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DESCRIPTION

FIELD OF THE INVENTION

[0001] The present invention relates to compounds acting both as muscarinic receptor antagonists and beta2 adrenergic receptor agonists, to processes for their preparation, to compositions comprising them, to therapeutic uses and combinations with other pharmaceutical active ingredients.

BACKGROUND OF THE INVENTION

[0002] Pulmonary disorders, such as asthma and chronic obstructive pulmonary disease (COPD), are commonly treated with bronchodilators. A known class of bronchodilators consists of beta-2 adrenergic receptor agonists, such as salbutamol, fenoterol, formoterol and salmeterol. These compounds are generally administered by inhalation.

[0003] Another known class of bronchodilators consists of muscarinic receptor antagonists (anticholinergic compounds), such as ipratropium and tiotropium. These compounds are also typically administered by inhalation.

[0004] Inhaled formulations of both beta-2 agonists and muscarinic receptor antagonists are valuable agents in the treatment of asthma and COPD, with both classes of agents providing symptomatic relief due to their ability to relax constricted airways. Observations that the bronchodilator effects of the two classes of agents were additive, prompted studies with combinations of the two agents. In 1975, it was shown that that beneficial effects could be achieved by combining two ingredients such as fenoterol and ipratropium bromide in a single aerosol. This prompted the development of fixed dose combinations of ipratropium bromide firstly with fenoterol (Berodual, introduced in 1980), and then with salbutamol (Combivent, introduced in 1994).

[0005] More recently the availability of both long-acting muscarinic antagonists and long-acting beta-2 agonists prompted to the development of combinations of these agents. For example, WO 00/69468 and US 2009/181935 disclose medicament compositions containing a muscarinic receptor antagonist, such as tiotropium bromide, and beta-2 adrenergic receptor agonists, such as formoterol fumarate or salmeterol, and WO 2005/115467 discloses a combination which comprises a beta-2 agonist and an antagonist of M3 muscarinic receptors which is a salt of 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo [2.2.2] octane.

[0006] An alternative approach to the development of fixed dose combinations is the identification of molecules that combine both activities of muscarinic antagonism and beta-2 agonism. In fact compounds possessing both beta-2 adrenergic receptor agonist and muscarinic receptor antagonist activity are highly desirable since such bifunctional compounds would provide bronchodilation through two independent mechanisms of action while having a single molecule pharmacokinetics.

[0007] Such kind of compounds was described in some patent applications, such as WO 2004/074246, WO 2004/074812, WO 2005/051946, WO 2006/023457, WO 2006/023460, WO 2010/123766, WO 2011/048409 and co-pending patent application PCT/EP2012/060795 as well as in Adam D. Hughes et al., Bioorganic & Medicinal Chemistry Letters Vol.21, no.5, 1 March 2011.

[0008] It has now been found that some particular carbamate derivatives, besides possessing both beta-2 adrenergic receptor agonist and muscarinic receptor antagonist activity, possess elevated affinity for the M3 muscarinic receptors and long lasting bronchodilating activity.

SUMMARY OF THE INVENTION

[0009] The present invention relates to compounds acting both as muscarinic receptor antagonists and beta2

adrenergic receptor agonists, to processes for their preparation, to compositions comprising them, to therapeutic uses and combinations with other pharmaceutical active ingredients among which are, for instance, those currently used in the treatment of respiratory disorders, among which beta2-agonists, antimuscarinic agents, mitogen-activated protein kinases (P38 MAP kinase) inhibitors, nuclear factor kappa-B kinase subunit beta (IKK2) inhibitors, human neutrophil elastase (HNE) inhibitors, phosphodiesterase 4 (PDE4) inhibitors, leukotriene modulators, non-steroidal anti-inflammatory agents (NSAIDs), antitussive agents, mucus regulators, mucolytics, expectorant/mucokinetic modulators, peptide mucolytics, antibiotics, inhibitors of JAK, SYK inhibitors, inhibitors of PI3Kdelta or PI3Kgamma, corticosteroids and M3-antagonists/PDE4-inhibitors (MAPI).

DETAILED DESCRIPTION OF THE INVENTION

[0010] In particular, the invention is directed to compounds as recited below and pharmaceutically acceptable salts or solvates thereof.

[0011] Whenever basic amino or quaternary ammonium groups are present in the compounds of the invention, physiological acceptable anions, selected among chloride, bromide, iodide, trifluoroacetate, formate, sulfate, phosphate, methane sulfonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate, p-toluenesulfonate, pamoate and naphthalene disulfonate may be present. Likewise, in the presence of acidic groups such as COOH groups, corresponding physiological cation salts may be present as well, for instance including alkaline or alkaline earth metal ions.

[0012] The present invention also provides pharmaceutical compositions of compounds of the invention alone or in combination with or in admixture with one or more pharmaceutically acceptable carriers and/or excipients.

[0013] The present invention also provides the use of compounds of the invention for preparing a medicament.

[0014] In a further aspect, the invention provides compounds of the invention for use in the prevention and/or treatment of any broncho-obstructive or inflammatory disease, preferably asthma or chronic bronchitis or chronic obstructive pulmonary disease (COPD).

[0015] In a further aspect, the invention provides the use of compounds of the invention for the manufacture of a medicament for the prevention and/or treatment of any broncho-obstructive or inflammatory disease, preferably asthma or chronic bronchitis or chronic obstructive pulmonary disease (COPD).

[0016] The present invention also provides pharmaceutical compositions suitable for administration by inhalation.

[0017] Inhalable preparations include inhalable powders, propellant-containing metering aerosols or propellant-free inhalable formulations.

[0018] The invention is also directed to a device which may be a single- or multi-dose dry powder inhaler, a metered dose inhaler and a soft mist nebulizer comprising the compounds of the invention.

[0019] The invention is also directed to a kit comprising the pharmaceutical compositions of compounds of the invention alone or in combination with or in admixture with one or more pharmaceutically acceptable carriers and/or excipients and a device which may be a single- or multi-dose dry powder inhaler, a metered dose inhaler and a soft mist nebulizer comprising the compounds of the invention.

[0020] According to specific embodiments, the present invention provides the compounds reported below, and pharmaceutically acceptable salts or solvates thereof:

Cpd	Chemical Name
1	2-(4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-2-methylphenoxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate

Cpd	Chemical Name
2	2-(4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)phenoxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
3	2-(2-Chloro-4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)phenoxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
4	2-(4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-2-methoxyphenoxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
5	2-(2-Bromo-4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)phenoxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
6	2-(2-Chloro-3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)phenoxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
7	2-((4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)5aphthalene-1-yl)oxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
8	2-(3-Chloro-4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)phenoxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
9	2-(3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)phenoxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
10	2-(4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-2,6-dimethylphenoxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
11	2-(2-Chloro-4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-6-methoxyphenoxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
12	2-(4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-3-methoxyphenoxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
13	2-(2-Bromo-4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-5-methoxyphenoxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
14	2-(2,6-Dichloro-4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)phenoxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
15	2-(2-Fluoro-4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)phenoxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
16	2-(4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-2,6-dimethoxyphenoxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
17	2-(2-Chloro-4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-5-methoxyphenoxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
18	4-(2-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzyl 3-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
19	2-Fluoro-4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
	4-(2-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)-3-

Cpd	Chemical Name
20	methoxybenzyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
21	3-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzyl 3-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
22	3-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)benzyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
23	(6-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)pyridin-3-yl)methyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
24	(5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)furan-2-yl)methyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
25	2-Fluoro-4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)benzyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
26	5-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-2-methoxybenzyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
27	(4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)furan-2-yl)methyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
28	(5-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)thiophen-2-yl)methyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
29	(5-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)thiophen-3-yl)methyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
30	3-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)benzyl 3-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
31	4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-3-methoxybenzyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
32	3-(4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)phenyl)propyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
33	4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)phenethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
34	(1-(3-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)propyl)-1H-pyrazol-4-yl)methyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
35	2-(4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-1H-pyrazol-1-yl)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
36	4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 1-methyl-5-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)-1H-pyrazole-3-carboxylate
37	4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)thiophene-2-carboxylate
38	4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 5-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)nicotinate
39	(R)-Quinuclidin-3-yl ((S)-3-((3-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)carbamoyl)-1-methyl-1H-pyrazol-5-yl)methoxy)phenyl)(phenyl)methyl)carbamate

Cpd	Chemical Name
40	(R)-Quinuclidin-3-yl ((S)-(3-((5-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)carbamoyl)furan-2-yl)methoxy)phenyl)(phenyl)methyl)carbamate
41	(R)-Quinuclidin-3-yl((S)-(3-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)carbamoyl)oxazol-2-yl)methoxy)phenyl)(phenyl)methyl)carbamate
42	(R)-3-((S)-(3-((5-((4-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)butoxy)carbonyl)furan-2-yl)methoxy)phenyl)(phenyl)methylcarbamoyloxy)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-1-azoniabicyclo[2.2.2]octane chloride hydrochloride

[0021] The present invention also provides pharmaceutical compositions comprising a compound of the invention, either as such or as pharmaceutically acceptable salt, and one or more pharmaceutically acceptable carriers and/or excipients.

[0022] The compounds of the invention may be administered as the sole active agent or in combination with other pharmaceutical active ingredients including those currently used in the treatment of respiratory disorders, e.g. beta2-agonists, antimuscarinic agents, mitogen-activated protein kinases (P38 MAP kinase) inhibitors, nuclear factor kappa-B kinase subunit beta (IKK2) inhibitors, human neutrophil elastase (HNE) inhibitors, phosphodiesterase 4 (PDE4) inhibitors, leukotriene modulators, non-steroidal anti-inflammatory agents (NSAIDs), antitussive agents, mucus regulators, mucolytics, expectorant/mucokinetic modulators, peptide mucolytics, antibiotics, inhibitors of JAK, SYK inhibitors, inhibitors of PI3Kdelta or PI3Kgamma, corticosteroids and M3-antagonists/PDE4-inhibitors (MAPI).

[0023] The present invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, with a β 2-agonist selected from the group consisting of carmoterol, GSK-642444, indacaterol, milveterol, arformoterol, arformoterol tartrate, formoterol, formoterol fumarate, salmeterol, salmeterol xinafoate, salbutamol, albuterol, levalbuterol, terbutaline, indacaterol (QAB-149), AZD-3199, BI-1744-CL, LAS-100977, GSK159797, GSK59790, GSK159802, GSK642444, GSK678007, GSK96108, bambuterol, isoproterenol, procaterol, clenbuterol, reproterol, fenoterol, bitolterol, brodxatelor and ASF-1020 and salts thereof.

[0024] The present invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, with an antimuscarinic agent selected from the group consisting of acridinium, tiotropium, tiotropium bromide (Spiriva®), ipratropium, ipratropium bromide, trospium, glycopyrrolate, NVA237, LAS34273, GSK656398, GSK233705, GSK57319, LAS35201, QAT370 and oxitropium salts.

[0025] The present invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, with a PDE4 inhibitor selected from the group consisting of AN-2728, AN-2898, CBS-3595, apremilast, ELB-353, KF-66490, K-34, LAS-37779, IBFB-211913, AWD-12-281, cipamfylline, cilomilast, roflumilast, BAY19-8004 and SCH-351591, AN-6415, indus-82010, TPI-PD3, ELB-353, CC-11050, GSK-256066, oglemilast, OX-914, tetomilast, MEM-1414 and RPL-554.

[0026] The present invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, with a P38 MAP kinase inhibitor selected from the group consisting of semapimod, talmapimod, pirfenidone, PH-797804, GSK-725, GSK856553, GSK681323, minokine and losmapimod and salts thereof.

[0027] In a preferred embodiment, the present invention provides combinations of a compound of the invention with an IKK2 inhibitor.

[0028] The invention also provides combinations of a compound of the invention with a HNE inhibitor selected from the group consisting of AAT, ADC-7828, aeriva, TAPI, AE-3763, KRP-109, AX-9657, POL-6014, AER-002, AGTC-0106, respriva, AZD-9668, zemaira, AAT IV, PGX-100, elafin, SPHD-400, prolactin C and prolactin inhaled.

[0029] The invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, with a leukotriene modulator selected from the group consisting of montelukast,

zafirlukast and pranlukast.

[0030] The invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, with a NSAID selected from the group consisting of ibuprofen and ketoprofen.

[0031] The invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, with an antitussive agent, selected from the group consisting of codeine and dextramorphane.

[0032] The invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, with a mucolytic, selected from the group consisting of N acetyl cysteine and fudostein.

[0033] The invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, with an expectorant/mucokinetic modulator, selected from the group consisting of ambroxol, hypertonic solutions (e.g. saline or mannitol) and surfactant.

[0034] The invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, with a peptide mucolytic, selected from the group consisting of recombinant human deoxyribonuclease I (dornase-alfa and rhDNase) and helicidin.

[0035] The invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, with an antibiotic, selected from the group consisting of azithromycin, tobramycin and aztreonam.

[0036] The invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, with a mucus regulator selected from the group consisting of INS-37217, diquafosol, sibenadet, CS-003, talnetant, DNK-333, MSI-1956 and gefitinib.

[0037] The invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, with an inhibitor of JAK, selected from the group consisting of CP-690550 and GLPG0634.

[0038] The invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, with a SYK inhibitor selected from the group consisting of R406, R343 and PRT062607.

[0039] The invention also provides combinations of a compound of the invention with a corticosteroid selected from the group consisting of dexamethasone, fluticasone, fluticasone furoate, fluticasone propionate, prednisolone, betamethasone, budesonide, mometasone, mometasone furoate, triamcinolone acetate, ciclesonide, TPI-1020, beclomethasone, beclomethasone dipropionate, prednisone, deflazacort, hydrocortisone, QAE-397 and flunisolide.

[0040] The compounds of the invention can be prepared from readily available starting materials using the following general methods and procedures or by using other information readily available to those of ordinary skill in the art. Although a particular embodiment of the present invention may be shown or described herein, those skilled in the art will recognize that all embodiments or aspects of the present invention can be prepared using the methods described herein or by using other methods, reagents and starting materials known to those skilled in the art. It will also 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. While the optimum reaction conditions may vary depending on the particular reactants or solvent used, such conditions can be readily determined by one skilled in the art by routine optimisation procedures.

[0041] Compounds of the invention may be prepared according to the Examples

[0042] The LCMS methods A, B, C and D used for the characterization of the compounds of the present invention,

are described in the following:

LCMS/HPLC methods

Method A (10cm_ESCI_FORMIC)

HPLC Setup

[0043]

Solvents: Acetonitrile (Far UV grade) with 0.1% (V/V) formic acid Water (High purity via PureLab Option unit) with 0.1% formic acid

Column: - Phenomenex Luna 5 μ C18 (2), 100 x 4.6mm. (Plus guard cartridge)

Flow Rate: - 2ml/min

Gradient: - A: Water / formic B: MeCN/formic

Time	A%	B%
0.00	95	5
3.50	5	95
5.50	5	95
5.60	95	5
6.50	95	5

Typical Injections 2-7 μ l (concentration ~ 0.2 -1mg/ml).

UV detection via HP or Waters DAD

Start Range (nm) 210 End Range (nm) 400 Range interval (nm)4.0 Other wavelength traces are extracted from the DAD data.

Optional ELS detection using Polymer Labs ELS-1000.

MS detection: Micromass ZQ, single quadrapole LC-MS or Quattro Micro LC-MS-MS.

Flow splitter gives approximately 300 μ l/min to mass spec

Scan range for MS Data (m/z)

Start (m/z) 100

End (m/z) 650 or 1500 when required

With +ve / -ve switching

Ionisation is routinely ESCI an option which gives both ESI and APCI data from a single run.

[0044] Typical ESI voltages and temperatures are:

Source 120-150C 3.5KV capillary 25V cone

[0045] Typical APCI voltages and temperatures are:

Source 140-160C 17 μ A corona 25V cone

Method B (HPLC Conditions - 15cm_Formic_Ascentis_HPLC_CH3CN) HPLC Setup

[0046]

Solvents: - Acetonitrile (Far UV grade) with 0.1% (V/V) formic acid
 Water (High purity via PureLab Ultra unit) with 0.1% formic acid

Column: - Supelco, Ascentis® Express C18 or Hichrom Halo C18, 2.7µm C18, 150 x 4.6mm.

Flow Rate: - 1ml/min

Gradient: - A: Water / formic B: MeCN/formic

Time	A%	B%
0.00	96	4
3.00	96	4
9.00	0	100
13.6	0	100
13.7	96	4
15	96	4

Typical Injections 0.2-10µl

Maximum pressure setting 400 bar.

Instrument: Agilent 1100, Binary Pump, Agilent Sampler and Agilent DAD detector

Diode array detection: (300nm, Band Width 200nm; Ref. 450nm, Band Width 100nm)

Method C (HPLC Conditions - 10cm_Formic_ACE-AR_HPLC_CH3CN)**HPLC Setup****[0047]**

Solvents: - Acetonitrile (Far UV grade) with 0.1% (V/V) formic acid
 Water (High purity via PureLab Ultra unit) with 0.1% formic acid

Column: - Hichrom ACE 3 C18-AR mixed mode column 100x4.6mm

Flow Rate: - 1ml/min

Gradient: - A: Water / formic B: MeCN/formic

Time	A%	B%
0.00	98	2
3.00	98	2
12.00	0	100
15.4	0	100
15.5	98	2
17	98	2

Typical Injections 0.2-10µl

Maximum pressure setting 400 bar.

Instrument: Agilent 1100, Binary Pump, Agilent Sampler and Agilent DAD detector

Diode array detection: (300nm, Band Width 200nm; Ref. 450nm, Band Width 100nm)

Method D (HPLC Conditions - 25cm_Acidic_Prodigy_HPLC)

HPLC Setup

[0048]

Solvents: - Acetonitrile (Far UV grade) with 0.1% formic acid

Water (High purity via PureLab Option unit) with 0.1% formic acid

Column: - Phenomenex Prodigy 5 μ ODS 3, 250 x 4.6mm.

Flow Rate: - 1ml/min

Gradient: - A: Water / formic B: MeCN/formic

Time	A%	B%
0.00	95.5	4.5
1.0	95.5	4.5
22	0	100
23	0	100
25	95.5	4.5
30	95.5	4.5

Typical Injections 2-7 μ l

Instrument: Agilent 1100, Binary Pump, Agilent Sampler and Agilent DAD detector

[0049] The invention also provides pharmaceutical compositions of compounds of the invention in admixture with one or more pharmaceutically acceptable carriers, for example those described in Remington's Pharmaceutical Sciences Handbook, XVII Ed., Mack Pub., N.Y., U.S.A.

[0050] Administration of the compounds of the present invention may be accomplished according to patient needs, for example, orally, nasally, parenterally (subcutaneously, intravenously, intramuscularly, intrasternally and by infusion), by inhalation, rectally, vaginally, topically, locally, transdermally, and by ocular administration.

[0051] Various solid oral dosage forms can be used for administering compounds of the invention including such solid forms as tablets, gelcaps, capsules, caplets, granules, lozenges and bulk powders. The compounds of the present invention can be administered alone or combined with various pharmaceutically acceptable carriers, diluents (such as sucrose, mannitol, lactose, starches) and known excipients, including suspending agents, solubilizers, buffering agents, binders, disintegrants, preservatives, colorants, flavorants, lubricants and the like. Time release capsules, tablets and gels are also advantageous in administering the compounds of the present invention.

[0052] Various liquid oral dosage forms can also be used for administering compounds of the invention, including aqueous and non-aqueous solutions, emulsions, suspensions, syrups, and elixirs. Such dosage forms can also contain suitable known inert diluents such as water and suitable known excipients such as preservatives, wetting agents, sweeteners, flavorants, as well as agents for emulsifying and/or suspending the compounds of the invention.

The compounds of the present invention may be injected, for example, intravenously, in the form of an isotonic sterile solution. Other preparations are also possible.

[0053] Suppositories for rectal administration of the compounds of the invention can be prepared by mixing the compound with a suitable excipient such as cocoa butter, salicylates and polyethylene glycols.

[0054] Formulations for vaginal administration can be in the form of cream, gel, paste, foam, or spray formula containing, in addition to the active ingredient, such as suitable carriers, are also known.

[0055] For topical administration the pharmaceutical composition can be in the form of creams, ointments, liniments, lotions, emulsions, suspensions, gels, solutions, pastes, powders, sprays, and drops suitable for administration to the skin, eye, ear or nose. Topical administration may also involve transdermal administration via means such as transdermal patches.

[0056] For the treatment of the diseases of the respiratory tract, the compounds according to the invention are preferably administered by inhalation.

[0057] Inhalable preparations include inhalable powders, propellant-containing metering aerosols or propellant-free inhalable formulations.

[0058] For administration as a dry powder, single- or multi-dose inhalers known from the prior art may be utilized. In that case the powder may be filled in gelatine, plastic or other capsules, cartridges or blister packs or in a reservoir.

[0059] A diluent or carrier, generally non-toxic and chemically inert to the compounds of the invention, e.g. lactose or any other additive suitable for improving the respirable fraction may be added to the powdered compounds of the invention.

[0060] Inhalation aerosols containing propellant gas such as hydrofluoroalkanes may contain the compounds of the invention either in solution or in dispersed form. The propellant-driven formulations may also contain other ingredients such as co-solvents, stabilizers and optionally other excipients.

[0061] The propellant-free inhalable formulations comprising the compounds of the invention may be in form of solutions or suspensions in an aqueous, alcoholic or hydroalcoholic medium and they may be delivered by jet or ultrasonic nebulizers known from the prior art or by soft-mist nebulizers such as Respimat®.

