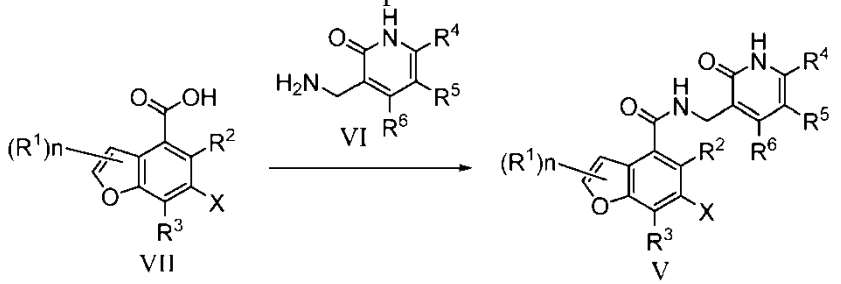


WO2019091450A also discloses a method of preparing a previously described compound, and the present disclosure provides a new method of preparing a pharmaceutically acceptable salt of the compound in consideration of simplifying the preparation process and reducing production costs.

Summary

The present disclosure provides a method of preparing a compound of Formula V or a pharmaceutically acceptable salt thereof, comprising the step of reacting the compound of Formula VI with the compound of Formula VII:



wherein:

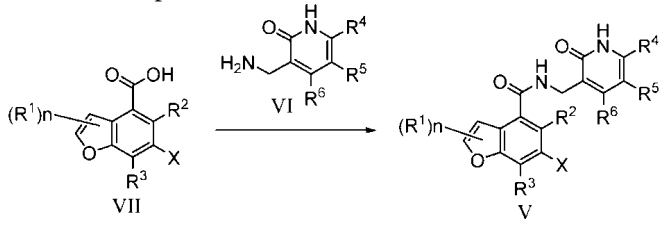
R^1 is the same or different, each independently selected from halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl. The alkyl, alkoxy, cycloalkyl, or heterocycloalkyl optionally substituted with one or more R^A. The R^A is selected from halogen, hydroxy,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

n is selected from 1 or 2.

X is selected from halogen.

In one aspect, the present disclosure refers to 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:



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

n is selected from 1 or 2; and

X is halogen.

In an optional example, the method of preparing a compound of formula V or a pharmaceutically acceptable salt thereof, wherein the compound of formula VI reacts with the compound of formula VII under the action of a condensing agent.

In an optional example, the condensing agent is 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), 2-(7-azabenzotriazole)-N,N',N',' N'-tetramethylureahexafluorophosphate (HATU), and O-benzotriazole-tetramethylureahexafluorophosphate (HBTU).

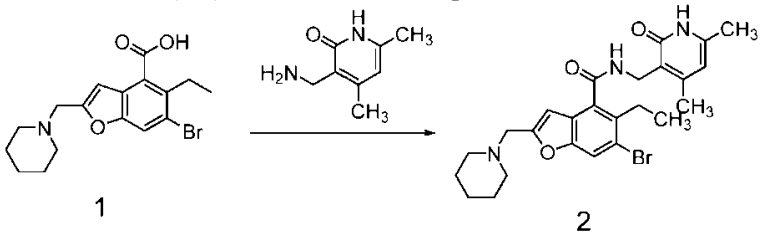
In an optional example, the condensing agent is selected from a combination of EDCI and HOBT.

In an optional example, the compound of Formula V or a pharmaceutically acceptable salt thereof is prepared and reacted in a basic environment.

In an optional example, the method of preparing a compound of Formula V or a pharmaceutically acceptable salt thereof provides a basic environment selected from the group consisting of triethylamine, pyridine, and N,N-diisopropylethylamine (DIPEA).

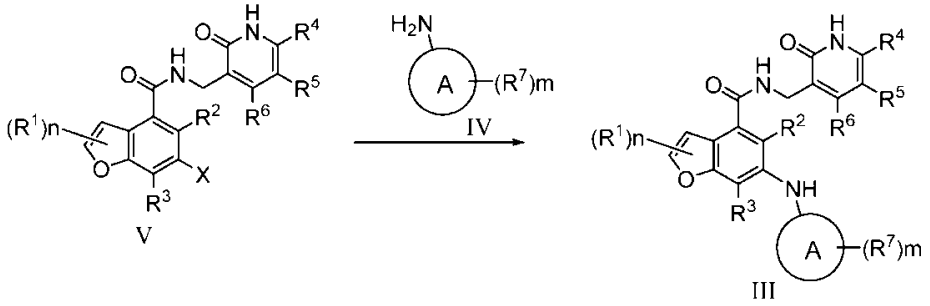
In an optional example, in the method of preparing a compound of formula V in the present disclosure or a pharmaceutically acceptable salt thereof, the reaction solvent is selected from N,N-dimethylformamide (DMF) or dichloromethane.

