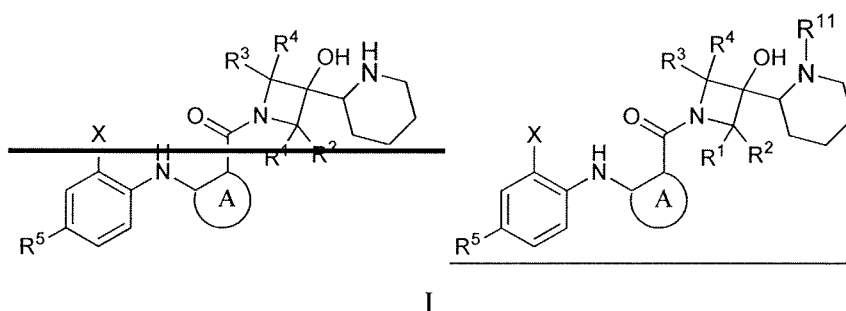


Claims

1. A process for making a compound of formula I:



wherein:

A is arylene or heteroarylene optionally substituted with one, two, three, or four groups selected from R^6 , R^7 , R^8 , and R^9 , each of which are independently selected from hydrogen, halo, (C₁-C₈)alkyl, halo(C₁-C₈)alkyl, hydroxy, (C₁-C₆)alkoxy, and halo(C₁-C₆)alkoxy;

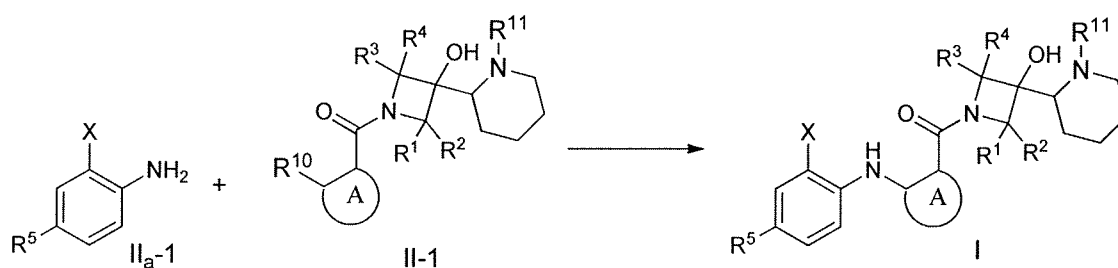
X is alkyl, halo, or halo(C₁-C₈)alkyl, or halo(C₁-C₆)alkoxy;

R^1 , R^2 , R^3 , and R^4 are each independently hydrogen, (C₁-C₈)alkyl, or halo(C₁-C₈)alkyl;

R^5 is hydrogen, halo, or (C₁-C₈)alkyl;

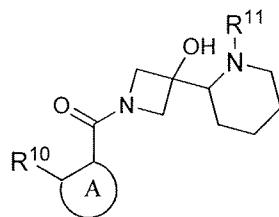
comprising:

contacting a compound of formula II-1 wherein X and R^5 are as defined above with a compound of formula II_a-1 wherein R^{10} is F, Br, Cl, I, or -OSO₂-CF₃ and R^{11} is H or a protecting group to provide a compound of formula I.



2. The process of ~~any one of claims claim~~ 1, wherein X and R^5 in a compound of formula II_a-1 are each independently F, Cl, Br, or I.
3. The process of any one of claims 1 or 2, wherein X is F and R^5 is I.

4. The process of any one of claims 1 to 3 wherein the compound of formula II-1 is the compound of formula II-2:

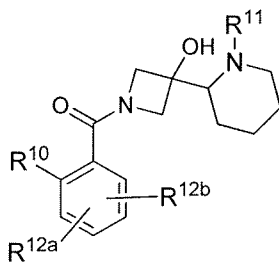


II-2

wherein R^{11} is H or a protecting group and Ring A is optionally substituted with one ~~or two, two,~~ ~~three or four~~ groups selected from R^6 , R^7 , R^8 , and R^9 , each of which are independently selected from hydrogen, halo, (C_1-C_8) alkyl, halo (C_1-C_8) alkyl, (C_1-C_6) alkoxy, and halo (C_1-C_6) alkoxy.

5. The process of ~~any one of claims 1 to 4~~ claim 4, wherein Ring A in the compound of formula II-2 is phenyl or pyridyl.

6. The process of ~~any one of claims 1 to 5~~ claim 5, wherein the compound of formula II-1 is the compound of formula II-3:



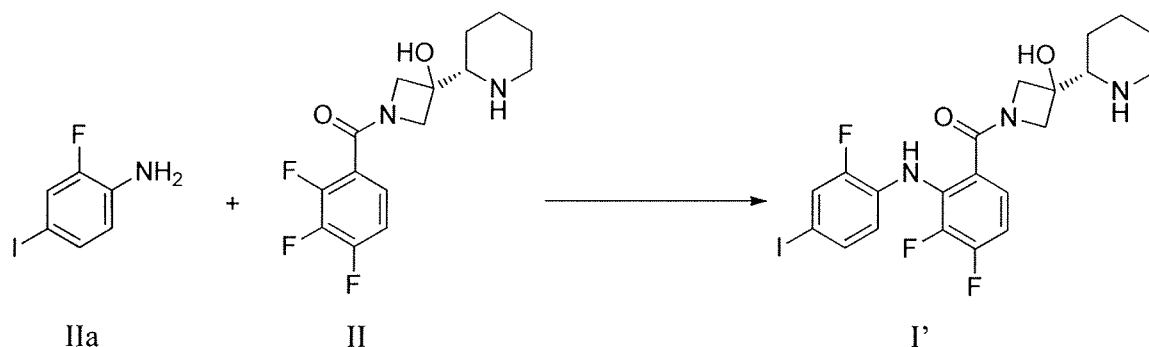
II-3

wherein R^{11} is as defined previously and R^{10} is F, Cl, Br, I, or OSO_2CF_3 , and R^{12a} and R^{12b} are each independently F, Cl, Br, I, alkyl, haloalkyl, alkoxy, or haloalkoxy.

7. The process of claim 6, wherein R^{10} in the compound of formula II-3 is F, Cl, Br, or I, and R^{12a} and R^{12b} are each independently F, Cl, Br, alkyl, haloalkyl, alkoxy, or haloalkoxy.

