[0004] Tropomyosin and troponin mediate the calcium effect on the interaction on actin and myosin. The troponin complex is comprised of three polypeptide chains: troponin C, which binds calcium ions; troponin I, which binds to actin; and troponin T, which binds to tropomyosin. The skeletal troponin-tropomyosin complex regulates the myosin binding sites extending over several actin units at once.

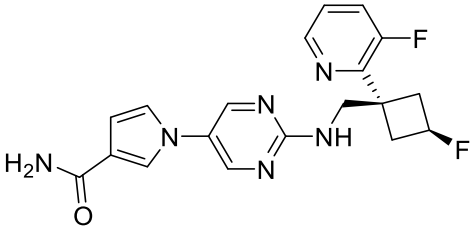
[0005] Troponin, a complex of the three polypeptides described above, is an accessory protein that is closely associated with actin filaments in vertebrate muscle. The troponin complex acts in conjunction with the muscle form of tropomyosin to mediate the Ca^{2+} dependency of myosin ATPase activity and thereby regulate muscle contraction. The troponin polypeptides T, I, and C, are named for their tropomyosin binding, inhibitory, and calcium binding activities, respectively. Troponin T binds to tropomyosin and is believed to be responsible for positioning the troponin complex on the muscle thin filament. Troponin I binds to actin, and the complex formed by troponins I and T, and tropomyosin inhibits the interaction of actin and myosin. Skeletal troponin C is capable of binding up to four calcium molecules. Studies suggest that when the level of calcium in the muscle is raised, troponin C exposes a binding site for troponin I, recruiting it away from actin. This causes the tropomyosin molecule to shift its position as well, thereby exposing the myosin binding sites on actin and stimulating myosin ATPase activity.

[0006] U.S. Patent No. 8962632 discloses 1-(2-((((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methyl)amino)pyrimidin-5-yl)-1H-pyrrole-3-carboxamide, a next-generation fast skeletal muscle troponin activator (FSTA) as a potential treatment for people living with debilitating diseases and conditions associated with neuromuscular or non-neuromuscular dysfunction, muscular weakness, and/or muscle fatigue.

[0007] There is a need for improved methods for preparing such compound with low cost and high overall yield and purity.

BRIEF SUMMARY

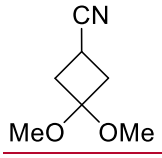
[0007a] In an aspect of the present disclosure, there is provided a method of preparing a compound of Formula (1):



(1) ,

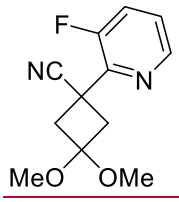
or a salt thereof, comprising:

(i) reacting a compound of Formula (1A):



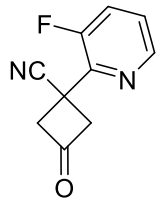
(1A)

with 2-chloro-3-fluoropyridine to form a compound of Formula (1B):



(1B);

(ii) reacting the compound of Formula (1B) with an aqueous acid to form a compound of Formula (1C):

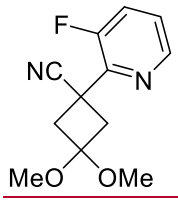


(1C);

and

(iii) converting the compound of Formula (1C) to the compound of Formula (1) or a salt thereof.

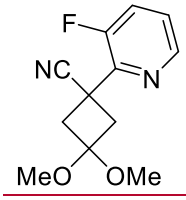
[0007b] In another aspect of the present disclosure, there is provided a compound of Formula (1B):



(1B),

or a salt thereof.

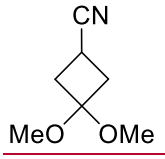
[0007c] In a further aspect of the present disclosure, there is provided a method of preparing a compound of Formula (1B):



(1B),

or a salt thereof, comprising:

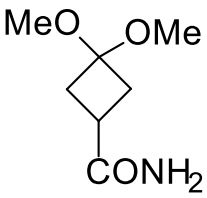
reacting a compound of Formula (1A):



(1A)

with 2-chloro-3-fluoropyridine to form the compound of Formula (1B).

