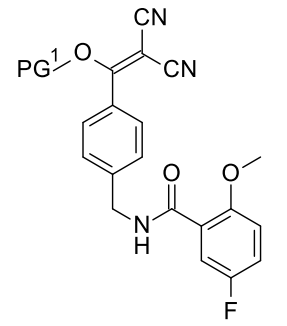
benzoyl)amino]methyl]phenyl]-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazole-4-carboxamide. The compound of Formula (I) is disclosed in WO 2017/103611 and/or WO 2020/028258. The compound of Formula (I) is a selective inhibitor of BTK. Formulations of the compound of Formula (I) are disclosed in WO 2020/028258.

The documents WO 2017/103611 and/or WO 2020/028258 noted above describe a synthesis method for the compound of Formula (I). The present disclosure provides a new process for preparing the compound of Formula (I). This new process provides an efficient, cost-effective, and facile synthesis of the compound of Formula (I), utilizing ecologically friendly reagents, allowing for optimal impurity control, and forming highly pure, crystalline materials. The pure, crystalline materials allow for facile purification of the product. Further, the present embodiments provide for novel intermediates that may be used to prepare the compound of Formula (I).

Summary

In one aspect of the present disclosure, there is provided a process for the preparation of (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I) comprising the steps of:

viii) coupling the compound of Formula (III):

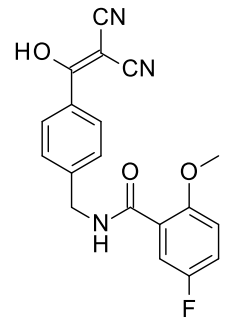


,

wherein PG^1 is $-CH_3$, $-CH_2CH_3$, $-C(CH_3)_3$, $-CH_2CH=CH_2$, methoxymethyl, tetrahydropyran, benzyl, trimethylsilyl, *tert*-butyl dimethylsilyl, di-*tert*-butylisobutylsilyl, di-*tert*-butyl[pyren-1-ylmethoxy]silyl, *tert*-butyl diphenylsilyl, acetyl, or benzoyl; and [(1S)-2,2,2-trifluoro-1-methyl-ethyl]hydrazine (8) or salt thereof to give N-[[4-[5-amino-4-cyano-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazol-3-yl]phenyl]methyl]-5-fluoro-2-methoxybenzamide (10) or a salt thereof; and

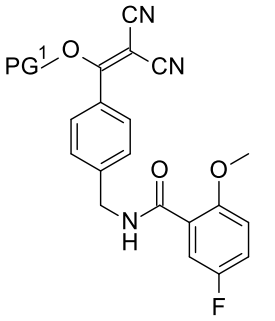
ix) synthesizing (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I) from N-[[4-[5-amino-4-cyano-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazol-3-yl]phenyl]methyl]-5-fluoro-2-methoxy-benzamide (10) or a salt thereof.

In another aspect of the present disclosure, there is provided a compound which is N-[[4-(2,2-dicyano-1-hydroxy-vinyl)phenyl]methyl]-5-fluoro-2-methoxy-benzamide:



.

In a further aspect of the present disclosure, there is provided a compound:



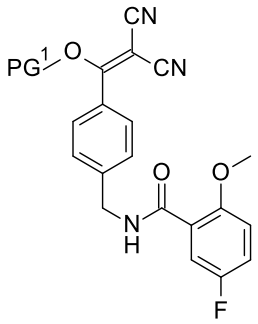
,

wherein PG^1 is $-CH_3$, $-CH_2CH_3$, $-C(CH_3)_3$, $-CH_2CH=CH_2$, methoxymethyl, tetrahydropyran, benzyl, trimethylsilyl, *tert*-butyl dimethylsilyl, di-*tert*-butylisobutylsilyl, di-*tert*-butyl[pyren-1-ylmethoxy]silyl, *tert*-butyl diphenylsilyl, acetyl, or benzoyl.

The present ~~embodiment~~examples provide for processes and new intermediates that may be used to prepare the compound of Formula (I).

One such ~~embodiment~~example includes a process for the preparation of (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I) comprising the steps of:

viii) coupling the compound of Formula (III):



,

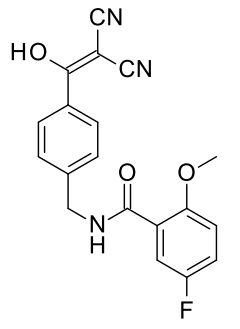
wherein PG^1 is $-CH_3$, $-CH_2CH_3$, $-C(CH_3)_3$, $-CH_2CH=CH_2$, methoxymethyl, tetrahydropyran, benzyl, trimethylsilyl, *tert*-butyl dimethylsilyl, di-*tert*-butylisobutylsilyl, di-*tert*-butyl[pyren-1-ylmethoxy]silyl, *tert*-butyl diphenylsilyl, acetyl, or benzoyl; and [(1S)-2,2,2-trifluoro-1-methyl-ethyl]hydrazine (8) thereof to give N-[[4-[5-amino-4-cyano-1-[(1S)-2,2,2-trifluoro-1-

methyl-ethyl]pyrazol-3-yl]phenyl]methyl]-5-fluoro-2-methoxy-benzamide (10) or a salt thereof;

ix) synthesizing (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I) from N-[[4-[5-amino-4-cyano-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazol-3-yl]phenyl]methyl]-5-fluoro-2-methoxy-benzamide (10) or a salt thereof; and

x) optionally crystallizing (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I) to provide a (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I) in crystalline form.

