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(54) Titre : PROCÉDE DE FABRICATION DE COMPOSÉS BIOLOGIQUEMENT ACTIFS ET D'INTERMÉDIAIRES
CONNEXES

(54) Title: PROCESS FOR MAKING BIOLOGICALLY ACTIVE COMPOUNDS AND INTERMEDIATES THEREOF

(57) Abrégé/Abstract:

A process of manufacturing biologically active compounds, their analogs, pharmaceutically acceptable salts, solvates, polymorphs, isotopic variants, and intermediates thereof. Notably, the compounds of the formula IA, 1B, 1C, 1D, 1E, 1F and 1G for which novel processes have been disclosed, selectively act on the cannabinoid receptors, and with high affinity. The processes for the preparation of the compounds enable the syntheses of cannabinoid modulators on a large-scale that are eco-friendly and economically viable. Additionally, the processes disclosed enable the synthesis of cannabinoid modulators with high purity and in high yield for their use in making drug substance and drug products.



Abstract

A process of manufacturing biologically active compounds, their analogs, pharmaceutically acceptable salts, solvates, polymorphs, isotopic variants, and intermediates thereof. Notably, the compounds of the formula IA, 1B, 1C. 1D. 1E, 5 1F and IG for which novel processes have been disclosed, selectively act on the cannabinoid receptors, and with high affinity. The processes for the preparation of the compounds enable the syntheses of cannabinoid modulators on a large-scale that are eco-friendly and economically viable. Additionally, the processes disclosed enable the synthesis of cannabinoid modulators with high purity and in 10 high yield for their use in making drug substance and drug products.

PROCESS FOR MAKING BIOLOGICALLY ACTIVE COMPOUNDS AND INTERMEDIATES THEREOF

Background

5 The present invention relates to a chemical process for the preparation of compounds of one of Formulae I, IA, IB, IC, ID, IE, 1F. and 1G. and IV, IVA, IVB, IVC, V and VI and intermediates thereof.

More specifically, the invention relates to a chemical process for the preparation of 5-[4-(4-cyano-1-butyn-1-yl)phenyl]-1-(2,4-dichlorophenyl)-N-(1,1-dioxido-4-thiomorpholinyl)-4-methyl-1H-pyrazole-3-carboxamide and 5-(4-(4-cyanobut-1-yn-1-yl)phenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-morpholino-1H-pyrazole-3-carboxamide and their analogs, solvates, polymorphs and isotopic variations thereof.

Compounds of this class with unique pharmacological properties and therapeutic value have been disclosed in WO200674445, WO2008154015 and WO2010104488.

Summary

Disclosed herein are processes for the preparation of compounds comprising, reacting a compound of Formula II with a compound of Formula III to provide a compound of Formula VII, second by reacting a compound of Formula VII with an alkyne in the presence of a palladium reagent and copper (I) iodide, in a basic medium and in an aprotic solvent to obtain a product of Formula I, third by hydrolysis of a compound of the Formula I using an alkali metal hydroxide to provide a compound of Formula V, and fourth by reacting a compound of Formula V with a substituted hydrazine.

Disclosed herein are processes for the preparation of compounds comprising, reacting a compound of Formula II with a compound of Formula III to provide a compound of Formula VII, second by reacting a compound of Formula VII with an alkyne in the presence of a palladium reagent and copper (I) iodide, in a basic medium and in an aprotic solvent to obtain a product of Formula I, third by reacting

a compound of Formula I with a substituted hydrazine, and fourth by reacting a compound of Formula V with a divinyl derivative.

Disclosed herein are processes for the preparation of compounds comprising, reacting a compound of Formula II with a compound of Formula III to provide a compound of Formula I, second by hydrolysis of a compound of the Formula I using an alkali metal hydroxide to provide a compound of Formula V, and third by reacting a compound of Formula V with a substituted hydrazine.

Also disclosed are alternative processes for preparing compounds comprising, reacting a compound of Formula II with a compound of Formula III to provide a compound of Formula I, second by hydrolysis of a compound of the Formula I using an alkali metal hydroxide to provide a compound of Formula V, and third by reacting a compound of Formula V with a substituted hydrazine.

Specifically, the disclosed herein are alternative processes for preparing compounds comprising, first reacting a compound of Formula II with a compound of Formula III to obtain product of the Formula VII, second by reacting a compound of Formula VII with an alkyne in the presence of a palladium reagent such as tetrakis(triphenylphosphine)palladium(0) and copper (I) iodide, in a basic medium and in an aprotic solvent to obtain a product of Formula I, and third by reacting the product of the Formula I using an alkali metal hydroxide to provide a compound of Formula V, fourth by reacting a compound of Formula V with 4-aminothiomorpholine 1,1-dioxide.

Specifically, the disclosed herein are alternative processes for preparing compounds comprising, first reacting a compound of Formula II with a compound of Formula III to obtain product of the Formula VII, second by reacting a compound of Formula VII with an alkyne in the presence of a palladium reagent such as tetrakis(triphenylphosphine)palladium(0) and copper (I) iodide, in a basic medium and in an aprotic solvent to obtain a product of Formula I, and third by reacting the product of the Formula I using an alkali metal hydroxide to provide a compound of Formula V, fourth by reacting a compound of Formula V with a substituted

hydrazine hydrate to obtain a product of the Formula VI, and fifth by reacting a compound of Formula VI with divinyl sulfone.

Disclosed herein are also processes for preparing compounds comprising, first reacting a compound of Formula III with a substituted hydrazide to obtain product
5 of the Formula IV, second by reacting a compound of Formula IV with Formula II

Disclosed herein are also processes for preparing compounds comprising, first reacting a compound of Formula III with a substituted hydrazide to obtain product of the Formula IV, second by reacting a compound of Formula IV with Formula II to obtain a compound of Formula ID, third by reacting compound of the Formula
10 1D with an alkyne in the presence of a palladium reagent such as tetrakis(triphenylphosphine)palladium(0) and copper (I) iodide, in a basic medium and in an aprotic solvent.

Certain embodiments disclose processes for the preparation of compounds of one of Formulae I, IA, IB, IC, ID, IE, 1F. and 1G. and IV, IVA, IVB, IVC, V and VI and
15 intermediates thereof.

Brief description of the drawings

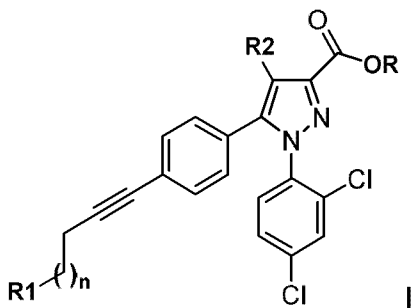
Figure 1 shows single-crystal X-ray diffraction data of 5-(4-(4-cyanobut-1-yn-1-yl)phenyl)-1-(2,4-dichlorophenyl)-N-(1,1dioxidothiomorpholino)-4-methyl-1H-pyrazole-3-carboxamide collected using Cu K α radiation and a Bruker Bruker
20 Photon 100 CMOS area detector.

Detailed Description

The disclosed embodiments concern a novel process for making each of biologically active compounds of one of Formulae I, IA, IB, IC, ID, IE, 1F. and 1G. and IV, IVA, IVB, IVC, V and VI and intermediates thereof.

25 More specifically, the disclosed invention concerns a novel process for making each of biologically active compounds of one of Formulae IA, IC and intermediates thereof.

