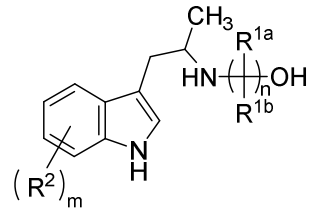
CLAIMS

1. A process for the preparation of a compound of formula (II):



(II)

or a stereoisomer or salt thereof

each of R^{1a} and R^{1b} is independently hydrogen, halogen, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, -CN, unsubstituted C_{3-6} cycloalkyl, or unsubstituted C_{3-6} spirocycloalkyl;

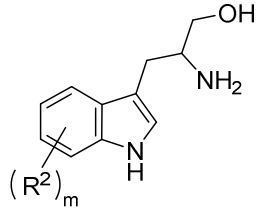
each R^2 is independently halogen, hydroxyl, -CN, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or unsubstituted C_{1-3} alkoxy;

m is 0, 1 or 2; and

n is 1, 2, or 3;

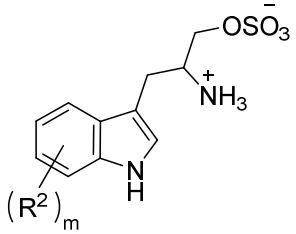
the process comprising:

(a) contacting a compound of formula (III),



(III)

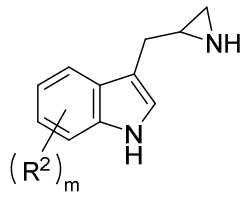
or a stereoisomer or salt thereof with a sulfonic acid to form a compound of formula (IIIa);



(IIIa)

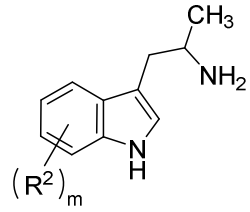
or a stereoisomer or salt thereof

(b) contacting the compound of formula (IIIa) or a stereoisomer or salt thereof with a base to form compound of formula (IV);


(IV)

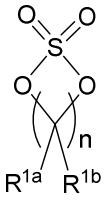
or a stereoisomer or salt thereof

(c) hydrogenating the compound of formula (IV) or a stereoisomer or salt thereof to form a compound of formula (V); and


(V)

or a stereoisomer or salt thereof

(d) contacting the compound of formula (V) or a stereoisomer or salt thereof with a compound of formula (VI);


(VI)

thereby forming a compound of formula (II) or a stereoisomer or salt thereof.

2. The process of claim 1, wherein the compound of formula (III) is a compound of formula (III*).

3. The process of claim 2, wherein the compound of formula (III*) is a compound of formula (3*), (3x*), (3y*), or (3z*).

4. The process of claim 2, wherein the compound of formula (III*) is a compound of formula (3*).

5. The process of any one of claims 1-4, wherein the sulfonic acid is H_2SO_4 or $ClSO_3H$.

6. The process of any one of claims 1-5, wherein the base is a hydroxide base.

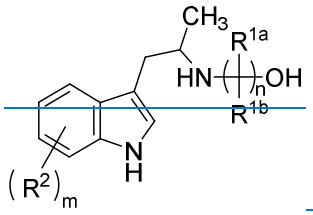
7. The process of claim 6, wherein the base is KOH, NaOH, or LiOH.

8. The process of any one of claims 1-7, wherein the hydrogenation is performed using a catalyst comprising Pd, Pt, or Ni.

9. The process of claim 8, wherein the catalyst is Pd/C, Pt/C, or Raney Ni.

10. The process of any one of claims 1-9, wherein the hydrogenation is performed using catalytic transfer hydrogenation in the presence of isopropanol, formic acid, formate, or ammonium.