In an optional example, the method of preparing a compound of formula V or a pharmaceutically acceptable salt thereof, comprising the step of reacting Compound 1 with 3-(aminomethyl)-4,6-lutidine-2(1H)-one to obtain Compound 2:



1 2

Another example of the present disclosure provides a method of preparing a compound of Formula III or a pharmaceutically acceptable salt thereof, which comprises the step of reacting the compound of Formula V with the compound of Formula IV:



wherein:

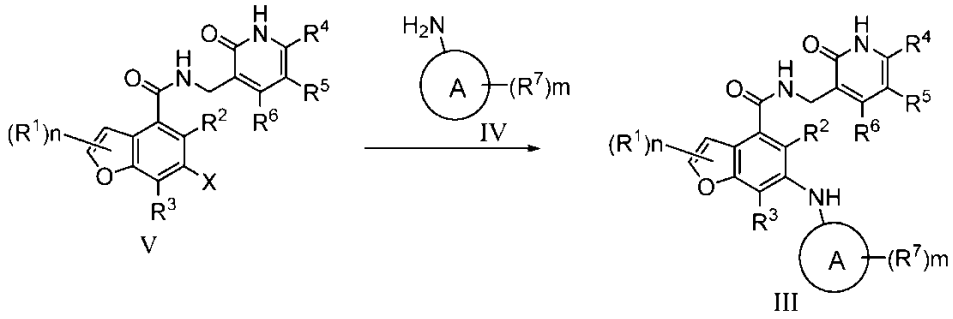
ring A is selected from cycloalkyl and heterocycloalkyl.

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

R^1, R^2, R^3, R^4, R^5, R^6, and n are defined in the compounds of formula V, respectively.

In one aspect, the present disclosure refers to 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,



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.

In an optional example, the compound of Formula V in the preparation method of a compound of Formula III or a pharmaceutically acceptable salt thereof reacts with the compound of Formula IV in the presence of a palladium catalyst and a phosphine ligand catalyst.

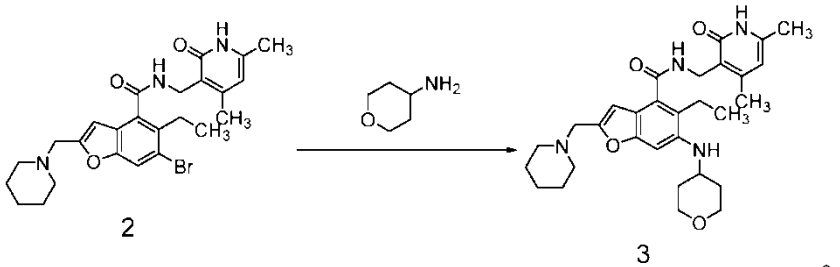
The palladium catalyst in an optional example is bis(dibenzylideneacetone)palladium ($Pd(dba)_2$).

In an optional example, the phosphine ligand catalyst is R-(+)-2,2'-bis(diphenylphosphine)-1,1'-binaphthalene (BINAP).

In an optional example, a compound of Formula III or a pharmaceutically acceptable salt thereof is reacted in a basic environment.

In an optional example, the method of preparing a compound of Formula III or a pharmaceutically acceptable salt thereof provides a basic environment selected from potassium tert-butanol (tBuOK) and/or sodium tert-butanol (tBuONa).

