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(54) **Title:**
ALKALOID AMINOESTER DERIVATIVES AND MEDICINAL COMPOSITION THEREOF

(57) **Abstract:**
The present invention relates to alkaloid aminoester derivatives acting as muscarinic receptor antagonists, to methods of preparing such derivatives, to compositions comprising them and therapeutic use thereof.

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(54) Title: ALKALOID AMINOESTER DERIVATIVES AND MEDICINAL COMPOSITION THEREOF

(57) Abstract: The present invention relates to alkaloid aminoester derivatives acting as muscarinic receptor antagonists, to methods of preparing such derivatives, to compositions comprising them and therapeutic use thereof.

ALKALOID AMINOESTER DERIVATIVES AND MEDICINAL COMPOSITION THEREOF

FIELD OF THE INVENTION

The present invention relates to alkaloid aminoester derivatives acting as muscarinic receptor antagonists, processes for the preparation thereof, compositions comprising them and the therapeutic use thereof.

BACKGROUND OF THE INVENTION

Quaternary ammonium salts acting as muscarinic (M) receptor antagonist drugs are currently used in therapy to induce bronchodilation for the treatment of respiratory diseases. Examples of well known M receptor antagonists are represented by ipratropium bromide and tiotropium bromide.

Several chemical classes acting as selective M3 receptor antagonist drugs have been developed for the treatment of inflammatory or obstructive airway diseases such as asthma and chronic obstructive pulmonary disease (COPD).

Quinuclidine carbamate derivatives and their use as M3 antagonists are disclosed in WO 02051841, WO 03053966 and WO 2008012290.

Said M and M3 receptor antagonists are currently administered through inhalation in order to deliver the drug directly at the site of action and hence limiting the systemic exposure.

However, even though the systemic exposure may be reduced through the inhalatory route, the compounds of the prior art may still exhibit undesired side effects due to systemic absorption.

It is hence highly desirable to provide M3 receptor antagonists able to act locally, while having high potency and long duration of action. Said drugs, once adsorbed, are degraded to inactive compounds which are deprived of any systemic side effects typical of muscarinic antagonists.

The present invention provides alkaloid aminoester derivatives with these therapeutically desirable characteristics.

The compounds of general formula (I) behave as soft-drugs, since they are able to produce a persistent bronchodilating effect in the lung but are consistently and rapidly transformed into inactive metabolites after passing into human plasma.

This behaviour gives great advantages in terms of safety.

US2824106 discloses quaternary alkyl derivatives of the tropeine series with increased spasmolytic activity and in particular N-phenyl amino acetyl derivatives.

J.Med.Chem. 1994, 37, 1712-1719 refers to presynaptic cholinergic modulators as potent cognition enhancers and analgesic drugs and in particular to N-phenyl amino acetyl derivatives.

US 2856407 discloses aminoacid esters of hydroxypiperidines; among them are N-methyl-3-piperidyl-2'-N'-dimethylaminoacetate and N-methyl-4-piperidyl-2'-N'-dimethylaminoacetate.

WO 99/20612 describes compounds that inhibit the farnesylation of mutant ras gene products and in particular 4-(methylsulfanyl) butanoate derivatives.

WO 2008/053158 refers to inhibitors of p38 MAP kinase activity, useful in the treatment of inflammatory and autoimmune disease and in particular to methylpiperidin-4-yl L-leucinate derivatives.

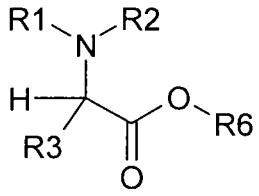
Khimiko-Farmatsevticheskii Zhurnal (1977), 11(7), 30-5 refers to tropine ester of phenylglyoxylic acid and in particular to phenylalanine ester derivatives.

Chemical & Pharmaceutical Bulletin (1971), 19(12), 2603-8 describes the one-step synthesis of atropine and other related alkaloids from dl-phenylalanine 3.alpha.-tropanyl ester and in particular to phenylalanine

ester derivatives.

SUMMARY OF THE INVENTION

The invention concerns alkaloid aminoester derivatives of general formula (I)



(I)

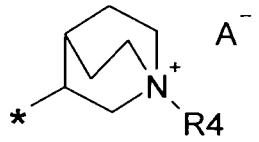
wherein:

R1 is selected from the group consisting of H, (C_1-C_{10})-alkyl, aryl, (C_3-C_8)-cycloalkyl, arylalkyl and heteroaryl, optionally substituted by one or more substituents selected from the group consisting of halogen atoms, OH, oxo (=O), SH, NO_2, CN, CON(R5)$_2$, COOH, NHCOR5, COR5, CO_2R5, CF_3, (C_1-C_{10})-alkoxycarbonyl, (C_1-C_{10})-alkylsulfanyl, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_1-C_{10})-alkyl and (C_1-C_{10})-alkoxyl;

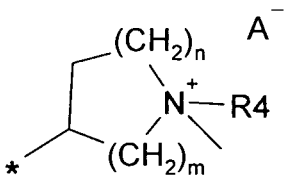
R2 is selected from the group consisting of (C_1-C_{10})-alkyl, aryl, (C_3-C_8)-cycloalkyl, arylalkyl and heteroaryl, optionally substituted by one or more substituents selected from the group consisting of halogen atoms, OH, oxo (=O), SH, NO_2, CN, CON(R5)$_2$, COOH, NHCOR5, COR5, CO_2R5, CF_3, (C_1-C_{10})-alkoxycarbonyl, (C_1-C_{10})-alkylsulfanyl, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_1-C_{10})-alkyl and (C_1-C_{10})-alkoxyl;

R3 is selected from the group consisting of H, (C_1-C_{10})-alkyl, aryl, (C_3-C_8)-cycloalkyl, heteroaryl, arylalkyl and heteroarylalkyl, optionally substituted by one or more substituents selected from the group consisting of halogen atoms, OH, oxo (=O), SH, NO_2, CN, CON(R5)$_2$, COOH, CO_2R5, CF_3, (C_1-C_{10})-alkoxycarbonyl, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_1-C_{10})-alkyl and (C_1-C_{10})-alkoxyl;

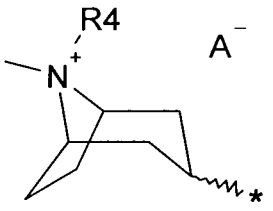
R6 represents a group of formula (i) or (ii) or (iii) or (iv)



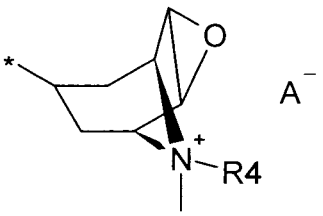
(i)



(ii)



(iii)



iv)

wherein

m = 1, 2 or 3;

n =1, 2 or 3;

A^- is a physiologically acceptable anion;

R4 is a group of formula (Y)

$$---(CH_2)p---P---(CH_2)q---W$$

(Y)

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, SO, SO_2, CO, NR5 CH=CH, $N(R5)SO_2$, N(R5)COO, N(R5)C(O), $SO_2N(R5)$, CO(O)N(R5) and C(O)N(R5);

W is selected from the group consisting of H, $(C_1$-$C_6)$-alkyl, $(C_3$-$C_8)$-cycloalkyl, aryl and heteroaryl, optionally substituted by one or more substituents selected from the group consisting of halogen atoms, OH, oxo

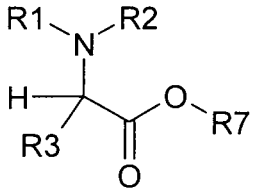
(=O), SH, NO_2, CN, $CON(R5)_2$, COOH, NH_2, NHCOR5, CO_2R5, (C_1-C_{10})-alkoxycarbonyl, (C_1-C_{10})-alkylsulfanyl, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_1-C_{10})-alkyl and (C_1-C_{10})-alkoxyl;

R5 is selected from the group consisting of H, (C_1-C_{10})alkyl, (C_1-C_6)alkylhalo, (C_2-C_6)alkynyl, (C_2-C_6)alkenyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, heteroaryl, (C_1-C_6)alkyl-heteroaryl and aryl optionally substituted by one or more substituents selected from the group consisting of halogen atoms, OH, oxo (=O), SH, NO_2, CN, $CONH_2$, COOH, (C_1-C_{10})-alkoxycarbonyl, (C_1-C_{10})-alkylsulfanyl, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_1-C_{10})-alkyl and (C_1-C_{10})-alkoxyl;

and pharmaceutically acceptable salts thereof,

with the proviso that when R1 is H, R2 is phenyl, R3 is H, then R6 is not a group of formula (iii).

The invention also refers to compounds of general formula (VI):

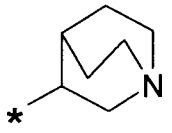


(VI)

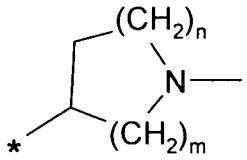
wherein:

R1, R2 and R3 are as described above;

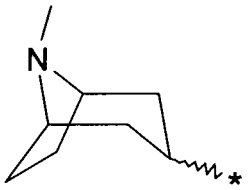
R7 represents a group of formula (vi) or (vii) or (viii) or (ix)



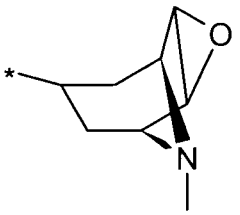
(vi)



(vii)



(viii)



(ix)

wherein

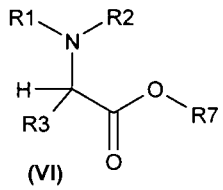
m and n are as described above;

and pharmaceutically acceptable salts thereof,

with the provisos that:

- when R1 is H or CH_3, R2 is phenyl, R3 is H or CH_3, then R6 is not a group of formula (viii) and
- the compounds of general formula (VI) are not N-methyl-3-piperidyl-2'-N'dimethylaminoacetate and N-methyl-4-piperidyl-2'-N'-dimethylaminoacetate.

The invention also refers to a process for the preparation of a compound of formula (I) as reported in Scheme 1, which comprises the alkylation of compounds of general formula (VI)



(VI)

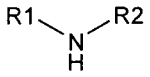
by alkylating agents of general formula (XI)



(XI)

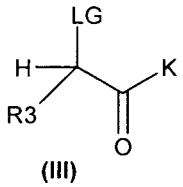
in which A is a suitable leaving group selected from the group consisting of halide and sulfonate, and R6 has the above reported meanings.

The invention also concerns a process for the preparation of a compound of formula (I) as reported in Scheme 1, which comprises the alkylation of amine compounds of general formula (II)



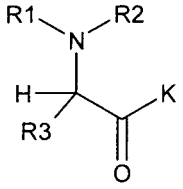
(II)

with compounds of general formula (III),



(III)

in which LG is a suitable leaving group and K may be either a hydroxyl group or a suitably protected hydroxyl group, to yield a compound of formula (IV),



(IV)

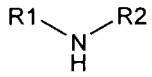
which is condensed with a compound of formula (V)



(V)

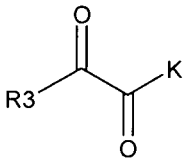
to obtain compound (VI), and converting the compound to a further compound of formula (I).

The invention also concerns a process for the preparation of a compound of formula (I) as reported in Scheme 1, which comprises coupling an amine of general formula (II)



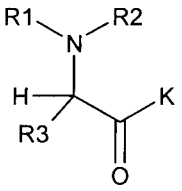
(II)

with ketones of formula (VII),



(VII)

to yield a compound of formula (IV),



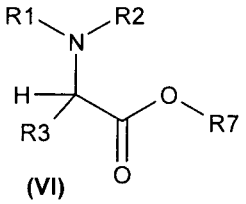
(IV)

which is condensed with a compound of formula (V)



(V)

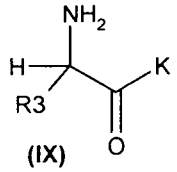
to obtain compound (VI)



(VI)

and converting the compound to a further compound of formula (I).

The invention also concerns a process for the preparation of a compound of formula (I) as reported in scheme 1, which comprises reacting compound (IX)



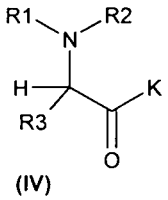
(IX)

with an alkylating agent of general formula (VIII),



(VIII)

in which z is a carbonyl group or a suitable leaving group such as a an halide, to yield a compound of formula (IV) in which R2 is hydrogen,



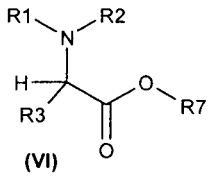
(IV)

which is condensed with a compound of formula (V)



(V)

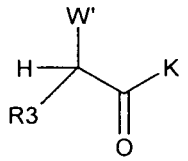
to obtain compound (VI)



(VI)

and converting the compound to a further compound of formula (I).

The invention also concerns a process for the preparation of a compound of formula (I) as reported in Scheme 1, which comprises coupling compounds of general formula (III)



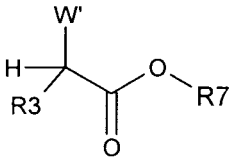
(III)

to compound of general formula (V)



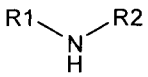
(V)

to yield compound (X),



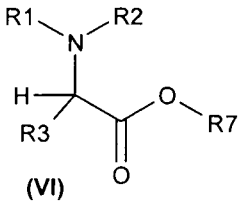
(X)

which is reacted with an amine of formula (II),



(II)

to obtain compound (VI)



(VI)

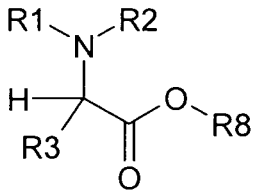
and converting the compound into a further compound of formula (I).

The invention also provides pharmaceutical compositions of compounds of general formula (I) or of general formula (VI) alone or in combination with or in admixture with one or more pharmaceutically acceptable carriers and/or excipients.

The invention also provides compounds of general formula (I) and (VI) for use as a medicament.

In a further aspect, the invention provides the use of compounds of formula (I) or of general formula (VI) 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).

In a further aspect the invention provides the use of the compounds of general formula (XIX)



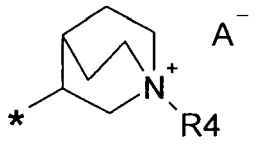
(XIX)

wherein:

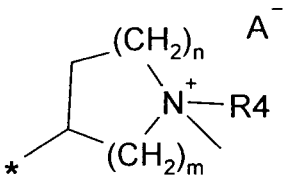
R1 and R2 is independently selected from the group consisting of H, (C_1-C_{10})-alkyl, aryl, (C_3-C_8)-cycloalkyl, arylalkyl and heteroaryl optionally substituted by one or more substituents selected from the group consisting of halogen atoms, OH, oxo (=O), SH, NO_2, CN, $CON(R5)_2$, COOH, NHCOR5, COR5, CO_2R5, CF_3, (C_1-C_{10})-alkoxycarbonyl, (C_1-C_{10})-alkylsulfanyl, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_1-C_{10})-alkyl and (C_1-C_{10})-alkoxyl;

R3 is selected from the group consisting of H, (C_1-C_{10})-alkyl, aryl, (C_3-C_8)-cycloalkyl, heteroaryl, arylalkyl and heteroarylalkyl optionally substituted by one or more substituents selected from the group consisting of halogen atoms, OH, oxo (=O), SH, NO_2, CN, $CON(R5)_2$, COOH, CO_2R5, CF_3, (C_1-C_{10})-alkoxycarbonyl, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_1-C_{10})-alkyl and (C_1-C_{10})-alkoxyl;

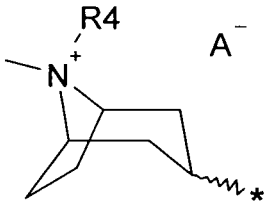
R8 represents a group of formula (i) or (ii) or (iii) or (iv) or (vi) or (vii) or (viii) or (ix)



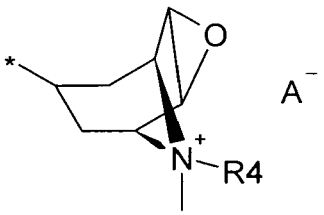
(i)



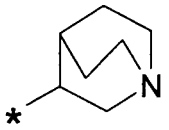
(ii)



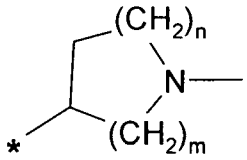
(iii)



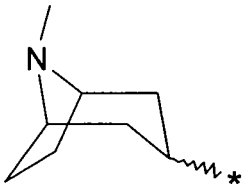
(iv)



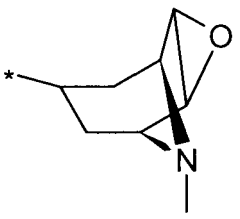
(vi)



(vii)



(viii)



(ix)

wherein

m = 1, 2 or 3;

n =1, 2 or 3;

A^- is a physiologically acceptable anion;

R4 is a group of formula (Y)

$$---(CH_2)p---P---(CH_2)q---W$$

(Y)

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, SO, SO_2, CO, NR5 CH=CH, $N(R5)SO_2$, N(R5)COO, N(R5)C(O), $SO_2N(R5)$, CO(O)N(R5) and C(O)N(R5);

W is selected from the group consisting of H, (C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyl, aryl and heteroaryl, optionally substituted by one or more substituents selected from the group consisting of halogen atoms, OH, oxo (=O), SH, NO_2, CN, $CON(R5)_2$, COOH, NH_2, NHCOR5, CO_2R5, (C_1-C_{10})-alkoxycarbonyl, (C_1-C_{10})-alkylsulfanyl, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_1-C_{10})-alkyl and (C_1-C_{10})-alkoxyl;

R5 is selected from the group consisting of H, (C_1-C_{10})alkyl, (C_1-C_6)alkylhalo, (C_2-C_6)alkynyl, (C_2-C_6)alkenyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, heteroaryl, (C_1-C_6)alkyl-heteroaryl and aryl optionally substituted by one or more substituents selected from the group consisting of halogen atoms, OH, oxo (=O), SH, NO_2, CN, $CONH_2$, COOH, (C_1-C_{10})-alkoxycarbonyl, (C_1-C_{10})-alkylsulfanyl, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_1-C_{10})-alkyl and (C_1-C_{10})-alkoxyl,

for the preparation 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).

The invention also provides a method for the prevention and/or treatment of broncho-obstructive or inflammatory diseases, 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), (VI) or (XIX).

The invention also provides pharmaceutical preparations suitable for

administration by inhalation, such as inhalable powders, propellant-containing metering aerosols or propellant-free inhalable formulations.

The invention also refers 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 general formula (I) or (VI).

The invention also refers to a kit comprising the pharmaceutical compositions of compounds of general formula (I) or (VI) 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) or (VI).

DEFINITIONS

The term "halogen atoms" includes fluorine, chlorine, bromine, and iodine.

The expression "(C_1-C_{10}) alkyl", refers to straight or branched chain alkyl groups wherein the number of carbon atoms is from 1 to 10. Examples of said groups are methyl, ethyl, n-propyl, isopropyl, t-butyl, pentyl, hexyl, heptyl, octanyl, nonenyl and decenyl.

Optionally, as reported above, one or more hydrogen atoms can be replaced by halogen atoms in alkyl groups. The derived expressions "(C_1-C_{10})-alkoxycarbonyl", (C_1-C_{10})-alkylsulfanyl", "(C_1-C_{10})-alkylsulfinyl", "(C_1-C_{10})-alkylsulfonyl" and "(C_1-C_{10})-alkoxyl" should be construed in an analogous manner.

The derived expressions "(C_2-C_{10}) alkenyl" and "(C_2-C_{10}) alkynyl", should be construed in an analogous manner, as referring to groups at least comprising one double or triple bond.

The expression "aryl" refers to mono, bi- or tricyclic ring systems which have 5 to 20 ring atoms, preferably from 5 to 15 and wherein at least one ring is aromatic. In said rings one or more hydrogen atoms may be

replaced by one or more halogen atoms.

The expression "heteroaryl" refers to mono, bi- or tricyclic ring systems which have 5 to 20 ring atoms, preferably from 5 to 15, in which at least one ring is aromatic and in which at least one ring atom is a heteroatom or heteroaromatic group (e.g. N, NH, S or O). In said rings one or more hydrogen atoms may be replaced by one or more halogen atoms.

The expression "arylalkyl" refers to a "(C_1-C_4) alkyl" optionally substituted by aryl as above defined.

Examples of suitable arylalkyl groups include benzyl and diphenylmethyl.

The expression "heteroarylalkyl" refers to a "(C_1-C_4) alkyl" optionally substituted by a heteroaryl group as above defined.

Examples of suitable heteroarylalkyl groups include thiophenylmethyl.

Examples of suitable monocyclic systems include thiophene, cyclopentadiene, benzene, pyrrole, pyrazole, imidazole, isoxazole, oxazole, isothiazole, thiazole, pyridine, imidazolidine, piperidine and furan radicals.

Examples of suitable bicyclic systems include naphthalene, biphenyl, purine, pteridine, benzotriazole, quinoline, isoquinoline, indole, isoindole and benzothiophene radicals.

Examples of suitable tricyclic systems include fluorene radicals.

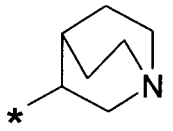
DETAILED DESCRIPTION OF THE INVENTION

The invention refers to alkaloid aminoester derivatives of formula (I) and (VI) acting as muscarinic receptor antagonists, and to the salts thereof, said derivatives preferably acting on the M3 receptors.

Advantageously, physiologically acceptable anions A^- include those selected from chloride, bromide, iodide, trifluoroacetate, formate, sulfate, phosphate, methanesulfonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate, and p-toluenesulfonate, preferably chloride, bromide and iodide.

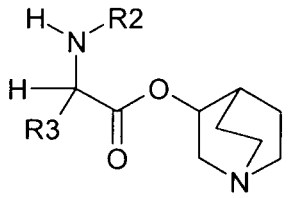
In preferred compounds of general formula (I) R1 is hydrogen, R2 is arylalkyl or (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or heteroaryl and R3 is (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or heteroaryl, preferably substituted with one or more halogen atoms and wherein R6 is as defined above.

In preferred compounds of general formula (VI) R1 is H, R2 is arylalkyl or (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or heteroaryl and R3 is (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or heteroaryl, preferably substituted with one or more halogen atoms and wherein R7 is a group of formula (vi)



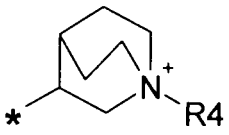
(vi)

according to the general formula (XII):



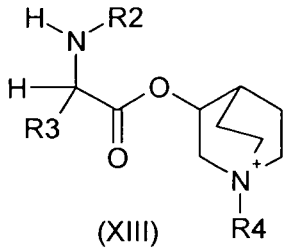
(XII)

In a preferred group of compounds of general formula (I) R1 is H, R2 is arylalkyl or (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or heteroaryl and R3 is (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or arylalkyl or heteroaryl, preferably substituted with one or more halogen atoms and wherein R6 is a group of formula (i)



(i)

according to the general formula (XIII):



(XIII)

In a preferred group of compounds of general formula (XII) R2 and R3 are phenyl.

In a preferred group of compounds of general formula (XIII) R2 and R3 are phenyl.

In a preferred group of compounds of general formula (XIII) R4 is a group of formula (Y)

$$---(CH_2)_p---P---(CH_2)_q---W$$

(Y)

wherein p is 1, P is CO, q is 0 and W is aryl or heteroaryl.

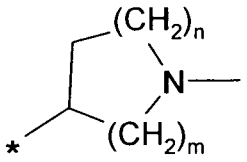
In a preferred group of compounds of general formula (XIII) R4 is a group of formula (Y), wherein p is 1, P is CO, q is 0 and W is an optionally phenyl.

In a preferred group of compounds of general formula (XIII) R4 is a group of formula (Y), wherein p is 1, P is CO, q is 0 and W is thienyl or thiazolyl.

In a preferred group of compounds of general formula (XIII) R4 is a group of formula (Y), wherein p is 2, P is O, q is 0 and W is phenyl.

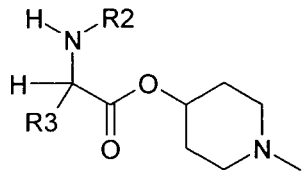
In a preferred group of compounds of general formula (XIII) R4 is a group of formula (Y), wherein p is 3, P is O, q is 0 and W is phenyl.

In a preferred group of compounds of general formula (VI) R1 is H, R2 is arylalkyl or (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or heteroaryl and R3 is (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or arylalkyl or heteroaryl, preferably substituted with one or more halogen atoms and wherein R7 is a group of formula (vii)



(vii)

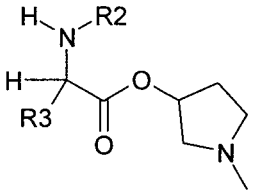
wherein m=2 and n=1, according to the general formula (XIV):



(XIV)

In a preferred group of compounds of general formula (XIV) R2 and R3 are phenyl, preferably substituted with one or more halogen atoms.

In a preferred group of compounds of general formula (VI) R1 is H, R2 is arylalkyl or (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or heteroaryl and R3 is (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or arylalkyl or heteroaryl, preferably substituted with one or more halogen atoms and wherein R7 is a group of formula (vii), wherein m=1 and n=1, according to the general formula (XV):

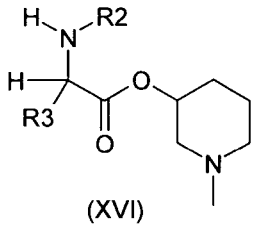


(XV)

In a preferred group of compounds of general formula (XV) R2 and R3 are phenyl, preferably substituted with one or more halogen atoms.

In a preferred group of compounds of general formula (VI) R1 is H, R2 is arylalkyl or (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or heteroaryl and R3 is (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or arylalkyl or arylalkyl or heteroaryl, preferably substituted with one or more halogen atoms and wherein

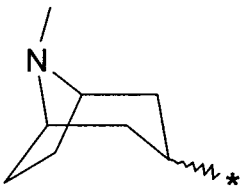
R7 is a group of formula (vii), wherein m=1 and n=2, according to the general formula (XVI):



(XVI)

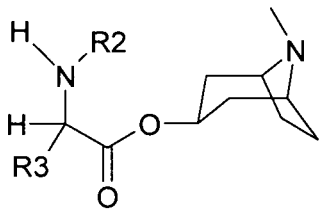
In a preferred group of compounds of general formula (XVI) R2 and R3 are phenyl, preferably substituted with one or more halogen atoms.

In a preferred group of compounds of general formula (VI) R1 is H, R2 is arylalkyl or $(C_1\text{-}C_{10})$-alkyl or aryl or $(C_3\text{-}C_8)$-cycloalkyl or heteroaryl and R3 is $(C_1\text{-}C_{10})$-alkyl or aryl or $(C_3\text{-}C_8)$-cycloalkyl or arylalkyl or arylalkyl or heteroaryl, preferably substituted with one or more halogen atoms and wherein R7 is a group of formula (viii)



(viii)

according to the general formula (XVII):

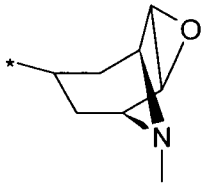


(XVII)

In a preferred group of compounds of general formula (XVII) R2 and R3 are phenyl, preferably substituted with one or more halogen atoms.

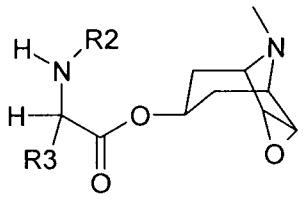
In a preferred group of compounds of general formula (VI) R1 is H, R2

is arylalkyl or (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or heteroaryl and R3 is (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or arylalkyl or arylalkyl or heteroaryl, preferably substituted with one or more halogen atoms and wherein R7 is a group of formula (ix)



(ix)

according to the general formula (XVIII):



(XVIII)

In a preferred group of compounds of general formula (XVIII) R2 and R3 are phenyl.

A preferred group of compounds are the corresponding quaternary ammonium salts of compounds of general formula (XII), (XIV), (XV), (XVII) and (XVIII).

It will be apparent that the compounds of general formula (I) and (VI) may contain asymmetric centers. Therefore the invention also includes the optical stereoisomers and mixtures thereof.

Where the compounds according to the invention have at least one asymmetric center, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centers, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed

within the scope of the present invention.

The active compounds of general formula (VI) and in particular compounds of general formula (XII), (XIII), (XV) and (XVI) wherein R3 is different from H, show at least two chiral centers, which are respectively represented by the alkaloid carbon atom bearing the aminoester group and the carbon atom bearing H, R3 and NHR2. Compounds of general formula (XII), (XIII), (XV) and (XVI) wherein R3 is different from H can be obtained in S-R, R-R, R-S, S-S configuration or as a mixture of diastereoisomers (R-R and S-R configuration or R-S and S-S configuration).

According to a preferred embodiment, compounds of general formula (XII), (XIII), (XV) and (XVI) wherein R3 is different from H, show a (R,R) configuration.

The active compounds of formula (I) and (VI) show at least one chiral center, which is represented by the alkaloid carbon atom bearing the aminoester group.

According to a further embodiment, compound (I) is in the form of (S)-enantiomer when R6 is a group of formula (i).

According to a preferred embodiment, compound (I) is in the form of (R)-enantiomer when R6 is a group of formula (i).

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

Compound	Chemical name
C2	(R)-quinuclidin-3-yl 2-phenyl-2-(phenylamino)acetate
C3	(R)-quinuclidin-3-yl 2-(4-fluorophenyl)-2-(4-fluorophenylamino)acetate
C4	(R)-quinuclidin-3-yl 2-(methyl(phenyl)amino)-2-phenylacetate

(continue)

C12	(R)-quinuclidin-3-yl 2-(3-fluorophenyl)-2-(3-fluorophenylamino)acetate
C13	(R)-1-methylpiperidin-4-yl-2-phenyl-2-(phenylamino)acetate
C14	(R)-1-methylpyrrolidin-4-yl-2-phenyl-2-(phenylamino)acetate
C15	(S)-1-methylpyrrolidin-4-yl-2-phenyl-2-(phenylamino)acetate
C16	(R)-1-methylpiperidin-3-yl 2-phenyl-2-(phenylamino)acetate
C17	8-methyl-8-azabicyclo[3.2.1]octan-3-yl 2-phenyl-2-(phenylamino)acetate
C18	Phenyl-phenylamino-acetic acid 9-methyl-3-oxa-9-aza-tricyclo[3.3.1.0*2,4*]non-7-yl ester
C20	(R)-quinuclidin-3-yl) 2-amino-3-phenylpropanoate di-trifluoroacetate
C22	3-phenyl-2-phenylamino-propionic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C24	(R)-quinuclidin-3-yl 2-(benzylamino)-2-phenylacetate
C25	(R)-quinuclidin-3-yl 2-amino-2-phenylacetate di-hydrochloride
C26	(R)-quinuclidin-3-yl 2-(cyclopentylamino)-2-phenylacetate di-trifluoroacetate
C27	(R)-quinuclidin-3-yl 2-(cyclohexylamino)-2-phenylacetate
C29	((4-chloro-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C30	4-({[(R)-(1-aza-bicyclo[2.2.2]oct-3-yl)oxycarbonyl]-phenyl-methyl}-amino)-benzoic acid methyl ester
C31	3-({[(R)-(1-aza-bicyclo[2.2.2]oct-3-yl)oxycarbonyl]-phenyl-methyl}-amino)-thiophene-2-carboxylic acid methyl ester
C32	(4-fluoro-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester

(continue)

C33	(4-fluoro-phenyl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C35	2-({[(R)-(1-aza-bicyclo[2.2.2]oct-3-yl)oxycarbonyl]-phenyl-methyl}-amino)-benzoic acid methyl ester
C37	(2-methoxy-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C39	phenyl-o-methyl phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C41	phenyl-(3-trifluoromethoxy-phenylamino)-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C43	(3-ethyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C46	(3-acetylamino-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C47	(3-methylcarbamoyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C52	(3-methylsulfanyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C53	(3-acetyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C55	(2,5-dimethoxy-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C58	(2,5-difluoro-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C59	(2,6-dimethyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester

(continue)

C61	(2-ethyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C64	(2-acetyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C65	(3,5-difluoro-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C67	3-({[(R)-(1-aza-bicyclo[2.2.2]oct-3-yl)oxycarbonyl]-phenyl-methyl}-amino)-benzoic acid ethyl ester
C69	(3-methoxy-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C72	[(4-fluoro-phenyl)-methyl-amino]-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C75	(methyl-phenyl-amino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C77	(4-methyl-benzylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C78	(4-fluoro-benzylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C79	(4-methoxy-benzylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C80	benzylamino-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C82	(4-fluoro-benzylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C84	(4-fluoro-phenyl)-(3-fluoro-phenylamino)-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester

(continue)

C85	(4-fluoro-phenyl)-(2-fluoro-phenylamino)-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C90	(R)-quinuclidin-3-yl 2-(phenylamino)-2-(thiophen-2-yl)acetate hydrochloride
C93	(4-methoxy-phenyl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C95	4-{[(R)-(1-aza-bicyclo[2.2.2]oct-3-yl)oxycarbonyl]-phenylamino-methyl}-benzoic acid methyl ester
C99	(3-fluoro-phenyl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C100	(4-fluoro-phenyl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C105	phenylamino-(4-trifluoromethyl-phenyl)-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C106	(S)-quinuclidin-3-yl 2-phenyl-2-(phenylamino)-acetate
C107	phenyl-phenylamino-acetic acid 1-methyl-azepan-4-yl ester
C108	(R)-1-(2-phenoxyethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C109	(R)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C110	(R)-1-(3-phenoxypropyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C111	(R)-1-methyl-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C112	(R)-1-(2-phenoxyethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

(continue)

C113	(R)-1-(2-oxo-2-phenylethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C114	(3R)-1-(2-oxo-2-(thiophen-3-yl)ethyl)-3-(2-phenyl-2-(phenylamino)-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C115	(3R)-1-(2-(4-fluorophenyl)-2-oxoethyl)-3-(2-phenyl-2-(phenylamino)-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C116	(R)-1-phenethyl-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C117	(R)-1-(2-(benzo[b]thiophen-2-yl)-2-oxoethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C118	(3R)-3-(2-(4-fluorophenyl)-2-(4-fluorophenylamino)acetoxy)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C119	(3R)-3-(2-(4-fluorophenyl)-2-(4-fluorophenylamino)acetoxy)-1-(2-oxo-2-phenylethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C120	(3R)-3-(2-(4-fluorophenyl)-2-(4-fluorophenylamino)acetoxy)-1-methyl-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C121	(3R)-3-(2-(3-fluorophenyl)-2-(3-fluorophenylamino)acetoxy)-1-(2-oxo-2-phenylethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C122	(3R)-3-(2-(methyl(phenyl)amino)-2-phenylacetoxy)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C123	(3R)-3-(2-(methyl(phenyl)amino)-2-phenylacetoxy)-1-(2-oxo-2-phenylethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C124	(R)-1-(2-phenoxyethyl)-3-(3-phenyl-2-(phenylamino)propanoyloxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C125	(R)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-3-((S)-3-phenyl-2-(phenylamino)propanoyloxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

(continue)

C126	(R)-1-methyl-3-(3-phenyl-2-(phenylamino)propanoyloxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C127	(R)-1-(2-oxo-2-phenylethyl)-3-((S)-3-phenyl-2-(phenylamino)propanoyloxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C128	(3R)-3-(2-(benzylamino)-2-phenylacetoxy)-1-(2-oxo-2-phenylethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C129	(R)-1-(2-oxo-2-pyridin-4-yl-ethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C130	(R)-1-[2-(3-chloro-thiophen-2-yl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C131	(R)-1-[2-(5-methyl-thiophen-2-yl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C132	(R)-1-[2-(1-methyl-1H-pyrrol-2-yl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C133	(R)-1-[2-(2,4-dimethyl-oxazol-5-yl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C134	(R)-3-(2-phenyl-2-phenylamino-acetoxy)-1-(3-phenylsulfanyl-propyl)-1-azonia-bicyclo[2.2.2]octane formate
C135	(R)-3-[2-(3-ethyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane formate
C136	(R)-3-[2-(4-methoxycarbonyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C137	(3R)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-(2-(phenylthio)ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C138	(3R)-1-(cyclohexylmethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

(continue)

C139	(3R)-1-(4-methylpent-3-enyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C140	(3R)-1-(2-(3,4-dichlorophenyl)-2-oxoethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C141	(R)-1-(2-oxo-2-phenylethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C142	3-(3-(3-fluorophenyl)-3-(3-fluorophenylamino)-2-oxopropyl)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-1-azonia-bicyclo[2.2.2]octane chloride
C143	(R)-1-(2-amino-2-oxoethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C144	(R)-1-(2-oxo-2-(phenylamino)ethyl)-3-(2-phenyl-2-(phenylamino)-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C145	(3R)-1-(2-oxo-2-phenylethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C146	(3R)-3-(2-(benzylamino)-2-phenylacetoxy)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-1-azonia-bicyclo[2.2.2]octane chloride
C147	(R)-1-(2-oxo-2-phenyl-ethyl)-3-((R)-2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C149	(R)-3-((S)-2-amino-phenylpropanoyloxy)-1-(2-phenoxyethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C150	(R)-3-((S)-2-amino-3-phenylpropanoyloxy)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C151	(R)-3-((S)-2-amino-3-phenylpropanoyloxy)-1-(3-phenoxypropyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C152	(R)-3-((S)-2-amino-3-phenylpropanoyloxy)-1-(2-oxo-2-phenylethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

(continue)

C153	(R)-1-(2-oxo-2-phenylethyl)-3-((R)-3-phenyl-2-(phenylamino)-propanoyloxy)-1-azoniabicyclo[2.2.2]octane bromide
C154	(R)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-3-((R)-3-phenyl-2-(phenylamino)-propanoyloxy)-1-azonia-bicyclo[2.2.2]octane chloride
C155	(R)-1-[2-(4-methoxy-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C156	(R)-1-(4-oxo-4-phenyl-butyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C157	(R)-1-(4-oxo-4-phenyl-butyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C158	(R)-1-benzyl-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C159	(R)-1-benzyl-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C160	(R)-1-benzyl-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C161	(R)-1-[2-(4-methoxy-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C162	(R)-1-[2-(4-methylsulfonyl-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C163	(R)-1-[2-(3-hydroxy-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C164	(R)-1-dimethylcarbamoylmethyl-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C165	(R)-1-(2-oxo-propyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

(continue)

C166	(R)-3-[2-(2-methoxycarbonyl-thiophen-3-yl)-2-phenylamino-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C167	(R)-3-[2-(2-methoxycarbonyl-thiophen-3-yl)-2-phenylamino-acetoxy]-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C168	(R)-3-[2-(4-methoxy-phenyl)-2-phenylamino-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane formate
C169	(R)-3-[2-(4-chloro-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C170	(R)-1-(2-oxo-2-phenyl-ethyl)-3-[2-phenylamino-2-(4-trifluoromethyl-phenyl)-acetoxy]-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C171	(R)-1-methyl-1-(2-oxo-2-phenyl-ethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-pyrrolidinium trifluoroacetate
C172	1,1-dimethyl-4-(2-phenyl-2-phenylamino-acetoxy)-piperidinium trifluoroacetate
C173	(R)-1-[2-(5-methyl-thiophen-3-yl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C174	(R)-1-[2-(2,4-difluoro-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C175	(R)-1-[2-(3,4-difluoro-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C176	(R)-1-[2-(2-fluoro-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C177	(R)-1-[2-(3-fluoro-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C178	(R)-1-[2-(2,4-dibromo-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane chloride

(continue)

C179	(R)-1-[2-(4-nitro-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C180	(R)-1-[2-(4-hydroxy-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C181	(R)-1-[2-oxo-2-(2-oxo-2,3-dihydro-1H-indol-5-yl)-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C182	(R)-1-(2-benzo[1,3]dioxol-5-yl-2-oxo-ethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C183	(R)-1-(2-oxo-2-thiazol-2-yl-ethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C184	(R)-1-[2-(3-ethoxycarbonyl-isoxazol-5-yl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C185	(R)-1-[2-(4-methyl-thiophen-2-yl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C186	(R)-1-(2-benzo[b]thiophen-5-yl-2-oxo-ethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C187	(R)-3-(2-phenyl-2-phenylamino-acetoxy)-1-phenylsulfanylmethyl-1-azonia-bicyclo[2.2.2]octane chloride
C188	(R)-1-(2-oxo-2-piperidin-1-yl-ethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane chloride
C189	(R)-3-(2-phenyl-2-phenylamino-acetoxy)-1-(thiazol-2-ylcarbamoylmethyl)-1-azonia-bicyclo[2.2.2]octane chloride
C190	(R)-1-(isoxazol-3-ylcarbamoylmethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane chloride
C191	(R)-1-(2-oxo-2-phenyl-ethyl)-3-(2-phenyl-2-p-methylphenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide

(continue)

C192	(R)-3-[2-(4-fluoro-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C193	(R)-3-[2-(4-fluoro-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane chloride
C194	(R)-3-[2-(2-methoxycarbonyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C195	(R)-3-[2-(2-methoxy-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C196	(R)-1-(2-oxo-2-phenyl-ethyl)-3-[2-phenyl-2-(3-trifluoromethoxy-phenylamino)-acetoxy]-1-azonia-bicyclo[2.2.2]octane bromide
C197	(R)-1-(2-oxo-2-phenyl-ethyl)-3-(2-phenyl-2-(phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C198	(R)-3-[2-(3-acetylamino-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C199	(R)-3-[2-(3-methylcarbamoyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C200	(R)-3-[2-(3-methylsulfanyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C201	(R)-3-[2-(4-fluoro-phenyl)-2-(3-fluoro-phenylamino)-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C202	(R)-3-[2-(4-fluoro-phenyl)-2-(3-fluoro-phenylamino)-acetoxy]-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane chloride
C203	(R)-3-[2-(4-fluoro-phenyl)-2-(2-fluoro-phenylamino)-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C204	(R)-3-[2-(4-fluoro-phenyl)-2-(2-fluoro-phenylamino)-acetoxy]-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane chloride

(continue)

C205	(R)-3-[2-(4-methoxycarbonyl-phenyl)-2-phenylamino-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C206	(R)-3-(2-cyclohexylamino-2-phenyl-acetoxy)-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C207	(R)-3-(2-cyclohexylamino-2-phenyl-acetoxy)-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane chloride
C208	(R)-1-(2-oxo-2-phenyl-ethyl)-3-(2-phenylamino-2-thiophen-2-yl-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C209	(R)-3-[2-(3-fluoro-4-methyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C210	(R)-3-[2-(2,5-dimethoxy-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C211	(R)-3-[2-(2,5-difluoro-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C212	(R)-3-[2-(2,6-dimethyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C213	(R)-3-[2-(2-ethyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C214	(R)-3-[2-(2-acetyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C215	(R)-3-[2-(3-ethoxycarbonyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C216	(R)-3-[2-(3,5-difluoro-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C217	(R)-3-[2-(3-methoxy-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide

(continue)

C218	(R)-3-[2-(3-fluoro-phenyl)-2-phenylamino-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C219	(R)-3-[2-(4-fluoro-phenyl)-2-phenylamino-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C220	(R)-1-cyanomethyl-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C221	(R)-1-tert-butoxycarbonylmethyl-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C222	(S)-1-(2-oxo-2-phenyl-ethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane chloride
C223	(R)-3-[2-(3-acetyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane formate
C224	(R)-1-[2-(4-acetylamino-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C225	(R)-1-[2-(4-methoxycarbonyl-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C226	(R)-3-(2-phenyl-2-phenylamino-acetoxy)-1-pyridin-2-ylmethyl-1-azonia-bicyclo[2.2.2]octane trifluoroacetate trifluoroacetate anion
C227	(R)-1-(2-oxo-2-pyridin-2-yl-ethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane formate formate anion
C229	(R)-1-(2-(2-methylthiazol-4-yl)-2-oxoethyl)-3-((R)-2-phenyl-2-(phenylamino)acetoxy)-1-azoniabicyclo[2.2.2]octane bromide
C233	(R)-1-(6-amino-pyridin-2-ylmethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate trifluoroacetate anion
C234	(R)-3-{2-[(4-fluoro-phenyl)-methyl-amino]-2-phenyl-acetoxy}-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane chloride

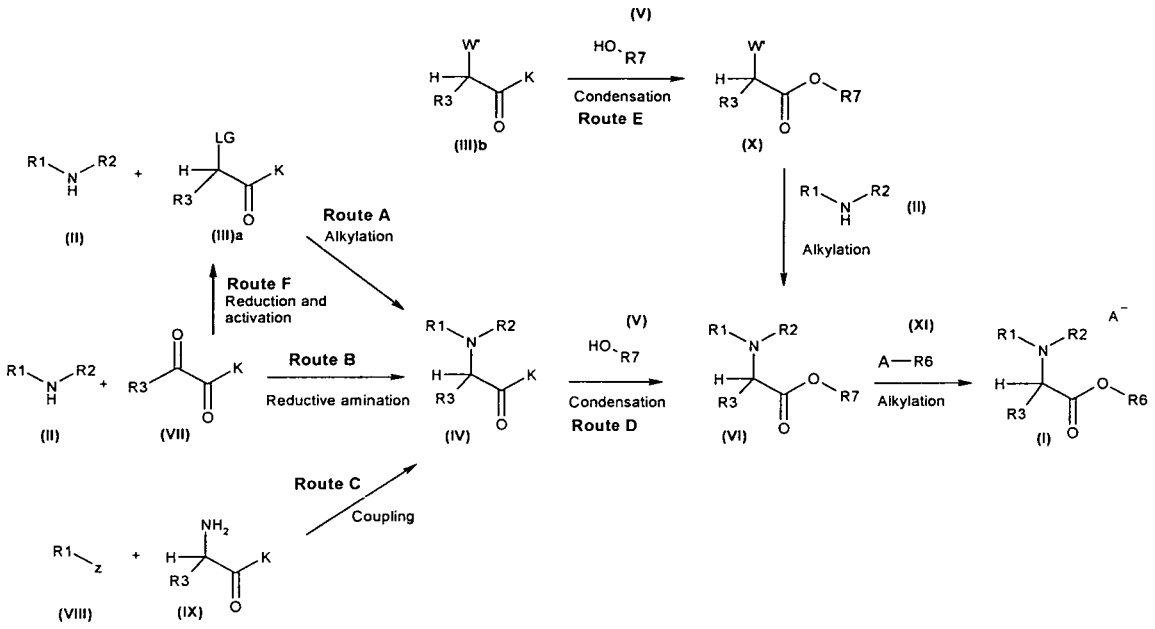
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C235	(R)-3-[2-(methyl-phenyl-amino)-2-phenyl-acetoxy]-1-(2-oxo-2-thiazol-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C236	(R)-3-[2-(methyl-phenyl-amino)-2-phenyl-acetoxy]-1-(2-oxo-2-thiophen-3-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane
C237	(R)-3-(2-benzylamino-2-phenyl-acetoxy)-1-[2-(3-ethoxycarbonyl-isoxazol-5-yl)-2-oxo-ethyl]-1-azonia-bicyclo[2.2.2]octane bromide
C238	(R)-3-(2-benzylamino-2-phenyl-acetoxy)-1-(2-oxo-2-thiazol-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate trifluoroacetate anion
C239	(R)-3-(2-benzylamino-2-phenyl-acetoxy)-1-(2-oxo-2-thiophen-3-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C240	(R)-3-[2-(4-methyl-benzylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane formate formate anion
C241	(R)-3-[2-(4-methoxy-benzylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane formate formate anion
C242	(R)-3-[2-(4-fluoro-benzylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane chloride
C243	(R)-3-[2-(4-fluoro-benzylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide
C245	4-methyl-phenyl-amino-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C246	(R)-1-(2-oxo-2-phenyl-ethyl)-3-(2-phenyl-4-methyl-phenyl-amino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide
C248	(2-fluoro-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C249	(R)-3-[2-(2-fluoro-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

(continue)

C250	(R)-3-[2-(3-fluoro-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C251	(R)-3-[2-(3-fluoro-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C254	(R)-(4-fluoro-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C255	(R)-3-[(R)-2-(4-fluoro-phenylamino)-2-phenyl-acetoxyl-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane chloride
C257	(4-chloro-phenyl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C258	(R)-3-[2-(4-chloro-phenyl)-2-phenylamino-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C262	(2-fluoro-phenyl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C263	(R)-3-[2-(2-fluoro-phenyl)-2-phenylamino-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C269	(5-methyl-thiophen-2-yl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester
C270	(R)-3-[2-(5-methyl-thiophen-2-yl)-2-phenylamino-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
C271	(R)-1-[2-(4-amino-phenyl)-2-oxo-ethyl]-3-((R)-2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane formate
C272	(R)-1-(2-hydroxy-2-phenyl-ethyl)-3-((R)-2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate

The compounds of general formula (I) and (VI) may be prepared according to methods known or evident to a person skilled in the art. Some of the processes which may be used are described below and reported in Scheme 1.



Scheme 1

Procedure for the preparation of compounds of formula (I)

Compounds of general formula (IV) may be prepared according to three different routes: A, B and C.

Route A - Alkylation of amine compounds of general formula (II), wherein R1 and R2 are as described above, with compounds of general formula (III), in which LG is a suitable leaving group (e.g. an halide such as bromine) and K may be either a hydroxyl group or a suitably protected hydroxyl group (e.g. K=OAlkyl such as OMe). The reaction may be promoted by a base selected from the group consisting of triethylamine, pyridine and 4-dimethylaminopyridine, either neat or in a suitable solvent (e.g. acetonitrile). This reaction is usually performed in a temperature range from 0°C to 130°C over a period of 1 hour up to 74 hours. The reaction may be conducted under conventional heating (using an oil bath) or under microwave heating. The reaction may be carried out in an open vessel or in a sealed tube.

Reagents of general formula (III) are commercially available or may be conveniently prepared according to standard procedures extensively reported in literature. For instance compounds of general formula (III) in which LG is a

halogen such as a bromine, may be prepared by halogenation of the opportunely substituted phenyl acetic ester (for example following the procedure reported by Epstein, J.W. in J.Med.Chem., 1981, 24/5, 481). Alternatively, compounds of general formula (III) may be prepared starting from the appropriately substituted mandelic derivative, using procedures readily apparent to those skilled in the art (a survey of the suitable reactions is given by Larock, L.C., Comprehensive Organic Transformation, Second edition (1999), John Wiley & Son Inc, pg 689-700).

Route B -. The coupling of amine of general formula (II) and ketones of general formula (VII) may be carried out using a reductive amination reaction, following one of the different procedures reported in literature (e.g.: Suwa T., Synthesis, 2000, 6, 789 or Fache, F. Tetrahedron, 1996, 52/29, 9777 or Quiang, K., Adv.Synth. Catal. 2007, 349, 1657).

Alternatively, compounds of general formula (VII) can be most conveniently converted into compounds of general formula (III) (Route F) using conditions well known to those skilled in the art. In a typical procedure, ketones (VII) are treated with a reducing agent such as sodium borohydride and the like, in a suitable solvent (e.g. ethanol and methanol) to smoothly provide the corresponding alcohol intermediate. The subsequent conversion of the alcohol moiety in a leaving group (LG) affords compounds of general formula (III). This activation can be effected according to one of the standard procedures broadly reported in the literature (a survey of the suitable reactions is given by Carey, F.A. and Sundeberg, R.J. Advanced Organic Chemistry, Third Edition (1990), Plenum Press, New York and London, pg 121). For instance, the alcohol intermediate could be treated with methanesulphonyl chloride (LG=Ms) in presence of a base such as triethylamine, pyridine, 4-dimethylaminopyridine and the like, either neat or in aprotic solvent (e.g. dichloromethane). This reaction is usually performed in a temperature range

from 0°C to 130°C over a period of 1 hour up to 74 hours.

Route C - Compound (IX) may be reacted with an alkylating agent of general formula (VIII), in which z is a suitable leaving group such as a carbonyl group or an halide (i.e. bromine, iodine, chlorine) or sulfonate ester (i.e. tosylate, triflates, mesylate), according to procedures readily available to those skilled in the art (e.g. Huang, Tetrahedron, 1997, 53/37, 12391).

In case z=O, compounds (IX) are reacted with aldehydes or ketones of general formula (VIII) to achieve the corresponding imines that are reduced to compound (IV) by treatment with a suitable reducing agent, following one of the procedures reported in literature (a survey of the suitable reactions is given by Carey, F.A. and Sundeberg, R.J. Advanced Organic Chemistry, Third Edition (1990), Plenum Press, New York and London, chapter 5, 219 or Ando, A., Tetrahedron, 1989, 45/16, 4969).

In case R1 is an aryl or heteroaryl and z is a halogen (typically a iodine or bromine), the coupling between compounds of general formula (VIII) and (IX) may be promoted by a suitable catalyst. In a typical procedure the catalyst is a copper catalyst (e.g. copper iodide), and the reaction is performed in the presence of a suitable base selected from the group consisting of potassium and cesium carbonate or amines such as triethylamine, in solvents selected from the group consisting of dimethyl sulfoxide (DMSO) and DMF, at a temperature ranging from ambient to 110°C, over a period ranging from one to 48 hours. The reaction may be carried out under conventional heating (using an oil bath) or under microwave irradiation. The reaction may be conducted either in an open vessel or in a sealed tube (Ma, D., Tetrahedron Asymmetry 1996, 7/11, 3075 or Kurokawa, M., Heterocycles, 2007, 71/4, 847).

In case R1 is an aryl or heteroaryl and z is a halogen (typically fluorine or chlorine), compound of general formula (VIII) and (IX) may react under the

typical conditions of the aromatic nucleophilic substitution to afford compound (IV).

Compounds of general formula (VI) may then be prepared according to two different routes.

Route D - Compounds of formula (VI) may be prepared by coupling alcohols of formula (V) with compounds of formula (IV).

The method for the preparation of compounds of formula (VI) from alcohols (V) and compounds (IV) is chosen on the basis of the reactivity of the alcohol (V), the commercial availability of reagents such as (IV) and the compatibility with the groups present in both the starting materials.

The coupling between (IV) and (V) may be conducted in several ways, in which K may be either a hydroxyl group or a halide such as chlorine (a survey of the suitable reactions is given by Carey, F.A. and Sundeberg, R.J. Advanced Organic Chemistry, Third Edition (1990), Plenum Press, New York and London, pg 145 and Montalbetti, C., Tetrahedron, 2005, 61, 10827).

In particular, in the case K is a protected hydroxyl group, the protecting group has to be removed before performing the coupling with (V). For instance, if K=OMe, hydrolysis of ester moiety may be performed treating the compound (IV; K=OMe) with a suitable aqueous base selected from the group consisting of sodium, lithium and potassium hydroxide in the opportune solvents (e.g. tetrahydrofuran, dioxane etc). The reaction proceeds at room temperature (RT), over a period of 1 hour up to 36 hours.

Alternative one - In a typical procedure compounds (VI) may be prepared by condensation between (V) and acid (IV) (K=OH) under standard amidation and peptide coupling conditions. For instance, treatment of the acid (IV) (K=OH) with one or more equivalents of a commercially available condensing agent such as a carbodiimide (e.g. 1-(3-dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDC) and the like) for example in the

presence of N-hydroxybenzotriazole (HOBt) followed by reaction of the activated intermediate with alcohol (V), results in the formation of compounds (VI). An organic base such as triethylamine may be also present in the reaction mixture. The activated intermediate may be either isolated, or pre-formed or generated in situ. Suitable solvents for the coupling include, but are not limited to, halocarbon solvents (e.g. dichloromethane), tetrahydrofuran, dioxane and acetonitrile. The reaction proceeds at temperature range from 0°C up to 170°C, for a time in the range of about 1 hour up to 72 hours. The reaction may be carried out under conventional heating (using an oil bath) or under microwave irradiation. The reaction may be conducted either in an open vessel or in a sealed tube.

Alternative two - In the case where K is halogen such as chlorine, the alcohol (V) is reacted with the suitable acyl halide (IV), using methods that are readily apparent to those skilled in the art. The reaction may be promoted by a base such as triethylamine, pyridine and 4-dimethylaminopyridine, in a suitable solvent (e.g. dichloromethane). This reaction is performed in a temperature range from 0°C to 130°C over a period of 1 hour up to 74 hours. The reaction may be conducted under conventional heating (using an oil bath) or under microwave heating. The reaction may be carried out in an open vessel or in a sealed tube.

In some embodiments of the present invention, the needed acyl halide (IV) may be readily prepared from the corresponding acid (IV) (K=OH). This activation may be effected according to one of the standard procedures reported in the literature. For instance, treatment of acid (IV) (K=OH) with one or more equivalents of oxalyl chloride in the presence of a catalytic amount of dimethylformamide (DMF) in a halocarbon solvent, such as dichloromethane, at temperature ranging form 0°C to 35°C, affords the required acyl chloride (IV) (K=Cl).

Alternative three - Alternatively, acylation of alcohol (V) to give compounds of general formula (VI) may be accomplished using procedures which convert in situ the acid (IV) (K=OH) into the corresponding acyl halides. For example, alcohols (V) are reacted with acids (IV) (K=OH) in presence of triphenylphosphine and a halocarbon solvent such as carbon tetrachloride or dichloromethane, at about RT, in a maximum period of time of 16 hours (Lee, J.B. J.Am.Chem.Soc., 1966, 88, 3440).

Alternative four - In another process for the preparation of the compounds of the present invention, acid (IV) (K=OH) may be activated with other commercially available activating agents such as bromotripyrrolidinophosphonium hexafluorophosphate (PyBrOP) or carbonylimidazole, in the suitable aprotic solvent (e.g. dichloromethane, tetrahydrofuran), at about RT. Subsequent reaction of the activated intermediate with alcohol (V) provides the desired compound of formula (VI). The reaction may also require the use of an organic base such as diisopropylethylamine and usually proceeds at about RT.

Alternative five - In another process for the preparation of the compounds of the present invention, compounds (VI) can be efficiently prepared by the condensation between acids (IV) (K=OH) and alcohol (V) under typical Mitsunobu conditions (Kumara Swamy, K.C., Chem. Rev. 2009, 109, 2551-2651). For example, acids (IV) and alcohol (V) are reacted in presence of a phosphine (e.g. triphenylphosphine) and an azadicarboxylate ester (e.g. diethyl azodicarboxylate or diisopropyl azodicarboxylate) in an aprotic solvent such as tetrahydrofuran. The reaction typically proceeds at temperature range from 0°C up to 100°C, for a time in the range of about 30 minutes up to 72 hours.

Alternatively compounds of formula (VI) may be prepared according to route E.

W' may be LG or hydroxy. Compounds of general formula (III) may be coupled to compound of general formula (V) to yield compound (X), applying one of the procedures readily apparent to those skilled in the art. For instance, the conditions used to perform the coupling may be selected among those described to produce the coupling between compound (IV) and (V) in Scheme 1.

In case W' is a halide, the resulting intermediate (X) may then be used as the alkylating agent of amines of general formula (II) to furnish the desired intermediate (VI). This reaction may be performed under the typical conditions extensively reported in literature, such as those described to obtain compound (IV) by coupling (II) and (III) (Scheme 1).

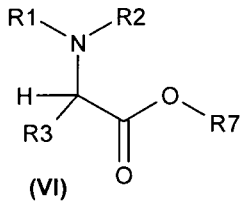
In case W' in compound (III) is hydroxy, it must be converted into a opportune leaving group selected from the group consisting of halide (i.e. bromine, iodine, chlorine) and sulfonate ester (i.e. tosylate, triflates, mesylate), according to procedures available to those skilled in the art (a general overview is given by Carey, F.A. and Sundeberg, R.J. Advanced Organic Chemistry, Third Edition (1990), Plenum Press, New York and London, chapter 3, 121), before performing the coupling with amines (II). In case W' is a suitably protected hydroxyl group, it must be deprotected and activated as above before performing the coupling with amines (II).

Compound of general formula (VI), in which R3 and R7 are defined hereinbefore, can be achieved either as single diastereoisomer or as a mixture of diastereoisomers. For instance, in the case R7 is a group of formula (vi), the alcohol can feature either a R or a S configuration. If R-enantiomer is used, compound VI can be obtained in S-R configuration, in R-R configuration or as a mixture of diastereoisomers (R-R and S-R configuration).

The mixture of diastereoisomers may be converted to compounds of formula (I) of Scheme 1 or can be most conveniently resolved to give the two

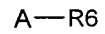
single diastereoisomers, which in turn may be converted to compounds of formula (I) of Scheme 1. This separation can be accomplished using procedures well known to those skilled in the art. These procedures include, but are not limited to, chromatography purification, preparative HPLC purification and crystallization. For example, the two diastereoisomers can be separated by flash chromatography on silica gel eluting with suitable solvents or mixture of solvents such as DCM and Methanol and the like. In another process of the present invention separation of diastereoisomers may be obtained using a column filled with a chiral stationary phase, for example Chiralpack AY or Chiralcel OD or Chiralcel OZ, and eluting, for example, with acetonitrile and/or with mixtures of acetonitrile and an alcohol. Alternatively the separation of diastereoisomers may be most conveniently achieved by crystallization from an opportune solvent (e.g. ethyl ether), as a free base or after the formation of a suitable salt (e.g. (+)-tartaric acid)).

The alkylation of compounds of general formula (VI)



(VI)

by alkylating agents of general formula (XI)



(XI)

in which A is a suitable leaving group selected from the group consisting of halide (i.e. bromine, iodine, chlorine) and sulfonate ester (i.e. tosylate, triflates, mesylate) provides compounds of general formula (I).

This kind of reaction is largely described in literature under several different conditions, for instance, the reaction may be performed neat or in a

suitable solvent selected from the group consisting of acetonitrile, DMF, DMSO and tetrahydrofuran. The reaction typically proceeds at temperature range from 0°C up to 170°C, for a time in the range of few minutes up to 72 hours. The reaction may be carried out under conventional heating (using an oil bath) or under microwave irradiation. The reaction may be conducted either in an open vessel or in a sealed tube.

Compounds of general formula (I) in Scheme 1 can be either considered as final products or can be further reacted to prepare other compounds of general formula (I). Thus, a moiety of R1, R2, R3 or R6 group in general formula (I) could undergo reactions of oxidation, reduction or cleavage (e.g to remove a needed protecting group) to afford other final compounds of general formula (I).

The present invention also provides pharmaceutical compositions of compounds of general formula (I) and (VI) 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 accomplished according to patient needs, for example, orally, nasally, parenterally (subcutaneously, intravenously, intramuscularly, intrasternally and by infusion), by inhalation, rectally, vaginally, topically, locally, transdermally, and by ocular administration.

Various solid oral dosage forms can be used for administering compounds of the invention including such solid forms as tablets, gelcaps, capsules, caplets, granules, lozenges and bulk powders. The compounds of the invention can be administered alone or combined with various pharmaceutically acceptable carriers, diluents (such as sucrose, mannitol, lactose, starches) and excipients known in the art, including but not limited to

suspending agents, solubilizers, buffering agents, binders, disintegrants, preservatives, colorants, flavorants, lubricants and the like. Time release capsules, tablets and gels are also advantageous in administering the compounds of the present invention.

Various liquid oral dosage forms can also be used for administering compounds of the invention, including aqueous and non-aqueous solutions, emulsions, suspensions, syrups, and elixirs. Such dosage forms can also contain suitable inert diluents known in the art such as water and suitable excipients known in the art such as preservatives, wetting agents, sweeteners, flavorants, as well as agents for emulsifying and/or suspending the compounds of the invention. The compounds of the present invention may be injected, for example, intravenously, in the form of an isotonic sterile solution. Other preparations are also possible.

Suppositories for rectal administration of the compounds of the present 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 suitable carriers as are known in the art.

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

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

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.

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

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

The propellant-free inhalable formulations comprising the compounds of the invention may be in form of solutions or suspensions in an aqueous, alcoholic or hydroalcoholic medium and they may be delivered by jet or ultrasonic nebulizers or by soft-mist nebulizers.

The compounds of the invention may be administered as the sole active agent or in combination with other pharmaceutical active ingredients including those currently used in the treatment of respiratory disorders, e.g. beta2-agonists, corticosteroids and anticholinergic or antimuscarinic agents.

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, 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 any disease wherein M3 antagonists are active. Said disease include: diseases involving inflammation such as asthma and COPD, acute rhinitis; diseases involving the gastrointestinal tract such as peptic ulcer; diseases involving the cardiovascular system such as acute myocardial infarction; diseases involving the genitourinary tract such as renal colic; anticholinesterase and mushroom poisoning; uses in anesthesia; uses in ophthalmology.

They also include neurological and psychiatric disorders such as Parkinsonism and motion sickness.

Preferably, the compounds of formula (I) may be administered for the prevention and/or treatment of respiratory diseases such as from mild to acute severe conditions of asthma and COPD.

Other respiratory diseases include bronchitis, bronchiolitis, bronchiectasis, acute nasopharyngitis, acute and chronic sinusitis, maxillary sinusitis, pharyngitis, tonsillitis, laryngitis, tracheitis, epiglottitis, croup, chronic disease of tonsils and adenoids, hypertrophy of tonsils and adenoids, peritonsillar abscess, rhinitis, abscess or ulcer and nose, pneumonia, viral and bacterial pneumonia, bronchopneumonia, influenza, extrinsic allergic alveolitis, coal workers' pneumoconiosis, asbestosis, pneumoconiosis, pneumonopathy, respiratory conditions due to chemical fumes, vapors and other external agents, emphysema, pleurisy, pneumothorax, abscess of lung and mediastinum, pulmonary congestion and hypostasis, postinflammatory pulmonary fibrosis, other alveolar and parietoalveolar pneumonopathy, idiopathic fibrosing alveolitis, Hamman-Rich syndrome, atelectasis, ARDS, acute respiratory failure, mediastinitis.

