

COMPOUNDS HAVING MUSCARINIC RECEPTOR ANTAGONIST AND BETA2 ADRENERGIC RECEPTOR AGONIST ACTIVITY

FIELD OF THE INVENTION

The present invention relates to compounds of general formula **I**, acting both as muscarinic receptor antagonists and beta2 adrenergic receptor agonists, to processes for their preparation, to compositions comprising them, to therapeutic
5 uses and combinations with other pharmaceutical active ingredients.

BACKGROUND OF THE INVENTION

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,
10 fenoterol, formoterol and salmeterol. These compounds are generally administered by inhalation.

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.

15 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
20 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).

25 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 discloses 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 5 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-ylacetox)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane.

An alternative approach to the development of fixed dose combinations is the identification of molecules that combine both activities of muscarinic 10 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.

15 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.

It has now been found that some particular carbamate derivatives, besides 20 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.

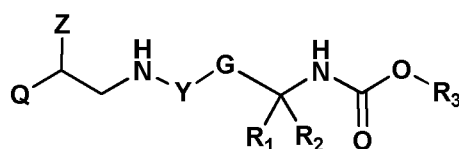
SUMMARY OF THE INVENTION

The present invention relates to compounds of general formula **I**, acting 25 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

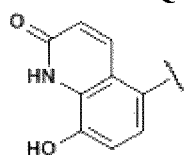
In particular, the invention is directed to compounds of general formula I



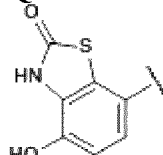
(I)

wherein

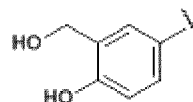
Q is a group of formula Q1, Q2 or Q3



Q1



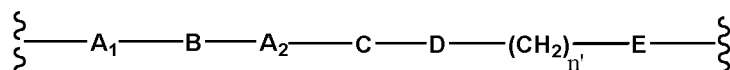
Q2



Q3

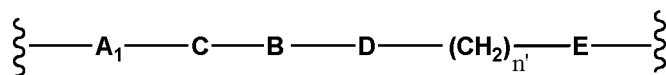
Z is H or OH;

Y is selected from Y' and Y1 which are divalent groups of formula



Y'

or



Y1

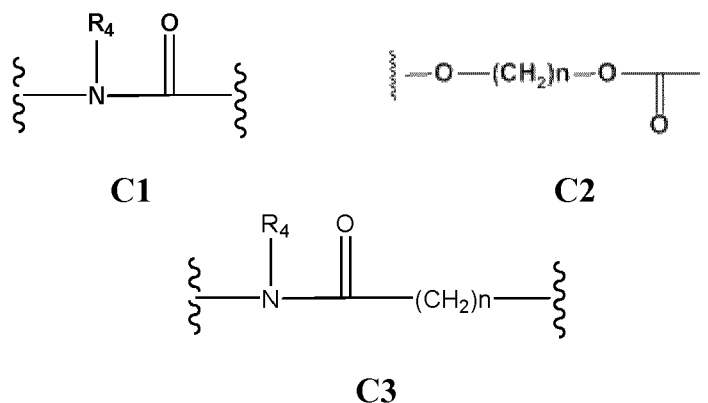
wherein

A1 and **A2** are independently absent or (C₁-C₆)alkylene;

B is absent or is selected from the group consisting of arylene and heteroarylene, optionally substituted by one or more groups selected from halogens, (C₁-C₆)alkyl,

5 halo(C₁-C₆)alkyl and (C₁-C₆)alkoxy;

C is absent or is -OC(O)- or is one of the following groups **C1-C3**



wherein **R₄** is H or linear or branched (C₁-C₄)alkyl;

D is absent or is selected from the group consisting of arylene and heteroarylene, optionally substituted by one or more (C₁-C₆)alkyl groups;

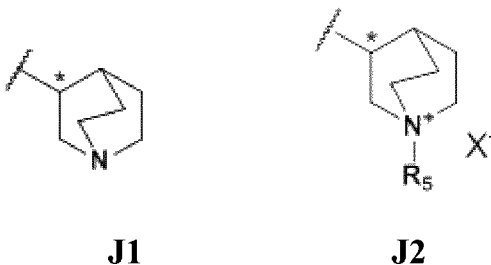
15 **n** and **n'** are independently 0 or an integer from 1 to 3;

E is absent or is selected from -O- and -OC(O)-;

G is arylene;

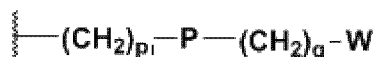
R₁ and **R₂** are independently H or aryl;

R₃ is a group of formula **J1** or **J2**



wherein **R₅** is a group of formula **K**

5



K

wherein p' is 0 or 1, P is absent or is CO, q is absent or is 1 and W is heteroaryl; and pharmaceutically acceptable salts or solvates thereof.

The expression “(C₁-C_x)alkyl” refers to straight or branched chain alkyl groups wherein the number of carbon atoms is from 1 to x. Examples of groups are methyl, ethyl, n-propyl, isopropyl, t-butyl, pentyl, hexyl and the like.

The expression “halo(C₁-C₆)alkyl” refers to straight or branched chain alkyl groups wherein the number of carbon atoms is from 1 to 6, substituted by one or more halogen atoms.

In an analogous manner, the expression “(C₁-C_x)alkylene” refers to divalent groups, such as methylene, ethylene, n-propylene, isopropylene, t-butylene, pentylene, hexylene, octylene, nonylene, decylene, undecylene, dodecylene and the like.

The expression “(C₁-C₁₀)alkoxy” refers to alkyl-oxy (e.g. alkoxy) groups, being the alkyl portion as above defined. Examples of said groups comprise methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, hexoxy and the like.

The expression “aryl” refers to mono, bi- or tricyclic ring systems having 5 to 20, preferably from 5 to 15, ring atoms, and wherein at least one ring is aromatic.

The expression “heteroaryl” refers to mono, bi- or tri-cyclic systems with 5 to 20 ring atoms, preferably from 5 to 15, in which at least one ring is aromatic and in which at least one carbon ring atom is a heteroatom or heteroaromatic group (e.g. N, NH, S or O).

Examples of suitable aryl or heteroaryl monocyclic systems include, for instance, thiophene, benzene, pyrrole, pyrazole, imidazole, isoxazole, oxazole,

isothiazole, thiazole, pyridine, imidazolidine, furan radicals and the like.

Examples of suitable aryl or heteroaryl bicyclic systems include naphthalene, biphenylene, purine, pteridine, benzotriazole, quinoline, isoquinoline, indole, isoindole, benzothiophene, dihydrobenzo dioxin, dihydro-indene,
5 dihydrobenzo dioxepin, benzo oxazin radicals and the like.

Examples of suitable aryl or heteroaryl tricyclic systems include fluorene radicals as well as benzocondensed derivatives of the aforementioned heteroaryl bicyclic systems.

In an analogous manner, the expressions “arylene” and “heteroarylene”
10 refer to divalent groups, such a phenylene, biphenylene and thienylene.

Whenever basic amino or quaternary ammonium groups are present in the compounds of formula **I**, physiological acceptable anions, selected among chloride, bromide, iodide, trifluoroacetate, formate, sulfate, phosphate, methanesulfonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate,
15 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.

It will be apparent that the compounds of general formula **I** may contain
20 asymmetric centers. Therefore, the invention also includes any of the optical stereoisomers, diastereoisomers and mixtures thereof, in any proportion.

In particular, the carbon atom linked to **R**₁, **R**₂, **G** and –NH– groups, depending on the meanings provided to **R**₁ and **R**₂ among those formerly reported, may represent a chiral center.

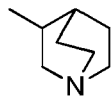
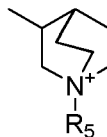
25 In an embodiment, the configuration is (S).

In another embodiment, the absolute configuration of this chiral center is preferably (R).

In another preferred embodiment, the compounds of general formula **I**

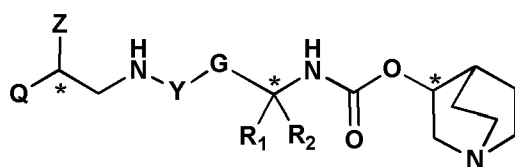
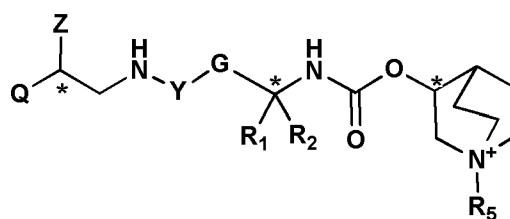
described in the present invention are present as mixtures of diastereoisomers.

It is apparent for those skilled in the art that compounds of general formula I wherein **R₃** is **J1** or **J2**

**J1****J2**

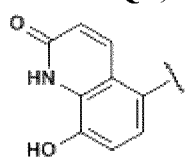
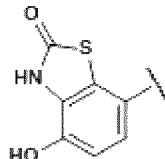
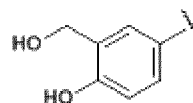
5 contain three stereogenic centers, as indicated below with an asterisk (*).

This means that the structure of formula I is characterized by eight different stereoisomers.

**(I)**

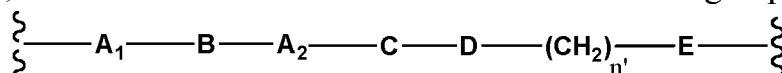
10 It is to be understood that all preferred groups or embodiments described herebelow for compounds of formula I may be combined among each other and apply as well *mutatis mutandis*.

A first preferred group of compounds is that of general formula I wherein **Q** is a group of formula **Q1**, **Q2** or **Q3**

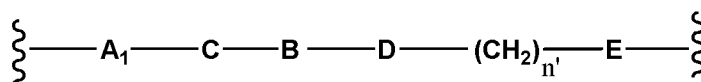
**Q1****Q2****Q3**

15

Z is H or OH; **Y** is selected from **Y'** and **Y1** which are divalent groups of formula

**Y'**

or

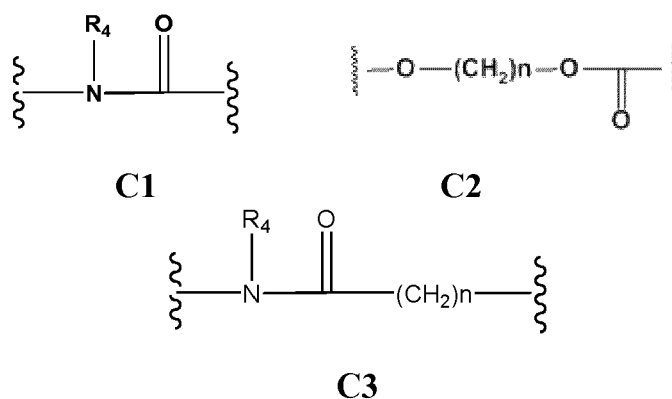


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Y1

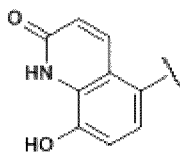
wherein **A1** and **A2** are independently absent or (C₁-C₆)alkylene; **B** is absent or is selected from the group consisting of arylene and heteroarylene, optionally substituted by one or more groups selected from halogens, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl and (C₁-C₆)alkoxy; **C** is absent or is -OC(O)- or is one of the following

5 groups **C1-C3**



10 wherein **R₄** is H or linear or branched (C₁-C₄)alkyl; **D** is absent or is selected from the group consisting of arylene and heteroarylene, optionally substituted by one or more (C₁-C₆)alkyl groups; **n** and **n'** are independently 0 or an integer from 1 to 3; **E** is absent or is selected from -O- and -OC(O)-; **G** is arylene; **R₁**, **R₂** and **R₃** are as defined above.

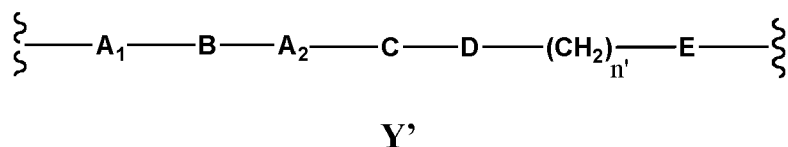
15 Still more preferred within this first group, are the compounds of general formula **I**, wherein **Q** is **Q1**



Q1

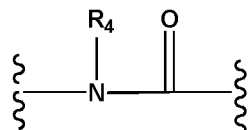
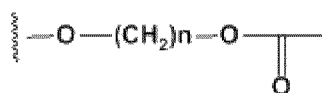
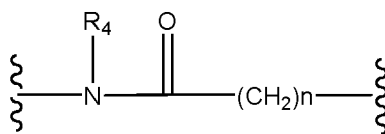
Z is -OH, **Y** is **Y'** which is a divalent group of formula

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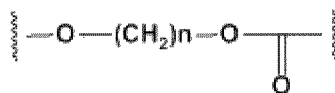
A1 and **A2** are independently absent or (C₁-C₆)alkylene; **B** is absent or is selected from the group consisting of arylene and heteroarylene, optionally

substituted by one or more groups selected from halogens, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl and (C₁-C₆)alkoxy; C is absent or is -OC(O)- or is one of the following groups **C1**-**C3**

**C1****C2****C3**

wherein **R**₄ is H or linear or branched (C₁-C₄)alkyl; **D** is absent or is arylene, optionally substituted by one or more (C₁-C₆)alkyl groups; **n** and **n'** are independently 0 or an integer from 1 to 3; **E** is absent or is -O-; and **G** is arylene.

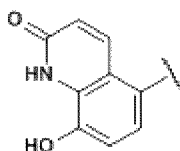
Still more preferred within this first group, are the compounds of general formula **I**, wherein **A1** is selected from the group consisting of methylene, ethylene and propylene; **A2** is absent or is selected from the group consisting of methylene, ethylene and propylene; **B** is absent or is selected from the group consisting of phenylene, naphthalene, pyridinediyl, furanediyl, thiophenediyl and pyrazolediyl; C is absent or is -OC(O)- or is a group of formula **C2**



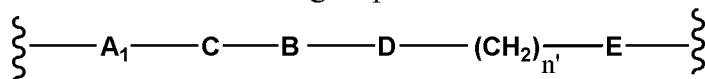
wherein **n** is 2; **n'** is 1; **D** is absent or is phenylene; **E** is absent or is -O- and **G** is phenylene.

A second group of preferred compounds of general formula **I**, is that wherein **Q** is **Q1**

10

**Q1**

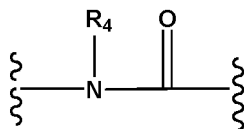
Z is -OH, **Y** is **Y1** which is a divalent group of formula



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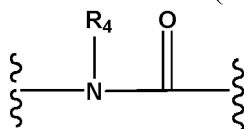
Y1

A1 is absent or (C₁-C₆)alkylene; **C** is absent or is -OC(O)- or is **C1**

**C1**

wherein **R₄** is H; **B** is absent or is selected from the group consisting of arylene and heteroarylene, optionally substituted by one or more groups selected from halogens, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl and (C₁-C₆)alkoxy; **D** is absent or is arylene; **n'** is 0 or an integer from 1 to 3; **E** is absent or is -O-; and **G** is arylene.

Still more preferred within this class, are the compounds of general formula **I**, wherein **A1** is butylene, **C** is absent or is -OC(O)- or is **C1**

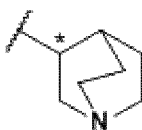
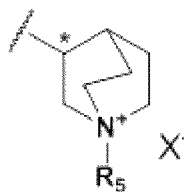


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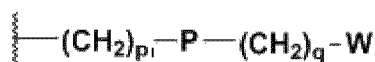
C1

wherein **R₄** is H; **B** is absent or is selected from the group consisting of pyrazolediyl, thiophenediyl, pyridinediyl, furanediyl and oxazolendiyl, optionally substituted by one or more groups selected from methyl; **D** is absent; **n'** is 1; **E** is -O-; **G** is phenylene and **R₃** is a group of formula **J1** or **J2**

20

**J1****J2**

wherein **R₅** is a group of formula **K**



K

wherein **p'** is 0 or 1, **P** is absent or is CO, **q** is absent or is 1 and **W** is heteroaryl;
and pharmaceutically acceptable salts or solvates thereof.

5 The present invention also provides pharmaceutical compositions of compounds of formula **I** alone or in combination with or in admixture with one or more pharmaceutically acceptable carriers and/or excipients.

The present invention also provides the use of compounds of formula **I** for preparing a medicament.

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

In a further aspect, the invention provides the use of compounds of formula
15 **I** 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).

The present invention further provides a method for prevention and/or treatment of any broncho-obstructive or inflammatory disease, preferably asthma
20 or chronic bronchitis or chronic obstructive pulmonary disease (COPD), which comprises administering to a subject in need thereof a therapeutically effective amount of a compound of general formula **I**.

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

25 Inhalable preparations include inhalable powders, propellant-containing metering aerosols or propellant-free inhalable formulations.

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 formula **I**.

The invention is also directed to a kit comprising the pharmaceutical compositions of compounds of formula **I** 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 general formula **I**.

According to specific embodiments, the present invention provides the compounds reported below:

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
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

(continued)

7	2-((4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)13aphthalene-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

(continued)

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-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
20	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)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

(continued)

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
31A	(5-((((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)thiazol-2-yl)methyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
31B	(5-((((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)isoxazol-3-yl)methyl 4-((3-((S)-phenyl((((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
31C	(5-((((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-1-methyl-1H-pyrazol-3-yl)methyl 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

(continued)

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
39A	(R)-Quinuclidin-3-yl ((S)-(3-((3-(ethyl(3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)propyl)carbamoyl)-1-methyl-1H-pyrazol-5-yl)methoxy)phenyl)(phenyl)methyl)carbamate
39B	(R)-Quinuclidin-3-yl ((S)-(3-((3-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)benzyl)carbamoyl)-1-methyl-1H-pyrazol-5-yl)methoxy)phenyl)(phenyl)methyl)carbamate
39C	(R)-Quinuclidin-3-yl ((S)-(3-((3-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-3-methoxybenzyl)carbamoyl)-1-methyl-1H-pyrazol-5-yl)methoxy)phenyl)(phenyl)methyl)carbamate
39D	(R)-quinuclidin-3-yl ((S)-(3-((3-((3-fluoro-4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)benzyl)carbamoyl)-1-methyl-1H-pyrazol-5-yl)methoxy)phenyl)(phenyl)methyl)carbamate
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
40A	(R)-Quinuclidin-3-yl ((S)-(3-((5-(ethyl(3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)propyl)carbamoyl)furan-2-yl)methoxy)phenyl)(phenyl)methyl)carbamate
41	(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
41A	(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)thiazol-2-yl)methoxy)phenyl)(phenyl)methyl)carbamate
41B	(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)benzyl)-oxy)phenyl)(phenyl)methyl)carbamate
41C	(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-3-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)ethyl)amino)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

(continued)

43	(R)-Quinuclidin-3-yl ((S)-(3-((4-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)benzyl)-carbamoyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate
44	(R)-Quinuclidin-3-yl ((S)-(3-((4-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-3-methoxybenzyl)carbamoyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate
45	(R)-Quinuclidin-3-yl ((S)-(3-((5-((3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)propyl)(methyl)carbamoyl)-1-methyl-1H-pyrazol-3-yl)methoxy)phenyl)(phenyl)methyl)carbamate
46	(R)-Quinuclidin-3-yl ((S)-(3-((5-((3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)propyl)(methyl)carbamoyl)-1-ethyl-1H-pyrazol-3-yl)methoxy)phenyl)(phenyl)methyl)carbamate
47	(R)-Quinuclidin-3-yl ((S)-(3-((4-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)(methyl)carbamoyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate
48	(R)-Quinuclidin-3-yl ((S)-(3-((4-(ethyl(4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)carbamoyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate
49	(R)-Quinuclidin-3-yl ((S)-(3-((3-((3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)propyl)(methyl)carbamoyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate
50	(R)-Quinuclidin-3-yl ((S)-(3-((3-(ethyl(3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)propyl)carbamoyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate
51	(R)-Quinuclidin-3-yl ((S)-(3-((4-(2-((3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)propyl)(methyl)amino)-2-oxoethyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate
52	(R)-Quinuclidin-3-yl ((S)-(3-((4-(2-((3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)propyl)amino)-2-oxoethyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate
53	(R)-Quinuclidin-3-yl ((S)-(3-((5'-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-2'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)phenyl)(phenyl)methyl)carbamate
54	(R)-Quinuclidin-3-yl ((S)-(3-((4'-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-3'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)phenyl)(phenyl)methyl)carbamate

(continued)

55	(R)-Quinuclidin-3-yl ((S)-(3-((3'-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-4'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)phenyl)(phenyl)methyl)carbamate
56	(R)-Quinuclidin-3-yl ((S)-(3-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate
57	(R)-Quinuclidin-3-yl ((S)-(3-((5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)furan-2-yl)methoxy)phenyl)(phenyl)methyl)carbamate
58	(R)-Quinuclidin-3-yl ((S)-(3-((3-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate
59	(R)-quinuclidin-3-yl ((S)-(3-((3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate
60	(R)-Quinuclidin-3-yl ((S)-(3-((6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)pyridin-3-yl)methoxy)phenyl)(phenyl)methyl)carbamate
61	(R)-Quinuclidin-3-yl ((S)-(3-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-3-methoxybenzyl)oxy)phenyl)(phenyl)methyl)carbamate
62	(R)-Quinuclidin-3-yl ((S)-(3-(2-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)phenyl)amino)-2-oxoethoxy)phenyl)(phenyl)methyl)carbamate
63	(R)-Quinuclidin-3-yl ((S)-(3-(2-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-3-methoxyphenyl)amino)-2-oxoethoxy)phenyl)(phenyl)methyl)carbamate
64	(R)-Quinuclidin-3-yl ((S)-(3-(2-((2-chloro-4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-5-methoxyphenyl)amino)-2-oxoethoxy)phenyl)(phenyl)methyl)carbamate
65	(R)-Quinuclidin-3-yl ((S)-(3-(2-((3-ethoxy-4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)phenyl)amino)-2-oxoethoxy)phenyl)(phenyl)methyl)carbamate
66	(R)-Quinuclidin-3-yl ((S)-(3-((4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)-3-(trifluoromethyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate
67	(R)-quinuclidin-3-yl ((S)-(3-((3-chloro-4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate
68	(R)-quinuclidin-3-yl ((S)-(3-((4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)-2-methylbenzyl)oxy)phenyl)(phenyl)methyl)carbamate

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.

5 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
10 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-
15 inhibitors (MAPI).

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,
20 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.

25 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 acclidinium, tiotropium, tiotropium bromide (Spiriva®), ipratropium, ipratropium bromide, trospium,

glycopyrrolate, NVA237, LAS34273, GSK656398, GSK233705, GSK57319, LAS35201, QAT370 and oxitropium salts.

The present invention also provides combinations of a compound of the invention, either as such or as pharmaceutically acceptable salt, with a PDE4
5 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.

10 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.

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

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,
20 respriva, AZD-9668, zemaira, AAT IV, PGX-100, elafin, SPHD-400, prolactin C and prolactin inhaled.

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.

25 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.

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 dexamorphane.

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

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.

10 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.

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

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,
20 talnetant, DNK-333, MSI-1956 and gefitinib.

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.

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

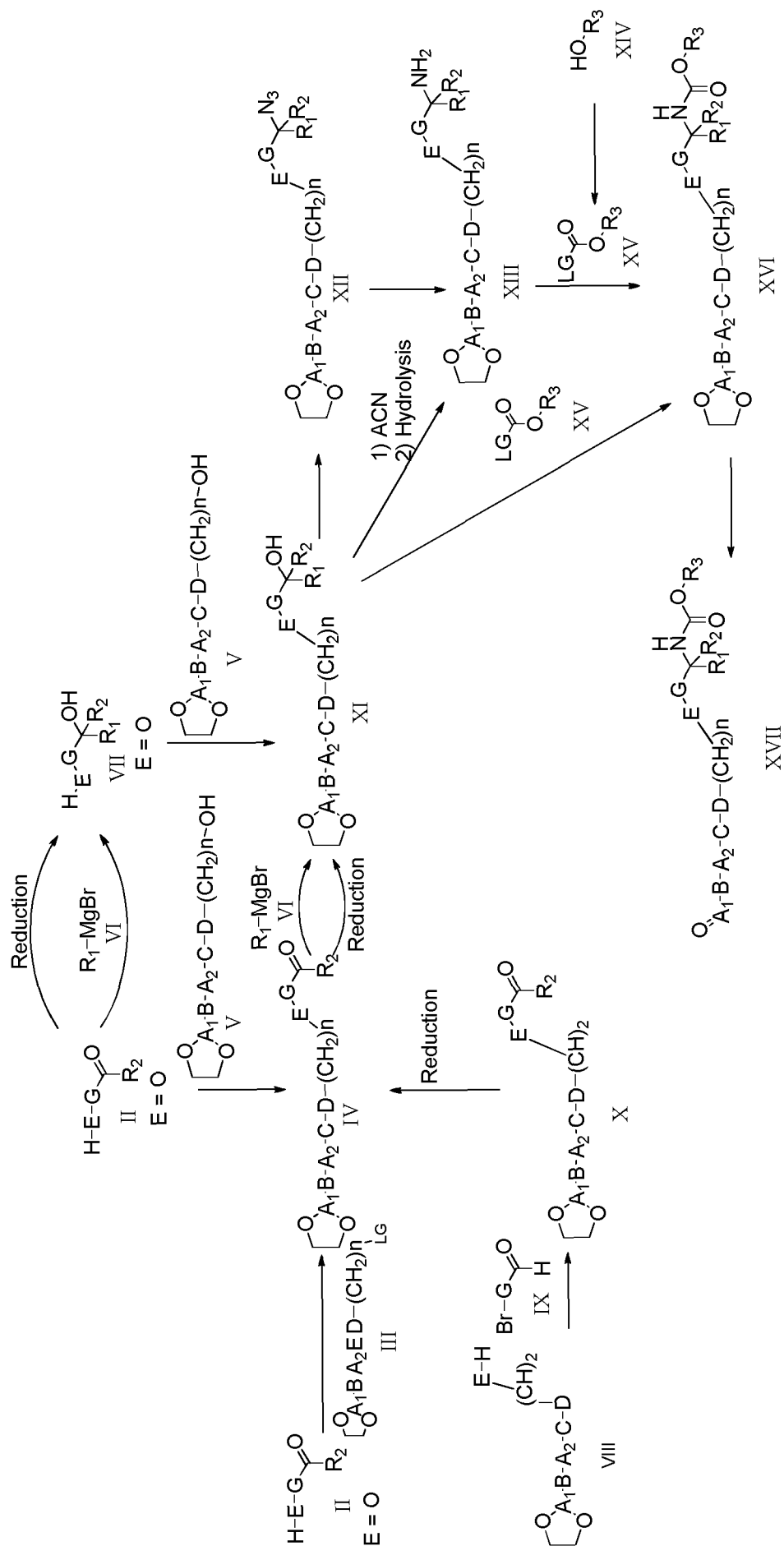
The invention also provides combinations of a compound of formula (I) with a corticosteroid selected from the group consisting of dexamethasone,

fluticasone, fluticasone furoate, fluticasone propionate, prednisolone, betamethasone, budesonide, mometasone, mometasone furoate, triamcinolone acetonide, ciclesonide, TPI-1020, beclomethasone, beclomethasone dipropionate, prednisone, deflazacort, hydrocortisone, QAE-397 and flunisolide.

