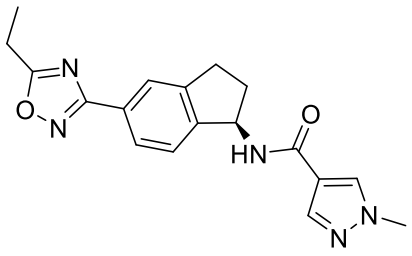
[0005] Current agents that target the cardiac sarcomere, such as inotropes (drugs that increase the contractile ability of the heart) are poorly selective for cardiac tissue, which leads to recognized adverse effects that limit their use. These adverse effects include cell damage caused by an increased rate of energy expenditure, exacerbation of relaxation abnormalities, and potential arrhythmogenic side effects that may result from increased cytosolic Ca++ and cyclic AMP concentrations in the inotropically stimulated myocardium. Given the limitations of current agents, new approaches are needed to improve cardiac function in HCM and HFpEF.

[0006] U.S. Patent No. 10,836,755 discloses (R)-N-(5-(5-ethyl-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-inden-1-yl)-1-methyl-1H-pyrazole-4-carboxamide, a selective allosteric inhibitor of cardiac myosin that has little to no effect on smooth muscle myosin. Benefits of this compound include a wider therapeutic index, less impact on cardiac relaxation, better pharmacokinetics, and better safety, and therefore it provides a potential treatment for cardiac diseases and conditions.

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

BRIEF SUMMARY

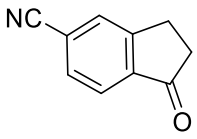
[0007a] In an aspect of the present disclosure, there is provided a method of preparing a compound of Formula (1):



(1),

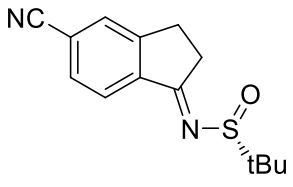
or a salt thereof, comprising:

(i) converting a compound of Formula (7)

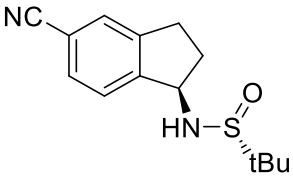


(7),

to a compound of Formula (6)

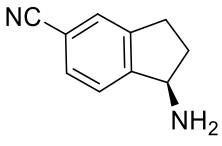
 (6);

(ii) converting the compound of Formula (6) to a compound of Formula (5)

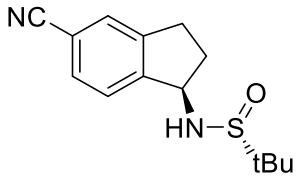
 (5);

(iii) converting the compound of Formula (5) to the compound of Formula (1) or salt thereof.

[0007b] In another aspect of the present disclosure, there is provided a method of preparing a compound of Formula (4)

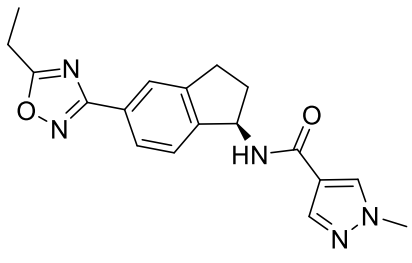
 (4),

or a salt thereof, comprising converting a compound of Formula (5):

 (5)

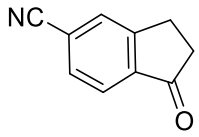
to the compound of Formula (4) or salt thereof.

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

 (1) ,

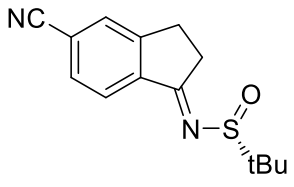
or a salt thereof, comprising

(i) converting a compound of Formula (7)



(7),

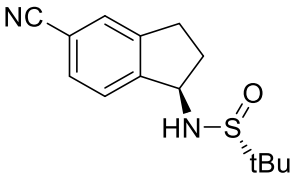
or a salt thereof, to a compound of Formula (6)



(6),

or salt thereof;

(ii) converting the compound of Formula (6) or salt thereof, to a compound of Formula (5)



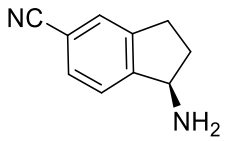
(5),

or a salt thereof; and

(iii) converting the compound of Formula (5) or salt thereof to the compound of Formula (1) or a salt thereof. In some examples, converting the compound of Formula (7) or salt thereof to the compound of Formula (6) or salt thereof comprises reacting the compound of Formula (7) with (R)-tert-butanesulfinamide. In some examples, reacting the compound of Formula (7) with (R)-tert-butanesulfinamide is performed in the presence of a Lewis acid. In some examples, reacting the compound of Formula (7) with (R)-tert-butanesulfinamide is performed in the presence of a water scavenger. In some examples, reacting the compound of Formula (7) with (R)-tert-butanesulfinamide is performed in the presence of titanium ethoxide. In some examples, reacting the compound of Formula (7) with (R)-tert-butanesulfinamide is performed in the presence of toluene at a temperature of between about 75 °C and about 85 °C.

