

**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 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 well known class of bronchodilators consists of beta-2 adrenergic receptor agonists, such as salbutamol, fenoterol, formoterol and salmeterol. These compounds are generally administered by inhalation.

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

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

1994).

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
5 medicament compositions containing a muscarinic receptor antagonist, such as tiotropium bromide, and beta-2 adrenergic receptor agonists, such as formoterol fumarate or salmeterol, and WO 2005/115467 discloses a combination which comprises a beta-2 agonist and an antagonist of M3 muscarinic receptors which is a salt of 3(R)-(2-hydroxy-2,2-dithien-2-
10 ylacetoxy)-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 antagonism and beta-2 agonism. In fact compounds possessing both beta-2 adrenergic receptor agonist and muscarinic receptor antagonist activity are
15 highly desirable since such bifunctional compounds would provide bronchodilation through two independent mechanisms of action while having a single molecule pharmacokinetics.

Such kind of compounds was described in some patent applications, such as WO 2004/074246, WO 2004/074812, WO 2005/051946, WO
20 2006/023457, WO 2006/023460, WO 2010/123766 and WO 2011/048409.

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

25 SUMMARY 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,

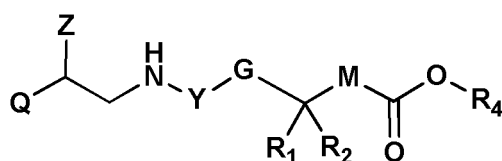
to therapeutic uses and combinations with other pharmaceutical active ingredients among which are, for instance, those currently used in the treatment of respiratory disorders, e.g. corticosteroids, P38 MAP kinase inhibitors, IKK2, HNE inhibitors, PDE4 inhibitors, leukotriene modulators,

5 NSAIDs and mucus regulators.

DETAILED DESCRIPTION OF THE INVENTION

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

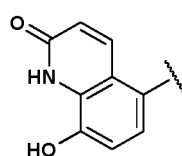
I



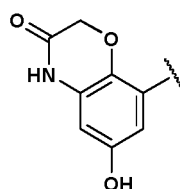
(I)

10 wherein

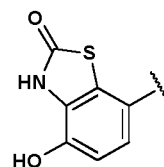
Q is a group of formula **Q1**, **Q2**, **Q3**, **Q4**, **Q5** or **Q6**



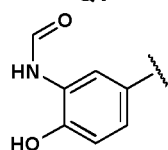
Q1



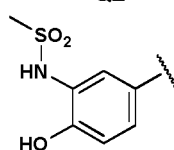
Q2



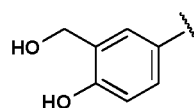
Q3



Q4



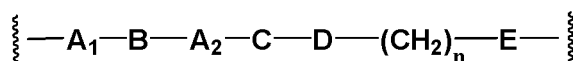
Q5



Q6

Z is H or OH;

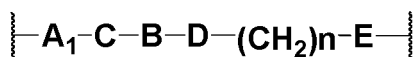
15 **Y** is selected from **Y'** and **Y1** which are divalent groups of formula



Y'

4

or

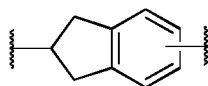


Y1

wherein

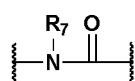
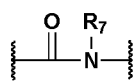
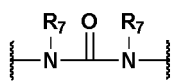
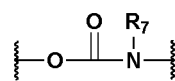
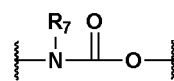
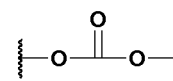
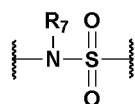
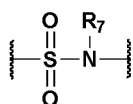
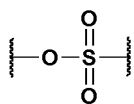
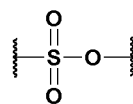
A1 and **A2** are independently absent or are selected from the group consisting of (C₁-C₁₂)alkylene, (C₃-C₈)cycloalkylene and (C₃-C₈)heterocycloalkylene optionally substituted by one or more substituents selected from the group consisting of (C₁-C₆)alkyl, aryl(C₁-C₆)alkyl and heteroaryl(C₁-C₆)alkyl;

B is absent or is selected from the group consisting of (C₃-C₈)cycloalkylene, (C₃-C₈)heterocycloalkylene, arylene, heteroarylene or is a group of formula

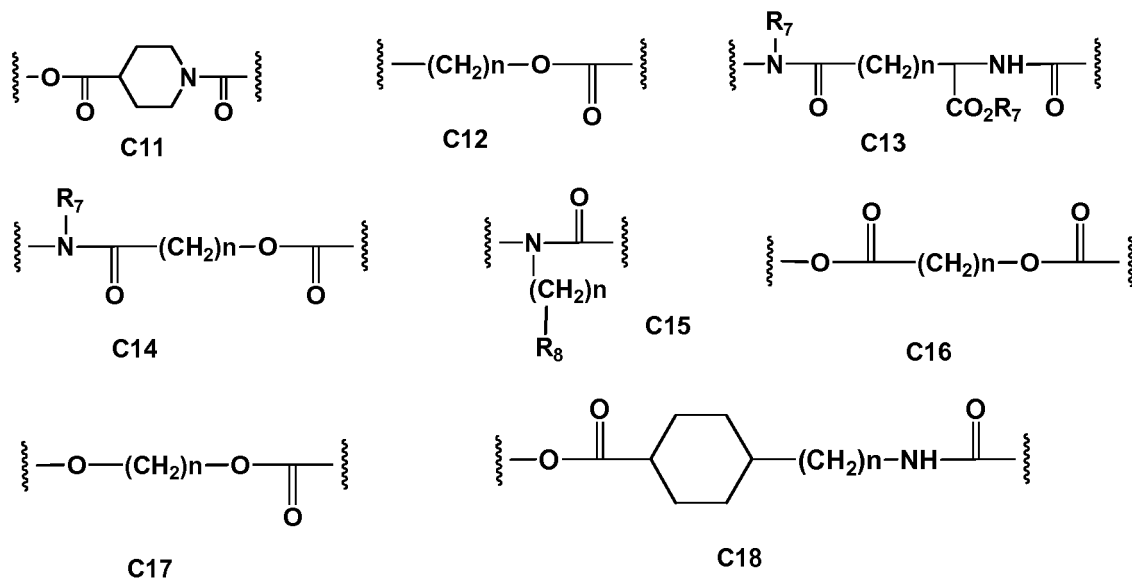
10 **B1****B1**

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

C is absent or is selected from the group consisting of -O-, -CO-, -OC(O)-, -C(OO)-, -S-, -S(O)-, -S(O)₂- and -N(R₇)-, or is one of the following groups

C1-C18**C1****C2****C3****C4****C5****C6****C7****C8****C9****C10**

5



wherein **R₇** is H or is selected from the group consisting of linear or branched (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)heterocycloalkyl, aryl, aryl(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl and heteroaryl and **R₈** is (C₁-C₈)alkoxycarbonyl;

D is absent or is selected from the group consisting of (C₁-C₁₂)alkylene, -C(CH₃)₂-, arylene, (C₂-C₁₂)alkenylene, heteroarylene, (C₃-C₈)heterocycloalkylene and (C₂-C₆)alkynylene;

n is 0 or an integer from 1 to 3;

E is absent or is selected from -O-, -NR₇-, -OC(O)- and -S-;

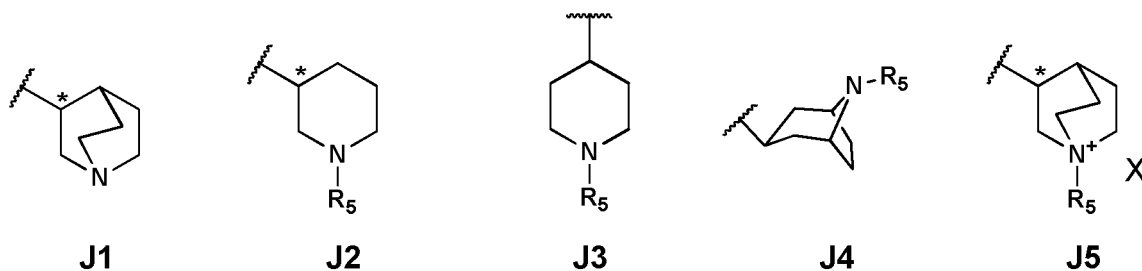
G is arylene or heteroarylene, optionally substituted by one or more substituents selected from the group consisting of halogen atoms, -OH, oxo (=O), -SH, -NO₂, -CN, -CON(R₆)₂, -NH₂, -NHCOR₆, -CO₂R₆, (C₁-C₁₀)alkylsulfanyl, (C₁-C₁₀)alkylsulfinyl, (C₁-C₁₀)alkylsulfonyl, (C₁-C₁₀)alkyl, aryl, haloaryl, heteroaryl and (C₁-C₁₀)alkoxy;

R₁ and **R₂** are independently H or selected from the group consisting of (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)heterocycloalkyl, aryl, heteroaryl, aryl(C₁-C₆)alkyl, heteroaryl(C₁-C₆)alkyl and (C₃-C₈)cycloalkyl(C₁-C₆)alkyl, optionally substituted by one or more halogen atoms or (C₁-C₈)alkyl groups or, taken together with the carbon atom to which they are bounded, **R₁** and **R₂**

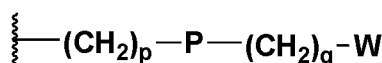
may form a (C₃-C₈)cycloalkyl, wherein **R**₁ and **R**₂ are not simultaneously H;
M is -O- or -N(R₃)-;

R₃ is H or is selected from the group consisting of (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, aryl and heteroaryl;

5 **R**₄ is a group of formula **J1**, **J2**, **J3**, **J4** or **J5**



R₅ is a group of formula **K**



10

K

wherein **p** is 0 or an integer from 1 to 4; **q** is 0 or an integer from 1 to 4;

P is absent or is selected from the divalent group consisting of O, S, SO, SO₂, CO, NR₆, CH=CH, N(R₆)SO₂, N(R₆)COO, N(R₆)C(O), SO₂N(R₆), CO(O)N(R₆) and C(O)N(R₆);

15 **W** is selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₈)cycloalkyl, aryl and heteroaryl, optionally substituted by one or more substituents selected from the group consisting of halogen atoms, -OH, oxo (=O), -SH, -NO₂, -CN, -CON(R₆)₂, -NH₂, -NHCOR₆, -CO₂R₆, (C₁-C₁₀)alkylsulfanyl, (C₁-C₁₀)alkylsulfinyl, (C₁-C₁₀)alkylsulfonyl, (C₁-C₁₀)alkyl and (C₁-C₁₀)alkoxy;

20 **X**⁻ is a physiological acceptable anion;

R₆ is H or is selected from the group consisting of (C₁-C₁₀)alkyl, (C₁-C₆)haloalkyl, (C₂-C₆)alkynyl, (C₂-C₆)alkenyl, (C₃-C₈)cycloalkyl, (C₃-C₈)cycloalkyl(C₁-C₆)alkyl, heteroaryl and aryl optionally substituted by

one or more substituents selected from the group consisting of halogen atoms, -OH, oxo (=O), -SH, -NO₂, -CN, -CONH₂, -COOH, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylsulfanyl, (C₁-C₁₀)alkylsulfinyl, (C₁-C₁₀)alkylsulfonyl, (C₁-C₁₀)alkyl and (C₁-C₁₀)alkoxy;

5 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, octyl, nonyl, decyl, undecyl, dodecyl and the like.

10 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-C₆)haloalkyl” refers to the above “(C₁-C₆)alkyl”
15 group wherein one or more hydrogen atoms are replaced by one or more halogen atoms, which can be the same or different from each other.

Examples of said (C₁-C₆)haloalkyl groups include halogenated, poly-halogenated and fully halogenated alkyl groups wherein one or more of the hydrogen atoms are replaced by halogen atoms, e.g. trifluoromethyl group.

20 The expressions “(C₁-C₁₀)alkylsulfanyl”, “(C₁-C₁₀)alkylsulfinyl” or “(C₁-C₁₀)alkylsulfonyl” refer, respectively, to alkyl-S-, alkyl-SO- or alkyl-SO₂- groups.

The expression “hydroxy(C₁-C₆)alkyl” refers to -alkyl-OH groups.

The expression “(C₂-C_x)alkenyl” refers to straight or branched carbon
25 chains with one or more double bonds, wherein the number of carbon atoms is from 1 to x. Examples of said groups comprise ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, dodecenyl and the like.

In an analogous manner, the expression “(C₂-C_x)alkenylene” refers to divalent groups, such as ethenylene, propenylene, butenylene, pentenylene, hexenylene, heptenylene, octenylene, nonenylene, decenylene, undecenylene, dodecenylene and the like.

5 The expression “(C₂-C_x)alkynyl” refers to straight or branched carbon chains with one or more triple bonds, wherein the number of carbon atoms is from 1 to x. Examples of said groups comprise ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like.

10 In an analogous manner, the expression “(C₂-C_x)alkynylene” refers to divalent groups, such as ethynylene, propynylene, butynylene, pentynylene, hexynylene and the like.

15 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 “(C₃-C₈)cycloalkyl” refers to mono or bi-cycloaliphatic hydrocarbon groups with 3 to 8 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]hept-2-yl and the like.

20 The expression “(C₃-C₈)heterocycloalkyl” refers to (C₃-C₈)cycloalkyl groups, in which at least one ring carbon atom is replaced by a heteroatom or heteroaromatic group (e.g. N, NH, S or O). Examples include quinuclidinyl, pyrrolidinyl, piperidinyl, azabicyclo[3.2.1]octan-3-yl and azoniabicyclo[2.2.2]octanyl and the like.

25 In an analogous manner, the expressions “(C₃-C₈)cycloalkylene” and “(C₃-C₈)heterocycloalkylene” refer to divalent groups, such as, respectively, cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, cycloheptylene, bicyclo[2.2.1]hept-2-ylene and quinuclidinylene,

pyrrolidinylene, piperidinylene, azabicyclo[3.2.1]octan-3-ylene, azoniabicyclo[2.2.2]octanylene 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
5 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).

10 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,
15 isoquinoline, indole, isoindole, benzothiophene, dihydrobenzo dioxin, dihydro-indene, 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.

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

The expressions “aryl(C₁-C₆)alkyl”, “heteroaryl(C₁-C₆)alkyl” and “(C₃-C₈)cycloalkyl(C₁-C₆)alkyl” refer to a “(C₁-C₆)alkyl” respectively substituted by one or more aryl, heteroaryl or (C₃-C₈)cycloalkyl groups, as
25 defined above.

Examples of aryl(C₁-C₆)alkyl include triphenylmethyl.

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, 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 asymmetric centers. Therefore, the invention also includes any of the optical stereoisomers, diastereoisomers and mixtures thereof, in any proportion.

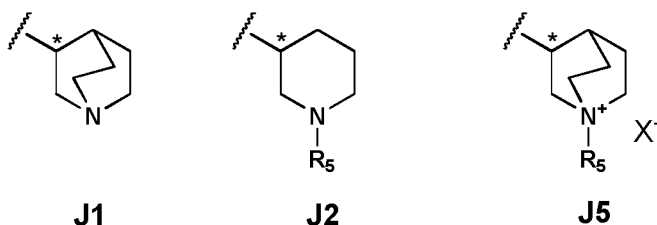
In particular, the carbon atom linked to **R**₁, **R**₂, **G** and **M** groups, depending on the meanings provided to **R**₁ and **R**₂ among those formerly reported, may represent a chiral center.

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.

In another embodiment, when in the compounds of general formula **I**, **R**₄ is a group of formula **J1**, **J2** or **J5**

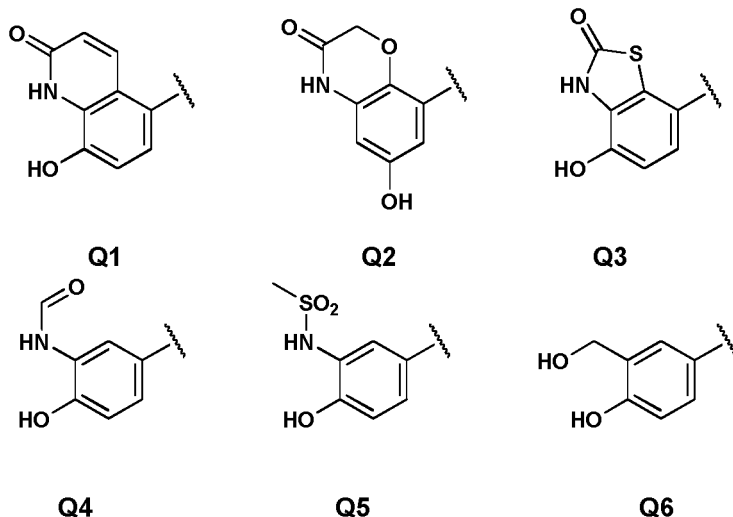


the carbon atom marked with an asterisk represents a chiral center.

In a preferred embodiment, this chiral center has (R) configuration.

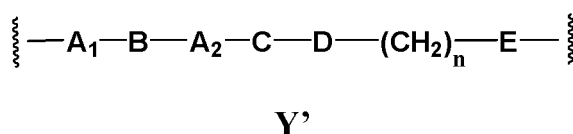
It is to be understood that all preferred groups or embodiments described herebelow for compounds of formula **I** may be combined among each other and apply as well *mutatis mutandis*.

A first preferred group of compounds is that of general formula **I** wherein **Q** is a group of formula **Q1**, **Q2**, **Q3**, **Q4**, **Q5** or **Q6**.



5 **Z** is H or OH;

Y is a group of formula



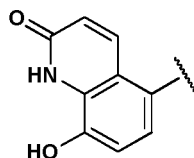
10 wherein

A1 and **A2** are, each independently, absent or are selected from the group consisting of (C₁-C₁₂)alkylene, (C₃-C₈)cycloalkylene and (C₃-C₈)heterocycloalkylene; **B** is absent or is selected from the group consisting of (C₃-C₈)cycloalkylene, (C₃-C₈)heterocycloalkylene, arylene and heteroarylene; **C** is absent or is selected from the group consisting of -O-, -CO-, -OC(O)-, -C(OO)-, -S-, -S(O)-, -S(O)₂- and -N(R₇)- wherein **R₇** is H or is selected from the group consisting of (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)heterocycloalkyl, aryl, aryl(C₁-C₈)alkyl, (C₁-C₈)alkoxy(C₁-C₈)alkyl and heteroaryl; **D** is absent or is selected from the group consisting of

20 (C₁-C₁₂)alkylene, arylene, (C₂-C₁₂)alkenylene, heteroarylene, (C₃-C₈)heterocycloalkylene and (C₂-C₆)alkynylene; **n** is 0; **E** is absent or is

selected from -O-, -NR₇- and -S-; **G** is arylene or heteroarylene, optionally substituted by one or more substituents selected from the group consisting of halogen atoms, -OH, oxo (=O), -SH, -NO₂, -CN, -CON(R₆)₂, -NH₂, -NHCOR₆, -CO₂R₆, (C₁-C₁₀)alkylsulfanyl, (C₁-C₁₀)alkylsulfinyl, (C₁-C₁₀)alkylsulfonyl, (C₁-C₁₀)alkyl, aryl, haloaryl, heteroaryl and (C₁-C₁₀)alkoxy; **R**₁, **R**₂, **M**, **R**₄ and **R**₆ are as defined above.

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

**Q1**

10

Z is -OH, **A1** is absent or is selected from the group consisting of (C₃-C₈)heterocycloalkylene and (C₁-C₁₂)alkylene, **A2** is absent or is selected from the group consisting of (C₁-C₆)alkylene, **B** is absent or arylene, **C** is absent, **D** is absent or is selected from the group consisting of (C₁-C₁₂)alkylene, heteroarylene and arylene, **n** is 0, **E** is absent or is -O-, **G** is arylene optionally substituted by one or more halogen atoms.

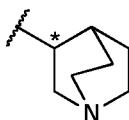
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Still more preferred within this class, are the compounds of general formula **I**, wherein **A1** is absent or is selected from the group consisting of methylene, ethylene, propylene, butylene, pentylene, hexylene, heptylene, octylene and nonylene, **A2** is absent or is selected from the group consisting of methylene and oxadiazolene, **B** is selected from the group consisting of phenylene and cyclohexylene or is absent, **C** is absent, **D** is absent or is selected from methylene, ethylene, propylene, butylene, pentylene, hexylene, heptylene, octylene, nonylene, phenylene and oxadiazolene; **n** is 0, **G** is selected from the group consisting of fluoro-biphenylene and phenylene.

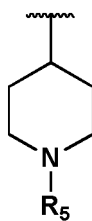
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Even still more preferred within this class are the compounds of general formula **I**, wherein **A1** is selected from the group consisting of ethylene, pentylene, hexylene, heptylene, octylene and nonylene, **D** is absent, **n** is 0, **R₁** is H, **R₂** is selected from the group consisting of phenyl, biphenyl, naphthyl, pyridinyl, difluorophenyl, methylphenyl, fluorophenyl and thiophenyl, **M** is -N(H)-, **R₄** is a group of formula **J1**

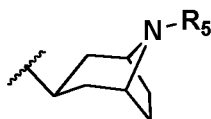
**J1**

or **J3**

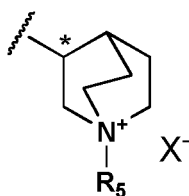
**J3**

10

or **J4**

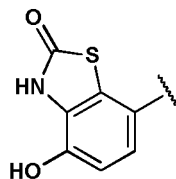
**J4**

or **J5**

**J5**

15 wherein **R₅** is a group of formula **K**, wherein **p** is 0 or 1, **P** is absent or is CO, **q** is absent or is 1 and **W** is H or is selected from the group consisting of (C₁-C₆)alkyl and aryl.

Another class of preferred compounds of general formula **I** is that wherein **Q** is **Q3**

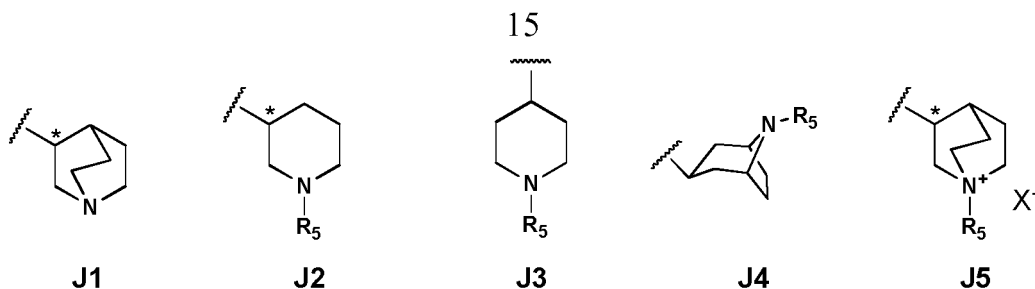
**Q3**

Z is H, **A1** is absent or is (C₁-C₁₂)alkylene, **A2** is absent, **B** is absent, **C** is absent, **D** is absent or (C₁-C₁₂)alkylene, **E** is -O-, **G** is arylene.

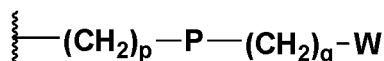
Still more preferred within this class, are the compounds of general formula **I**, wherein **A1** is absent or is selected from the group consisting of methylene, ethylene, propylene, butylene, pentylene, hexylene, heptylene, octylene and nonylene, **A2** is absent, **B** is absent, **C** is absent, **D** is absent or is selected from methylene, ethylene, propylene, butylene, pentylene, hexylene, heptylene, octylene and nonylene; **n** is 0, **G** is phenylene.

Even still more preferred within this class, are the compounds of general formula **I**, wherein **A1** is nonylene, **A2**, **B** and **C** are absent, **D** is absent, **n** is 0, **R₁** is H, **R₂** is phenyl, **M** is -N(H)- and **R₄** is **J1**.

Another preferred group of compounds is that of general formula **I** wherein **R₁** and **R₂** are independently H or selected from the group consisting of (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)heterocycloalkyl, aryl, heteroaryl, aryl(C₁-C₆)alkyl, heteroaryl(C₁-C₆)alkyl and (C₃-C₈)cycloalkyl(C₁-C₆)alkyl, optionally substituted by one or more halogen atoms or (C₁-C₈)alkyl groups or, taken together with the carbon atom they are linked to, **R₁** and **R₂** may form a (C₃-C₈)cycloalkyl group, wherein **R₁** and **R₂** are not simultaneously H; **M** is -O- or -N(R₃)-; **R₃** is H or is selected from the group consisting of (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, aryl and heteroaryl; **R₄** is a group of formula **J1**, **J2**, **J3**, **J4** or **J5**



R₅ is a group of formula **K**



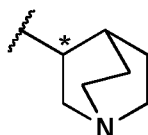
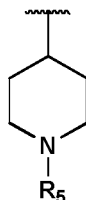
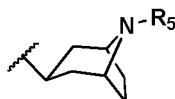
K

- 5 wherein **p** is 0 or an integer from 1 to 4; **q** is 0 or an integer from 1 to 4; **P** is absent or is selected from the group consisting of -O-, -S-, -S(O)-, -S(O₂)-, -C(O)-, -N(R₆)-, -CH=CH-, -N(R₆)S(O₂)-, -N(R₆)CO(O)-, -N(R₆)C(O)-, -SO₂N(R₆)-, -CO(O)N(R₆)- and -C(O)N(R₆)-; **W** is selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₈)cycloalkyl, aryl and heteroaryl, optionally
- 10 substituted by one or more substituents selected from the group consisting of halogen atoms, -OH, oxo (=O), -SH, -NO₂, -CN, -CON(R₆)₂, -NH₂, -NHCOR₆, -CO₂R₆, (C₁-C₁₀)alkylsulfanyl, (C₁-C₁₀)alkylsulfinyl, (C₁-C₁₀)alkylsulfonyl, (C₁-C₁₀)alkyl and (C₁-C₁₀)alkoxy; **R₆** is selected from the group consisting of H, (C₁-C₁₀)alkyl, (C₁-C₆)haloalkyl, (C₃-C₈)cycloalkyl, heteroaryl and aryl; **G**,
- 15 **Y**, **Z** and **Q** are as defined above.

Still more preferred within this class, are the compounds of general formula **I** wherein **R₁** and **R₂** are independently H or selected from the group consisting of (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, aryl and heteroaryl, optionally substituted by one or more halogen atoms or (C₁-C₈)alkyl groups or, taken

20 together with the carbon atom to which they are bounded, **R₁** and **R₂** may form a (C₃-C₈)cycloalkyl group, wherein **R₁** and **R₂** are not simultaneously H; **M** is -N(R₃)-; **R₃** is H; **R₄** is a group of formula **J1**

16

**J1**or **J3****J3**or **J4****J4**

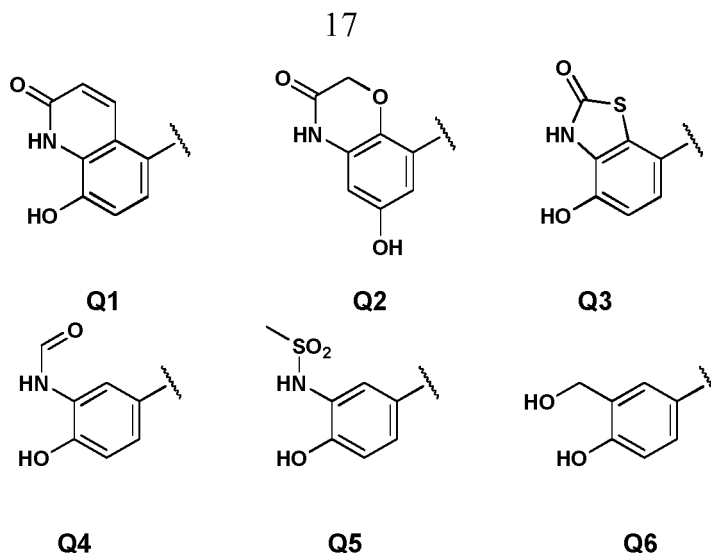
5

wherein **R**₅ is a group of formula **K**, wherein **p** is 0, **P** is absent, **q** is 1 and **W** is H or is selected from the group consisting of (C₁-C₆)alkyl and aryl.

Still more preferred within this class are the compounds of general formula **I** wherein **W** is H or phenyl; **R**₁ is H, **R**₂ is selected from the group consisting of phenyl, biphenyl, naphthyl, thiophenyl, pyridinyl, difluorophenyl, methylphenyl and fluorophenyl; **M** is -N(H)-; **R**₄ is selected from the group consisting of quinuclidinyl, benzylpiperidinyl, methylpiperidinyl, benzyl-8-azabicyclo[3.2.1]octan-3-yl and azoniabicyclo[2.2.2]octanyl.

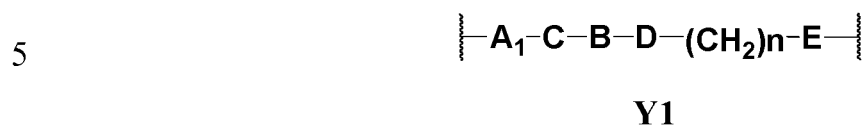
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A second group of preferred compounds is that of general formula **I** wherein **Q** is a group of formula **Q1**, **Q2**, **Q3**, **Q4**, **Q5** or **Q6**.



Z is H or OH;

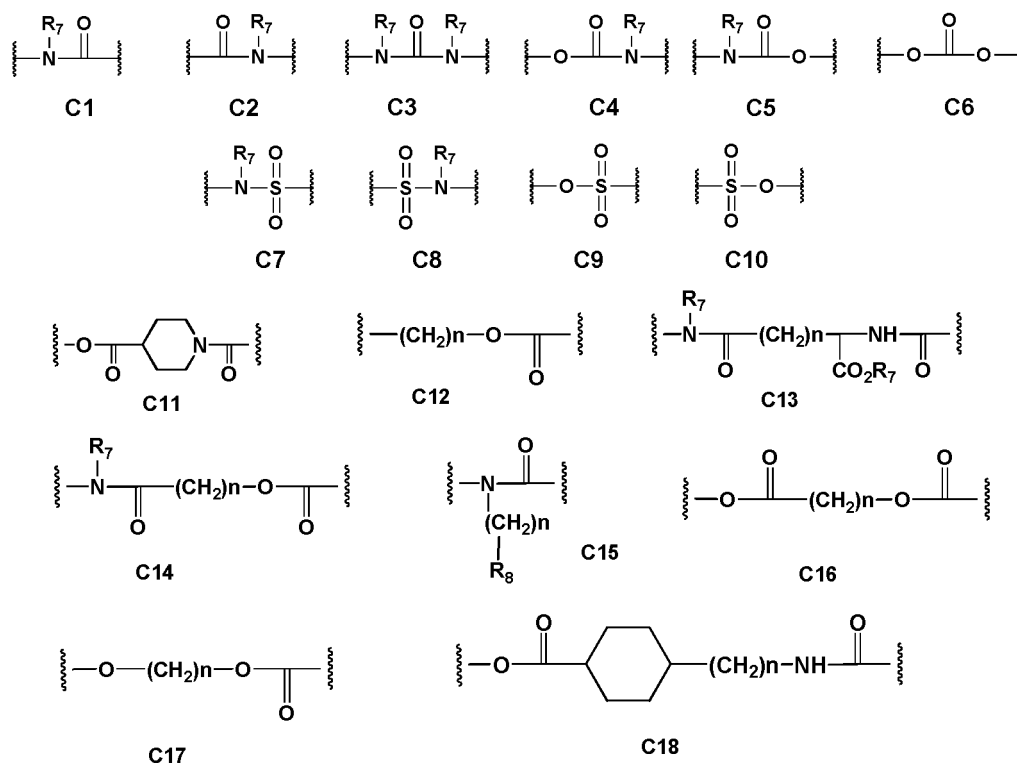
Y1 is a group of formula



wherein

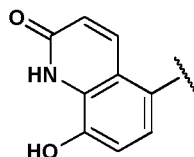
A1 is (C₁-C₁₂)alkylene; **C** is absent or is selected from the group consisting of -O-, -CO-, -OC(O)- or is a group of formula C1-C18

10



wherein **R**₇ is H or is selected from the group consisting of linear or branched (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)heterocycloalkyl, aryl, (C₁-C₆)arylalkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl and heteroaryl and **R**₈ is (C₁-C₈)alkoxycarbonyl; **B** is absent or is selected from the group consisting of (C₃-C₈)cycloalkylene, arylene and heteroarylene, optionally substituted by one or more groups selected from halogens, nitrile, (C₁-C₆)alkyl, (C₁-C₆)alkoxy and aryl(C₁-C₆)alkyl; **D** is absent or is selected from the group consisting of (C₁-C₁₂)alkylene, -C(CH₃)₂-, heteroarylene and arylene; **n** is 0 or an integer from 1 to 2; **E** is -O-; **G** is arylene or heteroarylene, optionally substituted by one or more substituents selected from the group consisting of halogen atoms, -OH, oxo (=O), -SH, -NO₂, -CN, -CON(R₆)₂, -NH₂, -NHCOR₆, -CO₂R₆, (C₁-C₁₀)alkylsulfanyl, (C₁-C₁₀)alkylsulfinyl, (C₁-C₁₀)alkylsulfonyl, (C₁-C₁₀)alkyl, aryl, haloaryl, heteroaryl and (C₁-C₁₀)alkoxy; **R**₁, **R**₂, **M** and **R**₄ are as defined above.

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

**Q1**

Z is -OH, **A1** is selected from (C₁-C₁₂)alkylene and (C₃-C₈)heterocycloalkylene; **C** is absent or is selected from the group consisting of -O-, -CO-, -OC(O)-, C11, C13, C14, C16, C17, C18 wherein **R**₇ is H or linear or branched (C₁-C₈)alkyl, C7 wherein **R**₇ is H and C15 wherein **R**₈ is (C₁-C₈)alkoxycarbonyl; **B** is absent or is selected from the group consisting of (C₃-C₈)cycloalkylene, (C₃-C₈)heterocycloalkylene, arylene and heteroarylene, optionally substituted by one or more halogens; **D** is absent or

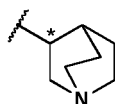
is selected from the group consisting of (C₁-C₁₂)alkylene, -C(CH₃)₂-, arylene and heteroarylene; **n** is 0 or an integer from 1 to 2; **E** is -O-; **G** is arylene, optionally substituted by one or more substituents selected from the group consisting of halogen atoms, aryl and heteroaryl.

5 Still more preferred within this class, are the compounds of general formula **I**, wherein **A1** is selected from the group consisting of methylene, ethylene, propylene, butylene, pentylene and hexylene; **C** is absent or is selected from the group consisting of -O-, -CO-, -OC(O)-, C11, C13, C14, C16, C17, C18 wherein **R₇** is H or is selected from the group consisting of
10 methyl, ethyl, isopropyl and C15 wherein **n** is 0 or 1 and **R₈** is ethoxycarbonyl; **B** is absent or is selected from phenylene, piperidinylene, cyclopropylene, cyclohexylene, piridinediyl, furanediyl and oxazolediyl, optionally substituted by one or more halogens; **D** is absent or is selected from methylene, -C(CH₃)₂-, phenylene and oxadiazolylene; **n** is 0 or an integer from 1 to 2; **E** is -O-; **G** is
15 selected from phenylene and biphenylene, optionally substituted by one or more substituents selected from the group consisting of fluorine, phenyl and 2-thiophenyl.

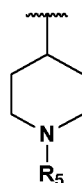
Even still more preferred within this class are the compounds of general formula **I**, wherein **A1** is selected from the group consisting of methylene,
20 ethylene, propylene, butylene, pentylene and hexylene; **C** is absent or is selected from the group consisting of -O-, -CO-, -OC(O)-, C11, C13, C14, C16, C17, C18 wherein **R₇** is H or is selected from the group consisting of methyl, ethyl and isopropyl and C15 wherein **n** is 0 or 1 and **R₈** is ethoxycarbonyl; **B** is absent or is selected from phenylene, piperidinylene,
25 cyclopropylene, cyclohexylene, piridinediyl, furanediyl and oxazolediyl, optionally substituted by one or more halogens; **D** is absent or is selected from methylene, -C(CH₃)₂-, phenylene and oxadiazolylene; **n** is 0 or an integer from 1 to 2; **E** is -O-; **G** is selected from phenylene and biphenylene, optionally

substituted by one or more substituents selected from the group consisting of fluorine, phenyl and 2-thiophenyl; R_1 is H, R_2 is selected from the group consisting of phenyl, cyclohexyl, fluorophenyl and chlorophenyl, M is -N(H)-, R_4 is a group of formula **J1**

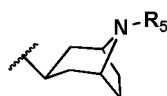
5

**J1**

or **J3**

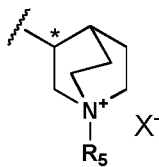
**J3**

or **J4**

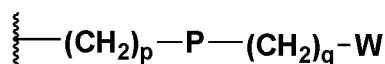
**J4**

10

or **J5**

**J5**

wherein R_5 is a group of formula **K**

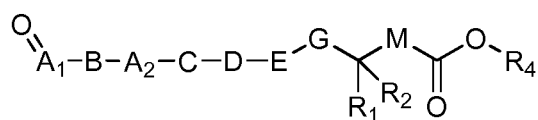
**K**

15

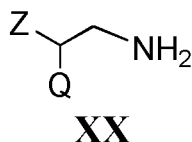
wherein p is 0 or 1, P is absent or is CO, q is absent or is 1 and W is H or is selected from the group consisting of (C₁-C₆)alkyl and aryl.

Even still more preferred within this class, are the compounds of general formula **I**, wherein **A1** is selected from the group consisting of methylene, ethylene, propylene, butylene, pentylene and hexylene; **C** is absent or is selected from the group consisting of -O-, -CO-, -OC(O)-, C11, C13, C14, C16, C17 and C18 wherein **R₇** is H or is selected from the group consisting of methyl, ethyl and isopropyl and C15 wherein **n** is 0 or 1 and **R₈** is ethoxycarbonyl; **B** is absent or is selected from phenylene, piperidinylene, cyclopropylene, cyclohexylene, piridinediyl, furanediyl and oxazolediyl, optionally substituted by one or more halogens; **D** is absent or is selected from methylene, -C(CH₃)₂-, phenylene and oxadiazolylene; **n** is 1; **E** is -O-; **G** is phenylene optionally substituted by one or more substituents selected from the group consisting of phenyl and 2-thiophenyl; **R₁** is H, **R₂** is selected from the group consisting of phenyl, cyclohexyl, fluorophenyl and chlorophenyl, **M** is -N(H)-, **R₄** is a group of formula **J1** or **J5**, wherein **R₅** is a group of formula **K**, wherein **p** is 0 or an integer from 1 to 4; **q** is 0 or an integer from 1 to 4; **P** is absent or is selected from the group consisting of -O- and -C(O)-; **W** is aryl; **G**, **Y**, **Z** and **Q** are as defined above.

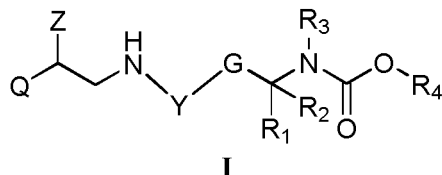
The present invention is also directed to a process for the preparation of the compounds of general formula **I**, which process comprises the reaction of a compound of general formula **XIX**

**XIX**

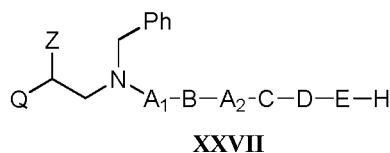
with a compound of general formula **XX**



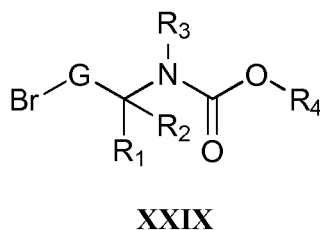
The present invention is also directed to a process for the preparation of the compounds of general formula **I**



5 which process comprises the reaction of a compound of general formula **XXVII**



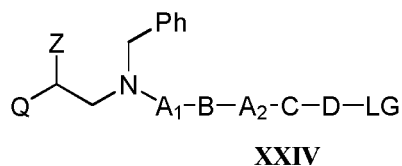
with a compound of formula **XXIX**



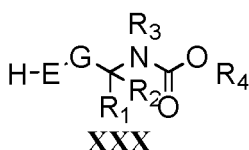
under the transition metal catalyzed cross-coupling reaction condition.

The present invention is also directed to a process for the preparation of the compounds of general formula **I**, which process comprises the reaction of

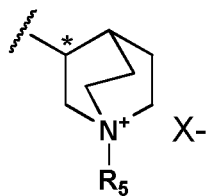
15 a compound of general formula **XXIV**



with a compound of formula **XXX**



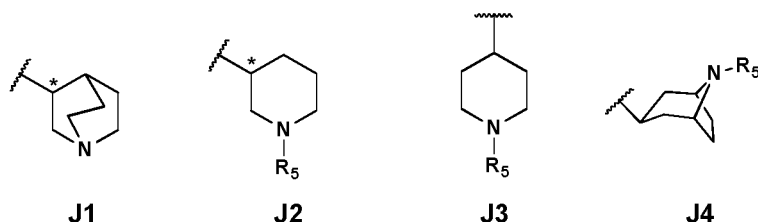
The present invention is also directed to a process for the preparation of the compounds of general formula **I** wherein **R₄** is **J5**



5

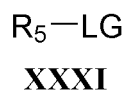
J5

this process comprising the reaction of the corresponding tertiary amine precursor of formula **I** wherein **R₅** is a **J1-J4** group



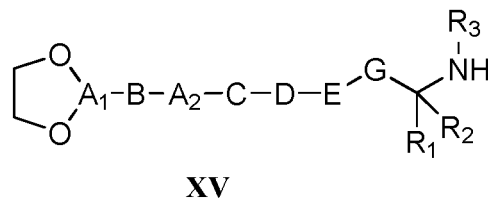
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with a compound of formula **XXXI**

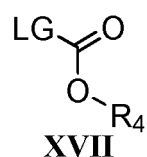


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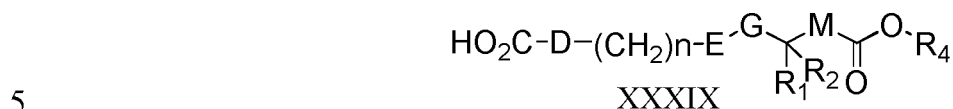
The present invention is also directed to a process for the preparation of the compounds of general formula **I** wherein **M** is $\text{—NR}_3\text{—}$, this process comprising the treatment of a compound of general formula **XV**



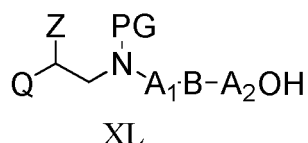
with a compound of general formula **XVII**



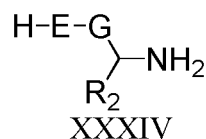
The present invention is also directed to a process for the preparation of the compounds of general formula **I** wherein **M** is $-\text{NR}_3-$, this process comprising the treatment of a compound of general formula **XXXIX**



with a compound of general formula **XL** followed by removal of the protecting group (PG)



10 The present invention is also directed to a process for the preparation of a compound of general formula **XXXIV**



15 in its two enantiomeric forms, by mean of crystallization of the corresponding diastereomeric salt, obtained by salification of the racemic mixture with an enantiomerically pure carboxylic acid.

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.

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

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).

25 In a further aspect, the invention provides the use of compounds of

formula **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).

5 The present invention further provides a method for prevention and/or treatment of any broncho-obstructive or inflammatory disease, preferably asthma 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**.

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

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

15 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**.

20 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	(R)-quinuclidin-3-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)-(phenyl)methylcarbamate
2	(R)-quinuclidin-3-yl (3-(8-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)octyloxy)phenyl)-(phenyl)methylcarbamate
3	(R)-quinuclidin-3-yl(3-(7-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)heptyloxy)phenyl)-(phenyl)methylcarbamate
4	(R)-quinuclidin-3-yl (3-(6-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)-(phenyl)methylcarbamate
5	(R)-quinuclidin-3-yl (3-(5-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)pentyloxy)phenyl)-(phenyl)methylcarbamate
6	1-benzylpiperidin-4-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)-(phenyl)methylcarbamate
7	1-methylpiperidin-4-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)-(phenyl)methylcarbamate
8	8-benzyl-8-azabicyclo[3.2.1]octan-3-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)-(phenyl)methylcarbamate
9	(R)-quinuclidin-3-yl (4-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)-(phenyl)methylcarbamate
10	(R)-quinuclidin-3-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)(thiophen-2-yl)methylcarbamate
11	(R)-quinuclidin-3-yl biphenyl-4-yl(3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)-methylcarbamate
12	(R)-quinuclidin-3-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)(naphthalen-1-yl)methylcarbamate
13	(R)-quinuclidin-3-yl biphenyl-3-yl(3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)-methylcarbamate
14	(R)-quinuclidin-3-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)(pyridin-2-yl)methylcarbamate

(continued)

15	(R)-quinuclidin-3-yl (3,5-difluorophenyl)(3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)-phenyl)methylcarbamate
16	(R)-quinuclidin-3-yl (3,4,5-difluorophenyl)(3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)-phenyl)methylcarbamate
17	(R)-quinuclidin-3-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)(o-tolyl)-methylcarbamate
18	(R)-quinuclidin-3-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)(m-tolyl)-methylcarbamate
19	(R)-quinuclidin-3-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)(p-tolyl)-methylcarbamate
20	(R)-quinuclidin-3-yl (4-difluorophenyl)(3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)-nonyloxy)phenyl)methylcarbamate
1B	(R)-quinuclidin-3-yl (3-fluorophenyl)(3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)methylcarbamate
2B	(R)-quinuclidin-3-yl (3-chlorophenyl)(3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)methylcarbamate
1C	(R)-quinuclidin-3-yl (cyclohexyl(3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)methyl)carbamate
2C	(R)-quinuclidin-3-yl ((3-((6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)(thiophen-2-yl)methyl)carbamate
3C	(R)-quinuclidin-3-yl ((3-((6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)(thiophen-3-yl)methyl)carbamate
21	(R)-quinuclidin-3-yl (3-(9-(2-(4-hydroxy-2-oxo-2,3-dihydrobenzo[d]thiazol-7-yl)ethylamino)nonyloxy)-phenyl)(phenyl)methylcarbamate
22	(R)-quinuclidin-3-yl (3-(4-(2-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)ethyl)benzyloxy)-phenyl)(phenyl)methylcarbamate
23	(R)-quinuclidin-3-yl (3-(2-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)ethyl)phenyl)(phenyl)methylcarbamate

(continued)

24	(3R)-3-((3-(6-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)(phenyl)-methylcarbamoyloxy)-1-(2-oxo-2-phenylethyl)-1-azoniabicyclo[2.2.2]octane
3B	(R)-quinuclidin-3-yl (3-(3-(2-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)ethyl)benzyloxy)phenyl)-(phenyl)methylcarbamate formate
4B	(3R)-3-((((3-((4-(2-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzyl)oxy)-phenyl)-(phenyl)-methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
5B	(3R)-3-((((3-chlorophenyl)(3-((9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)-methyl)-carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
6B	(3R)-3-((((3-bromo-5-((9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)(phenyl)-methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
7B	(R)-quinuclidin-3-yl (2-chloro-3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)-(phenyl)methylcarbamate
8B	(R)-quinuclidin-3-yl ((2,6-difluoro-3-((9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)(phenyl)methyl)carbamate
9B	(R)-quinuclidin-3-yl ((2-bromo-5-((9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)-(phenyl)methyl)carbamate
10B	(3R)-3-((((2-chloro-3-((9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)(phenyl)-methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
11B	(3R)-3-((((2,6-difluoro-3-((9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)(phenyl)-methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
12B	(3R)-3-((((2-bromo-5-((9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)(phenyl)-methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
13B	(3R)-3-((((3-((9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-4-methylphenyl)(phenyl)-methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
14B	(R)-quinuclidin-3-yl ((3-((9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-4-methoxyphenyl)(phenyl)methyl)carbamate
15B	(R)-quinuclidin-3-yl ((3-((9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-5-methoxyphenyl)(phenyl)methyl)carbamate

(continued)

16B	(3R)-3-((((3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-4-methoxyphenyl)(phenyl)-methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
17B	(3R)-3-((((3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-5-methoxyphenyl)(phenyl)-methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
18B	(3R)-3-((((5-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-[1,1'-biphenyl]-3-yl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
19B	(R)-quinuclidin-3-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)-5-(thiophen-2-yl)phenyl)(phenyl)methylcarbamate
20B	(3R)-3-((((3-((3-(4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)benzyl)oxy)-phenyl)(phenyl)-methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
21B	(3R)-3-((((3-((3-(4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)benzyl)oxy)-phenyl)(phenyl)-methyl)carbamoyl)oxy)-1-(2-phenoxyethyl)quinuclidin-1-ium
22B	(3R)-3-((((3-((3-((5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl)oxy)benzyl)oxy)phenyl)-(phenyl)-methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
23B	(3R)-3-((((3-((3-((5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl)oxy)benzyl)oxy)-phenyl)(phenyl)-methyl)carbamoyl)oxy)-1-(2-phenoxyethyl)quinuclidin-1-ium
24B	(R)-quinuclidin-3-yl (3-fluorophenyl)(3-(6-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)methylcarbamate
25B	(3R)-3-((((3-((5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl)oxy)phenyl)(phenyl)-methyl)carbamoyl)oxy)-1-(4-phenylbutyl)quinuclidin-1-ium
26B	(R)-Quinuclidin-3-yl (3-fluorophenyl)(3-(3-(2-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)ethyl)benzyloxy)phenyl)methylcarbamate
27B	(3R)-3-((((3-fluorophenyl)(3-((3-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzyl)oxy)phenyl)-methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium

(continued)

28B	(3R)-3-(((3-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)benzyl)oxy)-phenyl)(phenyl)-methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
29B	(R)-Quinuclidin-3-yl (3-((4'-(2-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)ethyl)biphenyl-3-yl)methoxy)phenyl)(phenyl)methylcarbamate
30B	(R)-quinuclidin-3-yl ((3-((4-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)carbamoyl)-benzyl)-oxy)phenyl)(phenyl)methyl)carbamate
31B	(R)-quinuclidin-3-yl (3-(4-(3-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)propylcarbamoyl)benzyloxy)-phenyl)(phenyl)methylcarbamate
32B	(3R)-3-(((3-((4-((3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)propyl)carbamoyl)benzyl)oxy)-phenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
33B	4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
34B	5-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)pentyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
35B	6-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
4C	7-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)heptyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
5C	4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)benzyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
6C	4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)phenyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
7C	4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)phenyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
8C	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
36B	(3R)-3-(((3-((4-(1-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)carbonyl)cyclopropyl)-benzyl)oxy)phenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium

(continued)

37B	(R)-quinuclidin-3-yl (3-(2-(3'-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)methyl)biphenyl-4-yl)ethoxy)phenyl)(phenyl)methylcarbamate
38B	(R)-quinuclidin-3-yl (3-(2-(3'-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)methyl)biphenyl-4-yl)ethoxy)phenyl)(phenyl)methylcarbamate
39B	6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyl 2-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonylamino)methyl)phenoxy)acetate
40B	(R)-quinuclidin-3-yl ((3-(((6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)-(phenyl)methyl)carbamate
41B	(R)-quinuclidin-3-yl ((3-(((6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)-(phenyl)methyl)carbamate
42B	(3R)-3-((((3-(((6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)(phenyl)-methyl)-carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
43B	(3R)-3-((((3-(((6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)(phenyl)-methyl)-carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
44B	4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
45B	4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
9C	5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl 2-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)acetate
10C	4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 2-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)acetate
11C	5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl 2-methyl-2-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)propanoate
12C	4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 2-methyl-2-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)propanoate
13C	5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl 2,2-dimethyl-3-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)propanoate

(continued)

14C	4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)-ethyl)amino)butyl 1-(2-(3-(phenyl(((R)-quinuclidin-3-yloxy)-carbonyl)amino)methyl)phenoxy)acetyl)piperidine-4-carboxylate
15C	4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzyl 2-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)acetate
16C	(R)-quinuclidin-3-yl ((3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-4-methylphenyl)(phenyl)methyl)carbamate
17C	(R)-Quinuclidin-3-yl ((3-bromo-5-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)-oxy)phenyl)(phenyl)methyl)carbamate
18C	(R)-quinuclidin-3-yl ((5-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-[1,1'-biphenyl]-3-yl)(phenyl)methyl)carbamate
19C	(R)-quinuclidin-3-yl ((2-bromo-3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-phenyl)(phenyl)methyl)carbamate
20C	(R)-quinuclidin-3-yl ((3'-fluoro-5-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-[1,1'-biphenyl]-3-yl)(phenyl)methyl)carbamate
21C	(R)-quinuclidin-3-yl ((3-((3-(4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)benzyl)-oxy)phenyl)(phenyl)methyl)carbamate
22C	(R)-quinuclidin-3-yl ((3-((3-((5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl)oxy)benzyl)-oxy)phenyl)(phenyl)methyl)carbamate
23C	(3R)-3-(((cyclohexyl(3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)-methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
24C	(3R)-3-(((3-((6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)(thiophen-2-yl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
25C	(3R)-3-(((3-fluorophenyl)(3-((6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)-methyl)-carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
26C	(3R)-3-(((3-((6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)(thiophen-3-yl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
27C	(3R)-3-(((3-((4-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)carbamoyl)benzyl)oxy)-phenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium

(continued)

28C	(3R)-3-((((3-((7-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)heptyl)oxy)phenyl)(phenyl)-methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
29C	(3R)-3-((((3-((7-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)heptyl)oxy)phenyl)(phenyl)-methyl)-carbamoyl)oxy)-1-(3-phenylpropyl)quinuclidin-1-ium
30C	(3R)-3-((((3-((5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl)oxy)phenyl)(phenyl)-methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
31C	4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)-ethyl)amino)butyl 1-(4-((3-(phenyl(((R)-quinuclidin-3-yloxy)-carbonyl)amino)methyl)phenoxy)methyl)phenyl)cyclopentane-carboxylate
32C	4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)-ethyl)amino)butyl 1-(4-((3-(phenyl(((R)-quinuclidin-3-yloxy)-carbonyl)amino)methyl)phenoxy)methyl)phenyl)cyclohexane-carboxylate
33C	4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 2-methyl-2-(4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)-phenyl)propanoate
34C	8-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)octyl 3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)benzoate
35C	9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl 3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)benzoate
36C	7-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)heptyl 3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)benzoate
37C	6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl 3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)benzoate
38C	5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl 3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)benzoate
39C	4-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)carbamoyl)benzyl 3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)benzoate
40C	4-(N-(4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)sulfamoyl)benzyl 3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)benzoate
41C	4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzyl 3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)benzoate

(continued)

42C	4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 4-(((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)benzamido)methyl)benzoate
43C	(2S)-4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 3-phenyl-2-(4-(((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)-benzamido)propanoate
44C	(R)-quinuclidin-3-yl ((3-((3-(4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)phenyl)-1,2,4-oxadiazol-5-yl)methoxy)phenyl)(phenyl)methyl)carbamate
45C	(R)-quinuclidin-3-yl ((5-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)pyridin-3-yl)(phenyl)methyl)carbamate
46C	(R)-quinuclidin-3-yl ((3-fluorophenyl)(5-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)pyridin-3-yl)methyl)carbamate
47C	4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 2-chloro-4-(((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
48C	4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 2-fluoro-4-(((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
49C	4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 6-(((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)nicotinate
50C	4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 5-(((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)furan-2-carboxylate
51C	4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 2-(((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)oxazole-4-carboxylate
52C	4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 3-(((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
53C	5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl 2-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)acetate
54C	5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl 2-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)acetate
55C	5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl 2-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)acetate

(continued)

56C	5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl 2-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)acetate
57C	(R)-quinuclidin-3-yl ((3-((4-((3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)propyl)carbamoyl)-benzyl)oxy)phenyl)(phenyl)methyl)carbamate
58C	(R)-quinuclidin-3-yl ((3-((4-((3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)carbamoyl)-benzyl)oxy)phenyl)(phenyl)methyl)carbamate
59C	(R)-quinuclidin-3-yl ((3-((4-(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
60C	(R)-quinuclidin-3-yl ((3-((4-((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
61C	(R)-quinuclidin-3-yl ((3-((4-((3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)propyl)(isopropyl)-carbamoyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate
62C	(1R,4R)-4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 4-((4-((3-(phenyl(((R)-quinuclidin-3-yloxy)-carbonyl)amino)methyl)phenoxy)methyl)-benzamido)methyl)-cyclohexanecarboxylate
63C	(2S)-methyl 4-((2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)(methyl)amino)-4-oxo-2-(4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)-phenoxy)methyl)benzamido)butanoate
64C	((1R,4R)-4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)cyclohexyl)methyl 4-((3-(phenyl-(((quinuclidin-4-yloxy)carbonyl)amino)methyl)phenoxy)-methyl)benzoate
65C	2-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)amino)-2-oxoethyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)-methyl)benzoate
66C	2-((3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)propyl)amino)-2-oxoethyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)-methyl)benzoate
67C	2-(4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)-2-oxoethyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)-methyl)benzoate
68C	2-((5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl)oxy)-2-oxoethyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)-methyl)benzoate

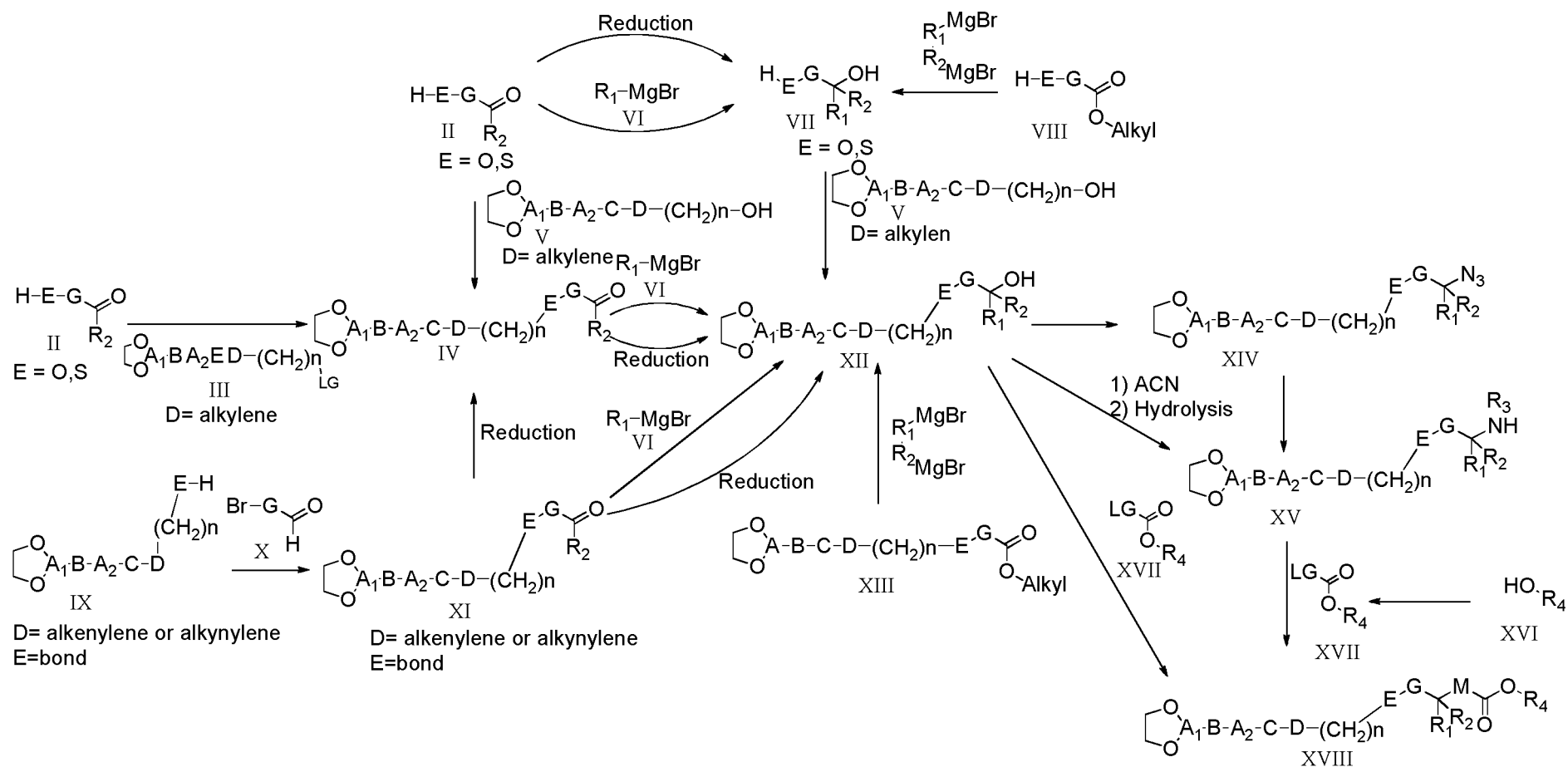
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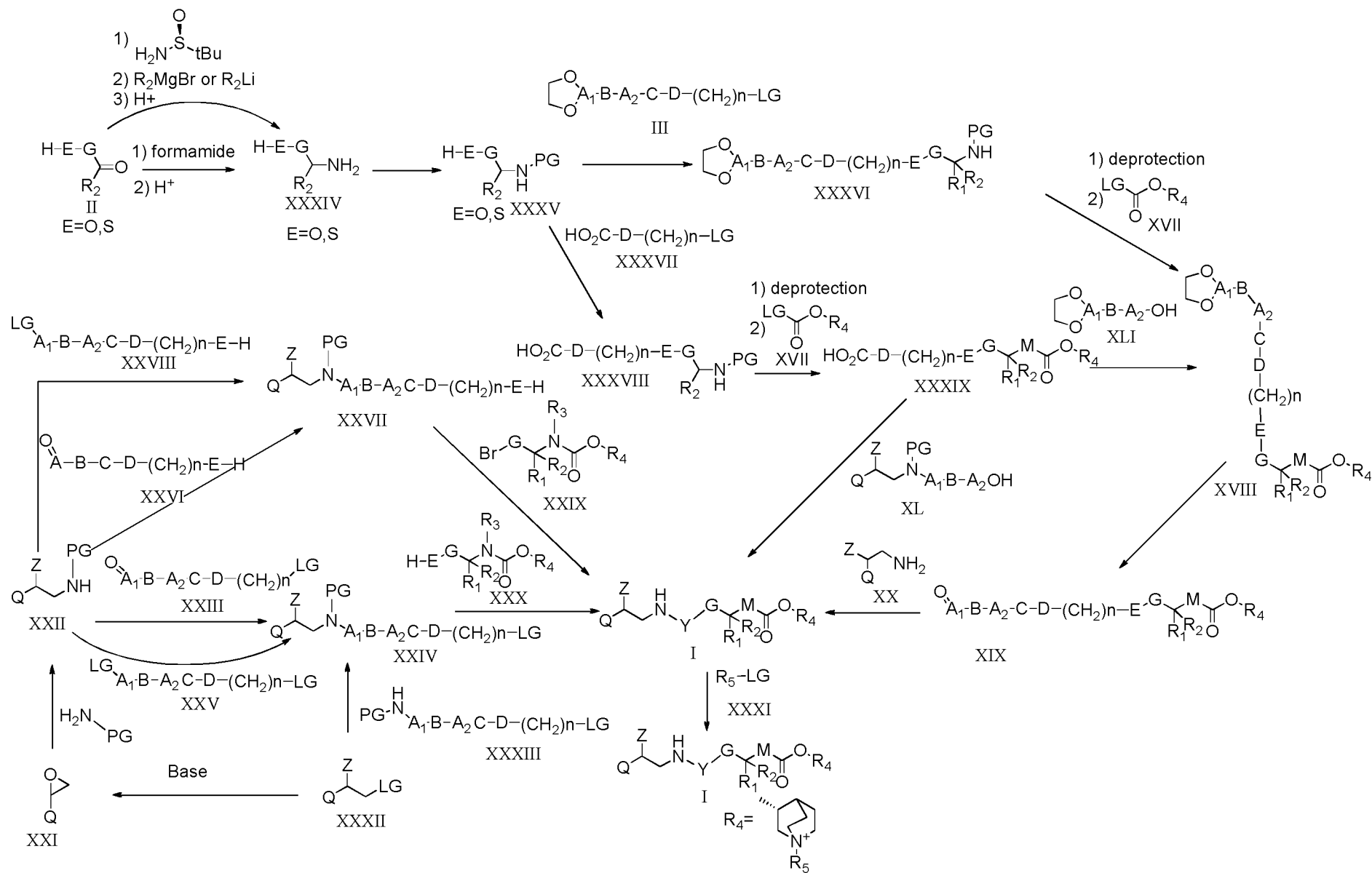
69C	2-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethoxy)ethyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
70C	2-(4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)ethyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
71C	2-((5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl)oxy)-2-oxoethyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)-phenoxy)methyl)benzoate
72C	2-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethoxy)ethyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
73C	2-(4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)ethyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
74C	3-(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
75C	3-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)-phenoxy)propyl 4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzoate
76C	4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 4-(2-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)ethyl)benzoate
77C	4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)-ethyl)amino)butyl 4-(5-((3-(phenyl(((R)-quinuclidin-3-yloxy)-carbonyl)amino)methyl)phenoxy)methyl)-1,2,4-oxadiazol-3-yl)benzoate
78C	4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 4-((4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)piperidin-1-yl)methyl)benzoate
79C	2-(4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)ethyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
80C	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
81C	2-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethoxy)ethyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
82C	4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 2-chloro-4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate
83C	4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 2-fluoro-4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate

The compounds of the invention can be prepared from readily available starting materials using the following general methods and procedures or by using other information readily available to those of ordinary skill in the art. Although a particular embodiment of the present invention may be shown or described herein, those skilled in the art will recognize that all embodiments or aspects of the present invention can be prepared using the methods described herein or by using other methods, reagents and starting materials known to those skilled in the art. It will also be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. While the optimum reaction conditions may vary depending on the particular reactants or solvent used, such conditions can be readily determined by one skilled in the art by routine optimisation procedures.