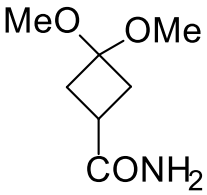
[0007d] In another aspect of the present disclosure, there is provided a compound of Formula (1D):



(1D),

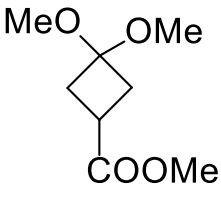
or a salt thereof.

[0007e] In a further aspect of the present disclosure, there is provided a method of preparing a compound of Formula (1D):



(1D),

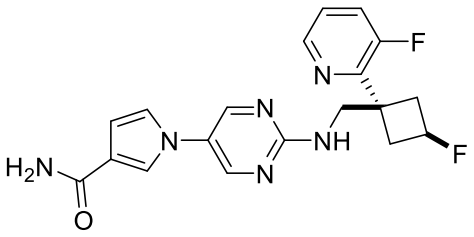
or a salt thereof, comprising converting a compound of Formula (1E):



(1E)

to the compound of Formula (1D) or a salt thereof.

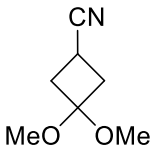
[0008] In one ~~aspect~~example, provided herein is method of preparing a compound of Formula (1):



(1),

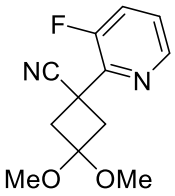
or a salt thereof, comprising:

(i) reacting a compound of Formula (1A):



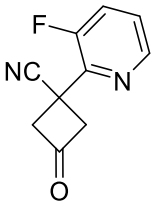
(1A),

with 2-chloro-3-fluoropyridine to form a compound of Formula (1B):



(1B);

(ii) reacting the compound of Formula (1B) with an aqueous acid to form a compound of Formula (1C):

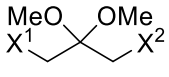


(1C);

and

(iii) converting the compound of Formula (1C) to the compound of Formula (1) or a salt thereof.

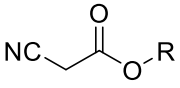
[0009] In some ~~embodiment~~examples, the method further comprises obtaining the compound of Formula (1A) by reacting a compound of Formula (2A):



(2A),

wherein X^1 and X^2 are each independently a leaving group,

with a compound of Formula (2B):



(2B),

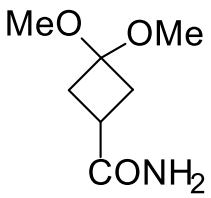
where R is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl, to form the compound of Formula (1A). In some ~~embodiment~~examples, X^1 and X^2 are independently halo, triflate, tosylate, mesylate, or acetoxy. In some ~~embodiment~~examples, X^1 and X^2 are independently halo.

[0010] In some ~~embodiment~~examples, the method further comprises obtaining the compound of Formula (1A) by reacting 1,3-dibromo-2,2-dimethoxypropane with *tert*-butyl 2-cyanoacetate to form the compound of Formula (1A).

[0011] In some ~~embodiment~~examples, the reaction of the 1,3-dibromo-2,2-dimethoxypropane with the *tert*-butyl 2-cyanoacetate is performed in the presence of a base.

[0012] In some ~~embodiment~~examples, the base is potassium *tert*-butoxide.

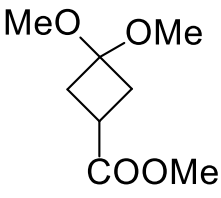
[0013] In some ~~embodiment~~examples, the method further comprises obtaining the compound of Formula (1A) by converting a compound of Formula (1D):



(1D)

to the compound of Formula (1A).

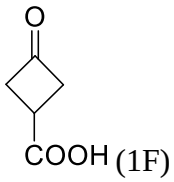
[0014] In some ~~embodiment~~examples, the method further comprises obtaining the compound of Formula (1D) by converting a compound of Formula (1E):



(1E)

to the compound of Formula (1D).