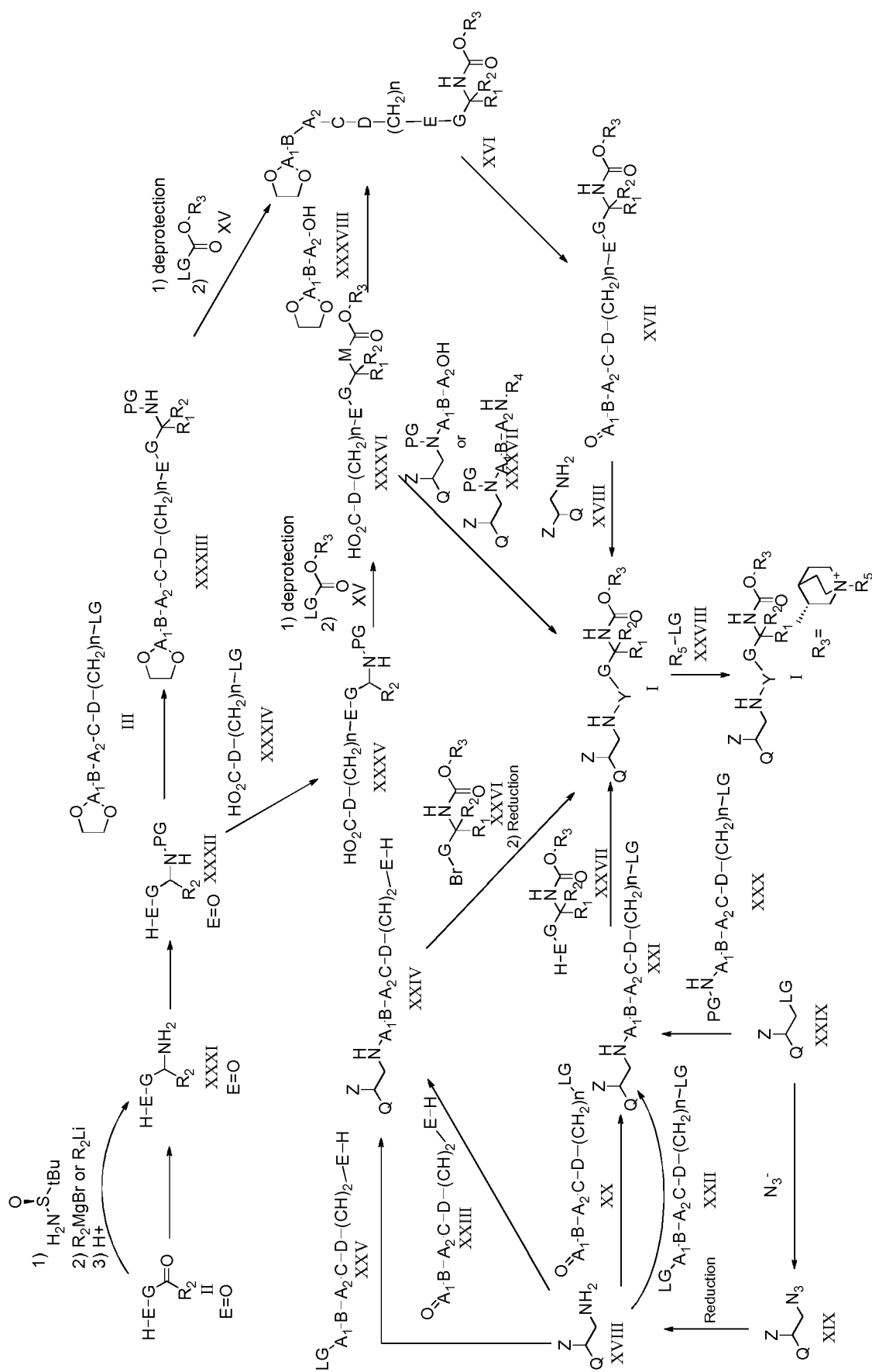
5 The compounds of the invention can be prepared from readily available starting materials using the following general methods and procedures or by using other information readily available to those of ordinary skill in the art. Although a particular embodiment of the present invention may be shown or described herein, those skilled in the art will recognize that all embodiments or aspects of the present
10 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
15 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.

Compounds of general formula **I** may be prepared according to the following synthetic **Schemes 1** and **2**.

Scheme 1



Scheme 2



General procedure for the preparation of compounds of formula I

The compounds of general formula **VIII** represent a compound wherein **A1** is alkylene substituted with oxo, leading to an aldehyde or ketone protected as cyclic acetal. The cyclic acetal protecting group (PG) can be removed leading to a
5 compound of general formula **XXIII**.

The synthesis of compounds of general formula **I** may require the protection of potential reactive functionality in addition to those methods already described. In such a case, examples of compatible protecting groups (PG) and their particular methods of protection and deprotection are described in "Protecting groups in
10 organic Synthesis" by T.W. Green and P. Wutz (Wiley-Interscience publication, 1999). Compounds of general formula **I** can be prepared for example by reaction of a compound of general formula **XVII** with a compound of general formula **XVIII**. This reductive amination reaction can be performed following several different protocols described in the literature and known for the skilled in the art.
15 For example, it can be performed in solvent such as methanol, ethanol, tetrahydrofuran (THF) or dichloromethane (DCM) using a reducing agent such as NaBH₄, NaCNBH₃ or NaBAcO₃H. It could be useful to obtain the imine before adding the reducing agent. The reaction proceeds smoothly at RT over 1 to 12 hours.

20 The intermediate of general formula **XVII** can be easily prepared by reaction of a compound of general formula **XIII** with a compound of general formula **XV**. The reaction occurs smoothly at RT or lower temperature in a solvent such as DCM or pyridine over 1-16 hours leading to compounds of formula **XVI** that can be easily deprotected in aqueous acidic solution, leading to a compound of
25 general formula **XVII** (see **Scheme 1**).

Compounds of general formula **XV** are either commercially available or can be prepared by reacting an alcohol of general formula **XIV** with for example diphosgene in a solvent such as DCM, THF or acetonitrile (ACN) at RT or lower

temperature, over a period of time ranging from 0.5 to 12 hours, leading to a compound of general formula **XV** wherein the leaving group LG is chlorine. Alternatively alcohol of general formula **XIV** can be reacted with for example carbonyldiimidazole (CDI) leading to the same intermediate wherein LG is imidazole. Other possible intermediates with other known LGs can be prepared as described in the literature.

Compound of general formula **XIII** may be prepared from a compound of general formula **XI** *via* Ritter reaction (acetonitrile and sulphuric acid at RT) followed by hydrolysis of the intermediate acetamide performed under basic condition.

Alternatively compounds of general formula **XIII** can be prepared by reduction of azide formula **XII** *via* hydrogenation under hydrogen atmosphere or hydrogen transfer conditions. The reaction occurs in alcohols at RT or higher temperature and stops in 1 to 12 hours. An alternative reduction method could be the Staudinger reaction, which involves treatment of the azide, first with for example triphenylphosphine, followed by hydrolysis of the iminophosphorane intermediate with water. This reaction occurs at RT in a water miscible solvent such as for example THF. The use of a strong reducing agent such as for example LiAlH_4 in THF or ether at -40°C or lower temperature could easily allow to perform the required conversion of compound **XIV** into **XIII**.

Azide **XII** is obtained from compound of formula **XI** by reaction with diphenyl phosphoryl azide. The reaction is performed in a high boiling point such as toluene or xylene in the presence of a strong base such as, but not limited to, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at a temperature ranging from 80 to 120°C and it completes over 12 to 24 hour. Alternatively the hydroxyl moiety of intermediate of formula **XI** can be converted into a suitable leaving group (LG), such as for example mesyl, tosyl or halogen and then reacted with an alkaline azide in a polar solvent such as acetonitrile, DMF or N-Methyl-2-pyrrolidone (NMP) at

RT or higher temperature.

Intermediates of general formula **XI** can be prepared in several different ways. For example they can be prepared from reaction of a compound of general formula **VII**, wherein **E** is -O-, and an aldehyde of general formula **V** featuring a
5 suitable hydroxyl group that can conveniently react under standard Mitsunobu conditions. The reaction is done in solvents such as THF or N-methyl-morpholine (NMM) at a temperature from -10 °C to RT and completes in 1 to 24 hours. It occurs in the presence of diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) and an organic phosphine such as, but not limited to,
10 triphenylphosphine.

Alcohol of general formula **VII** is either commercially available or it can be prepared from compound of formula **II** by addition of a Grignard reagent of formula **VI**. The reaction is normally done in an aprotic solvent such as ether or THF at RT or lower temperature and completes over 0.5 to 12 hours. Alternatively
15 it can be prepared by reduction of a compound of general formula **II**, wherein **R₂** is not hydrogen, with a reducing agent such as, but not limited to, NaBH₄, leading in this case to a compound of formula **VII** wherein **R₁** is hydrogen. The reaction is performed in a solvent such as methanol, ethanol or THF and completes over a period of time ranging from 1 to 12 hours. A similar synthetic protocol can be used
20 for the preparation of intermediate **XI** from compounds of general formula **IV**.

It is clear to a person skilled in the art that the preparation of compound of general formula **VII** or **XI** can be accomplished *via* inverse Grignard reaction in which Grignard of formula G-MgBr react with a compound of formula R₁C(O)R₂ under the same reaction conditions described above.

25 Compounds of general formula **IV** wherein **E** is -O-, can be prepared from a compound of general formula **II**, following an approach similar to that described for the preparation of compounds of formula **XI** from **VII**. Alternatively the compounds of general formula **IV** can be obtained by alkylation of a compound of

general formula **II**, with a compound of general formula **III** wherein LG is a suitable leaving group such as tosylate, mesylate or halogen. The reaction is normally done in polar solvents such as acetonitrile or DMF, occurs in a presence of a base such as for example alkaline carbonate, bicarbonates or organic bases and
5 completes over a period of time varying from 1 to 24 hours.

Preparation of compounds of formula **X** can be achieved by reaction of a compound of general formula **IX**, or the analogue wherein the bromine is substituted by iodine or triflate, with a compound of general formula **VIII**, wherein n is 2, under transition metal catalyzed cross-coupling reaction conditions. The
10 terminal alkene **VIII** can be reacted under for example the heck reaction condition with **IX**, leading to an alkenylene intermediate **X** that can be easily reduced by mean of a classical catalytic hydrogenation of double bond to give compounds of formula **IV**. A great number of protocols, reagents and catalysts can be conveniently used to achieve the desired conversion, as it is known to a person
15 skilled in the art.

Alternatively, compounds of general formula **I** featuring an ester moiety in the linker **Y**, can be prepared by treating a compound of general formula **XXXVI** with a compound of general formula **XXXVII**, wherein **A2** is functionalized with OH, under the condensation reaction condition for the preparation of esters. It is
20 possible prepare a compound of general formula **I**, wherein **C** is equal to **C1**, reacting a compound of general formula **XXXVI** with a compound **XXXVII** wherein **A2** is substituted with $-NR_4$ under the known reaction condition for the preparation of amide starting from carboxylic acid and amines.

In another embodiment of the present invention, compounds of general
25 formula **I** can be prepared following a different synthetic approach in which a compound of general formula **XXIV** is reacted with a compound of formula **XXVI** under the transition metal catalyzed cross-coupling reaction conditions, followed by reduction of the double bond $-(CH)_2-$, leading to a compound of formula **I**

wherein $n = 2$ or $n=3$ if the reaction is performed with a compound of formula LG-A₁-B-A₂-C-D-CH₂-(CH)₂-E-H. Alternatively it can be prepared by reaction of a compound of formula **XXI** with a compound of formula **XXVII** under the condition described above for the reaction of a compound of formula **II** with a
5 compound of formula **III**.

Intermediates of formula **XXIV** and **XXI** can be prepared by reaction of compound of formula **XVIII** under reductive amination conditions, described above for the reaction of compound of formula **XVII** with **XVIII**, starting from compound of formula **XXIII** and **XX** respectively. Alternatively compounds of
10 formula **XXIV** and **XXI** can be prepared by alkylation of compound **XVIII** with compound of formula **XXV** and **XXII** respectively under alkylation condition described above for the preparation of compound **IV** by reaction of compound **II** with compound **III**.

Compounds of general formula **XVIII** can be obtained from by simple
15 reduction of the azide of formula **XIX**. The reaction can be accomplished by mean of a catalytic hydrogenation in the presence Palladium catalyst. The reaction occurs, in polar solvent such as methanol or ethanol, under hydrogen atmosphere or under hydrogen transfer condition, using for example 1,4-cyclohexadiene or 1-methyl1,4-cyclohexadiene as source of hydrogen. The reaction proceeds at room
20 temperature (RT). In case it is performed under hydrogen transfer conditions higher temperature can be required.

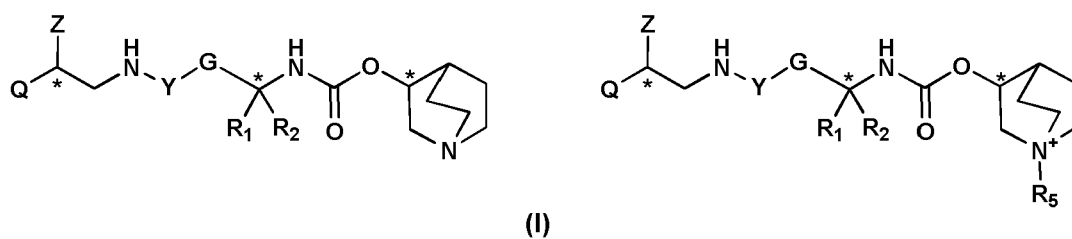
The azide **XIX** can be easily prepared from **XXIX** by the known nucleophilic substitution of alkyl bromide with alkaline azide. The reaction proceeds at a temperature ranging from 50 to 80°C and in a polar solvent such as
25 for example DMF or NMP and can be accelerated by the presence of alkaline iodide.

In an additional embodiment of the present invention, compounds of formula **I**, wherein **R₃** is **J2** or another group featuring a quaternary ammonium

salt, can be prepared reacting the corresponding tertiary amine precursor of formula **I** where **R₃** is **J1** with a compound of formula **XXVIII**. The reaction proceeds smoothly at RT or higher temperature in solvent such as DCM, acetonitrile, methanol or AcOEt over a period of time ranging from 1 to 24 hours.

5 In another embodiment of the present invention, compounds of general formula **XXI** can be prepared by reacting an intermediate of general formula **XXIX** with an amine of general formula **XXX**. This reaction is a common alkylation of amine in which the leaving group LG (normally chlorine, bromine or sulphate) is displaced by a nucleophile like the amine **XXX** as such or protected at
10 the amine moiety. Several methods to perform this reaction, that normally occurs in a polar solvent at a temperature higher than RT, are described in the literature. A similar reaction can be used for the preparation of a compound of general formula **XXXVII**.

It is apparent for those skilled in the art that compounds of general formula **I**
15 wherein **R₃** is **J1** or **J2** contain three stereogenic centers, as indicated below with the symbol asterisk (*). This means that the structure of formula **I** is characterized by eight different stereoisomers.



20 Each diastereoisomer can be obtained theoretically by chromatographic separation of the mixture obtained by reacting racemic mixtures of the required intermediates. It is clear that this approach it is not convenient and that it can be used only for the separation of mixtures containing few diastereoisomers.

In a more convenient approach, the synthesis of each single stereoisomer
25 can be accomplished using, in the reactions described above, only enantiomerically

pure intermediates.

The enantiomerically pure alcohol required for the preparation of compounds of general formula **I** wherein **R3** is **J1** or **J2** are commercially available.

5 The preparation of single enantiomerically pure compounds of general formula **XXIX** wherein LG is bromine are described in WO2005/080324, US2005-2222128, WO2004/032921, US2005/215590 and WO2005/092861 (cited by WO2007/107228). Enantiomerically pure compounds of general formula **XXXII** can be obtained by chiral chromatographic separation of the racemic
10 mixture or starting from enantiomerically pure amine compounds of general formula **XXXI**. Intermediate compounds of formula **XXXI** contains a basic group, it is possible to obtain the two enantiomers by mean of crystallization of the diastereomeric salt, obtained by salification of the racemic mixture with an enantiomerically pure carboxylic acid. Widely used carboxylic acids used for this
15 purpose are for example mandelic acid, tartaric acid and its derivatives. The base **XXXI** is dissolved in a suitable polar solvent and then treated with enantiomerically pure carboxylic acid causing precipitation of one of the two diastereoisomeric salts. It could be required to repeat the procedure several times to obtain the desired level of enantiomeric excess.

20 Alternatively the amines of formula **XXXI** can be obtained via enantioselective synthesis following for example the approach described in the literature (Tetrahedron: *Asymmetry* 13 (2002) 303–310) in which the aldehyde of formula **II**, wherein **R2** is H, is treated first with a enantiomerically pure tert-butyl sulfinimide and then with R₂MgBr or R₂Li (wherein **R2** is not H), followed by
25 hydrolysis of the intermediate leading to the formation of enantiomerically enriched compounds of formula **XXXI** that can be used as such or further purified to increase the enantiomeric excess.

The racemic amine of general formula **XXXI** can be prepared in several

different way, for example by addition of hydroxylamine to a compound of general formula **II** followed by the reduction of the oxime intermediate obtained than can be performed under several reaction condition known for the skilled in the art. For example catalytic hydrogenation, or the use of reducing agent such as LiAlH₄ or
5 Zinc in the presence of ammonium formate are all very efficient method to accomplished the reduction of oxime to amine.

The available amine of formula **XXXI** can be easily further derivatized under the reaction conditions described above. For example it can be treated with a protected aldehyde of formula **III**, under the conditions described for the
10 alkylation of compounds of formula **II** with compounds of formula **III**, leading to compound or general formula **XXXIII**. Deprotection of the amino group and reaction of compounds of formula **XV**, lead to the preparation of a compound of general formula **XVI**.

Alternatively, compound of general formula **I** can be prepared coupling a
15 compound of general formula **XXXVI** with a compound of general formula **XXXVII** leading to a compound of general formula **I** wherein **C** is -OCO- or **C1**. This ester or amide can be obtained under different reaction condition known to the skilled in the art. The reaction requires the activation of the acid **XXXVI** with reactant such as N,N'-Dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-
20 dimethylaminopropyl)carbodiimide (EDC), 2-(1H-Benzotriazole-1-yl)-1,1,3,3-Tetramethyluronium hexafluorophosphate (HBTU), (O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) or it may be converted into the corresponding acyl chloride. The activated ester can smoothly react, in DCM, pyridine or other aprotic solvents, with compound of formula
25 **XXXVII**.

Compound of formula **XXXVI** can be prepared starting from **XXXII** via alkylation with compound of formula **XXXIV**, deprotection and reaction with compound of formula **XV**. The reaction conditions for this conversion are

described above and described in the literature. Acid **XXXVI** can be easily reacted with a compound of formula **XXXVIII**, as described above for the reaction with a compound of formula **XXXVII**, leading to compound of formula **XVI**.

A compound of general formula **XXXVII** can be prepared by reaction of a
 5 compound of general formula **XXIX** with an amine of formula $\text{NH}_2\text{-A}_1\text{-B-A}_2\text{-OH}$ or $\text{NH}_2\text{-A}_1\text{-B-A}_2\text{-NHR}_4$, under the reaction conditions described for the reaction of compounds of general formula **XXIX** with compounds of general formula **XXX**.

For all the above, the synthesis of compounds of general formula **I** can be performed following several different approaches. In particular it must be noted
 10 that the sequence of reaction required, strongly depends on the nature of the linkers **Y** and **Y1** and on the functional groups present on the linker. The example given above for the preparation of compounds of formula **I** wherein **C** is -OC(O)- or **C1**, allows a person skilled in the art to appreciate this aspect of the invention.

The LCMS methods A, B, C and D used for the characterization of the
 15 compounds of the present invention, are described in the following:

LCMS/HPLC methods

Method A (10cm _ESCI_FORMIC)

HPLC Setup

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

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

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

Flow Rate: - 2ml/min

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

Time	A%	B%
25 0.00	95	5
3.50	5	95
5.50	5	95
5.60	95	5

6.50 95 5

Typical Injections 2-7ul (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

- 5 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 300ul/min to mass spec

- 10 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
15 single run.

Typical ESI voltages and temperatures are:

Source 120-150C 3.5KV capillary 25V cone

Typical APCI voltages and temperatures are:

Source 140-160C 17uA corona 25V cone

- 20 **Method B (HPLC Conditions - 15cm_Formic_Ascentis_HPLC_CH3CN)**

HPLC Setup

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,
25 150 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
5	13.7	96	4
	15	96	4

Typical Injections 0.2-10ul

Maximum pressure setting 400 bar.

Instrument: Agilent 1100, Binary Pump, Agilent Sampler and Agilent DAD
10 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

15 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

20	Time	A%	B%
	0.00	98	2
	3.00	98	2
	12.00	0	100
	15.4	0	100
25	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)

5 **Method D (HPLC Conditions - 25cm_Acidic_Prodigy_HPLC)**

HPLC Setup

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

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

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

10 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
15	22	0	100
	23	0	100
	25	95.5	4.5
	30	95.5	4.5

Typical Injections 2-7 μ l

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

The invention also provides pharmaceutical compositions of compounds of formula **I** in admixture with one or more pharmaceutically acceptable carriers, for example those described in Remington's Pharmaceutical Sciences Handbook, 25 XVII Ed., Mack Pub., N.Y., U.S.A.

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.

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.

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.

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.

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.

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.

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

5 Inhalable preparations include inhalable powders, propellant-containing metering aerosols or propellant-free inhalable formulations.

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.

10 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.

Inhalation aerosols containing propellant gas such as hydrofluoroalkanes
15 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.

The propellant-free inhalable formulations comprising the compounds of the invention may be in form of solutions or suspensions in an aqueous, alcoholic
20 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®.

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-
25 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).

5 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.

10 Advantageously, the compounds of formula **I** can be administered for example, at a dosage comprised between 0.001 and 1000 mg/day, preferably between 0.1 and 500 mg/day.

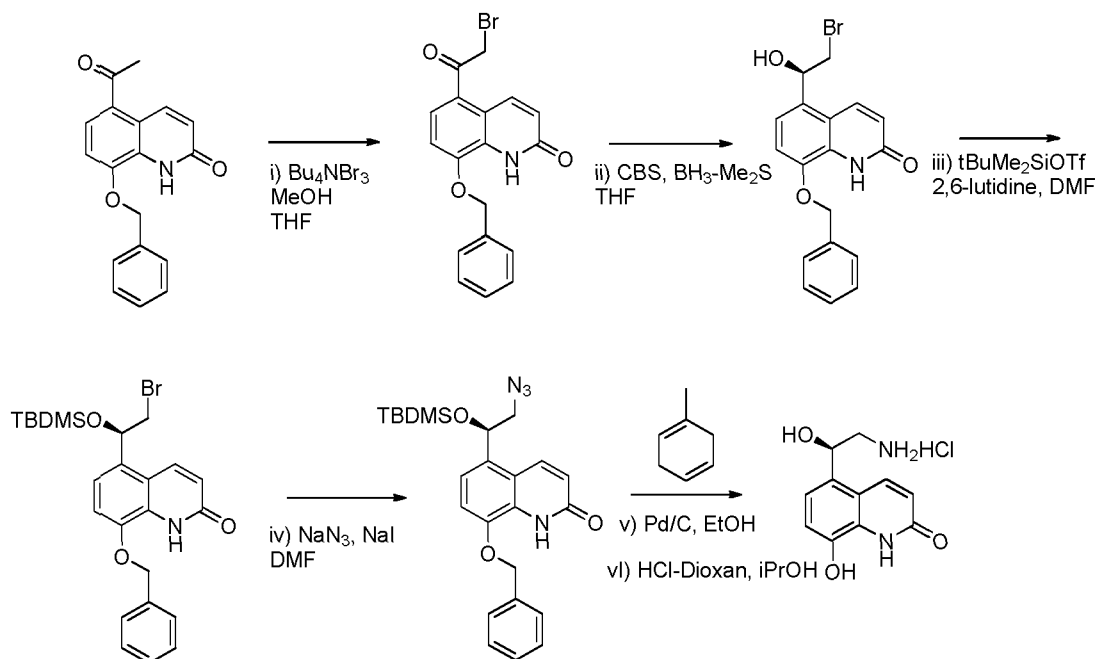
 When the compounds of formula **I** are administered by inhalation route, they are preferably given at a dosage comprised between 0.001 and 500 mg/day,
15 preferably between 0.1 and 200 mg/day.

 The compounds of formula **I** 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
20 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.

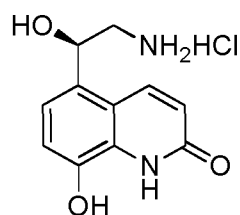
25 The present invention will now be further described by way of the following examples.

 The intermediate compounds for the synthesis of final compounds of general formula (I) were obtained through the preparations herebelow described.

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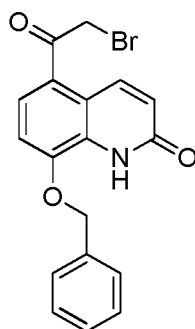


Preparation of (R)-5-(2-amino-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one hydrochloride



5

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



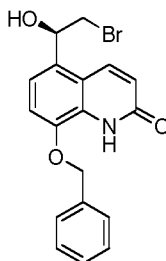
A suspension of 5-acetyl-8-(benzyloxy)quinolin-2(1H)-one (19.4 g, 66.4 mmol) in anhydrous THF (240 mL) and anhydrous methanol (165 mL) was added with a solution of *tetra*-*n*-butylammonium tribromide (Bu_4NBr_3) (54.5 g, 113.0 mmol) in anhydrous THF (130 mL) dropwise over 1.5 hours. The resulting solution 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

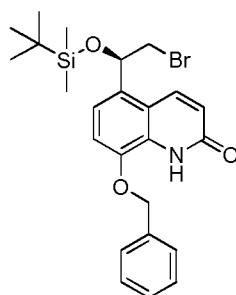


8-(Benzyloxy)-5-(2-bromoacetyl)quinolin-2(1H)-one (26.0 g, 69.9 mmol) and (*R*)-3,3-diphenyl-1-methyltetrahydro-3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole (21.3 g, 76.8 mmol) were azeotroped with toluene (× 3) then suspended in anhydrous THF (400 mL) under an atmosphere of nitrogen. The suspension was cooled 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).

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

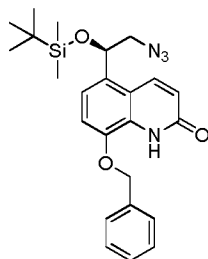


2,6-Lutidine (6.9 mL, 59.5 mmol) was added to a solution of (*R*)-8-(benzyloxy)-5-(2-bromo-1-hydroxyethyl)quinolin-2(1H)-one (10.1 g, 27.0 mmol) in DCM (100 mL) at 0 °C. The reaction mixture was stirred for 5 minutes then *tert*-butyldimethylsilyl trifluoromethanesulfonate (tBuMe₂SiOtf) (13.0 mL, 56.8 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 (x 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



(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

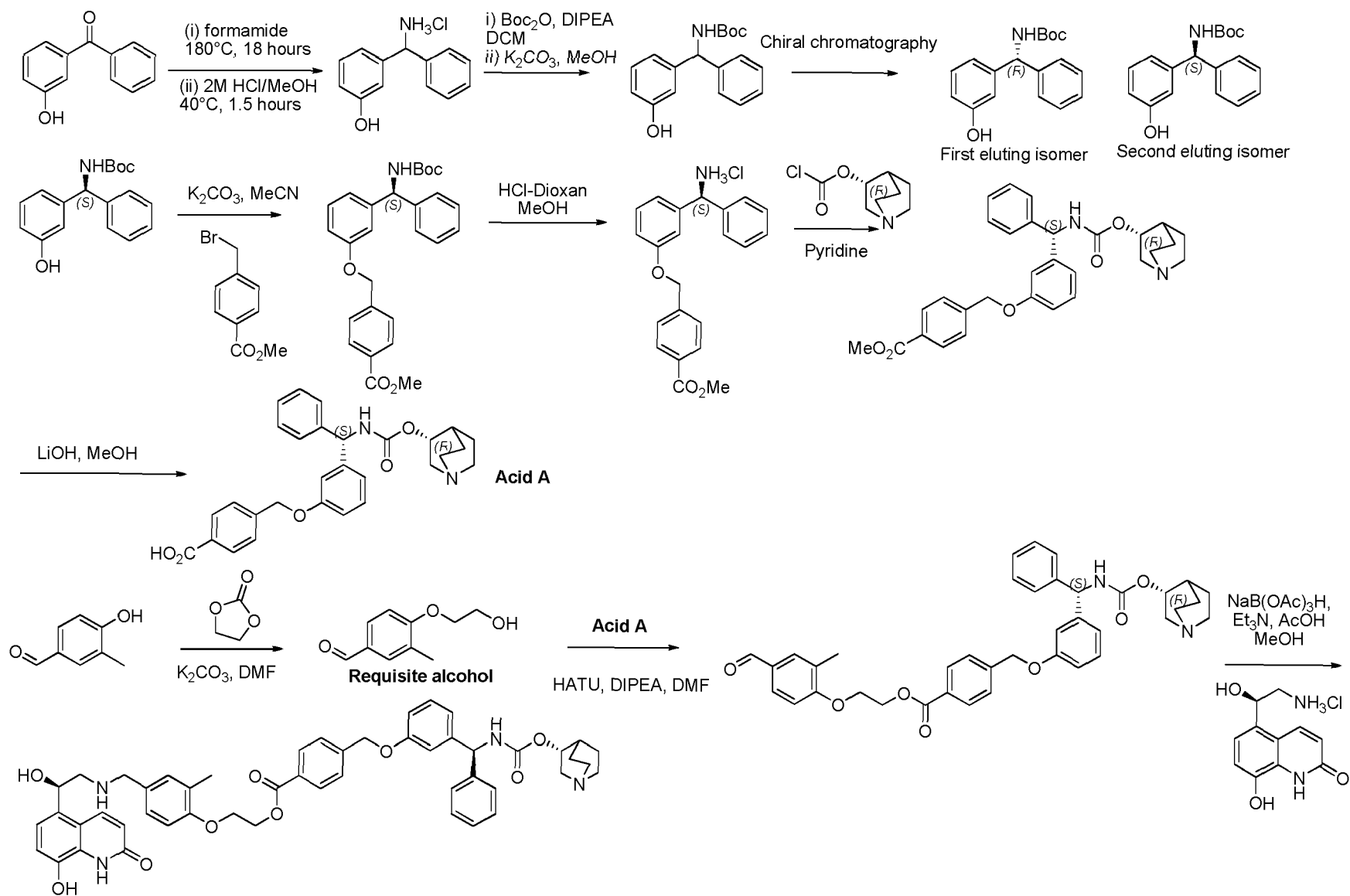
hydrochloride



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%).