[0009] In some examples, converting the compound of Formula (6) or salt thereof to the compound of Formula (5) or salt thereof comprises reacting the compound of Formula (6) with a reducing agent. In some examples, reacting the compound of Formula (6) with a reducing agent is performed in the presence of tetrahydrofuran at a temperature of between about -15 °C and about -5 °C. In some examples, the reducing agent is sodium borohydride. In some examples, the compound of Formula (6) is used without work-up or purification.

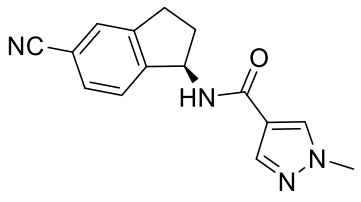
[0010] In some examples, converting the compound of Formula (5) or salt thereof to the compound of Formula (1) or a salt thereof comprises converting the compound of Formula (5) or salt thereof to the compound of Formula (4) or salt thereof.



(4)

In some examples, converting the compound of Formula (5) or salt thereof to the compound of Formula (4) or salt thereof comprises hydrolyzing the sulfinamide of the compound of Formula (5) or salt thereof. In some examples, hydrolyzing the sulfinamide of the compound of Formula (5) or salt thereof is performed in the presence of an aqueous acid. In some examples, the salt of the compound of Formula (4) is (R)-1-amino-2,3-dihydro-1H-indene-5-carbonitrile hydrochloride. In some examples, the salt of the compound of Formula (4) is (R)-1-amino-2,3-dihydro-1H-indene-5-carbonitrile 4-methylbenzenesulfonate. In some examples, the method further comprises obtaining the compound of Formula (4) by reacting the salt of the compound of Formula (4) with a base.

[0011] In some examples, converting the compound of Formula (5) or salt thereof to the compound of Formula (1) further comprises converting the compound of Formula (4) or salt thereof to a compound of Formula (3) or salt thereof.

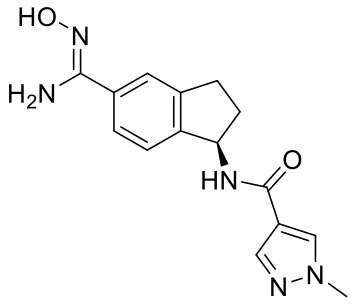


(3)

In some examples, converting the compound of Formula (4) or salt thereof to a compound of Formula (3) or salt thereof comprises: (i) reacting 1-methyl-1H-pyrazole-4-carboxylic acid with a carboxylic acid activating agent to form an activated 1-methyl-1H-pyrazole-4-carboxylic acid, and (ii) reacting the activated 1-methyl-1H-pyrazole-4-carboxylic acid with the compound of Formula (4) or a salt thereof, to form the compound of Formula (3) or salt thereof. In some examples, carboxylic acid activating agent is oxalyl chloride. In some examples, the

carboxylic acid activating agent comprises a carbodiimide reagent. In some examples, the carboxylic acid activating agent comprises a carbodiimide reagent and hydroxybenzotriazole.

[0012] In some examples, converting the compound of Formula (5) or salt thereof to the compound of Formula (1) or salt thereof further comprises converting the compound of Formula (3) or salt thereof to a compound of Formula (2) or salt thereof.

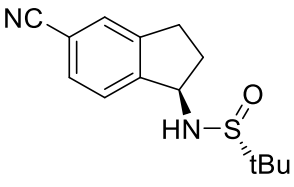


(2)

In some examples, converting the compound of Formula (3) or salt thereof to a compound of Formula (2) or salt thereof comprises reacting hydroxylamine with the compound of Formula (3) or salt thereof. In some examples, reacting the compound of Formula (3) or salt thereof with hydroxylamine is performed at a temperature of 25 °C or lower. In some examples, reacting the compound of Formula (3) or salt thereof with hydroxylamine is performed in the presence of N-methylpyrrolidone.

[0013] In some examples, converting the compound of Formula (5) or salt thereof to the compound of Formula (1) further comprises converting the compound of Formula (2) or salt thereof to the compound of Formula (1) or salt thereof. In some examples, converting the compound of Formula (2) or salt thereof to the compound of Formula (1) or salt thereof comprises: (i) reacting propionic acid with a second carboxylic acid activating agent to form an activated propionic acid, and (ii) reacting the activated propionic acid with the compound of Formula (2) or salt thereof. In some examples, the second carboxylic acid activating agent is carbonyldiimidazole.

