtained as an oil (680mg, 16%) from tert-butyl [2-(4-hydroxyphenyl)ethyl]carbamate (In-termediate 55; 1.73g, 0.007mol), 4-bromobut-1-ene (0.88mL, 0.008mol) and potassium carbonate (1.21g, 0.008mol) following the experimental procedure as described for Inter-mediate 51 and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane: Ether.

LRMS (m/z): 292 (M+1)+

Intermediate 57.

trans-4-tert-butylaminocyclohexyl {4-[(1E)-4-(4-{2-[(tert-butoxycarbonyl)amino]ethyl}phenoxy)but-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a solid (246mg, 50%) from tert-butyl {2-[4-(but-3-en-1-yloxy)phenyl]ethyl}carbamate (194mg, 0.67mmol), trans-4-benzyl-aminocyclohexyl (4-bromobiphenyl-2-yl)carbamate (Intermediate 43; 350mg, 0.67mmol), tri-o-tolylphosphine (203mg, 0.67mmol), N,N-Diisopropylethylamine (233µL, 1.34mmol) and palladium acetate (110mg, 0.33mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform: ethanol

LRMS (m/z): 734 (M+1)+

Intermediate 58.

trans-4-tert-butylaminocyclohexyl (4-{(1E)-4-[4-(2-aminoethyl)phenoxy]but-1-en-1-yl}biphenyl-2-yl)carbamate

To a solution of trans-4-tert-butylaminocyclohexyl {4-[(1E)-4-(4-{2-[(tert-butoxycarbonyl)amino]ethyl}phenoxy)but-1-en-1-yl]biphenyl-2-yl}carbamate (Intermediate 57; 240mg, 0.33mmol) was added hydrogen chloride 4N in dioxane (2.04mL, 8.18mmol). The mixture was stirred for 2 hours at room temperature. The solvent was removed under re-duced pressure and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2). The title com-pound was obtained as solid (135mg, 65%).

LRMS (m/z): 634 (M+1)+

Intermediate 59.

trans-4-tert-butylaminocyclohexyl {4-[(1E)-4-(4-{2-[((2R)-2-[8-(benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl]-2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)amino] ethyl}phenoxy)but-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a solid (145m, 75%) from trans-4-tert-butylaminocyclohexyl (4-{(1E)-4-[4-(2-aminoethyl)phenoxy]but-1-en-1-yl}biphenyl-2-yl)carbamate (100mg, 0.16mmol), 8-(benzyloxy)-5-((1R)-2-bromo-1-{[tert-butyl(dimethyl)silyl]oxy}ethyl)quinolin-2(1H)-one (US20040059116) (77mg, 0.16mmol), sodium bicarbonate (39mg, 0.47mmol) and sodium iodine (35mg, 0.24mmol) following the experimental procedure as described for Interme-diate 13 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 1042 (M+1)+

Intermediate 60.

trans-4-aminocyclohexyl (4-{4-[4-(2-{[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy] butyl}biphenyl-2-yl)carbamate

trans-4-tert-butylaminocyclohexyl {4-[(1E)-4-(4-{2-[((2R)-2-[8-(benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl]-2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)amino]ethyl}phenoxy)but-1-en-1-yl]biphenyl-2-yl}carbamate (Intermediate 59; 16mg) was dissolved in MeOH (2mL) and submitted to submitted twice to an H-Cube® Continuous-flow Hydrogenation Reactor. Conditions used: Pressure: Full H2, Flow 1mL/min, T^a 35°C. The solvent was removed under reduced pressure and the title compound was obtained as a solid (5mg, 33%), which was used in the final step without further manipulation.

LRMS (m/z): 820 (M+1)+

EXAMPLE 11.

trans-4-aminocyclohexyl (4-{4-[4-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]butyl}biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a white solid (4mg, 84%) from trans-4-aminocyclohexyl (4-{4-[4-(2-{[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]butyl}biphenyl-2-yl)carbamate (Intermediate 60; 5mg, 33%) and triethylamine trihydrofluoride (6µL, 0.04mmol) following the experimental procedure as described for Example 1.

LRMS (m/z): 705 (M+1)+

1H NMR (300 MHz, dmso) δ 8.55 (bs, 1H), 7.34-7.33 (m, 7H), 7.04 -7.02 (m. 4H), 6.86 (bs, 3H), 6.42 (bs, 1H), 5.41 (bs, 1H), 4.44 – 4.22 (m, 1H), 3.95 (s, 1H), 2.82-2.70 (m, 6H), 2.10 – 1.65 (m, 4H), 1.22 (bs, 4H), 1.07 (bs, 4H), 0.98 – 0.65 (m, 3H).

Intermediate 61.

methyl 3-amino-4-hydroxybenzoate

Hydrogen chloride (1.25M in Methanol, 100mL) was placed in a reactor at 0°C. Then 3-amino-4-hydroxybenzoic acid (5g, 0.032mol) was added in portions. The reaction mixture was stirred 5 minutes at 0°C and 24 hours at room temperature. The solvent was removed under reduced pressure and the crude was partitioned between ethyl acetate and satu-rated bicarbonate. The organics layer were combined, dried, filtered and the solvent was removed under reduced pressure to obtain the title compound as a solid (5.38g, 98%), which was used in the next step without further purification.

LRMS (m/z): 168 (M+1)+

Intermediate 62.

methyl 2-but-3-en-1-yl-1,3-benzoxazole-5-carboxylate

A round-bottomed flask fitted with stir bar was charged with methyl 3-amino-4-hydroxybenzoate (498mg, 2.98mmol) in xylenes (15mL). Triethylamine (0.46mL, 3.3mmol) and pyridine 4-methylbenzenesulfonate (256mg, 1.02mmol) were added suc-cessively, and the mixture was stirred 5 min until (almost) complete dissolution of the starting materials. Pent-4-enoyl chloride (0.35mL, 3.3mmol) was added drop wise to the cooled (ice/water bath) mixture, and then stirred at room temperature for 1 h. After having performed the first step, the flask is coupled to a Dean-Stark condenser system, and the mixture is heated at reflux overnight (T display = 170 °C). The mixture is diluted with ethyl acetate, washed with saturated bicarbonate, the aqueous layer was extracted with ethyl acetate, and combined organic layers were washed with brine, dried over MgSO4, filtered and concentrated to give 540 mg (70%) of a brown solid, which was used in the next step without further purification.

LRMS (m/z): 232 (M+1)+

Intermediate 63.

(2-but-3-en-1-yl-1,3-benzoxazol-5-yl)methanol

A round-bottomed flask fitted with stir bar was charged with methyl 2-but-3-en-1-yl-1,3-benzoxazole-5-carboxylate (Intermediate 62; 540mg, 2.34mmol) in 10 mL anhydrous tet-rahydrofurane and under Argon atmosphere. The mixture was cooled with an ice/water bath and lithium aluminium hydride was added cautiously. The solution is stirred at 0 °C for 30 min, and then a further 30 min at rt. The reaction is quenched by sequentially addi-tion of n:n:3n (where n is the LiAlH4 mass), that is 100 µL H2O:100 µL NaOH 4N:300 µL H2O, and then is stirred 15 min at rt. The solid formed is filtered and the resulting solution is concentrated under reduced pressure to give 450 mg (90%) of a dark brown oil, which was used in the next step without further purification.

LRMS (m/z): 204 (M+1)+

Intermediate 64.

2-but-3-en-1-yl-1,3-benzoxazole-5-carbaldehyde

A round-bottomed flask fitted with stir bar was charged with (2-but-3-en-1-yl-1,3-benzoxazol-5-yl)methanol (Intermediate 63; 430mg, 2.12mmol) in wet DCM. Dess-Martin periodinane (1.03g, 2.44mmol) was added portion wise and the mixture stirred at room temperature for 30 minutes. The reaction was quenched by addition of saturated bicarbonate (little bubbling)and thiosulfate solutions, and diluted with DCM. The organic layer was washed with more bicarbonate solution (twice), brine, dried over MgSO4, filtered and concentrated. The residue was purified by usual column chromatography (Ethyl acetate in hexanes gradient, 0-10-25-40%) to give 300 mg (67%) as a brown oil.

LRMS (m/z): 202 (M+1)+

Intermediate 65.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-4-(5-formyl-1,3-benzoxazol-2-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as an orange gum (287mg, 81%) from 2-but-3-en-1-yl-1,3-benzoxazole-5-carbaldehyde (Intermediate 64; 150mg, 0.75mmol), (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-bromobiphenyl-2-yl)carbamate (Intermediate 5; 300mg, 0.75mmol), tri-o-tolylphosphine

(226mg, 0.74mmol), N,N-Diisopropylethylamine (260µL, 1.49mmol) and palladium acetate (84mg, 0.37mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 522 (M+1)+

Intermediate 66.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl] oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1,3-benzoxazol-2-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a solid (240mg, 28%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-4-(5-formyl-1,3-benzoxazol-2-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate (Intermediate 65; 418mg, 0.8mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (316mg, 0.80mmol) (prepared according to prepara-tion 8 from US20060035931) and sodium triacetoxyborohydride (510mg, 2.41mmol) fol-lowing the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloro-form:methanol:ammonium (40:4:0.2)

LRMS (m/z): 841 (M+1)+

Intermediate 67.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1,3-benzoxazol-2-yl]butyl}biphenyl-2-yl)carbamate

A round-bottomed flask fitted with stir bar was charged with (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1,3-benzoxazol-2-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 66; 137mg, 0.16mmol) in MeOH (5mL) The flask was filled with Argon, and then Pd/C (145mg, 0.14mmol) was added employing an Argon cone stream to avoid solvent ignition. The flask was coupled with a quick-fit T-adaptor with one outlet to the hydrogen balloon and the other to the vacuum line. The flask was emptied by connecting it to the vacuum and then filled with hydrogen. This operation was repeated twice. The mixture was stirred vigorously at room temperature for 1.5 h. A further 40 mg of Pd/C were added employing the previously described procedure. The mixture was vigor-ously stirred at room temperature for 1 h. The Pd/C was filtered off and the solution con-centrated under reduced pressure. The solid was again dissolved in 5 mL MeOH and 71 mg of Pd/C were added. The mixture is stirred at room temperature for 5.5 h. The solid was filtered through a Celite pad and concentrated under reduced pressure to give 50 mg of a dark green/brown oil/gum. The residue was purified by column chromatography using as eluents CHCl3-MeOH-NH4OH 40:2:0.2 to give the title compound as a pale yellow gum (12mg, 7%).

LRMS (m/z): 843 (M+1)+

EXAMPLE 12.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)ethyl]amino}methyl)-1,3-benzoxazol-2-yl]butyl}biphenyl-2-yl)carbamate dihydrofluoride

Obtained as solid (8mg, 80%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1,3-benzoxazol-2-yl]butyl}biphenyl-2-yl)carbamate (Intermediate 67; 12mg, 0.01mmo) and triethylamine trihydrofluoride (25µL, 0.15mmol) following the experimental procedure as described for Example 1.

LRMS (m/z): 730 (M+1)+

1H NMR (300 MHz, cd3od) δ 7.76 (s, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.50 – 7.29 (m, 5H), 7.23 (d, J = 7.7 Hz, 1H), 7.18 – 6.98 (m, 3H), 6.80 – 6.68 (m, 2H), 4.23 (s, 1H), 3.37 – 3.33 (m, 5H), 3.30-3.26 (m , 5H), 3.16 – 2.89 (m, 5H), 2.83 – 2.67 (m, 2H), 2.62 – 2.42 (m, 2H), 2.12 (s, 1H), 2.07 – 1.86 (m, 3H), 1.80 (bs, 2H), 1.44 – 1.22 (m, 2H), 1.23 – 1.05 (m, 1H).

Intermediate 68.

tert-butyl {2-[3-(benzyloxy)phenyl]ethyl}carbamate

To a solution of 2-(3-(benzyloxy)phenyl)ethanamine (500mg, 2.2mmol) in dioxane (25mL) was added at 0°C a solution of sodium hydroxide (88mg, 2.2mmol) in water (2mL). Then a solution of di-tert-butyl dicarbonate (488mg, 2.24mmol) in dioxane (5mL) was added drop wise. The reaction mixture was stirred at 0°C for 1hour and 4 hours at room temperature. The solvent was removed under reduced pressure and the crude obtained was partitioned between ethyl acetate and water. The organic layer was dried, filtered and the solvent was removed under reduced pressure. The residue obtained was purified by column chroma-tography eluting with Hexane:ethyl acetate (15:1) to give the title compound as a solid (329mg, 45%).

LRMS (m/z): 328 (M+1)+

Intermediate 69.

tert-butyl [2-(3-hydroxyphenyl)ethyl]carbamate

A round-bottomed flask fitted with stir bar was charged with tert-butyl {2-[3-(benzyloxy)phenyl]ethyl}carbamate (Intermediate 68; 1.43g, 0.004mol)in MeOH (50mL) The flask was filled with Argon, and then Pd/C (143mg, 0.001mol) was added employing an Argon cone stream to avoid solvent ignition. The flask was coupled with a quick-fit T-adaptor with one outlet to the hydrogen balloon and the other to the vacuum line. The flask was emptied by connecting it to the vacuum and then filled with hydrogen. This op-eration was repeated twice. The reaction mixture was stirred overnight at room tempera-ture. The solid was filtered through a Celite pad and concentrated under reduced pressure to give the title compound as a white solid (980mg, 98%).

LRMS (m/z): 238 (M+1)+

Intermediate 70.

tert-butyl {2-[3-(allyloxy)phenyl]ethyl}carbamate

To a suspension of tert-butyl [2-(3-hydroxyphenyl)ethyl]carbamate (500mg, 2.11mol) in acetonitrile (5mL) was added potassium carbonate (437mg, 3.16mmol) and 3-bromoprop-1-ene (0.22mL, 2.54mmol). The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the crude was partitioned between ether and water. The organic layer was washed with further water, dried, filtered and evaporated, giving a crude which was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether. The title compound was obtained as a gum (488mg, 83%).

LRMS (m/z): 278 (M+1)+

Intermediate 71.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-3-(3-{2-[(tert-butoxycarbonyl)amino] ethyl}phenoxy)prop-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a solid (125mg, 28%) from tert-butyl {2-[3-(allyloxy)phenyl]ethyl}carbamate (207mf, 0.75mmol), (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-bromobiphenyl-2-yl)carbamate (Intermediate 5; 300mg, 0.75mmol), tri-o-tolylphosphine (227mg, 0.75mmol), N,N-Diisopropylethylamine (261µL, 1.49mmol) and palladium acetate (84mg, 0.37mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 598 (M+1)+

Intermediate 72.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[3-(3-{2-[(tert-butoxycarbonyl)amino] ethyl}phenoxy)propyl]biphenyl-2-yl}carbamate

Obtained as a solid (161mg, 53%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-3-(3-{2-[(tert-butoxycarbonyl)amino]ethyl}phenoxy)prop-1-en-1-yl]biphenyl-2-yl}carbamate (Inter-mediate 71; 300mg, 0.5mmol) following the experimental procedure as described for In-termediate 60. The crude obtained was used in the next step without further purification.

LRMS (m/z): 600 (M+1)+

Intermediate 73.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[3-(2-aminoethyl)phenoxy]propyl}biphenyl-2-yl)carbamate

Obtained as a solid (82mg, 61%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[3-(3-{2-[(tert-butoxycarbonyl)amino]ethyl}phenoxy)propyl]biphenyl-2-yl}carbamate (Intermediate 72; 161mg, 0.27mmol) and hydrogen chloride (4M in dioxane, 1.5mL) following the experimental procedure as described for Intermediate 58. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 500 (M+1)+

Intermediate 74.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[3-(3-{2-[((2R)-2-[8-(benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl]-2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)amino]ethyl} phenoxy)propyl]biphenyl-2-yl}carbamate

Obtained as a solid (52mg, 34%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[3-(2-aminoethyl)phenoxy]propyl}biphenyl-2-yl)carbamate (Intermediate 73; 84mg, 0.17mmol), 8-(benzyloxy)-5-((1R)-2-bromo-1-{[tert-butyl(dimethyl)silyl] oxy} ethyl)quinolin-2(1H)-one (US20040059116) (82mg, 0.17mmol), sodium bicarbonate (42mg, 0.50mmol) and sodium iodine (38mg, 0.24mmol) following the experimental procedure as described for Intermediate 13 and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 908 (M+1)+

Intermediate 75.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[3-(2-{[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy] propyl}biphenyl-2-yl)carbamate

A solution of (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[3-(3-{2-[((2R)-2-[8-(benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl]-2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)amino]ethyl} phenoxy) propyl]biphenyl-2-yl}carbamate (52mg, 0.06mmol) in methanol (3mL) was submitted tree times to an H-Cube® Continuous-flow Hydrogenation Reactor. Conditions used: Pressure: Full H2, Flow 1mL/min, T^{a} 60°C. The solvent was removed under reduced pressure and the title compound was obtained as a solid (23mg, 49%), which was used in the final step without further manipulation.

LRMS (m/z): 818 (M+1)+

EXAMPLE 13.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[3-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]propyl}biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a solid (11mg, 55%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[3-(2-{[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]propyl}biphenyl-2-yl)carbamate (23mg, 0.03mmol) and triethylamine trihydrofluoride (100μL, 0.61mmol) following the experimental procedure as described for Example 1.

LRMS (m/z): 703 (M+1)+

1H NMR (300 MHz, dmso) δ 8.72 (s, 1H), 8.15 (d, J = 9.9 Hz, 1H), 7.56 (bs, 1H), 7.46 – 7.28 (m, 5H), 7.29 – 7.04 (m, 3H), 6.95 bs, 1H), 6.83 (s, 2H), 6.56 (d, J = 9.9 Hz, 1H), 5.27 – 5.14 (m, 1H), 4.54 (s, 1H), 3.99 (s, 1H), 3.21 – 3.03 (m, 2H), 3.02 – 2.89 (m, 2H), 2.75 (bs, 4H), 2.36 (s, 1H), 2.27 (s, 1H), 2.18 (s, 1H), 2.07 -2.05(m, 4H), 1.88 (d, J = 15.4 Hz, 1H), 1.57 (s, 3H), 1.35 (s, 2H), 1.11 (s, 1H).

Intermediate 76.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-3-hydroxyprop-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a gum (282mg, 32%) from prop-2-en-1-ol (168mg, 2.89mmol), (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-bromobiphenyl-2-yl)carbamate (Intermediate 5; 658mg, 1.64 mmol), tri-o-tolylphosphine (300mg, 0.99mmol), N,N-Diisopropylethylamine (572μL, 3.28mmol) and palladium acetate (110mg, 0.49mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 379 (M+1)+

Intermediate 77.

(3R)-1-azabicyclo[2.2.2]oct-3-yl [4-(3-hydroxypropyl)biphenyl-2-yl]carbamate

A solution of (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-3-hydroxyprop-1-en-1-yl]biphenyl-2-yl}carbamate (Intermediate 76; 282mg, 0.75mmol) in acid acetic (10mL) was submitted tree times to an H-Cube® Continuous-flow Hydrogenation Reactor. Conditions used: Pressure: Full H2, Flow 1mL/min, T^a 30°C. The solvent was removed under reduced pres-sure and the title compound was obtained as a solid (79mg, 62%), which was used in the final step without further manipulation.

LRMS (m/z): 381 (M+1)+

Intermediate 78.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[({[4-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-chloro-5-methoxyphenyl]amino}carbonyl)oxy]propyl}biphenyl-2-yl)carbamate

To a solution of (3R)-1-azabicyclo[2.2.2]oct-3-yl [4-(3-hydroxypropyl)biphenyl-2-yl]carbamate (Intermediate 77; 20mg, 0.05mmol) and diisopropylethylenediamine (18μL, 0.1mmol) in tetrahydrofurane (5mL) was a added a solution of tert-butyl[(5-chloro-4-isocyanato-2- methoxybenzyl)oxy]dimethylsilane (Intermediate 59 WO2011/141180A1; 30mg, 0.09mmol) in tetrahydrofurane (5mL). The reaction mixture was stirred overnight at 80°C. The solvent was removed under reduced pressure and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2). The title compound was obtained as a solid (9.9mg, 26%).

LRMS (m/z): 709 (M+1)+

Intermediate 79.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[({[2-chloro-4-(hydroxymethyl)-5-methoxyphenyl]amino}carbonyl)oxy]propyl}biphenyl-2-yl)carbamate

To a solution of (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[({[4-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-chloro-5-methoxyphenyl]amino} carbonyl)oxy] propyl}biphenyl-2-yl)carbamate (Intermediate 78; 9.9mg, 0.01mmol) in tetrahydrofurane (5mL) was added triethylamine trihydrofluoride (14μL, 0.09mmol). The reaction mixture was stirred at room temperature 24 hours. The solvent was removed under reduced

pressure. The crude obtained was treated with ace-tonitrile to obtain the title compound as a gum (4mg, 48%), and it was used in the next step without further manipulation.
LRMS (m/z): 595 (M+1)+

Intermediate 80.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[3-({[(2-chloro-4-formyl-5-methoxyphenyl) amino]carbonyl}oxy)propyl]biphenyl-2-yl}carbamate

Obtained as a foam (37mg, 63%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[({[2-chloro-4-(hydroxymethyl)-5-methoxyphenyl]amino}carbonyl)oxy]propyl}biphenyl-2-yl)carbamate (Intermediate 79; 50mg, 0.08mmol) and Dess-Martin periodinane (39mg, 0.09mmol) fol-lowing the experimental procedure as described for Intermediate 64. The crude obtained was used in the next step without further purification.
LRMS (m/z): 593 (M+1)+

Intermediate 81.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[({[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-chloro-5-methoxyphenyl]amino}carbonyl)oxy]propyl}biphenyl-2-yl)carbamate

Obtained as a solid (74mg, 62%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[3-({[(2-chloro-4-formyl-5-methoxyphenyl)amino]carbonyl}oxy)propyl]biphenyl-2-yl}carbamate (Intermediate 80; 37mg, 0.06mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (25mg, 0.07mmol) (prepared according to preparation 8 from US20060035931)and sodium triacetoxyborohydride (40mg, 0.19mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was used in the final step without further purification.
LRMS (m/z): 911 (M+1)+

EXAMPLE 14.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[({[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl] amino}carbonyl)oxy]propyl}biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a solid (6mg, 24%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[({[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-chloro-5-methoxyphenyl]amino}carbonyl)oxy]propyl}biphenyl-2-yl)carbamate (Intermediate 81; 56mg, 0.03mmol) and triethylamine trihydrofluoride (83µL, 0.5mmol) following the experimental procedure as described for Example 1. The crude obtained was purified by column chromatography in reverse phase using as eluents water and acetonitrile.

LRMS (m/z): 797 (M+1)+

1H NMR (300 MHz, cd3od) δ 8.17 (d, J = 9.7 Hz, 1H), 7.46 (s, 1H), 7.43 – 7.23 (m, 5H), 7.22 – 7.12 (m, 4H), 7.09 (bs, 1H), 6.90 (d, J = 8.1 Hz, 1H), 6.53 (d, J = 9.8 Hz, 1H), 5.10 (s, 1H), 4.60 – 4.53 (m, 1H), 4.25 (d, J = 7.3 Hz, 1H), 4.15 (s, 1H), 3.69 (t, J = 6.7 Hz, 2H), 3.15 (s, 2H), 2.86 – 2.60 (m, 4H), 2.00 (bs, 2H), 1.89 (bs, 2H), 1.82 (bs, 2H), 1.67 b(s, 1H), 1.53 (bs, 1H), 1.37 (bs, 1H), 1.26 (d, J = 24.5 Hz, 2H).

Intermediate 82.

1-but-3-en-1-yl-1H-indole-5-carbaldehyde

To a solution of 1H-indole-5-carbaldehyde (500mg, 3.44mmol) in dimethylformamide (5mL) was added at 0°C sodium hydride (124mg, 5.17mmol) and the solution was stirred for some minutes. Then 4-bromobut-1-ene (0.524mL, 5.16mmol) was added into the solu-tion and the mixture was stirred at room temperature overnight. Water was poured into the mixture and the crude was extracted with chloroform. The organic layer was washed sev-eral times with water, dried, filtered and the solvent was removed under reduced pressure to give the title compound as an oil (510mg, 59%), which was used in the next step with-out further purification.

LRMS (m/z): 200 (M+1)+

Intermediate 83.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-4-(5-formyl-1H-indol-1-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a foam (320mg, 94%) from 1-but-3-en-1-yl-1H-indole-5-carbaldehyde (217mg, 0.76mmol), (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-bromobiphenyl-2-yl)carbamate (Intermediate 5; 250mg, 0.62mmol), tri-o-tolylphosphine (150mg, 0.49mmol), N,N-Diisopropylethylamine (300µL, 1.72mmol) and palladium acetate (29mg, 0.13mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 520 (M+1)+

Intermediate 84.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[5-({[(2R)-2-{[tert-butyl(dimethyl) silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-indol-1-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a foam (185mg, 25%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-4-(5-formyl-1H-indol-1-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate (Intermediate 83; 320mg, 0.62mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (278mg, 0.70mmol) (prepared according to preparation 8 from US20060035931) and sodium triacetoxyborohydride (449mg, 2.12mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 839 (M+1)+

Intermediate 85.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-indol-1-yl]butyl}biphenyl-2-yl)carbamate

Obtained as a solid diacetate salt (123mg, 77%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-indol-1-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 84; 160mg, 0.19mmol) following the experimental procedure as described for Intermediate 77 and the crude obtained was used in the final step without further purification.

LRMS (m/z): 841 (M+1)+

EXAMPLE 15.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-indol-1-yl]butyl}biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a white solid (49mg, 27%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-indol-1-yl]butyl}biphenyl-2-yl)carbamate (Intermediate 85; 225m, 0.23mmol) and triethylamine trihydrofluoride (162µL, 0.99mmol) following the ex-perimental procedure as described for Example 1.

LRMS (m/z): 726 (M+1)+

1H NMR (300 MHz, dmso) δ 8.83 (s, 1H), 8.23 (d, J = 9.9 Hz, 1H), 7.69 (s, 1H), 7.66 – 7.40 (m, 5H), 7.41 – 7.15 (m, 4H), 7.08 (bs, 2H), 6.75 – 6.64 (m, 1H), 6.56 (d, J = 9.8 Hz, 1H), 5.30 (s, 1H), 4.65 (s, 1H), 4.37 (d, J = 6.6 Hz, 2H), 4.10 (s, 2H), 3.20 (s, 2H), 2.93 (s, 2H), 2.79 (d, J = 7.2 Hz, 3H), 1.98 (s, 2H), 1.72 (s, 4H), 1.43 (bs, 2H), 1.14 (bs, 1H), 1.00 (s, 1H).

Intermediate 86.

3-but-3-en-1-yl-2-oxo-2,3-dihydro-1,3-benzothiazole-6-carbaldehyde

To a solution of 2-oxo-2,3-dihydrobenzo[d]thiazole-6-carbaldehyde (120mg, 0.67mmol) in a mixture of acetonitrile:tetrhydrofurane (5:2) was added 4-bromobut-1-ene (361mg, 2.68mmol), potassium iodide (22m, 0.13mmol) and potassium carbonate (185mg, 1.34mmol). The reaction mixture was stirred for 4 hours at 70°C. The mixture was filtered and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane: Ether.

LRMS (m/z): 234 (M+1)+

Intermediate 87.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-4-(6-formyl-2-oxo-1,3-benzothiazol-3(2H)-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a foam (114mg, 55%) from 3-but-3-en-1-yl-2-oxo-2,3-dihydro-1,3-benzothiazole-6-carbaldehyde (87mg, 0.37mmol), (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-bromobiphenyl-2-yl)carbamate (Intermediate 5; 150mg, 0.37mmol), tri-o-tolylphosphine (114mg, 0.37mmol), N,N-Diisopropylethylamine (130µL, 0.75mmol) and palladium acetate (49mg, 0.15mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 554 (M+1)+

Intermediate 88.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[6-({[(2R)-2-{[tert-butyl(dimethyl) silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzothiazol-3(2H)-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a foam (168mg, 79%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-4-(6-formyl-2-oxo-1,3-benzothiazol-3(2H)-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate (Intermedi-ate 87; 114mg, 0.21mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (69mg, 0.21mmol) (prepared according to preparation 8 from US20060035931), sodium triacetoxyborohydride (131mg, 0.62mmol) and diisopro-pylethylenamine (0.054mL, 0.31mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was used in the next step without further purifica-tion.

LRMS (m/z): 873 (M+1)+

Intermediate 89.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzothiazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate

Obtained as a foam (83mg, 23%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzothiazol-3(2H)-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 88; 200mg, 0.23mmol) following the experimental procedure as described for Intermediate 77. The crude obtained was used in the final step without further manipulation.

LRMS (m/z): 875 (M+1)+

EXAMPLE 16.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzothiazol-3(2H)-yl]butyl} biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a white solid (8.4mg, 11%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzothiazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate (In-termediate 89; 83mg, 0.09mol) and triethylamine trihydrofluoride (42µL, 0.26mmol) follow-ing the experimental procedure as described for Example 1 and the crude obtained was purified by column chromatography in reversed phase, eluting with a mixture of methanol and water.

LRMS (m/z): 760 (M+1)+

1H NMR (300 MHz, cd3od) δ 8.26 (d, J = 9.8 Hz, 1H), 7.57 (d, J = 15.1 Hz, 1H), 7.38 (d, J = 5.1 Hz, 5H), 7.29 – 7.13 (m, 4H), 7.12 (s, 1H), 6.99 (bs 2H), 6.61 (d, J = 9.8 Hz, 1H), 5.31 (s, 1H), 4.76 – 4.59 (m, 2H), 4.07 (d, J = 10.4 Hz, 2H), 3.67 – 3.53 (m, 1H), 3.45 (s, 1H), 3.33 (d, J = 8.1 Hz, 1H), 3.23 – 2.95 (m, 3H), 2.68 (d, J = 12.8 Hz, 1H), 2.07-2.05 (m 4H), 1.77 (s, 3H), 1.26 (bs, 4H), 1.25 – 1.07 (m, 2H).

Intermediate 90.

tert-butyl {2-[4-(allyloxy)phenyl]ethyl}carbamate

Obtained as a solid (291mg, 62%) from tert-butyl [2-(4-hydroxyphenyl)ethyl]carbamate (Intermediate 20 described in the patent WO2009/068177 A1; 400mg, 1.69mmol), 3-bromoprop-1-ene (0.29mL, 3.37mmol) and potassium carbonate (466mg, 3.37mmol) fol-lowing the experimental procedure as described for Intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane: Ether.

LRMS (m/z): 278 (M+1)+

Intermediate 91.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-3-(4-{2-[(tert-butoxycarbonyl)amino]ethyl}phenoxy)prop-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a solid (105mg, 28%) from tert-butyl {2-[4-(allyloxy)phenyl]ethyl}carbamate (Intermediate 90; 173mg, 0.62mmol), (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-bromobiphenyl-2-yl)carbamate (Intermediate 5; 250mg, 0.62mmol), tri-o-tolylphosphine (190mg, 0.62mmol), N,N-Diisopropylethylamine (220µL, 1.26mmol) and palladium acetate (70mg, 0.31mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 598 (M+1)+

Intermediate 92.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[3-(4-{2-[(tert-butoxycarbonyl)amino] ethyl}phenoxy)propyl]biphenyl-2-yl}carbamate

Obtained as a foam (150mg, 68%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-3-(4-{2-[(tert-butoxycarbonyl)amino]ethyl}phenoxy)prop-1-en-1-yl]biphenyl-2-yl}carbamate (Inter-mediate 91; 220mg, 0.37mmol) and palladium on charcoal (10%; 44mg, 0.04mmol) follow-ing the experimental procedure as described for Intermediate 67. The crude obtained was used in the next step without further purification.

LRMS (m/z): 600 (M+1)+

Intermediate 93.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[4-(2-aminoethyl)phenoxy]propyl}biphenyl-2-yl)carbamate

Obtained as a gum (51mg, 41%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[3-(4-{2-[(tert-butoxycarbonyl)amino]ethyl}phenoxy)propyl]biphenyl-2-yl}carbamate (Intermediate 92; 150mg, 0.25mol) and hydrogen chloride (4M in dioxane, 1.5mL, 6mmol) following the experimental procedure as described for Intermediate 58. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 500 (M+1)+

Intermediate 94.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[3-(4-{2-[((2R)-2-[8-(benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl]-2-{[tert-butyl(dimethyl)silyl]oxy}ethyl) amino]ethyl} phenoxy)propyl]biphenyl-2-yl}carbamate

Obtained as a solid (20mg, 21%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[4-(2-aminoethyl)phenoxy]propyl}biphenyl-2-yl)carbamate (Intermediate 93; 50mg, 0.1mmol), 8-(benzyloxy)-5-((1R)-2-bromo-1-{[tert-butyl(dimethyl)silyl]oxy}ethyl)quinolin-2(1H)-one (US20040059116) (50mg, 0.1mmol), sodium bicarbonate (26mg, 0.31mmol) and sodium iodine (23mg, 0.15mmol) following the experimental procedure as described for Intermediate 13. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 908 (M+1)+

Intermediate 95.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[4-(2-{[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy] propyl}biphenyl-2-yl)carbamate

A solution of (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[3-(4-{2-[((2R)-2-[8-(benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl]-2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)amino]ethyl}phenoxy)propyl]biphenyl-2-yl}carbamate (Inter-mediate 94; 20mg, 0.02mmol) in acetic acid (8mL) was submitted once to an H-Cube® Continuous-flow Hydrogenation Reactor. Conditions used: Pressure: 20 bars, Flow 1mL/min, T^a 40°C. The solvent was removed under reduced pressure and the title com-pound was obtained as a solid (16mg, 88%), which was used in the final step without fur-ther manipulation.

LRMS (m/z): 818 (M+1)+

EXAMPLE 17.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[4-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]propyl}biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a white solid (5mg, 40%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[4-(2-{[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

yl)ethyl]amino}ethyl)phenoxy]propyl}biphenyl-2-yl)carbamate (Intermediate 95; 16mg, 0.05mmol) and triethylamine trihydrofluoride (14μL, 0.09mmol) following the experimental procedure as described for Example 1.

LRMS (m/z): 703 (M+1)+

1H NMR (300 MHz, cd3od) δ 8.34 (d, J = 9.5 Hz, 1H), 7.97 (bs, 2H), 7.38 (bs, 6H), 7.14-7.12 (m, 4H), 6.95 (d, J = 8.1 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.65 (d, J = 10.0 Hz, 1H), 5.20 (bs, 1H), 3.98 (bs, 2H), 3.58 – 3.43 (m, 2H), 2.97 (bs, 3H), 2.84-2.70 (m, 4H), 2.62 – 2.46 (m, 2H), 2.06 (bs 3H), 1.94 (s, 1H), 1.89 (s, 1H), 1.77 – 1.66 (m, 1H), 1.64 – 1.50 (m, 2H), 1.39 (s, 2H), 1.28 (s, 1H).

Intermediate 96.

methyl 2-but-3-en-1-yl-1,3-benzoxazole-6-carboxylate

Obtained as a brown oil (1.32g, 86%) from methyl 4-amino-3-hydroxybenzoate (1g, 5.98mmol), triethylamine (0.92mL, 6.6mmol), pyridine 4-methylbenzenesulfonate (0.45g, 1.79mmol), pent-4-enoyl chloride (0.7mL, 6.32mmol) following the experimental procedure as described for Intermediate 62 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 232 (M+1)+

Intermediate 97.

(2-but-3-en-1-yl-1,3-benzoxazol-6-yl)methanol

Obtained as a dark brown oil (311mg, 47%) from methyl 2-but-3-en-1-yl-1,3-benzoxazole-6-carboxylate (646mg, 2.79mmol) following the experimental procedure as described for Intermediate 63 and the crude obtained was used in the next step without further purifica-tion.

LRMS (m/z): 204 (M+1)+

Intermediate 98.

2-but-3-en-1-yl-1,3-benzoxazole-6-carbaldehyde

Obtained as a brown oil (294mg, 86%) from (2-but-3-en-1-yl-1,3-benzoxazol-6-yl)methanol (311mg, 1.53mmol) and Dess-Martin periodinane (746mg, 1.76mmol) following the experimental procedure as described for Intermediate 64. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Ethyl acetate:Hexane.

LRMS (m/z): 202 (M+1)+

Intermediate 99.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-4-(6-formyl-1,3-benzoxazol-2-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as an orange gum (280mg, 68%) from 2-but-3-en-1-yl-1,3-benzoxazole-6-carbaldehyde (Intermediate 98; 150mg, 0.75mmol),), (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-bromobiphenyl-2-yl)carbamate (Intermediate 5; 300mg, 0.75mmol), tri-o-tolylphosphine (227mg, 0.75mmol), N,N-Diisopropylethylamine (0.26mL, 1.49mmol) and palladium acetate (84mg, 0.37mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 522 (M+1)+

Intermediate 100.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[6-({[(2R)-2-{[tert-butyl(dimethyl) silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1,3-benzoxazol-2-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a yellow/orange gum (262mg, 29%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-4-(6-formyl-1,3-benzoxazol-2-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate (280mg, 0.54mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (212mg, 0.54mmol) (prepared according to preparation 8 from US20060035931) and sodium triacetoxyborohydride (341mg, 1.61mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was used in the next step without further purification.

LRMS (m/z): 841 (M+1)+

Intermediate 101.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1,3-benzoxazol-2-yl]butyl}biphenyl-2-yl)carbamate

Obtained as a gum (50mg, 96%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1,3-benzoxazol-2-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate (Inter-mediate 100; 132mg, 0.08mmol) following the experimental procedure as described for Intermediate 77 and the crude obtained was used in the next step without further purifica-tion.

LRMS (m/z): 843 (M+1)+

EXAMPLE 18.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1,3-benzoxazol-2-yl]butyl}biphenyl-2-yl)carbamate

Obtained as a solid (3mg, 4%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1,3-benzoxazol-2-yl]butyl}biphenyl-2-yl)carbamate (Intermediate 101; 160mg, 0.09mmol) and triethylamine trihydrofluoride (14µL, 0.09mmol) following the experimental procedure as described for Example 1. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 728 (M+1)+

1H NMR (300 MHz, cd3od) δ 8.26 (d, J = 9.9 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.52 – 7.27 (m, 6H), 7.18-7.05 (m, 5H), 6.99 (d, J = 8.1 Hz, 1H), 6.59 (d, J = 9.8 Hz, 1H), 5.37 – 5.25 (m, 1H), 4.19 (s, 1H), 3.64 – 3.50 (m, 1H), 3.25 – 2.95 (m, 4H), 2.77 (dd, J = 25.9, 18.3 Hz, 3H), 2.15 (s, 1H), 1.95-1.9 (m, 5H), 1.80 (bs, 4H), 1.31 (bs, 4H), 1.22 – 1.07 (m, 2H).

Intermediate 102.

ethyl 1H-1,2,3-benzotriazole-5-carboxylate

To a solution of 1H-benzo[d][1,2,3]triazole-5-carboxylic acid (5g, 0.03mol) in ethanol (60mL) was added sulphuric acid (7.35mL, 0.13mol). The reaction mixture was stirred at 90°C for 8 hours. The solvent was removed and the crude was basified until pH 7-8 then extracted with ethyl acetate. The organic layer was dried, filtered and the solvent was re-moved under reduced pressure giving the title compound as a white solid (5g, 85%), which was used in the next step without further purification.

LRMS (m/z): 192 (M+1)+

Intermediate 103.

ethyl 2-but-3-en-1-yl-2H-1,2,3-benzotriazole-5-carboxylate

Obtained as a foam (2.5g, 39%) from ethyl 1H-1,2,3-benzotriazole-5-carboxylate (Intermediate 102; 5g, 0.026mol), 4-bromobut-1-ene (3.19mL, 0.031mol) and potassium carbonate (7.23g, 0.052mol) following the experimental procedure as described for Intermediate 51. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether.

LRMS (m/z): 246 (M+1)+

Intermediate 104.

(2-but-3-en-1-yl-2H-1,2,3-benzotriazol-5-yl)methanol

Obtained as an oil (1.5g, 90%) from ethyl 2-but-3-en-1-yl-2H-1,2,3-benzotriazole-5-carboxylate (Intermediate 103; 2g, 0.008mol) and lithium aluminium hydride (370mg, 0.009mol) following the experimental procedure as described for Intermediate 63 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 204 (M+1)+

Intermediate 105.

2-but-3-en-1-yl-2H-1,2,3-benzotriazole-5-carbaldehyde

Obtained as an oil (300mg, 32%) from (2-but-3-en-1-yl-2H-1,2,3-benzotriazol-5-yl)methanol (Intermediate 104; 750mg, 3.69mmol) and Dess-Martin periodinane (1.72g, 4.06mmol) following the experimental procedure as described for Intermediate 64 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 202 (M+1)+

Intermediate 106.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-4-(5-formyl-2H-1,2,3-benzotriazol-2-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a solid (345mg, 76%) from 2-but-3-en-1-yl-2H-1,2,3-benzotriazole-5-carbaldehyde (Intermediate 105; 219mg, 1.09mmol), (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-bromobiphenyl-2-yl)carbamate (Intermediate 5; 350mg, 0.87mmol), tri-o-tolylphosphine (265mg, 0.87mmol), N,N-Diisopropylethylamine (0.304mL, 1.74mmol) and palladium acetate (144mg, 0.44mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 522 (M+1)+

Intermediate 107.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[5-({[(2R)-2-{[tert-butyl(dimethyl) silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2H-1,2,3-benzotriazol-2-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a solid (244mg, 44%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-4-(5-formyl-2H-1,2,3-benzotriazol-2-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate (Intermediate 106; 345mg, 0.66mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (221mg, 0.66mmol) (prepared according to preparation 8 from US20060035931), sodium triacetoxyborohydride (420mg, 1.98mmol) and isopropyl ethylene diamine (173µL, 1.74mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 841 (M+1)+

Intermediate 108.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2H-1,2,3-benzotriazol-2-yl]butyl}biphenyl-2-yl)carbamate

Obtained as a diacetate salt (239mg, 84%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2H-1,2,3-benzotriazol-2-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 107; 240mg, 0.29mmol) following the experimental procedure as described for Intermediate 77. The crude obtained was used in the final step without further purifica-tion.

LRMS (m/z): 843 (M+1)+

EXAMPLE 19.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2H-1,2,3-benzotriazol-2-yl]butyl} biphenyl-2-yl)carbamate

Obtained as a solid (60mg, 26%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2H-1,2,3-benzotriazol-2-yl]butyl}biphenyl-2-yl)carbamate (Intermediate 108; 242mg, 0.29mmol) and triethylamine trihydrofluoride (230µL, 1.44mmol) following the experimental procedure as described for Example 1. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 728 (M+1)+

1H NMR (400 MHz, dmso) δ 8.56 (s, 1H), 8.09 (d, J = 9.9 Hz, 1H), 7.80 (d, J = 9.0 Hz, 1H), 7.75 (s, 1H), 7.41 – 7.23 (m, 6H), 7.16 (t, J = 6.1 Hz, 2H), 7.07 (d, J = 7.8 Hz, 1H), 7.03 (d, J = 8.2 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H), 6.39 (d, J = 9.9 Hz, 1H), 5.04 (dd, J = 7.8, 4.4 Hz, 1H), 4.73 (t, J = 7.0 Hz, 2H), 4.44 (s, 1H), 3.85 (s, 2H), 2.97 (d, J = 14.6 Hz, 3H), 2.65-2.63 (m. 8H), 2.30 (s, 1H), 2.08 – 1.97 (m, 2H), 1.73 (s, 1H), 1.61 – 1.51 (m, 2H), 1.39 (s, 1H), 1.28 – 1.13 (m, 1H).

Intermediate 109.

trans-4-tert-butylaminocyclohexyl {4-[4-(6-formyl-2-oxo-1,3-benzoxazol-3(2H)-yl)butyl]biphenyl-2-yl}carbamate

Obtained as a solid (233mg, 60%) from 3-but-3-en-1-yl-2-oxo-2,3-dihydro-1,3-benzoxazole-6-carbaldehyde (Intermediate 38; 150mg, 0.69mmol), trans-4-benzyl-aminocyclohexyl (4-bromobiphenyl-2-yl)carbamate (Intermediate 43; 300mg, 0.57mmol),), tri-o-tolylphosphine (174mg, 0.57mmol), N,N-Diisopropylethylamine (0.199mL, 1.15mmol) and palladium acetate (95mg, 0.29mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane:Ether.