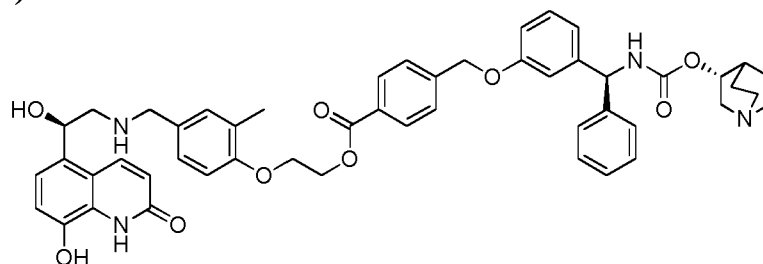
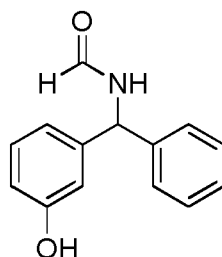
¹H NMR (400 MHz, MeOD): δ 7.71 (d, *J* = 9.8 Hz, 1 H), 6.57 (d, *J* = 8.2 Hz, 1 H), 6.31 (d, *J* = 8.2 Hz, 1 H), 6.02 (dd, *J* = 9.8, 6.5 Hz, 1 H), 4.58 (dd, *J* = 9.6, 3.5 Hz, 1 H), 2.47-2.31 (m, 2 H).

Synthesis of Compounds 1 to 17

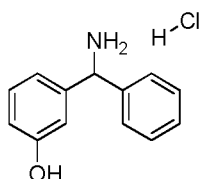


Example 1

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

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

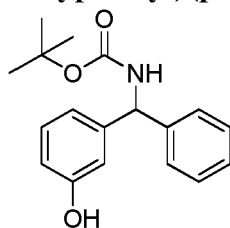
10 3-Hydroxybenzophenone (25 g, 126.1 mmol) in formamide (130 mL, 3.3 mmol) was heated to 180 °C for 18 hours. The reaction was allowed to cool slightly then poured into ice-cooled water and stirred for 30 minutes, filtered and washed with water. The solid was stirred in water (60 mL) and ethanol (60 mL) and heated to 50 °C for 1 hour, then allowed to cool. The solid was filtered and
15 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

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-d₆): 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

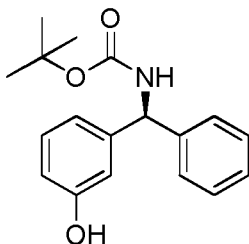


3-(Amino(phenyl)methyl)phenol hydrochloride (29.09 g, 123.4 mmol) in dichloromethane (450 mL) was cooled to 0 °C and diisopropylethylamine (65.9 mL, 370.2 mmol) and di-*tert*-butyl dicarbonate (59.2 g, 271.5 mmol) was added slowly. The reaction was stirred at 0 °C for 2 hours then warmed to RT over 16 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) was 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%).

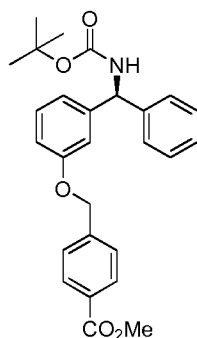
- 5 ¹H NMR (400 MHz, CDCl₃): δ 7.36-7.16 (m, 6 H); 6.80 (d, J = 7.79 Hz, 1 H); 6.74-6.69 (m, 2 H); 5.83 (s, 1 H); 5.15 (s, 1 H); 1.53-1.30 (s, 9 H).

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



- The racemic mixture from **step 3** was purified by SFC using a
 10 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**
 15



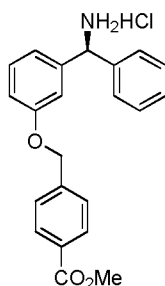
- A mixture of **(*S*)-*tert*-butyl ((3-hydroxyphenyl)(phenyl)methyl)carbamate** (3.20 g, 10.7 mmol), methyl 4-(bromomethyl)benzoate (2.70 g, 11.8 mmol) and potassium carbonate (2.20 g, 16.1 mmol) in acetonitrile (54 mL) was stirred at RT for 16 hours. The reaction

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.

- 5 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, CDCl₃): 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).

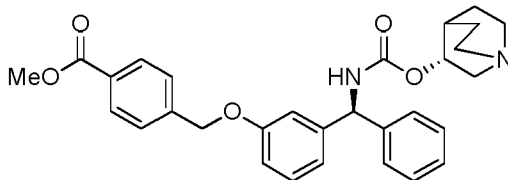
10 **Step 6; (S)-Methyl 4-((3-**
(amino(phenyl)methyl)phenoxy)methyl)benzoate hydrochloride



- A solution of **methyl 4-((3-(((tert-butoxycarbonyl)amino)**
 15 **(phenyl)methyl)phenoxy)methyl)benzoate** (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 %).

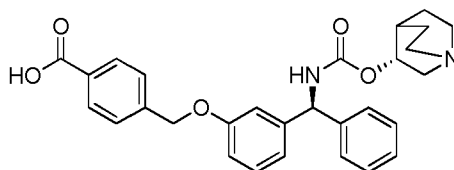
- ¹H NMR (400 MHz, CDCl₃): δ 9.21 (s, 2 H); 8.03 (d, *J* = 8.1 Hz, 2 H); 7.64 (d, *J* =
 20 8.1 Hz, 2 H); 7.59 (d, *J* = 7.6 Hz, 2 H); 7.49-7.34 (m, 5 H); 7.17 (d, *J* = 7.7 Hz, 1 H); 7.06 (dd, *J* = 8.3, 2.4 Hz, 1 H); 5.64 (s, 1 H); 5.28 (s, 2 H); 3.91 (s, 3 H).

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



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)methyl)benzoic acid

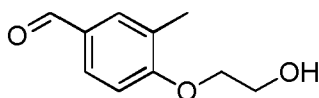


A stirred solution of methyl 4-((3-((*S*)-phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate (2.27 g, 4.50 mmol) in THF (23 mL) was added with an aqueous solution of lithium hydroxide (2.0 M, 9.0 ml, 18.0 mmol). The mixture was stirred at RT for 16 hours. The pH of the reaction 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, DMSO-d₆): 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



10

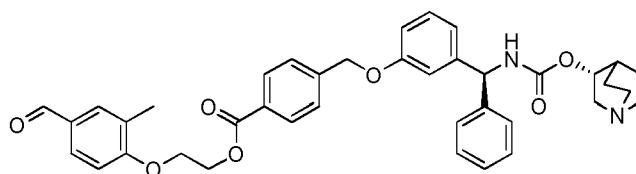
A stirred solution of 4-hydroxy-3-methyl-benzaldehyde (0.545 g, 4.00 mmol) in DMF (10 mL) was added with potassium carbonate (1.10 g, 7.97 mmol). The reaction mixture was stirred at RT for 5 minutes and then a solution of ethylene carbonate (0.705 g, 8.00 mmol) in DMF (2 mL) was added. The resultant 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%).

15

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).

20

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



25

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).

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)

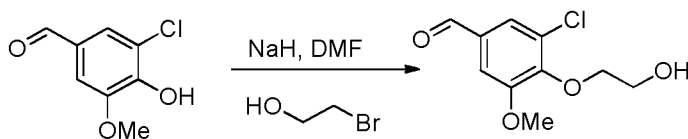
A suspension of **(*R*)-5-(2-amino-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one hydrochloride** (0.211 g, 0.83 mmol) in methanol (6 mL) was added with triethylamine (0.229 mL, 1.65 mmol). The mixture was stirred for 10 minutes and then a solution of **2-(4-formyl-2-methylphenoxy)ethyl 4-((3-((*S*)-phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)-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%).

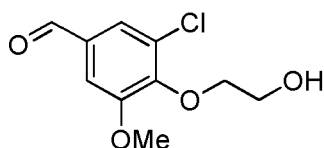
^1H NMR (400 MHz, DMSO- d_6): δ 8.29-8.20 (m, 2 H); 8.10 (d, J = 9.9 Hz, 1 H); 7.97 (d, J = 8.0 Hz, 2 H); 7.57 (d, J = 8.0 Hz, 2 H); 7.32-7.18 (m, 6 H); 7.17-7.01 (m, 4 H); 6.98-6.85 (m, 4 H); 6.47 (d, J = 9.9 Hz, 1 H); 5.81 (s, 1 H); 5.17 (s, 2 H); 5.09 (dd, J = 7.9, 4.7 Hz, 1 H); 4.60 (d, J = 16.8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

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.

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



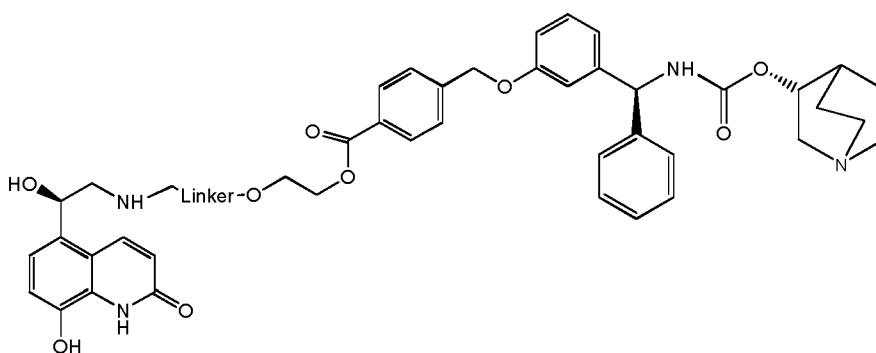
15 Preparation of 3-chloro-4-(2-hydroxyethoxy)-5-methoxybenzaldehyde



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%).

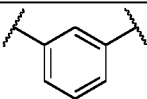
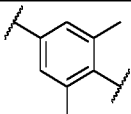
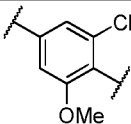
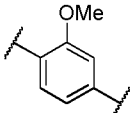
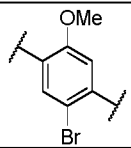
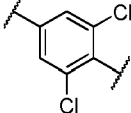
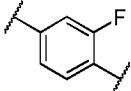
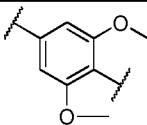
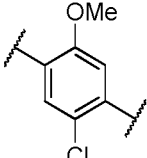
^1H NMR (400 MHz, CDCl_3): δ 9.87 (s, 1 H); 7.53 (d, $J = 1.6$ Hz, 1 H); 7.38 (d, $J = 1.6$ Hz, 1 H); 4.29-4.27 (m, 2 H); 3.96 (s, 3 H); 3.90-3.85 (m, 2 H); 2.77 (t, d, $J = 6.4$ Hz, 1 H).

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

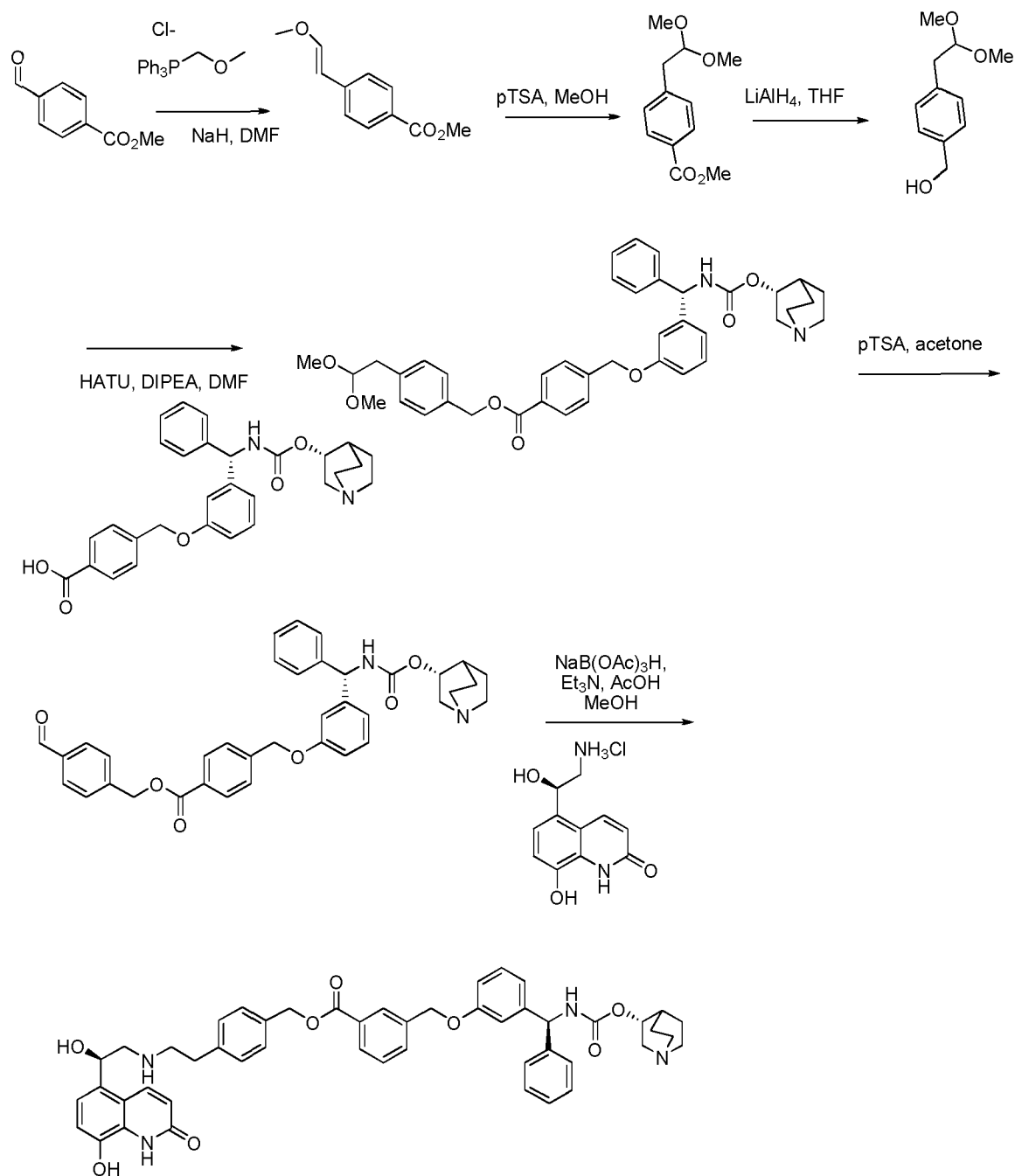


Compound number	Linker
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(continued)

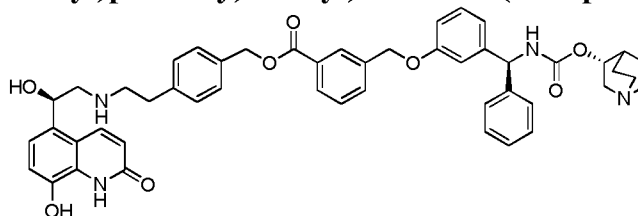
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Synthesis of Compounds 18 to 21

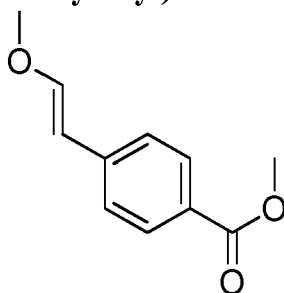


Example 2

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)



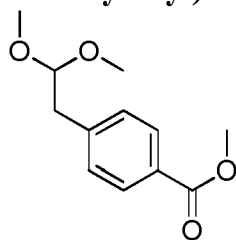
5

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

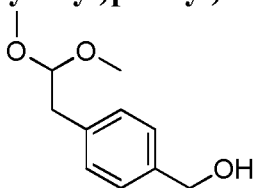
An ice-cooled suspension of (methoxymethyl)triphenylphosphonium chloride (6.48 g, 20.0 mmol) in THF (40 mL) was added portion wise with sodium hydride (60 % dispersion in mineral oil, 0.88 g, 22.0 mmol). The reaction mixture was stirred at this temperature for 10 minutes followed by 50 minutes at RT. 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, CDCl₃): 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).

20

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

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.

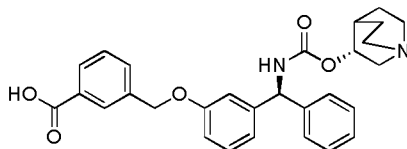
Step 3; (4-(2,2-Dimethoxyethyl)phenyl)methanol

A cooled (-78 °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, CDCl₃): δ 7.32-7.30 (m, 2 H); 7.26-7.23 (m, 2 H); 4.68 (d, *J*

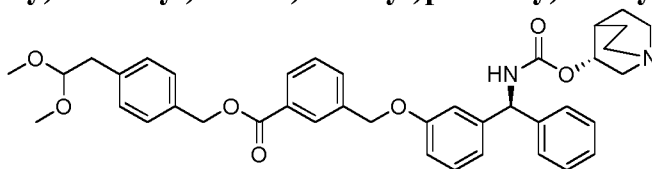
= 5.6 Hz, 2 H); 4.55-4.52 (m, 1 H); 3.34 (s, 6 H); 2.92 (d, J = 5.6 Hz, 1 H); 1.28 - 1.24 (m, 1 H).

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



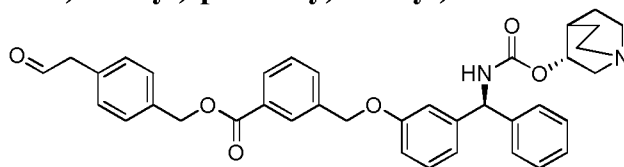
The title compound was prepared as described in **Example 1 Steps 5** though **8** with methyl 3-(bromomethyl)benzoate replacing methyl 4-(bromomethyl)benzoate in **Step 5**.

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



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 4-(2-hydroxyethoxy)-3-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



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*-

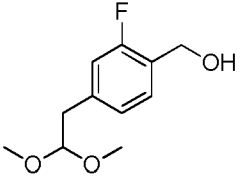
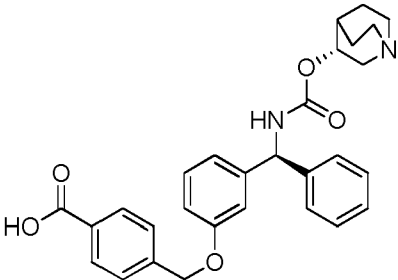
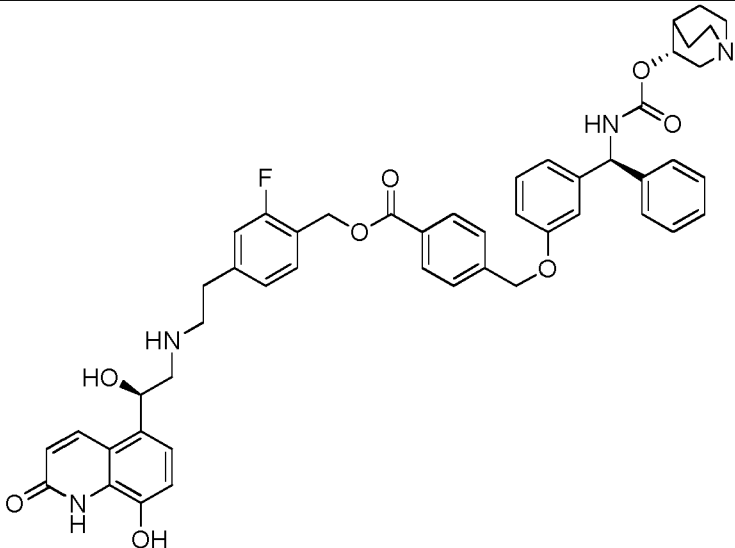
toluenesulfonic acid monohydrate (0.086 g, 0.45 mmol) and the mixture stirred at RT for 1 hour. The reaction mixture was diluted with saturated sodium hydrogen carbonate and extracted with ethyl acetate. The combined organic extracts were dried (magnesium sulfate), filtered and the solvent evaporated 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)

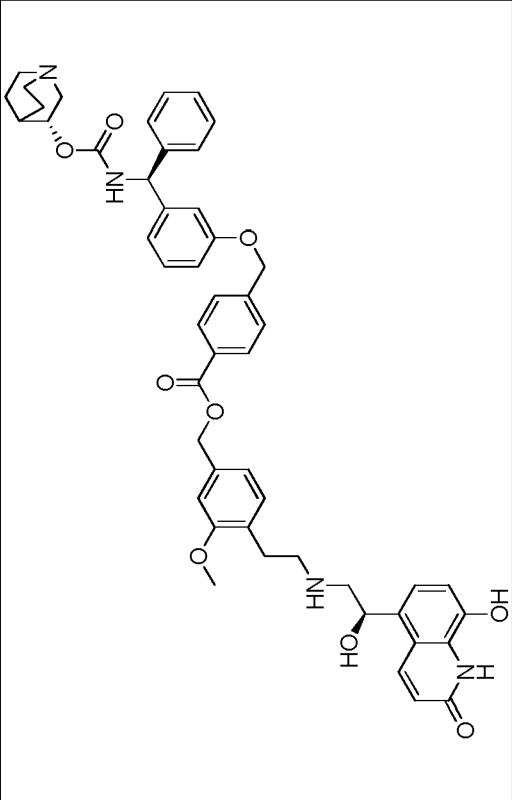
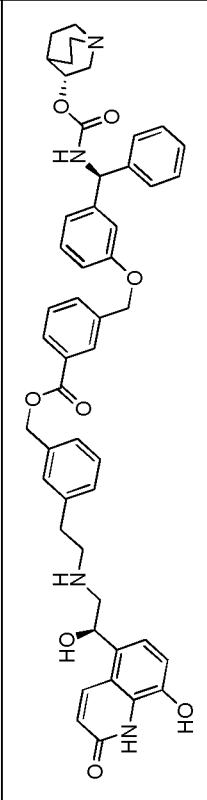
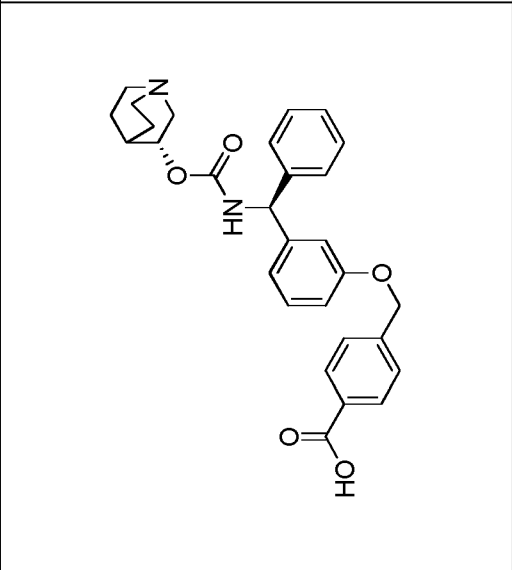
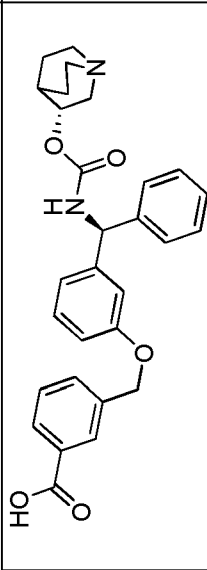
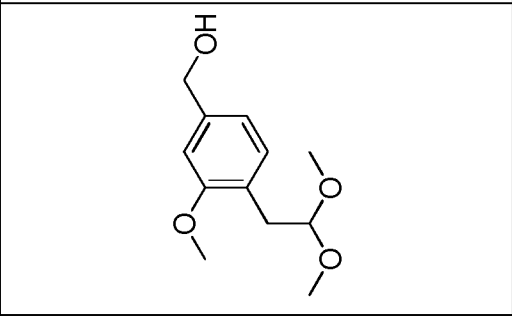
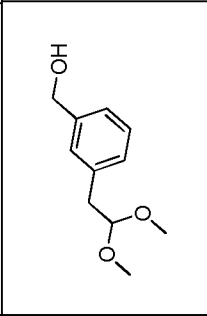
The title compound was prepared as described in **Example 1 Step 11** with 4-(2-oxoethyl)benzyl 3-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate replacing 2-(4-formyl-2-methylphenoxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)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

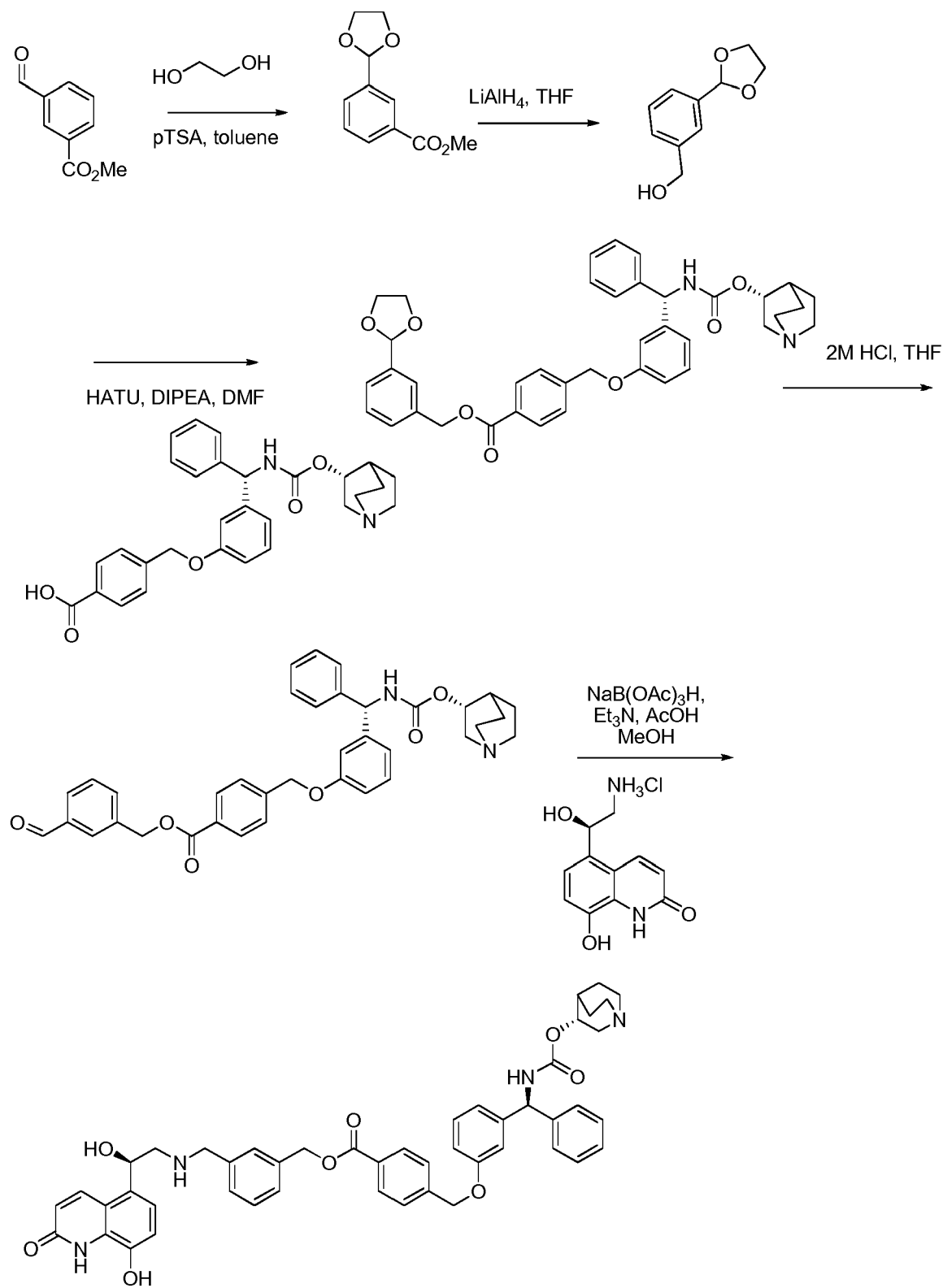
The following compounds were prepared in an analogous manner to **Example 2** coupling the requisite alcohol (prepared as described in **Example 2 Steps 1 to 3**) to the requisite acid as described in **Example 2 Step 5** and the subsequent product used in **Example 2 Step 6** and 7.