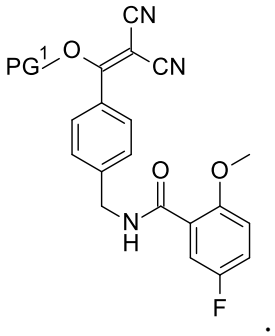
Another ~~embodiment~~example is an intermediate referred to as the compound of Formula (II) and is shown below. The compound of Formula (II) is N-[[4-(2,2-dicyano-1-hydroxy-vinyl)phenyl]methyl]-5-fluoro-2-methoxy-benzamide:



(II)

Accordingly, in another ~~embodiment~~example, the present process comprises employing the compound of Formula (II) to obtain the compound of Formula (I). In other words, described herein is a method of using N-[[4-(2,2-dicyano-1-hydroxy-vinyl)phenyl]methyl]-5-fluoro-2-methoxy-benzamide (II) in the preparation of (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I).

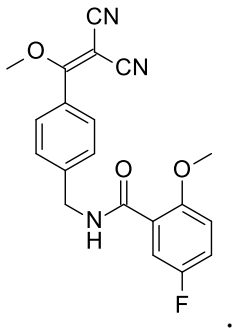
In another ~~embodiment~~example, a different intermediate may be used to prepare the compound of Formula (I). Specifically, this intermediate is a compound of Formula (III):



(III)

Wherein in Formula (III), "PG^1" refers to protecting group. Examples of what may constitute this PG^1 are $-CH_3$, $-CH_2CH_3$, $-C(CH_3)_3$, $-CH_2CH=CH_2$, methoxymethyl, tetrahydropyranyl, benzyl, silyl, acetyl, or benzoyl; or a pharmaceutically acceptable salt thereof. Silyl groups include but are not limited to trimethylsilyl, *tert*-butyl dimethylsilyl, di-*tert*-butylisobutylsilyl, di-*tert*-butyl[pyren-1-ylmethoxy]silyl, and *tert*-butyl diphenylsilyl.

A preferred ~~embodiment~~example of the present ~~invention~~disclosure is made in which the compound of Formula (III) has the PG^1 being methyl. This compound is N-[[4-(2,2-dicyano-1-methoxy-vinyl)phenyl]methyl]-5-fluoro-2-methoxy-benzamide and is represented below as Formula (IIIA) :

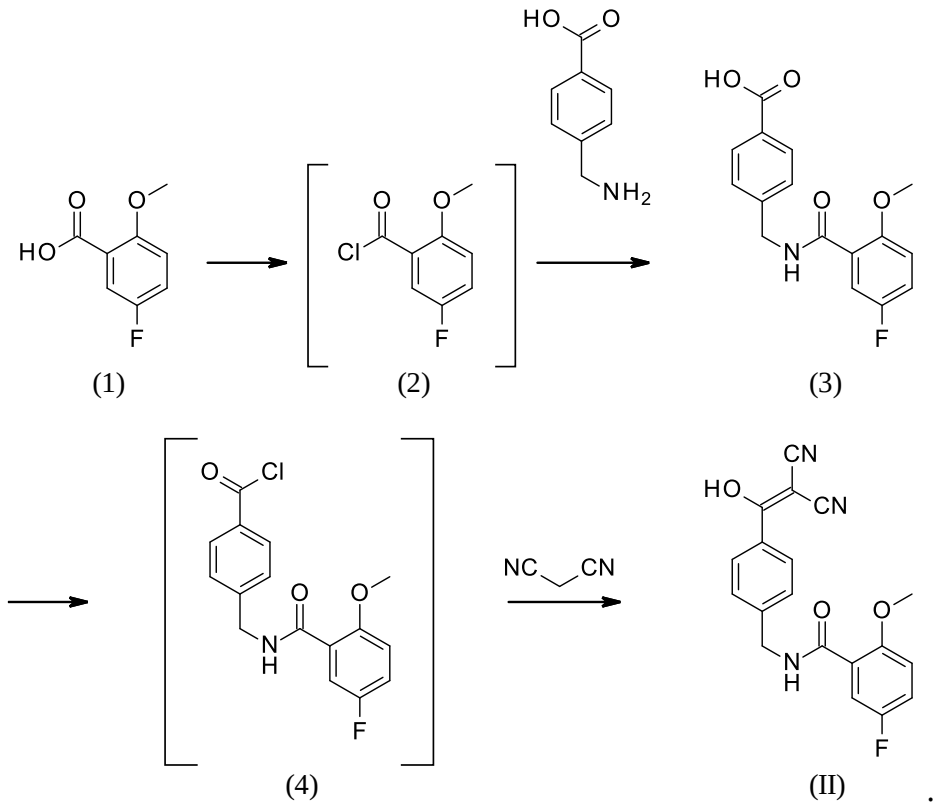


(IIIA)

Accordingly, in one ~~embodiment~~example, the present process comprises employing the compound of Formula (III) to obtain the compound of Formula (I). In other words, the present ~~embodiment~~examples include a method of using the compound of Formula (III) in the preparation of (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I). In some ~~embodiment~~examples, this may involve reacting the compound of Formula (IIIA) to obtain the compound of Formula (I).