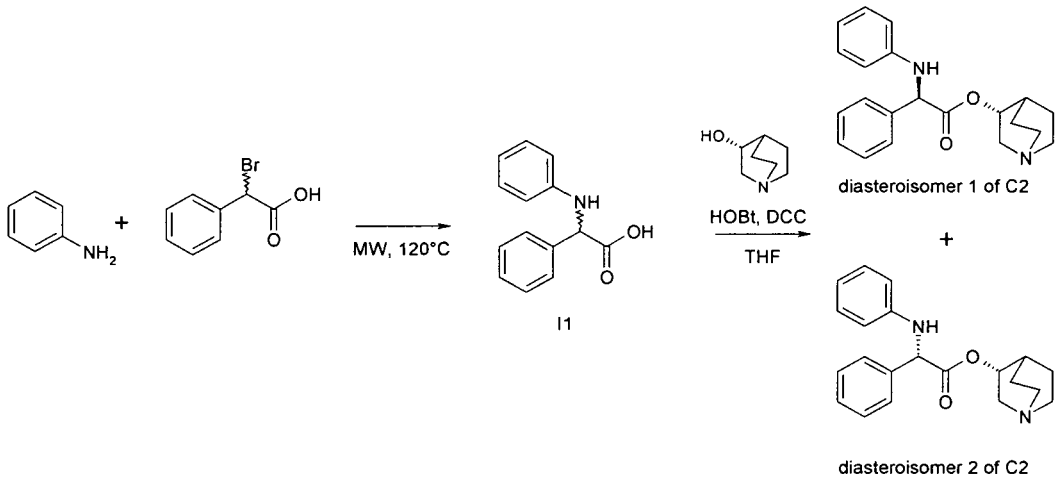
The present invention will now be further described by the following examples.

I = intermediates

C = compounds

EXAMPLE 1

Preparation of (R)-quinuclidin-3-yl 2-phenyl-2-(phenylamino)-acetate (Diastereoisomers 1 and 2 of C2)



Scheme 2

Preparation of 2-phenyl-2-(phenylamino)acetic acid (I1):

α-Bromophenylacetic acid (5.01 g, 23.2 mmol.) is dissolved in aniline (25 mL, 274 mmol) and the mixture reacted in a closed vessel under MW irradiation at 120°C for 5 min (LC-MS monitoring: complete conversion). Dichloromethane (DCM) (100 mL) is added to the reaction mixture and the resulting solid is filtered; 2M Na_2CO_3 (50 mL) is added to the solution, and the aqueous layer is washed with DCM (3x100 mL). The aqueous layer is acidified with 12N HCl (36 mL) and the title compound is recovered as racemic mixture by filtration (5.1 g, 97% yield, white solid).

Preparation of (R)-quinuclidin-3-yl 2-phenyl-2-(phenylamino)-acetate (Diastereoisomers 1 and 2 of C2)

A solution of 2-phenyl-2-(phenylamino)acetic acid (I1) (1.90 g,

8.41 mmol) in dioxane, is added with with a 4M solution of HCl in dioxane (5 mL) and the reaction is stirred at RT for 1 h; the solvent is evaporated under reduced pressure to obtain a white solid which is dissolved in dry THF (40 mL). DCC (2.12 g, 10.0 mmol), HOBt (1.33 g, 10.0 mmol) and 3(R)-quinuclidinol (3.10 g, 25.1 mmol) are added to the resulting solution and the mixture is stirred for 96 h at RT under nitrogen flowstream (LC-MS monitoring: complete conversion). The solvent is evaporated, 1N HCl (50 mL) is added to the resulting crude and the aqueous layer is washed with EtOAc (2x100 mL); a saturated solution of $NaHCO_3$ is added to the aqueous layer (pH=7-8) and the desired compound is extracted with DCM. The resulting crude is purified by flash chromatography (DCM/MeOH=95/5, 0.1% NH_3 (aq.)) recovering diastereoisomer 1 of C2 as a white solid (0.8 g; 28% yield, single diastereoisomer), and subsequently diastereoisomer 2 of C2 as a white solid (0.4 g, 14% yield, single diastereoisomer).

Diastereoisomer 1 of C2 (80 mg) is further purified by preparative LC-MS to obtain 55.3 mg of a pale yellow oil (TFA salt).

Diastereoisomer 2 of C2 (65 mg) is further purified by preparative LC-MS to obtain 28.3 mg of a pale yellow oil (TFA salt).

Diastereoisomer 1 of C2:

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 9.38 (br. s., 1H), 7.50 - 7.72 (m, 2H), 7.26 - 7.50 (m, 3H), 6.98 - 7.25 (m, 2H), 6.68 - 6.83 (m, 2H), 6.52 - 6.68 (m, 1H), 5.34 (s, 1H), 4.92 - 5.18 (m, 1H), 3.57 - 3.67 (m, 1H), 3.05 - 3.33 (m, 3H), 2.57 - 2.81 (m, 2H), 2.08 - 2.30 (m, 1H), 1.63 - 1.94 (m, 4H);

LC-MS (ESI POS): 337.3 (MH+);

$[\alpha]_D$= -32.0° (c=0.5, MeOH).

Diastereoisomer 2 of C2:

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 9.49 (br. s., 1H), 7.48 - 7.64 (m, 2H), 7.25 - 7.48 (m, 3H), 7.00 - 7.15 (m, 2H), 6.66 - 6.78 (m, 2H),

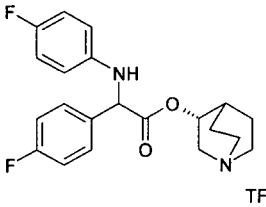
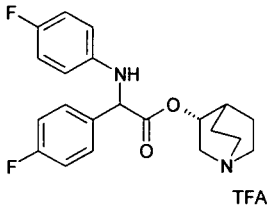
6.52 - 6.65 (m, 1H), 5.30 (s, 1H), 4.94 - 5.16 (m, 1H), 3.54 - 3.76 (m, 1H), 3.03 - 3.28 (m, 5H), 2.03 (br. s., 1H), 1.65 - 1.93 (m, 2H), 1.33 - 1.65 (m, 2H);

LC-MS (ESI POS): 337.3 (MH+);

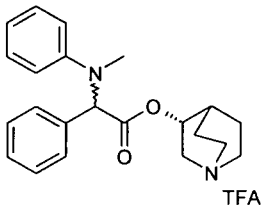
$[\alpha]_D$= 2.4° (c=0.5, MeOH).

The compounds listed in Table 1 are obtained by LC-MS purification as previously described for C2, starting from the suitable commercially available 2-bromo-phenylacetic acid derivatives and anilines.

Table 1

Compound	Structure	Yield and appearance	Analytical
Diastereoisomer 1 of C3	 TFA Single diastereoisomer	10% overall yield Pale yellow oil	LC-MS (ESI POS): 373.2 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 9.50 (br. s., 1H), 7.47 - 7.72 (m, 2H), 7.13 - 7.38 (m, 2H), 6.83 - 7.04 (m, 2H), 6.60 - 6.82 (m, 2H), 5.36 (s, 1H), 4.92 - 5.14 (m, 1H), 3.61 (ddd, 1H), 3.05 - 3.29 (m, 3H), 2.61 - 2.85 (m, 2H), 2.16 - 2.34 (m, 1H), 1.75 - 2.03 (m, 3H), 1.53 - 1.75 (m, 1H)
Diastereoisomer 2 of C3	 TFA Single diastereoisomer	8% overall yield Pale yellow oil	LC-MS (ESI POS): 373.2 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 9.58 (br. s., 1H), 7.51 - 7.67 (m, 2H), 7.15 - 7.32 (m, 2H), 6.83 - 7.02 (m, 2H), 6.58 - 6.81 (m, 2 H), 5.32 (s, 1H), 4.92 - 5.13 (m, 1H), 3.52 - 3.78 (m, 1H), 3.04 - 3.29 (m, 5H), 1.97 - 2.10 (m, 1H), 1.66 - 1.97 (m, 2H), 1.42 - 1.64 (m, 2H)

(continue)

C4	 Mixture of diastereoisomers	13% overall yield Pale yellow oil	LC-MS (ESI POS): 351.3 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 9.57 (br. s., 1H), 7.31 - 7.57 (m, 5H), 7.14 - 7.31 (m, 2H), 6.85 - 7.02 (m, 2H), 6.67 - 6.85 (m, 1H), 5.92 (s, 1H), 5.00 - 5.27 (m, 1H), 3.59 - 3.76 (m, 1H), 2.79 - 3.29 (m, 5H), 2.75 (s, 3H), 2.08 - 2.24 (m, 1H), 1.73 - 2.00 (m, 2H), 1.45 - 1.73 (m, 2H)

EXAMPLE 2

Alternative preparation of (R)-quinuclidin-3-yl 2-phenyl-2-(phenylamino)-acetate (Diastereoisomers 1 and 2 of C2):

A solution of 2-phenyl-2-(phenylamino)acetic acid (I1) (3.40 g, 14.9 mmol) in THF (600 mL), is added with with DCC (4.02 g, 19.4 mmol), HOBt (3.06 g, 19.44 mmol) and 3(R)–quinuclidinol (3.80 g, 29.9 mmol). The resulting mixture is stirred for 16 h at RT (LC-MS monitoring: complete conversion). The solvent is evaporated, the residue is taken up with EtOAc and the insoluble is filtered off. The clear solution is washed with 1M K_2CO_3 and then with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The resulting crude is purified by flash chromatography (DCM/MeOH=95/5, 0.1% NH_3 (aq.)) recovering first diastereoisomer 1 of C2 as a white solid (1.13 g, 22.5% yield, single diastereoisomer), and subsequently diastereoisomer 2 of C2 as a white solid (0.69 g, 13.7% yield, single diastereoisomer).

Diastereoisomer 1 of C2:

^1H NMR (300 MHz, DMSO-d_6) ppm: 7.48 - 7.59 (m, 2 H), 7.26 - 7.46 (m, 3 H), 7.02 - 7.14 (m, 2 H), 6.67 - 6.79 (m, 2 H), 6.51 - 6.64 (m, 1 H), 6.27 (d, 1 H), 5.26 (d, 1 H), 4.61 - 4.78 (m, 1 H), 2.96 (ddd, 1 H), 2.55 - 2.67 (m, 3 H), 2.16 - 2.37 (m, 1 H), 2.06 (d, 1 H), 1.79 - 1.94 (m, 1 H), 1.59 - 1.76 (m, 1 H), 1.35 - 1.59

(m, 2 H), 1.20 - 1.34 (m, 1 H);

LC-MS (ESI POS): 337.04 (MH+);

$[\alpha]_D$= -44.6 (c=0.25 MeOH).

Diastereoisomer 2 of C2:

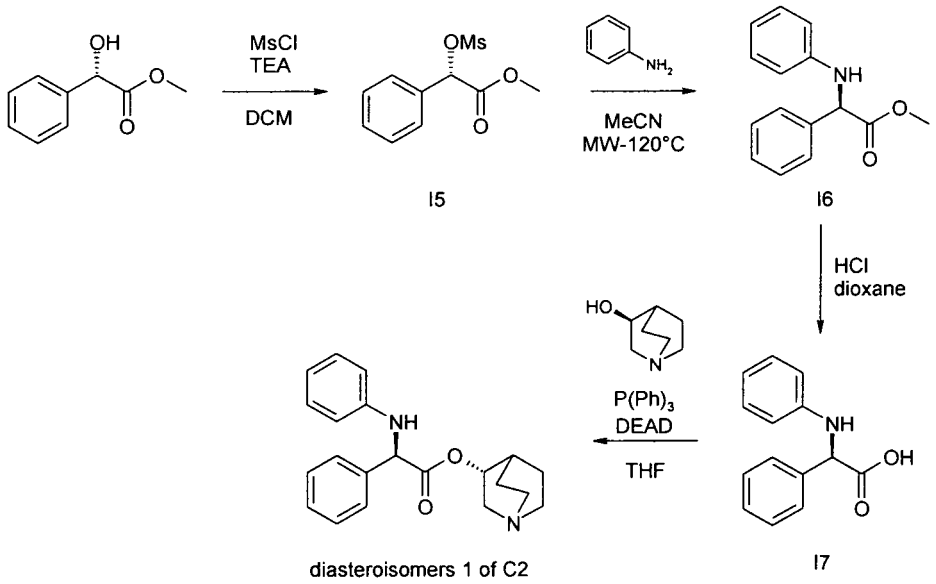
^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.48 - 7.60 (m, 2 H), 7.24 - 7.43 (m, 3 H), 6.97 - 7.14 (m, 2 H), 6.66 - 6.78 (m, 2 H), 6.51 - 6.66 (m, 1 H), 6.26 (d, 1 H), 5.24 (d, 1 H), 4.62 - 4.81 (m, 1 H), 3.08 (ddd, 1 H), 2.54 - 2.70 (m, 5 H), 1.64 - 1.79 (m, 1 H), 1.32 - 1.64 (m, 2 H), 1.16 - 1.32 (m, 1 H), 0.93 - 1.16 (m, 1 H);

LC-MS (ESI POS): 337.04 (MH+);

$[\alpha]_D$= +27.6 (c= 0.25 MeOH)

EXAMPLE 3

Alternative preparation of (R)-phenyl-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (Diastereoisomers 1 of C2)



Scheme 3

Preparation of (S)-methyl 2-(methylsulfonyloxy)-2-phenylacetate (I5):

A solution of (S)-methyl 2-hydroxy-2-phenylacetate (20.0 g, 120 mmol) in DCM (240 mL) maintained at 0°C under N_2 flowstream, is added with mesylchloride (11.2 mL, 144 mmol) and TEA (20.1 mL, 144 mmol) and the

mixture is stirred at RT for 1 h (UPLC-MS monitoring: complete conversion). The mixture is cooled to 0°C, 0.1N HCl (240 mL) is added and the desired compound is extracted with DCM (2x200 mL). The combined DCM phases are dried over Na_2SO_4, filtered and evaporated to dryness. The resulting crude is purified by filtration through a silica bed eluting with DCM, obtaining 22.4 g of the title compound as white solid (76% yield).

Preparation of (R)-methyl 2-phenyl-2-(phenylamino)acetate (I6):

Aniline (16.8 mL, 184 mmol) is added to a solution of (S)-methyl 2-(methylsulfonyloxy)-2-phenylacetate (I5) (22.4 g, 92.0 mmol) in CH_3CN (50 mL). The mixture is heated under MW irradiation at 120°C for 5 min (UPLC-MS monitoring: complete conversion). The resulting crude is partitioned between EtOAc (200 mL) and 1N HCl (200 mL) and the aqueous phase is extracted with EtOAc (3x200 mL). The combined organic layers are dried over Na_2SO_4, filtered and evaporated under vacuum to obtain 20.3 g of a pale yellow solid (92% yield), which is used in the next step without further purification.

Preparation of (R)-2-phenyl-2-(phenylamino)acetic acid (I7):

12N HCl (85 mL) is added to a solution of (R)-methyl 2-phenyl-2-(phenylamino)acetate (I6) (20.3 g, 84.0 mmol), in dioxane (85 mL) and the mixture is heated at 70°C for 18 h (UPLC-MS monitoring: complete conversion). The dioxane is evaporated, the mixture is cooled to 0°C and the resulting solid is collected by filtration to obtain 19.1g of intermediate I7 as a white solid (99% yield).

Preparation of (R)-((R)-quinuclidin-3-yl) 2-phenyl-2-(phenylamino)acetate) (Diastereoisomers 1 of C2):

(R)-2-Phenyl-2-(phenylamino)acetic acid (I7) (6.50 g, 28.7 mmol), is dissolved in dry THF (140 mL) under inert atmosphere. 3S-Quinuclidinol (4.0 g, 31.6 mmol), triphenylphosphine (8.90 g, 43.0 mmol) and diethyl azodicarboxylate (6.8 mL, 43.0 mmol) are added and the resulting

mixture is refluxed for 30 min (UPLC-MS monitoring: complete conversion). The solvent is evaporated and the residue is partitioned between water (100 mL) and EtOAc (100 mL). The aqueous phase is further extracted with EtOAc (3x100 mL). The combined organic layers are dried over Na_2SO_4, filtered and evaporated under vacuum. The resulting crude is purified by flash chromatography (DCM/MeOH=95/5) recovering 8.7 g of diastereoisomer 1 of compound C2 as a pale yellow solid (90% yield, single diastereoisomer).

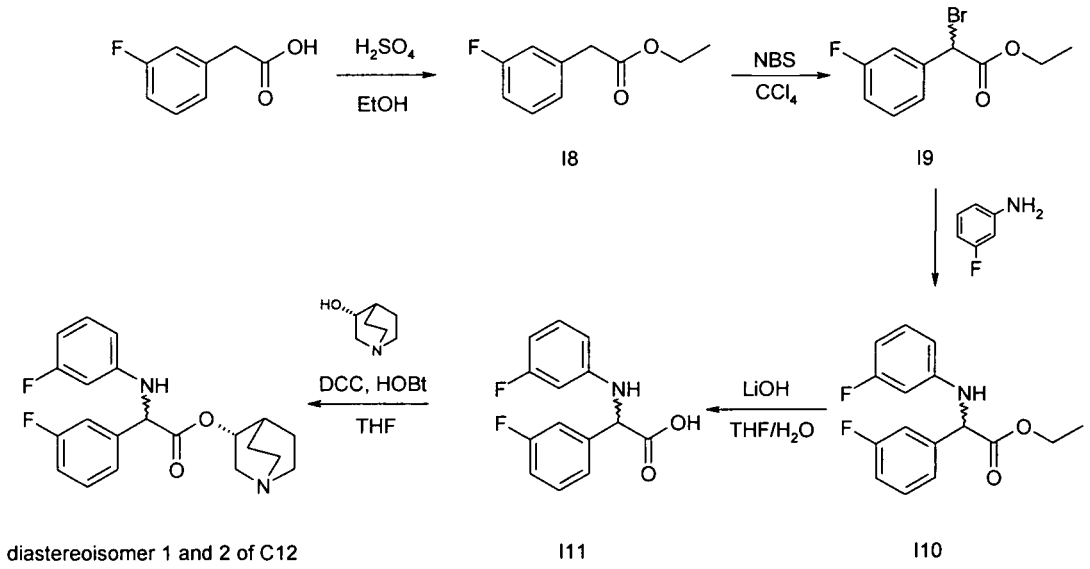
Diastereoisomer 1 of C2:

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.49 - 7.58 (m, 2 H) 7.25 - 7.47 (m, 3 H) 7.00 - 7.12 (m, 2 H) 6.66 - 6.78 (m, 2 H) 6.51 - 6.63 (m, 1 H) 6.27 (d, 1 H) 5.20 - 5.31 (m, 1 H) 4.62 - 4.73 (m, 1 H) 2.95 (ddd, 1 H) 2.53 - 2.68 (m, 3 H) 2.17 - 2.34 (m, 1 H) 2.01 - 2.13 (m, 1 H) 1.83 - 1.93 (m, 1 H) 1.38 - 1.71 (m, 3 H) 1.17 - 1.34 (m, 1 H)

LC-MS (ESI POS): 337.2 (MH+).

EXAMPLE 4

Preparation of (R)-quinuclidin-3-yl 2-(3-fluorophenyl)-2-(3-fluorophenylamino)acetate (Diastereoisomer 1 and 2 of C12)



Scheme 4

Preparation of ethyl 2-(3-fluorophenyl)acetate (I8):

A solution of 3-fluorophenyl acetic acid (10.0 g, 64.9 mmol) in ethanol

(300 mL), is added with a catalytic amount of H_2SO_4 (98%, 1 mL) and the mixture reacted for 12 h at 100°C (LC-MS monitoring: complete conversion). The solvent is evaporated and the residue is partitioned between EtOAc and water; the organic layer is separated and dried over Na_2SO_4 to obtain 10.1 g of (I8) as a white solid (85% yield).

Preparation of ethyl 2-bromo-2-(3-fluorophenyl)acetate (I9):

A solution of ethyl 2-(3-fluorophenyl)acetate (I8) (10.1 g, 55.0 mmol) in CCl_4 (250 mL), is added with NBS (9.70 g, 55.0 mmol) and the mixture refluxed for 2 h at 80°C (LC-MS monitoring: complete conversion). The solvent is evaporated and the resulting crude is dissolved in DCM and purified by filtration on a silica bed to obtain 7.80 g of (I9) as a colorless oil (54% yield).

Preparation of ethyl 2-(3-fluorophenyl)-2-(3-fluorophenylamino)-acetate (I10):

A solution of ethyl 2-bromo-2-(3-fluorophenyl)acetate (I9) (1.80 g, 6.84 mmol) in 3-fluoroaniline (6.50 mL, 68.0 mmol) is heated at 100°C for 5 min under MW irradiation (LC-MS monitoring: complete conversion). The solvent is evaporated and the resulting crude is purified by flash chromatography (Hexane/EtOAc=9/1) to obtain 2.00 g of I10 as a yellow oil (99% yield).

Preparation of 2-(3-fluorophenyl)-2-(3-fluorophenylamino)acetic acid (I11):

A solution of ethyl 2-(3-fluorophenyl)-2-(3-fluorophenylamino)-acetate (2.00 g, 6.81 mmol) in THF/H_2O (1:1 mixture, 10 mL), is added with LiOH (816 mg, 34.0 mmol) and the mixture is reacted for 2 h at RT (LC-MS monitoring: complete conversion). 1N HCl (15 mL) is added and the desired compound is extracted with EtOAc. The resulting crude is purified by flash chromatography (Hexane/EtOAc=1/1) to obtain 1.79 g of I11 as a pale yellow solid (99% yield).

Preparation of (R)-quinuclidin-3-yl 2-(3-fluorophenyl)-2-(3-

fluorophenylamino)acetate (Diastereoisomer 1 and 2 of C12):

A solution of 2-(3-fluorophenyl)-2-(3-fluorophenylamino)acetic acid (I11) (1.79 g, 6.80 mmol) in dioxane (70 mL), is added with a 4M solution of HCl in dioxane (5 mL). The reaction is stirred at RT for 1 h, then the solvent is evaporated under reduced pressure to obtain a white solid. The compound is dissolved in dry THF (70 mL) and DCC (1.71 g, 8.20 mmol), HOBt (1.10 g, 8.20 mmol) and 3(R)-quinuclidinol (2.60 g, 20.4 mmol) are added. The reaction is stirred at RT for 96h under nitrogen flowstream (LC-MS monitoring: complete conversion). The solvent is evaporated and the residue is partitioned between EtOAc and water; the organic layer is separated, dried over Na_2SO_4, filtered and evaporated to dryness. The crude is purified by flash chromatography (DCM/MeOH=97/3) recovering first 150 mg of diastereoisomer 1 of C51 as pale yellow solid (6% yield, single diastereoisomer) and subsequently 830 mg of mixture of diastereoisomers 1 and 2 of C12 as a pale yellow oil (32% yield, mixture of diastereoisomers).

Diastereoisomer 1 of C12 (80 mg) is further purified by preparative LC-MS to obtain 53.0 mg of a pale yellow oil (TFA salt).

Diastereoisomer 1 of C12

^{1}H NMR (300 MHz, DMSO-d6) ppm: 9.48 (br. s., 1 H), 7.31 - 7.58 (m, 3 H), 7.15 - 7.26 (m, 1 H), 7.10 (td, 1 H), 6.77 (d, 1 H), 6.47 - 6.65 (m, 2 H), 6.27 - 6.47 (m, 1 H), 5.48 (d, 1 H), 4.95 - 5.20 (m, 1 H), 3.63 (ddd, 1 H), 3.07 - 3.31 (m, 3 H), 2.74 - 2.91 (m, 2 H), 2.16 - 2.33 (m, 1 H), 1.65 - 1.95 (m, 4 H);

LC-MS (ESI POS): 373.2 (MH^+);

$[\alpha]_D$= -37.80° (c=0.2, MeOH).

Mixture of diastereoisomers 1 and 2 of C12

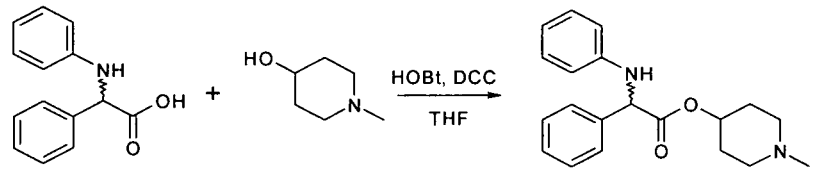
1H NMR (300 MHz, DMSO-d6) ppm: 9.58 (br. s., 1 H), 7.31 - 7.58 (m, 3 H), 7.15 - 7.26 (m, 1 H), 7.10 (td, 1 H), 6.77 (d, 1 H), 6.47 - 6.65 (m, 2 H), 6.27 - 6.47 (m, 1 H), 5.44 (d, 1 H), 4.95 - 5.20 (m, 1 H), 3.67 (ddd, 1 H), 3.07

- 3.31 (m, 3 H), 2.74 - 2.91 (m, 2 H), 2.05 (m, 1 H), 1.65 - 1.95 (m, 4 H);

LC-MS (ESI POS): 373.2 (MH^+).

EXAMPLE 5

Preparation of (R)-1-methylpiperidin-4-yl-2-phenyl-2-(phenylamino)-acetate (C13)



I1 C13

Scheme 5

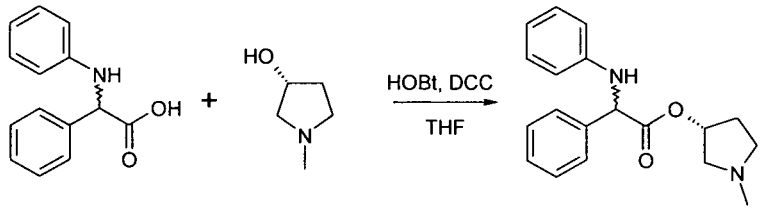
A solution of 2-phenyl-2-(phenylamino)acetic acid (I1) (234 mg, 0.91 mmol) in dioxane, is added with a 4M solution of HCl in dioxane (5 mL) and the reaction is stirred at RT for 1 h; the solvent is evaporated under reduced pressure to obtain a white solid which is dissolved in dry THF (10 mL). DCC (222 mg, 1.12 mmol), HOBt (144 mg, 1.14 mmol) and N-methyl-4-piperidinol (307 mg, 2.71 mmol) are added and the mixture is stirred for 96h at RT under nitrogen flowstream (LC-MS monitoring: complete conversion). The solvent is evaporated and the residue is partitioned between DCM and water; the organic layer is separated and dried over Na_2SO_4. The crude compound is purified by preparative LC-MS and the collected fractions are portioned between 2M K_2CO_3 and EtOAc. The organic phase is dried over Na_2SO_4, filtered and evaporated to dryness to obtain 20.6 mg of the title compound as a white solid (7% yield, racemic mixture).

^1H NMR (300 MHz, DMSO-d6) ppm: 7.45 - 7.60 (m, 2H), 7.20 - 7.45 (m, 3H), 6.95 - 7.17 (m, 2H), 6.69 (d, 2H), 6.47 - 6.63 (m, 1H), 6.23 (d, 1H), 5.20 (d, 1H), 4.71 (tt, 1H), 2.34 - 2.48 (m, 1H), 2.11 - 2.25 (m, 2H), 2.09 (s, 3H), 1.94 - 2.08 (m, 1H), 1.71 - 1.90 (m, 1H), 1.51 - 1.71 (m, 2H), 1.29 - 1.51 (m, 1H);

LC-MS (ESI POS): 325.2 (MH^+).

EXAMPLE 6

Preparation of (R)-1-methylpyrrolidin-4-yl-2-phenyl-2-(phenylamino)acetate (C14)



I1 C14

Scheme 6

A mixture of 2-phenyl-2-(phenylamino)acetic acid (I1) (200 mg, 0.88 mmol), DCC (218 mg, 1.05 mmol), HOBt (142 mg, 1.05 mmol) and (R)-1-methylpyrrolidin-3-ol (289 uL, 2.64 mmol) in dry THF (10 mL) is stirred at room temperature overnight under nitrogen flowstream (LC-MS monitoring: complete conversion). The solvent is evaporated and the residue is taken up with aq. HCl (pH about 2) and washed with DCM. The aqueous phase is basified with $NaHCO_3$ and extracted with DCM (three times). The organic layers are combined, dried over Na_2SO_4, filtered and evaporated to dryness. The resulting crude is first purified by flash chromatography (DCM to DCM/MeOH=95/5) and then by preparative LC-MS. The purified compound is partitioned between sat. $NaHCO_3$ and DCM, the organic phase is dried over Na_2SO_4, filtered and evaporated under vacuum to give 90.8 mg of the title compound as brown oil (33% yield, mixture of diastereoisomers).

^1H NMR (300 MHz, CHLOROFORM-d) ppm

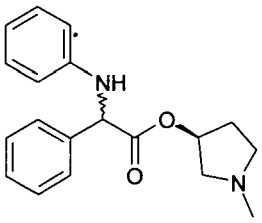
Diastereoisomer 1 of C14: 7.46 - 7.57 (m, 2 H), 7.29 - 7.45 (m, 3 H), 7.08 - 7.21 (m, 2 H), 6.67 - 6.81 (m, 1 H), 6.50 - 6.67 (m, 2 H), 5.20 - 5.37 (m, 1 H), 5.12 (d, 1 H), 4.84 - 5.05 (m, 1 H), 2.46 - 3.04 (m, 4 H), 2.44 (s, 3 H), 2.10 - 2.26 (m, 1 H), 1.63 - 1.82 (m, 1 H).

Diastereoisomer 2 of C14: 7.46 - 7.57 (m, 2 H), 7.29 - 7.45 (m, 3 H), 7.08 - 7.21 (m, 2 H), 6.67 - 6.81 (m, 1 H), 6.50 - 6.67 (m, 2 H), 5.20 - 5.37 (m, 1 H), 5.12 (d, 1 H), 4.84 - 5.05 (m, 1 H), 2.46 - 3.04 (m, 4 H), 2.33 (s, 3 H), 2.26 - 2.40 (m, 1 H), 1.86 - 2.05 (m, 1 H);

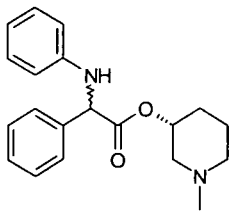
LC-MS (ESI POS): 311.3 (MH^+).

The compounds listed in Table 2 are prepared as previously described for diastereoisomers 1 and 2 of C14, coupling acid I1 with the commercially available (S)-1-methylpyrrolidin-3-ol and (R)-1-methylpiperidin-3-ol respectively.

Table 2

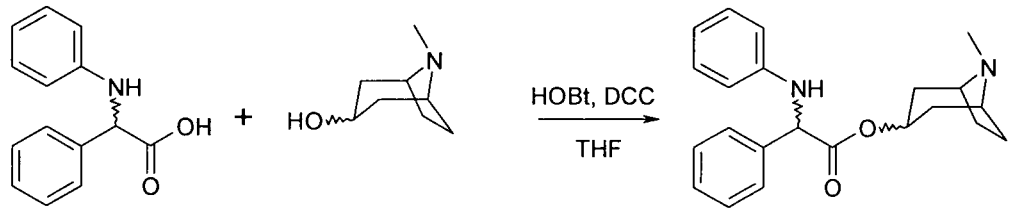
Compound	Structure	Yield and appearance	Analytical
C15	 Mixture of diastereoisomers	28% yield Colorless oil	LC-MS (ESI POS): 311.2 (MH^+) '1H NMR (300 MHz, CHLOROFORM-d) ppm Diastereoisomer 1 of C12: 7.46 - 7.57 (m, 2 H), 7.29 - 7.45 (m, 3 H), 7.08 - 7.21 (m, 2 H), 6.67 - 6.81 (m, 1 H), 6.50 - 6.67 (m, 2 H), 5.20 - 5.37 (m, 1 H), 5.12 (d, 1 H), 4.84 - 5.05 (m, 1 H), 2.46 - 3.04 (m, 4 H), 2.44 (s, 3 H), 2.10 - 2.26 (m, 1 H), 1.63 - 1.82 (m, 1 H) Diastereoisomer 2 of C12: 7.46 - 7.57 (m, 2 H), 7.29 - 7.45 (m, 3 H), 7.08 - 7.21 (m, 2 H), 6.67 - 6.81 (m, 1 H), 6.50 - 6.67 (m, 2 H), 5.20 - 5.37 (m, 1 H), 5.12 (d, 1 H), 4.84 - 5.05 (m, 1 H), 2.46 - 3.04 (m, 4 H), 2.33 (s, 3 H), 2.26 - 2.40 (m, 1 H), 1.86 - 2.05 (m, 1 H)

(continue)

C16	 Mixture of diastereoisomers	20% yield Colorless oil	LC-MS (ESI POS): 325.3 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.45 - 7.69 (m, 2 H), 7.22 - 7.45 (m, 3 H), 6.91 - 7.22 (m, 2 H), 6.66 - 6.91 (m, 2 H), 6.42 - 6.66 (m, 1 H), 6.27 (br. s., 1 H), 5.20 (s, 1 H), 4.77 (br. s., 1 H), 2.53 - 3.00 (m, 2 H), 1.64 - 2.44 (m, 6 H), 0.90 - 1.62 (m, 3 H)

EXAMPLE 7

Preparation of 8-methyl-8-azabicyclo[3.2.1]octan-3-yl 2-phenyl-2-(phenylamino)acetate (C17)



I1 C17

Scheme 7

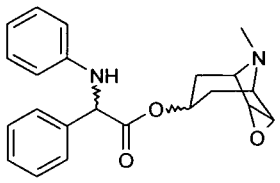
A mixture of 2-phenyl-2-(phenylamino)acetic acid I1 (250 mg, 0.90 mmol), EDC (255 mg, 1.35 mmol), HOBt (245 mg, 1.80 mmol) and 8-methyl-8-azabicyclo[3.2.1]octan-3-ol (380 mg, 2.71 mmol) in dry DMF (10 mL) is heated under microwave irradiation at 100°C for 1 h (LC-MS monitoring: complete conversion). The reaction is concentrated under reduced pressure and the residue is partitioned between EtOAc and water. The organic phase is dried over Na_2SO_4, filtered and evaporated to dryness. The resulting crude is purified by preparative HPLC. The collected compound is partitioned between 1N $NaHCO_3$ and DCM, the organic phase is separated dried over Na_2SO_4, filtered and evaporated under vacuum to give 20.1 mg of the title compound as a colorless oil (7% yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, CHLOROFORM-d) ppm: 7.45 - 7.57 (m, 2 H), 7.29 - 7.45 (m, 3 H), 7.04 - 7.21 (m, 2 H), 6.65 - 6.77 (m, 1 H), 6.51 - 6.65 (m, 2 H), 5.02 - 5.13 (m, 2 H), 5.00 (d, 1 H), 3.07 - 3.30 (m, 1 H), 2.81 - 3.07 (m, 1 H), 2.28 (s, 3 H), 2.19 - 2.27 (m, 1 H), 1.84 - 2.18 (m, 3 H), 1.70 - 1.82 (m, 2 H), 1.45 (d, 1 H), 1.17 (ddd, 1 H);

LC-MS (ESI POS): 351.3 (MH^+).

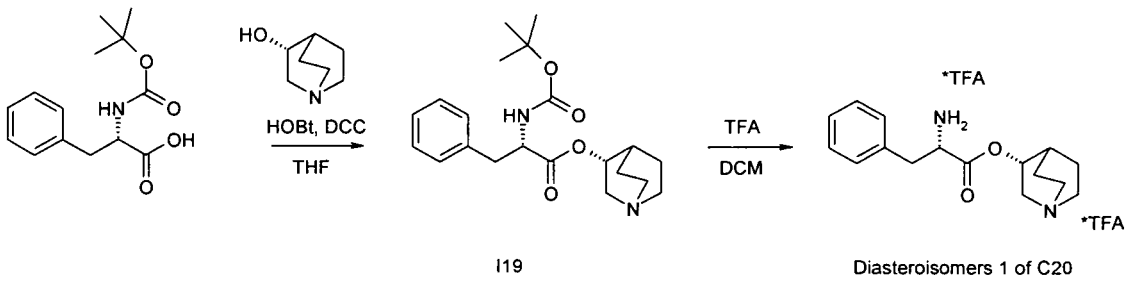
C18 listed in Table 3 is prepared as previously described for C17.

Table 3

Compound	Structure	Yield and appearance	Analytical
C18	 Mixture of diastereoisomers	5% yield Colorless oil	LC-MS (ESI POS): 365.2 (MH^+) ^{1}H NMR (300 MHz, Acetone-d6) ppm: 7.42 - 7.65 (m, 2H), 7.26 -7.46 (m, 3H), 7.01 - 7.15 (m, 2H), 6.67 - 6.76 (m, 2H), 6.56 - 6.65 (m, 1H), 5.57 - 5.65(m, 1H), 5.17 (d, 1H), 4.95 (t, 1H), 3.05 (dd, 1H), 2.89 (dd, 1H), 2.75 (d, 1H), 2.42 (s, 3H), 1.87 - 2.13(m, 2H), 1.66 (d, 1H), 1.28 (d, 1H).

EXAMPLE 8

Preparation of (S)-((R)-quinuclidin-3-yl) 2-amino-3-phenylpropanoate di-trifluoroacetate (Diastereoisomer 1 of C20)



I19 Diasteroisomers 1 of C20

Scheme 8

Preparation of (S)-((R)-quinuclidin-3-yl) 2-(tert-

butoxycarbonylamino)-3-phenylpropanoate (I19)

A solution of (S)-2-(tert-butoxycarbonylamino)-3-phenylpropanoic acid (1.03 g, 3.81 mmol) in THF (70 mL), is added with DCC (1.03 g, 4.91 mmol), HOBt (660 mg, 4.90 mmol) and 3(R)–quinuclidinol (1.18 g, 9.48 mmol) and the resulting mixture is stirred for 12hr at RT under nitrogen flowstream (LC-MS monitoring: complete conversion). The solvent is evaporated and the residue is partitioned between EtOAc (100 mL) and 2M K_2CO_3 (50 mL); the organic layer is separated, washed with brine and dried over Na_2SO_4. The resulting crude is purified by flash chromatography (DCM/MeOH=95/5, 0.1% NH_3 (aq.)) to obtain 1.12 g of I19 (80% yield).

Preparation of (S)-(R)-quinuclidin-3-yl) 2-amino-3-phenylpropanoate di-trifluoroacetate (Diastereoisomer 1 of C20)

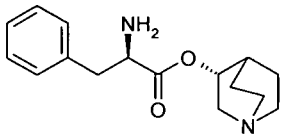
A solution of I19 (220 mg, 0.58 mmol) in DCM (5 mL), is added with trifluoroacetic acid (0.50 mL, 4.41 mmol) and the mixture stirred at RT overnight. The solvent is evaporated and the resulting crude is purified by preparative LC-MS to obtain 59.4 mg of diastereoisomer 1 of C20 as a brown gummy solid (56% yield, di-trifluoroacetate salt, single diastereoisomer).

^{1}H NMR (300 MHz, DMSO-d6) ppm: 9.81 (br. s., 1H), 8.52 (br. s., 3H), 7.24 - 7.41 (m, 5H), 5.02 - 5.09 (m, 1H), 4.20 - 4.46 (m, 1H), 3.60 - 3.73 (m, 1H), 3.00 - 3.33 (m, 7H), 2.01 (br. s., 1H), 1.79 - 1.95 (m, 1H), 1.76 (br. s., 1H), 1.60 (br. s., 2H);

LC-MS (ESI POS): 275.3 (MH^+).

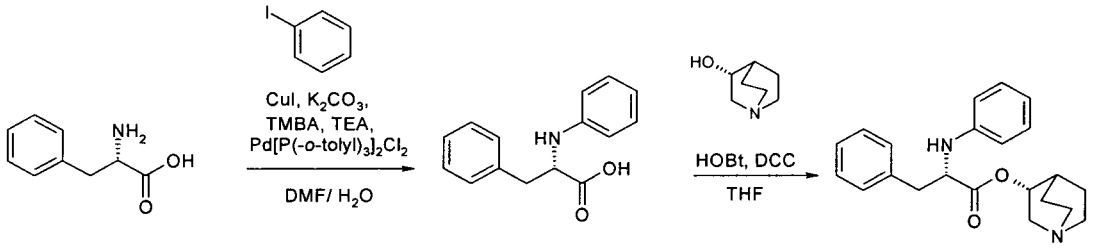
Diastereoisomer 2 of C20 listed in Table 4 is prepared as previously described for diastereoisomer 1 of C20, starting from the commercially available (R)-2-(tert-butoxycarbonylamino)-3-phenylpropanoic acid.

Table 4

Compound	Structure	Yield and appearance	Analytical
Diastereoisomer 2 of C20	 2TFA Single diastereoisomer	10% overall yield Pale yellow oil	LC-MS (ESI POS): 275.3 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 8.52 (br. s., 3H), 7.25 - 7.41 (m, 5H), 4.94 - 5.17 (m, 1H), 4.37 (dd, 1H), 3.61 (ddd, 1H), 3.00 - 3.30 (m, 5H), 2.86 - 2.97 (m, 1H), 2.82 (ddd, 1H), 2.08 - 2.22 (m, 1H), 1.61 - 1.94 (m, 4H)

EXAMPLE 9

Preparation of (S)-3-phenyl-2-phenylamino-propionic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (Diastereoisomers 1 of C22)



I21 Diasteroisomer 1 of C22

Scheme 9

Preparation of 3-phenyl-2-(phenylamino)propanoic acid (I21)

A solution of (S)-2-amino-3-phenylpropanoic acid (1.52 g, 9.12 mmol) in a DMF/H_2O mixture (10/1, 16.5 mL) maintained under nitrogen flowstream, is added with iodobenzene (1.00 mL, 9.12 mmol), dichlorobis(tri-o-tolylphosphine)palladium(II) (357 mg, 0.42 mmol) CuI (86.4 mg, 0.42 mmol), K_2CO_3 (1.21 g, 9.12 mmol), trimethylbenzylammonium chloride (286 mg, 1.51 mmol) and triethylamine (TEA) (2.50 mL, 18.0 mmol) and the mixture stirred for 24hr at 100°C under nitrogen flowstream (LC-MS monitoring: complete

conversion). The reaction mixture is partitioned between EtOAc and water; 1N HCl is added until pH =1 and the organic layer is separated, washed with brine and dried over Na_2SO_4. The resulting crude is purified by flash chromatography (DCM/MeOH=99/1) and 1.21 g of I21 is obtained (56% yield).

Preparation of (S)-3-phenyl-2-phenylamino-propionic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (Diastereoisomers 1 of C22)

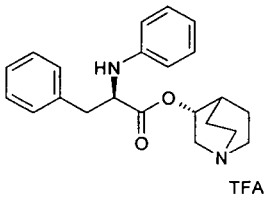
A solution of 3-phenyl-2-(phenylamino)propanoic acid (I21) (1.21 g, 5.01 mmol) in dioxane, is added with a 4M solution of HCl in dioxane (5 mL) and the reaction is stirred at RT for 1 hr; the solvent is evaporated under reduced pressure to obtain a white solid which is dissolved in dry THF (70 mL). DCC (1.22 g, 6.01 mmol), HOBt (0.8 g, 6.0 mmol) and 3(R)-quinuclidinol (1.31 g, 10.1 mmol) are added to the resulting solution and the mixture stirred for 24hr at RT under nitrogen flowstream (LC-MS monitoring: complete conversion). The solvent is evaporated. 1N HCl (20 mL) is added to the resulting crude and the aqueous layer is washed with EtOAc (2x50 mL); $NaHCO_3$ is added to the aqueous layer (pH=7-8) and the product is extracted with DCM and dried over Na_2SO_4, to obtain 530 mg (35% yield) of diastereoisomer 1 of C22, which is further purified by preparative LC-MS to obtain the title product as a brown oil (mixture of diastereoisomers that contains 20% of diastereoisomer 2 of C22, TFA salt).

^{1}H NMR (300 MHz, DMSO-d6) ppm: 9.58 (br. s., 1H), 7.19 - 7.38 (m, 5H), 6.91 - 7.15 (m, 2H), 6.55 - 6.68 (m, 3H), 4.94 (ddd, 1H), 4.34 (t, 1H), 3.62 (ddd, 1H), 2.92 - 3.25 (m, 7H), 1.63 - 1.95 (m, 3H), 1.36 - 1.63 (m, 2H);

LC-MS (ESI POS): 351.3 (MH^+).

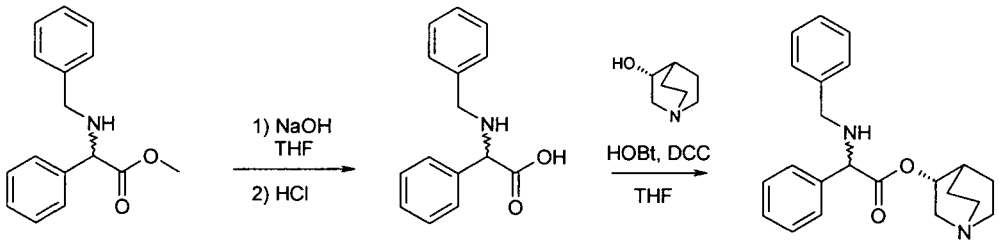
Diastereoisomer 2 of C22 listed in Table 5 is obtained as previously described for diastereoisomer 1 of C22, starting from the commercially available (R)-2-amino-3-phenylpropanoic acid.

Table 5

Compound	Structure	Yield and appearance	Analytical
Diastereoisomer 2 of C22	 TFA Single diastereoisomer	7% overall yield Brown oil	LC-MS (ESI POS): 351.3 (MH^+) ^1H NMR (300 MHz, DMSO-d6 +Na_2CO_3) ppm: 7.15 - 7.43 (m, 5H), 6.96 - 7.15 (m, 2H), 6.47 - 6.69 (m, 3H), 6.03 (d, 1H), 4.43 - 4.67 (m, 1H), 4.10 - 4.41 (m, 1H), 2.95 - 3.18 (m, 2H), 2.80 - 2.95 (m, 1H), 2.54 - 2.63 (m, 3H), 2.30 - 2.45 (m, 1H), 1.89 - 2.06 (m, 1H), 1.69 - 1.84 (m, 1H), 1.39 - 1.58 (m, 3H)

EXAMPLE 10

Preparation of (R)-quinuclidin-3-yl 2-(benzylamino)-2-phenylacetate (C24)



I23 C24

Scheme 10

Preparation of 2-(benzylamino)-2-phenylacetic acid (I23):

A solution of methyl 2-(benzylamino)-2-phenylacetate (1.00 g, 3.90 mmol) in THF (90 mL) and 1N NaOH (10 mL) is stirred at room temperature overnight (LC-MS monitoring: complete conversion). The solvent is removed under reduced pressure and the crude is partitioned between EtOAc and water. The aqueous phase is acidified with conc. HCl (pH about 3) and then extracted with EtOAc (three times). The organic phase is dried over Na_2SO_4, filtered and evaporated to dryness to give the title compound as a

white solid (940 mg, quantitative yield), which is used in the next step without any further purification.

Preparation of (R)-quinuclidin-3-yl 2-(benzylamino)-2-phenylacetate (Diastereoisomers 1 and 2 of C24):

A mixture of 2-(benzylamino)-2-phenylacetic acid (I23) (0.94 g, 3.90 mmol), DCC (0.97 g, 4.70 mmol), HOBt (0.63 g, 4.07 mmol) and 3(R)–quinuclidinol (1.51 g, 11.7 mmol) in dry THF (30 mL) is stirred at room temperature overnight under nitrogen flowstream (LC-MS monitoring: complete conversion). The solvent is evaporated and the residue is taken up with EtOAc and washed twice with water. The organic phase is dried over Na_2SO_4, filtered and evaporated to dryness. The resulting crude is purified by flash chromatography (DCM/MeOH=98/2, 0.2%$NH_{3(aq.)}$ to 95/5, 0.5%$NH_{3(aq.)}$) to give a mixture of diastereoisomers 1 and 2 of C24 (231 mg, 52% yield, mixture of diastereoisomers).

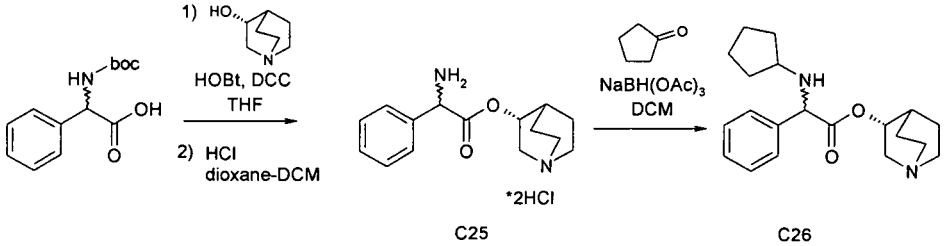
The mixture of diastereoisomers 1 and 2 of C24 (55 mg) is further purified by preparative HPLC.

^{1}H NMR (300 MHz, DMSO-d6 +Na_2CO_3) ppm: 7.20 - 7.45 (m, 11 H), 4.55 - 4.79 (m, 1 H), 4.35 (s, 1 H), 3.67 (d, 2 H), 2.85 - 3.14 (m, 2 H), 2.56 - 2.71 (m, 2 H), 2.31 - 2.46 (m, 1 H), 2.07 - 2.23 (m, 1 H), 1.82 - 1.93 (m, 1 H), 1.32 - 1.79 (m, 4 H);

LC-MS (ESI POS): 351.2 (MH^+).

EXAMPLE 11

Preparation of (R)-quinuclidin-3-yl 2-(cyclopentylamino)-2-phenylacetate di-trifluoroacetate (C26)



C25 C26

Scheme 11

Preparation of (R)-quinuclidin-3-yl 2-amino-2-phenylacetate di-hydrochloride (C25):

A mixture of 2-(tert-butoxycarbonylamino)-2-phenylacetic acid (0.90 g, 4.18 mmol), HOBt (0.68 g, 12.5 mmol), DCC (1.29 g, 6.27 mmol) and 3(R)–quinuclidinol (1.59 g, 12.5 mmol) in dry THF (50 mL) is stirred at room temperature for 16 hours (LC-MS monitoring: complete conversion). The solvent is removed under reduced pressure, the residue is taken up with EtOAc and washed twice with 2M K_2CO_3. The organic phase is dried over Na_2SO_4, filtered and evaporated to dryness. The compound is triturated with hexane to give (R)-quinuclidin-3-yl 2-(tert-butoxycarbonylamino)-2-phenylacetate as a white solid (1.46 g; 97% yield, mixture of diastereoisomers). This compound is dissolved in DCM (50 mL) and 4N HCl in dioxane (5 mL) is added. The reaction is stirred at room temperature for 1 hour (LC-MS monitoring: complete conversion) and then solvent is separated. The gummy solid is triturated with hexane to give C25 as a white solid (1.26 g, 94% yield, di hydrochloride, mixture of diastereoisomers).

Preparation of (R)-quinuclidin-3-yl 2-(cyclopentylamino)-2-phenylacetate di-trifluoroacetate (C26):

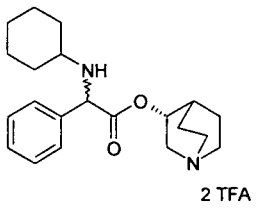
(R)-Quinuclidin-3-yl 2-amino-2-phenylacetate (C25) (200 mg, 0.60 mmol) is dissolved in dry DCM (10 mL) and treated with sodium triacetoxyborohydride (508 mg, 2.40 mmol). The reaction is stirred at room temperature for 30 minutes and then cyclopentanone (106 uL, 1.20 mmol) is added and the reaction is stirred at room temperature for additional 16 hours (LC-MS monitoring: complete conversion). The reaction is diluted with DCM and washed twice with 1N NaOH, the organic layer is dried over Na_2SO_4, filtered and evaporated to dryness. The crude compound is purified by preparative HPLC to give C26 as a white solid (53.1 mg, 16% yield, di trifluoroacetate salt, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d6) ppm: 10.02 (br. s., 2 H), 9.75 (br. s., 1 H), 7.43 - 7.76 (m, 5 H), 5.24 - 5.49 (m, 1 H), 5.01 - 5.24 (m, 1 H), 3.51 - 3.79 (m, 1 H), 3.12 - 3.37 (m, 4 H), 2.93 - 3.12 (m, 1 H), 2.75 - 2.94 (m, 1 H), 2.20 - 2.39 (m, 1 H), 1.78 - 2.14 (m, 4 H), 1.61 - 1.77 (m, 5 H), 1.31 - 1.57 (m, 3 H);

LC-MS (ESI POS): 329.2 (MH^+).

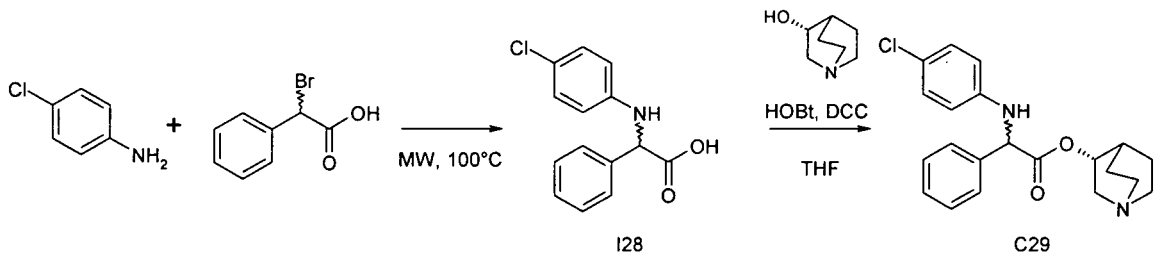
C27 listed in Table 6 is obtained as previously described for C26, using cyclohexanone instead of cyclopentanone.

Table 6

Compound	Structure	Yield and appearance	Analytical
C27	 2 TFA Mixture of diastereoisomers	24% yield White solid	LC-MS (ESI POS): 343.2 (MH^+) ^{1}1H NMR (300 MHz, DMSO-d6) ppm: 9.47 - 9.79 (m, 3 H), 7.36 - 7.85 (m, 5 H), 5.37 - 5.54 (m, 1 H), 5.10 - 5.20 (m, 1 H), 3.56 - 3.82 (m, 1 H), 2.68 - 3.28 (m, 5 H), 1.97 - 2.33 (m, 3 H), 1.66 - 1.94 (m, 5 H), 1.56 (br. s., 2 H), 1.29 (br. s., 2 H), 1.12 (br. S., 3 H)

EXAMPLE 12

Preparation of ((4-chloro-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C29)



Scheme 12

Preparation of (4-chloro-phenylamino)-phenyl-acetic acid (I28):

A solution of α-bromophenylacetic acid (1.00 g, 4.65 mmol) in acetonitrile (20 mL), is added with 4-chloro-phenylamine (1.18 g, 9.30 mmol) and the mixture reacted in a closed vessel under MW irradiation at 100°C for

1 h (UPLC-MS monitoring: complete conversion). Solvent is evaporated and residue is partitioned between EtOAc and 1N HCl. The organic phase is dried over Na_2SO_4, filtered and evaporated to dryness to get intermediate I76 as a yellow solid (0.57 g; 47% yield).

Preparation of ((4-chloro-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C29):

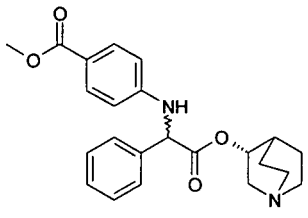
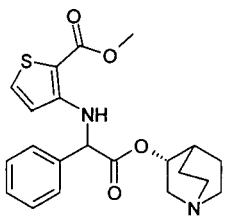
A solution of (4-chloro-phenylamino)-phenyl-acetic acid (I28) (574 mg, 2.20 mmol) in dry THF (20 mL), is added with DCC (543 mg, 2.64 mmol), HOBt (359 mg, 2.64 mmol) and 3(R)–quinuclidinol (558 mg, 4.40 mmol). The resulting mixture is stirred at RT overnight (UPLC-MS monitoring: complete conversion). The solvent is evaporated and the residue is partitioned between EtOAc and 2M K_2CO_3. The organic phase is dried over Na_2SO_4, filtered and evaporated to dryness. The resulting crude is purified by flash chromatography (DCM/MeOH=99/1 to 85/15) to obtain the title compound as a white solid (306 mg, 37% yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d6) ppm: 7.46 - 7.59 (m, 2 H), 7.22 - 7.45 (m, 3 H), 6.99 - 7.18 (m, 2 H), 6.65 - 6.80 (m, 2 H), 6.52 (d, 1 H), 5.28 (d, 1 H), 4.60 - 4.82 (m, 1 H), 3.04 (ddd, 1 H), 2.54 - 2.70 (m, 4 H), 2.03 - 2.36 (m, 1 H), 1.67 - 1.97 (m, 1 H), 1.36 - 1.68 (m, 2 H), 1.05 - 1.35 (m, 2 H);

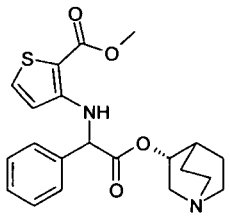
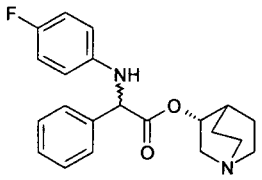
LC-MS (ESI POS): 371.1 (MH^+).

The compounds listed in Table 7 are obtained as previously described for C29, starting from the suitable commercially available 2-bromo-phenylacetic acid derivatives and anilines.

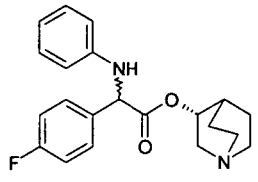
Table 7

Compound	Structure	Yield and appearance	Analytical
C30	 Mixture of diastereoisomer	9% yield White solid	LC-MS (ESI POS): 395.1 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.68 (m, 2 H), 7.47 - 7.58 (m, 2 H), 7.23 - 7.47 (m, 3 H), 7.15 (d, 1 H), 6.62 - 6.80 (m, 2 H), 5.39 (d, 1 H), 4.75 (ddd, 1 H), 3.74 (s, 3 H), 2.86 - 3.19 (m, 1 H), 2.54 - 2.69 (m, 4 H), 1.84 - 2.26 (m, 1 H), 1.35 - 1.80 (m, 3 H), 0.99 - 1.34 (m, 2 H)
Diastereoisomer 1 of C31	 Single diastereoisomer	28% yield Pale yellow solid	LC-MS (ESI POS): 401.1 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.76 (d, 1 H), 7.64 (d, 1 H), 7.22 - 7.54 (m, 5 H), 6.71 (d, 1 H), 5.60 (d, 1 H), 4.58 - 4.89 (m, 1 H), 3.78 (s, 3 H), 2.98 (ddd, 1 H), 2.54 - 2.69 (m, 3 H), 2.13 - 2.27 (m, 1 H), 1.96 - 2.09 (m, 1 H), 1.85 - 1.96 (m, 1 H), 1.51 - 1.73 (m, 2 H), 1.21 - 1.51 (m, 2 H)

(continue)

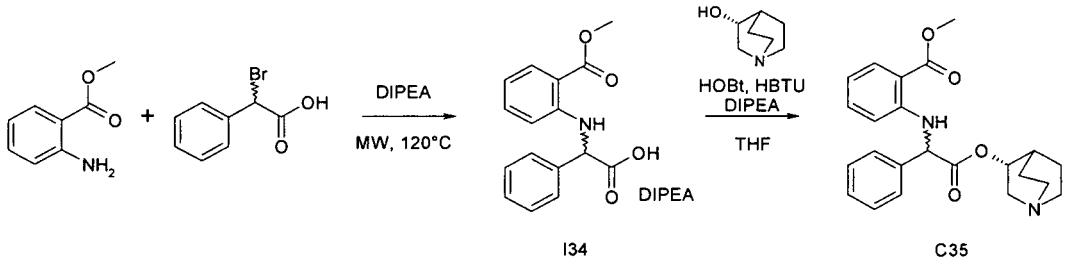
Diastereoisomer 2 of C31	 Single diastereoisomer	35% yield Pale yellow solid	LC-MS (ESI POS): 401.1 (MH^+) ^{1}H NMR (300 MHz, DMSO-d6) ppm: 7.78 (d, 1 H) 7.66 (d, 1 H) 7.17 - 7.53 (m, 5 H) 6.68 (d, 1 H) 5.63 (d, 1 H) 4.72 - 5.09 (m, 1 H) 3.78 (s, 3 H) 2.71 - 3.04 (m, 5 H) 1.10 - 2.07 (m, 6 H)
C32	 Mixture of diastereoisomer	17% yield over two steps yellow solid	LC-MS (ESI POS): 355.1 (MH^+) ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 9.38 (br. s., 1 H), 7.47 - 7.61 (m, 2 H), 7.28 - 7.46 (m, 3 H), 6.86 - 7.03 (m, 2 H), 6.64 - 6.79 (m, 2 H), 6.32 (br. s., 1 H), 5.32 (br. s., 1 H), 4.86 - 5.10 (m, 1 H), 3.55 - 3.70 (m, 1 H), 2.91 - 3.33 (m, 4 H), 2.64 - 2.73 (m, 1 H), 2.13 - 2.28 (m, 1 H), 1.46 - 2.01 (m, 4 H)

(continue)

C33	 Mixture of diastereoisomer	11% yield over two steps Pale yellow solid	LC-MS (ESI POS): 355.2 (MH^+) ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.36 - 7.66 (m, 2 H), 7.15 - 7.28 (m, 2 H), 7.00 - 7.12 (m, 2 H), 6.64 - 6.81 (m, 2 H), 6.50 - 6.64 (m, 1 H), 6.29 (d, 1 H), 5.29 (d, 1 H), 4.39 - 4.82 (m, 1 H), 3.01 - 3.12 (m, 1 H), 2.53 - 2.69 (m, 5 H), 1.67 - 1.80 (m, 1 H), 0.97 - 1.58 (m, 4 H)

EXAMPLE 13

Preparation of 2-({[(R)-(1-aza-bicyclo[2.2.2]oct-3-yl)oxycarbonyl]-phenyl-methyl}-amino)-benzoic acid methyl ester (C35)



I34 C35

Scheme 13

Preparation of N-ethyl-N-isopropylpropan-2-amine 2-[(carboxy-phenyl-methyl)-amino]-benzoic acid methyl ester (I34):

2-Bromo-2-phenylacetic acid (400 mg, 1.86 mmol), methyl 2-aminobenzoate (0.26 mL, 2.05 mmol), and N,N-diisopropylethylamine (DIPEA) (0.65 mL, 3.72 mmol) are dissolved in acetonitrile (8 mL). The resulting solution is heated under MW irradiation in a sealed vial at 100°C for 20 minutes. The mixture is evaporated and the crude residue is purified by

flash chromatography (DCM/MeOH=97/3) affording intermediate I82 as a white solid (611 mg, 79% yield, DIPEA salt).

Preparation of 2-({[(R)-(1-aza-bicyclo[2.2.2]oct-3-yl)oxycarbonyl]-phenyl-methyl}-amino)-benzoic acid methyl ester (C35):

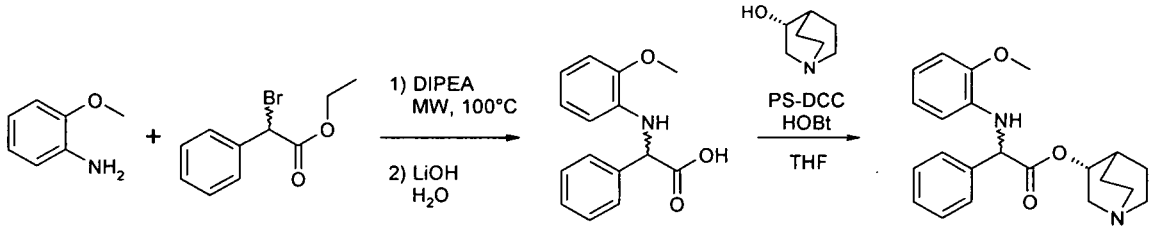
N-Ethyl-N-isopropylpropan-2-amine 2-(2-(methoxycarbonyl)-phenylamino)-2-phenylacetate (I34) (611 mg, 1.47 mmol), 2-(1H-benzo[d][1,2,3]triazol-1-yl)-1,1,3,3-tetramethylisouronium hexafluoro-phosphate(V) (559 mg, 1.47 mmol), and HOBT (226 mg, 1.47 mmol) are dissolved in THF (7 mL) and MeCN (3 mL). (R)-Quinuclidin-3-ol (375 mg, 2.95 mmol) is added and the mixture is stirred at RT for 1h. Solvents are evaporated, the residue is dissolved in EtOAc and washed with sat. $NaHCO_3$, water and brine. The organic layer is recovered, dried over Na_2SO_4, filtered and evaporated. The crude is purified by preparative HPLC and the collected fractions are evaporated, the residue is dissolved in EtOAc and washed with $NaHCO_3$ and brine. The organic layer is recovered, dried over Na_2SO_4, filtered and evaporated to afford compound the title compound as a colorless compound (95 mg, 16% yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 8.56 - 8.92 (m, 1 H), 7.80 - 7.94 (m, 1 H), 7.46 - 7.58 (m, 2 H), 7.22 - 7.45 (m, 4 H), 6.31 - 6.78 (m, 2 H), 5.53 and 5.51 (d, 1 H), 4.47 - 4.87 (m, 1 H), 3.86 (s, 3 H), 3.07 and 2.97 (ddd, 1 H), 2.54 - 2.68 (m, 4 H), 0.95 - 2.34 (m, 6 H);

LC-MS (ESI POS): 395.3 (MH+).