Cpd.	Requisite alcohol	Requisite acid	Structure
19			

(continued)

 <p>Chemical structure of compound 20: A complex molecule featuring a bicyclic amine (8-azabicyclo[3.2.1]octane) linked via an amide bond to a chiral center. This chiral center is further connected to a biphenyl system, which is linked via an ether bridge to a benzene ring. This benzene ring is connected via an ester linkage to a methoxy-substituted benzene ring, which is further connected via an amine linkage to a chiral center. This chiral center is connected to a benzene ring, which is linked via an amide bond to a bicyclic amine (8-azabicyclo[3.2.1]octane).</p>	 <p>Chemical structure of compound 21: A complex molecule featuring a bicyclic amine (8-azabicyclo[3.2.1]octane) linked via an amide bond to a chiral center. This chiral center is further connected to a biphenyl system, which is linked via an ether bridge to a benzene ring. This benzene ring is connected via an ester linkage to a methoxy-substituted benzene ring, which is further connected via an amine linkage to a chiral center. This chiral center is connected to a benzene ring, which is linked via an amide bond to a bicyclic amine (8-azabicyclo[3.2.1]octane).</p>
 <p>Chemical structure of compound 20: A complex molecule featuring a bicyclic amine (8-azabicyclo[3.2.1]octane) linked via an amide bond to a chiral center. This chiral center is further connected to a biphenyl system, which is linked via an ether bridge to a benzene ring. This benzene ring is connected via an ester linkage to a methoxy-substituted benzene ring, which is further connected via an amine linkage to a chiral center. This chiral center is connected to a benzene ring, which is linked via an amide bond to a bicyclic amine (8-azabicyclo[3.2.1]octane).</p>	 <p>Chemical structure of compound 21: A complex molecule featuring a bicyclic amine (8-azabicyclo[3.2.1]octane) linked via an amide bond to a chiral center. This chiral center is further connected to a biphenyl system, which is linked via an ether bridge to a benzene ring. This benzene ring is connected via an ester linkage to a methoxy-substituted benzene ring, which is further connected via an amine linkage to a chiral center. This chiral center is connected to a benzene ring, which is linked via an amide bond to a bicyclic amine (8-azabicyclo[3.2.1]octane).</p>
 <p>Chemical structure of compound 20: A complex molecule featuring a bicyclic amine (8-azabicyclo[3.2.1]octane) linked via an amide bond to a chiral center. This chiral center is further connected to a biphenyl system, which is linked via an ether bridge to a benzene ring. This benzene ring is connected via an ester linkage to a methoxy-substituted benzene ring, which is further connected via an amine linkage to a chiral center. This chiral center is connected to a benzene ring, which is linked via an amide bond to a bicyclic amine (8-azabicyclo[3.2.1]octane).</p>	 <p>Chemical structure of compound 21: A complex molecule featuring a bicyclic amine (8-azabicyclo[3.2.1]octane) linked via an amide bond to a chiral center. This chiral center is further connected to a biphenyl system, which is linked via an ether bridge to a benzene ring. This benzene ring is connected via an ester linkage to a methoxy-substituted benzene ring, which is further connected via an amine linkage to a chiral center. This chiral center is connected to a benzene ring, which is linked via an amide bond to a bicyclic amine (8-azabicyclo[3.2.1]octane).</p>
20	21

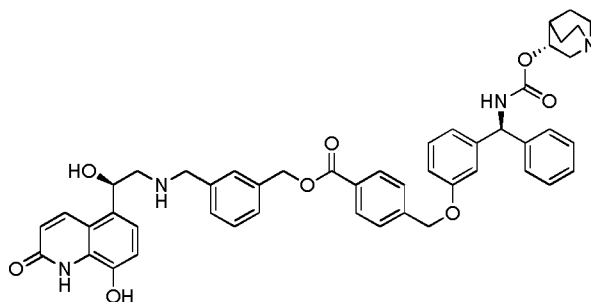
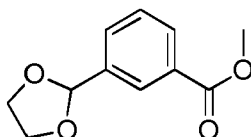
Synthesis of Compounds 22 to 31



Example 3

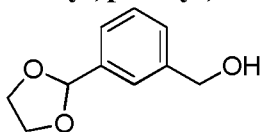
3-((((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)benzyl 4-(((3-(((*S*)-phenyl((((*R*)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate (Compound 22)

5

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

10 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
15 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

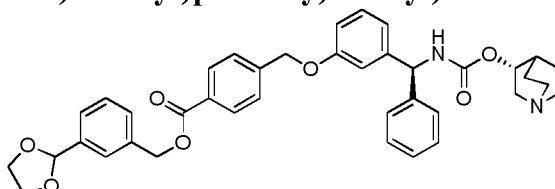
20

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.

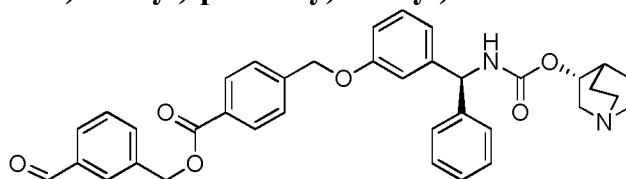
¹H NMR (400 MHz, DMSO-d₆): δ 7.40 (s, 1 H), 7.37-7.27 (m, 3 H), 5.77-5.68 (m, 1 H), 5.21 (t, 1 H), 4.53-4.46 (m, 2 H), 4.09-3.90 (m, 4 H).

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



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



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.

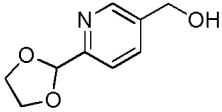
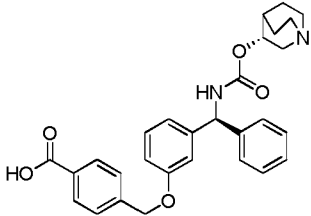
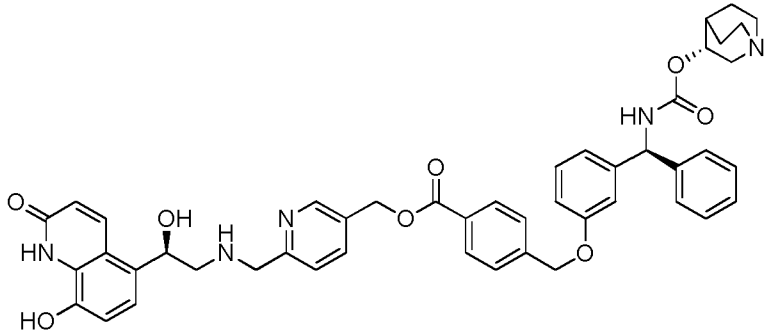
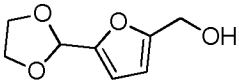
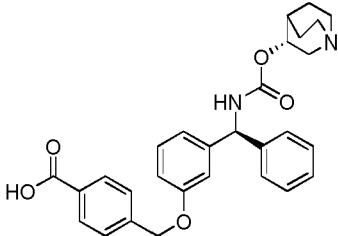
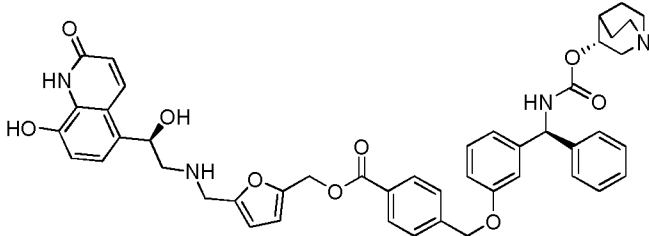
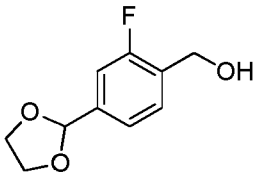
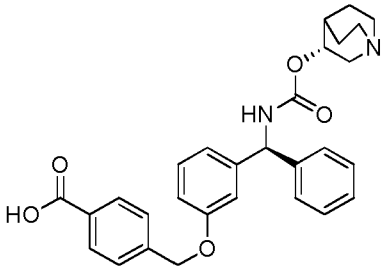
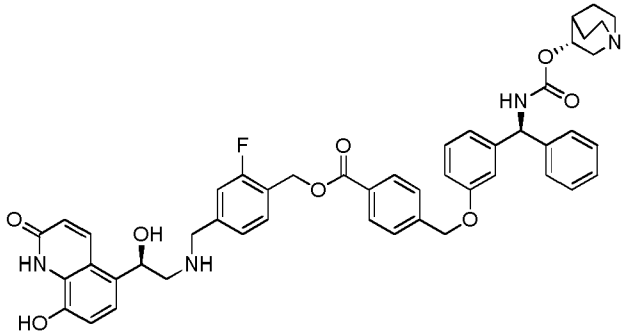
Step 5; 3-(((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)benzyl 4-((3-((*S*)-phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate (Compound 22)

The title compound was prepared as described in **Example 1 Step 11** with

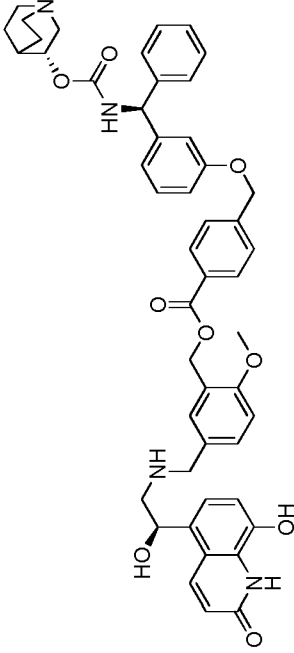
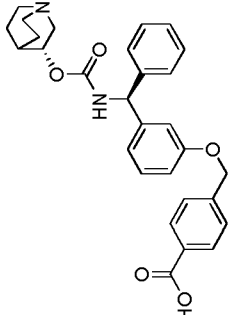
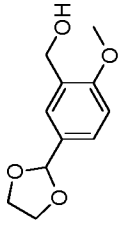
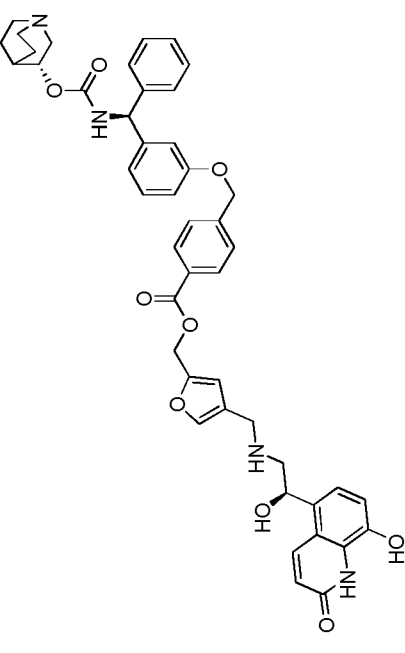
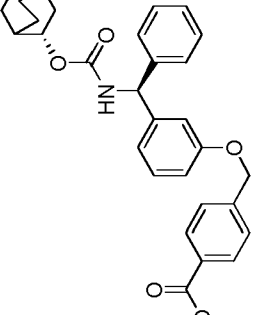
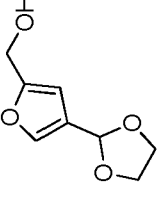
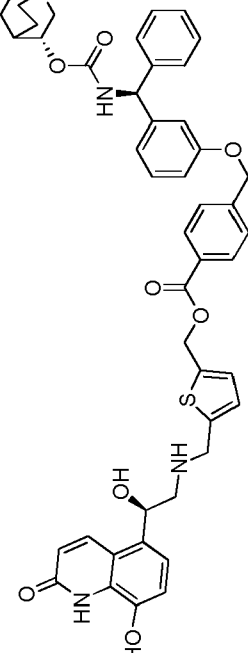
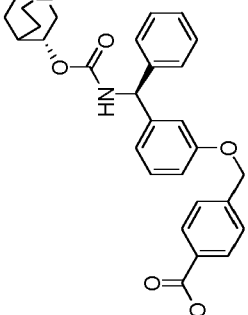
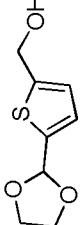
3-formylbenzyl 4-((3-((*S*)-phenyl((((*R*)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)benzoate replacing 2-(4-formyl-2-methylphenoxy)ethyl 4-((3-((*S*)-phenyl((((*R*)-quinuclidin-3-yloxy)carbonyl)-amino)methyl)phenoxy) methyl)benzoate.

- 5 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);
- 10 1.66 (s, 1 H); 1.53 (s, 1 H); 1.39 (s, 1 H).

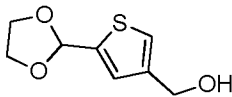
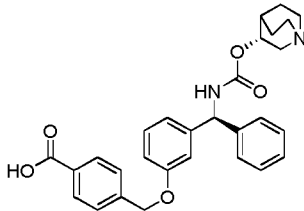
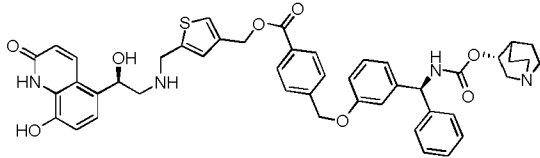
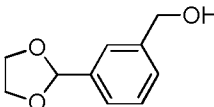
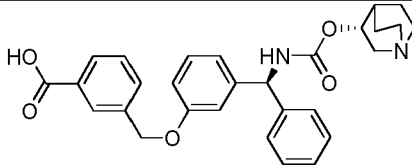
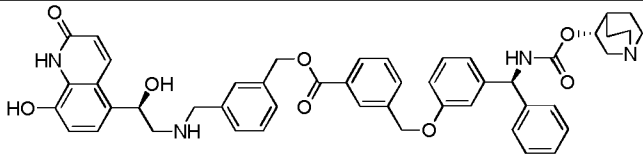
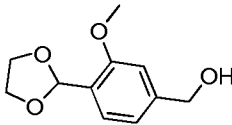
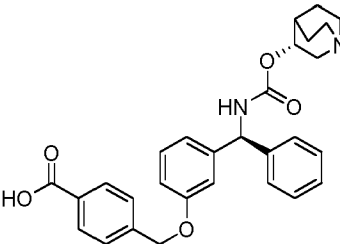
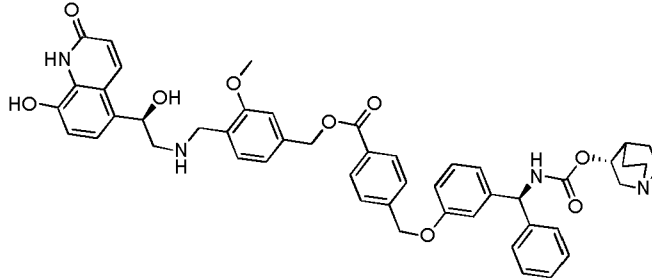
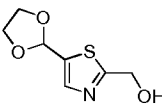
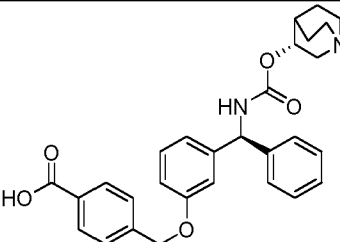
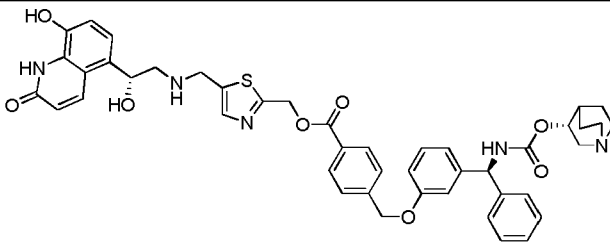
The following compounds were prepared in an analogous manner to **Example 3** coupling the requisite alcohol (prepared as described in **Example 3 Steps 1 to 2**) to the requisite acid as described in **Example 3 Step 3** and the subsequent product used in **Example 3 Step 4** and **5**.

Cpd.	Requisite alcohol	Requisite acid	Structure
23			
24			
25			

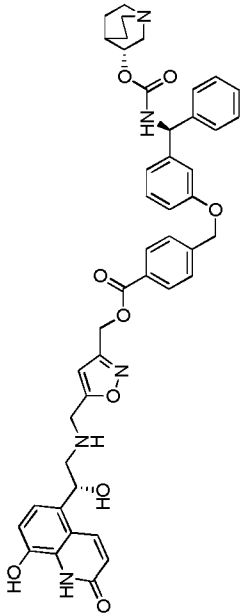
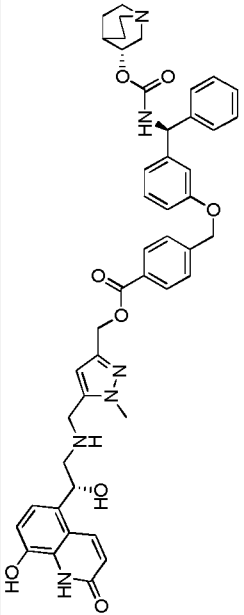
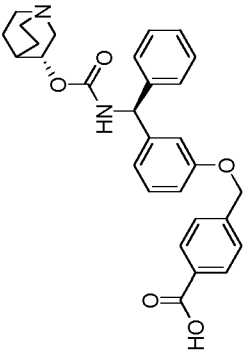
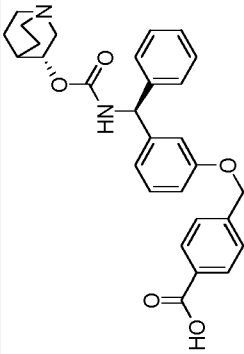
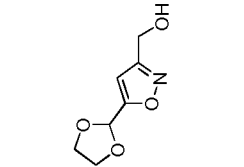
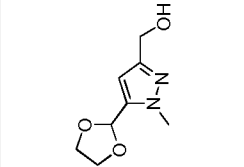
(continued)

			26
			27
			28

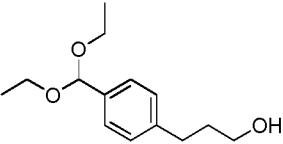
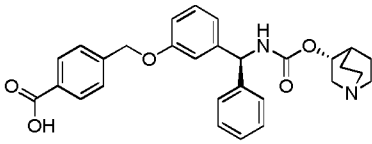
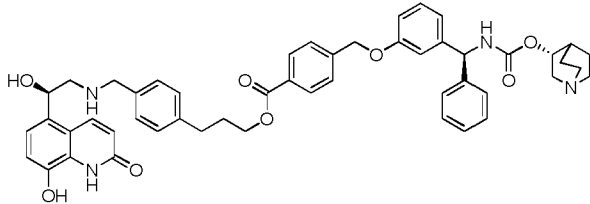
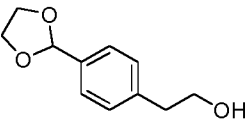
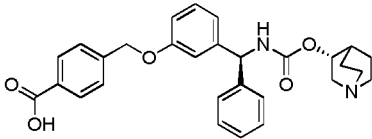
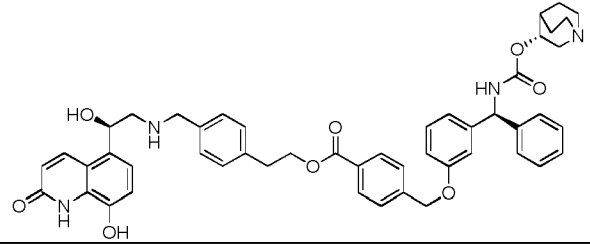
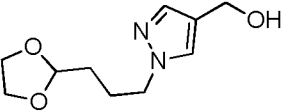
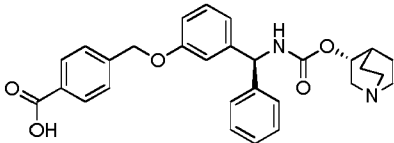
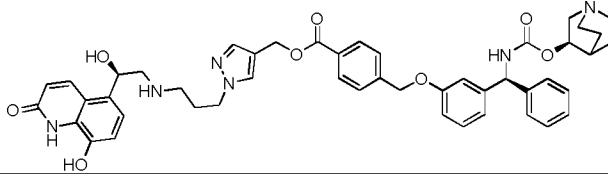
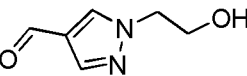
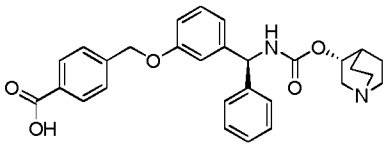
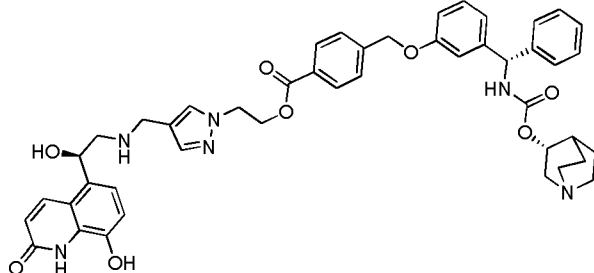
(continued)

29			
30			
31			
31A			

(continued)

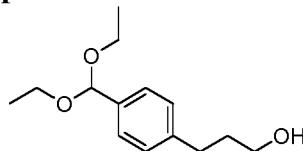
	
	
	
31B	31C

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**.

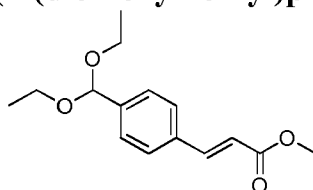
Cpd.	Requisite alcohol	Requisite acid	Structure
32			
33			
34			
35			

The synthesis of the requisite alcohol is detailed below;

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

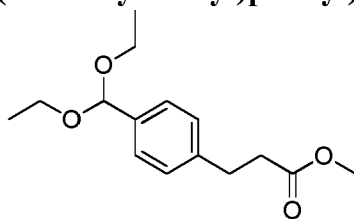


5 **Step 1; (E)-Methyl 3-(4-(diethoxymethyl)phenyl)acrylate**



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).

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

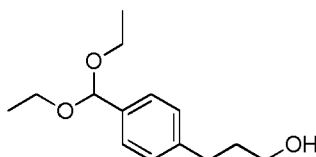


1-Methyl-1,4-cyclohexadiene (10.0 mL, 89 mmol) was added to a suspension of **(E)-methyl 3-(4-(diethoxymethyl)phenyl)acrylate** (2.41 g, 9.13 mmol) and 10% palladium on carbon (2.4 g) in ethanol (40 mL). The reaction mixture was heated at 60 °C for 1.5 hours. The reaction mixture was filtered through 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, CDCl₃): 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

5

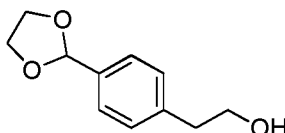


The title compound was prepared as described in **Example 2 Step 3** with **methyl 4-(2,2-dimethoxyethyl)benzoate** replacing **methyl 4-(2,2-dimethoxyethyl)benzoate**.

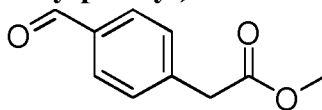
10 ¹H NMR (400 MHz, CDCl₃): δ 7.39 (d, *J* = 8.4 Hz, 2 H); 7.20-7.18 (m, 2 H); 5.47 (s, 1 H); 3.69-3.49 (m, 6 H); 2.73-2.69 (m, 2 H); 1.90-1.85 (m, 2 H); 1.28-1.24 (m, 6 H).

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

15



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

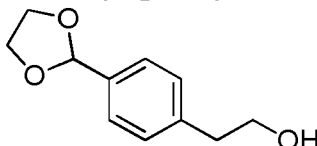


20 Acetyl chloride (5 mL) was added to an ice-cooled solution of 4-(hydroxymethyl)phenylacetic acid (5.78 g, 34.8 mmol) in methanol (200 mL). The reaction mixture allowed to warm to RT at stirred at this temperature for 42 hours. The solvent was evaporated under reduced pressure and the residue dissolved 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, CDCl₃): 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

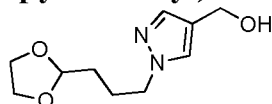


Methyl 2-(4-formylphenyl)acetate (1.72 g, 9.66 mmol) was dissolved in ethylene glycol (2.3 mL) and triethyl orthoformate (1.8 mL). Tetrabutylammonium tribromide (0.048 g) added and the reaction stirred at RT for 1 hour. Further tetrabutylammonium tribromide (0.434 g) added and the reaction stirred for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

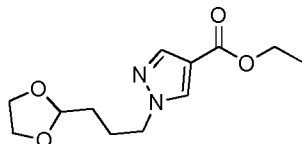
17%).

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).

- 5 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



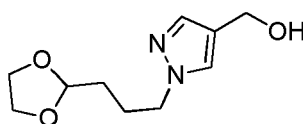
10

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.

- 15 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%).
- 20

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

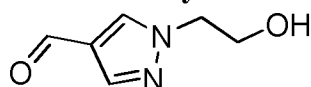


25

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).

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

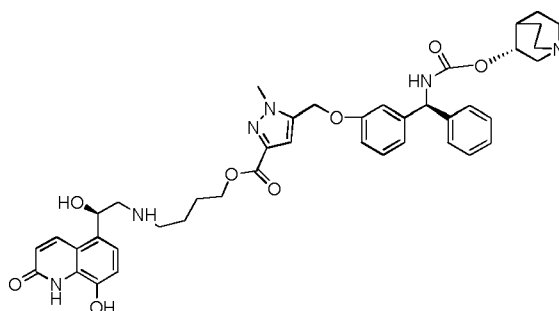


10 **1H-Pyrazole-4-carboxaldehyde** (0.50 g, 5.21 mmol), 2-bromoethanol (1.30 g, 10.41 mmol) and potassium carbonate (0.79 g, 5.73 mmol) combined with acetonitrile (5 mL) in a microwave vial. The microwave vial was heated at 150 °C in a microwave for 30 minutes. The reaction mixture was filtered and 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%).

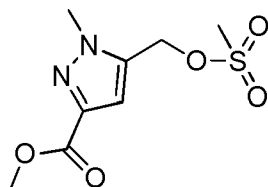
¹H NMR (400 MHz, CDCl₃): δ 9.86 (s, 1 H); 8.02 (s, 1 H); 7.99 (s, 1 H); 4.33-4.25 (m, 2 H); 4.05 (t, J = 4.8 Hz, 2 H).

Example 4

20 **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)**

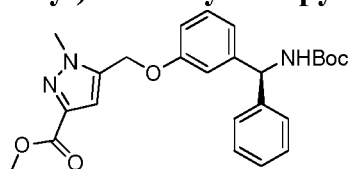


Step 1; Methyl 1-methyl-5-(((methylsulfonyl)oxy)methyl)-1H-pyrazole-3-carboxylate



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.

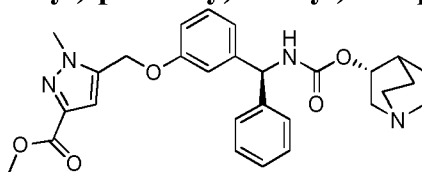
Step 2; (S)-Methyl 5-((3-(((tert-butoxycarbonyl)amino)(phenyl)methyl)phenoxy)methyl)-1-methyl-1H-pyrazole-3-carboxylate



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.

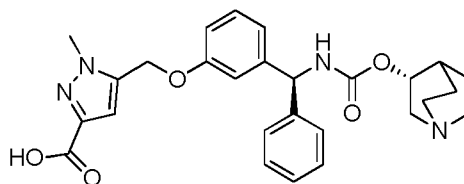
¹H NMR (400 MHz, CDCl₃): δ 7.37-7.21 (m, 7 H); 6.92 (d, J = 7.7 Hz, 1 H); 6.87-6.81 (m, 3 H); 5.88 (s, 1 H); 5.25-4.98 (m, 1 H); 5.00 (s, 2 H); 4.05-3.91 (m, 3 H); 3.92 (s, 3 H); 1.44 (s, 9 H).

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



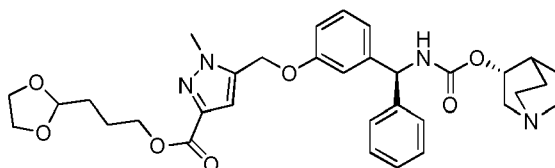
The title compound was prepared as described in **Example 1 Step 6** with
 5 (*S*)-methyl 5-((3-(((*tert*-butoxycarbonyl)amino)(phenyl)methyl)phenoxy)-methyl)-1-methyl-1*H*-pyrazole-3-carboxylate replacing methyl 4-((3-(((*tert*-butoxycarbonyl)amino)(phenyl)methyl)phenoxy)methyl)benzoate and the product 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)-1*H*-pyrazole-3-carboxylic acid



The title compound was prepared as described in **Example 1 Step 8** with
 15 methyl 1-methyl-5-((3-((*S*)-phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)-1*H*-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)-1*H*-pyrazole-3-carboxylate



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)-

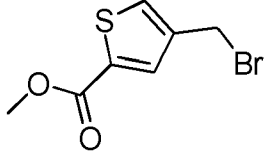
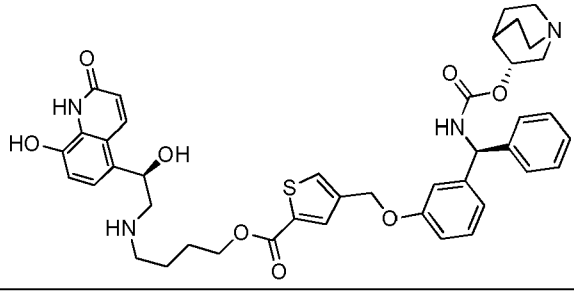
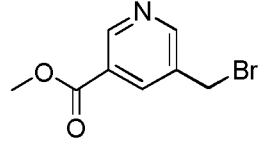
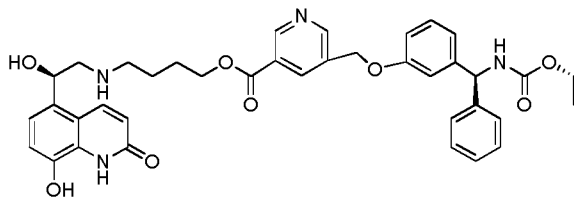
phenoxy)methyl)-1H-pyrazole-3-carboxylic acid and 3-(1,3-dioxolan-2-yl)propan-1-ol replacing 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino) methyl)phenoxy)methyl)benzoic acid and 4-(2-hydroxyethoxy)-3-methylbenzaldehyde respectively.