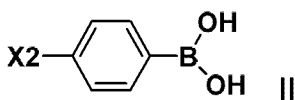
Particularly, in a certain embodiment, a subject of the present invention is a process for preparing a compound of Formula I:



in which:

- R1 is H, CN, OH, phthalimido, mesylate, tosylate, amide, ester, methoxy, halogen
- R2 is H, CH3 or CH2CH3, OCH3 or CN
- R is CH3 or CH2CH3
- n is 1-4

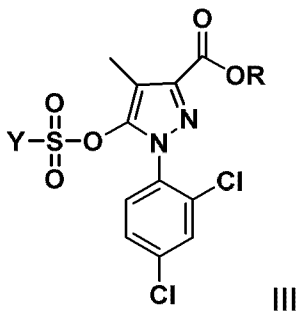
comprising steps of reacting a phenylboronic acid derivative of Formula II:



in which X2 is:

- halogen or
- $R_1-(CH_2)_n-C\equiv C-$ where R1 is as defined as in Formula I

with a compound of Formula III

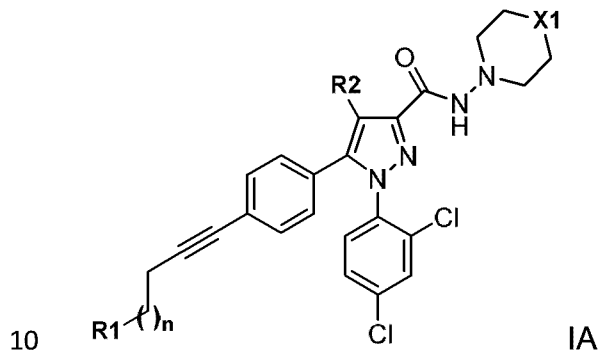


in which:

- R is as defined as in Formula I
- Y is selected from the group consisting of a (C₁-C₄)alkyl group, a (C₁-C₄)perfluoroalkyl group, a phenyl group that is unsubstituted or substituted with a methyl, chloro and nitro group

in a solvent, in the presence of a catalyst in a basic medium, at a suitable temperature.

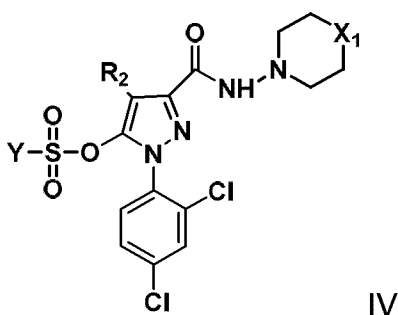
In another embodiment, a subject of the present invention is a process for preparing a compound of Formula 1A:



in which:

- R1 is H, CN, OH, phthalimido, amide, carboxylic ester, nitrate ester, halogen, methoxy, mesylate or tosylate;
- R2 is CH₃, CH₂CH₃, OCH₃ or CN
- n is 1-4
- X1 is CH₂, O or SO₂

comprising reacting a phenylboronic acid derivative of Formula II with a compound of Formula IV

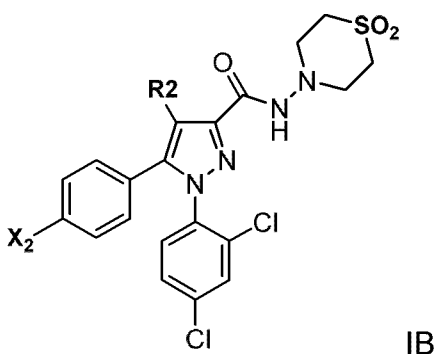


in which:

- R₂, Y and X₁ are defined as in Formula IA and Formula III

- 5 in a solvent, in the presence of a catalyst in a basic medium, at a suitable temperature.

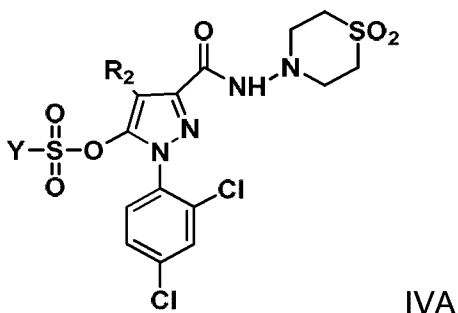
In another embodiment, a subject of the present invention is a process for preparing a compound of Formula 1B



- 10 in which:

- R₂ is CH₃, CH₂CH₃, OCH₃ or CN
- X₂ is defined as in Formula II

Comprising reacting a phenylboronic acid derivative of Formula II with a compound of Formula IVA



in which:

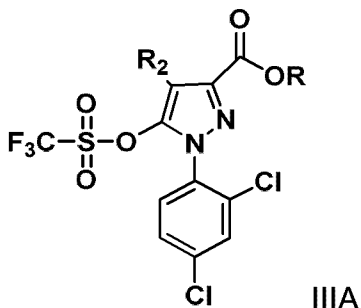
- Y is as defined as in Formula III and Formula IV
- R₂ is defined as in Formula IA and Formula IA

in a solvent, in the presence of a catalyst in a basic medium, at a suitable temperature.

Preferably, the reaction of a compound of Formula II with a compound of Formula III, Formula IV or Formula IVA is carried out in an aromatic solvent, for example toluene, xylene or in an ethereal solvent, for example tetrahydrofuran, dimethoxyethane or in dioxane, or in ethyl acetate, in the presence of a palladium reagent such as tetrakis(triphenylphosphine)palladium(0), and in a basic medium, for example in the presence of an alkali metal carbonate such as sodium carbonate or potassium carbonate. The reaction can be carried out at temperatures ranging from ambient room to 100 deg C.

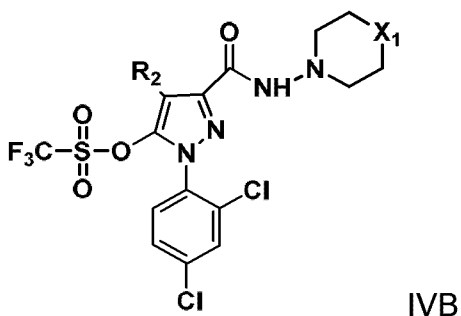
According to a preferred embodiment, the reaction is carried out in a two-phase medium, in the presence of tetrakis(triphenylphosphine)palladium(0), the basic medium consisting of sodium carbonate or potassium carbonate as an aqueous solution.

In a preferred process for preparing a compound of Formula I, a phenylboronic acid derivative of Formula II is reacted with a compound of Formula III in which Y represents a group CF₃, namely a compound of Formula IIIA



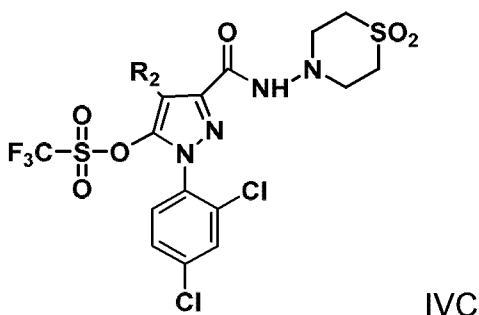
- R₂ is defined as in Formula IA and Formula IA
- R is as defined as in Formula I

In addition, according to a preferred process for preparing a compound of Formula
 5 IA, a phenylboronic acid derivative of Formula II is reacted with a compound of Formula IV in which Y represents a group CF₃, namely a compound of Formula IVB



- X₁ is CH₂, O or SO₂
- R₂ is defined as in Formula IA and Formula IA

In addition, in a preferred process for preparing a compound of Formula IB, a phenylboronic acid derivative of Formula II is reacted with a compound of Formula
 10 IVA in which Y represents a group CF₃, namely a compound of Formula IVC



- R2 is defined as in Formula IA and Formula IA

Preferably, (4-(4-(1,3-dioxoisindolin-2-yl)but-1-yn-1-yl)phenyl)boronic acid, (4-(4-hydroxybut-1-yn-1-yl)phenyl)boronic acid, (4-(4-cyanobut-1-yn-1-yl)phenyl)boronic acid, (4-(4-((methylsulfonyl)oxy)but-1-yn-1-yl)phenyl)boronic acid, (4-(4-(tosyloxy)but-1-yn-1-yl)phenyl)boronic acid or (4-(5-amino-5-oxopent-1-yn-1-yl)phenyl)boronic acid are reacted with a compound of Formula III or IIIA.