EXAMPLE 14

Preparation of (2-methoxy-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C37)



Scheme 14

Preparation of (2-methoxy-phenylamino)-phenyl-acetic acid hydrochloride (I36):

Ethyl 2-bromo-2-phenylacetate (500 mg, 2.06 mmol), 2-methoxyaniline (0.28 mL, 2.47 mmol) and DIPEA (0.47 ml, 2.67 mmol) are dissolved in acetonitrile (10 mL). The resulting solution is heated under microwave irradiation at 100°C for 30 minutes. DIPEA (47 ul, 0.27 mmol) and 2-methoxyaniline (28 uL, 0.25 mmol) are added and microwave heating is carried out for a further 15 minutes. Water (5 mL) and lithium hydroxide hydrate (259 mg, 6.17 mmol) are directly added to the reaction solution and the resulting mixture is vigorously stirred at RT for 1 hour. Acetonitrile is evaporated, the remaining water phase is cooled at 0°C and 4M HCl in 1,4-dioxane is added until pH is about 1. The solid obtained is collected by filtration and washed with water. The solid-cake is recovered and dried under vacuum to obtain intermediate I84 as a brown solid (377 mg, 62% yield).

Preparation of (2-methoxy-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C37):

PS-DCC (2.05 g, 2.57 mmol, loading: 1.25 mmol/g) is suspended in THF (15 mL) and shaken for few minutes. Then (2-methoxy-phenylamino)-phenyl-acetic acid hydrochloride (I36) (377 mg, 1.28 mmol) and HOBT

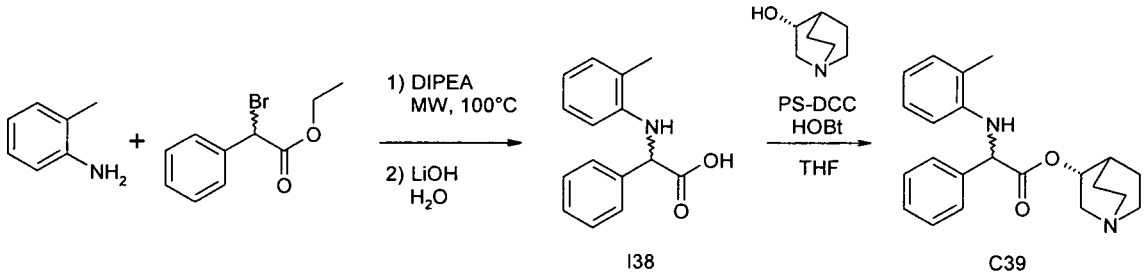
(393 mg, 2.57 mmol) are added. After 10 minutes, (R)-quinuclidin-3-ol (490 mg, 3.85 mmol) is added and the mixture is shaken at RT for 16 hours (Conversion complete by UPLC/MS-UV). PS-DCC is filtered off and the filtrate is evaporated to dryness. The residue is dissolved in EtOAc and washed with sat. $NaHCO_3$, water and brine. The organic layer is recovered, dried over Na_2SO_4, filtered and evaporated to afford the title compound as a yellow oil (548 mg, quantitative yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d6) ppm: 7.45 - 7.55 (m, 2 H), 7.13 - 7.43 (m, 3 H), 6.78 - 6.93 (m, 1 H), 6.64 (m, 2 H), 6.29 - 6.51 (m, 1 H), 5.40 (d, 1 H), 5.31 (d, 1 H), 4.58 - 4.85 (m, 1 H), 3.84 (s, 3 H), 2.91 - 3.14 (m, 1 H), 2.54 - 2.72 (m, 3 H), 1.95 - 2.47 (m, 2 H), 0.98 - 1.92 (m, 5 H);

LC-MS (ESI POS): 367.3 (MH+).

EXAMPLE 15

Preparation of phenyl-o-methylphenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C39)



Scheme 15

Preparation of phenyl-o-methyl phenylamino-acetic acid hydrochloride (I38):

Ethyl 2-bromo-2-phenylacetate (0.28 mL, 1.64 mmol), orto-toluidine (0.26 mL, 2.47 mmol) and DIPEA (0.43 mL, 2.47 mmol) are dissolved in acetonitrile (5 mL) and stirred under MW irradiation at 100°C for 1h (Conversion complete by UPLC/MS-UV). Lithium hydroxide hydrate (207 mg, 4.94 mmol) and water (3 mL) are added and the mixture is stirred at

RT for 16 hours. 4M HCl in dioxane is added until pH is about 1, then the solvents are evaporated, the residue is suspended in water, sonicated, cooled at 0°C and the resulting solid is recovered by filtration and dried under vacuum to get intermediate I86 as a off-white solid (290 mg, 63% yield).

Preparation of phenyl-o-methyl phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C39):

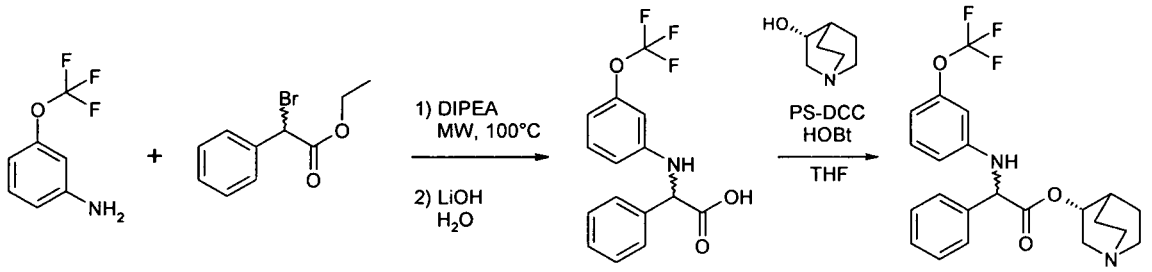
PS-DCC (1.15 g, 1.44 mmol, loading: 1.25 mmol/g) is suspended in THF (15 mL). Phenyl-o-methylphenylamino-acetic acid hydrochloride (I38) (200 mg, 0.72 mmol) and HOBT (221 mg, 1.44 mmol) are added, followed by (R)-quinuclidin-3-ol (275 mg, 2.16 mmol) and the mixture is shaken for 16 hours at RT. PS-DCC is filtered off and the filtrate is evaporated. The resulting residue is dissolved in EtOAc and washed sequentially with water, sat. $NaHCO_3$, water and brine. The organic layer is dried over Na_2SO_4, filtered and evaporated to give the title compound as a colorless oil (260 mg, quantitative yield, mixture of diastereoisomers).

^1H NMR (300 MHz, DMSO-d6) ppm: 7.50 - 7.62 (m, 2 H), 7.25 - 7.46 (m, 3 H), 7.00 - 7.07 (m, 1 H), 6.82 - 6.98 (m, 1 H), 6.51 - 6.66 (m, 1 H), 6.30 - 6.49 (m, 1 H), 5.32 (d, 1 H), 5.10 (d, 1 H), 4.65 - 4.85 (m, 1 H), 2.85 - 3.16 (m, 1 H), 2.56 - 2.69 (m, 3 H), 2.23 (s, 3 H), 2.13 - 2.46 (m, 2 H), 0.95 - 1.97 (m, 5 H);

LC-MS (ESI POS): 351.2 (MH+).

EXAMPLE 16

Preparation of phenyl-(3-trifluoromethoxy-phenylamino)-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C41)



I40 C41 ***S***

cheme 16

Preparation of phenyl-(3-trifluoromethoxy-phenylamino)-acetic acid hydrochloride (I40):

Ethyl 2-bromo-2-phenylacetate (400 mg, 1.64 mmol), 3-(trifluoromethoxy)aniline (0.33 mL, 2.47 mmol), and DIPEA (0.43 mL, 2.47 mmol) are dissolved in acetonitrile (5 mL) and heated under MW irradiation at 100°C for 1h (Conversion complete by UPLC/MS-UV). Water (5 mL) and lithium hydroxide hydrate (207 mg, 4.94 mmol) are directly added and the resulting mixture is stirred at RT for 1h. Then 4M HCl in dioxane is added to pH 1, the organic solvents are evaporated and the resulting crude oil is purified by filtration through a silica pad using DCM/MeOH= 9/1 as the eluent. Intermediate I88 is collected as a brown oil (569 mg, quantitative yield).

Preparation of phenyl-(3-trifluoromethoxy-phenylamino)-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C41):

PS-DCC (920 mg, 1.15 mmol, loading: 1.25 mmol/g) is suspended in THF (15 mL). Phenyl-(3-trifluoromethoxy-phenylamino)-acetic acid hydrochloride (I40) (200 mg, 0.57 mmol) and HOBT (176 mg, 1.15 mmol) are added, followed by (R)-quinuclidin-3-ol (219 mg, 1.73 mmol) and the mixture

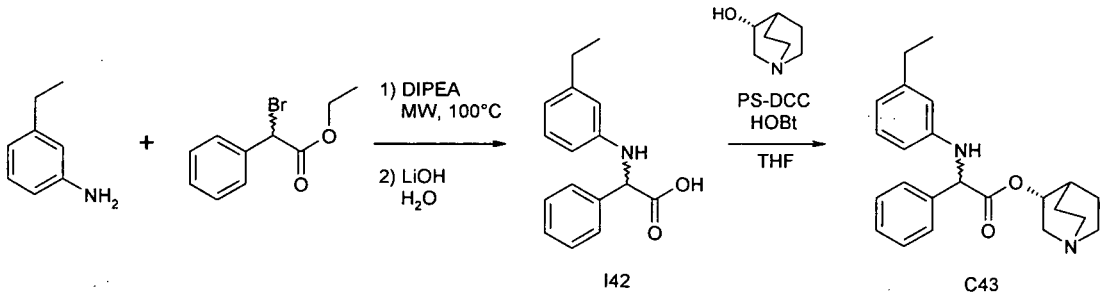
is shaken for 16 hours at RT. PS-DCC is filtered off and the filtrate is evaporated. The resulting residue is dissolved in EtOAc and washed with water, sat. $NaHCO_3$, water and brine. The organic phase is dried over Na_2SO_4, filtered and evaporated to give the title compound as a colorless oil (206 mg, 85% yield, mixture of diastereoisomers).

^1H NMR (300 MHz, DMSO-d6) ppm: 7.26 - 7.62 (m, 5 H), 7.16 (t, 1 H), 6.79 (d, 1 H), 6.38 - 6.75 (m, 3 H), 5.34 (d, 1 H), 4.66 - 4.80 (m, 1 H), 2.91 - 3.24 (m, 1 H), 2.53 - 2.76 (m, 3 H), 1.97 - 2.39 (m, 2 H), 1.67 - 1.96 (m, 1 H), 0.99 - 1.67 (m, 4 H);

LC-MS (ESI POS): 421.2 (MH^+).

EXAMPLE 17

Preparation of (3-ethyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C43)



Scheme 17

Preparation of (3-ethyl-phenylamino)-phenyl-acetic acid hydrochloride (I42):

Ethyl 2-bromo-2-phenylacetate (0.29 mL, 1.64 mmol), 3-ethylaniline (0.31 mL, 2.47 mmol), and N-ethyl-N-isopropylpropan-2-amine (0.43 mL, 2.47 mmol) are dissolved in acetonitrile (5 mL) and stirred under MW irradiation at 100°C for 1h (Conversion complete by UPLC/MS-UV). Lithium hydroxide hydrate (207 mg, 4.94 mmol) and water (3 mL) are added and the mixture is stirred at RT for 16 hours. 4M HCl in dioxane is added until pH 1 and the solvents are evaporated. The residue is suspended in water, sonicated,

cooled at 0°C and filtered under suction. The recovered white solid is dried under vacuum at 40°C overnight (414 mg, 86% yield).

Preparation of (3-ethyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C43):

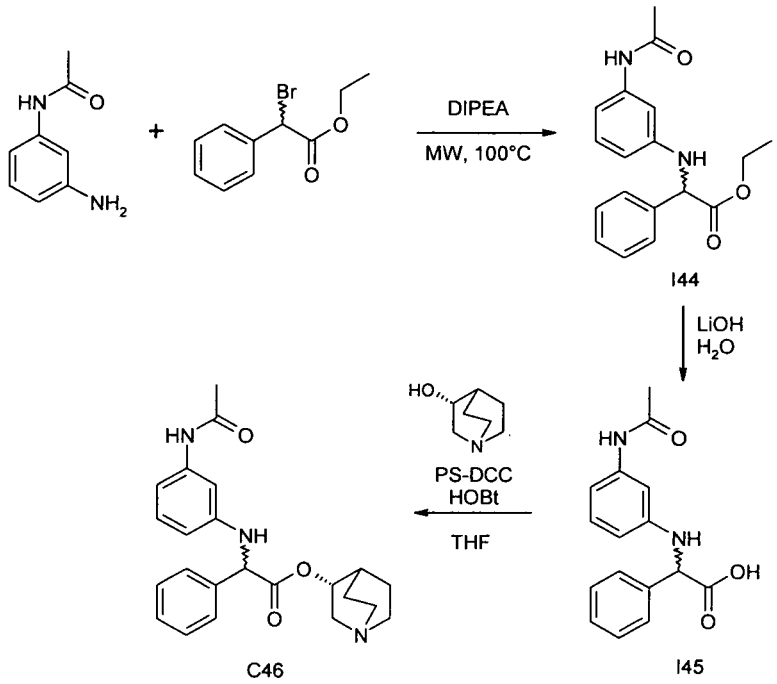
PS-DCC (1097 mg, 1.371 mmol, loading:1.25 mmol/g) is suspended in THF (15 mL). HOBT (210 mg, 1.37 mmol), (3-ethyl-phenylamino)-phenyl-acetic acid hydrochloride (I42) (200 mg, 0.68 mmol), and (R)-quinuclidin-3-ol (262 mg, 2.06 mmol) are added and the suspension is shaken at RT for 16h. PS-DCC is filtered off and the filtrate is evaporated. The resulting residue is dissolved in EtOAc and washed with water, sat. $NaHCO_3$, water and brine. The organic phase is dried over Na_2SO_4, filtered and evaporated. The crude is purified by flash chromatography (DCM/MeOH=95/5) to obtain the title compound as a colorless oil (72 mg, 30% yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.45 - 7.60 (m, 2 H), 7.21 - 7.47 (m, 3 H), 6.96 (t, 1 H), 6.56 - 6.66 (m, 1 H), 6.47 - 6.56 (m, 1 H), 6.38 - 6.47 (m, 1 H), 6.17 (d, 1 H), 5.16 - 5.39 (m, 1 H), 4.60 - 4.79 (m, 1 H), 2.89 - 3.16 (m, 1 H), 2.54 - 2.70 (m, 3 H), 2.45 (q, 2 H), 1.98 - 2.34 (m, 2 H), 1.66 - 1.96 (m, 1 H), 1.20 - 1.66 (m, 4 H), 1.11 (t, 3 H);

LC-MS (ESI POS): 365.3 (MH+).

EXAMPLE 18

Preparation of (3-acetylamino-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C46)



Scheme 18

Preparation of (3-acetylamino-phenylamino)-phenyl-acetic acid ethyl ester (I44):

N-(3-Aminophenyl)acetamide (371 mg, 2.47 mmol), ethyl 2-bromo-2-phenylacetate (0.29 mL, 1.64 mmol), and DIPEA (0.43 mL, 2.47 mmol) are dissolved in acetonitrile (5 mL). The reaction is heated under MW irradiation at 100°C for 30 minutes. Conversion complete by UPLC/MS-UV. Acetonitrile is evaporated and the crude residue is purified by flash chromatography (DCM/EtOAc=8/2) to obtain intermediate I92 as a colorless oil (440 mg, 86% yield).

Preparation of (3-acetylamino-phenylamino)-phenyl-acetic acid hydrochloride (I45):

(3-Acetylamino-phenylamino)-phenyl-acetic acid ethyl ester (I44) (440 mg, 1.41 mmol) and lithium hydroxide hydrate (118 mg, 2.82 mmol) are

dissolved in THF (5 mL) and water (3 mL). The reaction is stirred at RT for 2h. THF is evaporated, the resulting aqueous solution is cooled at 0°C and 1M HCl is added until pH is about 2. The precipitated is recovered by filtration, washed with cool water and dried under vacuum overnight to obtain intermediate I93 as a yellow solid (190 mg, 42% yield).

Preparation of (3-acetylamino-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C46):

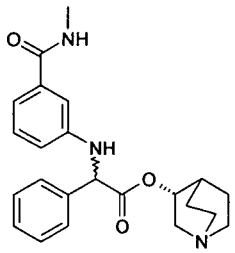
PS-DCC (798 mg, 0.10 mmol, loading: 1.25 mmol/g) is suspended in dry THF (10 mL). (3-Acetylamino-phenylamino)-phenyl-acetic acid hydrochloride (I45) (160 mg, 0.50 mmol), HOBT (153 mg, 0.10 mmol), and (R)-quinuclidin-3-ol (190 mg, 1.50 mmol) are added and the mixture is shaken for 16 h at RT (Conversion complete by UPLC/MS-UV). PS-DCC is filtered off and washed with THF and then with EtOAc. The filtrate is evaporated, the resulting residue is taken up with EtOAc and washed with 5% $NaHCO_3$, water and brine. The organic layer is separated, dried over Na_2SO_4, filtered and evaporated to afford the title compound as a yellow oil (196 mg, quantitative yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 9.62 (s, 1 H), 7.47 - 7.60 (m, 2 H), 7.25 - 7.47 (m, 3 H), 7.01 - 7.11 (m, 1 H), 6.96 (t, 1 H), 6.66 - 6.83 (m, 1 H), 6.36 - 6.46 (m, 1 H), 6.30 (d, 1 H), 5.15 (d, 1 H), 4.58 - 4.78 (m, 1 H), 2.95 and 3.06 (ddd, 1 H), 2.54 - 2.70 (m, 5 H), 1.99 (s, 3 H), 1.23 - 1.95 (m, 5 H);

LC-MS (ESI POS): 394.2 (MH+).

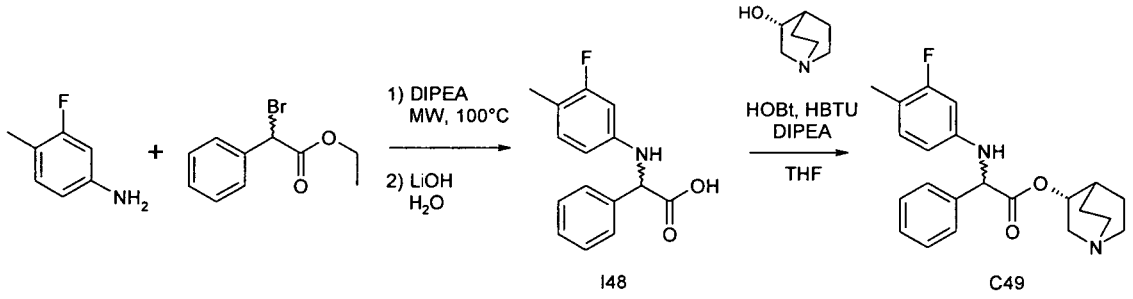
C47 listed in Table 8 is prepared as previously described for C46, using 3-amino-N-methyl-benzamide instead of N-(3-aminophenyl)acetamide.

Table 8

Compound	Structure	Yield and appearance	Analytical
C47	 Mixture of stereoisomer	Quantitative yield Yellow oil	LC-MS (ESI POS): 394.2 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 8.17 (q, 1 H), 7.48 - 7.59 (m, 2 H), 7.25 - 7.48 (m, 3 H), 7.17 - 7.23 (m, 1 H), 7.13 (t, 1 H), 6.99 - 7.08 (m, 1 H), 6.80 - 6.94 (m, 1 H), 6.49 (d, 1 H), 5.32 (d, 1 H), 4.59 - 4.79 (m, 1 H), 2.89 - 3.15 (m, 1 H), 2.74 (d, 3 H), 2.54 - 2.68 (m, 5 H), 1.07 - 1.96 (m, 5 H)

EXAMPLE 19

Preparation of (3-fluoro-4-methyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C49)



Scheme 19

Preparation of (3-fluoro-4-methyl-phenylamino)-phenyl-acetic acid hydrochloride (I48):

Ethyl 2-bromo-2-phenylacetate (0.29 mL, 1.64 mmol), 3-fluoro-4-methylaniline (247 mg, 1.97 mmol) and DIPEA (0.37 mL, 2.14 mmol) are dissolved in acetonitrile (8 mL). The reaction is heated in a microwave oven at 100°C for 1h and 15 min. Then, a solution of lithium hydroxide hydrate (207 mg, 4.94 mmol) in water (5 mL) is added and the mixture is stirred at RT

for 2h. Acetonitrile is evaporated under vacuum, the remaining aqueous solution is cooled at 0° and the pH is adjusted to 2 with 4M HCl in dioxane. The resulting white solid is recovered by filtration and dried at 45°C under vacuum overnight (367 mg, 75% yield).

Preparation of (3-fluoro-4-methyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C49):

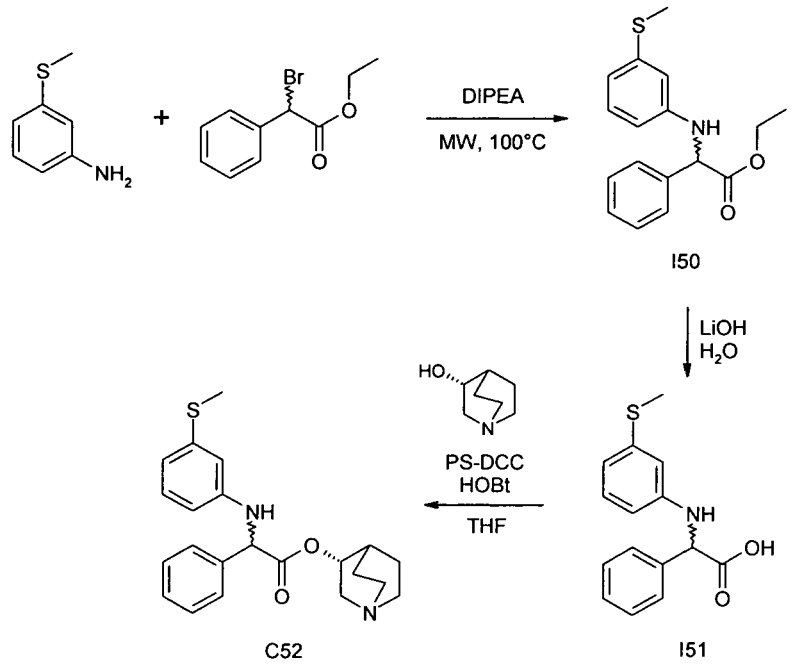
(3-Fluoro-4-methyl-phenylamino)-phenyl-acetic acid hydrochloride (I48) (250 mg, 0.84 mmol), 2-(1H-benzo[d][1,2,3]triazol-1-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (321 mg, 0.84 mmol), and HOBT (129 mg, 0.84 mmol) are dissolved in acetonitrile (6 mL). DIPEA (0.29 mL, 1.69 mmol) is added, followed by (R)-quinuclidin-3-ol (215 mg, 1.69 mmol) and the resulting yellow solution is stirred at RT overnight (Conversion complete by UPLC/MS-UV). MeCN is evaporated, the residue is dissolved in EtOAc and washed with sat. $NaHCO_3$, water and brine. The organic layer is recovered, dried over Na_2SO_4, filtered and evaporated. The crude compound is purified by filtration through a pad of silica using DCM/MeOH=9/1 as the eluent to obtain the title compound as a yellow oil (311 mg, quantitative yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.26 - 7.65 (m, 5 H), 6.94 (td, 1 H), 6.34 - 6.61 (m, 3 H), 5.25 - 5.33 (m, 1 H), 4.78 - 5.01 (m, 1 H), 3.42 and 3.52 (ddd, 1 H), 2.82 - 3.22 (m, 4 H), 2.54 - 2.66 (m, 1 H), 1.92 - 1.99 and 2.10 - 2.21 (m, 1 H), 2.04 (s, 3 H), 1.31 - 1.87 (m, 4 H);

LC-MS (ESI POS): 369.2 (MH+).

EXAMPLE 20

Preparation of (3-methylsulfanyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C52)



Scheme 20

Preparation of (3-methylsulfanyl-phenylamino)-phenyl-acetic acid ethyl ester (I50):

Ethyl 2-bromo-2-phenylacetate (0.22 mL, 1.23 mmol), 3-(methylthio)aniline (0.22 mL, 1.85 mmol), and DIPEA (0.32 mL, 1.85 mmol) are dissolved in acetonitrile (3 mL) and heated under microwave irradiation at 100°C for 1h. Acetonitrile is evaporated and the crude residue is purified by flash chromatography (petroleum ether/EtOAc=85/15) to obtain intermediate I98 as a colorless oil (292 mg, 79% yield).

Preparation of (3-methylsulfanyl-phenylamino)-phenyl-acetic acid hydrochloride (I51):

(3-Methylsulfanyl-phenylamino)-phenyl-acetic acid ethyl ester (I50) (292 mg, 0.97 mmol) and lithium hydroxide hydrate (81 mg, 1.94 mmol) are dissolved in THF (7 mL) and water (3 mL) and stirred at RT for 2h. THF is

evaporated, the solution is cooled at 0°C and 1M HCl is added dropwise until pH 1. The resulting mixture is concentrated and extracted several times with DCM. The collected organic phases are dried over Na_2SO_4, filtered and evaporated to afford intermediate I99 as a brown-solid (248 mg, 83% yield).

Preparation of (3-methylsulfanyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C52):

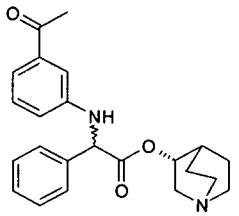
PS-DCC (602 mg, 0.80 mmol, loading: 1.33 mmol/g) is suspended in dry THF (15 mL). (3-Methylsulfanyl-phenylamino)-phenyl-acetic acid hydrochloride (I51) (124 mg, 0.40 mmol), HOBT (123 mg, 0.80 mmol), and (R)-quinuclidin-3-ol (153 mg, 1.20 mmol) are added and the suspension is shaken at RT overnight (16h). PS-DCC is filtered off, washed with THF and the filtrate is evaporated. The resulting residue is dissolved in EtOAc and washed with sat. $NaHCO_3$, water and brine. The organic layer is recovered, dried over Na_2SO_4, filtered and evaporated to afford the title compound as a brown oil (153 mg, quantitative yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.49 - 7.58 (m, 2 H), 7.28 - 7.48 (m, 3 H), 6.99 (t, 1 H), 6.58 - 6.69 (m, 1 H), 6.43 - 6.56 (m, 2 H), 6.38 (d, 1 H), 5.29 (d, 1 H), 4.59 - 4.78 (m, 1 H), 2.88 - 3.13 (m, 1 H), 2.54 - 2.69 (m, 3 H), 2.37 (s, 3 H), 1.68 - 2.24 (m, 3 H), 0.98 - 1.65 (m, 4 H);

LC-MS (ESI POS): 383.2 (MH+).

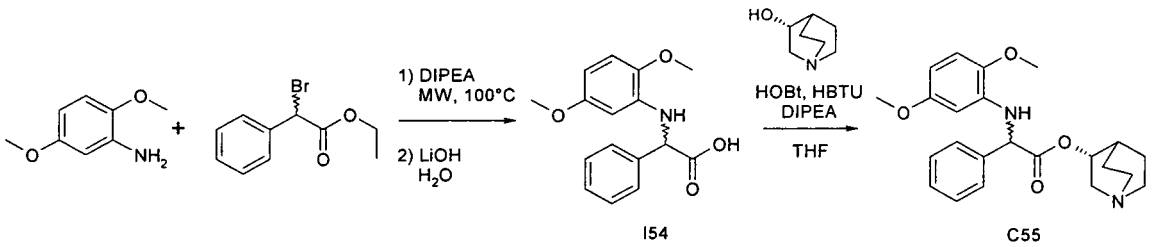
C53 listed in Table 9 is prepared as previously described for C52, using 1-(3-amino-phenyl)-ethanone instead of 3-(methylthio)aniline.

Table 9

Compound	Structure	Yield and appearance	Analytical
C53	 Mixture of stereoisomer	Quantitative yield Yellow oil	LC-MS (ESI POS): 379.3 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.49 - 7.64 (m, 2 H), 7.25 - 7.48 (m, 4 H), 7.13 - 7.26 (m, 2 H), 6.87 - 7.04 (m, 1 H), 6.63 (d, 1 H), 5.35 (d, 1 H), 4.56 - 4.82 (m, 1 H), 2.96 (ddd, 1 H), 2.55 - 2.68 (m, 4 H), 2.48 (s, 3 H), 2.02 - 2.32 (m, 1 H), 0.98 - 1.97 (m, 5 H)

EXAMPLE 21

Preparation of (2,5-dimethoxy-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C55)



Scheme 21

Preparation of (2,5-dimethoxy-phenylamino)-phenyl-acetic acid hydrochloride (I54):

2,5-Dimethoxyaniline (284 mg, 1.85 mmol), ethyl 2-bromo-2-phenylacetate (0.22 ml, 1.23 mmol), and DIPEA (0.32 mL, 1.85 mmol) are dissolved in acetonitrile (5 mL) and stirred under MW heating at 100°C for 1h. Water (2 mL, 111 mmol) and lithium hydroxide hydrate (104 mg, 2.47 mmol) are directly added and the resulting mixture is stirred at RT overnight. Acetonitrile is evaporated, 1M HCl is added and the acid aqueous

phase is extracted with DCM. The collected organic phases are washed with brine, dried (Na_2SO_4), filtered and evaporated to obtain intermediate I102 as a white solid (154 mg, 38% yield).

Preparation of (2,5-Dimethoxy-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C55):

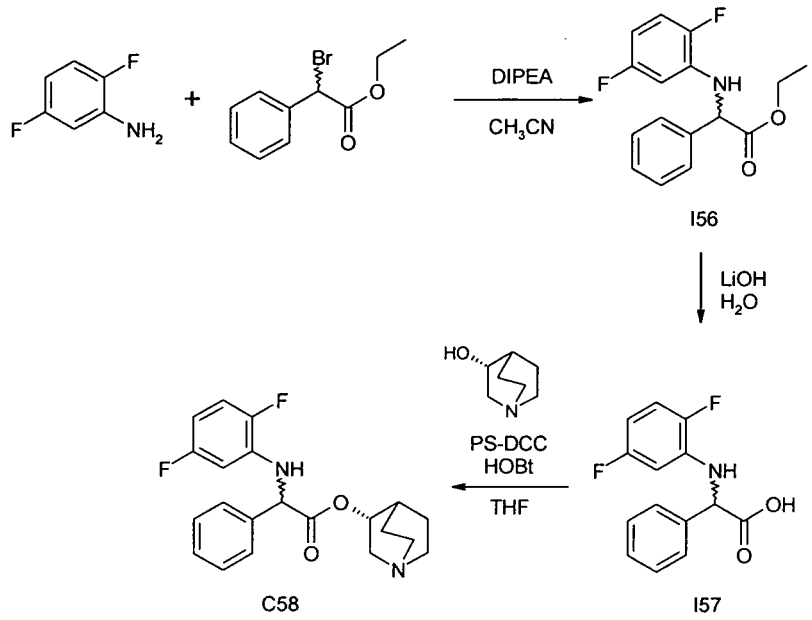
PS-DCC (715 mg, 0.951 mmol, loading: 1.33 mmol/g) is suspended in dry THF (10 mL). (2,5-Dimethoxy-phenylamino)-phenyl-acetic acid hydrochloride (I54) (154 mg, 0.48 mmol), HOBT (146 mg, 0.95 mmol) and (R)-quinuclidin-3-ol (181 mg, 1.43 mmol) are added and the mixture is shaken at RT overnight. PS-DCC is filtered off and the filtrate is evaporated. The residue is dissolved in EtOAc and washed with sat. $NaHCO_3$, water and brine. The organic layer is dried over Na_2SO_4, filtered and evaporated to dryness. The crude compound is purified by flash chromatography (DCM/MeOH=95/5) to afford the title compound as a colorless oil (108 mg, 57% yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.23 - 7.59 (m, 5 H), 6.74 (d, 1 H), 6.09 - 6.20 (m, 1 H), 6.04 (d, 1 H), 5.42 (d, 1 H), 5.33 (d, 1 H), 4.64 - 4.83 (m, 1 H), 3.79 (s, 3 H), 3.56 (s, 3 H), 2.90 - 3.03 and 3.04 - 3.15 (m, 1 H), 2.54 - 2.67 (m, 4 H), 1.96 - 2.25 (m, 1 H), 1.65 - 1.73 and 1.89 - 1.96 (m, 1 H), 0.98 - 1.66 (m, 4 H);

LC-MS (ESI POS): 397.3 (MH+).

EXAMPLE 22

Preparation of (2,5-difluoro-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C58)



Scheme 22

Preparation of (2,5-difluoro-phenylamino)-phenyl-acetic acid ethyl ester (I56):

2,5-Difluoroaniline (0.19 mL, 1.85 mmol), ethyl 2-bromo-2-phenylacetate (0.22 mL, 1.23 mmol), and DIPEA (0.32 mL, 1.85 mmol) are dissolved in acetonitrile (3 mL) and heated under MW irradiation at 100°C for 6h and then at 110°C for 4h. Acetonitrile is evaporated and the crude is purified by flash chromatography (Petroleum ether/EtOAc=97/3) to obtain intermediate I104 as a white solid (240 mg, 67% yield).

Preparation of (2,5-difluoro-phenylamino)-phenyl-acetic acid hydrochloride (I57):

(2,5-Difluoro-phenylamino)-phenyl-acetic acid ethyl ester (I56) (240 mg, 0.82 mmol) is dissolved in THF/water (7/3 mL). Lithium hydroxide hydrate (69.1 mg, 1.65 mmol) is added and the resulting mixture is stirred at RT for 16h. THF is evaporated under reduced pressure, the solution is cooled

at 0°C and 1M HCl is added dropwise until pH 1. The white solid is recovered by filtration, washed with cold water and dried under vacuum at 40°C overnight to obtain intermediate I105 as a white solid (198 mg, 80% yield).

Preparation of (2,5-difluoro-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C58):

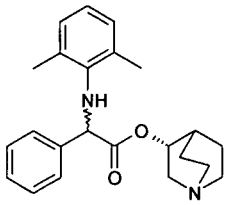
PS-DCC (914 mg, 1.301 mmol, loading: 1.33 mmol/g) is suspended in dry THF (15 mL). (2,5-Difluoro-phenylamino)-phenyl-acetic acid hydrochloride (I57) (195 mg, 0.65 mmol), HOBT (199 mg, 1.30 mmol), and (R)-quinuclidin-3-ol (248 mg, 1.95 mmol) are added and the suspension is shaken at RT for 16h (Conversion complete by UPLC/MS-UV). PS-DCC is filtered off under suction and the filtrate is evaporated. The resulting residue is dissolved in EtOAc and washed with sat. $NaHCO_3$, water and brine. The organic layer is separated, dried over Na_2SO_4, filtered and evaporated. The crude is purified by filtration through a silica-pad using DCM/MeOH=95/5 as the eluent. The title compound is collected as a colorless oil (195 mg, 80% yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.49 - 7.62 (m, 2 H) 7.28 - 7.47 (m, 3 H) 7.02 - 7.15 (m, 1 H) 6.46 - 6.60 (m, 1 H) 6.32 - 6.46 (m, 1 H) 5.85 - 6.00 (m, 1 H) 5.43 and 5.45 (d, 1 H) 4.66 - 4.82 (m, 1 H) 2.99 and 3.09(ddd, 1 H) 2.54 - 2.69 (m, 4 H) 2.01 - 2.31 (m, 1 H) 1.85 - 1.96 and 1.65 - 1.75 (m, 1 H) 0.92 - 1.66 (m, 4 H);

LC-MS (ESI POS): 373.2 (MH+).

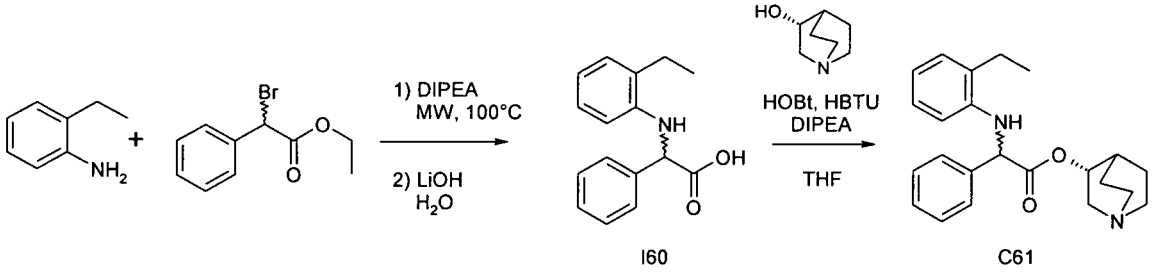
C59 listed in Table 10 is prepared as previously described for C58, using 2,6-dimethyl-phenylamineinstead of 2,5-difluoroaniline.

Table 10

Compound	Structure	Yield and appearance	Analytical
C59	 Mixture of diastereoisomer	34% yield Colorless oil	LC-MS (ESI POS): 365.1 (MH^+) ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.44 - 7.59 (m, 2 H), 7.25 - 7.44 (m, 3 H), 6.91 (d, 2 H), 6.60 - 6.79 (m, 1 H), 4.95 and 4.96 (d, 1 H), 4.62 - 4.82 (m, 2 H), 2.82 - 3.11 (m, 1 H), 2.55 - 2.61 (m, 3 H), 2.30 - 2.38 (m, 1 H), 2.22 (s, 6 H), 1.98 - 2.12 (m, 1 H), 1.70 - 1.75 and 1.77 - 1.89 (m, 1 H), 1.01 - 1.62 (m, 4 H)

EXAMPLE 23

Preparation of (2-ethyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C61)



Scheme 23

Preparation of (2-ethyl-phenylamino)-phenyl-acetic acid hydrochloride (I60):

2-Ethylaniline (0.23 mL, 1.85 mmol), ethyl 2-bromo-2-phenylacetate (0.22 mL, 1.23 mmol), and DIPEA (0.32 mL, 1.85 mmol) are dissolved in acetonitrile (3 mL) and stirred under MW irradiation at 100°C for 1h. Water (2 ml, 111 mmol) and lithium hydroxide hydrate (104 mg, 2.47 mmol) are added to the reaction and the resulting mixture is stirred at RT overnight

(16h). Acetonitrile is evaporated and 1M HCl is added until pH 1. The aqueous phase is extracted several times with DCM and the organic phases are collected and washed with water and brine, dried (Na_2SO_4), filtered and evaporated to give intermediate I108as an off-white solid (316 mg, 88% yield).

Preparation of (2-ethyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C61)

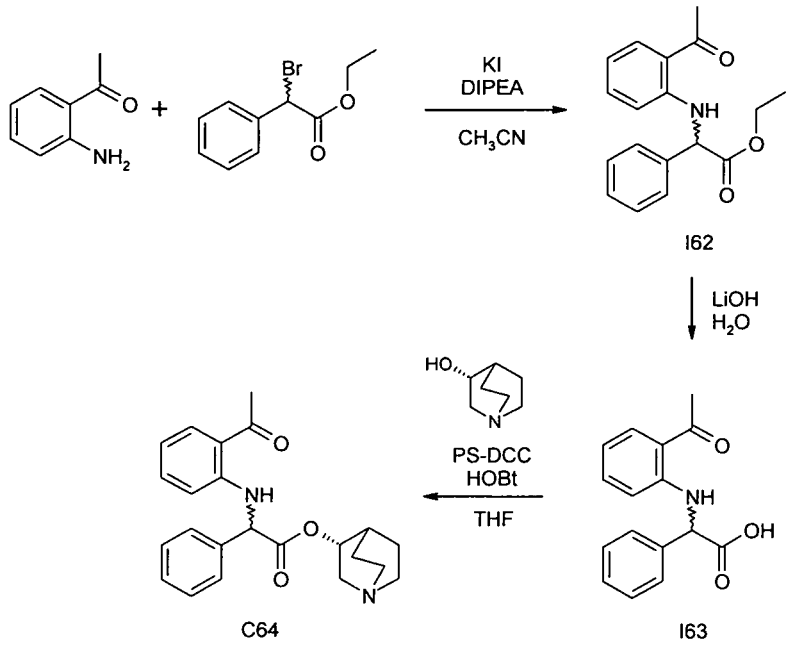
PS-DCC (962 mg, 1.37 mmol, loading:1.33 mmol/g) is suspended in THF (10 mL). HOBT (210 mg, 1.37 mmol), (2-ethyl-phenylamino)-phenyl-acetic acid hydrochloride (I60) (200 mg, 0.68 mmol), and (R)-quinuclidin-3-ol (262 mg, 2.06 mmol) are added and the mixture is shaken at RT overnight. PS-DCC is filtered off and washed with THF and the filtrate is evaporated under reduced pressure. The resulting residue is dissolved in EtOAc and washed with sat. $NaHCO_3$, water and brine. The organic layer is separated, dried over Na_2SO_4, filtered and evaporated. The residue is first purified by flash chromatography (DCM/MeOH=9/1) and then by preparative HPLC. The fractions containing the product are pooled, concentrated under vacuum, basified with sat. $NaHCO_3$ and extracted with EtOAc. The organic layer is dried (Na_2SO_4), filtered and evaporated to afford the title compound as a colorless oil (52 mg, 21% yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.47 - 7.60 (m, 2 H), 7.23 - 7.46 (m, 3 H), 7.00 - 7.08 (m, 1 H), 6.86 - 6.96 (m, 1 H), 6.53 - 6.66 (m, 1 H), 6.34 - 6.48 (m, 1 H), 5.32 and 5.33 (d, 1 H), 5.17 and 5.18 (d, 1 H), 4.66 - 4.84 (m, 1 H), 2.96 and 3.07 (ddd, 1 H), 2.61 (q, 2 H), 2.55 - 2.69 (m, 3 H), 1.98 - 2.39 (m, 2 H), 1.65 - 1.73 and 1.85 - 1.96 (m, 1 H), 1.24 (t, 3 H), 1.02 - 1.77 (m, 4 H);

LC-MS (ESI POS): 365.1 (MH+).

EXAMPLE 24

Preparation of (2-acetyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C64)



Scheme 24

Preparation of (2-acetyl-phenylamino)-phenyl-acetic acid ethyl ester (I62)

1-(2-Aminophenyl)ethanone (250 mg, 1.85 mmol), ethyl 2-bromo-2-phenylacetate (0.22 ml, 1.23 mmol), DIPEA (0.32 mL, 1.85 mmol) and a catalytic amount of potassium iodide are dissolved in acetonitrile (4 mL) and heated under MW irradiation at 100°C for 2h and then at 120°C for 1 h. Acetonitrile is evaporated and the crude is purified by flash chromatography (petroleum ether/EtOAc=93/7) to obtain intermediate I110 as a yellow oil (367 mg, quantitative yield).

Preparation of (2-acetyl-phenylamino)-phenyl-acetic acid hydrochloride (I63):

(2-Acetyl-phenylamino)-phenyl-acetic acid ethyl ester (I62) (367 mg, 1.23 mmol) and lithium hydroxide hydrate (104 mg, 2.47 mmol) are dissolved

in water (1.7 mL) and acetonitrile (5 mL). The reaction is stirred at RT overnight and then the solvents are evaporated. The residue is dissolved in EtOAc and washed several times with 1M HCl. The organic phase is recovered, dried (Na_2SO_4), filtered and evaporated to afford intermediate I111 as a brown solid (181 mg, 48% yield).

Preparation of (2-acetyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C64):

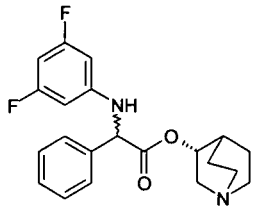
PS-DCC (890 mg, 1.184 mmol, loading: 1.33 mmol/g) is suspended in dry THF (10 mL). (2-Acetyl-phenylamino)-phenyl-acetic acid hydrochloride (I63) (181 mg, 0.59 mmol), HOBt (181 mg, 1.18 mmol), and (R)-quinuclidin-3-ol (226 mg, 1.78 mmol) are added and the mixture is shaken at RT overnight. PS-DCC is filtered off and the filtrate is evaporated. The residue is dissolved in EtOAc and washed with sat. $NaHCO_3$, water and brine, dried over Na_2SO_4, filtered and evaporated. The resulting crude oil is purified by flash chromatography (DCM/MeOH=9/1) to afford the title compound as a colorless oil (239 mg, quantitative yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 9.81 and 9.82 (d, 1 H), 7.83 - 7.94 (m, 1 H), 7.44 - 7.54 (m, 2 H), 7.22 - 7.44 (m, 4 H), 6.54 - 6.73 (m, 2 H), 5.52 and 5.53 (d, 1 H), 4.61 - 4.87 (m, 1 H), 2.99 and 3.10 (ddd, 1 H), 2.59 (s, 3 H), 2.54 - 2.69 (m, 3 H), 2.02 - 2.39 (m, 2 H), 1.69 - 1.78 and 1.87 - 1.97 (m, 1 H), 0.94 - 1.70 (m, 4 H);

LC-MS (ESI POS): 379.3 (MH+).

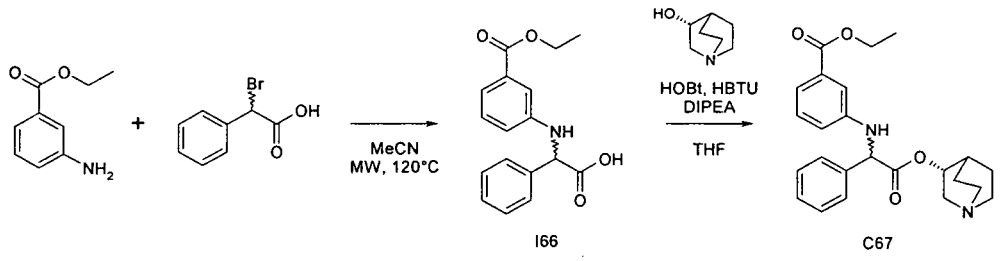
C65 listed in Table 11 is prepared as previously described for C64, using 3,5-difluoro-phenylamine instead of 1-(2-aminophenyl)ethanone.

Table 11

Compound	Structure	Yield and appearance	Analytical
C65	 Mixture of stereoisomer	86% yield White foam	LC-MS (ESI POS): 373.3 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.48 - 7.57 (m, 2 H), 7.28 - 7.46 (m, 3 H), 7.02 (d, 1 H), 6.19 - 6.49 (m, 3 H), 5.38 (d, 1 H), 4.66 - 4.80 (m, 1 H), 2.98 and 3.10 (ddd, 1 H), 2.54 - 2.69 (m, 3 H), 2.20 - 2.34 (m, 1 H), 2.01 - 2.13 (m, 1 H), 1.84 - 1.97 (m, 1 H), 1.05 - 1.78 (m, 4 H)

EXAMPLE 25

Preparation of 3-({[(R)-(1-aza-bicyclo[2.2.2]oct-3-yl)oxycarbonyl]-phenyl-methyl}-amino)-benzoic acid ethyl ester (C67)



Scheme 25

Preparation of 3-[(carboxy-phenyl-methyl)-amino]-benzoic acid ethyl ester hydrochloride (I66):

Ethyl 3-aminobenzoate (0.52 mL, 3.49 mmol), 2-bromo-2-phenylacetic acid (250 mg, 1.16 mmol), and DIPEA (0.41 mL, 2.32 mmol) are dissolved in acetonitrile (4 mL) and heated under MW irradiation at 100°C in a sealed vial for 30 minutes. Acetonitrile is evaporated and the crude is dissolved in DCM and washed with 1M HCl, water and brine. The organic layer is separated, dried (Na_2SO_4) and evaporated to obtain intermediate I114 as clear-brown oil

(348 mg, 89% yield).

Preparation of 3-({[(R)-(1-aza-bicyclo[2.2.2]oct-3-yl)oxycarbonyl]-phenyl-methyl}-amino)-benzoic acid ethyl ester (C67):

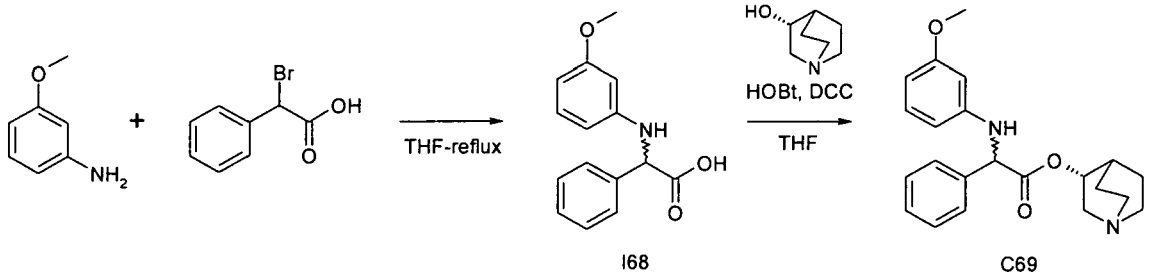
3-[(Carboxy-phenyl-methyl)-amino]-benzoic acid ethyl ester hydrochloride (I66) (161 mg, 0.48 mmol), 2-(1H-benzo[d][1,2,3]triazol-1-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (218 mg, 0.57 mmol), and HOBT (88 mg, 0.57 mmol) are dissolved in dry THF (10 mL). (R)-Quinuclidin-3-ol (61.0 mg, 0.48 mmol) and DIPEA (0.17 mL, 0.96 mmol) are added and the mixture is stirred under inert atmosphere overnight. THF is evaporated and the crude residue is dissolved in EtOAc and washed with sat. $NaHCO_3$, water and brine. The recovered organic layer is dried (Na_2SO_4), filtered and evaporated. The crude is purified by flash chromatography (DCM/MeOH=95/5) to afford the title compound as a yellow oil (154 mg, 79% yield, mixture of diastereoisomers).

^1H NMR (300 MHz, DMSO-d6) ppm: 7.50 - 7.61 (m, 2 H), 7.29 - 7.48 (m, 4 H), 7.14 - 7.29 (m, 2 H), 6.92 - 7.02 (m, 1 H), 6.70 (d, 1 H), 5.35 (d, 1 H), 4.56 - 4.92 (m, 1 H), 4.26 (q, 2 H), 3.09 - 3.25 (m, 1 H), 2.65 - 2.95 (m, 4 H), 2.21 - 2.38 (m, 1 H), 1.79 - 2.10 (m, 1 H), 1.36 - 1.80 (m, 4 H), 1.30 (t, 3 H);

LC-MS (ESI POS): 409.3 (MH+).

EXAMPLE 26

Preparation of (3-methoxy-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C69)



I68 C69

Scheme 26

Preparation of (3-methoxy-phenylamino)-phenyl-acetic acid (I68):

A solution of 2-bromo-2-phenylacetic acid (0.5 g, 2.28 mmol) and 3-methoxyaniline (0.54 mL, 4.56 mmol) in THF (12 mL) is refluxed for 4 hours. Solvent is removed under vacuum, the residue is taken up with 1M HCl and extracted with EtOAc. The organic phase is dried (Na_2SO_4), filtered and evaporated. The crude is purified by flash chromatography (DCM/MeOH=98/2 to 9/1) to obtain intermediate I116 as a white solid (0.58 g, 99% yield).

Preparation of (3-methoxy-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C69):

(3-Methoxy-phenylamino)-phenyl-acetic acid (0.58 g, 2.25 mmol), HOBT (0.45 g, 2.93 mmol) and DCC (0.60 g, 2.93 mmol) are dissolved in THF (100 mL) and stirred at RT for 20 minutes. Then, (R)-quinuclidin-3-ol (0.57 g, 4.51 mmol) is added and the resulting reaction is stirred at the same temperature for one day. The solvent is evaporated, the residue is taken up with EtOAc and the insoluble is filtered off. The organic solution is washed with 1M K_2CO_3 and then with brine. The crude is purified by flash chromatography (DCM/MeOH= 99/1 to 80:20) to obtain the title compound as a yellow solid (0.43 g, 52% yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm:

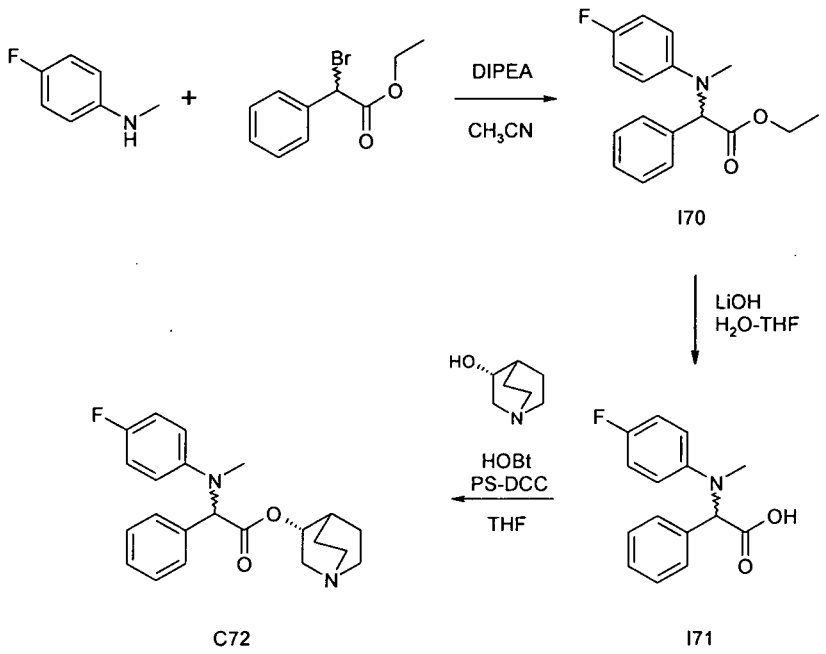
Diastereoisomer 1: 7.48 - 7.64 (m, 2 H), 7.22 - 7.47 (m, 3 H), 6.95 (t, 1 H), 6.23 - 6.38 (m, 3 H), 6.09 - 6.19 (m, 1 H), 5.25 (d, 1 H), 4.50 - 4.79 (m, 1 H), 3.64 (s, 3 H), 2.97 (ddd, 1 H), 2.20 - 2.71 (m, 4 H), 2.03 - 2.13 (m, 1 H), 1.83 - 1.95 (m, 1 H), 1.19 - 1.67 (m, 4 H);

Diastereoisomer 2: 7.48 - 7.64 (m, 2 H), 7.22 - 7.47 (m, 3 H), 6.95 (t, 1 H), 6.23 - 6.38 (m, 3 H), 6.09 - 6.19 (m, 1 H), 5.24 (d, 1 H), 4.50 - 4.79 (m, 1 H), 3.64 (s, 3 H), 3.04 - 3.14 (m, 1 H), 2.20 - 2.71 (m, 5 H), 1.68 - 1.74 (m, 1 H), 1.19 - 1.67 (m, 4 H);

LC-MS (ESI POS): 367.1 (MH+).

EXAMPLE 27

Preparation of [(4-fluoro-phenyl)-methyl-amino]-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C72)



Scheme 27

Preparation of [(4-fluoro-phenyl)-methyl-amino]-phenyl-acetic acid ethyl ester (I70):

4-Fluoro-N-methylaniline (0.33 g, 2.67 mmol) is added to a solution of ethyl 2-bromo-2-phenylacetate (0.36 mL, 2.06 mmol) in acetonitrile (6.86 mL) and DIPEA (0.47 ml, 2.67 mmol). The dark solution is stirred at 100°C under microwave irradiation for 1 hour. Then solvent is evaporated and the crude is purified by flash chromatography (Petroleum ether/EtOAc = 97/3) to obtain intermediate I118 as a yellow solid (0.59 g, 100 % yield).

Preparation of [(4-fluoro-phenyl)-methyl-amino]-phenyl-acetic acid hydrochloride (I71):

A solution of [(4-fluoro-phenyl)-methyl-amino]-phenyl-acetic acid ethyl ester (I70) (0.59 g, 2.05 mmol) in THF (10 mL) and water (10 mL) is

added lithium hydroxide hydrate (0.26 g, 6.14 mmol) is added. The reaction is stirred at RT for 3.5h and then at 70°C for 24h. 3N HCl is added till pH is about 1 and the mixture is evaporated. Water (15 mL) is added and the residue is triturated obtaining a pale brown suspension that is filtered on a buckner funnel, washed with water and then with acetonitrile. The solid is dried under vacuum at 40°C overnight to obtain intermediate I119 as a pale brown powder (0.44 g, 72 % yield).

Preparation of [(4-fluoro-phenyl)-methyl-amino]-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C72):

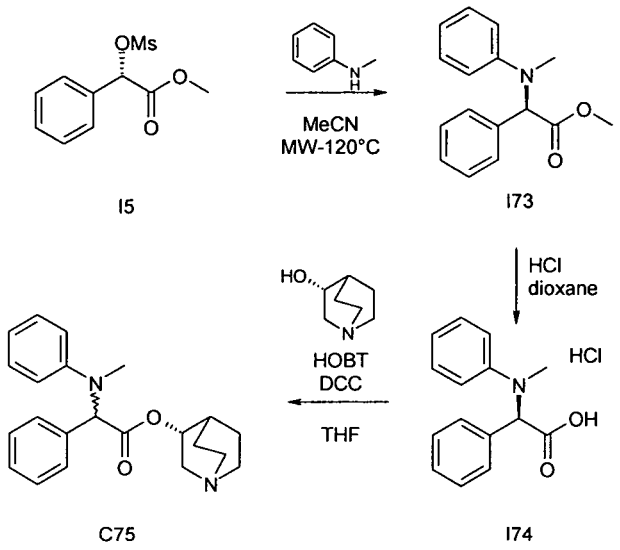
PS-DCC (1.02 g, 1.35 mmol, loading: 1.33 mmol/g) is suspended in dry THF (13.5 mL). Then HOBT (0.21 g, 1.35 mmol), [(4-fluoro-phenyl)-methyl-amino]-phenyl-acetic acid hydrochloride (I71) (0.20 g, 0.68 mmol) and (R)-quinuclidin-3-ol (0.26 g, 2.03 mmol) are added. The mixture is shaken at RT overnight. PS-DCC is filtered off, washed with EtOAc and THF. The solution is evaporated and the residue is partitioned between EtOAc and water. The organic phase is washed with sat. $NaHCO_3$, dried (Na_2SO_4) and evaporated. The crude is purified by flash chromatography (DCM/MeOH = 95/5) to afford the title compound as a colorless oil (209 mg, 84 % yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.26 - 7.49 (m, 5 H) 6.99 - 7.13 (m, 2 H) 6.83 - 6.99 (m, 2 H) 5.78 (d, 1 H) 4.74 - 4.88 (m, 1 H) 3.02 - 3.18 (m, 2 H) 2.56 - 2.79 (m, 5 H) 2.29 - 2.46 (m, 2 H) 1.76 - 1.93 (m, 1 H) 1.41 - 1.63 (m, 3 H) 1.19 - 1.39 (m, 1 H);

LC-MS (ESI POS): 369.2 (MH+).

EXAMPLE 28

Preparation of (methyl-phenyl-amino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C75)



Scheme 28

Preparation of (R)-(methyl-phenyl-amino)-phenyl-acetic acid methyl ester (I73):

N-methylaniline (299 ul, 2.76 mmol) is added to a solution of (S)-methyl 2-(methylsulfonyloxy)-2-phenylacetate (I5) (450 mg, 1.84 mmol) in acetonitrile (10 mL). The reaction is heated at 120°C for 15 minutes (microwave irradiation). 2N HCl (5 mL) is added and the mixture is extracted with EtOAc. The organic phase is dried over sodium sulphate and the solvent is evaporated to dryness. The crude is purified by flash chromatography on silica gel (Petroleum ether/Et_2O=9/1) to obtain intermediate I121 as an orange amorphous solid (125 mg, 27 % yield).

Preparation of (R)-(methyl-phenyl-amino)-phenyl-acetic acid hydrochloride (I74):

(R)-(Methyl-phenyl-amino)-phenyl-acetic acid methyl ester (I73) (125 mg, 0.49 mmol) is dissolved in dioxane (2 mL). 37% Hydrogen chloride in water (3.00 mL, 36.5 mmol) is added and the mixture is stirred at 70 °C for 18h. Then a

second portion of 37% hydrogen chloride in water (1.00 mL, 12.2 mmol) is added and the mixture is stirred at 70 °C for additional 36h. The mixture is cooled to RT and the white precipitate is filtered and washed with dioxane and Et_2O to obtain intermediate I122 as a white solid (97 mg, 71% yield).

Preparation of (methyl-phenyl-amino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C75):

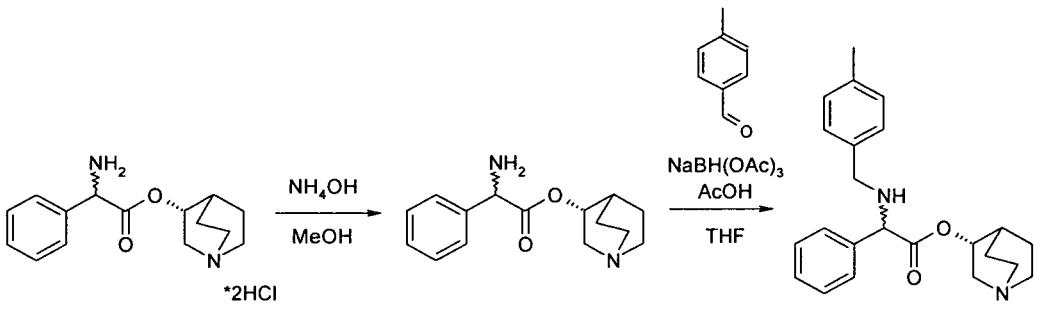
(R)-(Methyl-phenyl-amino)-phenyl-acetic acid hydrochloride (I74) (97 mg, 0.35 mmol), HOBT (107 mg, 0.70 mmol), DCC (144 mg, 0.70 mmol) and (R)-quinuclidin-3-ol (89 mg, 0.70 mmol) are dissolved in dioxane (5 mL) and the mixture is stirred at RT for 15h. The white precipitate is filtered and discarded whereas the clear solution is evaporated to dryness. The residue is dissolved in EtOAc and washed with sat. Na_2CO_3 and then brine. The organic phase is dried over sodium sulphate, filtered and evaporated to dryness. The resulting crude is purified by flash chromatography on silica gel (DCM/MeOH=97/3 to 95/5) to obtain the title compound as a pale yellow oil (46 mg, 38 % yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.29 - 7.53 (m, 5 H) 7.14 - 7.29 (m, 2 H) 6.86 - 6.99 (m, 2 H) 6.67 - 6.80 (m, 1 H) 5.84 and 5.83(s, 1 H) 4.73 - 4.88 (m, 1 H) 2.99 - 3.16 (m, 1 H) 2.75 and 2.71(s, 3 H) 2.53 - 2.69 (m, 3 H) 2.29 - 2.47 (m, 2 H) 1.74 - 1.95 (m, 1 H) 1.32 - 1.63 (m, 3 H) 1.12 - 1.30 (m, 1 H);

LC-MS (ESI POS): 351.3 (MH^+).

EXAMPLE 29

Preparation of (4-methyl-benzylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C77)



C25 I76 C77

Scheme 29

Preparation of amino-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (I76):

(R)-Quinuclidin-3-yl 2-amino-2-phenylacetate dihydrochloride (C25) (1.11 g, 3.33 mmol) is dissolved in MeOH (10 mL) and 32% NH_4OH (2.0 mL, 16.07 mmol) is added. The solution is stirred at RT for 30 sec. and then is evaporated under vacuum. The residue is dissolved in DCM/MeOH (4.5/0.5 mL) and about 1g of SiO_2 is added. The suspension is evaporated and the residue is loaded on a silica gel column and purified eluting with DCM/MeOH/NH_4OH = 9.2/0.8/0.1 to 9/1/0.1 to collect intermediate I124 as a pale yellow oil (635 mg, 73 % yield).

Preparation of (4-methyl-benzylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C77):

A solution of amino-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (I76) (100 mg, 0.38 mmol) in dry THF (3.84 mL), is added with 4-methylbenzaldehyde (68 mL, 0.57 mmol) and AcOH (0.5 mL, 8.73 mmol). The mixture is stirred at RT and sodium triacetoxyborohydride (163 mg, 0.77 mmol) is added. The reaction is stirred at RT for 1.5 hour then cyclohexane is added and the mixture is evaporated to dryness. The crude is purified by flash chromatography (DCM/MeOH/NH_4OH = 95/5/0.5) to obtain the title compound

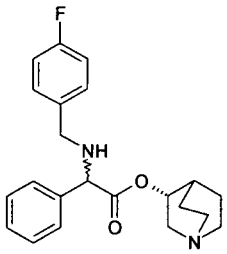
as a colorless oil (76 mg, 54 % yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d6) ppm: 7.25 - 7.51 (m, 5 H), 7.15 - 7.23 (m, 2 H), 7.03 - 7.15 (m, 2 H), 4.51 - 4.81 (m, 1 H), 4.33 (d, 1 H), 3.61 (s, 2 H), 2.85 - 3.19 (m, 1 H), 2.57 - 2.69 (m, 5 H), 2.28 (s, 3 H), 1.68 - 1.92 (m, 1 H), 0.91 - 1.64 (m, 4 H);

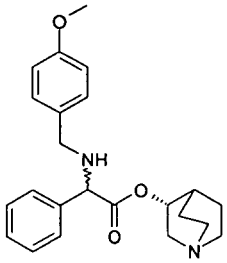
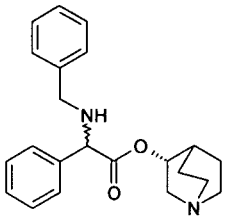
LC-MS (ESI POS): 365.2 (MH+).

The compounds listed in Table 12 are prepared as previously described for C77, using 4-fluorobenzaldehyde, 4-methoxybenzaldehyde and benzaldehyde instead of 4-methylbenzaldehyde.