LRMS (m/z): 662 (M+1)+

Intermediate 110.

trans-4-tert-butylaminocyclohexyl (4-{(1E)-4-[6-({[(2R)-2-{[tert-butyl(dimethyl) silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as an oil (50mg, 69%) from trans-4-tert-butylaminocyclohexyl {4-[4-(6-formyl-2-oxo-1,3-benzoxazol-3(2H)-yl)butyl]biphenyl-2-yl}carbamate (Intermediate 109; 358mg, 0.54mol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (163mg, 0.49mmol) (prepared according to preparation 8 from US20060035931) and sodium triacetoxyborohydride (575mg, 2.71mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was used in the next step without further purification.

LRMS (m/z): 979 (M+1)+

Intermediate 111.

trans-4-aminocyclohexyl (4-{4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate

Obtained as a foam (130mg, 92%) from trans-4-tert-butylaminocyclohexyl (4-{(1E)-4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 110; 140mg, 0.14mmol) following the experimental procedure as described for Intermediate 77 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 847 (M+1)+

EXAMPLE 20.

trans-4-aminocyclohexyl (4-{4-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a solid (21mg, 35%) from trans-4-aminocyclohexyl (4-{4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate (Intermediate 111; 70mg, 0.08mmol) and triethylamine trihydrofluoride (230µL, 1.44mmol) following the experimen-tal procedure as described for Example 1.

LRMS (m/z): 732 (M+1)+

1H NMR (300 MHz, dmso) δ 8.55 (s, 1H), 8.12 (d, J = 9.9 Hz, 1H), 7.46 – 7.26 (m, 6H), 7.13-7.09 (m, 5H), 6.87 (d, J = 8.3 Hz, 1H), 6.44 (d, J = 9.9 Hz, 1H), 5.04 (s, 1H), 4.32 (s, 1H), 3.84 (s, 2H), 3.75 (s, 2H), 2.82 (s, 1H), 2.63 (bs, 4H), 2.08 (bs, 3H), 1.85-1.7 (m, 4H), 1.60 (s, 2H), 1.26 (s, 3H).

Intermediate 112.

(5-bromobiphenyl-2-yl)amine

To a solution of biphenyl-2-amine (2.5g, 0.015mol) in dimethylformamide (5mL) was added at 0°C a solution of N-bromosuccinimide (3.16g, 0.018mol) in dimethylformamide (4mL). The reaction mixture was stirred at 0°C for 1 hour. Water was poured into the mixture and the crude was extracted with ethyl acetate. The organic layer was washed with water, dried, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane:Ether, giving the title compound as an orange solid (2.6g, 71%).

LRMS (m/z): 249 (M+1)+

Intermediate 113.

5-bromo-2-isocyanatobiphenyl

Obtained as a solution in toluene (550mg, 98%) from (5-bromobiphenyl-2-yl)amine (Inter-mediate 112; 500mg, 2.02mmol), triphosgene (239mg, 0.81mmol) and triethylamine (0.56mL, 4.04mmol) following the experimental procedure as described for Intermediate 4.

LRMS (m/z): 289 (M+16)+; (aliquot in MeOH and detection of methylic ester).

Intermediate 114.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (5-bromobiphenyl-2-yl)carbamate

Obtained as a solid (1.29g, 37%) from 5-bromo-2-isocyanatobiphenyl (Intermediate 113; 1.88g, 6.8mmol) and sodium (R)-quinuclidin-3-ol (1g, 6.7mmol) following the experimental procedure as described for Intermediate 5 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 402;403 (M+1/M+2)+

Intermediate 115.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {5-[(1E)-4-(4-{2-[(tert-butoxycarbonyl)amino]ethyl}phenoxy)but-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a foam (1.29g, 50%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (5-bromobiphenyl-2-yl)carbamate (Intermediate 114; 450mg, 1.12mmol), tert-butyl {2-[4-(but-3-en-1-yloxy)phenyl]ethyl}carbamate (Intermediate 9; 326mg, 1.12mmol), tri-o-tolylphosphine (341mg, 1.12mmol), N,N-Diisopropylethylamine (0.39mL, 2.23mmol) and palladium acetate (125mg, 0.56mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 612 (M+1)+

Intermediate 116.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (5-{(1E)-4-[4-(2-aminoethyl)phenoxy]but-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as solid (120mg, 65%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl {5-[(1E)-4-(4-{2-[(tert-butoxycarbonyl)amino]ethyl}phenoxy)but-1-en-1-yl]biphenyl-2-yl}carbamate (Intermediate 115; 130mg, 0.21mmol) and hydrogen chloride (2M in diethyl ether, 1.59mL) following the experimental procedure as described for Intermediate 58 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 512 (M+1)+

Intermediate 117.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {5-[(1E)-4-(4-{2-[((2R)-2-[8-(benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl]-2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)amino]ethyl}phenoxy) but-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as solid (92mg, 7%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (5-{(1E)-4-[4-(2-aminoethyl)phenoxy]but-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 116; 120mg, 0.23mmol), 8-(benzyloxy)-5-((1R)-2-bromo-1-{[tert-butyl(dimethyl)silyl]oxy}ethyl) quinolin-2(1H)-one (US20040059116) (66mg, 0.14mmol), sodium bicarbonate (69mg, 0.82mmol) and sodium iodine (61mg, 0.41mmol) following the experimental procedure as described for Intermediate 13. The crude obtained was used in the next step without further purifica-tion.

LRMS (m/z): 920 (M+1)+

Intermediate 118.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (5-{4-[4-(2-{[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]butyl}biphenyl-2-yl)carbamate

Obtained as a solid (46mg, 68%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl {5-[(1E)-4-(4-{2-[((2R)-2-[8-(benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl]-2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)amino]ethyl}phenoxy)but-1-en-1-yl]biphenyl-2-yl}carbamate (Intermediate 117; 71mg, 0.08mmol) following the experimental procedure as described for Intermediate 77 and the crude obtained was used in the final step without further manipulation.

LRMS (m/z): 832 (M+1)+

EXAMPLE 21.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (5-{4-[4-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]butyl}biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a solid (25mg, 68%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (5-{4-[4-(2-{[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]butyl}biphenyl-2-yl)carbamate (Intermediate 118; 46mg, 68%) and triethylamine trihydrofluoride (39µL, 0.24mmol) following the experimental pro-cedure as described for Example 1.

LRMS (m/z): 717 (M+1)+

1H NMR (300 MHz, dmso) δ 8.67 (s, 1H), 8.18 (bs, 1H), 7.38 (s, 5H), 7.29 – 7.12 (m, 3H), 7.07 (bs, 2H), 6.93 (bs, 1H), 6.82 (d, J = 7.5 Hz, 1H), 6.50 (bs, 1H), 5.16 (s, 1H), 4.49 (s, 1H), 3.94 (bs, 2H), 3.03 (bs, 2H), 2.84 (bs, 4H), 2.67 (s, 4H), 2.08 (bs, 2H), 1.76 -1.6 (m, 4H), 1.57 (s, 1H), 1.46 (bs, 2H), 1.29 (bs, 2H), 1.02 (bs, 2H).

Intermediate 119.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {5-[(1E)-4-(6-formyl-2-oxo-1,3-benzoxazol-3(2H)-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a foam (480mg, 53%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (5-bromobiphenyl-2-yl)carbamate (Intermediate 114; 554mg, 1.38mmol), 3-but-3-en-1-yl-2-oxo-2,3-dihydro-1,3-benzoxazole-6-carbaldehyde (Intermediate 38; 300mg, 1.38mmol), tri-o-tolylphosphine (336mg, 1.1mmol), N,N-Diisopropylethylamine (0.48mL, 2.76mmol) and palladium acetate (124mg, 0.37mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 538 (M+1)+

Intermediate 120.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (5-{(1E)-4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as solid (316mg, 51%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl {5-[(1E)-4-(6-formyl-2-oxo-1,3-benzoxazol-3(2H)-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate (Intermediate 119; 170mg, 0.43mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (321mg, 0.54mmol) (prepared according to prepara-tion 8 from US20060035931) and sodium triacetoxyborohydride (274mg, 1.29mmol) fol-lowing the experimental procedure as described for Intermediate 7. The crude obtained was used in the next step without further purification.

LRMS (m/z): 979 (M+1)+

Intermediate 121.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (5-{4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate

Obtained as a solid (138mg, 39%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (5-{(1E)-4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 120; 316mg, 0.37mmol) following the experimental procedure as described for Intermediate 67. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 859 (M+1)+

EXAMPLE 22.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (5-{4-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate

Obtained as a yellow solid (28mg, 42%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (5-{4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate (Intermediate 121; 77mg, 0.09mmol) and triethylamine trihydrofluoride (73µL, 0.45mmol) following the experimental procedure as described for Example 1. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 744 (M+1)+

1H NMR (300 MHz, cd3od) δ 8.28 (d, J = 9.8 Hz, 1H), 7.41-7.30 (m, 5H), 7.24 (bs, 2H), 7.15-7.05 (m, 5H), 6.92 (d, J = 8.2 Hz, 1H), 6.57 (d, J = 9.7 Hz, 1H), 5.17 (s, 1H), 4.66 – 4.56 (m, 1H), 3.88 (bs, 2H), 3.82 (bs, 2H), 3.22 (bs, 2H), 3.06 (bs, 2H), 2.99 (s, 1H), 2.92 – 2.64 (m, 3H), 1.96 – 1.63 (m, 3H), 1.57 (s, 1H), 1.40 (s, 1H), 1.37 – 1.22 (m, 3H), 1.15 (bs, 2H), 0.89 (s, 1H).

Intermediate 122.

ethyl 4-(2-aminobiphenyl-4-yl)butanoate

To a solution of (4-bromobiphenyl-2-yl)amine (Intermediate 3; 941mg, 3.79mmol) in tetra-hydrofurane (10mL) was added palladium acetate (9mg, 0.04mmol) and 2-diciclohexylamino-2',6'-dimethoxy-1,1'-biphenyl (31mg, 0.08mmol). Then (4-ethoxy-4-oxobutyl)zinc(II) bromide (9.1mL, 4.55mmol) was added drop wise under argon atmosphere. The reaction mixture was stirred overnight at room temperature. Ethyl ether was added into the mixture and the organics were extracted with hexane. The organic layer was washed with water, dried, filtered and the solvent was removed under reduced pres-sure giving the title compound as an orange oil (1.04g, 97%), which was used in the next step without further purification.

LRMS (m/z): 284(M+1)+

Intermediate 123.

ethyl 4-(2-((((trans)-4-(((benzyloxy)carbonyl)amino)cyclohexyl)oxy)carbonyl) amino)-[1,1'-biphenyl]-4-yl)butanoate

To a solution of triphosgene (0.4g, 1.35mmol) in dichloromethane (20mL) was added drop wise at 0°C a solution of ethyl 4-(2-aminobiphenyl-4-yl)butanoate (Intermediate 122; 1.04g, 3.67mmol), once the addition is finished triethylamine (1.02mL, 7.32mmol) was added. The mixture was stirred 2 hours at room temperature. The solvent was partially removed under reduced pressure without heating and hexane was added to precipitate the salts, the mixture was filtered and the filtrate was evaporated. The corresponding iso-cyanate was dissolved in tetrahydrofurane (10mL) and was added into a solution of benzyl (trans-4-hydroxycyclohexyl)carbamate (Intermediate 42; 0.96g, 3.85mmol) in tetrahydrofurane (5mL). The mixture was stirred for 24 hours at 70°C. The solvent was removed under reduced pressure and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether, giving the title compound as a solid (1.39g, 68%).

LRMS (m/z): 559 (M+1)+

Intermediate 124.

4-(2-(((((trans)-4-(((benzyloxy)carbonyl)amino)cyclohexyl)oxy)carbonyl)amino)-[1,1'-biphenyl]-4-yl)butanoic acid

To a solution of ethyl 4-(2-(((((trans)-4-(((benzyloxy)carbonyl)amino)cyclohexyl)oxy) carbonyl)amino)-[1,1'-biphenyl]-4-yl)butanoate (Intermediate 123; 394mg, 0.71mmol) in tetrahydrofurane (10mL) was added sodium hydroxide (2M, 2mL). The reaction mixture was stirred overnight at room tempera-ture. The solvent was removed under reduced pressure and the crude obtained was di-luted with water and acidified by hydrogen chloride 2N until pH 2-3. Then the crude was ex-tracted with diethyl ether. The organic layer was dried, filtered and the solvent was re-moved under reduced pressure giving the title compound as a white solid (370mg, 90%).

LRMS (m/z): 531 (M+1)+

Intermediate 125.

trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-(4-((4-formylphenyl)amino)-4-oxobutyl)-[1,1'-biphenyl]-2-yl)carbamate

To a solution of 4-(2-(((((trans)-4-(((benzyloxy)carbonyl)amino)cyclohexyl)oxy) carbonyl)amino)-[1,1'-biphenyl]-4-yl)butanoic acid (Intermediate 124; 378mg, 0.32mmol) was added 4-aminobenzaldehyde (80mg, 0.66mmol) and diisopropylethylenediamine (0.32mL, 1.86mmol) under nitrogen atmosphere. Then HATU (306mg, 0.80mmol) was added. The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the crude was partitioned between chloroform and water, the organic layer was washed with water several times, dried, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether, giving the title compound as a solid (198mg, 50%).

LRMS (m/z): 634 (M+1)+

Intermediate 126.

trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-(4-((4-((((R)-2-((tert-butyldimethylsilyl)oxy)-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl) amino)methyl)phenyl)amino)-4-oxobutyl)-[1,1'-biphenyl]-2-yl)carbamate

Obtained as solid (250mg, 98%) from trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-(4-((4-formylphenyl)amino)-4-oxobutyl)-[1,1'-biphenyl]-2-yl)carbamate (Intermediate 125; 198mg, 0.31mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (105mg, 0.27mmol) (prepared according to prepara-tion 8 from US20060035931) and sodium triacetoxyborohydride (199mg, 0.92mmol) fol-lowing the experimental procedure as described for Intermediate 7. The crude obtained was used in the next step without further purification.

LRMS (m/z): 953 (M+1)+

Intermediate 127.

trans-4-aminocyclohexyl [4-(4-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

Obtained as solid (338mg, 88%) from trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-(4-((4-((((R)-2-((tert-butyldimethylsilyl)oxy)-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)phenyl)amino)-4-oxobutyl)-[1,1'-biphenyl]-2-yl)carbamate (Intermediate 126; 418mg, 0.44mmol) following the experimental procedure as described for In-termediate 77 and the crude obtained was used in the next step without further purifica-tion.

LRMS (m/z): 819 (M+1)+

EXAMPLE 23.

trans-4-aminocyclohexyl [4-(4-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate dihydrofluoride

Obtained as a white solid (140mg, 56%) from trans-4-aminocyclohexyl [4-(4-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate

127; 338mg, 0.34mmol) and triethylamine trihydrofluoride (276µL, 1.69mmol) following the experimental procedure as described for Example 1.
LRMS (m/z): 704 (M+1)+
1H NMR (300 MHz, dmso) δ 8.55 (s, 1H), 8.06 (d, J = 10.3 Hz, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.45 – 7.26 (m, 5H), 7.27 – 7.10 (m, 5H), 7.03 (d, J = 8.2 Hz, 1H), 6.87 (s, 1H), 6.44 (d, J = 10.0 Hz, 1H), 5.02 (bs, 1H), 4.68 – 4.53 (m, 2H), 4.4-4.3 (m, 4H), 3.68 (s, 1H), 2.73 (s, 3H), 2.59 (bs, 4H), 2.34 (s, 6H), 1.87 (bs, 4H), 1.80 (bs, 4H), 1.20-1.1 (m, 4H).

Intermediate 128.

2-oxo-2,3-dihydro-1,3-benzoxazole-5-carbonitrile

A mixture of 5-bromobenzo[d]oxazol-2(3H)-one (1g, 4.67mmol) and copper (I) cyanide (0.71g, 7.93mmol) in 3 ml DMF is heated at 150°C under nitrogen atmosphere for 22 hr. After cooling to room temperature, a solution of 1.55 g (31.6 mmol) of sodium cyanide in 32 ml water is added followed by 1 hr stirring. The system is extracted thoroughly with ethyl acetate, washed with brine, dried and concentrated in vacuum to provide 1.04 of the crude mixture, which was carried out forward without further purification.

LRMS (m/z): 161 (M+1)+

Intermediate 129.

2-oxo-2,3-dihydro-1,3-benzoxazole-5-carbaldehyde

Obtained as a yellow solid (1.05g, 82%) from 2-oxo-2,3-dihydro-1,3-benzoxazole-5-carbonitrile (Intermediate 128; 1.09g, 6.81mmol) and Niquel-Aluminium (121.9mg, 1.42mmol) following the experimental procedure as described for Intermediate 2. The crude obtained was used in the next step without further manipulation.
LRMS (m/z): 164 (M+1)+

Intermediate 130.

3-allyl-2-oxo-2,3-dihydro-1,3-benzoxazole-5-carbaldehyde

Obtained as an oil (580mg, 39%) from 2-oxo-2,3-dihydro-1,3-benzoxazole-5-carbaldehyde (Intermediate 129; 1.19g, 0.007mol), potassium carbonate (2.02g, 0.014mmol), potassium iodide (240mg, 1.46mmol) and 3-bromoprop-1-ene (1.98mL, 0.022mol) following the experimental procedure as described for Intermediate 129. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether.

LRMS (m/z): 204 (M+1)+

Intermediate 131.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-3-(5-formyl-2-oxo-1,3-benzoxazol-3(2H)-yl)prop-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a solid (542mg, 90%) from 3-allyl-2-oxo-2,3-dihydro-1,3-benzoxazole-5-carbaldehyde (Intermediate 130; 200mg, 0.98mmol), (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-bromobiphenyl-2-yl)carbamate (Intermediate 5; 400mg, 1mmol), tri-o-tolylphosphine (303mg, 1mmol), N,N-Diisopropylethylamine (0.347mL, 1.99mmol) and palladium acetate (165mg, 0.5mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 553 (M+1)+

Intermediate 132.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]prop-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a foam (750mg, 94%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-3-(5-formyl-2-oxo-1,3-benzoxazol-3(2H)-yl)prop-1-en-1-yl]biphenyl-2-yl}carbamate (Intermedi-ate 131; 552mg, 1.05mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (374mg, 0.95mmol) (prepared according to prepara-tion 8 from US20060035931) and sodium triacetoxyborohydride (670mg, 3.16mmol) fol-lowing the experimental procedure as described for Intermediate 7. The crude obtained was used in the next step without further purification.

LRMS (m/z): 843 (M+1)+

Intermediate 133.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]propyl}biphenyl-2-yl)carbamate

Obtained as a foam (28mg, 14%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]prop-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 132; 200mg, 0.24mmol) and palladium on charcoal (10%, 20mg) following the experimental procedure as described for Intermediate 67. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 845 (M+1)+

EXAMPLE 24.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]propyl}biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a solid (20mg, 92%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]propyl}biphenyl-2-yl)carbamate (Intermediate 133; 28mg, 0.03mmol) and triethylamine trihydrofluoride (30µL, 0.18mmol) following the experimental procedure as described for Example 1.

LRMS (m/z): 730 (M+1)+

1H NMR (300 MHz, cd3od) δ 8.27 (d, J = 9.9 Hz, 1H), 7.47 – 7.26 (m, 6H), 7.23 – 7.03 (m, 6H), 6.95 (d, J = 7.8 Hz, 1H), 6.58 (d, J = 9.6 Hz, 1H), 5.22 (s, 1H), 4.71 (s, 2H), 3.92 (s, 2H), 2.99 (s, 1H), 2.97 – 2.77 (m, 3H), 2.75 (s, 2H), 2.16 (s, 2H), 2.00 (s, 1H), 1.84 (bs3H), 1.58 (bs 3H), 1.28 (s, 1H), 1.15 (bs, 2H).

Intermediate 134.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(5-hydroxy-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-8-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a yellow foam (256mg, 67%) from 8-[(R)-2-amino-1-(tert-butyl-dimethyl-silanoxy)-ethyl-5-hydroxy-4H-benzo[1,4]oxazin-3-one (preparation described in WO2008149110 intermediate 65; 123mg, 0.36mmol), (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-4-(6-formyl-2-oxo-1,3-benzoxazol-3(2H)-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate (Intermediate 39; 210mg, 0.33mmol and sodium triacetoxyborohydride (231mg, 1.09mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 861 (M+1)+

Intermediate 135.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(5-hydroxy-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-8-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate

Obtained as a yellow solid (218mg, 60%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(5-hydroxy-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-8-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 134; 256mg, 0.3mmol) following the experimental procedure as described for Intermediate 77 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 863 (M+1)+

EXAMPLE 25.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-({[(2R)-2-hydroxy-2-(5-hydroxy-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-8-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a white solid (64mg, 48%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(5-hydroxy-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-8-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate (Intermediate 135; 218mg, 0.18mmol) and triethylamine trihydrofluoride (30μL, 0.18mmol) following the experimental procedure as described for Example 1. The crude obtained was purified by column chromatography in reversed phase using as eluents Acetonitrile and Methanol.

LRMS (m/z): 745 (M+1)+

1H NMR (300 MHz, dmso) δ 9.96 (s, 1H), 8.74 (s, 1H), 7.48 – 7.16 (m,10H), 7.12 (bs, 1H), 6.86 (d, J = 8.5 Hz, 1H), 6.51 (d, J = 8.4 Hz, 1H), 4.98 – 4.91 (m, 1H), 4.56 (s, 1H), 4.45 (s, 2H), 3.94 (s, 2H), 3.86 (t, J = 6.5 Hz, 2H), 3.18 (d, J = 12.0 Hz, 2H), 2.88 – 2.69 (m, 4H), 2.63 (bs, 2H), 1.90 (d, J = 5.6 Hz, 1H), 1.74 (d, J = 6.5 Hz, 2H), 1.62 (d, J = 6.1 Hz, 4H), 1.40 (s, 2H).

Intermediate 136.

trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-((E)-3-(5-formyl-2-oxobenzo[d]oxazol-3(2H)-yl)prop-1-enyl)-[1,1'-biphenyl]-2-yl)carbamate

Obtained as a foam (250mg, 81%) from 3-allyl-2-oxo-2,3-dihydro-1,3-benzoxazole-5-carbaldehyde (Intermediate 130; 100mg, 0.49mmol), trans-4-benzylaminocyclohexyl (4-bromobiphenyl-2-yl)carbamate (Intermediate 43; 250mg, 0.48mmol), tri-o-tolylphosphine (150mg, 0.49mmol), N,N-Diisopropylethylamine (0.166mL, 0.95mmol) and palladium acetate (82mg, 0.25mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane:Ether:Ethanol.

LRMS (m/z): 646 (M+1)+

Intermediate 137.

trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-((E)-3-(5-((((R)-2-((tert-butyldimethylsilyl)oxy)-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl) amino)methyl)-2-oxobenzo[d]oxazol-3(2H)-yl)prop-1-enyl)-[1,1'-biphenyl]-2-yl)carbamate

Obtained as a yellow solid (331mg, 89%) from trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-((E)-3-(5-formyl-2-oxobenzo[d]oxazol-3(2H)-yl)prop-1-enyl)-[1,1'-biphenyl]-2-yl)carbamate (Intermediate 136; 250mg, 0.39mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (160mg, 0.41mmol) (prepared according to preparation 8 from US20060035931) and so-dium triacetoxyborohydride (250mg, 1.118mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was used in the next step without further purification.

LRMS (m/z): 965 (M+1)+

Intermediate 138.

trans-4-aminocyclohexyl (4-{3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]propyl}biphenyl-2-yl)carbamate

Obtained as foam (128mg, 45%) from trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-((E)-3-(5-((((R)-2-((tert-butyldimethylsilyl)oxy)-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-2-oxobenzo[d]oxazol-3(2H)-yl)prop-1-enyl)-[1,1'-biphenyl]-2-yl)carbamate (Intermediate 137;331mg, 0.34mmol) following the experimental procedure as described for Intermediate 77. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane:Ether:Ethanol.

LRMS (m/z): 833 (M+1)+

EXAMPLE 26.

trans-4-aminocyclohexyl (4-{3-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]propyl}biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a white solid (100mg, 90%) from trans-4-aminocyclohexyl (4-{3-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]propyl}biphenyl-2-yl)carbamate (Intermediate 138; 128mg, 0.15mmol) and triethylamine trihydrofluoride (125µL, 0.77mmol) following the experimental procedure as described for Example 1.

LRMS (m/z): 718 (M+1)+

1H NMR (300 MHz, dmso) δ 8.57 (s, 1H), 8.12 (d, J = 10.0 Hz, 1H), 7.45 – 7.28 (m, 2H), 7.28 – 6.99 (m, 6H), 6.88 (d, J = 8.1 Hz, 1H), 6.44 (d, J = 9.9 Hz, 1H), 5.07 (s, 1H), 4.31 (s, 1H), 3.85 (s, 1H), 3.77 (bs, 2H), 2.7-2.65 (m, 4H), 2.44 (t, J = 7.1 Hz, 2H), 2.27 (bs, 2H), 2.01 (bs, 1H), 1.80 (bs, 3H), 1.23 (bs, 2H).

Intermediate 139.

1-but-3-en-1-yl-1H-indole-5-carbaldehyde

Obtained as an oil (510mg, 59%) from 1H-indole-5-carbaldehyde (500mg, 3.44mmol), 4-bromobut-1-ene (0.524mL, 5.16mmol) and sodium hydride (60%, 124mg, 5.17mmol) following the experimental procedure as described for Intermediate 33. The crude obtained was used in the next step without further purification.

LRMS (m/z): 200 (M+1)+

Intermediate 140.

trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-((E)-4-(5-formyl-1H-indol-1-yl)but-1-enyl)-[1,1'-biphenyl]-2-yl)carbamate

Obtained as a foam (232mg, 51%) from 1-but-3-en-1-yl-1H-indole-5-carbaldehyde (Intermediate 139; 159mg, 0.8mmol), trans-4-benzylaminocyclohexyl (4-bromobiphenyl-2-yl)carbamate (Intermediate 43; 350mg, 0.67mmol), tri-o-tolylphosphine (203mg, 0.67mmol), N,N-Diisopropylethylamine (0.233mL, 1.34mmol) and palladium acetate (110mg, 0.33mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane:Ether:Ethanol.

LRMS (m/z): 646 (M+1)+

Intermediate 141.

trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-((E)-4-(5-((((R)-2-((tert-butyldimethylsilyl)oxy)-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-1H-indol-1-yl)but-1-enyl)-[1,1'-biphenyl]-2-yl)carbamate

Obtained as a solid (173mg, 50%) from trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-((E)-4-(5-formyl-1H-indol-1-yl)but-1-enyl)-

[1,1'-biphenyl]-2-yl)carbamate (Intermediate 140; 232mg, 0.36mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (121mg, 0.36mmol) (prepared according to preparation 8 from US20060035931) and sodium triacetoxyborohydride (383mg, 1.81mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane:Ether:Ethanol.

LRMS (m/z): 961 (M+1)+

Intermediate 142.

trans-4-aminocyclohexyl (4-{4-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-indol-1-yl]butyl}biphenyl-2-yl)carbamate

Obtained as solid (120mg, 77%) from trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-((E)-4-(5-((((R)-2-((tert-butyldimethylsilyl)oxy)-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-1H-indol-1-yl)but-1-enyl)-[1,1'-biphenyl]-2-yl)carbamate (Intermediate 141; 170mg, 0.18mmol) following the experimental procedure as described for Intermediate 77 and the crude obtained was used in the final step without further purification.

LRMS (m/z): 829 (M+1)+

EXAMPLE 27.

trans-4-aminocyclohexyl (4-{4-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-indol-1-yl]butyl}biphenyl-2-yl)carbamate

Obtained as a solid (42mg, 41%) from trans-4-aminocyclohexyl (4-{4-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-indol-1-yl]butyl}biphenyl-2-yl)carbamate (Intermediate 142; 120mg, 0.14mmol) and triethylamine trihydrofluoride (116µL, 0.72mmol) following the experimental procedure as described for Example 1. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 714 (M+1)+

1H NMR (300 MHz, dmso) δ 8.06 (d, J = 9.9 Hz, 1H), 7.45-7.3 (m, 7H), 7.17 (bs, 3H), 7.06 (bs, 3H), 6.86 (d, J = 8.2 Hz, 1H), 6.39 (d, J = 9.9 Hz, 1H), 6.35 (d, J = 3.0 Hz, 1H), 5.04 (s, 1H), 4.32 (s, 2H), 4.21-4.1 (m, 4H), 3.78 b(s, H), 3.17 (bs, 2H), 2.76 – 2.54 (m, 3H), 1.88 – 1.66 (m, 4H), 1.53 (s, 2H), 1.39 – 1.10 (m, 3H).

Intermediate 143.

3-but-3-en-1-yl-6-[(E)-2-methoxyvinyl]-1,3-benzoxazol-2(3H)-one

To a solution of (methoxymethyl)triphenylphosphonium chloride (5g, 0.014mol) in anhydrous tetrahydrofurane (25mL) was added drop wise at 0°C a solution of Lithium bis(trimethylsilyl)amide (1M in toluene, 15mL). The mixture was stirred for 30 minutes and then a solution of 3-but-3-en-1-yl-2-oxo-2,3-dihydro-1,3-benzoxazole-6-carbaldehyde (Intermediate 38; 1.26gm 0.005mol) in anhydrous tetrahydrofurane (25mL) was added into the mixture and it was allowed to stir for 30 minutes at 0°C and 20 hours at room temperature. A saturated solution of Ammonium chloride was poured into the mixture and the organics were extracted with ethyl acetate, dried, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether giving the title compound as a solid (0.68g, 48%).

LRMS (m/z): 246 (M+1)+

Intermediate 144.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[6-[(E)-2-methoxyvinyl]-2-oxo-1,3-benzoxazol-3(2H)-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a yellow foam (557mg, 66%) from 3-but-3-en-1-yl-6-[(E)-2-methoxyvinyl]-1,3-benzoxazol-2(3H)-one (Intermediate 143; 367mg, 1.5mmol),), (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-bromobiphenyl-2-yl)carbamate (Intermediate 5; 600mg, 1.5mmol), tri-o-tolylphosphine (364mg, 1.2mmol), N,N-Diisopropylethylamine (0.521mL, 2.99mmol) and palladium acetate (134mg, 0.4mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 566 (M+1)+

Intermediate 145.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[2-oxo-6-(2-oxoethyl)-1,3-benzoxazol-3(2H)-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate

To a solution of (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[6-[(E)-2-methoxyvinyl]-2-oxo-1,3-benzoxazol-3(2H)-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 144; 100mg, 0.18mmol) in dioxane (1mL) was added hydrogen chloride (4M in dioxane, 0.11mL, 0.44mmol). The mixture was stirred for 30 minutes and then a cool saturated solution of bicarbonate was poured into the mixture and the organics were extracted with ethyl acetate. The organic layer was washed with bicarbonate 4%, dried, filtered and the solvent was removed under reduced pressure. The title compound was obtained (85mg, 81%), which was used in the next step without further purification.

LRMS (m/z): 568/584 (M+16/M+32)+

Intermediate 146.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[6-(2-{[(2R)-2-{[tert-butyl(dimethyl) silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate

To a solution of (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[2-oxo-6-(2-oxoethyl)-1,3-benzoxazol-3(2H)-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 145; 85mg, 0.14mmol) in dichloromethane (4 mL) was added 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (55mg, 0.14mmol) (prepared according to preparation 8 from US20060035931) and methanol was added until complete dissolution of the mixture, then sodium cianoborohydride (0.4mmol) was added. The reaction is stirred overnight at room temperature. The solvent was removed under reduced pressure and the crude obtained was treated with chloroform giving a foam as the title compound (102mg, 45%), which was used in the next step without further purification.

LRMS (m/z): 871 (M+1)+

Intermediate 147.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-(2-{[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate

Obtained as a crude mixture (76mg) which was taken into the final step without purification, from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-4-[6-(2-{[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate (56mg, 0.04mmol) following the experimental procedure as described for Intermediate 77.

LRMS (m/z): 873 (M+1)+

EXAMPLE 28.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a white solid (33mg, 21%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-(2-{[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

yl)ethyl]amino}ethyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate (Intermediate 147; 400mg, 0.2mmol) and triethylamine trihydrofluoride (116μL, 0.72mmol) following the experimental procedure as described for Example 1. The crude obtained was purified by column chromatography in reversed phase using as eluents Acetonitrile and Methanol.

LRMS (m/z): 758 (M+1)+

1H NMR (300 MHz, dmso) δ 8.64 (s, 1H), 8.16 (d, J = 9.9 Hz, 1H), 7.45 – 7.27 (m, 4H), 7.20 (bs, 3H), 7.18-7.0 (m, 3H), 6.92 (d, J = 8.0 Hz, 2H), 6.49 (d, J = 9.9 Hz, 1H), 5.01 (bs, 1H), 4.45 (bs, 1H), 3.84 (bs, 2H), 3.04 – 2.91 (m, 2H), 2.73 b(s, 2H), 2.63 (bs, 2H), 2.57 (bs, 1H), 2.44 (bs, 2H), 1.76 (bs, 3H), 1.61 (bs, 3H), 1.4-1.3 (m, 4H), 1.31 – 1.24 (m, 4H).

Intermediate 148.

2-oxo-3-pent-4-en-1-yl-2,3-dihydro-1,3-benzoxazole-6-carbaldehyde

Obtained as a solid (460mg, 65%) from 2-oxo-2,3-dihydrobenzo[d]oxazole-6-carbaldehyde (500mg, 3.07mmol), 5-bromopent-1-ene (2.28g, 0.015mol) and potassium carbonate (423mg, 3.07mmol) following the experimental procedure as described for Intermediate 9. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane: Ether .

LRMS (m/z): 232 (M+1)+

Intermediate 149.

trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-((E)-5-(6-formyl-2-oxobenzo[d]oxazol-3(2H)-yl)pent-1-enyl)-[1,1'-biphenyl]-2-yl)carbamate

Obtained as a solid (221mg, 49%) from 2-oxo-3-pent-4-en-1-yl-2,3-dihydro-1,3-benzoxazole-6-carbaldehyde (Intermediate 148; 170mg, 0.74mmol), trans-4-benzylaminocyclohexyl (4-bromobiphenyl-2-yl)carbamate (Intermediate 43; 350mg, 0.67mmol), tri-o-tolylphosphine (203mg, 0.67mmol), N,N-Diisopropylethylamine (0.233mL, 1.34mmol) and palladium acetate (75mg, 0.33mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane:Ether:Ethanol.

LRMS (m/z): 674 (M+1)+

Intermediate 150.

trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-((E)-5-(6-((((R)-2-((tert-butyldimethylsilyl)oxy)-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino) methyl)-2-oxobenzo[d]oxazol-3(2H)-yl)pent-1-enyl)-[1,1'-biphenyl]-2-yl)carbamate

Obtained as a foam (147mg, 45%) from trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-((E)-5-(6-formyl-2-oxobenzo[d]oxazol-3(2H)-yl)pent-1-enyl)-[1,1'-biphenyl]-2-yl)carbamate (Intermediate 146; 221mg, 0.33mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (110mg, 0.33mmol) (prepared according to preparation 8 from US20060035931) and sodium triacetoxyborohydride (347mg, 1.64mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane:Ether:Ethanol.

LRMS (m/z): 993 (M+1)+

Intermediate 151.

trans-4-aminocyclohexyl (4-{5-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]pentyl}biphenyl-2-yl)carbamate

Obtained as a foam (51mg, 42%) from trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-((E)-5-(6-((((R)-2-((tert-butyldimethylsilyl)oxy)-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-2-oxobenzo[d]oxazol-3(2H)-yl)pent-1-enyl)-[1,1'-biphenyl]-2-yl)carbamate (Intermediate 150; 140mg, 0.14mmol) in Methanol following the experimental procedure as described for Intermediate 77 and the crude obtained was used in the final step without further purification.

LRMS (m/z): 861 (M+1)+

EXAMPLE 29.

trans-4-aminocyclohexyl (4-{5-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]pentyl}biphenyl-2-yl)carbamate dihydrofluoride

Obtained as white solid (30mg, 38%) from trans-4-aminocyclohexyl (4-{5-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]pentyl}biphenyl-2-yl)carbamate (Intermediate 151; 51mg, 0.06mmol) and triethylamine trihydrofluoride (48µL, 0.3mmol) following the experimental procedure as described for Example 1.

LRMS (m/z): 746 (M+1)+

1H NMR (300 MHz, dmso) δ 8.55 (s, 1H), 8.11 (d, J = 9.3 Hz, 1H), 7.4-7.2 (m, 4H), 7.18-7.0 (m, 6H), 6.89 (s, 2H), 6.44 (d, J = 10.0 Hz, 1H), 5.04 (s, 1H), 4.32 (s, 1H), 3.75 (bs, 3H), 2.08 (bs, 6H), 1.71 (d, J = 69.8 Hz, 8H), 1.26 (bs, 6H).

Intermediate 152.

3-allyl-6-[(E)-2-methoxyvinyl]-1,3-benzoxazol-2(3H)-one

Obtained as a foam (148mg, 27%) from 3-allyl-2-oxo-2,3-dihydro-1,3-benzoxazole-6-carbaldehyde (Intermediate 2; 485mg, 2.39mmol), (methoxymethyl)triphenylphosphonium chloride (4.1g, 0.012mmol) and Lithium bis(trimethylsilyl)amide (1M in toluene, 12mL) following the experimental procedure as described for Intermediate 143.

LRMS (m/z): 232 (M+1)+

Intermediate 153.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-3-[6-[(E)-2-methoxyvinyl]-2-oxo-1,3-benzoxazol-3(2H)-yl]prop-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a foam (308mg, 80%) from 3-allyl-6-[(E)-2-methoxyvinyl]-1,3-benzoxazol-2(3H)-one (Intermediate 152; 148mg, 0.64mmol), (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-bromobiphenyl-2-yl)carbamate (Intermediate 5; 257mg, 0.64mmol), tri-o-tolylphosphine (156mg, 0.51mmol), N,N-Diisopropylethylamine (0.223mL, 1.28mmol) and palladium acetate (85mg, 0.26mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 552 (M+1)+

Intermediate 154.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-3-[2-oxo-6-(2-oxoethyl)-1,3-benzoxazol-3(2H)-yl]prop-1-en-1-yl}biphenyl-2-yl)carbamate

The crude mixture obtained (209mg) in the previous preparation was used in the next step without further manipulation and it was obtained from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-3-[6-[(E)-2-methoxyvinyl]-2-oxo-1,3-benzoxazol-3(2H)-yl]prop-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 153; 200mg, 0.36mmol) and hydrogen chloride (4M in dioxane, 0.185mL) following the experimental procedure as described for Intermediate 145.

LRMS (m/z): 538 (M+1)+

Intermediate 155.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-3-[6-(2-{[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]prop-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a foam (40mg, 14%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-3-[2-oxo-6-(2-oxoethyl)-1,3-benzoxazol-3(2H)-yl]prop-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 154; 92mg, 0.16mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (63mg, 0.16mmol) (prepared according to preparation 8 from US20060035931) and sodium cianoborohydride (25mg, 0.4mmol) following the experimental procedure as described for Intermediate 146 and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 857 (M+1)+

Intermediate 156.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[6-(2-{[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]propyl}biphenyl-2-yl)carbamate

Obtained as a diacetate salt (83mg, 40%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-3-[6-(2-{[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]prop-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 155; 370mg, 0.22mmol) and palladium on charcoal (10%; 30mg) in a mixture of methanol:acid acetic (2:1) following the experimental procedure as described for Intermediate 67. The crude obtained was purified by column chromatography in reversed phase using as eluents Acetonitrile and Methanol.

LRMS (m/z): 859 (M+1)+

EXAMPLE 30.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[6-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]propyl}biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a white solid (66mg, 93%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[6-(2-{[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]propyl}biphenyl-2-yl)carbamate (Intermediate 156; 83mg, 0.08mmol) and triethylamine trihydrofluoride (45μL, 0.28mmol) following the experimental procedure as described for Example 1.

LRMS (m/z): 744 (M+1)+

1H NMR (300 MHz, dmso) δ 8.69 (s, 1H), 8.17 (d, J = 9.8 Hz, 1H), 7.42-7.3 (m, 5H), 7.19 (dd, J = 20.1, 8.1 Hz, 5H), 7.11 – 7.04 (m, 2H), 6.91 (d, J = 8.0 Hz, 1H), 6.51 (d, J = 9.7 Hz, 1H), 5.12 (s, 1H), 4.49 (s, 1H), 3.05 (bs, 2H), 2.89 (bs, 2H), 2.81 (bs, 4H), 2.66 (m, 6H), 2.37 (bs, 2H), 2.03 (d, J = 7.0 Hz, 2H) , 1.56 (bs, 2H), 1.46 (bs, 2H), 1.27 (bs, 2H).

Intermediate 157.

(3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-5-(6-formyl-2-oxo-1,3-benzoxazol-3(2H)-yl)pent-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a foam (244mg, 81%) from 2-oxo-3-pent-4-en-1-yl-2,3-dihydro-1,3-benzoxazole-6-carbaldehyde (Intermediate 148;120mg, 0.52mmol), (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-bromobiphenyl-2-yl)carbamate (Intermediate 5; 220mg, 0.5mmol), tri-o-tolylphosphine (150mg, 0.49mmol), N,N-Diisopropylethylamine (0.175mL, 1mmol) and palladium acetate (55mg, 0.24mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 552 (M+1)+

Intermediate 158.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-5-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]-oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]pent-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as solid (262mg, 50%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl {4-[(1E)-5-(6-formyl-2-oxo-1,3-benzoxazol-3(2H)-yl)pent-1-en-1-yl]biphenyl-2-yl}carbamate (Intermediate 157; 244mg, 0.44mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (190mg, 0.48mmol) (prepared according to preparation 8 from US20060035931) and sodium triacetoxyborohydride (285mg, 1.34mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 871 (M+1)+

Intermediate 159.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{5-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]pentyl}biphenyl-2-yl)carbamate

Obtained as a diacetate salt (158mg, 53%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{(1E)-5-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]pent-1-en-1-yl}-biphenyl-2-yl)carbamate (Intermediate 158; 262mg, 0.3mmol) and palladium on charcoal (10%, 35mg) following the experimental procedure as described for Intermediate 67. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 873 (M+1)+

EXAMPLE 31.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{5-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]pentyl} biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a white solid (124mg, 99%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{5-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]pentyl}biphenyl-2-yl)carbamate (Intermediate 159; 155mg, 0.16mmol) and triethylamine trihydrofluoride (80µL, 0.49mmol) following the experimental procedure as described for Example 1.

LRMS (m/z): 758 (M+1)+

1H NMR (300 MHz, dmso) δ 8.69 (s, 1H), 8.11 (d, J = 10.0 Hz, 1H), 7.45 – 7.27 (m, 6H), 7.27 – 7.13 (m, 4H), 7.12 – 7.02 (m, 2H), 6.90 (d, J = 8.1 Hz, 1H), 6.46 (d, J = 9.9 Hz, 1H), 5.12 – 5.05 (m, 1H), 4.50 (s, 1H), 3.81 (bs, 4H), 3.08 (dd, J = 13.9, 8.3 Hz, 2H), 2.67 (dd, J = 10.1, 7.7 Hz, 6H), 2.57 (t, J = 7.4 Hz, 2H), 2.42 (d, J = 14.1 Hz, 2H), 1.66 – 1.53 (m, 4H), 1.48 (s, 2H), 1.35 (s, 3H).