~~**11.** A process for the preparation of a compound of formula (II):~~



~~(II)~~

~~or a stereoisomer or salt thereof~~

~~each of R^{1a} and R^{1b} is independently hydrogen, halogen, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, -CN, unsubstituted C_{3-6} cycloalkyl, or unsubstituted C_{3-6} spirocycloalkyl;~~

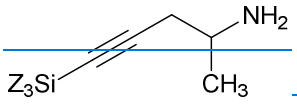
~~each R^2 is independently halogen, hydroxyl, -CN, C_{1-3} alkyl, or C_{1-3} haloalkyl, C_{1-3} alkoxy;~~

~~m is 0, 1 or 2; and~~

~~n is 1, 2 or 3;~~

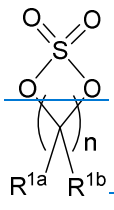
~~the process comprising:~~

~~**(a)** contacting a compound of formula (VII),~~



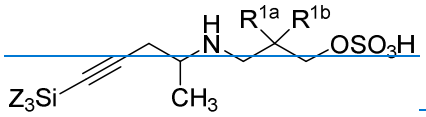
~~(VII)~~

~~or a stereoisomer or salt thereof wherein each Z is independently C_{1-3} alkyl or phenyl, with a compound of formula (VI),~~



~~(VI)~~

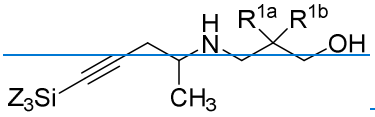
~~wherein R^{1a} and R^{1b} are as described herein, thereby synthesizing a compound of formula (VIIa);~~



(VIIa)

or a stereoisomer or salt thereof

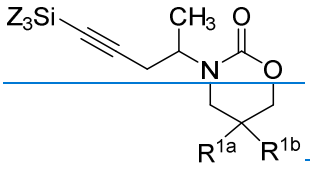
(b) contacting a compound of formula (VIIa) or a stereoisomer or salt thereof with an acid thereby synthesizing a compound of formula (VIIb);



(VIIb)

or a stereoisomer or salt thereof

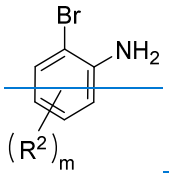
(c) contacting the compound of formula (VIIb) or a stereoisomer or salt thereof with 1,1'-carbonyldiimidazole thereby synthesizing a compound of formula (VIIc);



(VIIc)

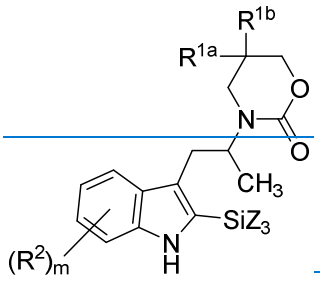
or a stereoisomer or salt thereof

(d) contacting the compound of formula (VIIc) or a stereoisomer or salt thereof with a compound of formula (VIII)



(VIII)

or a salt thereof to make a compound of formula (Va); and

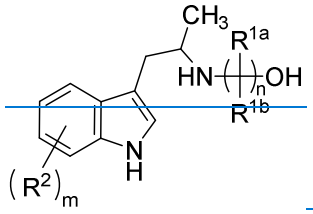


(Va)

or a stereoisomer or salt thereof

(e) contacting the compound of formula (Va) or stereoisomer or salt thereof with a base followed by an acid thereby making the compound of formula (II) or a stereoisomer or salt thereof.

12. A process for the preparation of a compound of formula (II):



(II)

or a stereoisomer or salt thereof

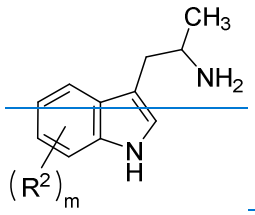
each of R^{1a} and R^{1b} is independently hydrogen, halogen, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, -CN, unsubstituted C_{3-6} cycloalkyl, or unsubstituted C_{3-6} spirocycloalkyl;

each R^2 is independently halogen, hydroxyl, -CN, C_{1-3} alkyl, or C_{1-3} haloalkyl, C_{1-3} alkoxy;

m is 0, 1 or 2; and

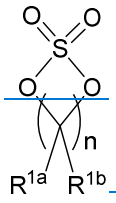
n is 1, 2 or 3;

the process comprising contacting a compound of formula (V),



(V)

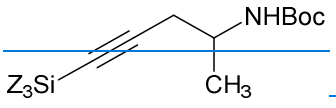
or a stereoisomer or salt thereof with a compound of formula (VI),



(VI)