Table 12

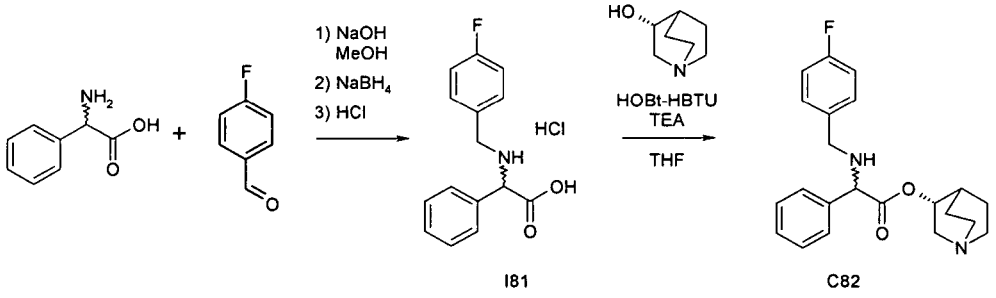
Compound	Structure	Yield and appearance	Analytical
C78	 Mixture of stereoisomer	64% yield Colorless oil	LC-MS (ESI POS): 369.1 (MH^+) ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.23 - 7.61 (m, 7 H), 7.01 - 7.23 (m, 2 H), 4.58 - 4.79 (m, 1 H), 4.34 (s, 1 H), 3.64 (s, 2 H), 2.99 and 3.07 (ddd, 1 H), 2.54 - 2.69 (m, 3 H), 2.08 - 2.46 (m, 2 H), 1.69 - 1.79 and 1.83 - 1.90 (m, 1 H), 1.03 - 1.64 (m, 4 H)

(continue)

C79	 Mixture of stereoisomer	55% yield Colorless oil	LC-MS (ESI POS): 381.2 (MH+) ^{1}H NMR (300 MHz, DMSO-d6) ppm: 7.25: - 7.50 (m, 5 H) 7.16 - 7.25 (m, 2 H) 6.81 - 6.92 (m, 2 H) 4.58 - 4.76 (m, 1 H) 4.32 (d, 1 H) 3.73 (s, 3 H) 3.59 (d, 2 H) 2.86 - 3.13 (m, 1 H) 2.53 - 2.67 (m, 5 H) 2.06 - 2.20 (m, 1 H) 1.68 - 1.90 (m, 1 H) 1.05 - 1.64 (m, 4 H)
C80	 Mixture of stereoisomer	64% yield Pale yellow oil	LC-MS (ESI POS): 351.3 (MH+) ^{1}H NMR (300 MHz, DMSO-d6) ppm: 7.07 - 7.54 (m, 10 H), 4.59 - 4.79 (m, 1 H), 4.35 (s, 1 H), 3.66 (s, 2 H), 2.97 - 3.14 (m, 1 H), 2.56 - 2.70 (m, 4 H), 2.17 - 2.40 (m, 1 H), 1.71 - 1.97 (m, 1 H), 0.99 - 1.69 (m, 4 H)

EXAMPLE 30

Alternative preparation of (4-fluoro-benzylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C82)



Scheme 30

Preparation of (4-fluoro-benzylamino)-phenyl-acetic acid hydrochloride (I81):

4-Fluorobenzaldehyde (0.25 mL, 2.38 mmol), 2-amino-2-phenylacetic acid

(300 mg, 1.98 mmol) and NaOH (79 mg, 1.98 mmol) are dissolved in MeOH (20 mL) and stirred at RT overnight. The reaction is cooled at 0°C and $NaBH_4$ (150 mg, 3.97 mmol) is added. After being stirred at 0°C for 30 min, the reaction is judged complete by UPLC-MS analysis. 4M HCl in dioxane is added dropwise till pH 5 and the precipitate is collected by suction filtration, washed with Et_2O and dried under vacuum at 40°C to obtain intermediate I129 as a white solid (587 mg, quantitative yield).

Preparation of (4-fluoro-benzylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C82):

A mixture of (4-fluoro-benzylamino)-phenyl-acetic acid hydrochloride (233 mg, 0.79 mmol), (R)-quinuclidin-3-ol (200 mg, 1.57 mmol), 2-(1H-benzo[d][1,2,3]triazol-1-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (596 mg, 1.57 mmol), TEA (0.22 mL, 1.57 mmol) and HOBT (241 mg, 1.57 mmol) in acetonitrile (10 mL) is stirred at RT for 48 hours. THF is removed under vacuum and the crude is partitioned between EtOAc and water. The organic phase is dried over sodium sulphate, filtered and evaporated to dryness. The crude is purified by preparative HPLC. The combined fractions are dried and partitioned between EtOAc and 2M K_2CO_3. The organic phase is dried over sodium sulphate, filtered and evaporated to dryness to afford the title compound as colorless oil (61 mg, 21% yield, mixture of diastereoisomers).

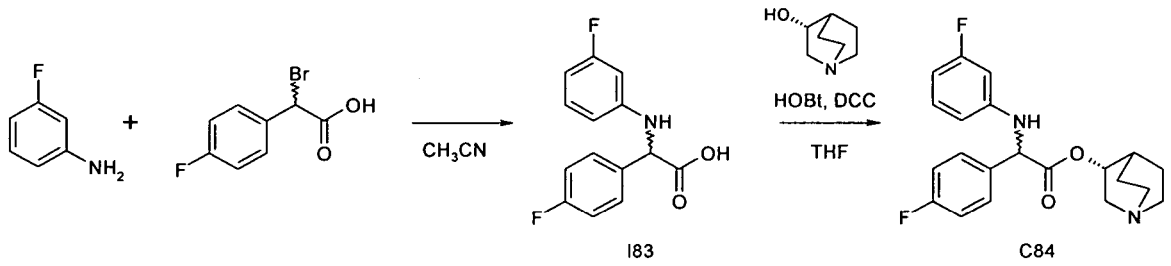
^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.25 - 7.63 (m, 7 H), 7.00 - 7.24 (m, 2 H), 4.58 - 4.79 (m, 1 H), 4.34 (s, 1 H), 3.64 (s, 2 H), 2.80 and 3.07 (ddd, 1 H), 2.54 - 2.69 (m, 3 H), 2.08 - 2.46 (m, 2 H), 1.69 - 1.79 and 1.83 - 1.90 (m, 1 H), 1.03 - 1.64 (m, 4 H);

LC-MS (ESI POS): 369.1 (MH^+).

EXAMPLE 31

Preparation of (4-fluoro-phenyl)-(3-fluoro-phenylamino)-acetic acid

(R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C84)



Scheme 31

Preparation of (4-fluoro-phenyl)-(3-fluoro-phenylamino)-acetic acid (I83):

A mixture of 2-bromo-2-(4-fluorophenyl)acetic acid (500 mg, 2.15 mmol) and 3-fluoroaniline (477 mg, 4.29 mmol) in acetonitrile (8 mL) is heated under microwave irradiation at 100°C for 50 minutes. Then 3-fluoroaniline (238 mg, 2.15 mmol) is added again and reaction is heated at 120°C for 45 minutes in a microwave oven (LC-MS monitoring: complete conversion). The organic solution is diluted with EtOAc and washed with 2N HCl and then with brine. The organic phase is dried over Na_2SO_4, filtered and the solvent is evaporated to give intermediate I131 as a white solid (510 mg, 90% yield).

Preparation of (4-fluoro-phenyl)-(3-fluoro-phenylamino)-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C84):

A mixture of (4-fluoro-phenyl)-(3-fluoro-phenylamino)-acetic acid (I83) (510 mg, 1.94 mmol), (R)-quinuclidin-3-ol (246 mg, 1.94 mmol), HOBT (356 mg, 2.32 mmol) and DCC (480 mg, 2.32 mmol) in THF (10 mL) is stirred at RT overnight (UPLC-MS monitoring: complete conversion). The solvent is evaporated, the crude is dissolved in EtOAc and the insoluble is filtered off. The clear solution is washed with 1N K_2CO_3 and then with brine. The organic layer is dried over Na_2SO_4, filtered and evaporated. The crude is purified by silica gel chromatography (EtOAc/MeOH= 8/2) to give the title compound as a yellow oil (360 mg, 50% yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d6):

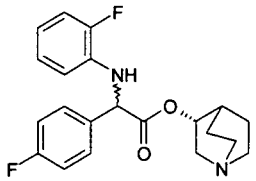
Diastereoisomer 1 of C84: 7.41 - 7.65 (m, 2 H), 7.15 - 7.33 (m, 2 H), 6.96 - 7.14 (m, 1 H), 6.67 (d, 1 H), 6.43 - 6.59 (m, 2 H), 6.20 - 6.42 (m, 1 H), 5.36 (d, 1 H), 4.46 - 4.88 (m, 1 H), 2.97 (ddd, 1 H), 2.53 - 2.72 (m, 3 H), 2.18 - 2.39 (m, 1 H), 2.01 - 2.16 (m, 1 H), 1.80 - 1.96 (m, 1 H), 1.21 - 1.66 (m, 4 H).

Diastereoisomer 2 of C84: 7.41 - 7.65 (m, 2 H), 7.15 - 7.33 (m, 2 H), 6.96 - 7.14 (m, 1 H), 6.67 (d, 1 H), 6.43 - 6.59 (m, 2 H), 6.20 - 6.42 (m, 1 H), 5.35 (d, 1 H), 4.46 - 4.88 (m, 1 H), 3.08 (ddd, 1 H), 2.53 - 2.72 (m, 5 H), 1.66 - 1.76 (m, 1 H), 1.21 - 1.66 (m, 4 H);

LC-MS (ESI POS): 373 (MH+).

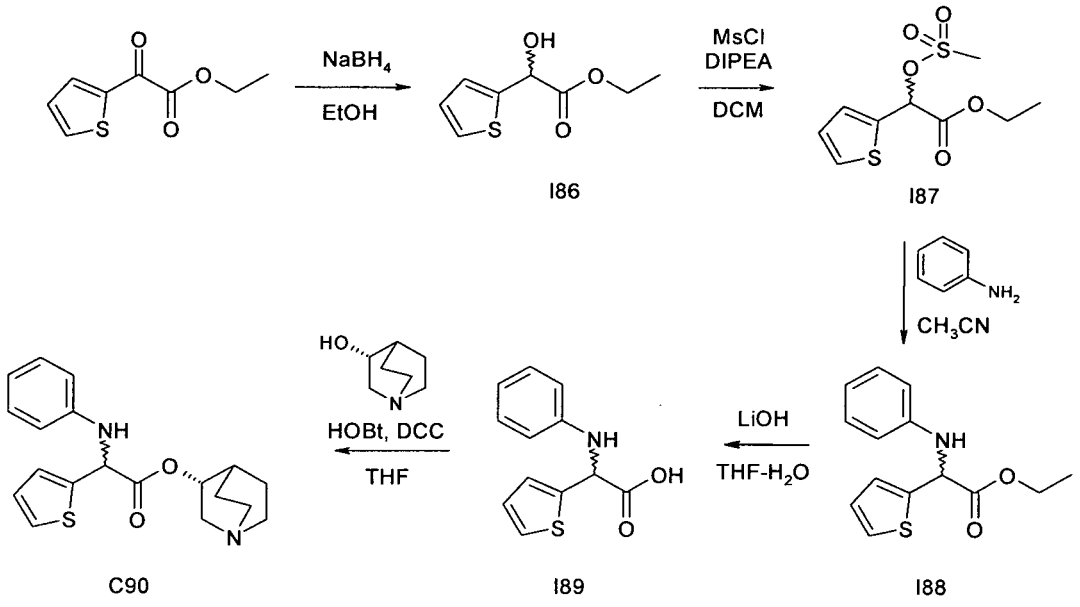
C85 listed in Table 13 is prepared as previously described for C84, using 2-fluoroaniline instead of 3-fluoroaniline.

Table 13

Compound	Structure	Yield and appearance	Analytical
C85	 Mixture of stereoisomer	53% yield White solid	LC-MS (ESI POS): 373.1 (MH^+) ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.49 - 7.66 (m, 2 H), 7.15 - 7.28 (m, 2 H), 7.07 (ddd, 1 H), 6.81 - 6.95 (m, 1 H), 6.50 - 6.78 (m, 2 H), 5.67 (d, 1 H), 5.40 (d, 1 H), 4.58 - 4.84 (m, 1 H), 3.07 (ddd, 1 H), 2.54 - 2.68 (m, 5 H), 1.64 - 1.77 (m, 1 H), 1.04 - 1.65 (m, 4 H)

EXAMPLE 32

Preparation of (R)-quinuclidin-3-yl 2-(phenylamino)-2-(thiophen-2-yl)acetate hydrochloride (C90)



Scheme 32

Preparation of hydroxy-thiophen-2-yl-acetic acid ethyl ester (I86):

A solution of ethyl 2-oxo-2-(thiophen-2-yl)acetate (5.00 g, 27.1 mmol) in ethanol (50 mL) is cooled at 0°C with an ice bath. $NaBH_4$ (0.31 g, 8.14 mmol) is added in four portion under stirring. The mixture is stirred at 0°C for 10 minutes, then allowed to warm at RT and stirred for additional 30 minutes. Reaction is concentrated under vacuum and the residue is partitioned between Et_2O and ice-cooled water. The organic layer is separated, washed with water and brine, dried over Na_2SO_4, filtered and evaporated to give a colorless liquid (5.05 g, 91% yield).

Preparation of ethyl 2-(methylsulfonyloxy)-2-(thiophen-2-yl)acetate (I87):

Hydroxy-thiophen-2-yl-acetic acid ethyl ester (4.58 g, 24.6 mmol) is dissolved in dry DCM (125 mL) and cooled at 0°C. DIPEA (5.15 mL, 29.5 mmol) and methanesulphonyl chloride (2.11 mL, 27.1 mmol) are added and the

resulting solution is stirred at RT for 1h. DIPEA (0.859 ml, 4.92 mmol) and methanesulphonyl chloride (0.19 mL, 2.46 mmol) are added again. After being stirred at room temperature for 1 additional hour, a third portion of DIPEA (0.43 mL, 2.46 mmol) and methanesulphonyl chloride (77 ul, 0.98 mmol) is added. After 1h the reaction is completed. The mixture is diluted with DCM, washed with sat. $NaHCO_3$, water and brine, dried (Na_2SO_4), filtered and evaporated. The resulting yellow oil is used in the next step without any further purification.

Preparation of ethyl 2-(phenylamino)-2-(thiophen-2-yl)acetate (I88):

Ethyl 2-(methylsulfonyloxy)-2-(thiophen-2-yl)acetate (I87) (5.7 g, 21.6 mmol), aniline (2.16 mL, 23.7 mmol) and DIPEA (4.52 mL, 25.9 mmol) are dissolved in acetonitrile (20 mL) to give a yellow solution which is heated under microwave irradiation in a sealed vial at 100°C for 15 minutes. Conversion complete by UPLC/MS-UV. Solvent is evaporated and the residue is dissolved in DCM and washed with water and brine, dried (Na_2SO_4), filtered and evaporated to dryness. The resulting crude is purified by flash chromatography (Petroleum ether/EtOAc = 85/15) to get desired compound as a yellow solid (4.33 g, 77% yield).

Preparation of 2-(phenylamino)-2-(thiophen-2-yl)acetic acid hydrochloride (I89):

Ethyl 2-(phenylamino)-2-(thiophen-2-yl)acetate (I88) (3.86 g, 14.8 mmol) and lithium hydroxide hydrate (1.24 g, 29.5 mmol) are dissolved in THF/water (20 mL/20 mL) and stirred at RT for 4h. THF is evaporated, the mixture is cooled to 0°C and 4M HCl in dioxane is added until pH is about 1. The resulting precipitate is collected by suction filtration and washed with water. The white solid is dried under vacuum at 40°C for 18h (3.09g, 78% yield).

Preparation of (R)-quinuclidin-3-yl 2-(phenylamino)-2-(thiophen-2-yl)acetate hydrochloride (C90):

2-(Phenylamino)-2-(thiophen-2-yl)acetic acid hydrochloride (I89) (359

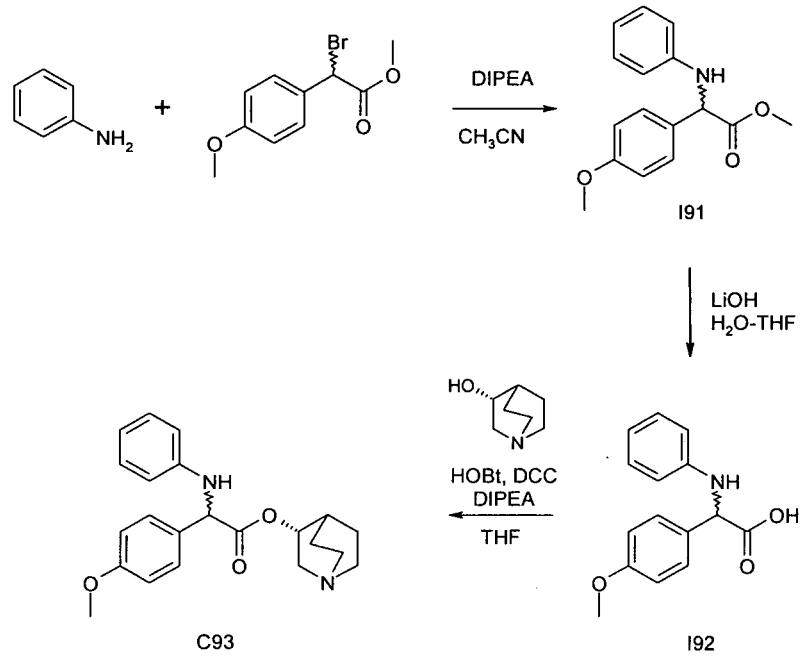
mg, 1.33 mmol), DCC (330 mg, 1.60 mmol) and HOBT (245 mg, 1.60 mmol) are dissolved in THF (15 mL). (R)-quinuclidin-3-ol (339 mg, 2.66 mmol) is added and the reaction mixture is stirred at RT for 16 hours. HOBT (20.4 mg, 0.13 mmol) and DCC (33.0 mg, 0.16 mmol) are added again and the mixture is stirred for additional 8 hours. HOBT (20.4 mg, 0.13 mmol), DCC (33.0 mg, 0.16 mmol), (R)-quinuclidin-3-ol (16.9 mg, 0.13 mmol) are added and the mixture is stirred for additional 16 hours. THF is evaporated and the resulting crude oil is dissolved in EtOAc and washed with water and brine. The organic phase is recovered, dried over Na_2SO_4, filtered and evaporated. The crude is first purified by flash chromatography (DCM/MeOH=9/1) and then by preparative HPLC. The pure fractions are collected and evaporated. The resulting TFA salt is dissolved in THF and passed through a PL-HCO_3 cartridge (Varian, 200 mg, 1.8 mmol/g HCO_3^-). THF is evaporated, the product is dissolved in dioxane (2 mL) and 4M HCl in dioxane (2 mL) is added. The solvent is evaporated and the residue is dried under vacuum for 24h to obtain the title compound as a brown solid (33 mg, 7% yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 10.01 (br. s., 1 H) 7.47 - 7.56 (m, 1 H) 7.21 - 7.29 (m, 1 H) 6.99 - 7.16 (m, 3 H) 6.71 - 6.82 (m, 2 H) 6.53 - 6.70 (m, 1 H) 5.64 and 5.61 (s, 1 H) 4.99 - 5.13 (m, 1 H) 3.03 - 3.28 (m, 4 H) 2.71 - 2.92 (m, 2 H) 1.42 - 2.28 (m, 5 H);

LC-MS (ESI POS): 343.1 (MH+).

EXAMPLE 33

Preparation of (4-methoxy-phenyl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C93)



Scheme 33

Preparation of (4-methoxy-phenyl)-phenylamino-acetic acid methyl ester (I91):

Methyl 2-bromo-2-(4-methoxyphenyl)acetate (1.10 g, 4.25 mmol), DIPEA (0.89 mL, 5.09 mmol), and aniline (0.43 mL, 4.67 mmol) are dissolved in acetonitrile (12 mL). The reaction is heated for 18 minutes at 100°C under microwave irradiation. Acetonitrile is evaporated and the residue is diluted with DCM and washed with water and brine, dried over Na_2SO_4, filtered and evaporated to dryness. The crude is purified by flash chromatography (Petroleum Ether/EtOAc = 9/1) to give intermediate I139 as a yellow oil (745 mg, 65% yield).

Preparation of (4-methoxy-phenyl)-phenylamino-acetic acid hydrochloride (I92):

(4-Methoxy-phenyl)-phenylamino-acetic acid methyl ester (953 mg,

3.51 mmol) and lithium hydroxide hydrate (295 mg, 7.03 mmol) are dissolved in THF (5 mL) and water (5 mL) and the resulting reaction is stirred overnight at RT (Conversion complete by UPLC-MS/UV). THF is evaporated, the aqueous phase is cooled at 0°C and acidified till pH 1 with 4M HCl in 1,4 dioxane. The precipitate is collected by suction filtration and the white solid is dried overnight at 45°C under vacuum (718 mg, 70% yield).

Preparation of (4-methoxy-phenyl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C93):

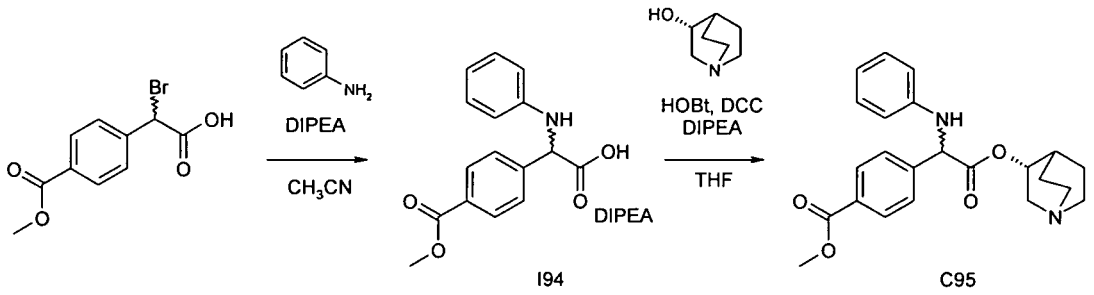
(4-Methoxy-phenyl)-phenylamino-acetic acid hydrochloride (I92) (300 mg, 1.02 mmol), DCC (253 mg, 1.23 mmol), and HOBT (188 mg, 1.23 mmol) are dissolved in THF (10 mL). DIPEA (0.36 mL, 2.04 mmol) and (R)-quinuclidin-3-ol (130 mg, 1.02 mmol) are added. The mixture is stirred ad RT for 16h. Then DCC (25.3 mg, 0.12 mmol), HOBT (18.8 mg, 0.12 mmol), DIPEA (36 uL, 0.204 mmol) and (R)-quinuclidin-3-ol (13.0 mg, 0.10 mmol) are added again and reaction is stirred for additional 32 hours. THF is evaporated and the residue is dissolved in EtOAc and washed with sat. $NaHCO_3$, H_2O and brine. The organic layer is dried (Na_2SO_4), filtered and evaporated. The crude residue is purified by flash chromatography (DCM/MeOH= 97/3 to 92/8) to obtain the title compound as a yellow solid (90 mg, 24% yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.34 - 7.63 (m, 2 H), 7.01 - 7.15 (m, 2 H), 6.87 - 7.01 (m, 2 H), 6.63 - 6.74 (m, 2 H), 6.52 - 6.62 (m, 1 H), 6.19 (d, 1 H), 5.17 (d, 1 H), 4.55 - 4.85 (m, 1 H), 3.74 (s, 3 H), 2.83 - 3.20 (m, 1 H), 2.03 - 2.69 (m, 5 H), 1.65 - 1.94 (m, 1 H), 0.93 - 1.63 (m, 4 H);

LC-MS (ESI POS): 367.3 (MH+).

EXAMPLE 34

Preparation of 4-{[(R)-(1-aza-bicyclo[2.2.2]oct-3-yl)oxycarbonyl]-phenylamino-methyl}-benzoic acid methyl ester (C95)



Scheme 34

Preparation of N-ethyl-N-isopropylpropan-2-amine 2-(4-(methoxycarbonyl)phenyl)-2-(phenylamino)acetate (I94):

2-Bromo-2-(4-(methoxycarbonyl)phenyl)acetic acid (700 mg, 2.56 mmol), aniline (0.23 mL, 2.56 mmol), and DIPEA (0.94 mL, 5.38 mmol) are dissolved in acetonitrile (5 mL). The reaction is stirred at 100°C under microwave irradiation for 15 minutes. Acetonitrile is evaporated and the residue is dissolved in DCM and washed with water and brine. The organic layer is dried (Na_2SO_4), filtered and evaporated. The crude compound is purified by flash chromatography (DCM/MeOH= 9/1) to obtain intermediate I142 as a white solid (381 mg, 37% yield).

Preparation of 4-{[(R)-(1-aza-bicyclo[2.2.2]oct-3-yl)oxycarbonyl]-phenylamino-methyl}-benzoic acid methyl ester (C95):

N-Ethyl-N-isopropylpropan-2-amine 2-(4-(methoxycarbonyl)phenyl)-2-(phenylamino)acetate (I94) (212 mg, 0.51 mmol), DCC (158 mg, 0.77 mmol), and HOBT (117 mg, 0.77 mmol) are dissolved in dry THF (5 mL). (R)-Quinuclidin-3-ol (195 mg, 1.53 mmol) is added and the mixture is stirred at RT for 2 days. A second portion of DCC (79 mg, 0.38 mmol), HOBT (58.7 mg, 0.38 mmol) and (R)-quinuclidin-3-ol (98 mg, 0.77 mmol) are added and the mixture is further stirred for 24h. Then THF is evaporated, the residue is

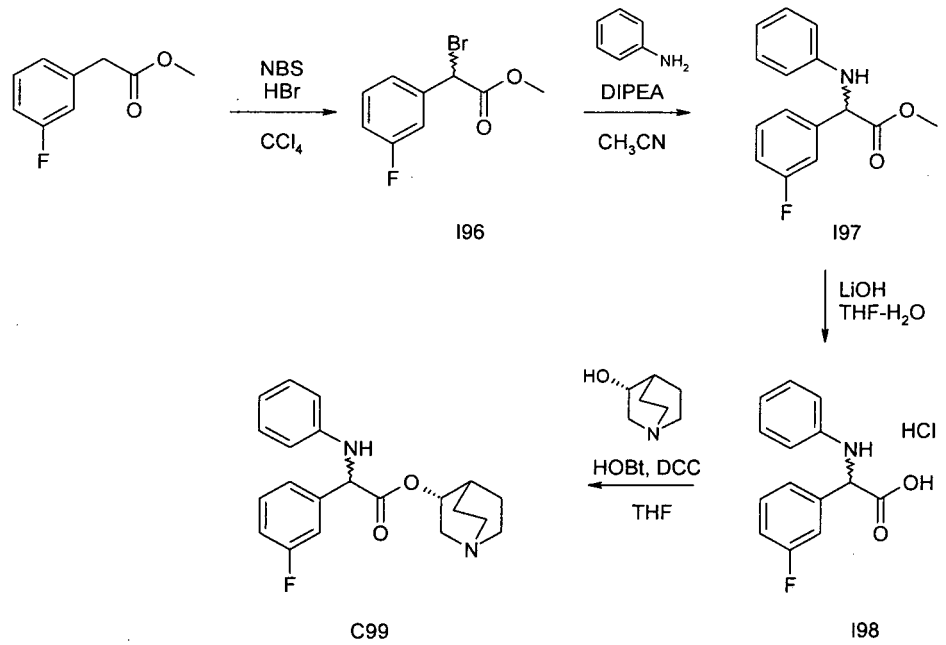
dissolved in EtOAc and washed with $NaHCO_3$, water and brine. The organic phase is dried (Na_2SO_4), filtered and evaporated. The crude is purified by preparative HPLC. The recovered fractions are evaporated, dissolved in EtOAc and washed with sat. $NaHCO_3$. The organic phase is dried (Na_2SO_4), filtered and evaporated to afford the desired compound as a colorless oil (42 mg, 21% yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.88 - 8.05 (m, 2 H), 7.51 - 7.76 (m, 2 H), 6.91 - 7.13 (m, 2 H), 6.71 (dd, 2 H), 6.50 - 6.64 (m, 1 H), 6.38 (d, 1 H), 5.42 (d, 1 H), 4.39 - 4.86 (m, 1 H), 3.85 (s, 3 H), 2.84 - 3.15 (m, 1 H), 2.54 - 2.67 (m, 4 H), 0.76 - 2.16 (m, 6 H);

LC-MS (ESI POS): 395.4 (MH+).

EXAMPLE 35

Preparation of (3-fluoro-phenyl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C99)



Scheme 35

Preparation of bromo-(3-fluoro-phenyl)-acetic acid methyl ester (I96):

Methyl 2-(3-fluorophenyl)acetate (1.90 g, 11.3 mmol) and N-bromo

succinimide (2.01 g, 11.3 mmol) are dissolved in CCl_4 (80 mL). HBr (64 ul, 0.56 mmol) is added and the mixture is stirred under reflux overnight. The mixture is cooled at RT, diluted with DCM and washed with sat. $NaHCO_3$, water and brine. The organic layer is dried (Na_2SO_4), filtered and evaporated obtaining intermediate I144 as a yellow oil (2.68 g, 96% yield).

Preparation of (3-fluoro-phenyl)-phenylamino-acetic acid methyl ester (I97):

Bromo-(3-fluoro-phenyl)-acetic acid methyl ester (I96) (300 mg, 1.21 mmol), DIPEA (0.32 mL, 1.82 mmol), and aniline (0.17 mL, 1.82 mmol) are dissolved in acetonitrile (4 mL) and heated under MW irradiation at 100°C for 1h. Acetonitrile is evaporated and the residue is purified by flash chromatography (Petroleum ether/EtOAc=95/5) to obtain intermediate I145 as a colorless oil (229 mg, 73% yield).

Preparation of (3-fluoro-phenyl)-phenylamino-acetic acid (I98):

(3-Fluoro-phenyl)-phenylamino-acetic acid methyl ester (I97) (229 mg, 0.88 mmol) and lithium hydroxide hydrate (74.1 mg, 1.77 mmol) are dissolved in THF/water (6 mL/2mL) and stirred at RT for 2h. THF is evaporated, the resulting basic aqueous solution is acidified till pH 1 with 1M HCl. The precipitate is recovered by suction filtration and washed with 1M HCl. The compound is dried at 40°C under vacuum overnight to get intermediate I146 as a white solid (186 mg, 75% yield).

Preparation of (3-fluoro-phenyl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C99):

PS-DCC (982 mg, 1.31 mmol, loading: 1.33 mmol/g) is suspended in dry THF (15 mL). (3-Fluoro-phenyl)-phenylamino-acetic acid hydrochloride (I98) (184 mg, 0.65 mmol), HOBT (200 mg, 1.31 mmol), and (R)-quinuclidin-3-ol (249 mg, 1.96 mmol) are added and the mixture is shaken at RT overnight. PS-DCC is filtered off and the filtrate is evaporated. The residue is dissolved in EtOAc and

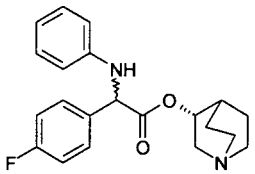
washed with $NaHCO_3$, water and brine. The organic layer is dried over Na_2SO_4, filtered and evaporated to dryness. The crude compound is purified by filtration through a pad of silica-gel using DCM/MeOH=9/1 as the eluent. The title compound is obtained as a colorless oil (129 mg, 56% yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d6) ppm: 7.31 - 7.52 (m, 3 H), 7.11 - 7.23 (m, 1 H), 6.98 - 7.11 (m, 2 H), 6.67 - 6.76 (m, 2 H), 6.51 - 6.63 (m, 1 H), 6.35 (d, 1 H), 5.35 and 5.36 (d, 1 H), 4.59 - 4.80 (m, 1 H), 2.97 and 3.07 (ddd, 1 H), 2.55 - 2.67 (m, 5 H), 1.67 - 1.74 and 1.81 - 1.95 (m, 1 H), 1.10 - 1.66 (m, 4 H);

LC-MS (ESI POS): 355.2 (MH^+).

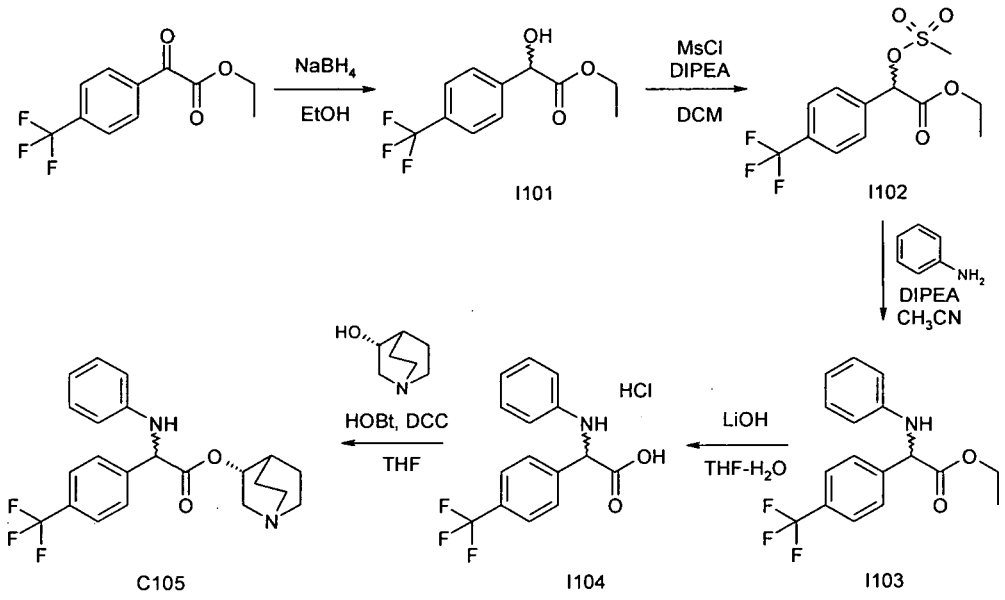
C100 listed in Table 14 is alternatively prepared as previously described for C99, using methyl 2-(4-fluorophenyl)acetate instead of methyl 2-(3-fluorophenyl)acetate.

Table 14

Compound	Structure	Yield and appearance	Analytical
C100	 Mixture of diastereoisomers	44% yield White solid	LC-MS (ESI POS): 355.0 (MH^+) ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.69 - 7.83 (m, 4 H), 7.01 - 7.16 (m, 2 H), 6.65 - 6.79 (m, 2 H), 6.53 - 6.64 (m, 1 H), 6.42 (d, 1 H), 5.46 and 5.47 (d, 1 H), 4.66 - 4.81 (m, 1 H), 2.99 and 3.10 (ddd, 1 H), 2.54 - 2.88 (m, 4 H), 2.04 - 2.41 (m, 1 H), 0.92 - 1.97 (m, 5 H)

EXAMPLE 36

Preparation of phenylamino-(4-trifluoromethyl-phenyl)-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C105)



Scheme 36

Preparation of hydroxy-(4-trifluoromethyl-phenyl)-acetic acid ethyl ester (I101):

Ethyl 2-oxo-2-(4-(trifluoromethyl)phenyl)acetate (500 mg, 2.03 mmol) is dissolved in absolute EtOH (10 mL) and cooled at 0°C under N_2. $NaBH_4$ (38.4 mg, 1.02 mmol) is added in two portions and the resulting suspension is allowed to warm to RT and stirred for 45 minutes. The solvent is evaporated, the resulting residue is diluted with Et_2O and cool water is added. The organic layer is separated, washed with water and brine, dried over Na_2SO_4, filtered and evaporated obtaining intermediate I149 as a colorless oil (440 mg, 87% yield).

Preparation of methanesulfonyloxy-(4-trifluoromethyl-phenyl)-acetic acid ethyl ester (I102):

Hydroxy-(4-trifluoromethyl-phenyl)-acetic acid ethyl ester (I101) (440 mg, 1.77 mmol) and DIPEA (0.43 mL, 2.48 mmol) are dissolved in dry DCM

(17 mL) and cooled at 0°C under N_2. Methanesulfonyl chloride (0.18 mL, 2.30 mmol) is added dropwise to the solution and the resulting mixture is allowed to warm to RT and stirred for 3h. The mixture is diluted with DCM and washed with sat. $NaHCO_3$, water and brine. The organic layer is dried (Na_2SO_4), filtered and evaporated to obtain intermediate I150 as a yellow oil (578 mg, quantitative yield), which is used in the next step without any further purification.

Preparation of phenylamino-(4-trifluoromethyl-phenyl)-acetic acid ethyl ester (I103):

Methanesulfonyloxy-(4-trifluoromethyl-phenyl)-acetic acid ethyl ester (I102) (594 mg, 1.82 mmol), aniline (0.25 mL, 2.73 mmol), and DIPEA (0.48 mL, 2.73 mmol) are dissolved in acetonitrile (4 mL). The reaction is heated under microwave irradiation at 100°C for 1 hour and 30 minutes. Aniline (0.17 mL, 1.820 mmol) is added again and the reaction is heated under microwave irradiation at 100°C for 3 hours. Acetonitrile is removed under vacuum and the residue is purified by flash chromatography (Petroleum ether/DCM=75/25) to afford intermediate I151 as a yellow oil (195 mg, 60% yield).

Preparation of phenylamino-(4-trifluoromethyl-phenyl)-acetic acid hydrochloride (I104):

Phenylamino-(4-trifluoromethyl-phenyl)-acetic acid ethyl ester (I103) (195 mg, 0.60 mmol) and lithium hydroxide hydrate (50.6 mg, 1.21 mmol) are dissolved in THF/water (9 mL/3mL) and stirred at RT for 4h and then at 40°C for 1h. THF is evaporated and the remaining aqueous solution is acidified with 1M HCl till pH 1. The resulting precipitate is recovered by suction filtration, washed with 1M HCl and dried under vacuum at 40°C overnight to obtain intermediate I152 as a white solid (200 mg, quantitative yield).

Preparation of phenylamino-(4-trifluoromethyl-phenyl)-acetic acid

(R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C105):

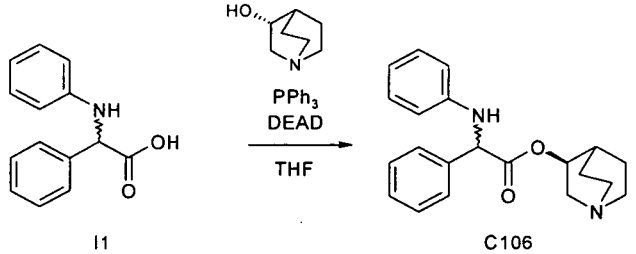
PS-DCC (907 mg, 1.21 mmol, loading: 1.33 mmol/g) is suspended in dry THF (10 mL). Phenylamino-(4-trifluoromethyl-phenyl)-acetic acid hydrochloride (I104) (200 mg, 0.60 mmol), HOBT (185 mg, 1.21 mmol), and (R)-quinuclidin-3-ol (230 mg, 1.81 mmol) are added and the mixture is shaken at RT overnight. PS-DCC is filtered off, the filtrate is evaporated and the residue is dissolved in EtOAc and washed with $NaHCO_3$, water and brine. The organic layer is dried over Na_2SO_4, filtered and evaporated to dryness. The resulting crude compound is purified by filtration through a pad of silica-gel using DCM/MeOH=9/1 as the eluent. The title compound is obtained as a colorless oil (110 mg, 45% yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.69 - 7.83 (m, 4 H), 7.01 - 7.16 (m, 2 H), 6.65 - 6.79 (m, 2 H), 6.53 - 6.64 (m, 1 H), 6.42 (d, 1 H), 5.46 and 5.47 (d, 1 H), 4.66 - 4.81 (m, 1 H), 2.99 and 3.10 (ddd, 1 H), 2.54 - 2.88 (m, 4 H), 2.04 - 2.41 (m, 1 H), 0.92 - 1.97 (m, 5 H);

LC-MS (ESI POS): 405.2 (MH^+).

EXAMPLE 37

Preparation of (S)-quinuclidin-3-yl 2-phenyl-2-(phenylamino)-acetate (C106)



I1 C106

Scheme 37

A solution of 2-phenyl-2-(phenylamino)acetic acid (I1) (500 mg, 2.20 mmol), (R)-quinuclidin-3-ol (280 mg, 2.20 mmol) and triphenylphosphine (577 mg, 2.20 mmol) in dry THF (7 mL) cooled at 0°C, is added with (E)-diethyl

diazene-1,2-dicarboxylate (0.35 mL, 2.20 mmol) and the reaction is stirred 2h at RT. The solvent is removed under vacuum and the residue is taken up with EtOAc, washed with 5% $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated to dryness. The resulting yellow oil is purified by flash chromatography (EtOAc/MeOH/NH_4OH =90/10/0.1 to 70/30/0.1) to obtain desired product as a white powder (78.0 mg, 10% yield, mixture of diastereoisomer).

^1H NMR (300 MHz, DMSO-d_6) ppm

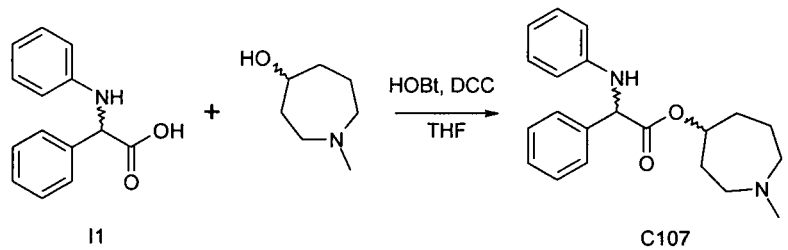
Diastereoisomer 1 of C106: 7.48 - 7.62 (m, 2 H), 7.24 - 7.45 (m, 3 H), 6.98 - 7.11 (m, 2 H), 6.66 - 6.75 (m, 2 H), 6.51 - 6.62 (m, 1 H), 6.27 (d, 1 H), 5.25 (d, 1 H), 4.58 - 4.82 (m, 1 H), 3.08 (dd, 1 H), 2.54 - 2.70 (m, 5 H), 1.62 - 1.75 (m, 1 H), 0.97 - 1.60 (m, 4 H);

Diastereoisomer 2 of C106: 7.48 - 7.62 (m, 2 H), 7.24 - 7.45 (m, 3 H), 6.98 - 7.11 (m, 2 H), 6.66 - 6.75 (m, 2 H), 6.51 - 6.62 (m, 1 H), 6.27 (d, 1 H), 5.26 (d, 1 H), 4.58 - 4.82 (m, 1 H), 2.95 (m, 1 H), 2.54 - 2.70 (m, 4 H), 2.02 - 2.14 (m, 1 H), 1.86 - 1.95 (m, 1 H), 0.97 - 1.60 (m, 4 H);

LC-MS (ESI POS): 337.2 (MH+).

EXAMPLE 38

Preparation of phenyl-phenylamino-acetic acid 1-methyl-azepan-4-yl ester (C107)



I1 C107

Scheme 38

A mixture of 2-phenyl-2-(phenylamino)acetic acid (I1) (175 mg, 0.77 mmol), DCC (192 mg, 0.92 mmol), HOBt (124 mg, 0.92 mmol) and 1-methyl-azepan-4-ol (100 mg, 0.77 mmol) in dry THF (100 mL) is stirred at RT overnight

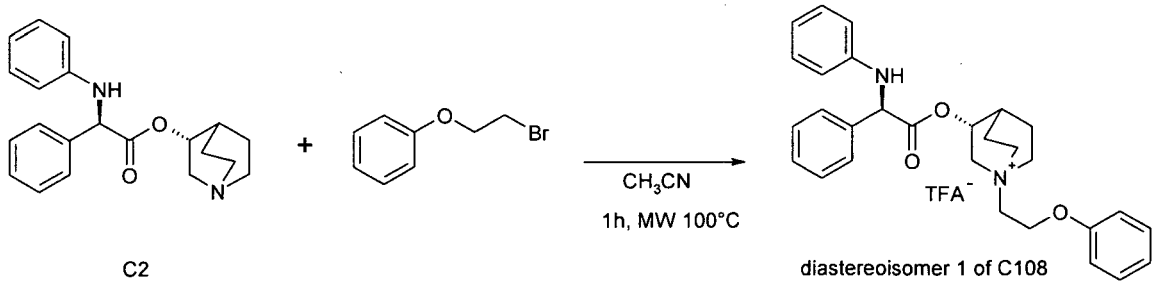
under nitrogen flowstream (UPLC-MS monitoring: complete conversion). The solvent is evaporated and the residue is taken up with aq. HCl and washed with EtOAc. The aqueous phase is basified with $NaHCO_3$ and extracted with DCM (three times). The organic layers are combined, dried over Na_2SO_4, filtered and evaporated to dryness. The resulting crude is first purified by flash chromatography (DCM to DCM/MeOH=95/5) and then by preparative LC-MS. The purified compound is partitioned between sat. $NaHCO_3$ and DCM, the organic phase is dried over Na_2SO_4, filtered and evaporated under vacuum to give 53 mg of the title compound as brown oil (20% yield, mixture of diastereoisomers).

^{1}H NMR (300 MHz, CHLOROFORM-d) ppm: 12.76 (br. s., 1 H), 7.30 - 7.62 (m, 6 H), 7.07 - 7.23 (m, 2 H), 6.50 - 6.84 (m, 3 H), 5.15 - 5.39 (m, 1 H), 5.09 (d, 1 H), 3.21 - 3.79 (m, 2 H), 2.60 (d, 3 H), 1.80 - 3.15 (m, 8 H);

LC-MS (ESI POS): 339.2 (MH^+).

EXAMPLE 39

Preparation of (R)-1-(2-phenoxy-ethyl)-3-((R)-2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane (Diastereoisomer 1 of C108)



C2 diastereoisomer 1 of C108

Scheme 39

A solution of (R)-quinuclidin-3-yl 2-phenyl-2-(phenylamino)acetate (diastereoisomer 1 of C2) (127 mg, 0.38 mmol), α-bromophenethole is added (91.2 mg, 0.45 mmol) and the mixture reacted in a closed vessel under MW irradiation for 1 hr at 100°C (LC-MS monitoring: complete conversion). The resulting crude is purified by preparative LC-MS to obtain the title compound

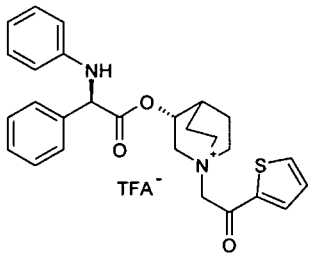
as a pale yellow solid (18.9 mg, 14% yield, trifluoroacetate salt, single diastereoisomer).

^{1}H NMR (300 MHz, DMSO-d6 + Na_2CO_3) ppm: 7.46 - 7.69 (m, 2H), 7.21 - 7.46 (m, 5H), 6.89 - 7.16 (m, 5H), 6.66 - 6.80 (m, 2H), 6.58 (t, 1H), 6.36 (d, 1H), 5.34 (d, 1H), 4.99 - 5.21 (m, 1H), 4.34 (t, 2H), 3.86 - 4.08 (m, 1H), 3.39 - 3.72 (m, 5H), 3.11 (d, 1H), 2.78 - 3.02 (m, 1H), 2.20 - 2.39 (m, 1 H), 1.61 - 2.15 (m, 4H);

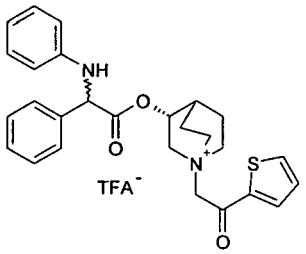
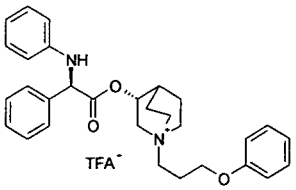
LC-MS (ESI POS): 457.3 (MH^+).

Final compounds listed in Table 15 are prepared as previously described for C108, by alkylation of suitable compounds (Diastereoisomer 1 of C2, Diastereoisomer 2 of C2, C2, Diastereoisomer 1 of C3, Diastereoisomer 2 of C3, C12, C4, Diastereoisomer 2 of C22, C43 and C30) and the commercially available alkylating agents.

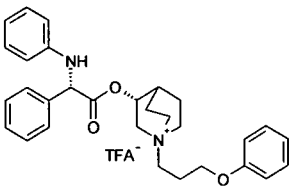
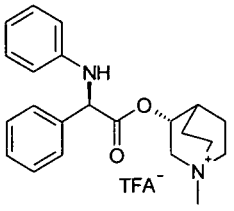
Table 15

Compound	Structure	Yield and Appearance	Analytical
Diastereoisomer 1 of C109	 Single diastereoisomer	16% yield Pale yellow oil	LC-MS (ESI POS): 461.2 (MH^+) ^{1}H NMR (300 MHz, DMSO-d6) ppm: 8.21 (dd, 1H), 8.05 (dd, 1H), 7.49 - 7.63 (m, 2H), 7.27 - 7.48 (m, 4H), 6.98 - 7.17 (m, 2H), 6.67 - 6.79 (m, 2H), 6.59 (t, 1H), 5.38 (s, 1H), 5.12 - 5.27 (m, 1H), 4.97 (s, 2H), 4.07 (ddd, 1H), 3.42 - 3.78 (m, 4H), 3.15 - 3.42 (m, 1H), 2.30 - 2.44 (m, 1H), 1.81 - 2.14 (m, 4H)

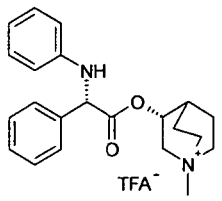
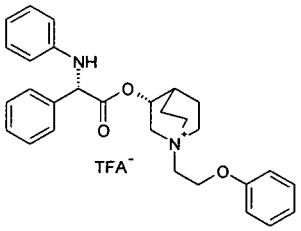
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C109	 Mixture of diastereoisomers	61% yield Pale yellow oil	LC-MS (ESI POS): 461.2 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 8.21 (dd, 1H), 8.07 (dd, 1H), 7.50 - 7.65 (m, 2H), 7.23 - 7.48 (m, 4H), 6.96 - 7.19 (m, 2H), 6.65 - 6.80 (m, 2H), 6.52 - 6.65 (m, 1H), 5.34 (s, 1H), 5.12 - 5.27 (m, 1H), 5.00 - 5.07 (m, 2H), 4.00 - 4.17 (m, 1H), 3.31 - 3.97 (m, 5H), 2.10 - 2.15 (m, 1H), 1.88 - 2.04 (m, 2H), 1.63 - 1.83 (m, 1H), 1.36 - 1.63 (m, 1H)
Diastereoisomer 1 of C110	 Single diastereoisomer	33% yield Brownish oil	LC-MS (ESI POS): 471.3 (MH^+) ^1H NMR (300 MHz, DMSO-d6 +Na_2CO_3) ppm: 7.50 - 7.65 (m, 2H), 7.25 - 7.50 (m, 5H), 7.03 - 7.25 (m, 2H), 6.87 - 7.03 (m, 3H), 6.69 - 6.83 (m, 2H), 6.61 (t, 1H), 6.37 (d, 1H), 5.35 (d, 1H), 5.01 - 5.22 (m, 1H), 4.01 (t, 2H), 3.72 - 3.91 (m, 1H), 3.36 - 3.50 (m, 3H), 3.10 - 3.25 (m, 2H), 2.89 (d, 1H), 2.67 - 2.82 (m, 1H), 2.22 - 2.38 (m, 1H), 1.56 - 2.15 (m, 6H)

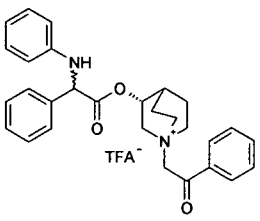
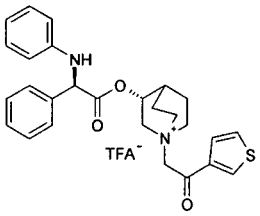
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Diastereoisomer 2 of C110	 Single diastereoisomer	79% yield Pale yellow oil	LC-MS (ESI POS): 471.3(MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.56 (dd, 2H), 7.24 - 7.49 (m, 5H), 7.05 - 7.13 (m, 2H), 6.92 - 7.00 (m, 3H), 6.66 - 6.80 (m, 2H), 6.53 - 6.66 (m, 1H), 5.31 (s, 1H), 5.01 - 5.21 (m, 1H), 3.88 - 4.16 (m, 3H), 3.21 - 3.52 (m, 7H), 1.77 - 2.42 (m, 5H), 1.58 - 1.73 (m, 1H), 1.36 - 1.57 (m, 1H) $[\alpha]_D$=-24.48° (c=0.14, MeOH)
Diastereoisomer 1 of C111	 Single diastereoisomer	28% yield Brownish oil	LC-MS (ESI POS): 351.3 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.50 - 7.64 (m, 2H), 7.29 - 7.50 (m, 3H), 7.01 - 7.23 (m, 2H), 6.68 - 6.83 (m, 2H), 6.53 - 6.68 (m, 1H), 5.34 (s, 1H), 5.00 - 5.24 (m, 1H), 3.80 (ddd, 1H), 3.21 - 3.42 (m, 3H), 2.97 (dt, 1H), 2.86 (s, 3H), 2.79 - 2.92 (m, 1H), 2.20 - 2.36 (m, 1H), 1.75 - 2.01 (m, 4H)

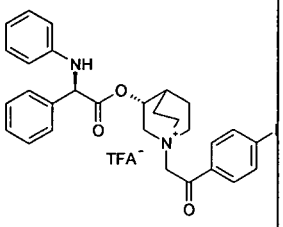
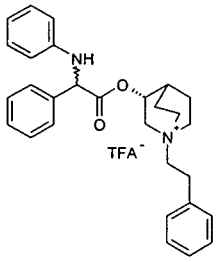
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Diastereoisomer 2 of C111	 Single diastereoisomer	72% yield Pale yellow oil	LC-MS (ESI POS): 351.3 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.48 - 7.63 (m, 2H), 7.24 - 7.48 (m, 3H), 6.99 - 7.17 (m, 2H), 6.50 - 6.80 (m, 3H), 5.29 (s, 1H), 4.99 - 5.19 (m, 1H), 3.71 - 3.94 (m, 1H), 3.08 - 3.54 (m, 5H), 2.95 (s, 3H), 1.94 - 2.15 (m, 1H), 1.68 - 1.94 (m, 2H), 1.56 - 1.68 (m, 1H), 1.29 - 1.56 (m, 1H) $[\alpha]_D$= -6.43° (c=0.14, MeOH)
Diastereoisomer 2 of C112	 Single diastereoisomer	65% yield Pale yellow oil	LC-MS (ESI POS): 457.3 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.47 - 7.65 (m, 2H), 7.22 - 7.47 (m, 5H), 6.86 - 7.19 (m, 5H), 6.65 - 6.81 (m, 2H), 6.50 - 6.65 (m, 1H), 6.34 (br. s., 1H), 5.31 (s, 1H), 5.01 - 5.21 (m, 1H), 4.40 - 4.46 (m, 2H), 3.88 - 4.13 (m, 1H), 3.66 - 3.74 (m, 2H), 3.43 - 3.51 (m, 5H), 2.02 - 2.17 (m, 1H), 1.72 - 2.02 (m, 3H), 1.39 - 1.72 (m, 1H) $[\alpha]_D$=-26.00° (c=0.14, MeOH)

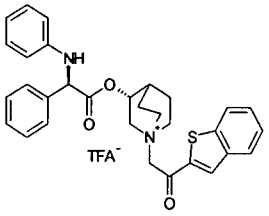
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C113	 Mixture of diastereoisomers	69% yield Pale yellow oil	LC-MS (ESI POS): 455.3 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 9.38 (br. s., 1H), 7.50 - 7.72 (m, 2H), 7.26 - 7.50 (m, 3H), 6.98 - 7.25 (m, 2H), 6.68 - 6.83 (m, 2H), 6.52 - 6.68 (m, 1H), 5.34 (s, 1H), 4.92 - 5.18 (m, 1H), 3.57 - 3.67 (m, 1H), 3.05 - 3.33 (m, 3H), 2.57 - 2.81 (m, 2H), 2.08 - 2.30 (m, 1H), 1.63 - 1.94 (m, 4H)
Diastereoisomer 1 of C114	 Single diastereoisomer	14% yield brown oil	LC-MS (ESI POS): 461.1 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 8.60 (dd, 1 H), 7.74 (dd, 1 H), 7.50 – 7.64 (m, 3 H), 7.26 – 7.49 (m, 3 H), 6.95 – 7.22 (m, 2 H), 6.66 – 6.81 (m, 2 H), 6.51 – 6.66 (m, 1 H), 6.36 (br. S., 1 H), 5.38 (s, 1 H), 5.12 – 5.29 (m, 1 H), 4.94 (s, 2 H), 3.95 – 4.17 (m, 1 H), 3.50 – 3.82 (m, 5 H), 2.31 – 2.43 (m, 1 H), 1.69 – 2.21 (m, 4 H)

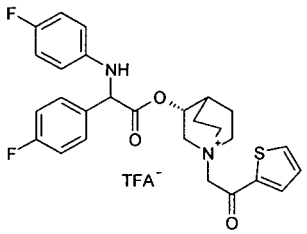
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Diastereoisomer 1 of C115	 Single diastereoisomer	59% yield colorless oil	LC-MS (ESI POS): 473.2 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.94 – 8.19 (m, 2 H), 7.53 – 7.68 (m, 2 H), 7.26 – 7.53 (m, 5 H), 7.00 – 7.22 (m, 2 H), 6.68 – 6.84 (m, 2 H), 6.52 – 6.68 (m, 1 H), 6.36 (br. S., 1 H), 5.38 (s, 1 H), 5.17 – 5.30 (m, 1 H), 5.07 (s, 2 H), 4.06 (ddd, 1 H), 3.54 – 3.74 (m, 3 H), 3.48 (d, 1 H), 3.30 – 3.43 (m, 1 H), 2.30 – 2.42 (m, 1 H), 1.85 – 2.14 (m, 4 H) $[\alpha]_D$= -46.15° (c=0.26, MeOH)
C116	 Mixture of diastereoisomers	67% yield colorless oil	LC-MS (ESI POS): 441.2 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.52 - 7.64 (m, 2 H), 7.21 - 7.51 (m, 8 H), 6.99 - 7.20 (m, 2 H), 6.67 - 6.83 (m, 2 H), 6.52 - 6.67 (m, 1 H), 6.35 (br. s., 1 H), 5.35 (s, 1 H), 5.07 - 5.24 (m, 1 H), 3.77 - 3.88 (m, 1 H), 3.43 - 3.57 (m, 1 H), 3.17 - 3.43 (m, 4 H), 2.92 - 3.12 (m, 2 H), 2.76 - 2.92 (m, 2 H), 2.32 (br. s., 1 H), 1.34 - 2.16 (m, 4 H)

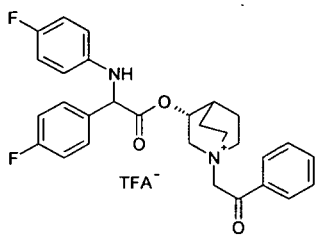
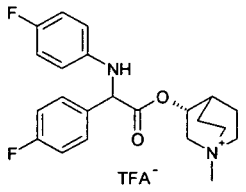
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Diastereoisomer 1 of C117	 Single diastereoisomer	13% yield brown amorphous solid	LC-MS (ESI POS): 511.2 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 8.46 (d, 1 H), 8.04 - 8.22 (m, 2 H), 7.49 - 7.69 (m, 4 H), 7.28 - 7.49 (m, 3 H), 7.00 - 7.18 (m, 2 H), 6.69 - 6.80 (m, 2 H), 6.54 - 6.67 (m, 1 H), 6.36 (d, 1 H), 5.39 (d, 1 H), 5.17 - 5.30 (m, 1 H), 5.11 (s, 2 H), 3.94 - 4.19 (m, 1 H), 3.37 - 3.77 (m, 5 H), 2.31 - 2.43 (m, 1 H), 1.88 - 2.12 (m, 4 H) $[\alpha]_D$= -47.81° (c=0.21, MeOH)

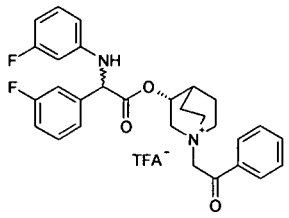
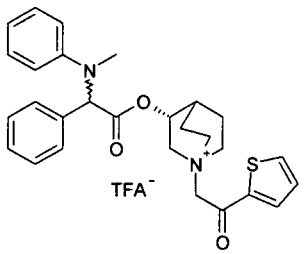
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Diastereoisomer 1 of C118	 Single diastereoisomer	22% yield Yellow oil	LC-MS (ESI POS): 497.1 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 8.20 (dd, 1H) 8.04 (dd, 1H) 7.53 - 7.68 (m, 2H) 7.34 (dd, 1H) 7.17 - 7.30 (m, 2H) 6.85 - 7.00 (m, 2H) 6.63 - 6.79 (m, 2H) 5.40 (s, 1H) 5.13 - 5.26 (m, 1H) 4.89 - 5.07 (m, 2H) 3.97 - 4.13 (m, 1H) 3.34 - 3.73 (m, 5H) 2.35 (br. s., 1H) 1.83 - 2.16 (m, 4H) $[\alpha]_D$= -33.13° (c=0.23, MeOH)

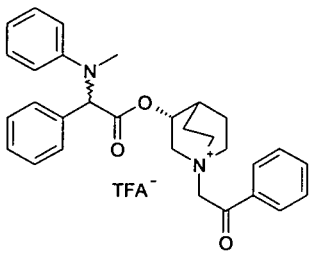
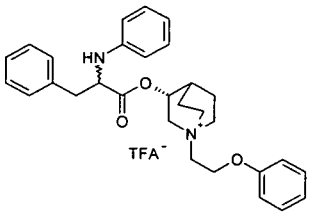
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Diastereoisomer 1 of C119	 Single diastereoisomer	16% yield Yellow oil	LC-MS (ESI POS): 491.2 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.91 - 8.00 (m, 2H) 7.70 - 7.82 (m, 1H) 7.55 - 7.69 (m, 4H) 7.20 - 7.32 (m, 2H) 6.84 - 7.01 (m, 2H) 6.65 - 6.80 (m, 2H) 5.41 (s, 1H) 5.18 - 5.27 (m, 1H) 5.10 (s, 2H) 3.97 - 4.13 (m, 1H) 3.33 - 3.73 (m, 6H) 2.37 (br. s., 1H) 1.80 - 2.16 (m, 4H) $[\alpha]_D$= -57.20° (c=0.20, MeOH)
Diastereoisomer 1 of C120	 Single diastereoisomer	19% yield Brown oil	LC-MS (ESI POS): 387.2 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.52 - 7.70 (m, 2 H), 7.13 - 7.35 (m, 2 H), 6.85 - 7.04 (m, 2 H), 6.61 - 6.82 (m, 2 H), 6.34 (br. s., 1 H), 5.35 (s, 1 H), 4.93 - 5.21 (m, 1 H), 3.72 - 3.91 (m, 1 H), 3.16 - 3.32 (m, 3 H), 2.94 - 3.11 (m, 2 H), 2.90 (s, 3 H), 2.24 - 2.31 (m, 1 H), 1.74 - 2.02 (m, 4 H)

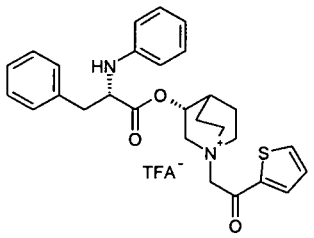
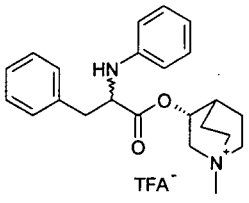
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C121	 Mixture of diastereoisomers	23% yield Pale yellow oil	LC-MS (ESI POS): 491.6 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.90 - 8.04 (m, 2 H), 7.69 - 7.83 (m, 1 H), 7.55 - 7.68 (m, 2 H), 7.34 - 7.55 (m, 3 H), 7.01 - 7.28 (m, 2 H), 6.79 (br. s., 1 H), 6.50 - 6.69 (m, 2 H), 6.29 - 6.50 (m, 1 H), 5.55 (br. s., 1 H), 5.21 - 5.32 (m, 1 H), 5.12 (s, 2 H), 3.99 - 4.13 (m, 1 H), 3.46 - 3.72 (m, 5 H), 2.31 - 2.45 (m, 1 H), 1.51 - 2.22 (m, 4 H)
C122	 Mixture of diastereoisomers	49% yield Pale yellow oil	LC-MS (ESI POS): 475.2 (MH^+) ^1H NMR (300 MHz, DMSO-d_6 +TFA) ppm: 8.21 (dd, 1H) 8.06 (dd, 1H) 7.31 - 7.50 (m, 6H) 7.17 - 7.30 (m, 2H) 6.89 - 6.99 (m, 2H) 6.70 - 6.80 (m, 1H) 5.96 (s, 1H) 5.25 - 5.37 (m, 1H) 5.03 (d, 2H) 4.08 - 4.24 (m, 1H) 3.53 - 3.74 (m, 4H) 3.39 - 3.51 (m, 1H) 2.76 (s, 3H) 2.21 - 2.33 (m, 1H) 1.92 - 2.11 (m, 2H) 1.67 - 1.90 (m, 1H) 1.47 - 1.65 (m, 1H)