Compounds of general formula **I** may be prepared according to the following synthetic **Scheme**.

Scheme





General procedure for the preparation of compounds of formula I

The compounds of general formula **IX** represent a compound wherein **A1** is alkylene, cycloalkylene or heterocycloalkylene 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 compound of general formula **XXVI**.

In the case **A1** is absent and **B** is a cycloalkylene, heterocycloalkylene or a group of formula **B1**, the carbonyl moiety, as such or protected, must be considered on group **B**.

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 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 **XIX** with a compound of general formula **XX**. This reductive amination reaction can be performed following several different protocols described in the literature and well known for those skilled in the art. 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 room temperature (RT) over 1 to 12 hours.

The intermediate of general formula **XIX** can be easily prepared by reaction of a compound of general formula **XIV** with a compound of general formula **XVII**. 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 **XVIII**, that can be easily deprotected in aqueous acidic solution, leading to a compound of general formula **XIX**.

Compounds of general formula **XVII** are either commercially available or can be prepared by reacting an alcohol of general formula **XVI** with for example diphosgene in a solvent such as DCM, THF or acetonitrile (ACN) at
5 RT or lower temperature, over a period of time ranging from 0.5 to 12 hours, leading to a compound of general formula **XVII** wherein the leaving group LG is chlorine. Alternatively alcohol of general formula **XVI** can be reacted with for example carbonyldiimidazole (CDI) leading to the same intermediate
10 wherein LG is imidazole. Other possible intermediates with other known LGs can be prepared as described in the literature.

Compound of general formula **XV**, wherein **R₃** is hydrogen, may be prepared from a compound of general formula **XII** *via* Ritter reaction (acetonitrile and sulphuric acid at RT) followed by hydrolysis of the
15 intermediate acetamide performed under basic condition.

Alternatively compounds of general formula **XV** can be prepared by reduction of azide formula **XIV** *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
20 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 LiAlH₄ in THF or ether at -40°C or lower
25 temperature could easily allow to perform the required conversion of compound **XIV** into **XV**.

Azide **XIV** is obtained from compound of formula **XII** 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 **XII** can be converted into a
5 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.

Compounds of general formula **XV** wherein **R₃** is alkyl, can be prepared from compounds of formula **XV** wherein **R₃** is hydrogen, by reductive
10 amination with a suitable aldehyde or ketone. The reaction can be conducted under the same reaction conditions described for the preparation of compounds of formula **I** from compounds of formula **XIX** and **XX**. Alternatively the alkylation of amine with alkyl halides, alkyl tosylates or mesylates under standard reaction conditions, well known to those skilled in
15 the art, can be considered to achieve the described conversion.

Compounds of general formula **I** wherein **M** is -O-, can be prepared treating a compound of general formula **XII** with a compound of general formula **XVII**. The reaction occurs in an aprotic solvent such as THF, DCM or DMF and requires the use of a strong base such as alkyl lithium or sodium
20 hydride. It proceeds rapidly at 0°C or lower temperature over a period of time ranging from 1 to 12 hours. The reaction can be performed using the compound of general formula **XVII** or alternatively the analogue compound in which the chlorine atom is substituted with another usual leaving group, such as imidazole or p-nitro phenol, typical reactant for the preparation of organic
25 asymmetric carbonates or carbamates.

Intermediates of general formula **XII** 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- or -S-, and an aldehyde of

general formula **V** wherein **D** is functionalized with and 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 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 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 for the preparation of intermediate **XII** from compounds of general formula **IV** or **XI**.

It is clear to a person skilled in the art that the preparation of compound of general formula **VII** or **XII** 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.

If the reaction is performed on a compound of general formula **XIII** with a bi-functional Grignard reagent such as for example BrMg-R₁-R₂-MgBr, a compound of general formula **XII**, wherein **R₁** and **R₂** are connected to form a cycle, can be obtained. A similar synthetic protocol can be used for the preparation of intermediates of formula **VII**, wherein **R₁** and **R₂** are connected to form a cycle, from compounds of general formula **VIII**.

Compounds of general formula **IV** wherein **E** is -O- or -S-, can be

prepared from a compound of general formula **II**, following an approach similar to that described for the preparation of compounds of formula **XII** 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
5 general formula **III** wherein **LG** is a suitable leaving group such as tosyl, mesyl 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 completes over a period of time varying from 1 to 24 hours.

10 Compounds of general formula **XII**, wherein **D** is alkenylene or alkynylene, **n** is 0 and **E** is absent, can be prepared by reacting a compound of formula **XI** under the same reaction condition described for the addition of a Grignard reagent of formula **VI** to a compound of formula **II**.

Preparation of compounds of formula **XI** can be achieved by reaction of
15 a compound of general formula **X**, or the analogue wherein the bromine is substituted by iodine or triflate, with a compound of general formula **IX**, under transition metal catalyzed cross-coupling reaction conditions. A great number of protocols, reagents and catalysts can be conveniently used to achieve the desired conversion, as it is known to a person skilled in the art. It
20 is clear that a compound of formula **XI**, wherein **n** is 0, **E** is absent and **D** is alkenylene or alkynylene, can be easily hydrogenated leading to the a compound of formula **IV** wherein **D** is the alkyl group derived from reduction of the unsaturated bond.

Alternatively, compounds of general formula **I** wherein **M** is -O-, can be
25 prepared by treating a compound of general formula **XXXIX** with a compound of general formula **XL**.

In another embodiment of the present invention, compounds of general formula **I** can be prepared following a different synthetic approach in which a

compound of general formula **XXVII** is reacted with a compound of formula **XXIX** under the transition metal catalyzed cross-coupling reaction condition. Alternatively it can be prepared by reaction of a compound of formula **XXIV** with a compound of formula **XXX** under the condition described above for the
5 reaction of a compound of formula **II** with a compound of formula **III**.

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

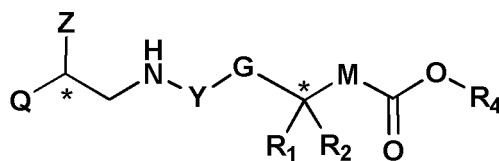
Compounds of general formula **XXII** can be obtained by opening the
15 epoxide intermediates **XXI** with a benzyl amine optionally substituted on the phenyl ring. The reaction can be performed neat or in high boiling point solvent such as toluene, xylene, isopropanol or butanol and occurs at temperature ranging from 80 to 120 °C. Classical thermal or microwaves heating is efficacious to drive the reaction to completion over 1 to 24 hours.

20 In an additional embodiment of the present invention, compounds of formula **I**, wherein **R₄** is **J5** or another group featuring a quaternary ammonium salt, can be prepared reacting the corresponding tertiary amine precursor of formula **I** where **R₅** is **J1-J4** with a compound of formula **XXXI**. The reaction proceeds smoothly at RT or higher temperature in solvent such as
25 DCM, acetonitrile, methanol or AcOEt over a period of time ranging from 1 to 24 hours.

In another embodiment of the present invention, compounds of general formula **XXIV** can be prepared by reacting an intermediate of general formula

XXXII with an amine of general formula **XXXIII**. 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 **XXXIII** wherein **R3** is H or an alkyl group that can increase the selectivity and it can
5 be removed after the reaction. Several methods to perform this reaction, that normally occurs in a polar solvent at a temperature higher than room temperature, are described in the literature.

It is apparent for those skilled in the art that compounds of general formula I wherein **R4** is **J1** or **J2** contain three stereogenic centers, as
10 indicated below with the symbol *. This means that the structure of formula I is characterized by eight different stereoisomers.



(I)

Each diastereoisomer can be obtained theoretically by chromatographic
15 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
20 stereoisomer 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 **R4** is **J1**, **J2** or **J5** are commercially available.

25 The preparation of single enantiomerically pure compounds of general

formula **XXXII** wherein LG is bromine are described in WO2005/080324, US2005-2222128, WO2004/032921, US2005/215590 and WO2005/092861 (cited by WO2007/107228). This compound can be easily converted into the epoxide **XXI** by heating the precursor (wherein Z is oxygen) in a suitable solvent in the presence of a base that catalyzes the epoxide formation.

Enantiomerically pure compounds of general formula **XXXV** can be obtained by chiral chromatographic separation of the racemic mixture or starting from enantiomerically pure amine compounds of general formula **XXXIV**. As intermediate compounds of formula **XXXIV** 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 purpose are for example mandelic acid, tartaric acid and its derivatives. The base **XXXIV** is dissolved in a suitable polar solvent and then treated with of the 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 optical purity.

Alternatively the amines of formula **XXXIV** 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 sulfiniimide and then with R_2MgBr or R_2Li (wherein **R2** is not H), followed by hydrolysis of the intermediate leading to the formation of enantiomerically enriched compounds of formula **XXXIV** that can be used as such or further purified to increase the optical purity.

The available amine of formula **XXXIV** 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 alkylation of compounds of formula **II** with compounds of formula **III**, leading to compound or general formula **XXXVI**. Deprotection of the amino group and reaction of compounds of formula **XVII**, lead to the preparation of a compound of general formula **XVIII**.

5 Alternatively, compound of general formula **I** can be prepared coupling a compound of general formula **XXXIX** with a compound of general formula **XL** leading to a compound of general formula **I** wherein **C** is $-\text{OCO}-$. This ester can be obtained under different reaction condition well known to those skilled in the art. The reaction requires the activation of the acid **XXXIX** with
10 reactant such as DCC, EDC, HBTU HATU or it may be converted into the corresponding acyl chloride. The activated ester can smoothly react, in DCM, pyridine or other apolar solvents, with the alcohol of formula **XL**.

 Compound of formula **XXXIX** can be prepared starting from **XXXV** via alkylation with compound of formula **XXXVII**, deprotection and reaction with
15 compound of formula **XVII**. The reaction conditions for this conversion are described above and well described in the literature. Acid **XXXIX** can be easily reacted with a compound of formula **XLI**, as described above for the reaction with a compound of formula **XL**, leading to compound of formula **XVIII**.

20 A compound of general formula **XL** can be prepared by reaction of a compound of general formula **XXXII** with an amine of formula $\text{PG-NH-A}_1\text{-B-A}_2\text{-OH}$, under the reaction conditions described for the reaction of compounds of general formula **XXXII** with compounds of general formula **XXXIII**.

 For all the above, the synthesis of compounds of general formula **I** can
25 be performed following several different approaches. In particular it must be noted 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 –OCO- allows appreciating this aspect of the invention.

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

Method A (IS 10cm_ESCI_Formic_MeCN)

5 HPLC Setup

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

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

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

Flow Rate: 2ml/min

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

Time	A%	B%
0.00	95	5
15 3.50	5	95
5.50	5	95
5.60	95	5
6.50	95	5

Typical Injections 2-7ul

20 UV detection via HP or Waters DAD

Start Range (nm) 210 End Range (nm) 400 Range interval (nm) 4.0

Optional ELS detection using Polymer Labs ELS-1000.

MS detection: Micromass ZQ, single quadrapole LC-MS instrument.

Scan range for MS Data (m/z)

25 Start (m/z) 100

End (m/z) 650 or 1000 when required

With +ve / -ve switching

Ionisation is either electrospray (ESI) or atmospheric-pressure chemical

ionization (APCI) dependent on compound types.

Method B (IS 15cm_Formic_ASCENTIS_HPLC_CH₃CN)

HPLC Setup

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

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

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

Flow Rate: 1 ml/min

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

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

Typical Injections 0.2-10 µl

Maximum pressure setting 400 bar.

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

20 DAD detector

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

Method C (IS 10cm_ESCI_Formic_MeCN)

HPLC Setup

25 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: ml/min

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

Time	A%	B%
0.00	98	2
3.00	98	2
5 12.00	0	100
15.4	0	100
15.5	98	2
17	98	2

Typical Injections 0.2-10ul

10 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

15 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, XVII Ed., Mack Pub., N.Y., U.S.A.

Administration of the compounds of the present invention may be
20 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
25 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.

5 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
10 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
15 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.

20 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.

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

 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.

5 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.

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

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

20 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. corticosteroids, P38 MAP kinase inhibitors, IKK2, HNE inhibitors, PDE4 inhibitors, leukotriene modulators, NSAIDs and mucus regulators.

25 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.

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.

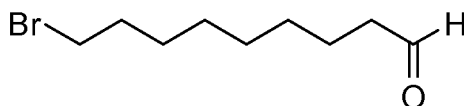
When the compounds of formula **I** are administered by inhalation route,
5 they are preferably given at a dosage comprised between 0.001 and 500 mg/day, preferably between 0.1 and 200 mg/day.

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

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

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

Preparation of 9-Bromononanal

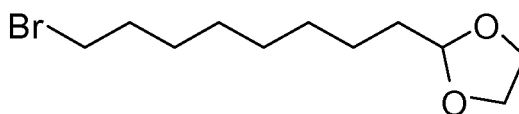


25 Pyridinium chlorochromate (38.7 g, 180 mmol) and silica 60A (39 g, particle size 35-70 micron) suspended in DCM (250 mL) were stirred at RT for 45 minutes. 9-Bromononanol (26.7 g, 120 mmol) was added, in one

portion, and the suspension was stirred at RT for 18 hours. The reaction mixture was filtered through a celite plug and the resulting filtrate concentrated under vacuum affording the title compound (28.0 g, >100%). The material was used without further purification in the next step.

- 5 ¹H NMR (400 MHz, CDCl₃): δ 9.77 (s, 1 H), 3.41 (t, 2 H), 2.43 (t, 2 H), 1.90-1.80 (m, 2 H), 1.63 (s, 2 H), 1.43 (s, 2 H), 1.32 (s, 6 H).

Preparation of 2-(8-Bromooctyl)-1,3-dioxolane



- 10 9-Bromononanal (28.0 g, assumed 120 mmol), ethylene glycol (33.6 mL, 600 mmol) and *para*-toluenesulphonic acid (2.7 g, 13 mmol) in toluene (210 mL) were heated at reflux for 20 hours. The reaction was cooled to RT and quenched with saturated aqueous sodium bicarbonate solution (300 mL). The resulting mixture was extracted with diethyl ether
- 15 (2 x 500 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (300 mL), water (300 mL), brine (100 mL), dried (magnesium sulfate), filtered and evaporated under reduced pressure to afford the title compound (25.2 g, 79%).

- 20 ¹H NMR (400 MHz, CDCl₃): δ 4.84 (t, J = 4.8 Hz, 1 H), 3.95-3.78 (m, 4 H), 3.43-3.37 (m, 2 H), 1.90-1.79 (m, 2 H), 1.69-1.54 (m, 2 H), 1.42 (s, 3 H), 1.32 (s, 7 H).

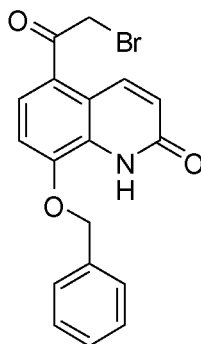
Alternatively **9-Bromononanal** could be prepared as follows:

- To a cooled (-78°C) solution of oxalyl chloride (11.66 g, 92 mmol) in DCM (250 mL), a solution of dimethylsulfoxide (DMSO) (13.0 mL, 183 mmol) in DCM (50 mL) was added over 15 minutes. After a further 5
- 25 minutes a solution of 9-bromononanol (10.25 g, 45.9 mmol) in DCM (50 mL) was added dropwise over 15 minutes. The resulting reaction mixture was

stirred at this temperature for 45 minutes. Triethylamine (32 mL, 230 mmol) was added and the reaction mixture stirred at this temperature for 10 minutes. The coolant was removed and allowed to warm to RT. The reaction mixture was stirred at RT for 40 minutes and then diluted with water. The organic
5 phase was removed and washed with 10% aqueous potassium hydrogen sulfate and dried (magnesium sulfate). The suspension was filtered and the filtrate evaporated under reduced pressure to afford the title compound.

All other 1,3-dioxalanes (i.e. 2-(7-bromoheptyl)-1,3-dioxolane; 2-(6-bromohexyl)-1,3-dioxolane; 2-(5-bromopentyl)-1,3-dioxolane and
10 2-(4-bromobutyl)-1,3-dioxolane) were prepared by the same method.

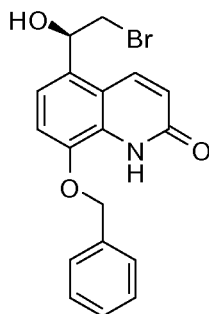
Preparation of 8-(Benzyloxy)-5-(2-bromoacetyl)quinolin-2(1H)-one



To 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)
15 was added a solution of *tetra*-n-butylammonium tribromide (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).
20 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- d_6): 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)

Preparation of (*R*)-8-(Benzyloxy)-5-(2-bromo-1-hydroxyethyl)-quinolin-2(1*H*)-one

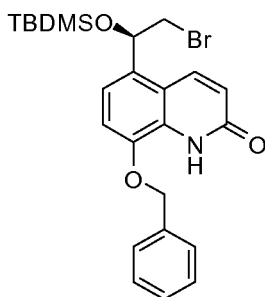


8-(Benzyloxy)-5-(2-bromoacetyl)quinolin-2(1*H*)-one (26.0 g, 69.9 mmol) and (*R*)-3,3-diphenyl-1-methyltetrahydro-3*H*-pyrrolo[1,2-
10 c][1,3,2]oxazaborole (21.3 g, 76.8 mmol) were azeotroped with toluene ($\times$ 3) then suspended in anhydrous THF (400 mL) under an atmosphere of nitrogen. The suspension was cooled to -20°C (external temperature) and borane dimethyl sulfide 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
15 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
20 (3×100 mL). The solid was partially dissolved in ethyl acetate and heated at reflux 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 heated at reflux 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).

Preparation of (R)-8-(Benzyloxy)-5-(2-bromo-1-(tert-butyltrimethylsilyloxy)ethyl)quinolin-2(1H)-one



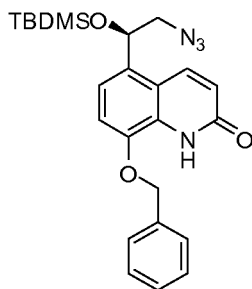
2,6-Lutidine (6.9 mL, 59.5 mmol) was added to a solution of (R)-8-(benzyloxy)-5-(2-bromo-1-hydroxyethyl)quinolin-2(1H)-one (10.1 g, 27.0 mmol) in DCM (100 mL) at 0°C. The reaction mixture was stirred for 5 minutes then *tert*-butyldimethylsilyl trifluoromethanesulfonate (13.0 mL, 56.8 mmol) was added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

Preparation of (R)-5-(2-Azido-1-(*tert*-butyldimethylsilyloxy)ethyl)-

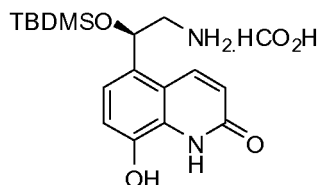
8-(benzyloxy)quinolin-2(1H)-one



(R)-8-(Benzyloxy)-5-(2-bromo-1-(*tert*-butyldimethylsilyloxy)ethyl)-quinolin-2(1H)-one (5.0 g, 10.2 mmol) was dissolved in dimethyl formamide (90 mL) and water (10 mL). Sodium iodide (1.7 g, 11.3 mmol) and sodium azide (0.7 g, 11.3 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 water (300 mL). The aqueous layer was extracted with DCM and the combined organic extracts were dried (magnesium sulfate), filtered and concentrated under reduced pressure. The crude residue was recrystallised from ethyl acetate and *iso*-hexane to afford the desired compound (3.6 g, 78%). 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).

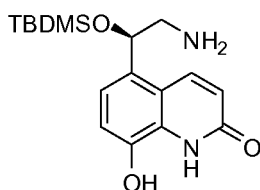
Preparation of (R)-5-(2-Amino-1-(tert-butyldimethylsilyloxy)ethyl)-8-hydroxyquinolin-2(1H)-one formate



5 Palladium on activated carbon (0.4 g, 10% w/w) was added to a suspension of (R)-5-(2-azido-1-(tert-butyldimethylsilyloxy)ethyl)-8-(benzyloxy)quinolin-2(1H)-one (2.05 g, 4.60 mmol) and ammonium formate (2.87 g, 63 mmol) in methanol (50 mL). The reaction mixture was heated at 80°C for 1 hour. If after this time the reaction had not reached completion; the reaction
10 mixture was filtered through celite, washing with methanol. The reaction mixture was concentrated to approximately 50 mL then ammonium formate (2.87 g, 63.0 mmol) and Palladium on activated carbon (0.40 g, 10% w/w) were added. The reaction mixture was heated at 80°C for 20 minutes, and then filtered through celite, washing with water. The reaction mixture was concentrated under reduced
15 pressure. The resulting solid was washed with water, triturated with ethyl acetate and collected by filtration to afford the title compound (1.32 g, 86%).

¹H NMR (400 MHz, DMSO-d₆): δ 8.34 (s, 1 H), 8.31-8.22 (m, 1 H), 7.03 (d, J = 8.1 Hz, 1 H), 6.98-6.90 (m, 1 H), 6.53 (d, J = 9.9 Hz, 1 H), 5.13 (t, J = 6.0 Hz, 1 H), 3.18 (s, 1 H), 2.84-2.73 (m, 2 H), 0.83 (s, 9 H), 0.06 (s, 3 H),
20 -0.17 (s, 3 H).

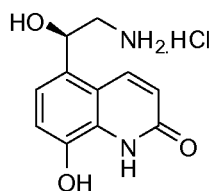
Preparation of (R)-5-(2-Amino-1-(tert-butyldimethylsilyloxy)ethyl)-8-hydroxyquinolin-2(1H)-one



To an ice-cooled suspension of (*R*)-5-(2-azido-1-(*tert*-butyldimethylsilyloxy)ethyl)-8-(benzyloxy)quinolin-2(1*H*)-one (5.77 g, 12.8 mmol) and palladium on activated charcoal (5.8 g, 10% w/w wet) in ethanol (50 mL), 1,4-cyclohexadiene (12.0 mL, 126 mmol) was added dropwise. After stirring at this temperature for 30 minutes the coolant was removed and replaced with a water bath at 30 °C. The reaction was stirred at this temperature for 1 hour. The suspension was filtered and the filter cake washed with further ethanol. The filtrate was evaporated under reduced pressure to dryness. The resulting solid was suspended in acetonitrile and stirred for 1 hour. The suspension was filtered and the resulting solid air-dried under vacuum to afford the title compound (2.90 g, 87%).

¹H NMR (400 MHz, DMSO-*d*₆): δ 8.43 (d, *J* = 10 Hz, 1 H), 7.18 (d, *J* = 8.0 Hz, 1 H), 7.08 (d, *J* = 8.4 Hz, 1 H), 6.68 (d, *J* = 10 Hz, 1 H), 5.14 (m, 1 H), 2.84-2.82 (m, 2 H), 0.96 (s, 9 H), 0.19 (s, 3 H), 0.00 (s, 3 H).

15 **Preparation of (*R*)-5-(2-Amino-1-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one hydrochloride**

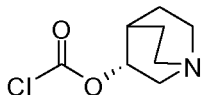


(*R*)-5-(2-Amino-1-(*tert*-butyldimethylsilyloxy)ethyl)-8-hydroxyquinolin-2(1*H*)-one formate (0.23 g, 0.61 mmol) was dissolved in hydrochloric acid (5 mL, 4 M solution in dioxane) and methanol (5 mL). The reaction mixture was stirred at RT for 16 hours before concentrating *in vacuo*. The resulting residue was washed with ethyl acetate and dried in a vacuum oven for 18 hours to afford the title compound (0.15 g, 99%).

25 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).

Preparation of (*R*)-Quinuclidin-3-yl carbonochloridate hydrochloride

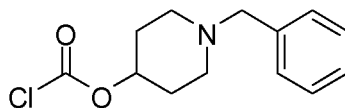


5 To a stirred solution of (*R*)-3-quinuclidinol (2.5 g, 19.66 mmol) in acetonitrile (200 mL), trichloromethyl chloroformate (3.06 mL, 25.57 mmol) was added dropwise at 0 °C and stirred for 1 hour. The reaction mixture was stirred at RT for 16 hours before concentrating *in vacuo* to afford the title compound (4.39 g, 98%).

10 ^1H NMR (400 MHz, DMSO- d_6): δ 10.29 (s, 1 H), 4.05-3.95 (m, 1 H), 3.43 (t, $J = 10.78$ Hz, 1 H), 3.12 (m, 3 H), 3.10-2.95 (m, 1 H), 2.79 (d, $J = 13.27$ Hz, 1 H), 2.12-2.02 (m, 1 H), 1.98 (m, $J = 3.36$ Hz, 1 H), 1.89-1.78 (m, 1 H), 1.75-1.59 (m, 2 H).

Preparation of 1-Benzylpiperidin-4-yl carbonochloridate hydrochloride

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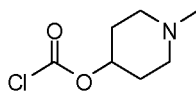


Title compound prepared as described above for (*R*)-quinuclidin-3-yl carbonochloridate to afford the title compound (0.6 g, 99%) which was used without further purification.

20 ^1H NMR (400 MHz, DMSO- d_6): δ 10.33 (s, 1 H), 7.60 (d, $J = 13.85$ Hz, 2 H), 7.47-7.44 (m, 3 H), 4.27 (dd, $J = 16.57, 5.30$ Hz, 2 H), 3.66-3.56 (m, 1 H), 3.28 (d, $J = 12.34$ Hz, 1 H), 3.12 (s, 2 H), 2.91 (q, $J = 11.35$ Hz, 1 H), 1.94 (d, $J = 13.65$ Hz, 2 H), 1.77-1.62 (m, 2 H).

Preparation of 1-Methylpiperidin-4-yl carbonochloridate hydrochloride

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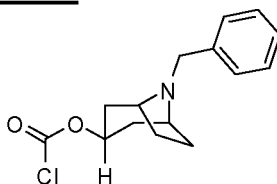


Title compound prepared as described above for (*R*)-quinuclidin-3-yl

carbonochloridate to afford the title compound (0.42 g, 90%) which was used without further purification.

^1H NMR (400 MHz, DMSO- d_6): δ 10.63 (s, 1 H); 3.93-3.89 (m, 1 H), 3.36-3.27 (m, 1 H), 3.19-3.04 (m, 2 H), 2.97-2.86 (m, 1 H), 2.70-2.63 (m, 3 H), 2.00-1.85 (m, 2 H), 1.76-1.61 (m, 2 H).

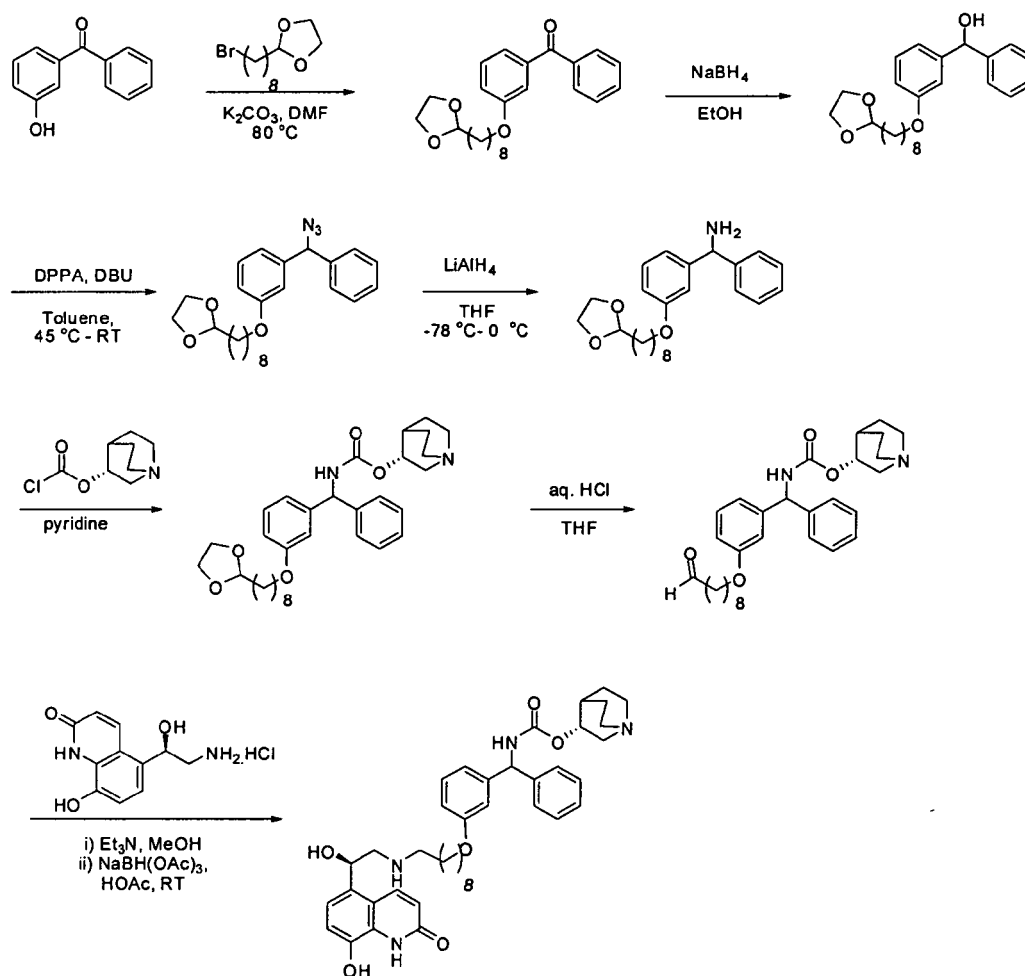
Preparation of 8-Benzyl-8-azabicyclo[3.2.1]octan-3-yl carbonochloridate hydrochloride



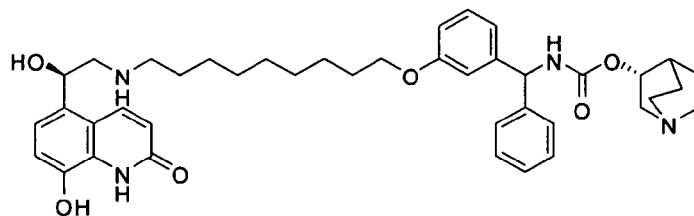
Title compound prepared as described above for (*R*)-quinuclidin-3-yl carbonochloridate to afford the title compound (0.31 g, 84%) which was used without further purification.

^1H NMR (400 MHz, DMSO- d_6): δ 7.68 (s, 2 H), 7.47 (s, 3 H), 4.13 (d, J = 6.31 Hz, 1 H), 3.99-3.90 (m, 2 H), 3.72 (s, 2 H), 2.27 (s, 2 H), 1.88 (t, J = 11.52 Hz, 6 H).

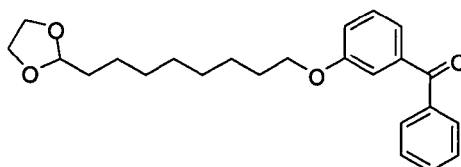
64

**Example 1**

(R)-Quinuclidin-3-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)(phenyl)-
5 methylcarbamate (compound 1)



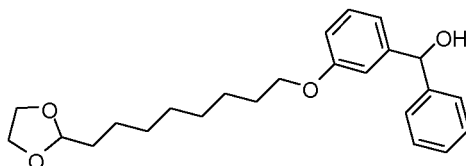
Step 1; (3-(8-(1,3-Dioxolan-2-yl)octyloxy)phenyl)(phenyl)methanone



2-(8-Bromooctyl)-1,3-dioxolane (3.89 g, 14.69 mmol) was added to a mixture of 3-hydroxybenzophenone (3 g, 15.13 mmol) and potassium carbonate (4.17 g, 30.21 mmol) in dimethyl formamide (50 mL). The reaction mixture was stirred at 80 °C for 16 hours. The reaction mixture was diluted with water and extracted with ethyl acetate (x 3). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution, saturated aqueous ammonium chloride solution and dried (sodium sulfate), filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 0-100% ethyl acetate in *iso*-hexane to afford the title compound (4.73 g, 84%).

¹H NMR (400 MHz, DMSO-d₆): δ 7.74 (d, J = 7.53 Hz, 2 H), 7.69-7.66 (m, 1 H), 7.60-7.53 (m, 2 H), 7.46-7.43 (m, 1 H), 7.28-7.20 (m, 3 H), 4.77-4.71 (m, 1 H), 4.04-3.97 (m, 2 H), 3.90-3.80 (m, 2 H), 3.79-3.69 (m, 2 H), 1.77-1.66 (m, 2 H), 1.57-1.50 (m, 2 H), 1.54-1.15 (m, 10 H).

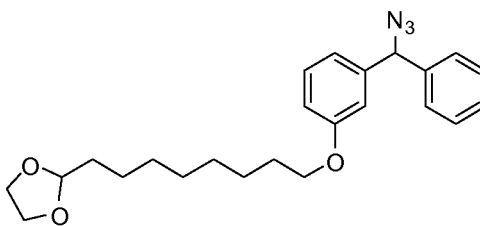
Step 2; (3-(8-(1,3-Dioxolan-2-yl)octyloxy)phenyl)(phenyl)methanol



To a solution of (3-(8-(1,3-dioxolan-2-yl)octyloxy)phenyl)(phenyl)methanone (4.73 g, 12.35 mmol) in ethanol (100 mL) at 0 °C sodium borohydride (1.88 g, 49.42 mmol) was added portion wise. The coolant was removed and the reaction mixture was allowed to warm to RT and stirred for 1 hour. The reaction mixture was quenched with water (30 mL) at 0 °C and then concentrated under reduced pressure. The crude material was dissolved in DCM and washed with saturated aqueous ammonium chloride, dried (sodium sulfate), filtered and concentrated under reduced pressure to afford the title compound (4.33 g, 91%).

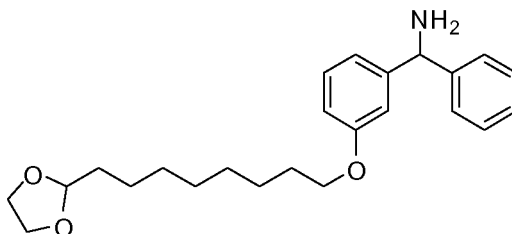
¹H NMR (400 MHz, DMSO-d₆): δ 7.37 (d, J = 1.27 Hz, 2 H), 7.32-7.28 (m, 2 H), 7.23-7.16 (m, 2 H), 6.96-6.90 (m, 2 H), 6.75 (dd, J = 8.11, 2.58 Hz, 1 H), 5.85 (d, J = 4.08 Hz, 1 H), 5.65 (d, J = 4.05 Hz, 1 H), 4.79-4.73 (m, 1 H), 3.93-3.80 (m, 4 H), 3.79-3.70 (m, 2 H), 1.73-1.62 (m, 2 H), 1.59-1.51 (m, 2 H), 1.73-0.95 (m, 10 H).

Step 3; 2-(8-(3-(Azido(phenyl)methyl)phenoxy)octyl)-1,3-dioxolane



To a stirred solution of (3-(8-(1,3-dioxolan-2-yl)octyloxy)phenyl)-(phenyl)methanol (1.63 g, 4.24 mmol) in toluene (10 mL) under an atmosphere of nitrogen diphenylphosphoryl azide (1.10 mL, 5.10 mmol) and DBU (0.77 mL, 5.11 mmol) was added. The reaction mixture was stirred at 45°C for 3 hours and then at RT for 16 hours. The reaction mixture was concentrated under reduced pressure. The crude material was purified by silica gel chromatography eluting with 0-100% ethyl acetate in *iso*-hexane to afford impure title compound (1.11 g, 64%). This material was used directly in the next step.

Step 4; (3-(8-(1,3-Dioxolan-2-yl)octyloxy)phenyl)(phenyl)methanamine

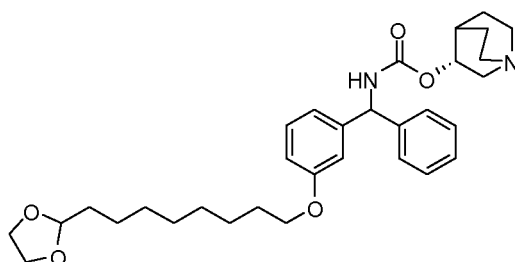


To a stirred solution of 2-(8-(3-(azido(phenyl)methyl)phenoxy)octyl)-1,3-dioxolane (1.11 g, 2.71 mmol) in THF (15 mL) at -78°C under an atmosphere of nitrogen a solution of lithium aluminium hydride (2.0M in

THF, 2.8 mL, 5.60 mmol) was added drop wise. After stirring the reaction at -78°C for 1 hour the reaction mixture was warmed up to 0°C for 1 hour. The reaction mixture was quenched with water (304 mL), 2M sodium hydroxide (304 mL) and water (304 mL x 3). Anhydrous magnesium sulphate and ethyl acetate were added and the reaction mixture filtered and concentrated under reduced pressure. The crude material was purified by column chromatography eluting with 100% *iso*-hexane to 100% DCM to 25:1 DCM:methanol (0.63 g, 39% based on (3-(8-(1,3-dioxolan-2-yl)octyloxy)phenyl)(phenyl)methanol).

¹H NMR (400 MHz, CDCl₃): δ 7.39-7.18 (m, 6 H), 7.00-6.91 (m, 2 H), 6.76-6.73 (m, 1H), 5.17 (s, 1 H), 4.84 (t, J = 4.8 Hz, 1H), 4.00-3.83 (m, 6 H), 1.79-1.53 (m, 8 H), 1.43-1.33 (m, 8 H).

Step 5; (*R*)-Quinuclidin-3-yl (3-(8-(1,3-dioxolan-2-yl)octyloxy)-phenyl)(phenyl)methylcarbamate

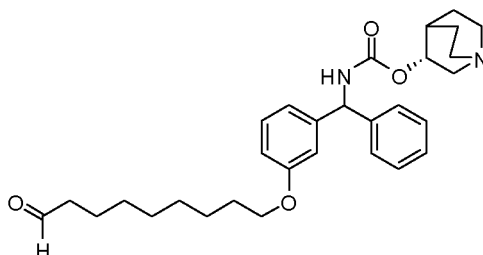


To a stirred solution of (3-(8-(1,3-dioxolan-2-yl)octyloxy)phenyl)-(phenyl)-methanamine (0.62 g, 1.62 mmol) in pyridine (10 mL) at 0°C, (*R*)-quinuclidin-3-yl carbonochloridate (0.48 g, 2.1 mmol) was added. The reaction was stirred at 0°C for 1 hour and then allowed to warm to RT for 16 hours. Water 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 concentrated 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 (0.67 g, 78%).

¹H NMR (400 MHz, CDCl₃): δ 7.41-7.18 (m, 6 H), 6.87-6.74 (m, 3 H),

5.96-5.82 (br m, 1 H), 5.32 (br s, 1 H), 4.86-4.82 (m, 1 H), 4.76-4.69 (m, 1 H), 4.01-3.81 (m, 6 H), 3.20 (br s, 1 H), 2.96-2.60 (m, 5 H), 2.00 (br s, 1 H), 1.79-1.19 (m, 17 H).

**Step 6; (*R*)-Quinuclidin-3-yl (3-(9-oxononyloxy)phenyl)(phenyl)-
5 methylcarbamate**



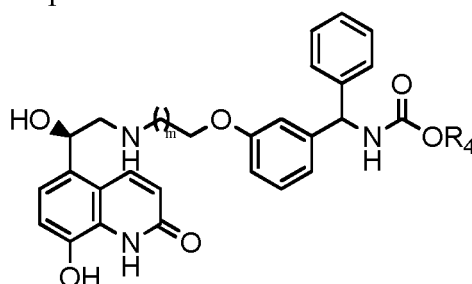
To a stirred solution of (*R*)-quinuclidin-3-yl (3-(8-(1,3-dioxolan-2-yl)octyloxy)phenyl)(phenyl)methylcarbamate (0.66 g, 1.23 mmol) in THF (10 mL) 2M hydrochloric acid was added (20 mL). The reaction mixture was stirred at RT for 3 hours. To the reaction mixture was added 10% aqueous potassium carbonate and the mixture extracted with DCM (x 3). The combined organic extracts were washed poured through a hydrophobic cartridge and concentrated under reduced pressure to afford the title compound (0.64 g, quantitative yield).
15 The material was used directly in the next step with no further purification.

**Step 7; (*R*)-Quinuclidin-3-yl (3-(9-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)-
(phenyl)methylcarbamate**

To a suspension of (*R*)-5-(2-amino-1-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one hydrochloride (0.17 g, 0.66 mmol) in methanol (2.5 mL), triethylamine (0.18 mL, 1.32 mmol) was added and the reaction mixture stirred for 10 minutes at RT. The reaction mixture was then added with a solution of (*R*)-quinuclidin-3-yl (3-(9-oxononyloxy)phenyl)(phenyl)-methylcarbamate (0.33 g, 0.66 mmol) in methanol (2.5 mL) and the reaction
20 mixture was stirred at RT for 1 hour. The reaction mixture was added with
25

sodium triacetoxyborohydride (0.26 g, 1.23 mmol) followed by acetic acid (0.15 mL, 2.64 mmol). The reaction mixture was stirred at RT for 16 hours. Water was added and the reaction mixture concentrated under reduced pressure. The crude material was purified by reverse phase preparative HPLC to afford the title compound (0.041 g, 9%).

The following compounds were prepared using the procedure described for the preparation of compound 1:

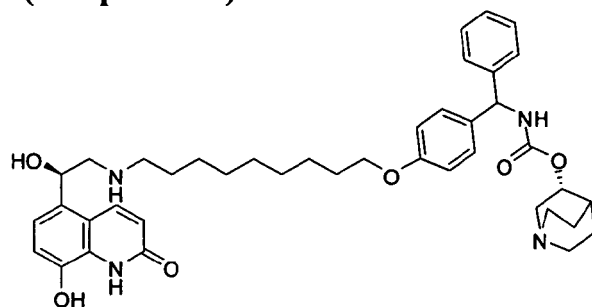


Compound	R ₄	m
2		7
3		6
4		5
5		4
6		8
7		8
8		8

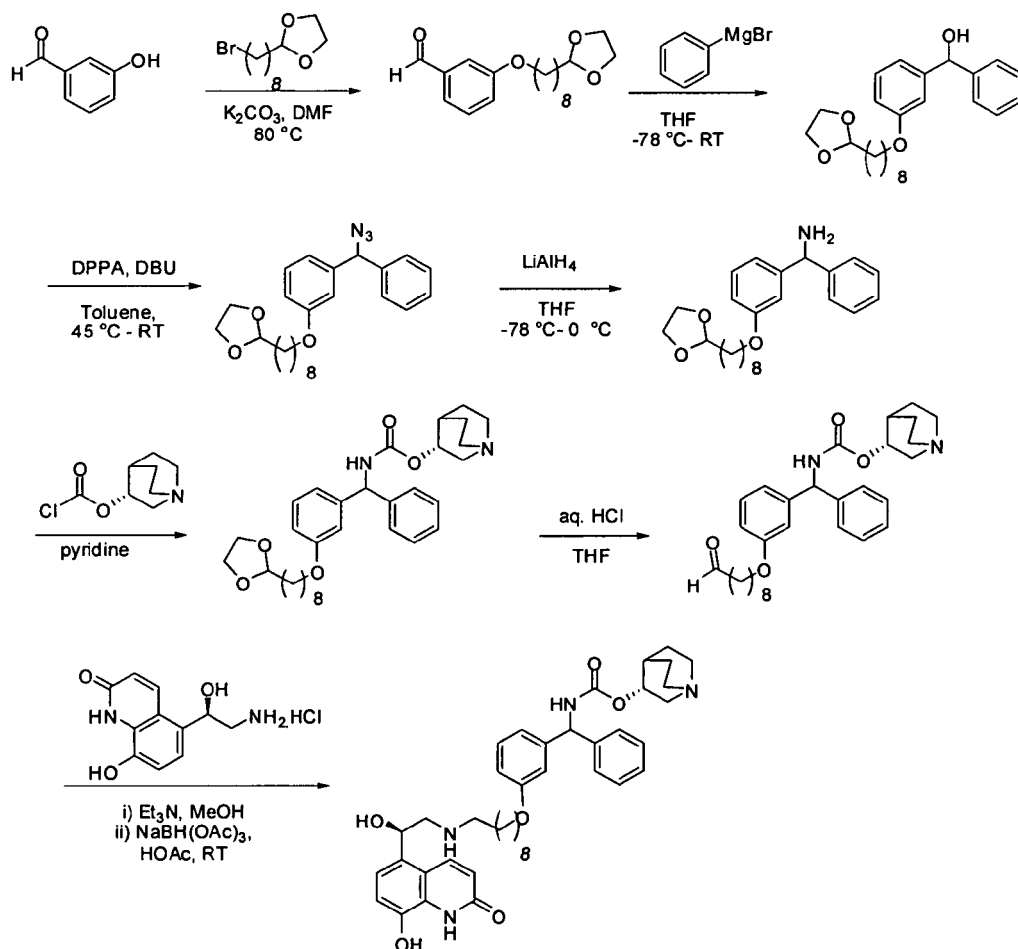
10

Example 9

(R)-Quinuclidin-3-yl (4-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)(phenyl)-

methylcarbamate (compound 9)

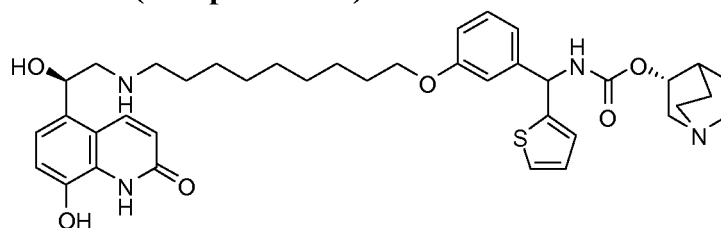
The title compound was prepared as in **Example 1** with 4-hydroxybenzophenone replacing 3-hydroxybenzophenone in **Step 1**. The additional steps required to make the target compound are described in the preparation of **Example 1**.

**Example 10**

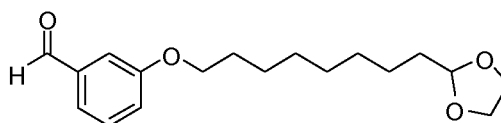
10

(R)-Quinuclidin-3-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-

dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)(thiophen-2-yl)methylcarbamate (compound 10)



Step 1; 3-(8-(1,3-Dioxolan-2-yl)octyloxy)benzaldehyde



5

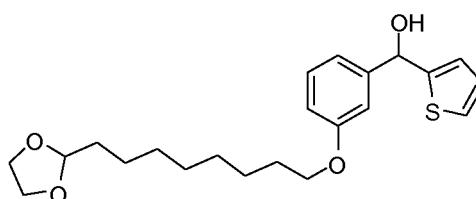
To a stirred solution of 2-(8-bromooctyl)-1,3-dioxolane (5 g, 18.85 mmol) in dimethyl formamide (100 mL) was added 3-hydroxybenzaldehyde (2.37 g, 19.42 mmol) and potassium carbonate (5.37 g, 38.83 mmol). The reaction mixture was stirred at 80°C for 16 hours.

10 The reaction mixture was diluted with water and extracted with ethyl acetate (x 3). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate solution and brine, dried (sodium sulfate), filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with 0-100% ethyl acetate in
15 *iso*-hexane to afford the title compound (4.66 g, 78%).

¹H NMR (400 MHz, CDCl₃): δ 9.97 (s, 1 H); 7.46-7.40 (m, 2 H); 7.38 (d, J = 2.59 Hz, 1 H); 7.20-7.14 (m, 1 H); 4.84 (t, J = 4.82 Hz, 1 H); 4.05-3.93 (m, 4 H); 3.89-3.81 (m, 2 H); 1.85-1.74 (m, 2 H); 1.55-1.27 (m, 12 H).

Step 2; (3-(8-(1,3-Dioxolan-2-yl)octyloxy)phenyl)(thiophen-2-yl)methanol

20

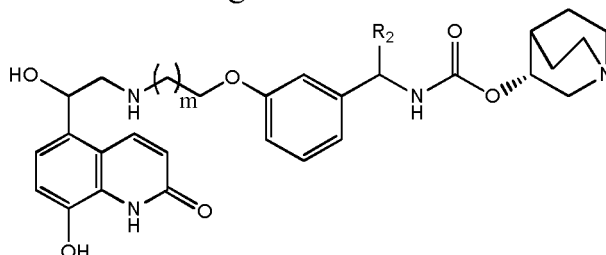


To a stirred solution of 3-(8-(1,3-dioxolan-2-yl)octyloxy)benzaldehyde (1.0 g, 3.25 mmol) in THF (30 mL) at -78°C under an atmosphere of nitrogen, a solution of 2-thienylmagnesium bromide (1M in THF, 4.23 mL, 4.23 mmol) was added over 10 minutes. After stirring at -78°C for 1 hour the reaction was allowed to warm to RT and stirred for 16 hours. The reaction was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (x 3). The combined organic extracts were washed with brine, dried (magnesium sulfate), filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography eluting with 0-50% ethyl acetate in *iso*-hexane to afford the title compound (1.12 g, 87%).

¹H NMR (400 MHz, CDCl₃): δ 7.29-7.22 (m, 2 H), 7.05-6.95 (m, 2 H), 6.96-6.92 (m, 1 H), 6.89 (dt, J = 3.58, 1.09 Hz, 1 H), 6.85-6.81 (m, 1 H), 6.02 (s, 1 H), 4.83 (t, J = 4.83 Hz, 1 H), 4.06-3.89 (m, 4 H), 3.89-3.81 (m, 2 H), 2.47 (s, 1 H), 1.81-1.69 (m, 2 H), 1.70-1.58 (m, 2 H), 1.49-1.21 (m, 10 H).

The title compound was prepared as described in **Example 1** with **(3-(8-(1,3-dioxolan-2-yl)octyloxy)phenyl)(thiophen-2-yl)methanol** replacing **(3-(8-(1,3-dioxolan-2-yl)octyloxy)phenyl)(phenyl)methanol** in **Step 3**. The additional steps required to make the target compound are described in the preparation of **Example 1**.

The following compounds were prepared using the methodology described for the preparation of compound 10 using the appropriate Grignard reagent to introduce suitable bromoacetals to generate alternate chain lengths (m)

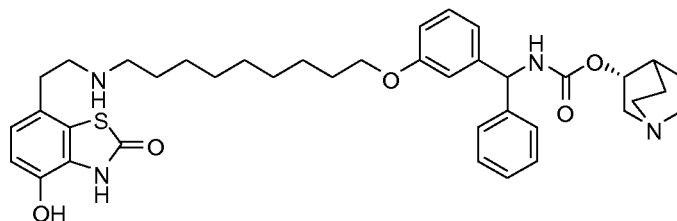


Compound	R ₂	m
11	4-biphenyl	8
12	naphthyl	8
13	3-biphenyl	8
14	2-pyridinyl	8
15	3,5-difluorophenyl	8
16	3,4,5-trifluorophenyl	8
17	2-methylphenyl	8
18	3-methylphenyl	8
19	4-methylphenyl	8
20	4-fluorophenyl	8
1B	3-fluorophenyl	8
2B	3-chlorophenyl	8
1C	cyclohexyl	8
2C	2-thienyl	5
3C	3-thienyl	5

Example 21

(*R*)-Quinuclidin-3-yl (3-(9-(2-(4-hydroxy-2-oxo-2,3-dihydrobenzo[d]thiazol-7-yl)ethylamino)nonyloxy)phenyl)-(phenyl)methylcarbamate (compound 21)

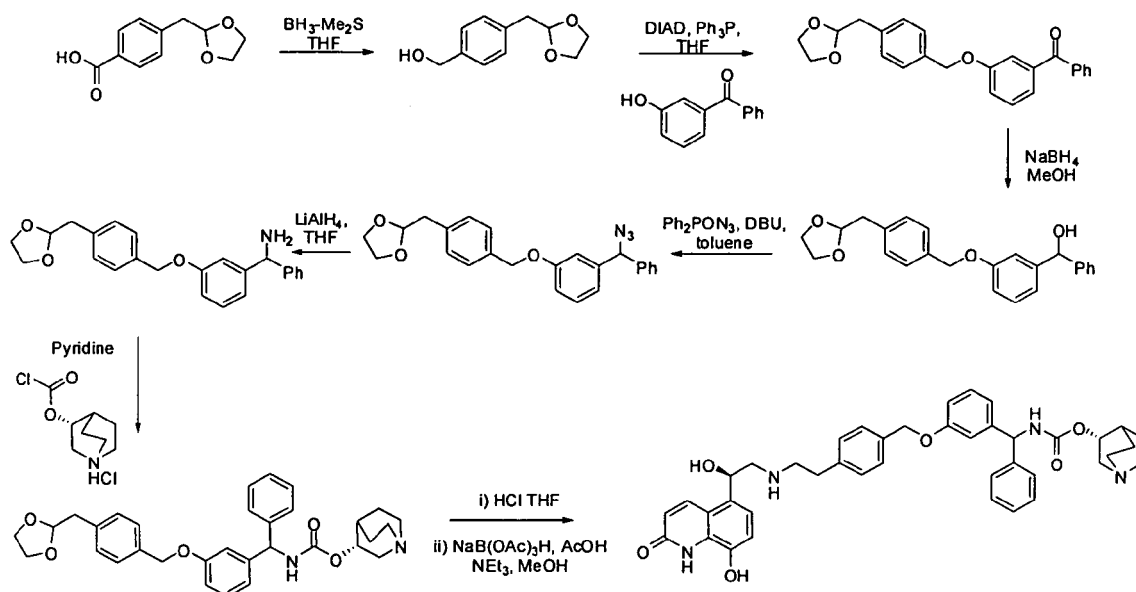
5



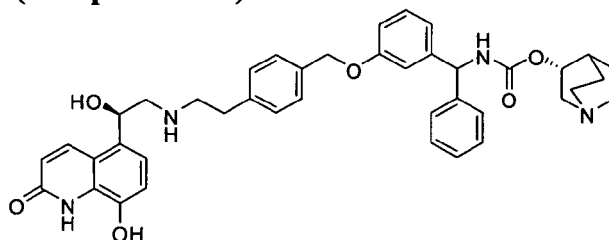
The preparation of **compound 21** requires **7-(2-aminoethyl)-4-hydroxybenzo[d]thiazol-2(3H)-one hydrobromide** (prepared as described in Organic Process Research & Development **2004**, 8, 628-642) replacing **(*R*)-5-(2-amino-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one hydrochloride** in **Example 1 Step 7**. The additional steps required to make the title compound are described in **Example 1**.

10

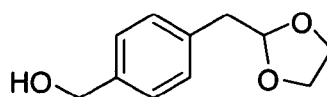
Scheme for Example 22

**Example 22**

- 5 **(*R*)-Quinuclidin-3-yl (3-(4-(2-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)ethyl)benzyloxy)phenyl)(phenyl)-methylcarbamate (compound 22)**

**Step 1; (4-((1,3-Dioxolan-2-yl)methyl)phenyl)methanol**

10

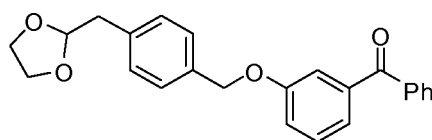


- To a cooled (0°C) solution of 4-((1,3-dioxolan-2-yl)methyl)benzoic acid (1.02 g, 4.92 mmol) in anhydrous THF (63.5 mL), a solution of borane dimethylsulfide complex (2.0 M in THF, 12.29 mL, 24.59 mmol) was added dropwise. The reaction mixture was stirred at this temperature for 5 minutes and then the coolant removed. The reaction mixture was stirred at RT for 16 hours. The reaction mixture was cooled to 0°C and methanol (1 mL) was
- 15

added. The reaction mixture was diluted with water and saturated aqueous sodium hydrogen carbonate and then extracted with ethyl acetate (x 2). The combined organic extracts were washed with brine, dried (magnesium sulphate) filtered and concentrated under reduced pressure. The crude material
5 was purified by silica gel chromatography eluting with 0-50% ethyl acetate in *iso*-hexane to afford the title compound (0.936 g, 98%).

^1H NMR (400 MHz, CDCl_3): δ 7.29 (m, 4 H), 5.08-5.02 (m, 1 H), 4.67 (d, J = 5.97 Hz, 2 H), 4.00-3.78 (m, 4 H), 2.97 (d, J = 4.82 Hz, 2 H), 1.61-1.58 (m, 1H).

**Step 2; (3-(4-((1,3-Dioxolan-2-yl)methyl)benzyloxy)phenyl)-
10 (phenyl)methanone**



To a cooled (0°C) solution of (4-((1,3-dioxolan-2-yl)methyl)phenyl)methanol (0.45 g, 2.317 mmol), 3-hydroxybenzophenone
15 (0.551 g, 2.78 mmol) and triphenylphosphine (0.729 g, 2.78 mmol) in anhydrous THF, di-*iso*-propylazodicarboxylate (1.027 mL, 2.78 mmol) was added dropwise. The reaction mixture was allowed to warm to RT and stirred at this temperature for 16 hours. The reaction mixture was diluted with ethyl acetate and washed with 10% aqueous potassium carbonate, brine and dried
20 (magnesium sulphate). The suspension was filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography eluting with 100% *iso*-hexane to 25% ethyl acetate in *iso*-hexane to afford the title compound (1.022 g, >100%).

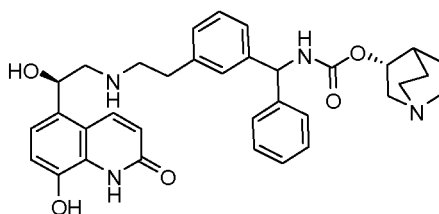
^1H NMR (400 MHz, CDCl_3): δ 7.82-7.76 (m, 2 H), 7.63-7.55 (m, 1 H),
25 7.51-7.16 (m, 10 H), 5.11-5.05 (m, 3 H), 3.98-3.92 (m, 2 H), 3.87-3.82 (m, 2 H), 2.98 (d, J = 4.8 Hz, 2 H).

The title compound was prepared as described in **Example 1** with (3-(4-

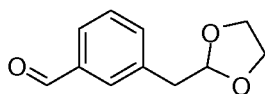
((1,3-Dioxolan-2-yl)methyl)benzyloxy)phenyl)(phenyl)methanone replacing (3-(8-(1,3-Dioxolan-2-yl)octyloxy)phenyl)(phenyl)methanone in **Step 2**. The additional steps required to make the target compound are described in **Example 1**.

Example 23

(*R*)-Quinuclidin-3-yl (3-(2-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)ethyl)phenyl)(phenyl)methylcarbamate (compound 23)



Step 1; 3-((1,3-Dioxolan-2-yl)methyl)benzaldehyde



To a solution of 3-((1,3-dioxolan-2-yl)methyl)phenyl)methanol (prepared as in **Example 22, Step 1** with 3-((1,3-dioxolan-2-yl)methyl)benzoic acid replacing 4-((1,3-dioxolan-2-yl)methyl)benzoic acid; 0.47 g, 2.42 mmol) in 1,4-dioxane (8 mL), manganese (IV) oxide (2.35 g) was added. The resulting suspension was heated at 100°C for 16 hours. The reaction mixture was allowed to cool and the suspension filtered through a pad of celite. The celite pad was washed with ethyl acetate and the filtrate evaporated at reduced pressure to afford the title compound (0.352 g, 76%).

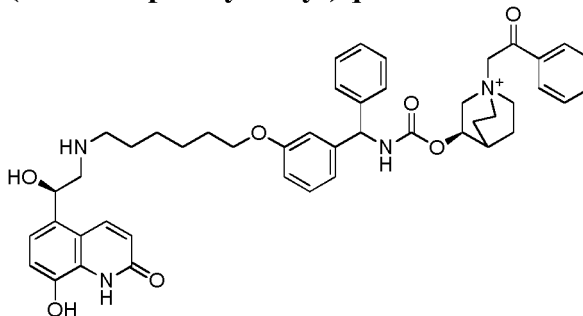
¹H NMR (400 MHz, CDCl₃): δ 10.01 (s, 1 H), 7.79-7.74 (m, 2 H), 7.56 (dt, J = 7.6, 1.5 Hz, 1 H), 7.51-7.43 (m, 1 H), 5.13-5.08 (m, 1 H), 3.96-3.81 (m, 4 H), 3.06 (d, J = 4.6 Hz, 2 H).

The title compound was prepared as described in **Example 2** with 3-((1,3-dioxolan-2-yl)methyl)benzaldehyde replacing 3-(8-(1,3-dioxolan-2-

yl)octyloxy)benzaldehyde in **Step 2**. The additional steps required to make the target compound are described in **Example 1**.

Example 24

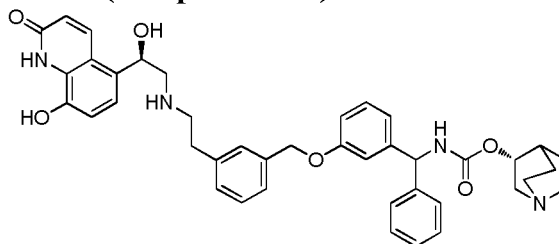
(3R)-3-((((3-((6-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)(phenyl)methyl)-
carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium



To a solution of (*R*)-quinuclidin-3-yl (3-(6-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)-phenyl)(phenyl)methylcarbamate (**Example 4**, 0.02 g, 0.03 mmol) in methanol (0.5 mL) was added a solution of 2-bromoacetophenone (0.007 g, 0.04 mmol) in methanol (0.5 mL). The reaction mixture was stirred at RT for 1 hour. Further 2-bromoacetophenone (0.007 g, 0.04 mmol) added and the reaction continued for 15 minutes. The solvent was evaporated at reduced pressure.
 The residue was purified by reverse phase preparative HPLC to afford the title compound (0.010 g, 43%).

Example 25

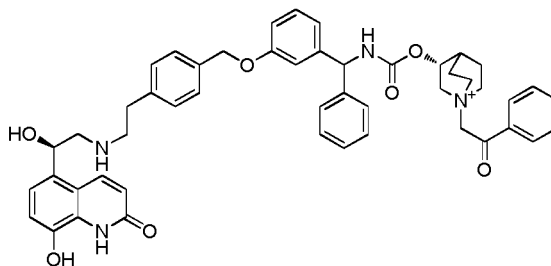
(*R*)-quinuclidin-3-yl (3-(3-(2-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)ethyl)benzyloxy)phenyl)(phenyl)-
methylcarbamate formate (compound 3B)



The title compound was prepared as described in **Example 22** with 3-((1,3-dioxolan-2-yl)methyl)benzoic acid replacing 4-((1,3-dioxolan-2-yl)methyl)benzoic acid in **Step 1**. The additional steps required to make the target compound are described in the preparation of **Example 1**.