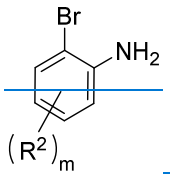
wherein the compound of formula (V) is prepared by:

(a) contacting a compound of formula (VIIp)



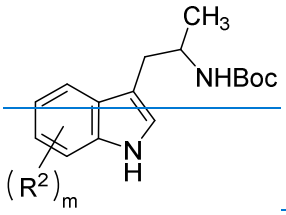
(VIIp)

or a stereoisomer or salt thereof wherein each Z is independently C_{1-3} alkyl or phenyl, with a compound of formula (VIII),



(VIII)

or a salt thereof to make a compound of formula (Vb); and



(Vb)

or a stereoisomer or salt thereof

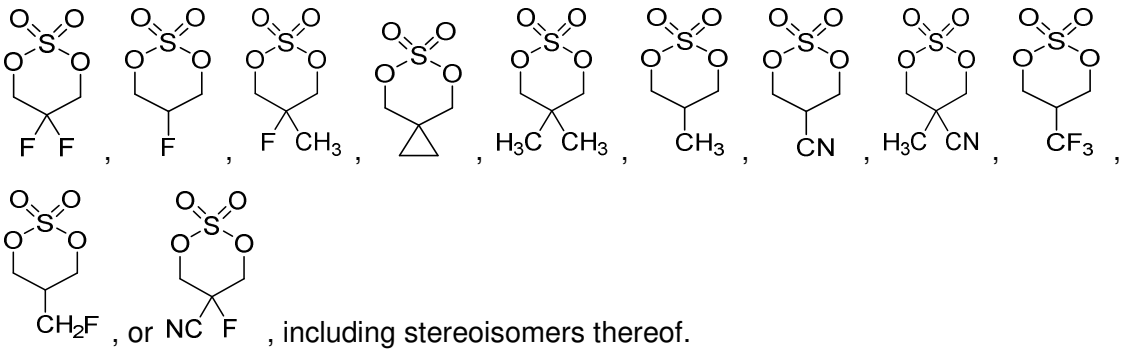
(b) contacting the compound of formula (Vb) with an acid thereby making the compound of formula (V).

13. The process of claim 11 or 12, wherein each Z is independently C_{1-4} alkyl.

14. The process of claim 11 or 12, wherein each Z is methyl, each Z is ethyl, each Z is isopropyl or wherein SiZ_3 is $Si(PhMe_2)$ or $Si(t\text{-}BuMe_2)$.

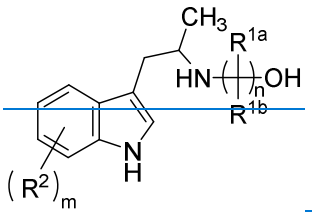
15. The process of claim 11 or 12, wherein each Z is ethyl.

16.11. The process of any one of claims 1-1510, wherein the compound of formula (VI) is:



, including stereoisomers thereof.

17. A process for the preparation of a compound of formula:



(II)

or a stereoisomer or salt thereof

each of R^{1a} and R^{1b} is independently hydrogen, halogen, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, -CN, unsubstituted C_{3-6} cycloalkyl, or unsubstituted C_{3-6} spirocycloalkyl;

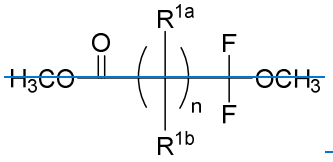
each R^2 is independently halogen, hydroxyl, -CN, C_{1-3} alkyl, or C_{1-3} haloalkyl, C_{1-3} alkoxy;

m is 0, 1 or 2;

n is 1, 2 or 3;

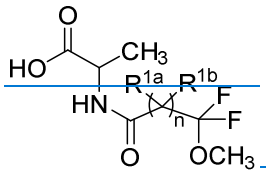
the process comprising

(a) contacting alanine with a compound of formula (IX),



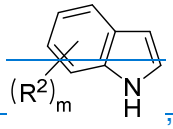
(IX)