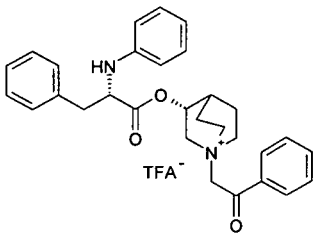
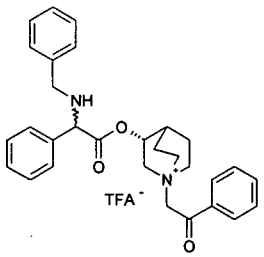
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C123	 Mixture of diastereoisomers	56% yield Yellow oil	LC-MS (ESI POS): 469.3(MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.89 - 8.06 (m, 2 H), 7.69 - 7.89 (m, 1 H), 7.55 - 7.69 (m, 2 H), 7.32 - 7.55 (m, 5 H), 7.18 - 7.32 (m, 2 H), 6.89 - 7.07 (m, 2 H), 6.67 - 6.86 (m, 1 H), 5.98 (s, 1 H), 5.26 - 5.44 (m, 1 H), 5.15 (br. s., 2 H), 4.02 - 4.30 (m, 1 H), 3.43 - 3.76 (m, 5 H), 2.77 (s, 3 H), 2.18 - 2.39 (m, 1 H), 1.41 - 2.15 (m, 4 H)
C124	 Mixture of diastereoisomers	60% yield Brown oil	LC-MS (ESI POS): 471.3 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.15 - 7.46 (m, 7H), 6.88 - 7.15 (m, 5H), 6.44 - 6.74 (m, 3H), 4.89 - 5.15 (m, 1H), 4.38 - 4.47 (m, 2H), 4.35 (t, 1H), 3.96 (ddd, 1H), 3.60 - 3.76 (m, 2H), 3.41 - 3.60 (m, 3H), 3.21 - 3.41 (m, 2H), 3.09 (d, 2H), 1.76 - 2.09 (m, 3H), 1.44 - 1.76 (m, 2H)

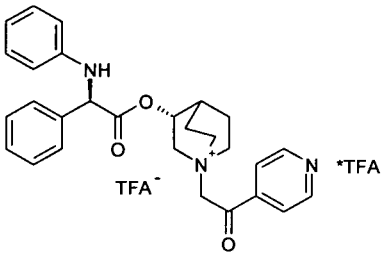
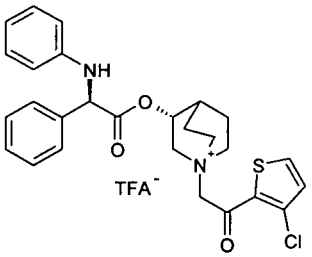
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Diastereoisomer 1 of C125	 Single diastereoisomer	35% yield Brown oil	LC-MS (ESI POS): 475.2 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 8.21 (dd, 1H), 8.07 (dd, 1H), 7.18 - 7.40 (m, 6H), 6.96 - 7.17 (m, 2H), 6.48 - 6.74 (m, 3H), 5.08 - 5.19 (m, 1H), 5.05 (d, 1H), 4.99 (d, 1H), 4.23 - 4.48 (m, 1H), 4.05 (dd, 1H), 3.26 - 3.83 (m, 5H), 2.94 - 3.24 (m, 2H), 1.84 - 2.06 (m, 3H), 1.60 - 1.84 (m, 2H) $[\alpha]_D$= -13.26° (c=0.35, MeOH)
C126	 Mixture of diastereoisomers	49% yield Brown oil	LC-MS (ESI POS): 365.3 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.17 - 7.45 (m, 5H), 6.98 - 7.17 (m, 2H), 6.56 - 6.67 (m, 3H), 4.85 - 5.14 (m, 1H), 4.23 - 4.43 (m, 1H), 3.80 (ddd, 1H), 3.14 - 3.51 (m, 5H), 3.09 (d, 2H), 2.92 (s, 3H), 1.71 - 1.98 (m, 3H), 1.39 - 1.69 (m, 2H)

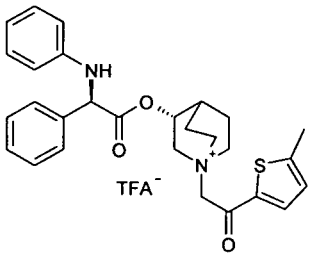
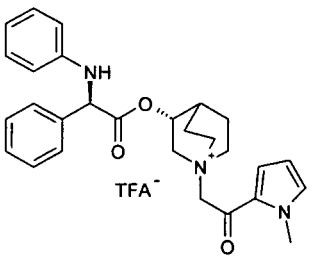
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Diastereoisomer 1 of C127	 Single diastereoisomer	25% yield Pale yellow oil	LC-MS (ESI POS): 469.2 (MH^+) 1H NMR (300 MHz, DMSO-d6) ppm: 7.88 - 8.05 (m, 2 H), 7.70 - 7.84 (m, 1 H), 7.51 - 7.70 (m, 2 H), 7.18 - 7.44 (m, 5 H), 6.98 - 7.18 (m, 2 H), 6.49 - 6.81 (m, 3 H), 6.12 (d, 1 H), 5.14 (s, 2 H), 5.02 - 5.14 (m, 1 H), 4.26 - 4.55 (m, 1 H), 3.92 - 4.21 (m, 1 H), 3.50 - 3.73 (m, 5 H), 3.14 (dd, 1 H), 3.08 (dd, 1 H), 1.82 - 2.07 (m, 3 H), 1.58 - 1.82 (m, 2 H) $[\alpha]_D$= -15.84° (c=0.365, MeOH)
C128	 Mixture of diastereoisomers	22% yield Colorless oil	LC-MS (ESI POS): 469.3 (MH^+) 1H NMR (300 MHz, DMSO-d6) ppm: 7.88 - 8.11 (m, 2 H), 7.69 - 7.88 (m, 1 H), 7.38 - 7.66 (m, 12 H), 5.25 - 5.46 (m, 2 H), 4.98 - 5.25 (m, 2 H), 3.95 - 4.28 (m, 3 H), 3.77 (d, 1 H), 3.43 - 3.70 (m, 4 H), 1.31 - 2.43 (m, 5 H)

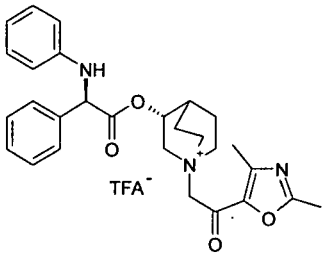
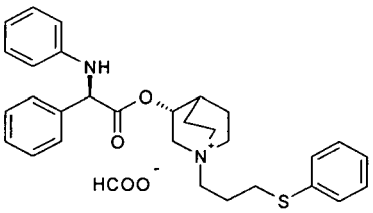
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Diastereoisomer 1 of C129	 Single diastereoisomer	45% yield amorphous brown solid	LC-MS (ESI POS): 456.1 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 8.80 - 9.01 (m, 2 H), 7.71 - 7.92 (m, 2 H), 7.51 - 7.67 (m, 2 H), 7.27 - 7.51 (m, 3 H), 7.01 - 7.18 (m, 2 H), 6.68 - 6.83 (m, 2 H), 6.51 - 6.67 (m, 1 H), 5.39 (s, 1 H), 5.15 - 5.30 (m, 1 H), 5.09 (s, 2 H), 3.97 - 4.16 (m, 1 H), 3.51 - 3.69 (m, 3 H), 3.32 - 3.49 (m, 2 H), 2.31 - 2.43 (m, 1 H), 1.82 - 2.15 (m, 4 H) $[\alpha]_D$=-36.13° (c=0.3, MeOH)
Diastereoisomer 1 of C130	 Single diastereoisomer	25% yield Light brown oil	LC-MS (ESI POS): 494.9 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 8.23 (d, 1 H), 7.53 - 7.62 (m, 2 H), 7.28 - 7.49 (m, 4 H), 6.99 - 7.18 (m, 2 H), 6.68 - 6.83 (m, 2 H), 6.60 (m, 1 H), 6.26 - 6.46 (m, 1 H), 5.32 - 5.47 (m, 1 H), 5.13 - 5.25 (m, 1 H), 4.94 (s, 2 H), 3.98 - 4.21 (m, 1 H), 3.51 - 3.69 (m, 2 H), 3.13 - 3.36 (m, 3 H), 2.32 - 2.41 (m, 1 H), 1.78 - 2.16 (m, 4 H)

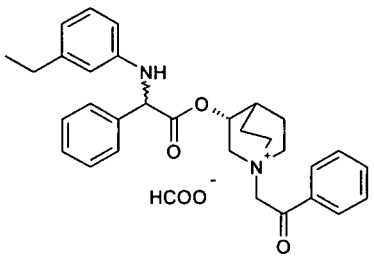
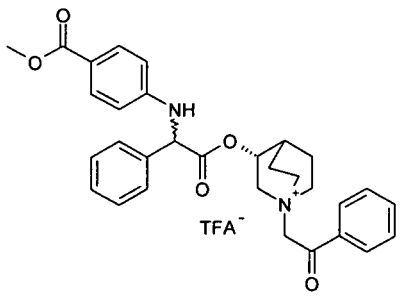
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Diastereoisomer 1 of C131	 Single diastereoisomer	22% yield Yellow oil	LC-MS (ESI POS): 475.03 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.89 (d, 1 H), 7.50 - 7.62 (m, 2 H), 7.27 - 7.48 (m, 3 H), 6.99 - 7.18 (m, 3 H), 6.67 - 6.82 (m, 2 H), 6.52 - 6.65 (m, 1 H), 6.24 - 6.46 (m, 1 H), 5.30 - 5.43 (m, 1 H), 5.15 - 5.27 (m, 1 H), 4.88 (s, 2 H), 3.97 - 4.13 (m, 1 H), 3.56 - 3.72 (m, 3 H), 3.10 - 3.38 (m, 2 H), 2.57 (s, 3 H), 2.31 - 2.41 (m, 1 H), 1.74 - 2.15 (m, 4 H)
Diastereoisomer 1 of C132	 Single diastereoisomer	21% yield Brown oil	LC-MS (ESI POS): 458.1 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.50 - 7.62 (m, 2 H), 7.29 - 7.48 (m, 4 H), 7.22 (dd, 1 H), 7.04 - 7.13 (m, 2 H), 6.69 - 6.78 (m, 2 H), 6.52 - 6.63 (m, 1 H), 6.39 (br. s., 1 H), 6.24 (dd, 1 H), 5.37 (br. s., 1 H), 5.08 - 5.23 (m, 1 H), 4.64 (s, 2 H), 3.94 - 4.16 (m, 1 H), 3.88 (s, 3 H), 3.62 - 3.79 (m, 2 H), 3.20 - 3.44 (m, 3 H), 2.31 - 2.41 (m, 1 H), 1.79 - 2.13 (m, 4 H)

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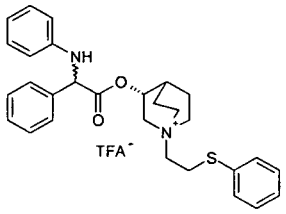
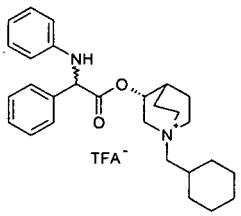
Diastereoisomer 1 of C133	 Single diastereoisomer	18% yield Brown oil	LC-MS (ESI POS): 474.1 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.53 - 7.63 (m, 2 H), 7.32 - 7.48 (m, 3 H), 7.10 (m, 2 H), 6.69 - 6.80 (m, 2 H), 6.50 - 6.65 (m, 1 H), 6.38 (s, 1 H), 5.29 - 5.49 (m, 1 H), 5.10 - 5.29 (m, 1 H), 4.74 (s, 2 H), 3.91 - 4.16 (m, 1 H), 3.40 - 3.70 (m, 5 H), 2.48 (br. s., 3 H), 2.41 (s, 3 H), 2.31 - 2.39 (m, 1 H), 1.66 - 2.07 (m, 4 H)
Diastereoisomer 1 of C134	 Single diastereoisomer	37% yield Pale yellow oil	LC-MS (ESI POS): 487.04 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.50 - 7.59 (m, 2 H), 7.20 - 7.48 (m, 9 H), 6.99 - 7.13 (m, 2 H), 6.67 - 6.81 (m, 2 H), 6.53 - 6.65 (m, 1 H), 6.36 (d, 1 H), 5.34 (d, 0 H), 4.93 - 5.16 (m, 0 H), 3.66 - 3.92 (m, 1 H), 3.14 - 3.39 (m, 8 H), 2.91 - 3.06 (m, 1 H), 1.32 - 2.16 (m, 7 H) formiate ion: 8.36 (s, 2 H) $[\alpha]_D$=-24.14° (c=0.29, MeOH)

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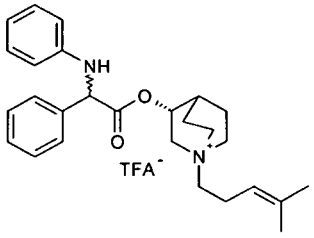
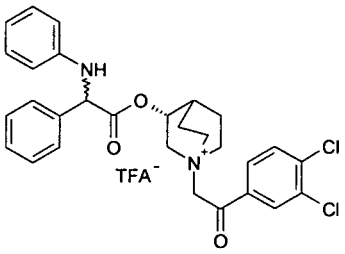
C135	 Mixture of diastereoisomer	18% yield Colorless oil	LC-MS (ESI POS): 483.2 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 8.51 (s, 1 H), 7.91 - 8.04 (m, 2 H), 7.67 - 7.82 (m, 1 H), 7.50 - 7.67 (m, 4 H), 7.30 - 7.49 (m, 3 H), 7.00 (t, 1 H), 6.59 - 6.66 (m, 1 H), 6.50 - 6.58 (m, 1 H), 6.44 - 6.50 (m, 1 H), 6.30 (d, 1 H), 5.29 - 5.44 (m, 1 H), 5.21 - 5.27 (m, 1 H), 5.12 and 5.20 (s, 2 H), 4.00 - 4.24 (m, 1 H), 3.45 - 3.85 (m, 5 H), 2.47 (q, 2 H), 2.10 - 2.17 and 2.31 - 2.40 (m, 1 H), 1.43 - 2.09 (m, 4 H), 1.12 (t, 3 H)
C136	 Mixture of diastereoisomers	41% yield Pale yellow solid	LC-MS (ESI POS): 513.2 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.89 - 8.07 (m, 2 H), 7.68 - 7.85 (m, 2 H), 7.52 - 7.67 (m, 5 H), 7.31 - 7.49 (m, 3 H), 7.06 - 7.28 (m, 1 H), 6.55 - 6.98 (m, 2 H), 5.37 - 5.60 (m, 1 H), 5.20 - 5.32 (m, 1 H), 4.99 - 5.20 (m, 2 H), 3.98 - 4.27 (m, 1 H), 3.75 (s, 3 H), 3.39 - 3.71 (m, 5 H), 2.07 - 2.45 (m, 1 H), 1.43 - 2.07 (m, 4 H)

The compounds listed in Table 16 are prepared as previously described for C108 by reaction of an equimolar mixture of diastereoisomer 1 and 2 of C2 with the suitable alkylating reagent.

Table 16

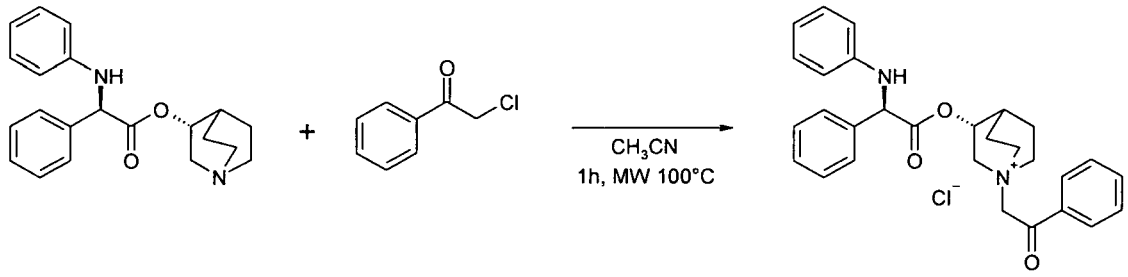
Compound	Structure	Yield and Appearance	Analytical
C137	 Mixture of diastereoisomers	10% yield Pale yellow oil	LC-MS (ESI POS): 473.2 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.50 - 7.63 (m, 2 H), 7.20 - 7.50 (m, 8 H), 7.07 (dd, 2 H), 6.64 - 6.83 (m, 2 H), 6.48 - 6.64 (m, 1 H), 6.35 (d, 1 H), 5.33 (d, 1 H), 5.00 - 5.20 (m, 1 H), 3.74 - 3.93 (m, 1 H), 3.36 - 3.55 (m, 9 H), 2.87 - 3.02 (m, 1 H), 2.31 - 2.45 (m, 1 H), 2.04 - 2.07 (m, 1 H), 1.75 - 2.01 (m, 4 H)
C138	 Mixture of diastereoisomers	15% yield Pale yellow oil	LC-MS (ESI POS): 433.2 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.48 - 7.65 (m, 2 H), 7.26 - 7.48 (m, 3 H), 6.93 - 7.21 (m, 2 H), 6.67 - 6.83 (m, 2 H), 6.55 - 6.67 (m, 1 H), 5.33 (s, 1 H), 5.00 - 5.19 (m, 1 H), 3.68 - 4.01 (m, 1 H), 3.36 (br. s., 4 H), 2.66 - 3.14 (m, 3 H), 1.41 - 2.15 (m, 10 H), 0.87 - 1.42 (m, 7 H)

(continue)

C139	 Mixture of diastereoisomers	15% yield Pale yellow oil	LC-MS (ESI POS): 419.3 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.51 - 7.67 (m, 2 H), 7.28 - 7.49 (m, 3 H), 6.99 - 7.19 (m, 2 H), 6.67 - 6.85 (m, 2 H), 6.52 - 6.67 (m, 1 H), 5.33 (s, 1 H), 5.07 - 5.21 (m, 1 H), 4.87 - 5.07 (m, 1 H), 3.66 - 3.94 (m, 1 H), 3.28 - 3.55 (m, 3 H), 3.09 - 3.28 (m, 2 H), 2.82 - 3.08 (m, 2 H), 1.74 - 2.43 (m, 7 H), 1.63 (s, 3 H), 1.69 (s, 3 H)
C140	 Mixture of diastereoisomers	16% yield Pale yellow oil	LC-MS (ESI POS): 523.3 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 8.16 - 8.27 (m, 1 H), 7.92 (d, 2 H), 7.53 - 7.66 (m, 2 H), 7.27 - 7.49 (m, 3 H), 7.00 - 7.16 (m, 2 H), 6.68 - 6.81 (m, 2 H), 6.52 - 6.66 (m, 1 H), 5.37 (s, 1 H), 5.17 - 5.27 (m, 1 H), 4.94 - 5.17 (m, 2 H), 3.92 - 4.25 (m, 1 H), 3.65 - 3.81 (m, 1 H), 3.54 - 3.69 (m, 3 H), 3.30 - 3.54 (m, 1 H), 1.38 - 2.45 (m, 5 H)

EXAMPLE 40

Preparation of (R)-1-(2-oxo-2-phenyl-ethyl)-3-((R)-2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane (Diastereoisomer 1 of C141)



diastereoisomer 1 of C2 — diastereoisomer 1 of C141

Scheme 40

A solution of (R)-phenyl-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (Diastereoisomer 1 of C2) (153 mg, 0.45 mmol), is added with α-chloroacetophenone (107 mg, 0.54 mmol) and the mixture reacted in a closed vessel under MW irradiation for 1hr at 100°C (LC-MS monitoring: complete conversion). The resulting crude is purified by flash

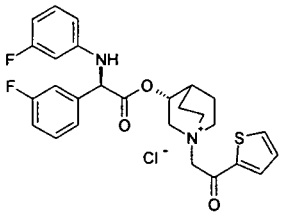
chromatography (DCM/MeOH=9/1) to obtain the title compound as a white solid (108.9 mg, 50% yield, chloride salt, single diastereoisomer).

^{1}H NMR (400 MHz, DMSO-d6) ppm: 7.96 (d, 2H) 7.70 - 7.81 (m, 1H) 7.58 (d, 2H) 7.62 (d, 2H) 7.29 - 7.47 (m, 3H) 7.09 (t, 2H) 6.74 (d, 2H) 6.59 (t, 1H) 6.41 (d, 1H) 5.39 (d, 1H) 5.16 - 5.26 (m, 1H) 5.13 (s, 2H) 4.08 (ddd, 1H) 3.47 - 3.71 (m, 4 H) 3.35 - 3.47 (m, 1H) 2.36 (br. s., 1H) 1.84 - 2.13 (m, 4H);

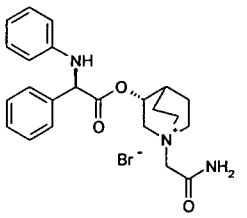
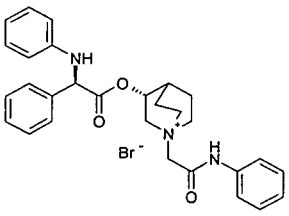
LC-MS (ESI POS): 455.27 (MH^+).

The compounds listed in Table 17 are prepared as previously described for C33 by reaction of C12, diastereoisomer 1 of C2 or C24 with the commercially available alkylating agents

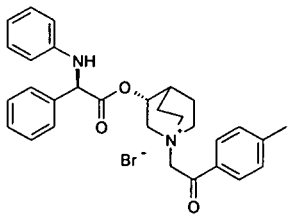
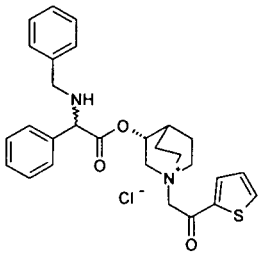
Table 17

Compound	**Structure**	**Yield and Appearance**	**Analytical**
Diastereoisomer 1 of C142	 Single diastereoisomer	25% yield Pale yellow solid	LC-MS (ESI POS): 497.1 (MH^+) ^{1}H NMR (300 MHz, DMSO-d6) ppm: 8.15 - 8.27 (m, 1 H), 7.99 - 8.15 (m, 1 H), 7.29 - 7.53 (m, 4 H), 7.02 - 7.27 (m, 2 H), 6.81 (d, 1 H), 6.48 - 6.66 (m, 2 H), 6.25 - 6.48 (m, 1 H), 5.44 - 5.62 (m, 1 H), 5.14 - 5.31 (m, 1 H), 5.05 (s, 2 H), 3.96 - 4.23 (m, 1 H), 3.74 - 3.93 (m, 1 H), 3.66 (br. s., 2 H), 3.37 - 3.61 (m, 2 H), 1.37 - 2.42 (m, 5 H) $[\alpha]_D$= -37.51° (c=0.225, MeOH)

(continue)

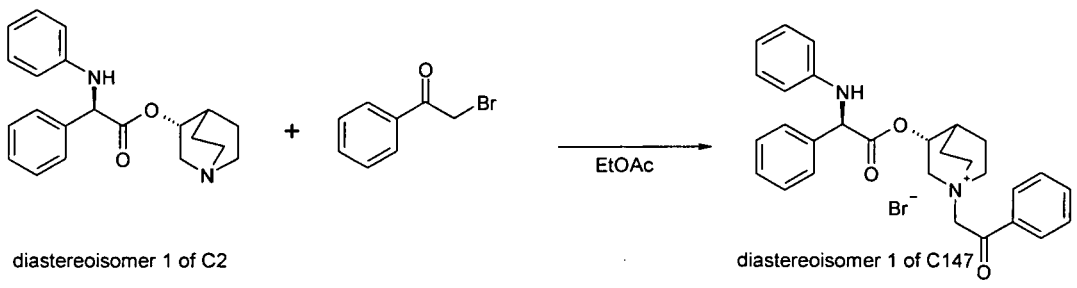
Diastereoisomer 1 of C143	 Single diastereoisomer	78% yield Yellow solid	LC-MS (ESI POS): 394.2 (MH+) ^{1}H NMR (300 MHz, DMSO-d6) ppm: 7.88 (br. s., 1 H), 7.68 (br. s., 1 H), 7.48 - 7.61 (m, 2 H), 7.26 - 7.48 (m, 3 H), 6.98 - 7.20 (m, 2 H), 6.67 - 6.81 (m, 2 H), 6.52 - 6.67 (m, 1 H), 6.34 (d, 1 H), 5.35 (d, 1 H), 5.03 - 5.25 (m, 1 H), 4.02 (ddd, 1 H), 3.93 (d, 1 H), 3.87 (d, 1 H), 3.37 - 3.69 (m, 4 H), 3.13 - 3.27 (m, 1 H), 2.21 - 2.40 (m, 1 H), 1.76 - 2.05 (m, 4 H) [α]D= -41.19° (c=0.27, MeOH)
Diastereoisomer 1 of C144	 Single diastereoisomer	86% yield Yellow solid	LC-MS (ESI POS): 470.3 (MH^+) ^{1}H NMR (300 MHz, DMSO-d6) ppm: 10.52 (s, 1 H), 7.47 - 7.70 (m, 4 H), 7.24 - 7.47 (m, 5 H), 6.98 - 7.24 (m, 3 H), 6.66 - 6.84 (m, 2 H), 6.51 - 6.66 (m, 1 H), 6.35 (d, 1 H), 5.37 (d, 1 H), 5.06 - 5.27 (m, 1 H), 4.17 (d, 1 H), 4.11 (d, 1 H), 3.99 - 4.09 (m, 1 H), 3.46 - 3.74 (m, 4 H), 3.20 - 3.36 (m, 1 H), 2.30 - 2.43 (m, 1 H), 1.80 - 2.13 (m, 4 H) $[\alpha]_D$= -55.2° (c=0.25, MeOH)

(continue)

Diastereoisomer 1 of C145	 Single diastereoisomer	50% yield White solid	LC-MS (ESI POS): 469.3 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.86 (m, 2 H), 7.50 - 7.68 (m, 2 H), 7.23 - 7.50 (m, 5 H), 6.99 - 7.18 (m, 2 H), 6.74 (m, 2 H), 6.50 - 6.67 (m, 1 H), 6.36 (d, 1 H), 5.38 (d, 1 H), 5.11 - 5.30 (m, 1 H), 5.06 (s, 2 H), 3.97 - 4.21 (m, 1 H), 3.58 - 3.83 (m, 2 H), 3.33 - 3.58 (m, 3 H), 2.42 (s, 3 H), 2.31 - 2.39 (m, 1 H), 1.84 - 2.12 (m, 4 H) $[\alpha]_D$= -57.92° (c=0.5, MeOH)
C146	 Mixture of diastereoisomers	28% yield Yellow solid	LC-MS (ESI POS): 475.2 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 8.21 (td, 1 H), 7.99 - 8.14 (m, 1 H), 7.21 - 7.50 (m, 11 H), 5.10 - 5.26 (m, 1 H), 4.92 - 5.10 (m, 2 H), 4.36 - 4.50 (m, 1 H), 4.00 - 4.19 (m, 1 H), 3.64 - 3.81 (m, 4 H), 3.46 - 3.64 (m, 3 H), 3.06 - 3.24 (m, 1 H), 1.34 - 2.40 (m, 5 H)

EXAMPLE 41

Preparation of (R)-1-(2-oxo-2-phenyl-ethyl)-3-((R)-2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide (Diastereoisomer 1 of C147)



Scheme 41

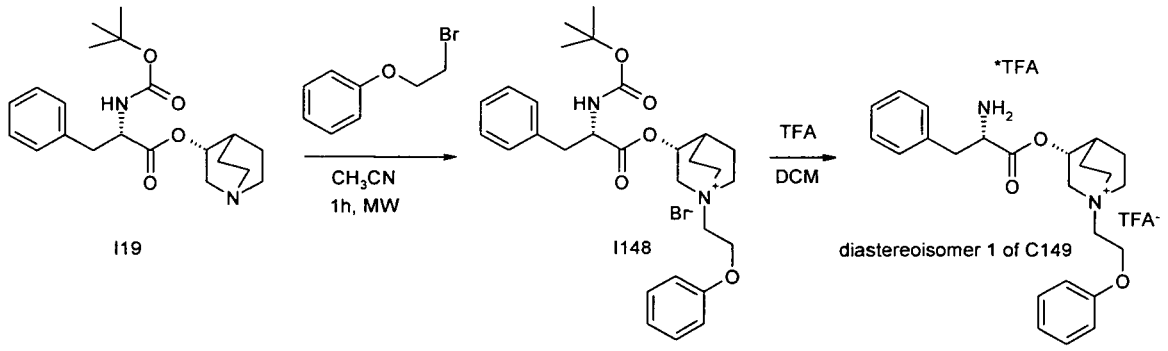
(R)-Quinuclidin-3-yl 2-phenyl-2-(phenylamino)acetate (Diastereoisomer 1 of C2) (20.3 mg, 0.06 mmol) is dissolved in EtOAc (0.60 mL) and 2-bromo-1-phenylethanone (12.0 mg, 0.06 mmol) is added. The reaction is stirred at room temperature for 2 hours (UPLC-MS: complete and clean conversion). Et_2O (0.20 mL) is added and the product is triturated to obtain a white solid which is isolated by filtration and dried under vacuum overnight (31 mg, 96% yield, bromide salt, single diastereoisomer).

^{1}H NMR (300 MHz, DMSO-d6) ppm: 7.89 - 8.08 (m, 2 H), 7.69 - 7.84 (m, 1 H), 7.52 - 7.69 (m, 4 H), 7.31 - 7.48 (m, 3 H), 6.99 - 7.17 (m, 2 H), 6.68 - 6.83 (m, 2 H), 6.51 - 6.66 (m, 1 H), 6.37 (d, 1 H), 5.39 (d, 1 H), 5.17 - 5.26 (m, 1 H), 5.13 (s, 2 H), 4.04 - 4.17 (m, 1 H), 3.34 - 3.79 (m, 5 H), 2.32 - 2.40 (m, 1 H), 1.83 - 2.16 (m, 4 H);

LC-MS (ESI POS): 455.3 (MH^+).

EXAMPLE 42

Preparation of (R)-3-((S)-2-amino-phenylpropanoyloxy)-1-(2-phenoxyethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate trifluoroacetate anion (Diastereoisomer 1 of C149)



Scheme 42

Preparation of (R)-3-((S)-2-tertbutoxycarbonylamino-phenylpropanoyloxy)-1-(2-phenoxyethyl)-1-azonia-bicyclo[2.2.2]octane bromide (I148)

A solution of (S)-((R)-quinuclidin-3-yl)-2-(tert-butoxycarbonylamino)-3-phenylpropanoate (I19) (200 mg, 0.53 mmol), is added with α-bromophenethole (130 mg, 0.64 mmol) and the mixture reacted in a closed vessel under MW irradiation for 1hr at 100°C (LC-MS monitoring: complete conversion). The solvent is evaporated under reduced pressure and the resulting crude is used without further purification.

Preparation of (R)-3-((S)-2-amino-phenylpropanoyloxy)-1-(2-phenoxyethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate trifluoroacetate anion (Diastereoisomer 1 of C149)

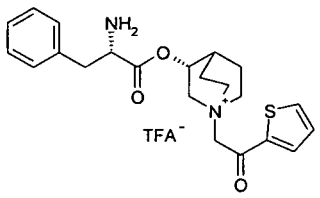
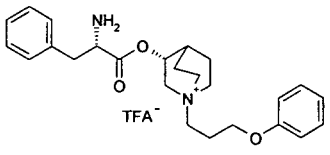
A solution of (R)-3-((S)-2-tertbutoxycarbonylamino-phenylpropanoyloxy)-1-(2-phenoxyethyl)-1-azonia-bicyclo[2.2.2]octane bromide (I148) (0.53 mmol) in DCM (5 mL), is added with trifluoroacetic acid (0.50 mL, 4.41 mmol) and the mixture stirred at RT overnight. The solvent is evaporated and the resulting crude is purified by preparative LC-MS to obtain the title compound as a brown gummy solid (112 mg, 43% overall yield, trifluoroacetate salt and trifluoroacetate anion, single diastereoisomer).

^{1}H NMR (300 MHz, DMSO-d6) ppm: 8.60 (br. s., 3H), 7.19 - 7.45 (m, 7H), 6.82 - 7.13 (m, 3H), 5.03 - 5.25 (m, 1H), 4.39 - 4.48 (m, 2H), 4.25 - 4.38 (m, 1H), 3.90 - 4.09 (m, 1H), 3.28 - 3.52 (m, 7 H), 3.19 (dd, 1H), 3.10 (dd, 1H), 2.09 (br. s., 1H), 1.81 - 2.04 (m, 2H), 1.66 - 1.79 (m, 2H);

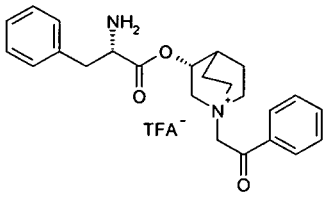
LC-MS (ESI POS): 395.4 (MH^+).

The compounds listed in Table 18 are prepared as previously described for C149, by reaction of I19 with 2-chloroacetylthiophene, 3-phenoxypropyl bromide and α-bromoacetophenone.

Table 18

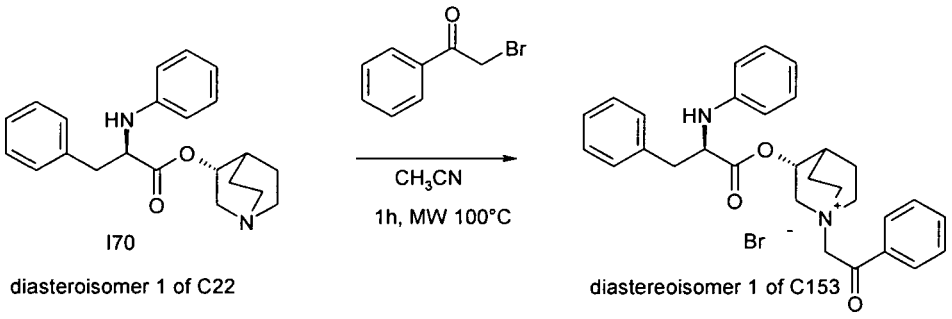
Compound	Structure	Yield and appearance	Analytical
Diastereoisomer 1 of C150	 Single diastereoisomer	45% yield Pale yellow oil	LC-MS (ESI POS): 399.2 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 8.62 (br. s., 3H), 8.22 (dd, 1H), 8.08 (dd, 1H), 7.15 - 7.47 (m, 6H), 5.14 - 5.30 (m, 1H), 5.06 (d, 1H), 4.99 (d, 1H), 4.38 (t, 1 H), 4.11 (dd, 1H), 3.44 - 3.74 (m, 5H), 3.22 (dd, 1H), 3.10 (dd, 1H), 2.06 - 2.14 (m, 1H), 1.90 - 2.07 (m, 2H), 1.56 - 1.90 (m, 2H)
Diastereoisomer 1 of C151	 Single diastereoisomer	41% yield Brown gummy solid	LC-MS (ESI POS): 409.3 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 8.62 (br. s., 3H), 7.22 - 7.41 (m, 7H), 6.90 - 7.01 (m, 3H), 4.99 - 5.29 (m, 1H), 4.22 - 4.49 (m, 1H), 4.04 (t, 2H), 3.78 - 3.94 (m, 1H), 3.25 - 3.50 (m, 7H), 3.20 (dd, 1H), 3.10 (dd, 1H), 2.02 - 2.15 (m, 3H), 1.80 - 2.02 (m, 2H), 1.65 - 1.78 (m, 2H)

(continue)

Diastereoisomer 1 of C152	 Single diastereoisomer	35% yield Pale yellow solid	LC-MS (ESI POS): 393.3 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 8.65 (br. s., 3H), 7.88 - 8.07 (m, 2H), 7.70 - 7.84 (m, 1H), 7.51 - 7.70 (m, 2H), 7.16 - 7.48 (m, 5H), 5.21 - 5.30 (m, 1H), 5.19 (d, 1H), 5.12 (d, 1H), 4.39 (dd, 1H), 4.11 (dd, H), 3.47 - 3.81 (m, 5H), 3.23 (dd, 1H), 3.10 (dd, 1H), 1.90 - 2.22 (m, 3H), 1.65 - 1.90 (m, 2H)

EXAMPLE 43

Preparation of (R)-1-(2-oxo-2-phenylethyl)-3-((R)-3-phenyl-2-(phenylamino)propanoyloxy)-1-azoniabicyclo[2.2.2]octane bromide (Diastereoisomer 1 of C153)



Scheme 43

A solution of (R)-((R)-quinuclidin-3-yl) 3-phenyl-2-(phenylamino)-propanoate (Diastereoisomer 1 of C22) (50.0 mg, 0.14 mmol), is added with 2-bromo-1-phenylethanone (28.4 mg, 0.14 mmol) and the mixture reacted in a closed vessel under MW irradiation for 1h at 100°C (LC-MS monitoring: complete conversion). Solvent is removed under reduced pressure and residue is triturated with EtOAc to obtain the title compound as a white solid (75.5 mg, 98% yield, bromide salt, single diastereoisomer).

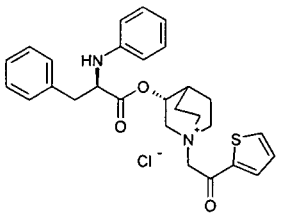
^{1}H NMR (300 MHz, DMSO-d6) ppm: 7.92 - 8.10 (m, 2 H), 7.71 - 7.85 (m, 1 H), 7.51 - 7.71 (m, 2 H), 7.27 - 7.44 (m, 4 H), 7.17 - 7.26 (m, 1 H), 6.95 - 7.16 (m, 2 H), 6.45 - 6.77 (m, 3 H), 6.11 (d, 1 H), 5.05 - 5.21 (m, 3 H), 4.23 - 4.50 (m, 1 H), 3.94 - 4.20 (m, 1 H), 3.49 - 3.81 (m, 3 H), 3.35 - 3.49 (m, 2 H), 3.15 (dd, 1 H), 3.08 (dd, 1 H), 2.17 - 2.37 (m, 1 H), 1.94 - 2.17 (m, 2 H), 1.70 - 1.94 (m, 2 H);

LC-MS (ESI POS): 469.3 (MH+);

$[\alpha]_D$= -8.19° (c=0.53, MeOH).

Diastereoisomer 2 of C154 listed in Table 19 is prepared as previously described for C153, by reaction of I70 with 2-chloroacetylthiophene

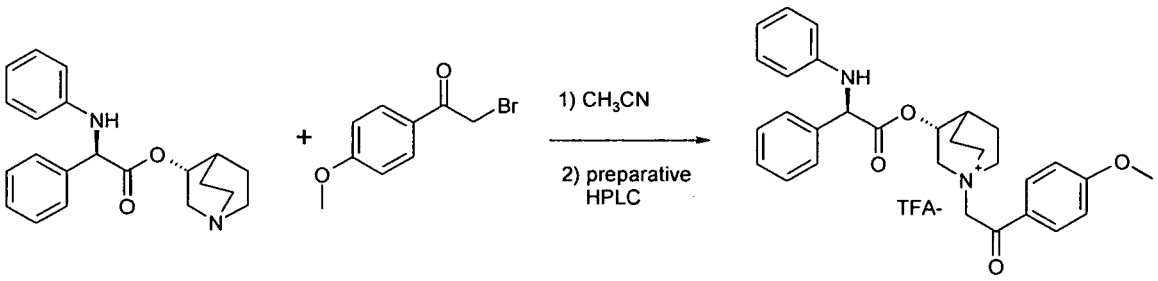
Table 19

Compound	Structure	Yield and appearance	Analytical
Diastereoisomer 2 of C154	 Single diastereoisomer	90% yield Yellow Solid	LC-MS (ESI POS): 475.2 (MH^+) ^{1}H NMR (300 MHz, DMSO-d6) ppm: 8.22 (dd, 1 H), 8.11 (dd, 1 H), 7.15 - 7.45 (m, 6 H), 6.92 - 7.15 (m, 2 H), 6.53 - 6.68 (m, 3 H), 6.12 (d, 1 H), 5.05 - 5.17 (m, 1 H), 5.02 (s, 2 H), 4.24 - 4.52 (m, 1 H), 4.06 (ddd, 1 H), 3.47 - 3.80 (m, 3 H), 3.33 - 3.47 (m, 2 H), 3.15 (dd, 1 H), 3.08 (dd, 1 H), 2.16 - 2.34 (m, 1 H), 1.77 - 2.10 (m, 4 H) $[\alpha]_D$= -14.2° (c=0.25, MeOH)

EXAMPLE 44

Preparation of (R)-1-[2-(4-methoxy-phenyl)-2-oxo-ethyl]-3-((R)-2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane

trifluoroacetate (diastereoisomer 1 of C155)



Diasteroisomer 1 of C2 Diasteroisomer 1 of C155

Scheme 44

A solution of (R)-phenyl-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (Diastereoisomer 1 of C2) (120 mg, 0.35 mmol) in acetonitrile (5 mL), is added with 2-bromo-1-(4-methoxy-phenyl)-ethanone (99 mg, 0.43 mmol) and the mixture is heated under MW irradiation for 1hr at 100°C (UPLC-MS monitoring: complete conversion). Solvent was evaporated and the resulting crude is first purified by flash chromatography (DCM/MeOH=99/1 to 9/1) and then purified by preparative LC-MS to obtain the title compound as a white solid (70.2 mg, 33% yield, trifluoroacetate salt, single diastereoisomer).

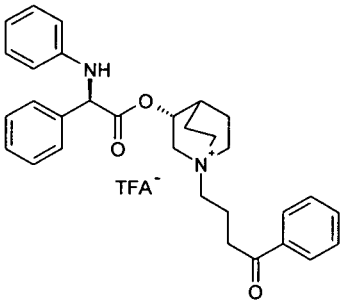
^{1}H NMR (300 MHz, DMSO-d6) ppm: 7.84 - 8.06 (m, 2 H), 7.51 - 7.71 (m, 2 H), 7.25 - 7.51 (m, 3 H), 6.95 - 7.22 (m, 4 H), 6.67 - 6.80 (m, 2 H), 6.53 - 6.67 (m, 1 H), 6.35 (br. s., 1 H), 5.38 (s, 1 H), 5.13 - 5.30 (m, 1 H), 5.01 (s, 2 H), 3.97 - 4.17 (m, 1 H), 3.88 (s, 3 H), 3.19 - 3.50 (m, 5 H), 2.31 - 2.42 (m, 1 H), 1.68 - 2.20 (m, 4 H);

LC-MS (ESI POS): 485.2 (MH^+);

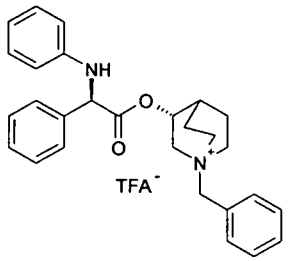
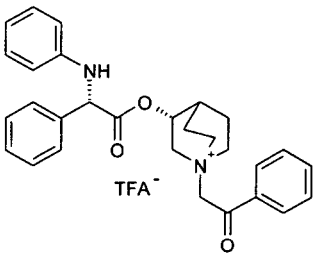
$[\alpha]_D$=-48.32° (c=0.25, MeOH).

Final compounds listed in Table 20 are prepared as previously described for C155, by alkylation of suitable intermediate (Diastereoisomer 1 of C2, Diastereoisomer 2 of C2, Diastereoisomer 1 of C37, C29, C105, C13, C14) and the commercially available alkylating agents.

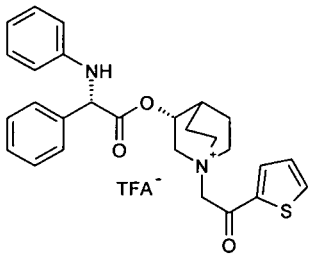
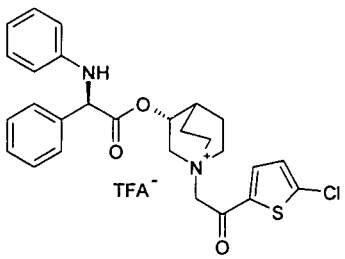
Table 20

Compound	Structure	Yield and Appearance	Analytical
Diastereoisomer 1 of C156	 Single diastereoisomer	10% yield colorless viscous oil	LC-MS (ESI POS): 483.1 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.84 - 8.11 (m, 2 H), 7.64 - 7.71 (m, 1 H), 7.52 - 7.61 (m, 4 H), 7.20 - 7.50 (m, 3 H), 6.95 - 7.20 (m, 2 H), 6.67 - 6.84 (m, 2 H), 6.52 - 6.67 (m, 1 H), 5.36 (s, 1 H), 5.04 - 5.19 (m, 1 H), 3.68 - 3.98 (m, 1 H), 3.29 - 3.56 (m, 3 H), 3.01 - 3.27 (m, 4 H), 2.80 - 2.93 (m, 1 H), 2.65 - 2.77 (m, 1 H), 2.20 - 2.37 (m, 1 H), 1.99 (br. s., 2 H), 1.75 - 1.94 (m0.0., 4 H)

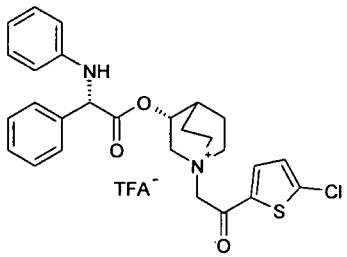
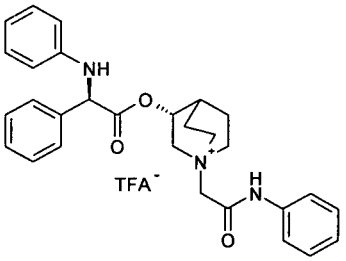
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Diastereoisomer 1 of C157	 Single stereoisomer	51% yield brown viscous oil	LC-MS (ESI POS): 427.2 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.29 - 7.62 (m, 10 H), 6.95 - 7.16 (m, 2 H), 6.64 - 6.78 (m, 2 H), 6.52 - 6.64 (m, 1 H), 5.31 (s, 1 H), 4.99 - 5.19 (m, 1 H), 4.40 (d, 1 H), 4.33 (d, 1 H), 3.81 (ddd, 1 H), 3.27 - 3.47 (m, 3 H), 2.87 - 3.03 (m, 1 H), 2.69 - 2.87 (m, 1 H), 2.20 - 2.38 (m, 1 H), 1.72 - 2.04 (m, 4 H)
Diastereoisomer 2 of C113	 Single stereoisomer	97% yield brown viscous oil	LC-MS (ESI POS): 455.1 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.91 - 8.03 (m, 2 H), 7.71 - 7.81 (m, 1 H), 7.54 - 7.67 (m, 4 H), 7.27 - 7.47 (m, 3 H), 6.97 - 7.17 (m, 2 H), 6.74 (m, 2 H), 6.50 - 6.66 (m, 1 H), 5.35 (s, 1 H), 5.20 - 5.27 (m, 1 H), 5.17 (s, 2 H), 4.12 (dd, 1 H), 3.42 - 3.84 (m, 5 H), 2.09 - 2.20 (m, 1 H), 1.85 - 2.07 (m, 2 H), 1.65 - 1.84 (m, 1 H), 1.38 - 1.60 (m, 1 H) $[\alpha]_D$=-14.60° (c=0.2, MeOH

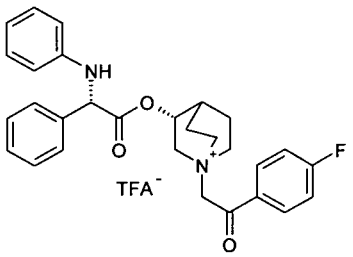
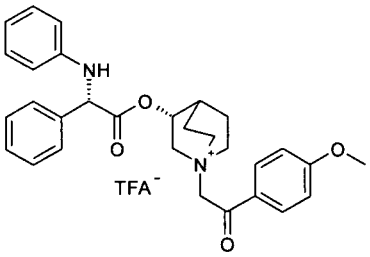
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Diastereoisomer 2 of C109	 Single diastereoisomer	81% yield brown viscous oil	LC-MS (ESI POS): 461.1 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 8.21 (dd, 1 H), 8.07 (dd, 1 H), 7.51 - 7.69 (m, 2 H), 7.27 - 7.49 (m, 4 H), 6.99 - 7.21 (m, 2 H), 6.66 - 6.80 (m, 2 H), 6.50 - 6.66 (m, 1 H), 5.34 (s, 1 H), 5.15 - 5.27 (m, 1 H), 5.07 (d, 1 H), 5.01 (d, 1 H), 4.11 (dd, 1 H), 3.60 - 3.87 (m, 4 H), 3.40 - 3.60 (m, 1 H), 2.06 - 2.21 (m, 1 H), 1.83 - 2.06 (m, 2 H), 1.63 - 1.83 (m, 1 H), 1.38 - 1.63 (m, 1 H) $[\alpha]_D$=-14.00° (c=0.2, MeOH
Diastereoisomer 1 of C158	 Single diastereoisomer	28% yield Yellow oil	LC-MS (ESI POS): 495.1 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.96 (d, 1 H), 7.50 - 7.68 (m, 2 H), 7.20 - 7.50 (m, 4 H), 6.93 - 7.20 (m, 2 H), 6.67 - 6.85 (m, 2 H), 6.50 - 6.67 (m, 1 H), 6.35 (br. s., 1 H), 5.37 (s, 1 H), 5.09 - 5.25 (m, 1 H), 4.91 (s, 2 H), 3.97 - 4.13 (m, 1 H), 3.50 - 3.70 (m, 2 H), 3.18 - 3.50 (m, 3 H), 2.31 - 2.42 (m, 1 H), 1.96 - 2.15 (m, 2 H), 1.74 - 1.96 (m, 2 H) $[\alpha]_D$=-40.32° (c=0.3, MeOH)

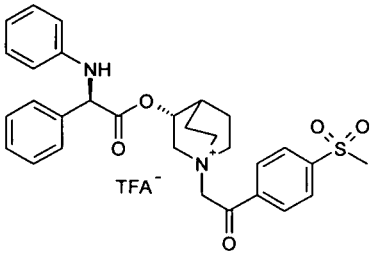
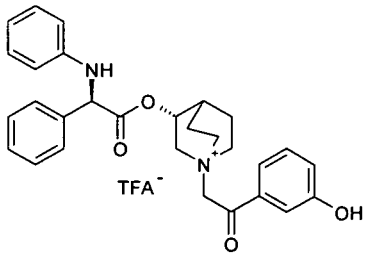
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Diastereoisomer 2 of C159	 Single diastereoisomer	57% yield brown viscous oil	LC-MS (ESI POS): 495.0 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.99 (d, 1 H), 7.52 - 7.64 (m, 2 H), 7.44 (d, 1 H), 7.30 - 7.42 (m, 3 H), 7.00 - 7.18 (m, 2 H), 6.69 - 6.76 (m, 2 H), 6.56 - 6.64 (m, 1 H), 5.33 (s, 1 H), 5.13 - 5.25 (m, 1 H), 5.02 (d, 1 H), 4.96 (d, 1 H), 4.08 (dd, 1 H), 3.67 - 3.83 (m, 1 H), 3.46 - 3.67 (m, 4 H), 2.06 - 2.19 (m, 1 H), 1.83 - 2.04 (m, 2 H), 1.63 - 1.82 (m, 1 H), 1.39 - 1.61 (m, 1 H) $[\alpha]_D$=-17.47° (c=0.3, MeOH)
Diastereoisomer 1 of C160	 Single diastereoisomer	47% yield brown viscous oil	LC-MS (ESI POS): 470.1 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 10.51 (s, 1 H), 7.49 - 7.67 (m, 4 H), 7.28 - 7.47 (m, 5 H), 7.12 - 7.23 (m, 1 H), 7.01 - 7.12 (m, 2 H), 6.72 (m, 2 H), 6.58 (m, 1 H), 6.35 (br. s., 1 H), 5.32 (br. s., 1 H), 5.10 - 5.24 (m, 1 H), 4.23 (d, 1 H), 4.17 (d, 1 H), 4.01 - 4.14 (m, 1 H), 3.75 - 3.85 (m, 1 H), 3.55 - 3.70 (m, 4 H), 2.06 - 2.20 (m, 1 H), 1.81 - 2.04 (m, 2 H), 1.62 - 1.79 (m, 1 H), 1.42 - 1.62 (m, 1 H) $[\alpha]_D$=-19.6° (c=0.25, MeOH)

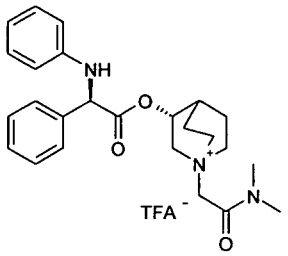
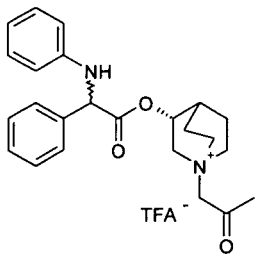
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Diastereoisomer 2 of C115	 Single diastereoisomer	58% yield brown viscous oil	LC-MS (ESI POS): 473.2 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.96 - 8.18 (m, 2 H), 7.54 - 7.63 (m, 2 H), 7.26 - 7.52 (m, 5 H), 6.98 - 7.16 (m, 2 H), 6.69 - 6.77 (m, 2 H), 6.55 - 6.67 (m, 1 H), 5.35 (s, 2 H), 5.18 - 5.28 (m, 1 H), 5.11 - 5.18 (m, 2 H), 3.83 - 4.27 (m, 1 H), 3.70 - 3.85 (m, 1 H), 3.47 - 3.70 (m, 4 H), 2.08 - 2.17 (m, 1 H), 1.86 - 2.04 (m, 2 H), 1.64 - 1.82 (m, 1 H), 1.44 - 1.64 (m, 1 H) $[\alpha]_D$=-11.44° (c=0.25, MeOH)
Diastereoisomer 2 of C161	 Single diastereoisomer	65% yield brown viscous oil	LC-MS (ESI POS): 485.2 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.84 - 8.03 (m, 2 H), 7.53 - 7.65 (m, 2 H), 7.28 - 7.49 (m, 3 H), 7.01 - 7.24 (m, 4 H), 6.69 - 6.79 (m, 2 H), 6.53 - 6.65 (m, 1 H), 5.34 (s, 1 H), 5.18 - 5.28 (m, 1 H), 5.02 - 5.12 (m, 2 H), 4.05 - 4.16 (m, 1 H), 3.89 (s, 3 H), 3.51 - 3.83 (m, 5 H), 2.08 - 2.18 (m, 1 H), 1.85 - 2.05 (m, 2 H), 1.65 - 1.81 (m, 1 H), 1.41 - 1.63 (m, 1 H) $[\alpha]_D$=-13.13° (c=0.3, MeOH)

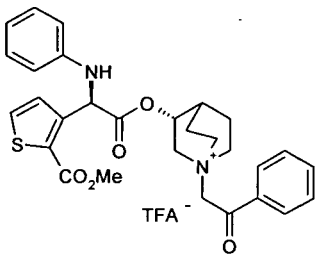
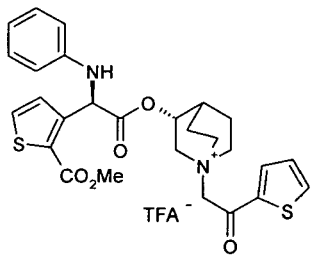
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Diastereoisomer 1 of C162	 Single diastereoisomer	36% yield brown viscous oil	LC-MS (ESI POS): 533.1 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.88 - 8.31 (m, 4 H), 7.52 - 7.68 (m, 2 H), 7.30 - 7.49 (m, 3 H), 7.01 - 7.17 (m, 1 H), 6.67 - 6.82 (m, 2 H), 6.51 - 6.67 (m, 1 H), 5.39 (s, 1 H), 5.17 - 5.27 (m, 1 H), 5.13 (s, 2 H), 3.99 - 4.15 (m, 1 H), 3.34 - 3.73 (m, 5 H), 3.31 (s, 3 H), 2.30 - 2.45 (m, 1 H), 1.69 - 2.21 (m, 5 H) $[\alpha]_D$=-34.15° (c=0.4, MeOH)
Diastereoisomer 1 of C163	 Single diastereoisomer	44% yield brown viscous oil	LC-MS (ESI POS): 471.2 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 9.99 (br. s., 1 H), 7.52 - 7.63 (m, 2 H), 7.26 - 7.49 (m, 6 H), 6.99 - 7.22 (m, 3 H), 6.69 - 6.81 (m, 2 H), 6.55 - 6.66 (m, 1 H), 5.38 (s, 1 H), 5.14 - 5.28 (m, 1 H), 5.04 (s, 2 H), 3.89 - 4.20 (m, 1 H), 3.19 - 3.85 (m, 5 H), 2.29 - 2.42 (m, 1 H), 1.71 - 2.14 (m, 4 H) $[\alpha]_D$=-42.75° (c=0.4, MeOH)

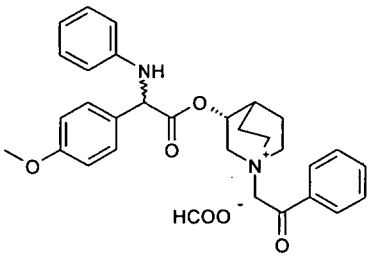
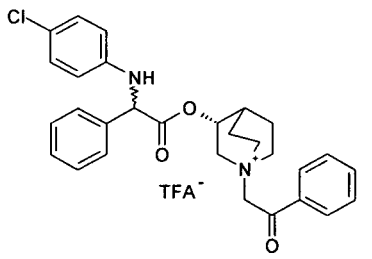
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Diastereoisomer 1 of C164	 Single diastereoisomer	38% yield brown viscous oil	LC-MS (ESI POS): 422.1 (MH+) ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.48 - 7.66 (m, 2 H), 7.25 - 7.47 (m, 3 H), 6.99 - 7.18 (m, 2 H), 6.73 (m, 2 H), 6.55 - 6.65 (m, 1 H), 5.35 (s, 1 H), 5.06 - 5.23 (m, 1 H), 4.25 (s, 2 H), 4.03 (ddd, 1 H), 3.43 - 3.73 (m, 4 H), 3.22 - 3.42 (m, 1 H), 2.92 (s, 3 H), 2.87 (s, 3 H), 2.29 - 2.38 (m, 1 H), 1.64 - 2.10 (m, 4 H) $[\alpha]_D$=-40.0° (c=0.1, MeOH)
Diastereoisomer 1 of C165	 single diastereoisomer	24% yield brown oil	LC-MS (ESI POS): 393.3 (MH+) ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.50 - 7.61 (m, 2 H), 7.26 - 7.47 (m, 3 H), 7.03 - 7.16 (m, 2 H), 6.68 - 6.78 (m, 2 H), 6.54 - 6.65 (m, 1 H), 5.36 (s, 1 H), 4.99 - 5.22 (m, 1 H), 4.37 (s, 2 H), 3.88 - 4.00 (m, 1 H), 3.36 - 3.57 (m, 3 H), 3.05 - 3.36 (m, 2 H), 2.28 - 2.38 (m, 1 H), 2.11 (s, 3 H), 1.70 - 2.07 (m, 4 H)

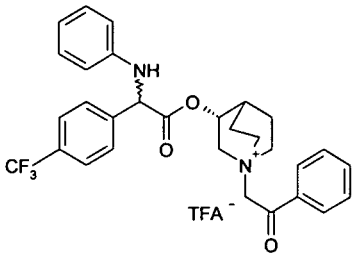
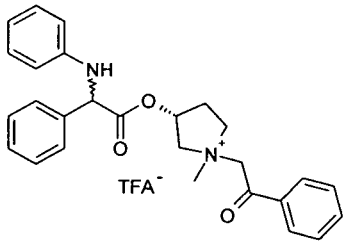
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Diastereoisomer 1 of C166	 Single stereoisomer	18% yield Pale yellow solid	LC-MS (ESI POS): 518.9 (MH+) ^{1}H NMR (300 MHz, DMSO-d6) ppm: 7.90 - 8.07 (m, 2 H), 7.72 - 7.82 (m, 2 H), 7.57 - 7.68 (m, 3 H), 7.33 - 7.55 (m, 5 H), 6.60 - 6.84 (m, 1 H), 5.57 - 5.87 (m, 1 H), 5.21 - 5.39 (m, 1 H), 4.98 - 5.21 (m, 2 H), 4.00 - 4.23 (m, 1 H), 3.78 (s, 3 H), 3.26 - 3.51 (m, 5 H), 2.30 - 2.47 (m, 1 H), 1.43 - 2.23 (m, 4 H)
Diastereoisomer 1 of C167	 Single diastereoisomer	27% yield Yellow solid	LC-MS (ESI POS): 525.0 (MH^+) ^{1}H NMR (300 MHz, DMSO-d6) ppm: 8.13 - 8.28 (m, 1 H) 8.05 (m, 1 H) 7.72 - 7.86 (m, 1 H) 7.66 (d, 1 H) 7.27 - 7.56 (m, 4 H) 6.72 (d, 1 H) 5.68 (d, 1 H) 5.19 - 5.32 (m, 1 H) 5.02 (s, 2 H) 4.02 - 4.24 (m, 1 H) 3.78 (s, 3 H) 3.37 - 3.68 (m, 7 H) 2.32 - 2.43 (m, 1 H) 1.88 - 2.23 (m, 3 H) 1.36 - 1.64 (m, 1 H)

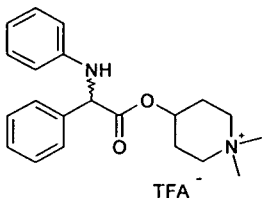
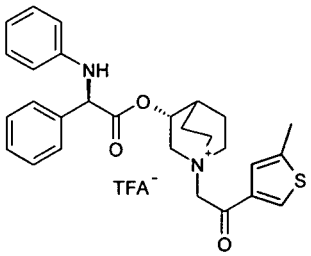
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C168	 Mixture of diastereoisomers	26% yield White solid	LC-MS (ESI POS): 485.0 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 8.47 (s, 1 H, *formiate ion*), 7.83 - 8.06 (m, 2 H), 7.68 - 7.82 (m, 1 H), 7.55 - 7.68 (m, 2 H), 7.39 - 7.55 (m, 2 H), 7.02 - 7.17 (m, 2 H), 6.90 - 7.02 (m, 2 H), 6.66 - 6.80 (m, 2 H), 6.52 - 6.63 (m, 1 H), 6.31 (d, 1 H), 5.24 - 5.38 (m, 1 H), 4.99 - 5.22 (m, 3 H), 3.98 - 4.20 (m, 1 H), 3.76 (s, 3 H), 3.45 - 3.83 (m, 5 H), 2.11 - 2.40 (m, 1 H), 1.45 - 2.10 (m, 4 H)
C169	 Mixture of diastereoisomers	58% yield Pale yellow oil	LC-MS (ESI POS): 489.1 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.88 - 8.09 (m, 2 H), 7.70 - 7.87 (m, 1 H), 7.50 - 7.70 (m, 4 H), 7.27 - 7.50 (m, 3 H), 7.12 (m, 2 H), 6.76 (m, 2 H), 6.60 (d, 1 H), 5.31 - 5.49 (m, 1 H), 5.19 - 5.31 (m, 1 H), 5.14 (s, 2 H), 3.91 - 4.21 (m, 1 H), 3.57 - 3.88 (m, 5 H), 1.35 - 2.44 (m, 5 H)

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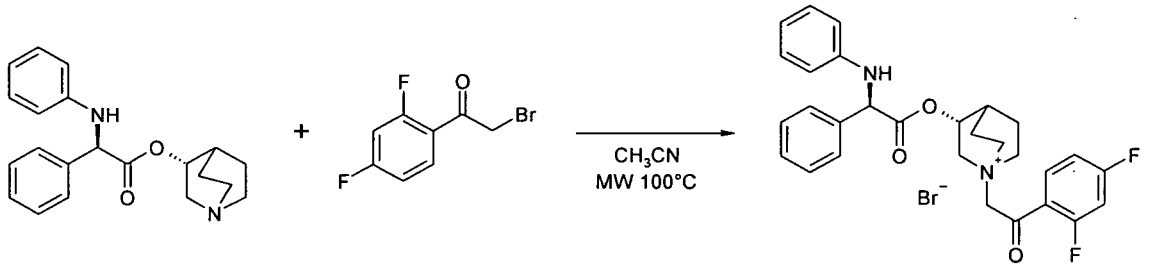
C170	 Mixture of diastereoisomer	41% yield White solid	LC-MS (ESI POS): 523.3 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: *8.45 (s, 1 H, formite ion)*, 7.91 - 8.04 (m, 2 H), 7.69 - 7.91 (m, 4 H), 7.48 - 7.69 (m, 3 H), 7.03 - 7.18 (m, 2 H), 6.70 - 6.80 (m, 2 H), 6.52 - 6.67 (m, 2 H), 5.50 - 5.64 (m, 1 H), 5.00 - 5.30 (m, 3 H), 3.51 - 4.32 (m, 6 H), 2.14 - 2.41 (m, 1 H), 1.54 - 2.14 (m, 4 H)
C171	 Mixture of diastereoisomers	38% yield yellow sticky oil	LC-MS (ESI POS): 429.1 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.90 - 8.09 (m, 2 H), 7.54 - 7.90 (m, 5 H), 6.90 - 7.52 (m, 5 H), 6.29 - 6.82 (m, 3 H), 5.43 - 5.57 (m, 1 H), 5.14 - 5.42 (m, 3 H), 3.72 - 4.19 (m, 4 H), 3.17 (s, 3 H), 2.55 - 2.73 (m, 1 H), 1.93 - 2.42 (m, 1 H)

(continue)

C172	 Mixture of stereoisomers	43% yield yellow sticky oil	LC-MS (ESI POS): 339.2 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.52 - 7.65 (m, 2 H), 7.29 - 7.49 (m, 3 H), 6.97 - 7.16 (m, 2 H), 6.66 - 6.79 (m, 2 H), 6.54 - 6.66 (m, 1 H), 6.32 (s, 1 H), 5.11 - 5.39 (m, 1 H), 4.81 - 5.01 (m, 1 H), 3.14 - 3.45 (m, 3 H), 3.04 (s, 6 H), 2.82 - 2.95 (m, 1 H), 1.35 - 2.25 (m, 4 H)
Diastereoisomer 1 of C173	 Single diastereoisomer	84% yield brown solid	LC-MS (ESI POS): 475.2 (MH+) ^1H NMR (300 MHz, DMSO-d6) ppm: 8.36 (d, 1 H), 7.54 - 7.60 (m, 2 H), 7.31 - 7.48 (m, 3 H), 7.24 (t, 1 H), 7.03 - 7.15 (m, 2 H), 6.68 - 6.80 (m, 2 H), 6.52 - 6.64 (m, 1 H), 5.37 (s, 1 H), 5.11 - 5.27 (m, 1 H), 4.89 (s, 2 H), 3.97 - 4.15 (m, 1 H), 3.20 - 3.51 (m, 5 H), 2.49 (s, 3 H), 2.32 - 2.40 (m, 1 H), 1.76 - 2.16 (m, 4 H) $[\alpha]_D$=-46.51° (c=0.35, MeOH)

EXAMPLE 45

Preparation of (R)-1-[2-(2,4-difluoro-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide(diastereoisomer 1 of C174)



Diastereoismer 1 of C2 Diastereoismer 1 of C174

Scheme 45

A solution of (R)-phenyl-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (Diastereoisomer 1 of C2) (50 mg, 0.15 mmol) in acetonitrile (1 mL), is added with 2-bromo-1-(2,4-difluoro-phenyl)-ethanone (35 mg, 0.15 mmol) and the mixture reacted in a closed vessel under MW irradiation for 1hr at 100°C (UPLC-MS monitoring: complete conversion). The solvent is evaporated and the resulting crude is purified by flash chromatography (DCM/MeOH=95/5) to obtain the title compound as a white solid (37.3 mg, 44% yield, bromide salt, single diastereoisomer).