5 **Example 26**

(3*R*)-3-((((3-((4-(2-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzyl)oxy)phenyl)(phenyl)-methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (compound 4B)



10

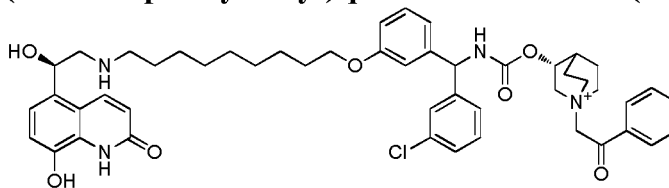
The title compound was prepared as described in **Example 24** with (*R*)-quinuclidin-3-yl (3-(4-(2-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzyloxy)phenyl)(phenyl)-methylcarbamate (**Example 22**) replacing (*R*)-quinuclidin-3-yl (3-(6-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyloxy)-phenyl)(phenyl)methylcarbamate.

15

Example 27

(3*R*)-3-((((3-chlorophenyl)(3-((9-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)methyl)-carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (compound 5B)

20

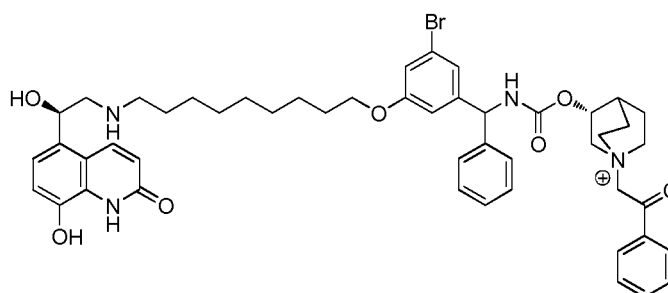


The title compound was prepared as described in **Example 24** with (*R*)-quinuclidin-3-yl (3-chlorophenyl)(3-(9-((*R*)-2-hydroxy-2-(8-hydroxy-

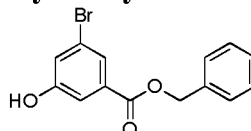
2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)-methylcarbamate (Example 26) replacing (*R*)-quinuclidin-3-yl (3-(6-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)-(phenyl)methylcarbamate.

5 **Example 28**

(3*R*)-3-((((3-bromo-5-((9-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)(phenyl)methyl)-carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (compound 6B)

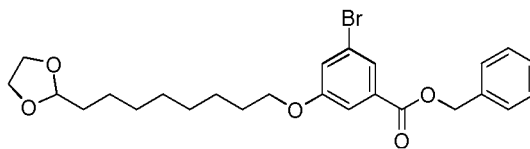


10 **Step 1; Benzyl 3-bromo-5-hydroxybenzoate**



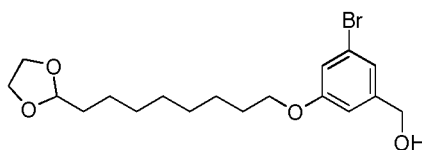
To a stirred solution of 3-bromo-5-hydroxybenzoic acid (2 g, 9.22 mmol) in dimethyl formamide (50 mL) was added potassium carbonate (1.27 g, 9.21 mmol) and stirred at 0°C for 20 minutes. Benzyl bromide (1.1 mL, 9.25 mmol) was added and the reaction mixture allowed to warm to room temperature over 16 hours. The reaction mixture was diluted with water and extracted with ethyl acetate (x 3). The combined organic extracts were washed with brine, dried (magnesium sulphate), filtered and concentrated under reduced pressure to afford the title compound (2.85 g, quantitative yield).

¹H NMR (400 MHz, CDCl₃): δ 7.75-7.72 (m, 1 H); 7.51-7.48 (m, 1 H); 7.45-7.34 (m, 5 H); 7.24-7.21 (m, 1 H); 5.34 (s, 2 H)

Step 2; Benzyl 3-((8-(1,3-dioxolan-2-yl)octyl)oxy)-5-bromobenzoate

To a stirred solution of benzyl 3-bromo-5-hydroxybenzoate (2.85 g, 9.22 mmol) in dimethyl formamide (50 mL) was added 2-(8-bromooctyl)-1,3-dioxolane (2.44 g, 9.21 mmol) and potassium carbonate (1.91 g, 13.8 mmol) and stirred at 80°C for 16 hours. The reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate (x 3). The combined organic extracts were washed with brine, dried (magnesium sulphate), filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography eluting with 0-7% ethyl acetate in *iso*-hexane to afford the title compound (2.94 g, 65%).

¹H NMR (400 MHz, CDCl₃): δ 7.76-7.75 (m, 1 H); 7.51-7.50 (m, 1 H); 7.45-7.34 (m, 5 H); 7.23-7.22 (m, 1 H); 5.35 (s, 2 H); 4.84 (t, J = 4.8 Hz; 1 H); 4.00-3.94 (m, 4 H); 3.86-3.83 (m, 2 H); 1.80-1.73 (m 2 H); 1.68-1.63 (m, 2 H); 1.44-1.22 (m, 10 H).

Step 3; (3-((8-(1,3-Dioxolan-2-yl)octyl)oxy)-5-bromophenyl)methanol

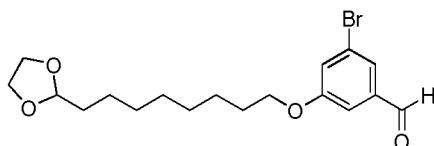
To a solution of benzyl 3-((8-(1,3-dioxolan-2-yl)octyl)oxy)-5-bromobenzoate in tetrahydrofuran (30 mL) at -78°C was added a solution of lithium aluminium hydride in THF (2.0 M, 3.3 mL, 6.60 mmol). The reaction mixture was stirred for 4 hours, then quenched with water (0.25 mL), 2 M sodium hydroxide (0.25 mL) and water (0.75 mL). The coolant was removed and ethyl acetate and magnesium sulphate was added and the mixture stirred at room temperature for 20 minutes. The suspension was filtered, washed with

ethyl acetate and the filtrate was concentrated under reduced pressure. The crude material was purified by silica gel chromatography eluting with 0-17% ethyl acetate in *iso*-hexane to afford the title compound as a 10:7 ratio of product to starting material (1.69 g, 73%).

5 ^1H NMR (400 MHz, CDCl_3): δ 7.08 (s, 1 H); 6.97-6.96 (m, 1 H); 6.84 (m, 1 H); 4.84 (t, $J = 4.8$ Hz, 1 H); 4.66-4.63 (m, 2 H); 3.99-3.89 (m, 4 H); 3.84-3.81 (m, 2 H); 1.79-1.74 (m, 2 H); 1.66-1.63 (m, 2 H); 1.45-1.42 (m, 10 H).

Step 4; 3-((8-(1,3-Dioxolan-2-yl)octyl)oxy)-5-bromobenzaldehyde

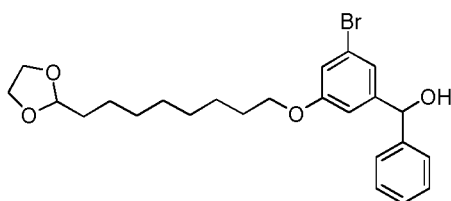
10



To a stirred solution of (3-((8-(1,3-dioxolan-2-yl)octyl)oxy)-5-bromophenyl)methanol (1.69 g, 4.36 mmol) in 1,4-dioxane (25 mL) was added magnesium (IV) oxide (1.90 g, 21.9 mmol). The reaction mixture was heated
15 to 100°C for 16 hours. The suspension was filtered, washed with ethyl acetate and the filtrate was concentrated under reduced pressure to afford the title compound (1.25 g, 74%).

^1H NMR (400 MHz, CDCl_3): δ 9.89 (s, 1 H); 7.56 (m, 1 H); 7.31 (m, 2 H); 4.85 (t, $J = 4.8$ Hz, 1 H); 4.10-3.95 (m 4 H); 3.86-3.83 (m, 2 H); 1.82-1.75
20 (m, 2 H); 1.69-1.63 (m, 2 H); 1.45-1.34 (m, 10 H).

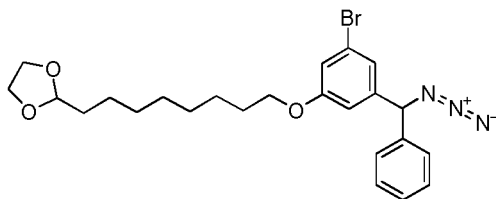
Step 5; (3-((8-(1,3-Dioxolan-2-yl)octyl)oxy)-5-bromophenyl)(phenyl)methanol



The title compound was prepared as described in **Example 10 Step 2** with **3-((8-(1,3-dioxolan-2-yl)octyl)oxy)-5-bromobenzaldehyde** and phenylmagnesium bromide replacing 3-(8-(1,3-dioxolan-2-yl)octyloxy)benzaldehyde and 2-thienylmagnesium bromide respectively.

¹H NMR (400 MHz, CDCl₃): δ 7.38-7.27 (m, 5 H); 7.10 (d, J = 1.52 Hz, 1 H); 6.95-6.91 (m, 1 H); 6.87 (s, 1 H); 5.74 (d, J = 3.46 Hz, 1 H); 4.84 (t, J = 4.83 Hz, 1 H); 3.99-3.93 (m, 2 H); 3.90 (t, J = 6.48 Hz, 2 H); 3.87-3.81 (m, 2 H); 2.28 (d, J = 4.43 Hz, 1 H); 1.78-1.60 (m, 4 H); 1.37 (d, J = 34.79 Hz, 10 H).

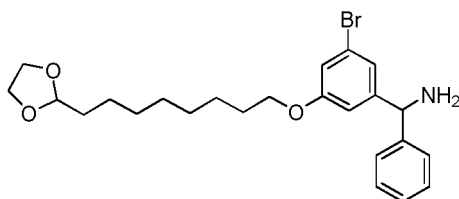
Step 6; 2-(8-(3-(Azido(phenyl)methyl)-5-bromophenoxy)octyl)-1,3-dioxolane



The title compound was prepared as described in **Example 1 Step 3** with **(3-((8-(1,3-dioxolan-2-yl)octyl)oxy)-5-bromophenyl)(phenyl)methanol** replacing **(3-(8-(1,3-dioxolan-2-yl)octyloxy)phenyl)(phenyl)methanol**.

¹H NMR (400 MHz, CDCl₃): δ 7.40-7.19 (m, 5 H); 7.11-6.91 (m, 1 H); 6.97-6.95 (m, 1 H); 6.78 (s, 1 H); 5.61 (s, 1 H); 4.84 (t, J = 4.83 Hz, 1 H); 3.98-3.93 (m, 2 H); 3.92-3.86 (m, 2 H); 3.88-3.82 (m, 2 H); 1.79-1.61 (m, 4 H); 1.53-1.25 (m, 10 H).

Step 7; (3-((8-(1,3-Dioxolan-2-yl)octyl)oxy)-5-bromophenyl)(phenyl)methanamine

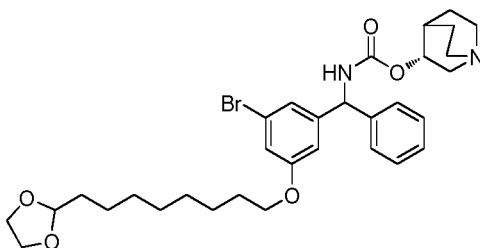


To a stirred reaction of **2-(8-(3-(Azido(phenyl)methyl)-5-**

bromophenoxy)octyl)-1,3-dioxolane (1.19 g, 2.45 mmol) in tetrahydrofuran (15 mL) and water (0.3 mL) was added triphenylphosphine (0.71 g, 2.69 mmol). The reaction mixture was heated to 60°C for 16 hours. The reaction mixture was cooled, concentrated and purified by silica gel chromatography eluting with 0-100% ethyl acetate in *iso*-hexane to afford impure title compound as a colourless oil (0.77 g, 68%).

¹H NMR (400 MHz, CDCl₃): δ 7.38-7.29 (m, 5 H); 7.11 (t, J = 1.55 Hz, 1 H); 6.94-6.84 (m, 2 H); 5.12 (s, 1 H); 4.84 (t, J = 4.83 Hz, 1 H); 3.99-3.94 (m, 2 H); 3.93-3.81 (m, 4 H); 1.77-1.60 (m, 4 H); 1.48-1.28 (m, 10 H).

Step 8; (*R*)-quinuclidin-3-yl ((3-((8-(1,3-dioxolan-2-yl)octyl)oxy)-5-bromophenyl)(phenyl)methyl)carbamate



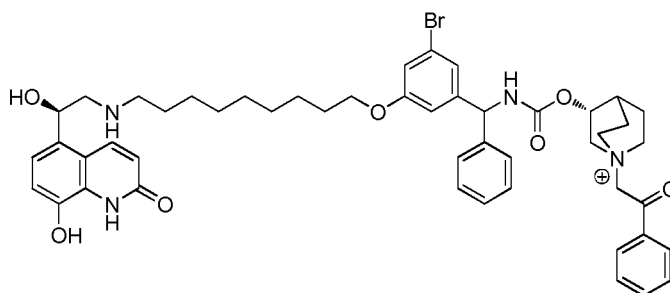
The title compound was prepared as described in **Example 1, Step 5** with **(3-((8-(1,3-dioxolan-2-yl)octyl)oxy)-5-bromophenyl)(phenyl)-methanamine** replacing **(3-(8-(1,3-dioxolan-2-yl)octyloxy)phenyl)(phenyl)-methanamine**.

Step 9; (*R*)-quinuclidin-3-yl ((3-bromo-5-((9-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)-(phenyl)methyl)carbamate

The title compound was prepared as described in **Example 1 Steps 6 and 7** with **(*R*)-quinuclidin-3-yl ((3-((8-(1,3-dioxolan-2-yl)octyl)oxy)-5-bromophenyl)(phenyl)methyl)carbamate** replacing **(*R*)-quinuclidin-3-yl (3-(8-(1,3-dioxolan-2-yl)octyloxy)phenyl)(phenyl)methylcarbamate** in **Step 6** and **(*R*)-Quinuclidin-3-yl ((3-bromo-5-((9-oxononyl)oxy)phenyl)(phenyl)-**

methyl)carbamate replacing (*R*)-quinuclidin-3-yl (3-(9-oxononyloxy)-phenyl)(phenyl)methylcarbamate in Step 7.

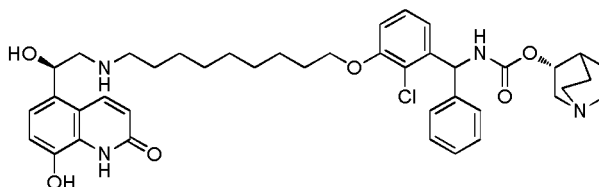
Step 10; (3*R*)-3-((((3-bromo-5-((9-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)(phenyl)-methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (compound 6B)



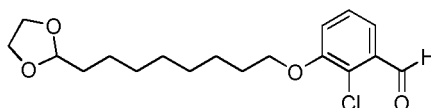
The title compound was prepared as described in **Example 24** with (*R*)-quinuclidin-3-yl ((3-bromo-5-((9-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)(phenyl)methyl)-carbamate replacing (*R*)-quinuclidin-3-yl (3-(6-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)-(phenyl)methylcarbamate.

Example 29

(*R*)-quinuclidin-3-yl (2-chloro-3-(9-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)(phenyl)-methylcarbamate (compound 7B)



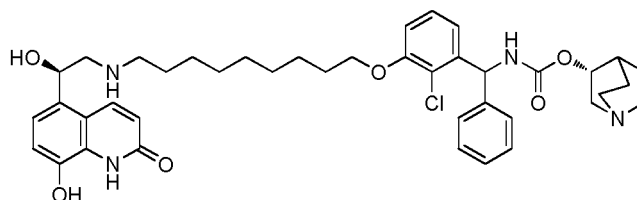
Step 1; 3-((8-(1,3-Dioxolan-2-yl)octyl)oxy)-2-chlorobenzaldehyde



The title compound was prepared as described in **Example 10 Step 1** with 2-chloro-3-hydroxybenzaldehyde replacing 3-hydroxybenzaldehyde.

¹H NMR (400 MHz, CDCl₃-d): δ 10.53 (d, J = 0.92 Hz, 1 H); 7.51 (d, J = 7.79 Hz, 1 H); 7.35-7.26 (m, 1 H); 7.15 (d, J = 8.16 Hz, 1 H); 4.86-4.81 (m, 1 H); 4.09-4.02 (m, 2 H); 4.00-3.93 (m, 2 H); 3.91-3.81 (m, 2 H); 1.91-1.76 (m, 3 H); 1.70-1.19 (m, 11 H).

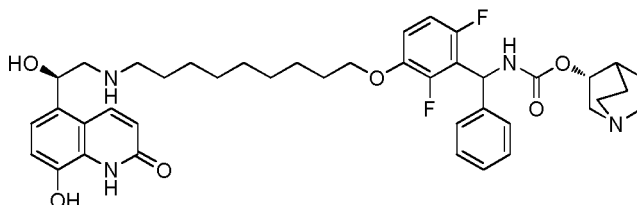
Step 2; (R)-quinuclidin-3-yl (2-chloro-3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)-(phenyl)methylcarbamate (compound 7B)



The title compound was prepared as in **Example 10** with 3-((8-(1,3-dioxolan-2-yl)octyl)oxy)-2-chlorobenzaldehyde replacing 3-((8-(1,3-dioxolan-2-yl)octyl)oxy)-benzaldehyde in **Step 2** and using the subsequent steps described in **Example 1**.

Example 30

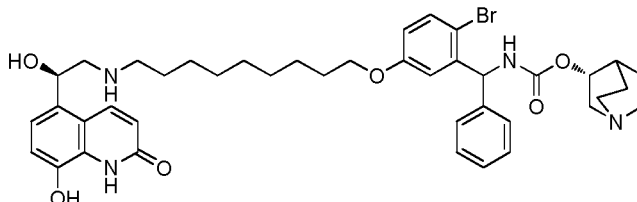
(R)-quinuclidin-3-yl ((2,6-difluoro-3-((9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)-(phenyl)methylcarbamate (compound 8B)



The title compound was prepared as described for **Example 29** from the commercially available 2,6-difluoro-3-hydroxybenzaldehyde.

Example 31

(*R*)-quinuclidin-3-yl ((2-bromo-5-((9-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)-(phenyl)methyl)carbamate (compound 9B)



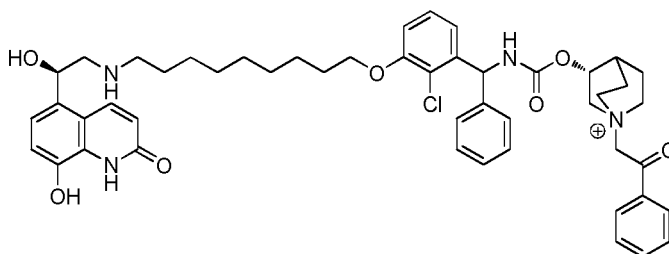
5

The title compound was prepared as described for **Example 19** from the commercially available 2-bromo-5-hydroxybenzaldehyde.

Example 32

(3*R*)-3-((((2-chloro-3-((9-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)(phenyl)methyl)-carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (compound 10B)

10



15

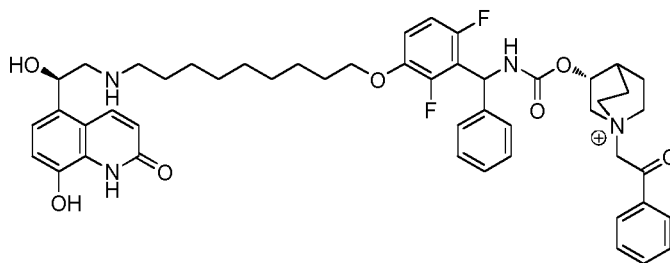
The title compound was prepared as described in **Example 24** with (*R*)-quinuclidin-3-yl (2-chloro-3-(9-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyloxy)phenyl)(phenyl)-methylcarbamate (**Example 31**) replacing (*R*)-quinuclidin-3-yl (3-(6-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyloxy)phenyl)(phenyl)methylcarbamate.

20

Example 33

(3*R*)-3-((((2,6-difluoro-3-((9-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-

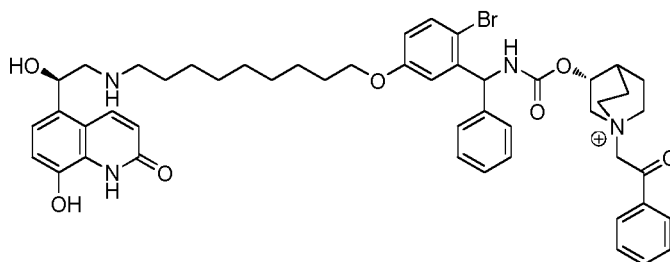
**1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)(phenyl)methyl)-
carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (compound
11B)**



5 The title compound was prepared as described in **Example 24** with (*R*)-
quinuclidin-3-yl ((2,6-difluoro-3-((9-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-
1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)(phenyl)methyl)-
carbamate (**Example 30**) replacing (*R*)-quinuclidin-3-yl (3-(6-((*R*)-2-
10 hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)-
hexyloxy)phenyl)(phenyl)methylcarbamate.

Example 34

(3*R*)-3-(((2-bromo-5-((9-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-
dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)(phenyl)methyl)-
carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (compound
15 **12B)**

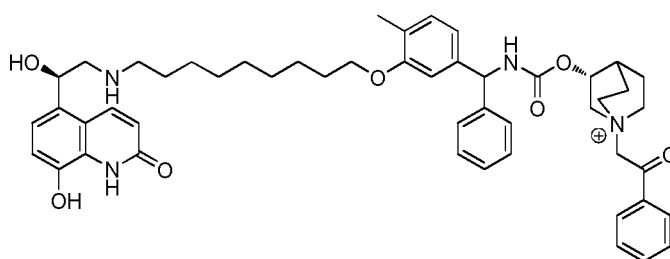


The title compound was prepared as described in **Example 24** with (*R*)-
quinuclidin-3-yl ((2-bromo-5-((9-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-
dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)(phenyl)methyl)-
20 carbamate replacing (*R*)-quinuclidin-3-yl (3-(6-((*R*)-2-hydroxy-2-(8-

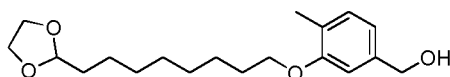
hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)-(phenyl)methylcarbamate.

Example 35

(3R)-3-((((3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-4-methylphenyl)(phenyl)-methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (compound 13B)



Step 1; (3-((8-(1,3-dioxolan-2-yl)octyl)oxy)-4-methylphenyl)-methanol

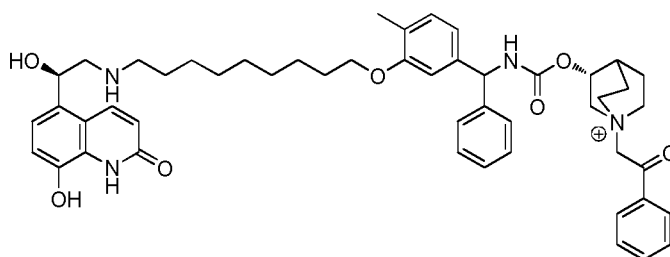


To a stirred solution of 5-(hydroxymethyl)-2-methylphenol (0.57 g, 4.15 mmol) in dimethyl formamide (15 mL) was added 2-(8-bromooctyl)-1,3-dioxolane (1.00 g, 3.77 mmol) and potassium carbonate (0.63 g, 4.57 mmol) and stirred at 80°C for 16 hours. The reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate (x 3). The combined organic extracts were washed with brine, dried (magnesium sulphate), filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography eluting with 0-7% ethyl acetate in *iso*-hexane to afford the title compound (0.5 g, 41%).

¹H NMR (400 MHz, DMSO-d₆): δ 7.06 (d, J = 8 Hz, 1 H); 6.86 (s, 1 H); 6.77 (d, J = 8 Hz, 1 H); 5.10 (d, J = 5.6 Hz, 1 H); 4.75 (t, J = 4.8 Hz, 1 H); 4.44 (d, J = 5.6 Hz, 2 H); 3.94 (t, J = 6.4 Hz, 2 H); 3.86-3.84 (m, 2 H); 3.76-

3.74 (m, 2 H); 2.11 (s, 3 H); 1.73 (m, 2 H); 1.53 (m, 2 H); 1.35-1.30 (m, 10 H).

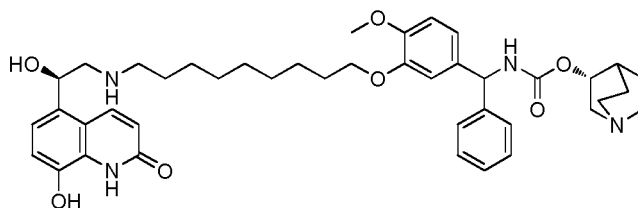
Step 2; (3R)-3-((((3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-4-methylphenyl)(phenyl)-methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
(compound 13B)



The title compound was prepared as described in **Example 18 Steps 4 to 9** with (3-((8-(1,3-dioxolan-2-yl)octyl)oxy)-4-methylphenyl)methanol replacing (3-((8-(1,3-dioxolan-2-yl)octyl)oxy)-5-bromophenyl)methanol in **Step 4** and the products used in the subsequent steps.

Example 36

(R)-quinuclidin-3-yl ((3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-4-methoxyphenyl)(phenyl)methyl)carbamate (compound 14B)

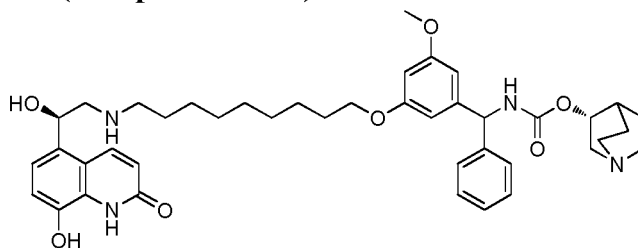


The title compound was prepared as described for **Example 29** from the commercially available 3-hydroxy-4-methoxybenzaldehyde.

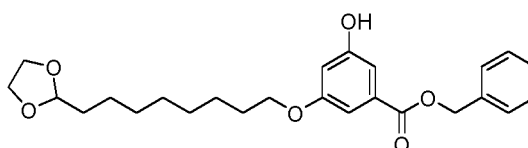
Example 37

(R)-quinuclidin-3-yl ((3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-5-methoxyphenyl)(phenyl)-

methyl)carbamate (compound 15B)



Step 1; Benzyl 3-((8-(1,3-dioxolan-2-yl)octyl)oxy)-5-hydroxybenzoate

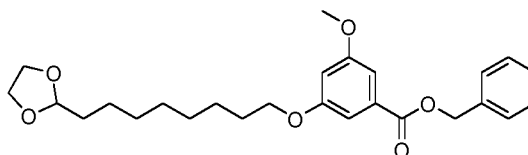


5

The title compound was prepared as described in **Example 28 Step 1** and **2** with 3,5-dihydroxybenzoic acid replacing 5-bromo-3-hydroxybenzoic acid in **Step 1** and the product used in the subsequent step.

Step 2; Benzyl 3-((8-(1,3-dioxolan-2-yl)octyl)oxy)-5-methoxybenzoate

10



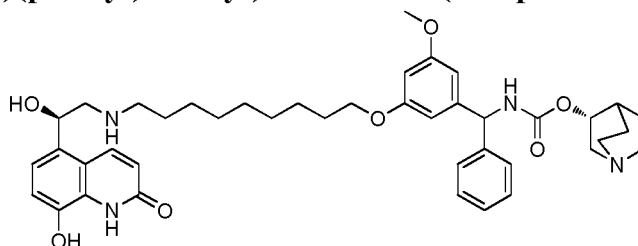
To an ice-cooled solution of benzyl 3-((8-(1,3-dioxolan-2-yl)octyl)oxy)-5-hydroxybenzoate (1.94 g, 4.53 mmol) in dimethyl formamide (25 mL) was added potassium carbonate (0.93 g, 6.75 mmol) followed by iodomethane (0.42 mL, 6.75 mmol). The reaction mixture was allowed to warm to room temperature over 16 hours and stood at room temperature for 3 days. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated under reduced pressure to afford the title compound (1.76 g, 88%).

20

¹NMR (400 MHz, CDCl₃-d): 7.45-7.32 (m, 5 H); 7.20-7.18 (m, 2 H); 6.64-6.63 (m, 1 H); 5.35 (s, 2 H); 4.84 (t, J = 4.8 Hz, 1 H); 4.10-3.92 (m, 4 H);

3.86-3.82 (m, 5 H); 1.80-1.73 (m, 2 H); 1.68-1.63 (m, 2 H); 1.46-1.34 (m, 10 H).

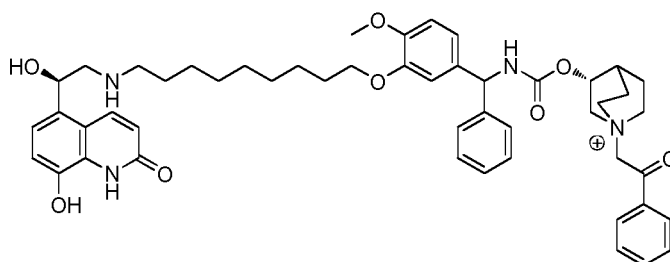
Step 3; (*R*)-quinuclidin-3-yl ((3-((9-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-5-methoxyphenyl)(phenyl)methyl)carbamate (compound 15B)



The title compound was prepared as described in **Example 28 Steps 3** through **9** with **benzyl 3-((8-(1,3-dioxolan-2-yl)octyl)oxy)-5-methoxybenzoate** replacing **benzyl 3-((8-(1,3-dioxolan-2-yl)octyl)oxy)-5-bromobenzoate** in **Step 3** and the product used in the subsequent steps.

Example 38

(3*R*)-3-(((3-((9-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-4-methoxyphenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (compound 16B)

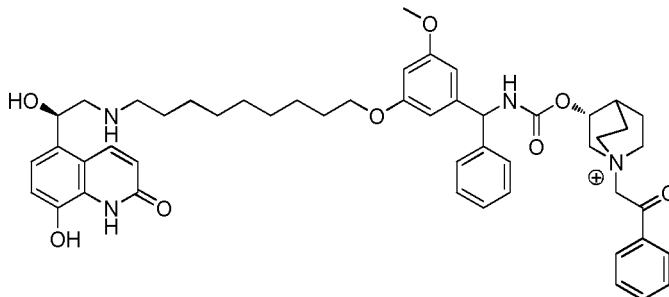


The title compound was prepared as described in **Example 24** with (*R*)-quinuclidin-3-yl ((3-((9-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-4-methoxyphenyl)(phenyl)methyl)carbamate (**Example 36**) replacing (*R*)-quinuclidin-3-yl (3-(6-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

yl)ethylamino)hexyloxy)phenyl)(phenyl)methylcarbamate.

Example 39

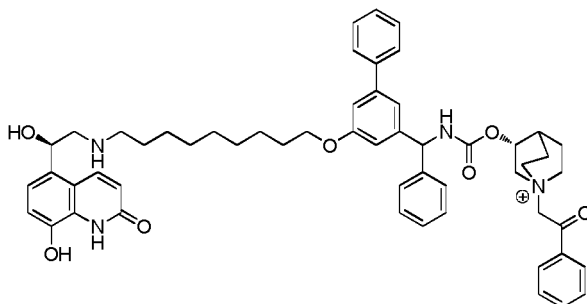
(3R)-3-((((3-((9-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-5-methoxyphenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (compound 17B)



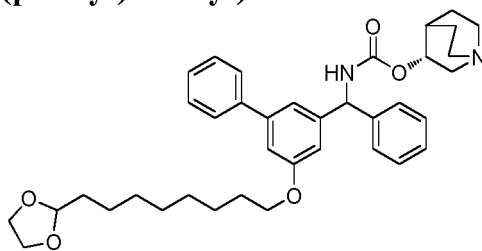
The title compound was prepared as described in **Example 24** with (*R*)-quinuclidin-3-yl ((3-((9-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-5-methoxyphenyl)(phenyl)-methyl)carbamate (**Example 36**) replacing (*R*)-quinuclidin-3-yl (3-(6-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)(phenyl)methylcarbamate.

Example 40

(3R)-3-((((5-((9-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-[1,1'-biphenyl]-3-yl)-(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (compound 18B)



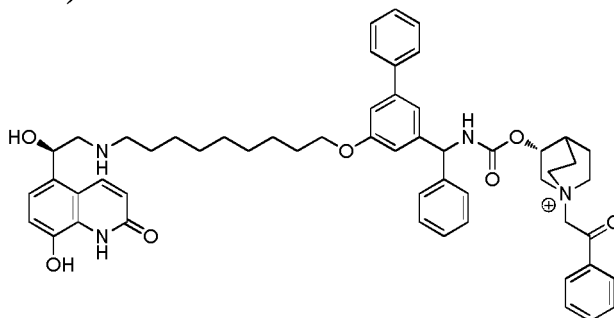
Step 1; (*R*)-quinuclidin-3-yl ((5-((8-(1,3-dioxolan-2-yl)octyl)oxy)-

[1,1'-biphenyl]-3-yl)(phenyl)methyl)carbamate

To a stirred solution of (*R*)-quinuclidin-3-yl ((3-((8-(1,3-dioxolan-2-yl)octyl)oxy)-5-bromophenyl)(phenyl)methyl)carbamate (0.2 g, 0.33 mmol) (prepared in **Example 28 Step 8**) in toluene (4 mL) and water (1 mL) was added phenyl boronic acid (0.04 g, 0.33 mmol), sodium carbonate (0.07 g, 0.66 mmol) and tetrakis (triphenylphosphine) palladium (0) (0.04 g, 0.03 mmol). The reaction mixture was heated in the microwave at 120°C for 30 minutes. The solvent was removed under reduced pressure, diluted with water and extracted with ethyl acetate (x 3). The combined organic extracts were dried (sodium sulphate), filtered and solvent removed under reduced pressure. The crude material was purified by silica gel chromatography eluting with 0-10% methanol in ethyl acetate to afford the title compound as a colourless oil (0.14 g, 71%).

¹H NMR (400 MHz, CDCl₃): δ 7.53 (d, *J* = 7.56 Hz, 2 H); 7.44-7.38 (m, 2 H); 7.38-7.27 (m, 6 H); 7.06 (s, 1 H); 7.01 (s, 1 H); 6.78 (s, 1 H); 5.95 (br s, 1 H); 5.4 (br s, 1 H); 4.86-4.81 (t, *J* = 4.81 Hz, 1 H); 4.77-4.71 (m, 1 H); 3.99-3.92 (m, 4 H); 3.86-3.81 (m, 2 H); 3.2-2.6 (m, 6 H); 2.03 (s, 1 H); 1.80-1.71 (m, 2 H); 1.7-1.3 (m, 15 H).

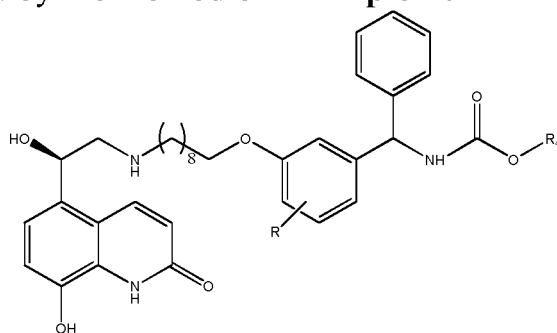
Step 2; 3R)-3-((((5-((9-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-[1,1'-biphenyl]-3-yl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (compound 18B)



5

The title compound was prepared as described in **Example 28 Steps 9 and 10** with (*R*)-quinuclidin-3-yl ((5-((8-(1,3-dioxolan-2-yl)octyl)oxy)-[1,1'-biphenyl]-3-yl)(phenyl)methyl)carbamate replacing (*R*)-quinuclidin-3-yl ((3-bromo-5-((9-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)(phenyl)methyl)carbamate in **Step 9** and the product used in the subsequent steps.

Also prepared by the method of **Example 40**

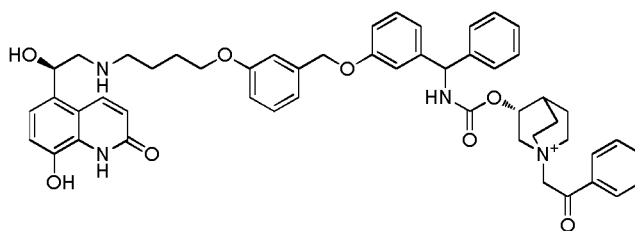
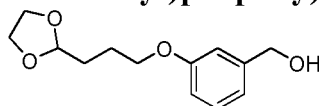


Compound	R	R ₄
19B	2-thienyl	

15

Example 41

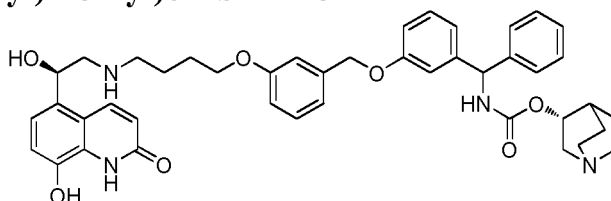
(3R)-3-((((3-((3-(4-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)benzyl)oxy)phenyl)-(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium

(compound 20B)**Step 1; (3-(3-(1,3-Dioxolan-2-yl)propoxy)phenyl)methanol**

5 To an ice-cooled solution of 3-(3-(1,3-dioxolan-2-yl)propoxy)benzaldehyde (prepared as in **Example 10; Step 1**) (3.08 g, 13.1 mmol) in ethanol (66 mL) was added sodium borohydride (1.98 g, 52.4 mmol). The reaction mixture was allowed to warm to ambient temperature and stirred at ambient temperature for 16 hours. The reaction mixture was
 10 carefully quenched with saturated aqueous ammonium chloride and extracted twice with DCM. The combined organic phases were poured through a hydrophobic column and the solvent evaporated at reduced pressure to afford the title compound as a colourless oil (2.96 g, 95%).

¹H NMR (400 MHz, CDCl₃): δ 7.25 (m, 1 H), 6.93-6.88 (m, 2 H), 6.82
 15 (m, 1 H), 4.93 (m, 1 H), 4.66 (m, 2 H), 4.02-3.92 (m, 4 H), 3.87 (m, 2 H), 1.96-1.77 (m, 5 H).

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



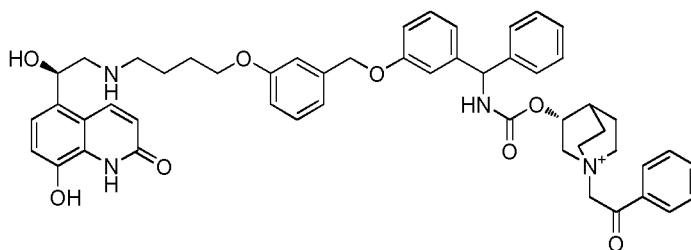
20

The title compound was prepared as described in **Example 22** with (3-(3-(1,3-dioxolan-2-yl)propoxy)phenyl)methanol replacing (4-((1,3-dioxolan-2-yl)methyl)phenyl)methanol in **Step 2**. The additional steps required to make the

target compound are described in the preparation of **Example 1**.

¹H NMR (400 MHz, CD₃OD): δ 8.56 (s, 1 H); 8.38 (d, J = 9.9 Hz, 1 H); 7.33-7.20 (m, 8 H); 7.07-6.85 (m, 7 H); 6.70-6.65 (m, 1 H); 5.87 (s, 1 H); 5.43-5.36 (m, 1 H); 5.03 (s, 2 H); 4.92 (m, 1H); 4.08-4.02 (m, 2 H); 3.51-3.50 (m, 1 H); 3.27-3.06 (m, 9 H); 2.30-1.60 (m, 9 H).

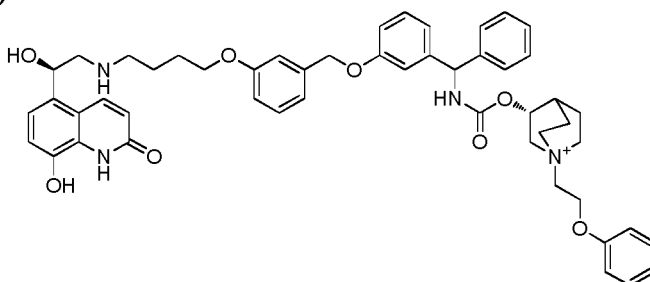
Step 3; (3R)-3-((((3-((3-(4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)benzyl)oxy)phenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium



The title compound was prepared as described in **Example 24** with (*R*)-quinuclidin-3-yl ((3-((3-(4-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)benzyl)oxy)phenyl)-(phenyl)methyl)carbamate replacing (*R*)-quinuclidin-3-yl (3-(6-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)(phenyl)methylcarbamate.

Example 42

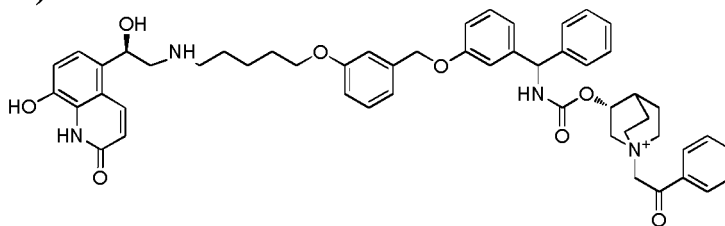
(3R)-3-((((3-((3-(4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)benzyl)oxy)phenyl)-(phenyl)methyl)carbamoyl)oxy)-1-(2-phenoxyethyl)quinuclidin-1-ium (compound 21B)



The title compound was prepared as in **Example 24** with **(R)-quinuclidin-3-yl** ((3-((3-(4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)benzyl)oxy)phenyl)-(phenyl)methyl)carbamate replacing **(R)-quinuclidin-3-yl** (3-(6-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)-hexyloxy)phenyl)(phenyl)methylcarbamate and β -bromophenetole replacing 2-bromoacetophenone.

Example 43

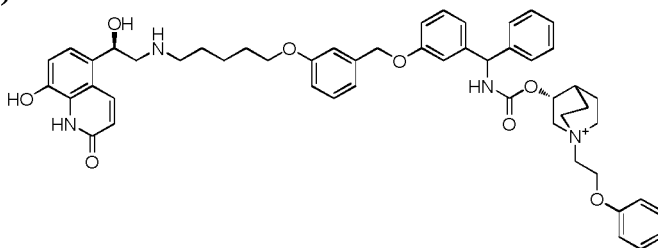
(3R)-3-((((3-(((5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl)oxy)benzyl)oxy)phenyl)-(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
(compound 22B)



The title compound was prepared as described in **Example 22** with **(3-(4-(1,3-dioxolan-2-yl)butyloxy)phenyl)methanol** replacing **(3-(3-(1,3-dioxolan-2-yl)propoxy)phenyl)methanol** in **Step 2**. The additional steps required to make the target compound are described in the preparation of **Example 1** and **Example 44**.

Example 44

(3R)-3-((((3-(((5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl)oxy)benzyl)oxy)phenyl)-(phenyl)methyl)carbamoyl)oxy)-1-(2-phenoxyethyl)quinuclidin-1-ium
(compound 23B)

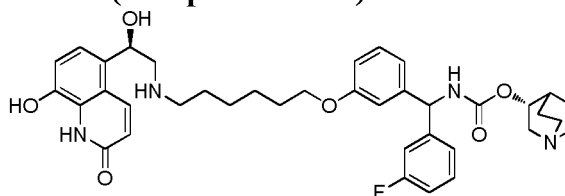


The title compound was prepared as in **Example 24** with **(R)-**

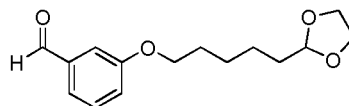
quinuclidin-3-yl ((3-((3-((5-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl)oxy)benzyl)oxy)phenyl)-(phenyl)methyl)carbamate replacing (*R*)-quinuclidin-3-yl (3-(6-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)-hexyloxy)phenyl)(phenyl)methylcarbamate and β -bromophenetole replacing 2-bromoacetophenone.

Example 45

(*R*)-quinuclidin-3-yl (3-fluorophenyl)(3-(6-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)-phenyl)methylcarbamate (compound 24B)



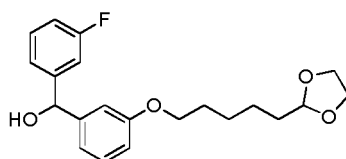
Step 1; 3-((5-(1,3-dioxolan-2-yl)pentyl)oxy)benzaldehyde



The title compound was prepared as described in **Example 10 Step 1** with 2-(5-bromopentyl)-1,3-dioxolane replacing 2-(8-bromooctyl)-1,3-dioxolane.

^1H NMR (400 MHz, CDCl_3): δ 9.99-9.92 (m, 1 H); 7.47-7.36 (m, 3 H); 7.19-7.13 (m, 1 H); 4.89-4.83 (m, 1 H); 4.04-3.82 (m, 6 H); 1.90-1.78 (m, 2 H); 1.74-1.65 (m, 2 H); 1.58-1.48 (m, 4 H).

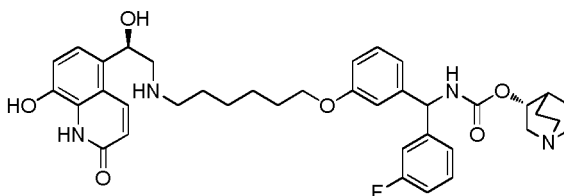
Step 2; (3-((5-(1,3-dioxolan-2-yl)pentyl)oxy)phenyl)(3-fluorophenyl)methanol



The title compound was prepared as described in **Example 10 Step 2** with 3-fluorophenylmagnesium bromide and 3-((5-(1,3-dioxolan-2-yl)pentyl)oxy)benzaldehyde replacing 2-thienylmagnesium bromide and 3-(8-(1,3-dioxolan-2-yl)octyloxy)benzaldehyde respectively.

¹H NMR (400 MHz, CDCl₃): δ 7.32- 7.08 (m, 4 H); 6.98-6.89 (m, 3 H); 6.87-6.77 (m, 1 H); 5.79-5.75 (m, 1 H); 4.88-4.82 (m, 1 H); 4.01-3.78 (m, 6 H); 2.35-2.25 (m, 1 H); 1.82-1.65 (m, 4 H); 1.54-1.44 (m, 4 H).

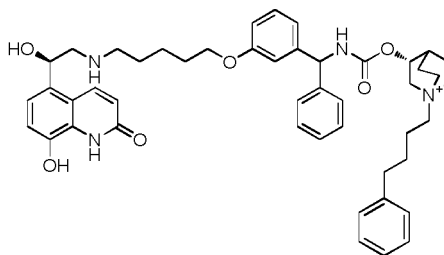
Step 3; (R)-quinuclidin-3-yl (3-(3-fluorophenyl)(3-(6-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)-phenyl)methylcarbamate



The additional steps required to prepare the title compound are described in **Example 1 Steps 3** through **7**.

Example 46

(3R)-3-((((3-((5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl)oxy)phenyl)(phenyl)-methyl)carbamoyl)oxy)-1-(4-phenylbutyl)quinuclidin-1-ium (compound 25B)

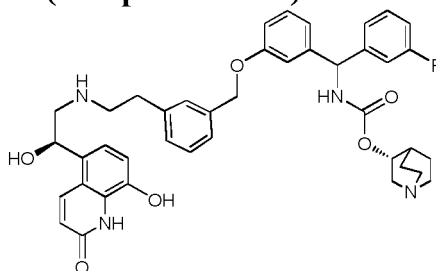


The title compound was prepared as in **Example 24** with **(R)-quinuclidin-3-yl (3-(5-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)pentyloxy)phenyl)(phenyl)-methylcarbamate (Example 5)** replacing **(R)-quinuclidin-3-yl (3-(6-((R)-2-**

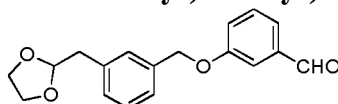
hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)-hexyloxy)phenyl)(phenyl)methylcarbamate and (4-bromobutyl)benzene replacing 2-bromoacetophenone.

Example 47

5 **(R)-Quinuclidin-3-yl (3-fluorophenyl)(3-(3-(2-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)ethyl)benzyloxy)-phenyl)methylcarbamate (compound 26B)**

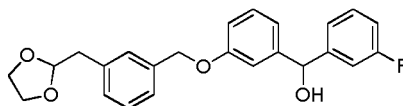


Step 1; 3-((3-((1,3-Dioxolan-2-yl)methyl)benzyl)oxy)benzaldehyde



10 The title compound was prepared as described in **Example 22** with (3-((1,3-dioxolan-2-yl)methyl)phenyl)methanol and 3-hydroxybenzaldehyde replacing (4-((1,3-dioxolan-2-yl)methyl)phenyl)methanol and 3-hydroxybenzophenone respectively in **Step 2**

15 **Step 2; (3-((3-((1,3-Dioxolan-2-yl)methyl)benzyl)oxy)phenyl)(3-fluorophenyl)methanol**

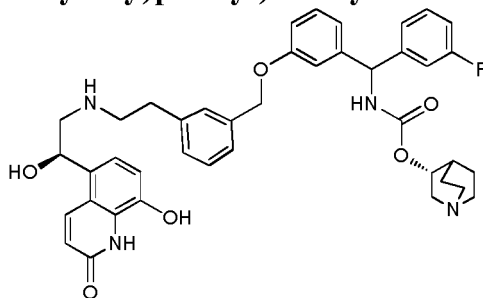


20 The title compound was prepared as described in **Example 10 Step 2** with 3-fluorophenylmagnesium bromide and 3-((3-((1,3-dioxolan-2-yl)methyl)benzyl)oxy)benzaldehyde replacing 2-thienylmagnesium bromide and 3-(8-(1,3-dioxolan-2-yl)octyloxy)benzaldehyde respectively.

¹H NMR (400 MHz, CDCl₃): δ 7.34-7.21 (m, 6 H); 7.13-7.06 (m, 2 H); 7.00 (t, J = 2.0 Hz, 1 H); 6.97-6.87 (m, 3 H); 5.77 (d, J = 3.5 Hz, 1 H);

5.10-4.99 (m, 3 H); 3.94-3.87 (m, 2 H); 3.88-3.78 (m, 2 H); 2.97 (d, J = 4.8 Hz, 2 H); 2.35 (d, J = 3.5 Hz, 1 H).

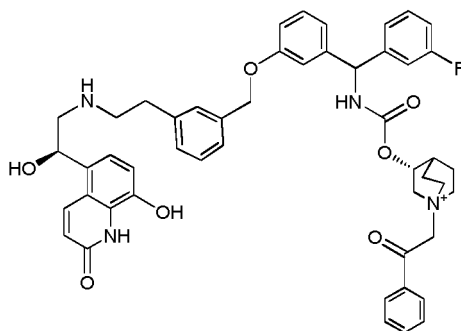
Step 3; (R)-Quinuclidin-3-yl (3-fluorophenyl)(3-(3-(2-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)ethyl)benzyloxy)phenyl)methylcarbamate (compound 27B)



The title compound was prepared using the additional steps described in **Example 1 Steps 3 through 7.**

Example 48

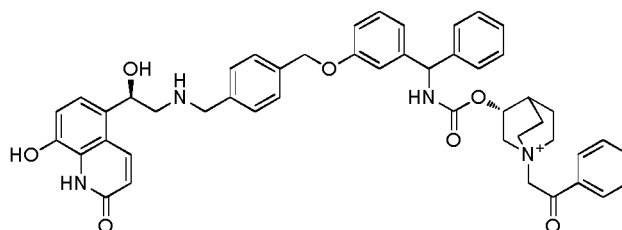
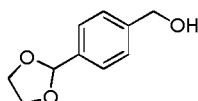
(3R)-3-((((3-fluorophenyl)(3-((3-(2-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzyl)oxy)phenyl)-methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (compound 27B)



The title compound was prepared as in **Example 24** with **(R)-quinuclidin-3-yl (3-fluorophenyl)(3-(3-(2-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)ethyl)benzyloxy)-phenyl)methylcarbamate** replacing **(R)-quinuclidin-3-yl (3-(6-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)(phenyl)methylcarbamate**.

Example 49

(3R)-3-((((3-(((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)benzyl)oxy)phenyl)(phenyl)-methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium
(compound 28B)

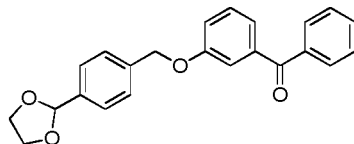
**Step 1; (4-(1,3-Dioxolan-2-yl)phenyl)methanol**

A mixture of terephthalaldehyde (5.4 g, 40 mmol), *para*-toluenesulfonic acid – monohydrate (0.4 g, 2 mmol) and ethylene glycol in toluene (80 mL) was heated at 110°C for 4 hours. The reaction mixture was allowed to cool and was washed with saturated sodium hydrogen carbonate and dried with anhydrous magnesium sulphate. The filtrate was evaporated at reduced pressure to afford a
 oil. The oil was dissolved in ethanol (200 mL) and then the reaction mixture cooled to 0°C. Sodium borohydride (5.9 g, 160 mmol) was added portionwise and the resultant reaction mixture allowed to warm to ambient temperature over 16 hours. The reaction mixture was quenched with saturated sodium hydrogen carbonate and subsequently extracted twice with ethyl acetate. The combined
 organic extracts were dried with anhydrous magnesium sulphate and the solvent evaporated at reduced pressure. The crude material was purified by silica gel chromatography eluting with 100% *iso*-hexane to 50% ethyl acetate in *iso*-hexane to afford the title compound as a colourless oil (3.4 g, 48%).

¹H NMR (400 MHz, CDCl₃): δ 7.47 (d, J = 8 Hz, 2 H); 7.37 (d, J = 8 Hz, 2 H); 5.81 (s, 1 H); 4.69 (d, J = 5.6 Hz, 2 H); 4.14 (m, 2 H); 4.05 (m, 2 H),

1.83 (d, $J = 6$ Hz, 1 H).

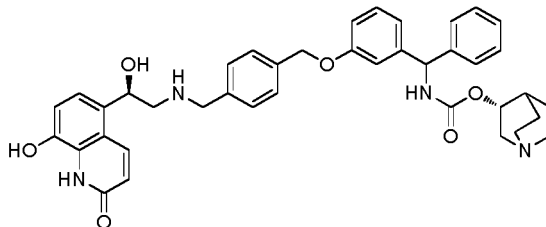
Step 2; (3-((4-(1,3-Dioxolan-2-yl)benzyl)oxy)phenyl)-(phenyl)methanone



5 The title compound was prepared as described in **Example 22** with **(4-(1,3-dioxolan-2-yl)phenyl)methanol** replacing **(4-((1,3-dioxolan-2-yl)methyl)phenyl)methanol** in **Step 2**.

^1H NMR (400 MHz, CDCl_3): δ 7.79-7.76 (m, 2 H); 7.58 (m, 1 H); 7.52-7.35 (m, 9 H); 7.20 (m, 1 H); 5.83 (s, 1 H); 5.13 (s, 2 H); 4.15 (m, 2 H);
10 4.06 (m, 2 H).

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

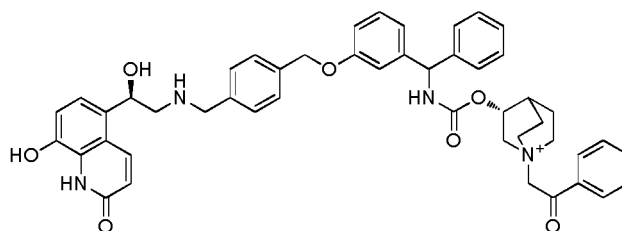


15 The title compound was prepared using the additional steps described in **Example 1 Steps 3 through 7**.

^1H NMR (400 MHz, DMSO-d_6): δ 8.37 (m, 1 H); 8.31 (s, 2 H); 8.16 (m, 1 H); 7.44-7.42 (m, 4 H); 7.38-7.34 (m, 5 H); 7.30-7.26 (m, 2 H); 7.13 (d, $J = 8.4$ Hz, 1 H); 7.08 (s, 1 H); 6.99-6.92 (m, 3 H); 6.55 (d, $J = 10$ Hz, 1 H); 5.87 (d, $J =$
20 9.6 Hz, 1 H); 5.21 (m, 1 H); 5.09 (s, 2 H); 4.72 (m, 1 H); 3.93 (s, 2 H); 3.32 (m, 1 H); 2.95-2.73 (m, 6 H); 2.06 (s, 1 H); 1.92 (s, 1 H); 1.74-1.51 (m, 3 H)

Step 4; (3R)-3-((3-(4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)methyl)benzyloxy)phenyl)(phenyl)-methylcarbamoyloxy)-1-(2-oxo-2-phenylethyl)-1-

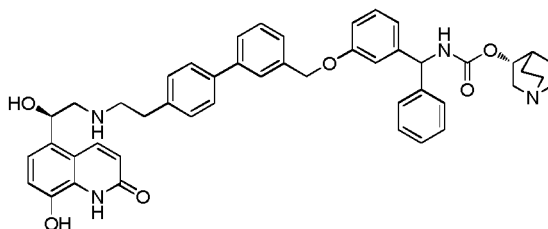
azoniabicyclo[2.2.2]octane



The title compound was prepared as in **Example 24** with *(R)*-
 5 **quinuclidin-3-yl** ((3-((4-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-
 dihydroquinolin-5-yl)ethyl)amino)methyl)benzyl)oxy)phenyl)(phenyl)-
 methyl)carbamate replacing *(R)*-quinuclidin-3-yl (3-(6-((*R*)-2-hydroxy-2-
 (8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)-
 (phenyl)methylcarbamate.

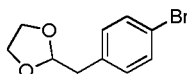
10 **Example 50**

(R)-Quinuclidin-3-yl (3-((4'-(2-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-
 1,2-dihydroquinolin-5-yl)ethylamino)ethyl)biphenyl-3-
 yl)methoxy)phenyl)(phenyl)methylcarbamate (compound 29B)



15

Step 1; 2-(4-Bromobenzyl)-1,3-dioxolane

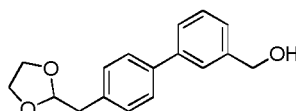


To a cooled (0°C) solution of 4-bromophenethylalcohol (3.9 g, 19.4
 20 mmol) in DCM (50 mL) was added the Dess-Martin reagent (8.22 g, 19.4
 mmol). After 10 minutes the coolant was removed and the reaction mixture
 was stirred at ambient temperature for 2 hours. The reaction mixture was
 quenched with 10% aqueous potassium carbonate and the mixture separated.
 The aqueous phase was extracted with further DCM (x 2) and the combined

organic phases were dried with anhydrous magnesium sulphate and the solvent evaporated at reduced pressure. The crude material was purified by silica gel chromatography eluting with 100% *iso*-hexane to 50% ethyl acetate in *iso*-hexane to afford a oil. The oil was dissolved in toluene (35 mL), *para*-toluenesulfonic acid – monohydrate (0.1 g, 0.52 mmol) and ethylene glycol (5.3 mL, 94.2 mmol) was added and the mixture heated at reflux under Dean and Stark conditions for 2 hours. The solvent was evaporated at reduced pressure and the residue dissolved in ethyl acetate. The solution was washed with 10% aqueous potassium carbonate, dried with anhydrous magnesium sulphate and the solvent evaporated at reduced pressure. The crude material was purified by silica gel chromatography eluting with 100% *iso*-hexane to 50% ethyl acetate in *iso*-hexane to afford an oil (2.3 g, 49%).

¹H NMR (400 MHz, CDCl₃): δ 7.52-7.36 (m, 2 H); 7.19-7.06 (m, 2 H); 5.03 (t, J = 4.6 Hz, 1 H); 3.95-3.85 (m, 2 H); 3.86-3.76 (m, 2 H); 2.93-2.86 (m, 2 H).

Step 2; (4'-((1,3-Dioxolan-2-yl)methyl)-[1,1'-biphenyl]-3-yl)methanol

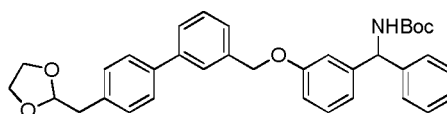


A mixture of 2-(4-bromobenzyl)-1,3-dioxolane (2.0 g, 8.2 mmol), 3-formylboronic acid (2.45 g, 16.4 mmol), tetrakis-(triphenylphosphine)-palladium (0) (0.763 g, 0.66 mmol) and sodium carbonate (1.74 g, 16.4 mmol) in dioxane/water (15 mL / 3 mL) in a microwave vessel was degassed in a stream of nitrogen for 10 minutes. The vessel was sealed and heated in the microwave at 125°C for 30 minutes. The solvent was decanted off and the solid residues washed with ethyl acetate. The organic phases were combined and the solvent evaporated at reduced pressure. The crude material was purified by silica gel chromatography eluting with 100% *iso*-hexane to 50% ethyl acetate in *iso*-hexane to afford an oil. The oil was dissolved in methanol

(25 mL) and cooled to 0°C. Sodium borohydride (0.393 g, 10.4 mmol) was added portion-wise and the reaction mixture was stirred at 0°C for 30 minutes followed by 1 hour at ambient temperature. The reaction mixture was quenched with water and extracted twice with ethyl acetate. The combined organic extracts were dried with anhydrous magnesium sulphate and the solvent evaporated at reduced pressure. The crude material was purified by silica gel chromatography eluting with 100% *iso*-hexane to 100% ethyl acetate in *iso*-hexane to afford the title compound (1.16 g, 52%).

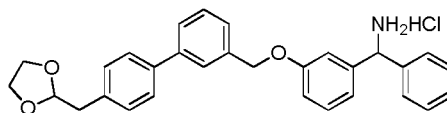
¹H NMR (400 MHz, CDCl₃): δ 7.58-7.45 (m, 4 H); 7.44-7.30 (m, 4 H); 5.09 (t, J = 4.8 Hz, 1 H); 4.73 (d, J = 5.0 Hz, 2 H); 3.99-3.83 (m, 4 H); 3.00 (d, J = 4.8 Hz, 2 H); 2.05-1.98 (m, 1 H).

Step 3; *tert*-butyl ((3-((4'-((1,3-dioxolan-2-yl)methyl)-[1,1'-biphenyl]-3-yl)methoxy)phenyl)(phenyl)methyl)carbamate



The title compound was prepared as described in **Example 22 Step 2** with (4'-((1,3-dioxolan-2-yl)methyl)-[1,1'-biphenyl]-3-yl)methanol and *tert*-butyl (3-hydroxyphenyl)(phenyl)methylcarbamate replacing (4-((1,3-dioxolan-2-yl)methyl)phenyl)methanol and 3-hydroxybenzophenone respectively.

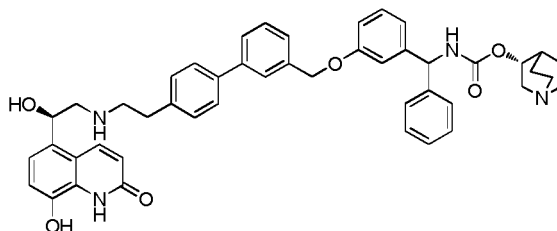
Step 4; (3-((4'-((1,3-dioxolan-2-yl)methyl)-[1,1'-biphenyl]-3-yl)methoxy)phenyl)(phenyl)methanamine hydrochloride



To a solution of *tert*-butyl ((3-((4'-((1,3-dioxolan-2-yl)methyl)-[1,1'-biphenyl]-3-yl)methoxy)phenyl)(phenyl)methyl)carbamate (1.44 g, 2.6 mmol) in methanol (6.5 mL) was added hydrogen chloride in dioxane (6.5 mL). The reaction mixture was stirred at ambient temperature for 16 hours. The solvent was evaporated to afford a mixture of the title compound and the

corresponding dimethyl acetal. The material was used in the next step without further purification.