Preferably, (4-(4-(1,3-dioxoisindolin-2-yl)but-1-yn-1-yl)phenyl)boronic acid, (4-(4-hydroxybut-1-yn-1-yl)phenyl)boronic acid, (4-(4-cyanobut-1-yn-1-yl)phenyl)boronic acid, (4-(4-((methylsulfonyl)oxy)but-1-yn-1-yl)phenyl)boronic acid, (4-(4-(tosyloxy)but-1-yn-1-yl)phenyl)boronic acid or (4-(5-amino-5-oxopent-1-yn-1-yl)phenyl)boronic acid is also reacted with a compound of Formulae IVA or IVC.

More preferably, 4-chlorophenylboronic acid or 4-bromophenylboronic acid is reacted with a compound of Formula IVA or Formula IVC.

In a preferred embodiment, the compound of Formula IV, Formula IVA, Formula IVB and Formula IVC are synthesized from Formula III.

In particular, compound of Formula IV, Formula IVA, Formula IV and Formula IVC are synthesized from Formula IIIA.

To prepare a compound of Formula IV, Formula IVA, Formula IVB and Formula IVC, a compound of Formula III or Formula IIIA is reacted with an appropriate substituted hydrazine, the reaction being carried out in the presence of a Lewis acid.

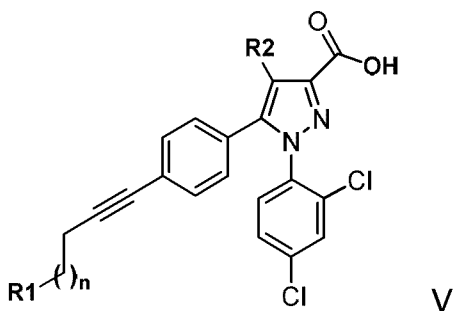
In particular, to prepare a compound of Formula IV, Formula IVA, Formula IVB and Formula IVC, a compound of Formula III or Formula IIIA is reacted with an appropriate substituted hydrazine, the reaction being carried out in the presence of aluminum chloride.

- 5 In particular, to prepare a compound of Formula IV, Formula IVA, Formula IVB and Formula IVC, a compound of Formula III or Formula IIIA is reacted with a substituted hydrazine, the reaction being carried out in the presence of aluminum chloride at temperatures ranging from -15 deg C to 100 deg C.

- 10 In particular, to prepare a compound of Formula IV, Formula IVA, Formula IVB and Formula IVC, a compound of Formula III or Formula IIIA is reacted with a substituted hydrazine, the reaction being carried out in the presence of aluminum chloride at temperatures ranging from - 15 deg C to 100 deg C in a solvent selected from dichloroethane, toluene, dioxane or tetrahydrofuran.

- 15 As a preferred embodiment, the substituted hydrazine can be hydrazine monohydrate, 1-aminopiperidine, 4-aminomorpholine, 4-aminothiomorpholine 1,1-dioxide or 4-aminothiomorpholine 1,1-dioxide-2,2,3,3,5,5,6,6-d8.

- 20 In another embodiment, disclosed herein is a process for preparing a compound of Formula IA characterized in that the hydrolysis of a compound of the Formula I using an alkali metal hydroxide such as lithium hydroxide, sodium hydroxide or potassium hydroxide will provide a compound Formula V



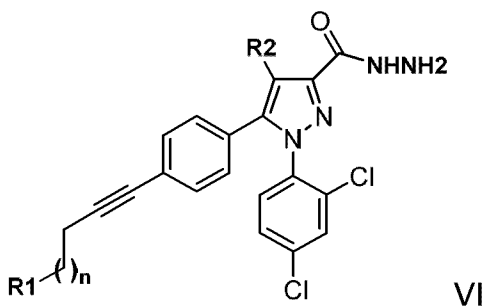
in which:

- R1 and R2 as defined as in Formula I and Formula IA
- n is 1-4

The subsequent steps involving, the sodium salt of a compound of Formula V being dissolved in water and then washed with a water immiscible solvent such as ethyl acetate, a chlorinated solvent such as dichloromethane or an aromatic solvent such as toluene, or an ethereal solvent such as diethyl ether. The washed
5 water layer containing the sodium salt of a compound of Formula V is then acidified with a mineral acid such as hydrochloric acid in water to obtain a compound of Formula V in highly purified form as free base.

The subsequent step involving stirring the compound of Formula V in an alcohol such as methanol, ethanol or 2-propanol in the presence of a catalytic amount of
10 mineral acid such as sulfuric acid to provide a highly purified ester of a compound of Formula I.

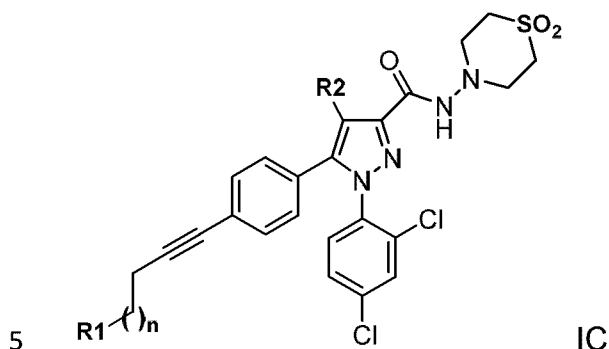
In the following step, as a preferred embodiment, a compound of Formula I is reacted with hydrazine monohydrate in an ethereal solvent such as tetrahydrofuran, dioxane, or a polar aprotic solvent such as dimethylformamide,
15 dimethylacetamide, or an alcohol such as methanol, ethanol or 2-propanol to provide a compound of Formula VI



- 20
- R1 and R2 as defined as in Formula I and Formula IA
 - n is 1-4

In a preferred embodiment, a compound of Formula IA is prepared by reacting a compound of Formula V with hydrazine monohydrate in ethanol at temperatures ranging from ambient room to 100 deg C to provide a compound of Formula VI.

Finally, in a certain embodiment, a compound of Formula VI is reacted with divinyl sulfone in the presence of an organic base, preferably a tertiary amine, in an alcohol such as methanol, ethanol or 2-propanol, at temperatures ranging from -15 deg C to 100 deg C. to provide a compound of Formula VII.