5 **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)**

 The title compound was prepared as described in **Example 2 Step 6** and
10 **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-
15 1.28 (m, 8 H).

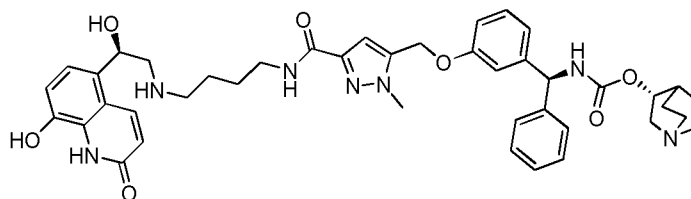
 The following compounds were prepared as described in **Example 4** with the appropriate alkylating agent in **Step 1** (methyl 1-methyl-5-(((methylsulfonyl)oxy)methyl)-1H-pyrazole-3-carboxylate in the case of **Compound 36**) used in **Step 2** and the product used in the subsequent steps in
20 **Example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

Compound number	Appropriate alkylating agent	Structure
37		
38		

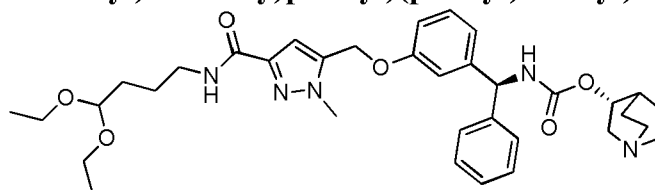
Example 5

(*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-1*H*-pyrazol-5-yl)methoxy)phenyl)(phenyl)methyl)carbamate (Compound 39)

5



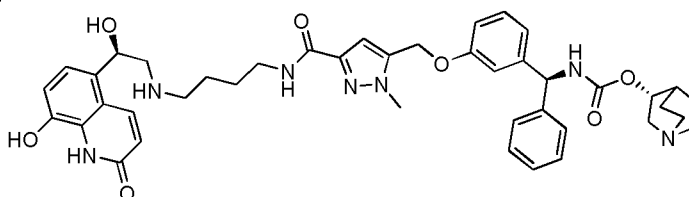
Step 1; (*R*)-Quinuclidin-3-yl ((*S*)-(3-((3-((4,4-diethoxybutyl)carbonyl)-1-methyl-1*H*-pyrazol-5-yl)methoxy)phenyl)(phenyl)methyl)carbamate



10 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
15 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.

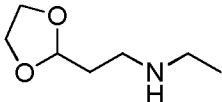
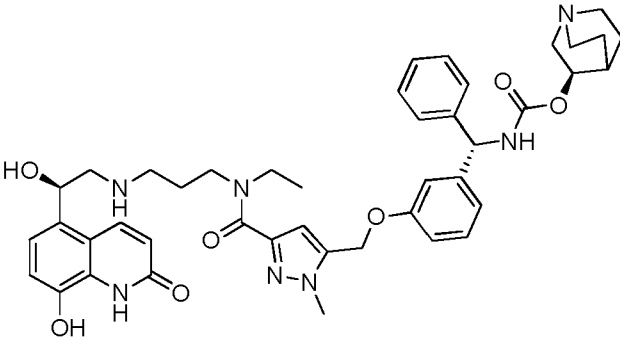
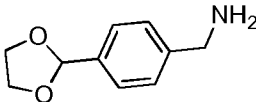
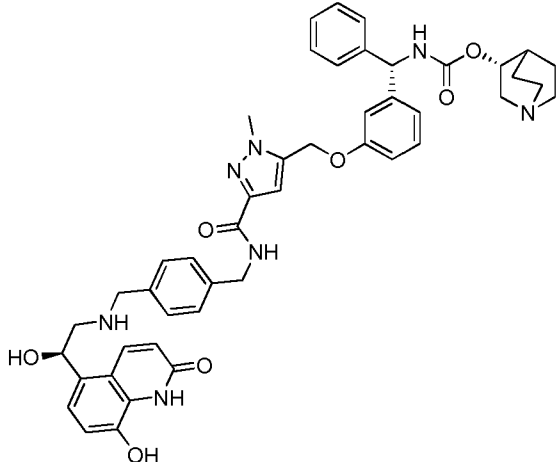
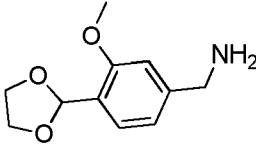
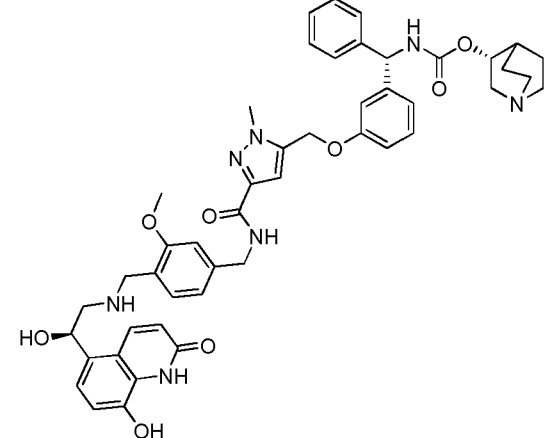
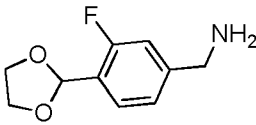
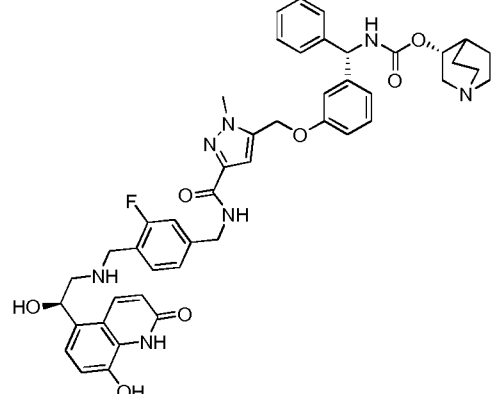
Step 2; (R)-Quinuclidin-3-yl ((S)-3-((3-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)carbamoyl)-1-methyl-1H-pyrazol-5-yl)methoxy)phenyl)(phenyl)methyl)carbamate (Compound 39)



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

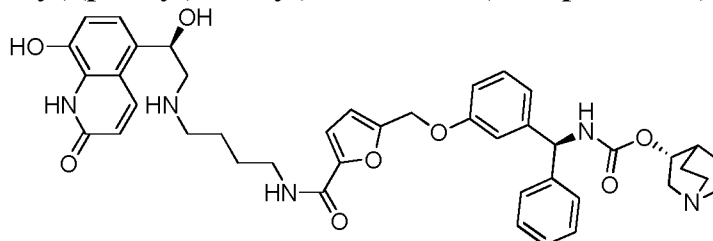
¹H NMR (400 MHz, DMSO-d₆): δ 10.30 (br s, 1 H); 8.48-8.07 (m, 3 H); 8.21-8.10 (m, 2 H); 7.34-7.19 (m, 6 H); 7.15-7.04 (m, 2 H); 7.00-6.91 (m, 2 H); 6.75 (s, 1 H); 6.53 (d, J = 9.86 Hz, 1 H); 5.84 (d, J = 8.57 Hz, 1 H); 5.31-5.10 (m, 3 H); 4.61 (s, 1 H); 3.88 (s, 3 H); 3.31-2.97 (m, 3 H); 2.95-2.56 (m, 7 H); 1.94 (s, 1 H); 1.82 (s, 1 H); 1.73-1.16 (m, 9 H).

The following compounds were prepared as described in **Example 5** with the appropriate amine used in **Step 1**.

Compound number	Appropriate amine	Structure
39A		
39B		
39C		
39D		

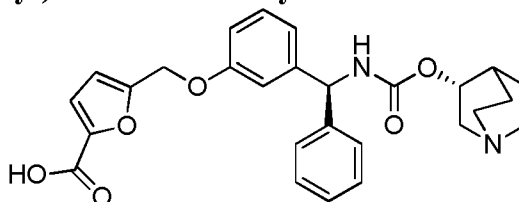
Example 6

(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)



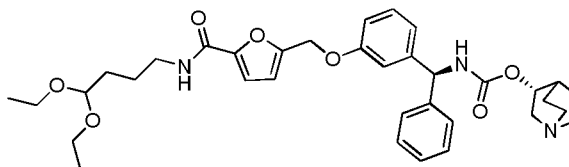
5

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



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



The title compound was prepared as described in **Example 5 Step 1** with 5-(((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)-methyl)furan-2-carboxylic acid replacing 1-methyl-5-(((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)-1H-pyrazole-3-

20

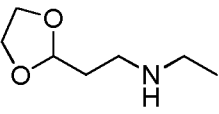
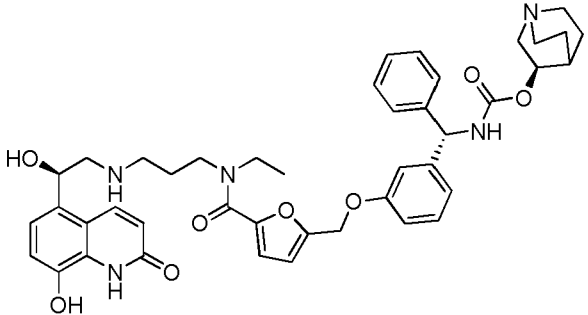
carboxylic acid. The crude reaction product was used in the next step without further purification.

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)carbamoyle)furan-2-yl)methoxy)phenyl)(phenyl)methyl)carbamate (Compound 40)

The title compound was prepared as described in **Example 5 Step 2**.

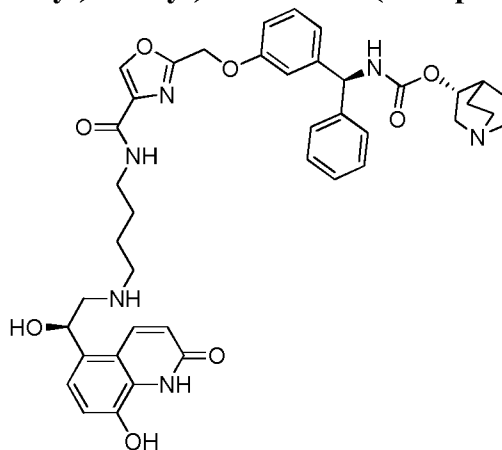
¹H NMR (400 MHz, DMSO-d₆): δ 10.38 (br s, 1 H); 8.46-8.39 (m, 1 H); 8.33-8.21 (m, 3 H); 8.18 (d, J = 9.93 Hz, 1 H); 7.34-7.19 (m, 6 H); 7.11 (d, J = 8.15 Hz, 1 H); 7.05 (t, J = 3.66 Hz, 2 H); 6.99-6.89 (m, 3 H); 6.69 (d, J = 3.44 Hz, 1 H); 6.54 (d, J = 9.86 Hz, 1 H); 5.84 (d, J = 8.95 Hz, 1 H); 5.20 (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).

The following compounds were prepared as described in **Example 6** with the requisite amine used in **Step 2**.

Compound number	Appropriate amine	Structure
40A		

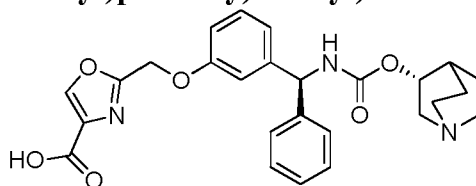
Example 7

(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 (Compound 41)



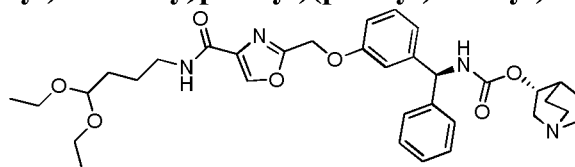
5

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



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.

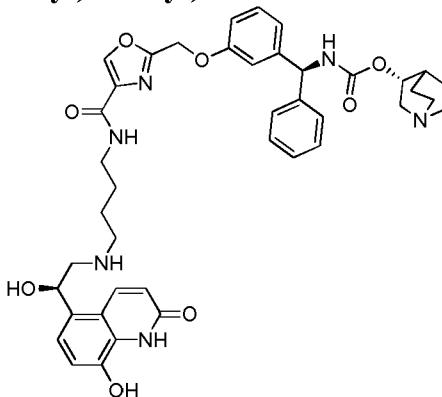
Step 2; (R)-Quinuclidin-3-yl ((S)-(3-((4-((4,4-diethoxybutyl)carbamoyl)oxazol-2-yl)methoxy)phenyl)(phenyl)methyl)-carbamate



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)-
1*H*-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-
 5 hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)carbamoyl)oxazol-
 2-yl)methoxy)phenyl)(phenyl)methyl)carbamate**



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 =
 10 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).

15 The following compounds were prepared as described in **Example 5** with
 the appropriate acid used in **Step 1**.

Compound number	Appropriate acid	Structure
41A		
41B		
41C		

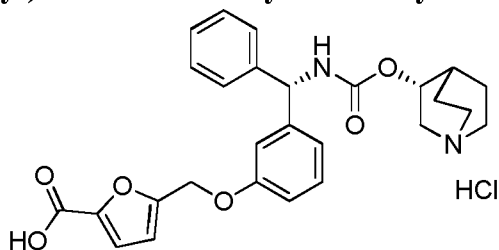
Example 8

(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-

5 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

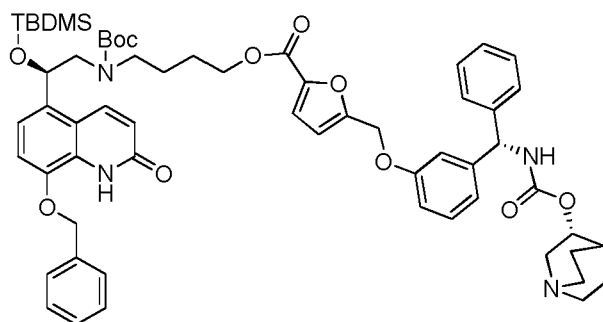


The **5-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonylamino)-methyl)phenoxy)methyl)furan-2-carboxylic acid** prepared as described in **Example 6 Step 1** was further purified by reverse phase column chromatography eluting with gradient of Eluent A: Water/ACN 95/5 + 0.1% HCOOH and Eluent B:

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



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)-**

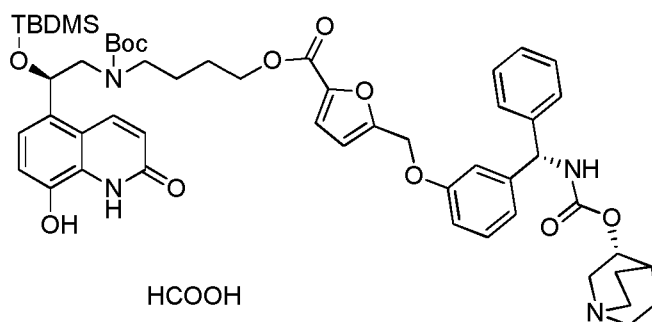
5-(2-amino-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one hydrochloride,

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

5

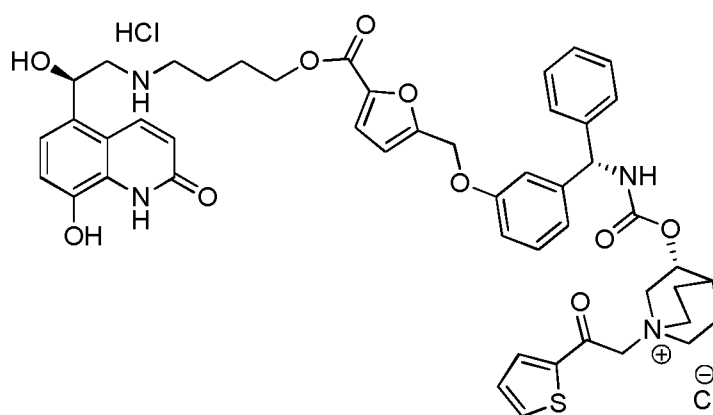


4-(((R)-2-(8-(Benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl)-2-(tert-butyldimethylsilyloxy)ethyl) (tert-butoxycarbonyl)amino)butyl 5-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonylamino)methyl)phenoxy) methyl)furan-2-carboxylate (2.1 g, 1.990 mmol), 10% Pd/C (0.106 g, 0.099 mmol) and formic acid (0.092 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



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

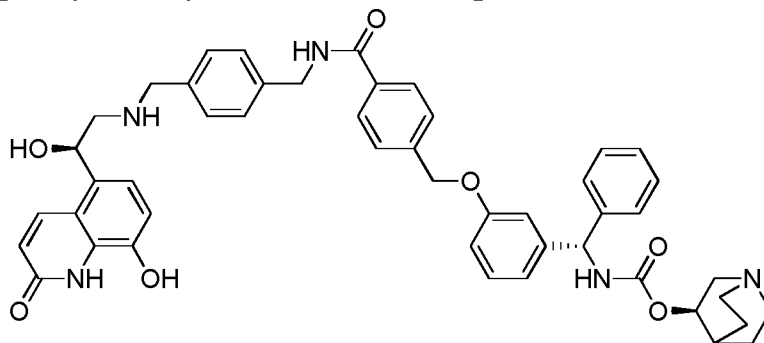
chromatography eluting with ACN:Water (gradient from 100% to 40 % of ACN leading to (R)-3-((S)-3-((5-((4-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)butoxy) carbonyl)furan-2-yl)methoxy)phenyl) (phenyl)-methylcarbamoyloxy)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-1-

- 5 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.

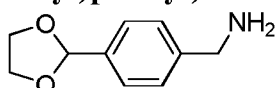
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.87 - 10.55 (bs, 1 H), 8.52 (d, *J*=9.26 Hz, 1 H), 8.33 (s, 2 H), 8.11 - 8.20 (m, 2 H), 8.05 (d, *J*=3.53 Hz, 1 H), 7.17 - 7.46 (m, 7 H), 6.87 - 7.10 (m, 5 H), 6.74 (d, *J*=3.53 Hz, 1 H), 6.48 (d, *J*=9.70 Hz, 1 H), 5.84 (d, *J*=9.26 Hz, 1 H), 4.93 - 5.23 (m, 6 H), 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)

Example 9

- 15 (R)-Quinuclidin-3-yl ((S)-3-((4-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)benzyl)carbamoyl)benzyl)-oxy)phenyl)(phenyl)methyl)carbamate (Compound 43)



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



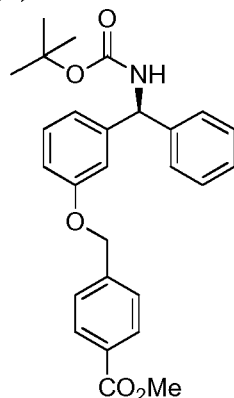
20

A stirred solution of 4-cyanobenzaldehyde (1.31 g, 10.0 mmol) and 4-toluenesulfonic acid hydrate (0.19 g, 1.0 mmol) in toluene (30 mL) was added with ethylene glycol (2.30 mL, 41.2 mmol). The reaction mixture was refluxed under

Dean and Stark conditions for 3 hours. The reaction mixture was diluted with ethyl acetate and washed with water, 10% aqueous potassium carbonate solution and brine. The organic phase was dried (magnesium sulfate), filtered and the solvent evaporated under reduced pressure. The residue was dissolved in anhydrous THF (10 mL) and added dropwise to an ice-cooled solution of lithium aluminium hydride in THF (2M in THF, 15.0 mL, 30.0 mmol). The reaction mixture was allowed to warm to room temperature at stirred at this temperature for 18 hours. Water (1.2 mL), 2M aqueous sodium hydroxide (1.2 mL) and water (3.6 mL) were added sequentially and the subsequent mixture stirred at room temperature for 30 minutes. Ethyl acetate and magnesium sulfate added and the mixture stirred for a further 30 minutes. The reaction mixture was filtered and the filtrate evaporated under reduced pressure to afford the title compound (1.56 g, 87%).

^1H NMR (400 MHz, CDCl_3): δ 7.46 (m, 2 H); 7.34 (d, J = 8.4 Hz, 2 H); 5.81 (s, 1 H); 4.17-4.00 (m, 2 H); 3.88 (s, 2 H); 1.55 (s, 2 H).

Step 2; (S)-Methyl 4-(((3-(((tert-butoxycarbonyl)amino)(phenyl)methyl)phenoxy)methyl)benzoate

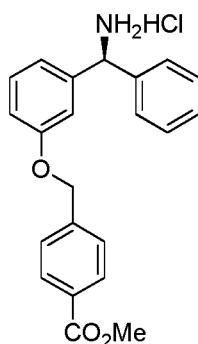


A mixture of (S)-tert-butyl ((3-hydroxyphenyl)(phenyl)methyl)carbamate (3.20 g, 10.7 mmol), methyl 4-(bromomethyl)benzoate (2.70 g, 11.8 mmol) and potassium carbonate (2.20 g, 16.1 mmol) in acetonitrile (54 mL) was stirred at RT for 16 hours. The reaction mixture was concentrated under reduced pressure 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, CDCl₃): 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).

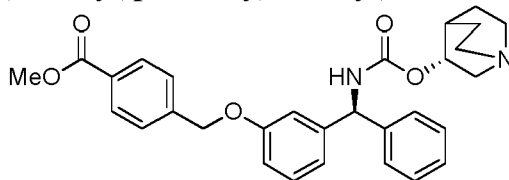
Step 3; (S)-Methyl 4-((3-(amino(phenyl)methyl)phenoxy)methyl)-benzoate hydrochloride



A solution of **methyl 4-((3-(((tert-butoxycarbonyl)amino)(phenyl)methyl)phenoxy)methyl)benzoate** (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 %).

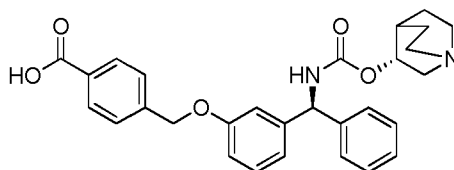
¹H NMR (400 MHz, CDCl₃): δ 9.21 (s, 2 H); 8.03 (d, *J* = 8.1 Hz, 2 H); 7.64 (d, *J* = 8.1 Hz, 2 H); 7.59 (d, *J* = 7.6 Hz, 2 H); 7.49-7.34 (m, 5 H); 7.17 (d, *J* = 7.7 Hz, 1 H); 7.06 (dd, *J* = 8.3, 2.4 Hz, 1 H); 5.64 (s, 1 H); 5.28 (s, 2 H); 3.91 (s, 3 H).

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



5 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
10 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%).

15 **Step 5; 4-((3-((*S*)-Phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoic acid**

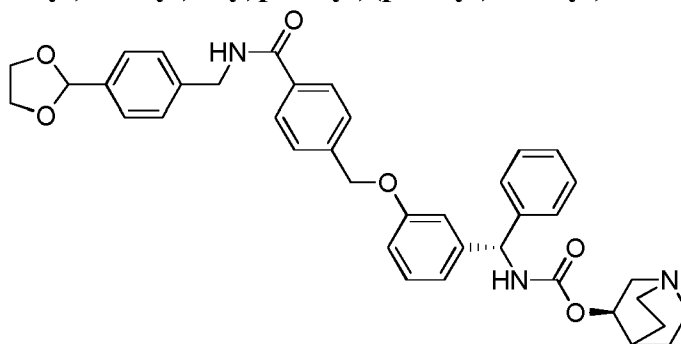


A stirred solution of methyl 4-((3-((*S*)-phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate (2.27 g, 4.50 mmol) in
20 THF (23 mL) was added with an aqueous solution of lithium hydroxide (2.0 M, 9.0 ml, 18.0 mmol). The mixture was stirred at RT for 16 hours. The pH of the 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, DMSO-d₆): 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 6; (R)-Quinuclidin-3-yl ((S)-(3-((4-((4-(1,3-dioxolan-2-yl)benzyl)carbamoyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate



The title was prepared as described in **Example 5 Step 1** with 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)-benzoic acid and (4-(1,3-dioxolan-2-yl)phenyl)methanamine replacing 1-methyl-5-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)-phenoxy)methyl)-1H-pyrazole-3-carboxylic acid and 4-aminobutyraldehyde diethyl acetal respectively.

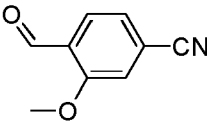
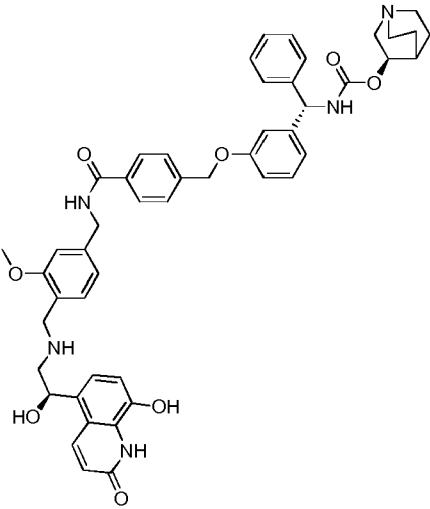
Step 7; (R)-Quinuclidin-3-yl ((S)-(3-((4-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)benzyl)-carbamoyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate (Compound 43)

The title compound was prepared as described in **Example 3 Step 4** and **Step 5** with (R)-quinuclidin-3-yl ((S)-(3-((4-((4-(1,3-dioxolan-2-yl)benzyl)carbamoyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate replacing 3-(1,3-dioxolan-2-yl)benzyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-

loxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate and the product used in **Step 5**.

¹H NMR (400 MHz, DMSO-d₆): δ 9.06-9.00 (m, 1 H); 8.31-8.23 (m, 3 H); 8.12 (d, J = 9.9 Hz, 1 H); 7.90 (d, J = 8.1 Hz, 2 H); 7.52 (d, J = 8.0 Hz, 2 H); 7.32-7.17 (m, 10 H); 7.05 (t, J = 4.2 Hz, 2 H); 6.96-6.85 (m, 3 H); 6.53-6.45 (m, 1 H); 5.82 (d, J = 9.2 Hz, 1 H); 5.18-5.06 (m, 3 H); 4.62 (s, 2 H); 4.47 (d, J = 5.9 Hz, 2 H); 3.92-3.68 (m, 2 H); 2.88-2.51 (m, 7 H); 1.95 (s, 1 H); 1.83 (s, 1 H); 1.62 (s, 1 H); 1.52 (s, 1 H); 1.39 (s, 1 H).

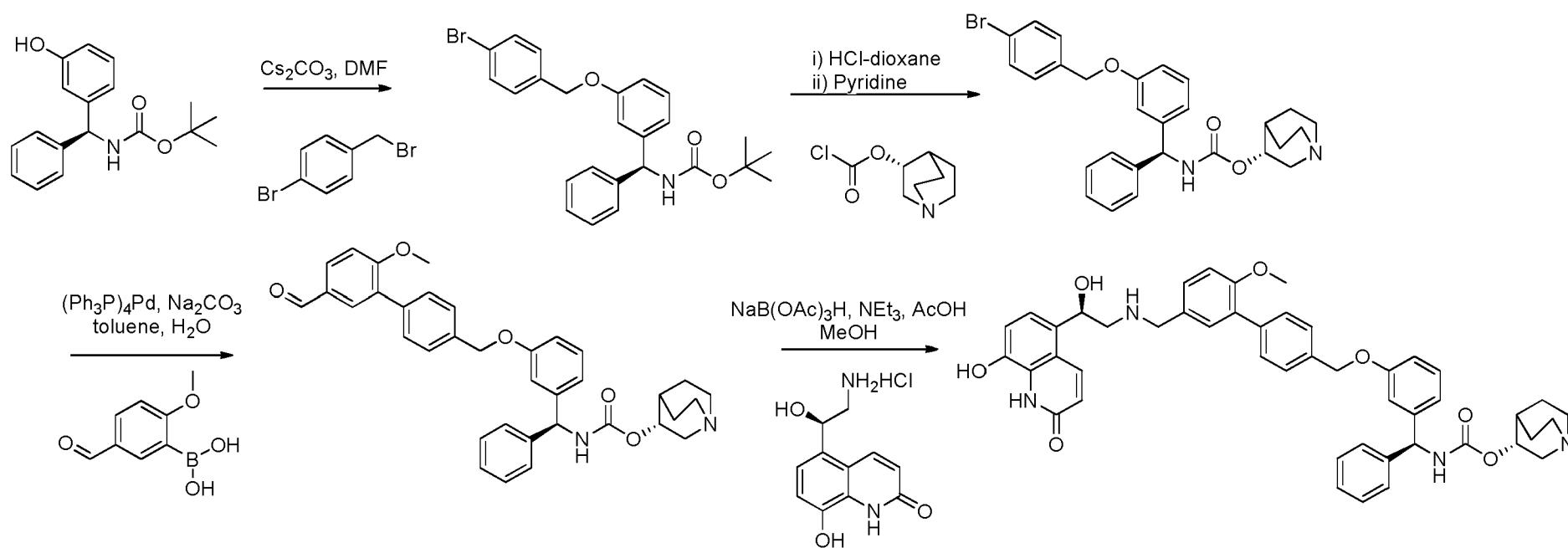
10 The following compounds were prepared as described in **Example 9** with the requisite aldehyde used in **Step 1**.