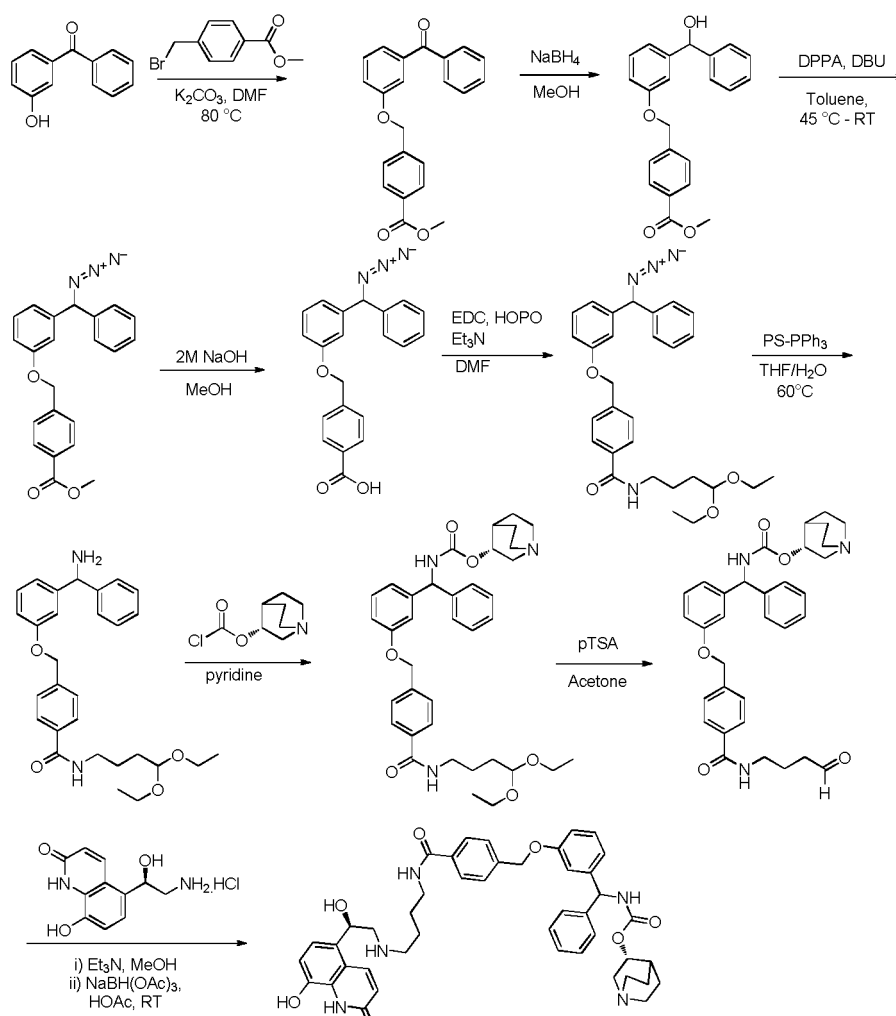
Step 5; (R)-Quinuclidin-3-yl (3-((4'-(2-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)ethyl)biphenyl-3-yl)methoxy)phenyl)(phenyl)methylcarbamate (compound 29B)



The title compound was prepared using the additional steps described in **Example 1 Steps 3 through 7.**

10

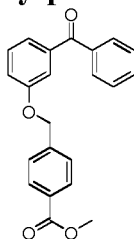
Synthetic scheme for the preparation of ester and amide analogues



Example 51

(R)-quinuclidin-3-yl ((3-((4-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)carbamoyl)benzyl)oxy)-phenyl)(phenyl)methyl)carbamate (compound 30B)

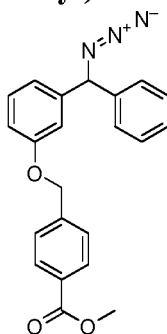
5 **Step 1; Methyl 4-((3-benzoylphenoxy)methyl)benzoate**



To a stirred solution of 3-hydroxybenzophenone (1.00 g, 5.04 mmol) in dimethyl formamide (10 mL) was added potassium carbonate (1.05 g, 7.61 mmol) and stirred for 10 minutes at room temperature. Methyl 4-
10 bromobenzoate (1.30 g, 6.05 mmol) in dimethyl formamide (5 mL) was added and the reaction mixture allowed to stir at room temperature for 16 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was washed with brine, dried (MgSO₄) and concentrated under reduced pressure. The crude material was purified by silica gel
15 chromatography eluting with 0-17% ethyl acetate in *iso*-hexane to afford the title compound (1.64 g, 99%).

¹H NMR (400 MHz, CDCl₃): δ 8.07 (d, J = 8.4 Hz, 2 H); 7.79 (d, J = 8.4 Hz, 2 H); 7.61-7.57 (m, 1 H); 7.52-7.37 (m, 8 H); 5.18 (s, 2 H); 3.93 (s, 3 H).

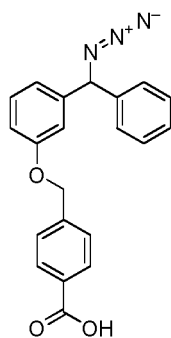
Step 2; Methyl 4-((3-(azido(phenyl)methyl)phenoxy)-methyl)benzoate



To an ice-cooled suspension of methyl 4-((3-benzoylphenoxy)methyl)benzoate (1.62 g, 4.88 mmol) in methanol (20 mL) was added sodium borohydride (0.27 g, 7.32 mmol). The reaction mixture was allowed to warm to room temperature over 2 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic extracts were washed with brine, dried (MgSO₄) and concentrated under reduced pressure to afford an oil. To a solution of the oil in toluene (25 mL) was added diphenylphosphoryl azide (1.26 mL, 5.85 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (881 µL, 5.85 mmol). The reaction mixture was stirred at 100°C for 3 hours. The reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate and washed with water, brine, dried (magnesium sulphate), filtered and concentrated. The crude material was purified by silica gel chromatography eluting with 0-10% ethyl acetate in *iso*-hexane to afford the title compound (1.62 g, 92% over 2 steps).

¹H NMR (400 MHz, CDCl₃): δ 8.05-8.03 (m, 2 H); 7.48-7.46 (m, 2 H); 7.39-7.25 (m, 6 H); 6.93-6.88 (m, 3 H); 5.67 (s, 1 H); 5.10 (s, 2 H); 3.92 (s, 3 H).

Step 3: 4-((3-(Azido(phenyl)methyl)phenoxy)methyl)benzoic acid

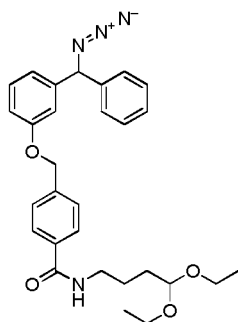


To a stirred suspension of methyl 4-((3-(azido(phenyl)methyl)phenoxy)methyl)benzoate (1 g, 2.79 mmol) in methanol (25 mL) was added 2M sodium hydroxide (25 mL). The reaction was allowed to stir at room temperature for 3 days. Tetrahydrofuran (10 mL)

was added to the reaction mixture and stirred at 50°C for 4 hours followed by 16 hours at room temperature. The reaction mixture was acidified with 10% hydrochloric acid, extracted with dichloromethane, dried (sodium sulphate), filtered and concentrated under reduced pressure to give the title compound (1 g, quantitative).

¹H NMR (400 MHz, CDCl₃): δ 8.10 (d, J = 8.09 Hz, 2 H); 7.51 (d, J = 8.03 Hz, 2 H); 7.38-7.27 (m, 6 H); 6.95-6.88 (m, 3 H); 5.67 (s, 1 H); 5.12 (s, 2 H).

Step 4; 4-((3-(Azido(phenyl)methyl)phenoxy)methyl)-N-(4,4-diethoxybutyl)benzamide

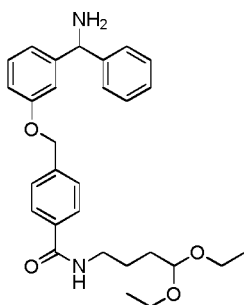


To a stirred solution of **4-((3-(azido(phenyl)methyl)phenoxy)-methyl)benzoic acid** (0.5 g, 1.39 mmol) in dimethyl formamide (14 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.29 g, 1.53 mmol), 2-hydroxypyridine-N-oxide (0.16 g, 1.53 mmol) and triethylamine (0.49 mL, 3.48 mmol). The reaction mixture was stirred at room temperature for 10 minutes. 4-Amino-butyraldehyde diethyl ether (0.27 g, 1.67 mmol) was added and the reaction mixture stirred at room temperature for 16 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic extracts were washed with brine, dried (sodium sulphate), filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography eluting with 0-100% ethyl

acetate in *iso*-hexane to afford the title compound as a colourless oil (0.51 g, 73%).

¹H NMR (400 MHz, CDCl₃): δ 7.78 (d, J = 8.08 Hz, 2 H); 7.46 (d, J = 7.94 Hz, 2 H); 7.40-7.24 (m, 6 H); 6.94-6.83 (m, 3 H); 6.52 (s, 1 H); 5.67 (s, 1 H); 5.08 (s, 2 H); 4.58-4.48 (m, 1 H); 3.72-3.62 (m, 2 H); 3.56-3.46 (m, 4 H); 1.83-1.69 (m, 4 H); 1.21 (t, J = 7.04 Hz, 6 H).

Step 5; 4-((3-(Amino(phenyl)methyl)phenoxy)methyl)-N-(4,4-diethoxybutyl)benzamide

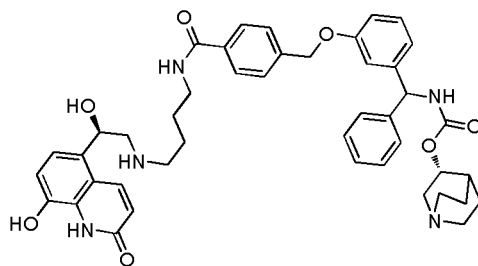


To a solution of 4-((3-(azido(phenyl)methyl)phenoxy)methyl)-N-(4,4-diethoxybutyl)benzamide (0.51 g, 1.03 mmol) in tetrahydrofuran (10 mL) was added polymer supported triphenylphosphine (3 mmol/g, 0.38 g, 1.13 mmol) and water (0.2 mL). The reaction mixture was stirred at 60°C for 16 hours. The reaction mixture was allowed to cool to room temperature, filtered, the filter-cake washed with dichloromethane and concentrated under reduced pressure to give the title compound (0.41 g, 83%).

¹H NMR (400 MHz, CDCl₃): δ 7.76 (d, J = 8.04 Hz, 2 H); 7.48 (d, J = 10.02 Hz, 2 H); 7.37-7.19 (m, 5 H); 7.03 (d, J = 2.34 Hz, 1 H); 6.98 (d, J = 7.60 Hz, 1 H); 6.83 (d, J = 2.79 Hz, 1 H); 6.41 (s, 1 H); 5.18 (s, 1 H); 5.02 (s, 2 H); 4.56-4.50 (m, 1 H); 3.67 (dq, J = 9.43, 7.05 Hz, 2 H); 3.56-3.45 (m, 4 H); 1.89-1.80 (m, 2 H); 1.73 (s, 2 H); 1.21 (t, J = 7.05 Hz, 6 H).

Step 6; (R)-Quinuclidin-3-yl ((3-((4-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)carbamoyl)-

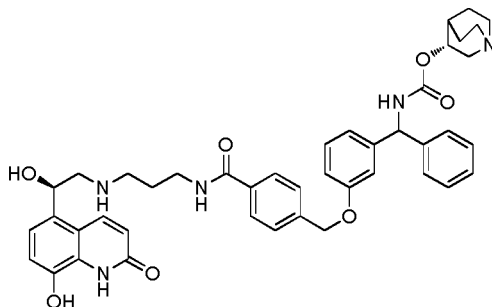
benzyl)oxy)phenyl)(phenyl)methyl)carbamate (compound 30B)



The title compound was prepared as described in **Example 1 Step 5**
 5 through 7 with 4-((3-(Amino(phenyl)methyl)phenoxy)methyl)-N-(4,4-
 diethoxybutyl)benzamide (3-(8-(1,3-dioxolan-2-yl)octyloxy)phenyl)-
 (phenyl)methanamine in **Step 5** and the product used in the subsequent steps.

Example 52

(*R*)-quinuclidin-3-yl (3-(4-(3-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-
 10 1,2-dihydroquinolin-5-yl)ethylamino)propylcarbamoyl)benzyloxy)-
 phenyl)(phenyl)methyl)carbamate (compound 31B)

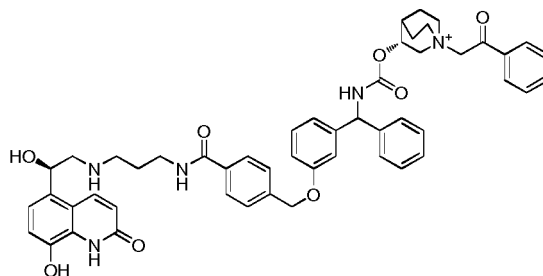


The title compound was prepared as described in **Example 51** with 3-
 15 amino-propylaldehyde diethyl ether replacing 4-amino-butyraldehyde diethyl
 ether in **Step 4** and the product used in the subsequent steps.

Example 53

(3*R*)-3-(((3-(((4-(((3-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-
 dihydroquinolin-5-yl)ethyl)amino)propyl)carbamoyl)benzyl)oxy)phenyl)-
 20 (phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium

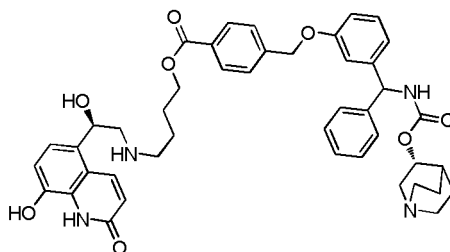
(compound 32B)



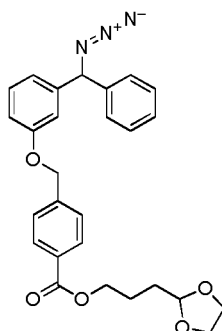
The title compound was prepared as in **Example 24** with (*R*)-quinuclidin-3-yl (3-(4-(3-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)propylcarbonyl)benzyloxy)phenyl)-(phenyl)methylcarbamate (**Example 52**) replacing (*R*)-quinuclidin-3-yl (3-(6-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)(phenyl)methylcarbamate.

Example 54

4-(((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 4-((3-(phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)-amino)methyl)phenoxy)methyl)benzoate (compound 33B)



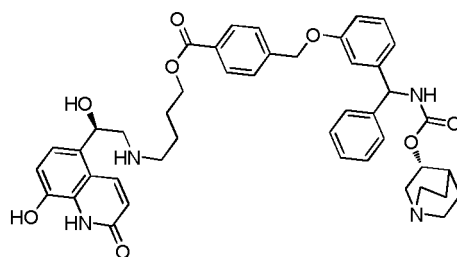
Step 1; 3-(1,3-Dioxolan-2-yl)propyl 4-((3-(azido(phenyl)methyl)phenoxy)methyl)benzoate



To a stirred solution of 3-chloropropyl-1,3-dioxolane (0.2 g, 1.35 mmol) in dimethyl formamide (14 mL) was added 4-((3-(azido(phenyl)methyl)phenoxy)methyl)benzoic acid (**Example 51 Step 3**) (0.5 g, 1.39 mmol) and potassium carbonate (0.38 g, 2.78 mmol). The reaction was allowed to stir at 80°C for 16 hours. The reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate (x 3). The organic extracts were washed with brine, dried (sodium sulphate), filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography eluting with 0-100% ethyl acetate in *iso*-hexane to afford the title compound (0.63 g, 96%).

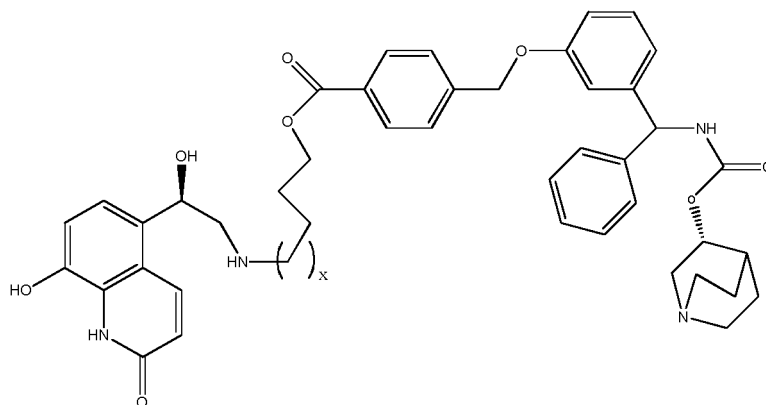
¹H NMR (400 MHz, CDCl₃): δ 7.53-7.43 (m, 2 H); 7.39-7.25 (m, 8 H); 6.92 (d, J = 5.57 Hz, 3 H); 5.67 (s, 1 H); 5.10 (s, 2 H); 4.94 (t, J = 4.40 Hz, 1 H); 4.40-4.33 (t, J = 6.39 Hz, 2 H); 4.03-3.93 (m, 2 H); 3.93-3.81 (m, 2 H); 1.96-1.79 (m, 4 H).

Step 2; 4-(((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 4-((3-(phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate (compound 33B)



The title compound was prepared as described in **Example 54 Steps 5 to 6** with 3-(1,3-dioxolan-2-yl)propyl 4-((3-(azido(phenyl)methyl)phenoxy)-methyl)benzoate replacing 4-((3-(azido(phenyl)methyl)phenoxy)methyl)-N-(4,4-diethoxybutyl)benzamide in **Step 5** and the product used in subsequent steps.

The following compounds were prepared using the appropriate bromides in **Example 55, Step 1**

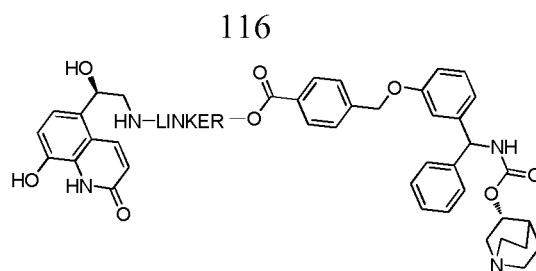


5

Compound	Bromide	x
34B	2-(4-bromobutyl)-1,3-dioxolane	2
35B	2-(5-bromopentyl)-1,3-dioxolane	3
4C	2-(6-bromohexyl)-1,3-dioxolane	4

The following compounds were prepared by coupling 4-((3-(azido(phenyl)methyl)phenoxy)methyl)benzoic acid (**Example 51 Step 3**) with the appropriate alcohol using the protocol below and the product so formed used in the subsequent steps for the preparation of **Example 51**.

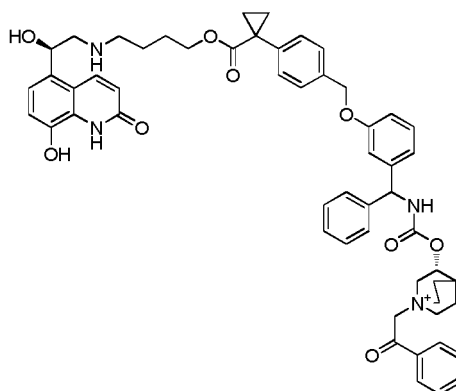
10 To a stirred solution of the 4-((3-(azido(phenyl)methyl)phenoxy)methyl)benzoic acid and the appropriate alcohol (2.0 equivalents) in DMF (0.2 M) was added diisopropylethylamine (1.5 equivalents) and HATU (1.2 equivalents). The reaction mixture was heated at 60°C for 24 hours. The reaction mixture was diluted with ethyl
 15 acetate and was washed sequentially with aqueous 1M sodium hydroxide, water and brine. The organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography eluting with 0-50% ethyl acetate in *iso*-hexane to afford the required compound.



Compound	LINKER	Appropriate alcohol
5C		
6C		
7C		
8C		

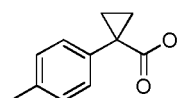
Example 56

(3R)-3-((((3-(((4-(1-(((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)carbonyl)cyclopropyl)benzyl)-oxy)phenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (compound 36B)



10

Step 1; Methyl 1-(p-tolyl)cyclopropanecarboxylate

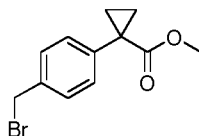


To a stirred solution of 1-(p-tolyl)cyclopropanecarboxylic acid (6 g,

34.05 mmol) in methanol (48 mL) was added para-toluenesulphonic acid monohydrate (0.648 g, 3.405 mmol). The reaction was stirred at 75°C for 16 hours. The mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic layer was washed with saturated aqueous sodium bicarbonate solution (x 2), brine and dried (magnesium sulfate), filtered and concentrated under reduced pressure to afford the title compound as an orange oil (6.279 g, 97%). The material was used directly in the next step with no further purification.

¹H NMR (400 MHz, CDCl₃): δ 7.25-7.21 (m, 2 H); 7.14-7.10 (m, 2 H); 3.62 (s, 3 H); 2.34 (s, 3 H); 1.60-1.56 (m, 2 H); 1.18-1.14 (m, 2 H).

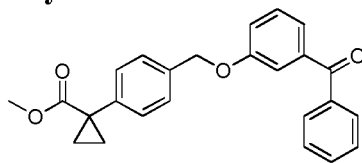
Step2; Methyl 1-(4-(bromomethyl)phenyl)cyclopropanecarboxylate



To a stirred solution of methyl 1-(p-tolyl)cyclopropanecarboxylate (3 g, 15.77 mmol) in acetonitrile (42 mL) was added N-bromosuccinimide (2.807 g, 15.77 mmol) followed by benzoyl peroxide (0.164 g, 0.473 mmol). The reaction was stirred at 80°C for 2 hours 40 minutes and then allowed to cool to room temperature. The reaction mixture was diluted with water and extracted with dichloromethane (x 3). The combined organic extracts were washed with brine and dried (magnesium sulfate), filtered and concentrated under reduced pressure to afford a red oil. The crude material was purified by silica gel column chromatography eluting with 0-9% ethyl acetate in *iso*-hexane to afford the title compound (2.478 g, 58%).

¹H NMR (400 MHz, CDCl₃): δ 7.36-7.30 (m, 4 H); 4.49 (s, 2 H); 3.62 (s, 3 H); 1.63-1.59 (m, 2 H); 1.20-1.16 (m, 2 H).

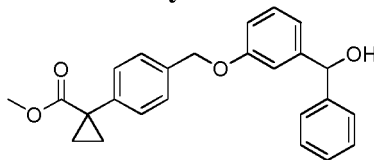
Step 3; Methyl 1-(4-((3-benzoylphenoxy)methyl)-phenyl)cyclopropanecarboxylate



Methyl 1-(4-(bromomethyl)phenyl)cyclopropanecarboxylate (2.478 g, 9.207 mmol) was added to a mixture of 3-hydroxybenzophenone (2.19 g, 11.05 mmol) and potassium carbonate (3.054 g, 22.10 mmol) in dimethyl formamide (46 mL). The reaction mixture was stirred at 60°C for 16 hours. The reaction mixture was diluted with water and extracted with ethyl acetate (x 3). The combined organic extracts were washed with 10% aqueous potassium carbonate (x 5), 2M NaOH (x 5), brine and dried (magnesium sulfate), filtered and concentrated under reduced pressure to afford the title compound (3.721 g, quantitative yield). The material was used directly in the next step with no further purification.

¹H NMR (400 MHz, CDCl₃): δ 7.81-7.77 (m, 2 H); 7.61-7.56 (m, 1 H); 7.50-7.35 (m, 9 H); 7.23-7.19 (m, 1 H); 5.10 (s, 2 H); 3.62 (s, 3 H); 1.64-1.59 (m, 2 H); 1.22-1.17 (m, 2 H).

Step 4; Methyl 1-(4-((3-(hydroxy(phenyl)methyl)phenoxy)-methyl)phenyl)cyclopropanecarboxylate

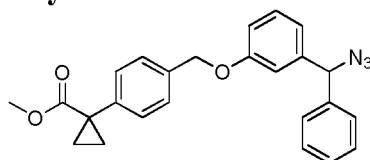


To a stirred solution of methyl 1-(4-((3-benzoylphenoxy)methyl)phenyl)cyclopropanecarboxylate (1.85 g, 4.787 mmol) in methanol (22.6 mL) at 0°C under an atmosphere of nitrogen was added sodium borohydride (0.181 g, 4.787 mmol) in one portion. The reaction mixture was stirred at 0 °C for 1 hour and then allowed to warm to

room temperature. After stirring for 40 minutes the reaction was cooled to 0 °C and additional sodium borohydride (0.091 g, 2.380 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 30 minutes. The reaction was quenched with water (3.5 mL), filtered to remove insoluble material and then concentrated under reduced pressure. Water was added to the residue and extracted with ethyl acetate (x 2). The combined organic extracts were washed with 10% aqueous potassium carbonate (x 2), brine, dried (magnesium sulfate), filtered and concentrated under reduced pressure to afford the title compound as a red oil (1.824 g, 98%). The material was used directly in the next step with no further purification.

¹H NMR (400 MHz, CDCl₃): δ 7.40-7.22 (m, 10 H); 7.05-7.03 (m, 1 H); 6.98 (d, J = 7.7 Hz, 1 H); 6.87 (dd, J = 8.3, 2.6 Hz, 1 H); 5.82 (d, J = 3.4 Hz, 1 H); 5.02 (s, 2 H); 3.62 (s, 3 H); 2.20 (d, J = 3.6 Hz, 1 H); 1.63-1.59 (m, 2 H); 1.20-1.16 (m, 2 H).

Step 5; Methyl 1-(4-((3-(azido(phenyl)methyl)phenoxy)methyl)-phenyl)cyclopropanecarboxylate

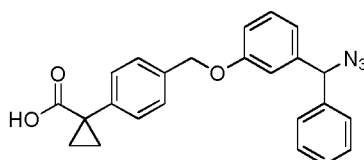


To a stirred solution of methyl 1-(4-((3-(hydroxy(phenyl)methyl)-phenoxy)methyl)phenyl)cyclopropanecarboxylate (1.824 g, 4.695 mmol) in toluene (21.8 mL) under an atmosphere of nitrogen was added diphenylphosphoryl azide (1.21 mL, 5.635 mmol) followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.84 mL, 5.635 mmol). The reaction mixture was stirred at 100°C for 3 hours and then allowed to cool to room temperature. The reaction was quenched by addition of saturated aqueous ammonium chloride solution and extracted with ethyl acetate (x 3). The combined organic extracts were washed with brine and dried (magnesium

sulfate), filtered and concentrated under reduced pressure to afford a brown oil. The crude material was purified by silica gel chromatography eluting with 0-14% ethyl acetate in *iso*-hexane to afford the title compound as a colourless oil (1.214 g, 62%).

¹H NMR (400 MHz, CDCl₃): δ 7.38-7.25 (m, 10 H); 6.95-6.89 (m, 3 H); 5.67 (s, 1 H); 5.01 (s, 2 H); 3.62 (s, 3 H); 1.63-1.59 (m, 2 H); 1.20-1.16 (m, 2 H).

Step 6; 1-(4-((3-(Azido(phenyl)methyl)phenoxy)methyl)phenyl)-cyclopropanecarboxylic acid

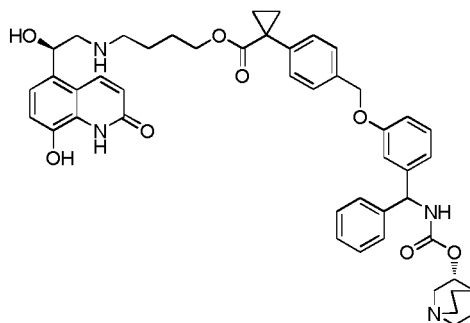


To a stirred solution of methyl 1-(4-((3-(azido(phenyl)methyl)phenoxy)methyl)phenyl)cyclopropanecarboxylate (0.569 g, 1.375 mmol) in methanol (12.9 mL) and tetrahydrofuran (5.1 mL) was added 2M aqueous sodium hydroxide (12.9 mL). The reaction was stirred at 50°C for 3 hours 30 minutes and then at room temperature for 16 hours. The reaction mixture was concentrated under reduced pressure and the pH adjusted to pH4 using 2M aqueous hydrochloric acid with stirring. The mixture was extracted with dichloromethane (x 3) and the combined organic extracts washed with brine, dried (magnesium sulfate), filtered and concentrated under reduced pressure to afford the title compound (0.552 g, quantitative yield). The material was used directly in the next step with no further purification

¹H NMR (400 MHz, CDCl₃): δ 7.39-7.24 (m, 10 H); 6.94-6.88 (m, 3 H); 5.67 (s, 1 H); 5.00 (s, 2 H); 1.69-1.65 (m, 2 H); 1.28-1.24 (m, 2 H).

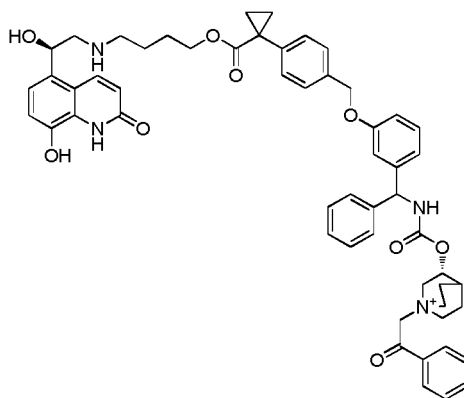
Step 7; 4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 1-(4-((3-(phenyl(((R)-quinuclidin-3-yl)oxy)-

carbonyl)amino)methyl)phenoxy)methyl)phenyl)cyclopropanecarboxylate



The title compound was prepared as described in **Example 54 Step 1**
 5 through **2** with **1-(4-(((3-(Azido(phenyl)methyl)phenoxy)methyl)phenyl)-**
cyclopropanecarboxylic acid replacing **4-((3-(azido(phenyl)methyl)-**
phenoxy)methyl)benzoic acid in **Step 1** and the product used in the
 subsequent steps.

Step 8; (3R)-3-((((3-(((4-(1-(((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-
 10 **1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)carbonyl)cyclopropyl)-**
benzyl)oxy)phenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-
phenylethyl)quinuclidin-1-ium (compound 36B)

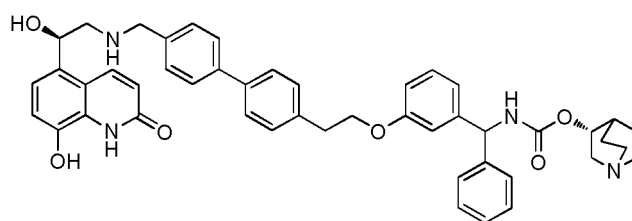


The title compound was prepared as in **Example 24** with **4-(((R)-2-**
 15 **hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl**
1-(4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)-
phenoxy)methyl)phenyl)cyclopropanecarboxylate replacing **(R)-**
quinuclidin-3-yl **(3-(6-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-**

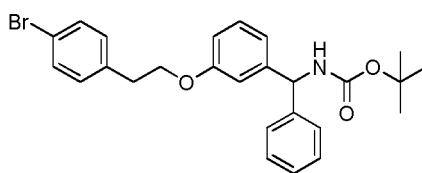
dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)(phenyl)-methylcarbamate.

Example 57

(*R*)-quinuclidin-3-yl ((3-(2-(4'-((((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-[1,1'-biphenyl]-4-yl)ethoxy)phenyl)(phenyl)methyl)carbamate (compound 37B)



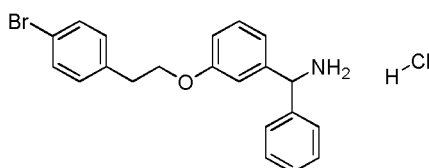
Step 1; *tert*-Butyl ((3-(4-bromophenethoxy)-phenyl)(phenyl)methyl)carbamate



The title compound was prepared as described in **Example 22 Step 2** with 4-bromophenethyl alcohol and *tert*-butyl (3-hydroxyphenyl)(phenyl)methylcarbamate replacing (4-((1,3-dioxolan-2-yl)methyl)phenyl)methanol and 3-hydroxybenzophenone respectively.

^1H NMR (400 MHz, CDCl_3): δ 7.44-7.39 (m, 2 H); 7.34-7.18 (m, 6 H); 7.16-7.11 (m, 2 H); 6.84-6.74 (m, 3 H); 5.86 (s, 1 H); 5.12 (s, 1 H); 4.15-4.08 (m, 2 H); 3.01 (t, $J = 6.8$ Hz, 2 H); 1.43 (s, 9 H).

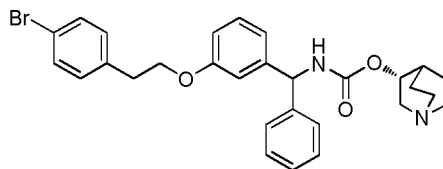
Step 2; (3-(4-bromophenethoxy)phenyl)(phenyl)methanamine hydrochloride



The title compound was prepared as described in **Example 50 Step 4** with ***tert*-butyl ((3-(4-bromophenoxy)phenyl)(phenyl)methyl)carbamate** replacing ***tert*-butyl ((3-((4'-((1,3-dioxolan-2-yl)methyl)-[1,1'-biphenyl]-3-yl)methoxy)phenyl)(phenyl)methyl)carbamate**

¹H NMR (400 MHz, DMSO-d₆): δ 8.95 (s, 3 H); 7.53-7.27 (m, 10 H); 7.14-7.10 (m, 1 H); 7.05-7.00 (m, 1 H); 6.96-6.90 (m, 1 H); 5.61-5.54 (m, 1 H); 4.18 (t, J = 6.7 Hz, 2 H); 3.02 (t, J = 6.7 Hz, 2 H).

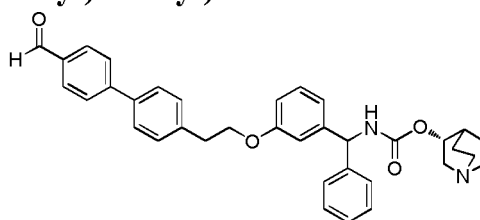
Step 3; (*R*)-quinuclidin-3-yl ((3-(4-bromophenoxy)phenyl)-(phenyl)methyl)carbamate



The title compound was prepared as described in **Example 1 Step 5** with **(3-(4-bromophenoxy)phenyl)(phenyl)methanamine hydrochloride** replacing **(3-(8-(1,3-dioxolan-2-yl)octyloxy)phenyl)(phenyl)methanamine**

¹H NMR (400 MHz, CDCl₃): δ 7.45-7.39 (m, 2 H); 7.37-7.19 (m, 6 H); 7.16-7.10 (m, 2 H); 6.87-6.75 (m, 3 H); 5.90 (s, 1 H); 5.29 (s, 1 H); 4.75-4.68 (m, 1 H); 4.16-4.07 (m, 2 H); 3.26-3.13 (m, 1 H); 3.01 (t, J = 6.8 Hz, 2 H); 2.93-2.62 (m, 5 H); 2.02-1.96 (m, 1 H); 1.86-1.75 (m, 1 H); 1.71-1.44 (m, 2 H); 1.42-1.29 (m, 1 H).

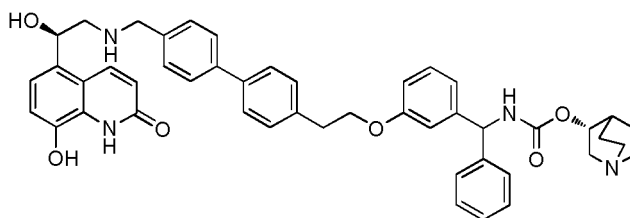
Step 4; (*R*)-quinuclidin-3-yl ((3-(2-(4'-formyl-[1,1'-biphenyl]-4-yl)ethoxy)phenyl)(phenyl)methyl)carbamate



(*R*)-quinuclidin-3-yl ((3-(4-bromophenoxy)phenyl)(phenyl)methyl)-

carbamate (0.40 g, 0.747 mmol), 4-formylphenylboronic acid (0.123 g, 0.822 mmol), sodium carbonate (0.158 g, 1.494 mmol) were combined in toluene (9.94 mL) and water (2.48 mL). The mixture was degassed with nitrogen for 10 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.087 g, 0.075 mmol) was added and the mixture heated at 120°C for 30 minutes in a microwave. The mixture was filtered and the filtrate partitioned between ethyl acetate and water. The organic layer was dried (sodium sulfate), filtered and concentrated under reduced pressure to afford a brown oil. The crude material was partially purified using a flash C18 cartridge eluting with 30-60% acetonitrile in water to afford a brown oil (0.174 g). The material was used directly in the next step with no further purification.

Step 5; (R)-quinuclidin-3-yl ((3-(2-(4'-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)-[1,1'-biphenyl]-4-yl)ethoxy)phenyl)(phenyl)methyl)carbamate



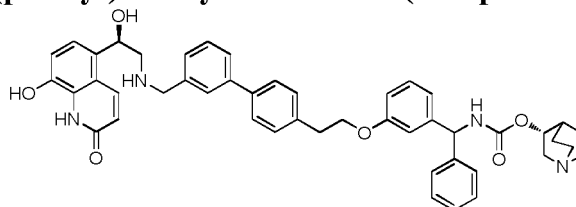
15

The title compound was prepared as described in **Example 1 Step 7** with **(R)-quinuclidin-3-yl ((3-(2-(4'-formyl-[1,1'-biphenyl]-4-yl)ethoxy)phenyl)(phenyl)methyl)carbamate** replacing **(R)-quinuclidin-3-yl (3-(9-oxononyloxy)phenyl)(phenyl)methylcarbamate**.

20

Example 58

(*R*)-quinuclidin-3-yl (3-(2-(3'-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)methyl)biphenyl-4-yl)ethoxy)phenyl)(phenyl)methylcarbamate (compound 38B)

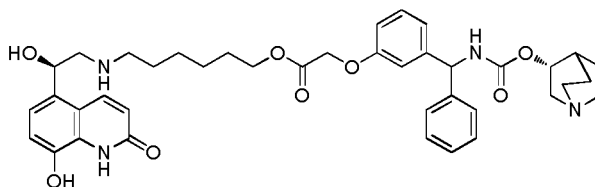


5

The title compound was prepared as described in **Example 57** with 3-formylboronic acid replacing 4-formylboronic acid in **Step 4** and the product used in the subsequent step.

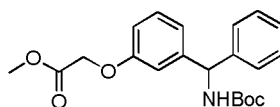
Example 59

6-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyl 2-(3-(phenyl(((*R*)-quinuclidin-3-yloxy)-carbonylamino)methyl)phenoxy)acetate (compound 39B)



15

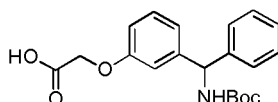
Step 1; Methyl 2-(3-(((*tert*-butoxycarbonyl)amino)-(phenyl)methyl)phenoxy)acetate



20

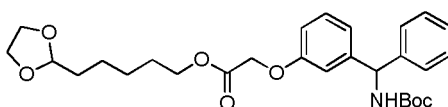
The title compound was prepared as described in **Example 1 Step 1** with *tert*-butyl (3-hydroxyphenyl)(phenyl)methylcarbamate and methyl bromoacetate replacing 3-hydroxybenzophenone and 2-(8-bromooctyl)-1,3-dioxolane respectively

Step 2; 2-(3-(((*tert*-Butoxycarbonyl)amino)(phenyl)-

methyl)phenoxy)acetic acid

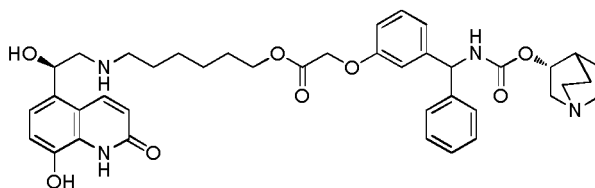
The title compound was prepared as described in **Example 56 Step 6** with methyl 2-(3-(((*tert*-butoxycarbonyl)amino)(phenyl)methyl)-phenoxy)acetate replacing methyl 1-(4-(((3-(azido(phenyl)methyl)phenoxy)-methyl)phenyl)cyclopropanecarboxylate.

Step 3; 5-(1,3-Dioxolan-2-yl)pentyl 2-(3-(((*tert*-butoxycarbonyl)amino)(phenyl)methyl)phenoxy)acetate



The title compound was prepared as described in **Example 54 Step 1** with 2-(3-(((*tert*-Butoxycarbonyl)amino)(phenyl)methyl)phenoxy)acetic acid and 2-(5-bromopentyl)-1,3-dioxolane 4-(((3-(azido(phenyl)methyl)phenoxy)-methyl)benzoic acid and 2-(3-chloropropyl)-1,3-dioxolane respectively.

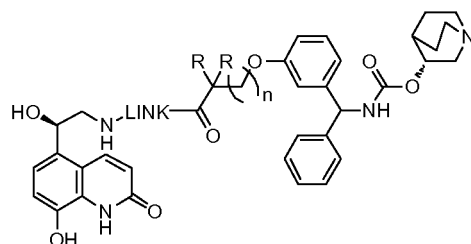
Step 4; 6-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyl 2-(3-(phenyl(((*R*)-quinuclidin-3-yloxy)-carbonylamino)methyl)phenoxy)acetate (compound 40B)



The title compound was prepared as described in **Example 53 Step 3** and **Step 4** with 5-(1,3-dioxolan-2-yl)pentyl 2-(3-(((*tert*-butoxycarbonyl)-amino)(phenyl)methyl)phenoxy)acetate replacing *tert*-butyl ((3-((4'-((1,3-dioxolan-2-yl)methyl)-[1,1'-biphenyl]-3-yl)methoxy)phenyl)(phenyl)-methyl)carbamate in **Step 3** and the product used in the subsequent steps.

The following compounds were prepared using the appropriate alkylating agent in **Example 59 Step 1** and the appropriate coupling partner

replacing 2-(5-bromopentyl)-1,3-dioxolane in **Example 59 Step 3**;

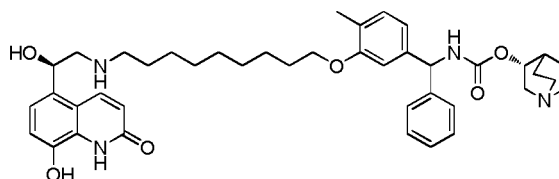


Cpd.	LINK	Coupling partner	Alkylating agent	n	R
9C	pentyl			0	H
10C	butyl			0	H
11C	pentyl			0	Me
12C	butyl			0	Me
13C	pentyl			1	Me
14C				0	H
15C				0	H

The coupling partner for **Compound 14C** was prepared from 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid and 2-(3-bromopropyl)-1,3-dioxolane using standard alkylation conditions detailed in **Example 1 Step 1**.

Example 60

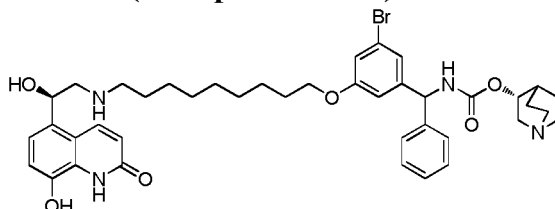
(R)-Quinuclidin-3-yl ((3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-4-methylphenyl)(phenyl)methyl)carbamate (Compound 16C)



The title compound was prepared as described in **Example 35**.

Example 61

(*R*)-Quinuclidin-3-yl ((3-bromo-5-((9-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)-(phenyl)methyl)carbamate (Compound 17C)



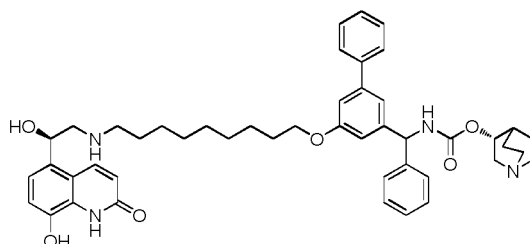
5

The title compound was prepared as described in **Example 28**.

Example 62

(*R*)-Quinuclidin-3-yl ((5-((9-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-[1,1'-biphenyl]-3-yl)(phenyl)methyl)carbamate (Compound 18C)

10

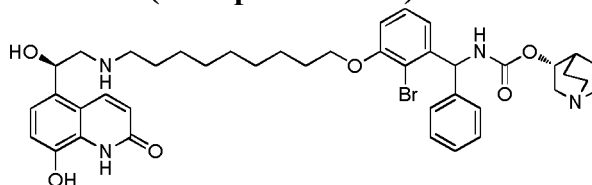


The title compound was prepared as described in **Example 40**.

Example 63

(*R*)-Quinuclidin-3-yl ((2-bromo-3-((9-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)-(phenyl)methyl)carbamate (Compound 19C)

15



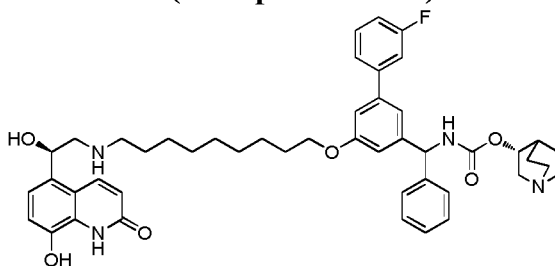
The title compound was prepared as described in **Example 29** with 2-bromo-3-hydroxybenzaldehyde used in **Step 1**.

20

Example 64

(*R*)-Quinuclidin-3-yl ((3'-fluoro-5-((9-(((*R*)-2-hydroxy-2-(8-hydroxy-

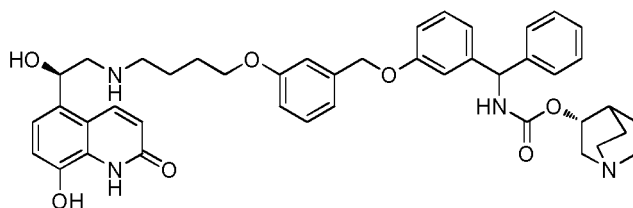
2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-[1,1'-biphenyl]-3-yl)(phenyl)methyl)carbamate (Compound 20C)



The title compound was prepared as described in **Example 40** with 3-fluorophenylboronic acid replacing phenyl boronic acid in **Step 1**.

Example 65

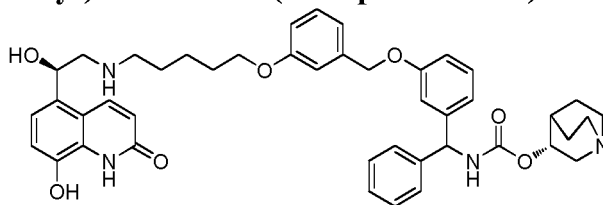
(*R*)-Quinuclidin-3-yl ((3-((3-(4-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)benzyl)oxy)phenyl)-(phenyl)methyl)carbamate (Compound 21C)



The title compound was prepared as described in **Example 42 Step 2**

Example 66

(*R*)-Quinuclidin-3-yl ((3-((3-((5-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl)oxy)benzyl)oxy)-phenyl)(phenyl)methyl)carbamate (Compound 22C)

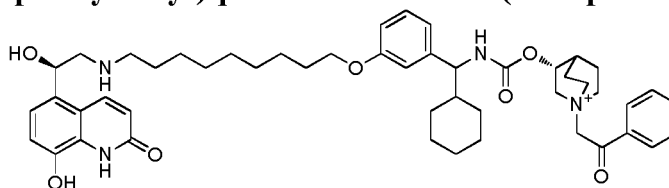


The title compound was prepared as described in **Example 44**.

Example 67

(3*R*)-3-(((Cyclohexyl(3-((9-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)methyl)carbamoyl)-

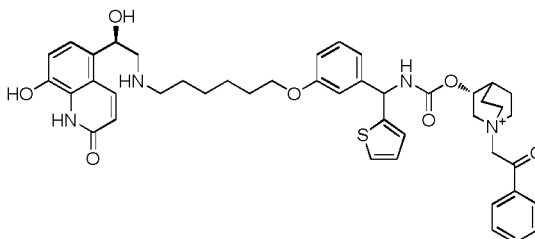
oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (Compound 23C)



The title compound was prepared as described in **Example 24** with **Compound 1C** replacing **(R)-quinuclidin-3-yl (3-(6-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)-phenyl)(phenyl)methylcarbamate**

Example 68

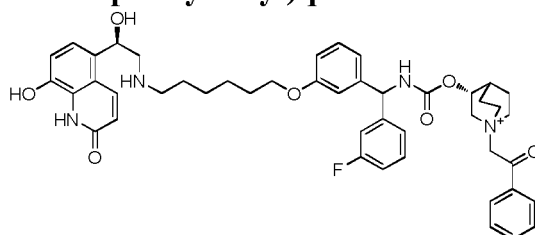
(3R)-3-((((3-(((6-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)(thiophen-2-yl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (Compound 24C)



The title compound was prepared as described in **Example 24** with **Compound 2C** replacing **(R)-quinuclidin-3-yl (3-(6-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)-(phenyl)methylcarbamate**.

Example 69

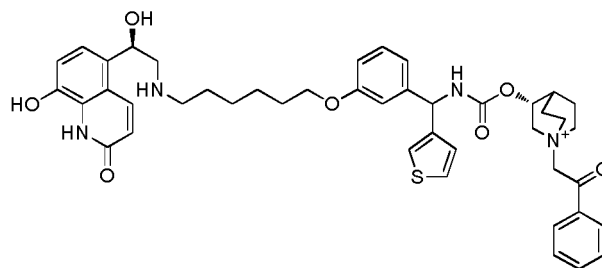
(3R)-3-((((3-Fluorophenyl)(3-(((6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)methyl)-carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (Compound 25C)



The title compound was prepared as described in **Example 24** with **Compound 24B** replacing (*R*)-quinuclidin-3-yl (3-(6-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)-(phenyl)methylcarbamate.

5 Example 70

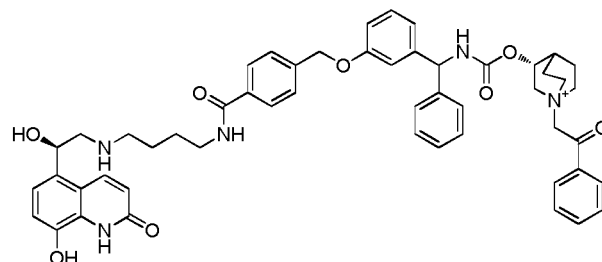
(3*R*)-3-((((3-(((6-(((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)(thiophen-3-yl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (Compound 26C)



The title compound was prepared as described in **Example 24** with **Compound 3C** replacing (*R*)-quinuclidin-3-yl (3-(6-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)-hexyloxy)phenyl)(phenyl)methylcarbamate.

15 Example 71

(3*R*)-3-((((3-(((4-(((4-(((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)carbamoyl)benzyl)oxy)phenyl)-(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (Compound 27C)

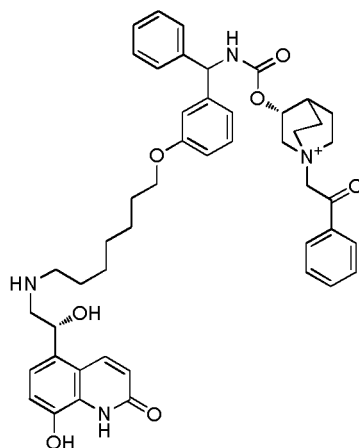


The title compound was prepared as described in **Example 24** with **Compound 31B** replacing (*R*)-quinuclidin-3-yl (3-(6-((*R*)-2-hydroxy-2-(8-

hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)(phenyl)methylcarbamate.

Example 72

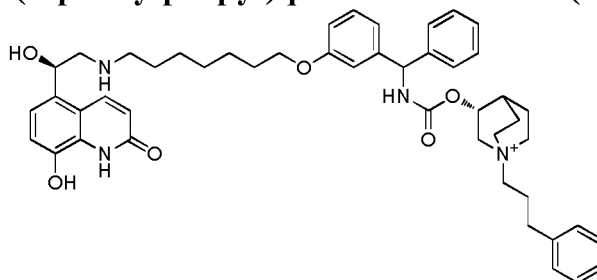
(3*R*)-3-((((3-((7-(((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)heptyl)oxy)phenyl)(phenyl)methyl-carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (Compound 28C)



The title compound was prepared as described in **Example 24** with **Compound 3** replacing (*R*)-quinuclidin-3-yl (3-(6-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)-(phenyl)methylcarbamate.

Example 73

(3*R*)-3-((((3-((7-(((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)heptyl)oxy)phenyl)(phenyl)methyl-carbamoyl)oxy)-1-(3-phenylpropyl)quinuclidin-1-ium (Compound 29C)

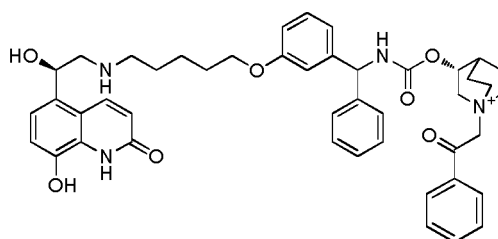


The title compound was prepared as described in **Example 24** with **Compound 3** replacing (*R*)-quinuclidin-3-yl (3-(6-((*R*)-2-hydroxy-2-(8-

hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)-(phenyl)methylcarbamate and (3-bromopropyl)benzene replacing bromoacetophenone.

Example 74

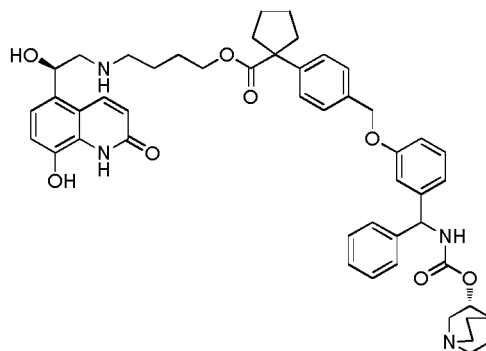
- 5 **(3*R*)-3-((((3-((5-((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl)oxy)phenyl)(phenyl)methyl-carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (Compound 30C)**



- 10 The title compound was prepared as described in **Example 24** with **Compound 5** replacing (*R*)-quinuclidin-3-yl (3-(6-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)(phenyl)methylcarbamate.

Example 75

- 15 **4-(((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 1-(4-((3-(phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)-amino)methyl)phenoxy)methyl)phenyl)cyclopentanecarboxylate (Compound 31C)**

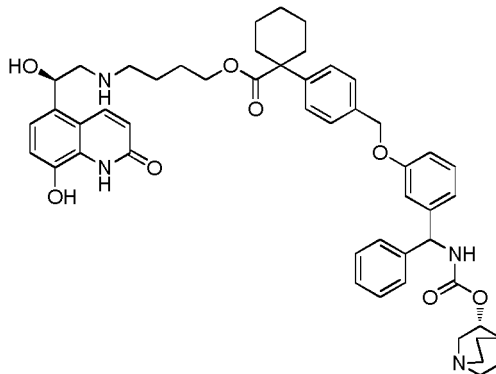


- 20 The title compound was prepared as described in **Example 56 Step1** through **Step 7** with 1-(p-tolyl)cyclopentanecarboxylic acid replacing

1-(p-tolyl)cyclopropanecarboxylic acid in **Step 1**.

Example 76

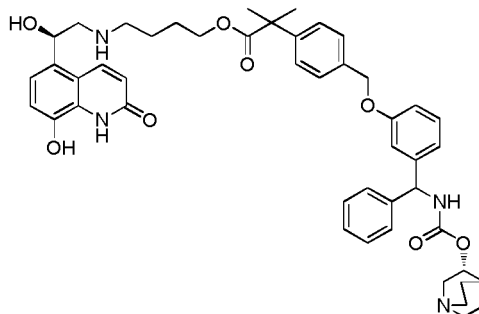
4-(((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 1-(4-((3-(phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)-amino)methyl)phenoxy)methyl)phenyl)cyclohexanecarboxylate
(Compound 32C)



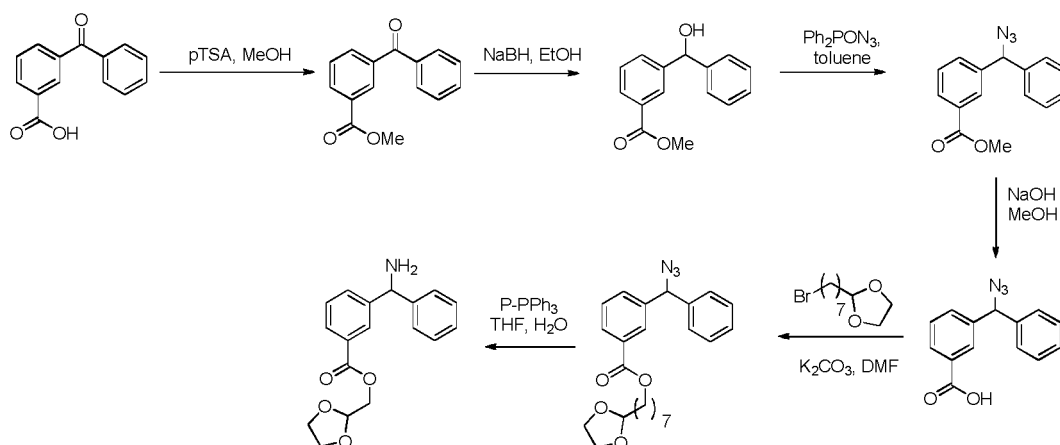
The title compound was prepared as described in **Example 56 Step1** through **Step 7** with 1-(p-tolyl)cyclohexanecarboxylic acid replacing 1-(p-tolyl)cyclopropanecarboxylic acid in **Step 1**.

Example 77

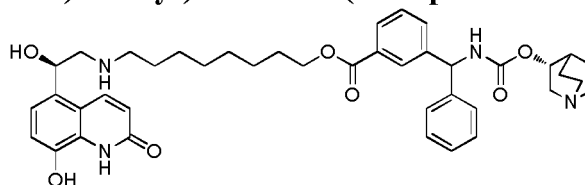
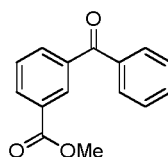
4-(((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 2-methyl-2-(4-((3-(phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)phenyl)propanoate
(Compound 33C)



The title compound was prepared as described in **Example 56 Step1** through **Step 7** with 2-methyl-2-(p-tolyl)propanoic acid replacing 1-(p-tolyl)cyclopropanecarboxylic acid in **Step 1**.

Synthesis of benzoic acid derivatives:**Example 78**

- 5 **8-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)octyl 3-(phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)amino)methyl)benzoate (Compound 34C)**

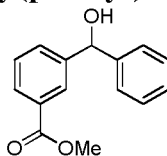
**Step 1; Methyl 3-benzoylbenzoate**

10

A stirred solution of 3-benzoylbenzoic acid (10.0 g, 44.4 mmol) and p-TSA (0.85 g, 4.39 mmol) in methanol (200 mL) was heated at 75°C for 18 hours. The reaction mixture was allowed to cool and the solvent evaporated at reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium hydrogen carbonate. The organic phase was dried with anhydrous sodium sulfate, filtered and the filtrate evaporated at reduced pressure to afford the title compound (9.55 g, 90%).

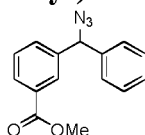
15

¹H NMR (400 MHz, CDCl₃): δ 8.44 (s, 1H); 8.27 (m, 1 H); 8.01 (m, 1 H); 7.86 (m 2 H); 7.61 (m, 2 H); 7.50 (m, 2 H); 3.94 (s, 3 H).

Step 2; Methyl 3-(hydroxy(phenyl)methyl)benzoate

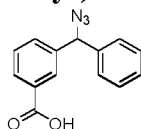
The title compound was prepared as described in **Example 1 Step 2** with **methyl 3-benzoylbenzoate** replacing **(3-(8-(1,3-dioxolan-2-yl)octyloxy)phenyl)(phenyl)methanone**.

^1H NMR (400 MHz, CDCl_3): δ 8.07 (s, 1 H); 7.90 (m, 2 H); 7.58 (m, 1 H); 7.40-7.21 (m, 6 H); 5.87 (s, 1 H); 3.88 (s, 3 H); 2.46 (s, 1 H).

Step 3; Methyl 3-(azido(phenyl)methyl)benzoate

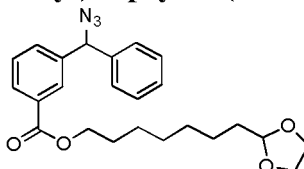
The title compound was prepared as described in **Example 1 Step 3** with **methyl 3-(hydroxy(phenyl)methyl)benzoate** replacing **(3-(8-(1,3-dioxolan-2-yl)octyloxy)phenyl)(phenyl)methanol**.

^1H NMR (400 MHz, CDCl_3): δ 8.09 (s, 1 H); 7.99 (m, 1 H); 7.50-7.20 (m, 7 H); 5.75 (s, 1 H); 3.93 (s, 3 H).

Step 4; 3-(Azido(phenyl)methyl)benzoic acid

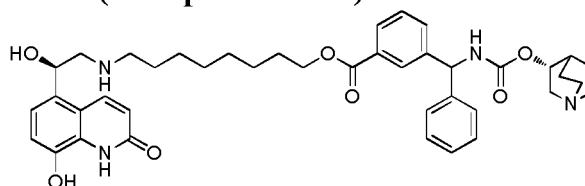
The title compound was prepared as described in **Example 56 Step 6** with **methyl 3-(azido(phenyl)methyl)benzoate** replacing **methyl 1-(4-((3-(azido(phenyl)methyl)phenoxy)methyl)phenyl)cyclopropanecarboxylate**.

^1H NMR (400 MHz, CDCl_3): δ 8.15 (s, 1 H); 8.00 (m, 1 H); 7.56 (m, 1 H); 7.47 (m, 1 H); 7.40-7.20 (m, 5 H); 5.72 (s, 1 H).

Step 5; 7-(1,3-Dioxolan-2-yl)heptyl 3-(azido(phenyl)methyl)benzoate

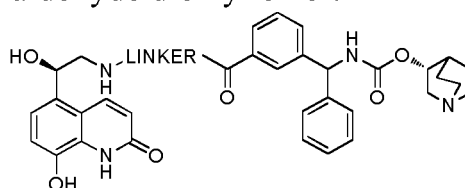
The title compound was prepared as described in **Example 54 Step 1** with 3-(7-bromoheptyl)-1,3-dioxolane and **3-(azido(phenyl)methyl)benzoic acid** replacing 2-(3-chloropropyl)-1,3-dioxolane and **4-((3-(azido(phenyl)methyl)phenoxy)methyl)benzoic acid** respectively.

Step 6; 8-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)octyl 3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)-amino)methyl)benzoate (Compound 34C)



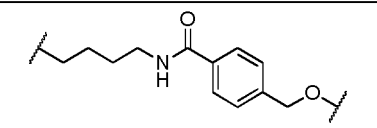
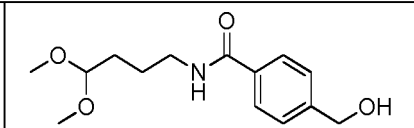
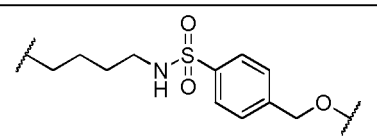
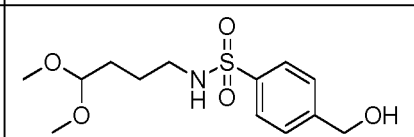
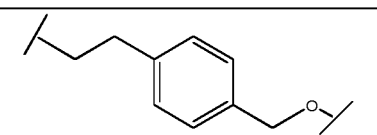
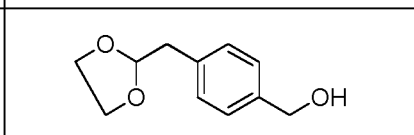
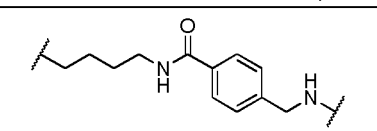
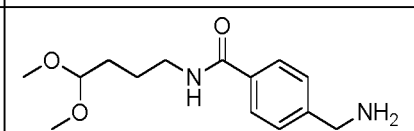
The title compound was prepared as described in **Example 54 Step 2**.

The following compounds were prepared using the appropriate alkylating agent in **Example 80 Step 5** and using the products in the subsequent steps. Alcohol based alkylating agents were coupled using the conditions described in **Example 22 Step 2** with the appropriate alcohol replacing 4-((1,3-dioxolan-2-yl)methyl)phenyl)methanol. Amine based alkylating agents were coupled using the conditions described in **Example 51 Step 4** with the appropriate amine replacing 4-amino-butyraldehyde diethyl ether.