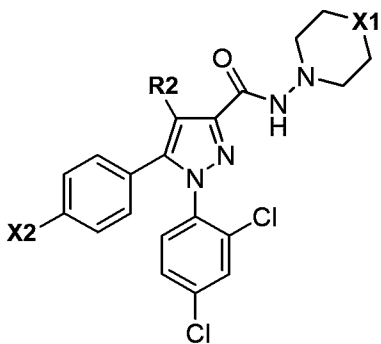
- R1 and R2 as defined as in Formula I and Formula IA
- n is 1-4

10 In a preferred embodiment, a compound of Formula VI is reacted with divinyl sulfone in an alcohol such as methanol, ethanol, or 2-propanol at temperatures ranging from -15 deg C to 100 deg C to provide a compound of Formula IC in highly purified form.

15 In another embodiment, to prepare a compound of the Formula IA, IB, IC, ID, IE, IF, and IG, a compound of the Formula V or Formula VII is reacted with a substituted hydrazine such as 1-aminopiperidine, 4-aminomorpholine, 4-aminothiomorpholine 1,1-dioxide or 4-aminothiomorpholine 1,1-dioxide-2,2,3,3,5,5,6,6-d8 in the presence of a peptide coupling reagent such as N,N,N',N'-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate or (1-cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate in the presence of an amine such as triethyl amine, 20 diisopropyl amine or diisopropyl ethylamine and in a solvent such as dichloromethane, an ethereal solvent such as tetrahydrofuran, a polar aprotic solvent such as dimethylformamide, or a more environmentally acceptable and

sustainable alternative such as dimethyl carbonate, ethyl acetate or methyltetrahydrofuran.

In one embodiment, 4-bromophenylboronic acid is reacted with a compound of Formula IVB to provide a compound of Formula VII.



5

ID

- R² as defined as in Formula I and Formula IA
- X₁ is CH₂, O or SO₂
- X₂ is defined as in Formula II

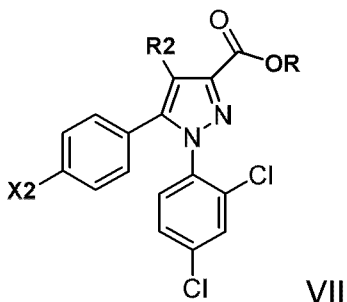
In a subsequent step, the compound of formula ID is reacted with an alkyne in the presence of a palladium reagent such as tetrakis(triphenylphosphine)palladium(0), copper (I) iodide, and in a basic medium, for example in the presence of an amine such as triethyl amine, diisopropyl amine or diisopropyl ethylamine and in an ethereal solvent such as tetrahydrofuran, dioxane or a polar aprotic solvent such as dimethylformamide, or in ethyl acetate to provide a compound of formula 1A.

10

15

The reaction can be carried out at temperatures ranging from ambient room to 100 deg C.

More preferably, in an embodiment, 4-bromophenylboronic acid is reacted with a compound of Formula III or IIIA to provide a compound of Formula VII



- R2 is defined as in Formula IA and Formula IA
- R is as defined as in Formula I
- X2 is is defined as in Formula II

5 In a subsequent step, the compound of formula VII is reacted with an alkyne in the presence of a palladium reagent such as tetrakis(triphenylphosphine)palladium(0), copper (I) iodide, and in a basic medium, for example in the presence of an amine such as triethyl amine, diisopropyl amine or diisopropyl ethylamine and in an ethereal solvent such as tetrahydrofuran, dioxane or a polar aprotic solvent such as dimethylformamide, or in ethyl acetate to provide a compound of Formula I. The reaction can be carried out at temperatures ranging from ambient room to 100 deg C.

Following this, in a preferred embodiment, hydrolysis of a compound of the Formula 1 using an alkali metal hydroxide such as lithium hydroxide, sodium hydroxide or potassium hydroxide will provide a compound Formula V.

The steps comprise the sodium salt of a compound of Formula V being dissolved in water and then washed with a water immiscible solvent such as ethyl acetate, a chlorinated solvent such as dichloromethane or an aromatic solvent, for example toluene, or an ethereal solvent such as diethyl ether, tetrahydrofuran, dioxane. The subsequent washed water layer containing the sodium salt of a compound of Formula V is then acidified with a mineral acid such as hydrochloric acid in water to obtain a compound of Formula V in highly purified form as free base.

The subsequent step comprises stirring the compound of Formula V in an alcohol such as methanol, ethanol or 2-propanol in the presence of a catalytic amount of mineral acid such as sulfuric acid to provide a highly purified ester of a compound of Formula I.

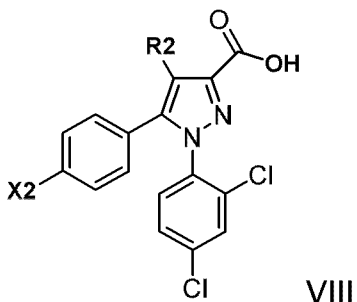
- 5 In the following step, a compound of Formula I is preferably reacted with hydrazine monohydrate in an ethereal solvent such as tetrahydrofuran, dioxane, or a polar aprotic solvent such as dimethylformamide, dimethylacetamide, or an alcohol such as ethanol or 2-propanol to provide a compound of Formula VI.

- 10 In a preferred embodiment, a compound of Formula IA is prepared by reacting a compound of Formula V with hydrazine monohydrate in ethanol at temperatures ranging from ambient room to 100 deg C to provide a compound of Formula VI.

- 15 Finally, a compound of Formula VI is reacted with divinyl sulfone in the presence of an organic base, preferably a tertiary amine, in an alcohol such as methanol, ethanol or 2-propanol at temperatures ranging from -15 deg C to 100 deg C to provide a compound of Formula 1A.

In a preferred embodiment, a compound of Formula VI is reacted with divinyl derivative such as divinyl sulfone in an alcohol such as methanol, ethanol, or 2-propanol at temperatures ranging from -15 deg C to 100 deg C to provide a compound of Formula 1A in highly purified form.

- 20 In a certain embodiment, hydrolysis of a compound of the Formula VII using an alkali metal hydroxide such lithium hydroxide, sodium hydroxide or potassium hydroxide in a solution containing water mixed with an ethereal solvent such as tetrahydrofuran and an alcohol such as methanol or ethanol will provide a compound Formula VIII.

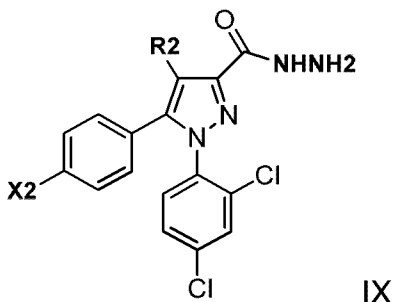


- R2 is defined as in Formula IA and Formula IA
- X2 is defined as in Formula II

The steps include the sodium salt of a compound of Formula VIII being dissolved
 5 in water and then washed with a water immiscible solvent such as ethyl acetate, a
 chlorinated solvent such as dichloromethane or an aromatic solvent, for example
 toluene, or an ethereal solvent such as diethyl ether, tetrahydrofuran, dioxane. The
 subsequent washed water layer containing the sodium salt of a compound of
 Formula IX is then acidified with a mineral acid such as hydrochloric acid in water
 10 to obtain a compound of Formula VIII in highly purified form as free base.

The subsequent step comprises stirring the compound of Formula VIII in an alcohol
 such as methanol, ethanol or 2-propanol in the presence of a catalytic amount of
 mineral acid such as sulfuric acid to provide a highly purified ester of a compound
 of Formula VII.

