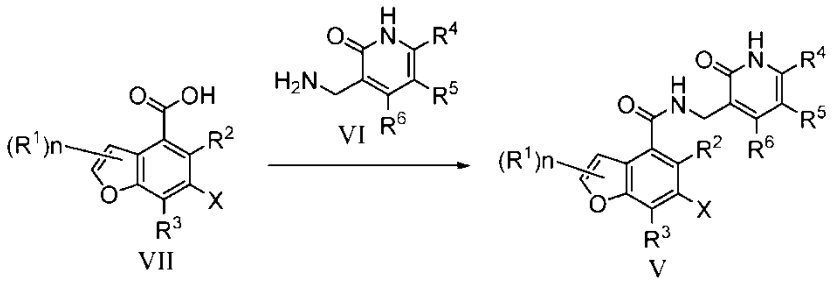
Claims

1. A method of preparing a compound of Formula V, or a pharmaceutically acceptable salt thereof, comprising the step of reacting a compound of Formula VI with a compound of Formula VII:



wherein:

each R^1 is the same or different, and each is independently selected from halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, or heterocycloalkyl is optionally substituted with one or more R^A, and wherein R^A is selected from halogen, hydroxy, cyano, amino, nitro, alkyl, alkoxy, cycloalkyl, and heterocycloalkyl;

R^2, R^3, R^4, R^5, R^6 are each independently selected from hydrogen, halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, and heterocycloalkyl, wherein the alkyl, alkoxy, cycloalkyl, or heterocycloalkyl is optionally substituted with one or more R^B, and wherein the R^B is selected from halogen, hydroxy, cyano, amino, and nitro;

n is selected from 1 or 2; and

X is halogen.

2. The method of preparing the compound of Formula V, or a pharmaceutically acceptable salt thereof, according to Claim 1, wherein:

R^1 is alkyl optionally substituted with R^A, wherein R^A is heterocycloalkyl.

3. The method of preparing the compound of Formula V, or a pharmaceutically acceptable salt thereof, according to Claim 1 or 2, wherein:

R^2, R^4, and R^6 are each independently alkyl.

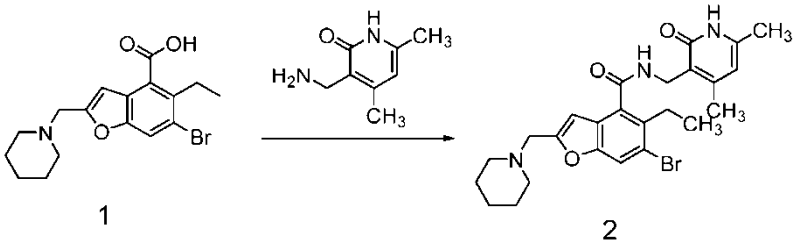
4. The method of preparing the compound of Formula V, or a pharmaceutically acceptable salt thereof, according to any one of Claims 1-3, wherein:

R^3 and R^5 are each independently hydrogen.

5. The method of preparing the compound of Formula V, or a pharmaceutically acceptable salt thereof, according to any one of Claims 1-4, wherein:

n is 1.

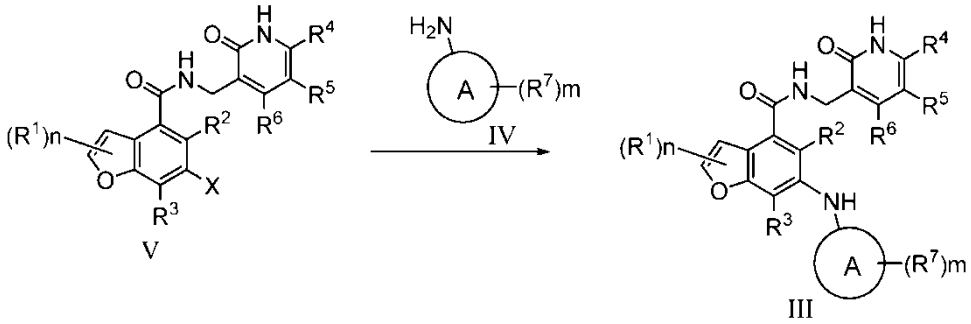
6. The method of preparing the compound of Formula V, or a pharmaceutically acceptable salt thereof, according to any one of Claims 1-5, comprising the step of reacting Compound 1, or a pharmaceutically acceptable salt thereof, with 3-(aminomethyl)-4,6-lutidine-2(1H)-one to obtain Compound 2, or a pharmaceutically acceptable salt thereof:



1 2

.