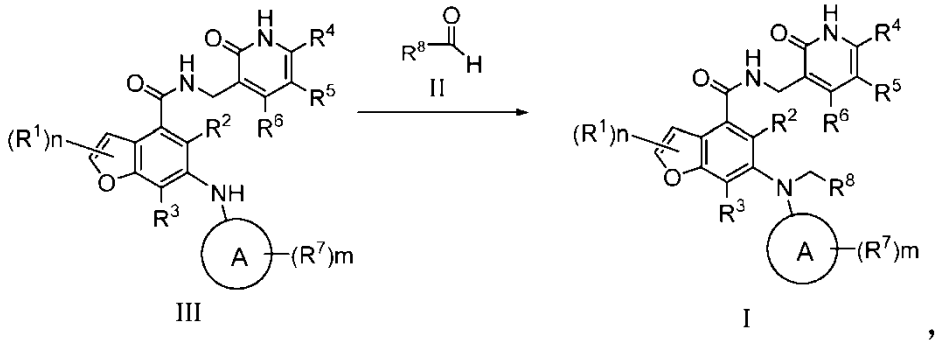
In an optional example, the method of preparing a compound of formula III or a pharmaceutically acceptable salt thereof comprises the step of reacting Compound 2 with 4-aminotetrahydropyran to obtain Compound 3:



2 3

In an optional example, the method of preparing a compound of Formula III provided in the present disclosure or a pharmaceutically acceptable salt thereof, further comprising the steps in the method of preparing the aforementioned compound of Formula V or a pharmaceutically acceptable salt thereof.

Another example of the present disclosure provides a method of preparing a compound of Formula I or a pharmaceutically acceptable salt thereof, which comprises the step of reacting the compound of Formula III with the compound of Formula II:



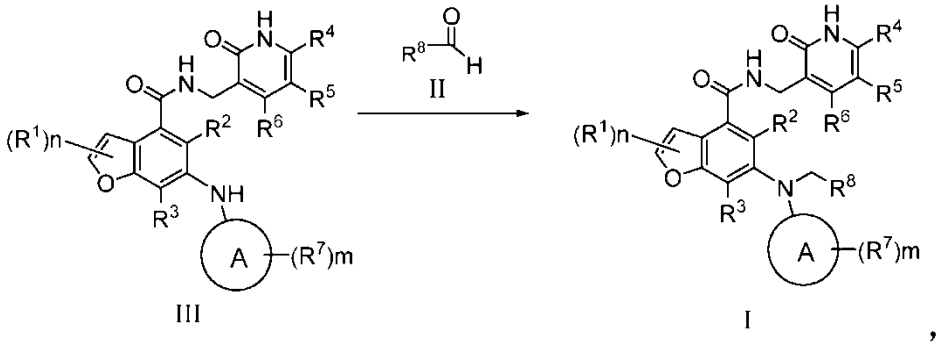
III I ,

wherein:

R^8 is alkyl.

R^1, R^2, R^3, R^4, R^5, R^6, R^7, Ring A, n, and m are defined in the compounds of Formula III, respectively.

In one aspect, the present disclosure refers to 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:



III I ,

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.

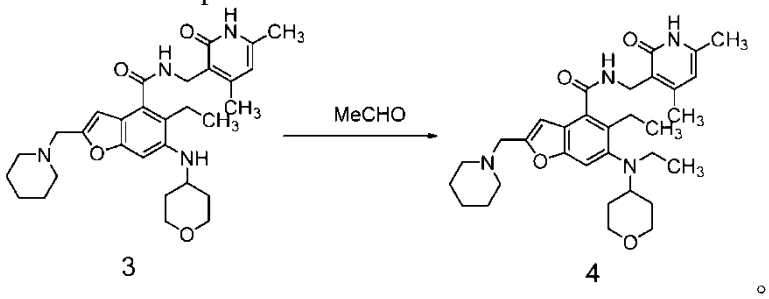
In an optional example, the method of preparing the compound of Formula I or a pharmaceutically acceptable salt thereof is reacted under a weak acid environment.

In an optional example, in the method of preparing a compound of Formula I or a pharmaceutically acceptable salt thereof, the weak acidic environment is provided by acetic acid.

In an optional example, in the method of preparing a compound of Formula I or a pharmaceutically acceptable salt thereof, the compound of Formula III reacts with a compound of Formula II in the presence of a reducing agent.

In an optional example, the reducing agent is selected from sodium borohydride or sodium cyanoborohydride.