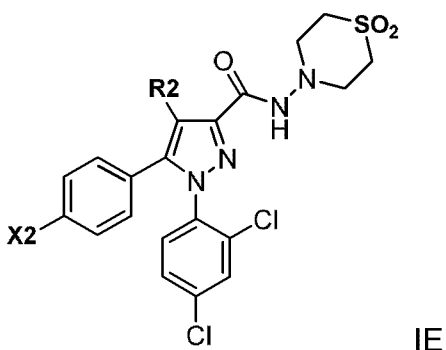
15 In the following step, a compound of Formula VII is reacted with hydrazine
 monohydrate in an ethereal solvent such as tetrahydrofuran, dioxane, or a polar
 aprotic solvent such as dimethylformamide, dimethylacetamide, or an alcohol such
 as ethanol or 2-propanol to provide a compound of Formula IX.



- R2 is defined as in Formula IA and Formula IA
- X2 is defined as in Formula II

In a preferred embodiment, a compound of Formula VII is reacted with hydrazine monohydrate in ethanol at temperatures ranging from ambient room to 100 deg C to provide a compound of Formula IX.

In a preferred embodiment, a compound of Formula IX is reacted with divinyl sulfone in the presence of an organic base, preferably a tertiary amine, in an alcohol such as methanol, ethanol or 2-propanol at temperatures ranging from -15 deg C to 100 deg C to provide a compound of Formula IE.

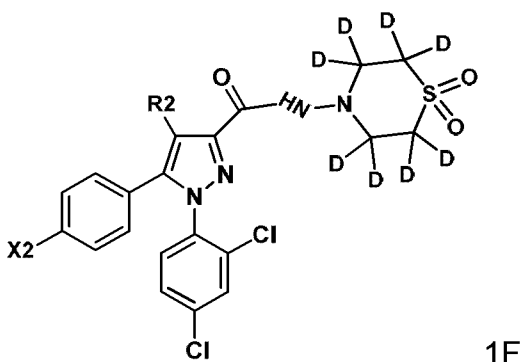


- R2 is defined as in Formula IA and Formula IA
- X2 is defined as in Formula II

In a preferred embodiment, a compound of Formula IX is reacted with divinyl sulfone in an alcohol such as methanol, ethanol, or 2-propanol at temperatures ranging from -15 deg C to 100 deg C to provide a compound of Formula IE in highly purified form.

In a subsequent step, the compound of formula IE is reacted with an alkyne in the presence of a palladium reagent such as tetrakis(triphenylphosphine)palladium(0), copper (I) iodide, and in a basic medium, for example in the presence of an amine such as triethyl amine, diisopropyl amine or diisopropyl ethylamine and in an
 5 etheral solvent such as tetrahydrofuran, dioxane or a polar aprotic solvent such as dimethylformamide, or in ethyl acetate to provide compound of Formula IC. The reaction can be carried out at temperatures ranging from ambient room to 100 deg C.

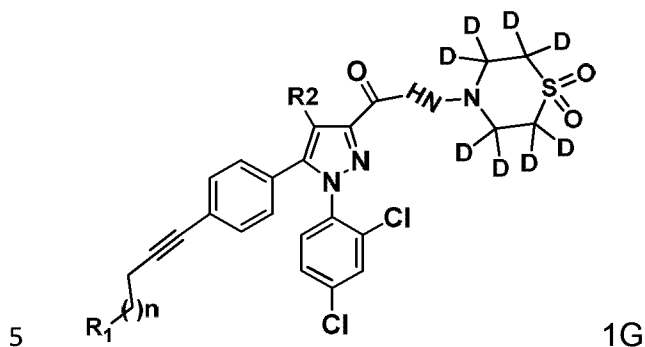
In another embodiment, a compound of Formula VIII is reacted with 4-
 10 aminothiophosphorine 1,1-dioxide-2,2,3,3,5,5,6,6-d8 in the presence of a peptide coupling reagent such as 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate and an amine such as triethyl amine, diisopropyl amine or diisopropyl ethylamine, and in a chlorinated solvent such as dichloroethane or dichloromethane, or an etheral solvent such as tetrahydrofuran, methyl
 15 tetrahydrofuran, dioxane, or a polar aprotic solvent such as dimethylformamide, or N-methyl pyrrolidinone to provide a compound of the formula 1F.



- R2 is defined as in Formula IA and Formula IA
- X2 is defined as in Formula II

20 Another embodiment includes a reaction wherein the compound of formula IE is reacted with an alkyne in the presence of a palladium reagent such as tetrakis(triphenylphosphine)palladium(0), copper (I) iodide, and in a basic medium, for example in the presence of an amine such as triethyl amine, diisopropyl amine

or diisopropyl ethylamine and in an ethereal solvent such as tetrahydrofuran, dioxane or a polar aprotic solvent such as dimethylformamide, or in ethyl acetate to provide compound of Formula 1G. The reaction can be carried out at temperatures ranging from ambient room to 100 deg C.



- R1 and R2 are defined as in Formula IA and Formula IA
- n is 1-4

As a variation, the compounds of the Formulae I, IA, IB, IC, ID, IE, 1F, 1G and intermediates thereof can also comprise isotopes at one or more of their atoms.

- 10 For example, the compounds can be radiolabeled with isotopes, such as ²H (deuterium written as D), ³H (tritium written as T), ¹¹C (carbon-11), ¹³C (carbon-13), ¹⁴C (carbon-14), ¹⁵O (oxygen-15), ¹⁷O (oxygen-17), ¹⁸O (oxygen-18), ¹³N (nitrogen-13), ¹⁵N (nitrogen-15), ¹⁸F (fluorine-18), ⁷⁵Br (bromine-75), ⁷⁶Br (bromine-76), ⁷⁷Br (bromine-77), ⁸²Br (bromine-82), ¹²³I (iodine-123), ¹²⁴I (iodine-124), ¹²⁵I (iodine-125) or ¹³¹I (iodine-131), ³⁶Cl (chlorine-36) or ³⁵S (sulphur-35), The present disclosure encompasses all isotopic variations of the described compounds, whether natural or unnatural, radioactive or not.
- 15

In some embodiments the amide is defined as any group with the formula -C(O)NH₂-,

- 20 -NH₂C(O)-, C(O)NHalkyl-, -alkylNHC(O)-,

In some embodiments, the ester group is defined as any group with the formula -C(O)Oalkyl- or -OC(O)-alkyl.

In some embodiments, the compounds have at least one isotope atom incorporated at or adjacent to a site that is susceptible to metabolism. The isotope atom can be part or adjacent to a substituent group as defined.

5 In some embodiments, the compounds have at least one deuterium atom incorporated at or adjacent to a site that is susceptible to metabolism. The deuterium atom can be part or adjacent to a group as defined.

In certain embodiments, the compounds disclosed herein are synthesized hydrates and also as solvates wherein solvent molecules able to become a partner of crystallization can include water; methanol, ethanol, 2-methoxyethanol,
10 isopropanol, 1-methyl butanol, DMF, NMP, DMSO, methylcyclohexane, dimethylacetamide, 1,4 dioxane and ethyl acetate.

The compounds disclosed herein can exist as various novel and stable polymorphs including hydrated and crystalline forms including solvates.

Several embodiments disclosed herein are described herein. It will be recognized
15 that one or more features of any embodiments disclosed herein may be combined and/or rearranged within the scope of the invention to produce further embodiments that are also within the scope of the invention.

Still other objects and advantages of the disclosed embodiments will become apparent by those of skill in the art from the disclosure herein, which are simply
20 illustrative and not restrictive. Thus, other embodiments will be recognized by the ordinarily skilled artisan without departing from the spirit and scope of the invention.