7. A method of preparing a compound of Formula III, or a pharmaceutically acceptable salt thereof, comprising the step of reacting a compound of Formula V, or a pharmaceutically acceptable salt thereof, with a compound of Formula IV,



V IV III

wherein:

ring A is selected from cycloalkyl and heterocycloalkyl;

R^7 is selected from halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl is optionally substituted with one or more R^c, wherein R^c is selected from halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

m is selected from 0, 1, 2, 3, 4, 5, or 6;

each R^1 is the same or different, and each is independently selected from halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, or heterocycloalkyl is optionally substituted with one or more R^A, and

wherein R^A is selected from halogen, hydroxy, cyano, amino, nitro, alkyl, alkoxy, cycloalkyl, and heterocycloalkyl;

R^2, R^3, R^4, R^5, R^6 are each independently selected from hydrogen, halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, and heterocycloalkyl, wherein the alkyl, alkoxy, cycloalkyl, or heterocycloalkyl is optionally substituted with one or more R^B, and

wherein R^B is selected from halogen, hydroxy, cyano, amino, and nitro;

n is selected from 1 or 2; and

X is halogen.

8. The method of preparing the compound of Formula III, or a pharmaceutically acceptable salt thereof, according to Claim 7, wherein:

ring A is heterocycloalkyl.

9. The method of preparing the compound of Formula III, or a pharmaceutically acceptable salt thereof, according to Claim 7 or 8, wherein:

m is 0.

10. The method of preparing the compound of Formula III, or a pharmaceutically acceptable salt thereof, according to any one of Claims 7-9, wherein:

R^1 is alkyl optionally substituted with R^A, wherein R^A is heterocycloalkyl.

11. The method of preparing the compound of Formula III, or a pharmaceutically acceptable salt thereof, according to any one of Claims 7-10, wherein:

R^2, R^4, and R^6 are each independently alkyl.

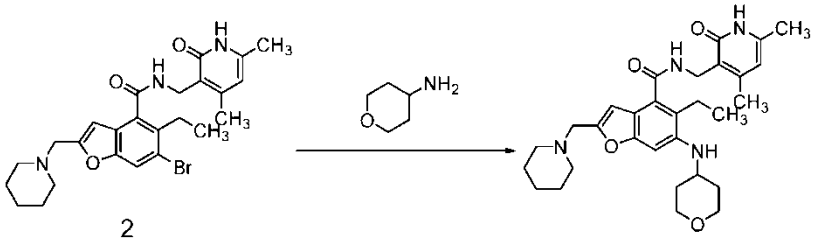
12. The method of preparing the compound of Formula III, or a pharmaceutically acceptable salt thereof, according to any one of Claims 7-11, wherein:

R^3 and R^5 are each independently hydrogen.

13. The method of preparing the compound of Formula III, or a pharmaceutically acceptable salt thereof, according to any one of Claims 7-12, wherein:

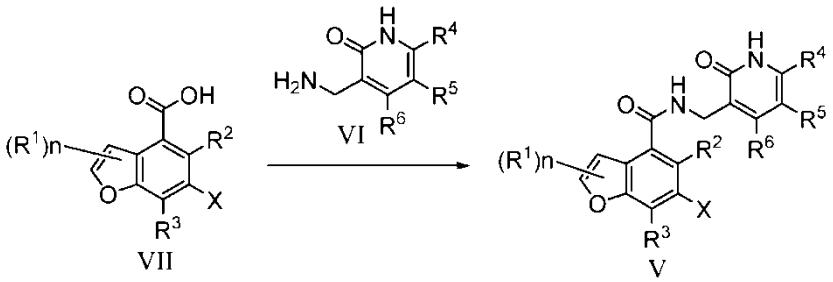
n is 1.