The compound of Formula (II) may be prepared using the following Scheme I, which is described in greater detail herein:

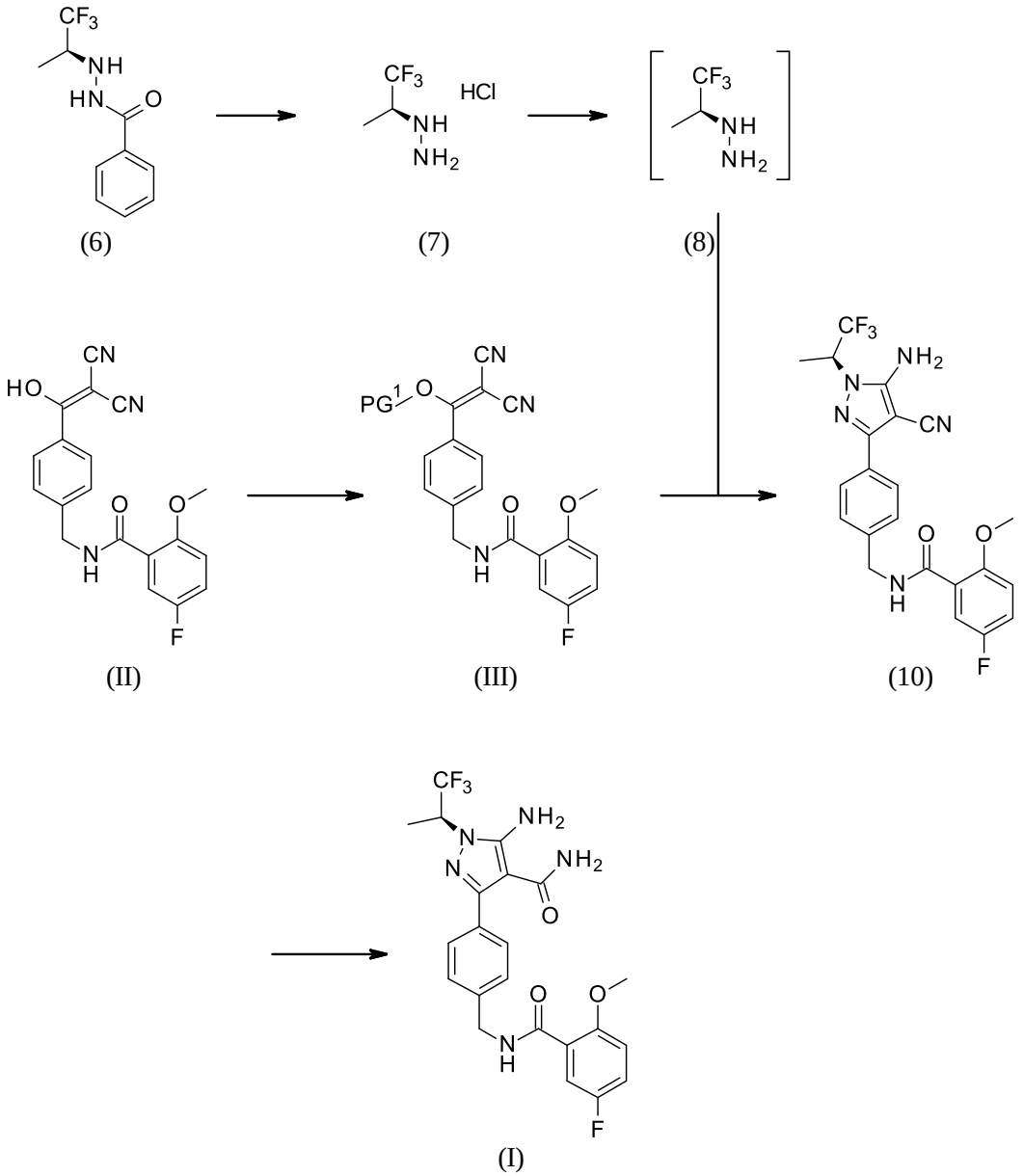
Scheme I



Additional ~~embodiment~~examples include a more efficient and ecologically friendly method of producing the compound of Formula (I). Such ~~embodiment~~examples may involve using the compound of Formula (II) and/or the compound of Formula (III).

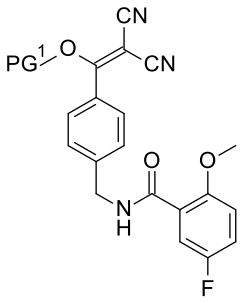
Other ~~embodiment~~examples may involve a process for the preparation of the compound of Formula (I), which involve using the reactions/compounds of Scheme II (which is described in greater detail herein). Scheme II uses the compound of Formula (II) and converts it into the compound of Formula (III), and then subsequently converts such compound into the compound of Formula (I):

Scheme II



The ~~embodiment~~examples shown in Scheme II are represented using the compound of Formula (III). As noted above, the compound of Formula (IIIA) is a sub-species of the compound of Formula (III), wherein the PG^1 is methyl. Those skilled in the art will appreciate that similar Scheme(s) may be used and constructed using other species as the PG^1 for the compound of Formula (III). All of these other ~~embodiment~~examples (e.g., where a different PG^1 is used in Formula (III)) may be used to prepare the compound of Formula (I) using similar techniques and schemes as those disclosed herein.

As shown in Schemes I and II, process may include one or more of the following steps:



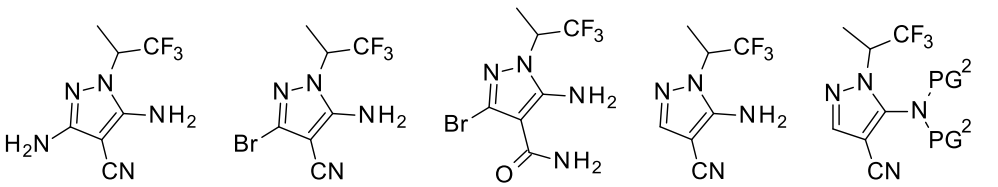
,

and [(1S)-2,2,2-trifluoro-1-methyl-ethyl]hydrazine (8) or a salt thereof to give N-[[4-[5-amino-4-cyano-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazol-3-yl]phenyl]methyl]-5-fluoro-2-methoxy-benzamide (10) or a salt thereof;