Compound number	Appropriate aldehyde	Structure
44		

The following compounds were prepared as described in **Example 9** with the requisite halide used in **Step 2** replacing methyl (4-bromomethyl)benzoate and the requisite amine used in **Step 6** replacing (4-(1,3-dioxolan-2-yl)phenyl)methanamine.

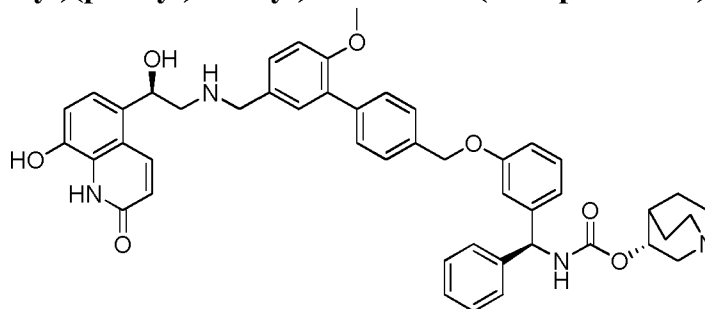
Compound number	Requisite halide	Requisite amine	Structure
45			
46			
47			
48			
49			
50			
51			
52			

Synthesis of compounds 53 to 55



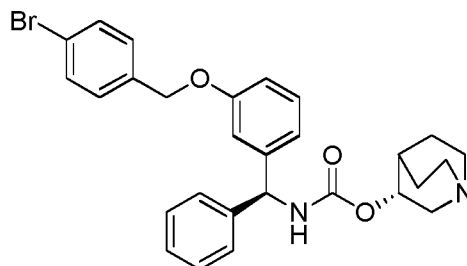
Example 10

(R)-Quinuclidin-3-yl ((S)-(3-((5'-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-2'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)phenyl)(phenyl)methyl)carbamate (Compound 53)



5

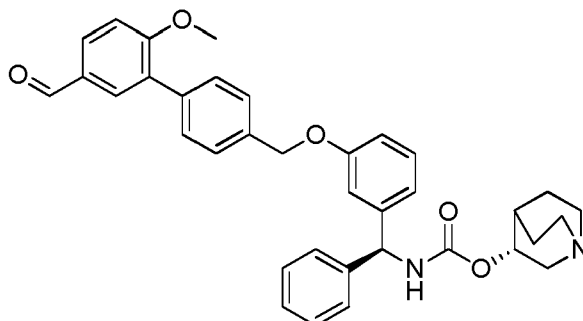
Step 1; (R)-Quinuclidin-3-yl ((S)-(3-((4-bromobenzyl)oxy)phenyl)(phenyl)methyl)carbamate



The title compound was prepared as described in **Example 1 Step 1 to Step 7** with 4-bromobenzyl bromide replacing methyl 4-(bromomethyl)benzoate in **Step 5**.

¹H NMR (400 MHz, DMSO-d₆): δ 8.23 (d, J = 9.2 Hz, 1 H); 7.59-7.56 (m, 2 H); 7.40-7.38 (m, 2 H); 7.32-7.22 (m, 6 H); 7.01 (s, 1 H); 6.95-6.86 (m, 2 H); 5.83 (d, J = 9.2 Hz, 1 H); 5.06 (s, 2 H); 4.57-4.55 (m, 1 H); 3.18 (m, 1 H); 2.72-2.47 (m, 5 H); 1.89 (s, 1 H); 1.78 (s, 1 H); 1.58 (m, 1 H); 1.46 (s, 1 H); 1.32 (s, 1 H).

Step 2; (R)-Quinuclidin-3-yl ((S)-(3-((5'-formyl-2'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)phenyl)(phenyl)methyl)carbamate

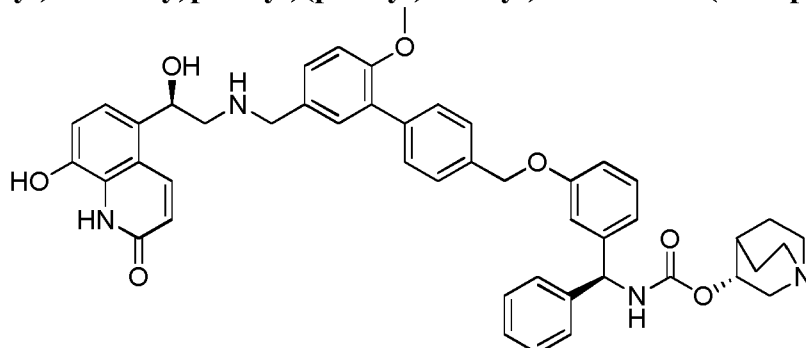


5 A solution of **(R)-quinuclidin-3-yl ((S)-(3-((4-bromobenzyl)oxy)phenyl)(phenyl)methyl)carbamate** (0.30 g, 0.57 mmol) and 5-formyl-2-methoxyphenyl boronic acid (0.15 g, 0.86 mmol) in toluene/water (2 mL/0.5 mL) was added with sodium carbonate (0.12 g, 1.14 mmol). Nitrogen was bubbled through the reaction mixture for 5 minutes that was then treated with

10 tetrakis(triphenylphosphine)palladium (0) (0.03 g, 0.03 mmol) and the reaction mixture heated under reflux for 2 hours. 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 loaded onto an SCX-2 cartridge and eluted with acetonitrile (4

15 column volumes) and then 10% triethylamine/acetonitrile (4 column volumes). 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 3; (R)-Quinuclidin-3-yl ((S)-(3-((5'-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-2'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)phenyl)(phenyl)methyl)carbamate (Compound 53)



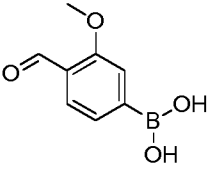
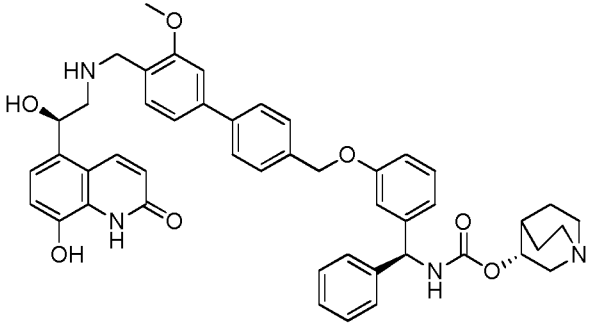
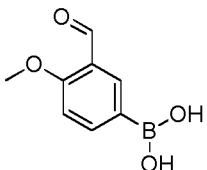
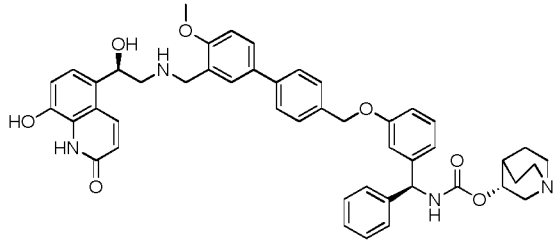
5 The title compound was prepared as described in **Example 1 Step11** with **(R)-quinuclidin-3-yl ((S)-(3-((5'-formyl-2'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)phenyl)(phenyl)methyl)carbamate** replacing **2-(4-formyl-2-methylphenoxy)ethyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate**.

10 ¹H NMR (400 MHz, DMSO-d₆): δ 8.32-8.23 (m, 3 H); 8.11 (d, J = 9.9 Hz, 1 H); 7.63-7.33 (m, 4 H); 7.35-7.21 (m, 8 H); 7.09-7.04 (m, 3 H); 6.96-6.88 (m, 3 H); 6.45 (d, J = 9.9 Hz, 1 H); 5.84 (d, J = 9.1 Hz, 1 H); 5.17-5.08 (m, 3 H); 4.66-4.59 (m, 1 H); 3.83 (s, 2 H); 3.76 (s, 3 H); 3.23-3.12 (m, 1 H); 2.85-2.51 (m, 7 H); 1.93 (s, 1 H); 1.83 (s, 1 H); 1.62 (s, 1 H); 1.52 (s, 1 H); 1.39 (s, 1 H).

15 The following compounds were prepared as described in **Example 10** with the requisite boronic acid used in **Step 2** replacing 5-formyl-2-methoxyphenyl boronic acid.

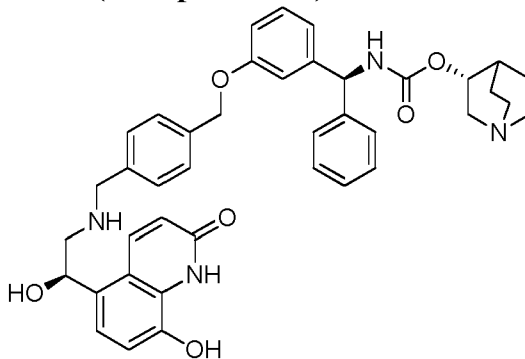
20

25

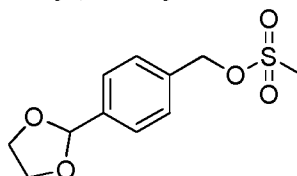
Compound number	Requisite boronic acid	Structure
54		
55		

Example 11

(R)-Quinuclidin-3-yl ((S)-(3-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)benzyl)oxy)phenyl) (phenyl)methyl)carbamate (Compound 56)



5

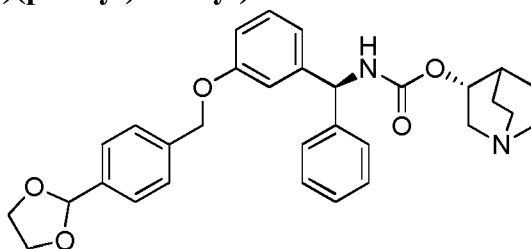
Step 1; 4-(1,3-Dioxolan-2-yl)benzyl methanesulfonate

An ice-cooled stirred solution of 4-(1,3-dioxolan-2-yl)phenylmethanol (prepared as described in WO2012168359, 1.2 g, 6.6 mmol) and triethylamine (2.8 mL, 20.0 mmol) in DCM (40 mL) was added dropwise with a solution of methanesulfonyl chloride (0.77 mL, 10.0 mmol) in DCM (10 mL). The reaction

10

mixture was stirred at this temperature for 40 minutes and then at room temperature for 18 hours. The reaction mixture was washed with water and the organic phase dried (magnesium sulfate). The filtrate was evaporated under reduced pressure to afford the title compound which was used immediately without further purification.

Step 2; (R)-Quinuclidin-3-yl ((S)-(3-((4-(1,3-dioxolan-2-yl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate



The title compound was prepared as described in **Example 1 Step 1 to Step 7** with **4-(1,3-dioxolan-2-yl)benzyl methanesulfonate** replacing methyl 4-(bromomethyl)benzoate. The product was used directly in the next step without any purification.

Step 3; (R)-Quinuclidin-3-yl ((S)-(3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate (Compound 56)

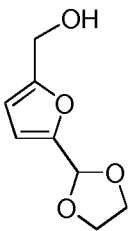
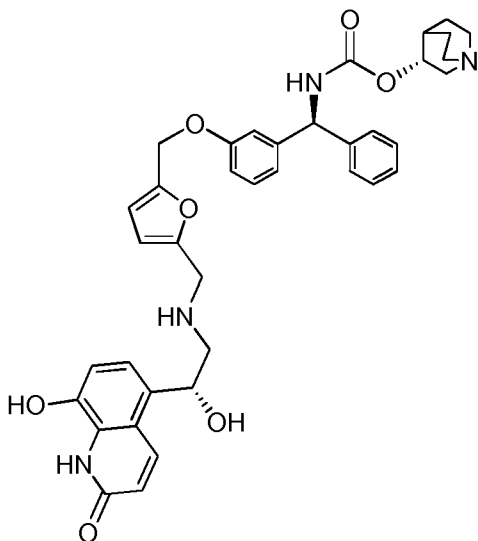
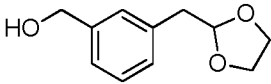
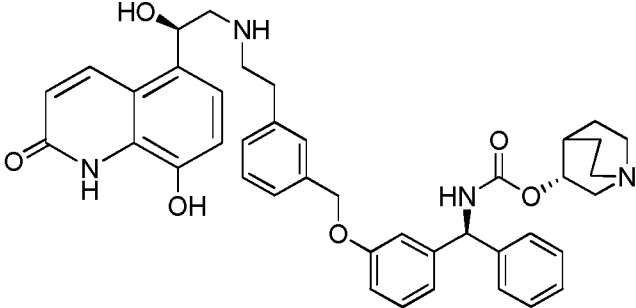
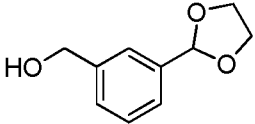
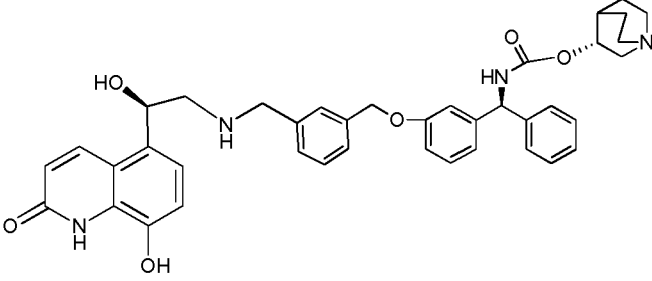
The title compound was prepared as described in **Example 3 Step 4 and Step 5** with **(R)-quinuclidin-3-yl ((S)-(3-((4-(1,3-dioxolan-2-yl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate** replacing **3-(1,3-dioxolan-2-yl)benzyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate** and the product used in **Step 5**.

¹H NMR (400 MHz, DMSO-d₆): δ 8.31-8.20 (m, 3 H); 8.11 (d, J = 9.9 Hz, 1 H); 7.41-7.27 (m, 8 H); 7.26-7.20 (m, 2 H); 7.12-7.00 (m, 2 H); 6.94-6.83 (m, 3 H); 6.48 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.3 Hz, 1 H); 5.10 (dd, J = 8.0, 4.5 Hz, 1 H); 5.04 (s, 2 H); 4.63-4.62 (m, 1 H); 3.81 (s, 2 H); 3.27-3.08 (m, 1 H); 2.82 (br s, 2 H); 2.81-2.56 (m, 5 H); 1.96 (br s, 1 H); 1.90-1.84 (m, 1 H); 1.70-1.60 (m, 1 H);

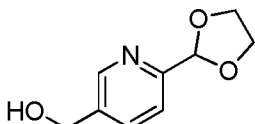
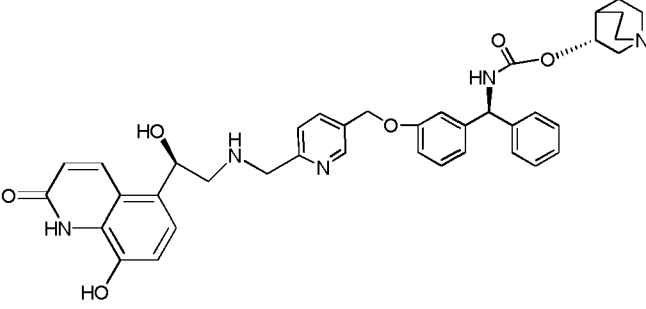
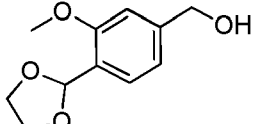
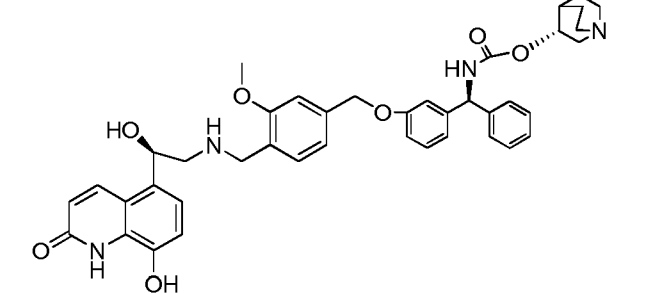
1.63-1.46 (m, 1 H); 1.44-1.38 (m, 1 H).

The following compounds were prepared as described in **Example 11** with the requisite alcohol used in **Step 1** replacing (4-(1,3-dioxolan-2-yl)phenyl)methanol.

5

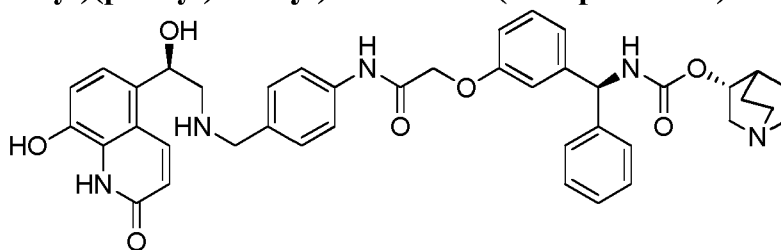
Compound number	Requisite alcohol	Structure
57	 <p>Prepared as described in Collection of Czechoslovak Chemical Communications, 57(1), 159-68; 1992</p>	
58	 <p>Prepared as described in PCT Int. Appl., 2012168359, 13 Dec 2012</p>	
59	 <p>Prepared as described in PCT Int. Appl., 2004101767, 25 Nov 2004</p>	

(continued)

60	<p>Prepared as described in Example 3 Step 1 and Step 2 starting from methyl 4-formyl nicotinate</p> 	
61	<p>Prepared as described in Example 3 Step 1 and Step 2 starting from methyl 4-formyl-3-methoxybenzoate</p> 	

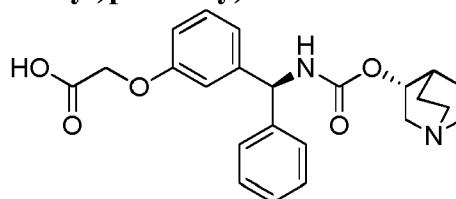
Example 12

(R)-Quinuclidin-3-yl ((S)-(3-(2-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)phenyl)amino)-2-oxoethoxy)phenyl)(phenyl)methyl)carbamate (Compound 62)



5

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

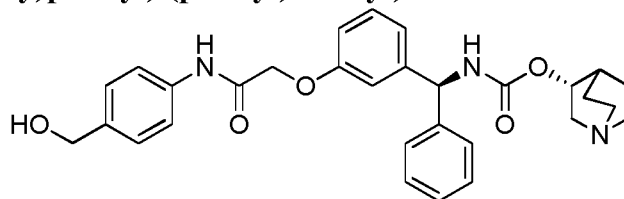


The title compound was prepared as described in **Example 1 Step 1** to **Step 7** with methyl bromoacetate replacing methyl 4-(bromomethyl)benzoate in **Step 5**.

10

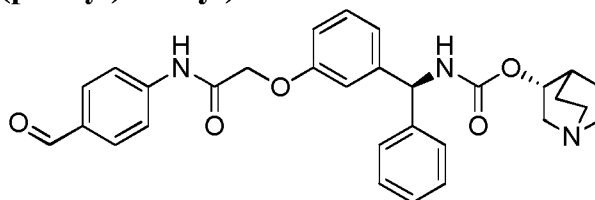
¹H NMR (400 MHz, DMSO-d₆): δ 8.32-8.24 (m, 1 H); 7.34-7.12 (m, 6 H); 6.89 (s, 1 H); 6.84 (d, J = 7.6 Hz, 1 H); 6.69 (dd, J = 8.2, 2.5 Hz, 1 H); 5.79 (d, J = 9.2 Hz, 1 H); 4.72-4.70 (m, 1 H); 4.37 (s, 2 H); 3.30-3.29 (m, 1 H); 2.93 (s, 2 H); 2.89-2.69 (m, 4 H); 2.05-2.03 (m, 1 H); 1.92-1.88 (m, 1 H); 1.70-1.50 (m, 3 H).

Step 2; (R)-Quinuclidin-3-yl ((S)-(3-(2-((4-(hydroxymethyl)phenyl)amino)-2-oxoethoxy)phenyl) (phenyl)methyl)carbamate



The title compound was prepared as described in **Example 1 Step 10** with **2-(3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)-phenoxy)acetic acid** replacing **4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl) phenoxy)methyl)benzoic acid** and **4-aminobenzyl alcohol** replacing **4-(2-hydroxyethoxy)-3-methylbenzaldehyde**.

Step 3; (R)-Quinuclidin-3-yl ((S)-(3-(2-((4-formylphenyl)amino)-2-oxoethoxy)phenyl)(phenyl)methyl)carbamate



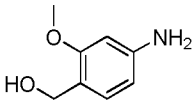
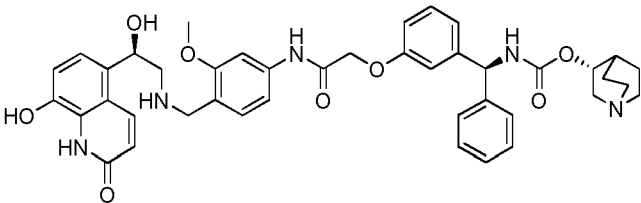
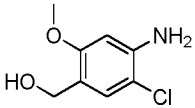
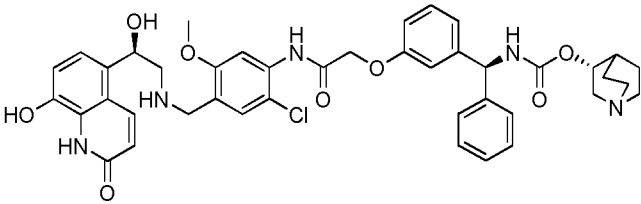
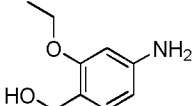
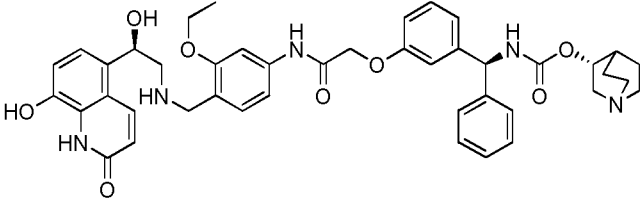
A stirred solution of **(R)-quinuclidin-3-yl ((S)-(3-(2-((4-(hydroxymethyl)phenyl)amino)-2-oxoethoxy)phenyl) (phenyl)methyl)-carbamate** (0.68 g, 1.31 mmol) in 1,4-dioxane (10 mL) was added with manganese (IV) oxide (0.57 g, 6.58 mmol). The reaction mixture was stirred at room temperature for 60 hours. The suspension was filtered and the filter cake was washed with ethyl acetate. The filtrate was evaporated under reduced pressure to afford the crude title compound. This material was used without further purification.

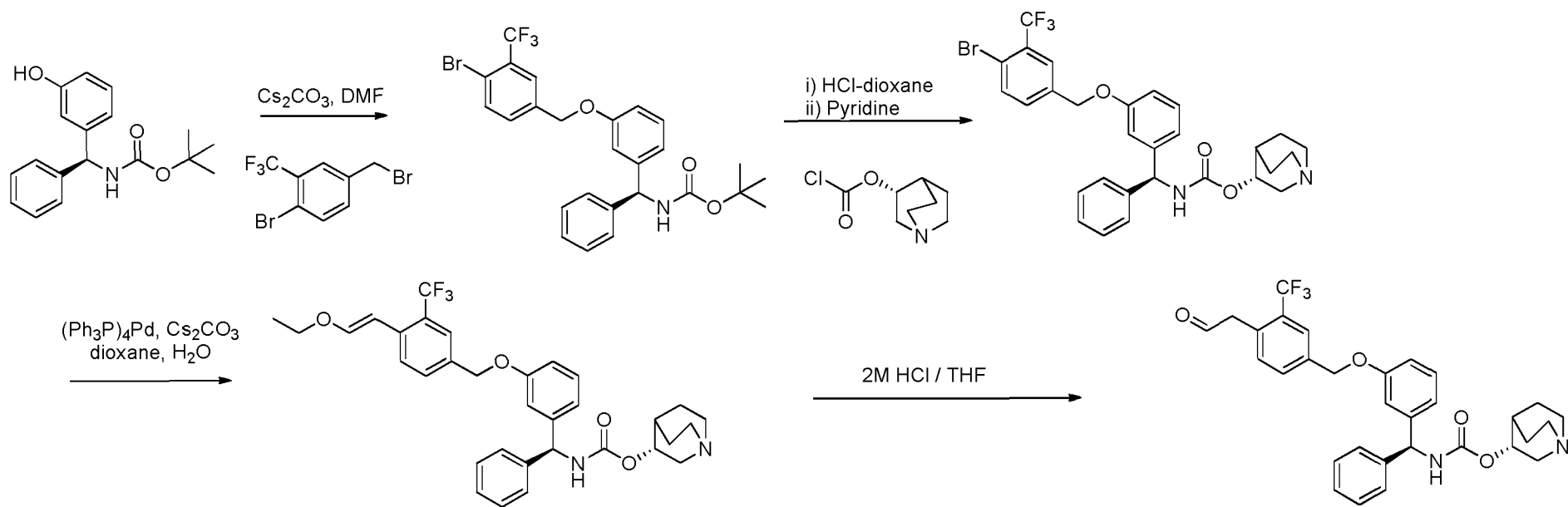
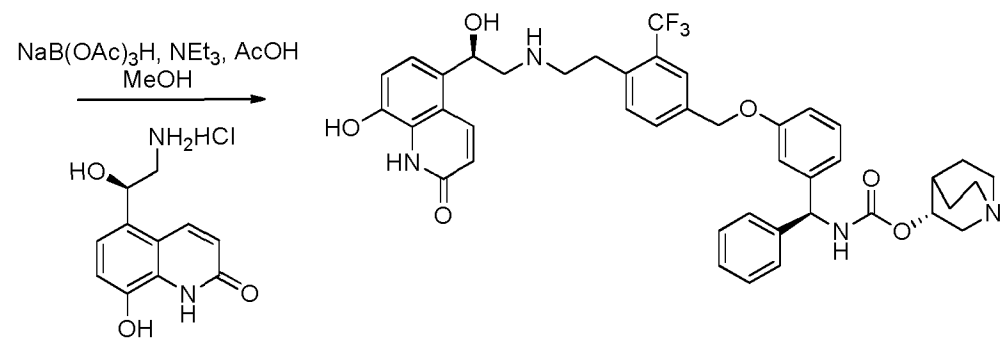
Step 4; (R)-Quinuclidin-3-yl ((S)-(3-(2-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)phenyl)amino)-2-oxoethoxy)phenyl)(phenyl)methyl)carbamate (Compound 62)

The title compound was prepared as described in **Example 11 Step 11**.

- 5 ¹H NMR (400 MHz, DMSO-d₆): δ 10.50 (s, 1 H); 10.23 (s, 1 H); 9.63 (s, 1 H); 9.05 (s, 1 H); 8.48 (d, J = 9.2 Hz, 1 H); 8.06 (d, J = 9.9 Hz, 1 H); 7.66 (d, J = 8.2 Hz, 2 H); 7.47 (d, J = 8.4 Hz, 2 H); 7.36-7.17 (m, 7 H); 7.12 (d, J = 8.2 Hz, 1 H); 7.05-6.95 (m, 3 H); 6.87 (dd, J = 8.3, 2.5 Hz, 1 H); 6.56 (d, J = 9.9 Hz, 1 H); 6.18 (s, 1 H); 5.86-5.81 (m, 1 H); 5.32 (d, J = 9.6 Hz, 1 H); 4.89-4.84 (m, 1 H); 4.69 (s, 2 H); 4.19 (s, 2 H); 3.71-3.60 (m, 1 H); 3.30-2.90 (m, 7 H); 2.24 (s, 1 H); 2.10-1.70 (m, 4 H).

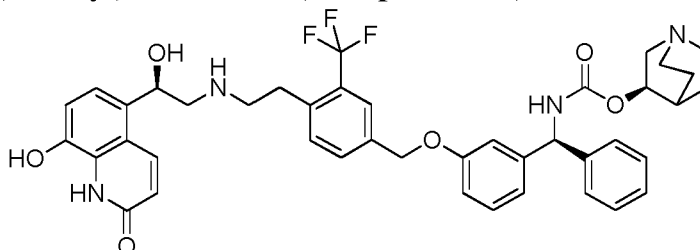
The following compounds were prepared as described in **Example 12** with the requisite amine used in **Step 2** in place of 4-aminobenzyl alcohol.