14. The method of preparing the compound of Formula III, or a pharmaceutically acceptable salt thereof, according to any one of Claims 7-13, comprising the step of reacting Compound 2, or a pharmaceutically acceptable salt thereof, with 4-aminotetrahydropyran to obtain Compound 3, or a pharmaceutically acceptable salt thereof:



2 3

15. The method of preparing the compound of Formula III, or a pharmaceutically acceptable salt thereof, according to any one of Claims 7-14, comprising the step of preparing a compound of Formula V, or a pharmaceutically acceptable salt thereof, with a compound of Formula VII



VII VI V

wherein:

each R^1 is the same or different, and each is independently selected from halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, or heterocycloalkyl is optionally substituted with one or more R^A, and

wherein R^A is selected from halogen, hydroxy, cyano, amino, nitro, alkyl, alkoxy, cycloalkyl, and heterocycloalkyl;

R^2, R^3, R^4, R^5, R^6 are each independently selected from hydrogen, halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, and heterocycloalkyl, wherein the alkyl,

alkoxy, cycloalkyl, or heterocycloalkyl is optionally substituted with one or more R^B, and

wherein R^B is selected from halogen, hydroxy, cyano, amino, and nitro;

n is selected from 1 or 2; and

X is halogen.

16. The method of preparing the compound of Formula III, or a pharmaceutically acceptable salt thereof, according to Claim 15, wherein:

R^1 is alkyl optionally substituted with R^A, wherein R^A is heterocycloalkyl.

17. The method of preparing the compound of Formula III, or a pharmaceutically acceptable salt thereof, according to Claim 15 or 16, wherein:

R^2, R^4, and R^6 are each independently alkyl.

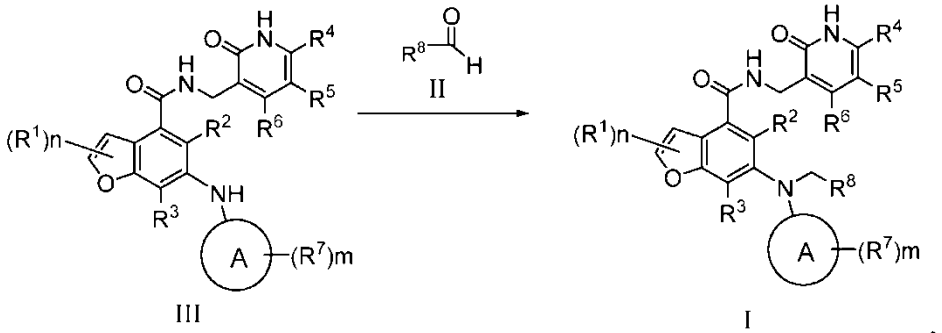
18. The method of preparing the compound of Formula III, or a pharmaceutically acceptable salt thereof, according to any one of Claims 15-17, wherein:

R^3 and R^5 are each independently hydrogen.

19. The method of preparing the compound of Formula III, or a pharmaceutically acceptable salt thereof, according to any one of Claims 15-18, wherein:

n is 1.

20. A method of preparing a compound of Formula I, or a pharmaceutically acceptable salt thereof, comprising the step of reacting a compound of Formula III, or a pharmaceutically acceptable salt thereof, with the compound of Formula II:



,

wherein:

R^8 is alkyl;

each R^1 is the same or different, and each is independently selected from halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, or heterocycloalkyl is optionally substituted with one or more R^A, and

wherein R^A is selected from halogen, hydroxy, cyano, amino, nitro, alkyl, alkoxy, cycloalkyl, and heterocycloalkyl;

R^2, R^3, R^4, R^5, R^6 are each independently selected from hydrogen, halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, and heterocycloalkyl, wherein the alkyl, alkoxy, cycloalkyl, or heterocycloalkyl is optionally substituted with one or more R^B, and

wherein R^B is selected from halogen, hydroxy, cyano, amino, and nitro;

n is selected from 1 or 2;

X is halogen;

ring A is selected from cycloalkyl and heterocycloalkyl;

R^7 is selected from halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl is optionally substituted with one or more R^c, and

wherein R^c is selected from halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; and

m is selected from 0, 1, 2, 3, 4, 5, or 6.