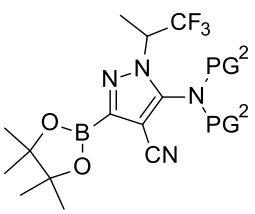
ix) synthesizing 5-amino-3-[4-[[(5-fluoro-2-methoxy-benzoyl)amino]methyl]phenyl]-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazole-4-carboxamide (I) from N-[[4-[5-amino-4-cyano-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazol-3-yl]phenyl]methyl]-5-fluoro-2-methoxy-benzamide (10) or a salt thereof; and

x) optionally crystallizing 5-amino-3-[4-[[(5-fluoro-2-methoxy-benzoyl)amino]methyl]phenyl]-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazole-4-carboxamide (I) to provide a 5-amino-3-[4-[[(5-fluoro-2-methoxy-benzoyl)amino]methyl]phenyl]-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazole-4-carboxamide (I) in crystalline form.

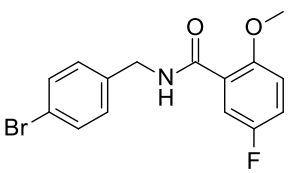
In a further ~~embodiment~~example, there is provided an intermediate compound selected from:



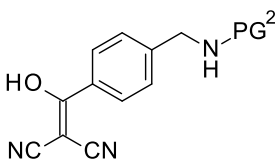
,



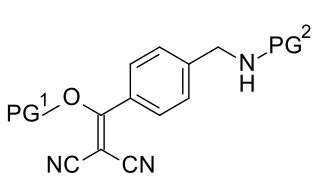
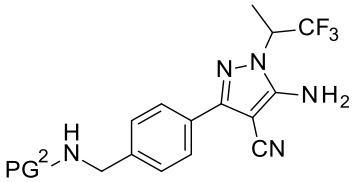
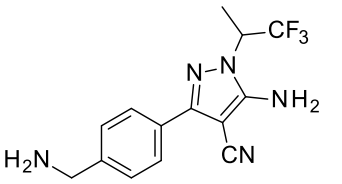
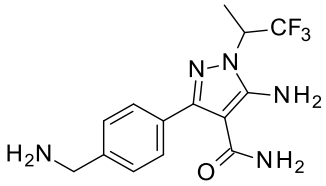
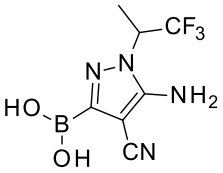
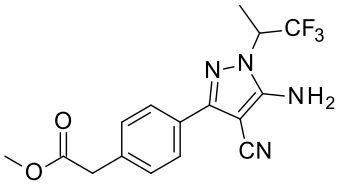
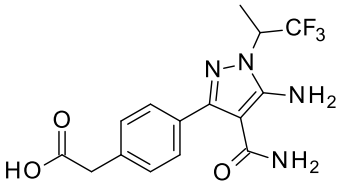
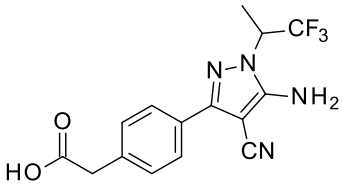
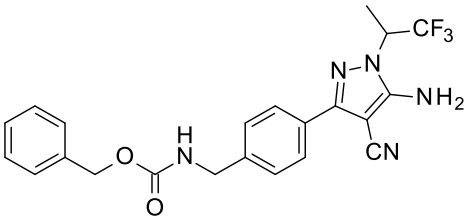
,



,



,


,

,

,

,

,

,

,

, and

or a salt thereof;

wherein PG^2 is fluorenylmethoxycarbonyl, *tert*-butoxycarbonyl, benzylcarbonyl, trifluoroacetamide, phthalimide, benzyl, triphenylmethyl, benzylideneamine, *p*-toluenesulfonamide, PG^1 is $-CH_3$, $-CH_2CH_3$, $-C(CH_3)_3$, $-CH_2CH{=}CH_2$, methoxymethyl, tetrahydropyranyl, benzyl, trimethylsilyl, *tert*-butyl dimethylsilyl, di-*tert*-butylisobutylsilyl, di-*tert*-butyl[pyren-1-ylmethoxy]silyl, *tert*-butyl diphenylsilyl, acetyl, or benzoyl. Some ~~embodiment~~examples of methods and processes whereby the above-recited compounds may be converted into the compound of Formula (I) will be described and shown herein.

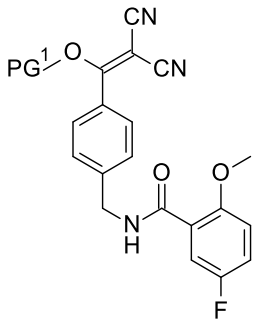
Description

Described herein is the compound, N-[[4-(2,2-dicyano-1-hydroxy-vinyl)phenyl]methyl]-5-fluoro-2-methoxy-benzamide:

WHAT IS CLAIMED IS:

1. A process for the preparation of (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I) comprising the steps of:

viii) coupling the compound of Formula (III):



,

wherein PG^1 is $-CH_3$, $-CH_2CH_3$, $-C(CH_3)_3$, $-CH_2CH=CH_2$, methoxymethyl, tetrahydropyran, benzyl, trimethylsilyl, *tert*-butyl dimethylsilyl, di-*tert*-butylisobutylsilyl, di-*tert*-butyl[pyren-1-ylmethoxy]silyl, *tert*-butyl diphenylsilyl, acetyl, or benzoyl; and [(1S)-2,2,2-trifluoro-1-methyl-ethyl]hydrazine (8) or salt thereof to give N-[[4-[5-amino-4-cyano-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazol-3-yl]phenyl]methyl]-5-fluoro-2-methoxy-benzamide (10) or a salt thereof; and

ix) synthesizing (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I) from N-[[4-[5-amino-4-cyano-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazol-3-yl]phenyl]methyl]-5-fluoro-2-methoxy-benzamide (10) or a salt thereof.~~; and~~

~~x) optionally crystallizing (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I) to provide a (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I) in crystalline form.~~

2. The process according to claim 1, further comprising crystallizing (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-

yl)-1H-pyrazole-4-carboxamide (I) to provide a (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I) in crystalline form.