Intermediate 160.

trans-4-(benzyloxy)carbonylaminocyclohexyl [4-(4-{[4-({[tert-butyl (dimethyl)silyl]oxy}methyl)-2-chloro-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

Obtained as a white solid (99mg, 83%) from 4-(2-(((((trans)-4-(((benzyloxy)carbonyl)amino)cyclohexyl)oxy)carbonyl)amino)-[1,1'-biphenyl]-4-yl)butanoic acid (Intermediate 124; 78 mg, 0.15mmol), 4-((tert-butyldimethylsilyloxy)methyl)-2-chloro-5-methoxyaniline (Intermediate 39 WO2011/141180A1; 50mg, 0.17mmol), diisopropylethylenediamine (77µL, 0.44mmol) and HATU (73mg, 0.19mmol) following the experimental procedure as described for Intermediate 125 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 683 (tropilic cation)+

Intermediate 161.

trans-4-(benzyloxy)carbonylaminocyclohexyl [4-(4-{[2-chloro-4-(hydroxymethyl)-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

To a solution of trans-4-(benzyloxy)carbonylaminocyclohexyl [4-(4-{[4-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-chloro-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 160; 99mg, 0.12mmol) in anhydrous tetrahydrofurane (1mL) was added triethylamine trihydrofluoride (100μL, 0.61mmol). The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the crude obtained was partitioned between methylene chloride and bicarbonate 4%. The organic layer was washed with water and brine, dried, filtered and the solvent was removed under reduced pressure giving the title compound as a foam (78mg, 91%), which was used in the next step without further purification.

LRMS (m/z): 701 (M+1)+

Intermediate 162.

trans-4-(benzyloxy)carbonylaminocyclohexyl (4-{4-[(2-chloro-4-formyl-5-methoxyphenyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate

Obtained as a foam (81mg, 80%) from trans-4-(benzyloxy)carbonylaminocyclohexyl [4-(4-{[2-chloro-4-(hydroxymethyl)-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 161; 78mg, 0.11mmol) and Dess-Martin periodinane (57mg, 0.13mmol) following the experimental procedure as described for Intermediate 64 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 699 (M+1)+

Intermediate 163.

trans-4-(benzyloxy)carbonylaminocyclohexyl [4-(4-{[4-({[(2R)-2-{[tert-butyl (dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl] amino}methyl)-2-chloro-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

Obtained as a white solid (30mg, 25%) from trans-4-(benzyloxy)carbonyl-aminocyclohexyl(4-{4-[(2-chloro-4-formyl-5-methoxyphenyl)-amino]-4-oxobutyl}-biphenyl-2-yl)-carbamate (Intermediate 162; 81mg, 0.12mmol), 5-((1R)-2-amino-1-

{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (46mg, 0.12mmol) (prepared according to preparation 8 from US20060035931) and sodium triacetoxyborohydride (74mg, 0.35mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane:Ethyl ether:Ethanol.
LRMS (m/z): 508 (M/2)+

Intermediate 164.

trans-4-aminocyclohexyl [4-(4-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-chloro-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

Obtained as a yellow solid (22mg, 84%) from trans-4-(benzyloxy)carbonylaminocyclohexyl [4-(4-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-chloro-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 163; 30mg, 0.03mmol) and palladium on charcoal (10%; 3mg) following the experimental procedure as described for Intermediate 67, and the crude obtained was used in the final step without further manipulation.
LRMS (m/z): 883 (M+1)+

EXAMPLE 32.

trans-4-aminocyclohexyl [4-(4-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate dihydrofluoride

Obtained as a solid (17mg, 80%) from trans-4-aminocyclohexyl [4-(4-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-chloro-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 164; 20mg, 0.02mmol) and triethylamine trihydrofluoride (80μL, 0.49mmol) following the experimental procedure as described for Example 1.
LRMS (m/z): 769 (M+1)+
1H NMR (300 MHz, dmso) δ 9.52 (s, 1H), 8.96 (s, 1H), 8.22 (d, J = 10.0 Hz, 1H), 7.67 (s, 1H), 7.53 (s, 1H), 7.50 – 7.06 (m, 10H), 7.02 (t, J = 6.1 Hz, 1H), 6.55 (d, J = 9.9 Hz, 1H), 5.48 (d, J = 7.1 Hz, 1H), 4.33 (s, 1H), 4.17 (d, J = 5.1 Hz, 2H), 3.80 (s, 3H), 2.99 (d, J = 10.3 Hz, 4H), 2.74 – 2.57 (m, 2H), 2.04 – 1.71 (m, 4H), 1.49 – 1.15 (m, 4H).

Intermediate 165.

2-nitrobiphenyl-4-ol

To a solution of 4-iodo-3-nitrophenol (1g, 0.0037mol) in dioxane (10mL) was added potassium carbonate (2g, 0.014mol) and phenyl boronic acid (0.6g, 0.0049mol), the mixture was placed under nitrogen atmosphere and then norbornylphosphino Pd II (0.11g, 0.002mol) was added into the reaction mixture, which was stirred for 2 hours at 90°C. The mixture was filtered through Celite and the solvent was removed under reduced pressure. The crude was partitioned between ethyl acetate and water, the organic layer was washed with brine, dried, filtered and the solvent was removed under reduced pressure giving the title compound as a solid (890mg, 95%), which was used in the next step without further purification.

LRMS (m/z): 216 (M+1)+

Intermediate 166.

tert-butyl(dimethyl)({6-[(2-nitrobiphenyl-4-yl)oxy]hexyl}oxy)silane

To a solution of 2-nitrobiphenyl-4-ol (Intermediate 165; 890mg, 3.64mmol) was added (6-bromohexyloxy)(tert-butyl)dimethylsilane (1.6mg, 5.7mmol) and potassium carbonate (760mg, 5.5mmol). The mixture was stirred at 70°C during 2 hours. Ethyl acetate was added into the mixture and the organic layer was washed several times with water, dried, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane:Ethyl ether, giving the title compound as a solid (1.5g, 93%).

LRMS (m/z): 430 (M+1)+

Intermediate 167.

{4-[(6-{[tert-butyl(dimethyl)silyl]oxy}hexyl)oxy]biphenyl-2-yl}amine

To a solution of tert-butyl(dimethyl)({6-[(2-nitrobiphenyl-4-yl)oxy]hexyl}oxy)silane (Intermediate 166; 3.53g, 0.008mol) in methanol (20mL) was added palladium on charcoal (10%, 0.1g). The reaction mixture was submitted to a hydrogenation with a hydrogen balloon overnight at room temperature. The catalyst was removed by filtration through Celite and the solvent was removed under reduced pressure giving the title compound an oil (1.52g, 46%), which was used in the next step without further purification.

LRMS (m/z): 400 (M+1)+

Intermediate 168.

tert-butyl({6-[(2-isocyanatobiphenyl-4-yl)oxy]hexyl}oxy)dimethylsilane

Obtained as a solution of toluene (4.2mL, 400mg; 93%) from {4-[(6-{[tert-butyl(dimethyl)silyl]oxy}hexyl)oxy]biphenyl-2-yl}amine (Intermediate 167; 400mg, 1mmol), triphosgene (120mg, 0.4mmol) and triethylamine (279µL, 2mmol) following the experimental procedure as described for Intermediate 4 and the crude obtained was used as a solution of the title compound in toluene.

LRMS (m/z): 426 (M+1)+

Intermediate 169.

trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-((6-((tert-butyldimethylsilyl) oxy)hexyl)oxy)-[1,1'-biphenyl]-2-yl)carbamate

Obtained as a solid (117mg, 37%) from benzyl (trans-4-hydroxycyclohexyl)carbamate (117mg, 0.47mmol) and tert-butyl({6-[(2-isocyanatobiphenyl-4-yl)oxy]hexyl}oxy)-dimethylsilane (200mg, 0.47mmol) following the experimental procedure as described for Intermediate 43 and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane:Ethyl ether: Ethanol.

LRMS (m/z): 675 (M+1)+

Intermediate 170.

trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-((6-hydroxyhexyl)oxy)-[1,1'-biphenyl]-2-yl)carbamate

Obtained as a foam (103mg, 98%) from trans-4-(((benzyloxy)carbonyl)amino)-cyclohexyl (4-((6-((tert-butyldimethylsilyl)oxy)hexyl)oxy)-[1,1'-biphenyl]-2-yl)carbamate (Intermediate 169; 120mg, 0.18mmol) and triethylamine trihydrofluoride (80µL, 0.49mmol) following the experimental procedure as described for Example 1. The crude obtained was used in the next step without further purification.

LRMS (m/z): 561 (M+1)+

Intermediate 171.

trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-((6-oxohexyl)oxy)-[1,1'-biphenyl]-2-yl)carbamate

Obtained as a foam (83mg, 98%) from trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-((6-hydroxyhexyl)oxy)-[1,1'-biphenyl]-2-yl)carbamate (Intermediate 170; 120mg, 0.18mmol) and Dess-Martin periodinane (63mg, 0.15mmol) following the experimental procedure as described for Intermediate 64 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 559 (M+1)+

Intermediate 172.

trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-((6-(((R)-2-((tert-butyldimethylsilyl)oxy)-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl) amino)hexyl)oxy)-[1,1'-biphenyl]-2-yl)carbamate

Obtained as a solid (30mg, 58%) from trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-((6-oxohexyl)oxy)-[1,1'-biphenyl]-2-yl)carbamate (Intermediate 171; 20mg, 0.04mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (14mg, 0.04mmol) (prepared according to preparation 8 from US20060035931) and sodium triacetoxyborohydride (40mg, 0.19mmol) following the experimental procedure as described for Intermediate 7. The crude mixture was used in the next step without further purification.

LRMS (m/z): 879 (M+1)

Intermediate 173.

trans-4-aminocyclohexyl {4-[(6-{[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}hexyl)oxy]biphenyl-2-yl}carbamate

Obtained as a foam (30mg, 41%) from trans-4-(((benzyloxy)carbonyl)amino)cyclohexyl (4-((6-(((R)-2-((tert-butyldimethylsilyl)oxy)-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)-[1,1'-biphenyl]-2-yl)carbamate (Intermediate 172; 81mg, 0.09mmol) following the experimental procedure as described for Intermediate 77 but using as a solvent methanol instead of acetic acid. The crude obtained was used in the next step without further purification.

LRMS (m/z): 744 (M+1)

EXAMPLE 33.

trans-4-aminocyclohexyl {4-[(6-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}hexyl)oxy]biphenyl-2-yl}carbamate dihydrofluoride

Obtained as a solid (18mg, 71%) from trans-4-aminocyclohexyl {4-[(6-{[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}hexyl)-oxy]biphenyl-2-yl}carbamate (Intermediate 173; 30mg, 0.04mmol) and triethylamine trihydrofluoride (80µL, 0.49mmol) following the experimental procedure as described for Example 1.

LRMS (m/z): 629 (M+1)+

1H NMR (300 MHz, cd3od) δ 8.36 (d, J = 9.7 Hz, 1H), 7.79 (s, 1H), 7.41 (bs, 2H), 7.45-7.25 (m, 4H), 7.17 (d, J = 8.5 Hz, 1H), 7.03 (d, J = 7.9 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 6.70 (d, J = 9.6 Hz, 1H), 5.38 (s, 1H), 4.91 (bs, 1H), 4.54 (bs, 1H), 4.04 (bs, 2H), 3.18

(d, J = 6.9 Hz, 2H), 3.06 (bs, 2H), 2.04 (bs, 4H), 1.83 (bs, 4H), 1.46 (bs, 6H), 1.36 – 1.26 (m, 2H).

Intermediate 174.

tert-butyl (trans-4-hydroxycyclohexyl)carbamate

To a solution of trans-4-aminocyclohexanol (15g, 0.13mol) in acetonitrile (250mL) was added in portions di-tert-butyldicarbonate (31g, 0.14mol). The mixture was stirred at room temperature overnight. The solid was filtered and washed with Hexane/Ethyl Acetate, obtaining the title compound as a white solid (23.7g, 84%), which was used in the next step without further purification.

1H NMR (300 MHz, cdcl3) δ 4.35 (bs, 1H), 3.60 (t, J = 10.5 Hz, 1H), 3.42 (bs, 1H), 2.05-1.78 (m, 4H), 1.60 (s, 2H), 1.42 (s, 9H), 1.38 – 1.26 (m, 2H), 1.26 – 1.06 (m, 2H).

Intermediate 175.

trans-4-tert-butylaminocyclohexyl (5-bromobiphenyl-2-yl)carbamate

Obtained as a white solid (890mg, 85%) from 5-bromo-2-isocyanatobiphenyl (Intermediate 113; 552mg, 2.01mmol) and tert-butyl (trans-4-hydroxycyclohexyl)-carbamate (Intermediate 174; 433mg, 2.01mmol) following the experimental procedure as described for Intermediate 43 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 490 (M+1)+

Intermediate 176.

trans-4-tert-butylaminocyclohexyl {5-[(1E)-4-(6-formyl-2-oxo-1,3-benzoxazol-3(2H)-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a yellow foam (235mg, 33%) from trans-4-tert-butylaminocyclohexyl (5-bromobiphenyl-2-yl)carbamate (Intermediate 175; 530mg, 1.08mmol), 3-but-3-en-1-yl-2-oxo-2,3-dihydro-1,3-benzoxazole-6-carbaldehyde (Intermediate 38; 235mg, 1.08mmol), tri-o-tolylphosphine (263mg, 0.86mmol), N,N-Diisopropylethylamine (0.377mL, 2.16mmol) and palladium acetate (69mg, 0.31mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether:ethanol.

LRMS (m/z): 626 (M+1)+

Intermediate 177.

trans-4-tert-butylaminocyclohexyl (5-{4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]-oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate

Obtained as a pale yellow solid (179mg, 50%) from trans-4-tert-butylaminocyclohexyl {5-[(1E)-4-(6-formyl-2-oxo-1,3-benzoxazol-3(2H)-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate (Intermediate 176; 230mg, 0.37mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (145mg, 0.37mmol) (prepared according to preparation 8 from US20060035931) and sodium triacetoxyborohydride (234mg, 1.1mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether:ethanol.

LRMS (m/z): 945 (M+1)+

Intermediate 178.

trans-4-tert-butylaminocyclohexyl (5-{4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]-oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate

Obtained as a foam (129mg, 69%) from trans-4-tert-butylaminocyclohexyl (5-{4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate (Intermediate 177; 174mg, 0.18mmol) and palladium on charcoal (10%, 20mg) following the experimental procedure as described for Intermediate 67 and the crude mixture obtained was used in the final step without further purification.

LRMS (m/z): 947 (M+1)+

EXAMPLE 34.

trans-4-aminocyclohexyl (5-{4-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate dihydrochloride

Obtained as a white solid (19mg, 33%) from trans-4-tert-butylaminocyclohexyl (5-{4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate (Intermediate 178; 74mg, 0.08mmol) and hydrogen chloride (4N in dioxane; 3mL) following the experimental procedure as described for Intermediate 21. The crude obtained was purified by column chromatography in reversed phase using as eluents Acetonitrile and Methanol.

LRMS (m/z): 732 (M+1)+

1H NMR (300 MHz, dmso) δ 8.52 (s, 1H), 8.12 (d, J = 10.0 Hz, 1H), 7.45 – 7.26 (m, 5H), 7.27 – 7.08 (m, 5H), 7.05 (d, J = 8.3 Hz, 1H), 6.90 (d, J = 8.1 Hz, 1H), 6.45 (d, J = 9.9 Hz, 1H), 5.04 (bs, 1H), 4.32 (bs, 2H), 4.12 (bs, 2H), 3.83 (bs, 2H), 3.73 (bs, 2H), 3.17 (bs, 4H), 2.63 (bs, 2H), 2.44 (bs, 2H), 1.77 (bs, 4H), 1.23 (bs, 4H).

Intermediate 179.

4-(but-3-en-1-ylamino)-3-nitrobenzonitrile

Obtained as a yellow solid (2g, 67%) from 4-amino-3-nitrobenzonitrile (2.5g, 0.015mol), 4-bromobut-1-ene (1.33mL, 0.014mol) and potassium carbonate (10.5g, 0.076mol) following the experimental procedure as described for Intermediate 9 and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether.

LRMS (m/z): 218 (M+1)+

Intermediate 180.

3-amino-4-(but-3-en-1-ylamino)benzonitrile

To a solution of 4-(but-3-en-1-ylamino)-3-nitrobenzonitrile (Intermediate 179; 2g, 0.009mol) in ethanol (20mL) was added Tin(II)chloride (11.1g, 0.049mol). The reaction mixture was stirred at 90°C for 4 hours. The solvent was partially removed and sodium hydroxide was added to precipitate salts, which were filtrated. The solvent was removed under reduced pressure to give the title compound (1.6g, 92%), which was used in the next step without further purification.

LRMS (m/z): 188 (M+1)+

Intermediate 181.

1-but-3-en-1-yl-1H-1,2,3-benzotriazole-5-carbonitrile

3-amino-4-(but-3-en-1-ylamino)benzonitrile (Intermediate 180; 1g, 5.34mmol) was dissolved in hydrogen chloride (5N, 9.6mL). The reaction mixture was cooled to 0°C and a solution of sodium nitrite (0.55g, 8.01mmol) in water (20mL) was added. The reaction mixture was stirred for 2 hours at room temperature. Water was added into the mixture and the crude was extracted with chloroform. The solvent was removed under reduced pressure and the crude obtained was crystallized with pentane giving the title compound as a solid (0.84g, 79%).

LRMS (m/z): 199 (M+1)+

Intermediate 182.

1-but-3-en-1-yl-1H-1,2,3-benzotriazole-5-carbaldehyde

Obtained as an oil (167mg, 33%) from 1-but-3-en-1-yl-1H-1,2,3-benzotriazole-5-carbonitrile (Intermediate 181; 350mg, 1.77mmol) in formic acid 80% and Niquel-aluminium (391mg, 4.4mmol) following the experimental procedure as described for Intermediate 2 and the crude was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether.

LRMS (m/z): 202 (M+1)+

Intermediate 183.

trans-4-tert-butylaminocyclohexyl (4-bromobiphenyl-2-yl)carbamate

Obtained as a solid (1.2g, 64%) from 4-bromo-2-isocyanatobiphenyl (Intermediate 4; 1.05g, 3.83mmol) and tert-butyl (trans-4-hydroxycyclohexyl)carbamate (Intermediate 174; 0.82g, 3.83mmol) following the experimental procedure as described for Intermediate 43 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 490 (M+1)+

Intermediate 184.

trans-4-tert-butylaminocyclohexyl {4-[(1E)-4-(5-formyl-1H-1,2,3-benzotriazol-1-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a yellow foam (130mg, 42%) from trans-4-tert-butylaminocyclohexyl (4-bromobiphenyl-2-yl)carbamate (Intermediate 183; 250mg, 0.51mmol), 1-but-3-en-1-yl-1H-1,2,3-benzotriazole-5-carbaldehyde (Intermediate 182; 161mg, 0.8mmol), tri-o-tolylphosphine (155mg, 0.51mmol), N,N-Diisopropylethylamine (0.177mL, 1.02mmol) and palladium acetate (57mg, 0.25mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether:ethanol.

LRMS (m/z): 610 (M+1)+

Intermediate 185.

trans-4-tert-butylaminocyclohexyl (4-{(1E)-4-[5-({[(2R)-2-{[tert-butyl(dimethyl)-silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a solid (81mg, 41%) from trans-4-tert-butylaminocyclohexyl {4-[(1E)-4-(5-formyl-1H-1,2,3-benzotriazol-1-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate (Intermediate 184; 130mg, 0.21mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (145mg, 0.37mmol) (prepared according to preparation 8 from US20060035931) and sodium triacetoxyborohydride (234mg, 1.1mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether:ethanol.

LRMS (m/z): 929 (M+1)+

Intermediate 186.

trans-4-tert-butylaminocyclohexyl (4-{4-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]-oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]butyl}biphenyl-2-yl)carbamate

Obtained as solid (74mg, 73%) from trans-4-tert-butylaminocyclohexyl (4-{(1E)-4-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 185; 85mg, 0.09mmol) and palladium on charcoal (10%, 10mg) following the experimental procedure as described for Intermediate 67 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 931 (M+1)+

EXAMPLE 35.

trans-4-aminocyclohexyl (4-{4-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]butyl} biphenyl-2-yl)carbamate

Obtained as solid (8mg, 12%) from trans-4-tert-butylaminocyclohexyl (4-{4-[5-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]butyl}biphenyl-2-yl)carbamate (Intermediate 186; 85mg, 0.09mmol) and hydrogen chloride (4N in dioxane; 5mL) following the experimental procedure as described for Intermediate 21. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 716 (M+1)+

1H NMR (300 MHz, cd3od) δ 8.25 (d, J = 9.8 Hz, 1H), 7.91 (d, J = 7.3 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.44 – 7.27 (m, 5H), 7.14 (bs, 2H), 6.99 (d, J = 7.7 Hz, 1H), 6.94 – 6.86 (m, 1H), 6.55 – 6.48 (m, 1H), 5.23 – 5.16 (m, 1H), 4.75 (dd, J = 14.0, 7.2 Hz, 2H), 4.45 (s, 1H), 3.97 (s, 1H), 3.84 (dd, J = 10.5, 7.8 Hz, 1H), 3.65 – 3.54 (m, 1H), 2.95 – 2.72 (m, 2H), 2.66 (s, 1H), 2.12 – 1.99 (m, 2H), 1.91 (d, J = 5.5 Hz, 2H), 1.67 (d, J = 7.0 Hz, 2H), 1.43 – 1.22 (m,5H).

Intermediate 187.

ethyl 4-(6-aminobiphenyl-3-yl)butanoate

Obtained as an orange oil (1g, 87%) from (5-bromobiphenyl-2-yl)amine (Intermediate 112; 1g, 4.03mmol), palladium acetate (9.05mg, 0.04mmol), 2-diciclohexylamino-2',6'-dimethoxy-1,1'-biphenyl (33mg, 0.08mmol) and (4-ethoxy-4-oxobutyl)zinc(II) bromide (9.67mL, 4.84mmol) following the experimental procedure as described for Intermediate 122 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 284 (M+1)+

Intermediate 188.

ethyl 4-(6-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy)carbonyl]amino}biphenyl-3-yl)butanoate

Obtained as a solid (0.94g, 51%) from ethyl 4-(6-aminobiphenyl-3-yl)butanoate (Intermediate 187; 1g, 3.53mmol), tert-butyl (trans-4-hydroxycyclohexyl)carbamate (Intermediate 174; 0.8g, 3.71mmol), triphosgene (0.42g, 1.41mmol) and triethylamine (0.983mL, 7.05mmol) following the experimental procedure as described for Intermediate 123 and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether:ethanol.

LRMS (m/z): 525 (M+1)+

Intermediate 189.

4-(6-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy) carbonyl]amino}-biphenyl-3-yl)butanoic acid

Obtained as a solid (880mg, 98%) from ethyl 4-(6-{[({trans-4-[(tert-butoxycarbonyl)-amino]cyclohexyl}oxy)carbonyl]amino}biphenyl-3-yl)butanoate (Intermediate 188; 940mg, 1.79mmol) and sodium hydroxide (2N, 4.48mL) following the experimental procedure as described for Intermediate 124 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 497 (M+1)+

Intermediate 190.

tert-butyl-trans-4-aminocyclohexyl (5-{4-[(4-formylphenyl)amino]-4-oxobutyl}-biphenyl-2-yl)carbamate

Obtained as a solid (740mg, 69%) from 4-(6-{[({trans-4-[(tert-butoxycarbonyl)amino]-cyclohexyl}oxy)carbonyl]amino}biphenyl-3-yl)butanoic acid (Intermediate 189; 880mg, 1.77mmol), 4-aminobenzaldehyde (236mg, 1.95mmol), diisopropylethylenediamine (0.925mL, 5.32mmol) and HATU (1g, 2.66mmol) following the experimental procedure as described for Intermediate 125 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 600 (M+1)+

Intermediate 191.

tert-butyl-trans-4-aminocyclohexyl [5-(4-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]-oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]-amino}-4-oxobutyl)biphenyl-2-yl]carbamate

Obtained as a solid (770mg, 68%) from tert-butyl-trans-4-aminocyclohexyl (5-{4-[(4-formylphenyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate (Intermediate 190; 740mg, 1.23mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (413mg, 1.23mmol) (prepared according to preparation 8 from US20060035931) and sodium triacetoxyborohydride (784mg, 3.7mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether:ethanol.

LRMS (m/z): 919 (M+1)+

EXAMPLE 36.

trans-4-aminocyclohexyl [5-(4-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

Obtained as a white solid (110mg, 18%) from tert-butyl-trans-4-aminocyclohexyl [5-(4-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 191; 770mg, 0.84mmol) and hydrogen chloride (8N in dioxane, 8mL) following the experimental procedure as described for Intermediate 21 and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 704 (M+1)+

1H NMR (400 MHz, dmso) δ 8.56 (s, 1H), 8.09 (d, J = 10.2 Hz, 1H), 7.50 (d, J = 8.3 Hz, 2H), 7.35 (t, J = 28.1 Hz, 5H), 7.20 (dd, J = 25.0, 16.9 Hz, 4H), 7.04 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.45 (d, J = 9.8 Hz, 1H), 5.04 (s, 1H), 4.33 (s, 2H), 2.69 (d, J = 20.4 Hz, 3H), 2.64 (s, 5H), 2.33 (s, 2H), 1.91 (s, 2H), 1.79 (s, 4H), 1.21 (s, 4H).

Intermediate 192.

methyl (4E)-5-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy)-carbonyl]amino}biphenyl-4-yl)pent-4-enoate

Obtained as a solid (0.57g, 44%) from trans-4-tert-butylaminocyclohexyl (4-bromobiphenyl-2-yl)carbamate (Intermediate 183; 1.2g, 2.45mmol), methyl pent-4-enoate (0.36mL, 2.94mmol), tri-o-tolylphosphine (0.8g, 2.63mmol), N,N-Diisopropylethylamine (0.85mL, 4.88mmol) and palladium acetate (280mg, 1.25mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether.

LRMS (m/z): 523 (M+1)+

Intermediate 193.

(4E)-5-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy) carbonyl]amino}biphenyl-4-yl)pent-4-enoic acid

Obtained as a solid (599mg, 97%) from methyl (4E)-5-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy)carbonyl]amino}biphenyl-4-yl)pent-4-enoate (Intermediate 192; 570mg, 1.09mmol) and sodium hydroxide (2N, 4.5mL) following the experimental procedure as described for Intermediate 124 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 509 (M+1)+

Intermediate 194.

trans-4-aminocyclohexyl (4-{(1E)-5-[(4-formylphenyl)amino]-5-oxopent-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a solid (400mg, 88%) from (4E)-5-(2-{[({trans-4-[(tert-butoxycarbonyl)-amino]cyclohexyl}oxy)carbonyl]amino}biphenyl-4-yl)pent-4-enoic acid (Intermediate 193; 300mg, 0.59mmol), 4-aminobenzaldehyde (80mg, 0.66mmol), diisopropylethylenediamine (0.31mL, 1.78mmol) and HATU (340mg, 0.89mmol) following the experimental procedure as described for Intermediate 125 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 612 (M+1)+

Intermediate 195.

trans-4-aminocyclohexyl [4-((1E)-5-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-5-oxopent-1-en-1-yl)biphenyl-2-yl]carbamate

Obtained as a solid (60mg, 12%) from trans-4-aminocyclohexyl (4-{(1E)-5-[(4-formylphenyl)amino]-5-oxopent-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 194; 400mg, 0.52mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (175mg, 0.52mmol) (prepared according to preparation 8 from US20060035931) and sodium triacetoxyborohydride (333mg, 1.57mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel twice, first, eluting with a mixture of hexane:ether:ethanol and second, in reversed phase using as eluents Acetonitrile and Methanol.

LRMS (m/z): 931 (M+1)+

Intermediate 196.

trans-4-aminocyclohexyl [4-(5-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-5-oxopentyl)biphenyl-2-yl]carbamate

Obtained as a crude mixture (60mg) from trans-4-aminocyclohexyl [4-((1E)-5-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-5-oxopent-1-en-1-yl)biphenyl-2-yl]carbamate (Intermediate 195; 60mg, 0.06mmol) and palladium on charcoal (10%, 10mg) following the experimental procedure as described for Intermediate 67 and the crude mixture obtained was taken forward without purification.

LRMS (m/z): 933 (M+1)+

EXAMPLE 37.

trans-4-aminocyclohexyl [4-(5-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-5-oxopentyl)biphenyl-2-yl]carbamate dihydrochloride

Obtained as a white salt (55mg, 97%) from trans-4-aminocyclohexyl [4-(5-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-5-oxopentyl)biphenyl-2-yl]carbamate (Intermediate 196; 65mg, 0.07mmol) and hydrogen chloride (4M in dioxane , 2mL) following the experimental procedure as described for Intermediate 21.

LRMS (m/z): 718 (M+1)+

1H NMR (400 MHz, dmso) δ 8.12 (d, J = 10.0 Hz, 1H), 7.92 (bs, 3H), 7.60 (bs, 2H), 7.48 – 7.25 (m, 5H), 7.14 (bs, 3H), 6.96 (bs, 1H), 6.53 (d, J = 9.8, Hz1H), 5.43 – 5.32 (m, 1H), 4.29 b(s, 1H), 4.11 (bs, 2H), 3.24 (bs, 4H), 2.96 (bs, 2H), 2.60 (bs, 2H), 2.34 (bs, 2H), 1.87 (bs, 3H), 1.61 (bs, 3H), 1.21 (bs, 3H).

Intermediate 197.

N-benzyl-trans-4-aminocyclohexyl (4-{4-[(4-{2-[((2R)-2-[8-(benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl]-2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-tert-butylamino]ethyl}phenyl)carbamateamino]-4-oxobutyl}biphenyl-2-yl)carbamate

Obtained as a solid (124mg, 50%) from 4-(2-(((((trans)-4-(((benzyloxy)carbonyl)amino)-cyclohexyl)oxy)carbonyl)amino)-[1,1'-biphenyl]-4-yl)butanoic acid (Intermediate 124; 85mg, 0.16mmol), tert-butyl [2-(4-aminophenyl)ethyl]((2R)-2-[8-(benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl]-2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)carbamate (Intermediate 121 from WO2009106351A1; 101mg, 0.16mmol), diisopropylethylenediamine (55µL, 0.32mmol) and HATU (132mg, 0.35mmol) following the experimental procedure as described for Intermediate 125. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 579 (M/2)

EXAMPLE 38.

trans-4-aminocyclohexyl [4-(4-{[4-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate dihydrochloride

To a solution of N-benzyl-trans-4-aminocyclohexyl (4-{4-[(4-{2-[((2R)-2-[8-(benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl]-2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-tert-butylamino]-ethyl}phenyl)carbamateamino]-4-oxobutyl}biphenyl-2-yl)carbamate (Intermediate 197; 125mg, 0.08mmol) was added hydrogen chloride (5N, 165µL) and the reaction mixture was stirred for 5 hours, then hydrogen chloride (4M in dioxane, 420µL) was added. The mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the crude obtained was dissolved with a mixture of Acetic Acid and Methanol (2:1) and palladium on charcoal (10%) was added. The reaction mixture was submitted to hydrogen with a balloon and it was stirred 24h at room temperature. The catalyst was filtered through Celite and the solvent was removed under reduced pressure to afford a crude, which was treated with hydrogen chloride (4M in dioxane; 2mL) and stirred 24h at room temperature. The solvent was removed under reduced pressure and the crude obtained was purified by column chromatography with silica gel in reversed phase using as eluents Acetonitrile and Methanol. The title compound was obtained as a yellow foam (61mg, 30%)

LRMS (m/z): 718 (M+1)+

1H NMR (300 MHz, dmso) δ 8.59 (s, 1H), 8.24 (d, J = 10.0 Hz, 1H), 8.00 (s, 2H), 7.56 (d, J = 8.6 Hz, 1H), 7.4-7.3 (m, 5H), 7.26 – 7.08 (m, 2H), 7.01 (d, J = 8.1 Hz, 1H), 6.57 (d, J = 10.0 Hz, 1H), 5.42 (s, 1H), 4.34 (bs, 2H), 3.17 (bs, 2H), 3.04 – 2.71 (m, 5H), 2.48 – 2.26 (m, 6H), 2.06 – 1.74 (m, 3H), 1.33 (bs, 4H).

Intermediate 198.

2-amino-4-methoxyphenol

To a solution of 4-methoxy-2-nitrophenol (5g, 0.029mol) in methanol (250mL) was added palladium on charcoal (10%, 0.5g). The mixture was submitted to a H2 balloon over weekend at room temperature. The catalyst was filtered through Celite and the solvent was removed under reduced pressure giving the title compound as a yellow solid (4.85g, 93%).

LRMS (m/z): 140 (M+1)+

Intermediate 199.

5-methoxy-1,3-benzoxazol-2(3H)-one

A mixture of 2-amino-4-methoxyphenol (Intermediate 198; 4.8g, 0.027mol) and urea (2.65g, 0.044mol) was heated at 180°C during 2 hours. Hydrogen chloride 1N (70mL) was poured into the mixture and the crude was extracted with Ethyl Acetate, the organic layer was washed with water and brine, dried, filtered and the solvent was removed under reduced pressure giving the title compound as a solid (4.5g, 99%).

LRMS (m/z): 166 (M+1)+

Intermediate 200.

6-bromo-5-methoxy-1,3-benzoxazol-2(3H)-one

To a solution of 5-methoxy-1,3-benzoxazol-2(3H)-one (Intermediate 199; 4.5g, 0.027mol) in acetic acid (16mL) was added drop wise at 15°C acid bromide (33% in acetic acid; 12.5mL, 0.069mol) and hydrogen peroxide (3.6mL, 0.035mol). The mixture was stirred at room temperature 2 hours. Water was poured into the mixture and the crude was extracted with ethyl acetate. The solvent was removed under reduced pressure, giving the title compound as a solid (5.5g, 82%).

LRMS (m/z): 245 (M+1)+

Intermediate 201.

5-methoxy-2-oxo-2,3-dihydro-1,3-benzoxazole-6-carbaldehyde

To a solution of 6-bromo-5-methoxy-1,3-benzoxazol-2(3H)-one (Intermediate 200; 1g, 4.1mmol) in anhydrous tetrahydrofurane (10mL) was added drop wise at -78°C Methyl magnesium bromide 3M in diethyl ether (1.5mL, 4.5mmol), then was slowly added 35mL of anhydrous tetrahydrofurane. Once the temperature was -78°C again, tert-butyl lithium (1.7M in pentane, 8.7mL, 14.7mmol) was added into the mixture. After some minutes dimethylformamide (1.9mL, 24.4mmol) was added and the reaction mixture was stirred 3 hours at room temperature. Water was slowly added into the mixture and tetrahydrofurane was partially evaporated. Ethyl acetate was added and the organic layer was washed with water, dried, filtered and evaporated to dryness. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether giving the title compound as a solid (310mg, 39%).

LRMS (m/z): 194 (M+1)+

Intermediate 202.

3-but-3-en-1-yl-5-methoxy-2-oxo-2,3-dihydro-1,3-benzoxazole-6-carbaldehyde

Obtained as foam (267mg, 68%) from 5-methoxy-2-oxo-2,3-dihydro-1,3-benzoxazole-6-carbaldehyde (Intermediate 201; 307mg, 1.59mmol), 4-bromobut-1-ene (200µL, 1.97mmol) and potassium carbonate (220mg, 1.59mmol) following the experimental procedure as described for Intermediate 9. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether.

LRMS (m/z): 248 (M+1)+

Intermediate 203.

N-benzylcarbamate-trans-4-aminocyclohexyl {4-[(1E)-4-(6-formyl-5-methoxy-2-oxo-1,3-benzoxazol-3(2H)-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as foam (194mg, 69%) from trans-4-benzylaminocyclohexyl (4-bromobiphenyl-2-yl)carbamate (Intermediate 43; 540mg, 1.03mmol), 3-but-3-en-1-yl-5-methoxy-2-oxo-2,3-dihydro-1,3-benzoxazole-6-carbaldehyde (Intermediate 202; 267mg, 1.08mmol), tri-o-tolylphosphine (314mg, 1.03mmol), N,N-Diisopropylethylamine (0.360mL, 2.07mmol) and palladium acetate (115mg, 0.51mmol) following the experimental procedure as described for intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether.

LRMS (m/z): 690 (M+1)+

Intermediate 204.

N-benzylcarbamate-trans-4-aminocyclohexyl (4-{(1E)-4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]-

amino}methyl)-5-methoxy-2-oxo-1,3-benzoxazol-3(2H)-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a solid (328mg, 61%) from N-benzylcarbamate-trans-4-aminocyclohexyl {4-[(1E)-4-(6-formyl-5-methoxy-2-oxo-1,3-benzoxazol-3(2H)-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate (Intermediate 203; 369mg, 0.53mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (211mg, 0.54mmol) (prepared according to preparation 8 from US20060035931) and sodium triacetoxyborohydride (345mg, 1.63mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel in reversed phase using as eluents Acetonitrile and Methanol.

LRMS (m/z): 504 (M/2)

Intermediate 205.

trans-4-aminocyclohexyl (4-{4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxy-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate

Obtained as a foam (214mg, 75%) from N-benzylcarbamate-trans-4-aminocyclohexyl (4-{(1E)-4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxy-2-oxo-1,3-benzoxazol-3(2H)-yl]but-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 204; 328mg, 0.33mmol) and palladium on charcoal (10%, 80mg) following the experimental procedure as described for Intermediate 67 and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 877 (M+1)+

EXAMPLE 39.

trans-4-aminocyclohexyl (4-{4-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxy-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a white solid (180mg, 92%) from trans-4-aminocyclohexyl (4-{4-[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxy-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate (Intermediate 205; 214mg, 0.24mmol) and triethylamine trihydrofluoride (140µL, 0.86mmol) following the experimental procedure as described for Example 1.

LRMS (m/z): 762 (M+1)+

1H NMR (300 MHz, cd3od) δ 8.25 (d, J = 9.6 Hz, 1H), 7.48 – 7.28 (m, 6H), 7.27 – 7.11 (m, 2H), 7.11 – 6.91 (m, 4H), 6.62 (d, J = 9.7 Hz, 1H), 5.39 (bs, 1H), 4.48 (bs, 1H), 4.29 (bs, 2H), 3.92 (bs, 3H), 3.19 (bs, 2H), 3.06 (bs, 2H), 2.72 (bs, 2H), 2.01 (bs, 3H), 1.86 (bs, 2H), 1.73 (bs, 4H), 1.5-1.4 (m, 4H).

Intermediate 206.

trans-4-[methyl(3-phenylpropyl)amino]cyclohexanol

Obtained as an oil (1.3g, 97%) from trans-4-(methylamino)cyclohexanol (0.7g, 5.42mmol), 3-phenylpropanal (0.78mL, 5.92mmol) and sodium triacetoxyborohydride (344mg, 1.63mmol) following the experimental procedure as described for Intermediate 7 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 248 (M+1)+

Intermediate 207.

ethyl 4-(2-{[({trans-4-[methyl(3-phenylpropyl)amino]cyclohexyl}oxy)carbonyl]amino}biphenyl-4-yl)butanoate

Obtained as a foam (350mg, 16%) from ethyl 4-(2-aminobiphenyl-4-yl)butanoate (Intermediate 122; 1g, 3.53mmol), trans-4-[methyl(3-phenylpropyl)amino]cyclohexanol (Intermediate 206; 0.87g, 3.53mmol), triphosgene (0.42g, 1.41mmol) and triethylamine (0.98mL, 7.05mmol) following the experimental procedure as described for Intermediate 123 and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether:ethanol.

LRMS (m/z): 557 (M+1)+

Intermediate 208.

4-(2-{[({trans-4-[methyl(3-phenylpropyl)amino]cyclohexyl}oxy)carbonyl]amino}biphenyl-4-yl)butanoic acid

Obtained as a solid (330mg, 98%) from ethyl 4-(2-{[({trans-4-[methyl(3-phenylpropyl)amino]cyclohexyl}oxy)carbonyl]amino}biphenyl-4-yl)butanoate (Intermediate 207; 350mg, 0.63mg) and lithium hydroxide monohydrate (79mg, 1.89mmol) following the experimental procedure as described for Intermediate 124 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 529 (M+1)+

Intermediate 209.

trans-4-[methyl(3-phenylpropyl)amino]cyclohexyl (4-{4-[(4-formylphenyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate

Obtained as an oil (143mg, 36%) from 4-(2-{[({trans-4-[methyl(3-phenylpropyl)amino]cyclohexyl}oxy)carbonyl]amino}biphenyl-4-yl)butanoic acid (Intermediate 208; 330mg, 0.62mmol), 4-aminobenzaldehyde (83mg, 0.69mmol), diisopropylethylenediamine (0.326mL, 1.87mmol) and HATU (356mg, 0.94mmol) following the experimental procedure as described for Intermediate 125 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 632 (M+1)+

Intermediate 210.

trans-4-[methyl(3-phenylpropyl)amino]cyclohexyl [4-(4-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]-amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

Obtained as a solid (70mg, 33%) from trans-4-[methyl(3-phenylpropyl)amino]cyclohexyl (4-{4-[(4-formylphenyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate (Intermediate 209; 141mg, 0.22mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (211mg, 0.54mmol) (prepared according to preparation 8 from US20060035931) and sodium triacetoxyborohydride (345mg, 1.63mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 951 (M+1)+

EXAMPLE 40

trans-4-[methyl(3-phenylpropyl)amino]cyclohexyl [4-(4-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate dihydrofluoride

Obtained as a white solid (13mg, 21%) from trans-4-[methyl(3-phenylpropyl)amino]cyclohexyl [4-(4-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 210; 70mg, 0.07mmol) and triethylamine trihydrofluoride (60µL, 0.37mmol) following the experimental procedure as described for Example 1 and the crude obtained was purified by column chromatography in reversed phase using as eluents Acetonitrile and Methanol.

LRMS (m/z): 877 (M+1)+

1H NMR (300 MHz, cd3od) δ 8.24 (d, J = 9.8 Hz, 1H), 7.52 (d, J = 8.4 Hz, 4H), 7.48 – 7.08 (m, 14H), 6.94 (d, J = 8.1 Hz, 1H), 6.59 (d, J = 9.8 Hz, 1H), 5.20 (bs, 1H), 4.42

(bs, 2H), 3.80 (bs, 2H), 2.93 – 2.68 (m, 4H), 2.52 (ddd, J = 29.8, 18.3, 7.5 Hz, 6H), 2.26 (s, 3H), 2.04 (bs, 2H), 1.97 (s, 2H), 1.80 (bs, 4H), 1.31 (d, J = 9.5 Hz, 4H).

Intermediate 211.

methyl (2E)-3-(4-chloro-3-nitrophenyl)acrylate

To a solution of (E)-3-(4-chloro-3-nitrophenyl)acrylic acid (1g, 4.39mmol) in a mixture of methanol/anhydrous dichloromethane (8mL-4mL) was added at -78°C tionyl chloride (200µL, 2.75mmol) and the mixture was stirred for 4.5h at 45°C. The solvent was removed under reduced pressure giving the title compound as a yellow solid (1.05g, 99%), which was used in the next step without further purification.

LRMS (m/z): 242 (M+1)+

Intermediate 212.

methyl (2E)-3-(2-nitrobiphenyl-4-yl)acrylate

To a solution of methyl (2E)-3-(4-chloro-3-nitrophenyl)acrylate (Intermediate 211; 1.05g, 4.35mmol) in dioxane (40mL) was added under nitrogen atmosphere phenylboronic acid (1.06g, 8.69mmol), cesium carbonate (2M, 6.6mL, 13.2mmol) and [1,1'-Bis(diphenilphosfine)-ferrocene]diclhoropaladium(II) (dichloromethane complex; 192mg, 0.22mmol). The reaction mixture was stirred 4h at 80°C. The catalyst was filtrated through Celite and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Ethyl acetate: Hexane to obtain the title compound as a solid (1.3g, 98%).

LRMS (m/z): 284 (M+1)+

Intermediate 213.

methyl 3-(2-aminobiphenyl-4-yl)propanoate

To a solution of methyl (2E)-3-(2-nitrobiphenyl-4-yl)acrylate (Intermediate 212; 1.3g, 4.73mmol) in methanol (15mL) was added palladium on charcoal (10%, 500mg). The crude mixture was submitted under an H2 balloon 2.5h at room temperature. The catalyst was filtered through Celite and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane:Ether to obtain the title compound as a solid (714mg, 59%).

LRMS (m/z): 256 (M+1)+

Intermediate 214.

methyl 3-(2-isocyanatobiphenyl-4-yl)propanoate

Obtained as a solid (764mg, 97%) from methyl 3-(2-aminobiphenyl-4-yl)propanoate (Intermediate 213; 710mg, 2.78mmol), triphosgene (330mg, 1.11mmol) and triethylamine (0.77mL, 5.56mmol) following the experimental procedure as described for Intermediate 4 and the crude obtained was used in the next step without further manipulation.