8. The process of any one of claims 1 to 6, wherein R^{10} in the compound of formula II-3 is F and R^{12a} and R^{12b} are each independently F, Cl, alkyl, or alkoxy.

9. A process according to claim 1 for preparing a compound of formula I', comprising contacting a compound of formula II_a with a compound of formula II.



10. The process of claim 9, further comprising a strong base is selected from the group consisting of butyllithium, t-butyllithium, the lithium, sodium, or potassium salts of mono or bis substituted alkyl or aromatic amines, and silylalkyl or silylaromatic amines.

~~11. The process of claim 10, wherein the strong base is selected from the group consisting of butyllithium, t-butyllithium, the lithium, sodium, or potassium salts of mono or bis substituted alkyl or aromatic amines, and silylalkyl or silylaromatic amines.~~

~~1211. The process of any one of claim 10 ~~claims 10 or 11~~, wherein the strong base is selected from the group consisting of the lithium, sodium, or potassium salts of diisopropyl amine, bis(trimethylsilyl)amine, diethylamine, and dimethylamine.~~

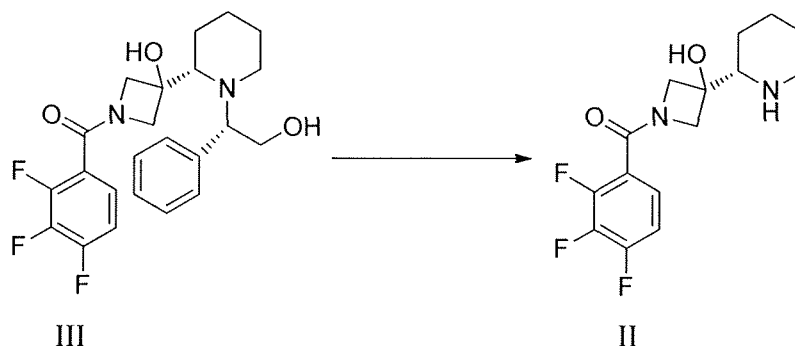
~~1312. The process of claim 11 ~~claim 12~~, wherein the strong base is selected from the group consisting of the lithium, sodium, and potassium salt of bis(trimethylsilyl)amine diisopropylamine, bis(trimethylsilyl)amine, diethylamine; and dimethylamine.~~

~~1413. The process of claim 12 ~~any one of claims 10 to 13~~, wherein the strong base is selected from the group consisting of lithium diisopropylamide, lithium bis(trimethylsilyl)amide, or lithium diethylamide.~~

~~1514. The process of claim 13 ~~any one of claims 10 to 14~~, wherein the strong base is lithium bis(trimethylsilyl)amide.~~

~~1615~~. The process of ~~14~~ any one of claims 10 to 15, wherein the reaction is performed in the presence of a solvent which is tetrahydrofuran.

~~1716~~. A process for preparing a compound of formula II, comprising deprotecting a compound of formula III.



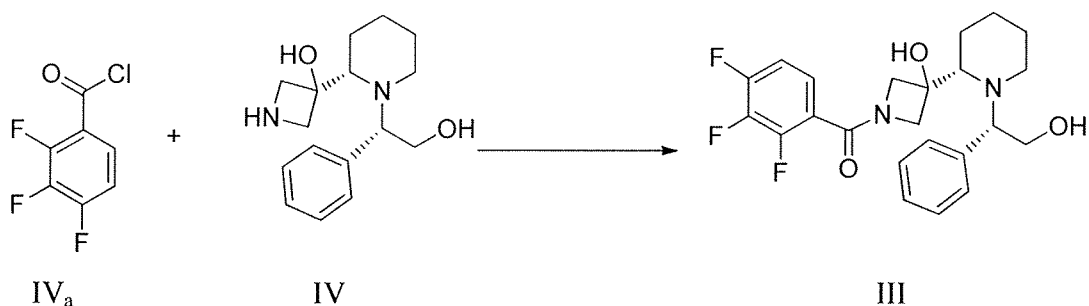
~~1817~~. The process of claim ~~1716~~, wherein deprotection comprises hydrogenation using H₂ in the presence of a heterogeneous transition metal hydrogenation catalyst or treatment with chloroethyl chloroformate in the presence of MeCN or Na/NH₃.

~~1918~~. The process of claim ~~1817~~, wherein the heterogeneous transition metal hydrogenation catalyst is selected from the group consisting of a Raney catalyst, Pd/C, Pd(OH)₂/C, Pd(OAc)₂, Au/TiO₂, Rh/C, Ru/Al₂O₃, Ir/CaCO₃, Pt/C, and Palladium(0) microencapsulated in polyurea matrix as a 45 percent mixture of nanoparticles of palladium approximately 2 nm in size in water, containing 0.4 mmol/g Pd(0) (dry basis), where the unit weight includes the weight of water (~~NP-Pd(0)-Eneat™ 30~~), or a mixture thereof.

~~2019~~. The process of claim ~~18-17~~ in the presence of HCl and acetic acid.

~~2120~~. The process of ~~claims 17~~ any one of claims 17 to 2019, wherein the heterogeneous transition metal hydrogenation catalyst is Pd/C.

~~2221~~. A process for preparing a compound of formula III, comprising contacting a compound of formula IV_a with a compound of formula IV.



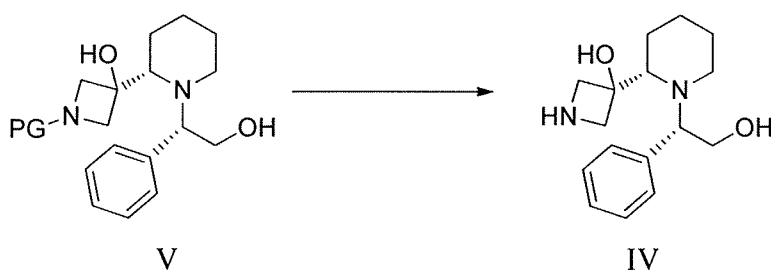
2322. The process of claim ~~22~~ 21 characterized by being performed in the presence of an inorganic base.

2423. The process of claim 22, wherein the inorganic base is an alkali or alkali earth metal hydroxide, phosphate, or carbonate.