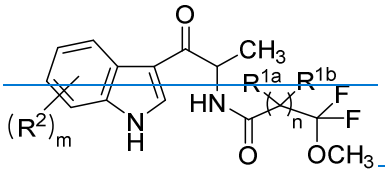
or a stereoisomer or salt thereof to form a compound of formula (XI);



(XI)

or a stereoisomer or salt thereof

(b) contacting the compound of formula (VIII) with a chlorinating agent, a compound of formula  , and an organoaluminum compound to form a compound of formula (Vc); and



(Vc)

or a stereoisomer or salt thereof

~~**(c)** contacting the compound of formula (Vc) or a stereoisomer or salt thereof with a reducing agent thereby forming a compound of formula (II) or a stereoisomer or salt thereof.~~

~~**18.** The process of claim 17, wherein the organoaluminum compound has the formula X_3Al, where X is independently Cl or C_{1-4} alkyl.~~

~~**19.** The process of claim 17, wherein X is independently methyl, ethyl, n-propyl, isopropyl, n-butyl, or isobutyl.~~

~~**20.** The process of any one of claims 17-19, wherein the organoaluminum compound is trimethyl aluminum, triethyl aluminum, triisobutyl aluminum, dimethyl aluminum chloride, diethyl aluminum chloride, or ethyl aluminum dichloride.~~

~~**21.** The process of any one of claims 17-20, wherein the organoaluminum compound is trimethyl aluminum.~~

~~**22.** The process of any one of claims 17-21, wherein the reducing agent is sodium aluminum hydride.~~

~~**23.** The process of any one of claims 17-22, wherein the chlorinating agent is SOCl2, methyl chloroformate, ethyl chloroformate, isobutyl chloroformate, pivaloyl chloride, or oxalyl chloride.~~

~~**24.** The process of claim 23, wherein the chlorinating agent is oxalyl chloride.~~

~~**25.** The process of claim 24, wherein the chlorinating agent is in the presence of N-formyl pyrrolidine or N,N-dimethylformamide.~~

~~**26.**__12.__ The process of any one of claims 1-~~25~~__10__, wherein R^{1a} and R^{1b} are independently hydrogen, halogen, cyano, unsubstituted C_{1-3} alkyl, or cyclopropyl.

~~**27.**__13.__ The process of any one of claims 1-~~25~~__10__, wherein R^{1a} and R^{1b} are independently hydrogen, halogen, or methyl.

~~**28.**__14.__ The process of any one of claims 1-~~25~~__10__, wherein R^{1a} is hydrogen and R^{1b} is halogen, methyl, cyano, or cyclopropyl.

~~**29.**__15.__ The process of any one of claims 1-~~25~~__10__, wherein R^{1a} is hydrogen and R^{1b} is halogen.

~~30.~~16. The process of any one of claims 1-~~25~~10, wherein R^{1a} is hydrogen and R^{1b} is methyl.

~~31.~~17. The process of any one of claims 1-~~25~~10, wherein R^{1a} is methyl and R^{1b} is halogen, methyl, cyano, or cyclopropyl.

~~32.~~18. The process of any one of claims 1-~~25~~10, wherein R^{1a} is halogen and R^{1b} is halogen, methyl, cyano, or cyclopropyl.

~~33.~~19. The process of any one of claims 1-~~25~~10, wherein R^{1a} and R^{1b} are independently halogen, or methyl.

~~34.~~20. The process of any one of claims 1-~~25~~10, wherein R^{1a} is halogen and R^{1b} is methyl.

~~35.~~21. The process of any one of claims 1-~~25~~10, wherein R^{1a} is halogen and R^{1b} is halogen.

~~36.~~22. The process of any one of claims 1-~~25~~10, wherein R^{1a} and R^{1b} are F.

~~37.~~23. The process of any one of claims 1-~~36~~10, wherein each R^2 is independently hydrogen, halogen, hydroxyl, -CN, or C_{1-3} alkyl.