21. The method of preparing the compound of Formula I, or a pharmaceutically acceptable salt thereof, according to Claim 20, wherein:

R^1 is alkyl optionally substituted with R^A, wherein R^A is heterocycloalkyl.

22. The method of preparing the compound of Formula I, or a pharmaceutically acceptable salt thereof, according to Claim 20 or 21, wherein:

R^2, R^4, and R^6 are each independently alkyl.

23. The method of preparing the compound of Formula I, or a pharmaceutically acceptable salt thereof, according to any one of Claims 20-22, wherein:

R^3 and R^5 are each independently hydrogen.

24. The method of preparing the compound of Formula I, or a pharmaceutically acceptable salt thereof, according to any one of Claims 20-23, wherein:

n is 1.

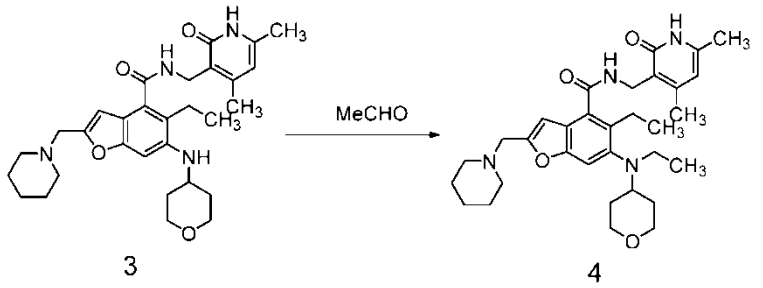
25. The method of preparing the compound of Formula I, or a pharmaceutically acceptable salt thereof, according to any one of Claims 20-24, wherein:

ring A is heterocycloalkyl.

26. The method of preparing the compound of Formula I, or a pharmaceutically acceptable salt thereof, according to any one of Claims 20-25, wherein:

m is 0.

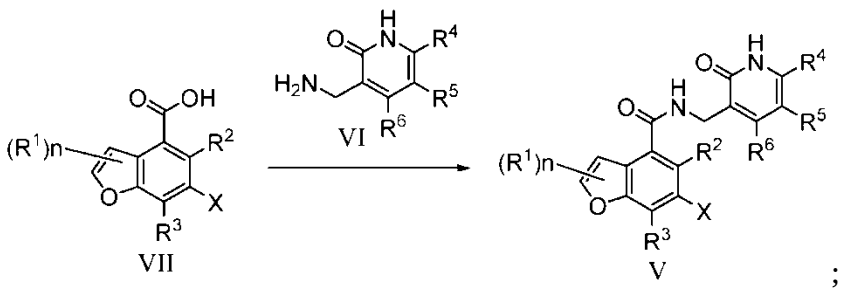
27. The method of preparing the compound of Formula I, or a pharmaceutically acceptable salt thereof, according to any one of Claims 20-26, comprising the step of reacting Compound 3, or a pharmaceutically acceptable salt thereof, with acetaldehyde to obtain Compound 4, or a pharmaceutically acceptable salt thereof:



3 4

.

28. The method of preparing the compound of Formula I, or a pharmaceutically acceptable salt thereof, according to any one of Claims 20-27, comprising the steps of preparing the compound of Formula V, or a pharmaceutically acceptable salt thereof, wherein the step comprises reacting a compound of Formula VII, or a pharmaceutically acceptable salt thereof, with a compound of Formula VI, or a pharmaceutically acceptable salt thereof:

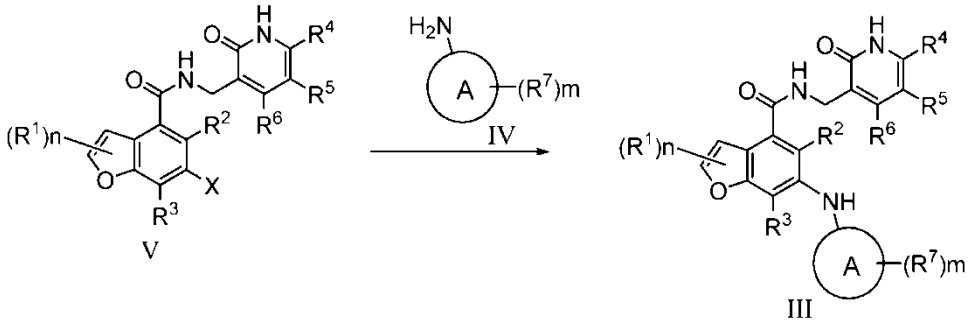


VII VI V

;

the method further comprising a step of preparing a compound of Formula III, or a

pharmaceutically acceptable salt thereof, wherein the step comprises reacting a compound of Formula V, or a pharmaceutically acceptable salt thereof, with a compound of Formula IV, or a pharmaceutically acceptable salt thereof:



wherein:

each R^1 is the same or different, and each is independently selected from halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, or heterocycloalkyl is optionally substituted with one or more R^A, and

wherein R^A is selected from halogen, hydroxy, cyano, amino, nitro, alkyl, alkoxy, cycloalkyl, and heterocycloalkyl;

R^2, R^3, R^4, R^5, R^6 are each independently selected from hydrogen, halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, and heterocycloalkyl, wherein the alkyl, alkoxy, cycloalkyl, or heterocycloalkyl is optionally substituted with one or more R^B, and

wherein R^B is selected from halogen, hydroxy, cyano, amino, and nitro;

n is selected from 1 or 2;

X is halogen;

ring A is selected from cycloalkyl and heterocycloalkyl;

R^7 is selected from halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl is optionally substituted with one or more R^c, and

wherein R^c is selected from halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; and

m is selected from 0, 1, 2, 3, 4, 5, or 6.

29. The method of preparing the compound of Formula I, or a pharmaceutically acceptable salt thereof, according to Claim 28, wherein:

R^1 is alkyl optionally substituted with R^A, wherein R^A is heterocycloalkyl.

30. The method of preparing the compound of Formula I, or a pharmaceutically acceptable salt thereof, according to Claim 28 or 29, wherein:

R^2, R^4, and R^6 are each independently alkyl.

31. The method of preparing the compound of Formula I, or a pharmaceutically acceptable salt thereof, according to any one of Claims 28-30, wherein:

R^3 and R^5 are each independently hydrogen.

32. The method of preparing the compound of Formula I, or a pharmaceutically acceptable salt thereof, according to any one of Claims 28-31, wherein:

n is 1.

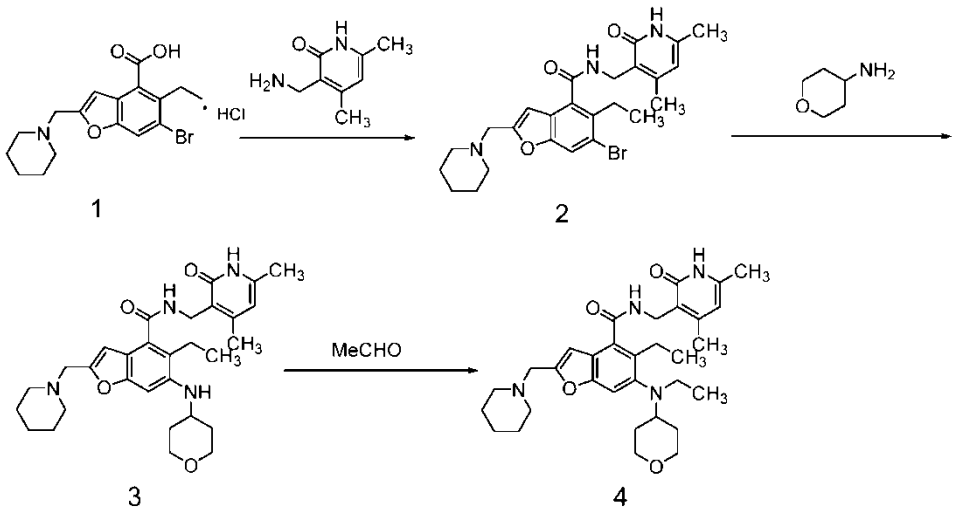
33. The method of preparing the compound of Formula I, or a pharmaceutically acceptable salt thereof, according to any one of Claims 28-32, wherein:

ring A is heterocycloalkyl.