^{1}H NMR (300 MHz, DMSO-d6) ppm: 7.97 - 8.07 (m, 1 H), 7.52 - 7.72 (m, 3 H), 7.39 - 7.52 (m, 2 H), 7.25 - 7.39 (m, 2 H), 6.92 - 7.21 (m, 2 H), 6.67 - 6.84 (m, 2 H), 6.51 - 6.67 (m, 1 H), 6.36 (d, 1 H), 5.38 (d, 1 H), 5.00 - 5.30 (m, 1 H), 4.88 (br. s., 2 H), 3.91 - 4.20 (m, 1 H), 3.51 - 3.74 (m, 3 H), 3.41 - 3.51 (m, 1 H), 3.31 - 3.41 (m, 1 H), 2.31 - 2.43 (m, 1 H), 1.86 - 2.09 (m, 4 H);

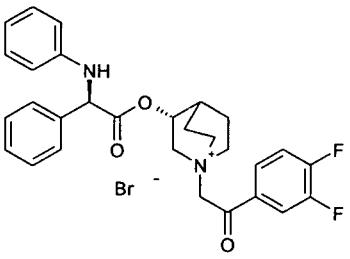
LC-MS (ESI POS): 491.1 (MH^+);

$[\alpha]_D$=-45.42° (c=0.24, MeOH).

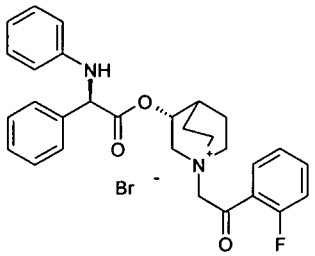
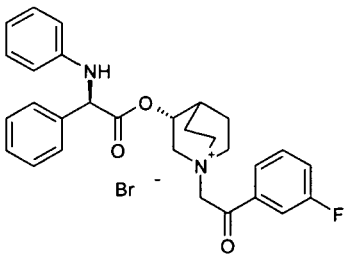
Final compounds listed in Table 21 are prepared as previously described for C174, by alkylation of suitable intermediate (Diastereoisomer 1

of C2, C2, C80, C83, C85, C89, C87, C95, C101, C94, C95 C100, C132, C133, C143, C27, C138) and the commercially available alkylating agents.

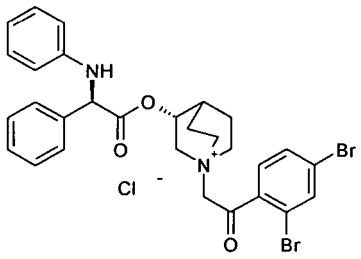
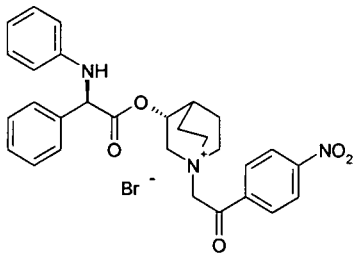
Table 21

Compound	Structure	Yield and Appearance	Analytical
Diastereoisomer 1 of C175	 Single diastereoisomer	69% yield White solid	LC-MS (ESI POS): 491.1 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.95 - 8.15 (m, 1 H), 7.81 - 7.95 (m, 1 H), 7.70 (s, 1 H), 7.50 - 7.63 (m, 2 H), 7.22 - 7.50 (m, 3 H), 6.95 - 7.21 (m, 2 H), 6.67 - 6.82 (m, 2 H), 6.50 - 6.67 (m, 1 H), 6.36 (d, 1 H), 5.38 (d, 1 H), 5.13 - 5.29 (m, 1 H), 5.06 (s, 2 H), 3.92 - 4.17 (m, 1 H), 3.53 - 3.67 (m, 3 H), 3.32 - 3.50 (m, 2 H), 2.31 - 2.43 (m, 1 H), 1.73 - 2.19 (m, 4 H) $[\alpha]_D$=-42.45° (c=0.22, MeOH)

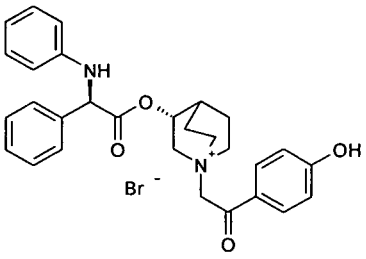
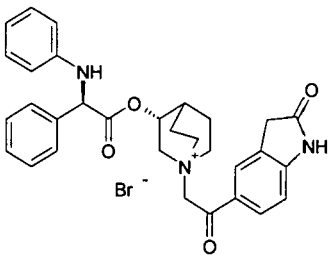
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Diastereoisomer 1 of C176	 Single diastereoisomer	25% yield Off-white solid	LC-MS (ESI POS): 473.0 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.87 - 8.02 (m, 1 H), 7.72 - 7.87 (m, 1 H), 7.52 - 7.68 (m, 2 H), 7.28 - 7.52 (m, 5 H), 6.98 - 7.23 (m, 2 H), 6.67 - 6.84 (m, 2 H), 6.48 - 6.69 (m, 1 H), 6.36 (d, 1 H), 5.38 (d, 1 H), 5.08 - 5.30 (m, 1 H), 4.91 (br. s., 2 H), 3.91 - 4.23 (m, 1 H), 3.35 - 3.73 (m, 5 H), 2.30 - 2.46 (m, 1 H), 1.55 - 2.20 (m, 4 H)
Diastereoisomer 1 of C177	 Single diastereoisomer	41% yield Yellow solid	LC-MS (ESI POS): 473.1 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 7.75 - 7.86 (m, 2 H), 7.51 - 7.73 (m, 4 H), 7.26 - 7.51 (m, 3 H), 6.95 - 7.25 (m, 2 H), 6.68 - 6.85 (m, 2 H), 6.51 - 6.68 (m, 1 H), 6.36 (d, 1 H), 5.39 (d, 1 H), 5.15 - 5.30 (m, 1 H), 5.10 (s, 2 H), 4.00 - 4.15 (m, 1 H), 3.60 - 3.75 (m, 2 H), 3.34 - 3.60 (m, 3 H), 2.31 - 2.42 (m, 1 H), 1.84 - 2.14 (m, 4 H)

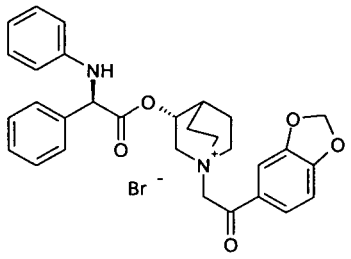
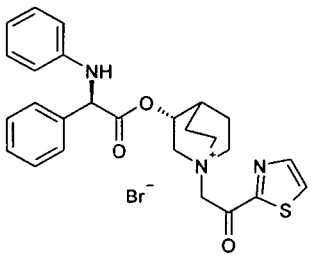
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Diastereoisomer 1 of C178	 Single diastereoisomer	47% yield White solid	LC-MS (ESI POS): 610.7 (MH^+) ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 8.12 (d, 1 H), 7.86 (dd, 1 H), 7.79 (d, 1 H), 7.53 - 7.64 (m, 2 H), 7.29 - 7.47 (m, 3 H), 7.00 - 7.17 (m, 2 H), 6.75 (m, 2 H), 6.53 - 6.68 (m, 1 H), 6.39 (d, 1 H), 5.39 (d, 1 H), 5.17 - 5.28 (m, 1 H), 5.03 (s, 2 H), 3.94 - 4.17 (m, 1 H), 3.34 - 3.77 (m, 5 H), 2.31 - 2.41 (m, 1 H), 1.68 - 2.19 (m, 4 H) $[\alpha]_D$=-50.30° (c=0.6, MeOH)
Diastereoisomer 1 of C179	 Single diastereoisomer	100% yield Orange solid	LC-MS (ESI POS): 500.1 (MH^+) ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 8.36 - 8.53 (m, 2 H), 8.10 - 8.25 (m, 2 H), 7.53 - 7.65 (m, 2 H), 7.32 - 7.48 (m, 3 H), 7.01 - 7.20 (m, 2 H), 6.70 - 6.84 (m, 2 H), 6.55 - 6.65 (m, 1 H), 6.37 (d, 1 H), 5.39 (d, 1 H), 5.19 - 5.30 (m, 1 H), 5.16 (s, 2 H), 4.00 - 4.17 (m, 1 H), 3.34 - 3.78 (m, 5 H), 2.31 - 2.42 (m, 1 H), 1.67 - 2.12 (m, 4 H)

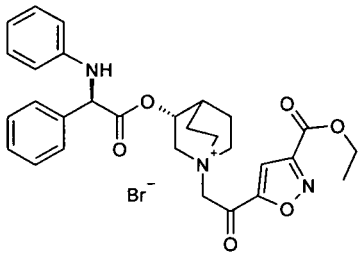
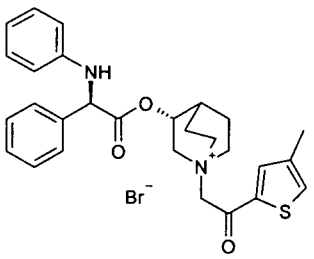
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Diastereoisomer 1 of C180	 Single diastereoisomer	64% yield light brown solid	LC-MS (ESI POS): 471.0 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.69 - 7.89 (m, 2 H), 7.51 - 7.65 (m, 2 H), 7.30 - 7.49 (m, 3 H), 6.98 - 7.15 (m, 2 H), 6.83 - 6.96 (m, 2 H), 6.70 - 6.79 (m, 2 H), 6.60 (m, 1 H), 6.36 (d, 1 H), 5.38 (d, 1 H), 5.15 - 5.25 (m, 1 H), 4.96 (s, 2 H), 3.89 - 4.20 (m, 1 H), 3.34 - 3.77 (m, 5 H), 2.31 - 2.43 (m, 1 H), 1.70 - 2.16 (m, 4 H) $[\alpha]_D$=-44.08° (c=0.25, MeOH)
Diastereoisomer 1 of C181	 Single diastereoisomer	81% yield Yellow solid	LC-MS (ESI POS): 510.0 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 10.95 (s, 1 H), 7.87 (dd, 1 H), 7.82 (d, 1 H), 7.53 - 7.65 (m, 2 H), 7.26 - 7.48 (m, 3 H), 7.03 - 7.15 (m, 2 H), 6.98 (d, 1 H), 6.69 - 6.81 (m, 2 H), 6.52 - 6.63 (m, 1 H), 6.38 (d, 1 H), 5.38 (d, 1 H), 5.15 - 5.26 (m, 1 H), 5.05 (s, 2 H), 3.98 - 4.22 (m, 1 H), 3.63 - 3.80 (m, 2 H), 3.61 (s, 2 H), 3.48 - 3.59 (m, 2 H), 3.34 - 3.47 (m, 1 H), 2.31 - 2.42 (m, 1 H), 1.65 - 2.19 (m, 4 H) $[\alpha]_D$=-47.07° (c=0.28, MeOH)

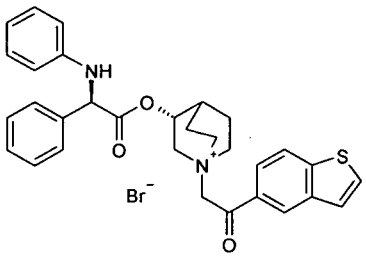
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Diastereoisomer 1 of C182	 Single diastereoisomer	33% yield Yellow solid	LC-MS (ESI POS): 499.0 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.53 - 7.64 (m, 3 H), 7.29 - 7.51 (m, 4 H), 7.14 (d, 1 H), 7.02 - 7.12 (m, 2 H), 6.69 - 6.82 (m, 2 H), 6.54 - 6.66 (m, 1 H), 6.36 (d, 1 H), 6.19 (s, 2 H), 5.38 (d, 1 H), 5.13 - 5.26 (m, 1 H), 4.98 (s, 2 H), 3.88 - 4.15 (m, 1 H), 3.35 - 3.75 (m, 5 H), 2.30 - 2.42 (m, 1 H), 1.70 - 2.12 (m, 4 H) $[\alpha]_D$=-62.80° (c=0.2, MeOH)
Diastereoisomer 1 of C183	 Single diastereoisomer	73% yield yellow solid	LC-MS (ESI POS): 461.9 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 8.39 (d, 1 H), 8.24 (d, 1 H), 7.51 - 7.65 (m, 2 H), 7.27 - 7.49 (m, 3 H), 6.98 - 7.18 (m, 2 H), 6.69 - 6.79 (m, 2 H), 6.60 (m, 1 H), 6.36 (d, 1 H), 5.38 (d, 1 H), 5.17 - 5.31 (m, 1 H), 5.12 (s, 2 H), 4.05 - 4.25 (m, 1 H), 3.58 - 3.77 (m, 3 H), 3.44 - 3.58 (m, 1 H), 3.33 - 3.41 (m, 1 H), 2.31 - 2.40 (m, 1 H), 1.76 - 2.16 (m, 4 H) $[\alpha]_D$=-58.16° (c=0.25, MeOH)

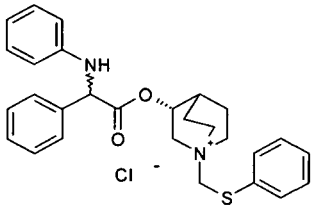
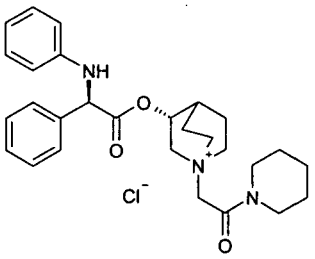
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Diastereoisomer 1 of C184	 Single diastereoisomer	27% yield yellow amorphous solid	LC-MS (ESI POS): 517.9 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.86 (s, 1 H), 7.49 - 7.65 (m, 2 H), 7.29 - 7.49 (m, 3 H), 6.95 - 7.18 (m, 2 H), 6.68 - 6.82 (m, 2 H), 6.55 - 6.67 (m, 1 H), 6.36 (d, 1 H), 5.38 (d, 1 H), 5.14 - 5.25 (m, 1 H), 4.93 (s, 2 H), 4.43 (q, 2 H), 3.96 - 4.15 (m, 1 H), 3.34 - 3.71 (m, 5 H), 2.31 - 2.40 (m, 1 H), 1.85 - 2.09 (m, 4 H), 1.35 (t, 3 H) $[\alpha]_D$=-45.40° (c=0.2, MeOH)
Diastereoisomer 1 of C185	 Single diastereoisomer	6% yield White solid	LC-MS (ESI POS): 475.0 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.89 (d, 1 H), 7.82 (s, 1 H), 7.51 - 7.62 (m, 2 H), 7.28 - 7.48 (m, 3 H), 7.01 - 7.18 (m, 2 H), 6.67 - 6.80 (m, 2 H), 6.52 - 6.65 (m, 1 H), 6.36 (d, 1 H), 5.37 (d, 1 H), 5.08 - 5.26 (m, 1 H), 4.92 (s, 2 H), 3.95 - 4.19 (m, 1 H), 3.41 - 3.75 (m, 5 H), 2.29 - 2.30 (m, 1 H), 2.29 (s, 3 H), 1.80 - 2.12 (m, 4 H)

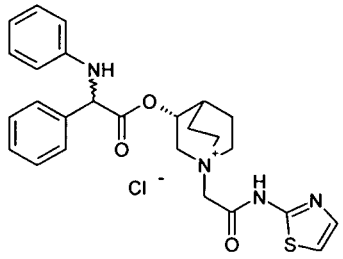
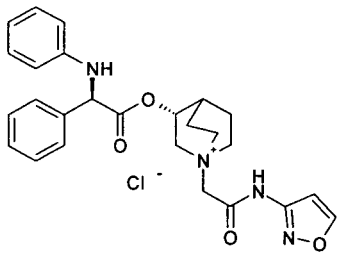
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Diastereoisomer 1 of C186	 Single diastereoisomer	67% yield Off-white solid	LC-MS (ESI POS): 510.9 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 8.56 (d, 1 H), 8.25 (d, 1 H), 7.97 (d, 1 H), 7.91 (dd, 1 H), 7.67 (d, 1 H), 7.52 - 7.62 (m, 2 H), 7.40 - 7.51 (m, 2 H), 7.28 - 7.40 (m, 1 H), 7.03 - 7.18 (m, 2 H), 6.69 - 6.84 (m, 2 H), 6.53 - 6.66 (m, 1 H), 6.38 (d, 1 H), 5.40 (d, 1 H), 5.20 (s, 2 H), 5.14 - 5.30 (m, 1 H), 4.06 - 4.23 (m, 1 H), 3.60 - 3.82 (m, 3 H), 3.50 - 3.60 (m, 1 H), 3.35 - 3.50 (m, 1 H), 2.34 - 2.42 (m, 1 H), 1.69 - 2.15 (m, 4 H) $[\alpha]_D$=-42.73° (c=0.3, MeOH)

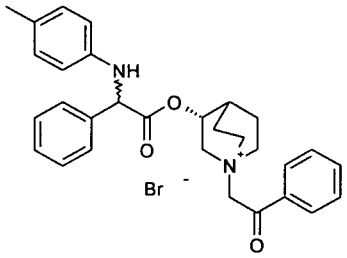
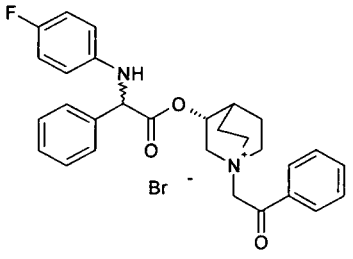
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C187	 Mixture of diastereoisomers	82% yield Off-white solid	LC-MS (ESI POS): 459.2 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.50 - 7.61 (m, 4 H), 7.29 - 7.49 (m, 6 H), 7.08 (dd, 2 H), 6.65 - 6.79 (m, 2 H), 6.55 - 6.65 (m, 1 H), 6.40 (d, 1 H), 5.35 (d, 1 H), 5.04 - 5.15 (m, 1 H), 4.96 (s, 2 H), 3.76 (ddd, 1 H), 3.33 - 3.50 (m, 3 H), 2.85 - 3.06 (m, 2 H), 2.23 - 2.34 (m, 1 H), 1.67 - 2.04 (m, 4 H) $[\alpha]_D$=-55.41° (c=1, MeOH)
Diastereoisomer 1 of C188	 Single diastereoisomer	37% yield white solid	LC-MS (ESI POS): 462.2 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.50 - 7.60 (m, 2 H) 7.29 - 7.46 (m, 3 H) 7.02 - 7.14 (m, 2 H) 6.67 - 6.79 (m, 2 H) 6.54 - 6.66 (m, 1 H) 6.37 (d, 1 H) 5.35 (d, 1 H) 5.06 - 5.22 (m, 1 H) 4.31 (s, 2 H) 3.97 - 4.15 (m, 1 H) 3.31 - 3.80 (m, 9 H) 2.23 - 2.39 (m, 1 H) 1.77 - 2.10 (m, 4 H) 1.38 - 1.69 (m, 6 H) $[\alpha]_D$=-40.7° (c=0.4, MeOH)

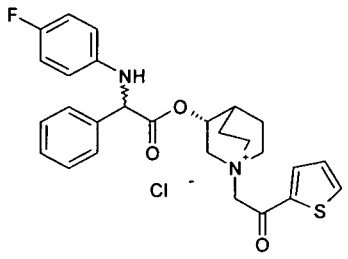
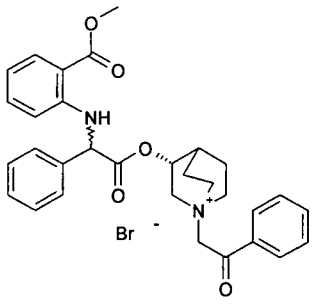
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C189	 Mixture of diastereoisomers	47% yield White solid	LC-MS (ESI POS): 476.9 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 12.82 (br. s., 1 H), 7.55 - 7.60 (m, 2 H), 7.53 (d, 1 H), 7.33 - 7.47 (m, 3 H), 7.32 (d, 1 H), 7.00 - 7.15 (m, 2 H), 6.69 - 6.81 (m, 2 H), 6.53 - 6.66 (m, 1 H), 6.39 (d, 1 H), 5.37 (d, 1 H), 5.06 - 5.21 (m, 1 H), 4.30 (s, 2 H), 4.00 - 4.17 (m, 1 H), 3.46 - 3.75 (m, 5 H), 2.29 - 2.39 (m, 1 H), 1.41 - 2.13 (m, 4 H)
Diastereoisomer 1 of C190	 Single stereoisomer	34% yield White solid	LC-MS (ESI POS): 461.0 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 11.82 (br. s., 1 H), 8.89 (d, 1 H), 7.52 - 7.63 (m, 2 H), 7.26 - 7.50 (m, 3 H), 7.02 - 7.17 (m, 2 H), 6.90 (d, 1 H), 6.70 - 6.80 (m, 2 H), 6.53 - 6.64 (m, 1 H), 6.39 (d, 1 H), 5.36 (d, 1 H), 5.04 - 5.25 (m, 1 H), 4.28 (s, 2 H), 3.99 - 4.15 (m, 1 H), 3.44 - 3.75 (m, 5 H), 2.27 - 2.39 (m, 1 H), 1.71 - 2.13 (m, 4 H) $[\alpha]_D$=-44.66° (c=1, DCM)

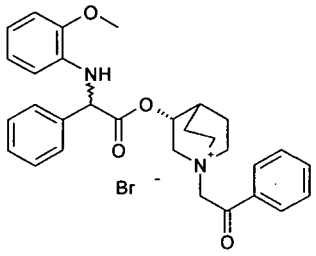
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C191	 Mixture of diastereoisomers	36% yield White solid	LC-MS (ESI POS): 469.1 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.88 - 8.07 (m, 2 H), 7.71 - 7.83 (m, 1 H), 7.51 - 7.68 (m, 4 H), 7.24 - 7.48 (m, 3 H), 6.91 (m, 2 H), 6.66 (m, 2 H), 6.16 (d, 1 H), 5.34 (d, 1 H), 5.15 - 5.27 (m, 1 H), 5.09 (s, 2 H), 3.92 - 4.19 (m, 1 H), 3.33 - 3.77 (m, 5 H), 2.31 - 2.41 (m, 1 H), 2.12 (s, 3 H), 1.77 - 2.08 (m, 4 H)
C192	 Mixture of diastereoisomers	32% yield Pale brown solid	LC-MS (ESI POS): 473.1 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.90 - 8.05 (m, 2 H), 7.72 - 7.84 (m, 1 H), 7.52 - 7.70 (m, 4 H), 7.23 - 7.50 (m, 3 H), 6.86 - 7.01 (m, 2 H), 6.64 - 6.80 (m, 2 H), 6.35 (d, 1 H), 5.37 (d, 1 H), 5.16 - 5.26 (m, 1 H), 5.12 (s, 1 H), 3.99 - 4.13 (m, 1 H), 3.38 - 3.84 (m, 6 H), 2.30 - 2.41 (m, 1 H), 1.39 - 2.18 (m, 4 H)

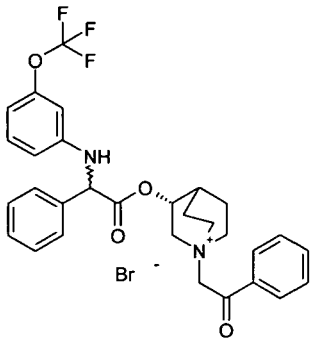
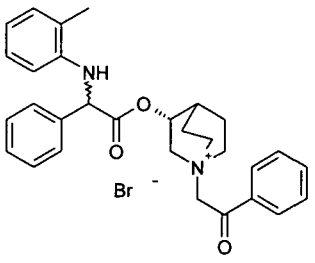
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C193	 Mixture of diastereoisomers	6% yield White solid	LC-MS (ESI POS): 479.0 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 8.14 - 8.29 (m, 1 H), 7.93 - 8.13 (m, 1 H), 7.51 - 7.63 (m, 2 H), 7.27 - 7.48 (m, 5 H), 6.86 - 7.04 (m, 2 H), 6.63 - 6.81 (m, 2 H), 6.11 - 6.43 (m, 1 H), 5.26 - 5.43 (m, 1 H), 5.13 - 5.26 (m, 1 H), 4.90 - 5.11 (m, 2 H), 3.92 - 4.25 (m, 1 H), 3.33 - 3.86 (m, 5 H), 2.30 - 2.42 (m, 0 H), 1.48 - 2.19 (m, 4 H)
C194	 Mixture of diastereoisomers	42% yield White powder	LC-MS (ESI POS): 513.0 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 8.82 (t, 1 H), 7.93 - 8.09 (m, 2 H), 7.82 - 7.91 (m, 1 H), 7.70 - 7.81 (m, 1 H), 7.51 - 7.70 (m, 4 H), 7.21 - 7.51 (m, 4 H), 6.56 - 6.79 (m, 2 H), 5.61 and 5.67 (d, 1 H), 5.22 - 5.36 (m, 1 H), 5.14 and 5.20 (s, 2 H), 3.94 - 4.27 (m, 1 H), 3.86 (s, 3 H), 3.35 - 3.77 (m, 5 H), 2.15 - 2-24 and 2.37 - 2.46 (m, 1 H), 1.38 - 2.14 (m, 4 H)

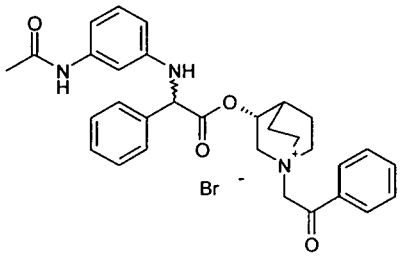
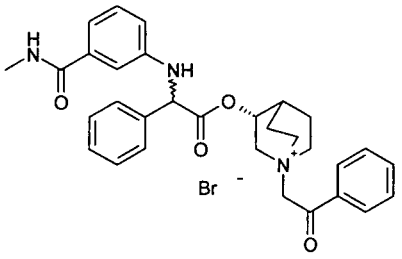
(continue)

C195	 Mixture of diastereoisomers	11% yield White powder	LC-MS (ESI POS): 485.1 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.89 - 8.10 (m, 2 H), 7.71 - 7.82 (m, 1 H), 7.58 - 7.70 (m, 2 H), 7.50 - 7.58 (m, 2 H), 7.24 - 7.48 (m, 3 H), 6.88 (d, 1 H), 6.71 (td, 1 H), 6.63 (td, 1 H), 6.37 - 6.52 (m, 1 H), 5.44 (d, 1 H), 5.39 (d, 1 H), 5.21 - 5.29 (m, 1 H), 5.13 and 5.20 (s, 2 H), 4.00 - 4.21 (m, 1 H), 3.85 (s, 3 H), 3.35 - 3.76 (m, 5 H), 2.14 - 2.20 and 2.35 - 2.45 (m, 1 H), 1.33 - 2.11 (m, 4 H)

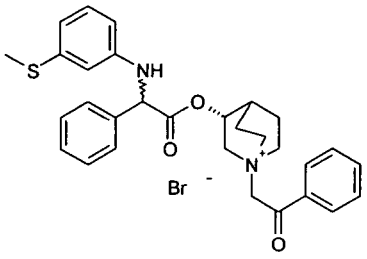
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C196	 Mixture of diastereoisomers	20% yield White solid	LC-MS (ESI POS): 539.0 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.89 - 8.07 (m, 2 H), 7.70 - 7.82 (m, 1 H), 7.52 - 7.70 (m, 4 H), 7.30 - 7.52 (m, 3 H), 7.19 (t, 1 H), 6.80 - 6.97 (m, 1 H), 6.69 - 6.80 (m, 2 H), 6.46 - 6.57 (m, 1 H), 5.44 and 5.48 (d, 1 H), 5.21 - 5.29 (m, 1 H), 5.14 and 5.20 (s, 2 H), 3.99 - 4.24 (m, 1 H), 3.39 - 3.87 (m, 5 H), 2.09 - 2.18 and 2.33 - 2.43 (m, 1 H), 1.42 - 2.18 (m, 4 H)
C197	 Mixture of diastereoisomers	37% yield White solid	LC-MS (ESI POS): 469.1 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.89 - 8.11 (m, 2 H), 7.69 - 7.85 (m, 1 H), 7.51 - 7.69 (m, 4 H), 7.27 - 7.49 (m, 3 H), 7.04 (d, 1 H), 6.87 - 7.01 (m, 1 H), 6.55 - 6.64 (m, 1 H), 6.46 (d, 1 H), 5.38 - 5.50 (m, 1 H), 5.09 - 5.31 (m, 4 H), 3.99 - 4.23 (m, 1 H), 3.45 - 3.89 (m, 5 H), 2.34 - 2.43 (m, 1 H), 2.25 (s, 3 H), 1.37 - 2.09 (m, 4 H)

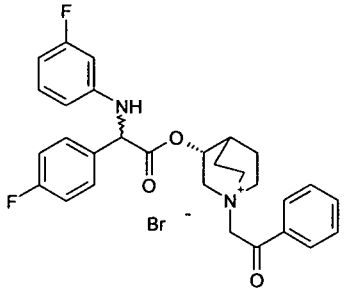
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C198	 Mixture of diastereoisomers	41% yield Off-white solid	LC-MS (ESI POS): 512.1 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 9.69 and 9.71 (d, 1 H), 7.89 - 8.07 (m, 2 H), 7.69 - 7.83 (m, 1 H), 7.50 - 7.68 (m, 4 H), 7.30 - 7.49 (m, 3 H), 7.09 - 7.25 (m, 1 H), 7.00 (t, 1 H), 6.61 - 6.81 (m, 1 H), 6.27 - 6.56 (m, 2 H), 5.03 - 5.32 (m, 4 H), 4.05 - 4.27 (m, 1 H), 3.44 - 3.90 (m, 5 H), 2.11 - 2.21 and 2.32 - 2.42 (m, 1 H), 1.94 and 1.96 (s, 3 H), 1.59 - 2.10 (m, 4 H)
C199	 Mixture of diastereoisomers	51% yield Off-white solid	LC-MS (ESI POS): 512.1 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 8.14 - 8.30 (m, 1 H), 7.92 - 8.05 (m, 2 H), 7.55 - 7.86 (m, 5 H), 7.30 - 7.50 (m, 3 H), 7.11 - 7.23 (m, 1 H), 6.99 - 7.10 (m, 1 H), 6.91 (d, 1 H), 6.62 (d, 2 H), 5.45 (d, 1 H), 5.19 - 5.24 (m, 1 H), 5.14 (s, 2 H), 4.03 - 4.26 (m, 1 H), 3.35 - 3.86 (m, 5 H), 2.70 (d, 3 H), 2.10 - 2.40 (m, 1 H), 1.61 - 2.09 (m, 4 H)

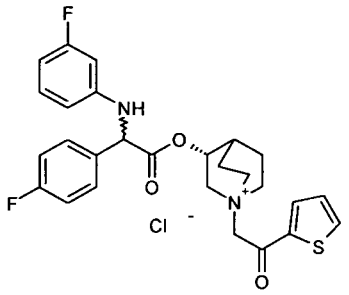
(continue)

C200	 Mixture of diastereoisomers	42% yield Off-white solid	LC-MS (ESI POS): 501.3 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.90 - 8.09 (m, 2 H), 7.71 - 7.84 (m, 1 H), 7.52 - 7.70 (m, 4 H), 7.28 - 7.49 (m, 3 H), 7.01 and 7.04 (d, 1 H), 6.67 (s, 1 H), 6.37 - 6.59 (m, 3 H), 5.40 and 5.43 (d, 1 H), 5.19 - 5.30 (m, 1 H), 5.14 and 5.21 (s, 2 H), 4.01 - 4.25 (m, 1 H), 3.40 - 3.88 (m, 5 H), 2.37 (s, 3 H), 1.38 - 2.21 (m, 5 H)

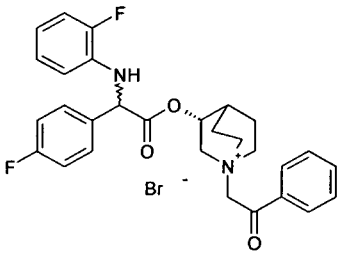
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C201	 Mixture of diastereoisomers	42% yield pale pink solid	LC-MS (ESI POS): 491.2 (MH^+) ^{1}H NMR (300 MHz, DMSO-d_6): Diastereoisomer 1: 7.88 - 8.07 (m, 2 H), 7.70 - 7.81 (m, 1 H), 7.49 - 7.68 (m, 4 H), 7.19 - 7.33 (m, 2 H), 6.99 - 7.16 (m, 1 H), 6.69 - 6.85 (m, 1 H), 6.49 - 6.62 (m, 2 H), 6.22 - 6.44 (m, 1 H), 5.49 (d, 1 H), 5.21 - 5.28 (m, 1 H), 5.13 (s, 2 H), 3.96 - 4.10 (m, 1 H), 3.43 - 3.88 (m, 5 H), 2.32 - 2.43 (m, 1 H), 1.46 - 2.21 (m, 4 H) Diastereoisomer 2: 7.88 - 8.07 (m, 2 H), 7.70 - 7.81 (m, 1 H), 7.49 - 7.68 (m, 4 H), 7.19 - 7.33 (m, 2 H), 6.99 - 7.16 (m, 1 H), 6.69 - 6.85 (m, 1 H), 6.49 - 6.62 (m, 2 H), 6.22 - 6.44 (m, 1 H), 5.46 (d, 1 H), 5.21 - 5.28 (m, 1 H), 5.18 (s, 2 H), 4.10 - 4.20 (m, 1 H), 3.43 - 3.88 (m, 5 H), 2.13 - 2.21 (m, 1 H), 1.36 - 2.11 (m, 4 H)

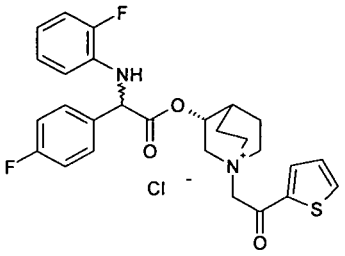
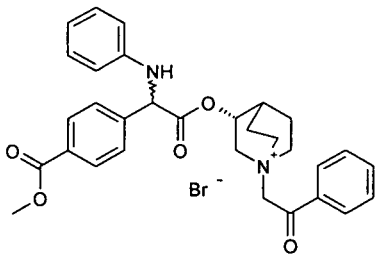
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C202	 Mixture of diastereoisomers	52% yield beige solid	LC-MS (ESI POS): 497.1 (MH^+) ^{1}H NMR (300 MHz, DMSO-d_6): Diastereoisomer 1: 8.20 (dd, 1.03 Hz, 1 H), 8.06 (dd, 1 H), 7.51 - 7.72 (m, 2 H), 7.31 - 7.41 (m, 1 H), 7.19 - 7.29 (m, 2 H), 6.98 - 7.17 (m, 1 H), 6.69 - 6.88 (m, 1 H), 6.45 - 6.62 (m, 2 H), 6.24 - 6.45 (m, 1 H), 5.48 (d, 1 H), 5.14 - 5.31 (m, 1 H), 5.03 (s, 2 H), 3.96 - 4.21 (m, 1 H), 3.36 - 3.86 (m, 5 H), 2.28 - 2.43 (m, 1 H), 1.46 - 2.11 (m, 4 H) Diastereoisomer 2: 8.21 (dd, 1 H), 8.10 (dd, *J*=3.96, 1.03 Hz, 1 H), 7.51 - 7.72 (m, 2 H), 7.31 - 7.41 (m, 1 H), 7.19 - 7.29 (m, 2 H), 6.98 - 7.17 (m, 1 H), 6.69 - 6.88 (m, 1 H), 6.45 - 6.62 (m, 2 H), 6.24 - 6.45 (m, 1 H), 5.44 (d, 1 H), 5.14 - 5.31 (m, 1 H), 5.09 (s, 2 H), 3.96 - 4.21 (m, 1 H), 3.36 - 3.86 (m, 5 H), 2.11 - 2.20 (m, 1 H), 1.46 - 2.11 (m, 4 H)

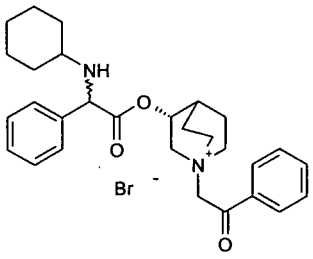
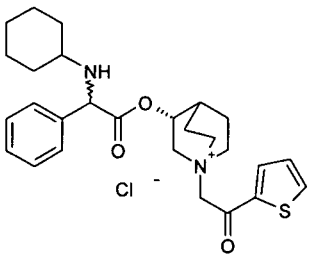
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C203	 Mixture of diastereoisomers	94% yield white solid	LC-MS (ESI POS): 491.2 (MH^+) ^{1}H NMR (300 MHz, DMSO-d_6): Diastereoisomer 1: 7.86 - 8.04 (m, 2 H), 7.70 - 7.83 (m, 1 H), 7.53 - 7.70 (m, 4 H), 7.19 - 7.33 (m, 2 H), 7.03 - 7.14 (m, 1 H), 6.89 - 7.00 (m, 1 H), 6.56 - 6.80 (m, 2 H), 5.73 - 5.89 (m, 1 H), 5.52 (d, 1 H), 5.20 - 5.29 (m, 1 H), 5.12 (s, 2 H), 3.95 - 4.29 (m, 1 H), 3.35 - 3.87 (m, 5 H), 2.32 - 2.42 (m, 1 H), 1.42 - 2.13 (m, 4 H) Diastereoisomer 2: 7.86 - 8.04 (m, 2 H), 7.70 - 7.83 (m, 1 H), 7.53 - 7.70 (m, 4 H), 7.19 - 7.33 (m, 2 H), 7.03 - 7.14 (m, 1 H), 6.89 - 7.00 (m, 1 H), 6.56 - 6.80 (m, 2 H), 5.73 - 5.89 (m, 1 H), 5.50 (d, 1 H), 5.20 - 5.29 (m, 1 H), 5.17 (s, 2 H), 3.95 - 4.29 (m, 1 H), 3.35 - 3.87 (m, 5 H), 2.14 - 2.23 (m, 1 H), 1.42 - 2.13 (m, 4 H)

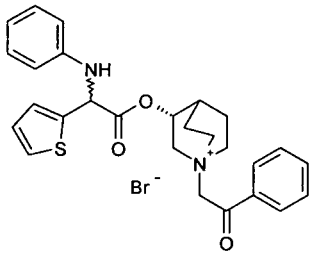
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C204	 Mixture of diastereoisomers	83% yield white solid	LC-MS (ESI POS): 497.1 (MH^+) ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 8.17 - 8.24 (m, 1 H), 8.03 - 8.14 (m, 1 H), 7.51 - 7.74 (m, 2 H), 7.28 - 7.41 (m, 1 H), 7.17 - 7.27 (m, 2 H), 7.02 - 7.14 (m, 1 H), 6.87 - 6.99 (m, 1 H), 6.44 - 6.78 (m, 2 H), 5.72 - 5.91 (m, 1 H), 5.50 (m, 1 H), 5.22 (br. s., 1 H), 5.07 (s, 2 H), 3.99 - 4.29 (m, 1 H), 3.35 - 3.94 (m, 5 H), 2.13 - 2.42 (m, 1 H), 1.41 - 2.12 (m, 4 H)
C205	 Mixture of diastereoisomers	81% yield Off-white solid	LC-MS (ESI POS): 513.0 (MH^+) ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.89 - 8.07 (m, 4 H), 7.70 - 7.80 (m, 3 H), 7.47 - 7.67 (m, 2 H), 7.03 - 7.17 (m, 2 H), 6.70 - 6.82 (m, 2 H), 6.55 - 6.65 (m, 1 H), 6.49 (d, 1 H), 5.56 and 5.52 (d, 1 H), 5.21 - 5.33 (m, 1 H), 5.20 and 5.12 (s, 2 H), 3.97 - 4.23 (m, 1 H), 3.85 (s, 3 H), 3.41 - 3.82 (m, 5 H), 2.33 - 2.42 and 2.10 - 2.21(m, 1 H), 1.49 - 2.11 (m, 4 H)

(continue)

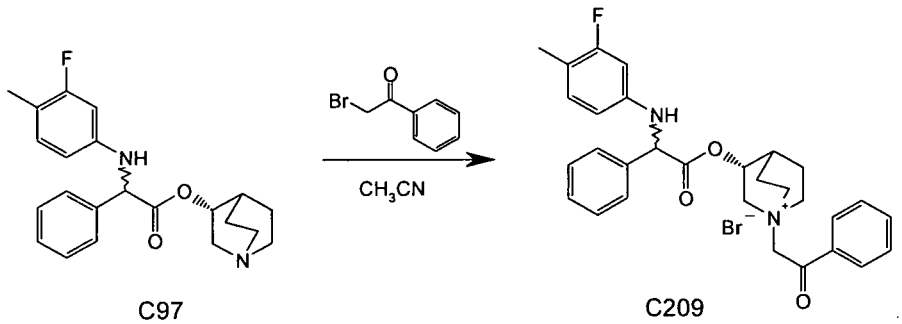
C206	 Mixture of diastereoisomers	46% yield Colorless sticky oil	LC-MS (ESI POS): 461.1 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 9.77 (br. s., 1 H), 9.58 (br. s., 1 H), 7.87 - 8.05 (m, 2 H), 7.72 - 7.82 (m, 1 H), 7.40 - 7.71 (m, 7 H), 5.45 - 5.70 (m, 1 H), 5.28 - 5.45 (m, 1 H), 5.06 - 5.26 (m, 2 H), 3.97 - 4.21 (m, 1 H), 3.81 (d, 1 H), 3.23 - 3.76 (m, 4 H), 2.77 - 3.04 (m, 1 H), 1.88 - 2.46 (m, 6 H), 1.69 - 1.86 (m, 3 H), 1.26 - 1.69 (m, 3 H), 0.80 - 1.26 (m, 3 H)
C207	 Mixture of diastereoisomers	41% yield White solid	LC-MS (ESI POS): 467.0 (MH^+) ^1H NMR (300 MHz, DMSO-d6) ppm: 9.56 (br. s., 2 H), 8.17 - 8.28 (m, 1 H), 7.94 - 8.12 (m, 1 H), 7.44 - 7.77 (m, 5 H), 7.24 - 7.39 (m, 1 H), 5.44 - 5.68 (m, 1 H), 5.26 - 5.44 (m, 1 H), 4.84 - 5.14 (m, 2 H), 3.92 - 4.24 (m, 1 H), 3.43 - 3.91 (m, 6 H), 2.78 - 3.08 (m, 1 H), 2.32 - 2.45 (m, 1 H), 1.84 - 2.23 (m, 3 H), 1.47 - 1.84 (m, 2 H), 0.83 - 1.47 (m, 8 H)

(continue)

C208	 Mixture of diastereoisomers	41% yield Off-white solid	LC-MS (ESI POS): 460.9 (MH^+) ^{1}H NMR (300 MHz, DMSO-d_6) ppm Diastereoisomer 1: 7.92 - 8.03 (m, 2 H), 7.71 - 7.82 (m, 1 H), 7.57 - 7.69 (m, 2 H), 7.50 - 7.57 (m, 1 H), 7.24 - 7.34 (m, 1 H), 7.01 - 7.17 (m, 3 H), 6.75 - 6.83 (m, 2 H), 6.58 - 6.67 (m, 1 H), 6.43 (d, 1 H), 5.69 (d, 1 H), 5.23 - 5.34 (m, 1 H), 5.17 (s, 2 H), 4.05 - 4.24 (m, 1 H), 3.44 - 3.86 (m, 5 H), 2.31 - 2.43 (m, 1 H), 1.64 - 2.14 (m, 4 H) Diastereoisomer 2: 7.92 - 8.03 (m, 2 H), 7.71 - 7.82 (m, 1 H), 7.57 - 7.69 (m, 2 H), 7.50 - 7.57 (m, 1 H), 7.24 - 7.34 (m, 1 H), 7.01 - 7.17 (m, 3 H), 6.75 - 6.83 (m, 2 H), 6.58 - 6.67 (m, 1 H), 6.42 (d, 1 H), 5.66 (d, 1 H), 5.23 - 5.34 (m, 1 H), 5.21 (s, 2 H), 4.05 - 4.24 (m, 1 H), 3.44 - 3.86 (m, 5 H), 2.18 - 2.24 (m, 1 H), 1.64 - 2.14 (m, 4 H)

EXAMPLE 46

Preparation of (R)-3-[2-(3-fluoro-4-methyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide (C209)



C97 C209

Scheme 46

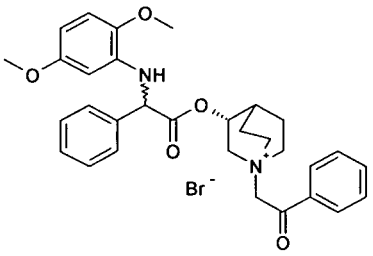
(R)-Quinuclidin-3-yl 2-(3-fluoro-4-methylphenylamino)-2-phenylacetate (C97) (80 mg, 0.22 mmol) and 2-bromo-1-phenylethanone (45.4 mg, 0.23 mmol) are dissolved in acetonitrile (3 mL) and stirred at RT overnight (Conversion complete by UPLC/MS). Acetonitrile is evaporated and the residue is purified by flash chromatography (DCM/MeOH=97/3) affording the title compound as a white solid (29 mg, 23% yield, bromide salt, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d6) ppm: 7.92 - 8.05 (m, 2 H), 7.71 - 7.86 (m, 1 H), 7.50 - 7.71 (m, 4 H), 7.28 - 7.50 (m, 3 H), 6.95 and 6.97 (d, 1 H), 6.38 - 6.62 (m, 3 H), 5.37 and 5.41 (d, 1 H), 5.19 - 5.27 (m, 1 H), 5.15 (s, 2 H), 4.00 - 4.27 (m, 1 H), 3.79 (d, 1 H), 3.40 - 3.72 (m, 4 H), 2.10 - 2.20 and 2.33 - 2.42 (m, 1 H), 2.04 (s, 3 H), 1.85 - 2.02 (m, 2 H), 1.65 - 1.85 (m, 1 H), 1.42 - 1.65 (m, 1 H);

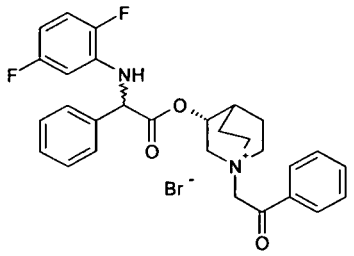
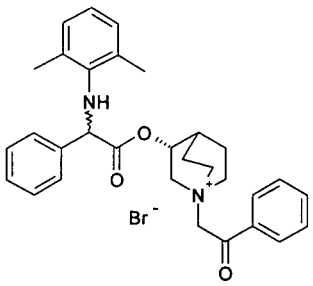
LC-MS (ESI POS): 487.1 (MH+).

Final compounds listed in Table 22 are prepared as previously described for C209, by alkylation of suitable intermediate (C103, C106, C107, C109, C112, C115, C117, C147, C148) and the commercially available alkylating agents.

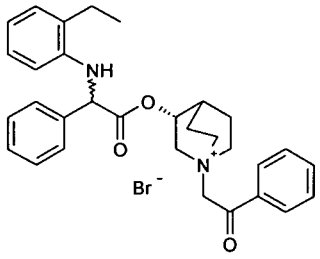
Table 22

Compound	Structure	Yield and Appearance	Analytical
C210	 Mixture of diastereoisomers	40% yield Yellow solid	LC-MS (ESI POS): 515.1 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.89 - 8.04 (m, 2 H), 7.70 - 7.83 (m, 1 H), 7.49 - 7.69 (m, 4 H), 7.27 - 7.49 (m, 3 H), 6.77 (d, 1 H), 6.15 (dd, 1 H), 6.03 and 6.06 (d, 1 H), 5.36 - 5.53 (m, 2 H), 5.21 - 5.30 (m, 1 H), 5.13 and 5.19 (s, 2 H), 3.94 - 4.28 (m, 1 H), 3.80 (s, 3 H), 3.59 - 3.73 (m, 3 H), 3.56 and 3.57 (s, 3 H), 3.34 - 3.54 (m, 2 H), 2.12 - 222 and 2.35 - 2.45 (m, 1 H), 1.29 - 2.12 (m, 4 H)

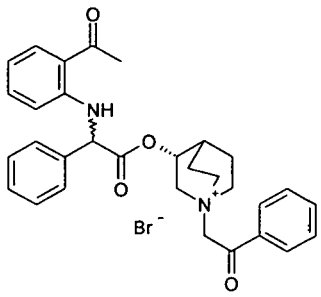
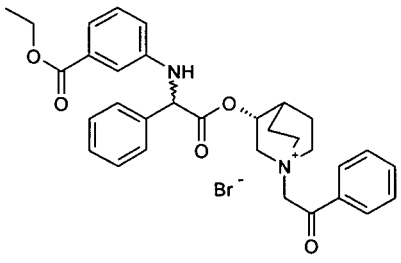
(continue)

C211	 Mixture of diastereoisomer	55% yield White solid	LC-MS (ESI POS): 491.3 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.92 - 8.03 (m, 2 H) 7.71 - 7.81 (m, 1 H) 7.54 - 7.67 (m, 4 H) 7.31 - 7.47 (m, 3 H) 7.11 (ddd, 1 H) 6.51 - 6.63 (m, 1 H) 6.36 - 6.47 (m, 1 H) 6.02 - 6.15 (m, 1 H) 5.54 and 5.56 (d, 1 H) 5.22 - 5.31 (m, 1 H) 5.19 (d, 1 H) 5.12 (d, 1 H) 4.01 - 4.22 (m, 1 H) 3.36 - 3.88 (m, 5 H) 1.34 - 2.43 (m, 5 H)
C212	 Mixture of diastereoisomer	58% yield White solid	LC-MS (ESI POS): 483.1 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.86 - 8.06 (m, 2 H), 7.68 - 7.83 (m, 1 H), 7.48 - 7.67 (m, 4 H), 7.24 - 7.46 (m, 3 H), 6.94 (d, 2 H), 6.75 (t, 1 H), 5.21 - 5.25 (m, 1 H), 5.15 and 5.18 (s, 2 H), 5.00 and 5.02 (d, 1 H), 4.70 and 4.75 (d, 1 H), 3.96 - 4.24 (m, 1 H), 3.44 - 3.75 (m, 5 H), 2.22 (s, 6 H), 1.27 - 2.19 (m, 5 H)

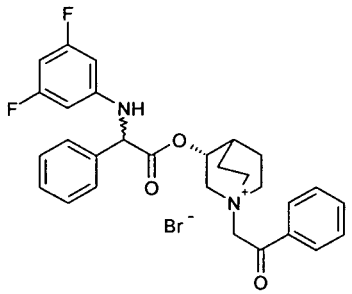
(continue)

C213	 Mixture of diastereoisomer	60% yield Yellow solid	LC-MS (ESI POS): 483.1 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.88 - 8.12 (m, 2 H), 7.71 - 7.84 (m, 1 H), 7.53 - 7.70 (m, 4 H), 7.26 - 7.49 (m, 3 H), 7.04 (d, 1 H), 6.90 - 7.01 (m, 1 H), 6.57 - 6.70 (m, 1 H), 6.47 (d, 1 H), 5.42 and 5.45 (d, 1 H), 5.19 - 5.30 (m, 2 H), 5.14 and 5.20 (s, 2 H), 4.01 - 4.24 (m, 1 H), 3.33 - 3.89 (m, 5 H), 2.64 (q, 2 H), 2.12 - 2.20 and 2.32 - 2.43 (m, 1 H), 1.37 - 2.13 (m, 4 H), 1.24 (t, 3 H)

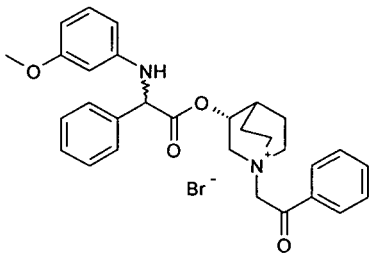
(continue)

C214	 Mixture of diastereoisomer	83% yield Off-white solid	LC-MS (ESI POS): 497.1 (MH^+) ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 9.84 and 9.86 (d, 1 H), 7.86 - 8.09 (m, 3 H), 7.69 - 7.84 (m, 1 H), 7.56 - 7.69 (m, 2 H), 7.49 - 7.56 (m, 2 H), 7.24 - 7.48 (m, 4 H), 6.54 - 6.73 (m, 2 H), 5.62 and 5.67 (d, 1 H), 5.23 - 5.31 (m, 1 H), 5.15 and 5.22 (s, 2 H), 4.00 - 4.27 (m, 1 H), 3.35 - 3.87 (m, 5 H), 2.60 (s, 3 H), 2.17 - 2.24 and 2.36 - 2.47 (m, 1 H), 1.42 - 2.16 (m, 4 H)
C215	 Mixture of diastereoisomer	24% yield Off-white solid	LC-MS (ESI POS): 527.3 (MH^+) ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.90 - 8.04 (m, 2 H) 7.71 - 7.82 (m, 1 H) 7.55 - 7.68 (m, 4 H) 7.30 - 7.49 (m, 4 H) 7.15 - 7.28 (m, 2 H) 6.93 - 7.04 (m, 1 H) 6.78 (t, 1 H) 5.44 (d, 1 H) 5.19 - 5.31 (m, 1 H) 5.14 (s, 2 H) 4.25 (q, 2 H) 3.97 - 4.19 (m, 1 H) 3.42 - 3.80 (m, 5 H) 1.85 - 2.22 (m, 4 H) 1.49 - 1.85 (m, 1 H) 1.28 (t, 3 H)

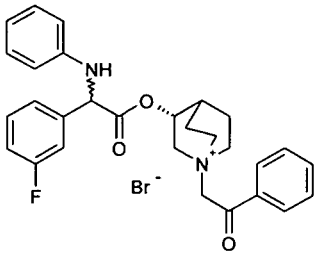
(continue)

C216	 Mixture of diastereoisomer	60% yield White solid	LC-MS (ESI POS): 491.2 (MH^+) ^{1}H NMR (300 MHz, DMSO-d_6) ppm Diastereoisomer 2: 7.90 - 8.06 (m, 2 H), 7.70 - 7.82 (m, 1 H), 7.51 - 7.68 (m, 4 H), 7.30 - 7.51 (m, 3 H), 7.09 (d, 1 H), 6.36 - 6.53 (m, 2 H), 6.20 - 6.36 (m, 1 H), 5.52 (d, 1 H), 5.22 - 5.29 (m, 1 H), 5.15 (s, 2 H), 3.95 - 4.27 (m, 1 H), 3.42 - 3.87 (m, 5 H), 2.31 - 2.44 (m, 1 H), 1.85 - 2.12 (m, 4 H) Diastereoisomer 2: 7.90 - 8.06 (m, 2 H), 7.70 - 7.82 (m, 1 H), 7.51 - 7.68 (m, 4 H), 7.30 - 7.51 (m, 3 H), 7.12 (d, 1 H), 6.36 - 6.53 (m, 2 H), 6.20 - 6.36 (m, 1 H), 5.48 (d, 0 H), 5.22 - 5.30 (m, 1 H), 5.20 (s, 2 H), 3.95 - 4.27 (m, 1 H), 3.42 - 3.87 (m, 5 H), 2.11 - 2.20 (m, 1 H), 1.87 - 2.10 (m, 3 H), 1.65 - 1.85 (m, 1 H), 1.38 - 1.62 (m, 1 H)

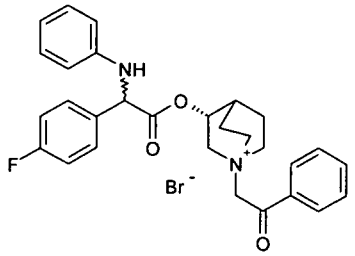
(continue)

C217	 Mixture of diastereoisomer	90% yield Yellow solid	LC-MS (ESI POS): 485.1 (MH^+) ^{1}H NMR (300 MHz, DMSO-d_6) ppm Diastereoisomer 1: 7.92 - 7.99 (m, 2 H), 7.70 - 7.81 (m, 1 H), 7.51 - 7.70 (m, 4 H), 7.26 - 7.49 (m, 3 H), 6.99 (t, 1 H), 6.29 - 6.42 (m, 3 H), 6.13 - 6.24 (m, 1 H), 5.38 (d, 1 H), 5.19 - 5.27 (m, 1 H), 5.10 (s, 2 H), 3.92 - 4.20 (m, 1 H), 3.65 (s, 3 H), 3.41 - 3.81 (m, 5 H), 2.31 - 2.43 (m, 1 H), 1.74 - 2.19 (m, 4 H) Diastereoisomer 2: 7.92 - 7.99 (m, 2 H), 7.70 - 7.81 (m, 1 H), 7.51 - 7.70 (m, 4 H), 7.26 - 7.49 (m, 3 H), 6.99 (t, 1 H), 6.29 - 6.42 (m, 3 H), 6.13 - 6.24 (m, 1 H), 5.35 (d, 1 H), 5.19 - 5.27 (m, 1 H), 5.17 (s, 2 H), 3.92 - 4.20 (m, 1 H), 3.65 (s, 3 H), 3.41 - 3.81 (m, 5 H), 2.31 - 2.43 (m, 1 H), 1.74 - 2.19 (m, 4 H)

(continue)

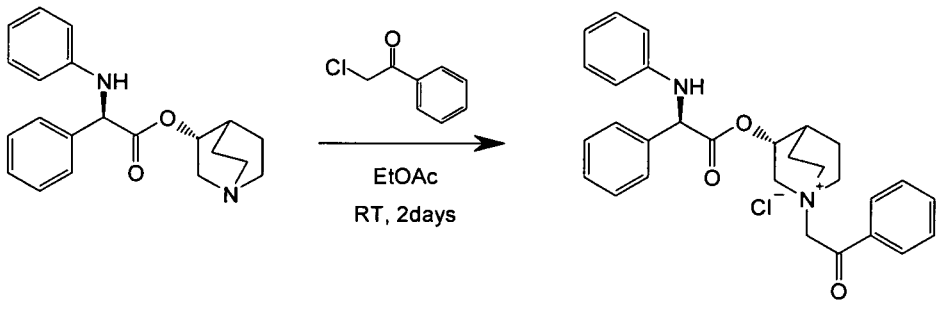
C218	 Mixture of diastereoisomer	52% yield White solid	LC-MS (ESI POS): 473.2 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.91 - 8.06 (m, 2 H), 7.69 - 7.84 (m, 1 H), 7.54 - 7.69 (m, 2 H), 7.30 - 7.54 (m, 3 H), 7.15 - 7.27 (m, 1 H), 7.00 - 7.15 (m, 2 H), 6.71 - 6.78 (m, 2 H), 6.54 - 6.66 (m, 1 H), 6.45 (d, 1 H), 5.45 and 5.49 (d, 1 H), 5.23 - 5.29 (m, 1 H), 5.14 and 5.20 (s, 2 H), 3.97 - 4.21 (m, 1 H), 3.37 - 3.90 (m, 5 H), 2.13 - 2.23 and 2.33 - 2.41 (m, 1 H), 1.46 - 2.10 (m, 4 H)

(continue)

C219	 Mixture of diastereoisomer	61% yield White solid	LC-MS (ESI POS): 473.3 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.91 - 8.05 (m, 2 H), 7.71 - 7.83 (m, 1 H), 7.55 - 7.71 (m, 4 H), 7.19 - 7.32 (m, 2 H), 7.04 - 7.16 (m, 2 H), 6.69 - 6.81 (m, 2 H), 6.56 - 6.67 (m, 1 H), 6.40 (d, 1 H), 5.40 and 5.43 (d, 1 H), 5.22 - 5.28 (m, 1 H), 5.13 and 5.21 (s, 2 H), 4.00 - 4.21 (m, 1 H), 3.74 - 3.87 (m, 1 H), 3.36 - 3.74 (m, 4 H), 2.12 - 2.21 and 2.33 - 2.44 (m, 1 H), 1.45 - 2.11 (m, 4 H)

EXAMPLE 47

Preparation of (R)-1-(2-oxo-2-phenylethyl)-3-((R)-2-phenyl-2-(phenylamino)acetoxy)-1-azoniabicyclo[2.2.2]octane chloride (Diastereoisomer 1 of C113)



Diastereoisomer 1 of C2 Diastereoisomer 1 of C113

Scheme 47

A mixture of 2-chloroacetophenone (6.20 g, 40.3 mmol) and (R)-((R)-

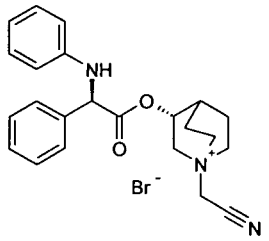
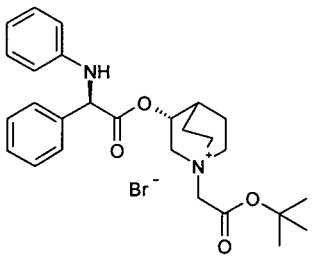
quinuclidin-3-yl) 2-phenyl-2-(phenylamino)acetate) (Diastereoisomer 1 of C2) (12.3 g, 36.6mmol) in EtOAc (100ml) is stirred at RT for 2 days (UPLC-MS monitoring: complete conversion). The solvent is evaporated and the crude is purified by flash chromatography eluting with DCM/MeOH=95/5 to get 10.1g of the title compound as a white solid (56% yield, chloride salt, single diastereoisomer).

^{1}H NMR (400 MHz, DMSO-d6): ppm 7.96 (d, 2H) 7.70 - 7.81 (m, 1H) 7.58 (d, 2H) 7.62 (d, 2H) 7.29 - 7.47 (m, 3H) 7.09 (t, 2H) 6.74 (d, 2H) 6.59 (t, 1H) 6.41 (d, 1H) 5.39 (d, 1H) 5.16 - 5.26 (m, 1H) 5.13 (s, 2H) 4.08 (ddd, 1H) 3.47 - 3.71 (m, 4 H) 3.35 - 3.47 (m, 1H) 2.36 (br. s., 1H) 1.84 - 2.13 (m, 4H);

LC-MS (ESI POS): 455.3 (MH+).

Diastereoisomer 1 of C220 and C221 listed in Table 23 are obtained as previously described for diastereoisomer 1 of C113, using bromo-acetonitrile and bromo-acetic acid tert-butyl ester instead of 2-chloroacetophenone.

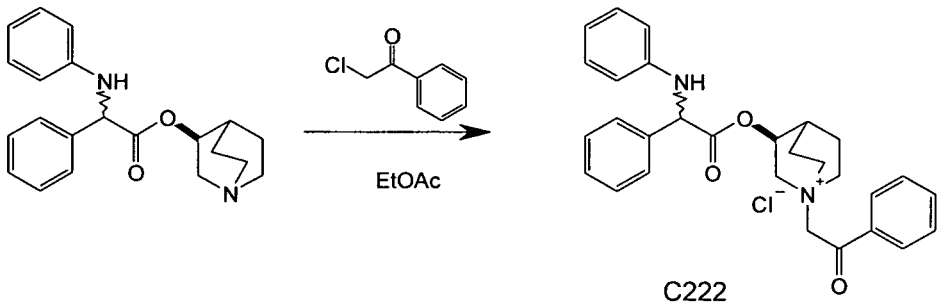
Table 23

Compound	Structure	Yield and Appearance	Analytical
Diastereoisomer 1 of C220	 Single stereoisomer	39% yield pale yellow solid	LC-MS (ESI POS): 467.0 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.50 - 7.68 (m, 2 H), 7.28 - 7.46 (m, 3 H), 6.96 - 7.17 (m, 2 H), 6.69 - 6.80 (m, 2 H), 6.54 - 6.65 (m, 1 H), 6.36 (d, 1 H), 5.37 (d, 1 H), 4.99 - 5.28 (m, 1 H), 4.77 (s, 2 H), 3.99 (ddd, 1 H), 3.35 - 3.69 (m, 3 H), 3.05 - 3.24 (m, 2 H), 2.29 - 2.42 (m, 1 H), 1.64 - 2.14 (m, 4 H)
Diastereoisomer 1 of C221	 Single stereoisomer	33% yield yellow solid	LC-MS (ESI POS): 451.3 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 7.49 - 7.60 (m, 2 H) 7.29 - 7.46 (m, 3 H) 7.03 - 7.14 (m, 2 H) 6.68 - 6.78 (m, 2 H) 6.54 - 6.65 (m, 1 H) 6.36 (d, 1 H) 5.36 (d, 1 H) 5.12 - 5.22 (m, 1 H) 4.22 (d, 1 H) 4.16 (d, 1 H) 3.89 - 4.04 (m, 1 H) 3.34 - 3.70 (m, 4 H) 3.18 - 3.27 (m, 1 H) 2.29 - 2.40 (m, 1 H) 1.75 - 2.15 (m, 4 H) 1.46 (s, 9 H)

(continue)

EXAMPLE 48

Preparation of (S)-1-(2-oxo-2-phenyl-ethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane chloride (C222)



C222

Scheme 48

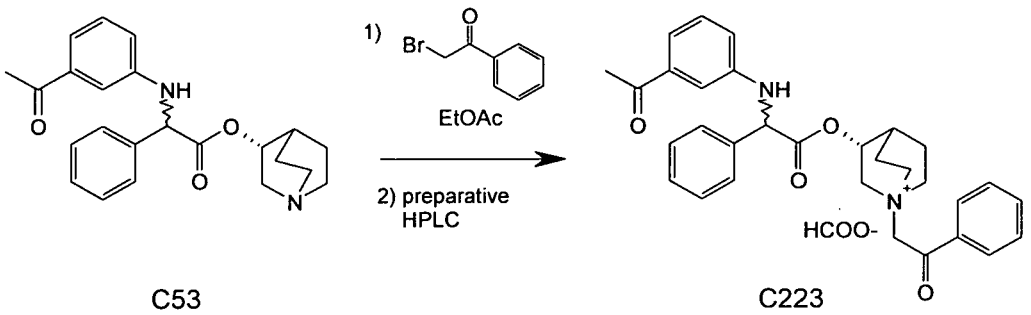
A solution of (S)-quinuclidin-3-yl 2-phenyl-2-(phenylamino)acetate (50.0 mg, 0.15 mmol) in EtOAc (2 mL), is added with 2-chloro-1-phenylethanone (23.0 mg, 0.15 mmol) and the reaction is stirred first at RT for 15h, then at 70°C for 7h and finally at RT for 3 days. The solvent is removed and the resulting crude is triturated with i-Pr_2O/Et_2O (3/1) and then with i-Pr_2O to afford the title compound as a beige solid (47.7 mg, 65% yield, chloride salt, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.92 - 8.03 (m, 2 H) 7.71 - 7.81 (m, 1 H) 7.52 - 7.67 (m, 4 H) 7.30 - 7.47 (m, 3 H) 7.04 - 7.15 (m, 2 H) 6.69 - 6.79 (m, 2 H) 6.55 - 6.64 (m, 1 H) 6.38 (d, 1 H) 5.39 (d, 1 H) 5.18 - 5.28 (m, 1 H) 5.13 (s, 2 H) 4.00 - 4.19 (m, 1 H) 3.48 - 3.78 (m, 4 H) 3.34 - 3.48 (m, 1 H) 2.31 - 2.42 (m, 1 H) 1.84 - 2.16 (m, 4 H);

LC-MS (ESI POS): 455.2 (MH+).