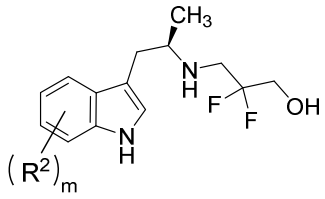
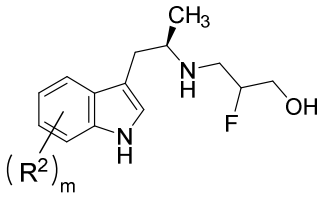
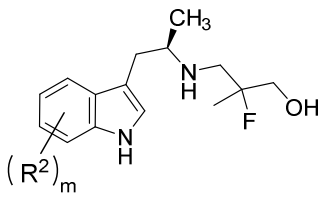
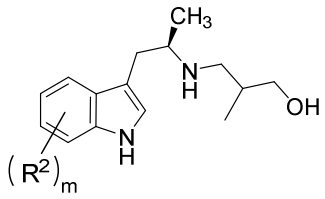
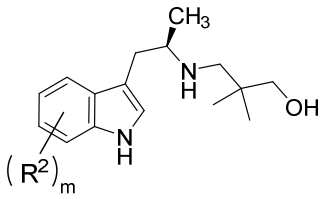
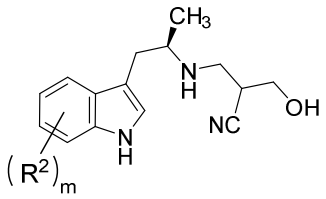
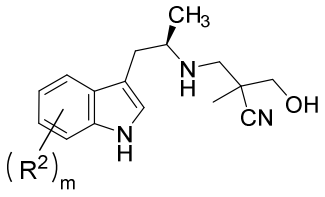
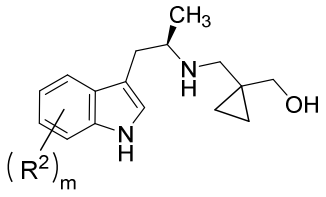
~~38.~~24. The process of any one of claims 1-~~37~~10 or 12-23, wherein m is 0.

~~39.~~25. The process of any one of claims 1-~~37~~10 or 12-23, wherein m is 1.

~~40.~~26. The process of any one of claims 1-~~37~~10 or 12-23, wherein R^2 is halogen or C_{1-3} alkyl and m is 1.

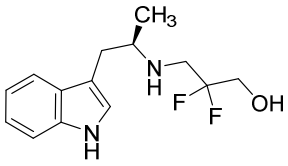
~~41.~~27. The process of any one of claims 1-~~37~~10 or 12-23, wherein R^2 is halogen and m is 1.

~~42.~~28. The process of any one of claims 1-~~41~~10 or 12-23, wherein the compound of formula (II) is:

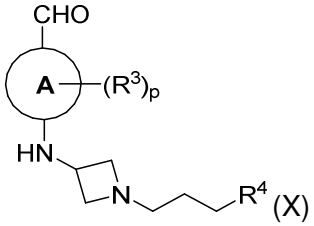
or a stereoisomer or salt thereof.

~~43.~~29. The process of any one of claims 1-~~38~~10, wherein the compound of formula (II) is:


(2)

or a salt thereof.

~~44.~~30. The process of any one of claims 1-~~43~~10 or 12-29, wherein the compound of formula (II) is contacted with a compound having formula (X):


(X)

or a stereoisomer or salt thereof

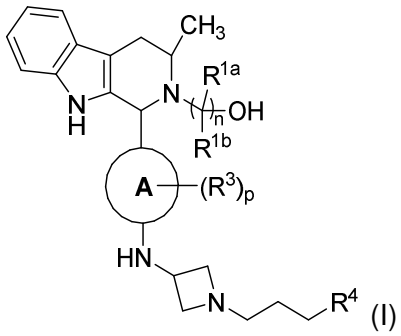
ring A is phenyl or pyridinyl;

each R^3 is independently hydrogen, halogen, or C_{1-3} alkyl,

R^4 is halogen or -CN; and

p is 1 or 2;