[0062] The compounds of the invention may be administered as the sole active agent or in combination with other pharmaceutical active ingredients including those currently used in the treatment of respiratory disorders, among which beta2-agonists, antimuscarinic agents, mitogen-activated protein kinases (P38 MAP kinase) inhibitors, nuclear factor kappa-B kinase subunit beta (IKK2) inhibitors, human neutrophil elastase (HNE) inhibitors, phosphodiesterase 4 (PDE4) inhibitors, leukotriene modulators, non-steroidal anti-inflammatory agents (NSAIDs), antitussive agents, mucus regulators, mucolytics, expectorant/mucokinetic modulators, peptide mucolytics, antibiotics, inhibitors of JAK, SYK inhibitors, inhibitors of PI3Kdelta or PI3Kgamma, corticosteroids and M3-antagonists/PDE4-inhibitors (MAPI).

[0063] The dosages of the compounds of the invention depend upon a variety of factors including the particular disease to be treated, the severity of the symptoms, the route of administration, the frequency of the dosage interval, the particular compound utilized, the efficacy, toxicology profile, and pharmacokinetic profile of the compound.

[0064] Advantageously, the compounds of the invention can be administered for example, at a dosage comprised between 0.001 and 1000 mg/day, preferably between 0.1 and 500 mg/day.

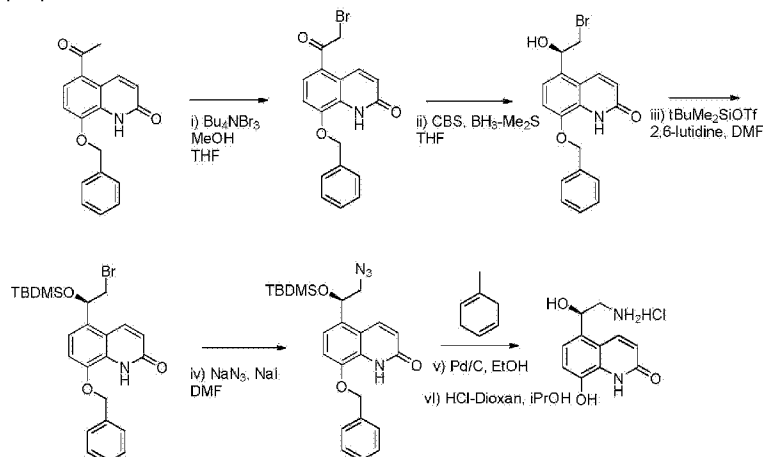
[0065] When the compounds of the invention are administered by inhalation route, they are preferably given at a dosage comprised between 0.001 and 500 mg/day, preferably between 0.1 and 200 mg/day.

[0066] The compounds of the invention may be administered for the prevention and/or treatment of broncho-obstructive or inflammatory diseases, such as asthma, chronic bronchitis, chronic obstructive pulmonary disease

(COPD), bronchial hyperreactivity, cough, emphysema or rhinitis; urological disorders such as urinary incontinence, pollakiuria, cystospasm, chronic cystitis and overactive bladder (OAB); gastrointestinal disorders such as bowel syndrome, spastic colitis, diverticulitis, peptic ulceration, gastrointestinal motility or gastric acid secretion; dry mouth; mydriasis, tachycardia; ophthalmic interventions cardiovascular disorders such as vagally induced sinus bradycardia.

[0067] The present invention will now be further described by way of the following examples.

[0068] The intermediate compounds for the synthesis of final compounds of the invention were obtained through the preparations herebelow described.



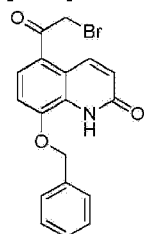
Preparation of (R)-5-(2-amino-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one hydrochloride

[0069]



Step 1; 8-(Benzyloxy)-5-(2-bromoacetyl)quinolin-2(1H)-one

[0070]



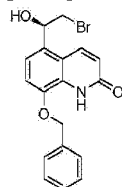
[0071] A suspension of 5-acetyl-8-(benzyloxy)quinolin-2(1H)-one (19.4 g, 66.4 mmol) in anhydrous THF (240 mL) and anhydrous methanol (165 mL) was added with a solution of *tetra*-n-butylammonium tribromide (Bu_4NBr_3) (54.5 g, 113.0 mmol) in anhydrous THF (130 mL) dropwise over 1.5 hours. The resulting solution was stirred at RT overnight before concentrating under reduced pressure without heating. The residue was re-dissolved in methanol (200 mL). Saturated aqueous ammonium chloride solution (390 mL) was added with ice-cooling. The resulting suspension was filtered and the solid washed with water and air-dried under vacuum. The solid was suspended in DCM and methanol

(1:1 v/v, 100 mL) for 90 minutes. The solid was collected by filtration, washed with DCM and air-dried to afford the title compound (18.0 g, 73%).

¹H NMR(400 MHz, DMSO-d₆): δ 11.07 (s, 1 H); 8.51 (d, *J* = 10.0 Hz, 1 H); 7.94-7.83 (m, 1 H); 7.60 (d, *J* = 7.5 Hz, 2 H); 7.44-7.27 (m, 4 H); 6.79-6.65 (m, 1 H); 5.53-5.39 (s, 2 H); 4.93 (s, 2 H)

Step 2; (*R*)-8-(Benzyloxy)-5-(2-bromo-1-hydroxyethyl)quinolin-2(1H)-one

[0072]

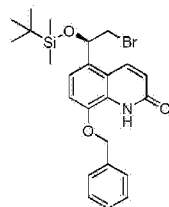


[0073] **8-(Benzyloxy)-5-(2-bromoacetyl)quinolin-2(1H)-one** (26.0 g, 69.9 mmol) and (*R*)-3,3-diphenyl-1-methyltetrahydro-3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole (21.3 g, 76.8 mmol) were azeotroped with toluene (× 3) then suspended in anhydrous THF (400 mL) under an atmosphere of nitrogen. The suspension was cooled to -20 °C (external temperature) and borane dimethyl sulfide (BH₃-Me₂S) complex solution (45.4 mL, 90.8 mmol, 2.0 M solution in THF) was added by syringe pump over 3 hours. After complete addition the reaction mixture was stirred for one hour before quenching with methanol (25 mL). The reaction was warmed to RT over 20 minutes. The mixture was concentrated under reduced pressure and the residue was suspended in aqueous hydrochloric acid (500 mL, 1 M solution) and stirred at RT for 18 hours. After this time the solid was collected by filtration and washed with water (3 × 100 mL). The solid was partially dissolved in ethyl acetate and refluxed for 2 hours. The remaining solid was removed by hot filtration and the filtrate was evaporated to afford the title compound. The solid collected from the hot ethyl acetate was again partially dissolved in ethyl acetate and refluxed for 2 hours then filtered to give filtrate containing pure product. This process was repeated four more times. The combined solid was recrystallised from ethyl acetate and petroleum ether to afford the title compound (20.0 g, 76%).

¹H NMR (400 MHz, DMSO-d₆): δ 10.68 (s, 1 H); 8.19 (d, *J* = 9.9 Hz, 1 H); 7.58 (d, *J* = 7.5 Hz, 2 H); 7.41-7.36 (m, 2 H); 7.34-7.29 (m, 1 H); 7.23-7.19 (m, 2 H); 6.57 (d, *J* = 9.8 Hz, 1 H); 5.94 (d, *J* = 4.7 Hz, 1 H); 5.31 (s, 2 H); 5.25-5.19 (m, 1 H); 3.71-3.58 (m, 2 H).

Step 3; (*R*)-8-(Benzyloxy)-5-(2-bromo-1-((*tert*-butyldimethylsilyl)oxy)ethyl)quinolin-2(1H)-one

[0074]



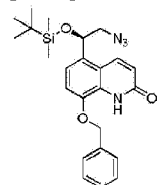
[0075] 2,6-Lutidine (6.9 mL, 59.5 mmol) was added to a solution of (*R*)-8-(benzyloxy)-5-(2-bromo-1-hydroxyethyl)quinolin-2(1H)-one (10.1 g, 27.0 mmol) in DCM (100 mL) at 0 °C. The reaction mixture was stirred for 5 minutes then *tert*-butyldimethylsilyl trifluoromethanesulfonate (tBuMe₂SiOTf) (13.0 mL, 56.8 mmol) was added dropwise over 15 minutes. The mixture was stirred at 0°C for 30 minutes, followed by RT overnight. After this time the reaction was quenched with saturated aqueous sodium bicarbonate solution and extracted with DCM (× 3). The combined organic extracts were dried (magnesium sulfate), filtered and concentrated under reduced pressure. *iso*-hexane (500 mL) was added to the crude material and the resulting solid collected by filtration. The solid was

recrystallised from ethyl acetate and petroleum ether (40 : 60) to afford the title compound (11.3 g, 85%).

¹H NMR (400 MHz, CDCl₃): δ 9.19 (s, 1 H); 8.23 (dd, *J* = 9.9, 4.4 Hz, 1 H); 7.43 (d, *J* = 4.6 Hz, 5 H); 7.17 (dd, *J* = 8.3, 4.5 Hz, 1 H); 7.03 (dd, *J* = 8.2, 4.4 Hz, 1 H); 6.71 (dd, *J* = 9.9, 3.7 Hz, 1 H); 5.18 (d, *J* = 4.5 Hz, 3 H); 3.63-3.56 (m, 1 H); 3.49 (dd, *J* = 10.4, 4.8 Hz, 1 H); 0.88 (t, *J* = 4.4 Hz, 9 H); 0.14 (d, *J* = 4.4 Hz, 3 H); - 0.11 (d, *J* = 4.4 Hz, 3 H).

Step 4: (*R*)-5-(2-Azido-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-8-(benzyloxy)quinolin-2(1H)-one

[0076]

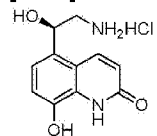


[0077] (*R*)-8-(Benzyloxy)-5-(2-bromo-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-quinolin-2(1H)-one (10.0 g, 20.5 mmol) was dissolved in dimethyl formamide (180 mL) and water (20 mL). Sodium iodide (3.39 g, 22.6 mmol) and sodium azide (1.47 g, 22.6 mmol) were added sequentially. The reaction mixture was stirred at RT until all the solid was in solution. The solution was heated at 80 °C for 40 hours then cooled to RT and diluted with ethyl acetate (300 mL). The mixture was washed with water, brine (x2) and the organic extract was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The crude residue was triturated with *iso*-hexane to afford the desired compound (8.16 g, 88%). Used without further purification in the next step.

¹H NMR (400 MHz, CDCl₃): δ 9.19 (s, 1 H), 8.18 (d, *J* = 9.9 Hz, 1 H), 7.45-7.36 (m, 4 H), 7.20 (d, *J* = 8.3 Hz, 1 H), 7.04 (d, *J* = 8.3 Hz, 1 H), 6.70 (dd, *J* = 9.9, 2.2 Hz, 1 H), 5.19-5.13 (m, 3 H), 3.48 (dd, *J* = 12.7, 8.1 Hz, 1 H), 3.26 (dd, *J* = 12.7, 3.8 Hz, 1 H), 0.89 (s, 9 H), 0.14 (s, 3 H), -0.11 (s, 3 H).

Step 5: (*R*)-5-(2-Amino-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one hydrochloride

[0078]

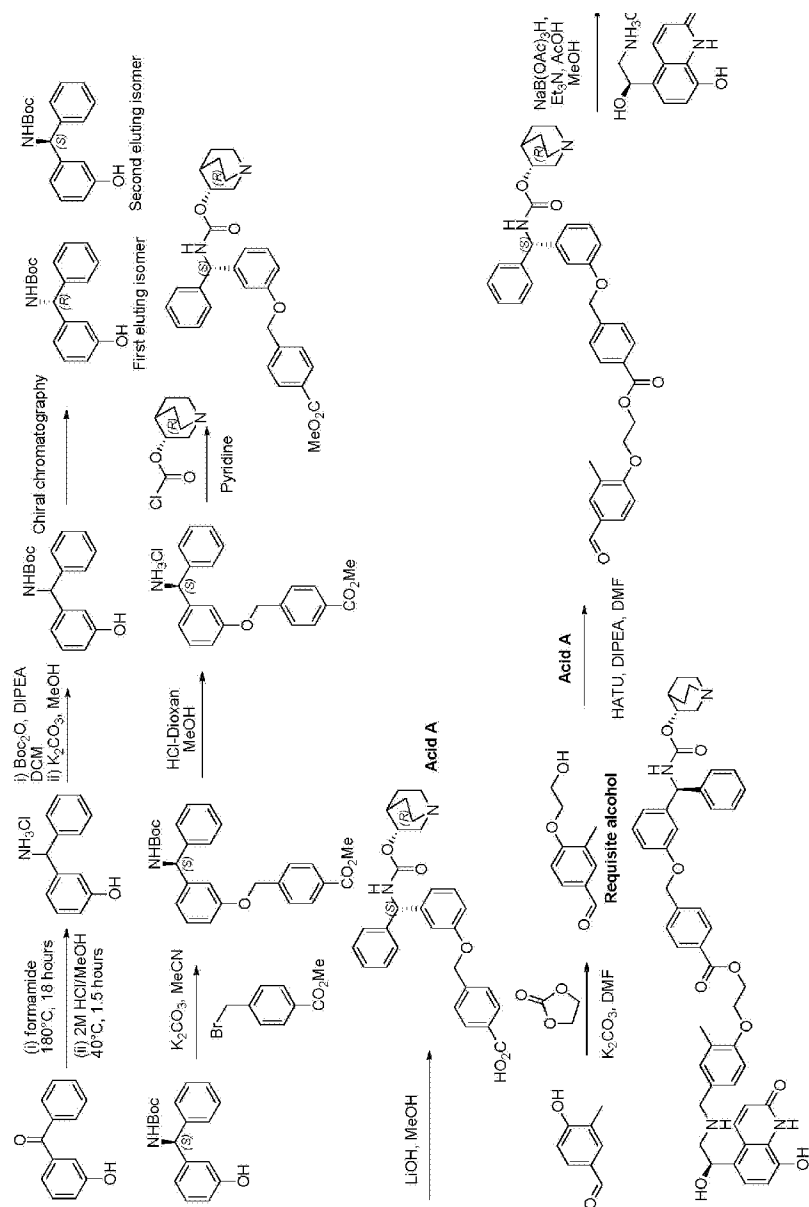


[0079] A solution of (*R*)-5-(2-azido-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-8-(benzyloxy)quinolin-2(1H)-one (4.50 g, 10.0 mmol) in ethanol (50 mL) was added with 10% palladium on charcoal (4.50 g) followed by 1-methyl-1,4-cyclohexadiene (11.0 mL, 97.9 mmol). The reaction was warmed to 60 °C and then stirred at 60 °C for 2 hours. The reaction mixture was allowed to cool and filtered through a pad of celite. The filtercake was washed with further ethanol and the filtrate was evaporated under reduced pressure. The residue was evaporated from *iso*-propanol (x2) and dissolved in *iso*-propanol (30 mL). HCl-dioxane (4M, 50 mL, 200 mmol) was added and the reaction mixture stirred at RT for 18 hours. The resultant suspension was filtered, the filtercake washed with ether and the solid dried under vacuum in the presence of P₂O₅ to afford the title compound (1.65 g, 62%).

¹H NMR (400 MHz, MeOD): δ 7.71 (d, *J* = 9.8 Hz, 1 H), 6.57 (d, *J* = 8.2 Hz, 1 H), 6.31 (d, *J* = 8.2 Hz, 1 H), 6.02 (dd, *J* = 9.8, 6.5 Hz, 1 H), 4.58 (dd, *J* = 9.6, 3.5 Hz, 1 H), 2.47-2.31 (m, 2 H).

Synthesis of Compounds 1 to 17

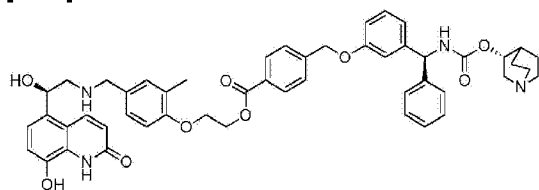
[0080]



Example 1

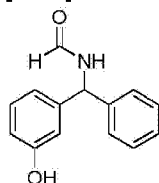
2-(4-((((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-2-methylphenoxy)ethyl 4-((3-((*S*)-phenyl((((*R*)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate (Compound 1)

[0081]



Step 1; *N*-((3-hydroxyphenyl)(phenyl)methyl)formamide

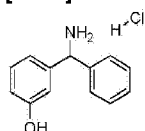
[0082]



[0083] 3-Hydroxybenzophenone (25 g, 126.1 mmol) in formamide (130 mL, 3.3 mmol) was heated to 180 °C for 18 hours. The reaction was allowed to cool slightly then poured into ice-cooled water and stirred for 30 minutes, filtered and washed with water. The solid was stirred in water (60 mL) and ethanol (60 mL) and heated to 50 °C for 1 hour, then allowed to cool. The solid was filtered and washed with water to give the title compound as a brown solid (33.94 g, 118 %). ¹H NMR (400 MHz, CD₃OD): δ 7.39-7.28 (m, 5 H); 7.21-7.13 (m, 1 H); 6.79 (d, J = 7.78 Hz, 1 H); 6.73-6.68 (m, 2 H); 5.45 (s, 1 H).

Step 2; 3-(Amino(phenyl)methyl)phenol hydrochloride

[0084]

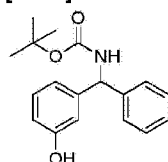


[0085] Methanol (125 mL), was cooled to 0 °C and acetyl chloride (17.8 mL) added dropwise to give a 2M solution of methanolic hydrogen chloride. ***N*-((3-hydroxyphenyl)(phenyl)methyl)formamide** was stirred at 40 °C for 1.5 hours with the 2M methanolic hydrogen chloride. The solvent was removed under reduced pressure and the residue re-dissolved in methanol and the solvent removed under reduced pressure. This process was repeated three times to give the title compound as a brown solid (29.09 g, 97.9 %)

¹H NMR (400 MHz, DMSO-*d*₆): δ 9.76 (s, 1 H); 9.07 (s, 3 H); 7.59-7.53 (m, 2 H); 7.51-7.37 (m, 3 H); 7.26 (t, J = 7.89 Hz, 1 H); 6.99 (d, J = 7.75 Hz, 1 H); 6.90 (t, J = 1.97 Hz, 1 H); 6.81 (dd, J = 8.10, 2.32 Hz, 1 H); 5.58 (d, J = 5.82 Hz, 1 H).

Step 3; *tert*-Butyl ((3-hydroxyphenyl)(phenyl)methyl)carbamate

[0086]



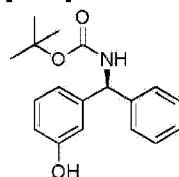
[0087] 3-(Amino(phenyl)methyl)phenol hydrochloride (29.09 g, 123.4 mmol) in dichloromethane (450 mL) was cooled to 0 °C and diisopropylethylamine (65.9 mL, 370.2 mmol) and di-*tert*-butyl dicarbonate (59.2 g, 271.5 mmol) was added slowly. The reaction was stirred at 0 °C for 2 hours then warmed to RT over 16 hours. The solvent was removed and compound purified through a silica plug, eluting with 0-20% ethyl acetate in *iso*-hexane to give a black oil. To this mixture in methanol (300 mL) was added potassium carbonate (51 g, 370.2 mmol) and stirred at RT for 16

hours. The suspension was filtered and the filtrate was evaporated under reduced pressure and the residue re-dissolved in ethyl acetate (370 mL). Silica (73 g) was added and the suspension was stirred for 30 minutes, filtered, and the filter cake washed with further ethyl acetate. The filtrate was evaporated to dryness. The dark solid residue was dissolved in ethyl acetate (200 mL) and charcoal added and the suspension was heated under reflux for 1 hour. The suspension was filtered through celite and solvent removed under reduced pressure. The dark solid was dissolved in dichloromethane and *iso*-hexane added then solvent evaporated (repeated 3 times) to give the title compound as a yellow solid (34.81 g, 92%).

^1H NMR (400 MHz, CDCl_3): δ 7.36-7.16 (m, 6 H); 6.80 (d, J = 7.79 Hz, 1 H); 6.74-6.69 (m, 2 H); 5.83 (s, 1 H); 5.15 (s, 1 H); 1.53-1.30 (s, 9 H).

Step 4; (S)-*tert*-Butyl ((3-hydroxyphenyl)(phenyl)methyl)carbamate

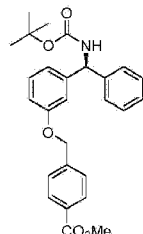
[0088]



[0089] The racemic mixture from **step 3** was purified by SFC using a CHIRALPAK® AD 20 μM 250 x 110 mm column using *n*-heptane / 2-propanol / diethylamine (60 / 40 / 0.1) as eluant with a flow rate of 570 mL / min at 25 °C. From 54.1 g of crude material **(S)-*tert*-butyl ((3-hydroxyphenyl) (phenyl)methyl)carbamate** (R_t = 8.5-8.6 min, 23.9 g, 99.2 e.e.) was obtained.

Step 5; (S)-Methyl 4-((3-(((*tert*-butoxycarbonyl)amino) (phenyl)methyl)phenoxy)methyl)benzoate

[0090]

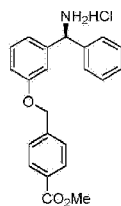


[0091] A mixture of **(S)-*tert*-butyl ((3-hydroxyphenyl)(phenyl)methyl)carbamate** (3.20 g, 10.7 mmol), methyl 4-(bromomethyl)benzoate (2.70 g, 11.8 mmol) and potassium carbonate (2.20 g, 16.1 mmol) in acetonitrile (54 mL) was stirred at RT for 16 hours. The reaction mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate and water. The aqueous phase was extracted with further ethyl acetate and the combined organic extracts combined, dried with anhydrous magnesium sulfate, filtered and the solvent evaporated under reduced pressure. The residue was re-crystallised from ethyl acetate and *iso*-hexane to afford the title compound as a white solid (3.25 g, 68 %).