[0015] In some ~~embodiment~~examples, the method further comprises obtaining the compound of Formula (1E) by converting a compound of Formula (1F):



(1F)

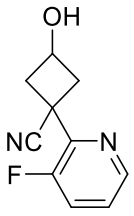
to the compound of Formula (1E).

[0016] In some ~~embodiment~~examples, step (i) is performed in the presence of a base.

[0017] In some ~~embodiment~~examples, the base is sodium bis(trimethylsilyl)amide.

[0018] In some ~~embodiment~~examples, the aqueous acid of step (ii) is aqueous hydrochloric acid.

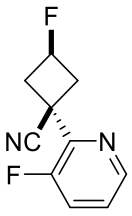
[0019] In some ~~embodiment~~examples, step (iii) comprises converting the compound of Formula (1C) to a compound of Formula (1G):



(1G),

and converting the compound of Formula (1G) to the compound of Formula (1) or a salt thereof.

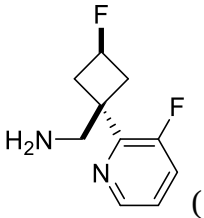
[0020] In some ~~embodiment~~examples, step (iii) further comprises converting the compound of Formula (1G) to a compound of Formula (1H):



(1H),

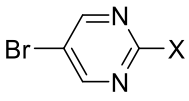
and converting the compound of Formula (1H) to the compound of Formula (1) or a salt thereof.

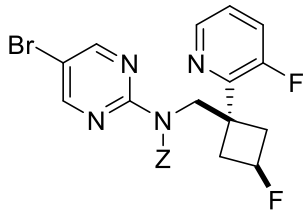
[0021] In some ~~embodiment~~examples, step (iii) further comprises converting the compound of Formula (1H) to a compound of Formula (1I)



(1I),

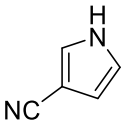
and converting the compound of Formula (1I) to the compound of Formula (1) or a salt thereof.

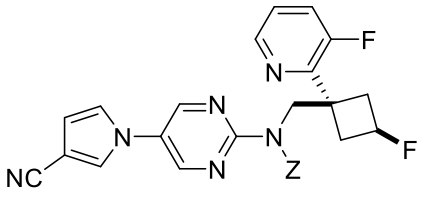
[0022] In some ~~embodiment~~examples, step (iii) further comprises reacting the compound of Formula (1I) with , wherein X is chloro or fluoro, to form a compound of Formula (1J):

 (1J),

wherein Z is a protecting group or hydrogen,

and converting the compound of Formula (1J) to the compound of Formula (1) or a salt thereof.

[0023] In some ~~embodiment~~examples, step (iii) further comprises reacting the compound of Formula (1J) with  to form a compound of Formula (1K):

 (1K),

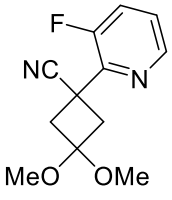
wherein Z is a protecting group or hydrogen,

and converting the compound of Formula (1K) to the compound of Formula (1) or a salt thereof.

[0024] In some ~~embodiment~~examples, Z is Boc. In some ~~embodiment~~examples, Z is hydrogen.

[0025] In some ~~embodiment~~examples, step (iii) comprises isolating the compound of Formula (1) or a salt thereof.

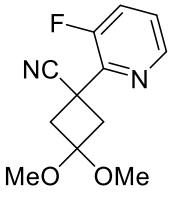
[0026] In another ~~aspect~~example, provided herein is a compound of Formula (1B):



(1B),

or a salt thereof.

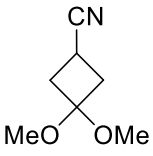
[0027] In some ~~embodiment~~examples, provided is a method of preparing a compound of Formula (1B):



(1B) ,

or a salt thereof, comprising:

reacting a compound of Formula (1A):



(1A)

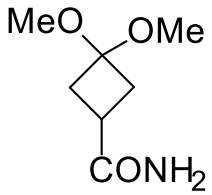
with 2-chloro-3-fluoropyridine to form the compound of Formula (1B).