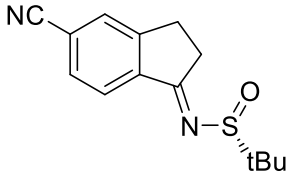
[0014] In another example, provided is a method of obtaining the compound of Formula (4) or salt thereof by converting a compound of Formula (5):



(5),

or a salt thereof, to the compound of Formula (4) or salt thereof.

[0015] In some examples, the method of obtaining the compound of Formula (4) further comprising obtaining the compound of Formula (5) or salt thereof by reacting a reducing agent with a compound of Formula (6):

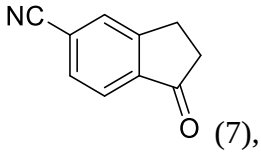


(6),

or a salt thereof, to form the compound of Formula (5) or salt thereof.

[0016] In some examples, the reducing agent is a borohydride reducing agent.

[0017] In some examples, the method of obtaining the compound of Formula (4) further comprises obtaining the compound of Formula (6) or salt thereof by reacting (R)-tert-butanesulfinamide with a compound of Formula (7):



(7),

to form the compound of Formula (6) or salt thereof.

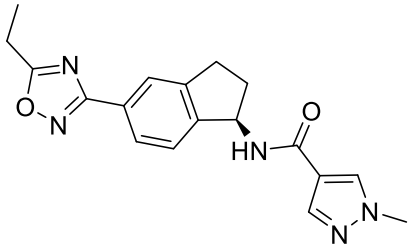
DETAILED DESCRIPTION

Definitions

[0018] 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

CLAIMS

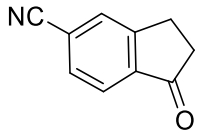
1. A method of preparing a compound of Formula (1):



(1),

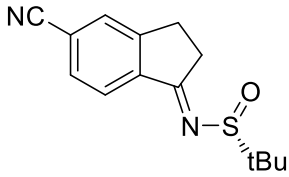
or a salt thereof, comprising:

(i) converting a compound of Formula (7)



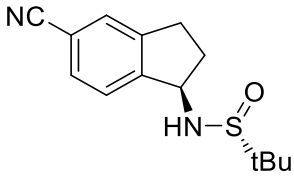
(7),

to a compound of Formula (6)



(6);

(ii) converting the compound of Formula (6) to a compound of Formula (5)



(5);

(iii) converting the compound of Formula (5) to the compound of Formula (1) or salt thereof.

2. The method of claim 1, wherein converting the compound of Formula (7) to the compound of Formula (6) comprises reacting the compound of Formula (7) with (R)-tert-butanesulfinamide.

3. The method of claim 2, wherein reacting the compound of Formula (7) with (R)-tert-butanesulfinamide is performed in the presence of a Lewis acid.

4. The method of claim 2 or 3, wherein reacting the compound of Formula (7) with (R)-tert-butanesulfinamide is performed in the presence of a water scavenger.

5. The method of any one of claims 2-4, wherein reacting the compound of Formula (7) with (R)-tert-butanesulfinamide is performed in the presence of titanium ethoxide.

6. The method of any one of claims 2-5, wherein reacting the compound of Formula (7) with (R)-tert-butanesulfinamide is performed in the presence of toluene at a temperature of between about 75 °C and about 85 °C.

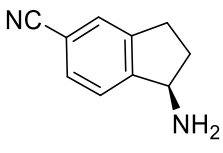
7. The method of any one of claims 1-6, wherein converting the compound of Formula (6) to the compound of Formula (5) comprises reacting the compound of Formula (6) with a reducing agent.

8. The method of claim 7, wherein reacting the compound of Formula (6) with a reducing agent is performed in the presence of tetrahydrofuran at a temperature of between about -15 °C and about -5 °C.

9. The method of claim 7 or 8, wherein the reducing agent is sodium borohydride.

10. The method of any one of claims 1-9, wherein the compound of Formula (6) is used without work-up or purification.

11. The method of any one of claims 1-10, wherein converting the compound of Formula (5) to the compound of Formula (1) or salt thereof comprises converting the compound of Formula (5) to the compound of Formula (4)



(4),

or a salt thereof.

12. The method of claim 11, wherein converting the compound of Formula (5) to the compound of Formula (4) or salt thereof comprises hydrolyzing the sulfinamide of the compound of Formula (5).

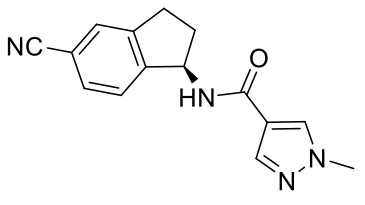
13. The method of claim 12, wherein hydrolyzing the sulfinamide of the compound of Formula (5) is performed in the presence of an aqueous acid.