LRMS (m/z): 281 (M+16;HPLC aliquot with MeOH).

Intermediate 215.

methyl 3-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy)carbonyl]-amino}biphenyl-4-yl)propanoate

Obtained as a solid (1.1g, 85%) from tert-butyl (trans-4-hydroxycyclohexyl)carbamate (640mg, 2.97mmol) and methyl 3-(2-isocyanatobiphenyl-4-yl)propanoate (Intermediate 214; 710mg, 2.7mmol) following the experimental procedure as described for Intermediate 123. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane:Ether.

LRMS (m/z): 497 (M+1)+

Intermediate 216.

3-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy)carbonyl]amino}-biphenyl-4-yl)propanoic acid

Obtained as a solid (1.07g, 96%) from methyl 3-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy)carbonyl]amino}biphenyl-4-yl)propanoate (Intermediate 215; 1.1g, 2.3mmol) and lithium hydroxide (290mg, 6.91mmol) following the experimental procedure as described for Intermediate 124 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 483 (M+1)+

Intermediate 217.

tert-butyl-trans-4-aminocyclohexyl [4-(3-{[4-(hydroxymethyl)phenyl]amino}-3-oxopropyl)biphenyl-2-yl]carbamate

Obtained as a foam (470mg) from 3-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]-cyclohexyl}oxy)carbonyl]amino}biphenyl-4-yl)propanoic acid (Intermediate 216; 300mg, 0.62mmol), (4-aminophenyl)methanol (92mg, 0.75mmol), diisopropylethylenediamine (0.33mL, 1.89mmol) and HATU (307mg, 0.81mmol) following the experimental procedure as described for Intermediate 125 and the crude obtained was taken forward without purification.

LRMS (m/z): 588 (M+1)+

Intermediate 218.

tert-butyl-trans-4-aminocyclohexyl (4-{3-[(4-formylphenyl)amino]-3-oxopropyl}-biphenyl-2-yl)carbamate

To a solution of tert-butyl-trans-4-aminocyclohexyl [4-(3-{[4-(hydroxymethyl)phenyl]-amino}-3-oxopropyl)biphenyl-2-yl]carbamate (Intermediate 217; 365mg, 0.62mmol) in chloroform (6mL) was added activated manganese oxide (430mg, 4.95mmol). The reaction mixture was stirred overnight at 45°C. The mixture was filtered and the solvent was removed under reduced pressure giving the title compound as an orange foam (390mg, 96%), which was used in the next step without further purification.

LRMS (m/z): 586 (M+1)+

Intermediate 219.

trans-4-aminocyclohexyl [4-(3-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-3-oxopropyl)biphenyl-2-yl]carbamate

Obtained as a grey solid (518mg, 95%) from tert-butyl-trans-4-aminocyclohexyl (4-{3-[(4-formylphenyl)amino]-3-oxopropyl}biphenyl-2-yl)carbamate (Intermediate 218; 390mg, 0.6mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (250mg, 0.63mmol) (prepared according to preparation 8 from US20060035931) and sodium triacetoxyborohydride (385mg, 1.82mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 905 (M+1)+

EXAMPLE 41.

trans-4-aminocyclohexyl [4-(3-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-3-oxopropyl)biphenyl-2-yl]carbamate dihydrochloride

Obtained as a yellow solid (380mg, 84%) from trans-4-aminocyclohexyl [4-(3-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-3-oxopropyl)biphenyl-2-yl]carbamate (Intermediate 219; 515mg, 0.57mmol) and hydrogen chloride (4M in dioxane, 5mL) following the experimental procedure as described for Intermediate 21.

LRMS (m/z): 690 (M+1)+

1H NMR (300 MHz, dmso) δ 10.52 (bs, 1H), 10.26 (s, 1H), 9.77 (bs, 1H), 9.10 (bs, 1H), 8.65 (s, 1H), 8.23 (d, J = 9.9 Hz, 1H), 8.12 (bs, 2H), 7.65 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.46 – 7.16 (m, 6H), 7.12 (d, J = 8.2 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 6.53 (d, J = 9.9 Hz, 1H), 5.50 (d, J = 8.5 Hz, 1H), 4.32 (bs, 2H), 4.14 (bs, 2H), 3.07 – 2.80 (m, 4H), 2.69 (t, J = 7.4 Hz, 2H), 1.86 (d, J = 31.8 Hz, 4H), 1.50 – 1.12 (m, 4H).

Intermediate 220.

ethyl 4-[2-({[(3R)-1-azabicyclo[2.2.2]oct-3-yloxy]carbonyl}amino)biphenyl-4-yl]butanoate

Obtained as an oil (503mg) from ethyl 4-(2-aminobiphenyl-4-yl)butanoate (Intermediate 122; 300mg, 1.06mmol), (R)-quinuclidin-3-ol (135mg, 1.06mmol), triphosgene (126mg, 0.42mmol) and triethylamine (0.3mL, 2.16mmol) following the experimental procedure as described for Intermediate 123 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 437 (M+1)+

Intermediate 221.

4-[2-({[(3R)-1-azabicyclo[2.2.2]oct-3-yloxy]carbonyl}amino)biphenyl-4-yl]butanoic acid

Obtained as a yellow-orange solid (608mg) from ethyl 4-[2-({[(3R)-1-azabicyclo-[2.2.2]oct-3-yloxy]carbonyl}amino)biphenyl-4-yl]butanoate (Intermediate 220; 503mg, 1.04mmol) and lithium hydroxide monohydrate (130mg, 3.1mmol) following the experimental proce-dure as described for Intermediate 124 and the crude obtained was taken forward without further manipulation.

LRMS (m/z): 409 (M+1)+

Intermediate 222.

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[(4-formylphenyl)amino]-4-oxobutyl}-biphenyl-2-yl)carbamate

To a solution of 4-[2-({[(3R)-1-azabicyclo[2.2.2]oct-3-yloxy]carbonyl}amino)biphenyl-4-yl]butanoic acid (Intermediate 221; 360mg, 0.75mmol) in dichloromethane (5mL) was added under nitrogen atmosphere oxalyl chloride (100µL, 1.15mmol) and a drop of dimethylformamide. The reaction mixture was stirred overnight at room temperature. Solvent was removed under reduced pressure and the crude (319mg, 0.66mmol) was taken into the next step without further manipulation. It was dissolved in dichloromethane (5mL) and 4-aminobenzaldehyde (115mg, 0.95mmol) and triethylamine (0.24mL, 1.72mmol) were added into the mixture. The reaction was stirred overnight at room temperature and 6 hours at 45°C. The solvent was removed under reduced pressure and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2), giving the title compound as a solid (22mg, 4%).

LRMS (m/z): 512 (M+1)+

Intermediate 223.

(3R)-1-azabicyclo[2.2.2]oct-3-yl [4-(4-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

Obtained as a yellow solid (17mg, 40%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[(4-formylphenyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate (Intermediate 222; 22mg, 0.03mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (16mg, 0.04mmol) (prepared according to preparation 8 from US20060035931) and sodium triacetoxyborohydride (30mg, 0.14mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 831 (M+1)+

EXAMPLE 42.

(3R)-1-azabicyclo[2.2.2]oct-3-yl [4-(4-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate dihydrofluoride

Obtained as a white solid (4mg, 40%) from (3R)-1-azabicyclo[2.2.2]oct-3-yl [4-(4-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 223; 17mg, 0.01mmol) and triethylamine trihydrofluoride (25μL, 0.15mmol) following the experimental procedure as described for Example 1 and the crude obtained was purified by column chromatography in reversed phase using as eluents Acetonitrile and Methanol.

LRMS (m/z): 716 (M+1)+

1H NMR (300 MHz, cd3od) δ 8.25 (d, J = 10.0 Hz, 1H), 7.69 – 7.54 (m, 2H), 7.42-7.25 (m, 7H), 7.22 (bs, 2H), 7.01 (t, J = 7.8 Hz, 2H), 6.62 (d, J = 9.8 Hz, 1H), 5.33 (bs, 1H), 4.68 (bs, 1H), 4.12 (bs, 1H), 3.51 – 3.32 (m, 2H), 3.12 (bs, 4H), 2.86 (bs, 1H), 2.74 (t, J

= 7.4 Hz, 2H), 2.44 (t, J = 7.4 Hz, 2H), 2.20 – 1.84 (m, 3H), 1.72 (d, J = 38.8 Hz, 2H), 1.31 (d, J = 13.5 Hz, 2H), 0.88 (d, J = 9.2 Hz, 2H).

Intermediate 224.

4-[(tert-butoxycarbonyl)amino]benzoic acid

To a solution of 4-aminobenzoic acid (1g, 7.29mmol) in a mixture of dioxane:water (20mL:10mL) was added sodium hydroxide (2M, 35mL). The mixture was stirred until complete dissolution and then it was added di-tert-butyl dicarbonate (3.18g, 14.57mmol) at 0°C. The reaction mixture was stirred 24 hours at room temperature. The solvent was removed under reduced pressure and the crude was acidified with hydrogen chloride 5N. The precipitate obtained was filtered and washed with water to obtain the title compound as a white solid (1.23g, 71%).

LRMS (m/z): 238 (M+1)+

Intermediate 225.

[4-(methylamino)phenyl]methanol

To a solution of 4-[(tert-butoxycarbonyl)amino]benzoic acid (Intermediate 224; 500mg, 2.11mmol) in tetrahydrofurane (20mL) was added slowly lithium aluminium hydride (450mg, 11.86mmol). The reaction mixture was refluxed for 1.5 hours. Hydride was destroyed and the solvent was removed under reduced pressure giving a crude, which was purified by reversed phase using as eluents Acetonitrile and Methanol. The title compound was obtained as an oil (159mg, 55%).

LRMS (m/z): 139 (M+1)+

Intermediate 226.

tert-butyl-trans-4-aminocyclohexyl (4-{4-[[4-(hydroxymethyl)phenyl](methyl)-amino]-4-oxobutyl}biphenyl-2-yl)carbamate

Obtained as a foam (78mg, 15%) from [4-(methylamino)phenyl]methanol (130mg, 0.95mmol), 4-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy)carbonyl]-amino}biphenyl-4-yl)butanoic acid (synthesized as Intermediate 189; 400mg, 0.81mmol), diisopropylethylenediamine (0.421mL, 2.42mmol) and HATU (613mg, 1.61mmol) following the experimental procedure as described for Intermediate 125 and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane:Ether.

LRMS (m/z): 616 (M+1)+

Intermediate 227.

trans-4-aminocyclohexyl (4-{4-[(4-formylphenyl)(methyl)amino]-4-oxobutyl}-biphenyl-2-yl)carbamate

Obtained as a foam (66mg, 85%) from tert-butyl-trans-4-aminocyclohexyl (4-{4-[[4-(hydroxymethyl)phenyl](methyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate (Intermediate 226; 78mg, 0.13mmol) and manganese oxide (110mg, 1.27mmol) following the experi-mental procedure as described for Intermediate 218 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 614 (M+1)+

Intermediate 228.

tert-butyl-trans-4-aminocyclohexyl (4-{4-[[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]-oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]-(methyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate

Obtained as a solid (16mg, 16%) from trans-4-aminocyclohexyl (4-{4-[(4-formylphenyl)(methyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate (Intermediate 227; 66mg, 0.11mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (36mg, 0.11mmol) (prepared according to preparation 8 from US20060035931), sodium cianoborohydride (17mg, 0.27mmol) and diethylethylenamine (19µL, 0.11mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform: methanol (9:1).

LRMS (m/z): 933 (M+1)+

EXAMPLE 43.

trans-4-aminocyclohexyl (4-{4-[[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl](methyl)amino]-4-oxobutyl}-biphenyl-2-yl)carbamate dihydrochloride

Obtained as white solid (10mg, 81%) from tert-butyl-trans-4-aminocyclohexyl (4-{4-[[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl](methyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate (Intermediate 228; 16mg, 0.02mmol) and hydrogen chloride (4M in dioxane, 1mL) following the ex-perimental procedure as described for Intermediate 21.

LRMS (m/z): 718 (M+1)+

1H NMR (300 MHz, dmso) δ 10.52 (bs, 1H), 9.70 (bs, 1H), 9.18 (bs,1H), 8.62 (s, 1H), 8.21 (d, J = 9.9 Hz, 1H), 7.98 (s,1H), 7.63 (d, J = 8.1 Hz, 1H), 7.51 – 7.22 (m, 6H), 7.22 – 7.07 (m, 3H), 6.99 (d, J = 8.2 Hz, 1H), 6.55 (d, J = 9.7 Hz, 1H), 5.49 (d, J = 8.7 Hz, 1H), 4.33 (s, 1H), 4.23 (s, 2H), 3.54 (d, J = 14.8 Hz, 4H), 3.18 (s, 2H), 2.92 (d, J = 20.2 Hz, 4H), 2.04 (d, J = 31.0 Hz, 2H), 2.01-1.59(m., 4H), 1.5-1.02 (m,4H).

Intermediate 229.

ethyl trans-4-aminocyclohexanecarboxylate

Hydrogen chloride (7 mL) was added to a suspension of the (1r,4r)-4-aminocyclohexanecarboxylic acid hydrochloride (6.32g, 0.035mol) in Ethanol (100 mL) and the mixture was stirred and heated to 60 oC and left overnight. The mixture was evaporated in vacuum, azeotroping the water with further Ethanol and finally toluene to give the title product as a white solid (7.2g, 98%).

1H NMR (300 MHz, dmso) δ 4.05 (q, J = 7.1 Hz, 2H), 2.95 (bs, 1H), 2.30 – 2.15 (m, 1H), 2.02 – 1.88 (m, 4H), 1.43 – 1.28 (m, 4H), 1.22 – 1.13 (t, J = 6.9 Hz, 3H).

Intermediate 230.

(trans-4-aminocyclohexyl)methanol

A suspension of ethyl trans-4-aminocyclohexanecarboxylate (Intermediate 229; 7.2g, 0.034mol) in tetrahydrofurane (200 mL) was added in rough portions at 0°C to lithium aluminium hydride (1M in tetrahydrofurane) and stirred 1h at 0°C, the ice bath was removed and the mixture was stirred at room temperature overnight. The stirred mixture was cooled in an ice bath and very carefully water (6.9 mL), 15% NaOH (21 mL) and water (21 mL) were added slowly. After stirring 30 minutes at room temperature the mixture was filtered through a thin layer (1 cm) of Celite and the filter cake was washed with tetrahydrofurane. The combined filtrate and washings were evaporated to give a white solid as the title compound (4.4g, 99%).

1H NMR (300 MHz, dmso) δ 3.18 (d, J = 6.3 Hz, 2H), 2.42 (m ,, 1H), 1.79 – 1.60 (m, 4H), 1.30 – 1.13 (m, 1H), 1.05 – 0.72 (m, 4H).

Intermediate 231.

trans-4-aminocyclohexyl [4-(4-{[trans-4-(hydroxymethyl)cyclohexyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

Obtained as an oil (455mg, 92%) from (trans-4-aminocyclohexyl)methanol (Intermediate 230; 114mg, 0.89mmol), 4-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]-cyclohexyl}oxy)carbonyl]amino}biphenyl-4-yl)butanoic acid (synthesized as Intermediate 189; 400mg, 0.81mmol), diisopropylethylenediamine (0.421mL, 2.42mmol) and HATU (613mg, 1.61mmol) following the experimental procedure as described for Intermediate 125 and the crude obtained was taken forward to the next step without purification.

LRMS (m/z): 608 (M+1)+

Intermediate 232.

trans-4-aminocyclohexyl (4-{4-[(trans-4-formylcyclohexyl)amino]-4-oxobutyl}-biphenyl-2-yl)carbamate

Obtained as an oil (525mg, 85%) from trans-4-aminocyclohexyl [4-(4-{[trans-4-(hydroxymethyl)cyclohexyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 231; 550mg, 0.9mmol) and Dess-Martin periodinane (422mg, 0.99mmol) following the experimental procedure as described for Intermediate 64.

LRMS (m/z): 606 (M+1)+

Intermediate 233.

trans-4-aminocyclohexyl [4-(4-{[trans-4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)cyclohexyl]-amino}-4-oxobutyl)biphenyl-2-yl]carbamate

Obtained as a yellow solid (246mg, 34%) from trans-4-aminocyclohexyl (4-{4-[(trans-4-formylcyclohexyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate (Intermediate 232; 525mg, 0.87mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (260mg, 0.78mmol) (prepared according to preparation 8 from US20060035931) and sodium triacetoxyborohydride (826mg, 3.9mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform: methanol (9:1).

LRMS (m/z): 925 (M+1)+

EXAMPLE 44.

trans-4-aminocyclohexyl [4-(4-{[trans-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)cyclohexyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate dihydrochloride

Obtained as a white solid (125mg, 66%) from trans-4-aminocyclohexyl [4-(4-{[trans-4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)cyclohexyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 233; 245mg, 0.27mmol) and hydrogen chloride (4M in dioxane; 3.31mL) following the experimental procedure as described for Intermediate 21.

LRMS (m/z): 710 (M+1)+

1H NMR (300 MHz, dmso) δ 8.68 (s, 1H), 8.32 (d, J = 10.0 Hz, 1H), 8.03 (s, 2H), 7.78 (d, J = 7.8 Hz, 1H), 7.41 (m, 4H), 7.30 – 7.13 (m, 3H), 7.04 (d, J = 8.2 Hz, 1H), 6.61 (d, J = 10.0 Hz, 1H), 5.51 (d, J = 9.3 Hz, 1H), 4.38 (bs, 2H), 3.58 – 3.52 (m, 2H), 3.04 (bs, 3H), 2.89 (bs, 2H), 2.61 (bs, 2H), 2.12 (bs, 4H), 1.90 (m, 6H), 1.50 – 1.26 (m, 4H), 1.13 (m, 4H).

Intermediate 234.

1-(4-nitrophenyl)propan-2-ol

To solution of 1-(4-nitrophenyl)propan-2-one (500mg, 2.79mmol) in methanol (9mL) was added in portions at 0°C sodium borohydride (106mg, 2.8mmol). The reaction mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure at room temperature and the crude obtained was partitioned between ether and water. The organic layer was washed with ammonium chloride, dried, filtered and the solvent was removed under reduced pressure giving the title compound as a solid (500mg, 98%).

LRMS (m/z): 182 (M+1)+

Intermediate 235.

1-(4-aminophenyl)propan-2-ol

To a solution of 1-(4-nitrophenyl)propan-2-ol (Intermediate 234; 500mg, 2.76mmol) in ethanol was added palladium on charcoal (10%, 30mg). The mixture was submitted to a H2 balloon pressure during 2 hours. The catalyst was filtered trough celite and the filtrate was evaporated giving a crude, which was the desired compound (412mg, 98%).

LRMS (m/z): 152 (M+1)+

Intermediate 236.

tert-butyl-trans-4-aminocyclohexyl [4-(4-{[4-(2-hydroxypropyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

Obtained as a foam (305mg, 98%) from 1-(4-aminophenyl)propan-2-ol (Intermediate 235; 74mg, 0.79mmol), 4-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy) carbonyl]amino}biphenyl-4-yl)butanoic acid (syn-thesized as Intermediate 189; 200mg, 0.4mmol), diisopropylethylenediamine (0.21mL, 1.21mmol) and HATU (199mg, 0.52mmol) following the experimental procedure as de-scribed for Intermediate 125 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 630 (M+1)+

Intermediate 237.

tert-butyl-trans-4-aminocyclohexyl [4-(4-oxo-4-{[4-(2-oxopropyl)phenyl]amino}-butyl)biphenyl-2-yl]carbamate

Obtained as an oil (275mg, 97%) from tert-butyl-trans-4-aminocyclohexyl [4-(4-{[4-(2-hydroxypropyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 236; 254mg, 0.4mmol) and Dess-Martin periodinane (190mg, 0.45mmol) following the experi-mental procedure as described for Intermediate 64 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 628 (M+1)+

Intermediate 238.

tert-butyl-trans-4-aminocyclohexyl [4-(4-{[4-(2-{[(2R)-2-{[tert-butyl(dimethyl)-silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}propyl)-phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

Obtained as a solid (127mg, 33%) from tert-butyl-trans-4-aminocyclohexyl [4-(4-oxo-4-{[4-(2-oxopropyl)phenyl]amino}butyl)biphenyl-2-yl]carbamate (Intermediate 237; 253mg, 0.4mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (170mg, 0.43mmol) (prepared according to preparation 8 from US20060035931) and sodium triacetoxyborohydride (275mg, 1.3mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform: methanol: ammonium (40:4:0.2).

LRMS (m/z): 947 (M+1)+

EXAMPLE 45.

trans-4-aminocyclohexyl [4-(4-{[4-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}propyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate dihydrochloride

Obtained as a white solid (22mg, 20%) from tert-butyl-trans-4-aminocyclohexyl [4-(4-{[4-(2-{[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}propyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 238; 127mg, 0.13mmol) and hydrogen chloride (4M in dioxane, 3.35mL) following the experimental procedure as described for Intermediate 21 and the crude obtained was purified by reversed phase using as eluents Water and Methanol.

LRMS (m/z): 732 (M+1)+

1H NMR (300 MHz, cd3od) δ 8.40 – 8.30 (m, 1H), 7.54 – 7.29 (m, 8H), 7.26 – 7.06 (m, 5H), 6.97 (d, J = 7.9 Hz, 1H), 6.66 (d, J = 9.8 Hz, 1H), 5.27 (bs, 1H), 4.49 (bs, 1H), 3.18

(bs, 2H), 3.12 – 2.81 (m, 4H), 2.74 (bs, 4H), 2.42 (d, J = 6.9 Hz, 2H), 2.03 (d, J = 14.1 Hz, 4H), 1.4-1.25 (m, 4H), 1.16 (d, J = 6.0 Hz, 3H).

Intermediate 239.

5-(methylamino)pentanoic acid

To 1-methylpiperidin-2-one (3.8g, 0.034mol) was added hydrogen chloride (5N, 19mL). The mixture was stirred over weekend at 150°C. The solvent was removed under reduced pressure at 50-60°C giving a solid, which was treated with ether. The title compound was obtained as a white solid (5.08g, 88%) and used in the next step without further purifica-tion.

LRMS (m/z): 132 (M+1)+

Intermediate 240.

5-[(tert-butoxycarbonyl)(methyl)amino]pentanoic acid

To a solution of 5-(methylamino)pentanoic acid (Intermediate 239; 3.7g, 0.022mol) in di-oxane/water (60mL, 2/1) was added sodium hydroxide (1N, 45mL) and at 0°C was added di-tert-butyl dicarbonate (5.4g, 0.024mol). The reaction mixture was stirred 10 minutes at 0°C and overnight at room temperature. The organic solvent was removed and the aque-ous phase was acidified and extracted with ethyl acetate. The organic layer was washed with brine, dried, filtered and the solvent was removed under reduced pressure, obtaining an oil, which was treated with pentane at low temperature to achieve a white solid as a title compound (4.4g, 80%)

LRMS (m/z): 230 (M+1)-

Intermediate 241.

tert-butyl (5-{[4-(hydroxymethyl)phenyl]amino}-5-oxopentyl)methylcarbamate

To a solution of 5-[(tert-butoxycarbonyl)(methyl)amino]pentanoic acid (Intermediate 240; 1.4g, 6.05mmol) in dimethylformamide (10mL) was added DIEA (3.14mL, 18.1mmol) and HATU (2.99g, 7.87mmol). The reaction mixture was stirred 1 hour at room temperature. Then (4-aminophenyl)methanol (820mg, 6.6mmol) was added into the mixture and it was stirred overnight at room temperature. The mixture was poured into 150mL of water and extracted with ethyl acetate. The organic layer was washed with brine, dried, filtered, and the solvent was removed under reduced pressure giving a crude, which was purified by column chromatography with silica gel, eluting with a mixture of chloroform: hexane.

LRMS (m/z): 337 (M+1)+

Intermediate 242.

N-[4-(hydroxymethyl)phenyl]-5-(methylamino)pentanamide

To a solution of tert-butyl (5-{[4-(hydroxymethyl)phenyl]amino}-5-oxopentyl)methylcarbamate (Intermediate 241; 812mg, 2.41mmol) in tetrahydrofurane (16mL) was added hydrogen chloride (2.5N aqueous, 5.8mL). The reaction mixture was stirred overnight at room temperature. Then 3eq more of hydrogen chloride were added and the reac-tion was stirred 24 hours at room temperature. The aqueous phase was saturated with sodium bicarbonate and extracted with chloroform. The organic solvent was removed un-der reduced pressure giving the title compound as a solid (377mg, 66%).

LRMS (m/z): 237 (M+1)+

Intermediate 243.

tert-butyl-trans-4-aminocyclohexyl (4-{4-[(5-{[4-(hydroxymethyl)phenyl]amino}-5-oxopentyl)(methyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate

Obtained as an oil (126mg, 44%) from N-[4-(hydroxymethyl)phenyl]-5-(methylamino)pentanamide (Intermediate 242; 104mg, 0.44mmol), 4-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy)carbonyl]amino}biphenyl-4-yl)butanoic acid (synthesized as Intermediate 189; 200mg, 0.4mmol), DIEA (0.21mL, 1.21mmol) and HATU (229mg, 0.60mmol) following the experimental procedure as described for Intermediate 125 and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform: ethanol (9:1).

LRMS (m/z): 715 (M+1)+

Intermediate 244.

tert-butyl-trans-4-aminocyclohexyl (4-{4-[{5-[(4-formylphenyl)amino]-5-oxopentyl}(methyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate

Obtained as an oil (125mg, 98%) from tert-butyl-trans-4-aminocyclohexyl (4-{4-[(5-{[4-(hydroxymethyl)phenyl]amino}-5-oxopentyl)(methyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate (Intermediate 243; 126mg, 0.18mmol) and Dess-Martin periodinane (82mg, 0.19mmol) following the experimental procedure as described for Intermediate 64 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 713 (M+1)+

Intermediate 245.

tert-butyl-trans-4-aminocyclohexyl (4-{4-[(5-{[4-({[(2R)-2-{[tert-butyl(dimethyl-)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-phenyl]amino}-5-oxopentyl)(methyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate

Obtained as a solid (160mg, 88%) from tert-butyl-trans-4-aminocyclohexyl (4-{4-[{5-[(4-formylphenyl)amino]-5-oxopentyl}(methyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate (Intermediate 244; 125mg, 0.18mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (58mg, 0.18mmol) (prepared according to preparation 8 from US20060035931) and sodium triacetoxyborohydride (185mg, 0.88mmol) following the experimental procedure as described for Intermediate 7 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 515 (M/2)+

EXAMPLE 46.

trans-4-aminocyclohexyl (4-{4-[(5-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-5-oxopentyl)(methyl) amino]-4-oxobutyl}biphenyl-2-yl)carbamate dihydrochloride

Obtained as a white solid (18mg, 23%) from tert-butyl-trans-4-aminocyclohexyl (4-{4-[(5-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-5-oxopentyl)(methyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate (Intermediate 245; 100mg, 0.1mmol) and hydrogen chloride (4M in dioxane, 4.85mL) following the experimental procedure as described for Intermediate 21 and the crude obtained was purified by reversed phase using as eluents Water and Methanol.

LRMS (m/z): 732 (M+1)+

1H NMR (300 MHz, dmso) δ 10.49 (d, J = 9.2 Hz, 2H), 10.10 (d, J = 13.0 Hz, 1H), 9.51 (s, 1H), 9.03 (s, 1H), 8.62 (s, 1H), 8.15 (d, J = 10.0 Hz, 1H), 7.99 (bs, 3H), 7.63 (d, J = 8.5 Hz, 2H), 7.54 – 7.27 (m, 6H), 7.27 – 7.04 (m, 4H), 6.98 (d, J = 8.2 Hz, 1H), 6.53 (d, J = 9.9 Hz, 1H), 6.15 (bs, 1H), 5.43 (d, J = 9.0 Hz, 1H), 4.34 (s, 1H), 4.13 (s, 3H), 3.29 (s,3H), 3.00 (d, J = 14.7 Hz, 2H), 2.92 (s, 2H), 2.80 (bs, 2H), 2.66 – 2.55 (m, 4H), 2.53 (d, J = 8.0 Hz, 2H), 2.31 (bs, 4H), 2.00 – 1.70 (m, 5H), 1.53 (bs, 4H), 1.42 – 1.17 (m, 4H).

Intermediate 246.

methyl 5-chloro-4-hydroxy-2-methoxybenzoate

To solution of 4-amino-5-chloro-2-methoxybenzoic acid (10g, 0.048mol) in water (50mL) was added HBF4 (48% in water, 16.2mL, 0.12mol) and acetyl chloride (2.24mL, 0.031mol) and the mixture was stirred for 1 hour at room temperature. The mixture was cooled to 0°C to add drop wise sodium nitrite (3.76g, 0.054mol) in water (30mL). The reaction was allowed to stirrer at 0°C for 30 minutes. Then the solid was filtered and it was treated with Acid Acetic (500mL). The mixture was heated at 100°C for 1 hour. The mixture was cooled and it was stand without further manipulation overnight. The solvent was removed under reduced pressure and the crude obtained was partitioned between Ethyl acetate and Brine. The organic layer was dried, filtered and the solvent was removed under reduced pressure. The crude was treated with sodium hydroxide (150mL) for 90 minutes at room temperature and overnight at 45°C. The crude was extracted with dichloromethane and purified over silica gel eluting with Dichloromethane/Ethanol (100/0 to 0/100) to give the title compound as a foam (1.1g, 10%)

LRMS (m/z): 217 (M+1)+

Intermediate 247.

2-chloro-4-(hydroxymethyl)-5-methoxyphenol

To a solution of methyl 5-chloro-4-hydroxy-2-methoxybenzoate (Intermediate 246; 1.1g, 5.08mmol) in THF (30mL) was added drop wise at 0°C lithium aluminium hydride (1M in THF, 9.65mL). The reaction mixture was stirred 10 minutes at 0°C , 1 hour at room temperature and 30 minutes at 65°C. The mixture was cooled at 0°C and a saturated solution of L-Tartrate (100mL) was added cautiously. Then Ethyl acetate was added and the mixture was stirred for 1 hour at room temperature. The organic layer was separated, dried, filtered and the solvent was removed under reduced pressure to give a crude, which was purified over silica gel eluting with Chloroform/Ethanol (100/0 to 0/100) to give the title compound as a foam (460mg, 450%)

LRMS (m/z): 189 (M+1)+

Intermediate 248.

ethyl [2-chloro-4-(hydroxymethyl)-5-methoxyphenoxy]acetate

To a solution of 2-chloro-4-(hydroxymethyl)-5-methoxyphenol (Intermediate 247; 459mg, 2.43mmol) in acetonitrile (5 mL) was added ethyl bromoacetate (0.26mL, 2.43mmol) and potassium carbonate (420mg, 3.04mmol) in a sealed tub. The mixture was stirred 2 hours at 90°C. The solid was filtrated, washed with acetonitrile and the solvent of the filtrate was removed under reduced pressure giving the title compound as a brown oil (640mg, 85%), which was used in the next step without further purification.

LRMS (m/z): 275 (M+1)+

Intermediate 249.

[2-chloro-4-(hydroxymethyl)-5-methoxyphenoxy]acetic acid

To a solution of ethyl [2-chloro-4-(hydroxymethyl)-5-methoxyphenoxy]acetate (Intermediate 248; 640mg, 2.33mmol) in THF (20mL) was added water (20mL) and lithium hydroxide (391mg, 9.32mmol). The reaction mixture was stirred for 1 hour at room temperature. The solvent was removed under reduced pressure and the aqueous phase was acidified until acid pH and then extracted with ethyl acetate. The organic layer was washed with brine, dried, filtered and the solvent was removed under reduced pressure to give the title compound as a red solid (550mg, 95%), which was used in the next step without further purification.

LRMS (m/z): 247 (M+1)+

Intermediate 250.

tert-butyl-trans-4-aminocyclohexyl [4-(3-hydroxypropyl)biphenyl-2-yl]carbamate

To a solution of methyl 3-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy) carbonyl]amino}biphenyl-4-yl)propanoate (Intermediate 215; 260mg, 0.52mmol) in tetrahydrofurane (7mL) was added at -10°C lithium boro-hydride (2.6mL, 5.2mmol). The reaction mixture was stirred 6 hours at room temperature. Ammonium chloride saturated was added into the mixture cautiously and with ethyl ace-tate was extracted. The organic layer was washed with water and brine, dried, filtered and the solvent was removed under reduced pressure to give the title compound as a foam (210mg, 85%), which was used in the next step without further purification.

LRMS (m/z): 469 (M+1)+

Intermediate 251.

tert-butyl-trans-4-aminocyclohexyl [4-(3-oxopropyl)biphenyl-2-yl]carbamate

Obtained as an oil (184mg, 88%) from tert-butyl-trans-4-aminocyclohexyl [4-(3-hydroxypropyl)biphenyl-2-yl]carbamate (Intermediate 250; 210mg, 0.45mmol) and Dess-Martin periodinane (230mg, 0.54mmol) following the experimental procedure as described for Intermediate 64 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 466 (M+1)+

Intermediate 252.

tert-butyl-trans-4-aminocyclohexyl {4-[3-(methylamino)propyl]biphenyl-2-yl}carbamate

To a solution of tert-butyl-trans-4-aminocyclohexyl [4-(3-oxopropyl)biphenyl-2-yl]carbamate (Intermediate 251; 210mg, 0.45mmol) in methanol (5mL) was added methanamine (225µL, 0.45mmol) and DIEA (80µL, 0.46mmol). The solution was stirred for 30 minutes at room temperature and then sodiumcyanoborohydride (71mg, 1.13mmol) was added. The reaction mixture was stirred over weekend at room temperature. The solvent was removed and the crude obtained was treated with chloroform, the solid was filtered and the filtrate was evaporated giving a crude which was purified by column chromatography with silica gel, eluting with a mixture of chloroform: methanol: ammonium (40:4:0.2). The title compound was obtained as a foam (82mg, 37%).

LRMS (m/z): 482 (M+1)+

Intermediate 253.

tert-butyl-trans-4-aminocyclohexyl (4-{3-[{[2-chloro-4-(hydroxymethyl)-5-methoxyphenoxy]acetyl}(methyl)amino]propyl}biphenyl-2-yl)carbamate

The title compound was obtained (22mg, 18%) from tert-butyl-trans-4-aminocyclohexyl {4-[3-(methylamino)propyl]biphenyl-2-yl}carbamate (Intermediate 252; 82mg, 0.17mmol), [2-chloro-4-(hydroxymethyl)-5-methoxyphenoxy]acetic acid (Intermediate 249; 42mg, 0.17mmol), HBTU (65mg, 0.17mmol) and DIEA (120µL, 0.69mmol) following the experimental procedure as described for Intermediate 125 and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane:ethyl acetate.

LRMS (m/z): 711 (M+1)+

Intermediate 254.

tert-butyl-trans-4-aminocyclohexyl (4-{3-[[(2-chloro-4-formyl-5-methoxyphenoxy)-acetyl](methyl)amino]propyl}biphenyl-2-yl)carbamate

Obtained as a yellow foam (22mg, 90%) from tert-butyl-trans-4-aminocyclohexyl (4-{3-[{[2-chloro-4-(hydroxymethyl)-5-methoxyphenoxy]acetyl}(methyl)amino]propyl}biphenyl-2-yl)carbamate (Intermediate 253; 22mg, 0.03mmol) and manganese oxide (30mg, 0.35mmol) following the experimental procedure as described for Intermediate 218 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 695 (M+1)+

Intermediate 255.

tert-butyl-trans-4-aminocyclohexyl (4-{3-[{[4-({[(2R)-2-{[tert-butyl(dimethyl) silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-chloro-5-methoxyphenoxy]acetyl}(methyl)amino]propyl}biphenyl-2-yl)carbamate

Obtained as a solid (12mg, 37%) from tert-butyl-trans-4-aminocyclohexyl (4-{3-[[(2-chloro-4-formyl-5-methoxyphenoxy)acetyl](methyl)amino]propyl}biphenyl-2-yl)carbamate (Intermediate 254; 22mg, 0.03mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (11mg, 0.03mmol) (prepared according to preparation 8 from US20060035931), sodium cyanoborohydride (5mg, 0.08mmol) and DIEA (6µL, 0.03mmol) following the experimental procedure as described for Intermediate 7 and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform: ethanol.

LRMS (m/z): 513 (M/2)+

EXAMPLE 47.

trans-4-aminocyclohexyl (4-{3-[{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenoxy]acetyl}(methyl)-amino]propyl}biphenyl-2-yl)carbamate dihydrochloride

Obtained as white solid (7mg, 73%) from tert-butyl-trans-4-aminocyclohexyl (4-{3-[{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)-ethylamino}methyl)-2-chloro-5-methoxyphenoxy]acetyl}(methyl)amino]propyl} biphenyl-2-yl)carbamate (Intermediate 255; 12mg, 0.01mmol) and hydrogen chloride (4M in dioxane, 0.1mL) following the experimental procedure as described for Intermediate 21.

LRMS (m/z): 813 (M+1)+

1H NMR (300 MHz, cd3od) δ 8.23 (d, J = 9.8 Hz, 1H), 7.49 – 7.23 (m, 5H), 7.23 – 6.99 (m, 6H), 6.77 (s, 1H), 6.69 (d, J = 10Hz, 1H), 5.47 – 5.34 (bs, 1H), 5.01 (bs, 1H), 4.48 (bs, 1H), 4.20 (bs, 2H), 3.96 – 3.82 (m, 2H), 3.70 (bs, 2H), 3.51 (bs, 2H), 3.13 (d, J = 20.5 Hz, 3H), 3.00 (bs, 2H), 2.72 (bs, 3H), 2.57 (bs, 2H), 1.97 (bs, 4H), 1.42 (bs, 4H).

Intermediate 256.

Ethyl (4-bromo-3-nitrophenyl)acetate

A round-bottomed flask fitted with stir bar was charged with fuming nitric acid (10.5mL, 0.25mol) and was cooled at -10° C, ethyl (4-bromophenyl)acetate (4.00g, 16.45mmol) was added dropwise. After stirring for 1h at -10 °C, the reaction was poured onto ice, after stirring 30 min, chloroform was added. The organic layer was dried, filtered and the solvent was removed under reduced pressure to give 3.05g (64%) of a yellow oil, which was used in the next step without further purification.

LRMS (m/z): 286,288 (M-1,M+1)-

Intermediate 257.

Ethyl (2-nitrobiphenyl-4-yl)acetate

To a solution of ethyl (4-bromo-3-nitrophenyl)acetate (Intermediate 256; 3.05g, 10.59mmol) in dioxane (8mL) and (12mL) was added under nitrogen atmosphere phenylboronic acid (1.55g, 12.70mmol), cesium carbonate (10.35g, 31.76mmol) and [1,1'-Bis(diphenilphosfine)-ferrocene]dichloropaladium(II) (dichloromethane complex; 0.26g, 0.03mmol). The reaction mixture was stirred 3h at 80°C. The catalyst was filtrated through Celite and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Hexane: Diethyl ether to obtain the title compound as a yellow oil (2.39g, 79%).

LRMS (m/z): 284 (M-1)-

Intermediate 258.

Ethyl (2-aminobiphenyl-4-yl)acetate

Obtained (2.12g, 99%) from ethyl (2-nitrobiphenyl-4-yl)acetate (Intermediate 257; 2.39g, 8.38mmol) and palladium on charcoal (10%, 250mg) in EtOH following the experimental procedure as described for Intermediate 67. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of Ethyl acetate: Hexane.

LRMS (m/z): 256 (M+1)+

Intermediate 259.

ethyl (2-isocyanatobiphenyl-4-yl)acetate

To a solution of triphosgene (0.60g, 2.04mmol) in dichloromethane (30mL) was added drop wise at 0°C a solution of ethyl (2-aminobiphenyl-4-yl)acetate (Intermediate 258; 1.30g, 5.09mmol) in dichloromethane (30mL), once the addition is finished triethylamine (1.42mL, 10.18mmol) was added. The mixture was stirred 2 hours at room temperature. The solvent was partially removed under reduced pressure without heating and pentane was added to precipitate the salts, the mixture was filtered and the filtrate was evaporated to get the title compound which was used in the next step without further manipulation.

Intermediate 260.

ethyl (2-{[({*trans*-4-[(*tert*-butoxycarbonyl)amino]cyclohexyl}oxy)carbonyl]amino} biphenyl-4-yl)acetate

To a solution of ethyl (2-isocyanatobiphenyl-4-yl)acetate (Intermediate 259) in toluene (20mL) was added tert-butyl (trans-4-hydroxycyclohexyl)carbamate (Intermediate 174; 1.10g, 5.9mmol). The mixture was stirred for 18 hours at 90°C. The solvent was removed under reduced pressure and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether, giving the title compound as a solid (1.12g, 44%).

LRMS (m/z): 495 (M-1)-

Intermediate 261.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(2-hydroxyethyl)biphenyl-2-yl]-carbamate

To a solution of ethyl (2-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy) carbonyl]amino}biphenyl-4-yl)acetate (Intermediate 260; 1.0g, 2.02mmol) in THF (30mL) was added drop wise at -5°C lithium borohydride solution (2M in THF, 10.07mL) and EtOH (4mL). The reaction mixture was stirred 2 hours at room temperature. Ammonium chloride saturated was added into the mixture cautiously and with ethyl acetate was extracted. The organic layer was washed with water and brine, dried, filtered and the solvent was removed under reduced pressure to give the title compound (0.9g, 98%), which was used in the next step without further purification.

LRMS (m/z): 453 (M-1)-

Intermediate 262.

2-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy)carbonyl]amino} biphenyl-4-yl)ethyl methanesulfonate

Methanesulfonyl chloride (56µL, 0.72 mmol) was added dropwise to a solution of trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(2-hydroxyethyl)biphenyl-2-yl]carbamate

(Intermediate 261; 0.3g, 0.66mmol) and triethylamine (183µL, 1.32 mmol) in dichloromethane at 0° C. The mixture was stirred for 2 hours at room temperature. The crude was partitioned between dichloromethane and sodium bicarbonate 4%, the organic layer was washed with brine, dried and the solvent was removed under reduced pressure to give the title compound as an off white solid (340mg, 96%), which was used in the next step without further purification.

LRMS (m/z): 533 (M+1)+, 531 (M-1)-

Intermediate 263.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl {4-[2-(methylamino)ethyl] biphenyl-2-yl}carbamate

Methylamine (1.70mL, 3.40mmol) was added to a solution of 2-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy)carbonyl]amino}biphenyl-4-yl)ethyl methanesulfonate (Intermediate 262; 351mg, 0.64mmol) in toluene, the mixture was stirred for 4 hours at 110° C. The solvent was removed under reduced pressure and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform: ethanol:ammonium (40:8:1) giving the title compound (0.30mg, 97%).

LRMS (m/z): 469 (M+1)+, 467 (M-1)-

Intermediate 264.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl (4-{2-[{[2-chloro-4-(hydroxymethyl)-5-methoxyphenoxy]acetyl}(methyl)amino]ethyl}biphenyl-2-yl)carbamate

The title compound was obtained (401mg, 62%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl (4-{2-[{[2-chloro-4-(hydroxymethyl)-5-methoxy-phenoxy]acetyl}(methyl)amino]ethyl}biphenyl-2-yl)carbamate (Intermediate 263; 305mg, 0.65mmol), [2-chloro-4-(hydroxymethyl)-5-methoxyphenoxy]acetic acid (Intermediate 249; 161mg, 0.65mmol), HBTU (247mg, 0.65mmol) and DIEA (454µL, 2.61mmol) following the experimental procedure as described for Intermediate 125 and the crude was used in the next step without further purification.