2524. The process of claim 22 ~~any one of claims 22 to 24~~, wherein the inorganic base is selected from the group consisting of LiOH, NaOH, KOH, CsOH, NH₄OH, RbOH, Mg(OH)₂, Ca(OH)₂, Ba(OH)₂, Li₂CO₃, Na₂CO₃, K₂CO₃, Cs₂CO₃, (NH₄)₂CO₃, and K₃PO₄.

2625. The process of any one of claims ~~22~~ 22 to 2524, wherein the inorganic base is K₃PO₄, K₂CO₃, or KOH.

2726. A process for preparing a compound of formula IV, comprising deprotecting a compound of formula V:

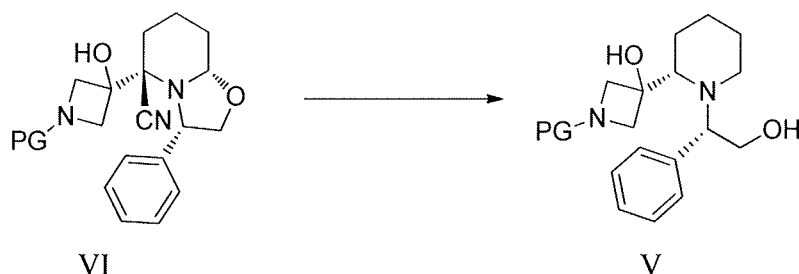


wherein PG is an amino protecting group.

2827. The process of claim 2726, wherein the protecting group is an FMoc, CBz, or BOC protecting group.

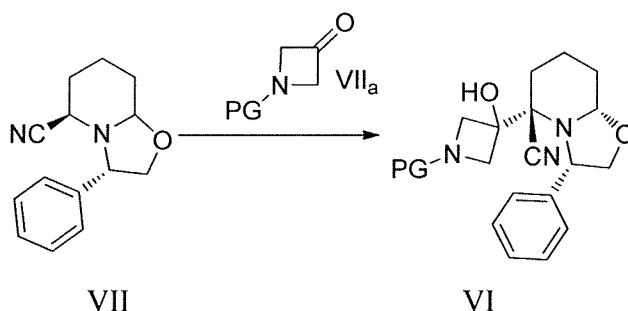
2928. The process of any one of claims 26 to claim 26 or 2827, wherein the protecting group is a BOC protecting group.

3029. A process for preparing a compound of formula V wherein PG is an amino protecting group, comprising reducing a compound of formula VI.



3130. A process according to claim 3029, in the presence of a reducing agent, in particular wherein the reducing agent is selected from the group consisting of borohydrides.

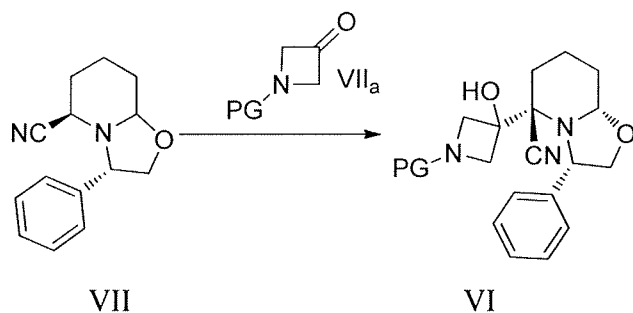
3231. A process for preparing a compound of formula VI comprising reacting a compound of formula VII with a compound of formula VII_a in the presence of base:



wherein PG is an amino protecting group.

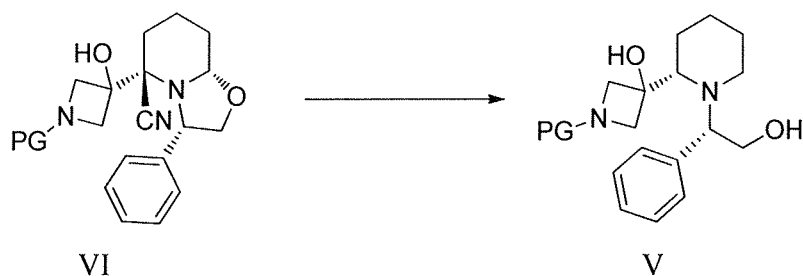
3332. A process for preparing a compound of formula V, comprising:

1) reacting a compound of formula VII with a compound of formula VII_a to provide a compound of formula VI;



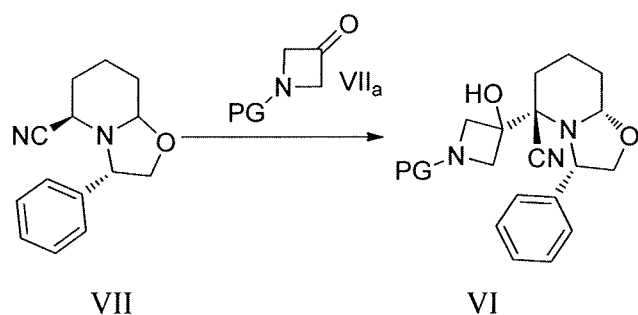
and

2) reducing a compound of formula VI with a reducing agent selected from the group consisting of borohydrides to provide a compound of formula V.

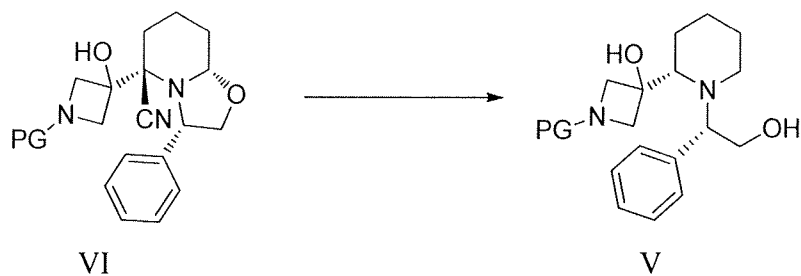


3433. A process for the preparation of the compound of formula IV, comprising:

1) reacting a compound of formula VII with a compound of formula VII_a to provide a compound of formula VI;

