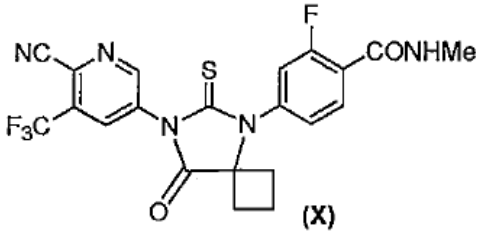
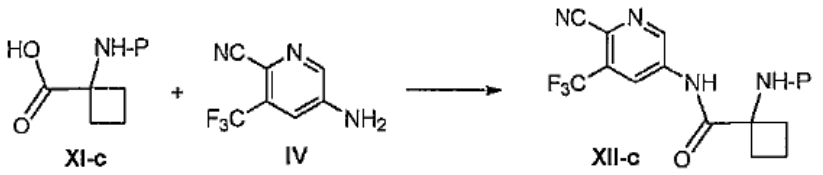
Claims

1. A process for the preparation of compound (X)



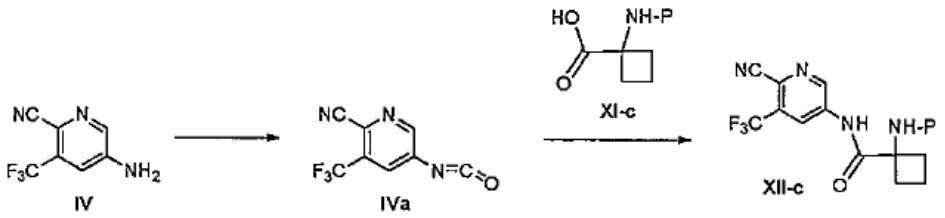
(X)

comprising



XI-c IV XII-c (2a)

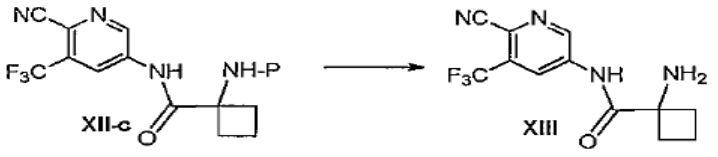
reacting a compound of formula (XI-c), wherein P is an amino protecting group, with compound (IV) under amide-bond formation conditions; in the presence of an amide coupling reagent; and in the presence of a catalyst; in an organic solvent; at a temperature in the range of from about 0 °C to about 50 °C; to yield the corresponding compound of formula (XII-c); or,



IV IVa XI-c XII-c

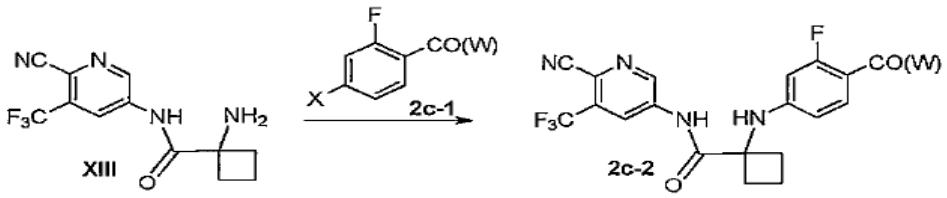
5-isocyanato-3-(trifluoromethyl)picolinonitrile (2a-1)

reacting compound (IV) with phosgene or a phosgene analog; in the presence of an organic base; in an aprotic solvent; then treating a resulting isocyanate intermediate (IVa), optionally without isolation, with a compound of formula (XI-c); in the presence of a non-nucleophilic base; at a temperature in the range of from about -20 °C to about 80 °C; to yield the corresponding compound of formula (XII-c);