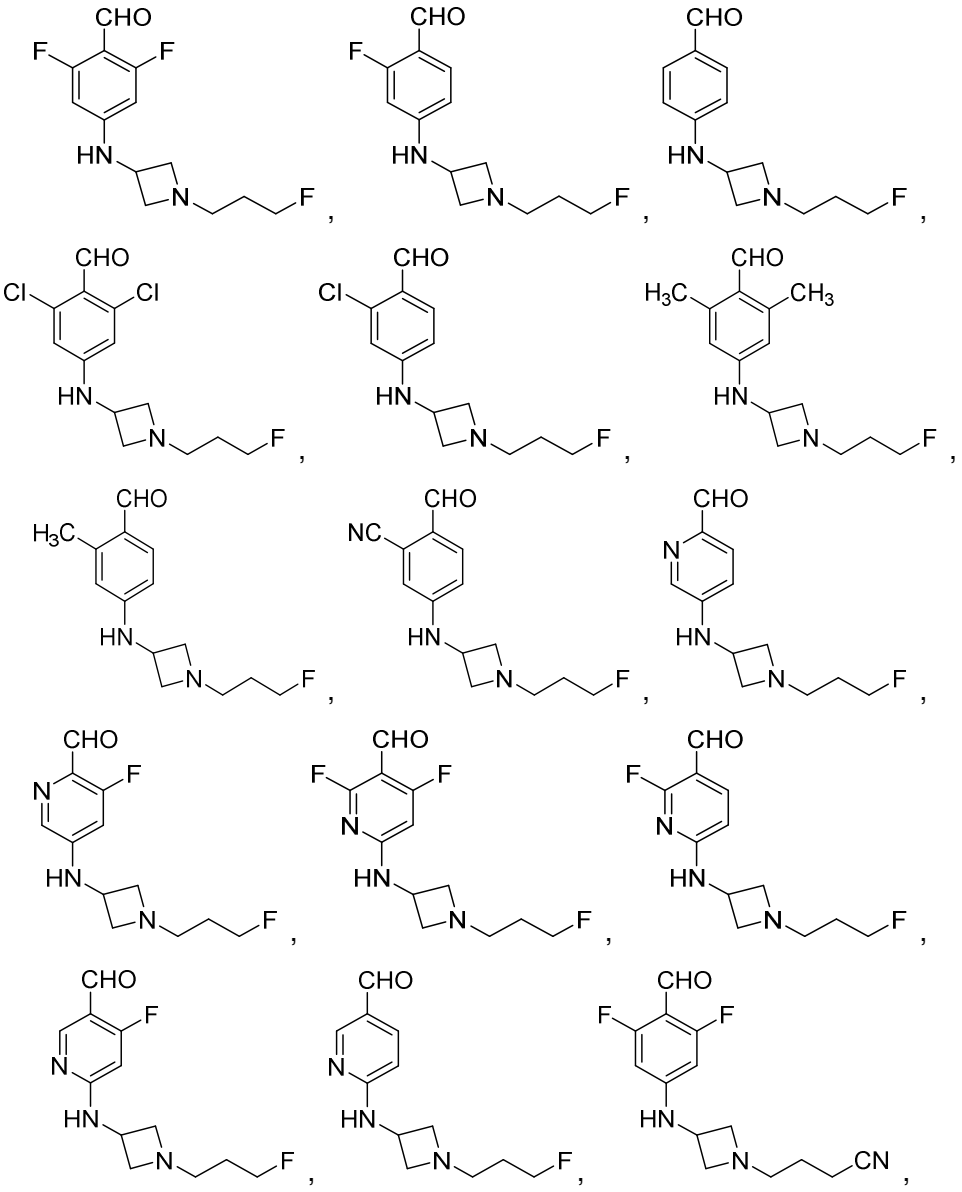
to form a compound of formula (I):