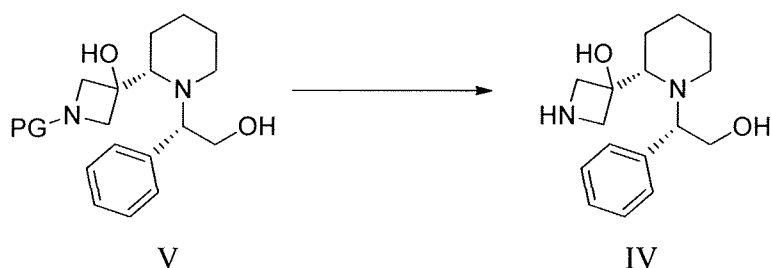


2) reducing a compound of formula VI with a reducing agent selected from the group consisting of borohydrides to provide a compound of formula V;



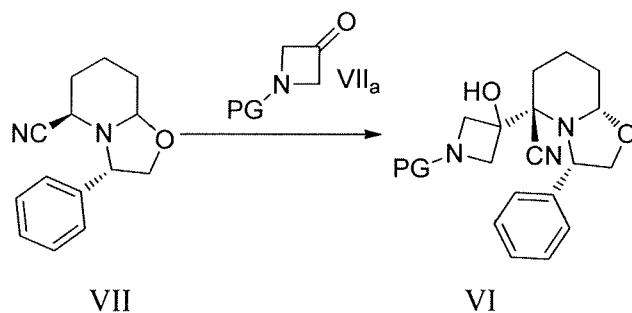
and

3) deprotecting the azetidiny ring of a compound of formula V to provide a compound of formula IV.

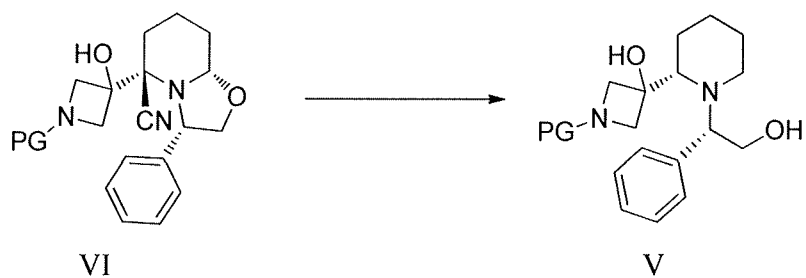


3534. A process for the preparation of the compound of formula III, comprising:

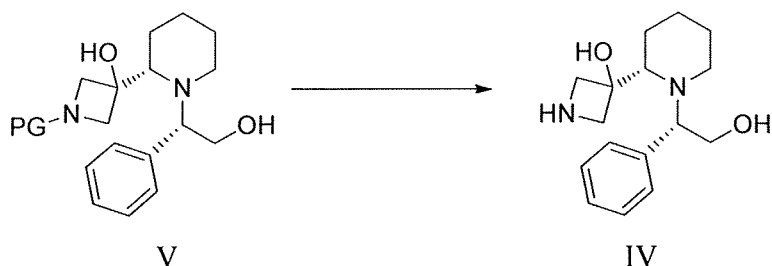
1) reacting a compound of formula VII with a compound of formula VII_a to provide a compound of formula VI;



2) reducing a compound of formula VI with a reducing agent selected from the group consisting of borohydrides to provide a compound of formula V;

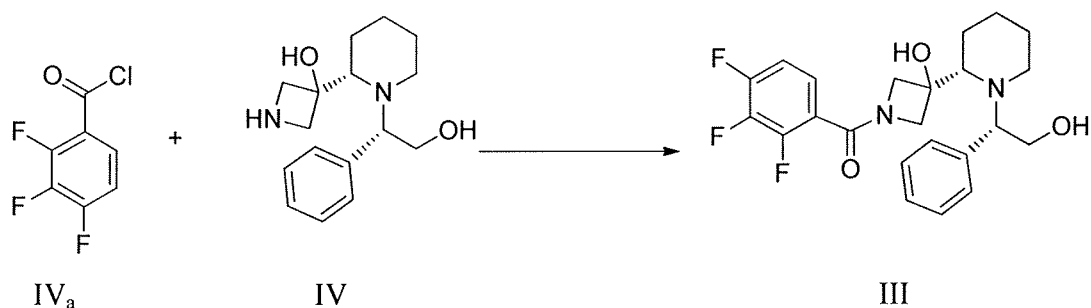


3) deprotecting the azetidinyl ring of a compound of formula V to provide a compound of formula IV;



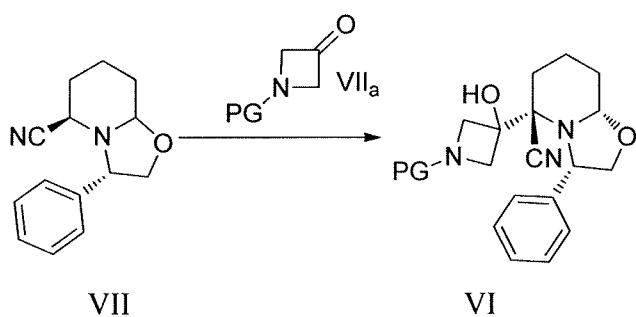
and

4) reacting a compound of formula IV with a compound of formula IV_a to provide a compound of formula III.

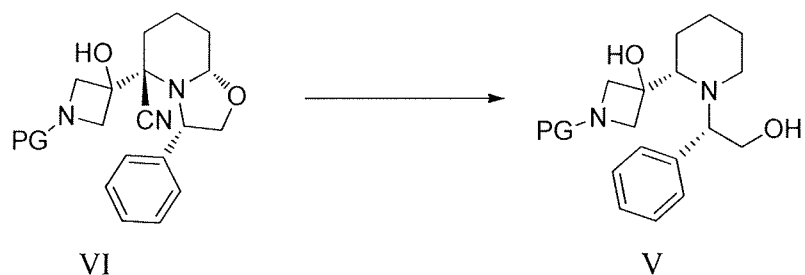


3635. A process for the preparation of the compound of formula II, comprising:

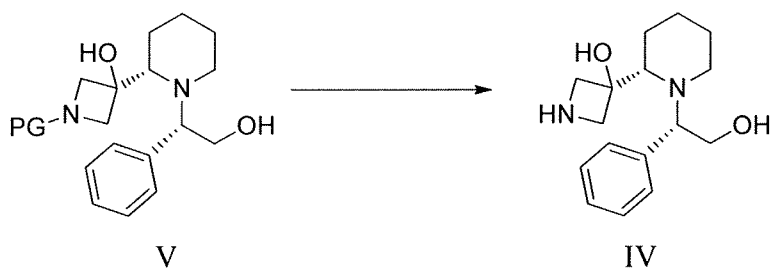
1) reacting a compound of formula VII with a compound of formula VII_a to provide a compound of formula VI;