^1H NMR (400 MHz, CDCl_3): δ 8.04 (d, J = 8.2 Hz, 2 H); 7.46 (d, J = 8.2 Hz, 2 H); 7.34-7.20 (m, 6 H); 6.90-6.81 (m, 3 H); 5.87 (s, 1 H); 5.13 (s, 1 H); 5.07 (s, 2 H); 3.92 (s, 3 H); 1.44 (s, 9 H).

Step 6; (S)-Methyl 4-((3-(amino(phenyl)methyl)phenoxy)methyl)benzoate hydrochloride

[0092]

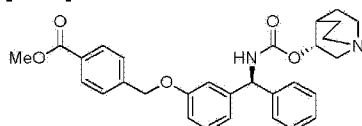


[0093] A solution of **methyl 4-((3-(((tert-butoxycarbonyl)amino)phenyl)methyl)phenoxy)methylbenzoate** (3.21 g, 7.20 mmol) in methanol (36 mL) was added with hydrogen chloride in dioxane (4 M, 9.0 mL, 36 mmol). The reaction mixture was stirred at RT for 16 hours. The solvent was removed under reduced pressure to afford the title compound (2.65 g, >95 %).

^1H NMR (400 MHz, CDCl_3): δ 9.21 (s, 2 H); 8.03 (d, J = 8.1 Hz, 2 H); 7.64 (d, J = 8.1 Hz, 2 H); 7.59 (d, J = 7.6 Hz, 2 H); 7.49-7.34 (m, 5 H); 7.17 (d, J = 7.7 Hz, 1 H); 7.06 (dd, J = 8.3, 2.4 Hz, 1 H); 5.64 (s, 1 H); 5.28 (s, 2 H); 3.91 (s, 3 H).

Step 7; Methyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methylbenzoate

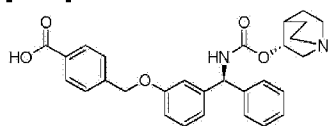
[0094]



[0095] A stirred solution of **(S)-methyl 4-((3-(amino(phenyl)methyl)phenoxy)methyl)benzoate hydrochloride** (12.0 g, 31.3 mmol) in pyridine (100 mL) at 0 °C was added portion-wise with *(R)*-quinuclidin-3-yl carbonochloridate (8.50 g, 37.5 mmol). The reaction was stirred at 0 °C for 1 hour and then allowed to warm to RT for 16 hours. Water was added to the reaction mixture and extracted with ethyl acetate (x 3). The combined extracts were washed with brine, dried (sodium sulfate), filtered and the solvent evaporated under reduced pressure. The crude material was purified by chromatography on a KP-NH Biotage cartridge eluting with 0-20% methanol in ethyl acetate to afford the title compound (10.3 g, 66%).

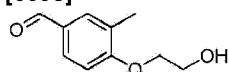
Step 8; 4-((3-((S)-Phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methylbenzoic acid

[0096]



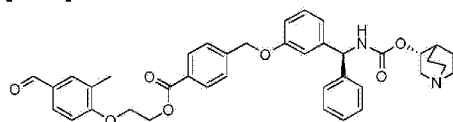
[0097] A stirred solution of **methyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methylbenzoate** (2.27 g, 4.50 mmol) in THF (23 mL) was added with an aqueous solution of lithium hydroxide (2.0 M, 9.0 mL, 18.0 mmol). The mixture was stirred at RT for 16 hours. The pH of the reaction mixture was adjusted to 6 by the addition of 4M aqueous hydrochloric acid. The mixture was then extracted with 10% methanolic ethyl acetate (x2) and the combined organic extracts evaporated under reduced pressure. The residue was then dissolved in ethanol and re-evaporated under reduced pressure to afford the title compound as a pale yellow solid (1.85 g, 84%).

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.41 (d, J = 9.4 Hz, 1 H); 7.99 (d, J = 7.9 Hz, 2 H); 7.58 (d, J = 8.0 Hz, 2 H); 7.42-7.26 (m, 6 H); 7.09 (s, 1 H); 7.02-6.91 (m, 2 H); 5.87 (d, J = 9 Hz, 1 H); 5.21 (s, 2 H); 4.76 (s, 1 H); 3.98-2.72 (m, 6 H); 2.12-1.54 (m, 5 H).

Step 9; 4-(2-Hydroxyethoxy)-3-methylbenzaldehyde**[0098]**

[0099] A stirred solution of 4-hydroxy-3-methyl-benzaldehyde (0.545 g, 4.00 mmol) in DMF (10 mL) was added with potassium carbonate (1.10 g, 7.97 mmol). The reaction mixture was stirred at RT for 5 minutes and then a solution of ethylene carbonate (0.705 g, 8.00 mmol) in DMF (2 mL) was added. The resultant mixture was heated at 80 °C for 90 hours. The reaction mixture was allowed to cool and diluted with ethyl acetate and water. The organic phase was removed, washed with brine (x2), dried (magnesium sulfate), filtered and the solvent evaporated under reduced pressure to afford the title compound (0.677 g, 94%). ¹H NMR (400 MHz, CDCl₃): δ 9.87 (s, 1 H); 7.72-7.70 (m, 2 H); 6.95-6.93 (m, 1 H); 4.20-4.18 (m, 2 H); 4.04-4.03 (m, 2 H); 2.29 (s, 3 H); 1.98 (s, 1 H).

Step 10; 2-(4-Formyl-2-methylphenoxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate

[0100]

[0101] A stirred solution of **4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoic acid** (0.778 g, 1.49 mmol) in DMF (6 mL) was added with di-*iso*-propylethylamine (0.649 mL, 1.79 mmol) and HATU (0.679 g, 1.79 mmol) and the mixture stirred at RT for 20 minutes. To the resultant solution was added a solution of **4-(2-hydroxyethoxy)-3-methylbenzaldehyde** (0.670 g, 3.72 mmol) in DMF (2 mL). The mixture was stirred at RT for 18 hours. The mixture was diluted with ethyl acetate washed with 10% aqueous potassium carbonate, brine (x2), dried (magnesium sulfate), filtered and the solvent evaporated under reduced pressure. The residue was loaded onto an SCX-2 cartridge and eluted with acetonitrile (4 column volumes) and then 10% triethylamine/acetonitrile (4 column volumes).

[0102] The 10% triethylamine/acetonitrile fractions analysed by TLC and product containing fractions combined and evaporated under reduced pressure. Material used directly in the next step with no further purification.

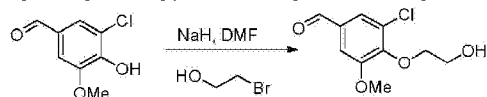
Step 11; 2-(4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-2-methylphenoxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate (Compound 1)

[0103] A suspension of **(R)-5-(2-amino-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one hydrochloride** (0.211 g, 0.83 mmol) in methanol (6 mL) was added with triethylamine (0.229 mL, 1.65 mmol). The mixture was stirred for 10 minutes and then a solution of **2-(4-formyl-2-methylphenoxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate** (0.445 g, 0.69 mmol) in methanol (2 mL) was added. The mixture was stirred at RT for 1 hour. Sodium triacetoxyborohydride (0.292 g, 1.38 mmol) followed by acetic acid (0.188 mL, 3.28 mmol) added and the reaction continued for a further 18 hours. The reaction mixture was quenched with water and evaporated under reduced pressure. The residue dissolved in *iso*-butanol and washed with water. The organic phase was evaporated under reduced pressure and the crude material was purified by reverse phase preparative HPLC to afford the title compound (0.065 g, 11%).

^1H NMR (400 MHz, DMSO- d_6): δ 8.29-8.20 (m, 2 H); 8.10 (d, J = 9.9 Hz, 1 H); 7.97 (d, J = 8.0 Hz, 2 H); 7.57 (d, J = 8.0 Hz, 2 H); 7.32-7.18 (m, 6 H); 7.17-7.01 (m, 4 H); 6.98-6.85 (m, 4 H); 6.47 (d, J = 9.9 Hz, 1 H); 5.81 (s, 1 H); 5.17 (s, 2 H); 5.09 (dd, J = 7.9, 4.7 Hz, 1 H); 4.60 (d, J = 16.8 Hz, 3 H); 4.31 (d, J = 5.0 Hz, 2 H); 3.71 (s, 2 H); 3.12 (m, 1 H); 2.81-2.52 (m, 6 H); 2.09 (s, 4 H); 1.92 (s, 1 H); 1.69-1.26 (m, 4 H).

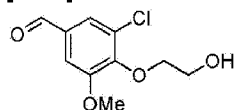
[0104] The following compounds were prepared in the same fashion coupling the requisite alcohol generated in **Step 9** with the acid from **Step 8** and using the product in the subsequent steps.

[0105] An alternative method for preparing the requisite alcohol is highlighted by the synthesis of **3-chloro-4-(2-hydroxyethoxy)-5-methoxybenzaldehyde**.



Preparation of 3-chloro-4-(2-hydroxyethoxy)-5-methoxybenzaldehyde

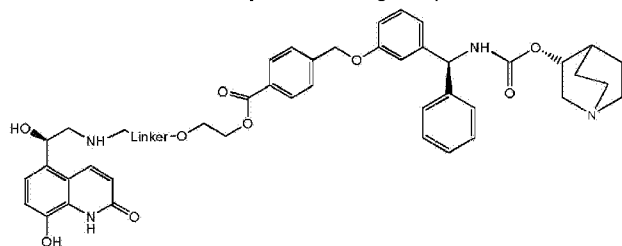
[0106]



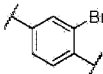
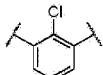
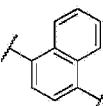
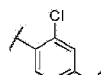
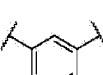
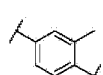
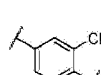
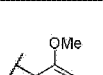
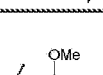
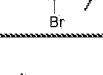
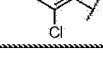
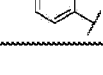
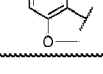
[0107] A suspension of sodium hydride (60% dispersion in mineral oil, 0.24 g, 6.00 mmol) in DMF (8 mL) was added with a solution of 5-chlorovanillin (0.746 g, 4.00 mmol) in DMF (2 mL). The reaction mixture was stirred at RT for 20 minutes and 2-bromoethanol (0.42 mL, 5.93 mmol) added. The reaction mixture was heated at 50 °C for 90 hours. The reaction mixture was diluted with ethyl acetate and washed with water, brine (x2), dried (magnesium sulfate), filtered and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with 0-50% ethyl acetate in *iso*-hexane to afford the title compound (0.413 g, 48%).

^1H NMR (400 MHz, CDCl_3): 8.9.87 (s, 1 H); 7.53 (d, J = 1.6 Hz, 1 H); 7.38 (d, J = 1.6 Hz, 1 H); 4.29-4.27 (m, 2 H); 3.96 (s, 3 H); 3.90-3.85 (m, 2 H); 2.77 (t, J = 6.4 Hz, 1 H).

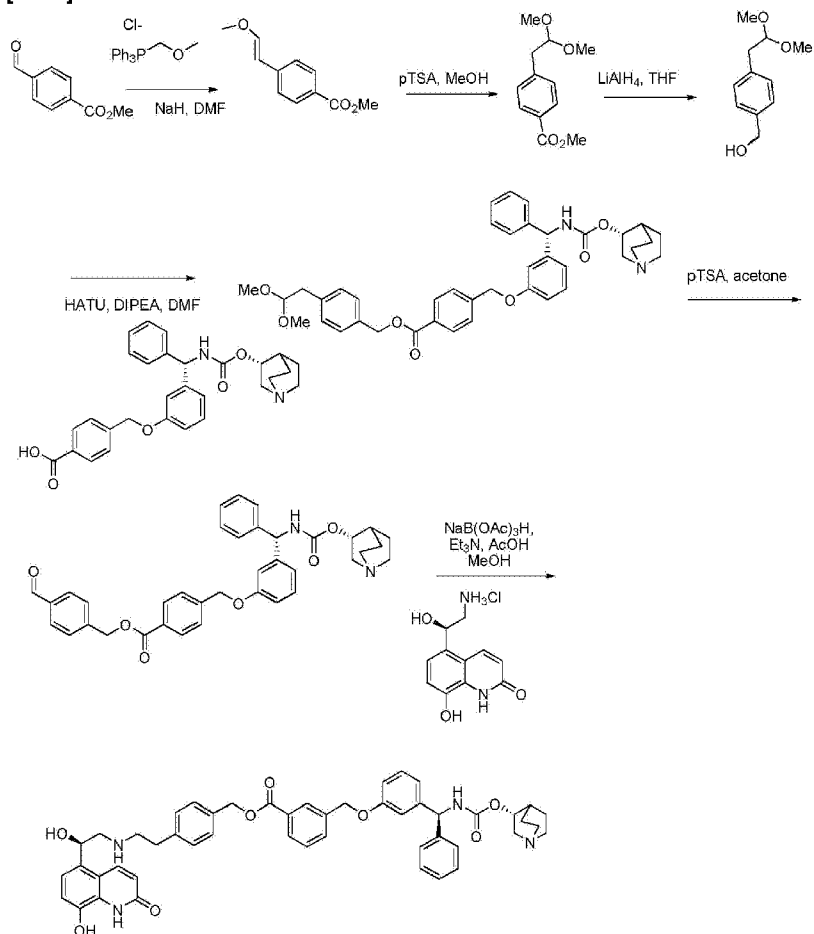
[0108] The following compounds were prepared in the same fashion coupling the requisite alcohol generated in **Step 9** with the acid from **Step 8** and using the product in the subsequent steps.



Compound number	Linker
2	
3	
4	

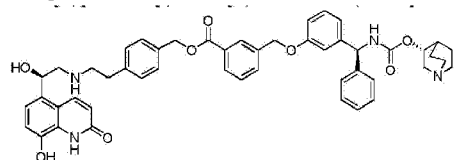
Compound number	Linker
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	

[0109]

**Example 2**

4-(2-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzyl 3-(((S)-phenyl(((R)-quinuclidin-3-yloxy)-carbonyl)amino)methyl)phenoxy)methyl)benzoate (Compound 18)

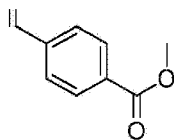
[0110]



Step 1; Methyl 4-(2-methoxyvinyl)benzoate

[0111]



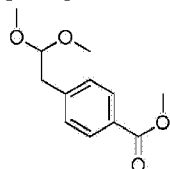


[0112] An ice-cooled suspension of (methoxymethyl)triphenylphosphonium chloride (6.48 g, 20.0 mmol) in THF (40 mL) was added portion wise with sodium hydride (60 % dispersion in mineral oil, 0.88 g, 22.0 mmol). The reaction mixture was stirred at this temperature for 10 minutes followed by 50 minutes at RT. A solution of methyl 4-formyl benzoate (1.16 g, 10.0 mmol) in THF (10 mL) was added and the mixture stirred at RT for 18 h. The reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate and extracted with DCM. The organic phase was poured through a hydrophobic frit and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with 0-10% ethyl acetate in *iso*-hexane to afford the title compound (1.36 g, 71%).

^1H NMR (400 MHz, CDCl_3): Mixture of isomers: δ 7.98-7.90 (m, 2 H); 7.63-7.59 (m, 1 H); 7.29-7.25 (m, 1 H); 7.17 (d, J = 13.0 Hz, 0.5 H); 6.25 (d, J = 7.0 Hz, 0.5 H); 5.82 (d, J = 13.0 Hz, 0.5 H); 5.31-5.25 (m, 0.5 H); 3.90 (s, 3 H); 3.83 (s, 1.5 H); 3.72 (s, 1.5 H).

Step 2; Methyl 4-(2,2-dimethoxyethyl)benzoate

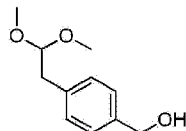
[0113]



[0114] A solution of **methyl 4-(2-methoxyvinyl)benzoate** (1.36 g, 7.08 mmol) in methanol (30 mL) was added with *para*-toluenesulfonic acid monohydrate (pTSA) (0.135 g, 0.71 mmol) and the reaction mixture heated under reflux for 18 hours. The solvent was evaporated under reduced pressure. The residue was partitioned between DCM and 10% aqueous potassium carbonate. The organic phase was poured through a hydrophobic frit and the solvent evaporated under reduced pressure. The crude material was used in the next step without further purification.

Step 3; (4-(2,2-Dimethoxyethyl)phenyl)methanol

[0115]

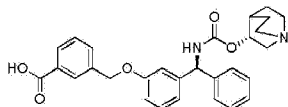


[0116] A cooled ($-78\text{ }^\circ\text{C}$) solution of **methyl 4-(2,2-dimethoxyethyl)benzoate** (assume 7.08 mmol) in THF (30 mL) was added drop wise with a solution of lithium aluminium hydride (2.0 M in THF, 3.50 mL, 7.00 mmol). The reaction mixture was allowed to warm to RT over 4 hours. The mixture was sequentially treated with water (0.266 mL), 2M aqueous sodium hydroxide (0.266 mL) and water (3 x 0.266 mL). The mixture was diluted with ethyl acetate and magnesium sulfate added. The mixture was stirred at RT for 1 hour and then filtered through celite. The filter cake was washed with further ethyl acetate and the filtrates combined. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography eluting with 0-30% ethyl acetate in *iso*-hexane to afford the title compound (0.854 g, 62%).

^1H NMR (400 MHz, CDCl_3): δ 7.32-7.30 (m, 2 H); 7.26-7.23 (m, 2 H); 4.68 (d, J = 5.6 Hz, 2 H); 4.55-4.52 (m, 1 H); 3.34 (s, 6 H); 2.92 (d, J = 5.6 Hz, 1 H); 1.28 - 1.24 (m, 1 H).

Step 4; 3-((3-((S)-Phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)benzoic acid

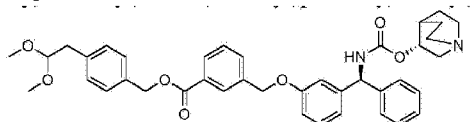
[0117]



[0118] The title compound was prepared as described in **Example 1 Steps 5** through **8** with methyl 3-(bromomethyl)benzoate replacing methyl 4-(bromomethyl)benzoate in **Step 5**.

Step 5; 4-(2,2-Dimethoxyethyl)benzyl 3-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate

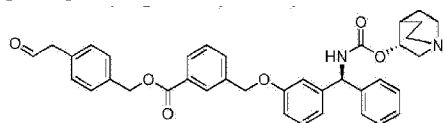
[0119]



[0120] The title compound was prepared as described in **Example 1 Step 10** with (4-(2,2-dimethoxyethyl)phenyl)methanol and 3-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoic acid replacing methylbenzaldehyde and methyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)-methyl)benzoate hydrochloride respectively.

Step 6; 4-(2-Oxoethyl)benzyl 3-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate

[0121]



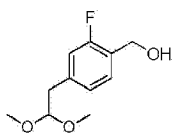
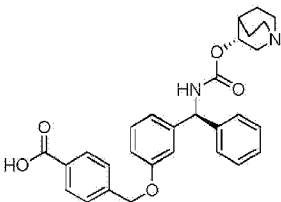
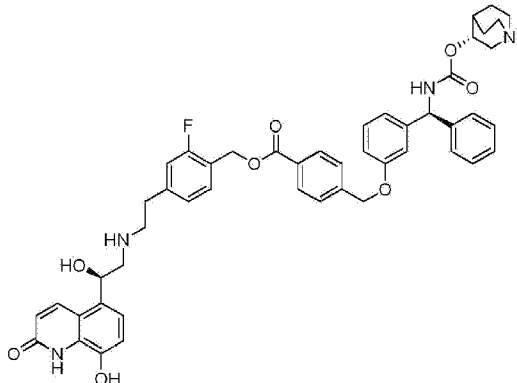
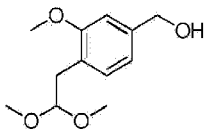
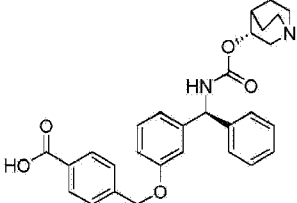
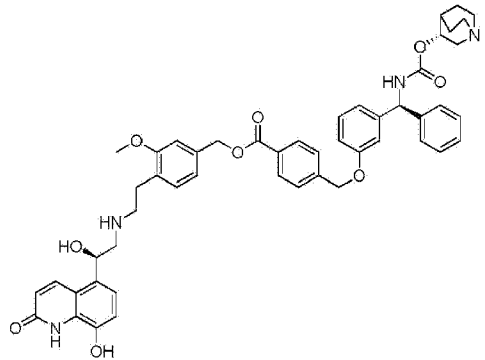
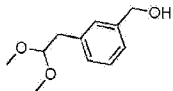
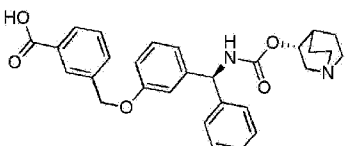
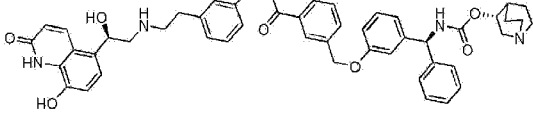
[0122] A stirred solution of **4-(2,2-dimethoxyethyl)benzyl 3-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)-benzoate** (0.100 g, 0.15 mmol) in acetone (5 mL) was added with *para*-toluenesulfonic acid monohydrate (0.086 g, 0.45 mmol) and the mixture stirred at RT for 1 hour. The reaction mixture was diluted with saturated sodium hydrogen carbonate and extracted with ethyl acetate. The combined organic extracts were dried (magnesium sulfate), filtered and the solvent evaporated under reduced pressure. The residue was used in the next step with no further purification.