3. The process according to claim 1 or 2, wherein PG^1 is $-CH_3$.

4. The process according to claim 1 or 2, wherein synthesizing (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I) from N-[[4-[5-amino-4-cyano-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazol-3-yl]phe-nyl]methyl]-5-fluoro-2-methoxy-benzamide (10) or a salt thereof is via a hydrolysis.

5. The process according to claim 4, wherein the hydrolysis is carried out under acidic, basic, oxidative, or metal-catalyzed/stoichiometric conditions.

6. The process according to claim 5, wherein the hydrolysis is carried out under acidic conditions.

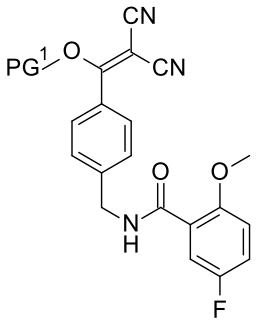
7. The process according to claim 6, wherein the hydrolysis employs methanesulfonic acid, trifluoroacetic acid, hydrochloric acid, polyphosphoric acid, or sulfuric acid.

8. The process according to claim 7, wherein the hydrolysis employs methanesulfonic acid.

9. The process according to claim 5, wherein the hydrolysis is carried out under basic, oxidative, or metal-catalyzed/stoichiometric conditions.

10. The process according to claim 9, wherein the hydrolysis employs potassium *tert*-butoxide, sodium hydroxide, peroxide, ruthenium hydroxide, manganese dioxide, copper (II) acetate, Parkin's catalyst or MnO_2/SiO_2.

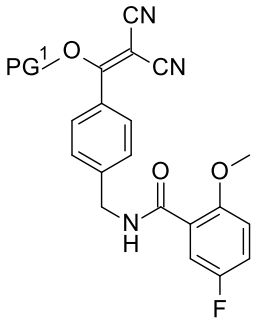
~~2.~~11. The process according to any one of claims 1-10, wherein prior to the coupling of the compound of Formula (III):



,

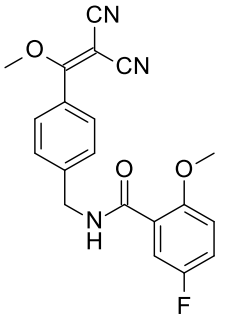
and [(1S)-2,2,2-trifluoro-1-methyl-ethyl]hydrazine (8) ~~step~~ or a salt thereof, the process further comprises the step of:

reacting N-[[4-(2,2-dicyano-1-hydroxy-vinyl)phenyl]methyl]-5-fluoro-2-methoxy-benzamide (II) with an alkylating agent to give the compound of Formula (III):



.

12. The process according to claim 11, wherein reacting N-[[4-(2,2-dicyano-1-hydroxy-vinyl)phenyl]methyl]-5-fluoro-2-methoxy-benzamide (II) with an alkylating agent gives the compound of Formula (IIIA):



13. The process according to claim 12, wherein the reaction employs trimethyl orthoformate, methyl triflate, trimethylammonium tetrafluoroborate, or *N,N'*-diisopropyl-*O*-methylisourea.

~~3.~~14. The process according to ~~either~~ any one of claims 1-11, ~~or 2~~ wherein prior to the coupling of the compound of Formula (III) and [(1S)-2,2,2-trifluoro-1-methyl-ethyl]hydrazine (8) ~~step~~, the process further comprises the step of:

converting [(1S)-2,2,2-trifluoro-1-methyl-ethyl]hydrazine hydrochloride (7) to [(1S)-2,2,2-trifluoro-1-methyl-ethyl]hydrazine (8).

~~4.~~15. The process according to claim 14~~3~~, wherein prior to converting [(1S)-2,2,2-trifluoro-1-methyl-ethyl]hydrazine hydrochloride (7) to [(1S)-2,2,2-trifluoro-1-methyl-ethyl]hydrazine (8), the process further comprises the step of:

reacting N'-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]benzohydrazide (6) or a salt thereof to give [(1S)-2,2,2-trifluoro-1-methyl-ethyl]hydrazine hydrochloride (7).

~~5. The process according to either claim 2 or 4, wherein prior to reacting N-[[4-(2,2-dicyano-1-hydroxy-vinyl)phenyl]methyl]-5-fluoro-2-methoxy-benzamide (II) with an alkylating agent, the process further comprises the step of:~~

~~reacting 4-[[(5-fluoro-2-methoxy-benzoyl)amino]methyl]benzoyl chloride (4) with malononitrile to give N-[[4-(2,2-dicyano-1-hydroxy-vinyl)phenyl]methyl]-5-fluoro-2-methoxy-benzamide (II).~~

6. The process according to claim 5, wherein prior to reacting 4-[[(5-fluoro-2-methoxy-benzoyl)amino]methyl]benzoyl chloride (4) with malononitrile, the process further comprises the step of:

converting 4-[[(5-fluoro-2-methoxy-benzoyl)amino]methyl]benzoic acid (3) or a salt thereof to 4-[[(5-fluoro-2-methoxy-benzoyl)amino]methyl]benzoyl chloride (4).