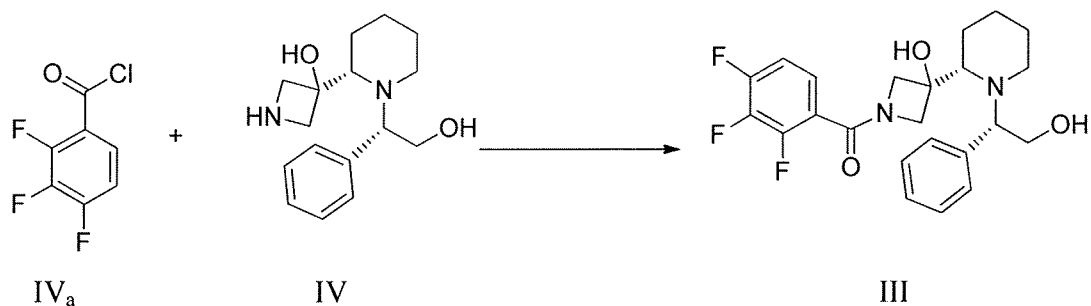
2) reducing a compound of formula VI with a reducing agent selected from the group consisting of borohydrides to provide a compound of formula V;



3) deprotecting the azetidiny ring of a compound of formula V to provide a compound of formula IV;

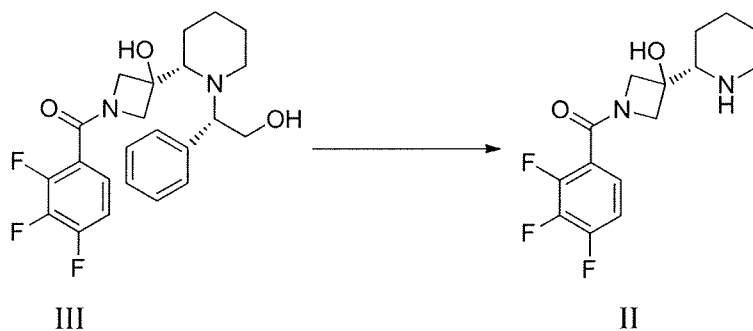


4) reacting a compound of formula IV with a compound of formula IV_a to provide a compound of formula III;



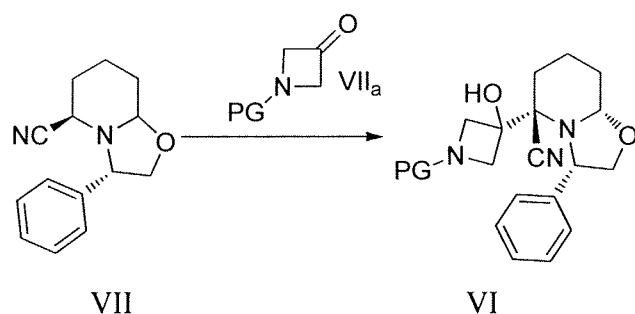
and

5) hydrogenation of a compound of formula III to provide a compound of formula II.

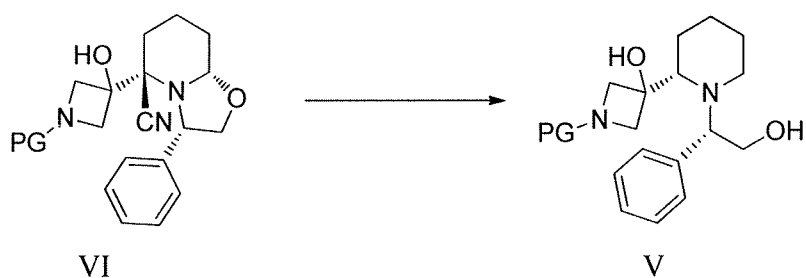


3736. A process for the preparation of the compound of formula I', comprising:

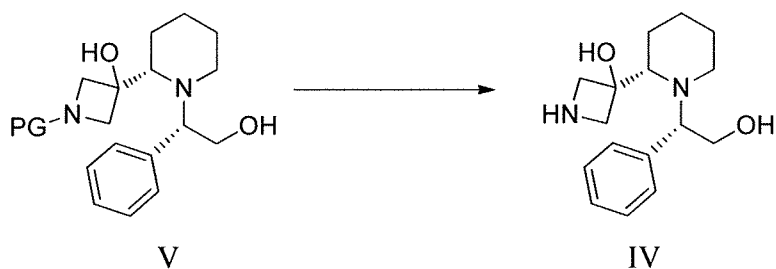
1) reacting a compound of formula VII with a compound of formula VII_a to provide a compound of formula VI;



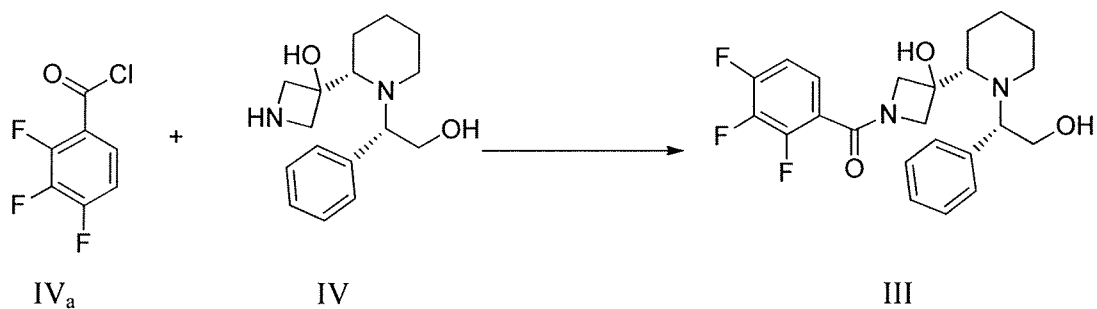
2) reducing a compound of formula VI with a reducing agent selected from the group consisting of borohydrides to provide a compound of formula V;