Compound	Linker	Alkylating agent
35C		
36C		
37C		
38C		

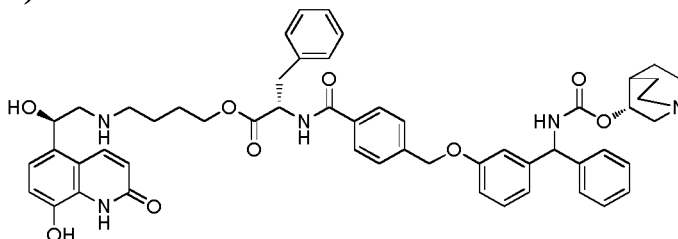
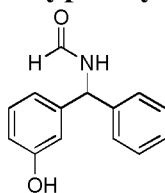
(continued)

39C		
40C		
41C		
42C		

Example 79

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

5 (Compound 43C)

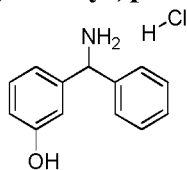
**Step 1; Step 1; N-((3-hydroxyphenyl)(phenyl)methyl)formamide**

3-Hydroxybenzophenone (25 g, 126.1 mmol) in formamide (130 mL, 3.3 mmol) was heated to 180°C for 18 hours. The reaction was allowed to cool slightly then poured into ice-cooled water and stirred for 30 minutes, filtered and washed with water. The solid was stirred in water (60 mL) and ethanol (60 mL) and heated to 50 °C for 1 hour, then allowed to cool. The solid was filtered and washed with water to give the title compound (33.94 g, 118%).

15 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).

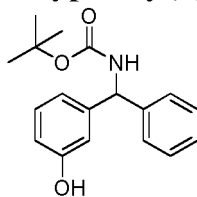
Step 2; 3-(Amino(phenyl)methyl)phenol hydrochloride



Methanol (125 mL), was cooled to 0°C and acetyl chloride (17.8 mL)
5 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
10 give the title compound (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).

15 **Step 3; *tert*-Butyl (3-hydroxyphenyl)(phenyl)methylcarbamate**

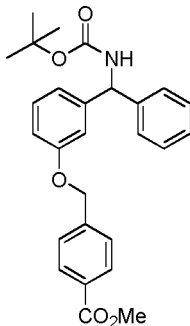


3-(Amino(phenyl)methyl)phenol hydrochloride (29.09 g, 123.4 mmol) in dichloromethane (450 mL) was cooled to 0°C and diisopropylethylamine (65.9 mL, 370.2 mmol) and di-*tert*-butyl dicarbonate (59.2 g, 271.5 mmol) was added slowly. The reaction was stirred at 0°C for 2
20 hours then warmed to room temperature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

room temperature for 16 hours. The suspension was filtered and the filtrate was evaporated at reduced pressure and the residue re-dissolved in ethyl acetate (370 mL). Silica (73 g) was added and the suspension was stirred for 30 minutes, filtered, and the filter cake washed with further ethyl acetate. The filtrate was evaporated to dryness. The dark solid residue was dissolved in ethyl acetate (200 mL) and charcoal added and the suspension was heated under reflux for 1 hour. The suspension was filtered through celite and solvent removed at reduced pressure. The dark solid was dissolved in dichloromethane and *iso*-hexane added then solvent evaporated (repeated 3 times) to give the title compound (34.81 g, 92%).

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

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



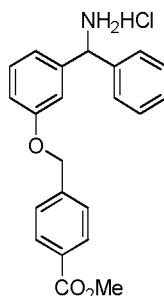
15

A mixture of *tert*-butyl (3-hydroxyphenyl)(phenyl)methylcarbamate (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 room temperature for 16 hours. The reaction mixture was concentrated at 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 at reduced pressure. The residue was re-crystallised from ethyl acetate and *iso*-hexane to afford the

title compound (3.25 g, 68%).

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

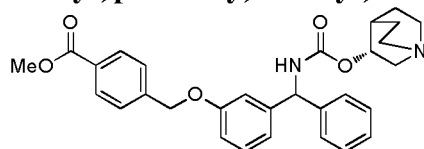
5 Step 5; Methyl 4-((3-(amino(phenyl)methyl)phenoxy)-methyl)benzoate hydrochloride



To 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 hydrogen chloride in dioxane (4 M, 9.0 mL, 36 mmol). The reaction mixture was stirred at room temperature for 16 hours. The solvent was removed at reduced pressure to afford the title compound (2.65 g, >95%).

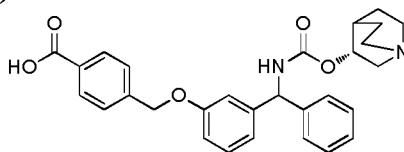
^1H NMR (400 MHz, CDCl_3): δ 9.21 (s, 2 H); 8.03 (d, $J = 8.1$ Hz, 2 H); 7.64 (d, $J = 8.1$ Hz, 2 H); 7.59 (d, $J = 7.6$ Hz, 2 H); 7.49-7.34 (m, 5 H); 7.17 (d, $J = 7.7$ Hz, 1 H); 7.06 (dd, $J = 8.3, 2.4$ Hz, 1 H); 5.64 (s, 1 H); 5.28 (s, 2 H); 3.91 (s, 3 H).

Step 6; Methyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate



The title compound was prepared as in **Example 1 Step 5** with **methyl 4-((3-(amino(phenyl)methyl)phenoxy)methyl)benzoate hydrochloride** replacing (3-(8-(1,3-dioxolan-2-yl)octyloxy)phenyl)(phenyl)methanamine.

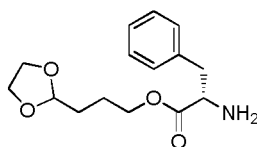
Step 7; 4-((3-(Phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)benzoic acid



To a stirred solution of methyl **4-((3-(phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate** (2.27 g, 4.50 mmol) in THF (23 mL) was added an aqueous solution of lithium hydroxide (2.0 M, 9.0 ml, 18.0 mmol). The mixture was stirred at room temperature 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 at reduced pressure. The residue was then dissolved in ethanol and re-evaporated at reduced pressure to afford the title compound (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).

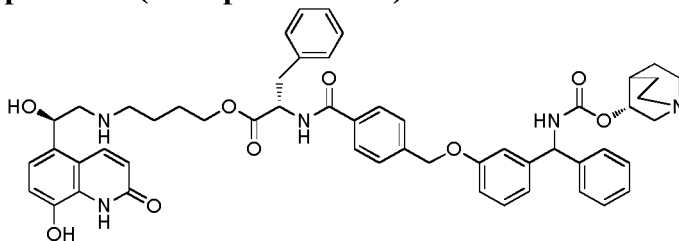
Step 8; (S)-3-(1,3-Dioxolan-2-yl)propyl 2-amino-3-phenylpropanoate



The title compound was prepared in two steps. Boc-Phe-OH was reacted with 2-(3-chloropropyl)-1,3-dioxolane according to **Example 10 Step 1** and the subsequent product reacted with hydrogen chloride in dioxane according to **Example 79 Step 5**.

Step 9; 2S)-4-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 3-phenyl-2-(4-((3-(phenyl(((*R*)-

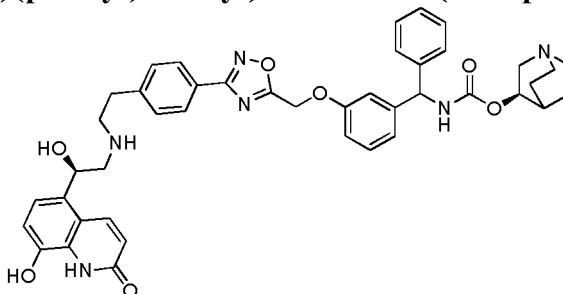
quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)-
benzamido)propanoate (Compound 43C)



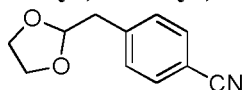
The title compound was prepared in three steps. The product from
5 **Example 79 Step 7** was coupled to the product from **Example 79 Step 8**
using the method described in **Example 51 Step 4**. The subsequent product
was then used in the methods of **Example 1 Step 6** followed by **Example 1**
Step 7.

Example 80

10 **(R)-Quinuclidin-3-yl ((3-((3-(4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-
oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)phenyl)-1,2,4-oxadiazol-5-
yl)methoxy)phenyl)(phenyl)methyl)carbamate (Compound 44C)**



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



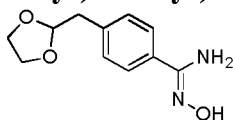
15

To a stirred solution of 4-(2-hydroxyethyl)benzonitrile (1.09 g, 7.41
mmol) in DCM (20 mL) was added Dess-Martin Periodinane (3.77 g, 8.84
mmol) and the reaction mixture stirred at room temperature for 1 hour. A 1:1
mixture of saturated aqueous sodium hydrogen carbonate and saturated
20 sodium thiosulfate was added and the bi-phasic mixture stirred for 1 hour. The
organic phase was separated and the aqueous phase extracted with further

DCM (x3). The combined organic extracts were dried with anhydrous magnesium sulfate and the solvent evaporated at reduced pressure. The crude material was dissolved in toluene (40 mL) and ethylene glycol (2.29 g, 37.05 mmol) and p-toluenesulfonic acid (0.14 g, 0.74 mmol) added. The mixture
5 was heated under Dean and Stark conditions for 2 hours. The solvent was evaporated under reduced pressure and the residue partitioned between saturated aqueous sodium hydrogen carbonate and ethyl acetate. The organic phase was removed and the aqueous phase was extracted with further ethyl acetate (x3). The combined organic phases were dried with anhydrous
10 magnesium sulfate and the solvent evaporated at reduced pressure to afford the title compound (1.40 g, 99%).

¹H NMR (400 MHz, CDCl₃): δ 7.69-7.53 (m, 2 H); 7.48-7.34 (m, 2 H); 5.08 (t, J = 4.5 Hz, 1 H); 3.94-3.81 (m, 4 H); 3.03 (t, J = 4.5 Hz, 2 H).

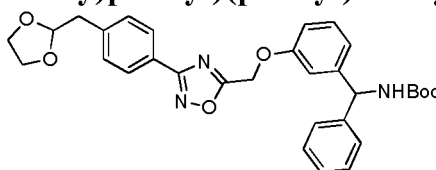
Step 2; 4-((1,3-Dioxolan-2-yl)methyl)-N'-hydroxybenzimidamide



To a solution of **4-((1,3-dioxolan-2-yl)methyl)benzonitrile** (1.40 g, 7.41 mmol) in ethanol (10 mL) was added 50% aqueous hydroxylamine (5 mL) and the resultant mixture heated at 80°C for 16 hours. The solvent was evaporated at reduced pressure and the residue partitioned between ethyl
20 acetate and brine. The organic phase was removed and the aqueous phase was extracted with further ethyl acetate (x2). The combined organic extracts were dried with aqueous magnesium sulfate and evaporated at reduced pressure to afford the title compound (1.21 g, 73%).

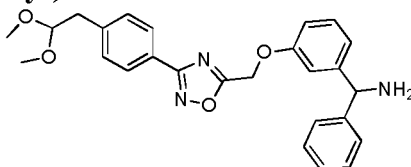
¹H NMR (400 MHz, DMSO-d₆): δ 9.57 (s, 1 H); 7.62-7.49 (m, 2 H);
25 7.34-7.23 (m, 2 H); 5.76 (s, 2 H); 5.03-4.90 (m, 1 H); 3.95-3.66 (m, 4 H); 2.91 (dd, J = 16.6, 4.9 Hz, 2 H).

Step 3, tert-butyl ((3-((3-(4-((1,3-Dioxolan-2-yl)methyl)phenyl)-

1,2,4-oxadiazol-5-yl)methoxy)phenyl)(phenyl)methyl)carbamate

To a stirred solution of **4-((1,3-dioxolan-2-yl)methyl)-N'-(hydroxybenzimidamido)-2-(3-(((tert-butoxycarbonyl)amino)(phenyl)methyl)phenoxy)acetic acid** (Example 59 Step 2, 1.0 g, 2.79 mmol) in acetonitrile (5 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.8 g, 4.18 mmol). The reaction mixture was stirred at ambient temperature for 16 hours. The reaction mixture was diluted with pyridine (1 mL) and heated at 150°C for 30 minutes in a microwave. The reaction was diluted with saturated brine and extracted with ethyl acetate (x3). The combined organic fractions were dried with magnesium sulfate and the solvent evaporated at reduced pressure. Material used directly in the next step without further purification (1.01 g, 65%).

¹H NMR (400 MHz, CDCl₃): δ 8.04-7.96 (m, 2 H); 7.45-7.37 (m, 2 H); 6.96-6.88 (m, 3 H); 5.88 (s, 1 H); 5.29 (s, 2 H); 5.19-5.07 (m, 2 H); 3.98-3.80 (m, 4 H); 3.03 (d, J = 4.6 Hz, 2 H); 1.44 (s, 9 H).

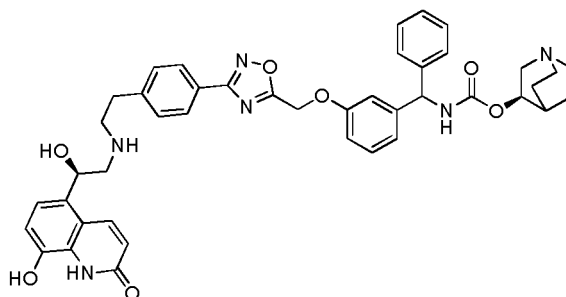
Step 4; (3-((3-(4-(2,2-dimethoxyethyl)phenyl)-1,2,4-oxadiazol-5-yl)methoxy)phenyl)(phenyl)methanamine

Hydrogen chloride in dioxane (4.0 M, 5 mL, 24 mmol) was added to a solution of *tert*-butyl ((3-((3-(4-((1,3-dioxolan-2-yl)methyl)phenyl)-1,2,4-oxadiazol-5-yl)methoxy)phenyl)(phenyl)methyl)carbamate (1.01 g, 1.85 mmol) in methanol (5 mL) and the resultant solution was stirred at ambient temperature for 2 hours. The solvent was evaporated at reduced pressure and the residue loaded onto an SCX-2 cartridge. The cartridge was eluted with

methanol (eight column volumes) followed by ammonia/methanol. Fractions containing the product were combined and evaporated at reduced pressure to afford the title compound (0.796 g, 96%).

¹H NMR (400 MHz, CDCl₃): δ 8.02 (d, J = 8.0 Hz, 2 H); 7.42-7.15 (m, 8 H); 7.12-7.01 (m, 2 H); 6.88 (dd, J = 8.2, 2.7 Hz, 1 H); 5.34-5.27 (m, 2 H); 5.19 (s, 1 H); 4.60-4.54 (m, 1 H); 3.38-3.31 (m, 6 H); 2.98 (d, J = 5.6 Hz, 2 H).

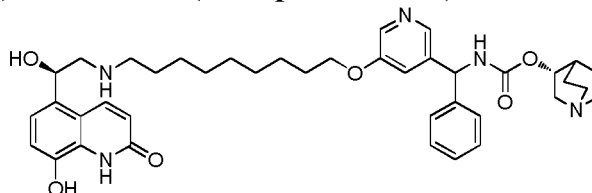
Step 5; (R)-quinuclidin-3-yl ((3-((3-(4-(2-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)phenyl)-1,2,4-oxadiazol-5-yl)methoxy)phenyl)(phenyl)methyl)carbamate (Compound 44C)



The title compound was prepared as described in **Example 1 Step 5, 6 and 7.**

15 **Example 81**

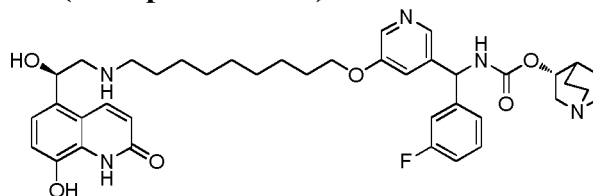
(R)-Quinuclidin-3-yl ((5-((9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)pyridin-3-yl)(phenyl)methyl)carbamate (Compound 45C)



20 The title compound was prepared as described in **Example 10** with 5-hydroxynicotinaldehyde replacing 3-hydroxybenzaldehyde in **Step 1** and phenyl magnesium bromide replacing 2-thienylmagnesium bromide in **Step 2.**

Example 82

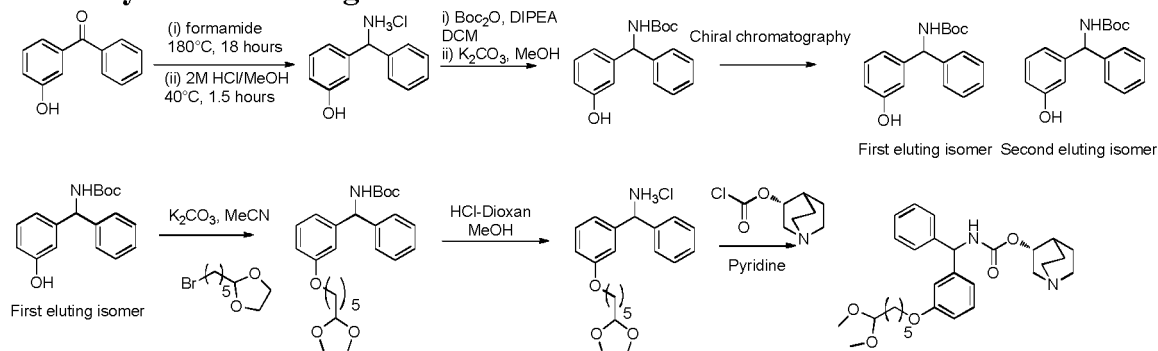
(*R*)-Quinuclidin-3-yl ((3-fluorophenyl)(5-(((9-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)pyridin-3-yl)methyl)carbamate (Compound 46C)



5

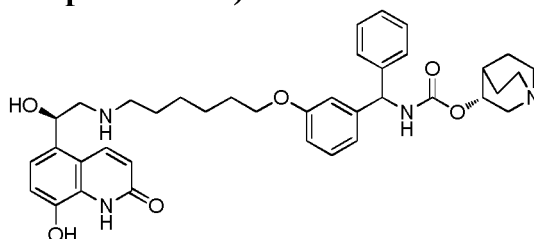
The title compound was prepared as described in **Example 10** with 5-hydroxynicotinaldehyde replacing 3-hydroxybenzaldehyde in **Step 1** and 3-fluorophenyl magnesium bromide replacing 2-thienylmagnesium bromide in **Step 2**.

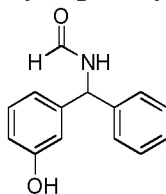
10

Synthesis of single diastereoisomers**Chiral Example 1**

(*R*)-Quinuclidin-3-yl ((3-(((6-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)(phenyl)-methyl)carbamate (compound 41B)

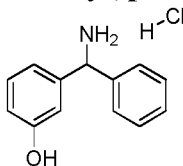
15



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

3-Hydroxybenzophenone (25 g, 126.1 mmol) in formamide (130 mL, 3.3 mmol) was heated to 180°C for 18 hours. The reaction was allowed to cool slightly then poured into ice-cooled water and stirred for 30 minutes, filtered and washed with water. The solid was stirred in water (60 mL) and ethanol (60 mL) and heated to 50 °C for 1 hour, then allowed to cool. The solid was filtered and washed with water to give the title compound (33.94 g, 118%).

¹H NMR (400 MHz, CH₃OH-d₄): 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 (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).

Step2a; Synthesis of enantiomerically pure 3-

(Amino(phenyl)methyl)phenol Mandelate (fast eluting enantiomer)

3-(Amino(phenyl)methyl)phenol (878 g, 4.4 mol) was dissolved in 17.5 l of iPrOH and heated to reflux. To the mixture a solution of R-mandelic acid (737 g, 4.8 mol) in 1760 ml of iPrOH was dropped. The mixture was
5 refluxed for 1 h and then allowed to cool to 10°C (overnight). The precipitate was filtered, washed with cold iPrOH and dried in vacuum oven at 35°C. The collected salt was refluxed in 95% iPrOH for 1h, then slowly cooled to 70°C (beginning of crystallization) and stirred at constant temperature for 5h. The mixture was allowed to cool down to 10°C overnight. The solid was filtered,
10 washed with cold iPrOH and dried in vacuum oven at 35°C.

Chiral analyses were made for free amine (the salt treated with sodium hydrogen carbonate, extracted with AcOEt and the organic layer concentrated).

Chiralpak IC, 4.6mmx250mm - (A) Ethanol + 0.1% TEA (B) Hexane +
15 0.1% TEA flow: 1ml/min (10%A; 90%B)

ee >99% retention time 10.58 min

¹H NMR (600 MHz, d₆-DMSO) 4.65 (s, 1H), 5.34 (s, 1H), 6.70 (m, 1H, Ar), 6.82 (m, 1H, Ar), 6.86 (m, 1H, Ar), 7.12 (m, 1H, Ar), 7.18 (m, 1H, Ar), 7.23-7.29 (m, 3H, Ar), 7.33-7.38 (m, 4H, Ar), 7.42 (m, 2H, Ar).

20 A sample of amine was converted into the corresponding hydrochloride.
 $[\alpha]_D^{20} = -0.019^\circ$ (c=4.4, MeOH)

A sample of amine was converted into the corresponding BOC derivatives as described in following Step 3 and analyzed by chiral HPLC that confirmed identical retention time of fast eluting enantiomer BOC protected.

25 **Step2b; Synthesis of enantiomerically pure 3-(Amino(phenyl)methyl)phenol Mandelate (slow eluting enantiomer)**

The product was prepared as described in Step 2a using S-mandelic acid.

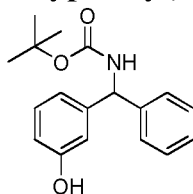
ee >99% retention time 16.37 min

A sample of amine was converted into the corresponding hydrochloride.

$[\alpha]_D^{20} = +0.019^\circ$ (c=4.4, MeOH)

A sample of amine was converted into the corresponding BOC
5 derivatives as described in following Step 3 and analyzed by chiral HPLC that
confirmed identical retention time of slow eluting enantiomer BOC protected.

Step 3; *tert*-Butyl (3-hydroxyphenyl)(phenyl)methylcarbamate



3-(Amino(phenyl)methyl)phenol hydrochloride (29.09 g, 123.4 mmol)
10 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
room temperature over 16 hours. The solvent was removed and compound
purified through a silica plug, eluting with 0-20% ethyl acetate in *iso*-hexane
15 to give a black oil. To this mixture in methanol (300 mL) was added
potassium carbonate (51 g, 370.2 mmol) and stirred at room temperature for
16 hours. The suspension was filtered and the filtrate was evaporated at
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
20 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. The dark solid
was dissolved in dichloromethane and *iso*-hexane added then solvent
25 evaporated (repeated 3 times) to give the title compound (34.81 g, 92%).

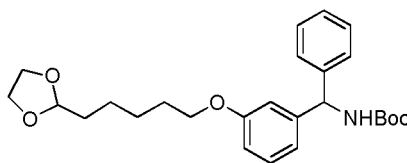
^1H NMR (400 MHz, CDCl_3 -d): δ 7.36-7.16 (m, 6 H); 6.80 (d, $J = 7.79$

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; Resolution of the racemic mixture into first and second eluting isomers

The racemic mixture was purified by SFC using a CHIRALPAK[®] AD 20 μ M 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 the first eluting enantiomer (R_t = 4.5 min, 26.7 g, >99.9% e.e.) and second eluting isomer (R_t = 8.5-8.6 min, 23.9 g, 99.2 e.e.) were separated.

Step 5; *tert*-Butyl ((3-((5-(1,3-dioxolan-2-yl)pentyl)oxy)phenyl)(phenyl)methyl)carbamate

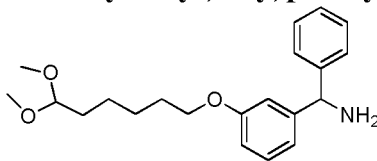


Potassium carbonate (0.566 g, 4.10 mmol) was added to a solution of *tert*-butyl (3-hydroxyphenyl)(phenyl)methylcarbamate (derived from the first eluting isomer, 0.614 g, 2.05 mmol) in acetonitrile (6 mL). The reaction mixture was stirred at ambient temperature for 10 minutes and 2-(5-bromopentyl)-1,3-dioxolane (0.549 g, 2.46 mmol) added. The reaction mixture was heated at 60°C for 20 hours. The reaction mixture was allowed to cool and diluted with water and DCM. The mixture was poured through a hydrophobic frit and the organic phase was evaporated at reduced pressure. The crude material was purified by silica gel chromatography eluting with 100% *iso*-hexane to 10% ethyl acetate in *iso*-hexane to afford the title compound as a colourless oil (0.503 g, 56%).

¹H NMR (400 MHz, CDCl₃): δ 7.34-7.13 (m, 6 H); 6.81-6.76 (m, 3 H); 5.85 (br s, 1 H); 5.10 (br s, 1 H); 4.86 (t, J = 4.8 Hz, 1 H); 3.97-3.83 (m, 6 H);

1.78-1.66 (m, 4 H); 1.50-1.44 (m, 4 H), 1.30 (s, 9 H).

Step 6; (3-((6,6-Dimethoxyhexyl)oxy)phenyl)(phenyl)methanamine



To a solution of *tert*-butyl ((3-((5-(1,3-dioxolan-2-yl)pentyl)oxy)phenyl)(phenyl)methyl)carbamate (0.483 g, 1.10 mmol) in methanol (4 mL) was added hydrogen chloride in dioxane (4 M, 4 mL, 16 mmol). The reaction was stirred at ambient temperature for 7 hours. The solvent was evaporated at reduced pressure and the residue loaded onto an SCX-2 cartridge. The cartridge was eluted with methanol (eight column volumes) followed by ammonia/methanol. Fractions containing the product were combined and evaporated at reduced pressure to afford the title compound as a colourless oil (0.322 g, 85%).

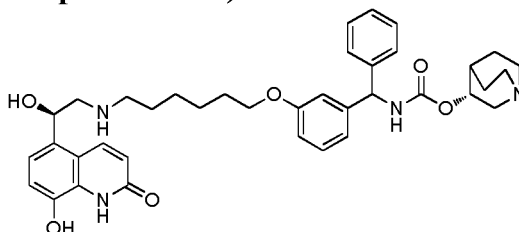
¹H NMR (400 MHz, CDCl₃): δ 7.38-7.18 (m, 6 H); 6.94-6.92 (m, 2 H); 6.73-6.73 (m, 1 H); 5.17 (s, 1 H); 4.38 (t, J = 5.6 Hz, 1 H); 3.93 (t, J = 6.4 Hz, 2 H); 3.32 (s, 6 H); 1.80-1.73 (m, 4 H); 1.65-1.60 (m, 2 H); 1.49-1.40 (m, 4 H).

Step 7; (*R*)-quinuclidin-3-yl ((3-((6-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)(phenyl)-methyl)carbamate (compound 41B)

The title compound was prepared using Step 5, 6 and 7 of Example 1.

Chiral Example 2

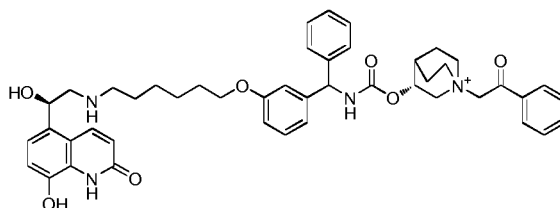
(*R*)-Quinuclidin-3-yl ((3-((6-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)(phenyl)-methyl)carbamate (compound 42B)



The title compound was prepared as in **Chiral Example 1** with the second eluting isomer from **Step 4** used in **Step 5**.

Chiral Example 3

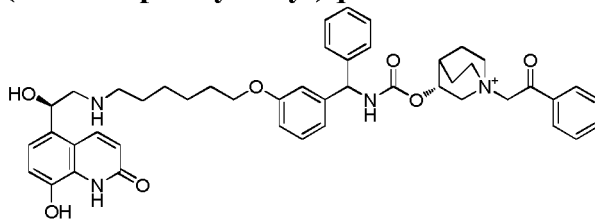
(3*R*)-3-((((3-((6-(((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)(phenyl)methyl)-
carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (compound
43B)



The title compound was prepared as in **Example 24** with **Chiral**
Example 1 replacing (*R*)-quinuclidin-3-yl (3-(6-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)(phenyl)methylcarbamate.

Chiral Example 4

(3*R*)-3-((((3-((6-(((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)(phenyl)methyl)-
carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium (compound 44B)

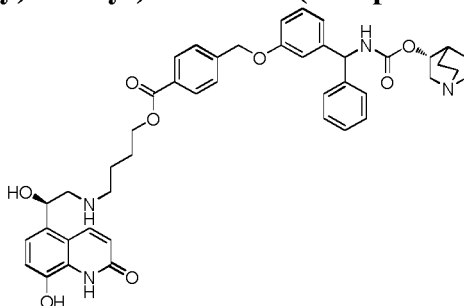


The title compound was prepared as in **Example 24** with **Chiral**
Example 2 replacing (*R*)-quinuclidin-3-yl (3-(6-((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)-(phenyl)methylcarbamate.

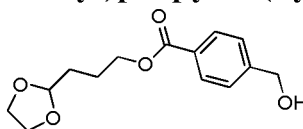
Chiral Example 5

4-(((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

yl)ethyl)amino)butyl 4-((3-(phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)-amino)methyl)phenoxy)methyl)benzoate (compound 45B)



Step 1; 3-(1,3-Dioxolan-2-yl)propyl 4-(hydroxymethyl)benzoate

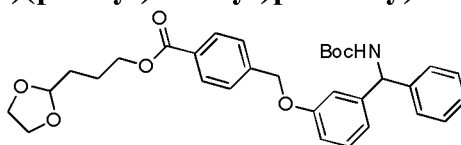


5

To a stirred solution of 4-hydroxymethylbenzoic acid (3.33 g, 21.9 mmol) in DMF (100 mL) was added potassium carbonate (5.67 g, 41.04 mmol) followed by 2-(3-bromopropyl)-1,3-dioxolane (3.0 g, 19.9 mmol). The resulting mixture was heated at 80°C for 16 hours. The reaction mixture was diluted with ethyl acetate and washed sequentially with water and twice with brine. The organic phase was dried with anhydrous magnesium sulphate, filtered and the filtrate evaporated at reduced pressure. The crude material was purified by silica gel chromatography eluting with 100% *iso*-hexane to 100% ethyl acetate in *iso*-hexane to afford the title compound as a colourless oil (2.55 g, 48%).

¹H NMR (400 MHz, CDCl₃): δ 8.06-7.98 (m, 2 H); 7.44 (d, J = 8.0 Hz, 2 H); 4.96-4.88 (m, 1 H); 4.77 (d, J = 4.0 Hz, 2 H); 4.36 (t, J = 6.4 Hz, 2 H); 4.02-3.94 (m, 2 H); 3.92-3.81 (m, 2 H); 1.96-1.80 (m, 4 H).

Step 2; 3-(1,3-Dioxolan-2-yl)propyl 4-((3-(((tert-butoxycarbonyl)amino)(phenyl)methyl)phenoxy)methyl)benzoate



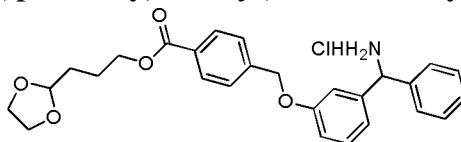
The title compound was prepared as described in **Example 22 Step 2**

20

with 3-(1,3-dioxolan-2-yl)propyl 4-(hydroxymethyl)benzoate and *tert*-butyl (3-hydroxyphenyl)(phenyl)methylcarbamate (first eluting isomer from **Chiral Example 1 Step 4**) replacing 4-((1,3-dioxolan-2-yl)methyl)phenyl)methanol and 3-hydroxybenzophenone respectively.

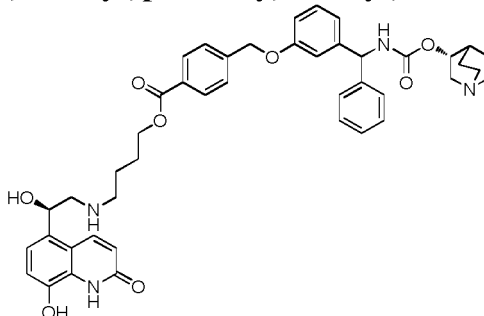
¹H NMR (400 MHz, CDCl₃): δ 8.04-8.02 (m, 2 H); 7.47-7.45 (m, 2 H); 7.33-7.21 (m, 6 H); 6.88-6.84 (m, 3 H); 5.87 (br s, 1 H); 5.15 (br s, 1 H); 5.08 (s, 2 H); 4.95-4.93 (m, 1 H); 4.38-4.35 (m, 2 H); 4.10-3.97 (m, 2 H); 3.88-3.85 (m, 2 H); 1.94-1.90 (m, 2 H); 1.86-1.83 (m, 2 H), 1.30 (s, 9 H).

Step 3; 3-(1,3-Dioxolan-2-yl)propyl 4-((3-(amino(phenyl)methyl)phenoxy)methyl)benzoate hydrochloride



Hydrogen chloride in dioxane (4.0 M, 6 mL, 24 mmol) was added to 3-(1,3-dioxolan-2-yl)propyl 4-((3-(((*tert*-butoxycarbonyl)amino)(phenyl)-methyl)phenoxy)methyl)benzoate (0.756 g, 1.38 mmol) and the resultant solution was stirred at ambient temperature for 2 hours. The solvent was evaporated at reduced pressure to afford the title compound (0.750 g, 100%).

Step 4; 4-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 4-((3-(phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate (compound 45B)

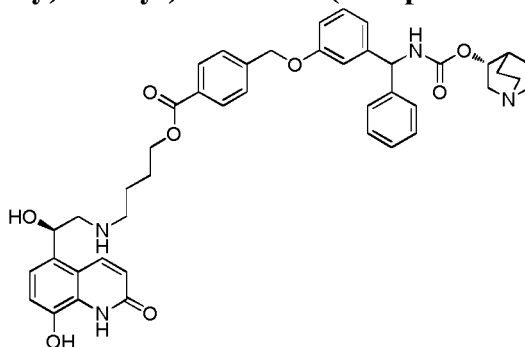


The title compound was prepared using **Step 5, 6 and 7 of Example 1.**

Chiral Example 6

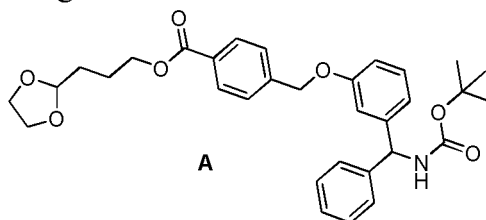
4-(((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

yl)ethyl)amino)butyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)-amino)methyl)phenoxy)methyl)benzoate (compound 46B)

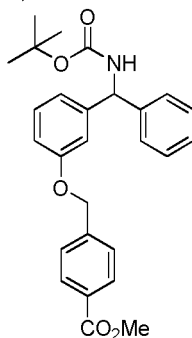


The title material was prepared as described in **Chiral Example 5** with
 5 *tert*-butyl (3-hydroxyphenyl)(phenyl)methylcarbamate (second eluting isomer from **Chiral Example 1 Step 4**) replacing *tert*-butyl (3-hydroxyphenyl)(phenyl)methylcarbamate (first eluting isomer from **Chiral Example 1 Step 4**) in **Step 2**.

An alternative method to prepare the key intermediate **A** in **Chiral**
 10 **Example 5** or **Chiral Example 6** is detailed below. The example below details the use of the second eluting isomer derived from **Chiral Example 1 Step 4**.



Step 1; Methyl 4-((3-(((tert-butoxycarbonyl)amino)-(phenyl)methyl)phenoxy)methyl)benzoate



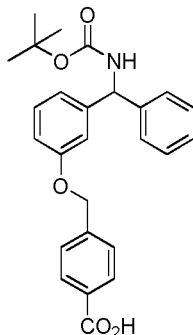
15

The title compound was prepared as described in **Example 106 Step 4** with the second eluting isomer from **Chiral Example 1 Step 4** replacing *tert*-

butyl (3-hydroxyphenyl)(phenyl)methylcarbamate.

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).

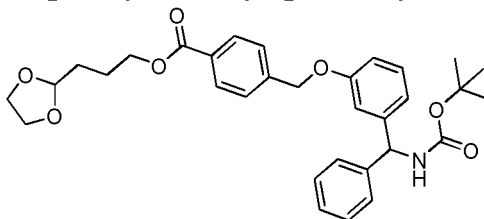
5 **Step 2; 4-((3-(((*tert*-Butoxycarbonyl)amino)(phenyl)methyl)-phenoxy)methyl)benzoic acid**



The title compound was prepared as described in **Example 81 Step 7** with methyl 4-((3-(((*tert*-butoxycarbonyl)amino)(phenyl)methyl)phenoxy)-methyl)benzoate replacing methyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate.

¹H NMR (DMSO-d₆): δ 7.94 (3 H, m), 7.54 (2 H, d, J = 7.97 Hz), 7.43 (1 H, d, J = 7.98 Hz), 7.37-7.15 (5 H, m), 7.02 (1 H, s), 6.96-6.84 (2 H, m), 5.79 (1 H, d, J = 9.68 Hz), 5.16 (2 H, s), 1.39 (9 H, s)

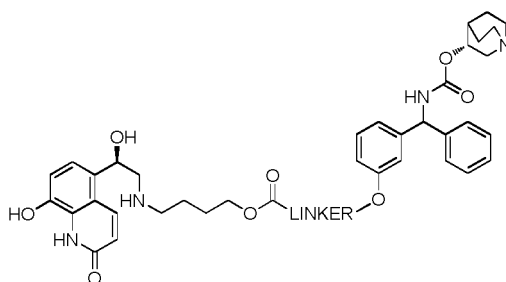
15 **Step 3; 3-(1,3-Dioxolan-2-yl)propyl 4-((3-(((*tert*-butoxycarbonyl)amino)(phenyl)methyl)phenoxy)methyl)benzoate**



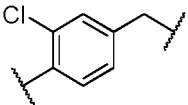
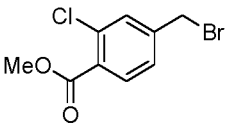
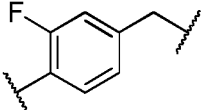
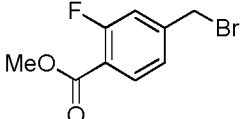
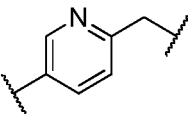
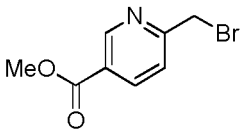
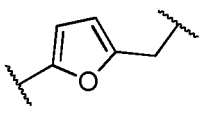
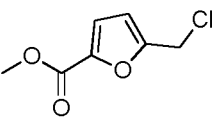
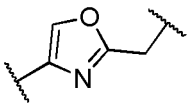
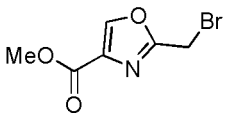
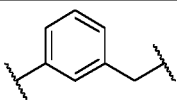
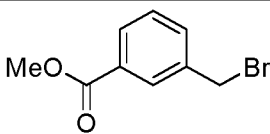
The title compound was prepared from 4-((3-(((*tert*-butoxycarbonyl)amino)(phenyl)methyl)phenoxy)methyl)benzoic acid and 2-(3-chloropropyl)-1,3-dioxolane according to the method of **Chiral Example 5 Step 1**.

¹H NMR (400 MHz, CDCl₃): δ 8.04-8.02 (m, 2 H); 7.47-7.45 (m, 2 H); 7.33-7.21 (m, 6 H); 6.88-6.84 (m, 3 H); 5.87 (br s, 1 H); 5.15 (br s, 1 H); 5.08 (s, 2 H); 4.95-4.93 (m, 1 H); 4.38-4.35 (m, 2 H); 4.10-3.97 (m, 2 H); 3.88-3.85 (m, 2 H); 1.94-1.90 (m, 2 H); 1.86-1.83 (m, 2 H), 1.30 (s, 9 H).

5 The following compounds were made using this alternative synthesis starting from the second eluting isomer of *tert*-butyl (3-hydroxyphenyl)(phenyl)methylcarbamate using the appropriate alkylating agent in **Step 1**.



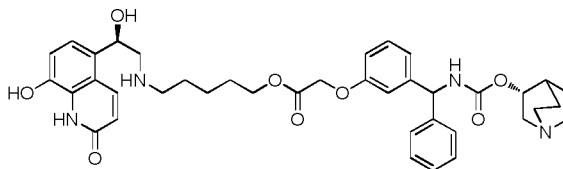
10

Compound	LINKER	Appropriate alkylating agent
47C		
48C		
49C		
50C		
51C		
52C		

Chiral Example 7

5-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

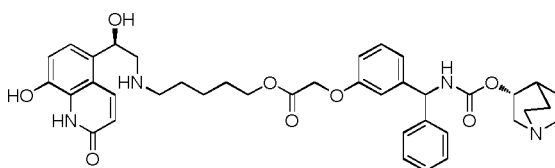
yl)ethyl)amino)pentyl 2-(3-(phenyl(((*R*)-quinuclidin-3-yloxy)-
carbonyl)amino)methyl)phenoxy)acetate (Compound 53C)



5 The title compound was prepared as described in **Compound 9C** but starting from the second eluting isomer from **Chiral Example 1 Step 4**.

Chiral Example 8

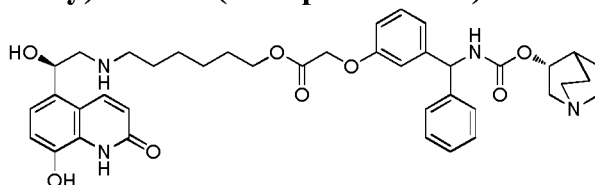
5-(((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl 2-(3-(phenyl(((*R*)-quinuclidin-3-yloxy)-
10 carbonyl)amino)methyl)phenoxy)acetate (Compound 54C)



The title compound was prepared as described in **Compound 9C** but starting from the first eluting isomer from **Chiral Example 1 Step 4**.

Chiral Example 9

6-(((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl 2-(3-(phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)-
amino)methyl)phenoxy)acetate (Compound 55C)

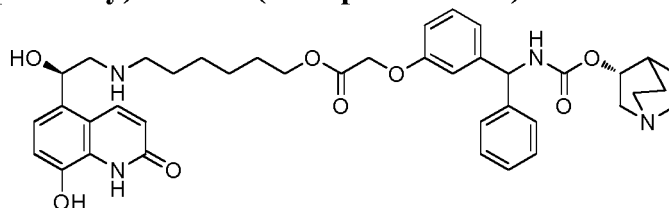


20 The title compound was prepared as described in **Example 59** but starting from the second eluting isomer from **Chiral Example 1 Step 4**.

Chiral Example 10

6-(((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

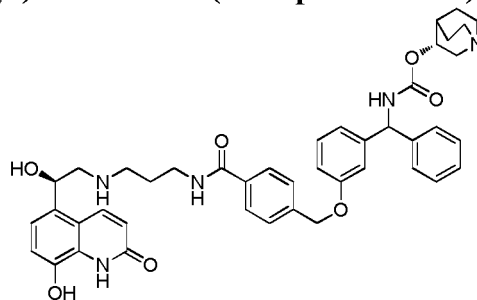
yl)ethyl)amino)hexyl 2-(3-(phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)-amino)methyl)phenoxy)acetate (Compound 56C)



The title compound was prepared as described in **Example 59** but starting from the first eluting isomer from **Chiral Example 1 Step 4**.

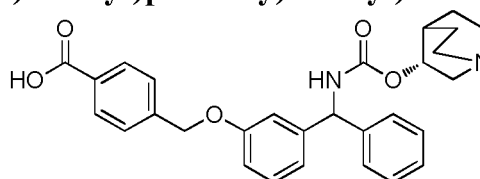
Chiral Example 11

(*R*)-Quinuclidin-3-yl ((3-((4-((3-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)propyl)carbamoyl)benzyl)oxy)-phenyl)(phenyl)methyl)carbamate (Compound 57C)



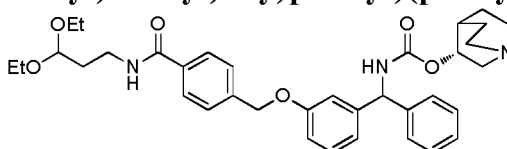
10

Step 1; 4-(((3-(Phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoic acid



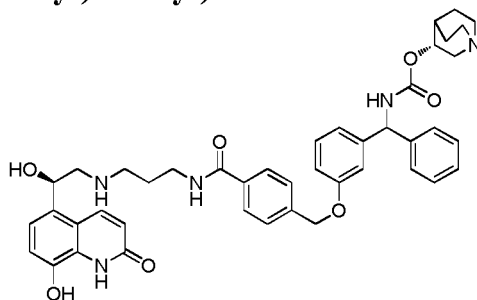
The title compound was prepared as described in **Example 79 Steps 4-7** with the second eluting isomer from **Chiral Example 1 Step 4** replacing the racemic *tert*-butyl (3-hydroxyphenyl)(phenyl)methylcarbamate in Step 4.

Step 2; (*R*)-Quinuclidin-3-yl ((3-((4-((3,3-diethoxypropyl)carbamoyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate



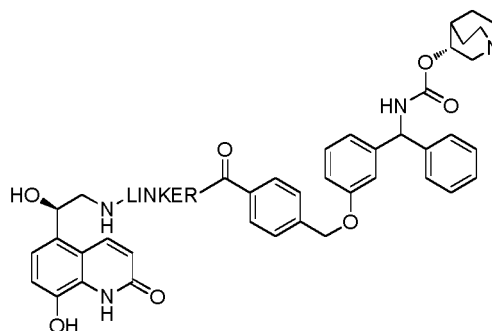
To a stirred solution of 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoic acid (0.300 g, 0.57 mmol) in DMF (2.5 mL) was added HATU (0.262 g, 0.69 mmol) and diisopropylethylamine (0.250 mL, 1.43 mmol) and the reaction mixture was stirred at room temperature for 30 minutes. 1-Amino-3,3-diethoxypropane (0.139 mL, 0.86 mmol) was added and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate and washed sequentially with saturated sodium hydrogen carbonate and brine (x2). The organic phase was dried with anhydrous sodium sulphate, filtered and the solvent evaporated at reduced pressure. The crude material was purified by silica gel chromatography eluting with 100% *iso*-hexane to 100% ethyl acetate in *iso*-hexane to afford the title compound (0.347 g, 99%), used directly in the next step.

Step 3; (R)-quinuclidin-3-yl ((3-((4-((3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)propyl)carbonyl)-benzyl)oxy)phenyl)(phenyl)methyl)carbamate



The title compound was prepared as described in **Example 1 Step 6** and **Step 7**.

The following compounds were prepared in the same fashion as **Chiral Example 11** using the appropriate amine in **Step 2**.



Compound No	Linker	Appropriate amine
58C		
59C		
60C		
61C		
62C		
63C		
64C		
65C		
66C		

The amines for **Compounds 59C, 60C, 61C, 65C and 66C** were prepared as detailed below (exemplified for the amine for **Compound 60C**);

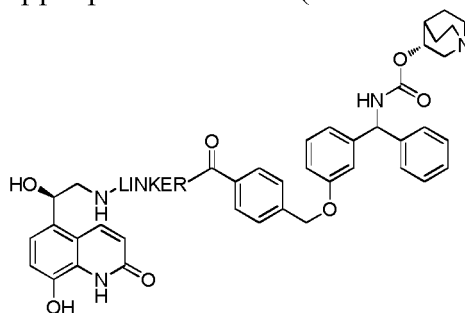
- 5 N-Benzylmethyalmine (1 equivalent), 2-(2-bromoethyl)-1,3-dioxalane (1.5 equivalents) and potassium carbonate (1.5 equivalents) in acetonitrile

(0.4 M) were heated at 80°C for 24 hours. The reaction mixture was diluted with ethyl acetate and washed sequentially with water and saturated aqueous brine. The organic phase was dried with anhydrous magnesium sulfate, filtered and the solvent evaporated at reduced pressure. The residue was
 5 purified by chromatography on an SCX-2 cartridge. The material was subjected to the procedure described in the synthesis of **(R)-5-(2-Amino-1-(tert-butylidimethylsilyloxy)ethyl)-8-hydroxyquinolin-2(1H)-one**.

The amine for **Compound 62C** was prepared by alkylating *trans*-4-(((*tert*-butoxycarbonyl)amino)methyl)cyclohexanecarboxylic acid with
 10 2-(3-chloropropyl)-1,3-dioxolane according to the protocol in **Example 54 Step 1** followed by removal of the protecting group according to the protocol in **Example 81 Step 5**.

The amine for **Compound 63C** was prepared by coupling (S)-3-(((*tert*-butoxycarbonyl)amino)-4-methoxy-4-oxobutanoic acid and 2,2-dimethoxy-N-methylethanamine according to the protocol in **Chiral Example 11 Step 2**
 15 followed by removal of the protecting group according to the protocol in **Example 81 Step 5**.

The following compounds were prepared in a similar fashion to **Chiral Example 11** but using the appropriate alcohol (heated at 60°C) in **Step 2**.

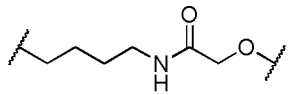
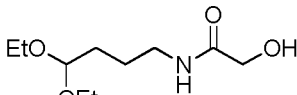
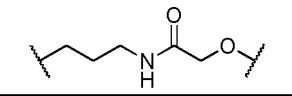
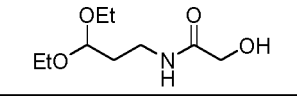
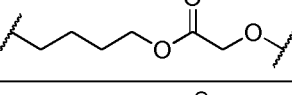
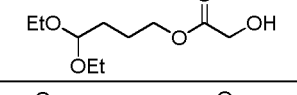
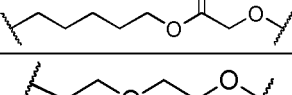
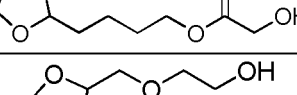
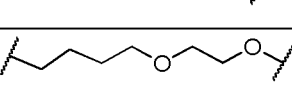
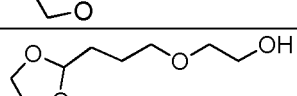
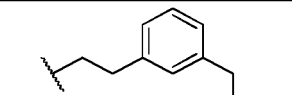
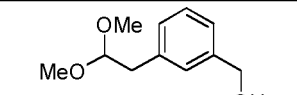
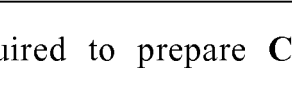
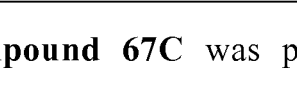


20

Compound No	Linker	Appropriate alcohol
67C		

(continued)

164

68C		
69C		
70C		
71C		
72C		
73C		
74C		

The alcohol required to prepare **Compound 67C** was prepared as described in Faming Zhuanli Shenqing Gongkai Shuomingshu, 101153000, 02 Apr 2008.

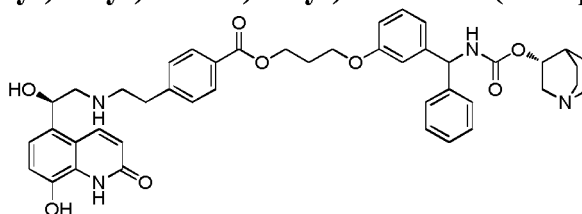
The alcohol required to prepare **Compound 68C** and **69C** was prepared from the requisite amine and hydroxyacetic acid.

The alcohol required to prepare **Compound 70C** and **71C** was prepared from the requisite alcohol and hydroxyacetic acid.

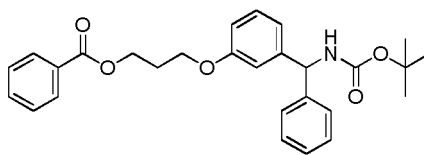
The alcohol required to prepare **Compound 72C** and **73C** was prepared from ethylene glycol and the requisite bromide.

10 Chiral Example 12

3-(3-(Phenyl((((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)-phenoxy)propyl 4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzoate (Compound 75C)

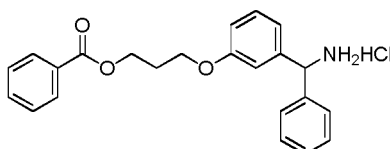


15 **Step 1; 3-(3-(((tert-Butoxycarbonyl)amino)(phenyl)methyl)-**

phenoxy)propyl benzoate

The title compounds was prepared as described in **Example 22 Step 3** with 3-hydroxypropyl benzoate (prepared as outlined in Organic & Biomolecular Chemistry, 8(24), 5505-5510; 2010) and *tert*-butyl ((3-hydroxyphenyl)(phenyl)methyl)carbamate (derived from the second eluting isomer **Chiral Example 1 Step 4**) replacing (4-((1,3-dioxolan-2-yl)methyl)phenyl)methanol and 3-hydroxybenzophenone respectively.

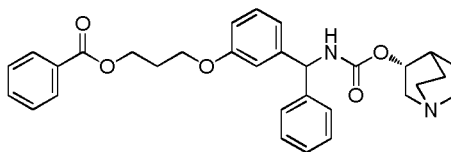
¹H NMR (400 MHz, CDCl₃): δ 8.03 (d, J = 7.7 Hz, 2 H); 7.60-7.52 (m, 1 H); 7.48-7.40 (m, 2 H); 7.35-7.19 (m, 6 H); 6.85-6.76 (m, 3 H); 5.86 (s, 1 H); 5.13 (s, 1 H); 4.54-4.47 (m, 2 H); 4.16-4.05 (m, 2 H); 2.29-2.19 (m, 2 H); 1.43 (s, 9 H).

Step 2; 3-(3-(Amino(phenyl)methyl)phenoxy)propyl benzoate hydrochloride

Hydrogen chloride in dioxane (4 M, 3.30 mL, 13.2 mmol) was added to 3-(3-(((*tert*-butoxycarbonyl)amino)(phenyl)methyl)phenoxy)propyl benzoate (0.359 g, 0.78 mmol) and the resultant mixture was stirred at room temperature for 2 hours. The solvent was evaporated at reduced pressure to afford the title compound (0.271 g, 88%).

¹H NMR (400 MHz, DMSO-d₆): δ 8.95 (s, 3 H); 7.98 (d, J = 7.7 Hz, 2 H); 7.71-7.63 (m, 1 H); 7.52 (dd, J = 15.3, 7.6 Hz, 4 H); 7.46-7.29 (m, 4 H); 7.17 (s, 1 H); 7.05 (d, J = 7.7 Hz, 1 H); 6.96 (d, J = 8.3 Hz, 1 H); 5.60 (s, 1 H); 4.47-4.40 (m, 2 H); 4.18-4.11 (m, 2 H); 2.24-2.16 (m, 2 H).

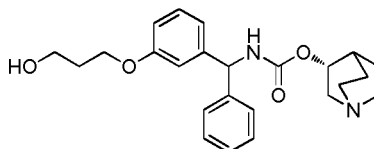
Step**3;****3-(3-(Phenyl(((R)-quinuclidin-3-**



5 with 3-(3-(amino(phenyl)methyl)phenoxy)propyl benzoate hydrochloride
replacing (3-(8-(1,3-dioxolan-2-yl)octyloxy)phenyl)(phenyl)methanamine.

¹H NMR (400 MHz, CDCl₃): δ 8.05-8.00 (m, 2 H); 7.60-7.53 (m, 1 H); 7.48-7.40 (m, 2 H); 7.37-7.29 (m, 2 H); 7.28-7.18 (m, 4 H); 6.88-6.78 (m, 3 H); 5.91 (s, 1 H); 5.31 (s, 1 H); 4.72 (s, 1 H); 4.54-4.47 (m, 2 H); 4.16-4.06 (m, 2 H); 3.20 (s, 1 H); 2.93-2.63 (s, 4 H); 2.28-2.19 (m, 2 H); 2.03-1.48 (br, 6 H).

Step 4; (R)-Quinuclidin-3-yl ((3-(3-hydroxypropoxy)phenyl)-(phenyl)methyl)carbamate

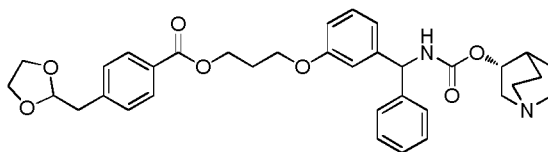


To a stirred solution of 3-(3-(phenyl(((R)-quinuclidin-3-ylloxy)carbonyl)amino)methyl)phenoxy)propyl benzoate (0.370 g, 0.72 mmol) in methanol (3.6 mL) was added a solution of lithium hydroxide monohydrate (0.060 g, 1.44 mmol) in water (1.2 mL). The reaction mixture was stirred at room temperature for 1 hour. Further lithium hydroxide monohydrate (0.060 g, 1.44 mmol) was added and the reaction stirred at room temperature for a further 16 hours. The reaction mixture was heated at 40°C for 3.5 hours and allowed to cool. The solvent was evaporate at reduced pressure and the residue partitioned between ethyl acetate and water. The aqueous phase was further extracted with ethyl acetate (x2). The combined organic extracts were washed with 10% aqueous potassium carbonate (x2), saturated brine and dried

with anhydrous sodium sulfate. The mixture was filtered and the solvent evaporated at reduced pressure to afford the title compound (0.275 g, 93%).

¹H NMR (400 MHz, CDCl₃): δ 7.38-7.20 (m, 6 H); 6.83 (t, J = 8.5 Hz, 3 H); 5.91 (s, 1 H); 5.30 (s, 1 H); 4.72 (s, 1 H); 4.16-4.06 (m, 2 H); 3.83 (t, J = 5.8 Hz, 2 H); 3.19 (s, 1 H); 2.94-2.62 (m, 4 H); 2.04-1.96 (m, 2 H); 1.90-1.32 m, 7 H).

Step 5; 3-(3-(Phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)propyl 4-((1,3-dioxolan-2-yl)methyl)benzoate



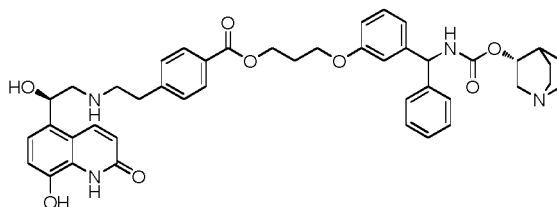
10

The title compound was prepared as described in **Chiral Example 11 Step 2** with (R)-quinuclidin-3-yl ((3-(3-hydroxypropoxy)phenyl)-(phenyl)methyl)carbamate and 4-(1,3-dioxolan-2-ylmethyl)-benzoic acid replacing 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)methyl)benzoic acid and 1-amino-3,3-diethoxypropane respectively.

15

Step 6; 3-(3-(Phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)-methyl)phenoxy)propyl 4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzoate (Compound 75C)

20

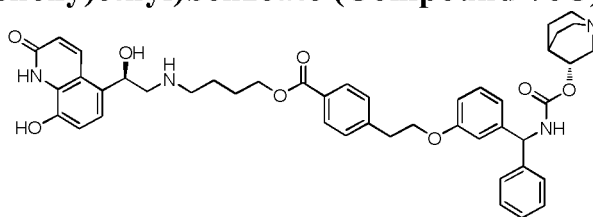


The title compound was prepared as described in **Example 1 Step 6** and 7.

Chiral Example 13

4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 4-(2-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)-

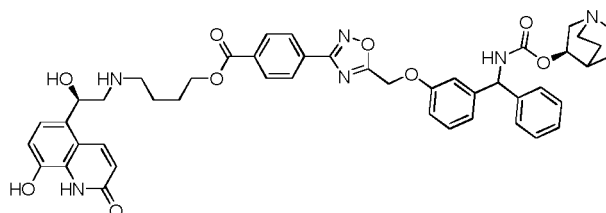
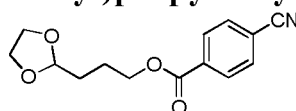
25

amino)methyl)phenoxy)ethyl)benzoate (Compound 76C)

The title compound was prepared as in **Chiral Example 5** with 4-(2-hydroxyethyl)benzoic acid replacing 4-hydroxymethylbenzoic acid and using *tert*-butyl (3-hydroxyphenyl)(phenyl)methylcarbamate (second eluting isomer from **Chiral Example 1 Step 4**) in **Step 1**.

Chiral Example 14

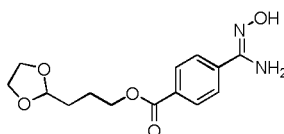
4-(((*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 4-(5-((3-(phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)-amino)methyl)phenoxy)methyl)-1,2,4-oxadiazol-3-yl)benzoate (Compound 77C)

**Step 1; 3-(1,3-Dioxolan-2-yl)propyl 4-cyanobenzoate**

The title compound was prepared as described in **Chiral Example 4 Step 1** with 4-cyanobenzoic acid replacing 4-hydroxymethylbenzoic acid.

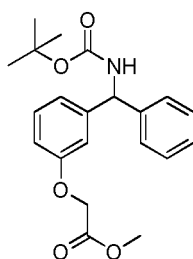
¹H NMR (400 MHz, CDCl₃): δ 8.16-8.12 (m, 2 H); 7.77-7.73 (m, 2 H); 4.97-4.89 (m, 1 H); 4.44-4.36 (m, 2 H); 4.04-3.83 (m, 4 H); 1.97-1.88 (m, 2 H); 1.86-1.79 (m, 2 H).

Step 2; 3-(1,3-Dioxolan-2-yl)propyl 4-(*N'*-hydroxycarbamimidoyl)benzoate



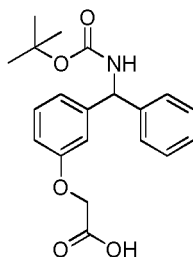
To a solution of 3-(1,3-dioxolan-2-yl)propyl 4-cyanobenzoate (1.00 g, 4.38 mmol) in ethanol (5 mL) was added hydroxylamine (50% aqueous solution, 5 mL) and the mixture heated at 80°C for 4 hours. The reaction was diluted with saturated brine and extracted with ethyl acetate (x3). The combined organic fractions were dried with magnesium sulfate and the solvent evaporated at reduced pressure. Material used directly in the next step without further purification.

Step 3; Methyl 2-(3-(((tert-butoxycarbonyl)amino)-(phenyl)methyl)phenoxy)acetate



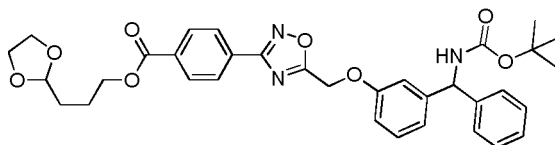
The title compound was prepared as described in **Example 79 Step 4** with the second eluting isomer from **Chiral Example 1 Step 4** replacing *tert*-butyl (3-hydroxyphenyl)(phenyl)methylcarbamate.

Step 4; 2-(3-(((tert-Butoxycarbonyl)amino)-(phenyl)methyl)phenoxy)acetic acid



The title compound was prepared as described in **Example 79 Step 7** with methyl 2-(3-(((tert-butoxycarbonyl)amino)(phenyl)methyl)phenoxy)-acetate acid replacing methyl 4-((3-(phenyl(((R)-quinuclidin-3-yl)oxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate.

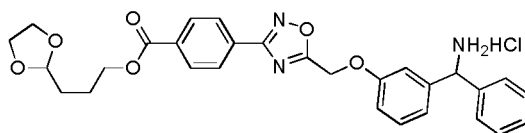
Step 5; 3-(1,3-Dioxolan-2-yl)propyl 4-(5-(((3-(((*tert*-butoxycarbonyl)-amino)(phenyl)methyl)phenoxy)methyl)-1,2,4-oxadiazol-3-yl)benzoate



5 To a solution of 2-(3-(((*tert*-butoxycarbonyl)amino)(phenyl)-methyl)phenoxy)acetic acid (0.087 g, 0.34 mmol) and 3-(1,3-dioxolan-2-yl)propyl 4-(N'-hydroxycarbamimidoyl)benzoate (0.10 g, 0.28 mmol) in acetonitrile (1 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (0.087 g, 0.42 mmol). The reaction mixture was
10 stirred at ambient temperature for 16 hours. The reaction mixture was diluted with pyridine and heated at 150°C for 30 minutes in a microwave. The reaction was diluted with saturated brine and extracted with ethyl acetate (x3). The combined organic fractions were dried with magnesium sulfate and the solvent evaporated at reduced pressure. Material used directly in the next step
15 without further purification (0.142 g, 87%).

¹H NMR (400 MHz, CDCl₃): δ 8.16 (s, 4H); 7.40-7.33 (m, 6 H); 7.00-6.88 (m, 3 H); 5.35-5.26 (m, 2 H); 4.97-4.92 (m, 1 H); 4.45-4.35 (m, 2 H); 4.04-3.93 (m, 2 H); 3.93-3.83 (m, 2 H); 2.01-1.81 (m, 4 H); 1.43 (s, 9 H).