34. The method of preparing the compound of Formula I, or a pharmaceutically acceptable salt thereof, according to any one of Claims 28-33, wherein:

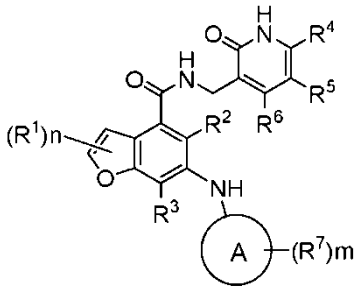
m is 0.

35. The method of preparing the compound of Formula I, or a pharmaceutically acceptable salt thereof, according to any one of Claims 28-34, comprising the steps of reacting Compound 1, or a pharmaceutically acceptable salt thereof, with 3-(aminomethyl)-4,6-lutidine-2(1H)-one to obtain Compound 2, or a pharmaceutically acceptable salt thereof; reacting Compound 2, or a pharmaceutically acceptable salt thereof, with 4-aminotetrahydropyran to obtain Compound 3; and reacting Compound 3, or a pharmaceutically acceptable salt thereof, with acetaldehyde to obtain Compound 4, or a pharmaceutically acceptable salt thereof:



1 2 3 4

36. A compound of Formula III, or a pharmaceutically acceptable salt thereof:



III ,

wherein each R^1 is the same or different, and each is independently selected from halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, or heterocycloalkyl is optionally substituted with one or more R^A, and

wherein R^A is selected from halogen, hydroxy, cyano, amino, nitro, alkyl, alkoxy, cycloalkyl, and heterocycloalkyl;

R^2, R^3, R^4, R^5, R^6 are each independently selected from hydrogen, halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, and heterocycloalkyl, wherein the alkyl, alkoxy, cycloalkyl, or heterocycloalkyl is optionally substituted with one or more R^B, and

wherein R^B is selected from halogen, hydroxy, cyano, amino, and nitro;

n is selected from 1 or 2;

X is halogen;

ring A is selected from cycloalkyl and heterocycloalkyl;

R^7 is selected from halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, heterocycloalkyl,

aryl, or heteroaryl is optionally substituted with one or more R^c, and

wherein R^c is selected from halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; and

m is selected from 0, 1, 2, 3, 4, 5, or 6.

37. The compound of Formula III, or a pharmaceutically acceptable salt thereof, according to Claim 36, wherein:

R^1 is alkyl optionally substituted with R^A, wherein R^A is heterocycloalkyl.

38. The compound of Formula III, or a pharmaceutically acceptable salt thereof, according to Claim 36 or 37, wherein:

R^2, R^4, and R^6 are each independently alkyl.

39. The compound of Formula III, or a pharmaceutically acceptable salt thereof, according to any one of Claims 36-38, wherein:

R^3 and R^5 are each independently hydrogen.

40. The compound of Formula III, or a pharmaceutically acceptable salt thereof, according to any one of Claims 36-39, wherein:

n is 1.

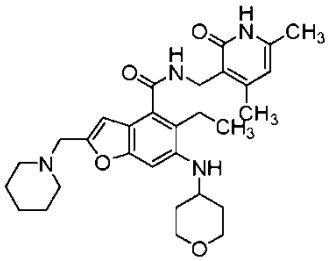
41. The compound of Formula III, or a pharmaceutically acceptable salt thereof, according to any one of Claims 36-40, wherein:

ring A is heterocycloalkyl.

42. The compound of Formula III, or a pharmaceutically acceptable salt thereof, according to any one of Claims 36-41, wherein:

m is 0.