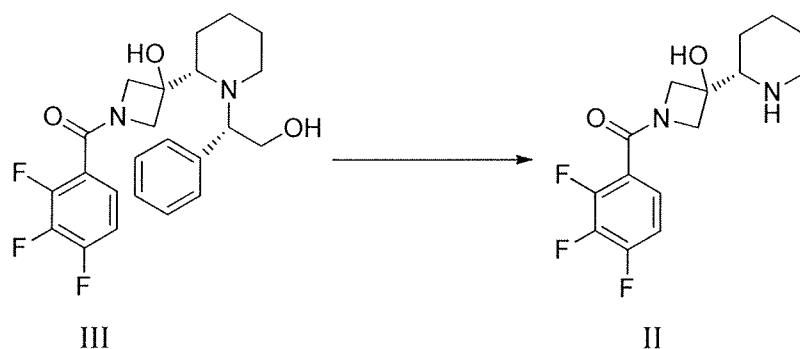
3) deprotecting the azetidinyl ring of a compound of formula V to provide a compound of formula IV;



4) reacting a compound of formula IV with a compound of formula IV_a to provide a compound of formula III;

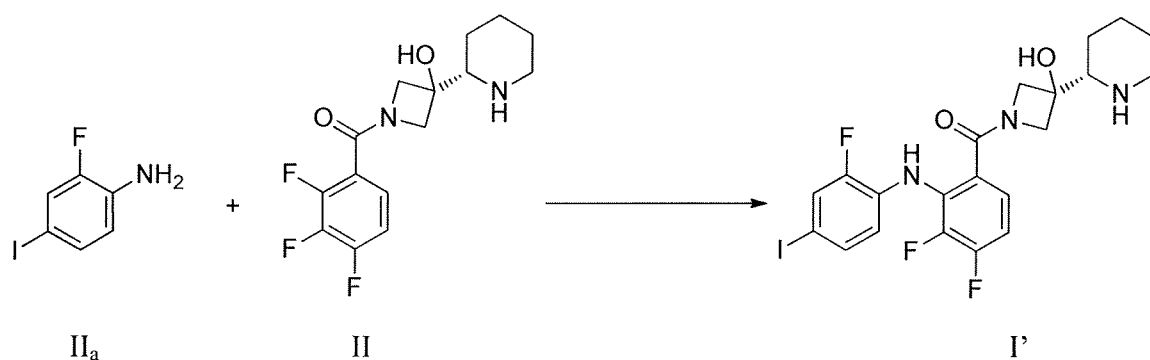


5) hydrogenation of a compound of formula III to provide a compound of formula II;



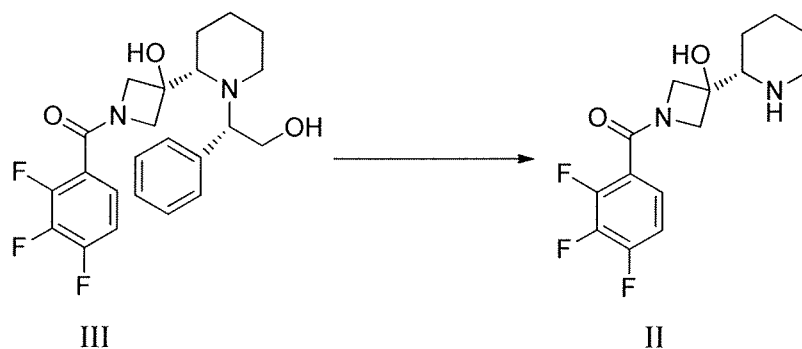
and

6) reacting a compound of formula II with a compound of formula II_a to provide a compound of formula I'.



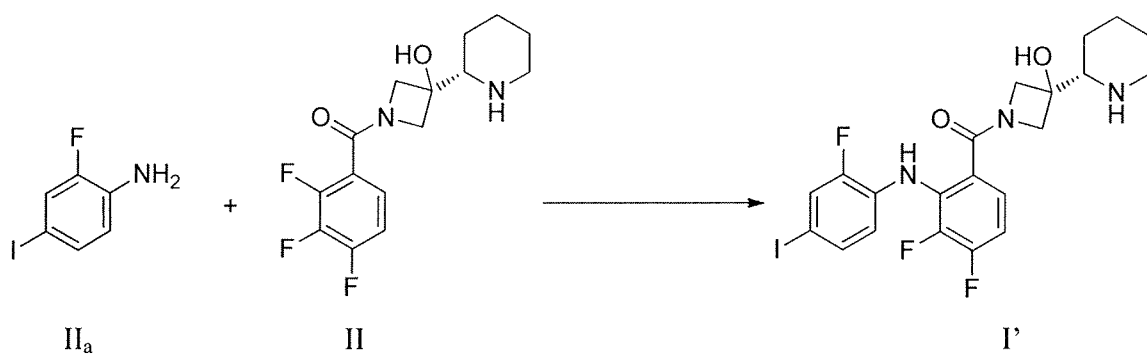
3837. A process for the preparation of the compound of formula I', comprising:

a) hydrogenation of a compound of formula III to provide a compound of formula II;