14. The method of any one of claims 11-13, wherein the compound of Formula (4) is prepared as a hydrochloride salt.

15. The method of any one of claims 11-13, wherein the compound of Formula (4) is prepared as a 4-methylbenzenesulfonate salt.

16. The method of any one of claims 11-15, further comprising obtaining the compound of Formula (4) by reacting the salt of the compound of Formula (4) with a base.

17. The method of any one of claims 11-16, wherein converting the compound of Formula (5) to the compound of Formula (1) or salt thereof further comprises converting the compound of Formula (4) or salt thereof to a compound of Formula (3)



(3),

or a salt thereof.

18. The method of claim 17, wherein converting the compound of Formula (4) or salt thereof to the compound of Formula (3) or salt thereof comprises:

(i) reacting 1-methyl-1H-pyrazole-4-carboxylic acid with a carboxylic acid activating agent to form an activated 1-methyl-1H-pyrazole-4-carboxylic acid, and

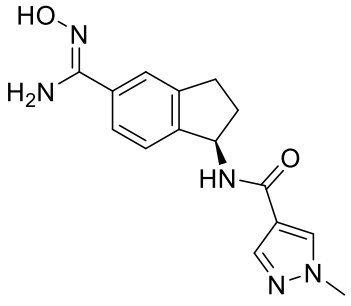
(ii) reacting the activated 1-methyl-1H-pyrazole-4-carboxylic acid with the compound of Formula (4) or salt thereof, to form the compound of Formula (3) or salt thereof.

19. The method of claim 18, wherein the carboxylic acid activating agent is oxalyl chloride.

20. The method of claim 18, wherein the carboxylic acid activating agent comprises a carbodiimide reagent.

21. The method of claim 18 or 20, wherein the carboxylic acid activating agent comprises a carbodiimide reagent and hydroxybenzotriazole.

22. The method of any one of claims 17-21, wherein converting the compound of Formula (5) to the compound of Formula (1) or salt thereof further comprises converting the compound of Formula (3) or salt thereof to a compound of Formula (2)



(2),

or a salt thereof.

23. The method of claim 22, wherein converting the compound of Formula (3) or salt thereof to the compound of Formula (2) or salt thereof comprises reacting hydroxylamine with the compound of Formula (3) or salt thereof.

24. The method of claim 23, wherein reacting the compound of Formula (3) or salt thereof with hydroxylamine is performed at a temperature of 25 °C or lower.

25. The method of claim 23 or 24, wherein reacting the compound of Formula (3) or salt thereof with hydroxylamine is performed in the presence of N-methylpyrrolidone.

26. The method of any one of claims 22-25, wherein converting the compound of Formula (5) to the compound of Formula (1) or salt thereof further comprises converting the compound of Formula (2) or salt thereof to the compound of Formula (1) or salt thereof.

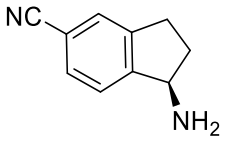
27. The method of claim 26, wherein converting the compound of Formula (2) or salt thereof to the compound of Formula (1) or salt thereof comprises:

(i) reacting propionic acid with a second carboxylic acid activating agent to form an activated propionic acid, and

(ii) reacting the activated propionic acid with the compound of Formula (2) or salt thereof.

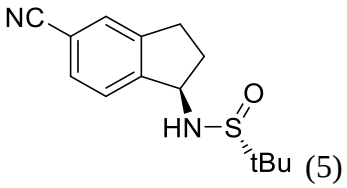
28. The method of claim 27, wherein the second carboxylic acid activating agent is carbonyldiimidazole.

29. A method of preparing a compound of Formula (4)



(4),

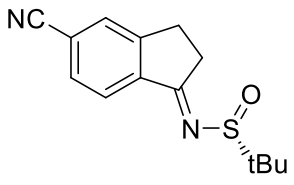
or a salt thereof, comprising converting a compound of Formula (5):



(5)

to the compound of Formula (4) or salt thereof.

30. The method of claim 29, further comprising obtaining the compound of Formula (5) by reacting a reducing agent with a compound of Formula (6):

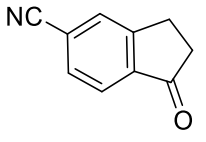


(6),

to form the compound of Formula (5).

31. The method of claim 30, wherein the reducing agent is a borohydride reducing agent.

32. The method of claim 30 or 31, further comprising obtaining the compound of Formula (6) by reacting (R)-tert-butanesulfinamide with a compound of Formula (7):



(7),

to form the compound of Formula (6).