Step 7; 4-(2-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzyl 3-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate (Compound 18)

[0123] The title compound was prepared as described in **Example 1 Step 11** with **4-(2-oxoethyl)benzyl 3-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)-amino)methyl)phenoxy)methyl)benzoate** replacing **2-(4-formyl-2-methylphenoxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)-amino)methyl)phenoxy)methyl)benzoate**.

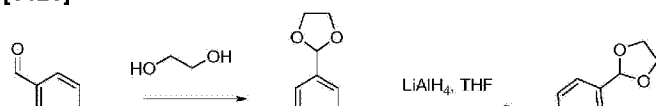
¹H NMR (400 MHz, DMSO-d₆): δ 8.28-8.19 (m, 3 H); 8.17 (d, J = 9.9 Hz, 1 H); 8.05 (s, 1 H); 7.94 (d, J = 7.8 Hz, 1 H); 7.72 (d, J = 7.7 Hz, 1 H); 7.58-7.52 (m, 1 H); 7.38 (d, J = 7.8 Hz, 2 H); 7.31-7.17 (m, 7 H); 7.10-7.02 (m, 2 H); 6.96-6.86 (m, 3 H); 6.51 (d, J = 9.9 Hz, 1 H); 5.81 (d, J = 9.0 Hz, 1 H); 5.33 (s, 2 H); 5.16 (s, 2 H); 5.07 (dd, J = 7.5, 4.8 Hz, 1 H); 4.57 (s, 1 H); 3.10 (s, 1 H); 2.86-2.65 (m, 8 H); 2.50 (m, 4 H); 1.90 (s, 1 H); 1.79 (s, 1 H); 1.46 (t, J = 49.4 Hz, 3 H).

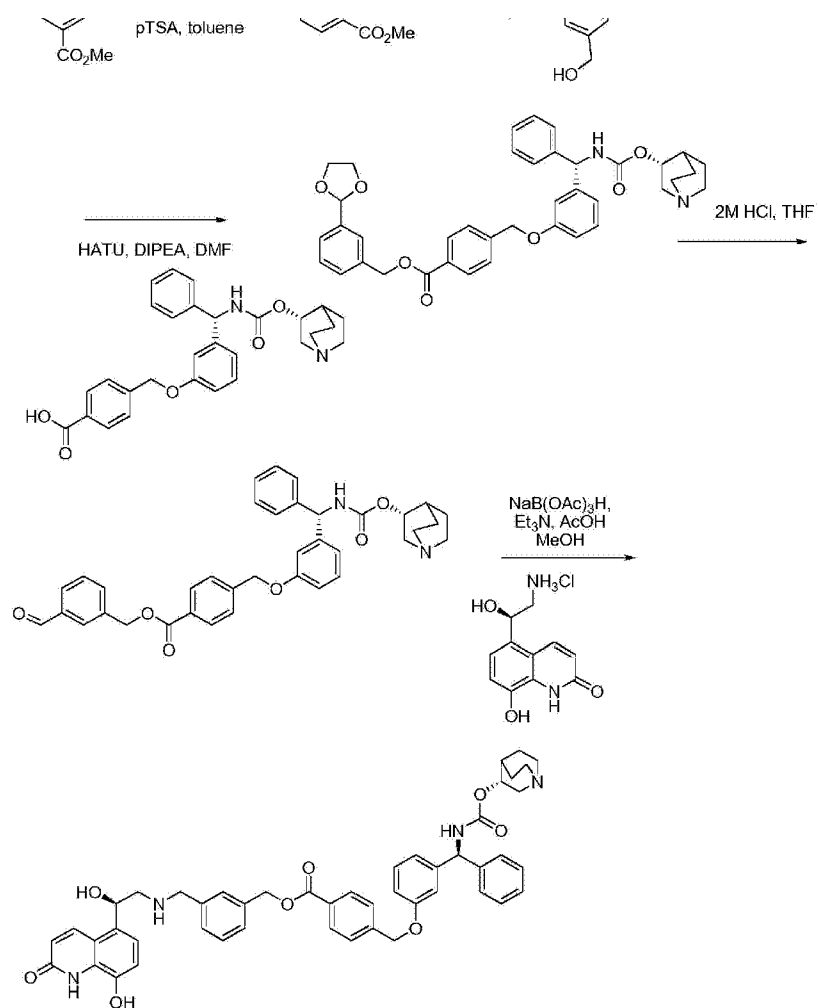
[0124] The following compounds were prepared in an analogous manner to **Example 2** coupling the requisite alcohol (prepared as described in **Example 2 Steps 1 to 3**) to the requisite acid as described in **Example 2 Step 5** and the subsequent product used in **Example 2 Step 6** and **7**.

Cpd.	Requisite alcohol	Requisite acid	Structure
19			
20			
21			

Synthesis of Compounds 22 to 31

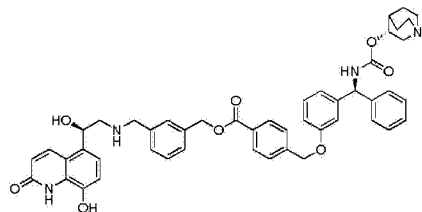
[0125]



**Example 3**

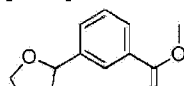
3-(((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)benzyl 4-(((3-(((*S*)-phenyl(((*R*)-quinclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate (Compound 22)

[0126]



Step 1; Methyl 3-(1,3-dioxolan-2-yl)benzoate

[0127]



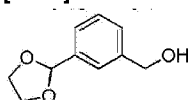


[0128] A mixture of methyl 3-formylbenzoate (2.5 g, 15.2 mmol), ethylene glycol (4.2 mL, 75 mmol) and *para*-toluenesulfonic acid monohydrate (0.29 g, 1.52 mmol) in toluene (60 mL) were refluxed under Dean and Stark conditions for 4 hours. The reaction mixture was diluted with ethyl acetate and washed sequentially with saturated sodium hydrogen carbonate and brine. The organic phase was dried (magnesium sulfate), filtered and the solvent evaporated under reduced pressure to afford the title compound (3.09 g, 98%).

^1H NMR (400 MHz, DMSO- d_6): δ 8.05-7.95 (m, 2 H), 7.72 (d, 1 H), 7.61-7.52 (m, 1 H), 5.82 (s, 1 H), 4.11-3.94 (m, 4 H), 3.87 (s, 2 H).

Step 2; (3-(1,3-Dioxolan-2-yl)phenyl)methanol

[0129]



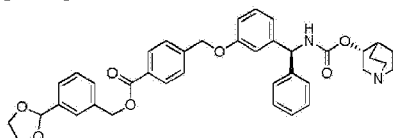
[0130] The title compound was prepared as described in **Example 2 Step 3** with **methyl 3-(1,3-dioxolan-2-yl)benzoate** replacing **methyl 4-(2,2-dimethoxyethyl) benzoate**.

^1H NMR (400 MHz, DMSO- d_6): δ 7.40 (s, 1 H), 7.37-7.27 (m, 3 H), 5.77-5.68 (m, 1 H), 5.21 (t, 1 H), 4.53-4.46 (m, 2 H), 4.09-3.90 (m, 4 H).

Step 3; 3-(1,3-Dioxolan-2-yl)benzyl
4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate

4-((3-((S)-phenyl(((R)-quinuclidin-3-

[0131]

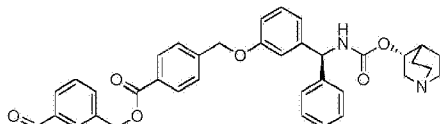


[0132] The title compound was prepared as described in **Example 1 Step 10** with **(3-(1,3-dioxolan-2-yl)phenyl) methanol** replacing **4-(2-hydroxyethoxy)-3-methylbenzaldehyde**.

Step 4; 3-Formylbenzyl
4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate

4-((3-((S)-phenyl(((R)-quinuclidin-3-

[0133]



[0134] A stirred solution of **3-(1,3-dioxolan-2-yl)benzyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate** (0.32 g, 0.57 mmol) in THF (8 mL) was added with 2M aqueous hydrochloric acid (8 mL). The reaction mixture was stirred at RT for 1 hour. The mixture was diluted with ethyl acetate and was washed sequentially with saturated aqueous sodium hydrogen carbonate and brine. The

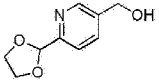
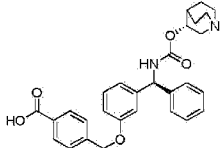
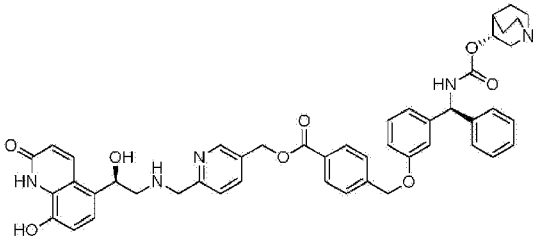
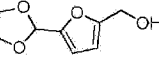
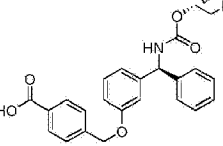
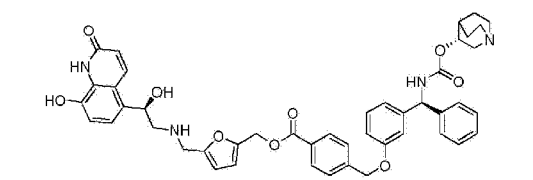
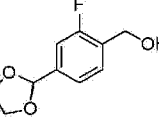
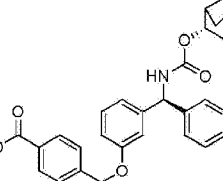
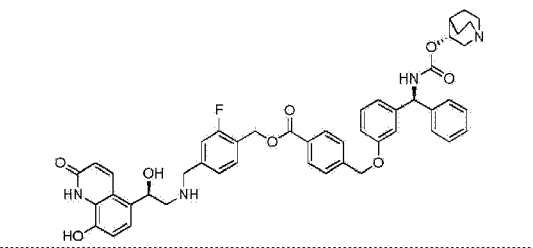
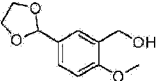
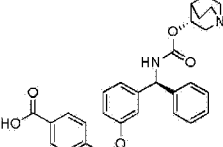
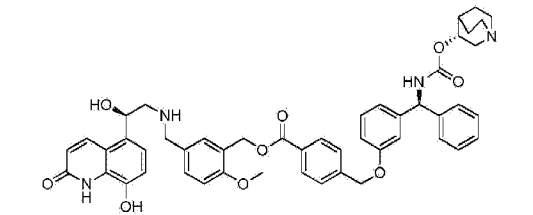
organic extract was dried (magnesium sulfate), filtered and the solvent evaporated under reduced pressure. The residue was used in the next step with no further purification.

Step 5; 3-((((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)benzyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate (Compound 22)

[0135] The title compound was prepared as described in **Example 1 Step 11** with **3-formylbenzyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)benzoate** replacing **2-(4-formyl-2-methylphenoxy)ethyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)-amino)methyl)phenoxy)methyl)benzoate**.

¹H NMR (400 MHz, DMSO-d₆): δ 8.26 (s, 2 H); 8.17 (d, J = 9.9 Hz, 1 H); 8.04 (d, J = 8.0 Hz, 2 H); 7.61 (d, J = 8.0 Hz, 2 H); 7.48 (s, 1 H); 7.41-7.22 (m, 9 H); 7.13-7.07 (m, 2 H); 7.01-6.90 (m, 3 H); 6.51 (d, J = 9.9 Hz, 1 H); 5.86 (d, J = 8.6 Hz, 1 H); 5.39 (s, 2 H); 5.23 (s, 2 H); 5.12 (dd, J = 7.9, 4.3 Hz, 1 H); 4.63 (s, 1 H); 3.85 (s, 2 H); 3.17 (d, J = 14.5 Hz, 1 H); 2.83-2.67 (m, 7 H); 1.96 (m, 2 H); 1.66 (s, 1 H); 1.53 (s, 1 H); 1.39 (s, 1 H).

[0136] The following compounds were prepared in an analogous manner to **Example 3** coupling the requisite alcohol (prepared as described in **Example 3 Steps 1 to 2**) to the requisite acid as described in **Example 3 Step 3** and the subsequent product used in **Example 3 Step 4 and 5**.

Cpd.	Requisite alcohol	Requisite acid	Structure
23			
24			
25			
26			
			

Cpd.	Requisite alcohol	Requisite acid	Structure
27			
28			
29			
30			
31			

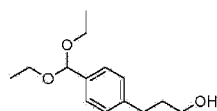
[0137] The following compounds were prepared in an analogous manner to **Example 3** coupling the requisite alcohol (as described below) to the requisite acid as described in **Example 3 Step 3** and the subsequent product used in **Example 3 Step 4** and **5**.

Cpd.	Requisite alcohol	Requisite acid	Structure
32			
33			
34			

Cpd.	Requisite alcohol	Requisite acid	Structure
35			

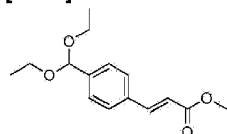
[0138] The synthesis of the requisite alcohol is detailed below;

[0139] The synthesis of the requisite alcohol for **Compound Number 32; 3-(4-(Diethoxymethyl)phenyl)propan-1-ol**



Step 1; (E)-Methyl 3-(4-(diethoxymethyl)phenyl)acrylate

[0140]

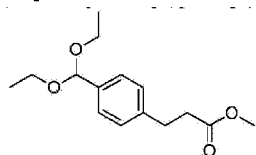


[0141] A solution of 4-(diethoxy)benzaldehyde (2.08 g, 10.0 mmol) and methyl (triphenylphosphoranylidene)acetate (3.68 g, 11.0 mmol) in toluene (30 mL) was heated under reflux for 18 hours. The solvent was evaporated under reduced pressure. The residue was by flash column chromatography eluting with 0-15% ethyl acetate in *iso*-hexane to afford the title compound (2.41 g, 91%).

¹H NMR (400 MHz, CDCl₃): δ 7.72 (d, *J* = 16 Hz, 1H); 7.54-7.48 (m, 4 H); 6.46 (d, *J* = 16 Hz, 1H); 5.51 (s, 1 H); 3.81 (s, 3 H); 3.65-3.50 (m, 4 H); 1.28-1.22 (m, 6 H).

Step 2; Methyl 3-(4-(diethoxymethyl)phenyl)propanoate

[0142]

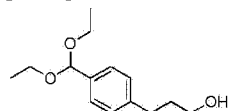


[0143] 1-Methyl-1,4-cyclohexadiene (10.0 mL, 89 mmol) was added to a suspension of **(E)-methyl 3-(4-(diethoxymethyl)phenyl)acrylate** (2.41 g, 9.13 mmol) and 10% palladium on carbon (2.4 g) in ethanol (40 mL). The reaction mixture was heated at 60 °C for 1.5 hours. The reaction mixture was filtered through celite and the filter cake washed with further ethanol. The solvent was evaporated under reduced pressure to afford the title compound (2.15 g, 89%).

^1H NMR (400 MHz, CDCl_3): δ 7.40 (m, 2 H); 7.20-7.18 (m, 2 H); 5.46 (s, 1 H); 3.73 (s, 3 H); 3.70-3.48 (m, 4 H); 2.97-2.92 (m, 2 H); 2.69-2.60 (m, 2 H); 1.26-1.23 (m, 6 H).

Step 3; 3-(4-(Diethoxymethyl)phenyl)propan-1-ol

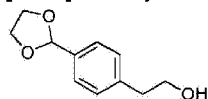
[0144]



[0145] The title compound was prepared as described in **Example 2 Step 3** with **methyl 4-(2,2-dimethoxyethyl)benzoate** replacing **methyl 4-(2,2-dimethoxyethyl)benzoate**.

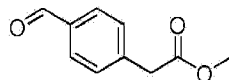
^1H NMR (400 MHz, CDCl_3): δ 7.39 (d, J = 8.4 Hz, 2 H); 7.20-7.18 (m, 2 H); 5.47 (s, 1 H); 3.69-3.49 (m, 6 H); 2.73-2.69 (m, 2 H); 1.90-1.85 (m, 2 H); 1.28-1.24 (m, 6 H).

[0146] The synthesis of the requisite alcohol for **Compound 33; 2-(4-(1,3-Dioxolan-2-yl)phenyl)ethanol**



Step 1; Methyl 2-(4-formylphenyl)acetate

[0147]

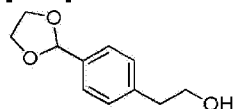


[0148] Acetyl chloride (5 mL) was added to an ice-cooled solution of 4-(hydroxymethyl)phenylacetic acid (5.78 g, 34.8 mmol) in methanol (200 mL). The reaction mixture allowed to warm to RT at stirred at this temperature for 42 hours. The solvent was evaporated under reduced pressure and the residue dissolved in DCM (100 mL). Manganese dioxide (29.47 g, 339 mmol) was added and the resultant suspension stirred at RT for 18 hours. The suspension was filtered through celite and the filter cake washed with further DCM. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography eluting with 0-25% ethyl acetate in *iso*-hexane to afford the title compound (1.72 g, 28%).

^1H NMR (400 MHz, CDCl_3): δ 10.0 (s, 1 H); 7.87-7.83 (m, 2 H); 7.46 (d, J = 8 Hz, 2 H); 3.69-3.65 (m, 5 H).

Step 2; 2-(4-(1,3-Dioxolan-2-yl)phenyl)ethanol

[0149]

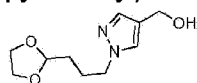


[0150] **Methyl 2-(4-formylphenyl)acetate** (1.72 g, 9.66 mmol) was dissolved in ethylene glycol (2.3 mL) and triethyl orthoformate (1.8 mL). Tetrabutylammonium tribromide (0.048 g) added and the reaction stirred at RT for 1 hour. Further tetrabutylammonium tribromide (0.434 g) added and the reaction stirred for 1 hour. The reaction mixture was

diluted with ethyl acetate and washed with water and brine. The organic phase was dried (magnesium sulfate), filtered and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with 0-15% ethyl acetate in *iso*-hexane to afford impure methyl 2-(4-(1,3-dioxolan-2-yl)phenyl)acetate (0.84 g). This material was dissolved in THF (15 mL) and cooled to -78 °C. A solution of lithium aluminium hydride (1.0 M in THF, 6.00 mL, 6.00 mmol) was added dropwise. The reaction mixture was allowed to warm to RT over 18 hours. The mixture was sequentially treated with water (0.228 mL), 2M aqueous sodium hydroxide (0.228 mL) and water (3 x 0.228 mL). The mixture was diluted with ethyl acetate and magnesium sulfate added. The mixture was stirred at RT for 1 hour and then filtered through celite. The filter cake was washed with further ethyl acetate and the filtrates combined. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography eluting with 0-40% ethyl acetate in *iso*-hexane to afford the title compound (0.315 g, 17%).

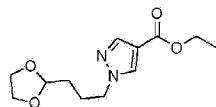
¹H NMR (400 MHz, CDCl₃): 7.44-7.42 (m, 2 H); 7.26-7.24 (m, 2 H); 5.80 (s, 1 H); 4.17-4.00 (m, 4 H); 3.88-3.83 (m, 2 H); 2.89-2.87 (m, 2 H); 1.39-1.34 (m, 1 H).

[0151] The synthesis of the requisite alcohol for **Compound Number 34; (1-(3-(1,3-Dioxolan-2-yl)propyl)-1H-pyrazol-4-yl)methanol**



Step 1; Ethyl 1-(3-(1,3-dioxolan-2-yl)propyl)-1H-pyrazole-4-carboxylate

[0152]

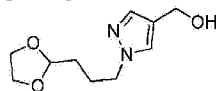


[0153] An ice-cooled stirred solution of ethyl 1H-pyrazole-4-carboxylate (2.0 g, 14.3 mmol) in DMF (10 mL) was added with sodium hydride (60% dispersion in mineral oil, 0.68 g, 17.1 mmol). The reaction mixture was allowed to warm to RT over 20 minutes and 2-(2-bromoethyl)-1,3-dioxolane (2.84 g, 15.7 mmol) added. The reaction mixture was heated at 60 °C for 16 hours. The reaction was partitioned between ethyl acetate and brine. The organic phase was washed with further brine, dried (magnesium sulfate), filtered and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with 0-100% ethyl acetate in *iso*-hexane to afford the title compound (2.14 g, 59%).

¹H NMR (400 MHz, CDCl₃): δ 7.91 (d, J = 4.3 Hz, 2 H); 4.92-4.83 (m, 1 H); 4.33-4.25 (m, 4 H); 4.03-3.80 (m, 4 H); 2.29-2.22 (m, 2 H); 1.39-1.31 (m, 3 H).

Step 2; (1-(3-(1,3-Dioxolan-2-yl)propyl)-1H-pyrazol-4-yl)methanol

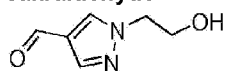
[0154]



[0155] The title compound was prepared as **Example 2 Step 2** with **ethyl 1-(3-(1,3-dioxolan-2-yl)propyl)-1H-pyrazole-4-carboxylate** replacing **methyl 4-(2-methoxyvinyl)benzoate**.

¹H NMR (400 MHz, CDCl₃): δ 7.69 (s, 1 H); 7.60-7.44 (m, 1 H); 4.94-4.84 (m, 1 H); 4.61-4.48 (m, 4 H); 4.06-3.82 (m, 4 H); 2.31-2.21 (m, 2 H); 1.70-1.64 (m, 1 H).