Step 6; 3-(1,3-dioxolan-2-yl)propyl 4-(5-(((3-(((*tert*-butoxycarbonyl)amino)(phenyl)methyl)phenoxy)methyl)-1,2,4-oxadiazol-3-yl)benzoate hydrochloride

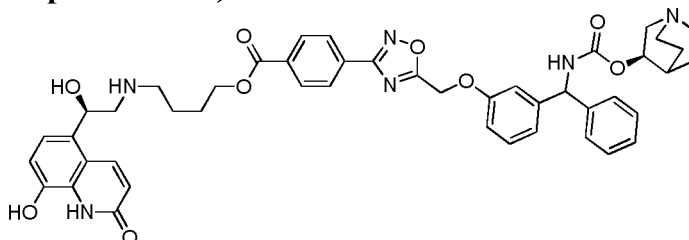


Hydrogen chloride in dioxane (4.0 M, 5 mL, 24 mmol) was added to 3-(1,3-dioxolan-2-yl)propyl 4-(5-(((3-(((*tert*-butoxycarbonyl)amino)(phenyl)-methyl)phenoxy)methyl)-1,2,4-oxadiazol-3-yl)benzoate (0.237 g, 0.41 mmol)
25 and the resultant solution was stirred at ambient temperature for 2 hours. The

solvent was evaporated at reduced pressure to afford the title compound (0.212 g, 100%).

¹H NMR (400 MHz, DMSO-d₆): δ 9.05 (s, 3 H); 8.18-8.07 (m, 4 H); 7.50 (d, J = 7.6 Hz, 2 H); 7.42-7.30 (m, 5 H); 7.15 (d, J = 7.8 Hz, 1 H); 7.10 (dd, J = 8.3, 2.6 Hz, 1 H); 5.71-5.53 (m, 3 H); 4.86-4.81 (m, 1 H); 4.35-4.27 (m, 2 H); 3.91-3.81 (m, 2 H); 3.79-3.73 (m, 2 H); 1.86-1.68 (m, 4 H).

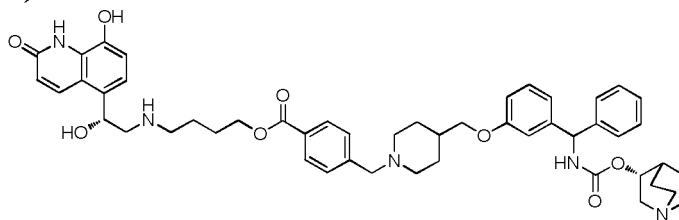
Step 7; 4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 4-(5-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)-1,2,4-oxadiazol-3-yl)benzoate (Compound 77C)



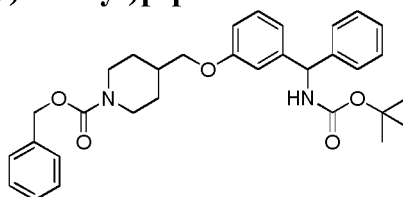
The title compound was prepared using **Step 5, 6 and 7 of Example 1.**

Chiral Example 15

4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 4-((4-((3-(phenyl(((R)-quinuclidin-3-yloxy)-carbonyl)amino)methyl)phenoxy)methyl)piperidin-1-yl)methyl)benzoate (Compound 78C)



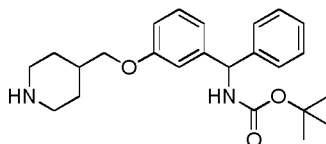
Step 1; Benzyl 4-((3-(((tert-butoxycarbonyl)amino)-(phenyl)methyl)phenoxy)methyl)piperidine-1-carboxylate



To a stirred solution of *tert*-butyl (3-hydroxyphenyl)(phenyl)methylcarbamate (the second eluting isomer from **Chiral Example 1 Step 4**, 1.00 g, 3.34 mmol) in DMF (15 mL) was added potassium carbonate (0.554 g, 4.01 mmol). The reaction mixture was stirred
5 for 10 minutes and benzyl 4-((tosyloxy)methyl)piperidine-1-carboxylate (prepared according to Bioorganic & Medicinal Chemistry Letters, 20(1), 380-382; 2010, 1.48 g, 3.67 mmol) added. The reaction mixture was heated at 60°C for 2 days followed by 80°C for 5 days. The reaction mixture was diluted with ethyl acetate and washed with water and saturated brine (x2). The
10 organic phase was dried with anhydrous magnesium sulfate and the solvent evaporated at reduced pressure. The crude material was purified by silica gel chromatography eluting with 100% *iso*-hexane to 50% ethyl acetate in *iso*-hexane to afford the title compound (1.12 g, 63%).

¹H NMR (400 MHz, CDCl₃): δ 7.40-7.18 (m, 11 H); 6.82 (d, J = 7.7 Hz, 1 H); 6.79-6.73 (m, 2 H); 5.86 (s, 1 H); 5.13 (s, 3 H); 4.23 (s, 2 H); 3.76 (d, J = 6.3 Hz, 2 H); 2.81 (m, 2 H); 1.99-1.89 (m, 1 H); 1.82 (d, J = 13.1 Hz, 2 H); 1.44 (s, 9 H); 1.33-1.22 (m, 2 H).

Step 2; *tert*-Butyl (phenyl(3-(piperidin-4-ylmethoxy)phenyl)methyl)carbamate

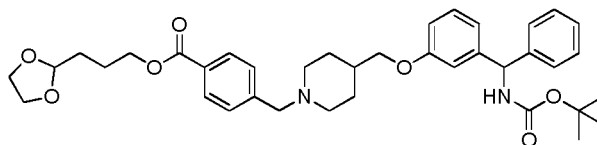


To a stirred solution of benzyl 4-((3-(((*tert*-butoxycarbonyl)amino)(phenyl)methyl)phenoxy)methyl)piperidine-1-carboxylate (1.12 g, 2.11 mmol) in ethanol (10 mL) was added 10% palladium on charcoal (0.22 g) and 1-methyl-1,4-cyclohexadiene (1.18 mL, 10.55 mmol).
25 The reaction mixture was heated to 80°C for 7 hours. The reaction mixture was filtered through a pad of celite and the filter-pad washed with further

ethanol. The filtrate was evaporated at reduced pressure to afford the title compound (0.716 g, 85%).

¹H NMR (400 MHz, CDCl₃): δ 7.38-7.17 (m, 6 H); 6.82-6.73 (m, 3 H); 5.86 (s, 1 H); 5.15 (s, 1 H); 3.78-3.68 (m, 2 H); 3.13 (d, J = 12.3 Hz, 2 H);
 5 2.65 (td, J = 12.1, 2.5 Hz, 2 H); 1.96-1.78 (m, 5 H); 1.33-1.18 (m, 9 H) (no exchangeable observed)

Step 3; 3-(1,3-Dioxolan-2-yl)propyl 4-(((4-(((3-(((*tert*-butoxycarbonyl)amino)(phenyl)methyl)phenoxy)methyl)piperidin-1-yl)methyl)benzoate



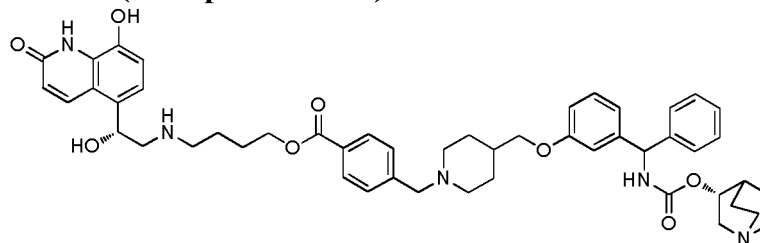
10

To a stirred solution of *tert*-butyl (phenyl(3-(piperidin-4-ylmethoxy)phenyl)methyl)carbamate (0.335 g, 0.84 mmol) and 3-(1,3-dioxolan-2-yl)propyl 4-formylbenzoate (0.706 g, 2.67 mmol) in DCM (5 mL) was added sodium triacetoxyborohydride (0.213 g, 1.01 mmol). The
 15 reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with DCM and washed with water, saturated aqueous sodium hydrogen carbonate and brine. The organic phase was dried with anhydrous magnesium sulfate and the solvent evaporated at reduced pressure. The residue was triturated with *iso*-hexane/diethyl ether (3:1) to afford the
 20 title compound (0.286 g, 0.44 mmol).

¹H NMR (400 MHz, CDCl₃): δ 7.98 (d, J = 8.0 Hz, 2 H); 7.39 (d, J = 8.0 Hz, 2 H); 7.35-7.16 (m, 6 H); 6.83-6.73 (m, 3 H); 5.86 (s, 1 H); 5.13 (s, 1 H); 4.96-4.91 (m, 1 H); 4.40-4.32 (m, 2 H); 4.00-3.95 (m, 2 H); 3.90-3.84 (m, 2 H); 3.76 (d, J = 5.8 Hz, 2 H); 3.55 (s, 2 H); 2.89 (d, J = 11.1 Hz, 2 H); 2.05-
 25 1.97 (m, 2 H); 1.97-1.77 (m, 7 H); 1.63-1.19 (m, 11 H).

Step 4; 4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-

5-yl)ethyl)amino)butyl 4-((4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)piperidin-1-yl)methyl)benzoate (Compound 78C)

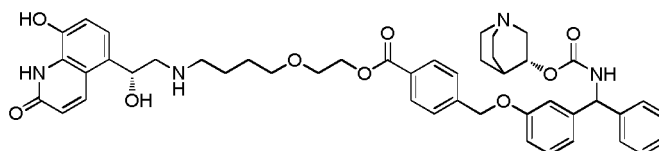


5 The title compound was prepared as described in **Chiral Example 5 Step 3** and **4**.

The following compounds were prepared as described above using the first eluting isomer of *tert*-butyl (3-hydroxyphenyl)(phenyl)methylcarbamate (**Chiral Example 1 Step 4**).

10 **Chiral Example 16**

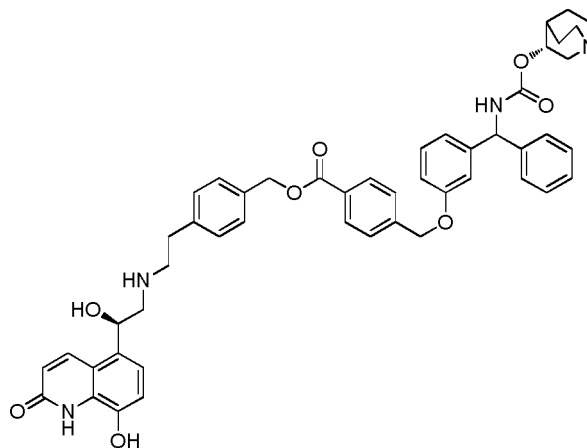
2-(4-(((R)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)ethyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate (Compound 79C)



15 The title compound was prepared as described for **Compound 73C** using the first eluting isomer of *tert*-butyl (3-hydroxyphenyl)(phenyl)methylcarbamate.

Chiral Example 17

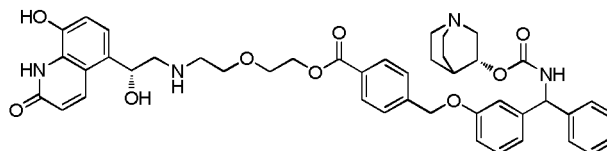
4-(2-(((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzyl 4-((3-(phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)-amino)methyl)phenoxy)methyl)benzoate (Compound 80C)



The title compound was prepared as described for **Compound 8C** using the first eluting isomer of *tert*-butyl (3-hydroxyphenyl)-(phenyl)methylcarbamate.

Chiral Example 18

2-(2-(((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethoxy)ethyl 4-((3-(phenyl(((*R*)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate (Compound 81C)

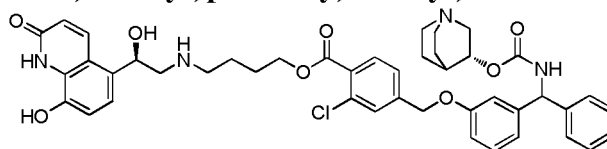


The title compound was prepared as described for **Compound 72C** using the first eluting isomer of *tert*-butyl (3-hydroxyphenyl)(phenyl)methylcarbamate.

Chiral Example 19

4-(((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 2-chloro-4-((3-(phenyl(((*R*)-quinuclidin-3-

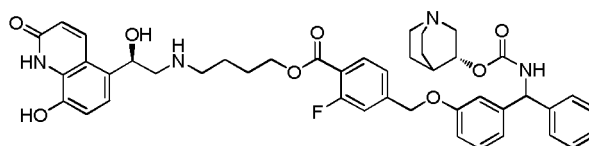
yl oxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate (Compound 82C)



The title compound was prepared as described for **Compound 47C** using the first eluting isomer of *tert*-butyl (3-hydroxyphenyl)(phenyl)methylcarbamate.

Chiral Example 20

4-(((*R*)-2-Hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 2-fluoro-4-(((3-(phenyl(((*R*)-quinuclidin-3-yl oxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate (Compound 83C)



The title compound was prepared as described for **Compound 48C** using the first eluting isomer of *tert*-butyl (3-hydroxyphenyl)(phenyl)methylcarbamate.

Cpd.	LCMS / HPLC method	NMR data at 400 MHz	Salt
1	B	(CD ₃ OD): δ 8.54 (s, 2 H); 8.37 (d, J = 9.88 Hz, 1 H); 7.36-7.18 (m, 7 H); 7.02 (d, J = 8.16 Hz, 1 H); 6.83-6.77 (m, 2 H); 6.68 (d, J = 9.88 Hz, 1 H); 5.86 (s, 1 H); 5.37 (dd, J = 7.81, 5.61 Hz, 1 H); 3.93 (t, J = 6.36 Hz, 2 H); 3.43 (d, J = 11.82 Hz, 1 H); 3.23-3.04 (m, 3 H); 3.06-2.93 (m, 7 H); 2.19 (s, 1 H); 2.09 (s, 1 H); 1.88 (s, 1 H); 1.78-1.66 (m, 8 H); 1.46 (s, 3 H); 1.38 (s, 9 H)	diformate
2	B	(CD ₃ OD): δ 8.56 (s, 2 H); 8.45-8.36 (m, 1 H); 7.38-7.20 (m, 7 H); 7.05 (d, J = 8.16 Hz, 1 H); 6.89-6.78 (m, 3 H); 6.70 (d, J = 9.84 Hz, 1 H); 5.88 (s, 1 H); 5.45-5.36 (m, 1 H); 4.90 (m, 1H, obscured by solvent); 3.95 (t, J = 6.34 Hz, 2 H); 3.59 (m, 1 H), 3.3-2.99 (m, 9 H), 2.30 (s, 1 H); 2.16 (s, 1 H); 2.03-1.69 (m, 7 H); 1.58-1.39 (m, 8 H)	diformate

(continued)

3	B	(CD ₃ OD): δ 8.56 (s, 2 H); 8.40 (d, 1 H); 7.37-7.20 (m, 7 H); 7.04 (d, J = 8.16 Hz, 1 H); 6.89-6.78 (m, 3 H); 6.72 (d, 1 H); 5.88 (s, 1 H); 5.39 (t, J = 6.73 Hz, 1 H); 4.90 (m, 1H, obscured by solvent); 3.96 (t, J = 6.30 Hz, 2 H); 3.51 (m, 1 H); 3.22-2.98 (m, 9 H); 2.25 (s, 1 H); 2.13 (s, 1 H); 1.99-1.64 (m, 7 H); 1.59-1.41 (m, 6 H)	diformate
4	B	(CD ₃ OD): δ 8.54 (s, 2H), 8.40 (d, J = 9.6 Hz, 1H), 7.36-7.23 (m, 7H), 7.05 (d, J = 8 Hz, 1H), 6.88-6.82 (m, 3H), 6.76 (d, J = 9.6 Hz, 1H), 5.88 (br s, 1H), 5.41-5.38 (m, 1H), 4.88 (m, 1H), 3.99-3.96 (m, 2H), 3.58 (m, 1H), 3.27-3.06 (m, 9H), 2.29 (br s, 1H), 2.17 (m, 1H), 1.98-1.73 (m, 6H), 1.60-1.45 (m, 5H)	diformate
5	B	(DMSO-d ₆): δ 8.32 (s, 2H), 8.27-8.25 (m, 1H), 8.21 (d, J = 10 Hz, 1H), 7.33-7.29 (m, 4H), 7.24-7.20 (m, 2H), 7.12 (d, J = 8.4 Hz, 1H), 6.98-6.90 (m, 3H), 6.80 (d, J = 8.0 Hz, 1H), 6.55 (d, J = 10 Hz, 1H), 5.82 (d, J = 8.8 Hz, 1H), 5.24-5.21 (m, 1H), 4.59 (br s, 1H), 3.94-3.91 (m, 2H), 3.13 (m, 1H), 2.91-2.33 (m, 8H), 1.93-1.39 (m, 12H)	diformate
6	B	(CD ₃ OD): δ 8.53 (s, 1 H), 8.38 (d, J = 9.87 Hz, 1 H), 7.45-7.21 (m, 12 H), 7.05 (d, J = 8.17 Hz, 1 H), 6.81 (s, 3 H), 6.70 (d, J = 9.84 Hz, 1 H), 5.86 (s, 1 H), 5.40 (t, J = 6.76 Hz, 1 H), 4.72 (s, 1 H), 3.95 (s, 2 H), 3.78 (s, 1 H), 3.26-3.20 (m, 2 H), 3.07 (t, J = 7.98 Hz, 2 H), 2.94 (s, 1 H), 2.60 (s, 2 H), 1.99 (s, 4 H), 1.84-1.71 (m, 6 H), 1.54-1.30 (s, 10 H).	formate
7	B	(DMSO-d ₆): δ 8.32 (s, 1 H); 8.20 (t, J = 9.75 Hz, 2 H); 7.35-7.26 (m, 4 H); 7.25-7.16 (m, 2 H); 7.11 (d, J = 8.17 Hz, 1 H); 6.96 (d, J = 8.14 Hz, 1 H); 6.93-6.85 (m, 2 H); 6.77 (dd, J = 8.21, 2.42 Hz, 1 H); 6.53 (d, J = 9.86 Hz, 1 H); 5.81 (d, J = 9.40 Hz, 1 H); 5.21 (dd, J = 8.51, 4.13 Hz, 1 H); 4.51 (m, 1 H); 3.91 (t, J = 6.48 Hz, 2 H); 2.94-2.85 (m, 2 H); 2.79-2.72 (m, 2 H); 2.61 (s, 2 H); 2.24-1.97 (m, 5 H); 1.81 (s, 2 H); 1.72-1.62 (m, 2 H); 1.61-1.45 (m, 4 H); 1.44-1.14 (m, 10H)	formate

(continued)

8	A	(DMSO-d ₆): δ 8.35 (s, 1 H); 8.19 (d, J = 9.86 Hz, 2 H); 7.37-7.15 (m, 10 H); 7.10 (d, J = 8.15 Hz, 1 H); 6.96 (d, J = 8.13 Hz, 1 H); 6.92-6.83 (m, 2 H); 6.77 (dd, J = 8.20, 2.50 Hz, 1 H); 6.52 (d, J = 9.84 Hz, 1 H); 5.79 (d, J = 9.39 Hz, 1 H); 5.18 (m, 1 H); 4.81 (m, 1 H); 3.91 (t, J = 6.50 Hz, 2 H); 3.54 (s, 2 H); 3.15 (d, J = 5.01 Hz, 2 H); 2.84 (m, 1 H); 2.73-2.65 (m, 1 H); 1.95 (s, 2 H); 1.79 (s, 2 H); 1.71-1.52 (m, 7 H); 1.49-1.21 (m, 13 H).	formate
9	B	(CD ₃ OD): δ 8.55 (s, 2 H); 8.36 (d, J = 9.84 Hz, 1 H); 7.34-7.21 (m, 6 H); 7.14 (s, 3 H); 7.01 (d, J = 8.24 Hz, 1 H); 6.85 (d, J = 8.24 Hz, 2 H); 6.67 (d, J = 9.82 Hz, 1 H); 5.84 (s, 1 H); 5.39-5.32 (m, 1 H); 3.93 (t, J = 3.20 Hz, 2 H); 3.46-3.29 (m, 1 H); 3.19-3.14 (m, 2 H); 3.11-2.87 (m, 8 H); 2.17 (s, 1 H); 2.07 (s, 1 H); 1.86 (s, 1 H); 1.77-1.66 (m, 7 H); 1.47 (s, 3 H); 1.38 (s, 9 H).	formate
10	A	(CD ₃ OD): δ 8.39 (d, J = 9.83 Hz, 1 H); 7.34-7.17 (m, 3 H); 6.97-6.92 (m, 4 H); 6.90-6.80 (m, 2 H); 6.65 (d, J = 9.79 Hz, 1 H); 6.07 (s, 1 H); 5.25 (dd, J = 9.11, 3.86 Hz, 1 H); 4.74 (d, J = 7.36 Hz, 1 H); 3.97 (t, J = 6.39 Hz, 2 H); 3.28-3.14 (m, 1 H); 3.03-2.63 (m, 9 H); 2.12-1.88 (m, 2 H); 1.84-1.70 (m, 3 H); 1.67-1.4 (m, 14 H)	none
11	B	(DMSO-d ₆): δ 8.34 (s, 1 H); 8.28 (d, J = 9.65 Hz, 1 H); 8.18 (d, J = 9.93 Hz, 1 H); 7.62 (t, J = 8.73 Hz, 4 H); 7.49-7.39 (m, 4 H); 7.35 (t, J = 7.35 Hz, 1 H); 7.23 (t, J = 7.90 Hz, 1 H); 7.10 (d, J = 8.16 Hz, 1 H); 6.95 (d, J = 8.34 Hz, 3 H); 6.79 (d, J = 8.37 Hz, 1 H); 6.52 (d, J = 9.86 Hz, 1 H); 5.86 (d, J = 9.33 Hz, 1 H); 5.17 (t, J = 6.14 Hz, 1 H); 4.59 (s, 1 H); 3.93 (t, J = 6.49 Hz, 2 H); 3.16-3.05 (m, 1 H); 2.86-2.81 (m, 2 H); 2.81-2.37 (m, 6 H); 1.92 (s, 1 H); 1.81 (s, 1 H); 1.74-1.11 (m, 18 H)	formate
12	A	(DMSO-d ₆): δ 8.35 (s, 2 H); 8.19 (d, J = 9.93 Hz, 1 H); 7.89-7.83 (m, 4 H); 7.54-7.45 (m, 3 H); 7.22 (t, J = 7.90 Hz, 1 H); 7.11 (d, J = 8.18 Hz, 1 H); 6.97 (d, J = 8.27 Hz, 3 H); 6.79 (d, J = 8.34 Hz, 1 H); 6.53 (d, J = 9.86 Hz, 1 H); 5.98 (s, 1 H); 5.22 (dd, J = 8.73, 4.00 Hz, 1 H); 4.61 (s, 1 H); 3.91 (t, J = 6.46 Hz, 2 H); 3.12 (m, 1 H); 2.94-2.81 (m, 2 H); 2.81-2.54 (m, 4 H); 1.93 (s, 1 H); 1.81 (s, 1 H); 1.73-1.1 (m, 20 H)	formate

(continued)

13	A	(DMSO-d ₆): δ 8.29 (d, J = 9.64 Hz, 1 H); 8.17 (d, J = 9.92 Hz, 1 H); 7.72-7.59 (m, 3 H); 7.52 (dd, J = 7.65, 1.84 Hz, 1 H); 7.48-7.31 (m, 5 H); 7.21 (t, J = 7.87 Hz, 1 H); 7.07 (d, J = 8.15 Hz, 1 H); 6.99-6.88 (m, 3 H); 6.77 (d, J = 8.21 Hz, 1 H); 6.50 (d, J = 9.86 Hz, 1 H); 5.89 (d, J = 9.31 Hz, 1 H); 5.03 (dd, J = 7.83, 4.59 Hz, 1 H); 4.57 (s, 1 H); 3.92 (t, J = 6.46 Hz, 2 H); 3.08 (s, 1 H); 2.78-2.54 (m, 6 H); 1.90 (s, 1 H); 1.80 (s, 1 H); 1.72-1.61 (m, 2 H); 1.57 (s, 1 H); 1.51-1.19 (m, 17 H)	none
14	A	(DMSO-d ₆): δ 8.51-8.48 (m, 1 H); 8.32 (s, 2 H); 8.19 (d, J = 9.9 Hz, 1 H); 8.10 (d, J = 9.1 Hz, 1 H); 7.80-7.73 (m, 1 H); 7.47 (d, J = 7.9 Hz, 1 H); 7.29-7.23 (m, 1 H); 7.19 (t, J = 7.9 Hz, 1 H); 7.10 (d, J = 8.2 Hz, 1 H); 6.99-6.87 (m, 3 H); 6.78 (d, J = 8.4 Hz, 1 H); 6.52 (d, J = 9.9 Hz, 1 H); 5.85 (d, J = 9.1 Hz, 1 H); 5.17 (t, J = 6.1 Hz, 1 H); 4.57 (m, 1 H); 3.91 (t, J = 6.8 Hz, 2 H); 3.16-3.04 (m, 1 H); 2.86-2.81 (m, 2 H); 2.79-2.38 (m, 4 H); 1.94-1.86 (m, 1 H); 1.86-1.73 (m, 1 H); 1.72-1.14 (m, 20 H).	diformate
15	B	(DMSO-d ₆): δ 8.34-8.25 (m, 2 H); 8.18 (d, J = 9.9 Hz, 1 H); 7.23 (t, J = 7.9 Hz, 1 H); 7.16-7.06 (m, 4 H); 6.97-6.88 (m, 3 H); 6.81 (d, J = 8.3 Hz, 1 H); 6.52 (d, J = 9.9 Hz, 1 H); 5.86 (d, J = 9.2 Hz, 1 H); 5.15 (t, J = 6.3 Hz, 1 H); 4.62-4.55 (m, 1 H); 3.93 (t, J = 6.5 Hz, 2 H); 3.15-3.05 (m, 1 H); 2.83 (d, J = 6.3 Hz, 2 H); 2.80-2.44 (m, 4 H); 1.95-1.21 (m, 22 H).	formate
16	B	(DMSO-d ₆): δ 8.32-8.24 (m, 2 H); 8.18 (d, J = 9.9 Hz, 1 H); 7.41-7.33 (m, 2 H); 7.23 (t, J = 7.9 Hz, 1 H); 7.09 (d, J = 8.2 Hz, 1 H); 6.97-6.87 (m, 3 H); 6.81 (d, J = 8.3 Hz, 1 H); 6.52 (d, J = 9.9 Hz, 1 H); 5.85 (d, J = 9.0 Hz, 1 H); 5.14 (t, J = 6.3 Hz, 1 H); 4.61-4.55 (m, 1 H); 3.92 (t, J = 6.5 Hz, 2 H); 3.14-3.05 (m, 1 H); 2.81 (d, J = 6.3 Hz, 2 H); 2.79-2.45 (m, 4 H); 1.93-1.21 (m, 22 H).	formate
17	B	(DMSO-d ₆): δ 8.22-8.06 (m, 2 H); 7.22-7.13 (m, 5 H); 7.04 (d, J = 8.14 Hz, 1 H); 6.87 (d, J = 8.11 Hz, 1 H); 6.80 (d, J = 7.85 Hz, 3 H); 6.48 (d, J = 9.85 Hz, 1 H); 5.97 (d, J = 8.81 Hz, 1 H); 4.99 (dd, J = 7.96, 4.44 Hz, 1 H); 4.54 (d, J = 7.42 Hz, 1 H); 3.93-3.86 (m, 2 H); 3.10-2.99 (m, 1 H); 2.74-2.60 (m, 6 H); 2.27 (d, J = 6.69 Hz, 3 H); 1.88 (s, 1 H); 1.77 (d, J = 13.00 Hz, 1 H); 1.73-1.61 (m, 2 H); 1.56 (s, 2 H); 1.31 (d, J = 46.22 Hz, 16 H).	none

(continued)

18	A	(DMSO-d ₆): δ 8.17 (d, J = 9.87 Hz, 2 H); 7.23-7.10 (m, 4 H); 7.08-7.00 (m, 2 H); 6.92-6.85 (m, 3 H); 6.77 (d, J = 8.40 Hz, 1 H); 6.49 (d, J = 9.86 Hz, 1 H); 5.75 (d, J = 9.21 Hz, 1 H); 5.00 (dd, J = 7.96, 4.49 Hz, 1 H); 4.55 (s, 1 H); 3.94-3.87 (m, 2 H); 3.07 (t, J = 10.34 Hz, 1 H); 2.74-2.60 (m, 6 H); 2.26 (s, 3 H); 1.88 (s, 1 H); 1.78 (s, 1 H); 1.73-1.61 (m, 2 H); 1.56 (s, 1 H); 1.31 (d, J = 46.94 Hz, 17 H)	none
19	A	(DMSO-d ₆): δ 8.21-8.10 (m, 2 H); 7.23-7.15 (m, 3 H); 7.11 (d, J = 7.79 Hz, 2 H); 7.05 (d, J = 8.15 Hz, 1 H); 6.92-6.84 (m, 3 H); 6.77 (d, J = 8.32 Hz, 1 H); 6.49 (d, J = 9.86 Hz, 1 H); 5.76 (d, J = 9.15 Hz, 1 H); 5.00 (dd, J = 7.91, 4.48 Hz, 1 H); 4.55 (s, 1 H); 3.94-3.87 (m, 2 H); 3.06 (s, 1 H); 2.73-2.60 (m, 6 H); 2.25 (s, 3 H); 1.88 (s, 1 H); 1.78 (s, 1 H); 1.73-1.61 (m, 2 H); 1.56 (s, 1 H); 1.57-1.14 (m, 17 H).	none
20	B	(DMSO-d ₆): δ 8.31 (s, 2 H); 8.27-8.15 (m, 2 H); 7.41-7.31 (m, 2 H); 7.24-7.07 (m, 4 H); 6.98-6.84 (m, 3 H); 6.81-6.75 (m, 1 H); 6.53 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.3 Hz, 1 H); 5.22-5.16 (m, 1 H); 4.62-4.54 (m, 1 H); 3.91 (t, J = 6.5 Hz, 2 H); 3.15-3.06 (m, 1 H); 2.92-2.81 (m, 2 H); 2.80-2.45 (m, 4 H); 1.94-1.20 (m, 22 H).	diformate
1B	A	(DMSO-d ₆): δ 8.25 (d, J = 9.8 Hz, 1 H); 8.17 (d, J = 9.9 Hz, 1 H); 7.40-7.32 (m, 1 H); 7.25-7.15 (m, 3 H); 7.09-7.02 (m, 2 H); 6.96-6.87 (m, 3 H); 6.82-6.77 (m, 1 H); 6.49 (d, J = 9.9 Hz, 1 H); 5.84 (d, J = 9.0 Hz, 1 H); 5.00 (dd, J = 7.9, 4.5 Hz, 1 H); 4.60-4.53 (m, 1 H); 3.92 (t, J = 6.5 Hz, 2 H); 3.12-3.02 (m, 1 H); 2.77-2.53 (m, 6H); 1.92-1.20 (m, 22 H)	none
2B	B	(DMSO-d ₆): δ 8.33-8.26 (m, 3 H); 8.18 (d, J = 9.9 Hz, 1 H); 7.42 (s, 1 H); 7.38-7.27 (m, 3 H); 7.22 (t, J = 8.0 Hz, 1 H); 7.10 (d, J = 8.2 Hz, 1 H); 6.98-6.87 (m, 3 H); 6.82-6.77 (m, 1 H); 6.53 (d, J = 9.9 Hz, 1 H); 5.84 (d, J = 9.2 Hz, 1 H); 5.18 (dd, J = 8.0, 4.6 Hz, 1 H); 4.62-4.55 (m, 1 H); 3.92 (t, J = 6.6 Hz, 2 H); 3.16-3.06 (m, 1 H); 2.90-2.83 (m, 2 H); 2.80-2.52 (m, 6 H); 1.94-1.22 (m, 20 H).	diformate
1C	C	(DMSO-d ₆ @105°C): δ 8.21-8.10 (m, 3 H); 7.19-7.11 (m, 1 H); 7.06 (d, J = 8.2 Hz, 1 H); 6.97-6.89 (m, 2 H); 6.86-6.77 (m, 2 H); 6.74 (d, J = 8.2 Hz, 1 H); 6.46 (d, J = 9.9 Hz, 1 H); 5.04-4.96 (m, 1 H); 4.55-4.47 (m, 1 H); 4.28-4.18 (m, 1 H); 3.99-3.89 (m, 2 H); 3.07-2.97 (m, 1 H); 2.81-2.50 (m, 8 H); 1.88-0.79 (m, 31 H).	diformate

(continued)

2C	C	(DMSO-d ₆): δ 8.38 (d, J = 9.86 Hz, 1 H); 8.31 (s, 1 H); 8.19 (d, J = 9.93 Hz, 1 H); 7.41-7.38 (m, 1 H); 7.29-7.20 (m, 1 H); 7.11 (d, J = 8.16 Hz, 1 H); 7.02-6.89 (m, 4 H); 6.87-6.79 (m, 2 H); 6.53 (d, J = 9.85 Hz, 1 H); 6.00 (d, J = 8.88 Hz, 1 H); 5.19 (dd, J = 8.24, 4.47 Hz, 1 H); 4.60 (s, 1 H); 3.97-3.90 (m, 2 H); 3.12 (d, J = 13.06 Hz, 1 H); 2.87 (d, J = 8.12 Hz, 2 H); 2.80-2.49 (m, 6 H); 1.99-1.86 (m, 1 H); 1.8-1.3 (m, 13 H).	formate
3C	B	(DMSO-d ₆): δ 8.30 (s, 2 H); 8.26-8.15 (m, 2 H); 7.46 (dd, J = 5.00, 2.93 Hz, 1 H); 7.30 (s, 1 H); 7.26-7.18 (m, 1 H); 7.12 (d, J = 8.17 Hz, 1 H); 7.07-7.03 (m, 1 H); 6.94 (dd, J = 19.65, 8.17 Hz, 3 H); 6.79 (d, J = 8.29 Hz, 1 H); 6.54 (d, J = 9.85 Hz, 1 H); 5.86 (d, J = 8.02 Hz, 1 H); 5.23 (dd, J = 8.83, 3.83 Hz, 1 H); 4.60 (s, 1 H); 3.96-3.90 (m, 2 H); 3.14 (s, 1 H); 2.99-2.83 (m, 2 H); 2.87-2.44 (m, 6 H); 1.92 (s, 1 H); 1.80 (s, 1 H); 1.72-1.31 (m, 12 H).	diformate
21	A	(DMSO-d ₆): δ 8.20 (br s, 1H), 7.34-7.18 (m, 6H), 6.92-6.88 (m, 2H), 6.79 (d, J= 8.4 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 5.80 (br s, 1H), 4.57-4.55 (m, 1H), 3.93-3.90 (m, 2H), 3.10-3.05 (m, 1H), 2.72-2.68 (m, 3H), 2.60-2.50 (m, 8H), 1.88 (s, 1H), 1.71-1.67 (m, 2H), 1.64 (br s, 1H), 1.57-1.25 (m, 15H)	none
22	A	(DMSO-d ₆): δ 8.29-8.21 (m, 2 H); 8.18 (d, J = 9.9 Hz, 1 H); 7.37-7.27 (m, 6 H); 7.26-7.18 (m, 4 H); 7.09 (d, J = 8.2 Hz, 1 H); 7.01 (s, 1 H); 6.97-6.84 (m, 3 H); 6.52 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.3 Hz, 1 H); 5.12 (t, J = 6.3 Hz, 1 H); 5.02 (s, 2 H); 4.63-4.56 (m, 1 H); 3.19-3.09 (m, 1 H); 2.97-2.52 (m, 11 H); 1.96-1.74 (m, 2 H); 1.67-1.30 (m, 3 H).	formate
23	B	(DMSO-d ₆): δ 8.30-8.21 (m, 3 H); 8.17 (d, J = 9.9 Hz, 1 H); 7.35-7.13 (m, 8 H); 7.08 (d, J = 8.0 Hz, 2 H); 6.94 (d, J = 8.1 Hz, 1 H); 6.51 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.3 Hz, 1 H); 5.13 (t, J = 6.3 Hz, 1 H); 4.63-4.55 (m, 1 H); 3.18-3.09 (m, 1 H); 2.95-2.52 (m, 11 H); 1.96-1.75 (m, 2 H); 1.65-1.28 (m, 3 H).	diformate
24	A	(DMSO-d ₆): δ 8.60 (br d, J = 8.8 Hz, 1H), 8.48 (s, 1H), 8.18-8.16 (m, 1H), 7.99-7.97 (m, 2H), 7.75-7.74 (m, 1H), 7.63-7.58 (m, 2H), 7.37-7.32 (m, 4H), 7.27-7.21 (m, 2H), 7.06-7.04 (m, 1H), 6.96-6.89 (m, 3H), 6.82-6.80 (m, 1H), 6.49-6.47 (m, 1H), 5.85 (br d, J = 8.8 Hz, 1H), 5.20 (br s, 2H), 5.04 (br m, 2H), 4.08 (m, 1H), 3.92 (t, J = 6 Hz, 2H), 3.75-3.69 (m, 3H), 3.44 (m, 2H), 2.72-2.67 (m, 2H), 2.56-2.51 (m, 2H), 2.34-2.33 (m, 1H), 2.20 (m, 1H), 2.09-1.98 (m, 3H), 1.69-1.66 (m, 2H), 1.44-1.30 (m, 6H)	formate

(continued)

3B	A	(DMSO-d ₆): δ 8.30-8.22 (m, 2 H); 8.18 (d, J = 9.9 Hz, 1 H); 7.38-7.14 (m, 10 H); 7.10-7.00 (m, 2 H); 6.97-6.86 (m, 3 H); 6.51 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 8.8 Hz, 1 H); 5.10 (t, J = 6.3 Hz, 1 H); 5.02 (s, 2 H); 4.62-4.54 (m, 1 H); 3.17-3.07 (m, 1 H); 2.95-2.52 (m, 11 H); 1.95-1.74 (m, 2 H); 1.66-1.28 (m, 3 H).	formate
4B	B	(DMSO-d ₆): δ 8.58 (dd, J = 9.2, 4.7 Hz, 1 H); 8.40 (s, 2 H); 8.17 (dd, J = 9.9, 1.7 Hz, 1 H); 7.97 (t, J = 7.5 Hz, 2 H); 7.75 (q, J = 6.8 Hz, 1 H); 7.60 (q, J = 8.0 Hz, 2 H); 7.40-7.16 (m, 10 H); 7.07-7.00 (m, 2 H); 6.97-6.87 (m, 3 H); 6.49 (dd, J = 9.9, 1.8 Hz, 1 H); 5.87-5.82 (m, 1 H); 5.22-5.14 (m, 2 H); 5.07-4.99 (m, 4 H); 4.13-4.04 (m, 1 H); 3.79-3.53 (m, 5 H); 2.85-2.66 (m, 6 H); 2.38-2.31 (m, 1 H); 2.24-2.13 (m, 1 H); 2.10-1.91 (m, 3 H).	diformate
5B	A	(DMSO-d ₆): δ 8.61 (d, J = 9.2 Hz, 1 H); 8.42 (s, 2 H); 8.18 (d, J = 9.9 Hz, 1 H); 8.02-7.94 (m, 2 H); 7.79-7.71 (m, 1 H); 7.65-7.57 (m, 2 H); 7.44 (d, J = 10.5 Hz, 1 H); 7.40-7.29 (m, 3 H); 7.28-7.21 (m, 1 H); 7.06 (d, J = 8.1 Hz, 1 H); 6.99-6.89 (m, 3 H); 6.83 (d, J = 8.3 Hz, 1 H); 6.49 (d, J = 9.8 Hz, 1 H); 5.87 (d, J = 8.4 Hz, 1 H); 5.24-5.13 (m, 2 H); 5.11-5.00 (m, 2 H); 4.14-4.02 (m, 1 H); 3.93 (t, J = 7.1 Hz, 2 H); 3.80-3.65 (m, 4 H); 2.79-2.66 (m, 2 H); 2.65-2.54 (m, 2 H); 2.39-2.31 (m, 1 H); 2.24-2.12 (m, 1 H); 2.11-1.91 (m, 3 H); 1.73-1.62 (m, 2 H); 1.48-1.18 (m, 13 H).	diformate
6B	A	(DMSO-d ₆): δ 8.59 (d, J = 8.87 Hz, 1 H); 8.43 (s, 2 H); 8.18 (d, J = 9.89 Hz, 1 H); 7.98 (d, J = 7.80 Hz, 2 H); 7.79-7.71 (m, 1 H); 7.65-7.57 (m, 2 H); 7.39-7.33 (m, 4 H); 7.27 (dd, J = 8.36, 5.16 Hz, 1 H); 7.15 (d, J = 10.12 Hz, 1 H); 7.09-7.01 (m, 2 H); 7.01-6.91 (m, 2 H); 6.49 (dd, J = 9.85, 1.23 Hz, 1 H); 5.86 (d, J = 8.44 Hz, 1 H); 5.19 (s, 2 H); 5.04 (d, J = 7.00 Hz, 2 H); 4.14-4.04 (m, 1 H); 3.98-3.91 (m, 2 H); 3.7-3.5 (m, 4 H); 2.74-2.64 (m, 2 H); 2.56 (d, J = 10.06 Hz, 2 H); 2.38-2.31 (m, 2 H); 2.19 (d, J = 17.51 Hz, 1 H); 2.09-1.92 (m, 3 H); 1.66 (d, J = 8.03 Hz, 2 H); 1.32 (d, J = 52.59 Hz, 12 H).	diformate
7B	B	(DMSO-d ₆): δ 8.32 (s, 1 H); 8.27 (d, J = 9.28 Hz, 1 H); 8.18 (d, J = 9.93 Hz, 1 H); 7.35-7.21 (m, 6 H); 7.15-7.03 (m, 3 H); 6.95 (d, J = 8.13 Hz, 1 H); 6.53 (d, J = 9.86 Hz, 1 H); 6.23 (d, J = 8.86 Hz, 1 H); 5.18 (dd, J = 8.02, 4.59 Hz, 1 H); 4.56 (s, 1 H); 4.06-3.99 (m, 2 H); 3.14-3.03 (m, 1 H); 2.86 (d, J = 7.36 Hz, 2 H); 2.79-2.53 (m, 6 H); 1.94-1.85 (m, 1 H); 1.79-1.68 (m, 3 H); 1.76-1.13 (m, 16 H).	formate

(continued)

8B	A	(DMSO-d ₆): δ 8.32 (s, 1 H); 8.22-8.11 (m, 2 H); 7.35-7.24 (m, 5 H); 7.16-7.07 (m, 2 H); 7.06-6.96 (m, 1 H); 6.95 (d, J = 8.13 Hz, 1 H); 6.53 (d, J = 9.86 Hz, 1 H); 6.23 (d, J = 8.18 Hz, 1 H); 5.20-5.14 (m, 1 H); 4.59 (s, 1 H); 4.02-3.95 (m, 2 H); 3.14-3.04 (m, 1 H); 2.88-2.83 (m, 2 H); 2.78-2.53 (m, 6 H); 1.99-1.77 (m, 2 H); 1.72-1.63 (m, 2 H); 1.73-1.12 (m, 16 H).	formate
9B	A	(DMSO-d ₆): δ 8.34-8.24 (m, 3 H); 8.18 (d, J = 9.9 Hz, 1 H); 7.51-7.43 (m, 1 H); 7.37-7.19 (m, 5 H); 7.18-7.07 (m, 2 H); 6.96 (d, J = 8.1 Hz, 1 H); 6.83 (dd, J = 8.8, 2.9 Hz, 1 H); 6.53 (d, J = 9.9 Hz, 1 H); 6.16-6.07 (m, 1 H); 5.20 (dd, J = 8.4, 4.3 Hz, 1 H); 4.63-4.54 (m, 1 H); 3.94 (t, J = 6.5 Hz, 2 H); 3.19-3.04 (m, 1 H); 2.93-2.82 (m, 2 H); 2.81-2.53 (m, 6 H); 1.97-1.86 (m, 1 H); 1.85-1.08 (m, 19 H).	diformate
10B	B	(DMSO-d ₆): δ 8.59 (dd, J = 8.88, 3.56 Hz, 1 H); 8.43 (s, 2 H); 8.18 (d, J = 9.92 Hz, 1 H); 8.01-7.94 (m, 2 H); 7.79-7.72 (m, 1 H); 7.61 (q, J = 6.64 Hz, 2 H); 7.39-7.21 (m, 6 H); 7.15-7.02 (m, 3 H); 6.95 (d, J = 8.10 Hz, 1 H); 6.49 (d, J = 9.83 Hz, 1 H); 6.28-6.20 (m, 1 H); 5.20 (d, J = 7.19 Hz, 2 H); 5.07-5.00 (m, 2 H); 4.09-4.00 (m, 3 H); 3.80-3.56 (m, 4 H); 2.72 (d, J = 7.37 Hz, 2 H); 2.6 (m, 2 H); 2.34 (m, 2 H); 2.2-1.9 (m, 4 H); 1.72 (d, J = 8.43 Hz, 2 H); 1.27 (t, J = 51.58 Hz, 12 H).	diformate
11B	A	(DMSO-d ₆): δ 8.54-8.45 (m, 1 H); 8.42 (s, 2 H); 8.17 (d, J = 9.92 Hz, 1 H); 8.01-7.90 (m, 2 H); 7.75 (dd, J = 14.66, 7.33 Hz, 1 H); 7.67-7.56 (m, 2 H); 7.41-7.27 (m, 5 H); 7.19-7.10 (m, 1 H); 7.08-6.99 (m, 2 H); 6.95 (t, J = 7.26 Hz, 1 H); 6.49 (d, J = 9.84 Hz, 1 H); 6.25 (dd, J = 14.03, 8.15 Hz, 1 H); 5.19 (d, J = 12.14 Hz, 2 H); 5.05 (s, 2 H); 4.09 (dd, J = 13.40, 8.00 Hz, 1 H); 4.03-3.96 (m, 2 H); 3.83-3.50 (m, 4 H); 2.74-2.66 (m, 2 H); 2.6 (m, 2 H); 2.39-2.22 (m, 3 H); 2.11-1.91 (m, 3 H); 1.69 (d, J = 7.79 Hz, 2 H); 1.32 (d, J = 55.24 Hz, 12 H).	diformate

(continued)

12B	B	(DMSO-d ₆): δ 8.67-8.58 (m, 1 H); 8.43 (s, 2 H); 8.18 (d, J = 9.9 Hz, 1 H); 8.02-7.93 (m, 2 H); 7.75 (q, J = 7.1 Hz, 1 H); 7.61 (q, J = 7.8 Hz, 2 H); 7.50 (d, J = 8.7 Hz, 1 H); 7.40-7.22 (m, 5 H); 7.14 (dd, J = 19.7, 3.0 Hz, 1 H); 7.06 (d, J = 8.2 Hz, 1 H); 6.95 (d, J = 8.1 Hz, 1 H); 6.85 (dd, J = 8.8, 2.9 Hz, 1 H); 6.49 (d, J = 9.8 Hz, 1 H); 6.21-6.11 (m, 1 H); 5.20 (d, J = 8.9 Hz, 2 H); 5.10-5.00 (m, 2 H); 4.14-4.04 (m, 1 H); 4.01-3.89 (m, 2 H); 3.81-3.51 (m, 5 H); 2.78-2.66 (m, 2 H); 2.63-2.53 (m, 2 H); 2.40-2.30 (m, 1 H); 2.23-1.90 (m, 4 H); 1.74-1.64 (m, 2 H); 1.47-1.17 (m, 12 H).	diformate
13B	A	(DMSO-d ₆): δ 8.51 (d, J = 9.58 Hz, 1 H); 8.43 (s, 2 H); 8.17 (d, J = 9.96 Hz, 1 H); 8.01-7.95 (m, 2 H); 7.80-7.72 (m, 1 H); 7.64-7.57 (m, 2 H); 7.36-7.30 (m, 4 H); 7.26-7.21 (m, 1 H); 7.08-7.04 (m, 2 H); 6.94 (d, J = 8.15 Hz, 2 H); 6.85-6.79 (m, 1 H); 6.49 (d, J = 9.86 Hz, 1 H); 5.81 (d, J = 8.39 Hz, 1 H); 5.19 (s, 2 H); 5.06-5.01 (m, 2 H); 4.08 (s, 1 H); 3.93 (d, J = 8.29 Hz, 2 H); 3.81-3.53 (m, 4 H); 2.72-2.65 (m, 2 H); 2.6-2.5 (m, 2 H); 2.34 (t, J = 3.03 Hz, 2 H); 2.20-1.95 (m, 7 H); 1.74-1.66 (m, 2 H); 1.33 (d, J = 57.30 Hz, 12 H).	diformate
14B	B	(CD ₃ OD): δ 8.45 (s, 2H), 8.40 (d, J = 10Hz, 1H); 7.36-7.27 (m, 6H); 7.06 (d, J = 8.4 Hz, 1H); 6.93 (d, J = 8 Hz, 1H); 6.86-6.83 (m, 2H); 6.72 (d, J = 9.6 Hz, 1H); 5.85 (br s, 1H); 5.42 (t, J = 6.8 Hz, 1H); 5.01-4.99 (m, 1H); 3.93 (t, J = 6.4 Hz, 2H); 3.83 (s, 3H); 3.70 (m, 1H), 3.27-3.15 (m, 6H); 3.10-3.06 (m, 2H); 2.37 (br s, 1H); 2.24 (br s, 1H); 2.05 (m, 1H); 1.95-1.86 (m, 2H); 1.77 -1.72 (m, 4H); 1.47-1.39 (m, 11H)	diformate
15B	B	(DMSO-d ₆): δ 8.32 (s, 1 H); 8.18 (m, 2 H); 7.35-7.27 (m, 4 H); 7.26-7.20 (m, 1 H); 7.10 (d, J = 8.16 Hz, 1 H); 6.99-6.91 (m, 1 H); 6.56-6.50 (m, 3 H); 6.34 (s, 1 H); 5.76 (d, J = 8.94 Hz, 1 H); 5.18 (dd, J = 8.05, 4.61 Hz, 1 H); 4.58 (s, 1 H); 3.93-3.87 (m, 2 H); 3.70 (d, J = 1.68 Hz, 3 H); 3.11 (d, J = 12.65 Hz, 1 H); 2.89-2.82 (m, 2 H); 2.74-2.5 (m, 6 H); 1.91 (s, 1 H); 1.81 (s, 1 H); 1.75-1.42 (m, 6 H); 1.67-0.96 (m, 12 H).	formate
16B	A	(CD ₃ OD): δ 8.57 (s, 2 H); 8.39 (d, J = 9.8 Hz, 1 H); 8.01 (d, J = 7.8 Hz, 2 H); 7.78-7.70 (m, 1 H); 7.62-7.55 (m, 2 H); 7.38-7.26 (m, 6 H); 7.03 (d, J = 8.2 Hz, 1 H); 6.93 (d, J = 8.2 Hz, 1 H); 6.90-6.81 (m, 2 H); 6.69 (dd, J = 9.8, 1.3 Hz, 1 H); 5.87 (s, 1 H); 5.41-5.34 (m, 1 H); 5.14 (s, 1 H); 4.23-4.13 (m, 1 H); 3.95-3.70 (m, 10 H); 3.20-3.14 (m, 2 H); 3.04-2.97 (m, 2 H); 2.50 (s, 1 H); 2.45-2.34 (m, 1 H); 2.27-2.17 (m, 1 H); 2.15-2.03 (m, 2 H); 1.77-1.69 (m, 5 H); 1.47-1.39 (s, 11 H)	diformate

(continued)

17B	B	(DMSO-d ₆): δ 8.55-8.48 (m, 1 H); 8.41 (s, 2 H); 8.18 (d, J = 9.92 Hz, 1 H); 8.01-7.95 (m, 2 H); 7.79-7.71 (m, 1 H); 7.64-7.57 (m, 2 H); 7.38-7.29 (m, 4 H); 7.27-7.22 (m, 1 H); 7.07 (d, J = 8.15 Hz, 1 H); 6.96 (d, J = 8.11 Hz, 1 H); 6.57-6.46 (m, 3 H); 6.37 (s, 1 H); 5.78 (d, J = 8.97 Hz, 1 H); 5.20 (s, 2 H); 5.13-5.06 (m, 1 H); 5.03 (s, 1 H); 4.14-4.03 (m, 1 H); 3.94-3.87 (m, 2 H); 3.71 (d, J = 2.10 Hz, 5 H); 3.60 (s, 2 H); 2.75 (d, J = 6.24 Hz, 2 H); 2.59 (d, J = 10.43 Hz, 2 H); 2.35 (d, J = 6.09 Hz, 1 H); 2.25-1.92 (m, 4 H); 1.71-1.62 (m, 2 H); 1.54-1.16 (m, 13 H).	diformate
18B	B	(DMSO-d ₆): δ 8.65-8.58 (m, 1 H); 8.42 (s, 2 H); 8.18 (d, J = 9.89 Hz, 1 H); 7.97 (dd, J = 12.34, 7.73 Hz, 2 H); 7.77-7.70 (m, 1 H); 7.68-7.56 (m, 4 H); 7.48-7.29 (m, 7 H); 7.26 (d, J = 9.96 Hz, 2 H); 7.06 (d, J = 7.09 Hz, 2 H); 6.99 (s, 1 H); 6.94 (d, J = 8.20 Hz, 1 H); 6.52-6.48 (m, 1 H); 5.92 (d, J = 8.66 Hz, 1 H); 5.19 (d, J = 7.20 Hz, 2 H); 5.05 (d, J = 6.31 Hz, 2 H); 4.11-3.98 (m, 3 H); 3.82-3.53 (m, 6 H); 2.74-2.66 (m, 2 H); 2.39-2.31 (m, 2 H); 2.22-1.89 (m, 4 H); 1.75-1.67 (m, 2 H); 1.33 (d, J = 56.95 Hz, 12 H).	diformate
19B	B	(CD ₃ OD): δ 8.57 (s, 2 H); 8.38 (d, J = 9.86 Hz, 1 H); 7.39-7.25 (m, 8 H); 7.17 (s, 1 H); 7.11-6.99 (m, 3 H); 6.76 (s, 1 H); 6.68 (dd, J = 9.83, 6.22 Hz, 1 H); 5.91 (s, 1 H); 5.35 (dd, J = 8.74, 4.54 Hz, 1 H); 4.81 (s, 1 H); 4.03-3.96 (m, 2 H); 3.18-3.07 (m, 2 H); 3.02-2.82 (m, 7 H); 2.09 (d, J = 36.56 Hz, 2 H); 1.90-1.62 (m, 6 H); 1.64-1.23 (m, 12 H).	diformate
20B	B	(CD ₃ OD): δ 8.56 (s, 1 H); 8.39 (d, J = 10 Hz, 1 H); 8.02-7.98 (m, 2 H); 7.73 (m, 1 H); 7.61-7.55 (m, 2 H); 7.36-7.24 (m, 8 H); 7.04-6.87 (m, 7 H); 6.69 (d, J = 12 Hz, 1 H); 5.90 (s, 1 H); 5.39 (m, 1 H); 5.14-4.90 (m, 6 H); 4.26-3.71 (m, 8 H); 3.18-3.11 (m, 4 H); 2.50-1.90 (m, 8 H)	formate
21B	A	(DMSO-d ₆): δ 8.57 (m, 1 H); 8.45 (s, 2 H); 8.24 (d, J = 12 Hz, 1 H); 7.38-7.23 (m, 10 H); 7.13-6.92 (m, 12 H); 6.54 (d, J = 8 Hz, 1 H); 5.89 (d, J = 8 Hz, 1 H); 5.16 (m, 1 H); 5.08 (s, 2 H); 4.98 (m, 1 H); 4.47 (m, 2 H); 4.08-4.00 (m, 3 H); 3.76-3.40 (m, 5 H); 2.84 (m, 2 H); 2.75 (m, 2 H); 2.36 (m, 1 H); 2.19 (m, 1 H); 2.03-1.93 (m, 3 H); 1.77 (m, 2 H); 1.66 (m, 2 H)	diformate

(continued)

22B	B	(CD ₃ OD): δ 8.56 (s, 1 H); 8.39 (d, J = 10 Hz, 1 H); 8.02-7.98 (m, 2 H); 7.73 (m, 1 H); 7.61-7.57 (m, 2 H); 7.36-7.23 (m, 8 H); 7.05-6.85 (m, 7 H); 6.69 (d, J = 10 Hz, 1 H); 5.90 (s, 1 H); 5.40 (t, J = 5.6 Hz, 1 H); 5.18-4.90 (m, 6 H); 4.18 (m, 1 H); 4.04-3.99 (m, 2 H); 3.85-3.60 (m, 5 H); 3.21-3.09 (m, 2 H); 3.10-3.06 (m, 2 H); 2.68-2.00 (m, 5 H); 1.85-1.79 (m, 3 H); 1.62-1.61 (m, 2 H)	formate
23B	B	(DMSO-d ₆): δ 8.58 (m, 1 H); 8.47 (s, 2 H); 8.24 (d, J = 12 Hz, 1 H); 7.38-7.23 (m, 10 H); 7.13-6.92 (m, 12 H); 6.53 (d, J = 12 Hz, 1 H); 5.89 (d, J = 8 Hz, 1 H); 5.16 (m, 1 H); 5.08 (s, 2 H); 4.98 (m, 1 H); 4.47 (m, 2 H); 4.08-3.97 (m, 3 H); 3.93-3.37 (m, 5 H); 2.83 (m, 2 H); 2.71 (m, 2 H); 2.34 (m, 1 H); 2.19 (m, 1 H); 2.03-1.85 (m, 3 H); 1.76 (m, 2 H); 1.53-1.47 (m, 4 H)	diformate
24B	A	(DMSO-d ₆): δ 8.29 (s, 3 H); 8.19 (d, J = 9.92 Hz, 1 H); 7.39-7.32 (m, 1 H); 7.21 (d, J = 9.99 Hz, 3 H); 7.15-7.02 (m, 2 H); 6.94 (dd, J = 19.08, 8.27 Hz, 3 H); 6.80 (d, J = 8.28 Hz, 1 H); 6.54 (d, J = 9.85 Hz, 1 H); 5.85 (d, J = 8.92 Hz, 1 H); 5.24 (dd, J = 8.95, 3.71 Hz, 1 H); 4.61 (s, 1 H); 3.96-3.89 (m, 2 H); 3.20-3.10 (m, 1 H); 3.0-2.9 (m, 2H); 2.85-2.5 (m, 6 H); 1.93 (s, 1 H); 1.81 (s, 1 H); 1.72-1.32 (m, 12 H).	diformate
25B	A	(CD ₃ OD): δ 8.55 (s, 2 H); 8.38 (d, J = 10 Hz, 1 H); 7.37-7.18 (m, 13 H); 7.04-6.76 (m, 3 H); 6.69 (m, 1 H); 5.88 (s, 1 H); 5.40-5.36 (m, 1 H); 5.11-4.97 (m, 1 H); 4.00-3.95 (m, 2 H); 3.88-3.77 (m, 1 H); 3.22-3.01 (m, 9 H); 2.78-2.65 (m, 2 H); 2.42 (br s, 1 H); 2.31 (br s, 1 H); 2.19-1.88 (m, 3 H); 1.87-1.58 (m, 12 H).	diformate
26B	B	(DMSO-d ₆): δ 8.34-8.21 (m, 2 H); 8.17 (d, J = 9.9 Hz, 1 H); 7.40-7.13 (m, 9 H); 7.11-7.00 (m, 3 H); 6.98-6.86 (m, 3 H); 6.50 (d, J = 9.9 Hz, 1 H); 5.85 (d, J = 8.7 Hz, 1 H); 5.10 (t, J = 6.3 Hz, 1 H); 5.02 (s, 2 H); 4.67-4.51 (m, 1 H); 3.17-3.07 (m, 1 H); 2.95-2.53 (m, 8 H); 1.98-1.84 (m, 1 H); 1.81-1.74 (m, 2 H); 1.73-1.20 (m, 4 H).	formate
27B	A	(DMSO-d ₆): δ 8.62 (d, J = 9.36 Hz, 1 H); 8.39 (s, 2 H); 8.17 (dd, J = 9.92, 2.70 Hz, 1 H); 8.00-7.90 (m, 2 H); 7.74 (q, J = 6.56 Hz, 1 H); 7.65-7.50 (m, 3 H); 7.37 (q, J = 7.36 Hz, 1 H); 7.30-7.12 (m, 7 H); 7.11-7.00 (m, 3 H); 6.98-6.87 (m, 3 H); 6.48 (dd, J = 9.87, 2.28 Hz, 1 H); 5.88 (d, J = 7.77 Hz, 1 H); 5.19 (s, 2 H); 5.03 (s, 4 H); 4.11-3.98 (m, 1 H); 3.65 (d, J = 55.36 Hz, 3 H); 2.85-2.66 (m, 2 H); 2.39-2.26 (m, 5 H); 2.33-2.03 (m, 1 H); 2.07-1.87 (m, 4 H).	diformate

(continued)

28B	A	(DMSO-d ₆): δ 8.40 (m, 1 H); 8.18 (s, 2 H); 7.92 (dd, J = 12.0, 8.0 Hz, 1 H); 7.82-7.77 (m, 2 H); 7.57 (m, 1 H); 7.46-7.39 (m, 2 H); 7.20-7.15 (m, 7 H); 7.09-7.03 (m, 2 H); 6.89-6.85 (m, 2 H); 6.77-6.72 (m, 3 H); 6.29 (dd, J = 12.0, 8.0 Hz, 1H); 5.67 (d, J = 8.0 Hz, 1 H); 5.02 (m, 2 H); 4.87 (m, 4 H); 3.92 (m, 1 H); 3.68-3.52 (m, 6 H); 3.42 (m, 1 H); 2.49 (m, 2 H); 2.17 (m, 1 H); 2.00 (m, 1 H); 1.89-1.53 (m, 3 H)	diformate
29B	B	(DMSO-d ₆): δ 8.30 (s, 2 H); 8.30-8.15 (m, 2 H); 7.70 (s, 1 H); 7.63-7.54 (m, 3 H); 7.50-7.37 (m, 2 H); 7.32-7.17 (m, 8 H); 7.12-7.04 (m, 2 H); 6.98-6.88 (m, 3 H); 6.52 (d, J = 9.9 Hz, 1 H); 5.83 (d, J = 9.2 Hz, 1 H); 5.21-5.05 (m, 3 H); 4.59 (s, 1 H); 3.15-3.10 (m, 1 H); 2.97-2.53 (m, 11 H); 1.92 (s, 1 H); 1.80 (s, 1 H); 1.72-1.24 (m, 3 H).	diformate
30B	B	(DMSO-d ₆): δ 8.54-8.46 (m, 1 H); 8.31-8.21 (m, 2 H); 8.18 (d, J = 9.94 Hz, 1 H); 7.84 (d, J = 8.04 Hz, 2 H); 7.50 (d, J = 7.91 Hz, 2 H); 7.34-7.27 (m, 4 H); 7.26-7.19 (m, 2 H); 7.10 (d, J = 8.17 Hz, 1 H); 7.04 (s, 1 H); 6.98-6.85 (m, 3 H); 6.53 (d, J = 9.86 Hz, 1 H); 5.82 (d, J = 8.54 Hz, 1 H); 5.20 (dd, J = 8.25, 4.32 Hz, 1 H); 5.13 (s, 2 H); 4.59 (s, 1 H); 3.27 (m, 2 H); 3.12 (s, 1 H); 2.93-2.63 (m, 6 H); 1.86 (d, J = 46.19 Hz, 2 H); 1.70-1.22 (m, 10 H).	formate
31B	B	(DMSO-d ₆): δ 8.62 (s, 1 H); 8.33-8.21 (m, 3 H); 8.19 (d, J = 9.93 Hz, 1 H); 7.85 (d, J = 7.99 Hz, 2 H); 7.50 (d, J = 7.90 Hz, 2 H); 7.35-7.19 (m, 6 H); 7.11 (d, J = 8.16 Hz, 1 H); 7.04 (s, 1 H); 6.99-6.85 (m, 3 H); 6.52 (d, J = 9.86 Hz, 1 H); 5.82 (d, J = 8.75 Hz, 1 H); 5.21 (dd, J = 8.34, 4.26 Hz, 1 H); 5.13 (s, 2 H); 4.60 (s, 1 H); 3.32 (t, J = 6.31 Hz, 2 H); 2.95-2.75 (m, 5 H); 2.67 (s, 3 H); 2.57 (d, J = 16.50 Hz, 1 H); 1.94 (s, 1 H); 1.81 (t, J = 7.70 Hz, 3 H); 1.61 (s, 2 H); 1.51 (s, 2 H).	diformate
32B	A	(DMSO-d ₆): 8.59-8.52 (m, 2 H); 8.40 (s, 2 H); 8.18 (m, 1 H); 7.97 (t, J = 8.2 Hz, 2 H); 7.84 (dd, J = 8.0, 2.1 Hz, 2 H); 7.77-7.71 (m, 1 H); 7.60 (q, J = 8.0 Hz, 2 H); 7.50 (d, J = 7.9 Hz, 2 H); 7.36-7.30 (m, 4 H); 7.28-7.21 (m, 2 H); 7.06 (t, J = 8.4 Hz, 2 H); 6.99-6.88 (m, 3 H); 6.49 (m, 1 H); 5.84 (d, J = 9.0 Hz, 1 H); 5.24-4.96 (m, 6 H); 4.15-4.03 (m, 1 H); 3.80-3.28 (m, 6 H); 2.75-2.63 (m, 4 H); 2.34 (s, 1 H); 2.23-1.89 (m, 5 H); 1.74-1.63 (m, 2 H)	diformate