7. The process according to claim 6, wherein prior to converting 4-[[(5-fluoro-2-methoxy-benzoyl)amino]methyl]benzoic acid (3) or a salt thereof, the process further comprises the step of:

coupling 5-fluoro-2-methoxy-benzoyl chloride (2) with 4-(aminomethyl)benzoic acid to give 4-[[(5-fluoro-2-methoxy-benzoyl)amino]methyl]benzoic acid (3) or a salt thereof.

8. The process according to claim 7, wherein prior to coupling 5-fluoro-2-methoxy-benzoyl chloride (2) with 4-(aminomethyl)benzoic acid, the process further comprises the step of:

converting 5-fluoro-2-methoxy-benzoic acid (1) or a salt thereof to give 5-fluoro-2-methoxy-benzoyl chloride (2).

9. A process for the preparation of (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I) comprising the steps of:

i) converting 5-fluoro-2-methoxy-benzoic acid (1) or a salt thereof to 5-fluoro-2-methoxy-benzoyl chloride (2);

ii) coupling 5-fluoro-2-methoxy-benzoyl chloride (2) with 4-(aminomethyl)benzoic acid to give 4-[[(5-fluoro-2-methoxy-benzoyl)amino]methyl]benzoic acid (3) or a salt thereof;

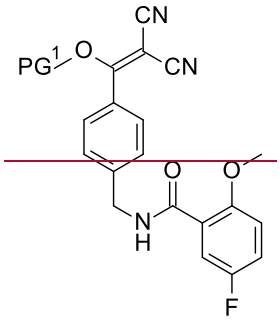
iii) converting 4-[[(5-fluoro-2-methoxy-benzoyl)amino]methyl]benzoic acid (3) or a salt thereof to 4-[[(5-fluoro-2-methoxy-benzoyl)amino]methyl]benzoyl chloride (4);

iv) reacting 4-[[(5-fluoro-2-methoxy-benzoyl)amino]methyl]benzoyl chloride (4) with malononitrile to give N-[[4-(2,2-dicyano-1-hydroxy-vinyl)phenyl]methyl]-5-fluoro-2-methoxy-benzamide (II);

v) converting N'-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]benzohydrazide (6) or a salt thereof to [(1S)-2,2,2-trifluoro-1-methyl-ethyl]hydrazine hydrochloride (7);

vi) converting [(1S)-2,2,2-trifluoro-1-methyl-ethyl]hydrazine hydrochloride (7) to [(1S)-2,2,2-trifluoro-1-methyl-ethyl]hydrazine (8)

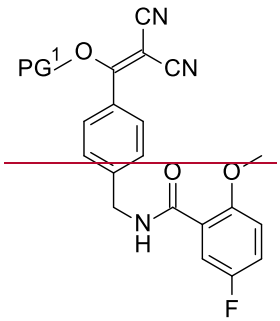
vii) converting N-[[4-(2,2-dicyano-1-hydroxy-vinyl)phenyl]methyl]-5-fluoro-2-methoxy-benzamide (II) to a compound of Formula (III):



;

wherein PG^1 is $-CH_3$, $-CH_2CH_3$, $-C(CH_3)_3$, $-CH_2CH=CH_2$, methoxymethyl, tetrahydropyran, benzyl, trimethylsilyl, *tert*-butyl dimethylsilyl, di-*tert*-butylisobutylsilyl, di-*tert*-butyl[pyren-1-ylmethoxy]silyl, *tert*-butyl diphenylsilyl, acetyl, or benzoyl;

viii) coupling the compound of Formula (III):



;

and [(1S)-2,2,2-trifluoro-1-methyl-ethyl]hydrazine (8) or a salt thereof to give N-[[4-[5-amino-4-cyano-1-[(1S)-2,2,2-trifluoro-1-methyl-

~~ethyl]pyrazol-3-yl]phenyl]methyl]-5-fluoro-2-methoxy-benzamide (10) or a salt thereof;~~

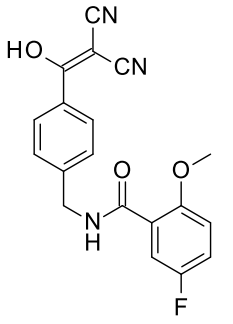
~~ix) synthesizing (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I) from N-[[4-[5-amino-4-cyano-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazol-3-yl]phenyl]methyl]-5-fluoro-2-methoxy-benzamide (10) or a salt thereof; and~~

~~x) optionally crystallizing (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I) to provide a (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I) in crystalline form.~~

~~10. A process for the preparation of (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I) comprising converting N-[[4-(2,2-dicyano-1-methoxy-vinyl)phenyl]methyl]-5-fluoro-2-methoxy-benzamide into S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I).~~

~~11. A process for the preparation of (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I) comprising converting N-[[4-(2,2-dicyano-1-hydroxy-vinyl)phenyl]methyl]-5-fluoro-2-methoxy-benzamide into S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I).~~

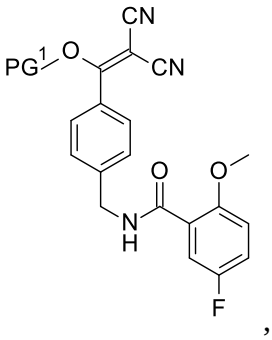
~~12.~~16. A compound which is N-[[4-(2,2-dicyano-1-hydroxy-vinyl)phenyl]methyl]-5-fluoro-2-methoxy-benzamide:



.