[0156] The synthesis of the requisite alcohol for **Compound Number 35**; **1-(2-Hydroxyethyl)-1H-pyrazole-4-carbaldehyde**



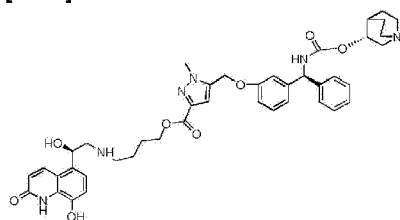
[0157] 1H-Pyrazole-4-carboxaldehyde (0.50 g, 5.21 mmol), 2-bromoethanol (1.30 g, 10.41 mmol) and potassium carbonate (0.79 g, 5.73 mmol) combined with acetonitrile (5 mL) in a microwave vial. The microwave vial was heated at 150 °C in a microwave for 30 minutes. The reaction mixture was filtered and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with 0-100% ethyl acetate in *iso*-hexane to afford the title compound (0.50 g, 69%).

¹H NMR (400 MHz, CDCl₃): δ 9.86 (s, 1 H); 8.02 (s, 1 H); 7.99 (s, 1 H); 4.33-4.25 (m, 2 H); 4.05 (t, J = 4.8 Hz, 2 H).

Example 4

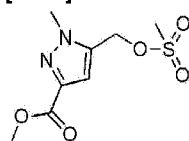
4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 1-methyl-5-(((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)-1H-pyrazole-3-carboxylate (Compound 36)

[0158]



Step 1; Methyl 1-methyl-5-(((methylsulfonyl)oxy)methyl)-1H-pyrazole-3-carboxylate

[0159]

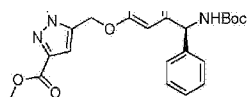


[0160] An ice-cooled solution of methyl 5-(hydroxymethyl)-1-methyl-1H-pyrazole-3-carboxylate (0.60 g, 3.51 mmol) and triethylamine (1.22 mL, 8.77 mmol) in DCM (10 mL) was added with methanesulfonyl chloride (0.41 mL, 5.26 mmol). The reaction mixture was stirred at this temperature for 15 minutes and the coolant removed. The reaction mixture was stirred at RT for 1 hour. The reaction mixture was diluted with DCM and washed with water and brine. The organic phase was dried (magnesium sulfate), filtered and the solvent evaporated under reduced pressure. The crude material was used in the next step without further purification.

Step 2; (S)-Methyl 5-(((3-(((tert-butoxycarbonyl)amino) (phenyl)methyl)phenoxy)methyl)-1-methyl-1H-pyrazole-3-carboxylate

[0161]



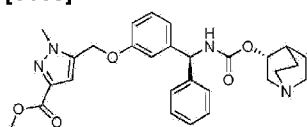


[0162] The title compound was prepared as described in **Example 1 Step 5** with **methyl 1-methyl-5-(((methylsulfonyl)oxy)methyl)-1H-pyrazole-3-carboxylate** replacing methyl 4-(bromomethyl)benzoate.

¹H NMR (400 MHz, CDCl₃): δ 7.37-7.21 (m, 7 H); 6.92 (d, J = 7.7 Hz, 1 H); 6.87-6.81 (m, 3 H); 5.88 (s, 1 H); 5.25-4.98 (m, 1 H); 5.00 (s, 2 H); 4.05-3.91 (m, 3 H); 3.92 (s, 3 H); 1.44 (s, 9 H).

Step 3; Methyl 1-methyl-5-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)-1H-pyrazole-3-carboxylate

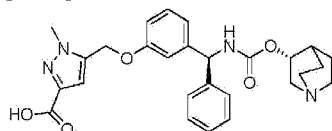
[0163]



[0164] The title compound was prepared as described in **Example 1 Step 6** with **(S)-methyl 5-((3-(((tert-butoxycarbonyl)amino)(phenyl)methyl)phenoxy)-methyl)-1-methyl-1H-pyrazole-3-carboxylate** replacing **methyl 4-((3-(((tert-butoxycarbonyl)amino)(phenyl)methyl)phenoxy)methyl)benzoate** and the product from this step used in **Example 1 Step 7**.

Step 4; 1-Methyl-5-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)-1H-pyrazole-3-carboxylic acid

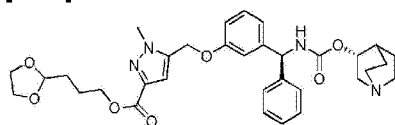
[0165]



[0166] The title compound was prepared as described in **Example 1 Step 8** with **methyl 1-methyl-5-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)-1H-pyrazole-3-carboxylate** replacing **4-((3-((phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl) benzoate**.

Step 5; 3-(1,3-Dioxolan-2-yl)propyl 1-methyl-5-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)-1H-pyrazole-3-carboxylate

[0167]



[0168] The title compound was prepared as described in **Example 1 Step 10** with **1-methyl-5-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)-phenoxy)methyl)-1H-pyrazole-3-carboxylic acid** and **3-(1,3-**

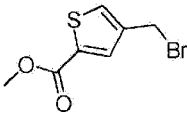
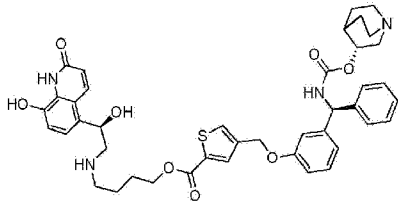
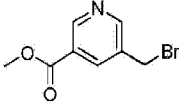
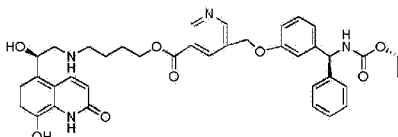
dioxolan-2-yl)propan-1-ol replacing 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoic acid and 4-(2-hydroxyethoxy)-3-methylbenzaldehyde respectively.

Step 6; 4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 1-methyl-5-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)-1H-pyrazole-3-carboxylate (Compound 36)

[0169] The title compound was prepared as described in **Example 2 Step 6** and **Step 7**.

¹H NMR (400 MHz, DMSO-d₆): δ 8.48-8.07 (m, 3 H); 8.18 (d, J = 9.93 Hz, 1 H); 7.33-7.19 (m, 6 H); 7.13-7.04 (m, 2 H); 7.00-6.90 (m, 3 H); 6.88 (s, 1 H); 6.51 (d, J = 9.86 Hz, 1 H); 5.83 (d, J = 8.56 Hz, 1 H); 5.32-5.03 (m, 3 H); 4.60 (s, 2 H); 4.26-4.19 (m, 2 H); 4.10-3.66 (m, 3 H); 3.20-3.08 (m, 1 H); 2.93-2.54 (m, 9 H); 2.06-1.28 (m, 8 H).

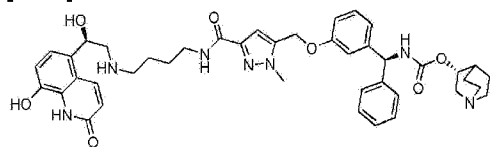
[0170] The following compounds were prepared as described in **Example 4** with the appropriate alkylating agent in **Step 1** (methyl 1-methyl-5-(((methylsulfonyl)oxy)methyl)-1H-pyrazole-3-carboxylate in the case of **Compound 36**) used in **Step 2** and the product used in the subsequent steps in **Example 4**.

Compound number	Appropriate alkylating agent	Structure
37		
38		

Example 5

(R)-Quinuclidin-3-yl ((S)-3-((3-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)carbonyl)-1-methyl-1H-pyrazol-5-yl)methoxy)phenyl)(phenyl)methyl)carbamate (Compound 39)

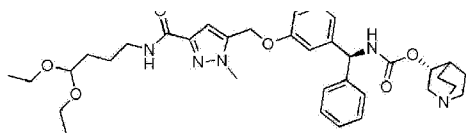
[0171]



Step 1; (R)-Quinuclidin-3-yl ((S)-3-((3-((4,4-diethoxybutyl)carbonyl)-1-methyl-1H-pyrazol-5-yl)methoxy)phenyl)(phenyl)methyl)carbamate

[0172]

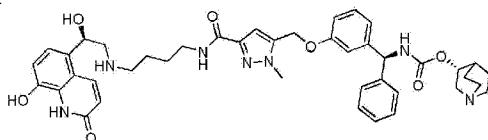




[0173] A stirred solution of **1-methyl-5-((3-((*S*)-phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)-1*H*-pyrazole-3-carboxylic acid** (0.30 g, 0.61 mmol) in DMF (6 mL) was added with triethylamine (0.2 mL, 1.53 mmol), 4-aminobutyraldehyde diethyl acetal (0.20 mL, 1.22 mmol), EDCI (0.18 g, 0.91 mmol) and 2-hydroxypyridine-*N*-oxide (0.09 g, 0.91 mmol). The reaction mixture stirred at RT for 90 h. The reaction mixture was diluted with ethyl acetate and washed with saturated sodium hydrogen carbonate, brine, dried (magnesium sulfate), filtered and the solvent evaporated under reduced pressure to afford the crude target material (0.22 g, 57%) which was used directly without further purification.

Step 2; (*R*)-Quinuclidin-3-yl ((*S*)-(3-((4-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)carbamoyl)-1-methyl-1*H*-pyrazol-5-yl)methoxy)phenyl)(phenyl)methyl)carbamate (Compound 39)

[0174]



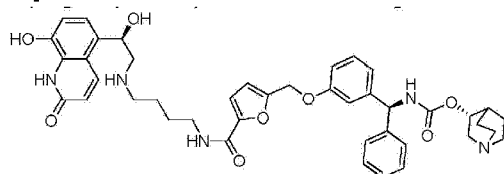
[0175] The title compound was prepared as described in **Example 2 Step 6** and **Step 7**.

¹H NMR (400 MHz, DMSO-*d*₆): δ 10.30 (br s, 1 H); 8.48-8.07 (m, 3 H); 8.21-8.10 (m, 2 H); 7.34-7.19 (m, 6 H); 7.15-7.04 (m, 2 H); 7.00-6.91 (m, 2 H); 6.75 (s, 1 H); 6.53 (d, *J* = 9.86 Hz, 1 H); 5.84 (d, *J* = 8.57 Hz, 1 H); 5.31-5.10 (m, 3 H); 4.61 (s, 1 H); 3.88 (s, 3 H); 3.31-2.97 (m, 3 H); 2.95-2.56 (m, 7 H); 1.94 (s, 1 H); 1.82 (s, 1 H); 1.73-1.16 (m, 9 H).

Example 6

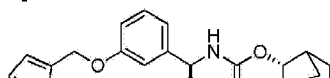
(*R*)-Quinuclidin-3-yl ((*S*)-(3-((5-((4-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)carbamoyl)furan-2-yl)methoxy)phenyl)(phenyl)methyl)carbamate (Compound 40)

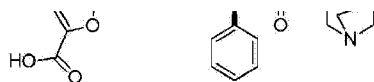
[0176]



Step 1; 5-((3-((*S*)-Phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)furan-2-carboxylic acid

[0177]

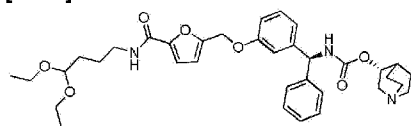




[0178] The title compound was prepared as described in **Example 4 Step 2** with methyl 5-(bromomethyl)furan-2-carboxylate replacing methyl 1-methyl-5-(((methylsulfonyl)oxy)methyl)-1H-pyrazole-3-carboxylate followed by the method of **Example 4 Step 3**. The crude product was used in the next step without further purification.

Step 2; (R)-Quinuclidin-3-yl ((S)-3-((5-((4,4-diethoxybutyl)carbamoyl)furan-2-yl)methoxy)phenyl)(phenyl)methyl)-carbamate

[0179]



[0180] The title compound was prepared as described in **Example 5 Step 1** with 5-(((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)-methylfuran-2-carboxylic acid replacing 1-methyl-5-(((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)-1H-pyrazole-3-carboxylic acid. The crude reaction product was used in the next step without further purification.

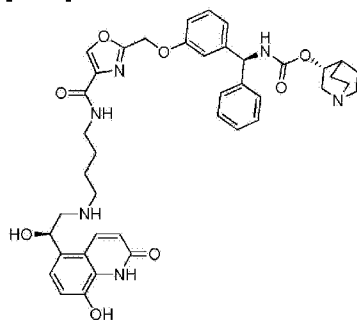
Step 3; (R)-Quinuclidin-3-yl ((S)-3-((5-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)carbamoyl)furan-2-yl)methoxy)phenyl)(phenyl)methyl)-carbamate (Compound 40)

[0181] The title compound was prepared as described in **Example 5 Step 2**. ^1H NMR (400 MHz, DMSO- d_6): δ 10.38 (br s, 1 H); 8.46-8.39 (m, 1 H); 8.33-8.21 (m, 3 H); 8.18 (d, J = 9.93 Hz, 1 H); 7.34-7.19 (m, 6 H); 7.11 (d, J = 8.15 Hz, 1 H); 7.05 (t, J = 3.66 Hz, 2 H); 6.99-6.89 (m, 3 H); 6.69 (d, J = 3.44 Hz, 1 H); 6.54 (d, J = 9.86 Hz, 1 H); 5.84 (d, J = 8.95 Hz, 1 H); 5.20 (dd, J = 8.44, 4.14 Hz, 1 H); 5.08 (s, 2 H); 4.60 (s, 1 H); 3.28-3.01 (m, 3 H); 2.88 (d, J = 8.88 Hz, 2 H); 2.79 (s, 6 H); 1.93 (s, 1 H); 1.88-1.73 (m, 1 H); 1.74-1.15 (m, 7 H).

Example 7

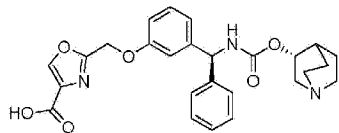
(R)-Quinuclidin-3-yl ((S)-3-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)carbamoyl)oxazol-2-yl)methoxy)phenyl)(phenyl)methyl)-carbamate (Compound 41)

[0182]



Step 1; 2-((3-((S)-Phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)oxazole-4-carboxylic acid

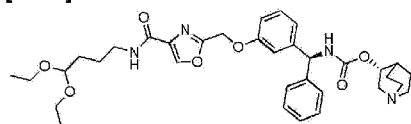
[0183]



[0184] The title compound was prepared as described in **Example 4 Step 2** with methyl 2-(chloromethyl)-1,3-oxazole-4-carboxylate replacing methyl 1-methyl-5-(((methylsulfonyl)oxy)methyl)-1H-pyrazole-3-carboxylate followed by the method of **Example 4 Step 3**. The crude product was used in the next step without further purification.

Step 2; (R)-Quinuclidin-3-yl ((S)-(3-((4-((4,4-diethoxybutyl)-carbamoyl)oxazol-2-yl)methoxy)phenyl)(phenyl)methyl)-carbamate

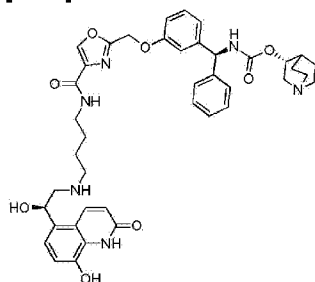
[0185]



[0186] The title compound was prepared as described in **Example 5 Step 1** with 2-((3-((S)-Phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)-phenoxy)methyl)oxazole-4-carboxylic acid replacing 1-methyl-5-(((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)-amino)methyl)phenoxy)methyl)-1H-pyrazole-3-carboxylic acid. The crude reaction product was used in the next step without further purification.

Step 3; (R)-Quinuclidin-3-yl ((S)-(3-((4-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)carbamoyl)oxazol-2-yl)methoxy)phenyl)(phenyl)methyl)carbamate

[0187]



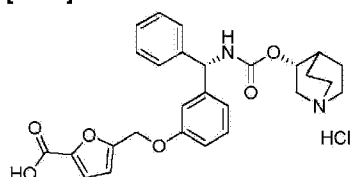
[0188] The title compound was prepared as described in **Example 5 Step 2**. ^1H NMR (400 MHz, DMSO- d_6): δ 10.31 (br s, 1 H); 8.61 (s, 1 H); 8.37 (t, J = 6.01 Hz, 1 H); 8.37-8.17 (m, 2 H); 8.17 (d, J = 9.92 Hz, 1 H); 7.33-7.19 (m, 6 H); 7.10 (d, J = 8.15 Hz, 1 H); 7.05-6.86 (m, 4 H); 6.53 (d, J = 9.86 Hz, 1 H); 5.83 (d, J = 8.65 Hz, 1 H); 5.25-5.14 (m, 3 H); 4.59 (s, 1 H); 3.23 (d, J = 6.27 Hz, 2 H); 3.21-3.06 (m, 1 H); 2.86-2.52 (m, 8 H); 1.92 (s, 1 H); 1.80 (s, 1 H); 1.71-1.16 (m, 8 H).

Example 8

(R)-3-((S)-3-((5-((4-((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)butoxy)carbonyl)furan-2-yl)methoxy)phenyl) (phenyl)methylcarbamoyloxy)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-1-azoniabicyclo[2.2.2]octane chloride hydrochloride (Compound 42)

Step 1: 5-((3-((S)-Phenyl(((R)-quinuclidin-3-yloxy)carbonylamino)-methyl)phenoxy)methyl)furan-2-carboxylic acid hydrochloride

[0189]

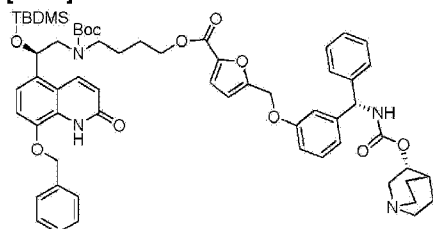


[0190] The **5-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonylamino)-methyl)phenoxy)methyl)furan-2-carboxylic acid** prepared as described in **Example 6 Step 1** was further purified by reverse phase column chromatography eluting with gradient of Eluent A: Water/ACN 95/5 + 0.1% HCOOH and Eluent B: ACN/water 95/5 + 0.1% HCOOH. 5-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonylamino)methyl)phenoxy) methyl)furan-2-carboxylic acid formate (1:1) (8.36 g, 16.12 mmol) was dispersed in Dioxane (50 mL) and then 4M HCl in dioxane (16.12 mL, 64.5 mmol) was added at 0°C and the mixture stirred at rt for 10 min until complete dissolution. The above mentioned solution was dropped in a 500 mL of Et₂O under vigorous stirring to give a white precipitate that was collected by filtration. After drying under vacuum **5-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonylamino)methyl)phenoxy)methyl)furan-2-carboxylic acid hydrochloride** (8.2 g, 15.98 mmol, 99 % yield) was isolate as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.90 - 13.34 (bs, 1 H), 10.10 (bs, 1 H), 8.43 (d, *J*=9.26 Hz, 1 H), 7.13 - 7.42 (m, 7 H), 7.04 (m., 1 H), 6.86 - 7.00 (m, 2 H), 6.72 (d, *J*=3.53 Hz, 1 H), 5.83 (d, *J*=9.26 Hz, 1 H), 5.11 (s, 2 H), 4.61 - 4.95 (m, 1 H), 3.57 - 3.75 (m, 1 H), 2.95 - 3.27 (m, 5 H), 2.22 (m, 1 H), 1.65 - 2.10 (m, 4 H)

Step 2: 4-(((R)-2-(8-(Benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl)-2-(tert-butyldimethylsilyloxy)ethyl)(tert-butoxycarbonyl)amino)butyl 5-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonylamino)methyl)phenoxy)-methyl)furan-2-carboxylate

[0191]

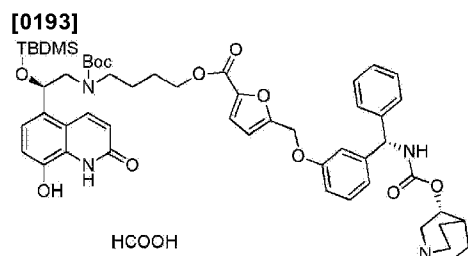


[0192] **5-((3-((S)-Phenyl(((R)-quinuclidin-3-yloxy)carbonylamino)methyl)-phenoxy)methyl)furan-2-carboxylic acid hydrochloride** (3.09 g, 6.03 mmol) and (R)-tert-butyl 2-(8-(benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl)-2-(tert-butyldimethylsilyloxy)ethyl(4-hydroxybutyl)carbamate (see **Preparation of (R)-5-(2-amino-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one hydrochloride, Step 3**) (3 g, 5.03 mmol) were dissolved in 15 mL of DMF, then EDC (1.445 g, 7.54 mmol) was added and the mixture cooled at 0°C. DMAP (0.307 g, 2.51 mmol) dissolved in 7 mL of

DMF was added dropwise at 0 °C and the mixture was stirred 5 min at 0 °C, 30 min at rt and heated at 50 °C for 3h and then left overnight at rt. Reaction was then partitioned between AcOEt (300 mL) and brine (600 mL). The organic layer was washed twice with 1:1 mixture water/brine (2x300 mL). Organic phase was washed with brine (300 mL), dried over Na₂SO₄ and evaporated to give a white foam. The foam was triturated in 300 mL of 95/5 Hexane/AcOEt for 3h and the precipitate was collected by filtration. A second crop was obtained by dilution with hexane of the mother liquor. 4-(((R)-2-(8-(benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl)-2-(tert-butyldimethylsilyloxy)ethyl) (tert-butoxycarbonyl)amino)butyl 5-(((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonylamino)methyl)phenoxy)methyl)furan-2-carboxylate (4.3 g from the 2 crops combined, 4.07 mmol, 81 % yield) was obtained as a white powder.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.64 (bs, 1 H), 8.32 (d, *J*=8.82 Hz, 2 H), 7.57 (d, *J*=7.50 Hz, 2 H), 7.12 - 7.44 (m, 11 H), 6.85 - 7.08 (m, 3 H), 6.73 (d, *J*=2.65 Hz, 1 H), 6.47 - 6.64 (m, 1 H), 5.82 (d, *J*=8.82 Hz, 1 H), 5.31 (s, 2 H), 5.10 (s, 2 H), 4.65 - 4.78 (m, 1 H), 4.21 (t, 2 H), 2.73 - 3.27 (m, 10 H), 1.46 - 2.18 (m, 9 H), 1.37 (s, 9 H), 0.81 (s, 9 H), -0.01 (s, 3 H), -0.20 (s, 3 H)