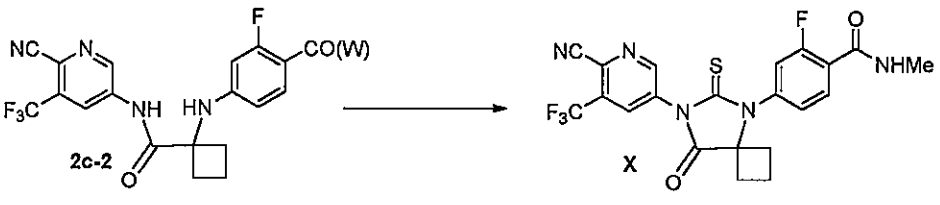
XII-c XIII (2b)

reacting a compound of formula (XII-c) under amino deprotection conditions; in an organic solvent; at a temperature greater than ambient temperature; to yield the corresponding compound (XIII);



XIII 2c-1 2c-2 (2c)

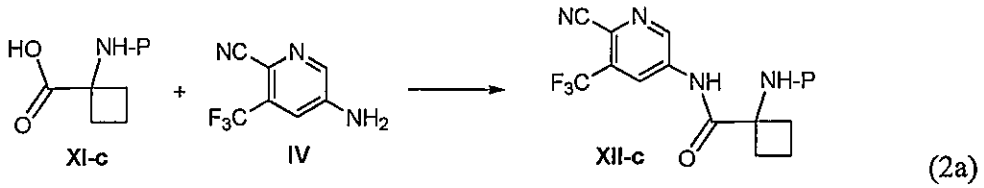
reacting compound (XIII) with a compound of formula (2c-1) wherein X is chloro, bromo, or iodo, and W is C_{1-8}alkoxy or methylamino; in the presence of a copper (0) source or a copper salt; in the presence of an inorganic base; in an organic solvent; optionally in the presence of a ligand; optionally in the presence of a reducing agent; at a temperature in the range of from about room temperature to about 140 °C; to yield the corresponding compound of formula (2c-2) wherein W is C_{1-8}alkoxy (2c-2B) or methylamino (XVII);



(2d)

converting a compound of formula (2c-2) to compound (X).

2. The process of claim 1 wherein step (2a) further comprises

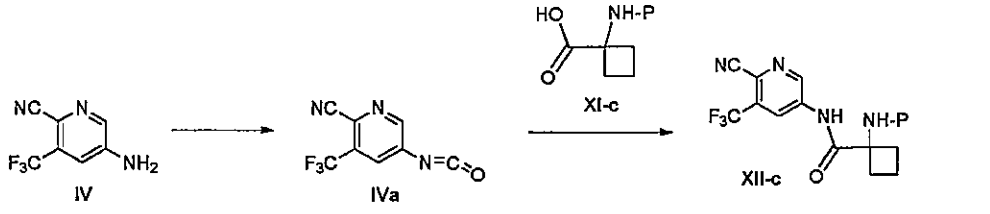


(2a)

reacting a compound of formula (XI-c), wherein P is an amino protecting group, with compound (IV) under amide-bond formation conditions; in the presence of an amide coupling reagent selected from the group consisting of 1,1-carbonyldiimidazole, T3P, EDCI, DMTMM, and EEDQ; in the presence of a catalyst selected from the group consisting of DBU, DBN, DABCO, triethylamine, DIPEA, TBD, TMG, MTBD, NaH, KOtBu, and LiHMDS; in an organic solvent selected from the group consisting of toluene, MeTHF, THF, iPrOAc, DCM, and IPA; at a temperature in the range of from about 0 °C to about 50 °C; to yield the corresponding compound of formula (XII-c).

3. The process of claim 2 wherein the amide coupling agent is 1,1-carbonyldiimidazole and the catalyst is DBU.

4. The process of claim 1 wherein step (2a-1) further comprises

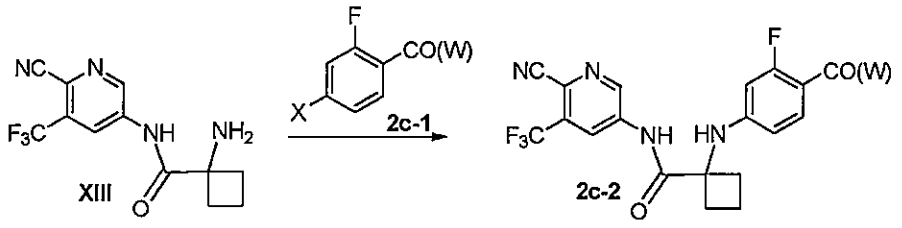


5-isocyanato-3-(trifluoromethyl)picolinonitrile

(2a-1)