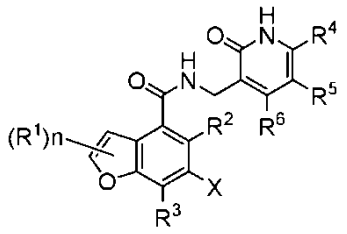
43. The compound of Formula III, or a pharmaceutically acceptable salt thereof, according to any one of Claims 36-42, wherein the compound is:



3

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44. A compound of Formula V, or a pharmaceutically acceptable salt thereof:



V

,

wherein,

each R^1 is the same or different, and each is independently selected from halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, or heterocycloalkyl is optionally substituted with one or more R^A, and wherein R^A is selected from halogen, hydroxy, cyano, amino, nitro, alkyl, alkoxy, cycloalkyl, and heterocycloalkyl;

R^2, R^3, R^4, R^5, R^6 are each independently selected from hydrogen, halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, and heterocycloalkyl, wherein the alkyl, alkoxy, cycloalkyl, or heterocycloalkyl is optionally substituted with one or more R^B, and wherein R^B is selected from halogen, hydroxy, cyano, amino, and nitro;

n is selected from 1 or 2; and

X is halogen.

45. The compound of Formula V, or a pharmaceutically acceptable salt thereof, according to Claim 44, wherein:

R^1 is alkyl optionally substituted with R^A, wherein R^A is heterocycloalkyl.

46. The compound of Formula V, or a pharmaceutically acceptable salt thereof, according to Claim 44 or 45, wherein:

R^2, R^4, and R^6 are each independently alkyl.

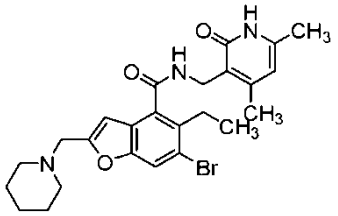
47. The compound of Formula V, or a pharmaceutically acceptable salt thereof, according to any one of Claims 44-46, wherein:

R^3 and R^5 are each independently hydrogen.

48. The compound of Formula V, or a pharmaceutically acceptable salt thereof, according to any one of Claims 44-47, wherein:

n is 1.

49. The compound of Formula V, or a pharmaceutically acceptable salt thereof, according to any one of Claims 44-48, wherein the compound is:



2 .

50. A pharmaceutical composition, comprising a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, prepared according to the methods of any one of Claims 20-35, and one or more pharmaceutically acceptable carriers, diluents, or excipients.

51. The method of preparing a compound of Formula V, or a pharmaceutically acceptable salt thereof, according to any one of Claims 1-6, comprising reacting the compound of Formula VI, or a pharmaceutically acceptable salt thereof, and the compound of Formula VII, or a pharmaceutically acceptable salt thereof, in the presence of a condensing agent selected from N,N-carbonyldiimidazole (CDI), dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), 4-dimethylaminopyridine (DMAP), 4-pyrrolidinylpyridine (4-PPY), 1-hydroxybenzotriazole (HOBT), 1-hydroxy-7-azabenzotriazazol (HOAT), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), O-benzotriazole-tetramethylureahexafluorophosphate (HBTU), or a combination thereof.

52. The method of preparing a compound of Formula V, or a pharmaceutically

acceptable salt thereof, according to Claim 51, wherein the condensing agent is a combination of EDCI and HOBT.

53. The method of preparing a compound of Formula III, or a pharmaceutically acceptable salt thereof, according to any one of Claims 7-19, comprising reacting the compound of Formula V, or a pharmaceutically acceptable salt thereof, and the compound of Formula IV, or a pharmaceutically acceptable salt thereof, in the presence of a palladium catalyst and a phosphine ligand.

54. The method of preparing a compound of Formula III, or a pharmaceutically acceptable salt thereof, according to Claim 53, wherein the palladium catalyst is bis(dibenzylideneacetone)palladium ($Pd(dba)_2$) and the phosphine ligand is R-(+)-2,2'-bis(diphenylphosphine)-1,1'-binaphthalene (BINAP).

55. The method of preparing a compound of Formula I, or a pharmaceutically acceptable salt thereof, according to any one of Claims 20-35, comprising reacting the compound of Formula III, or a pharmaceutically acceptable salt thereof, and the compound of Formula II, or a pharmaceutically acceptable salt thereof, in the presence of a reducing agent.

56. The method of preparing a compound of Formula I, or a pharmaceutically acceptable salt thereof, according to Claim 55, wherein the reducing agent is sodium borohydride acetate.