EXAMPLE 49

Preparation of (R)-3-[2-(3-acetyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane formate (C223)



C53 C223

Scheme 49

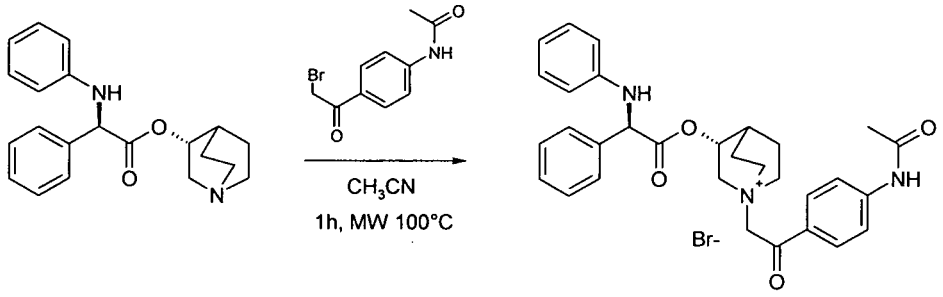
(R)-Quinuclidin-3-yl 2-(3-acetylphenylamino)-2-phenylacetate (C53) (134 mg, 0.35 mmol) and 2-bromo-1-phenylethanone (85.0 mg, 0.42 mmol) are dissolved in ethyl acetate (5 mL) and stirred at RT for 2h. EtOAc is evaporated and the resulting crude oil is first purified by flash chromatography (DCM/MeOH=95/5) and then by preparative HPLC. The fractions containing the product are combined and concentrated under vacuum to remove the organic solvent. The resulting aqueous solution is freeze-dried obtaining the title compound as a white-foam (77.7 mg, 40% yield, formate salt, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 8.44 (s, 1 H, formiate), 7.92 - 8.05 (m, 2 H), 7.69 - 7.80 (m, 1 H), 7.51 - 7.66 (m, 4 H), 7.15 - 7.49 (m, 6 H), 6.97 - 7.07 (m, 1 H), 6.76 and 6.78 (d, 1 H), 5.46 and 5.49 (d, 1 H), 5.23 - 5.28 (m, 1 H), 5.17 and 5.22 (s, 2 H), 4.01 - 4.26 (m, 1 H), 3.36 - 3.87 (m, 5 H), 2.48 (s, 3 H), 2.12 - 2.20 and 2.33 - 2.40 (m, 1 H), 1.48 - 2.11 (m, 4 H);

LC-MS (ESI POS): 497.1 (MH^+).

EXAMPLE 50

Preparation of (R)-1-[2-(4-acetylamino-phenyl)-2-oxo-ethyl]-3-((R)-2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide (C224)



Diastereoisomer 1 of C2 Diastereoisomer 1 of C224

Scheme 50

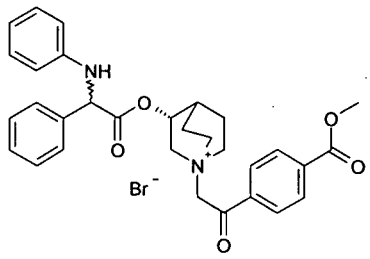
A mixture (R)-((R)-quinuclidin-3-yl) 2-phenyl-2-(phenylamino)acetate (Diastereoisomer 1 of C2) (80.0 mg, 0.24 mmol) and N-(4-(2-bromoacetyl)phenyl)acetamide (60.9 mg, 0.24 mmol) in acetonitrile (2 mL) is heated in a microwave oven at 100°C for 1 hour (UPLC-MS monitoring: complete conversion). The title compound is isolated by suction filtration and washed with Et_2O (98.2 mg, 81% yield, off-white solid, bromide salt, single diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d6) ppm: 10.44 (s, 1 H), 7.85 - 7.97 (m, 2 H), 7.69 - 7.84 (m, 2 H), 7.52 - 7.63 (m, 2 H), 7.25 - 7.49 (m, 3 H), 6.97 - 7.19 (m, 2 H), 6.70 - 6.79 (m, 2 H), 6.52 - 6.64 (m, 1 H), 6.37 (d, 1 H), 5.38 (d, 1 H), 5.14 - 5.27 (m, 1 H), 5.04 (s, 2 H), 3.88 - 4.20 (m, 1 H), 3.33 - 3.78 (m, 5 H), 2.31 - 2.43 (m, 1 H), 2.11 (s, 3 H), 1.84 - 2.05 (m, 4 H);

LC-MS (ESI POS): 512.2 (MH^+).

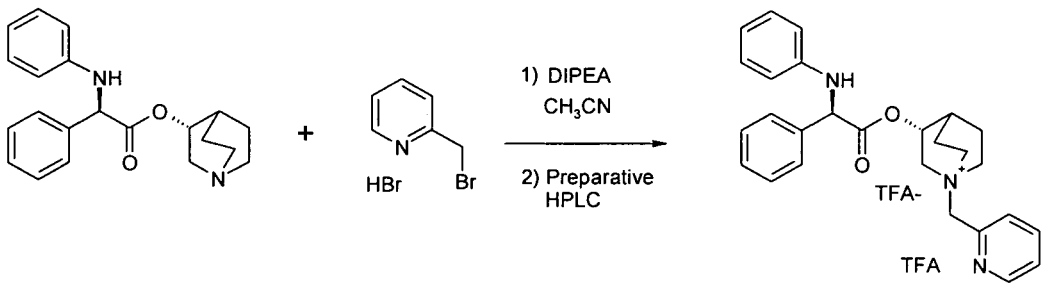
C225 listed in Table 24 is obtained as previously described for C224, using 4-(2-bromo-acetyl)-benzoic acid methyl ester instead of N-[4-(2-bromo-acetyl)-phenyl]-acetamide.

Table 24

Compound	Structure	Yield and Appearance	Analytical
C225	 Mixture of diastereoisomers	82% yield pale yellow powder	LC-MS (ESI POS): 513.2 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 8.13 - 8.25 (m, 2 H), 8.03 - 8.13 (m, 2 H), 7.54 - 7.66 (m, 2 H), 7.27 - 7.47 (m, 3 H), 6.98 - 7.17 (m, 2 H), 6.74 (m, 2 H), 6.56 - 6.64 (m, 1 H), 6.41 (d, 1 H), 5.39 (d, 1 H), 5.19 - 5.23 (m, 1 H), 5.16 (s, 2 H), 3.99 - 4.24 (m, 1 H), 3.91 (s, 3 H), 3.44 - 3.84 (m, 5 H), 2.34 - 2.41 (m, 1 H), 1.38 - 2.10 (m, 4 H)

EXAMPLE 51

Preparation of (R)-3-((R)-2-phenyl-2-phenylamino-acetoxy)-1-pyridin-2-ylmethyl-1-azonia-bicyclo[2.2.2]octane trifluoroacetate trifluoroacetate anion (Diastereoisomer 1 of C226)



Diastereoisomer 1 of C2

Diastereoisomer 1 of C226

Scheme 51

A solution of (R)-phenyl-phenylamino-acetic acid (R)-(1-aza-

bicyclo[2.2.2]oct-3-yl) ester (Diastereoisomer 1 of C2) (100 mg, 0.30 mmol) and DIPEA (61 uL, 0.36 mmol) in acetonitrile (4 mL), is added with 2-bromomethyl-pyridine hydrobromide (91.0 mg, 0.36 mmol) and the mixture is heated under MW irradiation for 1hr at 100°C (UPLC-MS monitoring: complete conversion). Solvent is evaporated and the resulting crude is first purified by flash chromatography (DCM/MeOH=98/2 to 9/1) and then by preparative LC-MS to obtain the title compound as a brown viscous oil (58 mg, 36% yield, trifluoroacetate trifluoroacetate anion, single diastereoisomer).

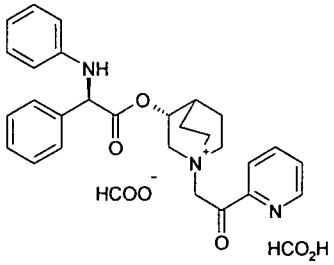
^{1}H NMR (300 MHz, DMSO-d6) ppm: 8.68 (ddd, 1 H), 7.96 (td, 1 H), 7.41 - 7.71 (m, 4 H), 7.23 - 7.41 (m, 3 H), 6.93 - 7.16 (m, 2 H), 6.70 (m, 2 H), 6.58 (m, 1 H), 5.32 (s, 1 H), 5.02 - 5.18 (m, 1 H), 4.46 (d, 1 H), 4.41 (d, 1 H), 3.90 (ddd, 1 H), 3.39 - 3.60 (m, 3 H), 3.17 (d, 1 H), 2.74 - 2.92 (m, 1 H), 2.20 - 2.35 (m, 1 H), 1.74 - 2.04 (m, 4 H);

LC-MS (ESI POS): 428.2 (MH^+);

$[\alpha]_D$=-40.80° (c=0.25, MeOH).

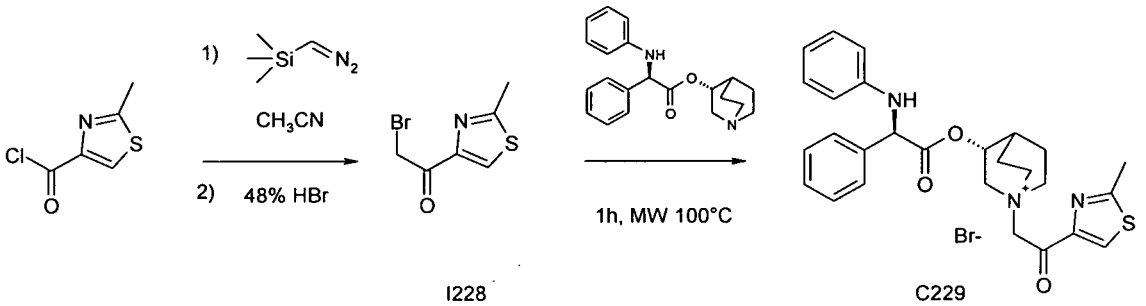
Diastereoisomer 1 of C227 listed in Table 25 is obtained as previously described for diastereoisomer 1 of C226, using 2-bromo-1-pyridin-2-yl-ethanone hydrobromide instead of 2-bromomethyl-pyridine hydrobromide.

Table 25

Compound	Structure	Yield and Appearance	Analytical
Diastereoisomer 1 of C227	 Single stereoisomer	50% yield yellow solid	LC-MS (ESI POS): 456.0 (MH^+) ^1H NMR (300 MHz, DMSO-d_6) ppm: 8.76 (ddd, 1 H), 8.37 (s, 1 H, formiate ion), 8.11 (ddd, 1 H), 8.05 (dt, 1 H), 7.78 (ddd, 1 H), 7.54 - 7.67 (m, 2 H), 7.30 - 7.50 (m, 3 H), 7.00 - 7.18 (m, 2 H), 6.69 - 6.81 (m, 2 H), 6.60 (m, 1 H), 6.37 (d, 1 H), 5.38 (d, 1 H), 5.10 - 5.29 (m, 3 H), 4.00 - 4.20 (m, 1 H), 3.26 - 3.84 (m, 5 H), 2.31 - 2.41 (m, 1 H), 1.80 - 2.18 (m, 4 H) $[\alpha]_D$=-51.68° (c=0.25, MeOH)

EXAMPLE 52

Preparation of (R)-1-(2-(2-methylthiazol-4-yl)-2-oxoethyl)-3-((R)-2-phenyl-2-(phenylamino)acetoxy)-1-azoniabicyclo[2.2.2]octane bromide (C229)



I228 C229

Scheme 52

Preparation of 2-bromo-1-(2-methyl-thiazol-5-yl)-ethanone (I228):

A solution of 2-methylthiazole-4-carbonyl chloride (0.34 g, 2.10 mmol) in dry MeCN (8 mL) cooled at 0°C, under nitrogen atmosphere, is slowly added with (diazomethyl)trimethylsilane (3.14 ml, 6.29 mmol, 2.0M in hexane). The reaction is stirred at RT for 15h (UPLC-MS monitoring: complete conversion). The reaction is cooled at 0°C and 48% hydrobromic acid (1.23 mL, 7.34 mmol) is added dropwise. The reaction is stirred at RT for 3h. Then EtOAc and water are added, the organic layer is separated and the aqueous phase is neutralized with 1M NaOH and extracted with EtOAc. The combined organic layers are dried over Na_2SO_4, filtered and evaporated to dryness to obtain compound I228 as a dark brown gummy solid (400 mg, 87% yield).

Preparation of (R)-1-(2-(2-methylthiazol-4-yl)-2-oxoethyl)-3-((R)-2-phenyl-2-(phenylamino)acetoxy)-1-azoniabicyclo[2.2.2]octane bromide (C229):

(R)-Phenyl-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl)

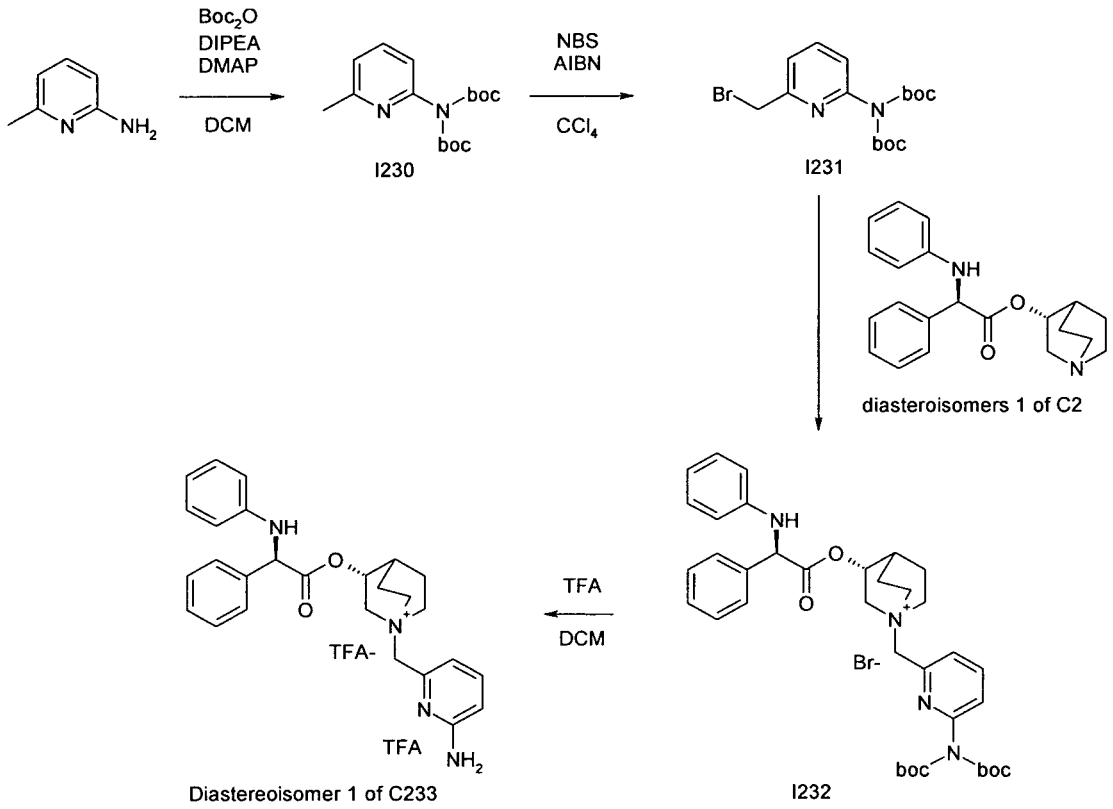
ester (Diastereoisomer 1 of C2) (75.0 mg, 0.22 mmol) and 2-bromo-1-(2-methylthiazol-4-yl)ethanone (I228) (49.1 mg, 0.22 mmol) in acetonitrile (5 mL) is heated at 100°C for 75 minutes under microwave irradiation (UPLC-MS monitoring: complete conversion). The solvent is removed and the resulting brown solid is triturated with iPr_2O/Et_2O (1/1) and then with iPrOH to obtain the title compound as a grey powder (43.3 mg, 35% yield, bromide salt, single diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 8.59 (s, 1 H) 7.53 - 7.66 (m, 2 H) 7.29 - 7.51 (m, 3 H) 7.01 - 7.15 (m, 2 H) 6.69 - 6.82 (m, 2 H) 6.56 - 6.66 (m, 1 H) 6.36 (d, 1 H) 5.37 (d, 1 H) 5.10 - 5.25 (m, 1 H) 5.02 (s, 2 H) 4.00 - 4.17 (m, 1 H) 3.45 - 3.75 (m, 4 H) 3.35 - 3.45 (m, 1 H) 2.75 (s, 3 H) 2.31 - 2.40 (m, 1 H) 1.80 - 2.10 (m, 4 H);

LC-MS (ESI POS): 476.2 (MH^+).

EXAMPLE 53

Preparation of (R)-1-(6-amino-pyridin-2-ylmethyl)-3-((R)-2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate trifluoroacetate anion (Diastereoisomers 1 of C233)



Scheme 53

Preparation of N,N-(bis-tert-butoxycarbonyl)-6-methylpyridin-2-amine (I230):

A mixture of 6-methylpyridin-2-amine (5.00 g, 46.3 mmol), di-tert-butyl dicarbonate (24.2 g, 111 mmol) and DIPEA (9.4 mL, 55.5 mmol) in DCM (40 mL) is stirred at RT for 3 days. The organic phase is washed with 5% citric acid and then with sat. $NaHCO_3$. The organic phase is dried over Na_2SO_4, filtered and evaporated to dryness. The crude is purified by flash chromatography (Petroleum ether/EtOAc=9/1) to obtain intermediate I230 as a white solid (3.0 g, 21% yield).

Preparation of N,N-(bis tert-butoxycarbonyl)- 6-

(bromomethyl)pyridin-2-amine (I231):

A catalytic amount of azobisisobutyronitrile (5% w/w) is added to a solution of N,N-(bis-tert-butoxycarbonyl)- 6-methylpyridin-2-amine (I230) (308 mg, 1.00 mmol) and N-bromo-succinimide (284 mg; 1.6 mmol) in carbon tetrachloride (8 mL). The reaction is refluxed for two hours, diluted with DCM and washed with water. The organic phase is dried over Na_2SO_4, filtered and evaporated to dryness. The crude is purified by flash chromatography (DCM) to obtain intermediate I231 as a yellow solid (240 mg, 83% yield).

Preparation of (R)-1-(N,N-(bis tert-butoxycarbonyl)-6-amino-pyridin-2-ylmethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide (I232):

A solution of (R)-phenyl-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (Diastereoisomer 1 of C2) (100 mg, 0.54 mmol) in acetonitrile (5 mL), is added with N,N-(bis tert-butoxycarbonyl)-6-(bromomethyl)pyridin-2-amine (240 mg, 1.15 mmol) and the mixture is heated under MW irradiation for 30 minutes at 100°C (UPLC-MS monitoring: complete conversion). The solvent is evaporated and the resulting crude is purified by flash chromatography (DCM to DCM/MeOH=9/1) to obtain intermediate I232 as a colorless oil (125 mg, 32% yield).

Preparation of (R)-1-(6-amino-pyridin-2-ylmethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate trifluoroacetate anion (diastereoisomers 1 of C233):

Trifluoroacetic acid (0.5 mL) is added to a solution of (R)-1-(N,N-(bis tert-butoxycarbonyl)-6-amino-pyridin-2-ylmethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide (I232) (125 mg, 0.19 mmol) in DCM (5 mL). The reaction is stirred at RT for 2 days. Solvent is removed under vacuum and the crude is purified by preparative LC-MS to obtain the title compound as a brown oil (21 mg, 16% yield, trifluoroacetate

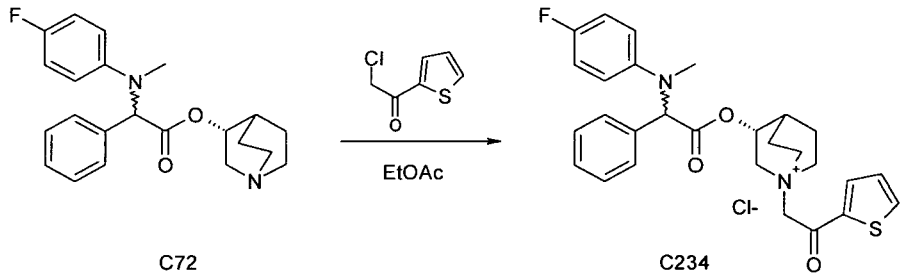
trifluoroacetate anion, single diastereoisomer).

^{1}H NMR (300 MHz, DMSO-d6) ppm: 7.42 - 7.59 (m, 3 H), 7.22 - 7.42 (m, 3 H), 6.97 - 7.17 (m, 2 H), 6.66 - 6.82 (m, 2 H), 6.44 - 6.66 (m, 3 H), 5.33 (s, 1 H), 5.03 - 5.21 (m, 1 H), 4.13 (s, 2 H), 3.75 - 3.95 (m, 1 H), 3.29 - 3.61 (m, 3 H), 3.14 (d, 1 H), 2.75 - 2.96 (m, 1 H), 2.18 - 2.35 (m, 1 H), 1.54 - 2.14 (m, 4 H);

LC-MS (ESI POS): 443.1 (MH+).

EXAMPLE 54

Preparation of (R)-3-{2-[(4-fluoro-phenyl)-methyl-amino]-2-phenyl-acetoxy}-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane chloride (C234)



C72 C234

Scheme 54

A solution of [(4-fluoro-phenyl)-methyl-amino]-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C120) (100 mg, 0.27 mmol) in ethyl acetate (2.7 mL), is added with 2-chloro-1-(thiophen-2-yl)ethanone (48.0 mg, 0.30 mmol). The reaction is stirred at RT for 3.5 days. The suspension is evaporated and the residue is triturated with Et_2O (8 mL). The solid is filtered on a buckner funnel and the sticky solid is dissolved in DCM. The solution is evaporated giving the title compound as a pale yellow solid (120 mg, 84 % yield, chloride salt, mixture of diastereoisomers).

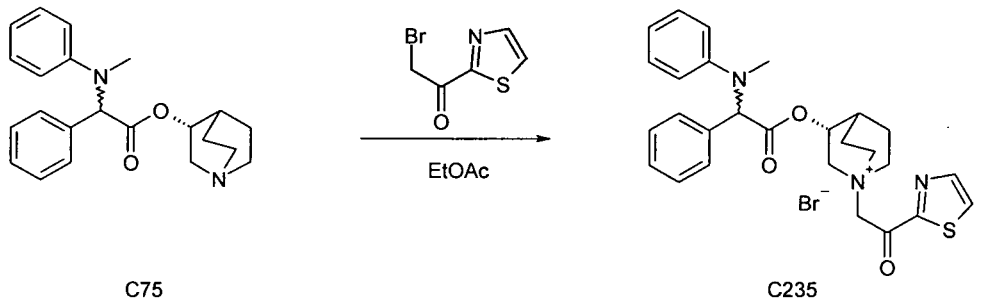
^{1}H NMR (300 MHz, DMSO-d_6) ppm: 8.21 (dd, 1 H), 8.11 (d, 1 H), 7.26 - 7.52 (m, 6 H), 7.02 - 7.15 (m, 2 H), 6.88 - 7.02 (m, 2 H), 5.91 and 5.92 (s, 1 H), 5.23 - 5.44 (m, 1 H), 5.19 (d, 1 H), 5.11 (d, 1 H), 4.07 - 4.34 (m, 1 H), 3.36 - 3.92

(m, 5 H), 2.73 (s, 3 H), 2.20 - 2.33 (m, 1 H), 1.47 - 2.12 (m, 4 H);

LC-MS (ESI POS): 493.1 (MH^+).

EXAMPLE 55

Preparation of (R)-3-[2-(methyl-phenyl-amino)-2-phenyl-acetoxy]-1-(2-oxo-2-thiazol-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide (C235)



C75 C235

Scheme 55

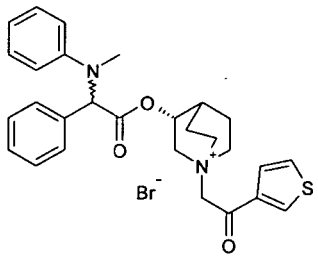
2-Bromo-1-(1,3-thiazol-2-yl)ethanone (54.2 mg, 0.26 mmol) is added to a solution of (R)-quinuclidin-3-yl 2-(methyl(phenyl)amino)-2-phenylacetate (C75) (92.2 mg, 0.26 mmol) in EtOAc (5 mL). The mixture is stirred at RT overnight. The solvent is evaporated to dryness and the crude is triturated with Et_2O. The yellow solid is collected by filtration (120 mg, 82% yield, bromide salt, mixture of diastereoisomers).

^1H NMR (300 MHz, DMSO-d_6) ppm: 8.39 (d, 1 H), 8.25 (d, 1 H), 7.32 - 7.50 (m, 5 H), 7.19 - 7.30 (m, 2 H), 6.84 - 7.00 (m, 2 H), 6.67 - 6.85 (m, 1 H), 5.97 (s, 1 H), 5.23 - 5.38 (m, 1 H), 5.19 and 5.20 (s, 2 H), 4.04 - 4.29 (m, 1 H), 3.44 - 3.82 (m, 5 H), 2.76 and 2.77 (s, 3 H), 2.24 - 2.36 (m, 1 H), 1.45 - 2.13 (m, 4 H);

LC-MS (ESI POS): 476.0 (MH+).

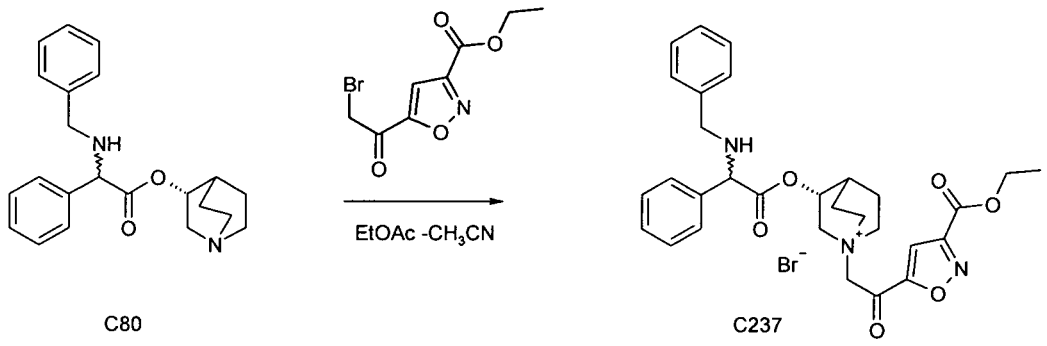
C236 listed in Table 26 is obtained as previously described for C235, using 2-bromo-1-thiophen-3-yl-ethanone instead of 2-bromo-1-(1,3-thiazol-2-yl)ethanone.

Table 26

Compound	Structure	Yield and Appearance	Analytical
C236	 Mixture of diastereoisomers	41% overall yield Off-yellow solid	LC-MS (ESI POS): 475.3 (MH+) ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 8.63 (dd, 1 H), 7.75 (dd, 1 H), 7.57 (dd, 1 H), 7.33 - 7.50 (m, 5 H), 7.17 - 7.31 (m, 2 H), 6.88 - 7.02 (m, 2 H), 6.68 - 6.80 (m, 1 H), 5.96 and 5.97 (s, 1 H), 5.14 - 5.41 (m, 1 H), 5.02 and 5.03 (s, 2 H), 4.10 - 4.24 (m, 1 H), 3.37 - 3.79 (m, 5 H), 2.76 and 2.77 (s, 3 H), 2.20 - 2.38 (m, 1 H), 1.44 - 2.15 (m, 4 H)

EXAMPLE 56

Preparation of (R)-3-(2-benzylamino-2-phenyl-acetoxy)-1-[2-(3-ethoxycarbonyl-isoxazol-5-yl)-2-oxo-ethyl]-1-azonia-bicyclo[2.2.2]octane bromide (C237)



C80 C237

Scheme 56

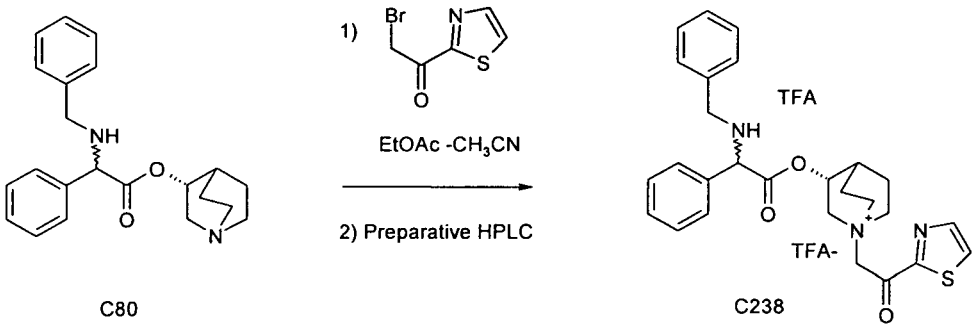
Benzylamino-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl)ester (C80) (100 mg, 0.28 mmol) is dissolved in ethyl acetate (1.90 mL) and acetonitrile (0.95 mL) and ethyl 5-(2-bromoacetyl)isoxazole-3-carboxylate (82.0 mg, 0.31 mmol) is added. The orange solution is stirred at RT overnight. The suspension is evaporated and the crude is purified by flash chromatography (DCM/EtOH= 93/7) to obtain the title compound as a pale brown solid (61 mg, 35 % yield, bromide salt, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d6) ppm: 7.86 and 7.89 (s, 1 H), 6.97 - 7.60 (m, 10 H), 5.10 - 5.24 (m, 1 H), 5.00 and 5.04 (s, 2 H), 4.33 - 4.53 (m, 3 H), 4.10 (dd, 1 H), 3.40 - 3.82 (m, 7 H), 2.15 - 2.24 and 2.29 - 2.38 (m, 1 H), 1.50 - 2.11 (m, 4 H), 1.35 (t, 3 H);

LC-MS (ESI POS): 532.3 (MH+).

EXAMPLE 57

Preparation of (R)-3-(2-benzylamino-2-phenyl-acetoxy)-1-(2-oxo-2-thiazol-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate trifluoroacetate anion (C238)



Scheme 57

Benzylamino-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl)ester (C80) (100 mg, 0.28 mmol) is dissolved in ethyl acetate (1.90 mL) and acetonitrile (0.95 mL) and 2-bromo-1-(thiazol-2-yl)ethanone (64.7 mg, 0.314 mmol) is added. The pale yellow solution is stirred at RT overnight. The suspension is evaporated and the crude is purified by flash chromatography (DCM/MeOH = 93/7). The resulting compound is further purified by preparative LC/MS. The collected fractions are first concentrated with rotary evaporator to remove organic solvent and then with freeze-drier overnight to get the title compound as a pale yellow oil (31 mg, 15 % yield, trifluoroacetate trifluoroacetate anion, mixture of diastereoisomers).

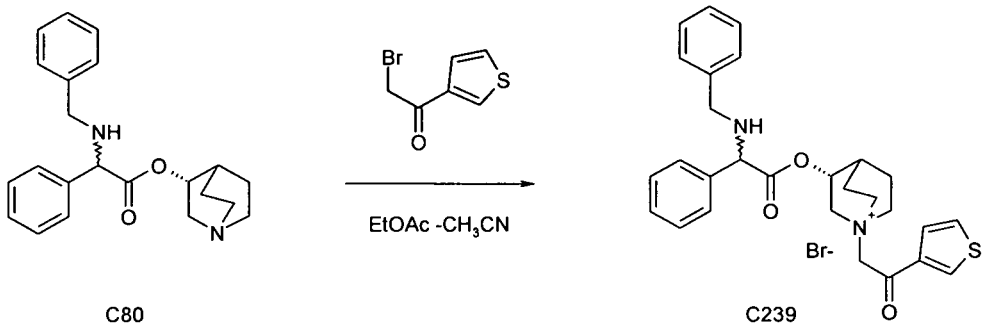
^{1}H NMR (300 MHz, DMSO-d6) ppm 8.40 (d, 1 H), 8.24 (d, 1 H), 7.36 - 7.71 (m, 10 H), 5.25 - 5.40 (m, 2 H), 5.17 and 5.21 (s, 2 H), 3.99 - 4.24 (m, 3 H), 3.46 - 3.84 (m, 5 H), 2.15 - 2.25 and 2.32 - 2.44 (m, 1 H), 1.35 - 2.14 (m, 4 H);

LC-MS (ESI POS): 475.9 (MH+).

EXAMPLE 58

Preparation of (R)-3-(2-benzylamino-2-phenyl-acetoxy)-1-(2-oxo-2-

thiophen-3-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide (C239)



C80 C239

Scheme 58

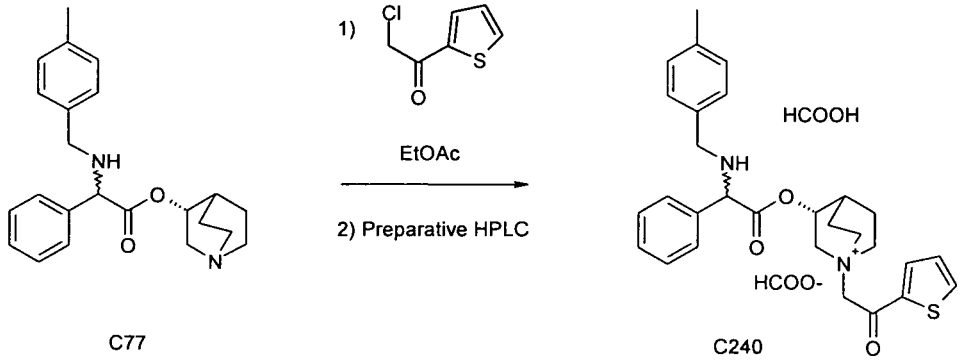
A solution of (R)-quinuclidin-3-yl 2-(benzylamino)-2-phenylacetate (C80) (116 mg, 0.33 mmol) in ethyl acetate (3.31 mL) and acetonitrile (3.31 mL), is added with 2-bromo-1-(thiophen-3-yl)ethanone (66.5 mg, 0.32 mmol). The mixture is stirred at RT overnight. The insoluble precipitate is filtered on a buckner funnel and washed with acetonitrile. The clear solution is evaporated and purified by flash chromatography (DCM/EtOH = 9/1) to obtain the title compound as a white solid (26 mg, 14% yield, bromide salt, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 8.63 (br. s., 1 H), 7.68 - 7.84 (m, 1 H), 7.10 - 7.63 (m, 11 H), 5.11 - 5.25 (m, 1 H), 5.03 and 5.06 (s, 2 H), 4.43 (br. s., 1 H), 3.99 - 4.24 (m, 1 H), 3.42 - 3.87 (m, 7 H), 2.18 and 2.23 (br. s., 1 H), 1.44 - 2.14 (m, 4 H);

LC-MS (ESI POS): 475.3 (MH+).

EXAMPLE 59

Preparation of (R)-3-[2-(4-methyl-benzylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane formate formate anion (C240)



Scheme 59

(R)-Quinuclidin-3-yl 2-(4-methylbenzylamino)-2-phenylacetate (C77) (73 mg, 0.20 mmol) is dissolved in ethyl acetate (2.00 mL) and 2-chloro-1-(thiophen-2-yl)ethanone (35.4 mg, 0.22 mmol) is added. The colorless solution is stirred at RT overnight. Solvent is evaporated and the residue is first purified by flash chromatography (DCM/MeOH = 9/1 to 85/15) and then by preparative LC/MS. Organic solvent is evaporated and then the aqueous solution is freeze-dried overnight to afford the title compound as a pale yellow oil (42 mg, 36% yield, formate formate anion, mixture of diastereoisomers).

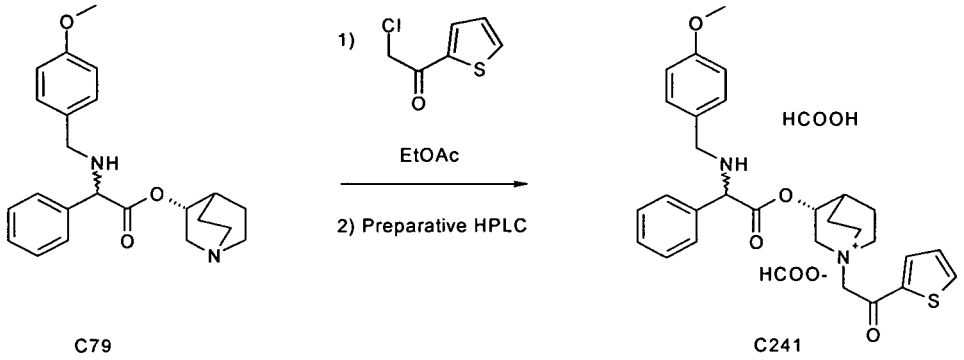
^{1}H NMR (300 MHz, DMSO-d6) ppm: 8.43 (s, 2 H) 8.16 - 8.24 (m, 1 H) 8.03 - 8.12 (m, 1 H) 7.28 - 7.51 (m, 6 H) 7.04 - 7.25 (m, 4 H) 4.94 - 5.26 (m, 3 H) 4.40 (s, 1 H) 4.00 - 4.18 (m, 1 H) 3.48 - 3.76 (m, 7 H) 2.29 (s, 3 H) 2.11 - 2.22 (m, 1 H) 1.39 - 2.12 (m, 5 H);

LC-MS (ESI POS): 489.1 (MH+).

EXAMPLE 60

Preparation of (R)-3-[2-(4-methoxy-benzylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane

formate formate anion (C241)



Scheme 60

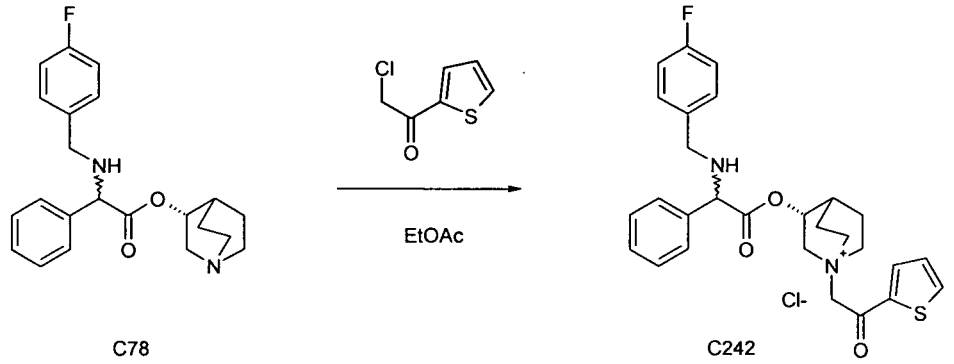
A solution of (R)-quinuclidin-3-yl 2-(4-methoxybenzylamino)-2-phenylacetate (C79) (78 mg, 0.21 mmol) in ethyl acetate (2.05 mL), is added with 2-chloro-1-(thiophen-2-yl)ethanone (36.2 mg, 0.23 mmol). The colorless solution is stirred at RT overnight. The residue is first purified by flash chromatography (DCM/MeOH = 90/10 to 85/15) and then by preparative LC/MS. MeOH is evaporated from the fractions collected and then the aqueous solution is freeze-dried overnight to obtain the title compound as a pale pink oil (44 mg, 36 % yield, formate formate anion, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 8.42 (s, 2 H) 8.17 - 8.25 (m, 1 H) 8.03 - 8.13 (m, 1 H) 7.15 - 7.50 (m, 8 H) 6.81 - 6.94 (m, 2 H) 4.97 - 5.23 (m, 3 H) 4.40 (s, 1 H) 3.88 - 4.22 (m, 1 H) 3.74 (s, 3 H) 3.46 - 3.71 (m, 6 H) 2.12 - 2.35 (m, 1 H) 1.70 - 2.10 (m, 3 H) 1.44 - 1.66 (m, 1 H);

LC-MS (ESI POS): 505.1 (MH+).

EXAMPLE 61

Preparation of (R)-3-[2-(4-fluoro-benzylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane chloride (C242)



Scheme 61

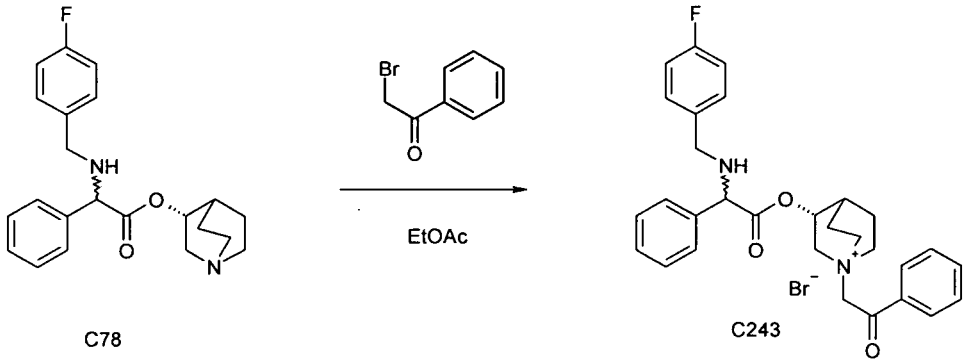
(R)-Quinuclidin-3-yl 2-(4-fluorobenzylamino)-2-phenylacetate (C78) (85 mg, 0.23 mmol) is dissolved in ethyl acetate (2.31 mL) and 2-chloro-1-(thiophen-2-yl)ethanone (40.8 mg, 0.25 mmol) is added. The solution is stirred at RT overnight. The suspension is evaporated and the white residue is first purified by flash chromatography (DCM/MeOH = 9/1 to 8/2) and then by trituration with Et_2O to afford the title compound as an off-white powder (83 mg, 68% yield, chloride salt, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 8.18 - 8.25 (m, 1 H), 8.04 - 8.18 (m, 1 H), 7.43 - 7.52 (m, 2 H), 7.26 - 7.43 (m, 6 H), 7.09 - 7.21 (m, 2 H), 5.16 - 5.24 (m, 1 H), 5.12 and 5.15 (s, 2 H), 4.42 (s, 1 H), 4.01 - 4.22 (m, 1 H), 3.67 (s, 2 H), 3.54 - 3.85 (m, 5 H), 2.13 - 2.23 and 2.29 - 2.33 (m, 1 H), 1.48 - 2.10 (m, 4 H);

LC-MS (ESI POS): 492.9 (MH+).

EXAMPLE 62

Preparation of (R)-3-[2-(4-fluoro-benzylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide (C243)



Scheme 62

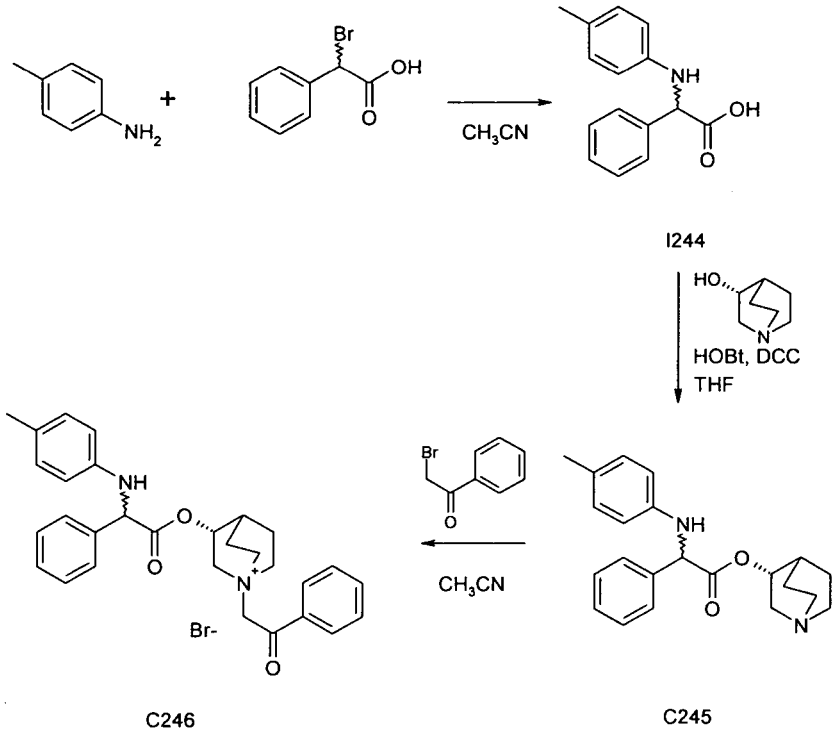
A mixture of (R)-quinuclidin-3-yl 2-(4-fluorobenzylamino)-2-phenylacetate (C78) (61 mg, 0.17 mmol) and 2-bromo-1-phenylethanone (33.0 mg, 0.17 mmol) in ethyl acetate (3 mL) is stirred at RT overnight. The solid is collected by suction filtration and washed with Et_2O. The product is further purified by flash chromatography (DCM/MeOH=95/5 to 92/8) to obtain the title compound as a white solid (35 mg, 37% yield, bromide salt, mixture of diastereoisomers).

^{1}H NMR (300 MHz, METHANOL-d_4) ppm: 7.91 - 8.07 (m, 2 H) 7.67 - 7.80 (m, 1 H) 7.53 - 7.64 (m, 2 H) 7.26 - 7.53 (m, 7 H) 6.97 - 7.13 (m, 2 H) 5.17 - 5.33 (m, 1 H) 4.50 (s, 1 H) 4.04 - 4.28 (m, 1 H) 3.49 - 3.89 (m, 8 H) 3.36 (s, 2 H) 2.40 - 2.52 (m, 1 H) 1.94 - 2.25 (m, 4 H);

LC-MS (ESI POS): 487.1 (MH+).

EXAMPLE 63

Preparation of (R)-1-(2-oxo-2-phenyl-ethyl)-3-(2-phenyl-2-p-methylphenyl-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide (C246)



Scheme 63

Preparation of 4-methyl-phenyl-amino-phenyl-acetic acid (I244):

A solution of α-bromophenylacetic acid (1.00 g, 4.65 mmol) in acetonitrile (20 mL), is added with 4-methyl-phenylamine (0.96 g, 9.30 mmol) and the mixture reacted in a closed vessel under MW irradiation at 100°C for 1 h (UPLC-MS monitoring: complete conversion). Solvent is evaporated and residue is partitioned between EtOAc and 2N HCl. The organic phase is dried over Na_2SO_4, filtered and evaporated to dryness to get desired compound as a yellow solid (0.88 g, 78% yield).

Preparation of 4-methyl-phenyl-amino-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C245):

A solution of 4-methyl-phenyl-amino-phenyl-acetic acid (I244) (870 mg, 3.60 mmol) in dry THF (35 mL), is added with DCC (891 mg, 4.32 mmol),

HOBt (583 mg, 4.32 mmol) and 3(R)–quinuclidinol (915 mg, 7.20 mmol). The resulting mixture is stirred at RT for 48 hours (UPLC-MS monitoring: complete conversion). The solvent is evaporated and the residue is partitioned between EtOAc and 1M K_2CO_3. The organic phase is dried over Na_2SO_4, filtered and evaporated to dryness. The resulting crude is dissolved in little DCM and filtered to remove the insoluble. The solution is concentrated under vacuum to obtain the title compound as a yellow solid, which is used in the next step without any further purification.

Preparation of (R)-1-(2-oxo-2-phenyl-ethyl)-3-(2-phenyl-4-methyl-phenyl-amino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide (C246)

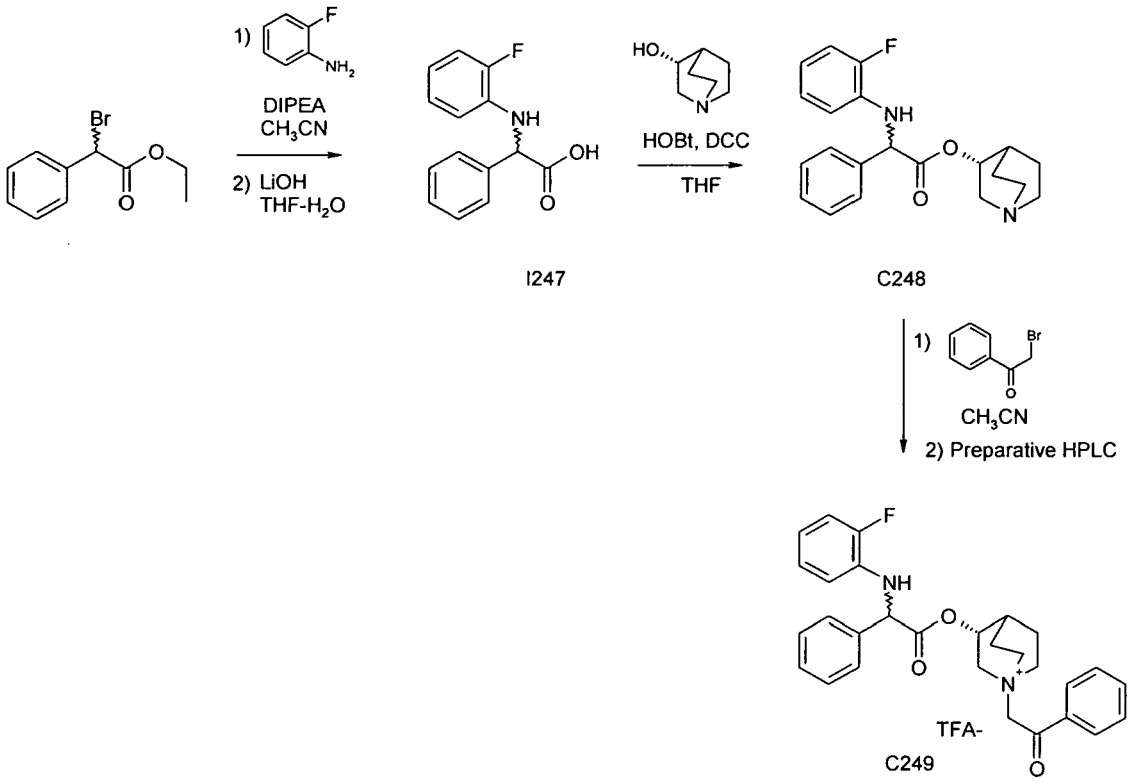
A solution of 4-methyl-phenyl-amino-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C245) (63.5 mg, 0.18 mmol) in acetonitrile (5 mL), is added with 2-bromo-1-phenyl-ethanone (36 mg, 0.18 mmol) and the mixture was heated at 100°C for 1 h in a MW oven (UPLC-MS monitoring: complete conversion). Solvent is evaporated and the resulting crude is purified by flash chromatography (DCM/MeOH = 95/5) to obtain the title compound as a white solid (58 mg, 32% yield, bromide salt, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.88 - 8.07 (m, 2 H), 7.71 - 7.83 (m, 1 H), 7.51 - 7.68 (m, 4 H), 7.24 - 7.48 (m, 3 H), 6.91 (m, 2 H), 6.66 (m, 2 H), 6.16 (d, 1 H), 5.34 (d, 1 H), 5.15 - 5.27 (m, 1 H), 5.09 (s, 2 H), 3.92 - 4.19 (m, 1 H), 3.33 - 3.77 (m, 5 H), 2.31 - 2.41 (m, 1 H), 2.12 (s, 3 H), 1.77 - 2.08 (m, 4 H);

LC-MS (ESI POS): 469.1 (MH^+).

EXAMPLE 64

Preparation of (R)-3-[2-(2-fluoro-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate (C249)



Scheme 64

Preparation of (2-fluoro-phenylamino)-phenyl-acetic acid hydrochloride (I247):

2-Fluoroaniline (347 ul, 3.60 mmol), ethyl 2-bromo-2-phenylacetate (420 ul, 2.40 mmol) and N-ethyl-N-isopropylpropan-2-amine (628 ul, 3.60 mmol) are dissolved in acetonitrile (5 mL) and stirred under MW irradiation at 100°C for 1 h and 30 minutes. Water (3.89 mL) and lithium hydroxide (230 mg, 9.59 mmol) are added to the reaction and the resulting mixture is stirred at RT overnight and then at 50°C for 3 h. Acetonitrile is removed and 1M HCl is added to the remaining aqueous solution until pH is about 1. The aqueous phase is extracted several time with DCM and the combined organic phases are washed with water

and brine, dried (Na_2SO_4), filtered and evaporated to give intermediate I247 as a brown solid (464 mg, 69% yield).

Preparation of (2-fluoro-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C248):

A solution of DCC (534 mg, 0.71 mmol), 1H-benzo[d][1,2,3]triazol-1-ol hydrate (217 mg, 1.42 mmol), (2-fluoro-phenylamino)-phenyl-acetic acid hydrochloride (I247) (200 mg, 0.71 mmol) and (R)-quinuclidin-3-ol (271 mg, 2.13 mmol) in THF (10 mL) is stirred at RT for 2 days. The solvent is evaporated and the residue is taken up with EtOAc, washed with sat $NaHCO_3$, water and brine. The organic layer is collected, dried over Na_2SO_4, filtered and evaporated to dryness. The residue is purified by preparative HPLC. The organic solvent is evaporated and the acid aqueous phase is basified with Na_2CO_3 and extracted with EtOAc. The organic layer is dried (Na_2SO_4), filtered and evaporated to afford the title compound as yellow oil (41 mg, 16% yield).

Preparation of (R)-3-[2-(2-fluoro-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate (C249):

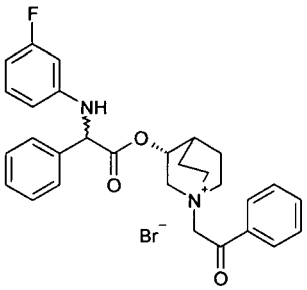
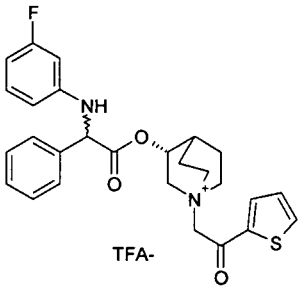
(2-Fluoro-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C248) (267 mg, 0.75 mmol) and 2-bromo-1-phenylethanone (157 mg, 0.79 mmol) are dissolved in CH_3CN (20 mL). The resulting reaction is stirred at RT for two days. The solvent is evaporated and the crude is purified with preparative HPLC to obtain the title compound as a yellow amorphous solid (178 mg, 40.3 % yield, trifluoroacetate salt, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.87 - 8.14 (m, 2 H), 7.67 - 7.81 (m, 1 H), 7.50 - 7.68 (m, 4 H), 7.26 - 7.50 (m, 3 H), 7.01 - 7.16 (m, 1 H), 6.85 - 7.00 (m, 1 H), 6.56 - 6.77 (m, 2 H), 5.75 (br. s., 1 H), 5.46 and 5.49 (s, 1 H), 5.24 (br. s., 1 H), 5.12 and 5.17 (s, 2 H), 4.00 - 4.20 (m, 1 H), 3.29 - 3.83 (m, 5 H), 2.12 - 2.23 and 2.31 - 2.42 (m, 1 H), 1.37 - 2.11 (m, 4 H);

LC-MS (ESI POS): 473.2 (MH+).

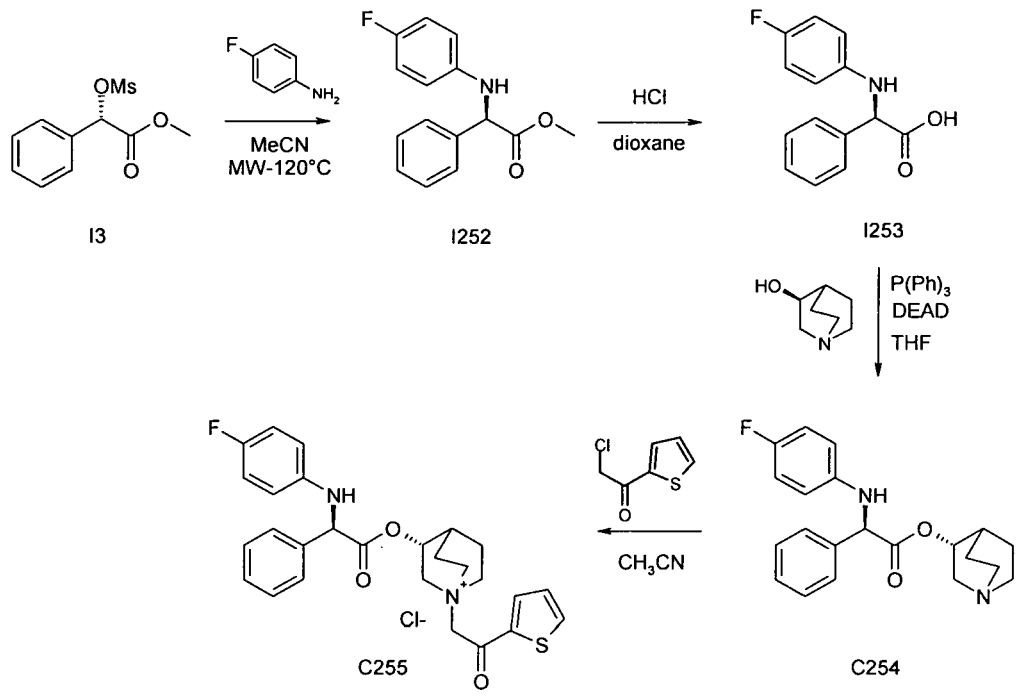
C250 and C251 listed in Table 27 are prepared as previously described for C249, using 3-fluoroaniline instead of 2-fluoroaniline and the suitable commercially available alkylating agents.

Table 27

Compound	Structure	Yield and appearance	Analytical
C250	 Mixture of diastereoisomer	14% overall yield White solid	LC-MS (ESI POS): 473.4 (MH+). ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.89 - 8.05 (m, 2 H), 7.69 - 7.83 (m, 1 H), 7.53 - 7.67 (m, 4 H), 7.30 - 7.49 (m, 3 H), 7.09 (td, 1 H), 6.74 and 6.76 (d, 1 H), 6.48 - 6.64 (m, 2 H), 6.37 (td, 1 H), 5.41 and 5.45 (d, 1 H), 5.23 - 5.30 (m, 1 H), 5.15 and 5.21 (s, 2 H), 3.96 - 4.29 (m, 1 H), 3.37 - 3.95 (m, 5 H), 2.11 - 2.19 and 2.36 - 2.42 (m, 1 H), 1.37 - 2.10 (m, 4 H)
C251	 Mixture of diastereoisomer	7% overall yield White solid	LC-MS (ESI POS): 479.3 (MH+). ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 8.20 and 8.22 (dd, 1 H), 8.04 and 8.08 (dd, 1 H), 7.50 - 7.63 (m, 2 H), 7.29 - 7.48 (m, 4 H), 7.09 (td, 1 H), 6.74 (br. s., 1 H), 6.47 - 6.63 (m, 2 H), 6.36 (td, 1 H), 5.39 and 5.44 (br. s., 1 H), 5.17 - 5.28 (m, 1 H), 4.99 and 5.04 (s, 2 H), 4.03 - 4.19 (m, 1 H), 3.25 - 3.85 (m, 5 H), 2.10 - 2.20 and 2.33 - 2.41 (m, 1 H), 1.45 - 2.09 (m, 4 H)

EXAMPLE 65

Preparation of (R)-3-[(R)-2-(4-fluoro-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane chloride (C255)



Scheme 65

Preparation of (R)-(4-fluoro-phenylamino)-phenyl-acetic acid methyl ester (I252):

A solution of (S)-methyl 2-(methylsulfonyloxy)-2-phenylacetate (I5) (520 mg, 2.13 mmol) in CH_3CN (10 mL), is added with 4-fluoroaniline (473 mg, 4.26 mmol) and the mixture is heated at 120°C for 5 min under MW irradiation. (UPLC-MS: complete conversion). Acetonitrile was evaporated and the resulting crude is dissolved in 1N HCl and extracted several times with EtOAc. The combined organic phase is dried over Na_2SO_4, filtered and evaporated to dryness to obtain intermediate I254 as a pale yellow oil (520 mg, 94% yield).

Preparation of (R)-(4-fluoro-phenylamino)-phenyl-acetic acid (I253):

A solution of (R)-(4-fluoro-phenylamino)-phenyl-acetic acid methyl ester (I252) (510 mg, 1.97 mmol) in dioxane (10 mL), is added with 12N HCl (10 mL) and the mixture is heated at 70°C for 12 h. The organic solvent is evaporated, the mixture is cooled to 0°C and the resulting solid is collected by filtration to obtain intermediate I255 as a brownish solid (420 mg, 87% yield).

Preparation of (R)-(4-fluoro-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C254):

A solution of (R)-(4-fluoro-phenylamino)-phenyl-acetic acid (I253) (420 mg, 1.71 mmol) in dry THF (40 mL), is sequentially added with (S)-quinuclidin-3-ol (218 mg, 1.71 mmol), DEAD (407 ul, 2.57 mmol) and triphenylphosphine (674 mg, 2.57 mmol). The reaction is refluxed for 30 min under N_2 flowstream and then the solvent is evaporated. The residue is partitioned between water and EtOAc, the organic layer is separated, dried over Na_2SO_4, filtered and evaporated to dryness. The resulting crude is purified by flash chromatography (DCM/MeOH=95/5) to obtain the title compound as a pale yellow oil (480 mg, 79% yield).

Preparation of (R)-3-[(R)-2-(4-fluoro-phenylamino)-2-phenyl-acetoxyl-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane chloride (C255):

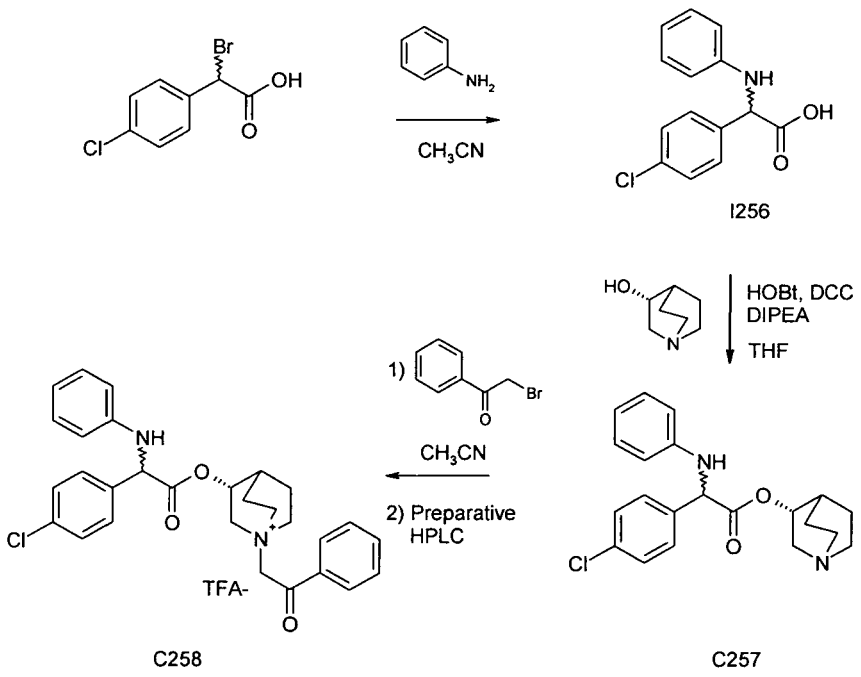
A solution of (R)-(4-fluoro-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C254) (200 mg, 0.56 mmol) in CH_3CN (2 mL), is added with 2-chloro-1-(thiophen-2-yl)ethanone (100 mg, 0.62 mmol). The reaction is heated at 100°C for 1 hr under MW irradiation. The solvent is evaporated and the crude is purified by flash chromatography (DCM/MeOH=9/1) recovering the title compound as a white solid (104 mg, 36% yield, chloride salt, single diastereoisomer).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 8.21 (d, 1 H), 8.08 (d, 1 H), 7.50 - 7.65 (m, 2 H), 7.23 - 7.48 (m, 4 H), 6.84 - 6.99 (m, 2 H), 6.61 - 6.84 (m, 2 H), 6.39 (d, 1 H), 5.36 (d, 1 H), 5.15 - 5.26 (m, 1 H), 5.06 (s, 2 H), 3.99 - 4.21 (m, 1 H), 3.38 - 3.85 (m, 5 H), 2.30 - 2.40 (m, 1 H), 1.70 - 2.17 (m, 4 H);

LC-MS (ESI POS): 478.9 (MH^+).