reacting compound (IV) with phosgene or a phosgene analog selected from the group consisting of triphosgene (bis(trichloromethyl) carbonate) and diphosgene (trichloromethyl chloroformate); in the presence of an organic base selected from the group consisting of triethylamine, ethyl diisopropylamine, and DABCO; in an aprotic solvent that is DCM, toluene, THF, or MeTHF; at a temperature in the range of from about -20 °C to about 50 °C; to form an isocyanate intermediate (IVa); then reacting said isocyanate intermediate (IVa) with a compound of formula (XI-c); in the presence of a non-nucleophilic base selected from the group consisting of DBU, DBN, DABCO, triethylamine, TBD, TMG, and MTBD; at a temperature in the range of from about -20 °C to about 80 °C; to yield the corresponding compound of formula (XII-c).

5. The process of claim 1 wherein step (2c) further comprises



(2c)

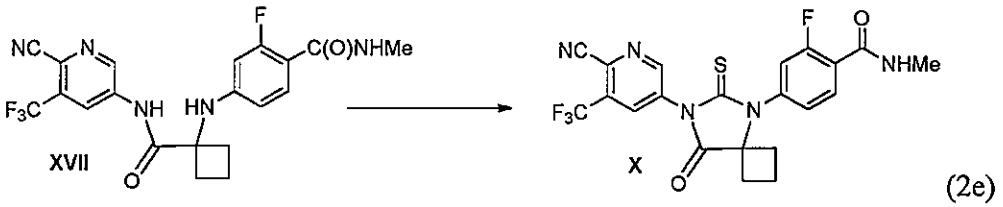
reacting compound (XIII) with a compound of formula (2c-1) wherein X is chloro, bromo, or iodo, and W is C_{1-8}alkoxy or methylamino; in the presence of either (1) a copper (0) source that is copper powder or copper sponge, or (2) a copper salt selected from the group consisting of cuprous chloride, cuprous iodide, cuprous bromide, cuprous acetate, and cupric bromide; in the presence of an inorganic base selected from the group consisting of potassium acetate, potassium carbonate, cesium carbonate, and CsF; in an organic solvent that is DMF, DMA, DMSO, acetonitrile, propionitrile, butyronitrile, or amyl alcohol; with or without the addition of a copper (I) salt selected from the group consisting of cuprous chloride, cuprous iodide, cuprous bromide, and cuprous acetate; and, optionally in the presence of a ligand selected from the group consisting of 2-acetylcyclohexanone, TMEDA, and phenanthroline; also, optionally in the presence of a reducing agent that is sodium ascorbate or sodium bisulfite; at a temperature in the range of from about room temperature to about 140 °C; to yield the corresponding compound of formula (2c-2) wherein W is C_{1-8}alkoxy (2c-2B) or methylamino (XVII).

6. The process of claim 5, comprising reacting compound (XIII) with a compound of formula (2c-1) in the presence of cuprous bromide; in the presence of TMEDA; in the presence of potassium acetate; in organic solvent DMA; at a temperature in the range of from about 80 °C to about 140 °C.

7. The process of claim 5, comprising reacting compound (XIII) with a compound of formula (2c-1) in the presence of a copper (0) source that is copper powder or copper sponge; in the presence of potassium acetate or sodium pivalate; in organic solvent DMSO; at a temperature in the range of from about 0 °C to about 80 °C.

8. The process of claim 5, comprising reacting compound (XIII) with a compound of formula (2c-1) in the presence of a copper (0) source that is copper powder or copper sponge; in the presence of potassium acetate; with the addition of a copper (I) salt selected from the group consisting of cuprous chloride, cuprous iodide, cuprous bromide, and cuprous acetate; in organic solvent DMSO; at a temperature in the range of from about 0 °C to about 80 °C.