LRMS (m/z): 695 (M-1)-

Intermediate 265.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl (4-{2-[[(2-chloro-4-formyl-5-methoxyphenoxy)acetyl](methyl)amino]ethyl}biphenyl-2-yl)carbamate

Obtained as a yellow foam (427mg, 85%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl (4-{2-[{[2-chloro-4-(hydroxymethyl)-5-methoxyphenoxy]-acetyl}(methyl)amino]ethyl}biphenyl-2-yl)carbamate (Intermediate 264; 401mg, 0.58mmol) and manganese oxide (500mg, 5.75mmol) following the experimental procedure as described for Intermediate 218 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 694 (M+1)+, 692 (M-1)-

Intermediate 266.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl (4-{2-[{[4-({[(2R)-2-{[tert-butyl (dimethyl) silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino} methyl)-2-chloro-5-methoxyphenoxy]acetyl}(methyl)amino]ethyl}biphenyl-2-yl)carbamate

Obtained (236mg, 38%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl (4-{2-[[(2-chloro-4-formyl-5-methoxyphenoxy)acetyl](methyl)amino]ethyl}biphenyl-2-yl)carbamate (Intermediate 265; 427mg, 0.62mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (206mg, 0.62mmol) (prepared according to preparation 8 from US20060035931) and sodium triacetoxyborohydride (97mg, 1.54mmol) and DIEA (118µL, 0.68mmol) following the experimental procedure as described for Intermediate 146. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform: methanol (9:1).

LRMS (m/z): 508 (M/2)+

EXAMPLE 48.

trans-4-aminocyclohexyl (4-{2-[{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenoxy]acetyl}(methyl)-amino]ethyl}biphenyl-2-yl)carbamate dihydrochloride

Obtained as a white solid (99mg, 80%) from trans-4-[(tert-butoxycarbonyl)amino] cyclohexyl (4-{2-[{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-chloro-5-methoxyphenoxy]acetyl}(methyl)-amino]ethyl}biphenyl-2-yl)carbamate (Intermediate 266; 158mg, 0.16mmol) and hydrogen chloride (4N in dioxane; 0.5mL) following the experimental procedure as described for Intermediate 21.

LRMS (m/z): 799 (M+1)+, 797 (M-1)-

1H NMR (400 MHz, dmso) δ 10.80 (s, 1H), 10.76 (s, 1H), 9.34 (bs, 1H), 9.06 (bs, 1H), 8.93 (d, J = 7.6 Hz, 1H), 8.41 (d, J = 9.9 Hz, 1H), 8.21 (bs, 3H), 7.82 (s, 1H), 7.65 (dd, J = 11.8, 5.4 Hz, 2H), 7.60 – 7.54 (m, 3H), 7.52 – 7.44 (m, 1H), 7.38 (dd, J = 8.8, 3.9 Hz, 1H), 7.24 (d, J = 8.2 Hz, 1H), 6.97 (d, J = 13.5 Hz, 1H), 6.82 (d, J = 9.9 Hz, 1H), 6.44 (s, 1H), 5.65 (d, J = 7.7 Hz, 1H), 5.32 (bs, 1H), 5.26 (bs, 1H), 4.58 (s, 1H), 4.36 (s, 2H), 4.06 (s, 3H), 4.03 (s, 2H), 3.92 – 3.73 (m, 2H), 3.66 (s, 3H), 3.25 (d, J = 31.6 Hz, 2H), 2.15 (d, J = 7.5 Hz, 2H), 2.07 (bs, 2H), 1.73 – 1.48 (m, 4H).

Intermediate 267

Tert-butyl[(5-chloro-4-isocyanato-2-methoxybenzyl)oxy]dimethylsilane

To a solution of 4-((tert-butyldimethylsilyloxy)methyl)-2-chloro-5-methoxyaniline (Intermediate 39 WO2011/141180A1; 300mg, 0.9mmol) in 4 mL of anhydrous dichloromethane at 0°C was added dropwise a solution of triphosgene (108mg; 0.36mmol) in 5mL of anhydrous dichloromethane.

Once the addition is finished triethylamine (280 uL, 2.01mmol) was added dropwise. The reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was concentrated under reduced pressure until half of the initial volume and 25 mL of pentane was added into the reaction mixture. The solid was filtrated and washed with more pentane and dried to get the title compound (307mg, 79%).

Intermediate 268

Trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{2-[({[4-({[tert-butyl(dimethyl) silyl]oxy}methyl)-2-chloro-5-methoxyphenyl]amino}carbonyl)oxy]ethyl}biphenyl-2-yl)carbamate

To a solution of tert-butyl[(5-chloro-4-isocyanato-2-methoxybenzyl)oxy]dimethylsilane (Intermediate 267; 150mg, 0.46mmol) in toluene (5mL) is added at 0°C trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl[4-(2-hydroxyethyl)biphenyl-2-yl]carbamate (Intermediate 261, 294mmol, 0.55 mmol) and triehylamine (75uL, 0.54mmol) and the mixture is stirred at room temperature for 4 hours.The solvent was removed under reduced pressure and the crude was purified by column chromatography in reverse phase using as eluents water and acetonitrile, giving the title compound (170mg, 47%).

Intermediate 269

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{2-[{[2-chloro-4-(hydroxy methyl)-5-methoxyphenoxy]acetyl}(methyl)amino]ethyl}biphenyl-2-yl)carbamate

To a solution of trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl (4-{2-[({[4-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-chloro-5-methoxyphenyl]amino}carbonyl)oxy]ethyl} biphenyl-2-yl)carbamate (Intermediate 268; 238mg, 0.30mmol) in tetrahydrofuran (8mL) was added dropwise TBAF 1M in THF (304 uL, 0.3 mmol). The reaction mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure and the crude was partitioned between dichloromethane and water, the organic layer was washed with water several times, dried, filtered and the solvent was removed under reduced pressure. The crude obtained was used in the next step without further purification (200mg, 98%).

Intermediate 270

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{2-[[(2-chloro-4-formyl-5-methoxy phenoxy)acetyl](methyl)amino]ethyl}biphenyl-2-yl)carbamate

A round-bottomed flask fitted with stir bar was charged with trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{2-[{[2-chloro-4-(hydroxymethyl)-5-methoxy phenoxy]acetyl}(methyl)amino]ethyl}biphenyl-2-yl)carbamate (Intermediate 269; 200mg, 0.3mmol) in DCM. Dess-Martin periodinane (139mg, 0.33mmol) was added portionwise and the mixture stirred at room temperature for 1 hour. The reaction was quenched by addition of saturated bicar-bonate (little bubbling) and diluted with DCM. The organic layer was washed with more bicarbonate solution (twice), brine, dried over MgSO4, filtered and concentrated. The residue was used in the next step without further purification (199mg, 99%).

LRMS (m/z): 667 (M+1)+

Intermediate 271

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{2-[({[4-({[(2R)-2-{[tert-butyl (dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino} methyl)-2-chloro-5-methoxyphenyl]amino}carbonyl)oxy]ethyl}biphenyl-2-yl) carbamate

To a mixture of trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl (4-{2-[[(2-chloro-4-formyl-5-methoxyphenoxy)acetyl](methyl)amino]ethyl}biphenyl-2-yl)carbamate (Intermediate 270; 199mg, 0.3mmol) and 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (99mg, 0.3mmol) (prepared according to preparation 8 from US20060035931) in 5mL of DCE/methanol (4:1) sodium triacetoxyborohydride (474mg, 2.22mmol) was added. The mixture was stirred over a weekend at room temperature. The solvent was removed under reduced pressure and the crude was partitioned between ethyl acetate and water, the organic layer was washed with sodium bicarbonate solution and water, dried, filtered and the solvent was removed under reduced pressure. The crude obtained was used in the next step without further purification (160mg, 54%).

EXAMPLE 49

trans-4-aminocyclohexyl(4-{2-[({[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino} carbonyl)oxy]ethyl}biphenyl-2-yl)carbamate dihydrochloride

A solution trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl (4-{2-[({[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino} methyl)-2-chloro-5-methoxyphenyl]amino}carbonyl)oxy]ethyl}biphenyl-2-yl)carbamate (Intermediate 271; 110mg, 0.11mmol) in 2.8mL of hydrogen chloride (4N in dioxane) was stirred for 3 hours at room temperature. The solvent was removed under reduced pressure and the crude obtained was treated with acetonitrile giving a white solid as the title compound (60mg, 54%)

LRMS (m/z): 771 (M+1)+

1H NMR (400 MHz, dmso) δ 10.50 (bs, 1H), 9.20 (s, 1H), 8.87 (s, 1H), 8.67 (s, 1H), 8.15 (d, J = 12.0 Hz, 1H), 8.01 (s, 2H), 7.60 (s, 1H), 7.48 – 7.16 (m, 10H), 7.11 (d, J = 9.3 Hz, 1H), 6.97 (d, J = 7.9 Hz, 1H), 6.54 (d, J = 10.9 Hz, 1H), 5.41 (d, J = 5.5 Hz, 1H), 4.32 (s, 3H), 4.15 (s, 2H), 3.77 (s, 3H), 2.96 (s, 6H), 1.84 (d, J = 29.6 Hz, 4H), 1.45 – 1.16 (m, 4H).

Intermediate 272.

4-(but-3-en-1-yloxy)benzaldehyde

To a solution of 4-hydroxybenzaldehyde (0.30g, 2.46mmol) in anhydrous DMF (3mL) were added potassium carbonate (1.65g, 12mmol) and 4-bromobut-1-ene (1.08mL, 11.1mmol) and the reaction mixture was heated at 60 °C for 28 hr. After cooling to room temperature, water (30mL) was added until complete dissolution of the solid. The aqueous phase was extracted with ether (3 x 20mL) and the combined organic extracts were washed with water (30mL) and brine (30mL), dried with anhydrous sodium sulphate, filtered and concentrated to dryness to afford the title compound as a colorless oil (426mg, 98%).

LRMS (m/z): 177 (M+1)+

Intermediate 273.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl {5-[(1E)-4-(4-formylphenoxy)but-1-en-1-yl]biphenyl-2-yl}carbamate

Obtained as a colorless oil (82mg of an 80% purity , 22%) from *trans*-4-tert-butylaminocyclohexyl (5-bromobiphenyl-2-yl)carbamate (Intermediate 175, 250 mg, 0.51 mmol), 4-(but-3-en-1-yloxy)benzaldehyde (Intermediate 272, 99mg, 0.56 mmol), tri-o-tolylphosphine (68mg, 0.22mmol), N,N-diisopropylethylamine (180µL, 1.03mmol) and palladium acetate (30mg, 0.13mmol) following the experimental procedure as described for Intermediate 6 using dioxane (3mL) as solvent. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether.

LRMS (m/z): 585 (M+1)+

Intermediate 274.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl (5-{(1E)-4-[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy]but-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a beige solid (66mg, 66%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl {5-[(1E)-4-(4-formylphenoxy)but-1-en-1-yl]biphenyl-2-yl}carbamate (Intermediate 273, 81mg, 0.11mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (44mg, 0.11mmol) (prepared according to preparation 8 from US20060035931), and sodium triacetoxyborohydride (140mg, 0.66mmol) following the experimental procedure as described for Intermediate 7 without DIEA and using a mixture of methanol:tetrahydrofuran 1:1 as solvent (2mL). The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform and chloroform:methanol:ammonium hydroxide(40:4:0.2)

LRMS (m/z): 904 (M+1)+

Intermediate 275.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl (5-{4-[4-({[(2R)-2-{[tert-butyl-(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}-methyl)phenoxy]butyl}biphenyl-2-yl)carbamate

To a solution of trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl (5-{(1E)-4-[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}-methyl)phenoxy]but-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 274, 66mg, 0.07mmol) in methanol (1.5mL) was added palladium on carbon (10% palladium on carbon, 8.0mg, 0.01mmol) and the resulting suspension was purged with argon and then filled with hydrogen. The mixture was stirred at room temperature for 3 hr. The reaction mixture is then filtered, the solid washed with a mixture of chloroform:ethanol 1:1 and the filtrate is concentrated to dryness to afford the title compound as a colorless foam (70mg, 100%)

LRMS (m/z): 906 (M+1)+

EXAMPLE 50.

trans-4-aminocyclohexyl (4-{5-[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy]pentyl}biphenyl-2-yl)carbamate

Obtained as white solid (40mg of a 95% purity, 68%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl (5-{4-[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy]butyl}biphenyl-2-yl)carbamate (Intermediate 275, 66mg, 0.01mmol) and hydrogen chloride (0.2mL of a 4M solution in dioxane, 0.8mmol) in tetrahydrofuran (1mL), following the experimental procedure as described for Intermediate 21.

LRMS (m/z): 692 (M+1)+

1H NMR (300 MHz, dmso) δ 10.48 (bs, 2H), 9.59 (bs, 1H), 9.01 (bs, 1H), 8.57 (s, 1H), 8.19 (d, J = 10.0 Hz, 1H), 8.05 (d, J = 3.4 Hz, 2H), 7.53 – 7.29 (m, 5H), 7.18 (m, 3H), 7.02 – 6.88 (m, 2H), 6.53 (d, J = 9.9 Hz, 1H), 5.46 (d, J = 8.2 Hz, 1H), 4.33 (m, 1H), 4.12 (bs, 2H), 4.02 (d, J = 11.6 Hz, 2H), 2.99 (m, 3H), 2.67 (bs, 2H), 2.01 – 1.64 (m, 6H), 1.48 – 1.15 (m, 4H).

Intermediate 276

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl[4-(4-{[trans-3-(hydroxymethyl) cyclobutyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

To a solution of 4-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy)carbonyl]amino}biphenyl-4-yl)butanoic acid (synthesized as Intermediate 189; 550mg, 1.11mmol) in DMF (5mL) was added ((1r,3r)-3-aminocyclobutyl)methanol (123mg, 1.22mmol) and diisopropylethylenediamine (0.578mL, 3.32mmol) under nitrogen atmosphere. Then HATU (631mg, 1.66mmol) was added. The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the crude was partitioned between ethyl acetate and water, the organic layer was washed with water several times, dried, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel giving the title compound as a solid (120mg, 18%).

LRMS (m/z): 581 (M+1)+

Intermediate 277

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{4-[(trans-3-formylcyclobutyl) amino]-4-oxobutyl}biphenyl-2-yl)carbamate

A round-bottomed flask fitted with stir bar was charged with trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl[4-(4-{[trans-3-(hydroxymethyl)cyclobutyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 276; 120mg, 0.21mmol) in DCM (10mL). Dess-Martin periodinane (115mg, 0.27mmol) was added portionwise and the mixture stirred at room temperature for 2 hours. The reaction was quenched by addition of saturated bicarbonate (little bubbling) and diluted with DCM. The organic layer was washed with more bicarbonate solution (twice), brine, dried over MgSO4, filtered and concentrated. The residue was used in the next step without further purification (119mg, 99%).

LRMS (m/z): 578 (M+1)+

Intermediate 278

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl[4-(4-{[trans-3-({[(2R)-2-{[tert-butyl (dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino} methyl)cyclobutyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

A mixture of trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{4-[(trans-3-formylcyclobutyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate (Intermediate 277; 119mg, 0.21mmol) and 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (62mg, 0.19mmol) (prepared according to preparation 8 from US20060035931) in 20mL of DCE/methanol (4:1) is stirred for 1 hour. Then sodium triacetoxyborohydride (474mg, 2.22mmol) was added. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with DCM and washed with sodium bicarbonate solution and water, dried, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel using basic media giving the title compound as a solid (49mg, 29%).

LRMS (m/z): 897 (M+1)+

EXAMPLE 51

trans-4-aminocyclohexyl [4-(4-{[trans-3-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)cyclobutyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate dihydrochloride

A solution trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(4-{[trans-3-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino} methyl)cyclobutyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 278; 49mg, 0.05mmol) in 2mL of hydrogen chloride (4N in dioxane) was stirred for 3 hours at room temperature. The solvent was removed under reduced pressure and the crude obtained was treated with acetonitrile and diethyl ether giving a white solid as the title compound (15mg, 40%)

LRMS (m/z): 683 (M+1)+

1H NMR (300 MHz, dmso) δ 10.74 (bs, 1H), 8.62 (s, 2H), 7.90 (d, J = 2.8 Hz, 2H), 7.36 (dd, J = 16.3, 6.0 Hz, 3H), 7.27 – 7.05 (m, 3H), 6.98 (d, J = 8.5 Hz, 1H), 6.58 (d, J = 7.3 Hz, 1H), 5.53 – 5.27 (m, 3H), 4.32 (d, J = 3.4 Hz, 3H), 4.18 – 3.95 (m, 1H), 3.57 (s, 2H), 2.99 (d, J = 9.0 Hz, 3H), 2.09 (d, J = 7.6 Hz, 2H), 1.97 – 1.72 (m, 5H), 1.67 (d, J = 6.2 Hz, 2H), 1.50 – 1.15 (m, 5H).

Intermediate 279.

5-chloro-4-cyano-2-methoxybenzoic acid

To a suspension of 4-amino-5-chloro-2-methoxybenzoic acid (4.0g, 19.8mmol) in water (66mL) was added concentrated hydrogen chloride (6.6mL of a 35% solution in water, 79.2mmol) and the resulting mixture was cooled to 0°C with vigorous stirring. Then, a solution of sodium nitrite (1.95g, 28.3mmol) in water (6mL) was added dropwise while maintaining the internal temperature below 4°C. After 5 min, the mixture containing the diazonium salt was slowly added, through an addition funnel and maintaining the temperature below 5°C, over a mechanically stirred solution of copper cyanide (2.4g, 26.8mmol) and sodium cyanide (3.7g, 75.5mmol) in water (20mL, this solution was freshly prepared from a suspension of the copper cyanide in water and slow addition of sodium cyanide while keeping the temperature below 40 °C and allowed to cool to rt). Once the addition was finished, the reaction mixture was allowed to warm to rt and vigorous stirring was maintained for 4 hours. Then, water and hydrogen chloride (5N) were added to the mixture and the aqueous phase was extracted with ethyl acetate. The whole mixture was filtered to remove the solids and the phases were separated. The aqueous phase was further extracted twice with ethyl acetate and the combined organic extracts were washed with brine, dried, decolorized with active carbon, filtered and concentrated to dryness to afford the title compound as light yellow solid (3.0g, 70%).

LRMS (m/z): 210 (M-1)-

Intermediate 280.

2-chloro-4-(hydroxymethyl)-5-methoxybenzonitrile

To a solution of 5-chloro-4-cyano-2-methoxybenzoic acid (Intermediate 279, 3.0g, 14.2mmol) in tetrahydrofuran (50mL) was added slowly, at 0 °C and under argon atmosphere, borane dimethylsufide complex (2.7mL, 28.4mmol). After the addition was finished, the reaction mixture was stirred at 0 °C for 5 min and then allowed to warm up to rt and stirred for 3 hours. Then, water was slowly added (6mL) and the mixture was concentrated to dryness. The residue was suspended in ethyl acetate and filtered. The solid was washed with further ethyl acetate and the combined organic phases were decolorized with active carbon, filtered and concentrated under reduced pressure to afford the title compound as a yellowish solid (2.3g, 80%).

LRMS (m/z): 215 (M+18[NH4+])+

Intermediate 281.

2-chloro-4-(hydroxymethyl)-5-methoxybenzoic acid

To a suspension of 2-chloro-4-(hydroxymethyl)-5-methoxybenzonitrile (Intermediate 280, 1.8g, 9.1mmol) in ethanol (20mL) in a sealed tube was added NaOH (8mL of a 32% aqueous solution, 64 mmol) and the reaction mixture was heated at 110 °C overnight. Then, water was added and the aqueous phase was washed with ethyl acetate twice, acidified with hydrochloric acid (5N) up to pH=2, and extracted with ethyl acetate twice. The combined organic extracts were dried and concentrated to dryness to provide the title compound as a white solid (1.3g, 66%)

LRMS (m/z): 215 (M-1)-

Intermediate 282.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(3-{[(benzyloxy)carbonyl]-amino}propyl)biphenyl-2-yl]carbamate

4-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy)carbonyl]amino}biphenyl-4-yl)butanoic acid (synthesized as Intermediate 189; 5g, 10.1mmol) was suspended in toluene (70mL) and cooled to -10 °C under nitrogen atmosphere. To this suspension, diphenylphosphorylazide (2.16mL, 10.1mmol) and triethylamine (1.95mL, 14.1mmol) were added and the mixture was heated to 70 °C for 3h. The reaction mixture was cooled to 50 °C, phenylmethanol (2.9mL, 28.2mmol) was added, and then heated again to 110 °C overnight. The solvent is removed and water and dichloromethane were added. The phases were separated and the organic phase was washed with water and brine, dried, filtered and concentrated to dryness. The residue is purified twice by column chromatography with silica gel and eluting with a mixture of hexane:ether. The title compound was obtained (4.7g of 87% purity, 66%) as a beige solid.

LRMS (m/z): 603 (M+1)+

Intermediate 283.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(3-aminopropyl)biphenyl-2-yl]carbamate

To a solution of trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl[4-(3-{[(benzyloxy)-carbonyl] amino}propyl)biphenyl-2-yl]carbamate (Intermediate 282, 3.7g, 6.1mmol) in a mixture of ethanol (20mL) and methanol (5mL) was added palladium on carbon (0.65g of a 10% suspension, 0.61mmol), and the reaction mixture was stirred under hydrogen atmosphere overnight. The suspension was filtered through a pad of Celite® and the solvent was removed under reduced pressure. The residue obtained was washed with hexane and dried to provide the title compound as a yellowish solid (2.5g, 82%).

LRMS (m/z): 468 (M+1)+

Intermediate 284.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(3-{[2-chloro-4-(hydroxymethyl)-5-methoxybenzoyl]amino}propyl)biphenyl-2-yl]carbamate

To a solution of 2-chloro-4-(hydroxymethyl)-5-methoxybenzoic acid (Intermediate 281, 240mg, 1.11mmol) and trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(3-aminopropyl)biphenyl-2-yl]carbamate (Intermediate 284, 622mg, 1.33mmol) in DMF (10mL) were added sequentially diisopropylethylenediamine (0.77mL, 4.43mmol) and HATU (843mg, 2.22mmol) under nitrogen atmosphere. After 3 hours the solvent was removed and the remaining residue was suspended in water and the aqueous phase was extracted with ethyl acetate (3 times). The combined organic extracts were washed with water and brine, dried, filtered and concentrated to dryness. The residue was purified by column chromatography over silica gel using a mixture hexane:ether:methanol as eluent, and the crude obtained was further purified over C18 modified silica gel using a mixture of water:methanol as eluent to afford the title compound as a white solid (70mg, 10%).

LRMS (m/z): 667 (M+1)+

Intermediate 285.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl (4-{3-[(2-chloro-4-formyl-5-methoxybenzoyl)amino]propyl}biphenyl-2-yl)carbamate

Obtained as a black oil (70mg, 100%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(3-{[2-chloro-4-(hydroxymethyl)-5-methoxy-benzoyl]amino}propyl)biphenyl-2-yl]carbamate (Intermediate 284, 70mg, 0.11mmol) and manganese dioxide (91mg, 1.1mmol) in chloroform (6mL) following the experimental procedure as described for Intermediate 218 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 665 (M+1)+

Intermediate 286.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(3-{[4-({[(2R)-2-{[tert-butyl-(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}-methyl)-2-chloro-5-methoxybenzoyl]amino}propyl)biphenyl-2-yl]carbamate

Obtained as a beige solid (25mg, 24%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl (4-{3-[(2-chloro-4-formyl-5-methoxybenzoyl)amino]-propyl}biphenyl-2-yl)carbamate (70mg, 0.11mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (35mg, 0.10mmol) (prepared according to preparation 8 from US20060035931), sodium cyanoborohydride (13mg, 0.21mmol) and DIEA (38µL, 0.22mmol) in MeOH (3mL), following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform and chloroform:methanol:amomonium hydroxide (40:4:0.2).

LRMS (m/z): 464 (M/2+1-56 (tert-butyl))+, 927 (M+1-56(tert-butyl))+

EXAMPLE 52.

trans-4-aminocyclohexyl [4-(3-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxybenzoyl]amino}propyl) biphenyl-2-yl]carbamate

Obtained as white solid (15mg of a 90% purity, 69%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(3-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-chloro-5-methoxy-benzoyl]amino}propyl) biphenyl-2-yl]carbamate (25mg, 0.03mmol) and hydrogen chloride (0.1mL of a 4M solution in dioxane, 0.4mmol) in dioxane (2mL), following the experimental procedure as described for Intermediate 21.

LRMS (m/z): 768 (M+1)+

1H NMR (300 MHz, dmso) δ 10.55 (d, J = 12.9 Hz, 2H), 9.40 (bs, 1H), 9.03 (bs, 1H), 8.67 (s, 1H), 8.61 (t, J = 12.9 Hz, 1H), 8.23 (d, J = 10.0 Hz, 1H), 8.07 – 7.89 (m, 3H), 7.70 (s, 1H), 7.51 – 7.35 (m, 4H), 7.31 – 7.25 (m, 2H), 7.20 (d, J = 7.9 Hz, 1H), 7.17 (d, J = 3.2 Hz, 1H), 7.03 (d, J = 8.2 Hz, 1H), 6.62 (d, J = 9.8 Hz, 1H), 6.25 (s, 1H), 5.50 (ddd, J = 10.3, 7.7, 3.7 Hz, 1H), 4.45 – 4.32 (m, 1H), 4.32 – 4.21 (m, 2H), 3.90 (s, 3H), 3.38 – 3.25 (m, 2H), 3.23 – 3.12 (m, 1H), 3.12 – 2.94 (m, 2H), 2.85 – 2.64 (m, 2H), 2.10 – 1.71 (m, 6H), 1.55 – 1.21 (m, 4H).

Intermediate 287.

4-allylphenol

To a solution of 1-allyl-4-methoxybenzene (2.0g, 13.5mmol) in dichloromethane (100mL) was added, at 0°C and under nitrogen atmosphere, boron tribromide (15 mL of a 1M solution in dichloromethane, 15.0mmol) and the reaction was stirred for 3 hours at 0°C and overnight at rt. The reaction mixture was poured over an ice-water mixture and the resulting phases were separated. The aqueous phase was extracted with dichloromethane (4 times) and the combined organic extracts were washed with water and brine, dried over sodium sulphate, filtered and concentrated. The oil obtained was purified by column chromatography with silica gel using a mixture of hexane:ethyl acetate as eluent. The title compound was obtained as a light yellow oil (0.73g, 41%).

1H NMR (300 MHz, cdcl3) d 7.05 (d, J = 8.6 Hz, 2H), 6.76 (d, J = 8.6 Hz, 2H), 6.07 - 5.76 (m, 1H), 5.09 - 5.04 (m, 1H), 5.02 (t, J = 1.4 Hz, 1H), 4.77 (s, 1H), 3.32 (d, J = 6.7 Hz, 2H).

Intermediate 288.

4-(4-allylphenoxy)benzaldehyde

4-fluorobenzaldehyde (0.16mL, 1.5mmol) and 4-allylphenol (200mg, 1.5mmol) were dissolved in DMF (5mL). To this solution, potassium carbonate was added (412mg, 2.98mmol) and the mixture was heated to 110°C for 2 days. The reaction mixture was filtered and the filtrate was diluted with ethyl acetate. The organic phase was washed with aqueous NaOH (2N), water and brine, dried, filtered and concentrated to dryness. The residue was purified by column chromatography with silica gel using a mixture of hexane:ether as eluent to provide the title compound as a colorless oil (224mg, 63%).

LRMS (m/z): 239 (M+1)+

Intermediate 289.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl (4-{(1E)-3-[4-(4-formylphenoxy)phenyl] prop-1-en-1-yl}biphenyl-2-yl)carbamate

Obtained as a brownish foam (263mg, 100%) from trans-4-tert-butylaminocyclohexyl (4-bromobiphenyl-2-yl)carbamate (Intermediate 183, 200mg, 0.41mmol), 4-(4-

allylphenoxy)benzaldehyde (Intermediate 288, 97mg, 0.41mmol), tri-o-tolylphosphine (125mg, 0.41mmol), N,N-diisopropylethylamine (142µL, 0.82mmol) and palladium acetate (46mg, 0.20mmol) in acetonitrile (2mL) following the experimental procedure as described for Intermediate 6. The crude obtained was used without further purification.

LRMS (m/z): 645 (M-1)-

Intermediate 290.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-((1E)-3-{4-[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]-amino}methyl)phenoxy]phenyl}prop-1-en-1-yl)biphenyl-2-yl]carbamate

Obtained as a beige solid (171mg of a 80% purity, 35%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl (4-{(1E)-3-[4-(4-formylphenoxy)phenyl] prop-1-en-1-yl}biphenyl-2-yl)carbamate (263mg, 0.41mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (136mg, 0.41mmol) (prepared according to preparation 8 from US20060035931), sodium cyanoborohydride (64mg, 1.02mmol) and DIEA (85µL, 0.49mmol) in MeOH (2mL), following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform and chloroform:methanol:amomonium hydroxide (40:4:0.2) and the residue was purified again using a mixture of hexane:ether:ethanol as eluent.

Intermediate 291.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(3-{4-[4-({[(2R)-2-{[tert-butyl-(dimethyl) silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}-methyl)phenoxy] phenyl}propyl)biphenyl-2-yl]carbamate

Obtained as a beige foam (184 mg of a 80% purity, 86%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-((1E)-3-{4-[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]-oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy]phenyl}-prop-1-en-1-yl)biphenyl-2-yl]carbamate (171mg, 0.18 mmol) and palladium on carbon (10% palladium on carbon, 20mg, 0.02mmol) under hydrogen atmosphere in methanol (20mL). The crude product was used without any further purification.

EXAMPLE 53.

trans-4-aminocyclohexyl [4-(3-{4-[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy]phenyl}propyl)biphenyl-2-yl]carbamate

Obtained as white solid (111mg, 71%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(3-{4-[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy]phenyl}propyl)-biphenyl-2-yl]carbamate (184mg, 0.19mmol) and hydrogen chloride (0.7mL of a 4M solution in dioxane, 2.8mmol) in dioxane (2mL), following the experimental procedure as described for Intermediate 21.

LRMS (m/z): 753 (M+1)+

1H NMR (300 MHz, dmso) δ 10.55 (bs, 2H), 9.67 (bs, 1H), 9.12 (bs, 1H), 8.65 (s, 1H), 8.24 (dd, J = 9.9, 3.3 Hz, 1H), 8.07 (bs, 2H), 7.60 (dd, J = 8.6, 2.1 Hz, 2H), 7.49 – 7.35 (m, 4H), 7.31 (d, J = 9.5 Hz, 1H), 7.27 (d, J = 9.8 Hz, 1H), 7.25 (bs, 1H), 7.19 (d, J = 7.5 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 7.09 – 6.91 (m, 5H), 6.58 (d, J = 9.9 Hz, 1H), 5.51 (dd, J = 6.2, 1.8 Hz, 1H), 4.45 – 4.29 (m, 1H), 4.21 (bs, 2H), 3.15 – 2.90 (m, 3H), 2.68 (t, J = 7.3 Hz, 2H), 2.05 – 1.79 (m, 6H), 1.50 – 1.18 (m, 4H).

Intermediate 292.

methyl 4-({[4-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}-oxy)carbonyl]-amino} biphenyl-4-yl)butanoyl]amino}methyl)benzoate

To a solution of 4-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy)carbonyl]amino}biphenyl-4-yl)butanoic acid (synthesized as Intermediate 189; 200mg, 0.40mmol) in DMF (4mL), were added diisopropylethylenediamine (0.28mL, 1.61mmol) and HATU (382mg, 1.00mmol) under nitrogen atmosphere. Then, methyl 4-(aminomethyl)benzoate hydrochloride (90mg, 0.45mmol) was added. The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the crude was partitioned between dichloromethane and water, the organic layer was washed with water several times and brine, dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by reverse phase column chromatography with C18 modified silica gel, eluting with a mixture of water:acetonitrile, giving the title compound as a colorless foam (189mg, 71%).

LRMS (m/z): 645 (M+1)+

Intermediate 293.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(4-{[4-(hydroxymethyl)-benzyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

To a suspension of lithium aluminum hydride (16mg, 0.42mmol) in tetrahydrofuran (0.5mL) was added, at 0°C and under argon atmosphere, a solution of methyl 4-({[4-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy)carbonyl]amino}biphenyl-4-

yl)butanoyl]amino}methyl) benzoate (Intermediate 292, 189mg, 0.29mmol) in tetrahydrofuran (1.5mL). The reaction mixture was allowed to warm to rt and stirring was maintained overnight. The reaction was then quenched by sequential addition of H_2O (20µL), NaOH (4N, 20µL) and H_2O (60µL), and was stirred for 30 min at rt. The solid formed was filtered, washed with dichloromethane, and the resulting solution was concentrated under reduced pressure. The residue obtained was purified by reverse phase column chromatography with C18 modified silica gel, eluting with a mixture of water:acetonitrile, to afford the title compound as colorless foam (95mg, 50%).

LRMS (m/z): 617 (M+1)+

Intermediate 294.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl (4-{4-[(4-formylbenzyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate

Obtained as a brownish foam (99mg of a 90% purity, 94%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(4-{[4-(hydroxymethyl)benzyl]amino}-4-oxobutyl)-biphenyl-2-yl]carbamate (Intermediate 293, 95mg, 0.15mmol) and Dess-Martin periodinane (80mg, 0.19mmol) in DCM (2mL) following the experimental procedure as described for Intermediate 64 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 615 (M+1)+

Intermediate 295.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(4-{[4-({[(2R)-2-{[tert-butyl(dimethyl) silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]-amino}methyl)benzyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

Obtained as a beige solid (83mg, 56%) from trans-4-[(tert-butoxycarbonyl)amino]-cyclohexyl (4-{4-[(4-formylbenzyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate (Intermediate 294, 98mg, 0.16mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (63mg, 0.16mmol) (prepared according to preparation 8 from US20060035931), sodium cyanoborohydride (26mg, 0.41mmol) and DIEA (28µL, 0.16mmol), following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol.

LRMS (m/z): 933 (M+1)+

EXAMPLE 54.

trans-4-aminocyclohexyl [4-(4-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-

dihydroquinolin-5-yl)ethyl]amino}methyl)benzyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate dihydrochloride

Obtained as white solid (55mg of a 92% purity, 72%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(4-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)benzyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 295; 83mg, 0.09mmol) and hydrogen chloride (0.45mL of a 4M solution in dioxane, 1.8mmol) in tetrahydrofuran (1mL), following the experimental procedure as described for Intermediate 21.

LRMS (m/z): 719 (M+1)+

1H NMR (300 MHz, dmso) δ 10.54 (bs, 1H), 9.78 (bs, 1H), 9.16 (bs, 1H), 8.66 (s, 1H), 8.47 (t, J = 5.9 Hz, 1H), 8.25 (d, J = 9.0 Hz, 1H), 8.10 (bs, 3H), 7.55 (d, J = 8.5 Hz, 2H), 7.49 – 7.28 (m, 7H), 7.25 (d, J = 9.0 Hz, 2H), 7.23 (bs, 1H) 7.15 (d, J = 8.5 Hz, 2H), 7.02 (d, J = 9.0 Hz, 1H), 6.57 (d, J = 9.5 Hz, 1H), 5.52 (d, J = 8.5 Hz, 1H), 4.43 – 4.28 (m, J = 9.5 Hz, 3H), 4.21 (bs, 2H), 3.10 – 2.87 (m, 3H), 2.61 (t, J = 7.5 Hz, 2H), 2.25 (t, J = 7.5 Hz, 2H), 2.02 – 1.79 (m, 6H), 1.52 – 1.21 (m, 4H).

Intermediate 296.

(5-aminopyridin-2-yl)methanol

To a suspension of lithium aluminium hydride (302mg, 7.96mmol) in tetrahydrofuran (0.5mL) was added, at 0°C and under argon atmosphere, a solution of ethyl 6-aminonicotinate (602mg, 3.62mmol) in tetrahydrofuran (1.5mL). The reaction mixture was allowed to warm to rt. After 5 hours the reaction was then quenched by sequential addition of H_2O (0.3mL), NaOH (4N, 0.3mL) and H_2O (0.6mL), and stirring was continued for 30 min at rt. The solid formed was filtered, washed with dichloromethane, and the resulting solution was concentrated under reduced pressure. The residue obtained was washed with ether and dried to afford the title compound as a colorless foam (500mg of a 90% purity, 100%). The compound was used without further purification.

LRMS (m/z): 125 (M+1)+

Intermediate 297.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(4-{[6-(hydroxymethyl)pyridin-3-yl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

Obtained as a colorless foam (244 mg of a 58% purity, 58%) from 4-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy)carbonyl]amino}biphenyl-4-yl)butanoic acid (synthesized as Intermediate 189; 200mg, 0.40mmol), (5-aminopyridin-2-yl)methanol

(Intermediate 296, 73mg, 0.53mmol) diisopropylethylenediamine (85µL, 0.49mmol) and HATU (170mg, 0.45mmol) in DMF (5mL) following the experimental procedure as described for intermediate 292. The crude residue was purified by column chromatography using a mixture of chloroform:methanol as eluent.

LRMS (m/z): 603 (M+1)+

Intermediate 298.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{4-[(6-formylpyridin-3-yl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate

Obtained as a brownish foam (145mg of a 63% purity, 27%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl[4-(4-{[6-(hydroxymethyl)pyridin-3-yl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 297, 243mg, 0.24mmol) and Dess-Martin periodinane (175mg, 0.41mmol) following the experimental procedure as described for Intermediate 64 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 601 (M+1)+

Intermediate 299.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl[4-(4-{[6-({[(2R)-2-{[tert-butyl(dimethyl) silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]-amino}methyl)pyridin-3-yl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

Obtained as a yellow foam (18mg, 28%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{4-[(6-formylpyridin-3-yl)amino]-4-oxobutyl}-biphenyl-2-yl)carbamate (Intermediate 298, 61mg of a 65% purity, 0.07mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (22mg, 0.07mmol) (prepared according to preparation 8 from US20060035931), sodium cyanoborohydride (11mg, 0.18mmol) and DIEA (12µL, 0.07mmol), following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol.

LRMS (m/z): 920 (M+1)+

EXAMPLE 55.

trans-4-aminocyclohexyl[4-(4-{[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)pyridin-2-yl]amino}-4-oxobutyl) biphenyl-2-yl]carbamate dihydrochloride

Obtained as a white solid (8mg, 53%) from trans-4-[(tert-butoxycarbonyl)amino]-cyclohexyl[4-(4-{[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)pyridin-3-yl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 299; 18mg, 0.02mmol) and hydrogen chloride (0.15mL of a 4M solution in dioxane, 0.6mmol) in tetrahydrofuran (0.5mL), following the experimental procedure as described for Intermediate 21.

LRMS (m/z): 705 (M+1)+

1H NMR (300 MHz, dmso) δ 10.73 (s, 1H), 10.55 (bs, 2H), 9.84 (bs, 1H), 9.19 (bs, 1H), 8.66 (s, 1H), 8.49 (s, 1H), 8.29 (d, J = 10.0 Hz, 1H), 8.16 (d, J = 8.5 Hz, 1H), 8.11 – 7.97 (m, 3H), 7.50 – 7.31 (m, 5H), 7.30 – 7.22 (m, 2H), 7.17 (d, J = 8.5 Hz, 2H), 7.03 (d, J = 8.5 Hz, 1H), 6.59 (d, J = 9.9 Hz, 1H), 5.53 (d, J = 9.2 Hz, 1H), 4.37 (m, 2H), 4.23 (bs, 2H), 3.18 – 2.90 (m, 4H), 2.67 (t, J = 7.5 Hz, 2H), 2.10 – 1.69 (m, 6H), 1.57 – 1.09 (m, 4H).

Intermediate 300.

trans-4-{[tert-butyl(dimethyl)silyl]oxy}-N-methylcyclohexanamine

To a solution of trans-4-(methylamino)cyclohexanol (3.4g, 26.32mmol) in dichloromethane (130mL) was added imidazole (2.70g, 39.66mmol). The mixture was cooled to 0°C and tert-butyldimethylsilyl chloride (4.40g, 29.19mmol) was added dropwise. The mixture was stirred at room temperature overnight. The crude was partitioned between water and more dichloromethane, the organic layer was washed with saturated solution of potassium carbonate, dried, filtered and evaporated to dryness. Pentane was added to the crude obtained, the mixture was filtered and the filtrate was evaporated giving the title compound (6.7g, 99%).

1H NMR (300 MHz, cdcl3) δ 3.60 – 3.43 (m, 1H), 2.36 (s, 3H), 2.31 – 2.18 (m, 1H), 1.83 (ddd, J = 16.2, 8.9, 3.6 Hz, 4H), 1.41 – 1.17 (m, 2H), 1.13 – 0.92 (m, 2H), 0.83 (s, 9H), 0.00 (s, 6H).

Intermediate 301.

trans-4-{[tert-butyl(dimethyl)silyl]oxy}-N-hexyl-N-methylcyclohexanamine

Obtained (1.53g, 978%) from trans-4-{[tert-butyl(dimethyl)silyl]oxy}-N-methylcyclohexanamine (Intermediate 300; 1.00g, 4.11mmol), hexanal (0.55mL, 4.58mmol) and sodium triacetoxyborohydride (2.60g, 12.27mmol) in dichloroethane (25mL) following the experimental procedure as described for Intermediate 146.

1H NMR (300 MHz, dmso) δ 3.53 (s, 2H), 3.29 (s, 3H), 2.84 (d, J = 3.1 Hz, 2H), 1.94 (d, J = 11.7 Hz, 2H), 1.85 – 1.72 (m, 3H), 1.60 – 1.34 (m, 4H), 1.23 (s, 9H), 0.02 – -0.02 (m, 6H).

Intermediate 302.

ethyl 4-(2-{[({trans-4-[hexyl(methyl)amino]cyclohexyl}oxy)carbonyl]amino} biphenyl-4-yl)butanoate

To a solution of triphosgene (0.29g, 0.96mmol) in toluene (8mL) was added dropwise at 0°C a solution of ethyl 4-(2-aminobiphenyl-4-yl)butanoate (Intermediate 122; 0.69g, 2.42mmol), once the addition is finished triethylamine (0.67mL, 4.84mmol) was added. The mixture was stirred 4 hours at room temperature. The solvent was partially removed under reduced pressure without heating and hexane was added to precipitate the salts, the mixture was filtered and the filtrate was evaporated. The corresponding isocyanate with trans-4-{[tert-butyl(dimethyl)silyl]oxy}-N-hexyl-N-methyl-cyclohexanamine (570mg, 2.67mmol) were stirred overnight at 110°C. The crude was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2), giving the title compound (174mg, 14%).

LRMS (m/z): 523 (M+1)+

Intermediate 303.

lithium 4-(2-{[({4-[hexyl(methyl)amino]cyclohexyl}oxy)carbonyl]amino}biphenyl-4-yl)butanoate

Obtained as a solid (160mg, 95%) from ethyl 4-(2-{[({trans-4-[hexyl(methyl)amino]-cyclohexyl}oxy)carbonyl]amino}biphenyl-4-yl)butanoate (Intermediate 302; 174mg, 0.34mg) and lithium hydroxide monohydrate (50mg, 1.19mmol) following the experimental procedure as described for Intermediate 124. After stirring overnight, and chloroform was added to precipitate the salts, the mixture was filtered and the filtrate was evaporated and the crude obtained was used in the next step without further purification.

LRMS (m/z): 493 (M-1)-

Intermediate 304.

4-[hexyl(methyl)amino]cyclohexyl [4-(4-{[4-({[tert-butyl(dimethyl)silyl]oxy}-methyl)-2-chloro-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

To a solution of lithium 4-(2-{[({4-[hexyl(methyl)amino]cyclohexyl}oxy)carbonyl]-amino}biphenyl-4-yl)butanoate (Intermediate 303; 160mg, 0.32mmol) in DMF (3mL) was added HATU (145mg, 0.38mmol) under nitrogen atmosphere. After 1 hour stirring at room temperature, 4-((tert-butyldimethylsilyloxy)methyl)-2-chloro-5-methoxyaniline (Intermediate 39 WO2011/141180A1; 104mg, 0.34mmol), was added. The reaction mixture was stirred at 50° C overnight. The solvent was removed under reduced pressure and the crude was partitioned between chloroform and water, the organic layer was washed with water several times, dried, filtered and the solvent was removed under reduced pressure. The crude obtained (242 mg of an 50% purity, 45%) was used in the next step without further purification.