[0028] In some ~~embodiment~~examples, the method further comprises obtaining the compound of Formula (1A) by reacting 1,3-dibromo-2,2-dimethoxypropane with *tert*-butyl 2-cyanoacetate to form the compound of Formula (1A).

[0029] In some ~~embodiment~~examples, the reaction of the 1,3-dibromo-2,2-dimethoxypropane with the *tert*-butyl 2-cyanoacetate is performed in the presence of a base.

[0030] In some ~~embodiment~~examples, the base is potassium *tert*-butoxide.

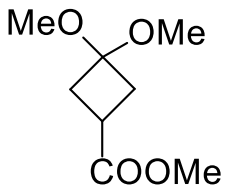
[0031] In some ~~embodiment~~examples, the method further comprises obtaining the compound of Formula (1A) by converting a compound of Formula (1D):



(1D)

to the compound of Formula (1A).

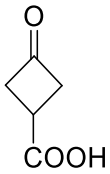
[0032] In some ~~embodiment~~examples, the method further comprises obtaining the compound of Formula (1D) by converting a compound of Formula (1E):



(1E)

to the compound of Formula (1D).

[0033] In some ~~embodiment~~examples, the method further comprises obtaining the compound of Formula (1E) by converting a compound of Formula (1F):



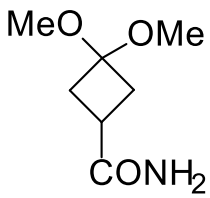
(1F)

to the compound of Formula (1E).

[0034] In some ~~embodiment~~examples, the reaction of the compound of Formula (1A) with the 2-chloro-3-fluoropyridine is performed in the presence of a base.

[0035] In some ~~embodiment~~examples, the base is sodium bis(trimethylsilyl)amide.

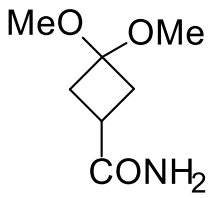
[0036] In another ~~aspect~~example, provided herein is a compound of Formula (1D):



(1D),

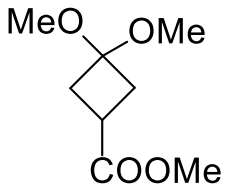
or a salt thereof.

[0037] In some ~~embodiment~~examples, provided herein is a method of preparing a compound of Formula (1D):



(1D),

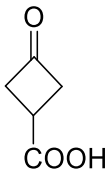
or a salt thereof, comprising converting a compound of Formula (1E):



(1E)

to the compound of Formula (1D) or a salt thereof.

[0038] In some ~~embodiment~~examples, the method further comprises obtaining the compound of Formula (1E) by converting a compound of Formula (1F):



(1F)

to the compound of Formula (1E).

DETAILED DESCRIPTION

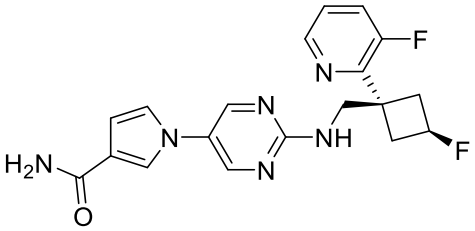
Definitions

[0039] As used herein and unless otherwise stated or implied by context, terms that are used herein have the meanings defined below. Unless otherwise contraindicated or implied, e.g., by including mutually exclusive elements or options, in those definitions and throughout this specification, the terms "a" and "an" mean one or more and the term "or" means and/or where permitted by context. Thus, as used in the specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise.

[0040] At various locations in the present disclosure, e.g., in any disclosed embodiments or in the claims, reference is made to compounds, compositions, or methods that "comprise" one or more specified components, elements or steps.