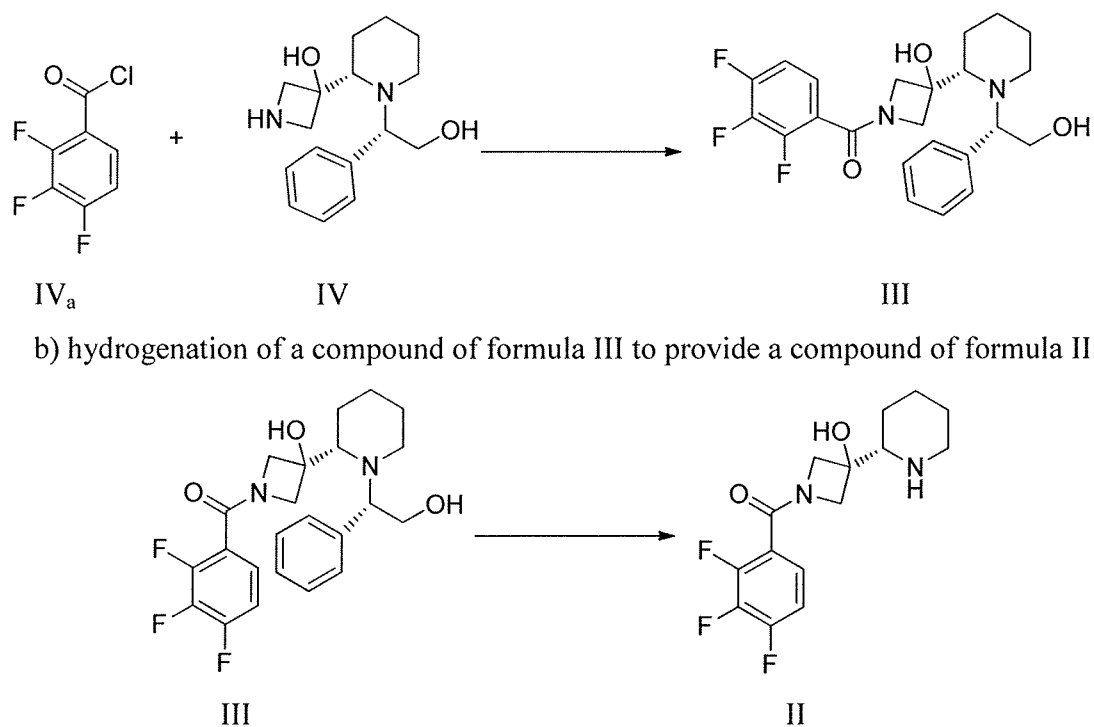
and

b) reacting a compound of formula II with a compound of formula II_a to provide a compound of formula I'.



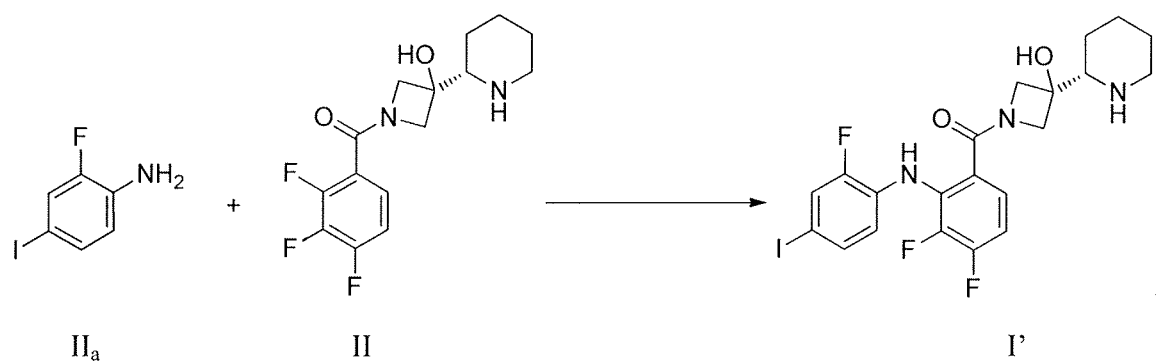
3938. A process for the preparation of the compound of formula I', comprising:

a) reacting a compound of formula IV with a compound of formula IV_a to provide a compound of formula III;



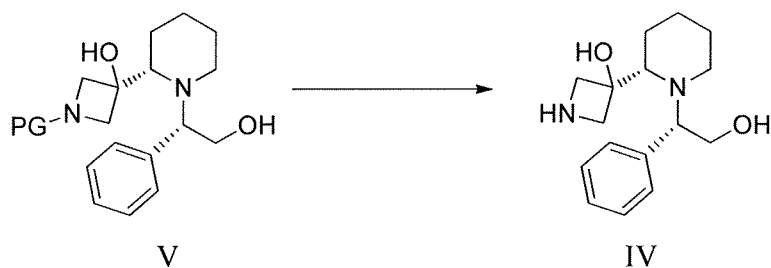
and

c) reacting a compound of formula II with a compound of formula II_a to provide a compound of formula I'.

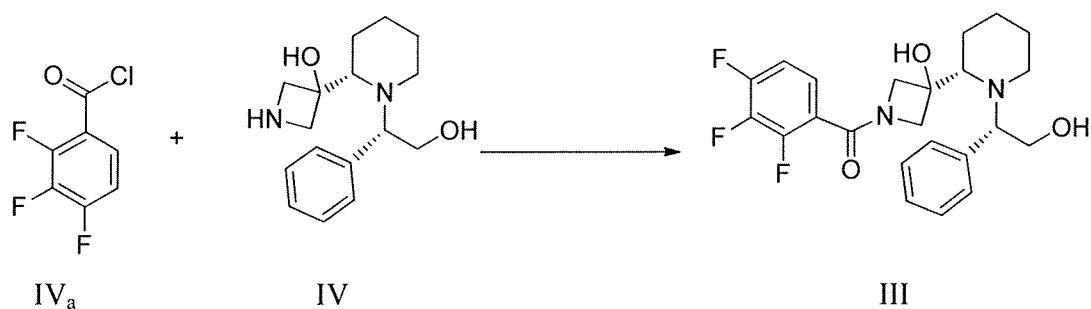


4039. A process for the preparation of the compound of formula I', comprising:

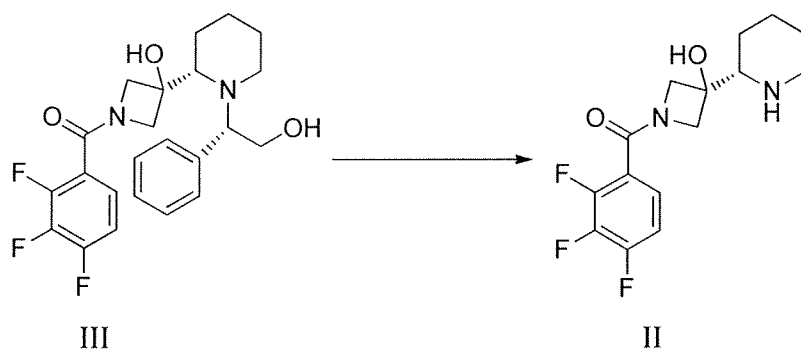
a) deprotecting the azetidiny ring of a compound of formula V to provide a compound of formula IV;



b) reacting a compound of formula IV with a compound of formula IV_a to provide a compound of formula III;