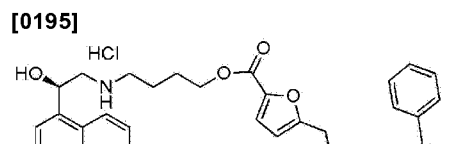
Step 3: 4-(((R)-2-(8-(Benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl)-2-(tert-butyldimethylsilyloxy)ethyl) (tert-butoxycarbonyl)amino)butyl 5-(((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonylamino)methyl)phenoxy)methyl)furan-2-carboxylate formate

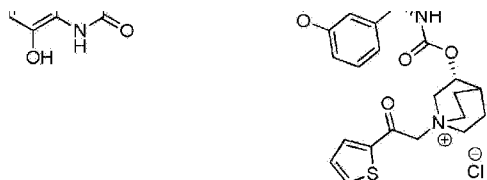


[0194] 4-(((R)-2-(8-(Benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl)-2-(tert-butyldimethylsilyloxy)ethyl) (tert-butoxycarbonyl)amino)butyl 5-(((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonylamino)methyl)phenoxy) methyl)furan-2-carboxylate (2.1 g, 1.990 mmol), 10% Pd/C (0.106 g, 0.099 mmol) and formic acid (0.092 mL, 2.388 mmol) were dissolved in MeOH (44.2 mL) and stirred at RT under balloon pressure of H₂. After 2h reaction was complete and it was filtered on a pad of celite and the filtrate concentrated under reduced pressure to give a colourless viscous oil. The oil was dispersed in Et₂O/AcOEt and evaporated 3 times in order to obtain a heavy white foam that was triturated in hexane/Et₂O/AcOEt to give a white solid that was collected by filtration. The mother liquor was concentrated to give 0.44 g of a second crop of a whitish foam. The 2 crops were combined to give 4-(tert-butoxycarbonyl((R)-2-(tert-butyldimethylsilyloxy)-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 5-(((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonylamino)-methyl)phenoxy)methyl)furan-2-carboxylate formate (1.95 g, 1.928 mmol, 97 % yield) as white amorphous solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.38 (br. s., 2 H), 8.33 (br. s., 2 H), 8.14 (s, 1 H), 7.16 - 7.40 (m, 7 H), 6.84 - 7.06 (m, 5 H), 6.73 (m, 1 H), 6.41 - 6.60 (m, 1 H), 5.82 (d, *J*=9.26 Hz, 1 H), 5.18 - 5.50 (m, 1 H), 5.10 (s, 2 H), 4.63 - 4.82 (m, 1 H), 4.20 (t, *J*=5.95 Hz, 2 H), 2.71 - 3.22 (m, 10 H), 1.44 - 2.16 (m, 9 H), 1.44 (s, 9 H), 0.80 (s, 9 H), -0.01 (s, 3 H), -0.19 (s, 3 H)

Step 4: 4-(tert-butoxycarbonyl((R)-2-(tert-butyldimethylsilyloxy)-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 5-(((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonylamino) methyl)phenoxy)methyl)-furan-2-carboxylate chloride hydrochloride



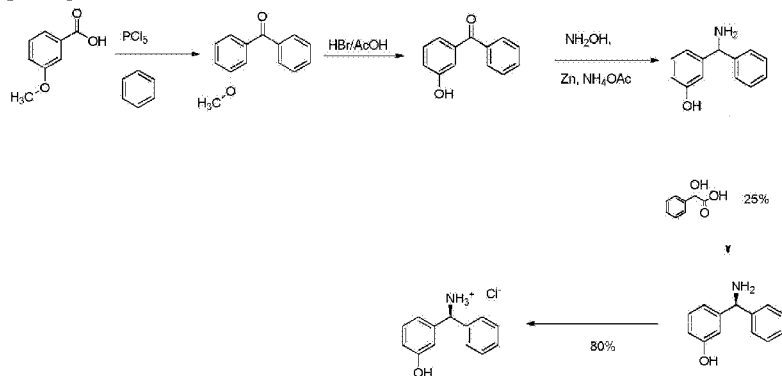


[0196] 4-(tert-Butoxycarbonyl((R)-2-(tert-butyldimethylsilyloxy)-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl) amino)butyl 5-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonylamino)methyl)phenoxy) methyl)furan-2-carboxylate formate (150 mg, 0.148 mmol) was dissolved in 500 μ L of dioxane and then a solution of 2-bromo-1-(thiophen-2-yl)ethanone (33.5 mg, 0.163 mmol) in 0.3 mL of dioxane was added. After 2 h a second eq. of alkylating agent was added and the mixture stirred at RT overnight. To drive the reaction to completion sodium bicarbonate (33 mg, 0.393 mmol) was added and the reaction mixture was heated at 50°C for 6 h. The reaction was cooled at RT and then Et₂O was added. The precipitate was collected as gummy solid dissolved in MeOH and evaporated to give a yellow residue that was dissolved in 2-propanol (1.8 ml). HCl in Dioxane (1.859 ml, 7.43 mmol) was added and the mixture stirred at RT overnight. The reaction mixture was diluted with Et₂O and the precipitate formed was collected by filtration and purified by reverse phase column chromatography eluting with ACN:Water (gradient from 100% to 40 % of ACN leading to (R)-3-((S)-3-((5-((4-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)butoxy) carbonyl)furan-2-yl)methoxy)phenyl) (phenyl)-methylcarbamoxyloxy)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-1-azoniabicyclo[2.2.2]octane chloride hydrochloride (96 mg, 0.101 mmol, 68.1 % yield) as pale yellow solid obtained by mean of trituration with EtOH and Et₂O of the residue.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.87 - 10.55 (bs, 1 H), 8.52 (d, *J*=9.26 Hz, 1 H), 8.33 (s, 2 H), 8.11 - 8.20 (m, 2 H), 8.05 (d, *J*=3.53 Hz, 1 H), 7.17 - 7.46 (m, 7 H), 6.87 - 7.10 (m, 5 H), 6.74 (d, *J*=3.53 Hz, 1 H), 6.48 (d, *J*=9.70 Hz, 1 H), 5.84 (d, *J*=9.26 Hz, 1 H), 4.93 - 5.23 (m, 6 H), 4.23 (t, *J*=6.39 Hz, 2 H), 3.98 - 4.12 (m, 2 H), 3.52 - 3.75 (m, 4 H), 2.57 - 2.80 (m, 4 H), 2.32 (m, 1 H), 1.86 - 2.23 (m, 4 H), 1.60 - 1.77 (m, 2 H), 1.44 - 1.57 (m, 2 H)

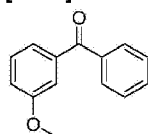
Large scale synthesis of (S)-3-(amino(phenyl)methyl)phenol hydrochloride

[0197]



Step 1; (3-Methoxyphenyl)(phenyl)methanone

[0198]

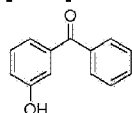


[0199] To the mixture of phosphorus pentachloride (3763 g, 18.1 mol) in 7500 mL of benzene, 3-methoxy benzoic acid (2500 g, 16.4 mol) was added in portions. The mixture was stirred for 50 minutes until it became homogenous. The formation of the acid chloride was controlled by TLC. After completion, the mixture was cooled down to 10 °C, reactor was covered with aluminum foil and aluminium trichloride (4820 g, 36.1 mol) was added in portions (internal temperature was held up to 30 °C maximum). Stirring was continued for 18 hours at RT. The reaction was monitored by TLC (AcOEt:hex 1:9). After completion, the reaction mixture was poured into ice and was diluted with AcOEt (7 L). Then organic layer was separated and the aqueous layer was extracted with AcOEt (2 x 10 L, 1 x 6 L). Combined organic layers were washed with water (5 x 3 L) to pH~6-7, saturated aqueous sodium hydrogen carbonate solution (15 L), dried (sodium sulfate), filtered and the solvent evaporated under reduced pressure to give a crude oil. The product was purified by vacuum distillation (130-139 °C, 2 mbar) to obtain title compound as a (2637 g 76%) of pale yellow oil.

^1H NMR (600 MHz, CDCl_3); δ 7.80 (m, 2 H); 7.57 (m, 1 H); 7.46 (m, 2 H); 7.32-7.37 (m, 3 H); 7.12(m, 1 H); 3.83 (s, 3 H).

Step 2; (3-Hydroxyphenyl)(phenyl)methanone

[0200]

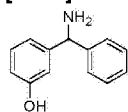


[0201] 1458 g (6.9 mol) of **(3-methoxyphenyl)(phenyl)methanone** was dissolved in 2090 mL of AcOH. To the solution, 2320 ml (20.6 mol) of 48% HBr was added and the mixture was stirred at 90 °C for 18 hours. The reaction was monitored by TLC (AcOEt:hex 1:9). After reaction was completed the mixture was cooled down to RT and poured into ice with stirring. The precipitated solid was filtered, washed with water and dried yielding the title compound as a white solid (1234 g, 91%).

^1H NMR (600 MHz, CDCl_3); δ 7.80 (m, 2 H); 7.58 (m, 1 H); 7.47 (m, 2 H); 7.39 (m, 1 H); 7.28-7.34 (m, 2 H); 7.11 (m, 1 H); 5.59 (brs, 1 H).

Step 3; 3-(Amino(phenyl)methyl)phenol

[0202]



[0203] **(3-Hydroxyphenyl)(phenyl)methanone** (400 g, 2 mol) was dissolved in methanol (4 L). Hydroxylamine hydrochloride (168 g, 2.4 mol) and sodium acetate (331 g, 4 mol) were added to the resulting solution. The mixture was refluxed for 18 hours. After cooling to RT solvent was evaporated under reduced pressure, then water (3 L) was added to the residue. The product was extracted with ethyl acetate (3 x 3L). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate, brine, dried (sodium sulfate), filtered and the solvent evaporated under reduced pressure. The crude residue (1085 g) was used in the next step without purification.

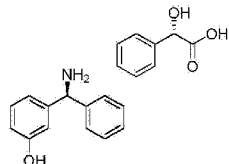
[0204] The crude oxime, 362 g, (287 g, 1.3 mol of pure oxime based on analysis) was dissolved in ethanol (860 mL) and 25% aqueous ammonia (3000 mL). To this mixture ammonium acetate (52 g, 0.7 mol) was added followed by portion wise addition of zinc powder (440 g, 6.7 mol) to maintain an internal not exceeding 40°C. The mixture was stirred without heating for 18 hours then filtered through a pad of celite. The filter cake was washed with ethyl acetate. The filtrate was collected and the formed layers were separated. The aqueous layer was extracted with ethyl acetate (5 x 5 L). the combined organic extracts layers were washed with brine (x 2) and the solvent was evaporated under

reduced pressure. The product was dried *in vacuo* (35 °C, 18 hours).

¹H NMR (600 MHz, DMSO-d₆); δ 9.25 (brs, 1 H); 7.36 (m, 2 H); 7.25 (m, 2 H); 7.15 (m, 1 H); 7.03 (m, 1 H); 6.79 (m, 2 H); 6.54 (m, 1 H); 4.98 (s, 1 H); 2.17 (brs, 2 H).

Step 4: Crystallization of (S)-3-(amino(phenyl)methyl)phenol (S)-mandelate

[0205]

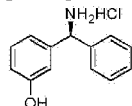


[0206] Salt formation: **3-(Amino(phenyl)methyl)phenol** (1081 g, 5.4 mol) was dissolved in *iso*-propanol (21.62 L) and heated to reflux. To the mixture a solution of S-mandelic acid (908 g, 6 mol) in *iso*-propanol (2160 mL) was added dropwise. The mixture was refluxed for 1 hour and then allowed to cool to 10 °C (over 18 hours). The precipitate formed was filtered, washed with cold *iso*-propanol and dried *n vacuo* at 35 °C.

[0207] The obtained salt was refluxed in 95% *iso*-propanol for 1 hour. The mixture was allowed to cool down to 10 °C over 18 hours. The solid was filtered, washed with cold *iso*-propanol and dried in vacuum oven at 35 °C. The crystallization process was repeated two or more times until the ee was >98% by chiral HPLC analysis .

Step 5: (S)-3-(Amino(phenyl)methyl)phenol hydrochloride

[0208]



[0209] **(S)-3-(Amino(phenyl)methyl)phenol (S)-mandelate** (1027 g, 2.9 mol) of was suspended in ethyl acetate. A solution of sodium hydrogen carbonate (737 g, 8.8 mol) in water (11.05 L) was added drop wise and the mixture was stirred at RT for 18 hours. The mixture was separated and aqueous layer was extracted with ethyl acetate (5 x10 L). The combined organic extracts were combined and the solvent evaporated under reduced pressure to give 464 g (85%) of amine as a pale yellow crystals.

[0210] The amine (464 g, 2.3 mol) was suspended in methanol and 4M HCl in AcOEt (3500 mL, 14 mol) was added drop wise. The mixture was stirred for 18 hours and the solvent evaporated under reduced pressure. The residue was triturated with ether (2740 mL) for 18 hours. The suspension was filtered, the filter cake washed with ether and dried.

¹H NMR (600 MHz, DMSO-d₆); δ 9.74 (s, 1 H); 9.19 (s, 3 H); 7.54 (m, 2 H); 7.40 (m, 2 H); 7.33 (m, 1 H); 7.19 (m, 1 H); 7.00 (m, 1 H); 6.89 (m, 1 H); 6.78 (m, 1 H); 5.49 (s, 1H, CH).

Cpd.	LCMS/H PLC method	NMR data at 400 MHz	Salt
1	A	(DMSO-d ₆): δ 8.29-8.20 (m, 2 H); 8.10 (d, J = 9.9 Hz, 1 H); 7.97 (d, J = 8.0 Hz, 2 H); 7.57 (d, J = 8.0 Hz, 2 H); 7.32-7.18 (m, 6 H); 7.17-7.01 (m, 4 H); 6.98-6.85 (m, 4 H); 6.47 (d, J = 9.9 Hz, 1 H); 5.81 (s, 1 H); 5.17 (s, 2 H); 5.09 (dd, J = 7.9, 4.7 Hz, 1 H); 4.60 (d, J = 16.8 Hz, 3 H); 4.31 (d, J = 5.0 Hz, 2 H); 3.71 (s, 2 H); 3.12 (m, 1 H); 2.81-2.52 (m, 6 H); 2.09 (s, 4 H); 1.92 (s, 1 H); 1.69-1.26 (m, 4 H).	Formate
2	C	(DMSO-d ₆): δ 10.31 (br s, 1 H); 8.26-8.19 (m, 2 H); 8.10 (d, J = 9.92 Hz, 1 H); 7.96 (d, J = 8.07 Hz, 2 H); 7.56 (d, J = 8.01 Hz, 2 H); 7.31-7.16 (m, 8 H); 7.07-7.00 (m, 2 H); 6.97-6.85 (m, 5 H); 6.47 (d, J = 9.86 Hz, 1 H); 5.81 (d, J = 9.03 Hz, 1 H); 5.17 (s, 2 H); 5.06 (dd, J = 7.90, 4.39 Hz, 1 H); 4.62-4.58 (m, 3 H); 4.34-4.29 (m, 2 H); 3.70 (s, 2 H); 3.16-3.04 (m, 1 H); 2.75-2.57 (m, 5 H); 2.34-2.31 (m, 1 H); 1.94-1.74 (m, 2 H); 1.64-1.28 (m, 4 H).	Formate
3	A	(DMSO-d ₆): δ 8.25 (s, 2 H); 8.12 (d, J = 9.9 Hz, 1 H); 7.95 (d, J = 8.0 Hz, 2 H); 7.56 (d, J = 8.0 Hz, 2 H); 7.37 (d, J = 2.0 Hz, 1 H); 7.32-7.14 (m, 8 H); 7.08-7.02 (m, 2 H); 6.98-6.86 (m, 3 H); 6.47 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 8.0 Hz, 1 H); 5.17 (s, 2 H); 5.06 (dd, J = 7.9, 4.4 Hz, 1 H); 4.65-4.54 (m, 3 H); 4.41 (d, J = 4.8 Hz, 2 H); 3.69 (s, 2 H); 3.11 (d, J = 13.0 Hz, 1 H); 2.77-2.55 (m, 5 H); 1.91 (s, 1 H); 1.79 (s, 1 H); 1.63-1.31 (m, 4 H).	Formate
4	A	(DMSO-d ₆): δ 8.32-8.20 (m, 2 H); 8.11 (d, J = 9.9 Hz, 1 H); 7.96 (d, J = 8.0 Hz, 2 H); 7.56 (d, J = 8.0 Hz, 2 H); 7.32-7.17 (m, 6 H); 7.10-6.82 (m, 8 H); 6.47 (d, J = 9.9 Hz, 1 H); 5.81 (s, 1 H); 5.18-5.06 (m, 3 H); 4.58 (m, 3 H); 4.30 (s, 2 H); 3.76 (s, 2 H); 3.71 (s, 3 H); 3.14 (m, 1 H); 2.81-2.63 (m, 6 H); 1.93 (s, 1 H); 1.81 (s, 1 H); 1.73-1.25 (m, 4 H).	Formate
5	C	(DMSO-d ₆): δ 8.27 (s, 2 H); 8.12 (d, J = 9.9 Hz, 1 H); 7.96 (d, J = 7.9 Hz, 2 H); 7.58-7.52 (m, 3 H); 7.34-7.11 (m, 8 H); 7.09-7.00 (m, 2 H); 6.97-6.85 (m, 3 H); 6.47 (d, J = 9.8 Hz, 1 H); 5.81 (s, 1 H); 5.16 (s, 2 H); 5.07 (dd, J = 8.0, 4.5 Hz, 1 H); 4.61 (s, 3 H); 4.41 (s, 2 H); 3.70 (s, 2 H); 3.12 (d, J = 11.3 Hz, 1 H); 2.81-2.51 (m, 5 H); 1.92 (s, 1 H); 1.80 (s, 1 H); 1.59 (s, 1 H); 1.48 (s, 2 H); 1.35 (s, 2 H).	Formate
6	C	(DMSO-d ₆): δ 10.32 (s, 1 H); 8.33-8.16 (m, 2 H); 8.14 (d, J = 9.9 Hz, 1 H); 7.96 (d, J = 8.1 Hz, 2 H); 7.56 (d, J = 8.0 Hz, 2 H); 7.30-7.16 (m, 7 H); 7.15-7.01 (m, 4 H); 6.97-6.85 (m, 3 H); 6.47 (d, J = 9.9 Hz, 1 H); 5.81 (d, J = 9.1 Hz, 1 H); 5.17 (s, 2 H); 5.05 (dd, J = 7.8, 4.5 Hz, 1 H); 4.69-4.55 (m, 3 H); 4.44-4.39 (m, 2 H); 3.85-3.74 (m, 2 H); 3.24-3.07 (m, 1 H); 2.81-2.40 (m, 7 H); 1.92 (s, 1 H); 1.80 (s, 1 H); 1.70-1.26 (m, 3 H).	Formate
7	C	(DMSO-d ₆): δ 10.32 (s, 1 H); 8.25 (s, 2 H); 8.21-8.08 (m, 3 H); 7.99 (d, J = 8.1 Hz, 2 H); 7.58-7.44 (m, 4 H); 7.40 (d, J = 7.9 Hz, 1 H); 7.30-7.16 (m, 6 H); 7.08-6.82 (m, 6 H); 6.46 (d, J = 9.9 Hz, 1 H); 5.81 (d, J = 9.1 Hz, 1 H); 5.16 (s, 2 H); 5.10 (dd, J = 7.9, 4.6 Hz, 1 H); 4.78 (s, 2 H); 4.58 (s, 1 H); 4.51 (s, 2 H); 4.14 (t, J = 3.4 Hz, 2 H); 3.19-3.08 (m, 1 H); 2.87-2.62 (m, 7 H); 1.91 (s, 1 H); 1.79 (s, 1 H); 1.68-1.25 (m, 3 H).	Formate
8	C	(DMSO-d ₆): δ 10.31 (s, 1 H); 8.23 (s, 2 H); 8.13 (d, J = 9.9 Hz, 1 H); 7.96 (d, J = 8.1 Hz, 2 H); 7.56 (d, J = 8.0 Hz, 2 H); 7.37 (d, J = 8.5 Hz, 1 H); 7.31-7.17 (m, 6 H); 7.09-7.02 (m, 3 H); 6.96-6.86 (m, 4 H); 5.81 (d, J = 9.1 Hz, 1 H); 5.17 (s, 2 H); 5.04 (dd, J = 7.7, 4.4 Hz, 1 H); 4.59 (s, 3 H); 4.36 (d, J = 4.8 Hz, 2 H); 3.75 (s, 2 H); 3.10 (m, 1 H); 2.75-2.61 (m, 8 H); 1.90 (s, 1 H); 1.78 (s, 1 H); 1.62-1.29 (m, 3 H).	Formate