LRMS (m/z): 779 (M+1)+

Intermediate 305.

trans-4-[hexyl(methyl)amino]cyclohexyl [4-(4-{[2-chloro-4-(hydroxymethyl)-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

Tetrabutylammonium fluoride solution (1M in THF, 311μM) was added dropwise to a solution of trans-4-[hexyl(methyl)amino]cyclohexyl [4-(4-{[2-chloro-4-(hydroxymethyl)-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 304; 242mg of an 50% purity, 0.16mmol) in tetrahydrofurane. The mixture was stirring 3h at room temperature. The solvent was removed under reduced pressure and the residue was suspended in MeOH and acidified by hydrogen chloride 1N. The solution was passed through an acidic sulphonic SCX column. The compound was released from the column with 33% ammonium in methanol and the solvent was removed under reduced pressure. The crude obtained (182mg of an 50% purity, 88%) was used in the next step without further purification.

LRMS (m/z): 664 (M+1)+

Intermediate 306.

trans-4-[hexyl(methyl)amino]cyclohexyl (4-{4-[(2-chloro-4-formyl-5-methoxyphenyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate

Obtained as a yellow foam (158mg of an 50% purity, 87%) from trans-4-[hexyl(methyl)amino]cyclohexyl [4-(4-{[2-chloro-4-(hydroxymethyl)-5-methoxyphenyl]-amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 305; 182 mg of an 50% purity, 0.13mmol) and manganese oxide (238mg, 2.74mmol) following the experimental procedure as described for Intermediate 218 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 662 (M+1)+

Intermediate 307.

trans-4-[hexyl(methyl)amino]cyclohexyl [4-(4-{[4-({[(2R)-2-{[tert-butyl(dimethyl)-silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-chloro-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

Obtained as a solid (10mg, 9%) from trans-4-[hexyl(methyl)amino]cyclohexyl (4-{4-[(2-chloro-4-formyl-5-methoxyphenyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate (Intermediate 306; 158mg of an 50% purity, 0.12mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (45mg, 0.13mmol) (prepared according to preparation 8 from US20060035931), sodium cianoborohydride (19mg, 0.30mmol) and diethylethylenamine (25µL, 0.14mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography in reverse phase using as eluents water and methanol.

LRMS (m/z): 491 (M/2+1)+

EXAMPLE 56

trans-4-[hexyl(methyl)amino]cyclohexyl [4-(4-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl] amino}-4-oxobutyl)biphenyl-2-yl]carbamate dihydrofluoride

Obtained as a white solid (8mg, 87%) from trans-4-[hexyl(methyl)amino]cyclohexyl [4-(4-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

yl)ethyl]amino}methyl)-2-chloro-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 307; 10mg, 0.01mmol) and triethylamine trihydrofluoride (10µL, 0.06mmol) following the experimental procedure as described for Example 1.

LRMS (m/z): 867 (M+1)+, 434 (M/2+1)+, 865 (M-1)-

Intermediate 308.

(5-aminopyridin-2-yl)methanol

Obtained as a solid (1.3g of an 85% purity, 30%) from ethyl 5-aminopicolinate (5,0g, 30.1mmol) and lithium aluminium hydride (2.28g, 60.1mmol) in tetrahydrofuran (21 mL), following the experimental procedure as described for Intermediate 296. The crude was purified by column chromatography on silica gel, eluting with a mixture of chloroform:methanol.

LRMS (m/z): 125 (M+1)+

Intermediate 309.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl[4-(4-{[6-(hydroxymethyl)pyridin-3-yl] amino}-4-oxobutyl)biphenyl-2-yl]carbamate

Obtained as an oil (326mg of an 82% purity, over 100%) from 4-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy)carbonyl]amino}biphenyl-4-yl)butanoic acid (synthesized as Intermediate 189; 200mg, 0.40mmol), (5-aminopyridin-2-yl)methanol (Intermediate 308, 55mg, 0.44mmol), diisopropylethylenediamine (85µL, 0.49mmol) and HATU (190mg, 0.50mmol) in DMF (5mL), following the experimental procedure as described for intermediate 292. The crude product was used without further purification.

LRMS (m/z): 604 (M+1)+

Intermediate 310.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{4-[(6-formylpyridin-3-yl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate

Obtained as a light brown foam (134 mg of an 83% purity, 97%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl[4-(4-{[6-(hydroxymethyl)pyridin-3-yl]amino}-4-oxobutyl) biphenyl-2-yl]carbamate (Intermediate 309, 138mg, 0.19mmol) and Dess-Martin periodinane (93mg, 0.22mmol) in dichloromethane (3mL), following the experimental procedure as described for Intermediate 64 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 601 (M+1)+

Intermediate 311.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl[4-(4-{[6-({[(2R)-2-{[tertbutyl(dimethyl)silyl] oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]-amino}methyl)pyridin-3-yl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

Obtained as a yellow foam (139mg, 81%) from trans-4-[(tert-butoxycarbonyl)-amino]cyclohexyl(4-{4-[(6-formylpyridin-3-yl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate (Intermediate 310, 134mg of a 83% purity, 0.18mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (80mg, 0.20mmol) (prepared according to preparation 8 from US20060035931), sodium cyanoborohydride (28mg, 0.45mmol) and DIEA (35µL, 0.20mmol), following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:ethanol.

LRMS (m/z): 920 (M+1)+

EXAMPLE 57.

trans-4-aminocyclohexyl[4-(4-{[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)pyridin-3-yl]amino}-4-oxobutyl)-biphenyl-2-yl] carbamate dihydrochloride

Obtained as a beige solid (108mg of a 94% purity, 86%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl[4-(4-{[6-({[(2R)-2-{[tertbutyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)pyridin-3-yl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 311; 139mg, 0.14mmol) and hydrogen chloride (1.0mL of a 4M solution in dioxane, 4.0mmol) in tetrahydrofuran (2.0mL), following the experimental procedure as described for Intermediate 21.

LRMS (m/z): 705 (M+1)+

^{1}H NMR (300 MHz, dmso) δ 10.57 (bs, 2H), 10.46 (s, 1H), 9.38 (bs, 1H), 8.91 (s, 1H), 8.68 (s, 1H), 8.25 (d, J = 10.1 Hz, 1H), 8.21 – 8.00 (m, 3H), 7.54 (d, J = 8.0 Hz, 1H), 7.49 – 7.33 (m, 4H), 7.29 – 7.24 (m, 2H), 7.19 (d, J = 8.2 Hz, 2H), 7.04 (d, J = 8.2 Hz, 1H), 6.61 (d, J = 9.6 Hz, 1H), 5.53 (d, J = 8.3 Hz, 1H), 4.37 (bs, 3H), 3.31 – 2.83 (m, 4H), 2.70 (t, J = 7.5 Hz, 2H), 2.47 (t, J = 7.5 Hz, 2H), 2.08 – 1.64 (m, 6H), 1.55 – 1.12 (m, 4H).

Intermediate 312.

trans-4-(hydroxymethyl)cyclohexanecarboxylic acid

To a solution of trans-methyl 4-(hydroxymethyl)cyclohexanecarboxylate (165mg, 0.96mmol) in tetrahydrofuran (4mL) and water (2mL) was added LiOH monohydrate (120mg, 2.86mmol) and the final solution was allowed to stir for 2 hours. The solvents were removed under vacuum providing the title compound as a white solid (150mg, 99%). The crude product was used without further purification.

Intermediate 313.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl{4-[3-({[trans-4-(hydroxymethyl) cyclohexyl]carbonyl}amino)propyl]biphenyl-2-yl}carbamate

To a solution of trans-4-(hydroxymethyl)cyclohexanecarboxylic acid (Intermediate 312, 100mg, 0.63mmol) and trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(3-aminopropyl)biphenyl-2-yl]carbamate (Intermediate 283, 295mg, 0.63mmol) in DMF (4mL) were added sequentially HATU (264mg, 0.70 mmol) and DIEA (143µL, 0.82mmol) and the reaction mixture was stirred overnight. Then, the solvent was removed under reduced pressure and ethyl acetate and water were added to the residue. The phases were separated and the organic phase was washed with saturated sodium bicarbonate solution and brine, dried over anhydrous sodium sulphate, filtered and concentrated to dryness. The title compound was obtained as a yellow oil (380mg of a 90% purity, 89%) and was used without any further purification.

LRMS (m/z): 609 (M+1)+

Intermediate 314.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl[4-(3-{[(trans-4-formylcyclohexyl) carbonyl]amino}propyl)biphenyl-2-yl]carbamate

Obtained as a brownish foam (374mg of a 80% purity, 80%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl{4-[3-({[trans-4-(hydroxymethyl)cyclohexyl]carbonyl}-amino)propyl]biphenyl-2-yl}carbamate (Intermediate 313, 243mg, 0.24mmol) and Dess-Martin periodinane (175mg, 0.41mmol) in chloroform (5mL) following the experimental procedure as described for Intermediate 64 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 607 (M+1)+

Intermediate 315.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl{4-[3-({[trans-4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]-amino}methyl)cyclohexyl]carbonyl}amino)propyl]biphenyl-2-yl}carbamate

Obtained as a yellow foam (110mg of a 90% purity, 24%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl[4-(3-{[(trans-4-formylcyclohexyl)carbonyl]amino}-propyl)biphenyl-2-yl]carbamate (Intermediate 314, 374mg of a 80% purity, 0.62mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (150mg, 0.45mmol) (prepared according to preparation 8 from US20060035931) and sodium cyanoborohydride (125mg, 1.98mmol), following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform and chloroform:methanol:ammonium hydroxide (40:4:0.2).

LRMS (m/z): 924 (M+1)+

EXAMPLE 58.

trans-4-aminocyclohexyl [4-(4-{[trans-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)cyclohexyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

Obtained as a beige solid (35mg, 41%) from trans-4-[(tert-butoxycarbonyl)-amino]cyclohexyl{4-[3-({[trans-4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)cyclohexyl]carbonyl}amino)propyl]-biphenyl-2-yl}carbamate (Intermediate 315, 110mg, 0.12mmol) and hydrogen chloride (2.0mL of a 4M solution in dioxane, 8.0mmol) in dioxane (3.0mL), following the experimental procedure as described for Intermediate 21. The crude residue was purified by reverse phase column chromatography with C18 modified silica gel using a mixture of water (with 0.1% of ammonium hydroxide):methanol.

LRMS (m/z): 711 (M+1)+

^{1}H NMR (300 MHz, dmso) δ 8.56 (s, 1H), 8.21 (d, J = 10.0 Hz, 1H), 7.80 (bt, J = 6.0 Hz, 1H), 7.49 – 7.30 (m, 4H), 7.26 – 7.21 (m, 2H), 7.15 (dd, J = 8.0, 1.4 Hz, 1H), 7.09 (d, J = 8.2 Hz, 1H), 6.93 (d, J = 8.1 Hz, 1H), 6.53 (d, J = 9.8 Hz, 1H), 5.04 (dd, J = 7.6, 4.4 Hz, 1H), 4.37 (m, 2H), 3.09 (dd, J = 11.9, 6.5 Hz, 2H), 2.77 (m, 1H), 2.73 – 2.50 (m, 6H), 2.47 – 2.34 (m, 2H), 2.31 (m, 1H), 2.07 (bt, J = 12:0 Hz, 2H), 1.89 – 1.65 (m, 5H), 1.52 – 1.05 (m, 7H), 0.99 – 0.80 (m, 3H).

Intermediate 316.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{3-[({[4-({[tert-butyl(dimethyl)-silyl]oxy}methyl)-2-chloro-5-methoxyphenyl]amino}carbonyl)amino]propyl}-biphenyl-2-yl)carbamate

To a solution of tert-butyl[(5-chloro-4-isocyanato-2- methoxybenzyl)oxy]dimethylsilane (Intermediate 267, 145mg, 0.44mmol) in toluene (10mL) was added a solution of trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(3-aminopropyl)biphenyl-2-yl]carbamate (Intermediate 283, 228mg, 0.49mmol) and triethylamine (74µL, 0.53mmol) in toluene (5mL) at 0°C and under argon atmosphere. After 2 hours, the suspension was filtered and the filtrate was concentrated under vacuum to afford the title compound (350mg, 89%) as a colorless oil.

LRMS (m/z): 664 (M-131, tropilium cation (100%))+, 796 (M+1)+

Intermediate 317.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{3-[({[2-chloro-4-(hydroxymethyl)-5-methoxyphenyl]amino}carbonyl)amino]propyl}biphenyl-2-yl)carbamate

To a solution of trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{3-[({[4-({[tert-butyl(dimethyl) silyl]oxy}methyl)-2-chloro-5-methoxyphenyl]amino}carbonyl)amino]-propyl}biphenyl-2-yl) carbamate (Intermediate 316, 350mg, 0.44 mmol) in tetrahydrofuran (10mL) was added TBAF (0.44mL of a1M solution in tetrahydrofuran, 0.44mmol) and the final solution was allowed to stir for 1 hour. The solvent is removed under reduced pressure and dichloromethane and water were added. The two phases were separated and the organic phase was dried, filtered and concentrated to dryness to provide the title compound (210mg of a 95% purity, 67%) as a colorless foam.

LRMS (m/z): 664 (M-131, tropilium cation (100%))+, 682 (M+1)+

Intermediate 318.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl{4-[3-({[(2-chloro-4-formyl-5-methoxyphenyl)amino]carbonyl}amino)propyl]biphenyl-2-yl}carbamate

Obtained as a brownish foam (209mg, 100%) from trans-4-[(tert-butoxycarbonyl)amino] cyclohexyl(4-{3-[({[2-chloro-4-(hydroxymethyl)-5-methoxyphenyl]amino}carbonyl)-amino]propyl} biphenyl-2-yl)carbamate (Intermediate 317, 210mg, 0.31mmol) and manganese dioxide (268mg, 3.10mmol) following the experimental procedure as described for Intermediate 218 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 679 (M+1)+

Intermediate 319.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{3-[({[4-({[(2R)-2-{[tert-butyl(dimethyl) silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]-amino}methyl)-2-chloro-5-methoxyphenyl]amino}carbonyl)amino]propyl}-biphenyl-2-yl)carbamate

Obtained as a yellow foam (90mg of a 90% purity, 26%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl{4-[3-({[(2-chloro-4-formyl-5-methoxyphenyl)amino]-carbonyl}amino)propyl]biphenyl-2-yl}carbamate (Intermediate 318, 210mg, 0.31mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (104mg, 0.31mmol) (prepared according to preparation 8 from US20060035931) and sodium cyanoborohydride (97mg, 1.55mmol), following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform and chloroform:methanol:ammonium hydroxide (40:4:0.2).

EXAMPLE 59.

trans-4-aminocyclohexyl (4-{3-[({[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino}-carbonyl)amino] propyl}biphenyl-2-yl)carbamate

Obtained as a beige solid (20mg, 26%) from trans-4-[(tert-butoxycarbonyl)-amino]cyclohexyl(4-{3-[({[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-chloro-5-methoxyphenyl]amino}-carbonyl)amino]propyl}biphenyl-2-yl)carbamate (Intermediate 319; 90mg, 0.12mmol) and hydrogen chloride (1.1mL of a 4M solution in dioxane, 4.4mmol) in dioxane (2.0mL), following the experimental procedure as described for Intermediate 21. The crude residue was purified by reverse phase column chromatography with C18 modified silica gel using a mixture of water (with 0.1% of ammonium hydroxide):methanol.

LRMS (m/z): 783 (M+1)+

Intermediate 320.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(4-hydroxybutyl)biphenyl-2-yl]-carbamate

To a solution of trans-4- [(tert-butoxycarbonyl)amino]cyclohexyl [4-(4-ethoxypent-4-en-1-yl)biphenyl-2-yl]carbamate (synthesized as Intermediate 188; 3.0g, 5.72mmol) in THF (30mL) was added cautiously at -5°C lithium borohydride (1.25g, 57.39mmol) and EtOH (9.5mL). The reaction mixture was stirred overnight at room temperature.

Ammonium chloride saturated was added into the mixture cautiously and was extracted with ethyl acetate. The organic layer was washed with water and brine, dried, filtered and the solvent was removed under reduced pressure to give the title compound (2.76g, 95%), which was used in the next step without further purification.

LRMS (m/z): 483 (M+1)+, 481 (M-1)-

Intermediate 321.

4-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy)carbonyl]amino}-biphenyl-4-yl)butyl methanesulfonate

Obtained as a solid (1.41g of an 80% purity, 97%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl[4-(4-hydroxybutyl)biphenyl-2-yl]carbamate (Intermediate 320; 1g, 2.07mmol), triethylamine (0.32mL, 2.31mmol) and methanesulfonyl chloride (0.16mL, 2.07mmol) in dichloromethane (10ml) following the experimental procedure as described for intermediate 262, the crude was used in the next step without further purification.

LRMS (m/z): 561 (M+1)+, 559 (M-1)-

Intermediate 322.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(4-azidobutyl)biphenyl-2-yl]-carbamate

Sodium azide (0.35g, 5.38mmol) was added cautiously to a solution of 4-(2-{[({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}oxy)carbonyl]amino}biphenyl-4-yl)butyl methanesulfonate (Intermediate 321; 1.41g of an 80% purity, 2.51mmol) in DMF (15mL). The reaction mixture was stirred 4h at 80° C. The reaction was poured onto ice, after stirring 30 min, dichloromethane was added. The organic layer was dried and the solvent was removed under reduced pressure to give 1.26g of an 80% purity (79%) of an off white solid, which was used in the next step without further purification.

LRMS (m/z): 508 (M+1)+

Intermediate 323.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(4-aminobutyl)biphenyl-2-yl]-carbamate

Triphenylphosphine (1.43g, 5.45mmol) was added to a solution of trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(4-azidobutyl)biphenyl-2-yl]carbamate (Intermediate 322; 1.26g of an 80% purity, 2.48mmol) in THF (25mL) and water (1.25mL). The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was suspended in MeOH. The solution was passed through an acidic sulphonic SCX column. The compound was released from the column with 33% ammonium in methanol and the solvent was removed under reduced pressure. The crude obtained (0.89g, 93%) was used in the next step without further purification.

LRMS (m/z): 482 (M+1)+

Intermediate 324.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(4-{[2-chloro-4-(hydroxyl-methyl)-5-methoxybenzoyl]amino}butyl)biphenyl-2-yl]carbamate

Obtained as a solid (0.48g, 71%) from 2-chloro-4-(hydroxymethyl)-5-methoxybenzoic acid (Intermediate 281; 0.15g, 0.69mmol), trans-4-[(tert-butoxycarbonyl)-amino]-cyclohexyl [4-(4-aminobutyl)biphenyl-2-yl]carbamate (Intermediate 323; 0.33g, 0.69mmol), diisopropylethylenediamine (0.48mL, 2.77mmol) and HATU (0.53g, 1.39mmol) in DMF (5mL) following the experimental procedure as described for Intermediate 125. The crude was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 681 (M+1)+

Intermediate 325.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl (4-{4-[(2-chloro-4-formyl-5-methoxybenzoyl)amino]butyl}biphenyl-2-yl)carbamate

Obtained as a yellow foam (255mg, 53%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(4-{[2-chloro-4-(hydroxymethyl)-5-methoxybenzoyl]-amino}butyl)biphenyl-2-yl]carbamate (Intermediate 324; 480mg, 0.71mmol) and manganese oxide (615mg, 7.07mmol) following the experimental procedure as described for Intermediate 218 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 678 (M+1)+

Intermediate 326.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl [4-(4-{[4-({[(2R)-2-{[tert-butyl-(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}-methyl)-2-chloro-5-methoxybenzoyl]amino}butyl)biphenyl-2-yl]carbamate

Obtained as a solid (92mg, 25%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl (4-{4-[(2-chloro-4-formyl-5-methoxybenzoyl)amino]butyl}biphenyl-2-yl)carbamate (Intermediate 325; 255mg, 0.38mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (126mg, 0.38mmol) (prepared according to preparation 8 from US20060035931), sodium cianoborohydride (60mg, 0.95mmol) and diethylethylenamine (80µL, 0.46mmol) following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 942 [M-56(tert-buthyl)+1]+

EXAMPLE 60

trans-4-aminocyclohexyl [4-(4-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxybenzoyl]amino}butyl)-biphenyl-2-yl]carbamate dihydrochloride

Obtained as a white solid (33mg, 46%) from trans-4-[(tert-butoxycarbonyl)-amino]cyclohexyl [4-(4-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-chloro-5-methoxybenzoyl]amino}butyl)-biphenyl-2-yl]carbamate (Intermediate 326; 92mg, 0.09mmol) and hydrogen chloride (4M in dioxane , 0.25mL) in dioxane (2mL) following the experimental procedure as described for Intermediate 21.

LRMS (m/z): 783 (M+1)+

1H NMR (300 MHz, dmso) δ 10.50 (d, J = 8.4 Hz, 2H), 9.35 (s, 1H), 8.98 (s, 1H), 8.60 (s, 1H), 8.49 (t, J = 5.5 Hz, 1H), 8.20 (d, J = 10.0 Hz, 1H), 7.95 (s, 2H), 7.68 – 7.55 (m, 1H), 7.46 – 7.27 (m, 4H), 7.22 (d, J = 7.8 Hz, 1H), 7.11 (dd, J = 13.3, 6.4 Hz, 2H), 6.99

(d, J = 8.2 Hz, 1H), 6.58 (d, J = 10.0 Hz, 1H), 5.44 (s, 1H), 5.35 (s, 1H), 4.33 (s, 1H), 4.22 (s, 2H), 3.84 (s, 3H), 3.35 – 3.24 (m, J = 5.5 Hz, 2H), 3.17 – 2.91 (m, 2H), 2.73 – 2.53 (m, 2H), 1.87 (d, J = 13.1 Hz, 3H), 1.74 – 1.52 (m, 3H), 1.45 – 1.28 (m, 4H).

Intermediate 327

Ethyl 4-(2-{[(1-azabicyclo[2.2.2]oct-4-yloxy)carbonyl]amino}biphenyl-4-yl)-butanoate

To a solution of triphosgene (0.42g, 1.42mmol) in toluene (5mL) was added dropwise at 0°C a solution of ethyl 4-(2-aminobiphenyl-4-yl)butanoate (Intermediate 122; 1.00g, 3.53mmol), once the addition is finished triethylamine (1.00mL, 7.21mmol) was added. The mixture was stirred 4 hours at room temperature. The solvent was partially removed under reduced pressure without heating and hexane was added to precipitate the salts, the mixture was filtered and the filtrate was evaporated. The corresponding isocyanate with quinuclidin-4-ol were stirred for 24 hours at 80°C. The crude was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2), giving the title compound as a solid (0.65mg, 42%).

LRMS (m/z): 437 (M+1)+

Intermediate 328

4-(2-{[(1-azabicyclo[2.2.2]oct-4-yloxy)carbonyl]amino}biphenyl-4-yl)butanoic acid hydrochloride

To a solution of ethyl 4-(2-{[(1-azabicyclo[2.2.2]oct-4-yloxy)carbonyl]amino}biphenyl-4-yl)butanoate (Intermediate 327; 500mg, 1.1mmol) in tetrahydrofurane (20mL) was added lithium hydroxide monohydrate (150mg, 3.6mmol) in water (10mL). The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the crude obtained was diluted with water and acidified by acid chloride 2N until pH 2-3. Then the crude was extracted with diethyl ether using a continuous extractor at 40°C overnight. The organic layer was dried, filtered and the solvent was removed under reduced pressure giving the title compound as a white solid (340mg, 67%).

LRMS (m/z): 409 (M+1)+

Intermediate 329

1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[4-(hydroxymethyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

To a solution of 4-(2-{[(1-azabicyclo[2.2.2]oct-4-yloxy)carbonyl]amino}biphenyl-4-yl)-butanoic acid hydrochloride (Intermediate 328; 50mg, 0.12mmol) in DMF (2mL) was added HATU (92mg, 0.24mmol) under nitrogen atmosphere. After 1 hour stirring at room temperature, (4-aminophenyl)methanol (16mg, 0.13mmol) was added. The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the crude was partitioned between chloroform and water, the organic layer was washed with water several times, dried, filtered and the solvent was removed under reduced pressure. The crude obtained was used in the next step without further purification.

LRMS (m/z): 514 (M+1)+

Intermediate 330

1-azabicyclo[2.2.2]oct-4-yl (4-{4-[(4-formylphenyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate

To a solution of 1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[4-(hydroxymethyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 329; 62mg, 0.12mmol) in chloroform (5mL) was added activated manganese oxide (105mg, 1.21mmol). The reaction mixture was stirred overnight at 45°C. The mixture was filtered and the solvent was removed under reduced pressure giving the title compound as an yellow foam (60mg, 97%), which was used in the next step without further purification.

LRMS (m/z): 512 (M+1)+

Intermediate 331

1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[4-({[(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

To a mixture of 1-azabicyclo[2.2.2]oct-4-yl (4-{4-[(4-formylphenyl)amino]-4-oxobutyl}-biphenyl-2-yl)carbamate (Intermediate 330; 60mg, 0.12mmol) and 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (40mg, 0.12mmol) (prepared according to preparation 8 from US20060035931) in 3mL of methanol was added sodium triacetoxyborohydride (75mg, 0.35mmol). The mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the crude obtained was suspended in chloroform, the solid was filtrated and the solvent was evaporated. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2) to give the title compound as a solid (37mg, 38%).

LRMS (m/z): 831 (M+1)+

EXAMPLE 61.

1-Azabicyclo[2.2.2]oct-4-yl [4-(4-{[4-({[(2*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate dihydrofluoride

Obtained as a white solid (31mg, 92%) from 1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[4-({[(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)-ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 331; 37mg, 0.04mmol) and triethylamine trihydrofluoride (50µL, 0.31mmol) following the experimental procedure as described for Example 1.

LRMS (m/z): 716 (M+1)+

1H NMR (300 MHz, dmso) δ 10.30 (bs, 1H), 9.86 (s, 1H), 8.39 (s, 1H), 8.09 (d, J = 10.0 Hz, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.46 – 7.28 (m, 5H), 7.26 – 7.17 (m, 3H), 7.12 (d, J = 6.3 Hz, 1H), 7.05 (d, J = 8.2 Hz, 1H), 6.90 (d, J = 8.1 Hz, 1H), 6.46 (d, J = 9.9 Hz, 1H), 5.05 (dd, J = 7.7, 4.5 Hz, 2H), 3.69 (s, 2H), 2.89 – 2.73 (m, 6H), 2.65 (dd, J = 12.2, 7.9 Hz, 2H), 2.35 (t, J = 7.4 Hz, 2H), 1.96 – 1.86 (m, 2H), 1.80 – 1.66 (m, 6H).

Intermediate 332.

trans-4-(hydroxymethyl)cyclohexanol

To a solution of *trans*-4-cyclohexanecarboxylic acid (1.0g, 6.9mmol) in THF (70mL) was added dropwise, at 0° C and under argon atmosphere, borane dimethylsulphide complex (2.8mL, 29.5mmol). The resulting suspension is allowed to warm to rt and stirring is maintained overnight. The reaction mixture is concentrated under reduced pressure and the solid obtained is dissolved in MeOH (20mL). The resulting solution is concentrated to dryness to afford the title compound as a white crystalline solid (0.95g, 100%).

1H NMR (300 MHz, dmso) δ 4.50 (d, J = 4.4 Hz, 1H), 4.40 (t, J = 5.3 Hz, 1H), 3.37 – 3.26 (m, 1H), 3.21 (t, J = 5.8 Hz, 1H), 1.84 (dd, J = 12.6, 2.9 Hz, 1H), 1.72 (bd, J = 13.5 Hz, 1H), 1.35 – 1.20 (m, 1H), 1.12 (ddd, J = 19.2, 13.4, 3.1 Hz, 2H), 0.89 (ddd, J = 19.0, 13.2, 2.9 Hz, 2H).

Intermediate 333.

trans-4-({[tert-butyl(diphenyl)silyl]oxy}methyl)cyclohexanol

To a solution of trans-4-(hydroxymethyl)cyclohexanol (Intermediate 332, 420mg, 3.23mmol) in DMF (15mL) were added sequentially imidazole (250mg, 3.67mmol) and tert-butyldiphenylsilyl chloride (0.85mL, 3.28mmol). After 4 hours the solvent was removed under reduced pressure and the residue was partitioned between water and ethyl acetate. The phases were separated and the aqueous phase was further extracted with ethyl acetate. The resulting organic phase was washed with water twice and brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Purification by column chromatography over silica gel using a mixture of hexane:ether provided the title compound (814mg, 69%) as a colorless oil.

LRMS (m/z): 391 (M+23[Na])+

Intermediate 334.

{[trans-4-({[tert-butyl(diphenyl)silyl]oxy}methyl)cyclohexyl]oxy}acetic acid

To a suspension of NaH (280mg of a 60% dispersion in oil, 7.0mmol) was added dropwise, at 0°C and under argon atmosphere, a solution of trans-4-({[tert-butyl(diphenyl)silyl]oxy}methyl) cyclohexanol (Intermediate 333, 790mg, 2.14mmol) and the reaction mixture was allowed to stir for 45 min. Then, 2-bromoacetic acid (300mg, 2.16mmol) was added and the resulting mixtures was heated at 90 °C for 4 hours. Upon cooling the reaction mixture, water was added and the organic solvent was removed under reduced pressure. Water and ether were added to the residue and the aqueous phase was further extracted with ether. The combined organic extracts were dried, filtered and concentrated to dryness. The crude was purified by column chromatography over silica gel using a mixture of hexane:ether providing the title compound (470mg, 51%) as a colorless oil.

LRMS (m/z): 444 (M+18[NH_4^+])+

Intermediate 335.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{3-[({[trans-4-({[tert-butyl-(diphenyl)silyl]oxy}methyl)cyclohexyl]oxy}acetyl)(methyl)amino]propyl}biphenyl-2-yl)carbamate

Obtained as an oil (113mg of a 70% purity, 29%) from tert-butyl-trans-4-amino-cyclohexyl{4-[3-(methylamino)propyl]biphenyl-2-yl}carbamate (Intermediate 252; 150mg, 0.31mmol), {[trans-4-({[tert-butyl(diphenyl)silyl]oxy}methyl)cyclohexyl]oxy}-acetic acid (Intermediate 334; 150mg, 0.35mmol), HATU (181mg, 0.48mmol) and DIEA (70µL, 0.40mmol) following the experimental procedure as described for Intermediate 125 and the crude obtained was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether:ethanol.

LRMS (m/z): 891 (M+1)+

Intermediate 336.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{3-[({[trans-4-(hydroxymethyl) cyclohexyl]oxy}acetyl)(methyl)amino]propyl}biphenyl-2-yl)carbamate

To a solution of trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{3-[({[trans-4-({[tert-butyl(diphenyl)silyl]oxy}methyl)cyclohexyl]oxy}acetyl)(methyl)amino]propyl}biphenyl-2-yl)carbamate (Intermediate 335, 113mg, 0.09mmol) in tetrahydrofuran (2.5mL) was added dropwise tetrabutylammonium fluoride (0.34 mL of a 1M solution in tetrahydrofuran, 0.34mmol). After stirring for 1.5 hours a rt, saturated ammonium chloride and ethyl acetate were added. The aqueous phase was further extracted with ethyl acetate and the combined organic extracts were washed with water and brine, dried over anhydrous sodium sulphate, filtered and concentrated to dryness. The residue was purified by column chromatography with silica gel, eluting with a mixture of hexane:ether:ethanol. The title compound was obtained as a yellow solid (44mg, 61%)

LRMS (m/z): 653 (M+1)+

Intermediate 337.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{3-[{[(trans-4-formyl-cyclohexyl)oxy] acetyl}(methyl)amino]propyl}biphenyl-2-yl)carbamate

Obtained as a colorless foam (41mg of an 81% purity, 95%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{3-[({[trans-4-(hydroxymethyl)cyclohexyl]oxy}acetyl) (methyl)amino]propyl}biphenyl-2-yl)carbamate (Intermediate 336, 44mg, 0.05mmol), Dess-Martin periodinane (50mg, 0.12mmol) and sodium bicarbonate (18mg, 0.21mmol) in dichloromethane (1mL), following the experimental procedure as described for Intermediate 64 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 651 (M+1)+

Intermediate 338.

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{3-[({[trans-4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]-amino}methyl)cyclohexyl]oxy}acetyl)(methyl)amino]propyl}biphenyl-2-yl)-carbamate

Obtained as a yellow foam (49mg, 100%) from trans-4-[(tert-butoxycarbonyl)amino]-cyclohexyl(4-{3-[{[(trans-4-formylcyclohexyl)oxy]acetyl}(methyl)amino] propyl}biphenyl-2-yl)carbamate (Intermediate 337, 41mg, 0.06mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (32mg, 0.08mmol) (prepared according to preparation 8 from US20060035931), sodium cyanoborohydride (12mg, 0.19mmol) and DIEA (13µL, 0.07mmol), following the experimental procedure as described for Intermediate 7. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol.

LRMS (m/z): 969 (M+1)+

EXAMPLE 62.

trans-4-aminocyclohexyl(4-{3-[({[trans-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)cyclohexyl]oxy}acetyl)(methyl)-amino] propyl} biphenyl-2-yl)carbamate dihydrochloride

Obtained as a white solid (38mg of a 93% purity, 85%) from trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{3-[({[trans-4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]-oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)cyclohexyl]oxy}-acetyl)(methyl)amino]propyl}biphenyl-2-yl)carbamate (Intermediate 338; 49mg, 0.05 mmol) and hydrogen chloride (0.255mL of a 4M solution in dioxane, 1.02mmol) in tetrahydrofuran (1.0mL), following the experimental procedure as described for Intermediate 21.

LRMS (m/z): 755 (M+1)+

1H NMR (300 MHz, dmso) δ 10.53 (bs, 2H), 9.25 (bs, 1H), 8.72 (bs, 1H), 8.65 (s, 1H), 8.37 (d, J = 9.7 Hz, 1H), 8.15 (bs, 3H), 7.49 – 7.31 (m, 5H), 7.28 – 7.22 (m, 2H), 7.19 (d, J = 8.2 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 6.58 (d, J = 9.7 Hz, 1H), 5.56 (d, J = 8.6 Hz, 1H), 4.37 (t, J = 11.5 Hz, 2H), 4.14 (d, J = 13.6 Hz, 2H), 3.60 (s, 2H), 2.99 (m, 5H), 2.85 (bs, 2H), 2.67 – 2.57 (m, 2H), 2.15 – 1.66 (m, 10H), 1.52 – 0.90 (m, 9H).

Intermediate 339

Ethyl 4-{[4-(2-{[(1-azabicyclo[2.2.2]oct-4-yloxy)carbonyl]amino}biphenyl-4-yl)butanoyl]amino}-5-chloro-2-methoxybenzoate

To a solution of 4-(2-{[(1-azabicyclo[2.2.2]oct-4-yloxy)carbonyl]amino}biphenyl-4-yl)butanoic acid hydrochloride (Intermediate 328; 2.0g, 4.9mmol) in thionyl chloride (20mL) was stirred at room temperature under nitrogen atmosphere. After 1 hour, the solvent was removed under reduced pressure, the crude was dissolved in chloroform (20mL) and ethyl 4-amino-5-chloro-2-methoxybenzoate (Intermediate 37 WO2011/141180A1; 1.24g, 5.4mmol) and triethylamine (1.0mL, 7.2mmol) were added. The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the crude was partitioned between chloroform and sodium bicarbonate 4%, the organic layer was washed with brine, dried, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:8:1) to give the title compound as a pale yellow foam (540mg, 18%).

LRMS (m/z): 621 (M+1)+

Intermediate 340

1-azabicyclo[2.2.2]oct-4-yl[4-(4-{[2-chloro-4-(hydroxymethyl)-5-methoxyphenyl]-amino}-4-oxobutyl)biphenyl-2-yl]carbamate

A round-bottomed flask fitted with stir bar was charged with ethyl 4-{[4-(2-{[(1-azabicyclo[2.2.2]oct-4-yloxy)carbonyl]amino}biphenyl-4-yl)butanoyl]amino}-5-chloro-2-methoxybenzoate (Intermediate 339; 540mg, 0.9mmol) in 20 mL anhydrous tetrahydrofurane and under Argon atmosphere. The mixture was cooled with an ice/water bath and lithium aluminium hydride 1M in tetrahydrofurane (1.37mL, 0.14mmol) was added cautiously. After stirring for 2h at 0 °C, the reaction was quenched by sequentially addition of n:n:3n (where n is the LiAlH4 mass), that was 50 µL H2O:50 µL NaOH 4N:150 µL H2O, and then was stirred 30 min at rt. The solid formed is filtered and the resulting solution is concentrated under reduced pressure to give 470 mg (90%) of an off white foam, which was used in the next step without further purification.

LRMS (m/z): 579 (M+1)+

Intermediate 341

1-azabicyclo[2.2.2]oct-4-yl (4-{4-[(2-chloro-4-formyl-5-methoxyphenyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate

Obtained as a yellow foam (334mg, 80%) from 1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[2-chloro-4-(hydroxymethyl)-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 340; 421mg, 0.73mmol) and manganese oxide (633mg, 7.28mmol) following the experimental procedure as described for Intermediate 330 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 576 (M+1)+

Intermediate 342

1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[4-({[(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-chloro-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

Obtained as a solid (285mg, 55%) from 1-azabicyclo[2.2.2]oct-4-yl (4-{4-[(2-chloro-4-formyl-5-methoxyphenyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate (Intermediate 341; 334mg, 0.58mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (194mg, 0.58mmol) (prepared according to preparation 8 from US20060035931), sodium triacetoxyborohydride (431mg, 2.03mmol) in MeOH (6mL) and tetrahydrofurane (1mL) following the experimental procedure as described for Intermediate 331. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 895 (M+1)+

EXAMPLE 63.

1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[2-chloro-4-({[(2*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate.

Obtained as a white solid (160mg, 64%) from 1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[4-({[(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)-ethyl]amino}methyl)-2-chloro-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]-carbamate (Intermediate 342; 285mg, 0.32mmol) and triethylamine trihydrofluoride (364µL, 2.23mmol) following the experimental procedure as described for Example 1. The crude residue was purified by reverse phase column chromatography with C18 modified silica gel using a mixture of water (with 0.1% of ammonium hydroxide):methanol.

LRMS (m/z): 781 (M+1)+

1H NMR (600 MHz, dmso) δ 9.41 (s, 1H), 8.37 (s, 1H), 8.10 (d, J = 9.9 Hz, 1H), 7.38 (t, J = 7.6 Hz, 2H), 7.30 (ddd, J = 11.2, 9.9, 4.2 Hz, 5H), 7.18 (d, J = 7.7 Hz, 2H), 7.10 (d, J = 7.8 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 6.43 (d, J = 9.8 Hz, 1H), 4.97 (dd, J = 7.9, 4.5 Hz, 1H), 3.69 (s, 3H), 3.62 (s, 2H), 2.80 – 2.70 (m, 6H), 2.65 – 2.59 (m, 2H), 2.40 (t, J = 7.1 Hz, 2H), 1.94 – 1.82 (m, 2H), 1.69 (d, J = 12.8 Hz, 6H).

Intermediate 343

Methyl 4-(but-3-en-1-ylamino)-3-nitrobenzoate

To a solution of methyl 4-fluoro-3-nitrobenzoate (1g; 5.02mmol) in THF (10mL) is added but-3-en-1-amine (1.01g, 14.2mmol) and the reaction mixture is stirred overnight at room temperature. The solvent was removed under reduced pressure and the crude was partitioned between ethyl acetate and water, the organic layer was washed with water several times, dried, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel giving the title compound as a solid (1.1g, 87%).

LRMS (m/z): 251 (M+1)+

Intermediate 344

Methyl 3-amino-4-(but-3-en-1-ylamino)benzoate

To a solution of methyl 4-(but-3-en-1-ylamino)-3-nitrobenzoate (Intermediate 343; 830mg, 3.32mol) in ethanol (5mL) was added 4 mL of Hydrochloric Acid (37%). Tin(II)chloride (2.62g, 11.6mol) was added and the reaction mixture was stirred at 50°C overnight. The solvent was partially removed and sodium hydroxide was added to precipitate salts, which were filtrated. The solvent was removed under reduced pressure and the residue was portioned between ethyl acetate and water. The organic layer was washed with brine, dried, filtered and the solvent was removed under reduced pressure. The crude obtained was used in the next step without further purification (684mg, 87%).

LRMS (m/z): 221 (M+1)+

Intermediate 345

Methyl 1-but-3-en-1-yl-1H-benzimidazole-5-carboxylate

methyl 3-amino-4-(but-3-en-1-ylamino)benzoate (Intermediate 344; 145mg, 0.66mmol) is solved in triethylorthoformiate (1.64mL, 9.85mmol) and two drops of formic acid are added. The reaction mixture is stirred for 1h at 80°C. The solvent was removed under reduced pressure and the crude obtained was used in the next step without further purification (142mg, 89%)

LRMS (m/z): 231 (M+1)+

Intermediate 346

(1-but-3-en-1-yl-1H-benzimidazol-5-yl)methanol

To a solution of methyl 1-but-3-en-1-yl-1H-benzimidazole-5-carboxylate (Intermediate 345; 140mg, 0.61mmol) in THF (3.6mL) was added dropwise at 0°C lithium aluminium hydride (1M in THF, 0.9mL). The reaction mixture was stirred 30 minutes at 0°C and 1 hour at room temperature. The stirred mixture was cooled in an ice bath and very carefully water (0.34 mL), NaOH 4N (0.34mL) and water (0.1mL) were added slowly. After stirring 15 minutes at room temperature the mixture was filtered through a thin layer (1 cm) of Celite and the filter cake was washed with dichloromethane. The combined filtrate and washings were evaporated to give a light pink solid as the title compound (118mg, 91%).

LRMS (m/z): 204 (M+1)+

Intermediate 347

1-but-3-en-1-yl-1H-benzimidazole-5-carbaldehyde

To a solution of (1-but-3-en-1-yl-1H-benzimidazol-5-yl)methanol (Intermediate 346; 581mg, 2.24mmol) in chloroform (19mL) was added activated manganese oxide (1.98g, 22.7mmol). The reaction mixture was stirred overnight at 45°C. The mixture was filtered and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel eluting with a mixture of diethyl ether/methanol giving the title compound as an oil (390mg, 96%).

LRMS (m/z): 201 (M+1)+

Intermediate 348

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl{4-[(1Z)-4-(5-formyl-1H-benzimidazol-1-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate

To a mixture of trans-4-tert-butylaminocyclohexyl (4-bromobiphenyl-2-yl)carbamate (Intermediate 183; 150mg, 0.31mmol) and 1-but-3-en-1-yl-1H-benzimidazole-5-carbaldehyde (Intermediate 347; 67mg, 0.34mmol) in acetonitrile (2 mL) in a sealed tube were added tri-o-tolylphosphine (93mg, 0.31mmol) and N,N-Diisopropylethylamine (0.106mL, 0.61mmol). The mixture was degassed under Argon during 5 minutes. Then palladium acetate (34mg, 0.15mmol) was added and the reaction mixture was stirred at 70°C for 4 hours. The crude was filtrated and the filtrate was evaporated to dryness. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2) to give the title compound as an oil (174mg, 83%).

LRMS (m/z): 610 (M+1)+

Intermediate 349

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl{4-[4-(5-formyl-1H-benzimidazol-1-yl)butyl]biphenyl-2-yl}carbamate

A round-bottomed flask fitted with stir bar was charged with trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl {4-[(1Z)-4-(5-formyl-1H-benzimidazol-1-yl)but-1-en-1-yl]biphenyl-2-yl}carbamate (Intermediate 348; 168mg, 0.28mmol) in Acetic acid (3mL) The flask was filled with Argon, and then Pd/C (29mg, 0.28mmol) was added under Argon athmosphere. The flask was coupled with a quick-fit T-adaptor with one outlet to the hydrogen balloon and the other to the vacuum line. The flask was emptied by connecting it to the vacuum and then filled with hydrogen. This operation was repeated twice. The mixture was stirred vigorously at room temperature for 4 h. The Pd/C was filtered off and the solution concentrated under reduced pressure. The residue was used without further purification (165mg, 48%).

LRMS (m/z): 612 (M+1)+

Intermediate 350

trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{4-[5-({[(2R)-2-{[tert-butyl (dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl] amino}methyl)-1H-benzimidazol-1-yl]butyl}biphenyl-2-yl)carbamate

A mixture of trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl {4-[4-(5-formyl-1H-benzimidazol-1-yl)butyl]biphenyl-2-yl}carbamate (Intermediate 349; 115mg, 0.19mmol) and 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (63mg, 0.19mmol) (prepared according to preparation 8 from US20060035931) in 4mL of methanol was stirred at room temperature for 2 hours. Then the crude was cooled to 0°C and sodium triacetoxyborohydride (118mg, 1.88mmol) was added. The mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the crude was portioned between ethyl acetate and water. The organic layer was washed with sodium bicarbonate, water and brine, dried, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel, using as eluents a mixture of hexane:ethyl acetate:methanol to give the title compound as an oil (98mg, 53%).