(continued)

33B	B	(DMSO- d ₆): δ 8.33-8.18 (m, 2 H); 8.18 (d, J = 9.93 Hz, 1 H); 8.00-7.92 (m, 2 H); 7.57 (d, J = 7.95 Hz, 2 H); 7.35-7.21 (m, 6 H); 7.10 (d, J = 8.16 Hz, 1 H); 7.04 (s, 1 H); 6.95 (d, J = 8.04 Hz, 2 H); 6.89 (d, J = 8.33 Hz, 1 H); 6.52 (d, J = 9.86 Hz, 1 H); 5.82 (d, J = 8.71 Hz, 1 H); 5.18 (s, 3 H); 4.59 (s, 1 H); 4.32-4.25 (m, 2 H); 3.18-3.08 (m, 1 H); 2.91-2.56 (m, 6 H); 1.92 (s, 1 H); 1.95-1.39 (m, 11 H).	formate
34B	A	(DMSO- d ₆): δ 8.28 (s, 1 H); 8.24 (d, J = 9.6 Hz, 1 H); 8.19 (d, J = 10 Hz, 1 H); 7.96 (d, J = 8.0 Hz, 2 H); 7.57 (d, J = 7.9 Hz, 2 H); 7.31-7.22 (m, 6 H); 7.10-6.87 (m, 5 H); 6.53 (d, J = 10 Hz, 1 H); 5.83 (d, J = 8.8 Hz, 1 H); 5.18-5.11 (m, 3 H); 4.56 (br s, 1 H); 3.13-3.08 (m, 1 H); 2.85-2.61 (m, 8 H); 1.94-1.86 (m, 1 H); 1.79-1.66 (m, 3 H), 1.63-1.24 (m, 10 H)	formate
35B	B	(DMSO- d ₆): 8.31 (s, 1 H); 8.26-8.14 (m, 2H); 7.96 (d, J = 8 Hz, 2 H); 7.56 (d, J = 8 Hz, 2 H); 7.34-7.20 (m, 6 H); 7.13-7.00 (m, 2 H); 6.97-6.87 (m, 3 H); 6.53 (d, J = 9.6 Hz, 1 H); 5.82 (d, J = 8.96 Hz, 1 H); 5.23-5.08 (m, 3 H); 4.57 (s, 1 H); 4.28 (t, J = 6.44 Hz, 2 H); 3.16-3.03 (m, 1 H); 2.83-2.49 (m, 8 H); 1.94-1.26 (m, 14 H)	formate
4C	B	(DMSO-d ₆): δ 8.29 (s, 2 H); 8.28-8.13 (m, 2 H); 7.96 (d, J = 7.9 Hz, 2 H); 7.57 (d, J = 7.9 Hz, 2 H); 7.34-7.19 (m, 6 H); 7.10 (d, J = 8.1 Hz, 1 H); 7.03 (s, 1 H); 6.92 (m, 3 H); 6.53 (d, J = 9.8 Hz, 1 H); 5.82 (d, J = 9.1 Hz, 1 H); 5.17 (s, 3 H); 4.57 (s, 1 H); 4.28 (t, J = 6.4 Hz, 2 H); 3.15-3.05 (m, 1 H); 2.85 (d, J = 6.4 Hz, 2 H); 2.73 (s, 5 H); 1.90 (s, 1 H); 1.85-1.66 (m, 3 H); 1.51 (s, 4 H); 1.40 (s, 3 H); 1.32 (s, 6 H).	diformate
5C	B	(DMSO-d ₆): δ 8.22 (s, 2 H); 8.12 (d, J = 9.9 Hz, 1 H); 7.99 (d, J = 7.9 Hz, 2 H); 7.57 (d, J = 7.9 Hz, 2 H); 7.45-7.33 (m, 4 H); 7.33-7.18 (m, 6 H); 7.10-6.99 (m, 2 H); 6.96-6.85 (m, 3 H); 6.47 (d, J = 9.8 Hz, 1 H); 5.81 (d, J = 9.0 Hz, 1 H); 5.33 (s, 2 H); 5.18 (s, 2 H); 5.08 (dd, J = 7.6, 4.2 Hz, 1 H); 4.58 (s, 1 H); 3.79 (s, 2 H); 3.42 (s, 7 H); 3.13 (s, 2 H); 2.78-2.62 (m, 3 H); 1.92 (s, 1 H).	diformate
6C	A	(DMSO-d ₆): δ 8.38 (s, 2 H); 8.28-8.16 (m, 2 H); 8.13 (d, J = 7.9 Hz, 2 H); 7.65 (d, J = 7.9 Hz, 2 H); 7.36-6.86 (m, 15 H); 6.52 (d, J = 10 Hz, 1 H); 5.87-5.78 (m, 1 H); 5.23 (s, 2 H); 5.05 (m, 1 H); 4.57 (br s, 1 H); 3.14-3.04 (m, 1 H); 2.91-2.63 (m, 11 H); 1.90 (br s, 1 H); 1.77 (br s, 1 H); 1.58 (br s, 1 H); 1.47 (br s, 1 H); 1.32 (br s, 1 H).	diformate

(continued)

7C	A	(DMSO-d ₆): δ 8.32-8.19 (m, 2 H); 8.21-8.10 (m, 2 H); 8.02 (d, J = 8.0 Hz, 2 H); 7.58 (d, J = 7.9 Hz, 2 H); 7.37-7.16 (m, 6 H); 7.10 (d, J = 8.2 Hz, 1 H); 7.05 (s, 1 H); 6.92 (dd, J = 23.2, 8.0 Hz, 3 H); 6.53 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.1 Hz, 1 H); 5.22-5.14 (m, 3 H); 4.70 (s, 2 H); 4.58 (s, 1 H); 3.17 (s, 1 H); 3.12 (d, J = 7.1 Hz, 3 H); 2.85 (d, J = 6.3 Hz, 2 H); 2.75 (s, 4 H); 2.65 (d, J = 20.1 Hz, 2 H); 1.92 (s, 1 H); 1.48 (s, 6 H); 1.35 (s, 2 H).	formate
8C	B	(DMSO-d ₆): δ 8.27 (s, 2 H); 8.25-8.15 (m, 2 H); 7.99 (d, J = 8.0 Hz, 2 H); 7.57 (d, J = 8.0 Hz, 2 H); 7.38 (d, J = 7.9 Hz, 2 H); 7.34-7.18 (m, 8 H); 7.09-7.00 (m, 2 H); 6.96-6.85 (m, 3 H); 6.52 (d, J = 10 Hz, 1 H); 5.82 (d, J = 9.2 Hz, 1 H); 5.32 (s, 2 H); 5.18 (s, 2 H); 5.07 (m, 1 H); 4.60-4.53 (m, 1 H); 3.15-3.05 (m, 1 H); 2.89-2.70 (m, 9 H); 1.89 (br s, 2 H); 1.78 (br s, 2 H); 1.59 (br s, 1 H); 1.46 (br s, 1 H); 1.31 (br s, 1 H)	formate
36B	B	(DMSO-d ₆): δ 8.58 (d, J = 8.9 Hz, 1 H); 8.37 (s, 2 H); 8.18 (d, J = 9.9 Hz, 1 H); 7.97 (t, J = 6.6 Hz, 2 H); 7.78-7.71 (m, 1 H); 7.60 (q, J = 7.4 Hz, 2 H); 7.40-7.21 (m, 10 H); 7.10-6.99 (m, 2 H); 6.99-6.86 (m, 3 H); 6.50 (dd, J = 9.8, 1.6 Hz, 1 H); 5.85 (d, J = 8.3 Hz, 1 H); 5.22-5.14 (m, 2 H); 5.09 (t, J = 6.2 Hz, 1 H); 5.07-4.97 (m, 3 H); 4.13-4.04 (m, 1 H); 4.01-3.94 (m, 2 H); 3.78-3.53 (m, 6 H); 2.72 (d, J = 6.1 Hz, 2 H); 2.62-2.53 (m, 1 H); 2.37-2.31 (m, 1 H); 2.24-2.13 (m, 1 H); 2.09-1.90 (m, 3 H); 1.55-1.33 (m, 6 H); 1.20-1.12 (m, 2 H).	diformate
37B	B	(DMSO-d ₆ @105°C): δ 8.21-8.14 (m, 3 H); 7.63-7.52 (m, 5 H); 7.41-7.18 (m, 10 H); 7.10 (d, J = 8.1 Hz, 1 H); 6.98-6.81 (m, 4 H); 6.46 (d, J = 9.9 Hz, 1 H); 5.83 (d, J = 8.8 Hz, 1 H); 5.09 (dd, J = 7.6, 4.8 Hz, 1 H); 4.64-4.58 (m, 1 H); 4.24 (td, J = 6.7, 2.0 Hz, 2 H); 3.82 (s, 2 H); 3.13-3.03 (m, 3 H); 2.90-2.77 (m, 1 H); 2.76-2.58 (m, 4 H); 2.57-2.52 (m, 2 H); 1.94-1.88 (m, 1 H); 1.82-1.70 (m, 1 H); 1.66-1.56 (m, 1 H); 1.54-1.43 (m, 1 H); 1.36-1.24 (m, 1 H).	diformate
38B	A	(DMSO-d ₆): δ 8.29-8.20 (m, 2 H); 8.12 (d, J = 9.9 Hz, 1 H); 7.65-7.49 (m, 4 H); 7.44-7.18 (m, 10 H); 7.08 (d, J = 8.2 Hz, 1 H); 6.99-6.80 (m, 4 H); 6.42 (d, J = 9.9 Hz, 1 H); 5.85-5.78 (m, 1 H); 5.11 (dd, J = 7.7, 4.5 Hz, 1 H); 4.63-4.56 (m, 1 H); 4.22-4.14 (m, 2 H); 3.86 (s, 2 H); 3.18-3.02 (m, 3 H); 2.81-2.53 (m, 5 H); 2.52-2.45 (m, 2 H); 1.95-1.73 (m, 2 H); 1.66-1.27 (m, 3 H).	formate

(continued)

39B	B	(DMSO-d ₆): δ 8.35 (s, 2 H); 8.26 (d, J = 9.9 Hz, 1 H); 8.20 (d, J = 9.9 Hz, 1 H); 7.35-7.27 (m, 4 H); 7.26-7.18 (m, 2 H); 7.11 (d, J = 8.2 Hz, 1 H); 6.99-6.92 (m, 4 H); 6.80-6.73 (m, 1 H); 6.53 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.5 Hz, 1 H); 5.24-5.18 (m, 1 H); 4.75 (d, J = 1.9 Hz, 2 H); 4.74-4.44 (m, 1 H); 4.08 (t, J = 6.6 Hz, 2 H); 3.19-3.08 (m, 1 H); 2.93-2.80 (m, 2 H); 2.81-2.60 (m, 6 H); 1.99-1.84 (m, 1 H); 1.91-1.70 (m, 1 H); 1.69-1.48 (m, 6 H); 1.48-1.24 (m, 1 H); 1.53-0.98 (m, 4 H)	diformate
40B	A	(DMSO-d ₆): δ 8.11 (s, 3 H); 8.02 (d, J = 9.9 Hz, 1 H); 7.22-7.05 (m, 4 H); 7.08-7.01 (m, 2 H); 6.95 (d, J = 8.2 Hz, 1 H); 6.81 (d, J = 8.2 Hz, 1 H); 6.76-6.69 (m, 2 H); 6.62 (d, J = 8.3 Hz, 1 H); 6.38 (d, J = 9.8 Hz, 1 H); 5.63 (s, 1 H); 5.11 (d, J = 9.2 Hz, 1 H); 4.45 (s, 1 H); 3.75 (t, J = 6.4 Hz, 2 H); 3.06-2.96 (m, 1 H); 2.85-2.39 (m, 9 H); 1.79 (s, 1 H); 1.66 (s, 1 H); 1.56-1.11 (m, 11 H)	diformate
41B	B	(DMSO-d ₆): δ 8.30 (s, 1 H); 8.24 (d, J = 10.10 Hz, 1 H); 8.19 (d, J = 9.93 Hz, 1 H); 7.37-7.17 (m, 6 H); 7.11 (d, J = 8.17 Hz, 1 H); 7.00-6.86 (m, 3 H); 6.78 (dd, J = 8.26, 2.44 Hz, 1 H); 6.56-6.48 (m, 1 H); 5.81 (d, J = 8.52 Hz, 1 H); 5.20 (dd, J = 8.28, 4.46 Hz, 1 H); 4.58 (s, 1 H); 3.95-3.88 (m, 2 H); 3.18-3.06 (m, 1 H); 2.86-2.55 (m, 8 H); 1.91 (s, 1 H); 1.80 (s, 1 H); 1.74-1.32 (m, 12 H).	formate
42B	A	(DMSO-d ₆): δ 8.55 (d, J = 9.19 Hz, 1 H); 8.40 (s, 2 H); 8.19 (d, J = 9.91 Hz, 1 H); 7.98 (d, J = 7.80 Hz, 2 H); 7.76 (t, J = 7.40 Hz, 1 H); 7.61 (t, J = 7.67 Hz, 2 H); 7.40-7.30 (m, 4 H); 7.29-7.19 (m, 2 H); 7.07 (d, J = 8.17 Hz, 1 H); 6.99-6.86 (m, 3 H); 6.81 (d, J = 8.37 Hz, 1 H); 6.50 (d, J = 9.84 Hz, 1 H); 5.84 (d, J = 8.86 Hz, 1 H); 5.20 (s, 2 H); 5.09 (s, 1 H); 5.03 (s, 1 H); 4.14-4.03 (m, 1 H); 3.96-3.88 (m, 2 H); 3.82-3.55 (m, 6 H); 2.75 (s, 2 H); 2.64-2.57 (m, 2 H); 2.34 (d, J = 6.23 Hz, 1 H); 2.18 (s, 1 H); 2.13-1.88 (m, 3 H); 1.67 (d, J = 8.37 Hz, 2 H); 1.51-1.21 (m, 5 H).	diformate
43B	A	(CD ₃ OD): δ 8.57 (s, 2H); 8.39 (d, J = 10 Hz, 1H); 8.02 (d, J = 9.6 Hz, 2 H); 7.75-7.70 (m, 1 H); 7.61-7.55 (m, 2 H); 7.40-7.24 (m, 7 H); 7.03 (d, J = 8.2 Hz, 1 H); 6.94-6.80 (m, 3 H); 6.70 (d, J = 9.6 Hz, 1 H); 5.90 (s, 1 H); 5.40-5.36 (m, 1 H); 5.15 (br s, 1 H); 4.92 (s, 2 H); 4.22-4.15 (m, 1 H); 4.00-3.66 (m, 8 H); 3.19-3.12 (m, 2 H); 3.01 (t, J = 8 Hz, 2 H); 2.51 (s, 1 H); 2.45-2.33 (m, 1 H); 2.26-2.17 (m, 1 H); 2.15-2.00 (m, 1 H); 1.84-1.69 (m, 4 H); 1.58-1.42 (m, 4 H)	diformate

(continued)

44B	C	(DMSO-d ₆): δ 8.34-8.22 (m, 3 H); 8.20 (d, J = 10 Hz, 1 H); 7.98 (d, J = 8.4 Hz, 2H); 7.58 (d, J = 8.4 Hz, 2 H); 7.38-7.20 (m, 6 H); 7.15-6.83 (m, 5 H); 6.54 (d, J = 9.6 Hz, 1 H); 5.82 (br s, 1 H); 5.24-5.13 (m, 3 H); 4.61-4.59 (m, 1 H); 4.31 (t, J = 6 Hz, 2 H); 3.21-3.09 (m, 1 H); 2.95-2.42 (m, 8 H); 1.95 (s, 1 H); 1.89-.29 (m, 9 H)	diformate
45B	B	(DMSO-d ₆): δ 8.29 (s, 1 H); 8.24 (d, J = 9.71 Hz, 1 H); 8.18 (d, J = 9.94 Hz, 1 H); 7.97 (d, J = 8.07 Hz, 2 H); 7.57 (d, J = 8.01 Hz, 2 H); 7.32-7.18 (m, 6 H); 7.09 (d, J = 8.16 Hz, 1 H); 7.04 (s, 1 H); 6.94 (d, J = 8.01 Hz, 2 H); 6.89 (dd, J = 8.27, 2.55 Hz, 1 H); 6.51 (d, J = 9.86 Hz, 1 H); 5.82 (d, J = 9.09 Hz, 1 H); 5.20-5.12 (m, 3 H); 4.58 (s, 1 H); 4.29 (t, J = 6.28 Hz, 2 H); 3.10 (d, J = 10.66 Hz, 1 H); 2.87-2.52 (m, 8 H); 2.06-1.30 (m, 10 H).	formate
9C	A	(DMSO-d ₆): δ 8.33 (s, 2 H); 8.27 (d, J = 9.9 Hz, 1 H); 8.19 (d, J = 9.9 Hz, 1 H); 7.35-7.27 (m, 4 H); 7.27-7.19 (m, 2 H); 7.11 (d, J = 8.2 Hz, 1 H); 6.99-6.92 (m, 3 H); 6.79-6.74 (m, 1 H); 6.53 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.3 Hz, 1 H); 5.25-5.19 (m, 1 H); 4.75 (d, J = 2.0 Hz, 2 H); 4.80-4.37 (m, 1 H); 4.08 (t, J = 6.7 Hz, 2 H); 3.20-3.08 (m, 1 H); 2.92-2.84 (m, 2 H); 2.79-2.70 (m, 4 H); 2.70-2.59 (m, 3 H); 1.99-1.86 (m, 1 H); 1.90-1.73 (m, 1 H); 1.62-1.47 (m, 6 H); 1.43-1.20 (m, 3 H).	diformate
10C	B	(DMSO-d ₆): δ 8.34 (s, 2 H); 8.29 (d, J = 10.0 Hz, 1 H); 8.19 (d, J = 9.9 Hz, 1 H); 7.35-7.27 (m, 4 H); 7.25-7.17 (m, 2 H); 7.10 (d, J = 8.2 Hz, 1 H); 6.99-6.92 (m, 3 H); 6.81-6.74 (m, 1 H); 6.52 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.6 Hz, 1 H); 5.22-5.16 (m, 1 H); 4.75 (s, 2 H); 4.67-4.53 (m, 1 H); 4.13-4.06 (m, 2 H); 3.21-3.04 (m, 1 H); 2.87-2.80 (m, 2 H); 2.79-2.46 (m, 7 H); 2.04-1.80 (m, 1 H); 1.95-1.68 (m, 1 H); 1.63-1.48 (m, 6 H); 1.63-1.12 (m, 1 H).	diformate
11C	B	(DMSO-d ₆): δ 8.32-8.21 (m, 1 H); 8.24 (s, 2 H); 8.17 (d, J = 9.9 Hz, 1 H); 7.33-7.29 (m, 4 H); 7.27-7.17 (m, 2 H); 7.11 (d, J = 8.2 Hz, 1 H); 6.99-6.91 (m, 2 H); 6.72 (s, 1 H); 6.61 (d, J = 8.2 Hz, 1 H); 6.54 (d, J = 9.9 Hz, 1 H); 5.79 (d, J = 9.0 Hz, 1 H); 5.21-5.15 (m, 1 H); 4.62-4.54 (m, 1 H); 4.00 (t, J = 6.4 Hz, 2 H); 3.22-3.02 (m, 1 H); 2.88-2.83 (m, 2 H); 2.80-2.71 (m, 2 H); 2.70-2.67 (m, 4 H); 1.93-1.88 (m, 1 H); 1.81-1.80 (m, 1 H); 1.59-1.58 (m, 1 H); 1.65-1.35 (m, 12 H); 1.43-1.31 (m, 1 H); 1.24-1.14 (m, 2 H)	diformate

(continued)

12C	B	(DMSO-d ₆): δ 8.31 (s, 2 H); 8.41-8.12 (m, 1 H); 8.17 (d, J = 9.9 Hz, 1 H); 7.41-7.21 (m, 4 H); 7.30-7.17 (m, 1 H); 7.18 (t, J = 8.1 Hz, 1 H); 7.09 (d, J = 8.2 Hz, 1 H); 6.95 (d, J = 8.3 Hz, 1 H); 6.99-6.83 (m, 1 H); 6.72 (s, 1 H); 6.61 (d, J = 8.1 Hz, 1 H); 6.51 (d, J = 9.8 Hz, 1 H); 5.79 (d, J = 9.0 Hz, 1 H); 5.23-5.06 (m, 1 H); 4.72-4.45 (m, 1 H); 4.01 (t, J = 6.4 Hz, 2 H); 3.25-2.98 (m, 1 H); 2.81-2.72 (m, 4 H); 2.83-2.46 (m, 4 H); 2.67-2.45 (m, 1 H); 2.01-1.80 (m, 1 H); 1.94-1.67 (m, 1 H); 1.85-1.14 (m, 11 H); 1.57-1.13 (m, 2 H).	diformate
13C	C	(CD ₃ OD): δ 8.57 (s, 2 H); 8.37 (d, J = 9.8 Hz, 1 H); 7.34-7.20 (m, 7 H); 7.04 (d, J = 8.1 Hz, 1 H); 6.86 (s, 1 H); 6.82 (d, J = 8.1 Hz, 2 H); 6.69 (d, J = 9.8 Hz, 1 H); 5.83 (d, J = 7.2 Hz, 1 H); 5.38-5.32 (m, 1 H); 4.90-4.74 (m, 1 H); 4.24-3.99 (m, 2 H); 4.11-3.84 (m, 2 H); 3.41-3.36 (m, 1 H); 3.10-3.03 (m, 3 H); 3.04-2.87 (m, 3 H); 2.92-2.58 (m, 2 H); 2.26-2.06 (m, 1 H); 2.25-1.90 (m, 1 H); 2.06-1.68 (m, 1 H); 1.79-1.67 (m, 1 H); 1.67-1.59 (m, 6 H); 1.69-0.95 (m, 8 H).	diformate
14C	A	(DMSO-d ₆): δ 8.36 (s, 2 H); 8.28 (d, J = 9.9 Hz, 1 H); 8.20 (d, J = 9.9 Hz, 1 H); 7.35-7.27 (m, 4 H); 7.26-7.20 (m, 2 H); 7.11 (d, J = 8.2 Hz, 1 H); 6.97 (d, J = 8.1 Hz, 1 H); 7.00-6.85 (m, 2 H); 6.81-6.70 (m, 1 H); 6.53 (d, J = 9.8 Hz, 1 H); 5.81 (d, J = 9.2 Hz, 1 H); 5.26 (dd, J = 8.9, 3.8 Hz, 1 H); 4.77 (s, 2 H); 4.74-4.52 (m, 1 H); 4.15 (d, J = 12.9 Hz, 1 H); 4.19-3.91 (m, 2 H); 3.77 (d, J = 13.3 Hz, 1 H); 3.24-3.05 (m, 2 H); 2.97-2.88 (m, 2 H); 2.86-2.53 (m, 8 H); 2.09-1.85 (m, 1 H); 2.04-1.65 (m, 3 H); 1.93-1.23 (m, 8 H); 1.58-1.24 (m, 2 H).	diformate
15C	C	(DMSO-d ₆): δ 8.31 (s, 2 H); 8.38-8.14 (m, 1 H); 8.18 (d, J = 9.9 Hz, 1 H); 7.34-7.15 (m, 9 H); 7.08 (d, J = 8.4 Hz, 1 H); 6.99-6.91 (m, 4 H); 6.82-6.75 (m, 1 H); 6.51 (d, J = 9.8 Hz, 1 H); 5.86-5.78 (m, 1 H); 5.28-4.95 (m, 3 H); 4.88-4.74 (m, 2 H); 4.70-4.49 (m, 1 H); 3.18-3.06 (m, 1 H); 2.98-2.57 (m, 11 H); 2.01-1.80 (m, 1 H); 1.97-1.64 (m, 1 H); 1.76-1.44 (m, 1 H); 1.60-1.36 (m, 1 H); 1.56-1.16 (m, 1 H).	diformate
16C	A	(DMSO-d ₆): δ 8.31 (s, 1 H); 8.24-8.14 (m, 2 H); 7.34-7.26 (m, 4 H); 7.23-7.18 (m, 1 H); 7.10 (d, J = 8.16 Hz, 1 H); 7.04 (d, J = 7.67 Hz, 1 H); 6.95 (d, J = 8.10 Hz, 2 H); 6.82-6.76 (m, 1 H); 6.53 (d, J = 9.86 Hz, 1 H); 5.79 (d, J = 9.14 Hz, 1 H); 5.20-5.14 (m, 1 H); 4.58 (s, 1 H); 3.94-3.88 (m, 2 H); 3.17-3.05 (m, 1 H); 2.86-2.81 (m, 2 H); 2.8-2.6 (m, 6 H); 2.09 (s, 3 H); 1.91 (s, 1 H); 1.80 (s, 1 H); 1.75-1.64 (m, 2 H); 1.76-1.12 (m, 16 H).	formate

(continued)

17C	A	(DMSO-d ₆): δ 8.32 (s, 1 H); 8.28 (d, J = 8.85 Hz, 1 H); 8.18 (d, J = 9.93 Hz, 1 H); 7.36-7.30 (m, 4 H); 7.27-7.22 (m, 1 H); 7.15-7.06 (m, 2 H); 6.98 (d, J = 15.67 Hz, 3 H); 6.53 (d, J = 9.86 Hz, 1 H); 5.82 (d, J = 9.15 Hz, 1 H); 5.18 (dd, J = 7.97, 4.67 Hz, 1 H); 4.58 (s, 1 H); 3.97-3.91 (m, 2 H); 3.16-3.05 (m, 1 H); 2.88-2.83 (m, 2 H); 2.80-2.53 (m, 7 H); 1.91 (s, 1 H); 1.80 (s, 1 H); 1.95-1.11 (m, 18 H).	formate
18C	B	(DMSO-d ₆): δ 8.31 (s, 2 H); 8.18 (d, J = 9.92 Hz, 1 H); 7.66-7.62 (m, 2 H); 7.48-7.28 (m, 7 H); 7.27-7.19 (m, 2 H); 7.10 (d, J = 8.17 Hz, 1 H); 7.04 (s, 1 H); 6.95 (d, J = 7.85 Hz, 2 H); 6.53 (d, J = 9.86 Hz, 1 H); 5.89 (d, J = 8.99 Hz, 1 H); 5.20-5.14 (m, 1 H); 4.59 (s, 1 H); 4.09-3.93 (m, 2 H); 3.12 (d, J = 13.08 Hz, 1 H); 2.87-2.82 (m, 2 H); 2.79-2.57 (m, 6 H); 1.92 (s, 1 H); 1.81 (s, 1 H); 1.75-1.67 (m, 2 H); 1.75-1.12 (m, 16 H).	formate
19C	A	(DMSO-d ₆ @105°C): δ 8.23-8.13 (m, 3 H); 7.60-7.49 (m, 1 H); 7.35-7.20 (m, 6 H); 7.15-7.05 (m, 2 H); 7.02-6.92 (m, 2 H); 6.51-6.45 (m, 1 H); 6.33-6.26 (m, 1 H); 5.06-5.00 (m, 1 H); 4.63-4.56 (m, 1 H); 4.10-4.01 (m, 2 H); 3.11-3.01 (m, 1 H); 2.84-2.52 (m, 8 H); 1.92-1.84 (m, 1 H); 1.82-1.54 (m, 4 H); 1.53-1.19 (m, 15 H).	diformate
20C	C	(DMSO-d ₆): δ 8.28 (s, 2 H); 8.18 (d, J = 9.88 Hz, 1 H); 7.54-7.44 (m, 3 H); 7.39 (s, 2 H); 7.36-7.28 (m, 3 H); 7.24-7.15 (m, 2 H); 7.10 (d, J = 7.01 Hz, 2 H); 7.00 (s, 1 H); 6.95 (d, J = 8.23 Hz, 1 H); 6.53 (d, J = 9.86 Hz, 1 H); 5.89 (d, J = 8.77 Hz, 1 H); 5.16 (d, J = 7.81 Hz, 1 H); 4.59 (s, 1 H); 4.08-3.96 (m, 2 H); 3.11 (s, 1 H); 2.94-2.76 (m, 2 H); 2.7-2.3 (m, 6 H); 1.92 (s, 1 H); 1.81 s, 1 H); 1.75-1.66 (m, 2 H); 1.75-1.13 (m, 16 H).	formate
21C	C	(CD ₃ OD): δ 8.56 (s, 1 H); 8.38 (d, J = 9.9 Hz, 1 H); 7.33-7.20 (m, 8 H); 7.07-6.85 (m, 7 H); 6.70-6.65 (m, 1 H); 5.87 (s, 1 H); 5.43-5.36 (m, 1 H); 5.03 (s, 2 H); 4.92 (m, 1H – obscured by water); 4.08-4.02 (m, 2 H); 3.51-3.50 (m, 1 H); 3.27-3.06 (m, 9 H); 2.30-1.60 (m, 9 H).	formate
22C	A	(CD ₃ OD): δ 8.56 (s, 1 H); 8.38 (d, J = 9.9 Hz, 1 H); 7.33-7.20 (m, 8 H); 7.07-6.85 (m, 7 H); 6.70-6.65 (m, 1 H); 5.87 (s, 1 H); 5.43-5.36 (m, 1 H); 5.03 (s, 2 H); 4.92 (m, 1H – obscured by water); 4.08-4.02 (m, 2 H); 3.51-3.50 (m, 1 H); 3.27-3.06 (m, 9 H); 2.30-1.60 (m, 11 H).	formate

(continued)

23C	C	(DMSO-d ₆): δ 8.43 (s, 2 H); 8.19 (d, J = 9.9 Hz, 1 H); 8.03-7.88 (m, 3 H); 7.80-7.69 (m, 1 H); 7.68-7.55 (m, 2 H); 7.20 (t, J = 7.9 Hz, 1 H); 7.06 (d, J = 8.2 Hz, 1 H); 6.96 (d, J = 8.1 Hz, 1 H); 6.92-6.75 (m, 3 H); 6.49 (dd, J = 9.8, 1.3 Hz, 1 H); 5.25-5.06 (m, 3 H); 5.01-4.91 (m, 1 H); 4.26-4.00 (m, 2 H); 3.94 (t, J = 6.8 Hz, 2 H); 3.84-3.50 (m, 5 H); 2.76 (d, J = 6.3 Hz, 2 H); 2.66-2.52 (m, 2 H); 2.38-1.78 (m, 6 H); 1.77-0.77 (m, 24 H).	diformate
24C	B	(DMSO-d ₆): δ 8.75-8.66 (m, 1 H); 8.39 (s, 2 H); 8.19 (dd, J = 9.92, 1.99 Hz, 1 H); 8.02-7.93 (m, 2 H); 7.77-7.70 (m, 1 H); 7.61 (dd, J = 15.40, 7.70 Hz, 2 H); 7.44-7.41 (m, 1 H); 7.30-7.24 (m, 1 H); 7.10-6.92 (m, 5 H); 6.89-6.81 (m, 2 H); 6.50 (dd, J = 9.85, 1.91 Hz, 1 H); 6.06-6.01 (m, 1 H); 5.20 (d, J = 10.80 Hz, 2 H); 5.16-5.10 (m, 1 H); 5.05 (s, 1 H); 4.14-4.06 (m, 1 H); 3.98-3.90 (m, 2 H); 3.72 (d, J = 14.98 Hz, 3 H); 3.61 (d, J = 12.36 Hz, 2 H); 2.81-2.75 (m, 2 H); 2.70-2.60 (m, 2 H); 2.44-2.29 (m, 1 H); 2.21-1.91 (m, 4 H); 1.73-1.64 (m, 2 H); 1.55-1.28 (m, 6 H).	diformate
25C	A	(DMSO-d ₆): δ 8.59 (d, J = 9.31 Hz, 1 H); 8.38 (s, 2 H); 8.18 (dd, J = 9.94, 2.25 Hz, 1 H); 7.98 (dd, J = 7.77, 3.44 Hz, 2 H); 7.78-7.71 (m, 1 H); 7.64-7.57 (m, 2 H); 7.38 (d, J = 8.14 Hz, 1 H); 7.28-7.17 (m, 3 H); 7.11-7.05 (m, 2 H); 6.95 (d, J = 8.55 Hz, 3 H); 6.83 (d, J = 8.19 Hz, 1 H); 6.50 (dd, J = 9.85, 1.97 Hz, 1 H); 5.88 (d, J = 8.38 Hz, 1 H); 5.19 (s, 2 H); 5.06 (d, J = 17.58 Hz, 2 H); 4.08 (s, 1 H); 3.96-3.89 (m, 2 H); 3.81-3.51 (d, J = 15.32 Hz, 4 H); 2.76-2.71 (m, 2 H); 2.58 (d, J = 16.78 Hz, 2 H); 2.38-2.32 (m, 2 H); 2.10-1.94 (m, 4 H); 1.67 (d, J = 7.71 Hz, 2 H); 1.48-1.25 (m, 6 H).	diformate
26C	C	(DMSO-d ₆): δ 8.54 (d, J = 9.47 Hz, 1 H); 8.40 (s, 2 H); 8.21-8.15 (m, 1 H); 8.02-7.94 (m, 2 H); 7.75 (dd, J = 13.60, 6.80 Hz, 1 H); 7.61 (dd, J = 14.38, 7.19 Hz, 2 H); 7.51-7.47 (m, 1 H); 7.36-7.29 (m, 1 H); 7.27-7.19 (m, 1 H); 7.09-7.02 (m, 2 H); 6.98-6.89 (m, 3 H); 6.82 (d, J = 8.31 Hz, 1 H); 6.50 (dd, J = 9.84, 2.05 Hz, 1 H); 5.89 (d, J = 8.63 Hz, 1 H); 5.20 (s, 2 H); 5.10 (s, 1 H); 5.03 (s, 1 H); 4.14-4.04 (m, 1 H); 3.96-3.89 (m, 2 H); 3.88-3.46 (m, 4 H); 2.77-2.72 (m, 2 H); 2.69-2.52 (m, 2 H); 2.34 (t, J = 3.91 Hz, 1 H); 2.17 (s, 1 H); 2.08-1.93 (m, 4 H); 1.68 (d, J = 8.24 Hz, 2 H); 1.51-1.26 (m, 6 H).	diformate

(continued)

27C	A	(DMSO-d ₆): δ 8.60-8.54 (m, 1 H); 8.50 (s, 1 H); 8.42 (s, 2 H); 8.17 (d, J = 9.87 Hz, 1 H); 8.01-7.92 (m, 2 H); 7.86-7.82 (m, 2 H); 7.75 (d, J = 7.15 Hz, 1 H); 7.65-7.56 (m, 2 H); 7.49 (d, J = 7.88 Hz, 2 H); 7.37-7.31 (m, 4 H); 7.29-7.23 (m, 2 H); 7.08-7.01 (m, 2 H); 6.99-6.89 (m, 3 H); 6.49 (dd, J = 9.83, 1.19 Hz, 1 H); 5.85 (d, J = 8.77 Hz, 1 H); 5.17 (d, J = 21.19 Hz, 4 H); 5.04 (d, J = 8.06 Hz, 2 H); 4.08 (s, 1 H); 3.79-3.55 (m, 4 H); 3.26 (s, 2 H); 2.73 (d, J = 7.03 Hz, 1 H); 2.69-2.52 (m, 3 H); 2.35 (d, J = 6.54 Hz, 1 H); 2.21-1.89 (m, 5 H); 1.51 (d, J = 22.95 Hz, 4 H).	diformate
28C	B	(CD ₃ OD): δ 8.56 (s, 2 H); 8.38 (dd, J = 9.9, 3.5 Hz, 1 H); 8.03-7.98 (m, 2 H); 7.77-7.69 (m, 1 H); 7.62-7.54 (m, 2 H); 7.36-7.21 (m, 7 H); 7.04 (d, J = 8.2 Hz, 1 H); 6.95-6.79 (m, 3 H); 6.69 (dd, J = 9.8, 3.3 Hz, 1 H); 5.90 (s, 1 H); 5.43-5.36 (m, 1 H); 5.14 (s, 1 H); 4.25-4.14 (m, 1 H); 4.00-3.97 (m, 2 H); 3.85-3.70 (m, 5 H); 3.34 (m, 2 H); 3.22-3.19 (m, 2 H); 3.10-3.05 (m, 2 H); 2.50 (s, 1 H); 2.45-2.33 (m, 1 H); 2.27-2.02 (m, 3 H); 1.82 (s, 4 H); 1.59 (s, 6 H).	diformate
29C	A	(CD ₃ OD): δ 8.56 (s, 2 H); 8.39 (d, J = 9.9 Hz, 1 H); 7.35-7.20 (m, 12 H); 7.04 (d, J = 8.2 Hz, 1 H); 6.90-6.77 (m, 3 H); 6.70 (d, J = 9.8 Hz, 1 H); 5.88 (s, 1 H); 5.39 (t, J = 6.7 Hz, 1 H); 5.04 (s, 1 H); 3.94 (t, J = 6.3 Hz, 2 H); 3.89-3.77 (m, 1 H); 3.55-3.18 (m, 6 H); 3.08-2.97 (m, 4 H); 2.69 (t, J = 7.1 Hz, 2 H); 2.41 (s, 1 H); 2.35-2.24 (m, 1H); 2.16-1.87 (m, 4 H); 1.81-1.68 n(m, 4 H); 1.56-1.39 (m, 6 H)	diformate
30C	C	(CD ₃ OD): δ 8.56 (s, 2 H); 8.38 (dd, J = 9.9, 3.5 Hz, 1 H); 8.03-7.98 (m, 2 H); 7.77-7.69 (m, 1 H); 7.62-7.54 (m, 2 H); 7.36-7.21 (m, 7 H); 7.04 (d, J = 8.2 Hz, 1 H); 6.95-6.79 (m, 3 H); 6.69 (dd, J = 9.8, 3.3 Hz, 1 H); 5.90 (s, 1 H); 5.43-5.36 (m, 1 H); 5.14 (s, 1 H); 4.25-4.14 (m, 1 H); 4.00-3.97 (m, 2 H); 3.85-3.70 (m, 5 H); 3.34 (m, 2 H); 3.22-3.19 (m, 2 H); 3.10-3.05 (m, 2 H); 2.50 (s, 1 H); 2.45-2.33 (m, 1 H); 2.27-2.02 (m, 3 H); 1.82 (s, 4 H); 1.59 (s, 2 H).	diformate
31C	B	(DMSO-d ₆): δ 8.32-8.21 (m, 3 H); 8.18 (d, J = 9.9 Hz, 1 H); 7.39-7.19 (m, 10 H); 7.09 (d, J = 8.2 Hz, 1 H); 7.01 (s, 1 H); 6.97-6.89 (m, 2 H); 6.88-6.82 (m, 1 H); 6.52 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.0 Hz, 1 H); 5.13 (t, J = 6.3 Hz, 1 H); 5.00 (s, 2 H); 4.62-4.55 (m, 1 H); 3.97 (t, J = 6.2 Hz, 2 H); 3.16-3.07 (m, 1 H); 2.81-2.52 (m, 9 H); 1.95-1.27 (m, 17 H).	diformate

(continued)

32C	B	(DMSO-d ₆): δ 8.32-8.22 (m, 3 H); 8.18 (d, J = 9.9 Hz, 1 H); 7.42-7.18 (m, 10 H); 7.10 (d, J = 8.2 Hz, 1 H); 7.03-6.89 (m, 3 H); 6.88-6.82 (m, 1 H); 6.53 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.1 Hz, 1 H); 5.18 (dd, J = 8.0, 4.5 Hz, 1 H); 5.00 (s, 2 H); 4.64-4.57 (m, 1 H); 4.02 (t, J = 6.2 Hz, 2 H); 3.20-3.09 (m, 1 H); 2.88-2.52 (m, 7 H); 2.40-2.30 (m, 2 H); 1.97-1.76 (m, 2 H); 1.73-1.16 (m, 17 H)	diformate
33C	B	(DMSO-d ₆): δ 8.33-8.23 (m, 3 H); 8.17 (d, J = 9.9 Hz, 1 H); 7.42-7.19 (m, 10 H); 7.10 (d, J = 8.2 Hz, 1 H); 7.01 (s, 1 H); 6.99-6.89 (m, 2 H); 6.88-6.83 (m, 1 H); 6.53 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.2 Hz, 1 H); 5.19 (dd, J = 8.2, 4.5 Hz, 1 H); 5.01 (s, 2 H); 4.64-4.56 (m, 1 H); 4.03 (t, J = 6.1 Hz, 2 H); 3.20-3.09 (m, 1 H); 2.89-2.52 (m, 9 H); 1.97-1.76 (m, 2 H); 1.67-1.28 (m, 13 H).	diformate
34C	A	(DMSO-d ₆): δ 8.39 (d, J = 9.32 Hz, 1 H); 8.30 (s, 2 H); 8.18 (d, J = 9.94 Hz, 1 H); 7.93 (s, 1 H); 7.83 (d, J = 7.72 Hz, 1 H); 7.65-7.53 (m, 1 H); 7.51-7.44 (m, 1 H); 7.35-7.30 (m, 4 H); 7.26 (d, J = 5.91 Hz, 1 H); 7.11 (d, J = 8.18 Hz, 1 H); 6.96 (d, J = 8.13 Hz, 1 H); 6.53 (d, J = 9.86 Hz, 1 H); 5.94 (d, J = 8.55 Hz, 1 H); 5.21 (dd, J = 8.61, 4.05 Hz, 1 H); 4.60 (s, 1 H); 4.28-4.21 (m, 2 H); 3.12 (s, 1 H); 2.96-2.85 (m, 2 H); 2.80-2.57 (m, 7 H); 1.92 (s, 1 H); 1.81 (s, 1 H); 1.86-1.39 (m, 5 H); 1.32 (d, J = 29.30 Hz, 10 H).	diformate
35C	A	(DMSO-d ₆): δ 8.39 (d, J = 9.08 Hz, 1 H); 8.32 (s, 2 H); 8.18 (d, J = 9.91 Hz, 1 H); 7.93 (s, 1 H); 7.83 (d, J = 7.65 Hz, 1 H); 7.58 (s, 1 H); 7.52-7.44 (m, 1 H); 7.34 (d, J = 4.53 Hz, 4 H); 7.26 (d, J = 6.13 Hz, 1 H); 7.11 (d, J = 8.14 Hz, 1 H); 6.99-6.91 (m, 1 H); 6.56-6.47 (m, 1 H); 5.94 (d, J = 7.51 Hz, 1 H); 5.24-5.18 (m, 1 H); 4.59 (s, 1 H); 4.29-4.21 (m, 2 H); 3.12 (d, J = 12.48 Hz, 1 H); 2.88 (d, J = 9.45 Hz, 2 H); 2.69 (d, J = 52.79 Hz, 6 H); 1.92 (s, 1 H); 1.81 (s, 1 H); 1.72-1.08 (m, 18 H).	diformate
36C	A	(DMSO-d ₆): δ 8.38 (d, J = 9.05 Hz, 1 H); 8.30 (d, J = 4.26 Hz, 2 H); 8.18 (d, J = 9.90 Hz, 1 H); 7.93 (s, 1 H); 7.83 (d, J = 7.68 Hz, 1 H); 7.58 (s, 1 H); 7.48 (t, J = 7.67 Hz, 1 H); 7.34 (d, J = 4.51 Hz, 4 H); 7.26 (d, J = 5.85 Hz, 1 H); 7.10 (d, J = 8.16 Hz, 1 H); 6.95 (d, J = 8.11 Hz, 1 H); 6.52 (d, J = 9.85 Hz, 1 H); 5.94 (d, J = 8.11 Hz, 1 H); 5.17 (s, 1 H); 4.58 (s, 1 H); 4.25 (t, J = 6.47 Hz, 2 H); 3.10 (s, 1 H); 2.91-2.52 (m, 8 H); 1.97-1.72 (m, 2 H); 1.73-1.65 (m, 2 H); 1.74-1.20 (m, 12 H).	diformate

(continued)

37C	A	(DMSO d ₆): δ 8.30 (s, 1 H); 8.27-8.20 (m, 1 H); 8.17-8.11 (m, 3 H); 7.65 (d, J = 7.9 Hz, 2 H); 7.41 (d, J = 8.0 Hz, 2 H); 7.36-7.15 (m, 8 H); 7.12-7.04 (m, 2 H); 6.98-6.87 (m, 3 H); 6.49 (d, J = 9.8 Hz, 1 H); 5.83 (d, J = 9.2 Hz, 1 H); 5.23 (s, 2 H); 5.08 (dd, J = 7.8, 4.3 Hz, 1 H); 4.57 (s, 1 H); 3.79 (s, 2 H); 3.10 (s, 2 H); 2.76-2.63 (m, 6 H); 1.90 (s, 1 H); 1.80 (s, 1 H); 1.58 (s, 1 H); 1.47 (s, 1 H); 1.33 (s, 1 H).	diformate
38C	A	(DMSO-d ₆): δ 8.39 (d, J = 8.88 Hz, 1 H); 8.29 (s, 2 H); 8.18 (d, J = 9.91 Hz, 1 H); 7.93 (s, 1 H); 7.84 (d, J = 7.67 Hz, 1 H); 7.59 (d, J = 7.47 Hz, 1 H); 7.52-7.44 (m, 1 H); 7.34 (d, J = 4.53 Hz, 4 H); 7.26 (d, J = 5.97 Hz, 1 H); 7.10 (d, J = 8.16 Hz, 1 H); 6.95 (d, J = 8.13 Hz, 1 H); 6.52 (d, J = 9.86 Hz, 1 H); 5.94 (d, J = 8.37 Hz, 1 H); 5.19-5.12 (m, 1 H); 4.58 (s, 1 H); 4.30-4.22 (m, 2 H); 3.10 (s, 1 H); 2.84 (d, J = 6.23 Hz, 2 H); 2.79-2.58 (m, 6 H); 1.91 (s, 1 H); 1.80 (s, 1 H); 1.76-1.64 (m, 2 H); 1.62-1.32 (m, 8 H).	diformate
39C	B	(DMSO-d ₆): δ 8.53 (s, 1 H); 8.39 (d, J = 9.67 Hz, 1 H); 8.28 (s, 2 H); 8.18 (d, J = 9.93 Hz, 1 H); 7.99 (s, 1 H); 7.87 (dd, J = 14.46, 7.77 Hz, 3 H); 7.65-7.58 (m, 1 H); 7.55-7.47 (m, 3 H); 7.34 (d, J = 4.80 Hz, 4 H); 7.28-7.23 (m, 1 H); 7.11 (d, J = 8.18 Hz, 1 H); 6.96 (d, J = 8.12 Hz, 1 H); 6.53 (d, J = 9.86 Hz, 1 H); 5.96 (d, J = 7.79 Hz, 1 H); 5.40 (s, 2 H); 5.21 (dd, J = 8.54, 4.15 Hz, 1 H); 4.59 (s, 1 H); 3.33-3.21 (m, 2 H); 3.12 (s, 1 H); 2.90-2.52 (m, 8 H); 1.85 (d, J = 49.16 Hz, 2 H); 1.71-1.21 (m, 8 H).	diformate
40C	B	(CD ₃ OD): δ 8.52 (s, 2 H); 8.38 (d, J = 9.94 Hz, 1 H); 8.00 (d, J = 11.22 Hz, 2 H); 7.88 (d, J = 7.98 Hz, 2 H); 7.64 (d, J = 7.97 Hz, 2 H); 7.59-7.45 (m, 2 H); 7.33 (dd, J = 24.56, 7.68 Hz, 6 H); 7.04 (d, J = 8.21 Hz, 1 H); 6.70 (d, J = 9.84 Hz, 1 H); 6.00 (s, 1 H); 5.45 (s, 2 H); 5.42-5.35 (m, 1 H); 4.60 (s, 1 H); 3.53 (m, 1 H); 3.23-3.16 (m, 9 H); 2.97-2.89 (m, 2 H); 2.23-1.48 (m, 9 H).	diformate
41C	B	(DMSO-d ₆): δ 8.40 (d, J = 8.99 Hz, 1 H); 8.27 (s, 2 H); 8.18 (d, J = 9.90 Hz, 1 H); 7.97 (s, 1 H); 7.86 (d, J = 7.68 Hz, 1 H); 7.67-7.52 (m, 1 H); 7.53-7.44 (m, 1 H); 7.38-7.31 (m, 6 H); 7.29-7.21 (m, 3 H); 7.15-7.05 (m, 1 H); 6.94 (d, J = 8.13 Hz, 1 H); 6.52 (d, J = 9.86 Hz, 1 H); 5.95 (d, J = 8.61 Hz, 1 H); 5.31 (s, 2 H); 5.17-5.10 (m, 1 H); 4.60 (s, 1 H); 3.14 (s, 1 H); 3.00-2.54 (m, 11 H); 1.93 (s, 1 H); 1.80 (s, 1 H); 1.60 (s, 1 H); 1.50 (s, 1 H); 1.36 (s, 1 H).	diformate

(continued)

42C	C	(DMSO-d ₆): δ 9.20-9.06 (m, 1 H); 8.32 (s, 2 H); 8.18 (d, J = 9.91 Hz, 1 H); 7.93 (d, J = 8.61 Hz, 3 H); 7.78 (d, J = 7.53 Hz, 1 H); 7.52-7.39 (m, 4 H); 7.34 (d, J = 5.28 Hz, 4 H); 7.25 (s, 1 H); 7.09 (d, J = 8.18 Hz, 1 H); 6.95 (d, J = 8.13 Hz, 1 H); 6.51 (d, J = 9.84 Hz, 1 H); 5.91 (d, J = 8.42 Hz, 1 H); 5.19-5.12 (m, 1 H); 4.61-4.50 (m, 3 H); 4.30-4.24 (m, 2 H); 3.21-3.02 (m, 1 H); 2.88-2.49 (m, 8 H); 1.91 (s, 1 H); 1.92-1.27 (m, 9 H).	diformate
43C	A	(CD ₃ OD): δ 8.54 (s, 2 H); 8.35 (d, J = 9.8 Hz, 1 H); 7.72 (d, J = 8.1 Hz, 2 H); 7.44 (d, J = 8.0 Hz, 2 H); 7.32-7.21 (m, 11 H); 7.03 (d, J = 8.2 Hz, 1 H); 6.91 (m, 4 H); 6.66 (dd, J = 9.8, 1.1 Hz, 1 H); 5.88 (s, 1 H); 5.39-5.34 (m, 1 H); 5.11 (s, 2 H); 4.78-4.73 (m, 1 H); 4.32-4.26 (m, 1 H); 4.14-4.09 (m, 1 H); 3.56 (s, 1 H); 3.30-3.03 (m, 11 H); 1.89-1.64 (m, 10 H).	diformate
44C	B	(DMSO-d ₆): δ 8.36 (s, 2 H); 8.27 (d, J = 9.3 Hz, 1 H); 8.18 (d, J = 9.9 Hz, 1 H); 7.98-7.89 (m, 2 H); 7.47-7.38 (m, 2 H); 7.35-7.22 (m, 5 H); 7.21-7.16 (m, 1 H); 7.13-6.91 (m, 5 H); 6.50 (d, J = 9.9 Hz, 1 H); 5.84 (d, J = 9.4 Hz, 1 H); 5.56 (s, 2 H); 5.13-5.07 (m, 1 H); 4.59 (d, J = 7.5 Hz, 1 H); 3.11 (d, J = 10.6 Hz, 1 H); 2.96-2.78 (m, 6 H); 2.73-2.44 (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).	diformate
45C	B	(DMSO-d ₆): δ 8.49-8.14 (m, 3 H); 8.20-8.13 (m, 3 H); 7.38-7.30 (m, 5 H); 7.29-7.22 (m, 1 H); 7.11 (d, J = 8.2 Hz, 1 H); 6.96 (d, J = 8.1 Hz, 1 H); 6.57-6.49 (m, 1 H); 5.92 (d, J = 9.1 Hz, 1 H); 5.21 (dd, J = 8.5, 4.2 Hz, 1 H); 4.60 (s, 1 H); 4.04-3.96 (m, 2 H); 3.18-3.07 (m, 1 H); 2.91-2.48 (m, 8 H); 1.92 (s, 1 H); 1.75-1.64 (m, 2 H); 1.52 (s, 4 H); 1.38 (d, J = 10.7 Hz, 4 H); 1.27 (s, 9 H).	diformate
46C	A	(DMSO-d ₆): δ 8.53-8.16 (m, 4H); 7.42-7.36 (m, 2 H); 7.24-7.22 (m, 2 H); 7.11-7.04 (m, 2 H); 6.91-6.89 (m, 2 H); 6.50 (d, J = 9.6 Hz, 1 H); 5.95 (s, 1 H); 5.02-4.99 (dd, J = 7.9, 4.5 Hz, 1 H); 4.60-4.53 (m, 1 H); 3.92 (t, J = 6.5 Hz, 2 H); 3.12-3.02 (m, 1 H); 2.77-2.53 (m, 6H); 1.92-1.20 (m, 21 H).	diformate

(continued)

47C	A	(DMSO-d ₆): δ 8.26 (s, 2 H); 8.20 (d, J = 9.51 Hz, 1 H); 8.13 (d, J = 9.93 Hz, 1 H); 7.76 (d, J = 7.99 Hz, 1 H); 7.57 (s, 1 H); 7.43 (d, J = 8.10 Hz, 1 H); 7.27-7.13 (m, 6 H); 7.04 (d, J = 8.17 Hz, 1 H); 6.98 (s, 1 H); 6.90 (d, J = 8.08 Hz, 2 H); 6.83 (dd, J = 8.27, 2.48 Hz, 1 H); 6.45 (d, J = 9.86 Hz, 1 H); 5.76 (d, J = 9.32 Hz, 1 H); 5.21-5.02 (m, 3 H); 4.53 (m, 1 H); 4.24 (t, J = 6.14 Hz, 2 H); 3.12-3.02 (m, 1 H); 2.88-2.49 (m, 9 H); 1.85 (m, 1 H); 1.80-1.20 (m, 8 H).	diformate
48C	C	(DMSO-d ₆): δ 8.32 (s, 2 H); 8.23 (d, J = 9.88 Hz, 1 H); 8.18 (d, J = 9.92 Hz, 1 H); 7.89 (t, J = 7.85 Hz, 1 H); 7.39-7.17 (m, 8 H); 7.13-6.98 (m, 2 H); 6.97-6.85 (m, 3 H); 6.50 (d, J = 9.85 Hz, 1 H); 5.82 (d, J = 9.01 Hz, 1 H); 5.18 (s, 2 H); 5.11 (t, J = 6.33 Hz, 1 H); 4.57 (s, 1 H); 4.29 (t, J = 6.33 Hz, 2 H); 3.09 (s, 1 H); 2.78 (d, J = 6.45 Hz, 2 H); 2.72 (s, 6 H); 1.90 (s, 1 H); 1.80-1.68 (m, 3 H); 1.73-1.40 (m, 6 H).	diformate
49C	C	(DMSO-d ₆): δ 9.09-9.05 (m, 1 H); 8.36-8.23 (m, 4 H); 8.18 (d, J = 9.94 Hz, 1 H); 7.63 (d, J = 8.19 Hz, 1 H); 7.32-7.18 (m, 6 H); 7.18-6.98 (m, 2 H); 6.98-6.88 (m, 3 H); 6.55-6.47 (m, 1 H); 5.82 (d, J = 9.28 Hz, 1 H); 5.37-5.19 (m, 2 H); 5.20 (dd, J = 8.41, 4.37 Hz, 1 H); 4.59 (s, 1 H); 4.36-4.30 (m, 2 H); 3.19-3.08 (m, 1 H); 2.92-2.55 (m, 8 H); 2.01-1.84 (m, 1 H); 1.95-1.39 (m, 9 H).	diformate
50C	B	(DMSO-d ₆): δ 8.39-8.12 (m, 3 H); 8.18 (d, J = 9.94 Hz, 1 H); 7.33-7.19 (m, 7 H); 7.15-7.07 (m, 1 H); 7.04 (s, 1 H); 6.99-6.89 (m, 3 H); 6.76 (d, J = 3.48 Hz, 1 H); 6.52 (d, J = 9.86 Hz, 1 H); 5.83 (d, J = 9.2 Hz, 1 H); 5.23-5.11 (m, 3 H); 4.60 (s, 1 H); 4.28-4.21 (m, 2 H); 3.14 (dd, J = 14.7, 8.6 Hz, 1 H); 2.88-2.75 (m, 5 H); 2.72-2.48 (m, 7 H); 1.92 (d, J = 5.8 Hz, 1 H); 1.72 (t, J = 6.7 Hz, 3 H); 1.62 (d, J = 10.3 Hz, 3 H); 1.56-1.29 (m, 3 H)..	diformate
51C	C	(DMSO-d ₆): δ 8.91-8.83 (m, 1 H); 8.37-8.12 (m, 3 H); 8.17 (d, J = 9.9 Hz, 1 H); 7.32-7.17 (m, 6 H); 7.10 (d, J = 8.1 Hz, 1 H); 7.05-6.87 (m, 4 H); 6.52 (d, J = 9.8 Hz, 1 H); 5.82 (d, J = 9.3 Hz, 1 H); 5.27 (s, 2 H); 5.18 (t, J = 5.9 Hz, 1 H); 4.59 (s, 1 H); 4.26 (t, J = 6.2 Hz, 2 H); 3.18-3.09 (m, 1 H); 2.86 (d, J = 7.2 Hz, 2 H); 2.79 (s, 5 H); 2.68-2.66 (m, 1 H); 1.92 (s, 1 H); 1.75-1.56 (m, 5 H); 1.50 (s, 2 H); 1.36 (s, 2 H).	diformate

(continued)

52C	A	(DMSO-d ₆): δ 8.31-8.22 (m, 3 H); 8.17 (d, J = 9.9 Hz, 1 H); 8.03 (s, 1 H); 7.92 (d, J = 7.8 Hz, 1 H); 7.71 (d, J = 7.7 Hz, 1 H); 7.54 (t, J = 7.7 Hz, 1 H); 7.36-7.18 (m, 6 H); 7.12-7.02 (m, 2 H); 6.98-6.87 (m, 3 H); 6.52 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.3 Hz, 1 H); 5.21-5.13 (m, 3 H); 4.63-4.56 (m, 1 H); 4.30 (t, J = 6.2 Hz, 2 H); 3.18-3.08 (m, 1 H); 2.91-2.52 (m, 9 H); 1.95-1.89 (m, 1 H); 1.86-1.30 (m, 8 H).	diformate
53C	A	(DMSO-d ₆): δ 8.30-8.24 (m, 3 H); 8.18 (d, J = 9.9 Hz, 1 H); 7.31-7.28 (m, 4 H); 7.26-7.20 (m, 2 H); 7.14-7.07 (m, 1 H); 6.96-6.94 (m, 3 H); 6.79-6.76 (m, 1 H); 6.54-6.51 (m, 1 H); 5.82-5.79 (m, 1 H); 5.19-5.16 (m, 1 H); 4.75 (s, 2 H); 4.60-4.56 (m, 1 H); 4.10-4.06 (m, 2 H); 3.11-3.09 (m, 1 H); 2.86-2.50 (m, 8 H); 1.92-1.88 (m, 1 H); 1.80-1.75 (m, 1 H); 1.58-1.48 (m, 7 H); 1.34-1.26 (m, 3 H).	diformate
54C	A	(DMSO-d ₆): δ 8.30-8.24 (m, 3 H); 8.18 (d, J = 9.9 Hz, 1 H); 7.32-7.28 (m, 4 H); 7.24-7.20 (m, 2 H); 7.11-7.09 (m, 1 H); 6.96-6.93 (m, 3 H); 6.78-6.76 (m, 1 H); 6.53-6.51 (m, 1 H); 5.82-5.80 (m, 1 H); 5.17-5.14 (m, 1 H); 4.75 (s, 2 H); 4.59-4.55 (m, 1 H); 4.09-4.06 (m, 2 H); 3.15-3.08 (m, 1 H); 2.83-2.50 (m, 8 H); 1.91-1.87 (m, 1 H); 1.81-1.75 (m, 1 H); 1.58-1.47 (m, 7 H); 1.33-1.25 (m, 3 H).	diformate
55C	C	(DMSO-d ₆): δ 8.32-8.27 (m, 3 H); 8.20 (d, J = 9.9 Hz, 1 H); 7.32-7.26 (m, 4 H); 7.25-7.20 (m, 2 H); 7.13-7.10 (m, 1 H); 6.98-6.94 (m, 3 H); 6.79-6.76 (m, 1 H); 6.55-6.52 (m, 1 H); 5.83-5.80 (m, 1 H); 5.29-5.26 (m, 1 H); 4.75 (s, 2 H); 4.63-4.59 (m, 1 H); 4.09-4.06 (m, 2 H); 3.20-3.15 (m, 1 H); 2.98-2.50 (m, 8 H); 1.98-1.87 (m, 1 H); 1.92-1.69 (m, 1 H); 1.76-1.28 (m, 5 H); 1.48-1.26 (m, 2 H); 1.45-1.09 (m, 4 H).	diformate
56C	A	(DMSO-d ₆): δ 8.35-8.20 (m, 3 H); 8.19 (d, J = 9.9 Hz, 1 H); 7.34-7.27 (m, 4 H); 7.26-7.19 (m, 2 H); 7.14-7.07 (m, 1 H); 7.00-6.90 (m, 3 H); 6.80-6.73 (m, 1 H); 6.56-6.50 (m, 1 H); 5.86-5.78 (m, 1 H); 5.24-5.19 (m, 1 H); 4.75 (s, 2 H); 4.68-4.52 (m, 1 H); 4.11-4.04 (m, 2 H); 3.23-3.03 (m, 1 H); 2.95-2.82 (m, 2 H); 2.91-2.61 (m, 4 H); 2.73-2.50 (m, 3 H); 1.98-1.87 (m, 1 H); 1.92-1.69 (m, 1 H); 1.76-1.28 (m, 5 H); 1.48-1.26 (m, 2 H); 1.45-1.09 (m, 4 H).	diformate

(continued)