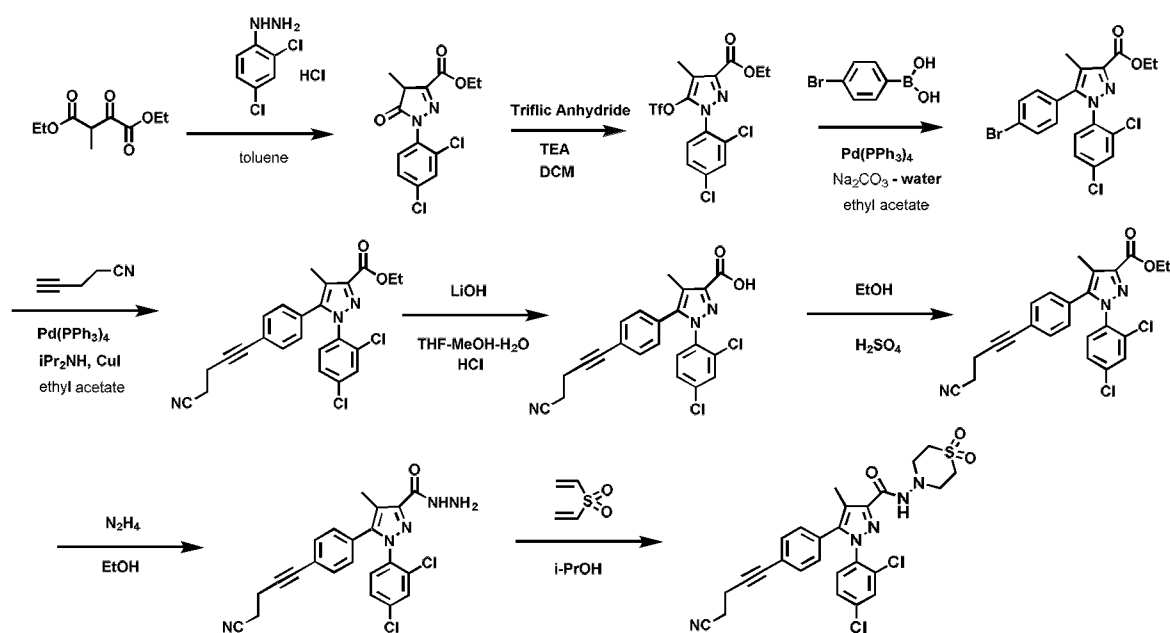
The disclosure is further illustrated by the following examples, which are not to be construed as limiting this disclosure in scope or spirit to the specific procedures
25 described in this disclosure. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the disclosure is intended thereby. It is to be further understood that resort may be had to various other embodiments, modifications, and equivalents thereof which

may suggest themselves to those skilled in the art without departing from the spirit of the present disclosure and/or scope of the appended claims.

Examples

The following examples (Examples 1-3), and schematically shown as Scheme 1, Scheme 2, Scheme 3A, Scheme 3B, and Scheme 4, illustrate specific exemplary steps for performing the above described processes forming the basis of the invention disclosed herein:

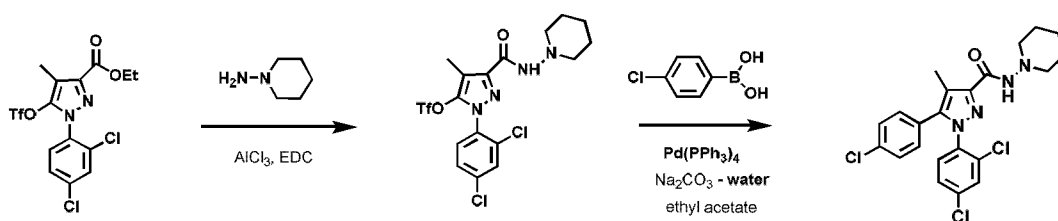
• Scheme 1:



Scheme 1

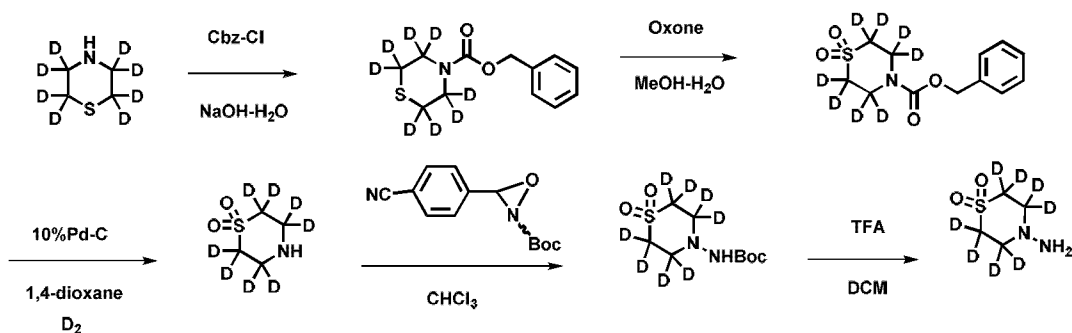
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• Scheme 2:



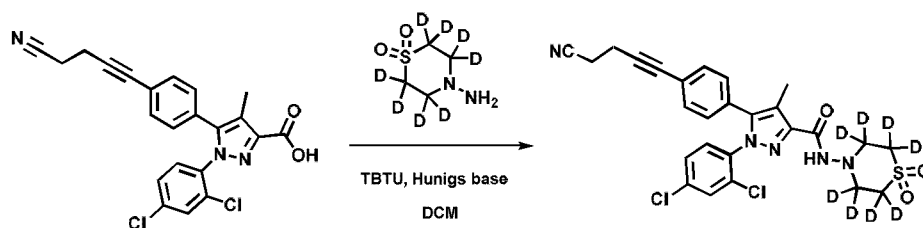
Scheme 2

• **Scheme 3A:**



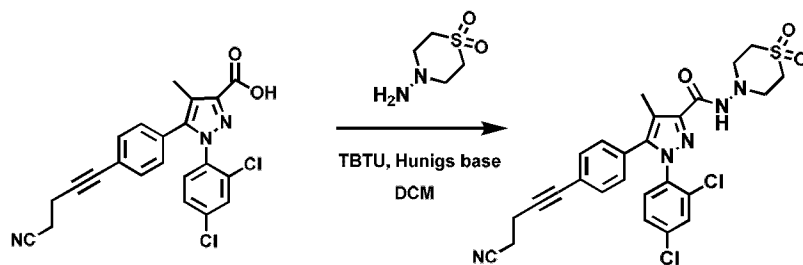
Scheme 3A

• **Scheme 3B:**



5 Scheme 3B

• **Scheme 4:**



Scheme 4

Example 1 (Scheme 1)

- 10 A) *Ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylate*

2,4-Dichlorophenylhydrazine hydrochloride(126 g) is dissolved in 1l of toluene and this solution is placed under nitrogen; after stirring, 100 g of diethyl 2-methyl-3-oxosuccinate are added and the mixture is then heated and 50 ml of TFA are added at 55° C. The mixture is left at the reflux of the solvent for 4 and a half hours, with stirring. The mixture is allowed to return to ambient temperature and is then heated to 75° C. and the reaction medium is hydrolyzed with 300 ml of water. The mixture is separated by settling out, the aqueous phase is discarded, and the organic phase is then evaporated in order to eliminate the residual TFA. The organic phase is taken up with 100 ml of toluene and the expected product then crystallizes (102 g).