CLAIMS

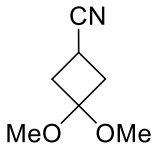
1. A method of preparing a compound of Formula (1):



(1) ,

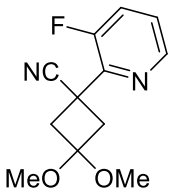
or a salt thereof, comprising:

(i) reacting a compound of Formula (1A):



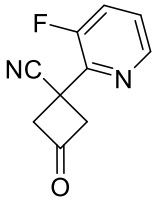
(1A)

with 2-chloro-3-fluoropyridine to form a compound of Formula (1B):



(1B);

(ii) reacting the compound of Formula (1B) with an aqueous acid to form a compound of Formula (1C):



(1C);

and

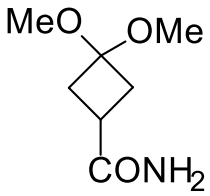
(iii) converting the compound of Formula (1C) to the compound of Formula (1) or a salt thereof.

2. The method of claim 1, further comprising obtaining the compound of Formula (1A) by reacting 1,3-dibromo-2,2-dimethoxypropane with *tert*-butyl 2-cyanoacetate to form the compound of Formula (1A).

3. The method of claim 2, wherein the reaction of the 1,3-dibromo-2,2-dimethoxypropane with the *tert*-butyl 2-cyanoacetate is performed in the presence of a base.

4. The method of claim 3, wherein the base is potassium *tert*-butoxide.

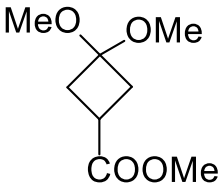
5. The method of claim 1, further comprising obtaining the compound of Formula (1A) by converting a compound of Formula (1D):



(1D)

to the compound of Formula (1A).

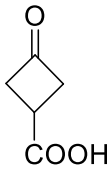
6. The method of claim 5, further comprising obtaining the compound of Formula (1D) by converting a compound of Formula (1E):



(1E)

to the compound of Formula (1D).

7. The method of claim 6, further comprising obtaining the compound of Formula (1E) by converting a compound of Formula (1F):



(1F)

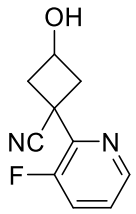
to the compound of Formula (1E).

8. The method of ~~any one of~~ claim~~s~~ 1~~-7~~, wherein step (i) is performed in the presence of a base.

9. The method of claim 8, wherein the base is sodium bis(trimethylsilyl)amide.

10. The method of ~~any one of~~ claim~~s~~ 1~~-9~~, wherein the aqueous acid of step (ii) is aqueous hydrochloric acid.

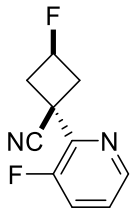
11. The method of ~~any one of~~ claim~~s~~ 1~~-10~~, wherein step (iii) comprises converting the compound of Formula (1C) to a compound of Formula (1G):



(1G),

and converting the compound of Formula (1G) to the compound of Formula (1) or a salt thereof.

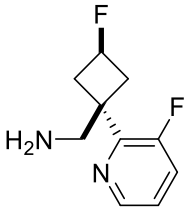
12. The method of claim 11, wherein step (iii) further comprises converting the compound of Formula (1G) to a compound of Formula (1H):



(1H),

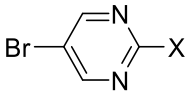
and converting the compound of Formula (1H) to the compound of Formula (1) or a salt thereof.

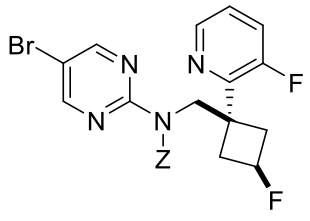
13. The method of claim 12, wherein step (iii) further comprises converting the compound of Formula (1H) to a compound of Formula (1I)



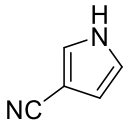
(1I),

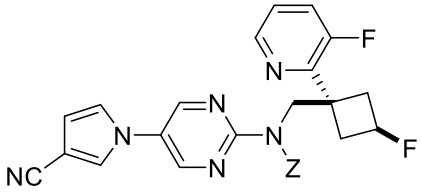
and converting the compound of Formula (1I) to the compound of Formula (1) or a salt thereof.