LRMS (m/z): 930 (M+1)+

EXAMPLE 64

trans-4-aminocyclohexyl(4-{4-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-benzimidazol-1-yl]butyl}biphenyl-2-yl) carbamate dihydrochloride

A solution trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl(4-{4-[5-({[(2R)-2-{[tert-butyl (dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino} methyl) - 1H-benzimidazol-1-yl]butyl}biphenyl-2-yl)carbamate (Intermediate 350; 98mg, 0.11mmol) in 2.64mL of hydrogen chloride (4N in dioxane) was stirred overnight at room temperature. The solvent was removed under reduced pressure and the crude obtained was treated with acetonitrile giving a white solid as the title compound (55mg, 73%)

LRMS (m/z): 716 (M+1)+

1H NMR (300 MHz, dmso) δ 10.49 (d, J = 16.5 Hz, 2H), 9.85 (bs, 1H), 9.45 (bs, 1H), 9.21 (bs, 1H), 8.62 (s, 1H), 8.20 (d, J = 9.9 Hz, 1H), 8.09 (s, 1H), 7.99 (dd, J = 15.2, 5.9 Hz, 2H), 7.73 (d, J = 10.4 Hz, 1H), 7.38 (d, J = 6.7 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 7.23 – 7.14 (m, 1H), 7.09 (d, J = 6.6 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 6.57 – 6.44 (m, 1H), 4.47 (dd, J = 7.3, 4.1 Hz, 1H), 4.39 (s, 2H), 4.31 (d, J = 1.7 Hz, 2H), 3.55 (s, 2H), 2.94 (d, J = 11.4 Hz, 2H), 2.71 (s, 1H), 2.67 – 2.56 (m, 2H), 2.25 (s, 1H), 1.99 – 1.85 (m, 4H), 1.81 (dd, J = 11.0, 4.9 Hz, 2H), 1.68 – 1.52 (m, 2H), 1.42 – 1.10 (m, 4H).

Intermediate 351

ethyl 4-(2-isocyanatobiphenyl-4-yl)butanoate

To a solution of triphosgene (840mg; 2.82mmol) in 15mL of dichloromethane was added dropwise at 0°C a solution of ethyl 4-(2-aminobiphenyl-4-yl)butanoate (Intermediate 122; 2g, 7.06mmol) in 5mL of dichloromethane. Once the addition is finished triethylamine (2.45mL, 17.65mmol) was added dropwise. The reaction mixture was stirred for 3 hours at room temperature. Cold pentane was added into the reaction mixture. The mixture was filtrated and the pentane of the filtrate was reduced under reduced pressure. The crude was solved in toluene, which was used in the next step without further manipulation.

Intermediate 352

trans-4-(dibenzylamino)-1-methylcyclohexanol

To a solution of 4-(Dibenzylamino)-cyclohexanone (5g, 17mmol) in 100 mL of tetrahydrofuran was added during one hour at -78°C methyl lithium 1.6M in diethyl ether (16mL, 25.5mmol). Once the addition finished, the reaction mixture was stirred for one hour and a half more. Saturated ammonium chloride was added to the reaction mixture as well as ethyl acetate. The aquous layer was extracted twice with ethyl acetate and the combined organic layer was dried, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel to give the title compound as an oil (570mg, 11%).

LRMS (m/z): 310 (M+1)+

Intermediate 353

ethyl4-{2-[({[trans-4-(dibenzylamino)-1-methylcyclohexyl]oxy}carbonyl)amino] biphenyl-4-yl}butanoate

A mixture of ethyl 4-(2-isocyanatobiphenyl-4-yl)butanoate (Intermediate 351; 1g, 3.23mmol) and trans-4-(dibenzylamino)-1-methylcyclohexanol (Intermediate 352; 1g, 3.23mmol) in toluene (1mL) is heated overnight at 70°C. The solvent was removed under reduced pressure and the crude was portioned between dichloromethane and water. The organic layer was washed with water, sodium bicarbonate and brine, dried, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel to give the title compound as an oil (1g, 50%)

LRMS (m/z): 619 (M+1)+

Intermediate 354

Ethyl 4-[2-({[(trans-4-amino-1-methylcyclohexyl)oxy]carbonyl}amino)biphenyl-4-yl] butanoate

To a solution of ethyl 4-{2-[({[trans-4-(dibenzylamino)-1-methylcyclohexyl]oxy} carbonyl)amino]biphenyl-4-yl}butanoate (Intermediate 353; 345mg, 0.56mmol) in ethanol (10mL) was added palladium on charcoal (10%, 154mg). The crude mixture was submitted under an H2 balloon 4 hours at room temperature. The catalyst was filtered through Celite and the solvent was removed under reduced pressure. The crude obtained was used without any further purification (242mg, 99%).

LRMS (m/z): 439 (M+1)+

Intermediate 355

ethyl4-{2-[({[trans-1-methyl-4-({[(4-nitrobenzyl)oxy]carbonyl}amino)cyclohexyl] oxy}carbonyl)amino]biphenyl-4-yl}butanoate

To a solution of ethyl 4-[2-({[(trans-4-amino-1-methylcyclohexyl)oxy]carbonyl} amino)biphenyl-4-yl]butanoate (Intermediate 354; 250mg, 0.57mmol) in tetrahydrofuran (5mL) was added triethylamine (119uL, 0.86mmol). The reaction mixture is cooled to 0°C and a solution of 4-nitrobenzyl carbonchloridate (122mg, 0.57mmol) in 2mL of tetrahydrofuran is added dropwise. The reaction mixture is stirred overnight at room temperature. The solvent was removed under reduced pressure and the crude was portioned between ethyl acetate and water. The organic layer was washed with water, brine, dried, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel to give the title compound (274mg, 70%)

LRMS (m/z): 618 (M+1)+

Intermediate 356

4-{2-[({[trans-1-methyl-4-({[(4-nitrobenzyl)oxy]carbonyl}amino)cyclohexyl]oxy} carbonyl)amino]biphenyl-4-yl}butanoic acid

To a solution of ethyl4-{2-[({[trans-1-methyl-4-({[(4-nitrobenzyl)oxy]carbonyl} amino)cyclohexyl] oxy}carbonyl)amino]biphenyl-4-yl}butanoate (Intermediate 355; 275mg, 0.45mmol) in THF (6mL) was added water (3mL) and lithium hydroxide (300mg, 6.69mmol). The reaction mixture was stirred for overnight at room temperature. The solvent was removed under reduced pressure and the aqueous phase was acidified until acid pH and then extracted with ethyl acetate. The organic layer was washed with brine, dried, filtered and the solvent was removed under reduced pressure to give the title compound (208mg, 79%), which was used in the next step without further purification.

LRMS (m/z): 588 (M-1)-

Intermediate 357

trans-4-({[(4-nitrobenzyl)oxy]carbonyl}amino)-1-methylcyclohexyl [4-(4-{[4-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-chloro-5-methoxyphenyl]amino}-4-oxobutyl) biphenyl-2-yl]carbamate

Obtained as an oil (308mg, 100%) from 4-{2-[({[trans-1-methyl-4-({[(4-nitrobenzyl)oxy]carbonyl}amino)cyclohexyl]oxy}carbonyl)amino]biphenyl-4-yl}butanoic acid (Intermediate 356; 208mg, 0.35mmol), 4-((tert-butyldimethylsilyloxy)methyl)-2-chloro-5-methoxyaniline (Intermediate 39 WO2011/141180A1; 106mg, 0.35mmol), DIEA (0.092mL, 0.53mmol) and HATU (147mg, 0.39mmol) following the experimental procedure as described for Intermediate 125 and the crude obtained was used without further purification

LRMS (m/z): 874 (M+1)+

Intermediate 358

trans-4-({[(4-nitrobenzyl)oxy]carbonyl}amino)-1-methylcyclohexyl[4-(4-{[2-chloro-4-(hydroxymethyl)-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

To a solution of trans-4-({[(4-nitrobenzyl)oxy]carbonyl}amino)-1-methylcyclohexyl [4-(4-{[4-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-chloro-5-methoxyphenyl]amino}-4-oxobutyl) biphenyl-2-yl]carbamate (Intermediate 357; 308mg, 0.42mmol) in tetrahydrofuran (30mL) was added dropwise TBAF 1M in THF (423 uL, 0.42 mmol). The reaction mixture was stirred at room temperature for 3 hours. The solvent was removed under reduced pressure and the crude obtained was used in the next step without further purification (267mg, 89%).

Intermediate 359

trans-4-({[(4-nitrobenzyl)oxy]carbonyl}amino)-1-methylcyclohexyl(4-{4-[(2-chloro-4-formyl-5-methoxyphenyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate

To a solution of trans-4-({[(4-nitrobenzyl)oxy]carbonyl}amino)-1-methylcyclohexyl [4-(4-{[2-chloro-4-(hydroxymethyl)-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl] carbamate (Intermediate 358; 265mg, 0.35mmol) in chloroform (10mL) was added activated manganese oxide (424mg, 4.88mmol). The reaction mixture was stirred overnight at 45°C. The mixture was filtered and the solvent was removed under reduced pressure. The crude obtained was used without further purification (264mg, 99%)

LRMS (m/z): 758 (M+1)+

Intermediate 360

trans-4-({[(4-nitrobenzyl)oxy]carbonyl}amino)-1-methylcyclohexyl[4-(4-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl) ethyl]amino}methyl)-2-chloro-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

A mixture of trans-4-({[(4-nitrobenzyl)oxy]carbonyl}amino)-1-methylcyclohexyl (4-{4-[(2-chloro-4-formyl-5-methoxyphenyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate (Intermediate 359; 265mg, 0.35mmol) and 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (117mg, 0.35mmol) (prepared according to preparation 8 from US20060035931) in 4mL of methanol was stirred at room temperature for 3 hours. Then the crude was cooled to 0°C and sodium cyanoborohydride (219mg, 3.5mmol) was added. The mixture was stirred overnight at room temperature overweekend. The solvent was removed under reduced pressure and the crude was portioned between ethyl acetate and water. The organic layer was washed with water, sodium bicarbonate and brine, dried, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel to give the title compound (115mg, 29%)

Intermediate 361

trans-4-amino-1-methylcyclohexyl[4-(4-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-chloro-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

To a solution of trans-4-({[(4-nitrobenzyl)oxy]carbonyl}amino)-1-methylcyclohexyl [4-(4-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-chloro-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl] carbamate (Intermediate 360; 115mg, 0.11mmol) in tetrahydrofuran was added palladium on charcoal (10%, 11mg). The mixture was submitted to a H2 balloon pressure during 3 hours. The catalyst was filtered trough celite and the filtrate was evaporated. The crude was partioned between ethyl acetate and water and the organic layer was washed with sodium bicartonate and brine, dried, filtered and the solvent was removed under reduced pressure. The crude obtained was used without any further purification (95mg, 99%)

LRMS (m/z): 897 (M+1)+

EXAMPLE 65

trans-4-amino-1-methylcyclohexyl[4-(3-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino}-3-oxopropyl)biphenyl-2-yl]carbamate dihydrofluoride

Obtained as a solid dihydrofluoride salt (20mg, 19%) from trans-4-amino-1-methylcyclohexyl[4-(4-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-chloro-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 361; 95mg, 0.11mmol) and triethylamine trihydrofluoride (69µL, 0.42mmol) following the experimental procedure as described for Example 1.

LRMS (m/z): 783 (M+1)+

1H NMR (300 MHz, dmso) δ 9.42 (d, J = 5.7 Hz, 1H), 8.35 (s, 1H), 8.09 (d, J = 11.9 Hz, 1H), 7.48 – 7.24 (m, 5H), 7.20 (d, J = 8.5 Hz, 1H), 7.12 (d, J = 8.3 Hz, 1H), 7.02 (d, J =

8.2 Hz, 1H), 6.92 – 6.79 (m, 1H), 6.54 – 6.37 (m, 2H), 5.08 – 4.92 (m, 1H), 4.76 (s, 1H), 3.69 (s, 3H), 3.63 (s, 2H), 2.63 (d, J = 7.7 Hz, 3H), 2.55 (s, 2H), 2.42 (s, 3H), 2.12 (d, J = 10.0 Hz, 2H), 1.91 (d, J = 4.7 Hz, 3H), 1.61 (d, J = 19.1 Hz, 3H), 1.27 (d, J = 8.8 Hz, 6H).

Intermediate 362

1-azabicyclo[2.2.2]oct-4-yl (4-bromobiphenyl-2-yl)carbamate

A mixture of 4-bromo-2-isocyanatobiphenyl (Intermediate 4; 1.65g, 6.05mmol) and (R)-quinuclidin-4-ol (0.77g, 6.05 mmol) in toluene (1mL) is heated overnight at 80°C. The solvent was removed under reduced pressure and the crude was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2) to give the title compound as an oil (1.99g, 80%).

LRMS (m/z): 401;403 (M+1/M+3)+

Intermediate 363

tert-butyl allyl(methyl)carbamate

To a solution of N-methylprop-2-en-1-amine (1g, 14.06mmol) in dichloromethane (10mL) was added triethylamine (2.35mL, 16.87mmol) and at 0°C was added di-tert-butyl dicarbonate (3.06g, 14.06mmol) in portions. The reaction mixture was stirred 10 minutes at 0°C and overnight at room temperature. The crude was partitioned between ethyl acetate and water, and the organic layer was washed with saturated ammonium chloride solution and brine. The organics were dried, filtered and the solvent was removed under reduced pressure giving the title compound as an oil. (1.92g, 79%)

Intermediate 364

1-azabicyclo[2.2.2]oct-4-yl (4-{(1E)-3-[(tert-butoxycarbonyl)(methyl)amino]prop-1-en-1-yl}biphenyl-2-yl)carbamate

To a mixture 1-azabicyclo[2.2.2]oct-4-yl (4-bromobiphenyl-2-yl)carbamate (Intermediate 362; 320mg, 0.80mmol) and tert-butyl allyl(methyl)carbamate (Intermediate 363; 216mg, 1.26mmol) in acetonitrile (4 mL) in a sealed tube were added tri-o-tolylphosphine (243mg, 0.80mmol) and N,N-Diisopropylethylamine (0.25mL, 1.43mmol). The mixture was degassed under Argon during 5 minutes. Then palladium acetate (106mg, 0.47mmol) was added and the reaction mixture was stirred at 90°C for 2 hours. The crude was filtrated and the filtrate was evaporated to dryness. The crude obtained was purified by column chromatography with silica gel, eluting with

a mixture of chloroform:methanol:ammonium (40:4:0.2) to give the title compound as an oil (511mg, 99%).
LRMS (m/z): 492 (M+1)+

Intermediate 365

1-azabicyclo[2.2.2]oct-4-yl(4-{3-[(tert-butoxycarbonyl)(methyl)amino]propyl} biphenyl -2-yl)carbamate

A round-bottomed flask fitted with stir bar was charged with 1-azabicyclo[2.2.2]oct-4-yl (4-{(1E)-3-[(tert-butoxycarbonyl)(methyl)amino]prop-1-en-1-yl}biphenyl-2-yl)carbamate (Intermediate 364; 511mg, 1.04mmol) in Acetic acid (7mL) The flask was filled with Argon, and then Pd/C (132mg, 1.24mmol) was added under Argon athmosphere. The flask was coupled with a quick-fit T-adaptor with one outlet to the hydrogen balloon and the other to the vacuum line. The flask was emptied by connecting it to the vacuum and then filled with hydrogen. This operation was repeated twice. The mixture was stirred vigorously at room temperature for 3 h. The Pd/C was filtered off and the solution concentrated under reduced pressure. The residue was partitioned between chloroform and sodium bicarbonate (solution 4%) and the organic layer was washed with water and brine. The organics were dried, filtered and the solvent was removed under reduced.The residue was purified by column chromatography using as eluents CHCl3-MeOH-NH4OH 40:2:0.2 to give the title compound as an oil (357mg, 64%).
LRMS (m/z): 495 (M+1)+

Intermediate 366

1-azabicyclo[2.2.2]oct-4-yl{4-[3-(methylamino)propyl]biphenyl-2-yl}carbamate

Obtained as an oil (323mg, 99%) from 1-azabicyclo[2.2.2]oct-4-yl (4-{3-[(tert-butoxycarbonyl)(methyl)amino]propyl}biphenyl-2-yl)carbamate (Intermediate 365; 357mg, 0.72mmol) and acid chloride (4M in dioxane, 1.1mL) following the experimental procedure as described for Intermediate 58. The crude was diluted with more chloroform and washed with sodium bicartonate (solution 4%). The organics were dried, filtered and the solvent was removed under reduced pressure.
LRMS (m/z): 394 (M+1)+

Intermediate 367

tert-butyl [2-chloro-4-(hydroxymethyl)-5-methoxyphenoxy]acetate

To a solution of 2-chloro-4-(hydroxymethyl)-5-methoxyphenol (Intermediate 247; 1.5g, 7.95mmol) in acetonitrile (5 mL) was added tert-butyl 2-bromoacetate (1.18mL, 7.95mmol) and potassium carbonate (1.37g, 9.94mmol) in a sealed tub. The mixture was stirred 3 hours at 90°C. The solid was filtrated, washed with acetonitrile and the solvent of the filtrate was removed under reduced pressure giving the title compound as a brown oil (1.6g, 59%), which was used in the next step without further purification.

Intermediate 368

tert-butyl (2-chloro-4-formyl-5-methoxyphenoxy)acetate

Obtained as a solid (700mg, 55%) from tert-butyl [2-chloro-4-(hydroxymethyl)-5-methoxyphenoxy]acetate (Intermediate 367; 1.60g, 4.23mmol) and manganese oxide (2.57g, 29.6mmol) following the experimental procedure as described for Intermediate 218 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 301 (M+1)+

Intermediate 369

(2-chloro-4-formyl-5-methoxyphenoxy)acetic acid

To a solution of tert-butyl (2-chloro-4-formyl-5-methoxyphenoxy)acetate (Intermediate 368; 1.15g, 3.82mmol) in chloroform (8mL) was added trifluoroacetic acid (2.95mL, 38.24mmol). The reaction mixture was stirred for 4 hours at 45°C. The solvent was removed under reduced pressure and the residue was treated with diethyl ether, filtered and dried to give the title compound as a solid (870mg, 93%), which was used in the next step without further purification.

LRMS (m/z): 245 (M+1)+

Intermediate 370

1-azabicyclo[2.2.2]oct-4-yl(4-{3-[[(2-chloro-4-formyl-5-(ethoxyphenoxy)acetyl] (methyl)amino]propyl}biphenyl-2-yl)carbamate

To a solution of 1-azabicyclo[2.2.2]oct-4-yl {4-[3-(methylamino)propyl]biphenyl-2-yl}carbamate (Intermediate 366; 322mg, 0.82mmol) in chloroform (8.4mL) was added (2-chloro-4-formyl-5-methoxyphenoxy)acetic acid (Intermediate 369; 183mg, 0.75mmol) and diisopropylethylendiamine (0.58mL, 3.36mmol) under nitrogen atmosphere. Then HATU (367mg, 0.97mmol) was added. The reaction mixture was stirred at room temperature for 5 hours. The solvent was removed under reduced pressure and the crude was partitioned between chloroform and water, the organic layer was washed with water several times, dried, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol, giving the title compound as an oil (370mg, 69%).

LRMS (m/z): 620 (M+1)+

Intermediate 371

1-azabicyclo[2.2.2]oct-4-yl(4-{3-[{[4-({[2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-chloro-5-methoxyphenoxy]acetyl}(methyl)amino]propyl}biphenyl-2-yl)carbamate

A mixture of 1-azabicyclo[2.2.2]oct-4-yl (4-{3-[[(2-chloro-4-formyl-5-methoxyphenoxy) acetyl](methyl)amino]propyl}biphenyl-2-yl)carbamate (Intermediate 370; 370mg, 0.60mmol) and 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (200mg, 0.60mmol) (prepared according to preparation 8 from US20060035931) in 4mL of methanol and 2mL of THF was stirred at room temperature for 4 hours. Then the crude was cooled to 0°C and sodium triacetoxyborohydride (476mg, 2.25mmol) was added. The mixture was stirred overnight at room temperature. Sodium bicarbonate (solution 4%) was added dropwise to the previously cooled reaction mixture and chloroform was added. The organic layer was washed with water and brine, dried, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel, using as eluents CHCl3-MeOH-NH4OH 40:2:0.2 to give the title compound as an oil (64mg, 11%).

LRMS (m/z): 939 (M+1)+

EXAMPLE 66

1-azabicyclo[2.2.2]oct-4-yl(4-{3-[{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenoxy]acetyl}(methyl)amino]propyl}biphenyl-2-yl)carbamate dihydrofluoride

Obtained as a pale yellow solid dihydrofluoride salt (49mg, 80%) from 1-azabicyclo[2.2.2]oct-4-yl(4-{3-[{[4-({[2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-chloro-5-methoxyphenoxy]acetyl} (methyl)amino]propyl}biphenyl-2-yl)carbamate (Intermediate 371; 64mg, 0.07mmol) and triethylamine trihydrofluoride (56μL, 0.34mmol) following the experimental procedure as described for Example 1.

LRMS (m/z): 825 (M+1)+

1H NMR (300 MHz, dmso) δ 10.34 (bs, 1H), 8.44 (d, J = 3.3 Hz, 1H), 8.09 (d, J = 10.0 Hz, 1H), 7.48 – 7.23 (m, 5H), 7.11 (ddd, J = 30.2, 16.3, 7.3 Hz, 4H), 6.88 (d, J = 8.1 Hz, 1H), 6.61 (d, J = 6.5 Hz, 1H), 6.46 (d, J = 9.9 Hz, 1H), 5.08 – 4.99 (m, 2H), 4.94 (d, J = 9.4 Hz, 3H), 3.69 (s, 3H), 3.63 (s, 2H), 3.01 (s, 2H), 2.84 (s, 6H), 2.69 – 2.62 (m, 2H), 2.54 (s, 2H), 2.41 (d, J = 3.6 Hz, 2H), 1.73 (s, 6H).

Intermediate 372

benzyl but-3-en-1-ylcarbamate

Benzyl chloridocarbonate (0.31mL, 2.19mmol) was added dropwise at 0°C a solution of but-3-en-1-amine (0.20mL, 2.19mmol) and triethylamine (0.50mL, 3.61mmol) in tetrahydrofurane (8mL). When the addition was finished, the mixture was stirred at room temperature. After overnight, water and ethyl acetate were added to the mixture, the organic layer washed with sodium bicarbonate 4%, dried (Na_2SO_4) and the solvent was removed under reduced pressure giving the title compound (315mg, 71%), which was used in the next step without further purification.

LRMS (m/z): 206 (M+1)+

Intermediate 373

1-azabicyclo[2.2.2]oct-4-yl [4-((1*E*)-4-{[(benzyloxy)carbonyl]amino}but-1-en-1-yl)biphenyl-2-yl]carbamate

Obtained (158mg, 48%) from 1-azabicyclo[2.2.2]oct-4-yl (4-bromobiphenyl-2-yl)carbamate (Intermediate 362; 250mg, 0.62mmol), benzyl but-3-en-1-ylcarbamate (Intermediate 372; 128mg, 0.62mmol), tri-o-tolylphosphine (76mg, 0.25mmol), N,N-diisopropylethylamine (196µL, 1.12mmol) and palladium acetate (28mg, 0.12mmol) following the experimental procedure as described for Intermediate 6. The crude obtained was purified by column chromatography with silica gel, eluting with a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 526 (M+1)+

Intermediate 374

1-azabicyclo[2.2.2]oct-4-yl [4-(4-aminobutyl)biphenyl-2-yl]carbamate

1-azabicyclo[2.2.2]oct-4-yl [4-((1*E*)-4-{[(benzyloxy)carbonyl]amino}but-1-en-1-yl)biphenyl-2-yl]carbamate (Intermediate 373; 158mg, 0.30mmol) in EtOH (5mL) and hydrogen chloride 1.25 M in EtOH (5mL) was added palladium on charcoal (10%, 0.16g). The reaction mixture was submitted to a hydrogenation with a hydrogen balloon 6h at room temperature. The catalyst was removed by filtration through Celite and the solvent was removed under reduced pressure giving the title compound an oil (140mg, 99%), which was used in the next step without further purification.

LRMS (m/z): 394 (M+1)+

Intermediate 375

1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[2-chloro-4-(hydroxymethyl)-5-methoxybenzoyl]amino}butyl)biphenyl-2-yl]carbamate

Obtained as a colorless foam (59mg, 33%) from 2-chloro-4-(hydroxymethyl)-5-methoxybenzoic acid (Intermediate 281; 70mg, 0.32mmol), 1-azabicyclo[2.2.2]oct-4-yl [4-(4-aminobutyl)biphenyl-2-yl]carbamate (Int 67C, 140mg, 0.30mmol), diisopropylethylenediamine (250µL, 1.44 mmol) and HATU (275mg, 0.72mmol) in chloroform (5mL) following the experimental procedure as described for Intermediate 329. The crude residue was purified by column chromatography using a mixture of chloroform:methanol:ammonium (40:4:0.2).

LRMS (m/z): 592 (M+1)+

Intermediate 376

1-azabicyclo[2.2.2]oct-4-yl (4-{4-[(2-chloro-4-formyl-5-methoxybenzoyl)amino]butyl}biphenyl-2-yl)carbamate

Obtained as a yellow foam (58mg, 99%) from 1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[2-chloro-4-(hydroxymethyl)-5-methoxybenzoyl]amino}butyl)biphenyl-2-yl]carbamate (Intermediate 375; 59mg, 0.10mmol) and manganese oxide (90mg, 10.4mmol) following the experimental procedure as described for Intermediate 330 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 590 (M+1)+

Intermediate 377

1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[4-({[(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-chloro-5-methoxybenzoyl]amino}butyl)biphenyl-2-yl]carbamate

Obtained as a solid (78mg, 86%) from 1-azabicyclo[2.2.2]oct-4-yl (4-{4-[(2-chloro-4-formyl-5-methoxybenzoyl)amino]butyl}biphenyl-2-yl)carbamate (Intermediate 376; 59mg, 0.10mmol), 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (34mg, 0.10mmol) (prepared according to preparation 8 from US20060035931), sodium triacetoxyborohydride (74mg, 0.35mmol) in MeOH (2mL) following the experimental procedure as described for Intermediate 331 and the crude obtained was used in the next step without further purification.

LRMS (m/z): 907 (M+1)+

EXAMPLE 67.

1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxybenzoyl] amino}butyl)biphenyl-2-yl]carbamate dihydrofluoride

Obtained as a white solid (48mg, 63%) from 1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[4-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-chloro-5-methoxybenzoyl]amino}butyl)biphenyl-2-yl]carbamate (Intermediate 377; 78mg, 0.09mmol) and triethylamine trihydrofluoride (70µL, 0.43mmol) following the experimental procedure as described for Example 1.

LRMS (m/z): 795 (M+1)+

1H NMR (300 MHz, dmso) δ 10.31 (bs, 1H), 8.36 (bs, 1H), 8.13 (d, J = 10.0 Hz, 1H), 7.47 – 7.25 (m, 5H), 7.22 – 7.13 (m, J = 7.9 Hz, 2H), 7.06 (dd, J = 17.4, 8.0 Hz, 2H), 6.95 – 6.84 (m, 3H), 6.46 (d, J = 9.9 Hz, 1H), 5.03 (bs, 1H), 3.75 (d, J = 4.5 Hz, 3H), 3.66 (s, 2H), 2.78 (bs, 6H), 2.72 – 2.58 (m, 4H), 2.55 (dd, J = 3.6, 1.8 Hz, 2H), 2.41 (dd, J = 3.6, 1.8 Hz, 2H), 1.70 (bs, 6H).

Intermediate 378

Ethyl 5-{[4-(2-{[(1-azabicyclo[2.2.2]oct-4-yloxy)carbonyl]amino}biphenyl-4-yl) butanoyl]amino}pyridine-2-carboxylate

To a solution of 4-(2-{[(1-azabicyclo[2.2.2]oct-4-yloxy)carbonyl]amino}biphenyl-4-yl)butanoic acid (Intermediate 328; 293mg, 0.72mmol) in chloroform (7.5mL) was added ethyl 5-aminopicolinate (119mg, 0.72mmol) and diisopropylethylendiamine (0.51mL, 2.94mmol) under nitrogen atmosphere. Then HATU (644mg, 1.7mmol) was added. The reaction mixture was stirred at room temperature for 48 hours. The reaction mixture was diluted with more chloroform and the organic layer was washed with sodium bicarbonate (solution 4%), water and brine, dried, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel, eluting using as eluents CHCl3-MeOH-NH4OH 40:4:0.2, giving the title compound as an oil (264mg, 64%).

LRMS (m/z): 557 (M+1)+

Intermediate 379

1-azabicyclo[2.2.2]oct-4-yl[4-(4-{[6-(hydroxymethyl)pyridin-3-yl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

A round-bottomed flask fitted with stir bar was charged with methyl ethyl 5-{[4-(2-{[(1-azabicyclo[2.2.2]oct-4-yloxy)carbonyl]amino}biphenyl-4-yl)butanoyl]amino}pyridine-2-carboxylate (Intermediate 378; 260mg, 0.47mmol) in 2.7 mL anhydrous tetrahydrofurane and under Argon atmosphere. The mixture was cooled with an acetone/CO2 bath at -10°C and lithium aluminium hydride 1M in THF (700uL, 0.7mmol) was added cautiously. The solution is stirred at -10 °C for 2 hours. The reaction is quenched by adding sodium hydroxide 1N (1.3mL) maintaining the temperature below 0°C. Ethyl acetate is added to the reaction mixture and the organic layer is washed with water, brine, dried, filtered and the solvent was removed under reduced pressure. The crude obtained was purified by column chromatography with silica gel, eluting using as eluents CHCl3-MeOH-NH4OH 40:8:1, giving the title compound as an oil (71mg, 25%).

LRMS (m/z): 516 (M+1)+

Intermediate 380

1-azabicyclo[2.2.2]oct-4-yl(4-{4-[(6-formylpyridin-3-yl)amino]-4-oxobutyl} biphenyl-2-yl)carbamate

A round-bottomed flask fitted with stir bar was charged with 1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[6-(hydroxymethyl)pyridin-3-yl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate (Intermediate 379; 71mg, 0.12mmol) in chloroform (1.5mL). Dess-Martin periodinane (64mg, 0.15mmol) was added portionwise and the mixture stirred at room temperature for 1 hour. The reaction was quenched by addition of saturated bicarbonate and sodium thiosulfate solution. The organic layer was dried over MgSO4, filtered and concentrated to give the title compound as a solid (80mg, 100%), which was used in the next step without further purification.

LRMS (m/z): 514 (M+1)+

Intermediate 381

1-azabicyclo[2.2.2]oct-4-yl[4-(4-{[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)pyridin-3-yl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate

A mixture of 1-azabicyclo[2.2.2]oct-4-yl (4-{4-[(6-formylpyridin-3-yl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate (Intermediate 380; 80mg, 0.12mmol) and 5-((1R)-2-amino-1-{[tert-butyl(dimethyl)-silyl]oxy}ethyl)-8-hydroxyquinolin-2(1H)-one acetate (48mg, 0.12mmol) (prepared according to preparation 8 from US20060035931) in 2mL of methanol and was stirred at room temperature for 4 hours. Then the crude was cooled to 0°C and sodium triacetoxyborohydride (20mg, 0.31mmol) was added. The mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography with silica gel, eluting using as eluents CHCl3-MeOH-NH4OH 40:4:0.2, giving the title compound as an oil (36mg, 32%).

LRMS (m/z): 832 (M+1)+

EXAMPLE 68

1-azabicyclo[2.2.2]oct-4-yl[4-(4-{[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)pyridin-3-yl]amino}-4-oxobutyl) biphenyl-2-yl]carbamate dihydrofluoride

Obtained as a pale yellow solid dihydrofluoride salt (29mg, 92%) from 1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[6-({[(2R)-2-{[tert-butyl(dimethyl)silyl]oxy}-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)pyridin-3-yl]amino}-4-oxobutyl) biphenyl-2-yl]carbamate (Intermediate 381; 36mg, 0.04mmol) and triethylamine trihydrofluoride (35µL, 0.21mmol) following the experimental procedure as described for Example 1.

LRMS (m/z): 718 (M+1)+

1H NMR (300 MHz, dmso) δ 10.38 (bs, 1H), 10.14 (s, 1H), 8.71 (d, J = 2.2 Hz, 1H), 8.56 (s, 1H), 8.15 (d, J = 9.9 Hz, 1H), 8.00 (d, J = 10.7 Hz, 1H), 7.48 – 7.26 (m, 5H), 7.24 – 7.01 (m, 4H), 6.98 – 6.84 (m, 1H), 6.49 (d, J = 9.9 Hz, 1H), 5.21 (bs, 2H), 4.00 (s, 2H), 3.13 – 2.89 (m, 6H), 2.84 (d, J = 4.2 Hz, 2H), 2.71 – 2.57 (m, 2H), 2.43 – 2.27 (m, 2H), 1.88 (d, J = 5.7 Hz, 6H).

Biological tests

Test 1: Human Adrenergic ß$_1$ and ß$_2$ Receptor Binding Assays

The study of binding to human adrenergic beta1 and beta2 receptors was performed using commercial membranes prepared from Sf9 cells where they are overexpressed (Perkin Elmer). The membrane suspensions (16 µg/well for beta1 and 5µg/well for beta2) in assay buffer (75mM Tris/HCl with 12.5mM MgCl2 and 2mM EDTA pH=7.4) were incubated with 0.14 or 0.6 nM of 3H-CGP12177 (Amersham) for beta 1 and beta 2 receptors respectively in a final volume of 250 µl, in GFC Multiscreen 96 well plates (Millipore) previously treated with assay buffer containing 0.3 % PEI (Sigma). Non specific binding was measured in the presence of 1µM propanolol. Incubation was maintained for 60 minutes at room temperature and with gentle shaking. The binding reactions were terminated by filtration and washing with 2.5 volumes of Tris/HCl 50mM pH=7.4. The affinity of each test compound to the receptor was determined by using ten different concentrations ran in duplicate. IC50s were calculated using Activity Base software from IDBS and the four parameters-log equation.

Compounds of the present invention were found to have IC_{50} values less than 10 nM for β_2 receptor and more than 60 nM for β_1 receptor, with β1/β2 ratios from 3 to 25.

Test 2: Human Muscarinic M_1, M_2, M_3, M_4 and M_5 receptors binding assays

The study of binding to human muscarinic M1, M2, M3, M4 and M5 receptors was performed using commercial membranes (Perkin Elmer) prepared from CHO-K1 cells. Radioligand binding experiments were conducted in 96 polypropylene well plates in a total volume of 200 μl. All reagents were dissolved in assay binding buffer (PBS with calcium and magnesium, SIGMA), except compounds that were dissolved in DMSO 100%. Non-specific binding (NSB) was measured in the presence of 1 μM atropine.

[3H]-NMS was used as the radioligand at a concentration of 1 nM for M2, M3 and M5 and 0.3 nM for M1 and M4. [3H]-NMS and antagonists were incubated with membranes that express human muscarinic receptors M1, M2, M3, M4 and M5 at concentrations of 8.1, 10, 4.9, 4.5 and 4.9 μg/well, respectively.

After an incubation period of two hours with gentle shaking, 150 μl of the reaction mix were transferred to 96 GF/C filter plates (Millipore), previously treated with wash buffer (Tris 50 mM ; NaCl 100 mM; pH:7.4), containing 0.05 % PEI (Sigma) during one hour. Bound and free [3H]-NMS were separated by rapid vacuum filtration in a manifold from Millipore and washed four times with ice cold wash buffer. After drying 30 min, 30 μl of OPTIPHASE Supermix were added to each well and radioactivity quantified using a Microbeta microplate scintillation counter.

The affinity of each test compound to the receptors was determined by using ten different concentrations ran in duplicate. IC50s were calculated using Activity Base software from IDBS and the four parameters-log equation.

In the table 1 are shown some IC_{50} values for β_2 and M_3 bindings.

Table 1

Compound Example nr	**Binding, IC_{50}, nM**	
	β_2	M_3
2	**18**	**0.24**

7	30	0.5
9	47	0.68
10	69	0.57
13	9.5	3.2
14	10	0.13
15	15	0.32
16	12	0.65
17	19	0.5
19	6.6	0.19
21	1.3	1.2
22	8.5	1
23	31	0.78
25	1.5	0.14
29	19	1.1
31	19	0.3
34	14	0.84
35	16	0.33
37	18	1.2
39	10	0.56
40	2	0.78
44	6.3	1.2
45	4.7	1.3
47	8.5	0.65
49	7.2	0.59
52	8.2	1.5
57	7.4	0.86
58	8.4	1.4
60	4.9	0.37
66	9.6	0.99
67	8.2	0.41
68	23	1.7

As it can be seen from Table1, compounds of the present invention exhibit potency at either beta2 adrenoceptor and M3 muscarinic receptors. For example, for the human M3 muscarininc receptor, compounds of the present invention were found to have an

IC_{50} values of less than 50 nM, preferably less than 10 nM, more preferably less than 5 nM, even less than 1 nM.

In case of beta2 of adrenoceptor, compounds of the present invention were found to have an IC_{50} values of less than 100 nM, preferably less than 50 nM, more preferably less than 10 nM, even less than 5 nM. This particular ratio balanced towards M3 activity makes the compounds safer in terms of cardiovascular adrenergic side-effects like tachycardia compared to pure LABA compounds. The combination of both activities, in addition to provide additive effect in terms of bronchodilation also combines the faster onset of action of the beta2 component and the duration of action of the M3 component. This long duration of action of the muscarinic activity is related to the long residence time at the human M3 receptor that show many compounds of this invention.

Pharmaceutical Compositions

The pharmaceutical formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient(s) into association with the carrier. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil- in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with flavouring or colouring agent.

Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, talc, gelatine, acacia, stearic acid, starch, lactose and sucrose.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent.

Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatine capsule. Where the composition is in the form of a soft gelatine capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and are incorporated in a soft gelatine capsule.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Formulations generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base (carrier substance) such as lactose or starch. Use of lactose is preferred.

Each capsule or cartridge may generally contain between 2μg and 150 μg of each therapeutically active ingredient. Alternatively, the active ingredient (s) may be presented without excipients.

Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi- dose delivery, the formulation can be pre-metered or metered in use. Dry powder inhalers are thus classified into three groups: (a) single dose, (b) multiple unit dose and (c) multi dose devices.

For inhalers of the first type, single doses have been weighed by the manufacturer into small containers, which are mostly hard gelatine capsules. A capsule has to be taken from a separate box or container and inserted into a receptacle area of the inhaler.

Next, the capsule has to be opened or perforated with pins or cutting blades in order to allow part of the inspiratory air stream to pass through the capsule for powder entrainment or to discharge the powder from the capsule through these perforations by means of centrifugal force during inhalation. After inhalation, the emptied capsule has to be removed from the inhaler again. Mostly, disassembling of the inhaler is necessary for inserting and removing the capsule, which is an operation that can be difficult and burdensome for some patients.

Other drawbacks related to the use of hard gelatine capsules for inhalation powders are (a) poor protection against moisture uptake from the ambient air, (b) problems with opening or perforation after the capsules have been exposed previously to extreme relative humidity, which causes fragmentation or indenture, and (c) possible inhalation of capsule fragments. Moreover, for a number of capsule inhalers, incomplete expulsion has been reported (e. g. Nielsen et al, 1997).

Some capsule inhalers have a magazine from which individual capsules can be transferred to a receiving chamber, in which perforation and emptying takes place, as described in WO 92/03175. Other capsule inhalers have revolving magazines with capsule chambers that can be brought in line with the air conduit for dose discharge (e. g. WO91/02558 and GB 2242134). They comprise the type of multiple unit dose inhalers together with blister inhalers, which have a limited number of unit doses in supply on a disk or on a strip.

Blister inhalers provide better moisture protection of the medicament than capsule inhalers. Access to the powder is obtained by perforating the cover as well as the blister foil, or by peeling off the cover foil. When a blister strip is used instead of a disk, the number of doses can be increased, but it is inconvenient for the patient to replace an empty strip. Therefore, such devices are often disposable with the incorporated dose system, including the technique used to transport the strip and open the blister pockets.

Multi-dose inhalers do not contain pre-measured quantities of the powder formulation. They consist of a relatively large container and a dose measuring principle that has to be operated by the patient. The container bears multiple doses that are isolated individually from the bulk of powder by volumetric displacement. Various dose measuring principles exist, including rotatable membranes (Ex. EP0069715) or disks (Ex. GB 2041763; EP 0424790; DE 4239402 and EP 0674533), rotatable cylinders (Ex.

EP 0166294; GB 2165159 and WO 92/09322) and rotatable frustums (Ex. WO 92/00771), all having cavities which have to be filled with powder from the container. Other multi dose devices have measuring slides (Ex. US 5201308 and WO 97/00703) or measuring plungers with a local or circumferential recess to displace a certain volume of powder from the container to a delivery chamber or an air conduit (Ex. EP 0505321, WO 92/04068 and WO 92/04928), or measuring slides such as the Genuair® (formerly known as Novolizer SD2FL), which is described in the following patent applications Nos.: WO97/000703, WO03/000325 and WO2006/008027.

Reproducible dose measuring is one of the major concerns for multi dose inhaler devices.

The powder formulation has to exhibit good and stable flow properties, because filling of the dose measuring cups or cavities is mostly under the influence of the force of gravity.

For reloaded single dose and multiple unit dose inhalers, the dose measuring accuracy and reproducibility can be guaranteed by the manufacturer. Multi dose inhalers on the other hand, can contain a much higher number of doses, whereas the number of handlings to prime a dose is generally lower.

Because the inspiratory air stream in multi-dose devices is often straight across the dose measuring cavity, and because the massive and rigid dose measuring systems of multi dose inhalers can not be agitated by this inspiratory air stream, the powder mass is simply entrained from the cavity and little de-agglomeration is obtained during discharge.

Consequently, separate disintegration means are necessary. However in practice, they are not always part of the inhaler design. Because of the high number of doses in multi-dose devices, powder adhesion onto the inner walls of the air conduits and the de-agglomeration means must be minimized and/or regular cleaning of these parts must be possible, without affecting the residual doses in the device. Some multi dose inhalers have disposable drug containers that can be replaced after the prescribed number of doses has been taken (e. g. WO 97/000703). For such semi-permanent multi dose inhalers with disposable drug containers, the requirements to prevent drug accumulation are even more strict.

Apart from applications through dry powder inhalers the compositions of the invention can be administered in aerosols which operate via propellant gases or by means of so-called atomisers, via which solutions of pharmacologically-active substances can be sprayed under high pressure so that a mist of inhalable particles results. The advantage of these atomisers is that the use of propellant gases can be completely dispensed with.

Such atomisers are described, for example, in PCT Patent Application No. W0 91/14468 and International Patent Application No. WO 97/12687, reference here is being made to the contents thereof.

Spray compositions for topical delivery to the lung by inhalation may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the active ingredient (s) and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, e. g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane, especially 1,1, 1, 2-tetrafluoroethane, 1,1, 1,2, 3,3, 3-heptafluoro-n-propane or a mixture thereof. Carbon dioxide or other suitable gas may also be used as propellant.

The aerosol composition may be excipient free or may optionally contain additional formulation excipients well known in the art such as surfactants, for example, oleic acid or lecithin and cosolvens, for example, ethanol. Pressurised formulations will generally be retained in a canister (for example, an aluminium canister) closed with a valve (for example, a metering valve) and fitted into an actuator provided with a mouthpiece.

Medicaments for administration by inhalation desirably have a controlled particle size. The optimum particle size for inhalation into the bronchial system is usually 1-10μ, preferably 2-5μ. Particles having a size above 20μ are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of the active ingredient as produced may be size reduced by conventional means, for example, by micronisation. The desired fraction may be separated out by air classification or sieving. Preferably, the particles will be crystalline.