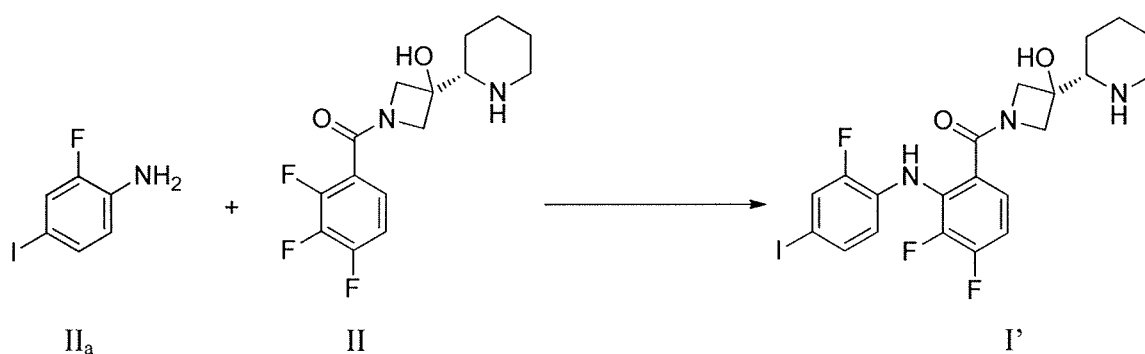


c) hydrogenation of a compound of formula III to provide a compound of formula II;



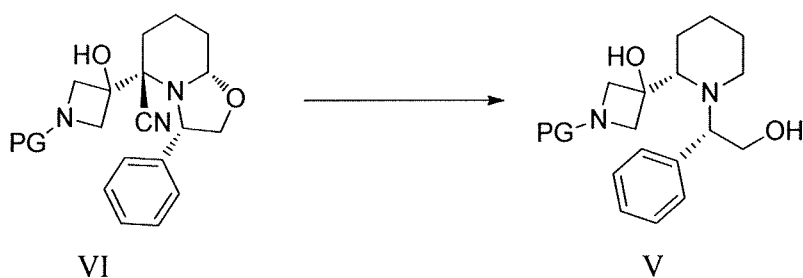
and

d) reacting a compound of formula II with a compound of formula II_a to provide a compound of formula I'.

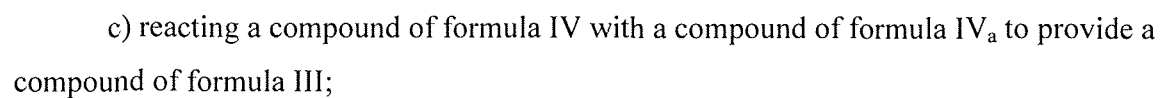
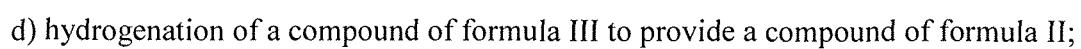


4140. A process for the preparation of the compound of formula I', comprising:

a) reducing a compound of formula VI with a reducing agent selected from the group consisting of borohydrides to provide a compound of formula V;



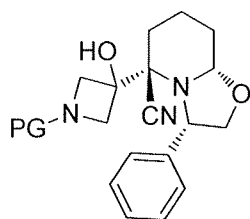
b) deprotecting the azetidiny ring of a compound of formula V to provide a compound of formula IV



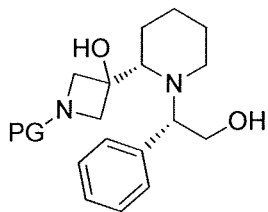
e) reacting a compound of formula II with a compound of formula II_a to provide a compound of formula I'.



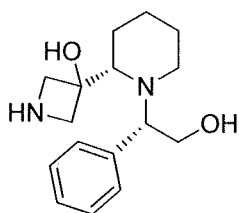
4241. A compound which is:



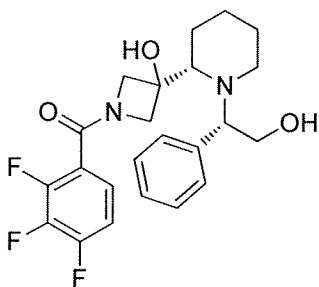
(VI), wherein PG is a protecting group;



(V), wherein PG is an amino protecting group;

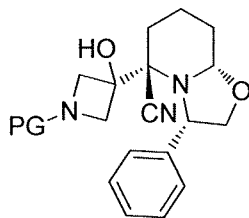


(IV); or



(III).

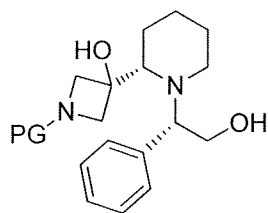
4342. The compound of claim 42-41 which is a compound of formula ~~V~~-VI:



~~V~~-VI

wherein PG is an amino protecting group.

4443. The compound of claim 37-41 which is a compound of formula ~~VI~~-V:

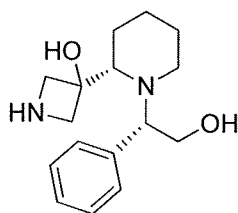


VI-V

wherein PG is an amino protecting group.

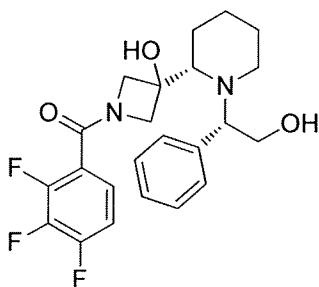
4544. The compounds of claims 43-42 or 44-43, wherein the amino protecting group is BOC.

4645. The compound of claim 41, characterized by having formula IV A compound of formula IV.



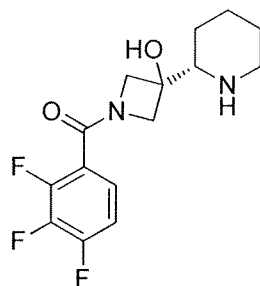
IV

4746. The compound of claim 41, characterized by having formula III A compound of formula III.



III

4847. A compound of formula II.



II

48. The process of claim 1, further comprising deprotection when R^{11} is a protecting group, to yield a compound of formula I, wherein R^{11} is H.