EXAMPLE 66

Preparation of (R)-3-[2-(4-chloro-phenyl)-2-phenylamino-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate (C258)



Scheme 66

Preparation of (4-chloro-phenyl)-phenylamino-acetic acid (I256):

2-Bromo-2-(4-chlorophenyl)acetic acid (1.2 g, 4.67 mmol) and aniline (0.85 mL, 9.33 mmol) are dissolved in acetonitrile (29 mL). The reaction is heated under microwave irradiation at 100°C for 5 minutes. The solvent is evaporated and the residue is dissolved in EtOAc and washed with 3M HCl and then brine. The organic layer is dried over Na_2SO_4, filtered and evaporated to dryness to give intermediate I258 as a white solid (1.22 g,

quantitative yield).

Preparation of (4-chloro-phenyl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C257):

(4-Chloro-phenyl)-phenylamino-acetic acid (I256) (1.22 g, 4.97 mmol), HOBT (0.99 g, 6.46 mmol) and DCC (1.33 g, 6.46 mmol) are dissolved in THF (250 mL). The reaction is stirred for 15 minutes and then (R)-quinuclidin-3-ol (1.26 g, 9.93 mmol) is added. The reaction is stirred at RT for 4 days. The solvent is evaporated and the residue is taken up with EtOAc. The insoluble is filtered off, the solution is washed with 1M K_2CO_3 and brine. The organic phase is dried (Na_2SO_4), filtered and evaporated to dryness. The crude is purified by flash chromatography (DCM/MeOH= 98/2 to 90/10) to afford compound C259 as a yellow solid (462 mg, 25 % yield).

Preparation of (R)-3-[2-(4-chloro-phenyl)-2-phenylamino-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate (C258):

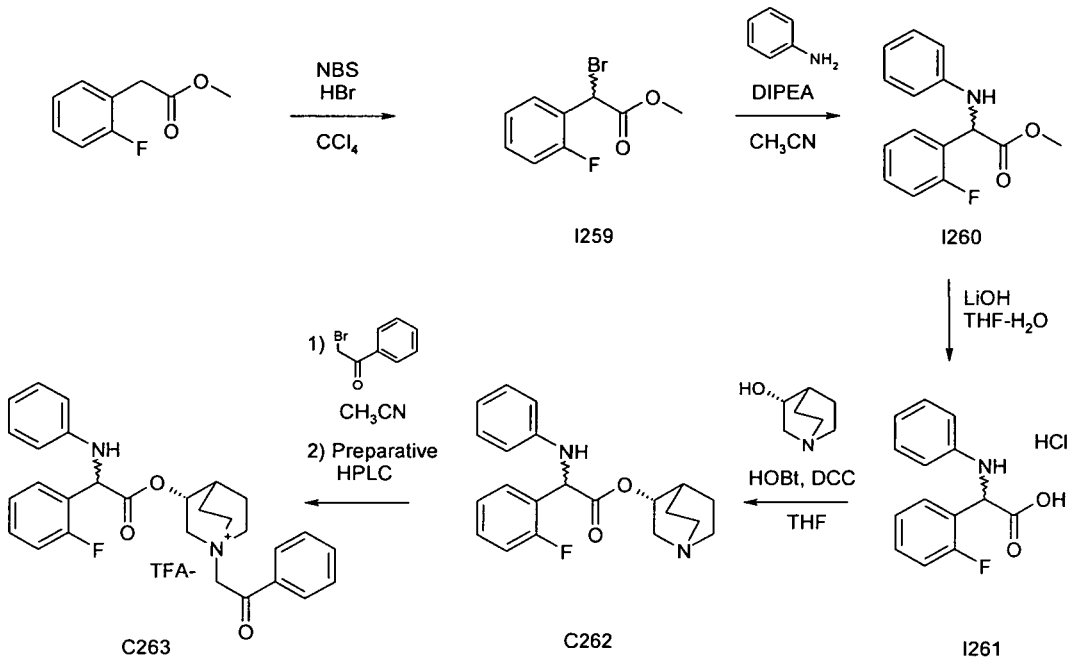
2-Bromo-1-phenylethanone (54.8 mg, 0.27 mmol) is added to a solution of (4-chloro-phenyl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C257) (100 mg, 0.27 mmol) in acetonitrile (4 mL). The reaction is heated in a microwave oven at 100°C for 1 hour. The solvent is evaporated and the crude is first purified by flash chromatography (DCM/MeOH=98/2 to 85/15) and then by preparative HPLC to collect the title compound as a brown viscous oil (37 mg, 22.76 % yield, trifluoroacetate salt, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.94 - 8.02 (m, 2 H), 7.72 - 7.83 (m, 1 H), 7.54 - 7.68 (m, 4 H), 7.40 - 7.54 (m, 2 H), 6.96 - 7.17 (m, 2 H), 6.68 - 6.78 (m, 2 H), 6.52 - 6.67 (m, 1 H), 5.42 (s, 1 H), 5.19 - 5.28 (m, 1 H), 5.16 (s, 2 H), 4.05 - 4.19 (m, 1 H), 3.44 - 3.86 (m, 5 H), 2.09 - 2.22 (m, 1 H), 1.90 - 2.08 (m, 2 H), 1.75 - 1.88 (m, 1 H), 1.54 - 1.73 (m, 1 H);

LC-MS (ESI POS): 488.9 (MH+).

EXAMPLE 67

Preparation of (R)-3-[2-(2-fluoro-phenyl)-2-phenylamino-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate (C263)



Scheme 67

Preparation of bromo-(2-fluoro-phenyl)-acetic acid methyl ester (I259):

A solution of methyl 2-(2-fluorophenyl)acetate (1.0 g, 5.95 mmol) in CCl_4 (15 mL), is added with N-bromo succinimide (1.06 g, 5.95 mmol) and 48% hydrogen bromide (33 uL, 0.30 mmol) and the reaction is refluxed for 15h. Reaction is diluted with DCM and washed with Na_2CO_3 and water. The organic phase is dried over Na_2SO_4, filtered and evaporated under vacuum to afford intermediate I261 as a dark brown oil (1.47 g, quantitative yield).

Preparation of (2-fluoro-phenyl)-phenylamino-acetic acid methyl ester (I260):

A solution of bromo-(2-fluoro-phenyl)-acetic acid methyl ester (I259)

(1.47 g, 5.95 mmol), aniline (814 ul, 8.93 mmol) and N-ethyl-N-isopropylpropan-2-amine (1.53 mL, 8.93 mmol) in acetonitrile (10 mL) is heated under microwave irradiation at 100°C for 1h. The solvent is evaporated, the residue is taken up with DCM and washed with water and brine, dried over Na_2SO_4 and evaporated to afford intermediate I262 as a dark brown oil (1.54 g, quantitative yield).

Preparation of (2-fluoro-phenyl)-phenylamino-acetic acid hydrochloride (I261):

A solution of (2-fluoro-phenyl)-phenylamino-acetic acid methyl ester (I260) (1.54 g, 5.95 mmol) in THF (15 mL), cooled at 0°C, is added with 2.0M lithium hydroxide (5.95 mL, 11.9 mmol) and the reaction is stirred at RT for 72 h. The solvent is evaporated, 1M HCl is added to the reaction until pH 1. The product is extracted with EtOAc, and the organic phase is washed with water and brine, dried over Na_2SO_4 and evaporated to provide intermediate I263 as a dark brown gummy solid (1.34 g, 80% yield).

Preparation of (2-fluoro-phenyl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C262):

A solution of (2-fluoro-phenyl)-phenylamino-acetic acid hydrochloride (I261) (217 mg, 0.77 mmol), (R)-quinuclidin-3-ol (338 mg, 2.66 mmol) and 1H-benzo[d][1,2,3]triazol-1-ol (180 mg, 1.332 mmol) in dry THF (15 mL), is added with PS-DCC (1.0 g, 1.33 mmol). The mixture is shaken at RT for 15h. Then (R)-quinuclidin-3-ol (49.0 mg, 0.38 mmol) and PS-DCC (290 mg, 0.38 mmol) are added again and the reaction is shaken for additional 3h at RT. The resin is removed by filtration and washed several time with EtOAc. The solvent is evaporated, the residue is taken up with EtOAc and washed with $NaHCO_3$, water and brine. The organic phase is dried (Na_2SO_4), filtered and evaporated to afford the title compound as a brown oil (225 mg, 82% yield).

Preparation of (R)-3-[2-(2-fluoro-phenyl)-2-phenylamino-acetoxy]-

1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate (C263):

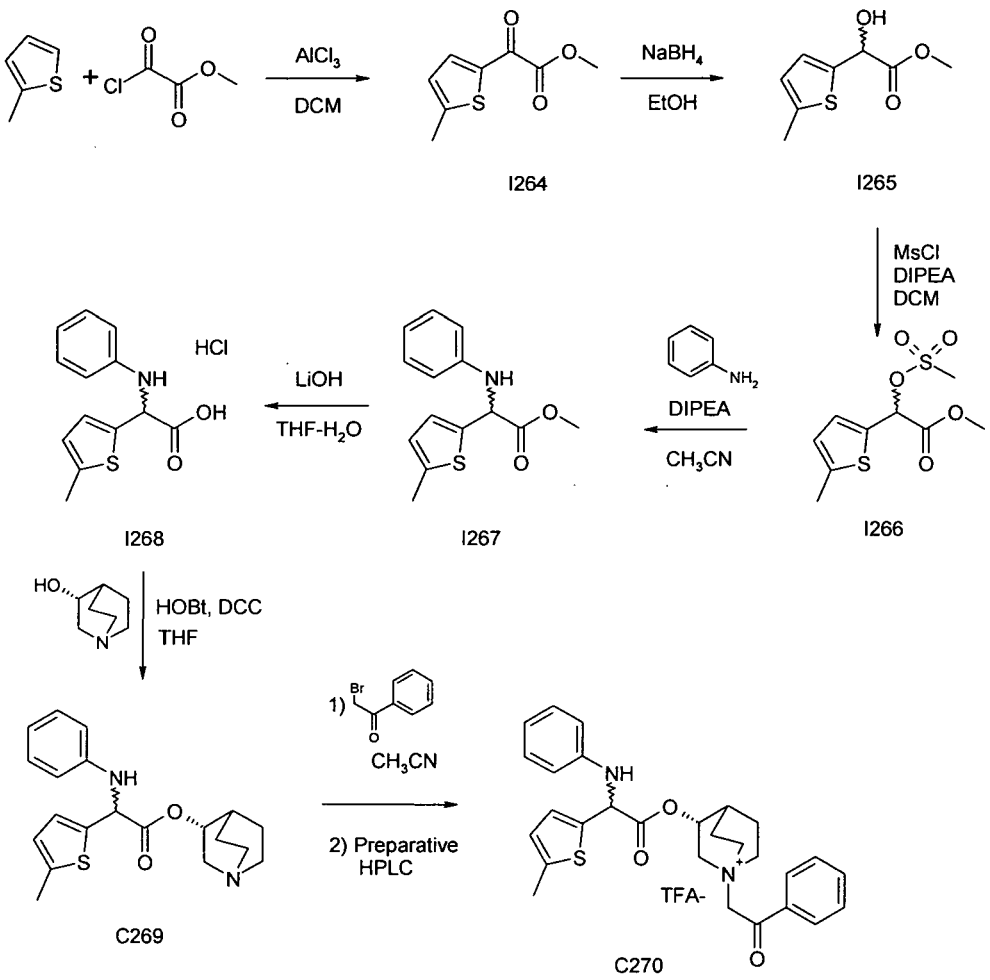
A solution of (2-fluoro-phenyl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C262) (225 mg, 0.63 mmol) in acetonitrile (8 mL), is added with 2-bromo-1-phenylethanone (126 mg, 0.63 mmol) and the reaction is stirred at RT for 15h. The solvent is evaporated and the resulting crude is purified by preparative HPLC to obtain the title compound as a brown oil (130 mg, 35%yield, trifluoroacetate salt, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.92 - 8.07 (m, 2 H), 7.69 - 7.82 (m, 1 H), 7.52 - 7.68 (m, 3 H), 7.35 - 7.49 (m, 1 H), 7.19 - 7.35 (m, 2 H), 7.05 - 7.15 (m, 2 H), 6.68 - 6.81 (m, 2 H), 6.56 - 6.67 (m, 1 H), 6.42 (br. s., 1 H), 5.57 and 5.59 (s, 1 H), 5.21 - 5.34 (m, 1 H), 5.12 and 5.17 (s, 2 H), 4.02 - 4.24 (m, 1 H), 3.27 - 3.83 (m, 5 H), 2.13 - 2.22 and 2.32 - 2.43 (m, 1 H), 1.34 - 2.13 (m, 4 H);

LC-MS (ESI POS): 473.4 (MH+).

EXAMPLE 68

Preparation of (R)-3-[2-(5-methyl-thiophen-2-yl)-2-phenylamino-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate (C270)



Scheme 68

Preparation of (5-methyl-thiophen-2-yl)-oxo-acetic acid methyl ester (I264):

A suspension of aluminum trichloride (2.75 g, 20.6 mmol) and methyl 2-chloro-2-oxoacetate (1.90 mL, 20.7 mmol) in dry DCM (25 mL), cooled at 0°C and under nitrogen atmosphere, is added with 2-methylthiophene (1.00 mL, 10.33 mmol) dropwise. The reaction is stirred at RT for 15h. Then the mixture is cooled at 0°C, ice-water is slowly added and the organic phase is washed with aq. $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated to obtain intermediate

I266 as a brown oil (1.9 g, quantitative yield).

Preparation of hydroxy-(5-methyl-thiophen-2-yl)-acetic acid methyl ester (I265):

A solution of methyl (5-methyl-thiophen-2-yl)-oxo-acetic acid methyl ester (I264) (1.90 g, 10.3 mmol) in MeOH (25 mL) cooled at 0°C, is added portionwise with sodium boron hydride (0.19 g, 5.17 mmol). The reaction is stirred at 0°C for 10 minutes then at RT for 1h. The solvent is evaporated, the residue is taken up with EtOAc and washed with ice-water and brine. The organic phase is dried over Na_2SO_4, filtered and evaporated to collect intermediate I267 as a brown oil (1.84 g, 96% yield).

Preparation of methanesulfonyloxy-(5-methyl-thiophen-2-yl)-acetic acid methyl ester (I266):

A solution of hydroxy-(5-methyl-thiophen-2-yl)-acetic acid methyl ester (I265) (1.84 g, 9.89 mmol) in dry DCM, cooled at 0°C under nitrogen atmosphere, is added with N-ethyl-N-isopropylpropan-2-amine (2.54 mL, 14.8 mmol) and methanesulfonyl chloride (1.16 mL, 14.8 mmol) and the reaction is stirred at RT for 2h. DCM is added and the organic phase is washed with aq. $NaHCO_3$, water and brine, dried over Na_2SO_4 and evaporated to obtain intermediate I268 as a dark brown oil (2.1 g, 80% yield).

Preparation of (5-methyl-thiophen-2-yl)-phenylamino-acetic acid methyl ester (I267):

A solution of methanesulfonyloxy-(5-methyl-thiophen-2-yl)-acetic acid methyl ester (I266) (2.10 g, 7.94 mmol), aniline (1.09 mL, 11.9 mmol) and N-ethyl-N-isopropylpropan-2-amine (2.04 mL, 11.9 mmol) in MeCN (10 mL) is heated under microwave irradiation at 100°C for 1h. The solvent is removed, DCM is added and the organic phase is washed with water and brine, dried over Na_2SO_4 and evaporated. The resulting brown oil is purified by silica gel flash chromatography (Hexane/EtOAc=9575 to 90/10) to obtain intermediate I269 as a

yellow oil (500 mg, 24% yield).

Preparation of (5-methyl-thiophen-2-yl)-phenylamino-acetic acid hydrochloride (I268):

A solution of (5-methyl-thiophen-2-yl)-phenylamino-acetic acid methyl ester (I267) (500 mg, 1.91 mmol) in THF (15 mL), cooled at 0°C, is added with 2.0M lithium hydroxide (1.91 mL, 3.83 mmol) and the reaction is stirred at RT for 72 hours. Then the solvent is evaporated, 1M HCl is added to the reaction until pH 1 and the product is extracted with EtOAc. The organic phase is washed with water and brine, dried over Na_2SO_4, filtered and evaporated to obtain intermediate I270 as a light brown solid (410 mg, 76% yield).

Preparation of (5-methyl-thiophen-2-yl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C269):

A solution of (5-methyl-thiophen-2-yl)-phenylamino-acetic acid hydrochloride (I268) (220 mg, 0.77 mmol), (R)-quinuclidin-3-ol (338 mg, 2.66 mmol) and 1H-benzo[d][1,2,3]triazol-1-ol (180 mg, 1.33 mmol) in dry THF (15 mL), is added with PS-DCC (1.0 g, 1.330 mmol) and the mixture is shaken at RT for 15h. Then (R)-quinuclidin-3-ol (49.3 mg, 0.39 mmol) and PS-DCC (291 mg, 0.39 mmol) are added again and the reaction is shaken at RT for other 3h. The resin is filtered off and washed several time with EtOAc. The solvent is concentrated and washed with aq. $NaHCO_3$, water and brine. The organic phase is dried over Na_2SO_4 and evaporated to obtain the title compound as a brown oil (175 mg, 63% yield).

Preparation of (R)-3-[2-(5-methyl-thiophen-2-yl)-2-phenylamino-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate (C270):

A solution of (5-methyl-thiophen-2-yl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester (C269) (175 mg, 0.49 mmol) in acetonitrile (8 mL), is added with 2-bromo-1-phenylethanone (98.0 mg, 0.49 mmol) and the

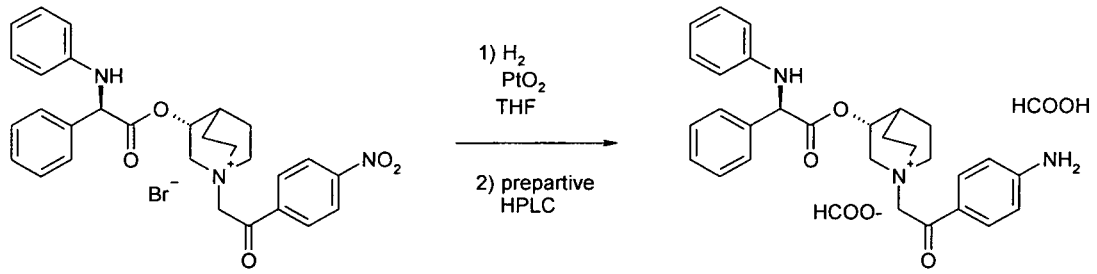
reaction is stirred at RT for 15h. The solvent is evaporated and the resulting brown crude is purified by preparative HPLC to obtain the title compound as a brown oil (60 mg, 21% yield, trifluoroacetate salt, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 7.91 - 8.08 (m, 2 H), 7.69 - 7.88 (m, 1 H), 7.54 - 7.69 (m, 2 H), 7.06 - 7.16 (m, 2 H), 6.99 - 7.07 (m, 1 H), 6.69 - 6.83 (m, 3 H), 6.54 - 6.69 (m, 1 H), 6.33 (br. s., 1 H), 5.52 and 5.56 (d, 1 H), 5.23 - 5.34 (m, 1 H), 5.13 and 5.17 (s, 2 H), 3.98 - 4.21 (m, 1 H), 3.55 - 3.86 (m, 5 H), 2.43 and 2.44 (d, 3 H), 2.19 - 2.25 and 2.33 - 2.40 (m, 1 H), 1.40 - 2.15 (m, 4 H);

LC-MS (ESI POS): 475.3 (MH^+).

EXAMPLE 69

Preparation of (R)-1-[2-(4-amino-phenyl)-2-oxo-ethyl]-3-((R)-2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane formate (diastereoisomer 1 of C271)



Diastereoisomer 1 of C179 Diastereoisomer 1 of C271

Scheme 69

A solution of (R)-1-[2-(4-nitro-phenyl)-2-oxo-ethyl]-3-((R)-2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide (Diastereoisomer 1 of C179) (88 mg, 0.152 mmol) in THF (30 mL) is hydrogenated in presence of a catalytic amount of Pt_2O at 15 psi for 2 hr and then at 20 psi for additional 2 hrs. (UPLC-MS monitoring: complete conversion). Catalyst is removed by filtration and the solution evaporated to dryness. The crude is purified by preparative HPLC to give the title compound as a pale yellow solid (31 mg, 37% yield, formate formate anion, single

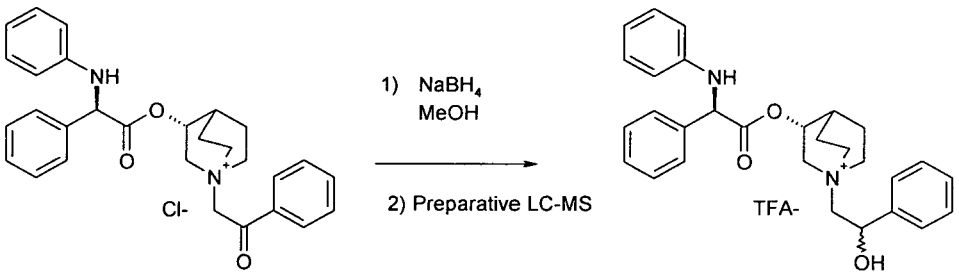
diastereoisomer).

^{1}H NMR (300 MHz, DMSO-d_6) ppm: 8.51 (s, 1 H, *formiate*), 7.63 - 7.77 (m, 2 H), 7.47 - 7.61 (m, 2 H), 7.30 - 7.46 (m, 3 H), 7.02 - 7.18 (m, 3 H), 6.68 - 6.81 (m, 2 H), 6.54 - 6.66 (m, 2 H), 6.41 (br. s., 2 H), 6.36 (d, 1 H), 5.37 (d, 1 H), 4.99 - 5.25 (m, 1 H), 4.82 (s, 2 H), 3.91 - 4.18 (m, 1 H), 3.41 - 3.74 (m, 5 H), 2.30 - 2.43 (m, 1 H), 1.56 - 2.09 (m, 4 H);

LC-MS (ESI POS): 470.1 (MH^+).

EXAMPLE 70

Preparation of (R)-1-(2-hydroxy-2-phenyl-ethyl)-3-((R)-2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate (C272)



Diastereoisomer 1 of C61 C272

Scheme 70

A solution of (R)-1-(2-oxo-2-phenyl-ethyl)-3-((R)-2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane chloride (Diastereoisomer 1 of C113) (80 mg, 0.163 mmol) in MeOH, is added with $NaBH_4$ (6.16 mg, 0.163 mmol) and the mixture is stirred at RT for 1 hour (UPLC-MS: complete conversion). The solvent is evaporated and the resulting crude is first purified by flash chromatography (DCM/MeOH =9/1) and then by preparative LC-MS to obtain the title compound as of a brown oil (31.2 mg, 39% yield, trifluoroacetate, mixture of diastereoisomers).

^{1}H NMR (300 MHz, DMSO-d_6) ppm 7.51 - 7.64 (m, 2 H), 7.28 - 7.50 (m, 8 H), 6.99 - 7.17 (m, 1 H), 6.66 - 6.86 (m, 2 H), 6.51 - 6.66 (m, 1 H), 5.01 - 5.54 (m,

3 H), 3.02 - 4.07 (m, 9 H), 2.29 - 2.42 (m, 1 H), 1.71 - 2.17 (m, 4 H);

LC-MS (ESI POS): 457.1 (MH^+).

Biological characterisation

EXAMPLE 71

Examples of Radioligand Binding Assay for Cloned Human Muscarinic Receptors and for Human beta Adrenergic Receptors:

CHO-K1 clone cells expressing the human M1-, M2-, M3- receptors (Euroscreen, Swissprot P11229, P08172, P20309, Genbank: J02960 respectively) were harvested in Ca^{++}/Mg^{++} free phosphate-buffered saline and collected by centrifugation at 1500 rpm for 10 min, at 4°C min. The pellets were resuspended in ice cold buffer A (15 mM Tris-HCl pH 7.4, 2 mM $MgCl_2$, 0.3 mM EDTA, 1 mM EGTA). Cloned cells expressing M1-, M2-, and M3- receptors were homogenized by a PBI politron (setting 5 for 15 s). The crude membrane fraction was collected by two consecutive centrifugation steps at 40000 g for 20 min at 4°C, separated by a washing step in buffer A.

The pellets obtained from the three cell lines were finally resuspended in buffer C (75 mM Tris HCl pH 7.4, 12.5mM $MgCl_2$, 0.3 mM EDTA, 1 mM EGTA, 250 mM sucrose) and aliquots were stored at – 80°C.

The day of experiment, M1-, M2-, and M3-receptor frozen membranes were resuspended in buffer D (50 mM Tris-HCl pH 7.4, 2.5 mM $MgCl_2$, 1 mM EDTA). The non selective muscarinic radioligand [3H]-N-methyl scopolamine (Mol. Pharmacol. 45:899-907) was used to label the M1, M2, and M3 binding sites. Binding experiments were performed in duplicate (ten point concentrations curves) in 96 well plates at radioligand concentration of 0.1-0.3 nM. The non specific binding was determined in the presence of cold N-methyl scopolamine 10 μM. Samples (final volume 0.75 mL) were incubated at RT for 120 min for M1, 60 min for M2 and 90 min for M3 binding assay.

The reaction was terminated by rapid filtration through GF/B Unifilter plates and two washes (0.75 mL) with cold buffer using a Packard Filtermate Harvester. Radioactivity on the filters was measured by a microplate scintillation counter TopCount NXT (Canberra Packard).

In the present assays, Ki values for the tested compounds were determined from the observed IC50 values according to known methods. A lower Ki value indicates that the tested compound has a higher binding affinity for the receptor.

The interaction with M3 muscarinic receptors can be estimated by the results of in vitro studies which evaluated the potency of the test compounds and the offset of the inhibitory activity produced after washout of the antagonists in isolated guinea pig trachea and by the in vivo duration of action against acetylcholine-induced bronchospasm in the guinea pig.

EXAMPLE 72

In vitro interaction with guinea pigs M3 receptors

The potency of the antagonist activity in isolated guinea pig trachea was investigated following a method previously described by Haddad EB et al. in Br J Pharmacol 127, 413-420, 1999, with few modifications.

A cumulative concentration-response curve to test antagonists was constructed on preparations precontracted by carbachol, until a complete inhibition of smooth muscle tone was achieved. The concentration of antagonist producing a 50% reversal of carbachol-induced tonic contraction (IC_{50}) was taken as a measure of its potency in this bioassay.

In the experiments aiming at assessing the offset of the inhibitory effects produced by test compounds, the minimal concentration of the test compounds known to produce a maximal inhibitory effect was administered to carbachol-precontracted preparations. As soon as the tonic contraction was completely reversed, the organ bath solution was renewed and preparations

were thoroughly washed with fresh Krebs solution. Carbachol (0.3 μM) was administered again (at 30 min interval between washout and next administration) during the next 4 hours.

After the administration of carbachol, the inhibitory effects of the compounds of the invention, administered at a concentration of 10 nM, were expressed as percentage of the recovery of the contracting response to carbachol. The percentage of recovery four hours after the washout was lower than 50%.

The compounds of the invention show a remarkable inhibitory M3 activity. In particular, the IC_{50} values being tested for some representative compounds result to be comprised between 0.03 and 10 nM.

EXAMPLE 73

In vivo studies

The in vivo tests on acetylcholine-induced bronchospasm in guinea pig were performed according to H. Konzett H and Rössler F Arch Exp Path Pharmacol 195, 71-74, 1940. Aqueous solutions of the test compounds were instilled intratracheally in anaesthetised mechanically ventilated guinea pigs. Bronchial response to intravenous acetylcholine challenge was determined before and after drug administration and changes in pulmonary resistance at several time-points were expressed as percent of inhibition of bronchospasm.

The bronchodilator activity of the tested compounds persisted unchanged up to 24 hours after the administration.

EXAMPLE 74

Plasma stability

In order to demonstrate that the compounds are degraded, stability in human plasma at 1 and 5 hours was tested for the compound of the invention. Briefly 10μl of a stock solution 250 μM of the compound in acetonitrile were added to 1ml of human plasma and samples were incubated at 37°C. Plasma

(50µL) was taken after 0, 1 and 5 hours of incubation and added to 140µl of acetonitrile with addition of verapamil as internal standard (250ng/ml). Samples were analysed by HPLC-MS/MS analysis.

Plasma stability is calculated as percentage remaining after 1 and 5 hours by dividing the peak area at 1 or 5 hours by the area of the peak at time 0.

After 1 and 5 hours of incubation, plasma stability being tested for some representative compounds of the invention result to be comprised between 0 and 25%, indicating that the compounds of the invention are very unstable in human plasma.

Legend

* NMR

s = singlet

d = doublet

t = triplet

q = quartet

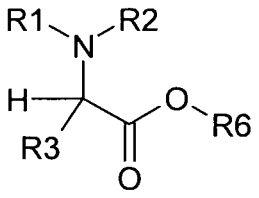
dd = doublet of doublets

m = multiplet

br = broad

CLAIMS

1. A compound of general formula (I),



(I)

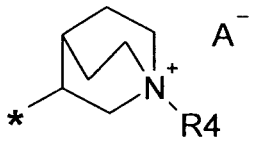
wherein:

R1 is selected from the group consisting of H, (C_1-C_{10})-alkyl, aryl, (C_3-C_8)-cycloalkyl, arylalkyl and heteroaryl, optionally substituted by one or more substituents selected from the group consisting of halogen atoms, OH, oxo (=O), SH, NO_2, CN, $CON(R5)_2$, COOH, NHCOR5, COR5, CO_2R5, CF_3, (C_1-C_{10})-alkoxycarbonyl, (C_1-C_{10})-alkylsulfanyl, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_1-C_{10})-alkyl and (C_1-C_{10})-alkoxyl;

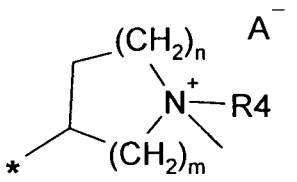
R2 is selected from the group consisting of (C_1-C_{10})-alkyl, aryl, (C_3-C_8)-cycloalkyl, arylalkyl and heteroaryl, optionally substituted by one or more substituents selected from the group consisting of halogen atoms, OH, oxo (=O), SH, NO_2, CN, $CON(R5)_2$, COOH, NHCOR5, COR5, CO_2R5, CF_3, (C_1-C_{10})-alkoxycarbonyl, (C_1-C_{10})-alkylsulfanyl, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_1-C_{10})-alkyl and (C_1-C_{10})-alkoxyl;

R3 is selected from the group consisting of H, (C_1-C_{10})-alkyl, aryl, (C_3-C_8)-cycloalkyl, heteroaryl, arylalkyl and heteroarylalkyl, optionally substituted by one or more substituents selected from the group consisting of halogen atoms, OH, oxo (=O), SH, NO_2, CN, $CON(R5)_2$, COOH, CO_2R5, CF_3, (C_1-C_{10})-alkoxycarbonyl, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_1-C_{10})-alkyl and (C_1-C_{10})-alkoxyl;

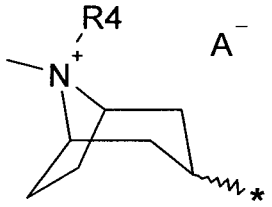
R6 represents a group of formula (i) or (ii) or (iii) or (iv)



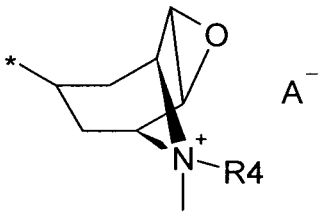
(i)



(ii)



(iii)



(iv)

wherein

m = 1, 2 or 3;

n =1, 2 or 3;

A^- is a physiologically acceptable anion;

R4 is a group of formula (Y)

$$---(CH_2)p---P---(CH_2)q---W$$

(Y)

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, SO, SO_2, CO, NR5 CH=CH, $N(R5)SO_2$, N(R5)COO, N(R5)C(O), $SO_2N(R5)$, CO(O)N(R5) and C(O)N(R5);

W is selected from the group consisting of H, $(C_1$-$C_6)$-alkyl, $(C_3$-$C_8)$-cycloalkyl, aryl and heteroaryl, optionally substituted by one or more substituents selected from the group consisting of halogen atoms, OH, oxo (=O), SH, NO_2, CN, $CON(R5)_2$, COOH, NH_2, NHCOR5, CO_2R5, $(C_1$-$C_{10})$-

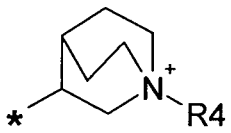
alkoxycarbonyl, (C_1-C_{10})-alkylsulfanyl, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_1-C_{10})-alkyl and (C_1-C_{10})-alkoxyl;

R5 is selected from the group consisting of H, (C_1-C_{10})alkyl, (C_1-C_6)alkylhalo, (C_2-C_6)alkynyl, (C_2-C_6)alkenyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, heteroaryl, (C_1-C_6)alkyl-heteroaryl and aryl optionally substituted by one or more substituents selected from the group consisting of halogen atoms, OH, oxo (=O), SH, NO_2, CN, $CONH_2$, COOH, (C_1-C_{10})-alkoxycarbonyl, (C_1-C_{10})-alkylsulfanyl, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_1-C_{10})-alkyl and (C_1-C_{10})-alkoxyl;

and pharmaceutically acceptable salts thereof,

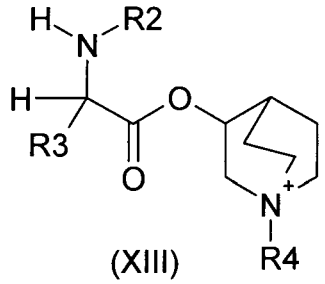
with the proviso that when R1 is H, R2 is phenyl, R3 is H, then R6 is not a group of formula (iii).

2. A compound of claim 1 wherein R1 is H, R2 is arylalkyl or (C1-C10)-alkyl or aryl or (C_3-C_8)-cycloalkyl or heteroaryl and R3 is (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or heteroaryl, preferably substituted with one or more halogen atoms and wherein R6 is a group of formula (i)



(i)

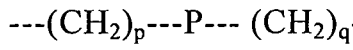
according to the general formula (XIII):



(XIII)

3. A compound of claim 2 wherein R1 is H, R2 and R3 are phenyl.

4. A compound of claim 3 wherein R1 is H, R2 and R3 are phenyl and wherein R4 is a group of formula (Y)



(Y)

wherein p is 1, P is CO, q is 0 and W is aryl.

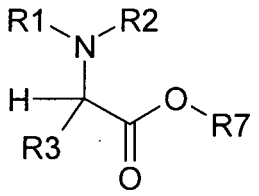
5. A compound of claim 4 wherein R4 is a group of formula (Y), wherein p is 1, P is CO, q is 0 and W is phenyl.

6. A compound of claim 4 wherein R4 is a group of formula (Y), wherein p is 1, P is CO, q is 0 and W is thienyl.

7. A compound of claim 4 wherein R4 is a group of formula (Y), wherein p is 2, P is O, q is 0 and W is phenyl.

8. A compound of claim 4 wherein R4 is a group of formula (Y), wherein p is 3, P is O, q is 0 and W is phenyl.

9. A compound of general formula (VI):

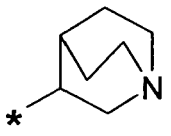


(VI)

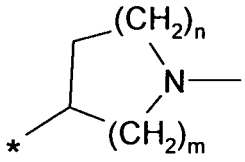
wherein:

R1, R2 and R3 are as described in claim 1;.

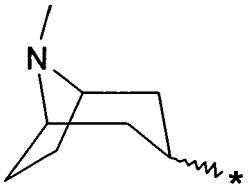
R7 represents a group of formula (vi) or (vii) or (viii) or (ix)



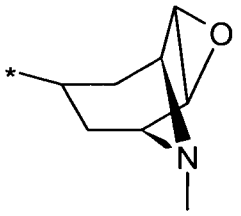
(vi)



(vii)



(viii)



(ix)

wherein

m and n are as described in claim 1;

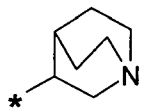
and pharmaceutically acceptable salts thereof,

with the provisos that:

- when R1 is H or CH_3, R2 is phenyl, R3 is H or CH_3, then R6 is not a group of formula (viii) and

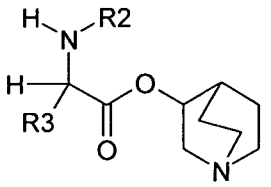
- the compounds of general formula (VI) are not N-methyl-3-piperidyl-2'-N'dimethylaminoacetate and N-methyl-4-piperidyl-2'-N'-dimethylaminoacetate.

10. A compound of claim 9 wherein R1 is H, R2 is (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or arylalkyl or heteroaryl and R3 is (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or arylalkyl or heteroaryl, preferably substituted with one or more halogen atoms and wherein R7 is a group of formula (vi)



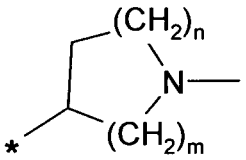
(vi)

according to the general formula (XII):



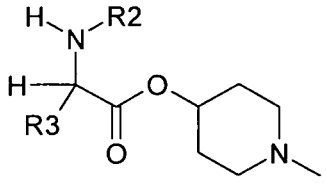
(XII)

11. A compound of claim 10 wherein R1 is H, R2 is arylalkyl or (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or heteroaryl and R3 is (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or arylalkyl or heteroaryl, preferably substituted with one or more halogen atoms and wherein R7 is a group of formula (vii)



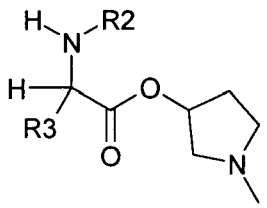
(vii)

according to the general formula (XIV)



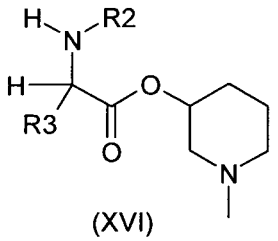
(XIV)

12. A compound of claim 10 wherein R1 is H, R2 is arylalkyl or (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or heteroaryl and R3 is (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or arylalkyl or heteroaryl, preferably substituted with one or more halogen atoms and wherein R7 is a group of formula (vii), according to the general formula (XV)



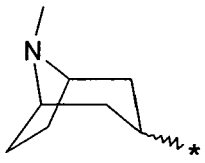
(XV)

13. A compound of claim 10 wherein R1 is H, R2 is arylalkyl or (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or heteroaryl and R3 is (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or arylalkyl or heteroaryl, preferably substituted with one or more halogen atoms and wherein R7 is a group of formula (vii), according to the general formula (XVI)

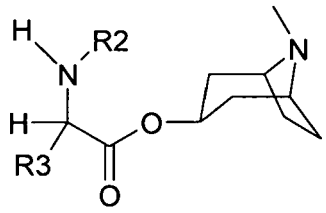


(XVI)

14. A compound of claim 10 wherein R1 is H, R2 is arylalkyl or (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or heteroaryl and R3 is (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or arylalkyl or heteroaryl, preferably substituted with one or more halogen atoms and wherein R7 is a group of formula (viii)

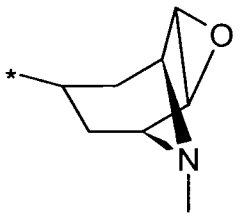


according to the general formula (XVII)

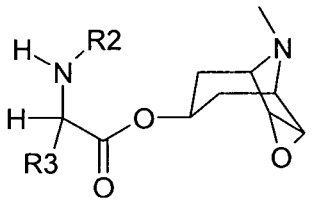


(XVII)

15. A compound of claim 10 wherein R1 is H, R2 is arylalkyl or (C1-C10)-alkyl or aryl or (C_3-C_8)-cycloalkyl or heteroaryl and R3 is (C_1-C_{10})-alkyl or aryl or (C_3-C_8)-cycloalkyl or arylalkyl or heteroaryl, preferably substituted with one or more halogen atoms and wherein R7 is a group of formula (ix)



according to the general formula (XVIII)



(XIII)

16. A compound according to any previous claim, selected from

(R)-quinuclidin-3-yl 2-phenyl-2-(phenylamino)acetate;

(R)-quinuclidin-3-yl 2-(4-fluorophenyl)-2-(4-fluorophenylamino)acetate;

(R)-quinuclidin-3-yl 2-(methyl(phenyl)amino)-2-phenylacetate;

(R)-quinuclidin-3-yl 2-(3-fluorophenyl)-2-(3-fluorophenylamino)acetate;

(R)-1-methylpiperidin-4-yl-2-phenyl-2-(phenylamino)acetate;

(R)-1-methylpyrrolidin-4-yl-2-phenyl-2-(phenylamino)acetate;

(S)-1-methylpyrrolidin-4-yl-2-phenyl-2-(phenylamino)acetate;

(R)-1-methylpiperidin-3-yl 2-phenyl-2-(phenylamino)acetate;

8-methyl-8-azabicyclo[3.2.1]octan-3-yl 2-phenyl-2-(phenylamino)acetate;

phenyl-phenylamino-acetic acid 9-methyl-3-oxa-9-aza-tricyclo[3.3.1.0*2,4*]non-7-yl ester;

(R)-quinuclidin-3-yl) 2-amino-3-phenylpropanoate di-trifluoroacetate;

3-phenyl-2-phenylamino-propionic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(R)-quinuclidin-3-yl 2-(benzylamino)-2-phenylacetate;

(R)-quinuclidin-3-yl 2-amino-2-phenylacetate di-hydrochloride;

(R)-quinuclidin-3-yl 2-(cyclopentylamino)-2-phenylacetate di-trifluoroacetate;

(R)-quinuclidin-3-yl 2-(cyclohexylamino)-2-phenylacetate;

(R)-1-(2-phenoxyethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-(3-phenoxypropyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-methyl-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-(2-phenoxyethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-(2-oxo-2-phenylethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(3R)-1-(2-oxo-2-(thiophen-3-yl)ethyl)-3-(2-phenyl-2-(phenylamino)-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(3R)-1-(2-(4-fluorophenyl)-2-oxoethyl)-3-(2-phenyl-2-(phenylamino)-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-phenethyl-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-(2-(benzo[b]thiophen-2-yl)-2-oxoethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(3R)-3-(2-(4-fluorophenyl)-2-(4-fluorophenylamino)acetoxy)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(3R)-3-(2-(4-fluorophenyl)-2-(4-fluorophenylamino)acetoxy)-1-(2-oxo-

2-phenylethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(3R)-3-(2-(4-fluorophenyl)-2-(4-fluorophenylamino)acetoxy)-1-methyl-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(3R)-3-(2-(3-fluorophenyl)-2-(3-fluorophenylamino)acetoxy)-1-(2-oxo-2-phenylethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(3R)-3-(2-(methyl(phenyl)amino)-2-phenylacetoxy)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(3R)-3-(2-(methyl(phenyl)amino)-2-phenylacetoxy)-1-(2-oxo-2-phenylethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-(2-phenoxyethyl)-3-(3-phenyl-2-(phenylamino)propanoyloxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-3-((S)-3-phenyl-2-(phenylamino)propanoyloxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-methyl-3-(3-phenyl-2-(phenylamino)propanoyloxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-(2-oxo-2-phenylethyl)-3-((S)-3-phenyl-2-(phenylamino)propanoyloxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(3R)-3-(2-(benzylamino)-2-phenylacetoxy)-1-(2-oxo-2-phenylethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-(2-oxo-2-pyridin-4-yl-ethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-[2-(3-chloro-thiophen-2-yl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-[2-(5-methyl-thiophen-2-yl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-[2-(1-methyl-1H-pyrrol-2-yl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-[2-(2,4-dimethyl-oxazol-5-yl)-2-oxo-ethyl]-3-(2-phenyl-2-

phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-3-(2-phenyl-2-phenylamino-acetoxy)-1-(3-phenylsulfanyl-propyl)-1-azonia-bicyclo[2.2.2]octane formate;

(R)-3-[2-(3-ethyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane formate;

(R)-3-[2-(4-methoxycarbonyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(3R)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-(2-(phenylthio)ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(3R)-1-(cyclohexylmethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(3R)-1-(4-methylpent-3-enyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(3R)-1-(2-(3,4-dichlorophenyl)-2-oxoethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-(2-oxo-2-phenylethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane chloride;

3-(3-(3-fluorophenyl)-3-(3-fluorophenylamino)-2-oxopropyl)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-1-azonia-bicyclo[2.2.2]octane chloride;

(R)-1-(2-amino-2-oxoethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane;

(R)-1-(2-oxo-2-(phenylamino)ethyl)-3-(2-phenyl-2-(phenylamino)-acetoxy)-1-azonia-bicyclo[2.2.2]octane;

(3R)-1-(2-oxo-2-phenylethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane;

(3R)-3-(2-(benzylamino)-2-phenylacetoxy)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-1-azonia-bicyclo[2.2.2]octane;

(R)-1-(2-oxo-2-phenylethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-

azonia-bicyclo[2.2.2]octane bromide;

(R)-3-((S)-2-amino-phenylpropanoyloxy)-1-(2-phenoxyethyl)-1-azonia-bicyclo[2.2.2]octane;

(R)-3-((S)-2-amino-3-phenylpropanoyloxy)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-3-((S)-2-amino-3-phenylpropanoyloxy)-1-(3-phenoxypropyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-3-((S)-2-amino-3-phenylpropanoyloxy)-1-(2-oxo-2-phenylethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-(2-oxo-2-phenylethyl)-3-((R)-3-phenyl-2-(phenylamino)-propanoyloxy)-1-azoniabicyclo[2.2.2]octane bromide;

(R)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-3-((R)-3-phenyl-2-(phenylamino)-propanoyloxy)-1-azonia-bicyclo[2.2.2]octane chloride;

((4-chloro-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

4-({[(R)-(1-aza-bicyclo[2.2.2]oct-3-yl)oxycarbonyl]-phenyl-methyl}-amino)-benzoic acid methyl ester;

3-({[(R)-(1-aza-bicyclo[2.2.2]oct-3-yl)oxycarbonyl]-phenyl-methyl}-amino)-thiophene-2-carboxylic acid methyl ester;

(4-fluoro-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(4-fluoro-phenyl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

2-({[(R)-(1-aza-bicyclo[2.2.2]oct-3-yl)oxycarbonyl]-phenyl-methyl}-amino)-benzoic acid methyl ester;

(2-methoxy-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

phenyl-o-methyl phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-

3-yl) ester;

phenyl-(3-trifluoromethoxy-phenylamino)-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(3-ethyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(3-acetylamino-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(3-methylcarbamoyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(3-fluoro-4-methyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(3-methylsulfanyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(3-acetyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(2,5-dimethoxy-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(2,5-difluoro-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(2,6-dimethyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(2-ethyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(2-acetyl-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(3,5-difluoro-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

3-({[(R)-(1-aza-bicyclo[2.2.2]oct-3-yl)oxycarbonyl]-phenyl-methyl}-

amino)-benzoic acid ethyl ester;

(3-methoxy-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

[(4-fluoro-phenyl)-methyl-amino]-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(methyl-phenyl-amino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(4-methyl-benzylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(4-fluoro-benzylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(4-methoxy-benzylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

benzylamino-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(4-fluoro-benzylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(4-fluoro-phenyl)-(3-fluoro-phenylamino)-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(4-fluoro-phenyl)-(2-fluoro-phenylamino)-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(R)-quinuclidin-3-yl 2-(phenylamino)-2-(thiophen-2-yl)acetate hydrochloride;

(4-methoxy-phenyl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

4-{[(R)-(1-aza-bicyclo[2.2.2]oct-3-yl)oxycarbonyl]-phenylamino-methyl}-benzoic acid methyl ester;

(3-fluoro-phenyl)-phenylamino-acetic acid (R)-(1-aza-

bicyclo[2.2.2]oct-3-yl) ester;

(4-fluoro-phenyl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

phenylamino-(4-trifluoromethyl-phenyl)-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(S)-quinuclidin-3-yl 2-phenyl-2-(phenylamino)-acetate;

phenyl-phenylamino-acetic acid 1-methyl-azepan-4-yl ester;

(R)-1-[2-(4-methoxy-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-(4-oxo-4-phenyl-butyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-benzyl-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-[2-(5-chloro-thiophen-2-yl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-benzyl-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-[2-(4-methoxy-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-[2-(3-hydroxy-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-dimethylcarbamoylmethyl-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-(2-oxo-propyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-(2-oxo-propyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-3-[2-(2-methoxycarbonyl-thiophen-3-yl)-2-phenylamino-acetoxy]-

1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-3-[2-(2-methoxycarbonyl-thiophen-3-yl)-2-phenylamino-acetoxy]-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-3-[2-(4-methoxy-phenyl)-2-phenylamino-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane formate;

(R)-3-[2-(4-chloro-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-(2-oxo-2-phenyl-ethyl)-3-[2-phenylamino-2-(4-trifluoromethyl-phenyl)-acetoxy]-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-methyl-1-(2-oxo-2-phenyl-ethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-pyrrolidinium trifluoroacetate;

1,1-dimethyl-4-(2-phenyl-2-phenylamino-acetoxy)-piperidinium trifluoroacetate;

(R)-1-[2-(5-methyl-thiophen-3-yl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-[2-(2,4-difluoro-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-1-[2-(3,4-difluoro-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-1-[2-(2-fluoro-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-1-[2-(3-fluoro-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-1-[2-(2,4-dibromo-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane chloride;

(R)-1-[2-(4-nitro-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-1-[2-(4-hydroxy-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-1-[2-oxo-2-(2-oxo-2,3-dihydro-1H-indol-5-yl)-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-1-(2-benzo[1,3]dioxol-5-yl-2-oxo-ethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-1-(2-oxo-2-thiazol-2-yl-ethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-1-[2-(3-ethoxycarbonyl-isoxazol-5-yl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-1-[2-(4-methyl-thiophen-2-yl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-1-(2-benzo[b]thiophen-5-yl-2-oxo-ethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-(2-phenyl-2-phenylamino-acetoxy)-1-phenylsulfanylmethyl-1-azonia-bicyclo[2.2.2]octane chloride;

(R)-1-(2-oxo-2-piperidin-1-yl-ethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane chloride;

(R)-3-(2-phenyl-2-phenylamino-acetoxy)-1-(thiazol-2-ylcarbamoylmethyl)-1-azonia-bicyclo[2.2.2]octane chloride;

(R)-1-(isoxazol-3-ylcarbamoylmethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane chloride;

(R)-1-(2-oxo-2-phenyl-ethyl)-3-(2-phenyl-2-p-methylphenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(4-fluoro-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(4-fluoro-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane chloride;

(R)-3-[2-(2-methoxycarbonyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(2-methoxy-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-1-(2-oxo-2-phenyl-ethyl)-3-[2-phenyl-2-(3-trifluoromethoxy-phenylamino)-acetoxy]-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-1-(2-oxo-2-phenyl-ethyl)-3-(2-phenyl-2-(phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(3-acetylamino-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(3-methylcarbamoyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(3-methylsulfanyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(4-fluoro-phenyl)-2-(3-fluoro-phenylamino)-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(4-fluoro-phenyl)-2-(3-fluoro-phenylamino)-acetoxy]-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane chloride;

(R)-3-[2-(4-fluoro-phenyl)-2-(2-fluoro-phenylamino)-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(4-fluoro-phenyl)-2-(2-fluoro-phenylamino)-acetoxy]-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane chloride;

(R)-3-[2-(4-methoxycarbonyl-phenyl)-2-phenylamino-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-(2-cyclohexylamino-2-phenyl-acetoxy)-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-(2-cyclohexylamino-2-phenyl-acetoxy)-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane chloride;

(R)-1-(2-oxo-2-phenyl-ethyl)-3-(2-phenylamino-2-thiophen-2-yl-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(3-fluoro-4-methyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(2,5-dimethoxy-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(2,5-difluoro-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(2,6-dimethyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(2-ethyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(2-acetyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(3-ethoxycarbonyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(3,5-difluoro-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(3-methoxy-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(3-fluoro-phenyl)-2-phenylamino-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(4-fluoro-phenyl)-2-phenylamino-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-1-cyanomethyl-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-1-tert-butoxycarbonylmethyl-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide;

(S)-1-(2-oxo-2-phenyl-ethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane chloride;

(R)-3-[2-(3-acetyl-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane formate;

(R)-1-[2-(4-acetylamino-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-1-[2-(4-methoxycarbonyl-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-(2-phenyl-2-phenylamino-acetoxy)-1-pyridin-2-ylmethyl-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-(2-oxo-2-pyridin-2-yl-ethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane formate;

(R)-1-(2-(2-methylthiazol-4-yl)-2-oxoethyl)-3-((R)-2-phenyl-2-(phenylamino)acetoxy)-1-azoniabicyclo[2.2.2]octane bromide;

(R)-1-(6-amino-pyridin-2-ylmethyl)-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-3-{2-[(4-fluoro-phenyl)-methyl-amino]-2-phenyl-acetoxy}-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane chloride;

(R)-3-[2-(methyl-phenyl-amino)-2-phenyl-acetoxy]-1-(2-oxo-2-thiazol-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(methyl-phenyl-amino)-2-phenyl-acetoxy]-1-(2-oxo-2-thiophen-3-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane;

(R)-3-(2-benzylamino-2-phenyl-acetoxy)-1-[2-(3-ethoxycarbonyl-isoxazol-5-yl)-2-oxo-ethyl]-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-(2-benzylamino-2-phenyl-acetoxy)-1-(2-oxo-2-thiazol-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-3-(2-benzylamino-2-phenyl-acetoxy)-1-(2-oxo-2-thiophen-3-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(4-methyl-benzylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane formate;

(R)-3-[2-(4-methoxy-benzylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane formate;

(R)-3-[2-(4-fluoro-benzylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane chloride;

(R)-3-[2-(4-fluoro-benzylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

4-methyl-phenyl-amino-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(R)-1-(2-oxo-2-phenyl-ethyl)-3-(2-phenyl-4-methyl-phenyl-amino-acetoxy)-1-azonia-bicyclo[2.2.2]octane bromide;

(2-fluoro-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(R)-3-[2-(2-fluoro-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-3-[2-(3-fluoro-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane bromide;

(R)-3-[2-(3-fluoro-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-(4-fluoro-phenylamino)-phenyl-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(R)-3-[(R)-2-(4-fluoro-phenylamino)-2-phenyl-acetoxy]-1-(2-oxo-2-thiophen-2-yl-ethyl)-1-azonia-bicyclo[2.2.2]octane chloride;

(4-chloro-phenyl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(R)-3-[2-(4-chloro-phenyl)-2-phenylamino-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(2-fluoro-phenyl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(R)-3-[2-(2-fluoro-phenyl)-2-phenylamino-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

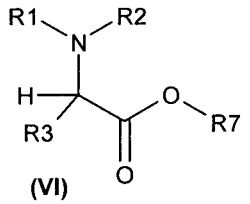
(5-methyl-thiophen-2-yl)-phenylamino-acetic acid (R)-(1-aza-bicyclo[2.2.2]oct-3-yl) ester;

(R)-3-[2-(5-methyl-thiophen-2-yl)-2-phenylamino-acetoxy]-1-(2-oxo-2-phenyl-ethyl)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate;

(R)-1-[2-(4-amino-phenyl)-2-oxo-ethyl]-3-(2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane formate;

(3R)-1-(2-hydroxy-2-phenylethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate.

17. A process for the preparation of a compound of formula (I) as defined in claim 1, which comprises the alkylation of compounds of general formula (VI)



(VI)

by alkylating agents of general formula (XI)

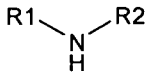


(XI)

in which A is a suitable leaving group selected from the group consisting of halide and sulfonate, wherein R1, R2, R3, R6 and R7 are defined according to claims 1 and 9.

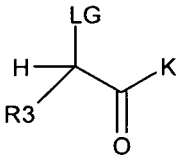
18. A process for the preparation of a compound of formula (I) as defined in claim 1, which comprises the alkylation of amine compounds of general

formula (II)



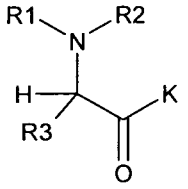
(II)

with compounds of general formula (III),



(III)

in which LG is a suitable leaving group and K may be either a hydroxyl group or a suitably protected hydroxyl group, to yield a compound of formula (IV),



(IV)

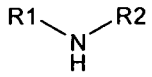
which is condensed with a compound of formula (V)



(V)

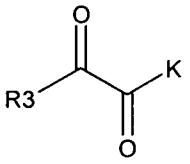
to obtain compound (VI), and converting the compound to a further compound of formula (I), according to claim 15 and wherein R1, R2, R3, R6 and R7 are defined according to claims 1 and 9.

19. A process for the preparation of a compound of formula (I) as defined in claim 1, which comprises coupling amine of general formula (II)



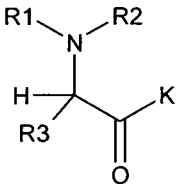
(II)

and ketones of formula (VII),



(VII)

to yield a compound of formula (IV),



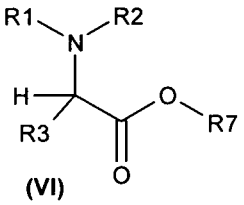
(IV)

which is condensed with a compound of formula (V)



(V)

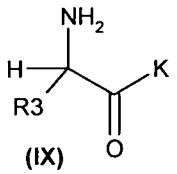
to obtain compound (VI)



(VI)

and converting the compound to a further compound of formula (I), wherein R1, R2, R3, R6 and R7 are defined according to claims 1 and 9.

20. A process for the preparation of a compound of formula (I) as reported in scheme 1, which comprises reacting compound (IX)



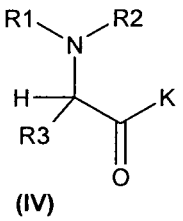
(IX)

with an alkylating agent of general formula (VIII),



(VIII)

in which z is a carbonyl group or a suitable leaving group such as a an halide, to yield a compound of formula (IV) in which R2 is hydrogen,



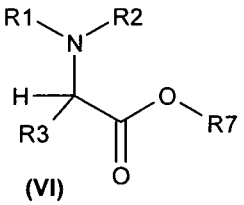
(IV)

which is condensed with a compound of formula (V)



(V)

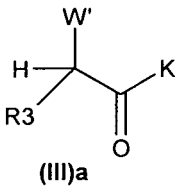
to obtain compound (VI)



(VI)

and converting the compound to a further compound of formula (I), wherein R1, R2, R3, R6 and R7 are defined according to claims 1 and 9.

21. A process for the preparation of a compound of formula (I) as reported in scheme 1, which comprises coupling compounds of general formula (IIIa)



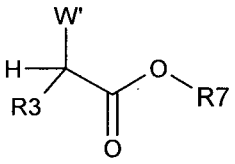
(III)a

to compound of general formula (V)



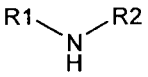
(V)

to yield compound (X),



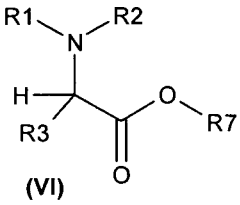
(X)

which is reacted with an amine of formula (II),



(II)

to obtain compound (VI)



(VI)

and converting the compound to a further compound of formula (I), wherein R1, R2, R3 and R7 are defined according to claims 1 and 9 and wherein W' is LG as defined in claim 18 or hydroxy.

22. A pharmaceutical composition comprising a compound of claims 1 to 16 in admixture with one or more pharmaceutically acceptable carriers and/or

excipients.

23. The pharmaceutical composition of claim 21 suitable for administration by inhalation.

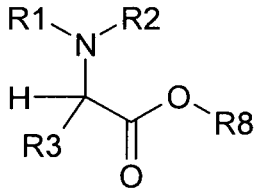
24. The pharmaceutical composition of claims 21 or 22 wherein said composition further comprises a second component selected from the classes of beta2-agonists and corticosteroids.

25. A compound of claims from 1 to 16 for use as a medicament.

26. The use of any of the compounds of the claims 1 to 16 for the manufacture of a medicament for the prevention and/or treatment of broncho-obstructive or inflammatory diseases.

27. The use as in claim 25 wherein the disease is selected from the group consisting of asthma or chronic bronchitis or chronic obstructive pulmonary disease (COPD).

28. The use of the compounds of general formula (XIX)



(XIX)

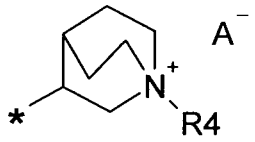
wherein:

R1 and R2 are independently selected from the group consisting of H, (C_1-C_{10})-alkyl, aryl, (C_3-C_8)-cycloalkyl, arylalkyl and heteroaryl, optionally substituted by one or more substituents selected from the group consisting of halogen atoms, OH, oxo (=O), SH, NO_2, CN, $CON(R5)_2$, COOH, NHCOR5, COR5, CO_2R5, CF_3, (C_1-C_{10})-alkoxycarbonyl, (C_1-C_{10})-alkylsulfanyl, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_1-C_{10})-alkyl and (C_1-C_{10})-alkoxyl;

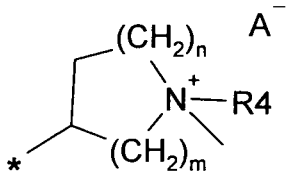
R3 is selected from the group consisting of H, (C_1-C_{10})-alkyl, aryl,

(C_3-C_8)-cycloalkyl, heteroaryl, arylalkyl and heteroarylalkyl, optionally substituted by one or more substituents selected from the group consisting of halogen atoms, OH, oxo (=O), SH, NO_2, CN, $CON(R5)_2$, COOH, CO_2R5, CF_3, (C_1-C_{10})-alkoxycarbonyl, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_1-C_{10})-alkyl and (C_1-C_{10})-alkoxyl;

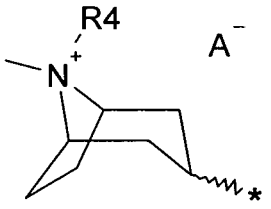
R8 represents a group of formula (i) or (ii) or (iii) or (iv) or (vi) or (vii) or (viii) or (ix)



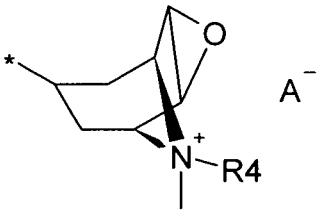
(i)



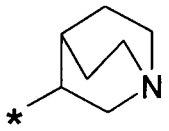
(ii)



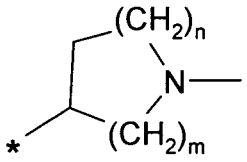
(iii)



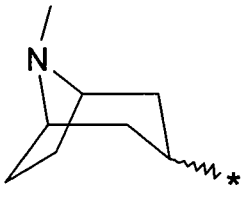
(iv)



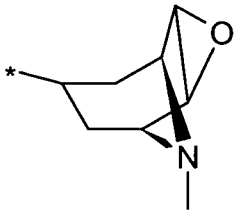
(vi)



(vii)



(viii)



(ix)

wherein

m = 1, 2 or 3;

n =1, 2 or 3;

A^- is a physiologically acceptable anion;

R4 is a group of formula (Y)

$$---(CH_2)p---P---(CH_2)q---W$$

(Y)

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, SO, SO_2, CO, NR5 CH=CH, $N(R5)SO_2$, N(R5)COO, N(R5)C(O), $SO_2N(R5)$, CO(O)N(R5) and C(O)N(R5);

W is selected from

the group consisting of H, (C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyl, aryl and heteroaryl, optionally substituted by one or more substituents selected from the group consisting of halogen atoms, OH, oxo (=O), SH, NO_2, CN, $CON(R5)_2$, COOH, NH_2, NHCOR5, CO_2R5, (C_1-C_{10})-alkoxycarbonyl, (C_1-C_{10})-alkylsulfanyl, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_1-C_{10})-alkyl and (C_1-C_{10})-alkoxyl;

R5 is selected from the group consisting of H, (C_1-C_{10})alkyl, (C_1-C_6)alkylhalo, (C_2-C_6)alkynyl, (C_2-C_6)alkenyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl-(C_1-C_6)alkyl, heteroaryl, (C_1-C_6)alkyl-heteroaryl and aryl optionally substituted by one or more substituents selected from the group consisting of halogen atoms, OH, oxo (=O), SH, NO_2, CN, $CONH_2$, COOH, (C_1-C_{10})-alkoxycarbonyl, (C_1-C_{10})-alkylsulfanyl, (C_1-C_{10})-alkylsulfinyl, (C_1-C_{10})-alkylsulfonyl, (C_1-C_{10})-alkyl and (C_1-C_{10})-alkoxyl

for the preparation 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).

29. A method for prevention and/or treatment of broncho-obstructive or inflammatory diseases, preferably selected from the group consisting of 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 according to claims 1 to 16.

30. A method for prevention and/or treatment of broncho-obstructive or inflammatory diseases, preferably selected from the group consisting of asthma or chronic bronchitis or chronic obstructive pulmonary disease (COPD), which comprises administering to a subject in need thereof a therapeutically effective amount of compound (XIX) as defined in claim 27.

31. A device comprising the pharmaceutical composition of claim 21.

32. The device according to claim 30 which is a single- or multi-dose dry powder inhaler.

33. The device according to claim 31 which is a metered dose inhaler or a soft mist nebulizer.