Achieving high dose reproducibility with micronised powders is difficult because of their poor flowability and extreme agglomeration tendency. To improve the efficiency of dry powder compositions, the particles should be large while in the inhaler, but small when discharged into the respiratory tract. Thus, an excipient such as lactose or glucose is generally employed. The particle size of the excipient will usually be much greater than the inhaled medicament within the present invention. When the excipient is lactose it will typically be present as milled lactose, preferably crystalline alpha lactose monohydrate.
Pressurized aerosol compositions will generally be filled into canisters fitted with a valve, especially a metering valve. Canisters may optionally be coated with a plastics material e. g. a fluorocarbon polymer as described in W096/32150. Canisters will be fitted into an actuator adapted for buccal delivery.

Typical compositions for nasal delivery include those mentioned above for inhalation and further include non-pressurized compositions in the form of a solution or suspension in an inert vehicle such as water optionally in combination with conventional excipients such as buffers, anti-microbials, tonicity modifying agents and viscosity modifying agents which may be administered by nasal pump.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer a single dose.

Each dosage unit contains suitably from 0.5 μg to 500 μg, and preferably from 5 μg to 100 μg of a compound according to the invention.

The amount of each active which is required to achieve a therapeutic effect will, of course, vary with the particular active, the route of administration, the subject under treatment, and the particular disorder or disease being treated.

The active ingredients may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity. Preferably, the active ingredients are administered once or twice a day.

Examples of suitable PDE4 inhibitors that can be combined with compounds of the present invention are benafentrine dimaleate, etazolate, denbufylline, rolipram, cipamfylline, zardaverine, arofylline, filaminast, tipelukast, tofimilast, piclamilast, tolafentrine, mesopram, drotaverine hydrochloride, lirimilast, roflumilast, cilomilast, oglemilast, apremilast, tetomilast, filaminast, (R)-(+)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine (CDP-840), N-(3,5-Dichloro-4-pyridinyl)-2-[1-(4-fluorobenzyl)-5-hydroxy-1H-indol-3-yl]-2-oxoacetamide (GSK-842470), 9-(2-Fluorobenzyl)-N6-methyl-2-(trifluoromethyl)adenine (NCS-613), N-(3,5-Dichloro-4-pyridinyl)-8-methoxyquinoline-5-carboxamide (D-4418), 3-[3-(Cyclopentyloxy)-4-methoxybenzyl]-6-(ethylamino)-8-isopropyl-3H-purine hydrochloride (V-11294A), 6-[3-(N,N-Dimethylcarbamoyl)phenylsulfonyl]-4-(3-methoxyphenylamino)-8-methylquinoline-3-carboxamide hydrochloride (GSK-256066), 4-[6,7-Diethoxy-2,3-bis(hydroxymethyl)naphthalen-1-yl]-1-(2-methoxyethyl)pyridin-2(1H)-one (T-440), (-)-trans-2-[3'-[3-(N-Cyclopropylcarbamoyl)-4-oxo-1,4-dihydro-1,8-naphthyridin-1-yl]-3-fluorobiphenyl-4-yl]cyclopropanecarboxylic acid (MK-0873), CDC-801, UK-500001, BLX-914, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluroromethoxyphenyl)cyclohexan1-one, *cis* [4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol, 5(S)-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3(S)-(3-methylbenzyl)piperidin-2-one (IPL-455903), ONO-6126 (Eur Respir J 2003, 22(Suppl. 45): Abst 2557) and the salts claimed in the PCT patent applications number WO03/097613, WO2004/058729, WO 2005/049581, WO 2005/123693 and WO 2005/123692

Examples of suitable corticosteroids and glucocorticoids that can be combined with compounds of the present invention are prednisolone, methylprednisolone, dexamethasone, dexamethasone cipecilate, naflocort, deflazacort, halopredone acetate, budesonide, beclomethasone dipropionate, hydrocortisone, triamcinolone acetonide, fluocinolone acetonide, fluocinonide, clocortolone pivalate, methylprednisolone aceponate, dexamethasone palmitoate, tipredane, hydrocortisone aceponate, prednicarbate, alclometasone dipropionate, halometasone, methylprednisolone suleptanate, mometasone, mometasone furoate, rimexolone, prednisolone farnesylate, ciclesonide, butixocort propionate, RPR-106541, deprodone propionate, fluticasone, fluticasone propionate, fluticasone furoate, halobetasol propionate, loteprednol etabonate, betamethasone butyrate propionate, flunisolide, prednisone, dexamethasone sodium phosphate, triamcinolone, betamethasone 17-valerate, betamethasone, betamethasone dipropionate, 21-Chloro-11beta-hydroxy-17alpha-[2-(methylsulfanyl)acetoxy]-4-pregnene-3,20-dione, Desisobutyrylciclesonide, hydrocortisone acetate, hydrocortisone sodium succinate, NS-126, prednisolone sodium phosphate and hydrocortisone probutate, Prednisolone sodium metasulfobenzoate and clobetasol propionate.

Particularly preferred pharmaceutical composition according to the invention comprises a compound of formula (I) and a therapeutically effective amount of one or more additional therapeutic agents selected from the group consisting of mometasone, mometasone furoate, ciclesonide, budesonide, fluticasone, fluticasone propionate, fluticasone furoate, rolipram, roflumilast, cilomilast and the compounds claimed in the PCT patent applications number WO03/097613, WO2004/058729, WO 2005/049581, WO 2005/123693 and WO 2005/123692

Still particularly preferred pharmaceutical composition according to the invention comprise a compound of formula (I) and a therapeutically effective amount of one or more additional therapeutic agents selected from the group consisting of mometasone furoate, ciclesonide, budesonide, fluticasone propionate, fluticasone furoate, rolipram, roflumilast and cilomilast

The combinations of the invention may be used in the treatment of respiratory diseases, wherein the use of bronchodilating agents is expected to have a beneficial effect, for example asthma, acute or chronic bronchitis, emphysema, or Chronic Obstructive Pulmonary Disease (COPD).

The active compounds in the combination and the PDE4 inhibitors, corticosteroids or glucocorticoids may be administered together in the same pharmaceutical composition or in different compositions intended for separate, simultaneous, concomitant or sequential administration by the same or a different route.

It is contemplated that all active agents would be administered at the same time, or very close in time. Alternatively, one or two actives could be taken in the morning and the other (s) later in the day. Or in another scenario, one or two actives could be taken twice daily and the other (s) once daily, either at the same time as one of the twice-a-day dosing occurred, or separately. Preferably at least two, and more preferably all, of the actives would be taken together at the same time. Preferably, at least two, and more preferably all actives would be administered as an admixture.

The active substance compositions according to the invention are preferably administered in the form of compositions for inhalation delivered with the help of inhalers, especially dry powder inhalers, however, any other form or parenteral or oral application is possible. Here, the application of inhaled compositions embodies the preferred application form, especially in the therapy of obstructive lung diseases or for the treatment of asthma.

Additional suitable carriers for formulations of the active compounds of the present invention can be found in Remington: The Science and Practice of Pharmacy, 20th Edition, Lippincott Williams & Wilkins, Philadelphia, Pa., 2000. The following non-limiting examples illustrate representative pharmaceutical compositions of the invention.

FORMULTION EXAMPLE

Formulation Example 1 (Oral suspension)

Ingredient	**Amount**
Active Compound	3 mg
Citric acid	0,5 g
Sodium chloride	2,0 g
Methyl paraben	0,1 g
Granulated sugar	25 g
Sorbitol (70% solution)	11 g
Veegum K	1,0 g
Flavoring	0,02 g
Dye	0,5 mg
Distilled water	q.s. to 100 mL

Formulation Example 2 (Hard gelatine capsule for oral administration)

Ingredient	Amount
Active Compound	1 mg
Lactose	150 mg
Magnesium stearate	3 mg

Formulation Example 3 (Gelatin cartridge for inhalation)

Ingredient	Amount
Active Compound (micronized)	0,2 mg
Lactose	25 mg

Formulation Example 4 (Formulation for inhalation with a DPI)

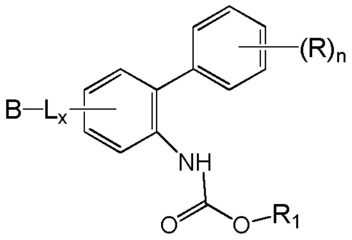
Ingredient	Amount
Active Compound (micronized)	15 mg
Lactose	3000 mg

Formulation Example 5 (Formulation for a MDI)

Ingredient	Amount
Active Compound (micronized)	10 g
1,1,1,2,3,3,3-heptafluoro-n-propane	q.s. to 200 ml

Claims

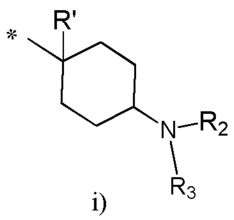
1. A compound of formula (A), and pharmaceutically acceptable salts, and deuterated derivates thereof



Formula (A)

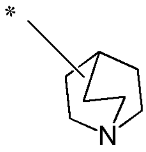
wherein

- R is selected from the group consisting of a hydrogen atom, a halogen atom, a hydroxyl group, a linear or branched C_{1-4} alkyl group, a linear or branched C_{1-4} hydroxyalkyl group and a linear or branched C_{1-4} alkoxy group,
- n has a value of 1 or 2,
- R_1 represents a group of formula:



i)

or

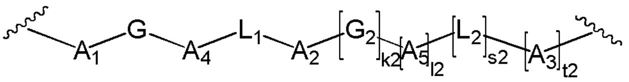


ii)

wherein:

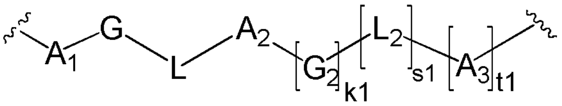
  - R_2 and R_3 independently represent a hydrogen atom, a linear or branched C_{1-4} alkyl group, a $(C_{5-6}$ aryl)-(C_{1-4})alkyl group or a linear or branched C_{1-4} alkoxy group,
  - R' represents a hydrogen atom or a linear or branched C_{1-4} alkyl group,
  - * represents the point of attachment of R_1 to the remainder of the molecule of formula (A),
- L_x is a suitable covalent linker, and
- B is a moiety having a beta2-adrenergic binding activity.

2. A compound according to claim 1, wherein the L_x has the following formula:



Formula (La)

or



Formula (Lb)

wherein k1, k2, s1, s2, l2, t1 and t2 independently have a value of 0 or 1;

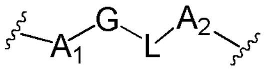
- A_1, A_2, A_3, A_4 and A_5 each independently are selected from the group consisting of a direct bond, a C_{1-10} alkylene group, a C_{2-10} alkenylene group and a C_{2-10} alkynylene group, wherein said groups are optionally substituted with one or more substituents selected from a halogen atom, a hydroxy group, a linear or branched C_{1-4} alkyl group, a linear or branched C_{1-4} alkoxy group, a C_{5-6} aryl group and a C_{3-7} cycloalkyl group,

- L, L_1 and L_2 independently are selected from a direct bond, -O-, -NR^c-, -S-, -S(O)-, -SO$_2$-, -NR^c(CO)-, -(CO)NR^c-, –NR^c(CO)(CH$_2$)$_q$O-, –O(CH$_2$)$_q$(CO)NR^c-, -NR^c(CO)(CH$_2$)$_q$NR^c(CO)-, –O(CH$_2$)$_q$NR^c-, –NR^c(CH$_2$)$_q$O-, –NR^c(CO)NR^d-, -C(O)-, -C(O)O-, -OC(O)-, -S(O)$_2$NR^c-, -NR^{c}S(O)$_2$-, -NR^{c}S(O)$_2$NR^d-, –C(O)NR^{c}S(O)$_2$- and –S(O)$_2$NR^{c}C(O)-, wherein R^c and R^d are independently selected from a hydrogen atom and a linear or branched C_{1-4} alkyl group and q has a value of 0, 1, 2, 3 or 4.

- G and G_2 independently are selected from the group consisting of a direct bond, a C_{3-10} mono- or bicyclic cycloalkyl group, a C_5-C_{14} mono- or bicyclic aryl group, a 3 to 14-membered saturated or unsaturated mono- or bicyclic heterocyclyl group having one or more heteroatoms selected from N, S and O, a 5- to 14-membered mono- or bicyclic heteroaryl group having one or more heteroatoms selected from N, S and O and a bicyclic ring system comprising two monocyclic ring systems which are linked between each other by a covalent bond or by a –O- or –NH- group, wherein said monocyclic ring systems are independently selected from a C_{3-8} cycloalkyl group, a C_{5-6} aryl group, a 3 to 8-membered saturated or unsaturated heterocyclyl group having one or more heteroatoms selected from N, S and O and a 5- to 6-membered heteroaryl group having one or more heteroatoms selected from N, S and O, wherein the cyclic groups independently are optionally substituted with one or more substituents selected from a halogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a carboxy group, a cyano group, a nitro group, a hydroxy group, an oxo group, a trifluoromethyl group and a trifluoromethoxy group.

3. A compound according to claim 2, wherein all of k1, k2, s1, s2, l2, t1 and t2 have a value of 0.

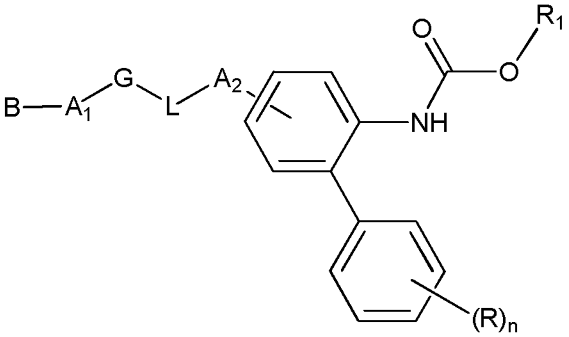
4. A compound according to claim 3, wherein L has the following formula (Lb1):



Formula (Lb1)

wherein A_1, A_2, L_1 and G are as defined in claim 2.

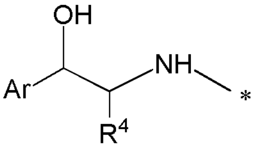
5. A compound according to any preceding claims, having the following formula (B):



Formula(B)

Wherein A_1, A_2, B, L, G, n, R and R_1 are as defined in any one of the preceding claims.

6. A compound according to any preceding claims, wherein B represents a group of formula (IB):



Formula (IB)

wherein:

- R^4 is selected from the group consisting of a hydrogen atom, a linear or branched C_{1-4} alkyl group and a linear or branched C_{1-4} alkoxy group,

- Ar is selected from the group consisting of a C_{3-10} saturated or unsaturated, mono- or bicyclic cycloalkyl group, a C_5-C_{14} mono- or bicyclic aryl group, a 3 to 14-membered saturated or unsaturated mono- or bicyclic heterocyclyl group having one or more heteroatoms selected from N, S and O, a 5- to 14-membered mono- or bicyclic heteroaryl group having one or more heteroatoms selected from N, S and O and wherein the cyclic groups independently are optionally substituted with one or more substituents selected from a halogen atom, a cyano group, a nitro group, an oxo group, a carboxy group, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, $-CF_3$, $–OCF_3$, $-NR^eR^f$, $-(CH_2)_p-OH$, $-NR^e(CO)R^f$, $-NR^e-SO_2-R^g$, $-SO_2NR^eR^f$, $-OC(O)R^h$, and $–NR^e(CH_2)_{(0-2)}-R^i$, wherein p has a value of 0, 1 or 2 and wherein:

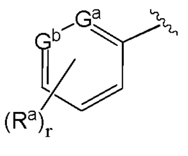
  R^e and R^f independently represent a hydrogen atom or a linear or branched C_{1-4} alkyl group,

  R^g is selected from the group consisting of a linear or branched C_{1-4} alkyl group, a C_{5-6} aryl group, a saturated or unsaturated C_{3-8} cycloalkyl, wherein the cyclic groups independently are optionally substituted with one or more substituents selected from a halogen atom, a C_{1-4} alkyl group and a C_{1-4} alkoxy group,

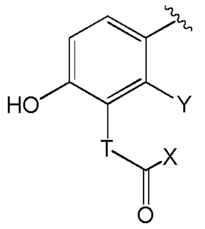
  R^h is selected from a hydrogen atom,$-NR^eR^f$ and a C_{5-6} aryl group which is optionally substituted with one or more substituents selected from a C_{1-4} alkyl group and a C_{1-4} alkoxy group,

  R^i is selected from the group consisting of a C_{5-6} aryl group, a C_{3-8} cycloalkyl group and a 3 to 8 membered saturated or unsaturated heterocyclyl group, which groups independently are optionally substituted with one or more substituents selected from a halogen atom, a C_{1-4} alkyl group and a C_{1-4} alkoxy group.

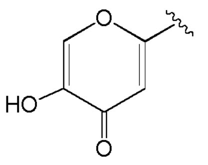
7. A compound according to claim 6, wherein Ar represents a group of formula:



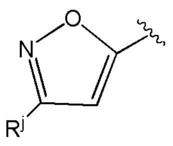
(a)



(b)



(c)



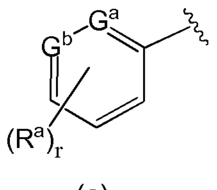
(d)

wherein

- G^a and G^b independently are selected from a nitrogen atom and a carbon atom,
- r has a value of 0, 1, 2 or 3 and

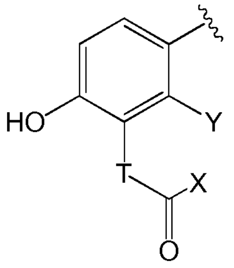
- R^a is seleted from the group consisting of a halogen atom, an amino group, a cyano group, a nitro group, an oxo group, a carboxy group, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, $-CF_3$, $-OCF_3$, $-(CH_2)_p-OH$, -NH(CO)H, $-NH-SO_2-R^g$, $-SO_2NH_2$, -OC(O)H, –O(CO)-(4-methyl)phenyl, $-O(CO)-N(CH_3)_2$, $-OC(O)NH_2$ and $-NH(CH_2)_{(1-2)}-R^i$, group, wherein p is as defined above and R^g and R^i independently are selected from a phenyl group optionally substituted with a one substituent selected from a methyl group or a methoxy group,
- R^j represents a halogen atom,
- T is selected from the group consisting of $-CH_2-$ and –NH-,
- Both X and Y represent a hydrogen atom or X together with Y form the group $-CH_2-CH_2-$, -CH=CH-, $-CH_2-O-$ or –S-, wherein in the case of $-CH_2-O-$ the methylene group is bound to the carbonyl group holding X and the oxygen atom is bound to the carbon atom in the phenyl ring holding Y.

8. A compound according to claim 7, wherein Ar represents a compound of formula (a) or (b) wherein:



(a)

or



(b)

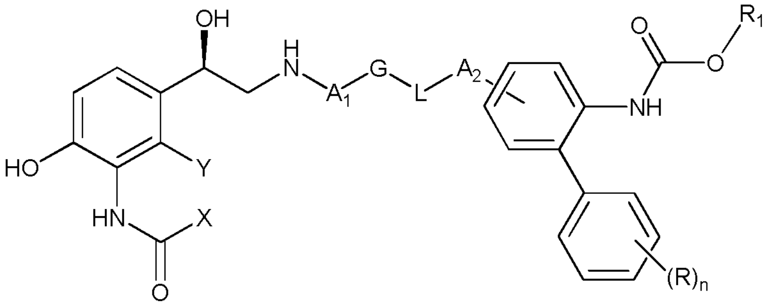
- Both G^a and G^b represent a carbon atom,
- R^a is seleted from the group consisting of halogen atom, amino group, cyano group, nitro group, $-(CH_2)_p-OH$, -NH(CO)H, $-NH-SO_2-CH_3$, $-SO_2NH_2$, -OC(O)H, –O(CO)-(4-methyl)phenyl, $-O(CO)-N(CH_3)_2$, $-OC(O)NH_2$ and $-CF_3$ group, wherein p has a value of 0, 1 or 2,
- T represents –NH- group,
- Both X and Y represent a hydrogen atom or X together with Y form the group –CH=CH-, $-CH_2-CH_2-$, $-CH_2-O-$ or –S-, wherein in the case of $-CH_2-O-$ the methylene group is bound to the carbon atom in the amido substituent holding X and the oxygen atom is bound to the carbon atom in the phenyl ring holding Y.

9. A compound according to claim 8, wherein Ar is selected from the group consisting of 3-bromoisoxazol-5-yl, 3,4-dihydroxyphenyl, 4-hydroxy-3-(methylsulfonamido)phenyl,

3,4-bis(4-methylbenzoyloxy)phenyl, 3,5-bis(dimethylcarbamoyloxy)phenyl, (5-hydroxy-6-hydroxymethyl)pyrid-2-yl, (4-amino-3,5-dichloro)phenyl, 4-hydroxyphenyl, 4-hydroxy-3-(2-hydroxyethyl)phenyl, 4-hydroxy-3-(hydroxymethyl)phenyl, [4-amino-3-chloro-5-(trifluoromethyl)]phenyl, (3-formamido-4-hydroxy)phenyl, 8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl, 8-hydroxy-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl, 5-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-8-yl, 4-hydroxy-2-oxo-2,3-dihydrobenzo[d]thiazol-7-yl, preferably Ar is selected from the group consisting of 4-hydroxy-3-(hydroxymethyl)phenyl, (3-formamido-4-hydroxy)phenyl, 8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl, 8-hydroxy-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl and 5-hydroxy-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-8-yl.

10. A compound according to claim 8, wherein Ar represents a compound of formula (b) wherein X and Y are as defined in claim 8 and T represents a –NH- group.

11. A compound according to any one of preceding claims, having the following formula (I):



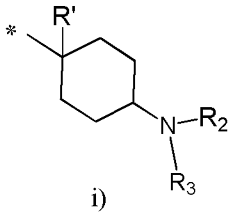
Formula (I)

Wherein:

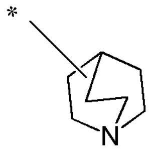
- R is selected from the group consisting of a hydrogen atom, a halogen atom, a hydroxyl group, a linear or branched C_{1-4} alkyl group, a linear or branched C_{1-4} hydroxyalkyl group and a linear or branched C_{1-4} alkoxy group,
- n has a value of 1 or 2,
- X and Y are both a hydrogen atom or X together with Y form the group –CH=CH-, -CH_2-O- or –S-, wherein in the case of -CH_2-O- the methylene group is bound to the carbon atom in the amido substituent holding X and the oxygen atom is bound to the carbon atom in the phenyl ring holding Y,
- A_1 and A_2 independently are selected from the group consisting of a direct bond, a C_{1-10} alkylene group, a C_{2-10} alkenylene group and a C_{2-10} alkynylene group, wherein said groups are optionally substituted with one or more substituents selected from a

halogen atom, a hydroxy group, a linear or branched C_{1-4} alkyl group, a linear or branched a C_{1-4} alkoxy group, a C_{5-6} aryl group and a C_{3-7} cycloalkyl group,

- G is selected from the group consisting of a direct bond, a C_{3-10} mono- or bicyclic cycloalkyl group, a C_{5-14} mono- or bicyclic aryl group, a 3- to 14-membered saturated or unsaturated mono- or bicyclic heterocyclyl group having one or more heteroatoms selected from N, S and O, a 5- to 14-membered mono- or bicyclic heteroaryl group having one or more heteroatoms selected from N, S and O and a bicyclic ring system consisting of two monocyclic ring systems which are linked between each other by a covalent bond or by a –O- group, wherein said monocyclic ring systems are independently selected from a C_{3-8} cycloalkyl group, a C_{5-6} aryl group, a 3- to 8-membered saturated or unsaturated heterocyclyl group having one or more heteroatoms selected from N, S and O and a 5- to 6-membered heteroaryl group having one or more heteroatoms selected from N, S and O, wherein the cyclic groups independently are optionally substituted with one or more substituents selected from a halogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a carboxy, group, a cyano group, a nitro group, a hydroxy group, an oxo group, a trifluoromethyl group and a trifluoromethoxy group.
- L is selected from a direct bond, -O-, $-NR^c-$, -S-, -S(O)-, $-SO_2-$, $-NR^c(CO)-$, $-(CO)NR^c-$, $–NR^c(CO)(CH_2)_qO-$, $–O(CH_2)_q(CO)NR^c-$, $-NR^c(CO)(CH_2)_qNR^c(CO)-$, $–O(CH_2)_qNR^c-$, $–NR^c(CH_2)_qO-$, $–NR^c(CO)NR^d-$, -C(O)-, -C(O)O-, -OC(O)-, $-S(O)_2NR^c-$, $-NR^cS(O)_2-$, $-NR^cS(O)_2NR^d-$, $–C(O)NR^cS(O)_2-$ and $–S(O)_2NR^cC(O)-$, wherein R^c and R^d are independently selected from a hydrogen atom and a linear or branched C_{1-4} alkyl group and q has a value of 0, 1, 2, 3 or 4.
- R_1 represents a group of formula:


i)

or


ii)

wherein R_2 and R_3 independently represent a hydrogen atom, a linear or branched C_{1-4} alkyl group or a $(C_{5-6}$ aryl)-(C_{1-4})alkyl group and R' represents a hydrogen atom or a linear or branched C_{1-4} alkyl group.

12. A compound according to any one of preceding claims, wherein A_1 and A_2 independently are selected from the group consisting of C_{1-6} alkylene group, C_{1-6} alkenylene group and C_{1-6} alkynylene group, wherein said groups are optionally substituted with one or more substituents selected from a halogen atom, a hydroxy

group, a C_{1-2} alkyl group, a C_{1-2} alkoxy group, a C_{5-6} aryl group and a C_{3-6} cycloalkyl group, preferably, A_1 and A_2 independently represent a C_{1-6} alkylene group optionally substituted with one or more substituents selected from a C_{1-2} alkyl group, a C_{1-2} alkoxy group and a phenyl group, preferably A_1 and A_2 independently represent a C_{1-4} alkylene group optionally substituted with one or two substituents selected from a methyl group and a methoxy group, more preferably substituted with one or two methyl groups.

13. A compound according to any one of preceding claims , wherein X together with Y form the group -CH=CH- or $-CH_2-O-$, preferably, X together with Y form the group –CH=CH-.

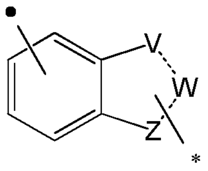
14. A compound according to any one of preceding claims, wherein L is selected from the group consisting a direct bond, -O-, $-NR^c-$, -S-, -S(O)-, $-SO_2-$, $-NR^c(CO)-$, $-(CO)NR^c-$, $-NR^c(CO)(CH_2)_qO-$, $-O(CH_2)_q(CO)NR^c-$, $-NR^c(CO)(CH_2)_qNR^c(CO)-$, $-O(CH_2)_qNR^c-$, $-NR^c(CH_2)_qO-$, $-NR^c(CO)NR^d-$, -C(O)-, -C(O)O-, -OC(O)-, $-S(O)_2NR^c-$, $-NR^cS(O)_2-$, $-NR^cS(O)_2NR^d-$, $-C(O)NR^cS(O)_2-$ and $-S(O)_2NR^cC(O)-$, wherein R^c and R^d are independently selected from a hydrogen atom and a linear or branched C_{1-4} alkyl group and q has a value of 0, 1, 2, 3 or 4, preferably, L is selected from the group consisting of direct bond, -O-, $-NR^c-$, $-NR^c(CO)-$, $-(CO)NR^c-$, $-NR^c(CO)(CH_2)_qO-$, $-O(CH_2)_q(CO)NR^c-$, $-NR^c(CO)(CH_2)_qNR^c(CO)-$, $-O(CH_2)_qNR^c-$, $-NR^c(CH_2)_qO-$, $-NR^c(CO)NR^d-$, -C(O)-, -C(O)O-, -OC(O)- wherein R^c and R^d independently are selected from a hydrogen atom and a methyl group, more preferably, L is selected from a direct bond, -O-, $-NR^c(CO)-$, $-(CO)NR^c-$, $-NR^c(CO)(CH_2)_qO-$, $-O(CH_2)_q(CO)NR^c-$ and -C(O)-, wherein R^c and R^d independently are selected from a hydrogen atom and a methyl group.

15. A compound according to claim 14, wherein L is selected from a direct bond, $-NR^c(CO)-$, $-(CO)NR^c-$,$-O(CH_2)_q(CO)NR^c-$ and -C(O)-, preferably a direct bond, $-NR^c(CO)-$ and $-(CO)NR^c-$, wherein R^c represents a hydrogen atom or a methyl group.

16. A compound according to any one of preceding claims, wherein G is selected from the group consisting of a direct bond, a C_{3-7} cycloalkyl group, a C_{5-14} mono- or bicyclic aryl group, a 3- to 14-membered saturated or unsaturated mono- or bicyclic heterocyclyl group having one or more heteroatoms selected from N, S and O, a 5- to 14-membered mono- or bicyclic heteroaryl group having one or more heteroatoms selected from N, S and O and a bicyclic ring system comprising two monocyclic ring systems which are linked between each other by a covalent bond or by a –O- group,

wherein said monocyclic ring system are independently selected from the group consisting of a C_{3-8} cycloalkyl group and a C_{5-6} aryl group, wherein the cyclic groups independently are optionally substituted with one or more substituents selected from a halogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a carboxy, group, a cyano group, a nitro group, a hydroxy group, an oxo group, a trifluoromethyl group and a trifluoromethoxy group, preferably G is selected from the group consisting of a direct bond, a C_{3-7} cycloalkyl group, a C_5-C_6 aryl group, a 8- to 10-membered saturated or unsaturated bicyclic heterocyclyl group having one or more heteroatoms selected from N, S and O, a 8- to 10-membered bicyclic heteroaryl group having one or more heteroatoms selected from N, S and O, wherein the cyclic groups independently are optionally substituted with one or more substituents selected from a halogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, a cyano group, a nitro group, a hydroxy group and an oxo group.

17. A compound according to claim 16, wherein, G is selected from the group consisting of a C_{3-7} cycloalkyl group, a C_5-C_6 aryl group, or a group of formula



Formula (Iwa)

wherein

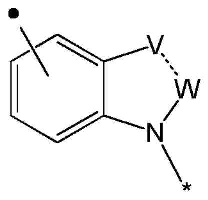
- V, W and Z are independently selected from a –N-, -NH-, -C-, -CH-, -S-, -O- and –C(O)-,

wherein the cyclic groups independently are optionally substituted with one or more substituents selected from a halogen atom, a C_{1-4} alkyl group and a C_{1-4} alkoxy group.

18. A compound according to claim 17, wherein W represents a –N-, -NH-, or a –C(O)- group, preferably W represents a –C(O)- group.

19. A compound according to claim 17, wherein V represents a -N-, -NH-, -S- or –O- group, preferably V is a –N-, -NH- or a –O- group, , more preferably, W represents a –C(O)- group and Z is a –N- or –NH- group.

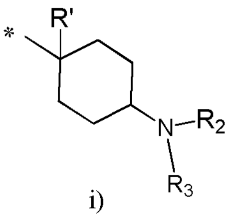
20. A compound according to claim 17 to 19, wherein G represents a phenylene group or a cylohexyl group or a group of formula



Formula (Iwb)

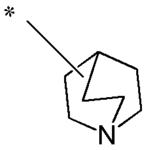
Wherein V represents a -N-, -NH- or a –O- group and W represents a –C(O)- group, and wherein the cyclic groups are independently optionally substituted with one or two substituents selected from a chlorine atom, methyl group and methoxy group.

21. A compound according to any one of preceding claims, wherein R_1 represents a group of formula:



i)

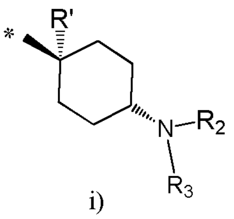
or



ii)

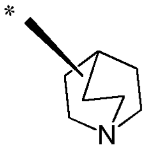
wherein R', R_2 and R_3 independently represent a hydrogen atom or a C_{1-2} alkyl group.

22. A compound according to claim 21, wherein R_1 represents a group of formula:



i)

or



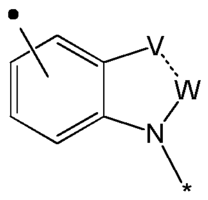
ii)

wherein R', R_2 and R_3 are as defined in claim 21, preferably, R', R_2 and R_3 independently represent a hydrogen atom or a methyl group, more preferably both R_2 and R_3 represent a hydrogen atom and R' represents a hydrogen atom or a methyl group.

23. A compound according to any one of preceding claims, wherein R is selected from the group consisting of a hydrogen atom, a halogen atom or a hydroxy group, preferably R represents a hydrogen atom or a hydroxy group, more preferably R represents a hydrogen.

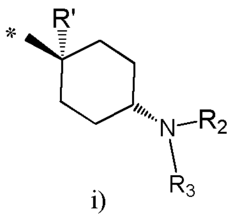
24. A compound according to any one of preceding claims, wherein n has a value of 1 or 2, preferably 1.

25. A compound according to any one of preceding claims, wherein A_1 and A_2 independently represent a C_{1-4} alkylene group optionally substituted with one or two methyl groups, X together with Y form the group –CH=CH-, L is selected from the group consisting of a direct bond, -NR^c(CO)- and -(CO)NR^c-, wherein R^c represents a hydrogen atom or a methyl group, G represents a phenylene group or a cyclohexyl group or a group of formula



Formula (Iwb)

Wherein V represents a –N-, -NH- or –O- group and W represents a –C(O) group, and wherein the cyclic groups are independently optionally substituted with one or two substituents selected from a chlorine atom, methyl group and methoxy group, and R_1 represents a group of formula:



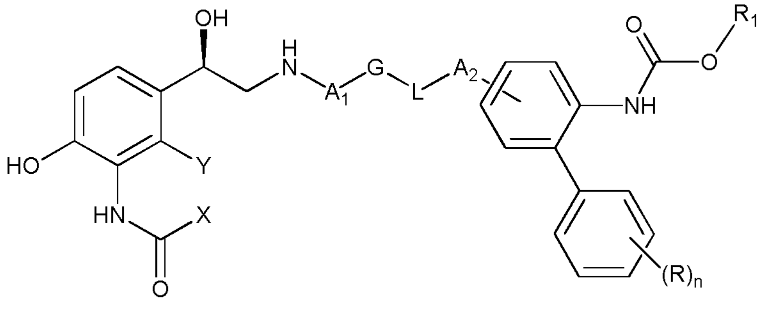
i)

or

ii)

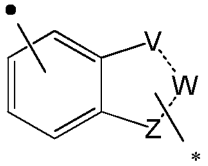
wherein both R_2 and R_3 represent a hydrogen atom and R' represents a hydrogen atom or a methyl group, R represents a hydrogen atom and n has a value of 1.

26. A compound according to claim 1, having the following formula (I):



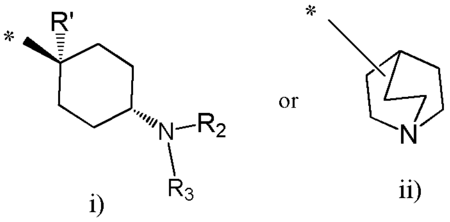
Formula (I)

Wherein, R represents a hydrogen atom and n has a value of 1, A_1 and A_2 independently represent a direct bond or a C_{1-6} alkylene group optionally substituted with a methyl group, X together with Y form the group –CH=CH- $-CH_2-CH_2-$ or $-CH_2-O-$, L is selected from the group consisting of a direct bond, -O-, $-NR^c(CO)O-$, $-O(CH_2)(CO)NR^c-$, $-NR^c(CO)-(CH_2)_4NR^c(CO)-$, $-(CH_2)_{(0-1)}NR^c(CO)-$, $-(CO)NR^c-$ and –NH(CO)NH-, wherein R^c represents a hydrogen atom or a methyl group, G represents a direct bond, a phenylene group, a pyridyl group, a cyclobutyl group, a cylohexyl group or a group of formula:



Formula (Iwa)

Wherein V and Z independently are selected from the group consisting of –N-, -NH-, -C-, -O- and –S-, and W represents a -N-, -NH-, -C-, or a –C(O)- group, and wherein the phenylene group, pyridyl group, cyclobutyl group, cylohexyl group and the group of formula (Iwa) are independently optionally substituted with one or two substituents selected from a chlorine atom, methyl group and methoxy group, R^1 represents a group of formula:



wherein both R_2 and R_3 are indenpendently selected from a hydrogen atom, a methyl group, a hexyl group and a propyl group substituted with a phenyl group and R' represents a hydrogen atom or a methyl group.

27. A compound according to any one of the preceding claims, which is one of:
    (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]propyl}biphenyl-2-yl)carbamate,
    (3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[4-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]butyl}biphenyl-2-yl)carbamate

trans-4-(methylamino)cyclohexyl (4-{3-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]propyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]propyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl]propyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-indol-1-yl]propyl}biphenyl-2-yl)carbamate,
(3*R*)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-({[(2*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2*H*)-yl]butyl}biphenyl-2-yl)carbamate,
trans-4-aminocyclohexyl (4-{3-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydro-quinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]propyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[3-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy]butyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy]butyl}biphenyl-2-yl)carbamate,
trans-4-aminocyclohexyl (4-{4-[4-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]butyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2,3,4-tetrahydroquinolin-5-yl)ethyl]amino}methyl)-1,3-benzoxazol-2-yl]butyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[3-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]propyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[({[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino}carbonyl)oxy]-propyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-indol-1-yl]butyl}biphenyl-2-yl)carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzothiazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[4-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]propyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1,3-benzoxazol-2-yl]butyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2H-1,2,3-benzotriazol-2-yl]butyl}biphenyl-2-yl)carbamate,
trans-4-aminocyclohexyl (4-{4-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (5-{4-[4-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenoxy]butyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (5-{4-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate,
trans-4-aminocyclohexyl [4-(4-{[4-({[(2*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]propyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-({[(2R)-2-hydroxy-2-(5-hydroxy-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-8-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate,
trans-4-aminocyclohexyl (4-{3-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]propyl}biphenyl-2-yl)carbamate,
trans-4-aminocyclohexyl (4-{4-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-indol-1-yl]butyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{4-[6-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl (4-{5-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]pentyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{3-[6-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]propyl}biphenyl-2-yl)carbamate,
(3R)-1-azabicyclo[2.2.2]oct-3-yl (4-{5-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]pentyl}biphenyl-2-yl)carbamate,
trans-4-aminocyclohexyl [4-(4-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,
trans-4-aminocyclohexyl {4-[(6-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}hexyl)oxy]biphenyl-2-yl}carbamate,
trans-4-aminocyclohexyl (5-{4-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate,
trans-4-aminocyclohexyl (4-{4-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-1,2,3-benzotriazol-1-yl]butyl}biphenyl-2-yl)carbamate,
trans-4-aminocyclohexyl [5-(4-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,
trans-4-aminocyclohexyl [4-(5-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-5-oxopentyl)biphenyl-2-yl]carbamate,
trans-4-aminocyclohexyl [4-(4-{[4-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}ethyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,
trans-4-aminocyclohexyl (4-{4-[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxy-2-oxo-1,3-benzoxazol-3(2H)-yl]butyl}biphenyl-2-yl)carbamate,
trans-4-[methyl(3-phenylpropyl)amino]cyclohexyl [4-(4-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl [4-(3-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-3-oxopropyl)biphenyl-2-yl]carbamate,

(3R)-1-azabicyclo[2.2.2]oct-3-yl [4-(4-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl (4-{4-[[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl](methyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl [4-(4-{[trans-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)cyclohexyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl [4-(4-{[4-(2-{[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}propyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl (4-{4-[(5-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-5-oxopentyl)(methyl)amino]-4-oxobutyl}biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl (4-{3-[{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenoxy]acetyl}(methyl)amino]-propyl}biphenyl-2-yl)carbamate,

trans-4-amino-1-methylcyclohexyl [4-(3-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino} methyl)-5-methoxyphenyl]amino}-3-oxopropyl)biphenyl-2-yl]carbamate,

trans-4-amino-1-methylcyclohexyl [4-(3-{[trans-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)cyclohexyl]amino}-3-oxopropyl)biphenyl-2-yl]carbamate,

1-azabicyclo[2.2.2]oct-4-yl [4-(3-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino}-3-oxopropyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl (4-{2-[{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5methoxyphenoxy]acetyl}(methyl)amino]ethyl}biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl (4-{2-[({[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino}carbonyl)oxy]ethyl}biphenyl-2-yl)carbamate, trans-4-aminocyclohexyl (4-{4-[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy]butyl}biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl [4-(4-{[trans-3-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)cyclobutyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl [4-(3-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxybenzoyl]amino}propyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl [4-(3-{4-[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenoxy]phenyl}propyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl [4-(4-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)benzyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl [4-(4-{[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)pyridin-2-yl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

trans-4-[hexyl(methyl)amino]cyclohexyl [4-(4-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

trans-4-aminocyclohexyl [4-(4-{[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)pyridin-3-yl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

Trans-4-aminocyclohexyl (4-(3-(Trans-4-((((2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)cyclohexanecarboxamido)propyl)-biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl (4-{3-[({[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino} carbonyl)amino] propyl}biphenyl-2-yl)carbamate,

trans-4-aminocyclohexyl [4-(4-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxybenzoyl]amino}butyl)biphenyl-2-yl] carbamate,

1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)phenyl]amino}-4-oxobutyl)biphenyl-2-yl]Carbamate,

trans-4-aminocyclohexyl (4-{3-[({[trans-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)cyclohexyl]oxy}acetyl)(methyl)amino] propyl}biphenyl-2-yl)carbamate,
1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate
trans-4-aminocyclohexyl (4-{4-[5-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-1H-benzimidazol-1-yl]butyl}biphenyl-2-yl)carbamate,
trans-4-amino-1-methylcyclohexyl [4-(4-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino} methyl)-5-methoxyphenyl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,
1-azabicyclo[2.2.2]oct-4-yl (4-{3-[{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxyphenoxy]acetyl}(methyl)amino propyl}biphenyl-2-yl)carbamate,
1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[2-chloro-4-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)-5-methoxybenzoyl]amino}butyl)biphenyl-2-yl]carbamate and
1-azabicyclo[2.2.2]oct-4-yl [4-(4-{[6-({[(2R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl]amino}methyl)pyridin-3-yl]amino}-4-oxobutyl)biphenyl-2-yl]carbamate,

and pharmaceutically acceptable salts and deuterated derivates thereof.

28. A compound according to any one of claims 1 to 27 for use in the treatment of a human or animal body by therapy.

29. A compound according to any one of claims 1 to 27 for use in the treatment of a pathological condition or disease associated with β2 adrenergic receptor agonist and M3 muscarinic receptor antagonist activities, which condition or disease is preferably selected from pulmonary diseases, pre-labor, glaucoma, neurological disorders, cardiac disorders, inflammation and gastrointestinal disorders, and is more preferably asthma and or chronic obstructive pulmonary disease.

30. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 27 in association with a pharmaceutically acceptable diluent or carrier.

31. A method for treating a subject afflicted with a pathological condition or disease as defined in claim 30, which comprises administering to said subject an effective amount of a compound as defined in any one of claims 1 to 27.

32. A combination product comprising (i) a compound according to any one of claims 1 to 27; and (ii) another compound selected from a corticosteroid and a PDE4 inhibitor, for simultaneous, separate or sequential use in the treatment of the human or animal body.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/076973

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K47/48 A61P11/08 A61K31/13 A61K31/439 A61K31/4184
C07D453/02 C07D235/24 C07C15/50 C07C271/38

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)

A61K A61P C07D C07C

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 practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2012/046467 A1 (MITSUYAMA ETSUKO [JP] ET AL) 23 February 2012 (2012-02-23)	1-26, 28-32
Y	paragraph [0081] column 13; compounds 5,6 column 13, chemical formula 13 paragraph [0258] claims 1,17 -----	1-26, 28-32

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☒ 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 application or patent 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 3 March 2014	Date of mailing of the international search report 11/03/2014
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Villard, Anne-Laure

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International application No
PCT/EP2013/076973

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	RAY NICHOLAS C ET AL: "Muscarinic antagonist-beta-adrenergic agonist dual pharmacology molecules as bronchodilators: a patent review", EXPERT OPINION ON THERAPEUTIC PATENTS, INFORMA HEALTHCARE, GB, vol. 19, no. 1, 1 January 2009 (2009-01-01), pages 1-12, XP002695097, ISSN: 1354-3776, DOI: 10.1517/13543770802630331 pages 2-5, paragraph 2.1.1 figure 1; compounds 1-3,6,8 -----	1-26, 28-32

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2013/076973

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