Compound number	Requisite amine	Structure
63		
64		
65		



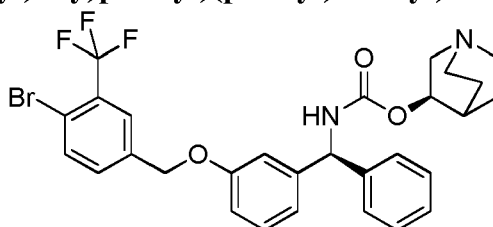
Example 13

(R)-Quinuclidin-3-yl ((S)-3-((4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)-3-(trifluoromethyl)benzyl)oxy)-phenyl)(phenyl)methyl)carbamate (Compound 66)



5

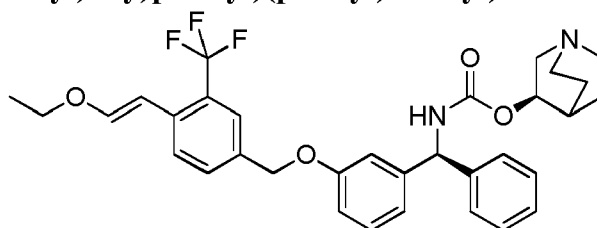
Step 1; (R)-Quinuclidin-3-yl ((S)-3-((4-bromo-3-(trifluoromethyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate



The title compound was prepared as described in **Example 1 Step 1 to Step 7** with 4-bromo-3-trifluoromethyl-benzyl bromide replacing methyl 4-(bromomethyl)benzoate in **Step 5**.

¹H NMR (400 MHz, DMSO-d₆): δ 8.22 (d, J = 9.6 Hz, 1 H); 7.90 (d, J = 7.0 Hz, 2 H); 7.65 (d, J = 8.3 Hz, 1 H); 7.32-7.18 (m, 6 H); 7.04 (s, 1 H); 6.97 (d, J = 7.7 Hz, 1 H); 6.90 (dd, J = 8.2, 2.5 Hz, 1 H); 5.83 (d, J = 9.5 Hz, 1 H); 5.16 (s, 2 H); 4.56 (s, 1 H); 3.07 (t, J = 10.7 Hz, 1 H); 2.79-2.54 (m, 5 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).

Step 2; (R)-quinuclidin-3-yl ((S)-3-((4-((E)-2-ethoxyvinyl)-3-(trifluoromethyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate



20

A mixture of **(R)-quinuclidin-3-yl ((S)-3-((4-bromo-3-**

(trifluoromethyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate (0.295 g, 0.50 mmol) and cesium carbonate (0.494 g, 1.50 mmol) was added with degassed 1,4-dioxane/water (4/1, 5 mL). This mixture was treated with 2-ethoxyethylenyl-1-boronic acid pinacol ester (0.152 g, 0.75 mmol) and the mixture de-gassed with nitrogen. Tetrakis(triphenylphosphine)palladium (0) (0.029 g, 0.025 mmol) was added and the reaction mixture refluxed for 3 hours. The reaction mixture was evaporated under reduced pressure and the residue partitioned between ethyl acetate and water. The organic phase was washed with brine, dried (magnesium sulfate), filtered and the solvent evaporated under reduced pressure. The crude material was purified by chromatography eluting with 0-20% methanol in ethyl acetate to afford the title compound (0.258 g, 89%).

¹H NMR (400 MHz, DMSO-d₆): δ 8.23 (d, J = 9.5 Hz, 1 H); 7.70 (d, J = 8.9 Hz, 2 H); 7.67-7.55 (m, 1 H); 7.34-7.20 (m, 6 H); 7.05 (s, 1 H); 6.97-6.85 (m, 2 H); 5.98 (dd, J = 12.6, 2.6 Hz, 1 H); 5.82 (d, J = 9.5 Hz, 1 H); 5.11 (s, 2 H); 4.56 (s, 1 H); 3.95 (q, J = 7.0 Hz, 2 H); 3.07 (t, J = 10.8 Hz, 1 H); 2.2.81-2.48 (m, 6 H); 1.89 (s, 1 H); 1.79 (s, 1 H); 1.57 (s, 1 H); 1.45 (s, 1 H); 1.28 (t, J = 7.0 Hz, 4 H).

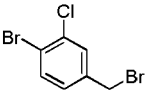
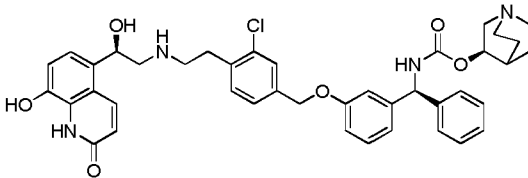
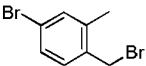
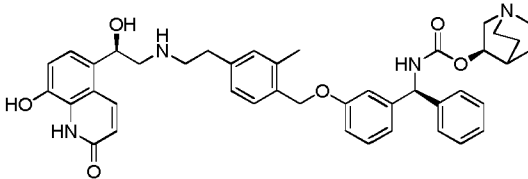
Step 3; (R)-Quinuclidin-3-yl ((S)-(3-((4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)-3-(trifluoromethyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate (Compound 66)

The title compound was prepared as described in **Example 3 Step 4** and **Step 5** with (R)-quinuclidin-3-yl ((S)-(3-((4-((E)-2-ethoxyvinyl)-3-(trifluoromethyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate replacing 3-(1,3-dioxolan-2-yl)benzyl 4-((3-((S)-phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate and the product used in **Step 5**.

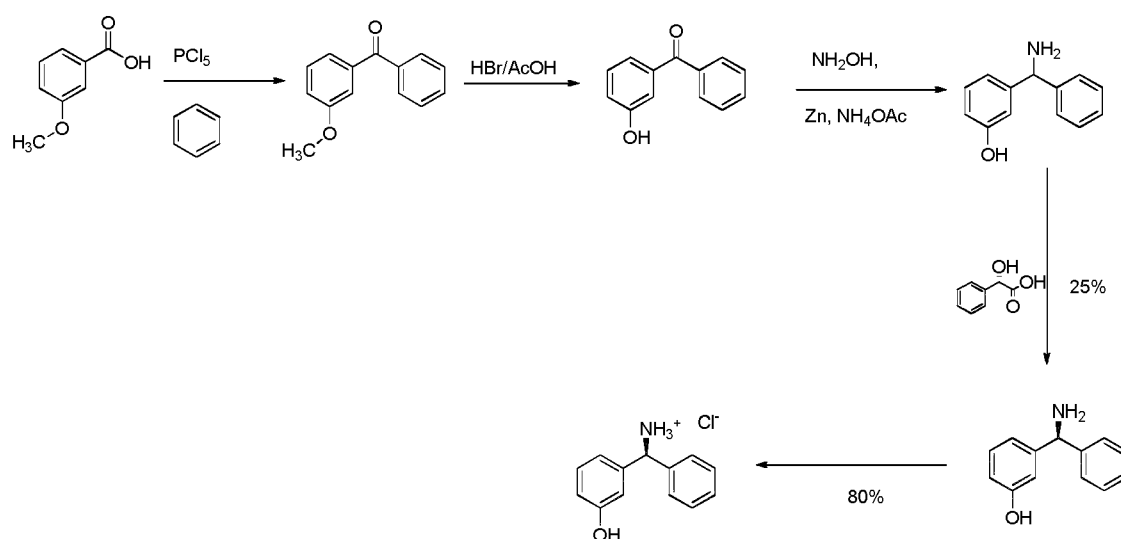
¹H NMR (400 MHz, DMSO-d₆): δ 10.51 (s, 2 H); 9.67 (s, 1 H); 8.94 (br s, 2 H); 8.46 (d, J = 9.25 Hz, 1 H); 8.18 (d, J = 9.95 Hz, 1 H); 7.80 (s, 1 H); 7.73 (d, J =

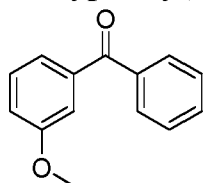
8.06 Hz, 1 H); 7.55 (d, J = 8.00 Hz, 1 H); 7.33-7.21 (m, 6 H); 7.17 (d, J = 8.19 Hz, 1 H); 7.05-6.97 (m, 3 H); 6.91 (dd, J = 8.27, 2.41 Hz, 1 H); 6.59 (m, 2 H); 6.24 (s, 1 H); 5.84 (d, J = 9.09 Hz, 1 H); 5.35 (d, J = 9.65 Hz, 1 H); 5.15 (s, 2 H); 4.88-4.83 (m, 1 H); 3.72-3.60 (m, 1 H); 3.27-3.11 (m, 10 H); 2.23 (br s, 1 H); 2.13-1.99 (m, 1 H); 1.96-1.68 (m, 3 H).

The following compounds were prepared as described in **Example 13** with the requisite benzyl bromide used in **Step 1** in place of 4-bromo-3-trifluoromethylbenzyl bromide.

Compound number	Requisite benzyl bromide	Structure
67		
68		

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



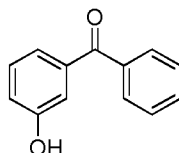
Step 1; (3-Methoxyphenyl)(phenyl)methanone

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.

5 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
10 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
15 (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, CDCl₃); 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).

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

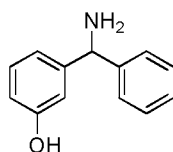


1458 g (6.9 mol) of **(3-methoxyphenyl)(phenyl)methanone** was dissolved in 2090 mL of AcOH. To the solution, 2320 ml (20.6 mol) of 48% HBr was added
25 and the mixture was stirred at 90 °C for 18 hours. The reaction was monitored by

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%).

- 5 ¹H NMR (600 MHz, CDCl₃); 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



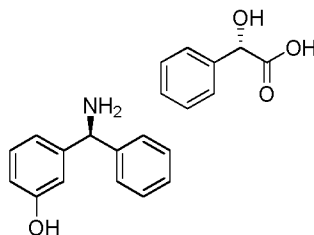
- 10 **(3-Hydroxyphenyl)(phenyl)methanone** (400 g, 2 mol) was dissolved in methanol (4 L). Hydroxylamine hydrochloride (168 g, 2.4 mol) and sodium acetate (331 g, 4 mol) were added to the resulting solution. The mixture was refluxed for 18 hours. After cooling to RT solvent was evaporated under reduced pressure, then water (3 L) was added to the residue. The product was extracted
15 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.

- The crude oxime, 362 g, (287 g, 1.3 mol of pure oxime based on analysis)
20 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
25 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).

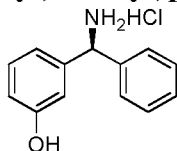
5 **Step 4; Crystallization of (S)-3-(amino(phenyl)methyl)phenol (S)-mandelate**



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
10 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.

The obtained salt was refluxed in 95% *iso*-propanol for 1 hour. The mixture
15 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



20

(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.

The amine (464 g, 2.3 mol) was suspended in methanol and 4M HCl in
 5 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
 10 (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

(continued)

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

(continued)

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
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

(continued)

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

(continued)

14	B	(CH ₃ OH-d ₆): 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
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

(continued)

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-trifluoro-acetate
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

(continued)

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

(continued)

23	C	(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); 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

(continued)

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

(continued)

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); 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).	Diformate
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
31A	C	(DMSO-d ₆): δ 10.54 (d, J = 9.45 Hz, 2 H); 9.61 (s, 1 H); 9.23 (s, 2 H); 8.49 (d, J = 9.16 Hz, 1 H); 8.15 (d, J = 9.94 Hz, 1 H); 8.07 (d, J = 8.16 Hz, 2 H); 7.98 (s, 1 H); 7.66 (d, J = 8.13 Hz, 2 H); 7.37-7.25 (m, 6 H); 7.18 (d, J = 8.17 Hz, 1 H); 7.10-7.00 (m, 3 H); 6.96 (dd, J = 8.23, 2.40 Hz, 1 H); 6.64-6.60 (m, 1 H); 6.23 (s, 1 H); 5.89 (d, J = 9.06 Hz, 1 H); 5.70 (s, 2 H); 5.37 (d, J = 9.50 Hz, 1 H); 5.24 (s, 2 H); 4.93-4.88 (m, 1 H); 4.58 (s, 2 H); 3.71 (t, J = 11.18 Hz, 1 H); 3.35-3.09 (m, 6 H); 2.28 (s, 1 H); 1.88 (d, J = 40.12 Hz, 3 H).	Di-trifluoroacetate

(continued)

31B	C	(DMSO-d ₆): δ 10.51 (d, J = 11.5 Hz, 2 H); 9.51 (s, 3 H); 8.46 (d, J = 9.2 Hz, 1 H); 8.14 (d, J = 9.9 Hz, 1 H); 8.00 (d, J = 8.1 Hz, 2 H); 7.60 (d, J = 8.1 Hz, 2 H); 7.32-7.19 (m, 6 H); 7.14 (d, J = 8.2 Hz, 1 H); 7.00 (t, J = 8.3 Hz, 3 H); 6.91 (dd, J = 8.3, 2.5 Hz, 1 H); 6.84 (s, 1 H); 6.59 (dd, J = 9.9, 1.9 Hz, 1 H); 6.21 (s, 1 H); 5.84 (d, J = 9.1 Hz, 1 H); 5.48 (s, 2 H); 5.36 (d, J = 9.6 Hz, 1 H); 5.19 (s, 2 H); 4.88-4.83 (m, 1 H); 4.53 (s, 2 H); 3.71-3.58 (m, 1 H); 3.28-3.05 (m, 4 H); 2.23 (s, 1 H); 2.14-1.47 (m, 5 H).	Di-trifluoroacetate
31C	C	(DMSO-d ₆): δ 8.23 (s, 2 H); 8.16 (d, J = 9.9 Hz, 1 H); 7.95 (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); 6.96-6.85 (m, 3 H); 6.48 (d, J = 9.9 Hz, 1 H); 6.24 (s, 1 H); 5.81 (d, J = 9.1 Hz, 1 H); 5.19 (d, J = 14.3 Hz, 4 H); 5.04 (dd, J = 7.9, 4.4 Hz, 1 H); 4.58 (s, 1 H); 3.81-3.71 (m, 5 H); 3.20-3.05 (m, 1 H); 2.78-2.60 (m, 5 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
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

(continued)

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

(continued)

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
39A	C	(DMSO-d ₆ , 105 °C): δ 8.25-8.16 (m, 3 H); 7.59 (s, 1 H); 7.34-7.19 (m, 6 H); 7.13-7.01 (m, 2 H); 6.98-6.91 (m, 3 H); 6.57 (s, 1 H); 6.48 (d, J = 9.9 Hz, 1 H); 5.84 (d, J = 7.5 Hz, 1 H); 5.21-5.12 (m, 2 H); 5.05 (dd, J = 7.4, 5.1 Hz, 1 H); 4.66-4.60 (m, 1 H); 3.93-3.81 (m, 3 H); 3.55 (d, J = 8.2 Hz, 4 H); 3.10 (dd, J = 14.4, 8.3 Hz, 1 H); 2.86-2.59 (m, 9 H); 1.94-1.90 (m, 1 H); 1.79-1.68 (m, 3 H); 1.67-1.56 (m, 1 H); 1.54-1.44 (m, 1 H); 1.37-1.26 (m, 1 H); 1.19-1.08 (m, 3 H).	Diformate
39B	C	(DMSO-d ₆): δ 8.66-8.60 (m, 1 H); 8.31-8.23 (m, 3 H); 8.11 (d, J = 9.9 Hz, 1 H); 7.33-7.18 (m, 10 H); 7.06 (d, J = 8.7 Hz, 2 H); 6.99-6.90 (m, 3 H); 6.79 (s, 1 H); 6.49 (dd, J = 9.9, 4.3 Hz, 1 H); 5.83 (d, J = 9.3 Hz, 1 H); 5.20 (s, 2 H); 5.10 (dd, J = 7.8, 4.7 Hz, 1 H); 4.62 (s, 2 H); 4.39 (d, J = 6.3 Hz, 2 H); 3.89 (s, 3 H); 3.93-3.61 (m, 2 H); 3.16 (d, J = 11.7 Hz, 1 H); 2.87-2.53 (m, 6 H); 1.95 (s, 1 H); 1.83 (s, 1 H); 1.62 (s, 1 H); 1.52 (s, 1 H); 1.39 (s, 1 H).	Diformate

(continued)

39C	C	(DMSO-d ₆): δ 10.54 (s, 1 H); 10.49 (s, 1 H); 9.84 (s, 1 H); 8.71 (t, J = 6.6 Hz, 1 H); 8.47 (d, J = 9.2 Hz, 1 H); 8.08 (d, J = 9.9 Hz, 1 H); 7.38-6.87 (m, 16 H); 6.79 (s, 1 H); 6.56 (d, J = 9.9 Hz, 1 H); 6.20 (s, 1 H); 5.84 (d, J = 9.1 Hz, 1 H); 5.34 (s, 1 H); 5.20 (s, 2 H); 4.89-4.84 (m, 1 H); 4.43 (d, J = 6.3 Hz, 2 H); 4.28-4.11 (m, 2 H); 3.90 (s, 3 H); 3.81 (s, 3 H); 3.66 (t, J = 18.0 Hz, 1 H); 3.38-2.92 (m, 7 H); 2.23 (s, 1 H); 2.06 (d, J = 15.5 Hz, 1 H); 1.96-1.68 (m, 3 H).	Di-trifluoroacetate
39D	C	(DMSO-d ₆): δ 8.72 (t, J = 6.3 Hz, 1 H); 8.30 (d, J = 9.6 Hz, 1 H); 8.25 (s, 2 H); 8.20-8.09 (m, 1 H); 7.40-7.16 (m, 7 H); 7.11-6.89 (m, 7 H); 6.80 (s, 1 H); 6.55-6.45 (m, 1 H); 5.83 (d, J = 9.3 Hz, 1 H); 5.20 (s, 2 H); 5.06 (dd, J = 8.1, 4.5 Hz, 1 H); 4.65 (s, 2 H); 4.39 (d, J = 6.2 Hz, 2 H); 3.90 (s, 3 H); 3.77 (s, 2 H); 3.23 (t, J = 10.2 Hz, 1 H); 2.87-2.56 (m, 6 H); 1.99 (s, 1 H); 1.86 (d, J = 11.1 Hz, 1 H); 1.65 (s, 1 H); 1.55 (s, 1 H); 1.43 (s, 1 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

(continued)

40A	C	(DMSO-d ₆ , 105 °C): δ 8.24-8.14 (m, 3 H); 7.57 (d, J = 8.8 Hz, 1 H); 7.33-7.27 (m, 4 H); 7.26-7.19 (m, 2 H); 7.08 (d, J = 8.1 Hz, 1 H); 7.01 (d, J = 2.3 Hz, 1 H); 6.97-6.89 (m, 3 H); 6.86 (d, J = 3.4 Hz, 1 H); 6.57 (d, J = 3.4 Hz, 1 H); 6.48 (d, J = 9.9 Hz, 1 H); 5.83 (d, J = 8.2 Hz, 1 H); 5.15-5.04 (m, 2 H); 5.03 (dd, J = 7.5, 4.9 Hz, 1 H); 3.51-3.43 (m, 4 H); 3.09 (dd, J = 14.4, 8.3 Hz, 1 H); 2.85-2.51 (m, 10 H); 1.93-1.89 (m, 1 H); 1.78-1.65 (m, 3 H); 1.66-1.57 (m, 1 H); 1.52-1.44 (m, 1 H); 1.34-1.26 (m, 1 H); 1.17-1.09 (m, 3 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
41A	C	(DMSO- d ₆): 8.49-8.42 (m, 1 H), 8.28 (d, J = 6.31 Hz, 3 H), 8.18 (d, J = 9.94 Hz, 1 H), 7.33-7.19 (m, 7 H), 7.15-7.07 (m, 2 H), 7.02 (d, J = 7.70 Hz, 1 H), 6.96 (d, J = 8.14 Hz, 2 H), 6.54 (d, J = 9.87 Hz, 1 H), 5.85 (s, 1 H), 5.43 (s, 2 H), 5.19 (dd, J = 8.25, 4.35 Hz, 1 H), 4.60 (s, 1 H), 3.29-3.04 (m, 3 H), 2.93-2.57 (m, 7 H), 1.93 (s, 1 H), 1.81 (s, 2 H), 1.68-1.20 (m, 8 H).	Diformate
41B	C	(DMSO- d ₆): δ 10.35 (s, 1 H); 8.63-8.56 (m, 1 H); 8.35 (d, J = 9.20 Hz, 1 H); 8.28-8.22 (m, 3 H); 7.95 (s, 1 H); 7.82 (d, J = 7.77 Hz, 1 H); 7.59 (d, J = 7.62 Hz, 1 H); 7.47 (t, J = 7.66 Hz, 1 H); 7.34-7.20 (m, 6 H); 7.18-7.09 (m, 1 H); 7.10-6.84 (m, 4 H); 6.55 (d, J = 9.85 Hz, 1 H); 5.84 (d, J = 9.15 Hz, 1 H); 5.40 (d, J = 9.38 Hz, 1 H); 5.12 (s, 2 H); 4.74-4.68 (m, 1 H); 3.38-3.18 (m, 3 H); 3.06-2.66 (m, 8 H); 2.05 (s, 1 H); 1.91 (s, 1 H); 1.75-1.45 (m, 7 H).	Diformate

(continued)

41C	C	(DMSO-d ₆): δ 8.43-8.36 (m, 1 H); 8.30 (s, 2 H); 8.24 (d, J = 9.5 Hz, 1 H); 8.17 (d, J = 9.9 Hz, 1 H); 7.89 (s, 1 H); 7.35-7.27 (m, 4 H); 7.27-7.18 (m, 2 H); 7.16-7.06 (m, 2 H); 7.01 (s, 1 H); 6.95 (d, J = 8.0 Hz, 2 H); 6.88 (dd, J = 8.3, 2.5 Hz, 1 H); 6.52 (d, J = 9.9 Hz, 1 H); 5.83 (d, J = 9.2 Hz, 1 H); 5.16-5.11 (m, 1 H); 4.95 (s, 2 H); 4.58 (s, 1 H); 3.11 (d, J = 14.4 Hz, 2 H); 2.85-2.70 (m, 7 H); 1.91 (s, 1 H); 1.80 (s, 1 H); 1.66-1.20 (m, 9 H).	Diformate
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
43	C	(DMSO-d ₆): δ 9.06-9.00 (m, 1 H); 8.31-8.23 (m, 3 H); 8.12 (d, J = 9.9 Hz, 1 H); 7.90 (d, J = 8.1 Hz, 2 H); 7.52 (d, J = 8.0 Hz, 2 H); 7.32-7.17 (m, 10 H); 7.05 (t, J = 4.2 Hz, 2 H); 6.96-6.85 (m, 3 H); 6.53-6.45 (m, 1 H); 5.82 (d, J = 9.2 Hz, 1 H); 5.18-5.06 (m, 3 H); 4.62 (s, 2 H); 4.47 (d, J = 5.9 Hz, 2 H); 3.92-3.68 (m, 2 H); 2.88-2.51 (m, 7 H); 1.95 (s, 1 H); 1.83 (s, 1 H); 1.62 (s, 1 H); 1.52 (s, 1 H); 1.39 (s, 1 H).	Diformate

(continued)

44	C	(DMSO-d ₆): δ 9.05-8.99 (m, 1 H); 8.29-8.21 (m, 2 H); 8.12 (d, J = 9.9 Hz, 1 H); 7.90 (d, J = 8.1 Hz, 2 H); 7.52 (d, J = 8.0 Hz, 2 H); 7.33-7.19 (m, 7 H); 7.05 (d, J = 7.8 Hz, 2 H); 6.97-6.81 (m, 5 H); 6.49 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.1 Hz, 1 H); 5.14 (s, 2 H); 5.07 (dd, J = 7.8, 4.6 Hz, 1 H); 4.60 (s, 1 H); 4.47 (d, J = 5.8 Hz, 2 H); 3.78-3.62 (m, 3 H); 3.23-3.06 (m, 1 H); 2.84-2.55 (m, 7 H); 2.08 (s, 2 H); 1.93 (t, J = 4.4 Hz, 1 H); 1.82 (s, 1 H); 1.61 (s, 1 H); 1.50 (s, 1 H); 1.37 (s, 1 H).	Formate
45	C	(DMSO-d ₆ , 120 °C): δ 8.21 (d, J = 9.9 Hz, 1 H); 8.16 (s, 2 H); 7.47-7.38 (m, 1 H); 7.32-7.27 (m, 4 H); 7.26-7.20 (m, 2 H); 7.08 (d, J = 8.1 Hz, 1 H); 7.02-7.00 (m, 1 H); 6.98-6.85 (m, 3 H); 6.48 (d, J = 9.9 Hz, 1 H); 6.41 (s, 1 H); 5.86-5.80 (m, 1 H); 5.07-4.96 (m, 3 H); 4.65-4.59 (m, 1 H); 3.84-3.77 (m, 3 H); 3.48-3.40 (m, 2 H); 3.09 (dd, J = 14.5, 8.3 Hz, 1 H); 2.96 (s, 3 H); 2.81-2.47 (m, 9 H); 1.93-1.88 (m, 1 H); 1.80-1.56 (m, 4 H); 1.53-1.44 (m, 1 H); 1.37-1.27 (m, 1 H).	Diformate
46	C	(DMSO-d ₆ , 120 °C): δ 8.21 (d, J = 10.0 Hz, 1 H); 8.16 (s, 2 H); 7.47-7.40 (m, 1 H); 7.32-7.27 (m, 4 H); 7.25-7.19 (m, 2 H); 7.08 (d, J = 8.1 Hz, 1 H); 7.01 (s, 1 H); 6.97-6.86 (m, 3 H); 6.48 (d, J = 9.9 Hz, 1 H); 6.37 (s, 1 H); 5.85-5.80 (m, 1 H); 5.06-4.98 (m, 3 H); 4.64-4.59 (m, 1 H); 3.82-3.75 (m, 3 H); 3.46-3.34 (m, 4 H); 3.09 (dd, J = 14.4, 8.3 Hz, 1 H); 2.80-2.47 (m, 9 H); 1.93-1.89 (m, 1 H); 1.79-1.56 (m, 4 H); 1.53-1.45 (m, 1 H); 1.34-1.27 (m, 1 H); 1.10 (t, J = 7.1 Hz, 3 H).	Diformate

(continued)

47	C	(DMSO-d ₆ , 105 °C): δ 8.24-8.15 (m, 3 H); 7.57 (s, 1 H); 7.46 (d, J = 7.9 Hz, 2 H); 7.37-7.28 (m, 6 H); 7.27-7.21 (m, 2 H); 7.09 (d, J = 8.1 Hz, 1 H); 7.03 (s, 1 H); 6.98-6.86 (m, 3 H); 6.49 (d, J = 9.9 Hz, 1 H); 5.83 (d, J = 7.0 Hz, 1 H); 5.21-5.04 (m, 2 H); 5.07-5.00 (m, 1 H); 4.64-4.59 (m, 2 H); 3.13-3.05 (m, 1 H); 2.92 (s, 3 H); 2.83-2.46 (m, 10 H); 1.91 (s, 1 H); 1.76 (s, 1 H); 1.69-1.29 (m, 7 H).	Diformate
48	C	(DMSO-d ₆ , 105 °C): δ 8.24-8.16 (m, 3 H); 7.58 (m, 1 H); 7.46 (d, J = 7.9 Hz, 2 H); 7.34-7.28 (m, 6 H); 7.27-7.21 (m, 2 H); 7.10-7.02 (m, 2 H); 6.97-6.86 (m, 3 H); 6.48 (d, J = 9.9 Hz, 1 H); 5.83 (d, J = 7.0 Hz, 1 H); 5.11 (s, 2 H); 5.03 (dd, J = 7.4, 5.0 Hz, 1 H); 4.65-4.59 (m, 1 H); 3.39-3.25 (m, 4 H); 3.15-3.04 (m, 1 H); 2.82-2.51 (m, 11 H); 1.93-1.89 (m, 1 H); 1.76 (s, 1 H); 1.64-1.53 (m, 3 H); 1.42-1.30 (m, 2 H); 1.10 (t, J = 7.0 Hz, 3 H).	Diformate
49	C	(DMSO-d ₆ , 105 °C): δ 8.23-8.13 (m, 3 H); 7.57 (m, 1 H); 7.48-7.37 (m, 2 H); 7.33-7.27 (m, 6 H); 7.26-7.19 (m, 2 H); 7.10-7.02 (m, 2 H); 6.96-6.85 (m, 3 H); 6.48 (d, J = 9.9 Hz, 1 H); 5.83 (d, J = 7.9 Hz, 1 H); 5.12 (s, 2 H); 5.01 (m, 1 H); 4.64-4.59 (m, 1 H); 3.43-3.31 (m, 2 H); 3.09 (m, 1 H); 2.89 (s, 3 H); 2.83-2.54 (m, 9 H); 1.91 (s, 1 H); 1.77-1.56 (m, 5 H); 1.31 (d, J = 11.1 Hz, 1 H).	Diformate

(continued)