Cpd.	LCMS/H PLC method	NMR data at 400 MHz	Salt
9	C	(DMSO-d ₆): δ 10.20 (s, 1 H); 8.29-8.20 (m, 2 H); 8.11 (d, J = 9.9 Hz, 1 H); 7.96 (d, J = 8.1 Hz, 2 H); 7.56 (d, J = 8.0 Hz, 2 H); 7.31-7.17 (m, 7 H); 7.09-7.01 (m, 2 H); 6.97-6.80 (m, 6 H); 6.46 (d, J = 9.9 Hz, 1 H); 5.81 (d, J = 9.1 Hz, 1 H); 5.17 (s, 2 H); 5.07 (dd, J = 7.9, 4.4 Hz, 1 H); 4.60 (m, 3 H); 4.33-4.28 (m, 2 H); 3.73 (s, 2 H); 3.11 (m, 1 H); 2.77-2.58 (m, 7 H); 1.90 (s, 1 H); 1.78 (s, 1 H); 1.66-1.25 (m, 3 H).	Formate
10	D	(DMSO-d ₆): δ 10.34 (s, 1 H); 8.28 (d, J = 9.7 Hz, 1 H); 8.21 (s, 2 H); 8.12 (d, J = 9.9 Hz, 1 H); 8.00 (d, J = 8.1 Hz, 2 H); 7.60 (d, J = 8.0 Hz, 2 H); 7.32-7.19 (m, 6 H); 7.09-7.02 (m, 2 H); 7.00-6.87 (m, 5 H); 6.48 (d, J = 9.9 Hz, 1 H); 5.83 (d, J = 8.6 Hz, 1 H); 5.19 (s, 2 H); 5.15-5.09 (m, 1 H); 4.68-4.53 (m, 3 H); 4.08 (s, 2 H); 3.72 (s, 2 H); 3.32-3.16 (m, 1 H); 2.87-2.56 (m, 7 H); 2.21 (s, 6 H); 1.96 (s, 1 H); 1.84 (s, 1 H); 1.73-1.31 (m, 3 H).	Diformate
11	A	(DMSO-d ₆): δ 10.29 (br s, 1 H); 8.27-8.19 (m, 2 H); 8.13 (d, J = 9.93 Hz, 1 H); 7.90 (d, J = 8.06 Hz, 2 H); 7.54 (d, J = 8.00 Hz, 2 H); 7.32-7.18 (m, 6 H); 7.09-7.02 (m, 2 H); 6.99-6.85 (m, 5 H); 6.45 (d, J = 9.86 Hz, 1 H); 5.82 (d, J = 7.84 Hz, 1 H); 5.16 (s, 2 H); 5.07 (dd, J = 7.64, 4.41 Hz, 1 H); 4.59 (s, 1 H); 4.53 (s, 2 H); 4.30 (s, 2 H); 3.74 (s, 3 H); 3.69 (s, 2 H); 3.13 (s, 1 H); 2.78-2.55 (m, 7 H); 1.92 (s, 1 H); 1.80 (s, 1 H); 1.67-1.29 (m, 3 H).	Formate
12	A	(DMSO-d ₆): δ 10.31 (br s, 1 H); 8.24 (s, 3 H); 8.11 (d, J = 9.93 Hz, 1 H); 7.97 (d, J = 8.04 Hz, 2 H); 7.57 (d, J = 8.01 Hz, 2 H); 7.33-7.15 (m, 8 H); 7.04 (t, J = 5.55 Hz, 2 H); 6.96-6.85 (m, 3 H); 6.60 (d, J = 2.32 Hz, 1 H); 6.57-6.47 (m, 2 H); 5.81 (s, 1 H); 5.18 (s, 2 H); 5.08 (dd, J = 7.86, 4.61 Hz, 1 H); 4.60 (s, 3 H); 4.34 (s, 2 H); 3.73 (d, J = 3.93 Hz, 5 H); 3.13 (d, J = 12.40 Hz, 1 H); 2.77-2.62 (m, 6 H); 1.92 (s, 1 H); 1.80 (s, 1 H); 1.71-1.25 (m, 3 H).	Diformate
13	A	(DMSO-d ₆): δ 10.29 (br s, 1 H); 8.30-8.20 (m, 3 H); 8.12 (d, J = 9.93 Hz, 1 H); 7.96 (d, J = 8.05 Hz, 2 H); 7.56 (d, J = 8.00 Hz, 2 H); 7.41 (s, 1 H); 7.32-7.18 (m, 6 H); 7.05 (d, J = 8.40 Hz, 2 H); 6.96-6.85 (m, 3 H); 6.82 (s, 1 H); 6.47 (d, J = 9.86 Hz, 1 H); 5.82 (d, J = 7.95 Hz, 1 H); 5.17 (s, 2 H); 5.03 (dd, J = 7.60, 4.58 Hz, 1 H); 4.63 (d, J = 5.03 Hz, 2 H); 4.58 (s, 1 H); 4.46 (d, J = 4.85 Hz, 2 H); 3.88-3.70 (m, 3 H); 3.63 (s, 2 H); 3.11 (d, J = 13.87 Hz, 1 H); 2.78-2.54 (m, 7 H); 1.90 (s, 1 H); 1.79 (s, 1 H); 1.46 (t, J = 49.22 Hz, 3 H).	Diformate
14	B	(CH ₃ OH-d ₄): δ 8.55 (s, 1 H); 8.28 (d, J = 9.87 Hz, 1 H); 8.00 (d, J = 8.13 Hz, 2 H); 7.50 (d, J = 8.09 Hz, 2 H); 7.32-7.21 (m, 5 H); 7.16 (d, J = 8.16 Hz, 1 H); 7.06 (s, 2 H); 6.98 (d, J = 8.15 Hz, 1 H); 6.95-6.87 (m, 4 H); 6.59 (d, J = 9.84 Hz, 1 H); 5.88 (s, 1 H); 5.20-5.13 (m, 4 H); 4.90 (m, 1 H); 4.70-4.65 (m, 2 H); 4.43-4.39 (m, 2 H); 4.13-4.05 (q, J = 10.6 Hz, 2 H); 3.51-3.48 (m, 1 H); 3.19-3.13 (m, 2 H); 3.08 (d, J = 14.26 Hz, 2 H); 2.92-2.88 (m, 2 H); 2.26 (s, 1 H); 2.2-2.07 (m, 1 H); 2.0-1.68 (m, 3 H).	Formate
15	A	(CH ₃ OH-d ₄): δ 8.53 (s, 2 H); 8.28 (d, J = 9.88 Hz, 1 H); 7.99 (d, J = 8.13 Hz, 2 H); 7.49 (d, J = 8.04 Hz, 2 H); 7.31-7.12 (m, 10 H); 7.01 (d, J = 8.15 Hz, 1 H); 6.96-6.88 (m, 3 H); 6.64 (d, J = 9.83 Hz, 1 H); 5.88 (s, 1 H); 5.31 (dd, J = 8.86, 4.22 Hz, 1 H); 5.14 (s, 2 H); 4.90 (m, 2 H); 4.71-4.66 (m, 2 H); 4.49-4.45 (m, 2 H); 4.01 (s, 2 H); 3.61-3.49 (m, 1 H); 3.25-3.16 (m, 2 H); 3.18-3.08 (m, 3 H); 3.04-2.98 (m, 1 H); 2.28 (s, 1 H); 2.21-2.1 (m, 1 H); 2.02-1.7 (m, 3 H).	Diformate

Cpd.	LCMS/H PLC method	NMR data at 400 MHz	Salt
16	A	(DMSO-d ₆): δ 10.29 (br s, 1 H); 8.30-8.19 (m, 2 H); 8.12 (d, J = 9.93 Hz, 1 H); 7.92 (d, J = 8.05 Hz, 2 H); 7.56 (d, J = 8.00 Hz, 2 H); 7.32-7.18 (m, 6 H); 7.11-7.02 (m, 2 H); 6.97-6.86 (m, 3 H); 6.63 (s, 2 H); 6.45 (d, J = 9.86 Hz, 1 H); 5.82 (d, J = 8.41 Hz, 1 H); 5.17 (s, 2 H); 5.10 (dd, J = 7.85, 4.46 Hz, 1 H); 4.59 (s, 1 H); 4.46 (d, J = 5.00 Hz, 2 H); 4.18 (t, J = 3.94 Hz, 2 H); 3.71 (s, 2 H); 3.65 (s, 6 H); 3.19-3.08 (m, 1 H); 2.77-2.62 (m, 7 H); 1.93 (s, 1 H); 1.81 (s, 1 H); 1.70-1.25 (m, 3 H).	Formate
17	C	(DMSO-d ₆): δ 10.49 (s, 2 H); 9.84 (s, 1 H); 9.01 (s, 1 H); 8.77 (s, 1 H); 8.45 (d, J = 9.11 Hz, 1 H); 8.13 (d, J = 9.94 Hz, 1 H); 7.98 (d, J = 8.08 Hz, 2 H); 7.57 (d, J = 9.33 Hz, 3 H); 7.32-7.19 (m, 6 H); 7.13 (d, J = 8.19 Hz, 1 H); 7.03 (s, 1 H); 7.02-6.86 (m, 4 H); 6.57 (d, J = 9.87 Hz, 1 H); 6.17 (s, 1 H); 5.83 (d, J = 9.06 Hz, 1 H); 5.38 (d, J = 8.92 Hz, 1 H); 5.17 (s, 2 H); 4.88-4.83 (m, 1 H); 4.66 (s, 2 H); 4.53 (s, 2 H); 4.21-4.07 (m, 1 H); 3.87 (s, 3 H); 3.71-3.59 (m, 1 H); 3.33-2.92 (m, 7 H); 2.23 (s, 1 H); 2.06 (d, J = 13.09 Hz, 1 H); 1.90-1.72 (m, 3 H).	Di-trifluoroacetate
18	C	(DMSO-d ₆): δ 8.28-8.19 (m, 3 H); 8.17 (d, J = 9.9 Hz, 1 H); 8.05 (s, 1 H); 7.94 (d, J = 7.8 Hz, 1 H); 7.72 (d, J = 7.7 Hz, 1 H); 7.58-7.52 (m, 1 H); 7.38 (d, J = 7.8 Hz, 2 H); 7.31-7.17 (m, 7 H); 7.10-7.02 (m, 2 H); 6.96-6.86 (m, 3 H); 6.51 (d, J = 9.9 Hz, 1 H); 5.81 (d, J = 9.0 Hz, 1 H); 5.33 (s, 2 H); 5.16 (s, 2 H); 5.07 (dd, J = 7.5, 4.8 Hz, 1 H); 4.57 (s, 1 H); 3.10 (s, 1 H); 2.86-2.65 (m, 8 H); 2.50 (m, 4 H); 1.90 (s, 1 H); 1.79 (s, 1 H); 1.46 (t, J = 49.4 Hz, 3 H).	Diformate
19	C	(DMSO-d ₆): δ 8.29 (s, 1 H); 8.16 (s, 1 H); 7.96 (d, J = 8.00 Hz, 2 H); 7.57 (d, J = 7.98 Hz, 2 H); 7.46 (t, J = 7.83 Hz, 1 H); 7.32-7.17 (m, 7 H); 7.17-6.99 (m, 4 H); 6.96-6.85 (m, 3 H); 6.50 (d, J = 9.84 Hz, 1 H); 5.80 (s, 1 H); 5.37 (s, 2 H); 5.18 (s, 2 H); 5.03 (dd, J = 7.70, 4.49 Hz, 1 H); 4.56 (s, 1 H); 3.16 (s, 3 H); 2.86-2.69 (m, 7 H); 2.68 (s, 1 H); 2.33 (s, 1 H); 1.89 (s, 1 H); 1.78 (s, 1 H); 1.57 (s, 1 H); 1.46 (s, 1 H); 1.32 (s, 1 H).	Formate
20	C	(DMSO-d ₆): δ 8.28 (s, 1 H); 8.23 (d, J = 9.5 Hz, 1 H); 8.17 (d, J = 9.9 Hz, 1 H); 8.00 (d, J = 8.0 Hz, 2 H); 7.58 (d, J = 8.0 Hz, 2 H); 7.31-7.17 (m, 6 H); 7.15 (d, J = 7.6 Hz, 1 H); 7.09-7.05 (m, 2 H); 7.03 (s, 1 H); 6.99-6.84 (m, 4 H); 6.51 (d, J = 9.9 Hz, 1 H); 5.81 (d, J = 9.2 Hz, 1 H); 5.32 (s, 2 H); 5.18 (s, 2 H); 5.10-5.03 (m, 1 H); 4.56 (s, 1 H); 3.79 (s, 3 H); 3.09 (m, 1 H); 2.82-2.65 (m, 11 H); 1.90 (d, J = 6.3 Hz, 1 H); 1.78 (s, 1 H); 1.58 (s, 1 H); 1.46 (s, 1 H); 1.33 (s, 1 H).	Formate
21	B	(DMSO-d ₆): δ 8.28-8.19 (m, 3 H); 8.17 (d, J = 9.9 Hz, 1 H); 8.05 (s, 1 H); 7.95 (d, J = 7.8 Hz, 1 H); 7.72 (d, J = 7.6 Hz, 1 H); 7.57-7.51 (m, 1 H); 7.33-7.17 (m, 10 H); 7.10-7.01 (m, 2 H); 6.96-6.85 (m, 3 H); 6.50 (d, J = 9.9 Hz, 1 H); 5.81 (d, J = 8.8 Hz, 1 H); 5.34 (s, 2 H); 5.16 (s, 2 H); 5.11-5.05 (m, 1 H); 4.58 (s, 1 H); 3.11 (m, 1 H); 2.95-2.60 (m, 11 H); 1.91 (s, 1 H); 1.79 (s, 1 H); 1.59 (s, 1 H); 1.48 (s, 1 H); 1.34 (s, 1 H).	Diformate
22	B	(DMSO-d ₆): δ 8.26 (s, 2 H); 8.17 (d, J = 9.9 Hz, 1 H); 8.04 (d, J = 8.0 Hz, 2 H); 7.61 (d, J = 8.0 Hz, 2 H); 7.48 (s, 1 H); 7.41-7.22 (m, 9 H); 7.13-7.07 (m, 2 H); 7.01-6.90 (m, 3 H); 6.51 (d, J = 9.9 Hz, 1 H); 5.86 (d, J = 8.6 Hz, 1 H); 5.39 (s, 2 H); 5.23 (s, 2 H); 5.12 (dd, J = 7.9, 4.3 Hz, 1 H); 4.63 (s, 1 H); 3.85 (s, 2 H); 3.17 (d, J = 14.5 Hz, 1 H); 2.83-2.67 (m, 7 H); 1.96 (m, 2 H); 1.66 (s, 1 H); 1.53 (s, 1 H); 1.39 (s, 1 H).	Formate
		(DMSO-d ₆): δ 8.62 (d, J = 2.2 Hz, 1 H); 8.24 (s, 2 H); 8.16 (d, J = 9.9 Hz, 1 H); 7.99 (d, J = 8.0 Hz, 2 H); 7.86 (dd, J = 8.0, 2.2 Hz, 1 H); 7.57 (d, J = 8.0 Hz, 2 H); 7.44 (d, J = 8.0 Hz, 1 H);	

Cpd.	LCMS/H PLC method	NMR data at 400 MHz	Salt
23	C	7.31-7.17 (m, 6 H); 7.07 (d, J = 8.1 Hz, 1 H); 7.03 (s, 1 H); 6.95-6.84 (m, 3 H); 6.49 (d, J = 9.9 Hz, 1 H); 5.81 (d, J = 9.0 Hz, 1 H); 5.38 (s, 2 H); 5.18 (s, 2 H); 5.09 (dd, J = 7.8, 4.5 Hz, 1 H); 4.57 (s, 1 H); 3.88 (s, 2 H); 3.12 (m, 1 H); 2.82-2.60 (m, 7 H); 1.91 (s, 1 H); 1.79 (s, 1 H); 1.66-1.28 (m, 3 H).	Formate
24	C	(DMSO-d ₆ @85°C): δ 8.22 (s, 2 H); 8.17 (d, J = 9.93 Hz, 1 H); 7.97-7.91 (m, 2 H); 7.54 (t, J = 7.70 Hz, 3 H); 7.31-7.19 (m, 6 H); 7.07 (d, J = 8.17 Hz, 1 H); 7.01 (s, 1 H); 6.95-6.86 (m, 3 H); 6.51-6.45 (m, 2 H); 6.23 (d, J = 3.12 Hz, 1 H); 5.82 (d, J = 8.64 Hz, 1 H); 5.28 (s, 2 H); 5.17 (s, 2 H); 5.03 (dd, J = 7.69, 4.73 Hz, 1 H); 4.60-4.57 (m, 1 H); 3.76 (s, 2 H); 3.07 (dd, J = 15.45, 8.55 Hz, 3 H); 2.82-2.76 (m, 1 H); 2.72-2.63 (m, 3 H); 2.62 (d, J = 4.93 Hz, 1 H); 2.59 (d, J = 4.88 Hz, 1 H); 1.89 (d, J = 3.93 Hz, 1 H); 1.58 (d, J = 8.96 Hz, 1 H); 1.49-1.47 (m, 1 H).	Formate
25	C	(DMSO-d ₆): δ 8.30-8.18 (m, 2 H); 8.14 (d, J = 9.9 Hz, 1 H); 7.96 (d, J = 8.1 Hz, 2 H); 7.57 (d, J = 8.0 Hz, 2 H); 7.52-7.45 (m, 1 H); 7.31-7.15 (m, 8 H); 7.10-6.99 (m, 2 H); 6.95-6.84 (m, 3 H); 6.47 (d, J = 9.9 Hz, 1 H); 5.81 (d, J = 9.0 Hz, 1 H); 5.37 (s, 2 H); 5.18 (s, 2 H); 5.06 (dd, J = 7.8, 4.4 Hz, 1 H); 4.58 (s, 1 H); 3.78 (s, 2 H); 3.12 (m, 1 H); 2.76-2.57 (m, 7 H); 1.91 (s, 1 H); 1.79 (s, 1 H); 1.65-1.27 (m, 3 H).	Formate
26	C	(DMSO-d ₆): δ 8.28-8.19 (m, 2 H); 8.10 (d, J = 9.9 Hz, 1 H); 7.96 (d, J = 8.0 Hz, 2 H); 7.56 (d, J = 8.0 Hz, 2 H); 7.39 (s, 1 H); 7.33-7.17 (m, 7 H); 7.08-6.97 (m, 3 H); 6.96-6.85 (m, 3 H); 6.46 (d, J = 9.9 Hz, 1 H); 5.81 (d, J = 9.0 Hz, 1 H); 5.31 (s, 2 H); 5.17 (s, 2 H); 5.07 (dd, J = 7.8, 4.5 Hz, 1 H); 4.58 (s, 1 H); 3.81 (s, 3 H); 3.75 (s, 2 H); 3.12 (m, 1 H); 2.79-2.63 (m, 7 H); 1.91 (s, 1 H); 1.79 (s, 1 H); 1.59 (s, 1 H); 1.48 (s, 1 H); 1.34 (s, 1 H).	Formate
27	C	(DMSO-d ₆): δ 8.23 (s, 3 H); 8.15 (d, J = 9.9 Hz, 1 H); 7.95 (d, J = 8.1 Hz, 2 H); 7.57 (d, J = 8.0 Hz, 3 H); 7.30-7.17 (m, 7 H); 7.07 (d, J = 8.1 Hz, 1 H); 7.03 (s, 1 H); 6.96-6.86 (m, 3 H); 6.60 (s, 1 H); 6.49 (d, J = 9.9 Hz, 1 H); 5.81 (d, J = 8.8 Hz, 1 H); 5.29 (s, 2 H); 5.18 (s, 2 H); 5.06 (dd, J = 7.6, 4.6 Hz, 1 H); 4.58 (s, 1 H); 3.61 (s, 2 H); 3.12 (m, 1 H); 2.78-2.60 (m, 6 H); 1.91 (s, 1 H); 1.79 (s, 1 H); 1.59 (s, 1 H); 1.48 (s, 1 H); 1.35 (s, 1 H).	Diformate
28	B	(DMSO-d ₆ /D ₂ O): δ 8.14 (d, J = 9.9 Hz, 1 H); 8.01 (d, J = 8.1 Hz, 2 H); 7.62 (d, J = 8.1 Hz, 2 H); 7.35-7.22 (m, 8 H); 7.17 (d, J = 8.2 Hz, 1 H); 7.05-6.99 (m, 3 H); 6.97-6.93 (m, 1 H); 6.61 (d, J = 9.9 Hz, 1 H); 5.87-5.84 (m, 1 H); 5.58 (s, 2 H); 5.21 (s, 2 H); 4.95-4.88 (m, 1 H); 4.44 (s, 2 H); 3.75-3.63 (m, 1 H); 3.30-3.07 (m, 9 H); 2.27 (s, 1 H); 2.10-1.76 (m, 3 H).	Trifluoroacetate
29	B	(DMSO-d ₆): δ 8.23 (s, 3 H); 8.13 (d, J = 9.9 Hz, 1 H); 7.98 (d, J = 8.0 Hz, 2 H); 7.56 (d, J = 8.0 Hz, 2 H); 7.46 (s, 1 H); 7.32-7.18 (m, 6 H); 7.10-6.99 (m, 3 H); 6.97-6.84 (m, 3 H); 6.47 (d, J = 9.9 Hz, 1 H); 5.81 (d, J = 8.8 Hz, 1 H); 5.26 (s, 2 H); 5.18 (s, 2 H); 5.06 (dd, J = 7.8, 4.5 Hz, 1 H); 4.58 (s, 1 H); 3.92 (d, J = 2.6 Hz, 2 H); 3.12 (d, J = 14.2 Hz, 1 H); 2.77-2.65 (m, 6 H); 1.91 (s, 1 H); 1.80 (s, 1 H); 1.59 (s, 1 H); 1.48 (s, 2 H); 1.35 (s, 1 H).	Diformate
30	A	(DMSO-d ₆): δ 8.27-8.19 (m, 3 H); 8.11 (d, J = 9.9 Hz, 1 H); 8.05 (s, 1 H); 7.94 (d, J = 7.7 Hz, 1 H); 7.72 (d, J = 7.7 Hz, 1 H); 7.57-7.51 (m, 1 H); 7.43 (s, 1 H); 7.35-7.16 (m, 9 H); 7.08-7.02 (m, 2 H); 6.96-6.85 (m, 3 H); 6.46 (d, J = 9.9 Hz, 1 H); 5.81 (d, J = 9.0 Hz, 1 H); 5.35 (s, 2 H); 5.16 (s, 2 H); 5.07 (dd, J = 8.0, 4.3 Hz, 1 H); 4.58 (s, 1 H); 3.79 (s, 2 H); 3.12 (m, 1 H);	Diformate