~~13. The use of the compound according to claim 12 in the preparation of (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I).~~

~~14.~~17. A compound:

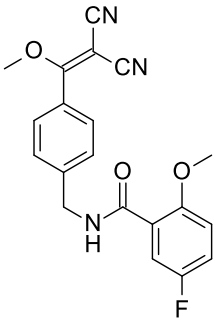


,

wherein PG^1 is $-CH_3$, $-CH_2CH_3$, $-C(CH_3)_3$, $-CH_2CH=CH_2$, methoxymethyl, tetrahydropyran, benzyl, trimethylsilyl, *tert*-butyl dimethylsilyl, di-*tert*-butylisobutylsilyl, di-*tert*-butyl[pyren-1-ylmethoxy]silyl, *tert*-butyl diphenylsilyl, acetyl, or benzoyl.

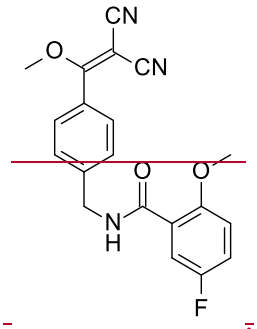
~~15. The compound according to claim 14 wherein PG^1 is $-CH_3$.~~

~~16.~~18. The compound according to claim ~~14~~17 which is:

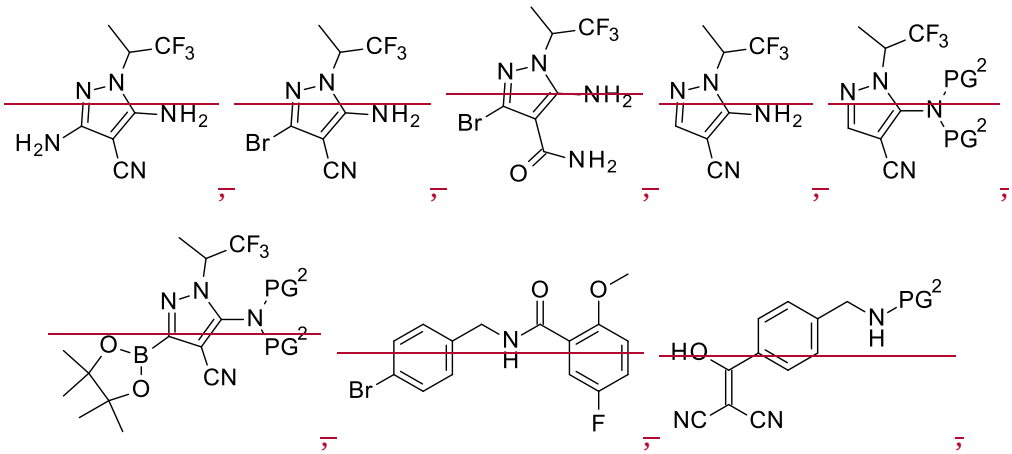


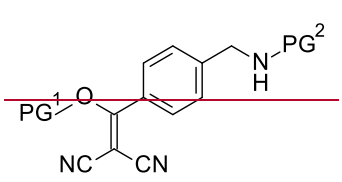
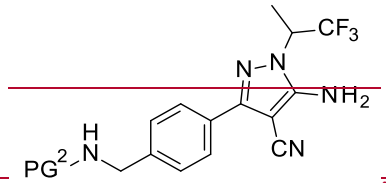
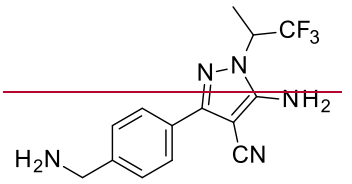
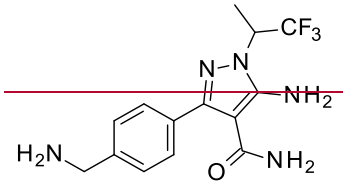
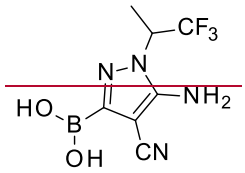
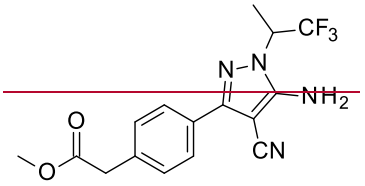
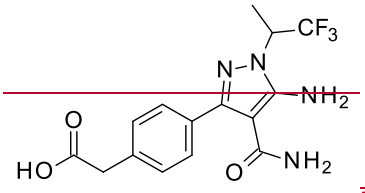
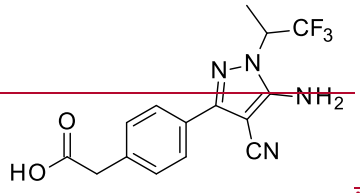
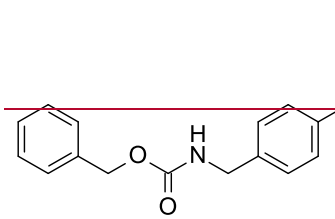
17. The use of the compound according to claim 14 to prepare (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I).

18. The process of any one of claims 1-3, wherein the compound of Formula (III) is the compound of Formula (IIIA):



19. A compound selected from a group consisting of the following:

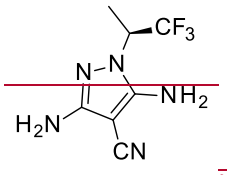


or a salt thereof;

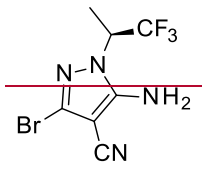
wherein PG^2 is fluorenylmethoxycarbonyl, *tert*-butoxycarbonyl, benzylcarbonyl, trifluoroacetamide, phthalimide, benzyl, triphenylmethyl, benzylideneamine, *p*-toluenesulfonamide, PG^1 is $-CH_3$, $-CH_2CH_3$, $-C(CH_3)_3$, $-CH_2CH{=}CH_2$, methoxymethyl, tetrahydropyranyl, benzyl, trimethylsilyl, *tert*-butyl dimethylsilyl, di-*tert*-butylisobutylsilyl, di-*tert*-butyl[pyren-1-ylmethoxy]silyl, *tert*-butyl diphenylsilyl, acetyl, or benzoyl.