50	C	(DMSO-d ₆ , 105 °C): δ 8.23-8.15 (m, 3 H); 7.57 (s, 1 H); 7.49-7.34 (m, 3 H); 7.33-7.19 (m, 7 H); 7.07 (d, J = 8.1 Hz, 1 H); 7.04-7.02 (m, 1 H); 6.97-6.85 (m, 3 H); 6.48 (d, J = 9.9 Hz, 1 H); 5.83 (d, J = 8.0 Hz, 1 H); 5.29-4.95 (m, 2 H); 5.02 (dd, J = 7.7, 5.1 Hz, 1 H); 4.65-4.59 (m, 1 H); 3.42-3.22 (m, 4 H); 3.09 (m, 1 H); 2.83-2.54 (m, 9 H); 1.93-1.89 (m, 1 H); 1.75-1.54 (m, 4 H); 1.54-1.44 (m, 1 H); 1.37-1.26 (m, 1 H); 1.12-1.02 (m, 3 H).	Di-formate
51	C	(DMSO-d ₆ , 110°C): δ 8.21-8.15 (m, 2 H); 7.86-7.78 (m, 3 H); 7.54-7.23 (m, 13 H); 7.15 (d, J = 8.2 Hz, 1 H); 7.05-6.95 (m, 3 H); 6.93 (dd, J = 8.3, 2.7 Hz, 1 H); 6.55 (d, J = 9.9 Hz, 1 H); 5.87-5.82 (m, 1 H); 5.36-5.31 (m, 1 H); 5.15-5.08 (m, 2 H); 4.95-4.90 (m, 1 H); 3.66 (ddd, J = 13.9, 8.5, 2.6 Hz, 1 H); 3.57-3.46 (m, 7 H); 3.59-2.72 (m, 9 H); 2.25 (d, J = 4.6 Hz, 1 H); 2.10-1.72 (m, 7 H).	Di-trifluoroacetate
52	C	(DMSO-d ₆ , 110 °C): δ 8.17 (d, J = 9.9 Hz, 1 H); 7.86-7.77 (m, 2 H); 7.36-7.21 (m, 9 H); 7.15 (d, J = 8.2 Hz, 1 H); 7.03-6.98 (m, 2 H); 6.95 (d, J = 7.8 Hz, 1 H); 6.90 (dd, J = 8.2, 2.5 Hz, 1 H); 6.56 (d, J = 9.9 Hz, 1 H); 5.84 (d, J = 8.7 Hz, 1 H); 5.35-5.30 (m, 1 H); 5.04 (s, 2 H); 4.95-4.90 (m, 1 H); 3.65 (ddd, J = 13.8, 8.5, 2.5 Hz, 1 H); 3.47 (s, 2 H); 3.28-2.97 (m, 12 H); 2.26-2.23 (m, 1 H); 2.07-1.73 (m, 6 H).	Di-trifluoroacetate

(continued)

53	C	(DMSO-d ₆): δ 8.32-8.23 (m, 3 H); 8.11 (d, J = 9.9 Hz, 1 H); 7.63-7.33 (m, 4 H); 7.35-7.21 (m, 8 H); 7.09-7.04 (m, 3 H); 6.96-6.88 (m, 3 H); 6.45 (d, J = 9.9 Hz, 1 H); 5.84 (d, J = 9.1 Hz, 1 H); 5.17-5.08 (m, 3 H); 4.66-4.59 (m, 1 H); 3.83 (s, 2 H); 3.76 (s, 3 H); 3.23-3.12 (m, 1 H); 2.85-2.51 (m, 7 H); 1.93 (s, 1 H); 1.83 (s, 1 H); 1.62 (s, 1 H); 1.52 (s, 1 H); 1.39 (s, 1 H).	Diformate
54	C	(DMSO-d ₆): δ 8.30-8.19 (m, 3 H); 8.14 (d, J = 9.9 Hz, 1 H); 7.70 (d, J = 8.0 Hz, 2 H); 7.51 (d, J = 7.9 Hz, 2 H); 7.39-7.17 (m, 10 H); 7.07 (d, J = 8.4 Hz, 2 H); 6.97-6.87 (m, 3 H); 6.49 (d, J = 9.9 Hz, 1 H); 5.83 (d, J = 9.0 Hz, 1 H); 5.14-5.06 (m, 3 H); 4.60 (s, 1 H); 3.86 (s, 3 H); 3.80 (s, 2 H); 3.14 (t, J = 8.6 Hz, 1 H); 2.81-2.56 (m, 6 H); 1.93 (s, 1 H); 1.82 (s, 1 H); 1.61 (s, 1 H); 1.50 (s, 1 H); 1.37 (s, 1 H).	Diformate
55	C	(DMSO-d ₆): δ 10.50 (s, 2 H); 9.61 (s, 1 H); 8.90 (s, 3 H); 8.46 (d, J = 9.2 Hz, 1 H); 8.08 (d, J = 9.9 Hz, 1 H); 7.83 (d, J = 2.4 Hz, 1 H); 7.76 (dd, J = 8.6, 2.3 Hz, 1 H); 7.67 (d, J = 8.1 Hz, 2 H); 7.52 (d, J = 8.0 Hz, 2 H); 7.34-7.17 (m, 6 H); 7.15 (d, J = 8.2 Hz, 1 H); 7.04 (s, 1 H); 6.98 (d, J = 8.1 Hz, 2 H); 6.92 (dd, J = 8.2, 2.4 Hz, 1 H); 6.53 (d, J = 9.9 Hz, 1 H); 6.22 (s, 1 H); 5.84 (d, J = 9.1 Hz, 1 H); 5.10 (s, 2 H); 4.89-4.84 (m, 1 H); 4.32 (s, 2 H); 3.89 (s, 3 H); 3.30-3.05 (m, 8 H); 2.24 (s, 1 H); 2.16-1.97 (m, 1 H); 1.97-1.57 (m, 4 H).	Di-trifluoroacetate

(continued)

56	C	(DMSO-d ₆): δ 8.31-8.20 (m, 3 H); 8.11 (d, J = 9.9 Hz, 1 H); 7.41-7.27 (m, 8 H); 7.26-7.20 (m, 2 H); 7.12-7.00 (m, 2 H); 6.94-6.83 (m, 3 H); 6.48 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.3 Hz, 1 H); 5.10 (dd, J = 8.0, 4.5 Hz, 1 H); 5.04 (s, 2 H); 4.63-4.62 (m, 1 H); 3.81 (s, 2 H); 3.27-3.08 (m, 1 H); 2.82 (br s, 2 H); 2.81-2.56 (m, 5 H); 1.96 (br s, 1 H); 1.90-1.84 (m, 1 H); 1.70-1.60 (m, 1 H); 1.63-1.46 (m, 1 H); 1.44-1.38 (m, 1 H).	Diformate
57	C	(DMSO-d ₆): δ 8.29-8.18 (m, 2 H); 8.15 (d, J = 9.9 Hz, 1 H); 7.35-7.27 (m, 4 H); 7.26-7.18 (m, 2 H); 7.11-6.98 (m, 2 H); 6.95-6.85 (m, 3 H); 6.51-6.43 (m, 2 H); 6.21 (d, J = 3.1 Hz, 1 H); 5.82 (d, J = 9.2 Hz, 1 H); 5.04 (dd, J = 8.0, 4.5 Hz, 1 H); 4.97 (s, 2 H); 4.61 (s, 1 H); 3.73 (s, 2 H); 3.23-3.11 (m, 1 H); 2.74-2.64 (m, 7 H); 1.94 (d, J = 5.2 Hz, 1 H); 1.82 (s, 1 H); 1.62 (s, 1 H); 1.52 (s, 2 H); 1.39 (s, 1 H).	Diformate
58	C	(DMSO-d ₆ /D ₂ O): δ 8.17 (d, J = 10.0 Hz, 1 H); 7.40-7.20 (m, 10 H); 7.17 (d, J = 8.2 Hz, 1 H); 7.04-6.92 (m, 3 H); 6.93-6.87 (m, 1 H); 6.60 (d, J = 9.9 Hz, 1 H); 5.84-5.78 (m, 1 H); 5.31 (dd, J = 9.7, 3.4 Hz, 1 H); 5.02 (s, 2 H); 4.87-4.82 (m, 1 H); 3.63-3.59 (m, 1 H); 3.28-3.07 (m, 8 H); 3.03-2.90 (m, 2 H); 2.22 (s, 1 H); 2.03 (s, 1 H); 2.01-1.72 (m, 4 H).	Di-trifluoroacetate

(continued)

59	C	(DMSO-d ₆): δ 10.50 (d, J = 17.4 Hz, 2 H); 9.53 (s, 1 H); 9.06 (s, 2 H); 8.45 (d, J = 9.2 Hz, 1 H); 8.07 (d, J = 9.9 Hz, 1 H); 7.60 (s, 1 H); 7.53-7.44 (m, 3 H); 7.32 (d, J = 4.5 Hz, 4 H); 7.28-7.21 (m, 2 H); 7.12 (d, J = 8.2 Hz, 1 H); 7.02-6.94 (m, 4 H); 6.90 (d, J = 8.3 Hz, 1 H); 6.57 (dd, J = 9.8, 1.9 Hz, 1 H); 6.17 (s, 1 H); 5.84 (d, J = 9.1 Hz, 1 H); 5.33 (d, J = 9.4 Hz, 1 H); 5.07 (s, 2 H); 4.89-4.84 (m, 1 H); 4.25 (s, 2 H); 3.72-3.60 (m, 1 H); 3.28-2.94 (m, 6 H); 2.23 (s, 1 H); 2.04 (s, 1 H); 1.92-1.73 (m, 3 H).	Di-trifluoroacetate
60	C	(DMSO-d ₆): δ 10.52 (s, 1 H); 10.47 (s, 1 H); 9.53 (s, 1 H); 9.19 (s, 2 H); 8.74 (d, J = 2.1 Hz, 1 H); 8.46 (d, J = 9.2 Hz, 1 H); 8.16 (d, J = 9.9 Hz, 1 H); 7.95 (dd, J = 8.0, 2.1 Hz, 1 H); 7.53 (d, J = 8.0 Hz, 1 H); 7.35-7.21 (m, 6 H); 7.16 (d, J = 8.2 Hz, 1 H); 7.06-6.96 (m, 3 H); 6.95-6.90 (m, 1 H); 6.61 (dd, J = 9.9, 2.0 Hz, 1 H); 6.18 (s, 1 H); 5.86-5.82 (m, 1 H); 5.44 (d, J = 9.5 Hz, 1 H); 5.16 (s, 2 H); 4.89-4.84 (m, 1 H); 4.43 (s, 2 H); 3.72-3.59 (m, 1 H); 3.27-3.07 (m, 6 H); 2.24 (s, 1 H); 2.07-1.69 (m, 5 H).	Di-trifluoroacetate
61	C	(DMSO-d ₆): δ 10.50 (d, J = 12.8 Hz, 2 H); 9.58 (s, 1 H); 8.81 (s, 2 H); 8.68 (d, J = 4.9 Hz, 1 H); 8.45 (d, J = 9.1 Hz, 1 H); 8.08-7.98 (m, 1 H); 7.57 (dd, J = 7.6, 5.3 Hz, 1 H); 7.43 (d, J = 7.7 Hz, 1 H); 7.33-7.20 (m, 4 H); 7.17 (s, 1 H); 7.14 (d, J = 8.2 Hz, 1 H); 7.10-6.94 (m, 3 H); 6.91 (dd, J = 8.2, 2.4 Hz, 1 H); 6.58 (d, J = 9.9 Hz, 1 H); 6.20 (s, 1 H); 5.86-5.82 (m, 1 H); 5.37-5.31 (m, 1 H); 5.08 (s, 2 H); 4.89-4.84 (m, 1 H); 4.33-4.15 (m, 2 H); 3.84 (s, 3 H); 3.71-3.60 (m, 1 H); 3.32-2.98 (m, 8 H); 2.24 (s, 1 H); 2.13-1.67 (m, 4 H).	Di-trifluoroacetate

(continued)

62	C	(DMSO-d ₆): δ 10.50 (s, 1 H); 10.23 (s, 1 H); 9.63 (s, 1 H); 9.05 (s, 1 H); 8.48 (d, J = 9.2 Hz, 1 H); 8.06 (d, J = 9.9 Hz, 1 H); 7.66 (d, J = 8.2 Hz, 2 H); 7.47 (d, J = 8.4 Hz, 2 H); 7.36-7.17 (m, 7 H); 7.12 (d, J = 8.2 Hz, 1 H); 7.05-6.95 (m, 3 H); 6.87 (dd, J = 8.3, 2.5 Hz, 1 H); 6.56 (d, J = 9.9 Hz, 1 H); 6.18 (s, 1 H); 5.86-5.81 (m, 1 H); 5.32 (d, J = 9.6 Hz, 1 H); 4.89-4.84 (m, 1 H); 4.69 (s, 2 H); 4.19 (s, 2 H); 3.71-3.60 (m, 1 H); 3.30-2.90 (m, 7 H); 2.24 (s, 1 H); 2.10-1.70 (m, 4 H).	Di-trifluoroacetate
63	C	(DMSO-d ₆): δ 10.50 (m, 2 H); 9.57 (s, 1 H); 8.74 (s, 2 H); 8.52-8.42 (m, 1 H); 8.05 (d, J = 9.9 Hz, 1 H); 7.47 (d, J = 1.9 Hz, 1 H); 7.39-7.18 (m, 8 H); 7.13 (d, J = 8.2 Hz, 1 H); 7.03-6.94 (m, 3 H); 6.89-6.85 (m, 1 H); 6.57 (d, J = 9.9 Hz, 1 H); 6.18 (d, J = 3.9 Hz, 1 H); 5.86-5.82 (m, 1 H); 5.36-5.28 (m, 1 H); 4.89-4.84 (m, 1 H); 4.69 (s, 2 H); 4.27-4.11 (m, 2 H); 3.80 (s, 3 H); 3.71-3.60 (m, 1 H); 3.31-3.05 (m, 5 H); 3.01 (s, 2 H); 2.24 (s, 1 H); 2.05 (s, 1 H); 1.91-1.72 (m, 4 H).	Di-trifluoroacetate
64	C	(DMSO-d ₆): δ 10.50 (2 H, d, J = 14.70 Hz), 9.64 (1 H, s), 9.52 (1 H, s), 8.82 (2 H, s), 8.48 (1 H, d, J = 9.18 Hz), 8.09 (1 H, d, J = 9.93 Hz), 7.70 (1 H, s), 7.63 (1 H, s), 7.34-7.27 (5 H, m), 7.26-7.19 (1 H, m), 7.14 (1 H, d, J = 8.18 Hz), 7.08-7.00 (2 H, m), 6.98 (1 H, d, J = 8.13 Hz), 6.93-6.89 (1 H, m), 6.59 (1 H, d, J = 9.88 Hz), 6.19 (1 H, s), 5.86 (1 H, d, J = 9.07 Hz), 5.36-5.31 (1 H, m), 4.89-4.84 (1 H, m), 4.79 (2 H, s), 4.21 (2 H, d, J = 9.15 Hz), 3.82 (3 H, s), 3.72-3.59 (2 H, m), 3.30-2.99 (7 H, m), 2.24 (1 H, s), 2.05 (1 H, s), 1.93-1.73 (3 H, m).	Di-trifluoroacetate

(continued)

65	C	(DMSO- d ₆): 10.51 (s, 2 H); 10.22 (s, 1 H); 9.64 (s, 1 H); 8.73 (m, 2 H); 8.48 (d, J = 9.12 Hz, 1 H); 8.06 (d, J = 9.94 Hz, 1 H); 7.45 (s, 1 H); 7.38-7.17 (m, 8 H); 7.13 (d, J = 8.18 Hz, 1 H); 7.00 (dd, J = 14.55, 8.56 Hz, 3 H); 6.89-6.85 (m, 1 H); 6.56 (d, J = 9.87 Hz, 1 H); 6.21 (s, 1 H); 5.86-5.81 (m, 1 H); 5.33 (dd, J = 9.07, 3.46 Hz, 1 H); 4.89-4.84 (m, 1 H); 4.69 (s, 2 H); 4.27-4.08 (m, 3 H); 4.03 (dd, J = 14.04, 7.02 Hz, 2 H); 3.70-3.61 (m, 1 H); 3.37-2.93 (m, 6 H); 2.24 (s, 1 H); 2.05 (s, 1 H); 1.93-1.70 (m, 3 H); 1.37-1.28 (m, 3 H).	Di-trifluoroacetate
66	C	(DMSO- d ₆): δ 10.51 (s, 2 H); 9.67 (s, 1 H); 8.94 (br s, 2 H); 8.46 (d, J = 9.25 Hz, 1 H); 8.18 (d, J = 9.95 Hz, 1 H); 7.80 (s, 1 H); 7.73 (d, J = 8.06 Hz, 1 H); 7.55 (d, J = 8.00 Hz, 1 H); 7.33-7.21 (m, 6 H); 7.17 (d, J = 8.19 Hz, 1 H); 7.05-6.97 (m, 3 H); 6.91 (dd, J = 8.27, 2.41 Hz, 1 H); 6.59 (m, 2 H); 6.24 (s, 1 H); 5.84 (d, J = 9.09 Hz, 1 H); 5.35 (d, J = 9.65 Hz, 1 H); 5.15 (s, 2 H); 4.88-4.83 (m, 1 H); 3.72-3.60 (m, 1 H); 3.27-3.11 (m, 10 H); 2.23 (br s, 1 H); 2.13-1.99 (m, 1 H); 1.96-1.68 (m, 3 H).	Di-trifluoroacetate
67	C	(DMSO- d ₆): δ 10.51 (d, J = 4.51 Hz, 2 H); 9.73 (s, 1 H); 8.91 (br s, 2 H); 8.46 (d, J = 9.22 Hz, 1 H); 8.18 (d, J = 9.94 Hz, 1 H); 7.55 (s, 1 H); 7.39 (s, 2 H); 7.33-7.19 (m, 6 H); 7.17 (d, J = 8.19 Hz, 1 H); 7.02-6.95 (m, 3 H); 6.89 (dd, J = 8.25, 2.42 Hz, 1 H); 6.63-6.53 (m, 2 H); 6.23 (s, 1 H); 5.83 (d, J = 9.08 Hz, 1 H); 5.35 (d, J = 9.58 Hz, 1 H); 5.06 (s, 2 H); 4.89-4.84 (m, 1 H); 3.71-3.60 (m, 1 H); 3.25-3.06 (m, 10 H); 2.23 (s, 1 H); 2.05 (s, 1 H); 1.96-1.68 (m, 3 H).	Di-trifluoroacetate

(continued)

68	C	(DMSO- d_6): δ 10.52 (d, J = 8.35 Hz, 2 H); 9.78 (s, 1 H); 8.85 (s, 1 H); 8.79 (s, 1 H); 8.46 (d, J = 9.24 Hz, 1 H); 8.17 (d, J = 9.94 Hz, 1 H); 7.39-7.21 (m, 6 H); 7.17 (d, J = 8.63 Hz, 1 H); 7.11 (s, 1 H); 7.07 (d, J = 8.05 Hz, 1 H); 7.05-6.95 (m, 3 H); 6.91 (d, J = 8.29 Hz, 1 H); 6.58 (d, J = 10.06 Hz, 2 H); 6.23 (s, 1 H); 5.84 (d, J = 9.07 Hz, 1 H); 5.35 (d, J = 9.56 Hz, 1 H); 5.02 (s, 2 H); 4.89-4.84 (m, 1 H); 3.71-3.60 (m, 1 H); 3.28-3.05 (m, 9 H); 3.04-2.87 (m, 2 H); 2.30 (s, 3 H); 2.23 (s, 1 H); 2.13-1.98 (m, 1 H); 1.97-1.54 (m, 3 H).	Di-trifluoroacetate
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Biological characterization

Example 14

M3 Receptor radioligand binding assay

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 μ M) 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 unifilter 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 50 μ l 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. Ki values were calculated from IC50 values by the Cheng and Prusoff equation.

The Ki values of the most of the compounds of the examples are less than

10 nM.

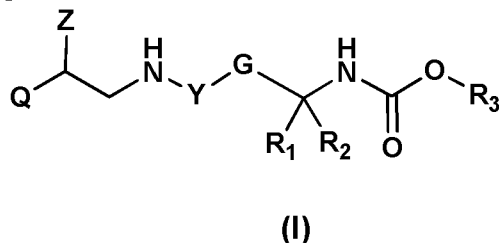
Example 15

β_2 adrenoceptor radioligand binding assay

Human β_2 adrenoceptor membranes (7.5 ug/well) from Perkin Elmer were
5 incubated with 0.3 nM ^{125} -I 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
10 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,
15 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 IC₅₀ 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.

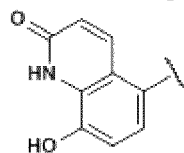
CLAIMS

1. A compound of general formula I

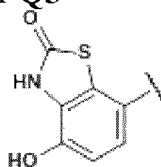


- 5 wherein

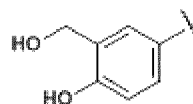
Q is a group of formula **Q1**, **Q2** or **Q3**



Q1



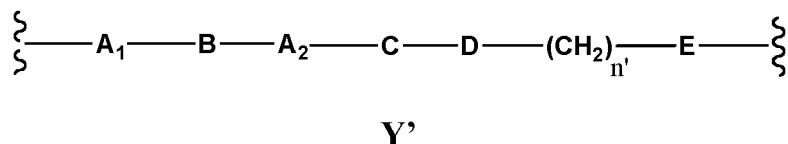
Q2



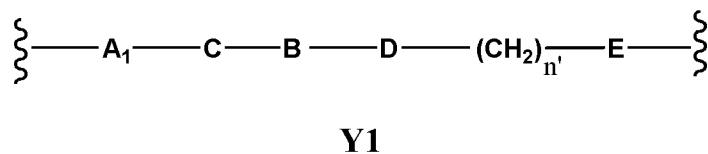
Q3

Z is H or OH;

- 10 **Y** is selected from **Y'** and **Y1** which are divalent groups of formula



or



wherein

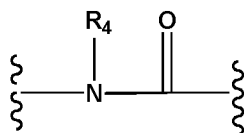
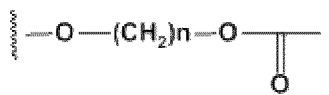
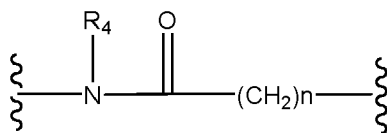
A1 and **A2** are independently absent or (C₁-C₆)alkylene;

B is absent or is selected from the group consisting of arylene and heteroarylene,

- 20 optionally substituted by one or more groups selected from halogens, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl and (C₁-C₆)alkoxy;

C is absent or is -OC(O)- or is one of the following groups **C1-C3**

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**C1****C2****C3**

5

wherein **R₄** is H or linear or branched (C₁-C₄)alkyl;

D is absent or is selected from the group consisting of arylene and heteroarylene, optionally substituted by one or more (C₁-C₆)alkyl groups;

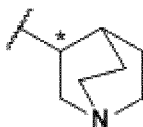
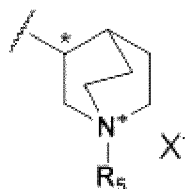
n and **n'** are independently 0 or an integer from 1 to 3;

10 **E** is absent or is selected from -O- and -OC(O)-;

G is arylene;

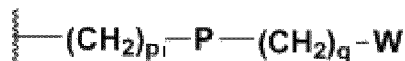
R₁ and **R₂** are independently H or aryl;

R₃ is a group of formula **J1** or **J2**

**J1****J2**

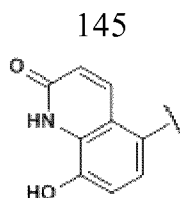
15

wherein **R₅** is a group of formula **K**

**K**

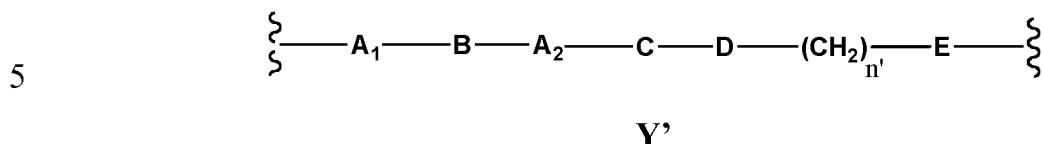
wherein **p'** is 0 or 1, **P** is absent or is CO, **q** is absent or is 1 and **W** is heteroaryl, and pharmaceutically acceptable salts or solvates thereof.

20 2. A compound according to claim 1, wherein **Q** is **Q1**



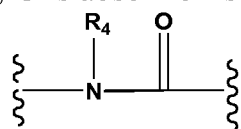
Q1

Z is -OH, **Y** is **Y'** which is a divalent group of formula

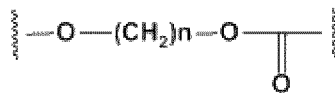


A1 and **A2** are independently absent or (C₁-C₆)alkylene, **B** is absent or is selected from the group consisting of arylene and heteroarylene, optionally substituted by one or more groups selected from halogens, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl and (C₁-C₆)alkoxy; **C** is absent or is -OC(O)- or is one of the following groups **C1-C3**

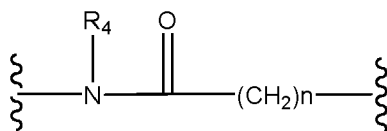
10



C1



C2

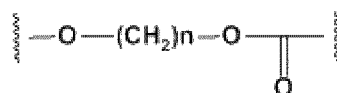


C3

wherein **R₄** is H or linear or branched (C₁-C₄)alkyl; **D** is absent or is selected from the group consisting of arylene and heteroarylene, optionally substituted by one or more (C₁-C₆)alkyl groups; **n** and **n'** are independently 0 or an integer from 1 to 3, **E** is absent or is -O- and **G** is arylene.

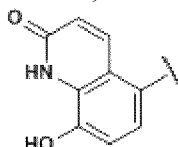
20 3. A compound according to claims 1 to 2, wherein **A1** is selected from the group consisting of methylene, ethylene and propylene, **A2** is absent or is selected from the group consisting of methylene, ethylene and propylene, **B** is absent or is selected from the group consisting of phenylene, naphthalene, pyridinediyl, furanediyl, thiophenediyl and pyrazolediyl, **C** is absent or is -OC(O)- or is a group

of formula **C2**



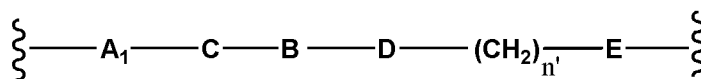
wherein **n** is 2, **n'** is 1, **D** is absent or is phenylene, **E** is absent or is—O- and **G** is phenylene.

- 5 4. A compound according to claim 1, wherein **Q** is **Q1**



Q1

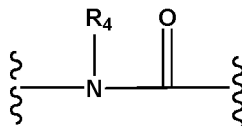
Z is -OH, **Y** is **Y1** which is a divalent group of formula



10

Y1

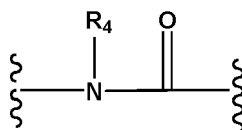
A1 is absent or (C₁-C₆)alkylene, **C** is absent or is -OC(O)- or is **C1**



C1

- 15 wherein **R₄** is H, **B** is absent or is selected from the group consisting of arylene and heteroarylene, optionally substituted by one or more groups selected from halogens, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl and (C₁-C₆)alkoxy, **D** is absent or is arylene, **n'** is 0 or an integer from 1 to 3, **E** is absent or is—O- and **G** is arylene.

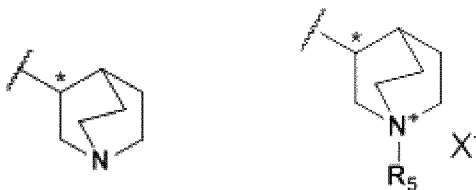
5. A compound according to claims 1 or 4, wherein **A1** is butylene, **C** is
20 absent or is -OC(O)- or is **C1**



C1

wherein **R₄** is H, **B** is absent or is selected from the group consisting of

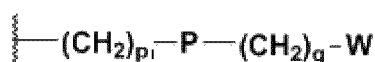
pyrazolediyl, thiophenediyl, pyridinediyl, furanediyl and oxazolendiyl, optionally substituted by one or more groups selected from methyl; **D** is absent, **n'** is 1, **E** is – O–, **G** is phenylene and **R₃** is a group of formula **J1** or **J2**



5

J1**J2**

wherein **R₅** is a group of formula **K**

**K**

wherein **p'** is 0 or 1, **P** is absent or is CO, **q** is absent or is 1 and **W** is heteroaryl, and pharmaceutically acceptable salts or solvates thereof.

10 6. A pharmaceutical composition comprising a compound of formula **I** as defined in any one of the claims 1 to 5, with one or more pharmaceutically acceptable carriers and/or excipients.

7. Use of a compound of formula **I** according to any one of claims 1 to 5 for the manufacture of a medicament for the prevention and/or treatment of broncho-
15 obstructive or inflammatory diseases, preferably asthma or chronic bronchitis or chronic obstructive pulmonary disease (COPD).

8. A combination of a compound of formula **I** as defined in any one of the claims 1 to 5 with one or more active ingredients selected from the classes consisting of beta2-agonists, antimuscarinic agents, mitogen-activated protein
20 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).

9. A pharmaceutical composition according to claim 6 to be administered by inhalation, such as inhalable powders, propellant-containing metering aerosols or
5 propellant-free inhalable formulations.
10. A device comprising the pharmaceutical composition according to claim 9, which may be a single- or multi-dose dry powder inhaler, a metered dose inhaler and a soft mist nebulizer.