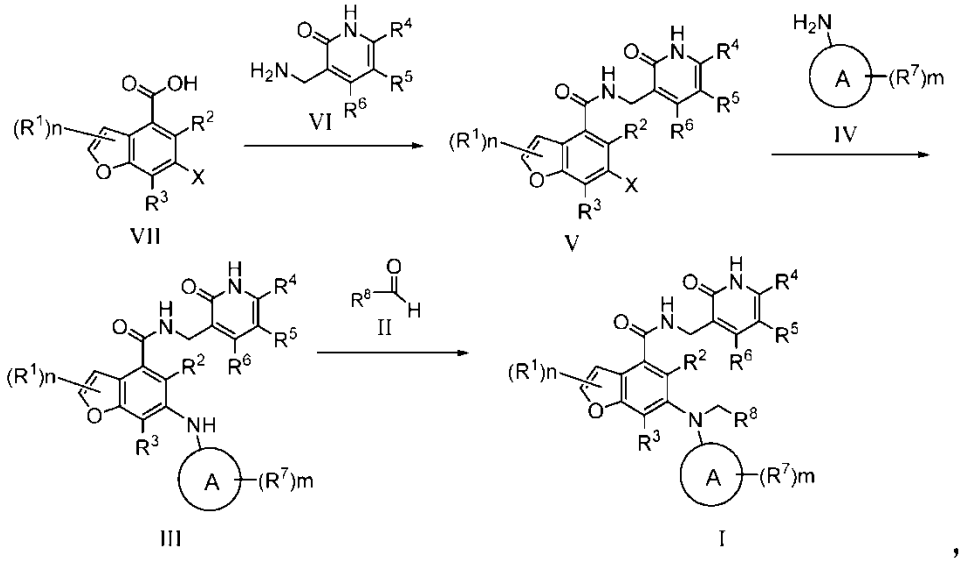
In an optional example, the method of preparing a compound of Formula I or a pharmaceutically acceptable salt thereof, comprising the step of reacting Compound 3 with acetaldehyde to obtain Compound 4:



3 4

In an optional example, the method of preparing a compound of Formula I provided in the present disclosure or a pharmaceutically acceptable salt thereof, further comprising the steps in the aforementioned method of preparing a compound of Formula V or a pharmaceutically acceptable salt thereof and/or the steps in the aforementioned method of preparing a compound of Formula III or a pharmaceutically acceptable salt thereof.

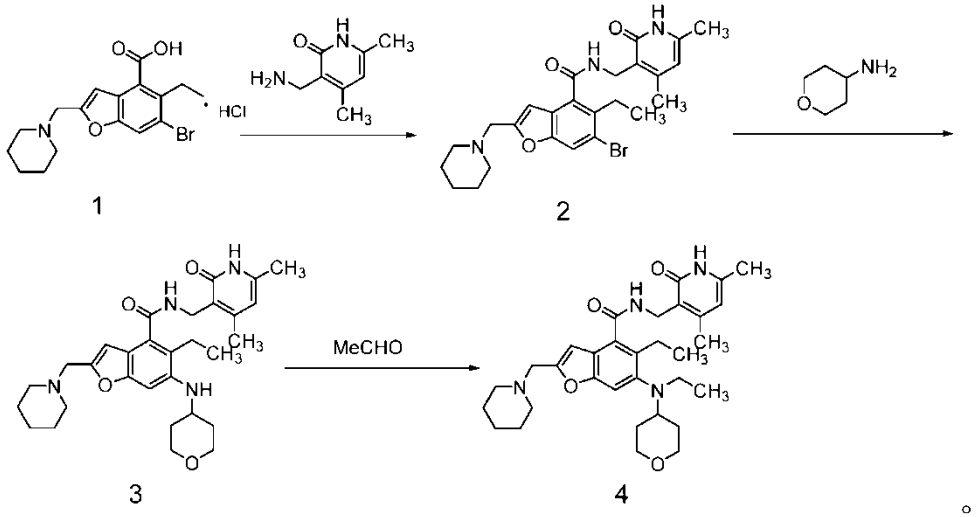
In an optional example, the present disclosure provides a method of preparing a compound of Formula I or a pharmaceutically acceptable salt thereof, which comprises the steps of:



VII VI V IV III II I

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, ring A, n, and m are as previously described, respectively.