14. The method of claim 13, wherein step (iii) further comprises reacting the compound of Formula (1I) with , wherein X is chloro or fluoro, to form a compound of Formula (1J):


(1J),

wherein Z is a protecting group or hydrogen,
and converting the compound of Formula (1J) to the compound of Formula (1) or a salt thereof.

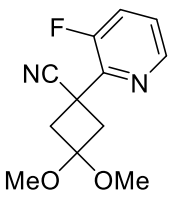
15. The method of claim 14, wherein step (iii) further comprises reacting the compound of Formula (1J) with  to form a compound of Formula (1K):


(1K),

wherein Z is a protecting group or hydrogen,
and converting the compound of Formula (1K) to the compound of Formula (1) or a salt thereof.

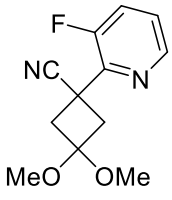
16. The method of claim 15, wherein step (iii) further comprises isolating the compound of Formula (1) or a salt thereof.

17. A compound of Formula (1B):


(1B),

or a salt thereof.

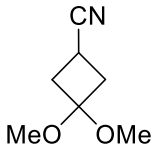
18. A method of preparing a compound of Formula (1B):



(1B),

or a salt thereof, comprising:

reacting a compound of Formula (1A):



(1A)

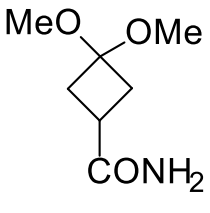
with 2-chloro-3-fluoropyridine to form the compound of Formula (1B).

19. The method of claim 18, further comprising obtaining the compound of Formula (1A) by reacting 1,3-dibromo-2,2-dimethoxypropane with *tert*-butyl 2-cyanoacetate to form the compound of Formula (1A).

20. The method of claim 19, wherein the reaction of the 1,3-dibromo-2,2-dimethoxypropane with the *tert*-butyl 2-cyanoacetate is performed in the presence of a base.

21. The method of claim 20, wherein the base is potassium *tert*-butoxide.

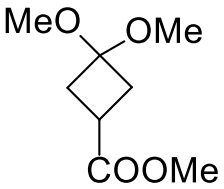
22. The method of claim 18, further comprising obtaining the compound of Formula (1A) by converting a compound of Formula (1D):



(1D)

to the compound of Formula (1A).

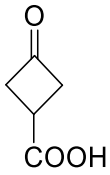
23. The method of claim 22, further comprising obtaining the compound of Formula (1D) by converting a compound of Formula (1E):



(1E)

to the compound of Formula (1D).

24. The method of claim 23, further comprising obtaining the compound of Formula (1E) by converting a compound of Formula (1F):



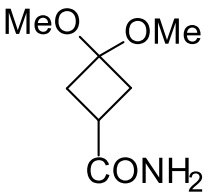
(1F)

to the compound of Formula (1E).

25. The method of ~~any one of~~ claim~~s~~ 18~~–24~~, wherein the reaction of the compound of Formula (1A) with the 2-chloro-3-fluoropyridine is performed in the presence of a base.

26. The method of claim 25, wherein the base is sodium bis(trimethylsilyl)amide.

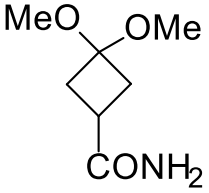
27. A compound of Formula (1D):



(1D),

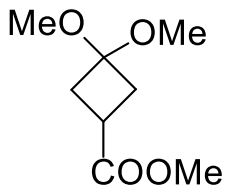
or a salt thereof.

28. A method of preparing a compound of Formula (1D):



(1D),

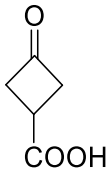
or a salt thereof, comprising converting a compound of Formula (1E):



(1E)

to the compound of Formula (1D) or a salt thereof.

29. The method of claim 28, further comprising obtaining the compound of Formula (1E) by converting a compound of Formula (1F):



(1F)

to the compound of Formula (1E).