57C	A	(DMSO-d ₆): δ 8.57 (t, J = 5.5 Hz, 1 H); 8.32 (s, 2 H); 8.27-8.15 (m, 2 H); 7.84 (d, J = 8.0 Hz, 2 H); 7.50 (d, J = 8.0 Hz, 2 H); 7.35-7.19 (m, 6 H); 7.11-7.02 (m, 2 H); 6.96-6.86 (m, 3 H); 6.50 (d, J = 9.9 Hz, 1 H); 5.84-5.79 (m, 1 H); 5.16-5.09 (m, 3 H); 4.60-4.54 (m, 1 H); 3.36-3.28 (m, 2 H); 3.15-3.05 (m, 1 H); 2.83-2.52 (m, 9 H); 1.94-1.68 (m, 4 H); 1.65-1.26 (m, 3 H).	diformate
58C	A	(DMSO-d ₆): δ 8.45 (t, J = 5.6 Hz, 1 H); 8.32 (s, 1 H); 8.27-8.16 (m, 2 H); 7.83 (d, J = 8.1 Hz, 2 H); 7.50 (d, J = 8.0 Hz, 2 H); 7.36-7.19 (m, 6 H); 7.12-7.03 (m, 2 H); 6.96-6.86 (m, 3 H); 6.48 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.2 Hz, 1 H); 5.14 (s, 2 H); 5.04 (t, J = 6.2 Hz, 1 H); 4.61-4.53 (m, 1 H); 3.40-3.32 (m, 2 H); 3.14-3.04 (m, 1 H); 2.83-2.52 (m, 9 H); 1.93-1.73 (m, 2 H); 1.65-1.26 (m, 3 H).	formate
59C	A	(DMSO-d ₆ 85°C): δ 8.22-8.11 (m, 2 H); 7.76-7.65 (m, 1 H); 7.48-7.38 (m, 2 H); 7.36-7.15 (m, 8 H); 7.10-6.82 (m, 5 H); 6.51-6.40 (m, 1 H); 5.85-5.75 (m, 1 H); 5.13-4.94 (m, 3 H); 4.64-4.52 (m, 1 H); 3.40-3.22 (m, 4 H); 3.14-3.00 (m, 1 H); 2.82-2.43 (m, 9 H); 1.94-1.83 (m, 1 H); 1.81-1.55 (m, 4 H); 1.53-1.40 (m, 1 H); 1.36-1.23 (m, 1 H); 1.12-1.00 (m, 3 H).	formate
60C	B	(DMSO-d ₆ 85°C): δ 8.22-8.15 (m, 3 H); 7.73 (s, 1 H); 7.46 (d, J = 7.85 Hz, 2 H); 7.37-7.27 (m, 6 H); 7.26-7.19 (m, 2 H); 7.08 (d, J = 8.12 Hz, 2 H); 7.03 (s, 1 H); 6.95 (d, J = 7.74 Hz, 2 H); 6.48 (d, J = 9.88 Hz, 1 H); 5.83 (d, J = 7.98 Hz, 1 H); 5.11 (s, 2 H); 5.05-4.99 (m, 1 H); 4.63-4.58 (m, 1 H); 3.39 (s, 2 H); 3.09 (dd, J = 14.46, 8.25 Hz, 1 H); 2.91 (s, 3 H); 2.81-2.49 (m, 9 H); 1.93-1.89 (m, 1 H); 1.73-1.55 (m, 4 H); 1.52-1.45 (m, 1 H); 1.31 (d, J = 11.44 Hz, 1 H).	diformate
61C	C	(DMSO-d ₆ 85°C): δ 8.25-8.15 (m, 3 H); 7.73 (s, 1 H); 7.46 (d, J = 7.85 Hz, 2 H); 7.33-7.20 (m, 7 H); 7.09 (d, J = 8.12 Hz, 1 H); 7.03 (m, 1 H); 6.97-6.87 (m, 3 H); 6.50 (d, J = 3.46 Hz, 1 H); 5.83 (d, J = 8.55 Hz, 1 H); 5.11 (s, 2 H); 5.07-5.03 (m, 1 H); 4.63-4.58 (m, 1 H); 4.00 (s, 1 H); 3.27 (t, J = 7.50 Hz, 2 H); 3.09 (dd, J = 14.43, 8.27 Hz, 1 H); 2.80-2.5 (m, 9 H); 1.93-1.89 (m, 1 H); 1.78-1.68 (m, 3 H); 1.66-1.56 (m, 1 H); 1.53-1.44 (m, 1 H); 1.32 (q, J = 9.86 Hz, 1 H); 1.15 (d, J = 6.72 Hz, 6 H).	diformate

(continued)

62C	A	(DMSO-d ₆): δ 8.46 (t, J = 5.7 Hz, 1 H); 8.29 (s, 2 H); 8.24 (d, J = 9.3 Hz, 1 H); 8.18 (d, J = 9.9 Hz, 1 H); 7.84 (d, J = 7.9 Hz, 2 H); 7.50 (d, J = 7.9 Hz, 2 H); 7.36-7.27 (m, 4 H); 7.27-7.18 (m, 2 H); 7.09 (d, J = 8.1 Hz, 1 H); 7.04 (s, 1 H); 6.98-6.85 (m, 3 H); 6.52 (d, J = 9.9 Hz, 1 H); 5.81 (d, J = 8.9 Hz, 1 H); 5.18-5.10 (m, 3 H); 4.62-4.54 (m, 1 H); 4.00 (t, J = 6.0 Hz, 2 H); 3.17-3.06 (m, 3 H); 2.86-2.53 (m, 9 H); 2.29-2.19 (m, 1 H); 1.96-1.86 (m, 3 H); 1.85-1.72 (m, 3 H); 1.66-1.20 (m, 10 H); 1.05-0.90 (m, 2 H).	diformate
63C	A	(DMSO-d ₆): 10.80-10.00 (br s, 1 H); 8.70 (t, J = 6.32 Hz, 1 H); 8.27 (s, 2 H); 8.19 (d, J = 9.92 Hz, 1 H); 7.84 (t, J = 6.84 Hz, 2 H), 7.51 (d, J = 7.83 Hz, 2 H); 7.31 (s, 4 H); 7.23 (t, J = 7.47 Hz, 2 H); 7.11-7.02 (m, 2 H); 6.96-6.85 (m, 3 H); 6.50 (dd, J = 9.80, 3.32 Hz, 1 H); 5.81 (s, 1 H); 5.14 (s, 2 H); 5.07 (d, J = 10.80 Hz, 1 H); 4.90 (t, J = 6.69 Hz, 1 H); 4.60 (s, 1 H); 3.63 (d, J = 2.45 Hz, 3 H); 3.50-3.32 (m, 3 H); 3.15 (s, 1 H); 2.98 (s, 3 H); 2.90 (d, J = 6.19 Hz, 1 H), 2.77 (m, 7 H); 2.68 (s, 3 H); 1.94 (s, 1 H); 1.81 (s, 1 H); 1.61 (s, 1 H); 1.51 (s, 1 H); 1.37 (s, 1 H).	diformate
64C	C	(DMSO-d ₆): δ 8.30-8.21 (m, 3 H); 8.19 (d, J = 9.9 Hz, 1 H); 7.97 (d, J = 7.9 Hz, 2 H); 7.57 (d, J = 7.9 Hz, 2 H); 7.30 (s, 4 H); 7.28-7.19 (m, 2 H); 7.10 (d, J = 8.1 Hz, 1 H); 7.03 (s, 1 H); 6.92 (dd, J = 24.4, 8.0 Hz, 3 H); 6.53 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.1 Hz, 1 H); 5.20-5.11 (m, 3 H); 4.59 (s, 1 H); 4.12 (d, J = 6.2 Hz, 2 H); 3.13 (m, 1 H); 2.88-2.55 (m, 8 H); 1.96-1.32 (m, 12 H); 1.14-0.88 (m, 4 H)	diformate
65C	B	(DMSO-d ₆): δ 8.30 (s, 1 H); 8.27-8.20 (m, 1 H); 8.17-8.11 (m, 3 H); 7.65 (d, J = 7.9 Hz, 2 H); 7.41 (d, J = 8.0 Hz, 2 H); 7.36-7.15 (m, 8 H); 7.12-7.04 (m, 2 H); 6.98-6.87 (m, 3 H); 6.49 (d, J = 9.8 Hz, 1 H); 5.83 (d, J = 9.2 Hz, 1 H); 5.23 (s, 2 H); 5.08 (dd, J = 7.8, 4.3 Hz, 1 H); 4.57 (s, 1 H); 3.79 (s, 2 H); 3.10 (s, 2 H); 2.76-2.63 (m, 6 H); 1.90 (s, 1 H); 1.80 (s, 1 H); 1.58 (s, 1 H); 1.47 (s, 1 H); 1.33 (s, 1 H).	diformate
66C	C	(DMSO-d ₆): δ 8.32-8.20 (m, 2 H); 8.17 (d, J = 10.0 Hz, 2 H); 8.02 (d, J = 7.9 Hz, 2 H); 7.58 (d, J = 7.9 Hz, 2 H); 7.31 (s, 4 H); 7.24 (t, J = 7.8 Hz, 2 H); 7.12-7.01 (m, 2 H); 6.98-6.85 (m, 3 H); 6.51 (d, J = 9.8 Hz, 1 H); 5.82 (d, J = 8.9 Hz, 1 H); 5.19 (s, 2 H); 5.11 (t, J = 6.2 Hz, 1 H); 4.70 (s, 2 H); 4.58 (s, 1 H); 3.16-3.09 (m, 4 H); 2.79 (d, J = 6.5 Hz, 2 H); 2.74-2.65 (m, 4 H); 1.91 (s, 1 H); 1.80 (s, 1 H); 1.64 (t, J = 11.6 Hz, 5 H); 1.48 (s, 1 H); 1.34 (s, 1 H).	diformate

(continued)

67C	A	(DMSO-d ₆): δ 8.30-8.16 (m, 3 H); 8.19 (d, J = 10.0 Hz, 1 H); 8.00 (d, J = 8.0 Hz, 2 H); 7.59 (d, J = 8.0 Hz, 2 H); 7.31 (s, 4 H); 7.28-7.19 (m, 2 H); 7.09 (d, J = 8.1 Hz, 1 H); 7.04 (s, 1 H); 6.97-6.86 (m, 3 H); 6.53 (d, J = 10.0 Hz, 1 H); 5.81 (m, 1 H); 5.19 (s, 2 H); 5.11 (t, J = 5.2 Hz, 1 H); 4.93 (s, 2 H); 4.58 (s, 1 H); 4.14 (t, J = 6.3 Hz, 2 H); 3.16-3.04 (m, 1 H); 2.86-2.62 (m, 8 H); 1.90 (s, 1 H); 1.79 (s, 1 H); 1.69-1.41 (m, 7 H); 1.34 (s, 1 H).	diformate
68C	A	(DMSO-d ₆): δ 8.30-8.16 (m, 3 H); 8.00 (d, J = 8.1 Hz, 2 H); 7.60 (d, J = 8.0 Hz, 2 H); 7.31-7.18 (m, 6 H); 7.12 (d, J = 8.2 Hz, 1 H); 7.03 (s, 1 H); 6.96 (t, J = 6.8 Hz, 2 H); 6.89 (dd, J = 8.2, 2.5 Hz, 1 H); 6.55 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.2 Hz, 1 H); 5.25 (dd, J = 8.9, 3.9 Hz, 1 H); 5.19 (s, 2 H); 4.94 (s, 2 H); 4.60 (s, 1 H); 4.14 (t, J = 6.4 Hz, 2 H); 3.16 (m, 1 H); 2.98-2.89 (m, 2 H); 2.85-2.59 (m, 7 H); 1.94 (s, 1 H); 1.81 (s, 1 H); 1.65-1.55 (m, 6 H); 1.40-1.30 (m, 4 H).	formate
69C	C	(DMSO-d ₆): δ 8.32-8.20 (m, 3 H); 8.17 (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); 7.32-7.18 (m, 6 H); 7.08-7.01 (m, 2 H); 6.97-6.84 (m, 3 H); 6.49 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.3 Hz, 1 H); 5.17 (s, 2 H); 5.09-5.02 (m, 1 H); 4.58 (s, 1 H); 4.42-4.37 (m, 2 H); 3.76-3.71 (m, 2 H); 3.61-3.55 (m, 2 H); 3.11 (t, J = 10.6 Hz, 1 H); 2.82-2.50 (m, 9 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
70C	C	(DMSO-d ₆): δ 8.31-8.19 (m, 2 H); 8.16 (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); 7.31-7.18 (m, 6 H); 7.08 (d, J = 8.2 Hz, 1 H); 7.03 (s, 1 H); 6.97-6.90 (m, 2 H); 6.88 (dd, J = 8.3, 2.5 Hz, 1 H); 6.52 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.1 Hz, 1 H); 5.18-5.09 (m, 3 H); 4.57 (s, 1 H); 4.42-4.37 (m, 2 H); 3.72-3.67 (m, 2 H); 3.46 (s, 2 H); 3.21-3.02 (m, 1 H); 2.81-2.50 (m, 10 H); 1.90 (s, 1 H); 1.79 (s, 1 H); 1.53 (s, 5 H); 1.34 (s, 1 H).	formate
71C	A	(DMSO-d ₆): δ 8.30-8.16 (m, 3 H); 8.00 (d, J = 8.1 Hz, 2 H); 7.60 (d, J = 8.0 Hz, 2 H); 7.31-7.18 (m, 6 H); 7.12 (d, J = 8.2 Hz, 1 H); 7.03 (s, 1 H); 6.96 (t, J = 6.8 Hz, 2 H); 6.89 (dd, J = 8.2, 2.5 Hz, 1 H); 6.55 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.2 Hz, 1 H); 5.25 (dd, J = 8.9, 3.9 Hz, 1 H); 5.19 (s, 2 H); 4.94 (s, 2 H); 4.60 (s, 1 H); 4.14 (t, J = 6.4 Hz, 2 H); 3.16 (m, 1 H); 2.98-2.89 (m, 2 H); 2.85-2.59 (m, 7 H); 1.94 (s, 1 H); 1.81 (s, 1 H); 1.65-1.55 (m, 6 H); 1.40-1.30 (m, 4 H).	formate

(continued)

72C	C	(DMSO-d ₆): δ 8.32-8.20 (m, 3 H); 8.17 (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); 7.32-7.18 (m, 6 H); 7.08-7.01 (m, 2 H); 6.97-6.84 (m, 3 H); 6.49 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.3 Hz, 1 H); 5.17 (s, 2 H); 5.09-5.02 (m, 1 H); 4.58 (s, 1 H); 4.42-4.37 (m, 2 H); 3.76-3.71 (m, 2 H); 3.61-3.55 (m, 2 H); 3.11 (t, J = 10.6 Hz, 1 H); 2.82-2.50 (m, 9 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
73C	C	(DMSO-d ₆): δ 8.31-8.19 (m, 2 H); 8.16 (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); 7.31-7.18 (m, 6 H); 7.08 (d, J = 8.2 Hz, 1 H); 7.03 (s, 1 H); 6.97-6.90 (m, 2 H); 6.88 (dd, J = 8.3, 2.5 Hz, 1 H); 6.52 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.1 Hz, 1 H); 5.18-5.09 (m, 3 H); 4.57 (s, 1 H); 4.42-4.37 (m, 2 H); 3.72-3.67 (m, 2 H); 3.46 (s, 2 H); 3.21-3.02 (m, 1 H); 2.81-2.50 (m, 10 H); 1.90 (s, 1 H); 1.79 (s, 1 H); 1.53 (s, 5 H); 1.34 (s, 1 H).	formate
74C	C	(DMSO-d ₆): δ 8.29 (s, 1 H); 8.22 (d, J = 9.8 Hz, 1 H); 8.17 (d, J = 9.9 Hz, 1 H); 7.99 (d, J = 8.0 Hz, 2 H); 7.57 (d, J = 8.0 Hz, 2 H); 7.34-7.18 (m, 9 H); 7.09-7.01 (m, 2 H); 6.96-6.84 (m, 3 H); 6.49 (d, J = 9.9 Hz, 1 H); 5.81 (d, J = 9.3 Hz, 1 H); 5.33 (s, 2 H); 5.17 (s, 2 H); 5.05 (dd, J = 7.7, 4.7 Hz, 1 H); 4.56 (s, 1 H); 3.10 (m, 1 H); 2.89-2.70 (m, 10 H); 1.89 (br s, 2 H); 1.78 (br s, 2 H); 1.59 (br s, 1 H); 1.46 (br s, 1 H); 1.31 (br s, 1 H)	formate
75C	B	(DMSO-d ₆): δ 8.40 (s, 1 H); 8.22 (d, J = 9.3 Hz, 1 H); 8.16 (d, J = 9.9 Hz, 1 H); 7.87 (d, J = 8.1 Hz, 2 H); 7.37-7.26 (m, 6 H); 7.26-7.18 (m, 2 H); 7.05 (d, J = 8.2 Hz, 1 H); 6.98-6.89 (m, 3 H); 6.82 (dd, J = 8.2, 2.4 Hz, 1 H); 6.49 (d, J = 9.9 Hz, 1 H); 5.84-5.77 (m, 1 H); 5.01 (dd, J = 7.9, 4.5 Hz, 1 H); 4.59-4.52 (m, 1 H); 4.40 (t, J = 6.2 Hz, 2 H); 4.10 (t, J = 6.2 Hz, 2 H); 3.12-3.02 (m, 1 H); 2.86-2.53 (m, 8 H); 2.20-2.11 (m, 2 H); 1.92-1.72 (m, 5 H); 1.63-1.22 (m, 3 H).	formate
76C	A	(DMSO-d ₆): δ 8.31 (s, 2 H); 8.28-8.14 (m, 2 H); 7.91 (d, J = 7.89 Hz, 2 H); 7.46 (d, J = 7.91 Hz, 2 H); 7.31 (d, J = 4.81 Hz, 4 H); 7.26-7.17 (m, 2 H); 7.10 (d, J = 8.15 Hz, 1 H); 6.98-6.87 (m, 3 H); 6.81 (d, J = 8.23 Hz, 1 H); 6.52 (d, J = 9.83 Hz, 1 H); 5.81 (d, J = 9.13 Hz, 1 H); 5.21-5.15 (m, 1 H); 4.59 (s, 2 H); 4.30-4.23 (m, 2 H); 4.19 (t, J = 6.64 Hz, 2 H); 3.13-3.07 (m, 3 H); 2.95-2.51 (m, 7 H); 1.92 (s, 1 H); 1.94-1.32 (m, 9 H).	diformate

(continued)

77C	C	(DMSO-d ₆): δ 8.41-8.12 (m, 3 H); 8.20-8.13 (m, 5 H); 7.35-7.23 (m, 5 H); 7.23-7.15 (m, 1 H); 7.13-7.05 (m, 2 H); 7.05-6.91 (m, 3 H); 6.51 (d, J = 9.9 Hz, 1 H); 5.88-5.80 (m, 1 H); 5.60 (s, 2 H); 5.18-5.11 (m, 1 H); 4.63-4.49 (m, 1 H); 4.36-4.29 (m, 2 H); 3.15-3.05 (m, 1 H); 2.86-2.71 (m, 7 H); 2.69-2.49 (m, 2 H); 1.97-1.82 (m, 1 H); 1.81-1.72 (m, 3 H); 1.69-1.60 (m, 3 H); 1.60-1.33 (m, 1 H); 1.47-1.20 (m, 1 H).	diformate
78C	C	(CD ₃ OD): δ 8.57 (s, 2 H); 8.38 (d, J = 9.9 Hz, 1 H); 8.01 (d, J = 8.0 Hz, 2 H); 7.48 (d, J = 8.0 Hz, 2 H); 7.35-7.19 (m, 7 H); 7.03 (d, J = 8.2 Hz, 1 H); 6.89-6.79 (m, 3 H); 6.67 (d, J = 9.8 Hz, 1 H); 5.88 (s, 1 H); 5.39 (t, J = 6.7 Hz, 1 H); 4.89 (br s, 1 H); 4.51-4.28 (m, 2 H); 3.80 (d, J = 5.5 Hz, 2 H); 3.65 (s, 2 H); 3.46 (m, 1 H); 3.18 (d, J = 6.7 Hz, 2 H); 3.24-2.98 (m, 3 H); 3.09-2.89 (m, 5 H); 2.28-2.13 (m, 1 H); 2.19-2.07 (m, 3 H); 1.98-1.82 (m, 5 H); 1.91-1.75 (m, 5 H); 1.88-1.45 (m, 1 H); 1.51-1.37 (m, 2 H)	diformate
79C	A	(DMSO-d ₆): δ 8.31 (s, 2 H); 8.23 (d, J = 8.1 Hz, 1 H); 8.17 (d, J = 9.9 Hz, 1 H); 7.95 (d, J = 8.1 Hz, 2 H); 7.55 (d, J = 8.1 Hz, 2 H); 7.34-7.19 (m, 6 H); 7.08 (d, J = 8.2 Hz, 1 H); 7.02 (s, 1 H); 6.96-6.84 (m, 3 H); 6.51 (d, J = 9.9 Hz, 1 H); 5.81 (d, J = 9.2 Hz, 1 H); 5.17-5.08 (m, 3 H); 4.57 (s, 1 H); 4.42-4.37 (m, 2 H); 3.70 (t, J = 4.6 Hz, 2 H); 3.46 (s, 2 H); 3.10 (m, 2 H); 2.79 (d, J = 6.3 Hz, 2 H); 2.75-2.63 (m, 8 H); 1.84 (d, J = 44.6 Hz, 2 H); 1.53 (s, 5 H).	diformate
80C	A	(DMSO-d ₆): δ 8.32 (s, 1 H); 8.25-8.12 (m, 2 H); 7.98 (d, J = 8.1 Hz, 2 H); 7.57 (d, J = 8.1 Hz, 2 H); 7.38-7.15 (m, 11 H); 7.09-6.98 (m, 2 H); 6.94-6.84 (m, 3 H); 6.50 (d, J = 9.9 Hz, 1 H); 5.81 (d, J = 9.4 Hz, 1 H); 5.32 (s, 2 H); 5.18 (s, 2 H); 5.03 (dd, J = 7.9, 4.6 Hz, 1 H); 4.55 (s, 1 H); 3.04 (m, 1 H); 2.83-2.65 (m, 10 H); 1.94-1.83 (m, 1 H); 1.77 (s, 1 H); 1.56 (d, J = 11.1 Hz, 1 H); 1.45 (s, 1 H); 1.30 (s, 1 H)	formate
81C	C	(CD ₃ OD): δ 8.55 (s, 1 H); 8.33 (d, J = 9.9 Hz, 1 H); 7.95 (d, J = 8.1 Hz, 2 H); 7.46 (d, J = 8.0 Hz, 2 H); 7.35-7.18 (m, 8 H); 7.02-6.88 (m, 4 H); 6.64 (d, J = 9.8 Hz, 1 H); 5.88 (s, 1 H); 5.32 (dd, J = 9.0, 4.3 Hz, 1 H); 5.14 (s, 2 H); 4.80 (m, 1 H); 4.53-4.49 (m, 2 H); 3.91-3.86 (m, 2 H); 3.86-3.80 (m, 2 H); 3.22-3.08 (m, 6 H); 3.01 (s, 3 H); 2.16 (d, J = 44.3 Hz, 2 H); 1.97-1.63 (m, 3 H).	formate

(continued)

82C	C	(DMSO-d ₆): δ 8.28 (s, 1 H); 8.23 (d, J = 9.8 Hz, 1 H); 8.17 (d, J = 9.9 Hz, 1 H); 7.81 (d, J = 8.0 Hz, 1 H); 7.62 (s, 1 H); 7.48 (d, J = 8.1 Hz, 1 H); 7.32-7.19 (m, 6 H); 7.09 (d, J = 8.2 Hz, 1 H); 7.03 (s, 1 H); 6.96-6.84 (m, 3 H); 6.51 (d, J = 9.9 Hz, 1 H); 5.82 (d, J = 9.2 Hz, 1 H); 5.18-5.06 (m, 3 H); 4.57 (s, 1 H); 4.29 (t, J = 6.3 Hz, 2 H); 3.10 (s, 2 H); 2.79 (d, J = 6.5 Hz, 2 H); 2.73 (t, J = 7.9 Hz, 4 H); 1.90 (s, 1 H); 1.76 (t, J = 10.9 Hz, 3 H); 1.66-1.57 (m, 4 H); 1.47 (s, 2 H); 1.33 (s, 1 H).	formate
83C	C	(CD ₃ OD): δ 8.55 (s, 2 H); 8.37 (d, J = 9.9 Hz, 1 H); 7.93 (t, J = 7.7 Hz, 1 H); 7.36-7.22 (m, 9 H); 7.03 (d, J = 8.2 Hz, 1 H); 6.95-6.86 (m, 3 H); 6.68 (d, J = 9.8 Hz, 1 H); 5.89 (s, 1 H); 5.40-5.34 (m, 1 H); 5.16 (s, 2 H); 4.95-4.79 (m, 1 H under solvent peak); 4.42 (s, 2 H); 3.56-3.42 (m, 1 H); 3.27-3.01 (m, 9 H); 2.24 (s, 1 H); 2.12 (s, 1 H); 1.94 (s, 7 H).	diformate

Legend

* NMR

s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; m = multiplet; br = broad.

5 **Biological characterization****Example 83****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 room temperature 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 50ul 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.

5 The Ki values of the tested compounds are less than 10 nM.

Example 84

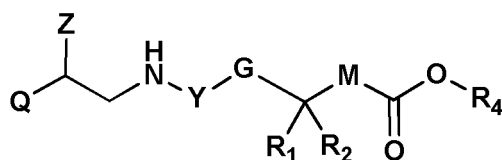
β₂ adrenoceptor radioligand binding assay

Human β₂ adrenoceptor membranes (7.5 ug/well) from Perkin Elmer were incubated with 0.3 nM ¹²⁵-I Cyanopindolol with or without test
10 compounds, or a saturating concentration of s-propranolol (2 μM) for the determination of non-specific binding. The assay was carried out in 96-well polypropylene plates in a volume of 200 ul. The assay buffer used was 25 mM HEPES, 0.5% BSA (w/v), 1 mM EDTA, 0.02% ascorbic acid (v/v), (pH 7.4). The final assay concentration of DMSO was 0.5% (v/v). The plates were
15 sealed and incubated for 1h at room temperature 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 ul of wash buffer containing 10 mM HEPES and 500 mM NaCl. The plates were dried before addition of 50 μl of microscint-0, sealed
20 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 tested compounds are less than 5 nM.

CLAIMS

1. A compound of general formula **I**

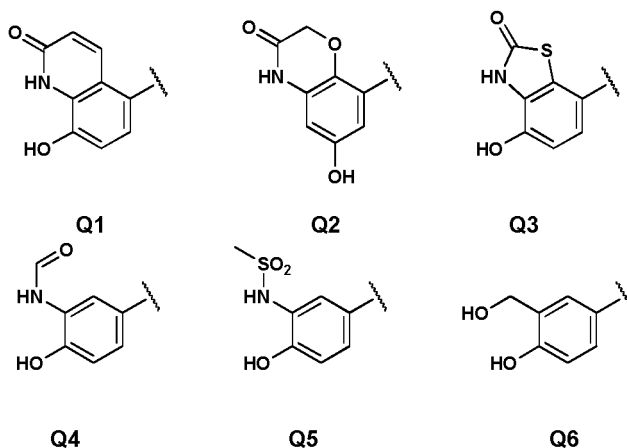


(I)

5

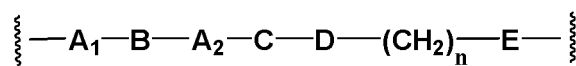
wherein

Q is a group of formula **Q1**, **Q2**, **Q3**, **Q4**, **Q5** or **Q6**



- 10 **Z** is H or OH;

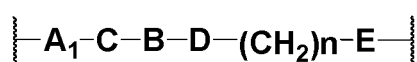
Y is selected from **Y'** and **Y1** which are divalent groups of formula



15

Y

or

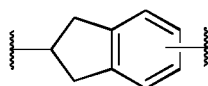
**Y1**

wherein

A1 and **A2** are independently absent or are selected from the group consisting of (C₁-C₁₂)alkylene, (C₃-C₈)cycloalkylene and (C₃-C₈)heterocycloalkylene optionally substituted by one or more substituents selected from the group consisting of (C₁-C₆)alkyl, (C₁-C₆)arylalkyl and (C₁-C₆)heteroarylalkyl;

- 5 **B** is absent or is selected from the group consisting of (C₃-C₈)cycloalkylene, (C₃-C₈)heterocycloalkylene, arylene, heteroarylene or is a group of formula

B1

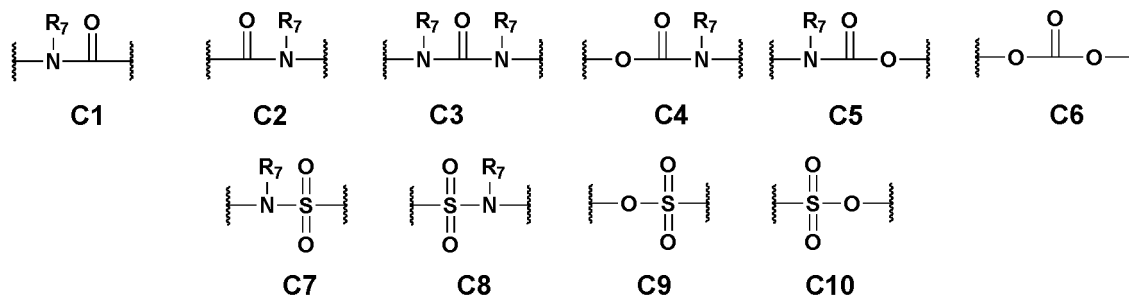


B1

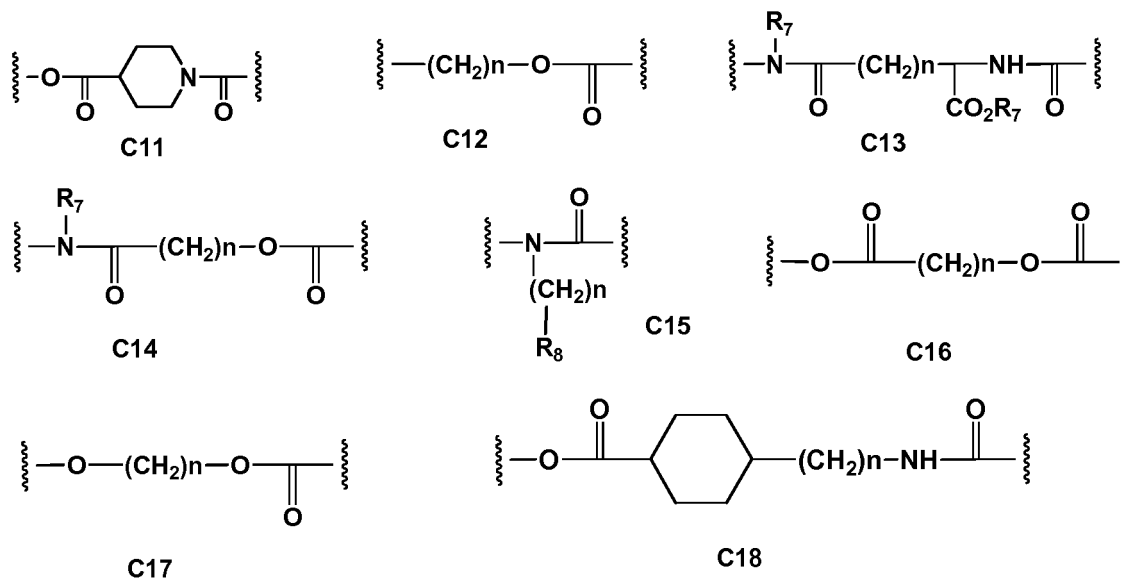
optionally substituted by one or more groups selected from halogens, nitrile,

- 10 (C₁-C₆)alkyl, (C₁-C₆)alkoxy and (C₁-C₆)arylalkyl;

C is absent or is selected from the group consisting of -O-, -CO-, -OC(O)-, -C(OO)-, -S-, -S(O)-, -S(O)₂-, -N(R₇)-, -N(CO)R₇-, -N(CO)NHR₇-, -N(SO₂)R₇- or is one of the following groups **C1-C18**



210



wherein **R**₇ is H or is selected from the group consisting of linear or branched (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)heterocycloalkyl, aryl, (C₁-C₆)arylalkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl and heteroaryl and **R**₈ is (C₁-C₈)alkoxycarbonyl;

D is absent or is selected from the group consisting of (C₁-C₁₂)alkylene, -C(CH₃)₂-, arylene, (C₂-C₁₂)alkenylene, heteroarylene, (C₃-C₈)heterocycloalkylene and (C₂-C₆)alkynylene;

n is 0 or an integer from 1 to 3;

E is absent or is selected from -O-, -NR₇-, -OC(O)- and -S-;

G is arylene or heteroarylene, optionally substituted by one or more substituents selected from the group consisting of halogen atoms, -OH, oxo (=O), -SH, -NO₂, -CN, -CON(R₆)₂, -NH₂, -NHCOR₆, -CO₂R₆, (C₁-C₁₀)alkylsulfanyl, (C₁-C₁₀)alkylsulfinyl, (C₁-C₁₀)alkylsulfonyl, (C₁-C₁₀)alkyl, aryl, haloaryl, heteroaryl and (C₁-C₁₀)alkoxy;

R₁ and **R**₂ are independently H or selected from the group consisting of (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)heterocycloalkyl, aryl, heteroaryl, aryl(C₁-C₆)alkyl, heteroaryl(C₁-C₆)alkyl and (C₃-C₈)cycloalkyl(C₁-C₆)alkyl, optionally substituted by one or more halogen atoms or (C₁-C₈)alkyl groups

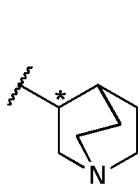
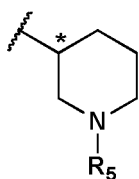
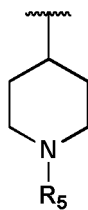
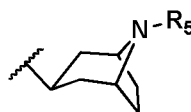
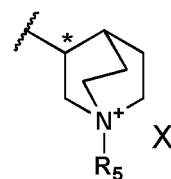
or, taken together with the carbon atom to which they are bounded, **R**₁ and **R**₂

may form a (C₃-C₈)cycloalkyl, wherein **R**₁ and **R**₂ are not simultaneously H;

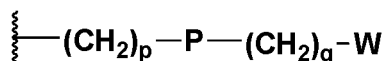
M is -O- or -N(R₃)-;

R₃ is H or is selected from the group consisting of (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, aryl and heteroaryl;

5 **R**₄ is a group of formula **J1**, **J2**, **J3**, **J4** or **J5**

**J1****J2****J3****J4****J5**

R₅ is a group of formula **K**

**K**

10

wherein **p** is 0 or an integer from 1 to 4; **q** is 0 or an integer from 1 to 4;

P is absent or is selected from the divalent group consisting of O, S, SO, SO₂, CO, NR₆ CH=CH, N(R₆)SO₂, N(R₆)COO, N(R₆)C(O), SO₂N(R₆), CO(O)N(R₆) and C(O)N(R₆);

15 **W** is selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₈)cycloalkyl, aryl and heteroaryl, optionally substituted by one or more substituents selected from the group consisting of halogen atoms, -OH, oxo (=O), -SH, -NO₂, -CN, -CON(R₆)₂, -NH₂, -NHCOR₆, -CO₂R₆, (C₁-C₁₀)alkylsulfanyl, (C₁-C₁₀)alkylsulfinyl, (C₁-C₁₀)alkylsulfonyl, (C₁-C₁₀)alkyl and (C₁-C₁₀)alkoxy;

20 **X**⁻ is a physiological acceptable anion;

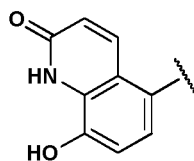
R₆ is H or is selected from the group consisting of (C₁-C₁₀)alkyl, (C₁-C₆)haloalkyl, (C₂-C₆)alkynyl, (C₂-C₆)alkenyl, (C₃-C₈)cycloalkyl, (C₃-C₈)cycloalkyl(C₁-C₆)alkyl, heteroaryl and aryl optionally substituted by

one or more substituents selected from the group consisting of halogen atoms, -OH, oxo (=O), -SH, -NO₂, -CN, -CONH₂, -COOH, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylsulfanyl, (C₁-C₁₀)alkylsulfinyl, (C₁-C₁₀)alkylsulfonyl, (C₁-C₁₀)alkyl and (C₁-C₁₀)alkoxy;

5 and pharmaceutically acceptable salts or solvates thereof.

2. A compound according to claim 1, wherein **B** is absent or is selected from the group consisting of (C₃-C₈)cycloalkylene, (C₃-C₈)heterocycloalkylene, arylene and heteroarylene; **C** is absent or is selected from the group consisting of -O-, -CO-, -OC(O)-, -C(OO)-, -S-,
 10 -S(O)-, -S(O)₂-, and -N(R₇)-, wherein **R**₇ is H or is selected from the group consisting of (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)heterocycloalkyl, aryl and heteroaryl; **G** is arylene or heteroarylene, optionally substituted by one or more substituents selected from the group consisting of halogen atoms, -OH, oxo (=O), -SH, -NO₂, -CN, -CON(R₆)₂, -NH₂, -NHCOR₆, -CO₂R₆,
 15 (C₁-C₁₀)alkylsulfanyl, (C₁-C₁₀)alkylsulfinyl, (C₁-C₁₀)alkylsulfonyl, (C₁-C₁₀)alkyl and (C₁-C₁₀)alkoxy and wherein **Q**, **Z**, **A1**, **A2**, **D**, **E**, **G**, **R**₁, **R**_{2, **M**, **R**₄ and **R**₆ are as defined in claim 1.}

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



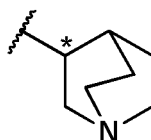
Q1

20

Z is -OH, **A1** is absent or is selected from the group consisting of (C₃-C₈)heterocycloalkylene and (C₁-C₁₂)alkylene, **A2** is absent or (C₁-C₆)alkylene, **B** is absent or arylene, **C** is absent, **D** is absent or is selected from the group consisting of (C₁-C₁₂)alkylene, heteroarylene and arylene, **E** is
 25 absent or is -O-, **G** is arylene optionally substituted by one or more halogen

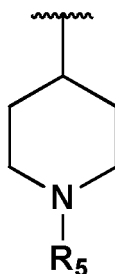
atoms.

4. A compound according to claim 3, wherein **A1** is absent or is selected from the group consisting of methylene, ethylene, propylene, butylene, pentylene, hexylene, heptylene, octylene and nonylene, **A2** is absent or is
- 5 selected from the group consisting of methylene and oxadiazolene, **B** is selected from the group consisting of phenylene and cyclohexylene or is absent, **C** is absent, **D** is absent or is selected from methylene, ethylene, propylene, butylene, pentylene, hexylene, heptylene, octylene, nonylene, phenylene and oxadiazolene; **G** is selected from the group consisting of
- 10 fluoro-biphenylene and phenylene.
5. A compound according to claim 4, wherein **A1** is selected from the group consisting of ethylene, pentylene, hexylene, heptylene, octylene and nonylene, **D** is absent, **R₁** is H, **R₂** is selected from the group consisting of phenyl, biphenyl, naphthyl, pyridinyl, difluorophenyl, methylphenyl,
- 15 fluorophenyl and thiophenyl, **M** is -N(H)-, **R₄** is a group of formula **J1**



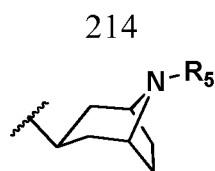
J1

or **J3**

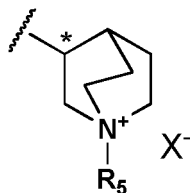


J3

20 or **J4**

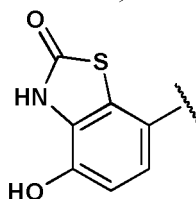
**J4**

or **J5**

**J5**

wherein **R**₅ is a group of formula **K**, wherein **p** is 0 or 1, **P** is absent or is CO,
 5 **q** is absent or is 1 and **W** is H or is selected from the group consisting of
 (C₁-C₆)alkyl and aryl.

6. A compound according to claim 2, wherein **Q** is **Q3**

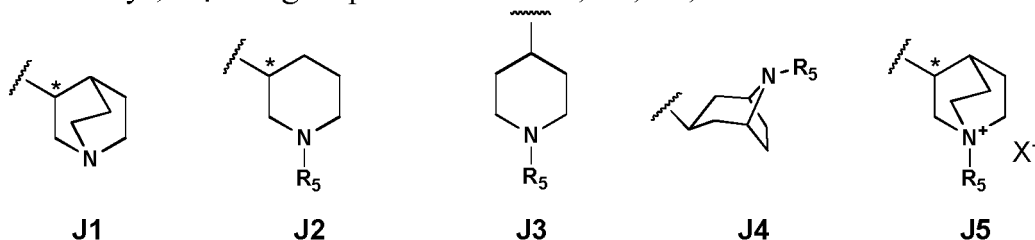
**Q3**

Z is H, **A1** is absent or is (C₁-C₁₂)alkylene, **A2** is absent, **B** is absent, **C** is
 10 absent, **D** is absent or (C₁-C₁₂)alkylene, **E** is -O-, **G** is arylene.

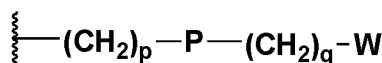
7. A compound according to claim 6, wherein **A1** is absent or is selected
 from the group consisting of methylene, ethylene, propylene, butylene,
 pentylene, hexylene, heptylene, octylene and nonylene, **A2** is absent, **B** is
 absent, **C** is absent, **D** is absent or is selected from methylene, ethylene,
 15 propylene, butylene, pentylene, hexylene, heptylene, octylene and nonylene;
G is phenylene.

8. A compound according to claim 1, wherein **R**₁ and **R**₂ are independently
 H or selected from the group consisting of (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl,
 (C₃-C₈)heterocycloalkyl, aryl, heteroaryl, aryl(C₁-C₆)alkyl, heteroaryl(C₁-

C₆)alkyl and (C₃-C₈)cycloalkyl(C₁-C₆)alkyl, optionally substituted by one or more halogen atoms or (C₁-C₈)alkyl groups or, taken together with the carbon atom they are linked to, **R**₁ and **R**₂ may form a (C₃-C₈)cycloalkyl group, wherein **R**₁ and **R**₂ are not simultaneously H; **M** is -O- or -N(**R**₃)-; **R**₃ is H or
 5 is selected from the group consisting of (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, aryl and heteroaryl; **R**₄ is a group of formula **J1**, **J2**, **J3**, **J4** or **J5**



R₅ is a group of formula **K**



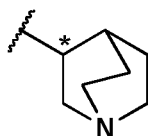
K

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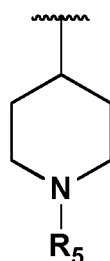
wherein **p** is 0 or an integer from 1 to 4; **q** is 0 or an integer from 1 to 4; **P** is absent or is selected from the group consisting of -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, -N(**R**₆)-, -CH=CH-, -N(**R**₆)S(O)₂-, -N(**R**₆)CO(O)-, -N(**R**₆)C(O)-, -SO₂N(**R**₆)-, -CO(O)N(**R**₆)- and -C(O)N(**R**₆)-; **W** is selected from the group
 15 consisting of (C₁-C₆)alkyl, (C₃-C₈)cycloalkyl, aryl and heteroaryl, optionally substituted by one or more substituents selected from the group consisting of halogen atoms, -OH, oxo (=O), -SH, -NO₂, -CN, -CON(**R**₆)₂, -NH₂, -NHCOR₆, -CO₂R₆, (C₁-C₁₀)alkylsulfanyl, (C₁-C₁₀)alkylsulfinyl, (C₁-C₁₀)alkylsulfonyl, (C₁-C₁₀)alkyl and (C₁-C₁₀)alkoxy; **R**₆ is selected from the group consisting of
 20 H, (C₁-C₁₀)alkyl, (C₁-C₆)haloalkyl, (C₃-C₈)cycloalkyl, heteroaryl and aryl; **G**, **Y**, **Z** and **Q** are as defined in claim 1.

9. A compound according to claim 8, wherein **R**₁ and **R**₂ are independently H or selected from the group consisting of (C₁-C₈)alkyl,

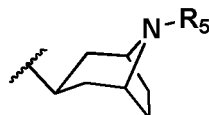
(C₃-C₈)cycloalkyl, aryl and heteroaryl, optionally substituted by one or more halogen atoms or (C₁-C₈)alkyl groups or, taken together with the carbon atom to which they are bounded, **R**₁ and **R**₂ may form a (C₃-C₈)cycloalkyl group, wherein **R**₁ and **R**₂ are not simultaneously H; **M** is -N(**R**₃)-; **R**₃ is H; **R**₄ is a
 5 group of formula **J1**

**J1**

or **J3**

**J3**

or **J4**

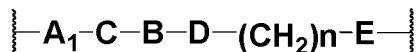
**J4**

10

wherein **R**₅ is a group of formula **K**, wherein **p** is 0, **P** is absent, **q** is 1 and **W** is H or is selected from the group consisting of (C₁-C₆)alkyl and aryl.

10. A compound according to claim 9, wherein **W** is H or phenyl; **R**₁ is H, **R**₂ is selected from the group consisting of phenyl, biphenyl, naphthyl, thiophenyl, pyridinyl, difluorophenyl, methylphenyl and fluorophenyl; **M** is
 15 -N(H)-; **R**₄ is selected from the group consisting of quinuclidinyl, benzylpiperidinyl, methylpiperidinyl, benzyl-8-azabicyclo[3.2.1]octan-3-yl and azoniabicyclo[2.2.2]octanyl.

11. A compound according to claim 1, wherein **Q** is a group of formula **Q1**, **Q2**, **Q3**, **Q4**, **Q5** or **Q6**, **Z** is H or OH; **Y1** is a group of formula



5

Y1

- wherein **A1** is (C₁-C₁₂)alkylene; **C** is absent or is selected from the group consisting of -O-, -CO-, -OC(O)- or is a group of formula C1-C18 wherein **R₇** is H or is selected from the group consisting of linear or branched (C₁-C₈)alkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)heterocycloalkyl, aryl, (C₁-C₆)arylalkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl and heteroaryl and **R₈** is (C₁-C₈)alkoxycarbonyl; **B** is absent or is selected from the group consisting of (C₃-C₈)cycloalkylene and arylene; **D** is absent or is selected from the group consisting of (C₁-C₁₂)alkylene, -C(CH₃)₂-, heteroarylene and arylene; **n** is 0 or an integer from 1 to 2; **E** is -O-; **G** is arylene or heteroarylene, optionally substituted by one or more substituents selected from the group consisting of halogen atoms, -OH, oxo (=O), -SH, -NO₂, -CN, -CON(R₆)₂, -NH₂, -NHCOR₆, -CO₂R₆, (C₁-C₁₀)alkylsulfanyl, (C₁-C₁₀)alkylsulfinyl, (C₁-C₁₀)alkylsulfonyl, (C₁-C₁₀)alkyl, aryl, haloaryl, heteroaryl and (C₁-C₁₀)alkoxy; **R₁**, **R₂**, **M** and **R₄** are as defined in claim 1.
12. A compound according to claim 11, wherein **A1** is selected from the group consisting of methylene, ethylene, propylene, butylene, pentylene and hexylene; **C** is absent or is selected from the group consisting of -O-, -CO-, -OC(O)-, C11, C13, C14, C16, C17, C18 wherein **R₇** is H or is selected from the group consisting of methyl, ethyl and isopropyl and C15 wherein **n** is 0 or 1 and **R₈** is ethoxycarbonyl; **B** is absent or is selected from phenylene, piperidinylene, cyclopropylene, cyclohexylene, piridinediyl, furanediyl, oxazolediyl, optionally substituted by one or more halogens; **D** is absent or is selected from methylene, -C(CH₃)₂-, phenylene and oxadiazolylene; **n** is 0 or

an integer from 1 to 2; **E** is -O-; **G** is selected from phenylene and biphenylene, optionally substituted by one or more substituents selected from the group consisting of fluorine, phenyl and 2-thiophenyl.

13. A compound according to claim 1, which is

(R)-quinuclidin-3-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)(phenyl)methylcarbamate;

(R)-quinuclidin-3-yl (3-(8-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)octyloxy)phenyl)(phenyl)methylcarbamate;

(R)-quinuclidin-3-yl(3-(7-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)heptyloxy)phenyl)(phenyl)methylcarbamate;

(R)-quinuclidin-3-yl (3-(6-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)(phenyl)methylcarbamate;

(R)-quinuclidin-3-yl (3-(5-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)pentyloxy)phenyl)(phenyl)methylcarbamate;

1-benzylpiperidin-4-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)(phenyl)methylcarbamate;

1-methylpiperidin-4-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)(phenyl)methylcarbamate;

8-benzyl-8-azabicyclo[3.2.1]octan-3-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

yl)ethylamino)nonyloxy)phenyl)(phenyl)methylcarbamate;

(R)-quinuclidin-3-yl (4-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)(phenyl)methylcarbamate;

(R)-quinuclidin-3-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)(thiophen-2-

yl)methylcarbamate;

(R)-quinuclidin-3-yl biphenyl-4-yl(3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)methylcarbamate;

(R)-quinuclidin-3-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)(naphthalen-1-yl)methylcarbamate;

5 (R)-quinuclidin-3-yl biphenyl-3-yl(3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)methylcarbamate;

(R)-quinuclidin-3-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)(pyridin-2-yl)methylcarbamate;

10 (R)-quinuclidin-3-yl (3,5-difluorophenyl)(3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)methylcarbamate;

(R)-quinuclidin-3-yl (3,4,5-difluorophenyl)(3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)methylcarbamate

15 (R)-quinuclidin-3-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)(o-tolyl)methylcarbamate;

(R)-quinuclidin-3-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)(m-tolyl)methylcarbamate;

20 (R)-quinuclidin-3-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)(p-tolyl)methylcarbamate;

(R)-quinuclidin-3-yl (4-difluorophenyl)(3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)methylcarbamate;

(R)-quinuclidin-3-yl (3-fluorophenyl)(3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)methylcarbamate;

25 (R)-quinuclidin-3-yl (3-chlorophenyl)(3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)methylcarbamate;

(R)-quinuclidin-3-yl (cyclohexyl(3-((9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)methyl)carbamate;

(R)-quinuclidin-3-yl ((3-((6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)(thiophen-2-yl)methyl)carbamate;

5 (R)-quinuclidin-3-yl ((3-((6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)(thiophen-3-yl)methyl)carbamate

(R)-quinuclidin-3-yl (3-(9-(2-(4-hydroxy-2-oxo-2,3-dihydrobenzo[d]thiazol-7-yl)ethylamino)nonyloxy)phenyl)(phenyl)methylcarbamate;

10 (R)-quinuclidin-3-yl (3-(4-(2-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)ethyl)benzyloxy)phenyl)(phenyl)methylcarbamate;

(R)-quinuclidin-3-yl (3-(2-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)ethyl)phenyl)(phenyl)methylcarbamate;

15 (3R)-3-((3-(6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)(phenyl)methylcarbamoxyloxy)-1-(2-oxo-2-phenylethyl)-1-azoniabicyclo[2.2.2]octane;

(R)-quinuclidin-3-yl (3-(3-(2-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)ethyl)benzyloxy)phenyl)(phenyl)methylcarbamate formate;

20 (3R)-3-(((3-((4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamoxyloxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;

(3R)-3-(((3-chlorophenyl)(3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)methyl)carbamoxyloxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;

25 1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;

(3R)-3-(((3-bromo-5-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)(phenyl)methyl)carbamoxyloxy)-1-(2-oxo-2-

phenylethyl)quinuclidin-1-ium;

phenylethyl)quinuclidin-1-ium;

(R)-quinuclidin-3-yl (2-chloro-3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)phenyl)(phenyl)methylcarbamate;

5 (R)-quinuclidin-3-yl ((2,6-difluoro-3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)(phenyl)methyl)carbamate;

(R)-quinuclidin-3-yl ((2-bromo-5-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)(phenyl)methyl)carbamate;

10 (3R)-3-(((2-chloro-3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;

15 (3R)-3-(((2,6-difluoro-3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;

(3R)-3-(((2-bromo-5-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;

20 (3R)-3-(((3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-4-methylphenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;

25 (R)-quinuclidin-3-yl ((3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-4-methoxyphenyl)(phenyl)methyl)carbamate;

(R)-quinuclidin-3-yl ((3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-

dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-5-

methoxyphenyl)(phenyl)methyl)carbamate;

(3R)-3-((((3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-4-methoxyphenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;

(3R)-3-((((3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-5-methoxyphenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;

(3R)-3-((((5-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-[1,1'-biphenyl]-3-yl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;

(R)-quinuclidin-3-yl (3-(9-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)nonyloxy)-5-(thiophen-2-yl)phenyl)(phenyl)methylcarbamate;

(3R)-3-((((3-((3-(4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)benzyl)oxy)phenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;

(3R)-3-((((3-((3-(4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)benzyl)oxy)phenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-phenoxyethyl)quinuclidin-1-ium;

(3R)-3-((((3-((3-((5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl)oxy)benzyl)oxy)phenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;

(3R)-3-((((3-((3-((5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl)oxy)benzyl)oxy)phenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-phenoxyethyl)quinuclidin-1-ium;

(R)-quinuclidin-3-yl (3-fluorophenyl)(3-(6-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyloxy)phenyl)methylcarbamate;

(3R)-3-((((3-((5-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl)oxy)phenyl)(phenyl)methyl)carbamoyl)oxy)-1-(4-phenylbutyl)quinuclidin-1-ium;

(R)-Quinuclidin-3-yl (3-fluorophenyl)(3-(3-(2-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)ethyl)benzyloxy)phenyl)methylcarbamate;

(3R)-3-((((3-fluorophenyl)(3-((3-(2-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzyl)oxy)phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;

(3R)-3-((((3-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;

(R)-Quinuclidin-3-yl (3-((4'-(2-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)ethyl)biphenyl-3-yl)methoxy)phenyl)(phenyl)methylcarbamate;

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

(R)-quinuclidin-3-yl (3-(4-(3-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)propyl)carbamoyl)benzyloxy)phenyl)(phenyl)methylcarbamate;

(3R)-3-((((3-((4-((3-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)propyl)carbamoyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;

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

5 5-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)pentyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonylamino)methyl)phenoxy)methyl)benzoate;

6-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonylamino)methyl)phenoxy)methyl)benzoate;

10 7-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)heptyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate;

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

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

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

25 (3R)-3-(((3-((4-(1-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)carbonyl)cyclopropyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;

(R)-quinuclidin-3-yl (3-(2-(3'-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)methyl)biphenyl-4-yl)ethoxy)phenyl)(phenyl)methylcarbamate;

5 (R)-quinuclidin-3-yl (3-(2-(3'-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)methyl)biphenyl-4-yl)ethoxy)phenyl)(phenyl)methylcarbamate;

6-((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyl 2-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonylamino)methyl)phenoxy)acetate;

10 (R)-quinuclidin-3-yl ((3-((6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyl)oxy)phenyl)(phenyl)methyl)carbamate;

15 (R)-quinuclidin-3-yl ((3-((6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyl)oxy)phenyl)(phenyl)methyl)carbamate;

(3R)-3-(((3-((6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyl)oxy)phenyl)(phenyl)methyl)carbonyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;

20 (3R)-3-(((3-((6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)hexyl)oxy)phenyl)(phenyl)methyl)carbonyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;

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

25 4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino)butyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate;

5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

yl)ethyl)amino)pentyl 2-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)acetate;

4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

5 yl)ethyl)amino)butyl 2-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)acetate;

5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

yl)ethyl)amino)pentyl 2-methyl-2-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)propanoate;

4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

10 yl)ethyl)amino)butyl 2-methyl-2-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)propanoate;

5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

yl)ethyl)amino)pentyl 2,2-dimethyl-3-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)propanoate;

15 4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

yl)ethyl)amino)butyl 1-(2-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)acetyl)piperidine-4-carboxylate;

4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

20 yl)ethyl)amino)ethyl)benzyl 2-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)acetate;

(R)-quinuclidin-3-yl ((3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-4-methylphenyl)(phenyl)methyl)carbamate;

(R)-Quinuclidin-3-yl ((3-bromo-5-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

25 yl)ethyl)amino)nonyl)oxy)phenyl)(phenyl)methyl)carbamate;

(R)-quinuclidin-3-yl ((5-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-[1,1'-biphenyl]-3-

yl)(phenyl)methyl)carbamate;

(R)-quinuclidin-3-yl ((2-bromo-3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

yl)ethyl)amino)nonyl)oxy)phenyl)(phenyl)methyl)carbamate;

5 (R)-quinuclidin-3-yl ((3'-fluoro-5-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)-[1,1'-biphenyl]-3-yl)(phenyl)methyl)carbamate;

(R)-quinuclidin-3-yl ((3-((3-(4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

10 yl)ethyl)amino)butoxy)benzyl)oxy)phenyl)(phenyl)methyl)carbamate;

(R)-quinuclidin-3-yl ((3-((3-((5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

yl)ethyl)amino)pentyl)oxy)benzyl)oxy)phenyl)(phenyl)methyl)carbamate;

(3R)-3-(((cyclohexyl(3-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-

15 dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;

(3R)-3-(((3-((6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)(thiophen-2-yl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;

20 (3R)-3-(((3-(3-fluorophenyl)(3-((6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;

(3R)-3-(((3-((6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl)oxy)phenyl)(thiophen-3-yl)methyl)carbamoyl)oxy)-1-

25 (2-oxo-2-phenylethyl)quinuclidin-1-ium;

(3R)-3-(((3-((4-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

yl)ethyl)amino)butyl)carbamoyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamoyl

- l)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;
- (3R)-3-((((3-((7-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)heptyl)oxy)phenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-2-phenylethyl)quinuclidin-1-ium;
- 5 (3R)-3-((((3-((7-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)heptyl)oxy)phenyl)(phenyl)methyl)carbamoyl)oxy)-1-(3-phenylpropyl)quinuclidin-1-ium;
- (3R)-3-((((3-((5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl)oxy)phenyl)(phenyl)methyl)carbamoyl)oxy)-1-(2-oxo-
- 10 2-phenylethyl)quinuclidin-1-ium;
- 4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 1-(4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)phenyl)cyclopentanecarboxylate;
- 4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-
- 15 yl)ethyl)amino)butyl 1-(4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)phenyl)cyclohexanecarboxylate;
- 4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-
- yl)ethyl)amino)butyl 2-methyl-2-(4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)phenyl)propanoate;
- 20 8-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)octyl 3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)benzoate;
- 9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-
- yl)ethyl)amino)nonyl 3-(phenyl(((R)-quinuclidin-3-
- 25 yloxy)carbonyl)amino)methyl)benzoate;
- 7-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)heptyl 3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)benzoate;

- 6-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl 3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)benzoate;
- 5 5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl 3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)benzoate;
- 4-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)carbamoyl)benzyl 3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)benzoate;
- 10 4-(N-(4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)sulfamoyl)benzyl 3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)benzoate;
- 4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzyl 3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)benzoate;
- 15 4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)benzamido)methyl)benzoate;
- (2S)-4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 3-phenyl-2-(4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzamido)propanoate;
- (R)-quinuclidin-3-yl ((3-((3-(4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)phenyl)-1,2,4-oxadiazol-5-yl)methoxy)phenyl)(phenyl)methyl)carbamate;
- 20 (R)-quinuclidin-3-yl ((5-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)pyridin-3-yl)(phenyl)methyl)carbamate;
- 25 (R)-quinuclidin-3-yl ((3-fluorophenyl)(5-((9-(((R)-2-hydroxy-2-(8-hydroxy-2-

- oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)nonyl)oxy)pyridin-3-yl)methyl)carbamate;
- 4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 2-chloro-4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate;
- 5 4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 2-fluoro-4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate;
- 4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 6-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)nicotinate;
- 10 4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 5-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)furan-2-carboxylate
- 15 4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 2-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)oxazole-4-carboxylate
- 4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 3-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate;
- 20 5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl 2-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)acetate;
- 5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl 2-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)acetate;
- 25 5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl 2-(3-(phenyl(((R)-quinuclidin-3-

- yl oxy)carbonyl)amino)methyl)phenoxy)acetate;
 5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)hexyl 2-(3-(phenyl(((R)-quinuclidin-3-yl oxy)carbonyl)amino)methyl)phenoxy)acetate;
- 5 (R)-quinuclidin-3-yl ((3-((4-((3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)propyl)carbamoyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate;
 (R)-quinuclidin-3-yl ((3-((4-((3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)carbamoyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate;
- 10 (R)-quinuclidin-3-yl ((3-((4-(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;
 (R)-quinuclidin-3-yl ((3-((4-((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;
- 15 (R)-quinuclidin-3-yl ((3-((4-((3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)propyl)(isopropyl)carbamoyl)benzyl)oxy)phenyl)(phenyl)methyl)carbamate;
- 20 (1R,4R)-4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 4-((4-((3-(phenyl(((R)-quinuclidin-3-yl oxy)carbonyl)amino)methyl)phenoxy)methyl)benzamido)methyl)cyclohexanecarboxylate;
- 25 (2S)-methyl 4-((2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)(methyl)amino)-4-oxo-2-(4-((3-(phenyl(((R)-quinuclidin-3-

- yl oxy)carbonyl)amino)methyl)phenoxy)methyl)benzamido)butanoate;
((1R,4R)-4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)methyl)cyclohexyl)methyl 4-((3-(phenyl(((quinuclidin-4-yl oxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate;
- 5 2-((4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl)amino)-2-oxoethyl 4-((3-(phenyl(((R)-quinuclidin-3-yl oxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate;
- 2-((3-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)propyl)amino)-2-oxoethyl 4-((3-(phenyl(((R)-quinuclidin-3-yl oxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate;
- 10 2-(4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)-2-oxoethyl 4-((3-(phenyl(((R)-quinuclidin-3-yl oxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate;
- 2-((5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl)oxy)-2-oxoethyl 4-((3-(phenyl(((R)-quinuclidin-3-yl oxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate;
- 15 2-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethoxy)ethyl 4-((3-(phenyl(((R)-quinuclidin-3-yl oxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate;
- 20 2-(4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)ethyl 4-((3-(phenyl(((R)-quinuclidin-3-yl oxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate;
- 2-((5-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)pentyl)oxy)-2-oxoethyl 4-((3-(phenyl(((R)-quinuclidin-3-yl oxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate;
- 25 2-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethoxy)ethyl 4-((3-(phenyl(((R)-quinuclidin-3-yl oxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate;

- 2-(4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)ethyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate;
- 3-(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;
- 3-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)propyl 4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzoate;
- 4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 4-(2-(3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)ethyl)benzoate;
- 4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 4-(5-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)-1,2,4-oxadiazol-3-yl)benzoate;
- 4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butyl 4-((4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)piperidin-1-yl)methyl)benzoate;
- 2-(4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)butoxy)ethyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate;
- 4-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethyl)benzyl 4-((3-(phenyl(((R)-quinuclidin-3-yloxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate;
- 2-(2-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethyl)amino)ethoxy)ethyl 4-((3-(phenyl(((R)-quinuclidin-3-

yl oxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate;

4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

yl)ethyl)amino)butyl 2-chloro-4-((3-(phenyl(((R)-quinuclidin-3-yl oxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate;

5 4-(((R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-

yl)ethyl)amino)butyl 2-fluoro-4-((3-(phenyl(((R)-quinuclidin-3-yl oxy)carbonyl)amino)methyl)phenoxy)methyl)benzoate.

14. A pharmaceutical composition comprising a compound of formula **I** as defined in any one of the claims 1-13, with one or more pharmaceutically
10 acceptable carriers and/or excipients.

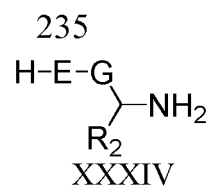
15. Use of a compound of formula **I** according to any one of claims 1-13 for the manufacture of a medicament for the prevention and/or treatment of broncho-obstructive or inflammatory diseases, preferably asthma or chronic bronchitis or chronic obstructive pulmonary disease (COPD).

15 16. A combination of a compound of formula **I** as defined in any one of the claims 1-13 with one or more active ingredients selected from the classes consisting of corticosteroids, P38 MAP kinase inhibitors, IKK2 inhibitors, HNE inhibitors, PDE4 inhibitors, leukotriene modulators, NSAIDs and mucus regulators.

20 17. A pharmaceutical composition according to claim 14 to be administered by inhalation, such as inhalable powders, propellant-containing metering aerosols or propellant-free inhalable formulations.

18. A device comprising the pharmaceutical composition according to claim 17, which may be a single- or multi-dose dry powder inhaler, a metered
25 dose inhaler and a soft mist nebulizer.

19. The present invention is also directed to a process for the preparation of a compound of general formula **XXXIV**



in its two enantiomeric forms, by mean of crystallization of the corresponding diastereomeric salt, obtained by salification of the racemic mixture with an enantiomerically pure carboxylic acid, wherein **E**, **G** and **R₂** are as defined in

5 claim 1.