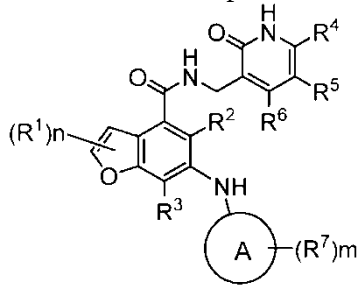
In an optional example, the method of preparing a compound of Formula I provided in the present disclosure or a pharmaceutically acceptable salt thereof, comprising the steps of:



1 2 3 4

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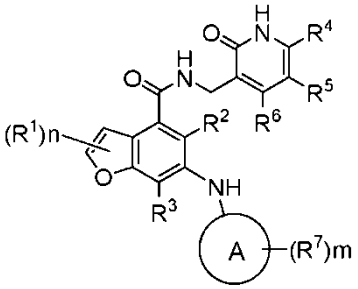
According to another example of the present disclosure, a compound of Formula III or a pharmaceutically acceptable salt thereof is provided:



III ,

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, ring A, n, and m are as previously described, respectively.

In one aspect, the present disclosure refers to 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;

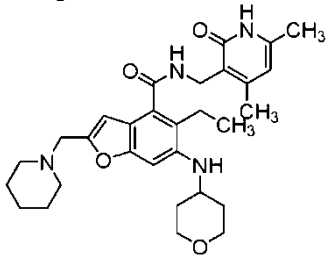
ring A is selected from cycloalkyl and heterocycloalkyl;

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

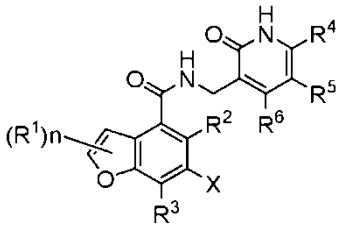
m is selected from 0, 1, 2, 3, 4, 5, or 6.

In an optional example, the compound of Formula III or a pharmaceutically acceptable salt thereof provided in the present disclosure are:



3

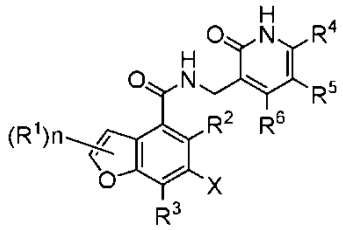
According to another example of the present disclosure, a compound of Formula V or a pharmaceutically acceptable salt thereof is provided:



V ,

wherein R^1, R^2, R^3, R^4, R^5, R^6, n, and m are as previously described, respectively.

In one aspect, the present disclosure refers to a compound of Formula V, or a pharmaceutically acceptable salt thereof:



V ,

wherein,

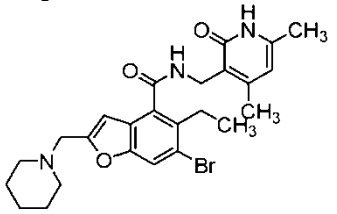
each R^1 is the same or different, and each is independently selected from halogen, alkyl, alkoxy, amino, nitro, hydroxy, cyano, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein the alkyl, alkoxy, cycloalkyl, or heterocycloalkyl is optionally substituted with one or more R^A, and wherein R^A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

In an optional example, a compound of Formula V provided in the present disclosure or a pharmaceutically acceptable salt thereof, which is:



2 。

In one aspect, the present disclosure refers to 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 disclosed herein, and one or more pharmaceutically acceptable carriers, diluents, or excipients.

Detailed Description of the Invention

Unless stated to the contrary, terms used in the Specification and Claims have the following meanings.

The term “alkyl” refers to a saturated aliphatic hydrocarbon group, which is a linear or branched group comprising 1 to 20 carbon atoms, preferably an alkyl group comprising 1 to 12 carbon atoms. Non-limiting examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, n-hexyl, n-octyl, n-heptyl, isooctyl, decyl, undecyl, dodecyl, and various branched isomers thereof, and the like.

The term “cycloalkyl” refers to a saturated or partially unsaturated monocyclic or polycyclic hydrocarbon substituent, with the cycloalkyl ring comprising 3 to 20 carbon atoms, preferably 3 to 12 carbon atoms, preferably 3 to 10 carbon atoms, more preferably 3 to 6 carbon atoms. Non-limiting examples of monocycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, cycloheptyl, cycloheptatrienyl, cyclooctyl, and the like. Polycycloalkyl groups include cycloalkyl groups of spirocyclic, fused, and bridged rings.