B) Ethyl 1-(2,4-dichlorophenyl)-4-methyl-5-(((trifluoromethyl)sulphonyl)oxy)-1H-pyrazole-3-carboxylate

Pyrazolone (50 gm) obtained in the preceding step is suspended in 250 ml of DCM, under nitrogen, and the mixture is cooled to 0° C. with stirring. 24 ml of TEA followed by 30 ml of triflic anhydride are added and the stirring is maintained at 0° C. for 15 minutes. The reaction medium is hydrolyzed with 200 ml of DCM. The reaction medium is separated by settling out and the organic phase is then washed with 200 ml of water. The aqueous phase is discarded. The organic phase is evaporated, and the oil obtained is chromatographed on silica, elution being carried out with a pentane/EtOAc mixture (90/10; v/v). The fractions containing the expected compound are combined and evaporated to dryness to obtain the final product (67.7 g).

C) Ethyl 5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylate

25.5 g of the pyrazole triflate of the preceding step, 10.8 g of 4-bromophenylboronic acid and 670 mg of tetrakis(triphenylphosphine)palladium are mixed, under nitrogen; 250 ml of ethyl acetate and 71 ml of a 2M aqueous sodium carbonate solution are added. The reaction medium is stirred at 65° C. for 6 hours. The reaction medium is separated by settling out, the aqueous phase is discarded, and the organic phase is then washed with 100 ml of water. After separation by

settling out, the organic phase is evaporated off. The crude product obtained is purified by chromatography on silica, elution being carried out with a cyclohexane/EtOAc mixture (85/15; v/v) to provide the final product (18.9 g).

5 *D) Ethyl 5-(4-(4-cyanobut-1-yn-1-yl)phenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylate*

To a stirred solution of bromo compound obtained from the previous step (18 g) in ethyl acetate (400 ml), under argon was added 4-cyano-1-butyne (10 g), and diisopropyl amine (7.8 ml). The reaction mixture was degassed by introducing a steady stream of argon into the solution for 5 min and to this was added
10 tetrakis(triphenylphosphine)palladium (0) (1.8 g) and copper(I) iodide (400 mg). The resulting mixture was refluxed for 3 h. The solvent was washed with deionized water (2×~100 mL). The organic layer was separated, dried over anhydrous MgSO₄, filtered and the filtrate was removed in vacuo. The residue obtained was carried to the next reaction without further purification.

15 *E) 5-(4-(4-Cyanobut-1-yn-1-yl)phenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid*

The acid (7.5 g, 15.8 mmol) obtained was taken in a 500 ml single neck flask equipped with a nitrogen inlet and to it 200 ml of anhydrous ethyl alcohol. To this was added few drops of sulfuric acid and the mixture was refluxed for 12 hours.
20 The solvents were removed, and the residue was dissolved in dichloromethane (100 ml) and washed with deionized water (2×~100 mL). The organic layer was separated, dried over anhydrous MgSO₄, filtered and the solvent was evaporated in vacuo to provide the ester as an off-white solid (7 g, 87 %).

25 *F) Ethyl 5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylate*

The acid (7.5 g, 15.8 mmol) obtained was taken in a 500 ml single neck flask equipped with a nitrogen inlet and to it 200 ml of anhydrous ethyl alcohol. To this was added few drops of sulfuric acid and the mixture was refluxed for 12 hours. The solvents were removed, and the residue was dissolved in dichloromethane

(100 ml) and washed with deionized water (2×~100 mL). The organic layer was separated, dried over anhydrous MgSO₄, filtered and the solvent was evaporated in vacuo to provide the ester as an off-white solid (7 g, 87 %).

G) *5-(4-(4-cyanobut-1-yn-1-yl)phenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carbohydrazide*

The ester (7 g, 15.4 mol) obtained was taken in a 500 ml single neck flask equipped with a nitrogen inlet and to it 50 ml of anhydrous ethyl alcohol followed by 20 g of hydrazine hydrate are added and the mixture is heated at reflux for 3 hours. The reaction medium is concentrated in vacuo with 10% residual solvent remaining.

10 The combined residue is dissolved in dichloromethane (150 ml) and washed with deionized water (2×~100 mL). The organic layer was separated, dried over anhydrous MgSO₄, filtered and the filtrate was removed in vacuo. The residue obtained was purified by crystallization from ethyl acetate and hexane to provide the hydrazide as a white solid (5.2 g, 76 %).

15 H) *5-[4-(4-cyano-1-butyn-1-yl)phenyl]-1-(2,4-dichlorophenyl)-N-(1,1-dioxido-4-thiomorpholinyl)-4-methyl-1H-pyrazole-3-carboxamide*

To a solution of the hydrazide (5 g, 11.4 mmol) in iPrOH (6 mL) was added divinyl sulfone (1.35 g, 11.4 mmol) dropwise and the contents were stirred overnight at room temperature. The white solids obtained were filtered and washed with iPrOH
20 (2 x 25 ml) and re-dissolved in hot ethyl acetate to provide crystals when kept on standing overnight (3.5 g, 55%).

¹H NMR (Varian Unity-INOVA spectrometer, 500 MHz, CDCl₃): 8.08 (s, 1H), 7.43 (s, 1H), 7.37 (d, J = 7.81 Hz, 2H), 7.28 - 7.34 (m, 1H), 7.24 (s, 1H), 7.06 (d, J = 7.81 Hz, 2H), 3.56 (d, J = 4.88 Hz, 4H), 3.26 (br. s., 4H), 2.72 - 2.87 (m, 2H), 2.57
25 - 2.71 (m, 2H), 2.37 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): 161.21, 144.23, 143.94, 136.69, 136.25, 133.36, 132.44, 130.97, 130.90, 129.92, 128.74, 128.49, 123.90, 118.92, 118.69, 87.43, 82.95, 53.50, 51.62, 18.12, 17.24, 9.85; HRMS-ESI (Q-TOF) calcd for C₂₆H₂₃Cl₂N₅O₃S (M⁺ +H), 556.0977, found 556.0980. Elemental analysis Anal. Calcd for C₂₆H₂₃Cl₂N₅O₃S: C% 56.12, H% 4.17, N% 12.59, S%
30 5.76; found C% 56.2, H% 4.04, N% 12.37, S% 5.59; m.p 278-280°C; Heavy

metals, USP<231> Method II less than 20 ppm; Palladium content not detectable by ICP-MS; Copper content 0.86 ppm by ICP-MS; Iron content 6.4 ppm by ICP-MS; Water content 0.3% (Karl Fisher).

Alternatively, the acid (15.8 mmol) obtained from step E scheme 1 was taken in a
5 500 ml 1 neck flask equipped with a nitrogen inlet and to it 200 ml of DCM, 4-aminothiophosphine 1,1-dioxide (16.4 mmol), TBTU (17.4 mmol) and DIPEA (17.4 mmol) were added and the contents were stirred for 1 hour (scheme 4). To the reaction mixture, 100 ml of water was added, and the contents were acidified to pH~7 using 2N HCl. The organic layer was separated, washed with brine, dried
10 over sodium sulphate and concentrated to provide 5-[4-(4-cyano-1-butyn-1-yl)phenyl]-1-(2,4-dichlorophenyl)-N-(1,1-dioxido-4-thiomorpholinyl)-4-methyl-1H-pyrazole-3-carboxamide in 74% yields.