Cpd.	LCMS/H PLC method	NMR data at 400 MHz	Salt
		2.77-2.63 (m, 7 H); 1.91 (s, 1 H); 1.80 (s, 1 H); 1.59 (s, 1 H); 1.48 (s, 1 H); 1.35 (s, 1 H).	
31	C	(DMSO-d ₆): δ 10.53 (d, J = 7.72 Hz, 2 H); 9.59 (s, 1 H); 8.83 (s, 2 H); 8.49 (d, J = 9.18 Hz, 1 H); 8.13 (d, J = 9.95 Hz, 1 H); 8.07 (d, J = 8.14 Hz, 2 H); 7.64 (d, J = 8.14 Hz, 2 H); 7.51 (d, J = 7.73 Hz, 1 H); 7.39-7.25 (m, 6 H); 7.17 (t, J = 8.05 Hz, 2 H); 7.09-6.98 (m, 3 H); 6.96 (dd, J = 8.21, 2.42 Hz, 1 H); 6.62 (dd, J = 9.87, 2.00 Hz, 1 H); 6.23 (d, J = 3.80 Hz, 1 H); 5.88 (d, J = 9.09 Hz, 1 H); 5.46-5.35 (m, 2 H); 5.23 (s, 2 H); 4.93-4.88 (m, 1 H); 4.30 (d, J = 13.50 Hz, 2 H); 3.92 (s, 3 H); 3.71 (t, J = 10.79 Hz, 1 H); 3.38-3.09 (m, 6 H); 3.11 (s, 3 H); 2.28 (s, 1 H); 1.98-1.78 (m, 3 H).	Di-trifluoroacetate
32	C	(DMSO-d ₆): δ 10.29 (s, 1 H); 8.28-8.20 (m, 2 H); 8.11 (d, J = 9.92 Hz, 1 H); 7.96 (d, J = 8.06 Hz, 2 H); 7.56 (d, J = 7.98 Hz, 2 H); 7.32-7.15 (m, 10 H); 7.07-7.02 (m, 2 H); 6.96-6.85 (m, 3 H); 6.46 (d, J = 9.87 Hz, 1 H); 5.82 (d, J = 9.23 Hz, 1 H); 5.18 (s, 2 H); 5.06 (m, 1 H); 4.57 (m, 1 H); 4.29-4.22 (t, J = 6.34 Hz, 2 H); 3.72 (s, 2 H); 3.10 (m, 1 H); 2.75-2.60 (m, 7 H); 2.08-1.96 (m, 3 H); 1.90 (s, 1 H); 1.79 (s, 1 H); 1.62-1.26 (m, 4 H).	Formate
33	A	(DMSO-d ₆): δ 8.30-8.18 (m, 2 H); 8.11 (d, J = 9.9 Hz, 1 H); 7.91 (d, J = 8.0 Hz, 2 H); 7.54 (d, J = 8.0 Hz, 2 H); 7.32-7.15 (m, 8 H); 7.07-7.01 (m, 2 H); 6.97-6.85 (m, 3 H); 6.46 (d, J = 9.8 Hz, 1 H); 5.82 (d, J = 9.2 Hz, 1 H); 5.16 (s, 2 H); 5.05 (dd, J = 8.0, 4.3 Hz, 1 H); 4.56 (s, 1 H); 4.50-4.42 (m, 2 H); 3.71 (s, 2 H); 3.10-2.98 (m, 3 H); 2.74-2.59 (m, 6 H); 1.99-1.32 (m, 8 H).	Formate
34	A	(DMSO-d ₆): δ 8.29-8.18 (m, 2 H); 8.17 (d, J = 9.9 Hz, 1 H); 7.94 (d, J = 8.1 Hz, 2 H); 7.84 (s, 1 H); 7.57-7.50 (m, 3 H); 7.31-7.17 (m, 6 H); 7.08 (d, J = 8.1 Hz, 1 H); 7.02 (s, 1 H); 6.96-6.90 (m, 2 H); 6.88 (dd, J = 8.2, 2.5 Hz, 1 H); 6.51 (d, J = 9.9 Hz, 1 H); 5.81 (d, J = 9.0 Hz, 1 H); 5.21 (s, 2 H); 5.16 (s, 2 H); 5.10-5.04 (m, 1 H); 4.63-4.53 (m, 1 H); 4.17-4.10 (m, 2 H); 3.15-3.09 (m, 2 H); 2.75-2.48 (m, 8 H); 1.97-1.88 (m, 3 H); 1.85-1.72 (m, 1 H); 1.68-1.52 (m, 1 H); 1.55-1.40 (m, 1 H); 1.42-1.27 (m, 1 H).	Formate
35	C	¹ H NMR (400 MHz, DMSO): δ 10.50 (s, 2 H); 9.66 (s, 1 H); 8.87 (s, 2 H); 8.46 (d, J = 9.2 Hz, 1 H); 8.08 (d, J = 9.9 Hz, 1 H); 7.95 (s, 1 H); 7.87 (d, J = 8.1 Hz, 2 H); 7.61 (s, 1 H); 7.51 (d, J = 8.1 Hz, 2 H); 7.33-7.20 (m, 6 H); 7.10 (d, J = 8.2 Hz, 1 H); 7.04-6.93 (m, 3 H); 6.90 (dd, J = 8.2, 2.4 Hz, 1 H); 6.56 (d, J = 9.9 Hz, 1 H); 6.17 (s, 1 H); 5.84 (d, J = 9.1 Hz, 1 H); 5.30 (d, J = 9.4 Hz, 1 H); 5.15 (s, 2 H); 4.89-4.84 (m, 1 H); 4.57 (dd, J = 19.0, 5.3 Hz, 4 H); 4.10 (s, 3 H); 3.67 (t, J = 12.4 Hz, 2 H); 3.31-2.98 (m, 5 H); 2.24 (s, 1 H); 2.12-1.72 (m, 3 H).	Di-trifluoroacetate
36	A	(DMSO-d ₆): δ 8.48-8.07 (m, 3 H); 8.18 (d, J = 9.93 Hz, 1 H); 7.33-7.19 (m, 6 H); 7.13-7.04 (m, 2 H); 7.00-6.90 (m, 3 H); 6.88 (s, 1 H); 6.51 (d, J = 9.86 Hz, 1 H); 5.83 (d, J = 8.56 Hz, 1 H); 5.32-5.03 (m, 3 H); 4.60 (s, 2 H); 4.26-4.19 (m, 2 H); 4.10-3.66 (m, 3 H); 3.20-3.08 (m, 1 H); 2.93-2.54 (m, 9 H); 2.06-1.28 (m, 8 H).	Diformate
37	C	(DMSO-d ₆): δ 8.30-8.20 (m, 2 H); 8.18 (d, J = 9.9 Hz, 1 H); 7.93 (s, 1 H); 7.82 (d, J = 1.5 Hz, 1 H); 7.34-7.26 (m, 4 H); 7.28-7.18 (m, 2 H); 7.09 (d, J = 8.2 Hz, 1 H); 7.02 (s, 1 H); 6.94 (d, J = 8.0 Hz, 2 H); 6.88 (dd, J = 8.2, 2.5 Hz, 1 H); 6.51 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 8.2 Hz, 1 H); 5.16-5.11 (m, 1 H); 5.07 (s, 2 H); 4.58 (s, 1 H); 4.28-4.21 (m, 2 H); 3.11 (d, J = 11.1 Hz, 1 H); 2.85-2.58 (m, 7 H); 1.96-1.33 (m, 11 H)	Formate

Cpd.	LCMS/H PLC method	NMR data at 400 MHz	Salt
38	C	(DMSO-d ₆): δ 9.06 (d, J = 2.1 Hz, 1 H); 8.89 (d, J = 2.2 Hz, 1 H); 8.35 (s, 1 H); 8.36-8.16 (m, 3 H); 8.21-8.12 (m, 1 H); 7.32-7.18 (m, 7 H); 7.11-7.04 (m, 2 H); 6.99-6.89 (m, 3 H); 6.51 (dd, J = 9.8, 5.1 Hz, 1 H); 5.83 (d, J = 8.8 Hz, 1 H); 5.23 (s, 2 H); 5.14-5.07 (m, 1 H); 4.57 (s, 1 H); 4.36-4.29 (m, 2 H); 3.10 (m, 1 H); 2.82-2.70 (m, 6 H); 1.90 (s, 1 H); 1.81-1.71 (m, 4 H); 1.65-1.55 (m, 4 H); 1.48 (s, 1 H); 1.34 (s, 1 H).	Diformate
39	C	(DMSO-d ₆): δ 10.30 (br s, 1 H); 8.48-8.07 (m, 3 H); 8.21-8.10 (m, 2 H); 7.34-7.19 (m, 6 H); 7.15-7.04 (m, 2 H); 7.00-6.91 (m, 2 H); 6.75 (s, 1 H); 6.53 (d, J = 9.86 Hz, 1 H); 5.84 (d, J = 8.57 Hz, 1 H); 5.31-5.10 (m, 3 H); 4.61 (s, 1 H); 3.88 (s, 3 H); 3.31-2.97 (m, 3 H); 2.95-2.56 (m, 7 H); 1.94 (s, 1 H); 1.82 (s, 1 H); 1.73-1.16 (m, 9 H).	Diformate
40	C	(DMSO-d ₆): δ 10.38 (br s, 1 H); 8.46-8.39 (m, 1 H); 8.33-8.21 (m, 3 H); 8.18 (d, J = 9.93 Hz, 1 H); 7.34-7.19 (m, 6 H); 7.11 (d, J = 8.15 Hz, 1 H); 7.05 (t, J = 3.66 Hz, 2 H); 6.99-6.89 (m, 3 H); 6.69 (d, J = 3.44 Hz, 1 H); 6.54 (d, J = 9.86 Hz, 1 H); 5.84 (d, J = 8.95 Hz, 1 H); 5.20 (dd, J = 8.44, 4.14 Hz, 1 H); 5.08 (s, 2 H); 4.60 (s, 1 H); 3.28-3.01 (m, 3 H); 2.88 (d, J = 8.88 Hz, 2 H); 2.79 (s, 6 H); 1.93 (s, 1 H); 1.88-1.73 (m, 1 H); 1.74-1.15 (m, 7 H).	Diformate
41	B	(DMSO-d ₆): δ 10.31 (br s, 1 H); 8.61 (s, 1 H); 8.37 (t, J = 6.01 Hz, 1 H); 8.37-8.17 (m, 2 H); 8.17 (d, J = 9.92 Hz, 1 H); 7.33-7.19 (m, 6 H); 7.10 (d, J = 8.15 Hz, 1 H); 7.05-6.86 (m, 4 H); 6.53 (d, J = 9.86 Hz, 1 H); 5.83 (d, J = 8.65 Hz, 1 H); 5.25-5.14 (m, 3 H); 4.59 (s, 1 H); 3.23 (d, J = 6.27 Hz, 2 H); 3.21-3.06 (m, 1 H); 2.86-2.52 (m, 8 H); 1.92 (s, 1 H); 1.80 (s, 1 H); 1.71-1.16 (m, 8 H).	Formate
42	C	(DMSO-d ₆): δ 9.87 - 10.55 (bs, 1 H), 8.52 (d, J=9.26 Hz, 1 H), 8.33 (s, 2 H), 8.11 - 8.20 (m, 2 H), 8.05 (d, J=3.53 Hz, 1 H), 7.17 - 7.46 (m, 7 H), 6.87 - 7.10 (m, 5 H), 6.74 (d, J=3.53 Hz, 1 H), 6.48 (d, J=9.70 Hz, 1 H), 5.84 (d, J=9.26 Hz, 1 H), 4.93 - 5.23 (m, 6 H), 4.23 (t, J=6.39 Hz, 2 H), 3.98 - 4.12 (m, 2 H), 3.52 - 3.75 (m, 4 H), 2.57 - 2.80 (m, 4 H), 2.32 (m, 1 H), 1.86 - 2.23 (m, 4 H), 1.60 - 1.77 (m, 2 H), 1.44 - 1.57 (m, 2 H)	Hydrochloride

Biological characterization

Example 14

M3 Receptor radioligand binding assay

[0211] Human M3 receptor membranes (15ug/well) from Perkin Elmer were incubated with 0.52nM Scopolamine Methyl Chloride, [N-methyl-3H] with or without test compounds, or a saturating concentration of Atropine (5 μM) for the determination of non-specific binding. The assay was carried out in 96-well polypropylene plates in a volume of 250ul. The assay buffer used was 50mM Tris-HCl, 154mM NaCl (pH 7.4). The final assay concentration of DMSO was 0.5% (v/v). The plates were sealed and incubated for 2h at RT on an orbital shaker (slow speed). Membranes were harvested onto 96-well unfilter GF/C filter plates pre-treated with 0.5% polyethyleneimine (v/v), using a filter manifold, washed four times with 200ul of assay buffer. The plates were dried before addition of 50μl of microscint-0, sealed then read in a Trilux Microbeta scintillation counter. IC50 values are determined from competition curves using

a non-linear curve fitting program. K_i values were calculated from IC_{50} values by the Cheng and Prusoff equation.

[0212] The K_i values of the most of the compounds of the examples are less than 10 nM.

Example 15

β_2 adrenoceptor radioligand binding assay

[0213] Human β_2 adrenoceptor membranes (7.5 ug/well) from Perkin Elmer were incubated with 0.3 nM 125-1 Cyanopindolol with or without test compounds, or a saturating concentration of s-propranolol (2 μ M) for the determination of non-specific binding. The assay was carried out in 96-well polypropylene plates in a volume of 200 μ l. The assay buffer used was 25 mM HEPES, 0.5% BSA (w/v), 1 mM EDTA, 0.02% ascorbic acid (v/v), (pH 7.4). The final assay concentration of DMSO was 0.5% (v/v). The plates were sealed and incubated for 1h at RT on an orbital shaker (slow speed). Membranes were harvested onto 96-well unifilter GF/C filter plates pre-treated with 0.5% polyethyleneimine (v/v), using a filter manifold, washed six times with 200 μ l of wash buffer containing 10 mM HEPES and 500 mM NaCl. The plates were dried before addition of 50 μ l of microscint-0, sealed then read in a Trilux Microbeta scintillation counter. IC_{50} values are determined from competition curves using a non-linear curve fitting program. K_i values were calculated from IC_{50} values by the Cheng and Prusoff equation. The K_i values of the most of the compounds of the examples are less than 10 nM.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- [WO0069468A \[0005\]](#)
- [US2009181935A \[0005\]](#)
- [WO2005116467A \[0005\]](#)
- [WO2004074246A \[0007\]](#)
- [WO2004074812A \[0007\]](#)
- [WO2005051946A \[0007\]](#)
- [WO2006023457A \[0007\]](#)
- [WO2006023460A \[0007\]](#)
- [WO2010123766A \[0007\]](#)
- [WO2011048409A \[0007\]](#)
- [EP2012060795W \[0007\]](#)

Non-patent literature cited in the description

- **ADAM D. HUGHES et al.** Bioorganic & Medicinal Chemistry Letters, 2011, vol. 21, 5 [\[0007\]](#)
- Remington's Pharmaceutical Sciences Handbook Mack Pub., N.Y. [\[0049\]](#)

Patentkrav

1. Forbindelse, som er udvalgt fra gruppen bestående af:

5 2-(4-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-methyl)-2-methylphenoxy)ethyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)-amino)methyl)phenoxy)methyl)benzoat;

10 2-(4-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-methyl)phenoxy)ethyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)benzoat;

15 2-(2-chlor-4-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)-amino)methyl)phenoxy)ethyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)benzoat;

20 2-(4-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-methyl)-2-methoxyphenoxy)ethyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)-amino)methyl)phenoxy)methyl)benzoat;

2-(2-brom-4-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)-amino)methyl)phenoxy)ethyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)benzoat;

25 2-(2-chlor-3-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)-amino)methyl)phenoxy)ethyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)benzoat;

30 2-((4-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-methyl)naphthalen-1-yl)oxy)ethyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)-amino)methyl)phenoxy)methyl)benzoat;

35 2-(3-chlor-4-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)-amino)methyl)phenoxy)ethyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)benzoat;

2-(3-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-methyl)phenoxy)ethyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)benzoat;

5 2-(4-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-methyl)-2,6-dimethylphenoxy)ethyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)-amino)methyl)phenoxy)methyl)benzoat;

10 2-(2-chlor-4-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)-amino)methyl)-6-methoxyphenoxy)ethyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)-carbonyl)amino)methyl)phenoxy)methyl)benzoat;

15 2-(4-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-methyl)-3-methoxyphenoxy)ethyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)-amino)methyl)phenoxy)methyl)benzoat;

20 2-(2-brom-4-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)-amino)methyl)-5-methoxyphenoxy)ethyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)-carbonyl)amino)methyl)phenoxy)methyl)benzoat;

2-(2,6-dichlor-4-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)phenoxy)ethyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)-amino)methyl)-phenoxy)methyl)benzoat;

25 2-(2-fluor-4-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)-amino)methyl)phenoxy)ethyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)benzoat;

30 2-(4-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-methyl)-2,6-dimethoxyphenoxy)ethyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)-amino)methyl)phenoxy)-methyl)benzoat;

35 2-(2-chlor-4-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)-amino)methyl)-5-methoxyphenoxy)ethyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)-carbonyl)amino)methyl)phenoxy)methyl)benzoat;

4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-ethyl)benzyl 3-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)-phenoxy)methyl)benzoat;

5 2-fluor-4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)-amino)ethyl)benzyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)-phenoxy)methyl)benzoat;

10 4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-ethyl)-3-methoxybenzyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)benzoat;

15 3-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-ethyl)benzyl 3-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)-phenoxy)methyl)benzoat;

20 3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-methyl)benzyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)-phenoxy)methyl)benzoat;

(6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-methyl)pyridin-3-yl)methyl 4-((3-(S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)benzoat;

25 (5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-methyl)furan-2-yl)methyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)benzoat;

30 2-fluor-4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)-amino)methyl)benzyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)-phenoxy)methyl)benzoat;

35 5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-methyl)-2-methoxybenzyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)benzoat;

(4-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-methyl)furan-2-yl)methyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)benzoat;

5 (5-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-methyl)thiophen-2-yl)methyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)benzoat;

10 (5-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-methyl)thiophen-3-yl)methyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)benzoat;

15 3-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-methyl)benzyl 3-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)-phenoxy)methyl)benzoat;

20 4-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-methyl)-3-methoxybenzyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)benzoat;

3-(4-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-methyl)phenyl)propyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)-phenoxy)methyl)benzoat;

25 4-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-methyl)phenethyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)-phenoxy)methyl)benzoat;

30 (1-(3-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-propyl)-1H-pyrazol-4-yl)methyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)-amino)methyl)phenoxy)methyl)benzoat;

35 2-(4-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)-methyl)-1H-pyrazol-1-yl)ethyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)benzoat;

4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 1-methyl-5-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)-methyl)-1H-pyrazol-3-carboxylat;

5 4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)-thiophen-2-carboxylat;

10 4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 5-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)-nicotinat;

15 (R)-quinuclidin-3-yl ((S)-3-((3-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)carbamoyl)-1-methyl-1H-pyrazol-5-yl)methoxy)-phenyl)(phenyl)methyl)carbamate;

(R)-quinuclidin-3-yl ((S)-3-((5-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)carbamoyl)furan-2-yl)methoxy)phenyl)(phenyl)-methyl)carbamate;

20 (R)-quinuclidin-3-yl ((S)-3-((4-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)carbamoyl)oxazol-2-yl)methoxy)phenyl)(phenyl)-methyl)carbamate, og

25 (R)-3-((S)-3-((5-((4-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)butoxy)carbonyl)furan-2-yl)methoxy)phenyl)(phenyl)methylcarbamoxyloxy)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-1-azoniabicyclo[2.2.2]octan- chlorid-hydrochlorid,

30 eller et farmaceutisk acceptabelt salt af forbindelsen.

2. Farmaceutisk sammensætning omfattende en forbindelse som defineret i krav 1, med en eller flere farmaceutisk acceptable bærere og/eller hjælpestoffer.

3. Anvendelse af en forbindelse som defineret i krav 1 til fremstilling af et medikament til forebyggelse og/eller behandling af broncho-obstruktive eller inflammatoriske sygdomme, fortrinsvis asthma eller kronisk bronchitis eller kronisk obstruktiv pulmonær sygdom (COPD).

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4. Kombination af en forbindelse som defineret i krav 1 med en eller flere aktive bestanddele udvalgt fra klasserne bestående af beta2-agonister, antimuskarine midler, mitogen-aktiverede proteinkinaser (P38 MAP-kinase) hæmmere, nukleær faktor kappa-B-kinase underenhed beta (IKK2)-hæmmere, humane neutrofile elastase (HNE)-hæmmere, phosphodiesterase 4 (PDE4)-hæmmere, leukotrien-modulatorer, non-steroidale anti-inflammatoriske midler (NSAIDs), antitussive midler, mucus-regulatorer, mucolytika, ekspektorante/mucokinetiske modulatorer, peptid-mucolytika, antibiotika, hæmmere af JAK, SYK-inhibitorer, inhibitorer af PI3Kdelta eller PI3Kgamma, corticosteroider og M3-antagonister/PDE4-hæmmere (MAPI).

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5. Farmaceutisk sammensætning ifølge krav 2 til indgivelse ved inhalation, såsom inhalerbare pulvere, doseringsaerosoler, der indeholder drivmidler, eller drivmiddelfrie inhalerbare formuleringer.

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6. Indretning omfattende den farmaceutiske sammensætning ifølge krav 5, som kan være en enkelt- eller multidosis-tørpulverinhalator, en doseringsinhalator og en soft mist-forstøver.