20. The compound according to claim 19 which is 3,5-diamino-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazole-4-carbonitrile:



~~or a salt thereof.~~

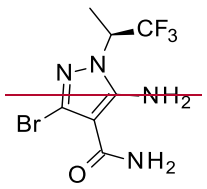
~~21. The compound according to claim 19 which is 5-amino-3-bromo-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazole-4-carbonitrile:~~



~~;~~

~~or a salt thereof.~~

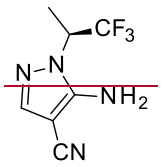
~~22. The compound according to claim 19 which is 5-amino-3-bromo-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazole-4-carboxamide:~~



~~;~~

~~or a salt thereof.~~

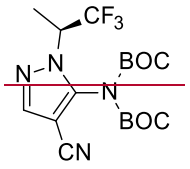
~~23. The compound according to claim 19 which is 5-amino-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazole-4-carbonitrile:~~



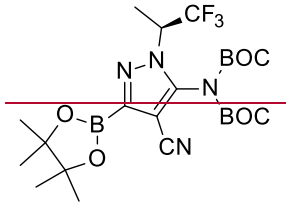
~~;~~

~~or a salt thereof.~~

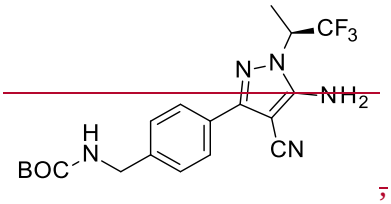
~~24. The compound according to claim 19 which is *tert*-butyl N-*tert*-butoxycarbonyl-N-[4-cyano-2-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazol-3-yl]carbamate:~~



25. The compound according to claim 19 which is *tert*-butyl N-*tert*-butoxycarbonyl-N-[4-cyano-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazol-3-yl]carbamate:

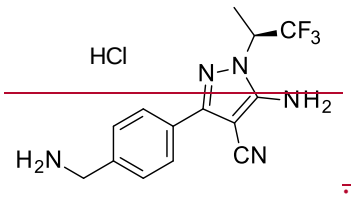


26. The compound according to claim 19 which is *tert*-butyl N-[[4-[5-amino-4-cyano-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazol-3-yl]phenyl]methyl]carbamate:

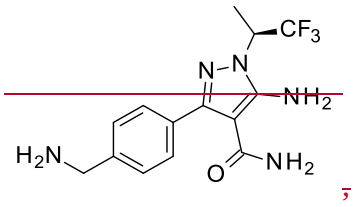


or a salt thereof.

27. The compound according to claim 19 which is 5-amino-3-[4-(aminomethyl)phenyl]-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazole-4-carbonitrile hydrochloride:

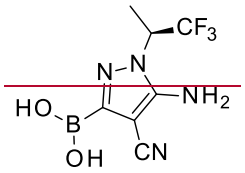


28. The compound according to claim 19 which is 5-amino-3-[4-(aminomethyl)phenyl]-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazole-4-carboxamide:



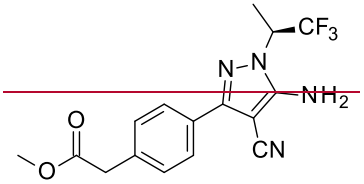
or a salt thereof.

29. The compound according to claim 19 which is [5-amino-4-cyano-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazol-3-yl]boronic acid:



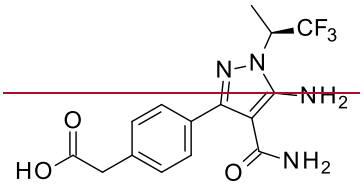
or a salt thereof.

30. The compound according to claim 19 which is methyl 2-[4-[5-amino-4-cyano-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazol-3-yl]phenyl]acetate:



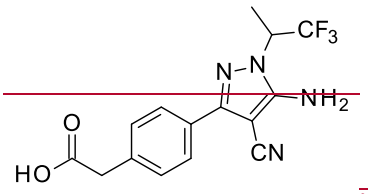
or a salt thereof.

31. The compound according to claim 19 which is 2-[4-[5-amino-4-carbamoyl-1-[(1S)-2,2,2-trifluoro-1-methyl-ethyl]pyrazol-3-yl]phenyl]acetic acid:



or a salt thereof.

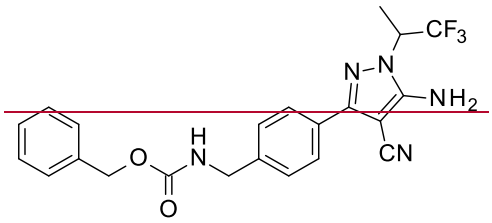
32. The compound according to claim 19 which is 2-[4-[5-amino-4-cyano-1-(2,2,2-trifluoro-1-methyl-ethyl)pyrazol-3-yl]phenyl]acetic acid:



;

or a salt thereof.

33. The compound according to claim 19 which is benzyl N-[[4-[5-amino-4-cyano-1-(2,2,2-trifluoro-1-methyl-ethyl)pyrazol-3-yl]phenyl]methyl]carbamate:



;

or a salt thereof.

34. The use of the compound according to any one of claims 19 to 33 or a salt thereof according to any one of claims 20 to 23, claim 26, or claims 28 to 33, to prepare (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide (I).