9. The process of claim 1, wherein step (2d) further comprises the conversion of compound (XVII) to compound (X) by



(2e)

reacting compound (XVII) with a thiocarbonyl source; in the presence of an activating agent; in an organic solvent; optionally in the presence of an organic base; at a temperature in the range of from about -20 °C to about 100 °C; to yield the corresponding compound (X).

10. The process of claim 9, wherein step (2e) further comprises reacting compound (XVII) with a thiocarbonyl source selected from the group consisting of *O,O'*-di(pyridin-2-yl)carbonothioate, 1,1'-thiocarbonylbis(pyridin-2(1*H*)-one), di(1*H*-imidazol-1-yl)methanethione, thiophosgene, phenyl thionochloroformate, *O*-(2-naphthyl) thionochloroformate, tolyl thionochloroformate, and thiocarbonyl bis(benzotriazole); in the presence of an activating agent selected from the group consisting of DMAP, NaH, and NaOH; in an organic solvent selected from the group consisting of DMA, DMF, toluene, DMSO, ACN, THF, DCM, EtOAc, acetone, MEK, and dioxane; optionally in the presence of an organic base selected from triethylamine or DIPEA; at a temperature in the range of from about -20 °C to about 100 °C; to yield the corresponding compound (X).

11. The process of claim 10 wherein the thiocarbonyl source is 1,1'-thiocarbonylbis(pyridin-2(1*H*)-one).

12. The process of claim 11 wherein the activating agent is DMAP.

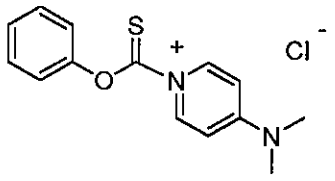
13. The process of claim 12 wherein the organic solvent is DMA.

14. The process of claim 10 wherein the thiocarbonyl source is phenyl thionochloroformate; the activating agent is DMAP; the organic base is triethylamine or DIPEA; the organic solvent is DMA; at a temperature in the range of from about - 20 °C to about 80 °C.

15. The process of claim 10 wherein the thiocarbonyl source is phenyl thionochloroformate; the activating agent is DMAP; the organic base is triethylamine or DIPEA; the organic solvent is acetone or ethyl acetate; at a temperature in the range of from about -20 °C to about 80 °C.

16. The process of claim 15 wherein immediately after cyclization, DMAPA is added.

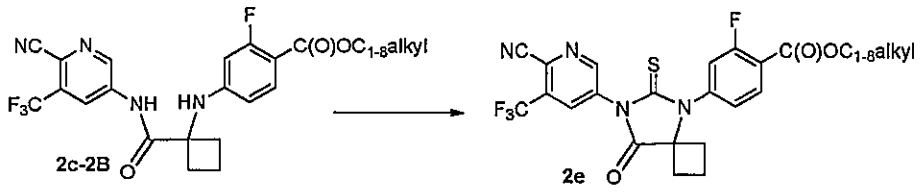
17. The process of claim 10, wherein step (2e) further comprises reacting phenyl thionochloroformate with DMAP to form an isolatable quaternary salt, compound **(S1)**,



S1 ;

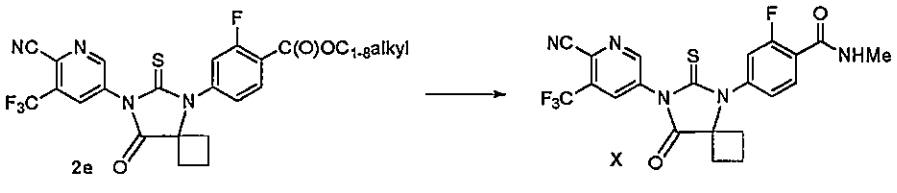
then, reacting compound (XVII) with compound **S1**; in the presence of an organic base selected from triethylamine or DIPEA; in DMA; at a temperature in the range of from about -20 °C to about 80 °C; to yield the corresponding compound **(X)**.