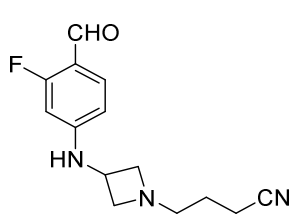
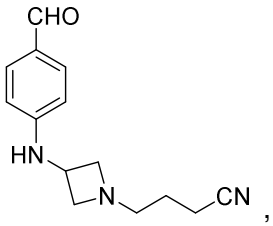
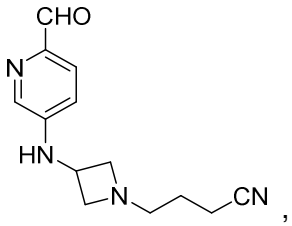
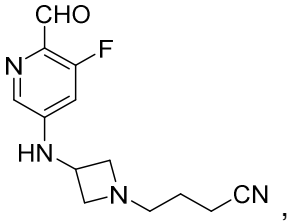
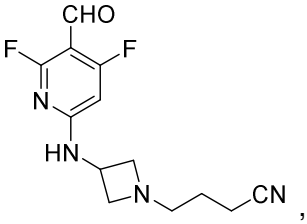
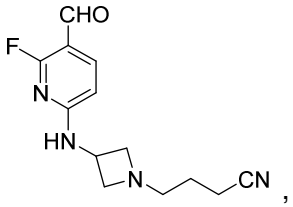
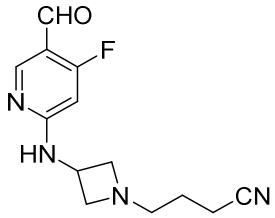
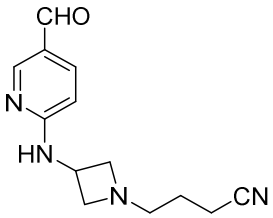


(I)

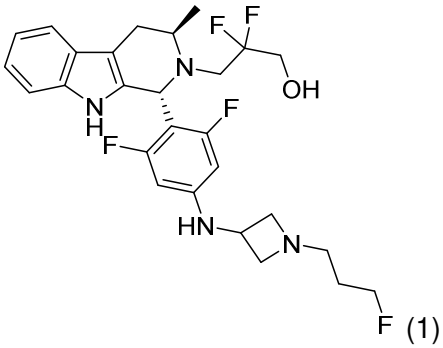
or a stereoisomer or pharmaceutically acceptable salt thereof.

~~45.~~31. The process of claim ~~44~~30, wherein the compound of formula (X) is:



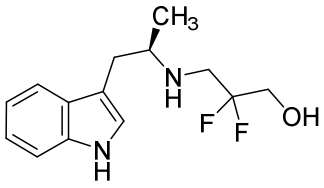







, or

, or a salt thereof.

~~46.~~32. A process for the synthesis of a compound having the formula (1), the process comprising:


(1)

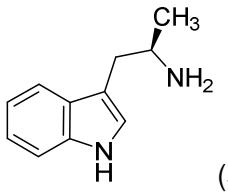
or a pharmaceutically acceptable salt thereof.

(a) contacting a compound of formula (2)

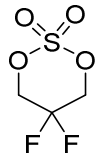

(2)

or a salt thereof

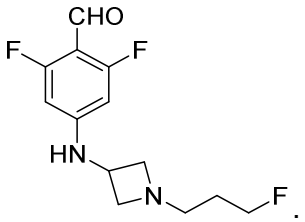
wherein the compound of formula (2) is synthesized according to the process of claim 1~~, 11, or 12~~ and wherein the compound of formula (V) has formula (5)


(5)

or a salt thereof and the compound of formula (VI) has formula (6):

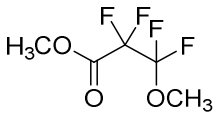
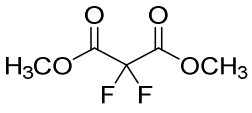

(6)

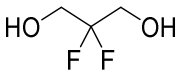
(b) with a compound of formula (10)

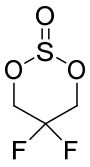

.

or a salt thereof thereby making a compound of formula (1) or a pharmaceutically acceptable salt thereof.

~~47.~~**33.** The process of claim ~~46~~32, wherein the compound of formula (6) is prepared by:

(a) contacting a compound of formula (12a)  (12a) with H_2SO_4 to make a compound of formula  (12b);

(b) reducing the compound of formula (12b) to make a compound of formula  (12c);

(c) cyclizing the compound of formula (12c) in the presence of $SOCl_2$ to make the compound of formula  (12d); and

(d) contacting the compound of formula (12d) with $FeCl_3$, NaOCl and a base, thereby making the compound of formula (6).