18. The process of claim 1, wherein step (2d) further comprises the conversion of a compound of formula (2c-2B) to a compound of formula (2e), by



(2f)

reacting a compound of formula (2c-2B) with a thiocarbonyl source; in the presence of an activating agent; in an organic solvent; at a temperature in the range of from about -20 °C to about 100 °C; to yield the corresponding compound of formula (2e); then,



(2g)

treating a compound of formula (2e) with methylamine; in an organic solvent; at about ambient temperature; to yield the corresponding compound (X).

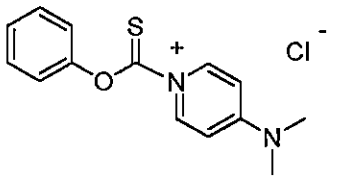
19. The process of claim 18, further comprising reacting a compound of formula (2c-2B) with a thiocarbonyl source selected from the group consisting of *O,O'*-di(pyridin-2-yl)carbonothioate, 1,1'-thiocarbonylbis(pyridin-2(1*H*)-one),

di(1*H*-imidazol-1-yl)methanethione, thiophosgene, phenyl thionochloroformate, *O*-(2-naphthyl) thionochloroformate, tolyl thionochloroformate, and thiocarbonyl bis(benzotriazole); in the presence of an activating agent selected from the group consisting of DMAP, NaH, and NaOH; in an organic solvent selected from the group consisting of dimethylacetamide, DMF, toluene, DMSO, THF, and dioxane; at a temperature in the range of from about -20 °C to about 100 °C; to yield the corresponding compound of formula (2e); then
treating the compound of formula (2e) with methylamine; in an organic solvent selected from the group consisting of THF, DMF, DMA, ethanol, and an aqueous mixture thereof; at about ambient temperature; to yield the corresponding compound (X).

20. The process of claim 19 wherein treating the compound of formula (2e) with methylamine further comprises using ethanol as the organic solvent.

21. The process of claim 19 further comprising reacting a compound of formula (2c-2B) wherein the thiocarbonyl source is phenyl thionochloroformate; the activating agent is DMAP; the organic solvent is acetone or ethyl acetate; at a temperature in the range of from about -20 °C to 40 °C; to yield the corresponding compound of formula (2e); then treating the compound of formula (2e) with methylamine; in ethanol; at about room temperature; to yield the corresponding compound (X).

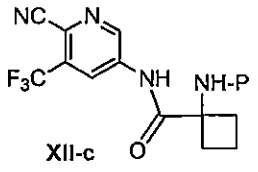
22. The process of claim 18, wherein step (2f) further comprises reacting phenyl thionochloroformate with DMAP to form an isolatable quaternary salt, compound **(S1)**,



S1 ;

then, reacting compound (2c-2B) with compound **S1**; in the presence of an organic base selected from triethylamine or DIPEA; in DMA; at a temperature in the range of from about -20 °C to about 80 °C; to yield the corresponding compound (**X**).

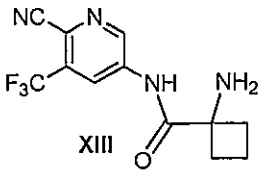
23. A compound of formula (XII-c), useful for the preparation of compound (X), wherein P is an amino protecting group



XII-c .

24. The compound of claim 23 wherein P is *t*-butoxycarbonyl.

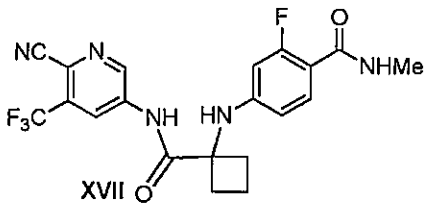
25. A compound (XIII)



XIII ,

useful for the preparation of compound (X).

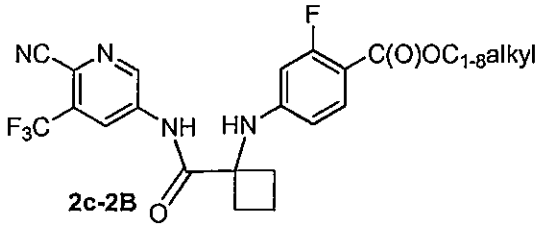
26. A compound (XVII)



,

useful for the preparation of compound (X).

27. A compound of formula (2c-2B)



,

useful for the preparation of compound (X).