Example 2

A) 1-(2,4-dichlorophenyl)-4-methyl-3-(piperidin-1-ylcarbamoyl)-1H-pyrazol-5-yl
15 trifluoromethanesulfonate

To magnetically stirred suspension of AlCl₃ (9.8 g, 3 eq) in anhydrous dichloroethane (30 ml) at 0 °C was added 1-aminopiperidine (8.6 g, 3.5 eq) under argon atmosphere, and the resulting mixture was stirred at 0-5 °C for 25 min. Ethyl
20 1-(2,4-dichlorophenyl)-4-methyl-5-(((trifluoromethyl)sulfonyl)oxy)-1H-pyrazole-3-carboxylate (11 g) in dichloroethane (250 ml) was added, and the reaction mixture was slowly brought to room temperature over 30 minutes, and stirred at this temperature for 5 h. Reaction was quenched by adding 10 % HCl (50 ml), and the biphasic mixture was stirred for 2 h. Organic layer was separate, and the aqueous layer was extracted with dichloromethane (3 × 50ml). Combined organic layers
25 were washed with water (2 × 80ml), and brine (1 × 80 ml), dried over anhydrous MgSO₄, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography on silica gel to give 9.5 g (77 % yield) of product as a white solid.

B) 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)-1H-
30 pyrazole-3-carboxamide

9 g of the pyrazole triflate of the preceding step, 2.8 g of 4-chlorophenylboronic acid and 350 mg of tetrakis(triphenylphosphine)palladium are mixed, under nitrogen; 250 ml of ethyl acetate and 35 ml of a 2M aqueous sodium carbonate solution are added. The reaction medium is stirred at 65° C. for 6 hours. The reaction medium is separated by settling out, the aqueous phase is discarded, and the organic phase is then washed with 100 ml of water. After separation by settling out, the organic phase is evaporated off. The crude product obtained is purified by filtration and crystallization from a mixture of ethyl acetate and hexane to provide the final product (6 g).

10 Example 3 (Schemes 3A and 3B)

A) Benzyl thiomorpholine-4-carboxylate-d8

To a solution of thiomorpholine-2,2,3,3,5,5,6,6-d8 (2 g) prepared as in WO2008070619, taken in 1N NaOH (11.6 mL) was added benzyl chloroformate (1.66 mL) under ice water cooling and the mixture was stirred at ambient temperature for 2 hours. The solution was neutralized with 1N HCl and extracted with EtOAc twice. The combined organic layer was washed with water and brine, dried over MgSO₄ and evaporated in vacuo. The residue was purified by silica gel column chromatography to give benzyl thiomorpholine-4-carboxylate-d8 as a colorless Solid (4.8 g).

20 *B) Benzyl thiomorpholine-4-carboxylate-2,2,3,3,5,5,6,6-d8 1,1-dioxide*

To a solution of benzyl thiomorpholine-4-carboxylate-d8 (4.8 g) in methanol (30 mL) and H₂O (20 mL) was added oxone (16.2 g) under ice water cooling and the mixture was stirred at ambient temperature for 2 hours. The solution was evaporated in vacuo and partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with water and brine, dried over MgSO₄ and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of hexane and EtOAc to give the title compound (3.8 g).

C) Thiomorpholine 1,1-dioxide-d9

To a solution of benzyl thiomorpholine-4-carboxylate-2,2,3,3,5,5,6,6-d8 1,1-dioxide

- (3.8 g) in methanol (32 mL) and 1,4-dioxane (8 mL) was added Palladium, 10 wt.%
5 on activated carbon (380 mg) at ambient temperature. The mixture was stirred at ambient temperature for 4 hours under an environment of D2. The mixture was filtered and evaporated in vacuo to give title compound (2.22 g).

D) tert-Butyl (1,1-dioxidothiomorpholino-2,2,3,3,5,5,6,6-d8)carbamate

- To a solution of thiomorpholine 1,1-dioxide-d9 (2 g) in CHCl₃ (20 mL) was treated
10 at 0 deg C by a solution of tert-butyl 3-(4-cyanophenyl)-1,2-oxaziridine-2-carboxylate

(3.4 g) in CHCl₃ (20 mL). At the end of the addition the cooling bath was removed, and the contents were allowed to stir overnight. The solvent was evaporated, and the residue obtained was carried to the next step directly.

- 15 *E) 4-Aminothiomorpholine 1,1-dioxide-2,2,3,3,5,5,6,6-d8*

- To a stirred solution of crude tert-butyl (1,1-dioxidothiomorpholino-2,2,3,3,5,5,6,6-d8)carbamate obtained in step D in dichloromethane (25 ml) at 0°C was added trifluoroacetic acid (15 ml). After stirred at room temperature for 1 hour, the mixture was evaporated to give an oil. Diethyl ether (100 ml) was added, and the white
20 precipitate was separated. The upper solution was then removed by decanting. This procedure was repeated three times to ensure complete removal of excess trifluoroacetic acid. The remaining white solids were dried in vacuo to give the title compound in quantitative yield.

- 25 *F) 5-(4-(4-Cyanobut-1-yn-1-yl)phenyl)-1-(2,4-dichlorophenyl)-N-(1,1-dioxidothiomorpholino-2,2,3,3,5,5,6,6-d8)-4-methyl-1H-pyrazole-3-carboxamide*

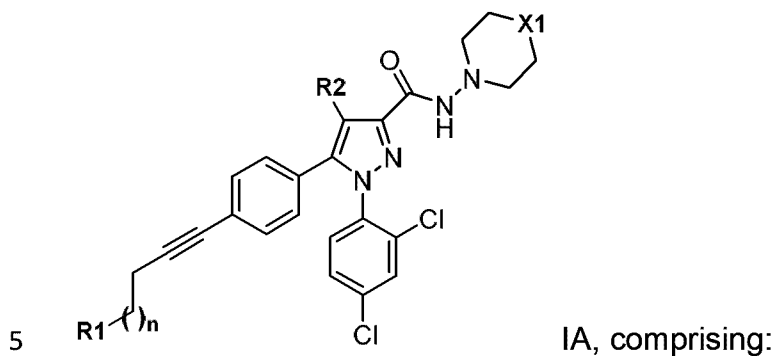
The acid (7.5 g, 15.8 mmol) obtained from step E scheme 1 was taken in a 500 ml 1 neck flask equipped with a nitrogen inlet and to it 200 ml of DCM, 4-aminothiomorpholine 1,1-dioxide-2,2,3,3,5,5,6,6-d8 (2.61 g, 16.4 mmol), TBTU (5.59g, 17.4 mmol) and DIPEA (2.25 g, 17.4 mmol) were added and the contents

were stirred for 1 hour. To the reaction mixture, 100 ml of water was added, and the contents were acidified to pH ~7 using 2N HCl. The organic layer was separated, washed with brine, dried over sodium sulphate and concentrated to give the title compound (3 g); ES m/z 554.14 (M^+H).

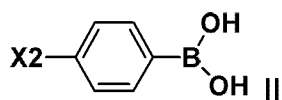
Claims

What is claimed is:

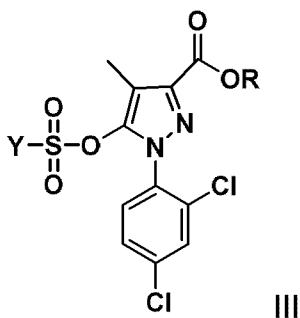
1. A process for preparing a compound represented by Formula IA, its solvates, polymorphs and isotopic variations thereof:



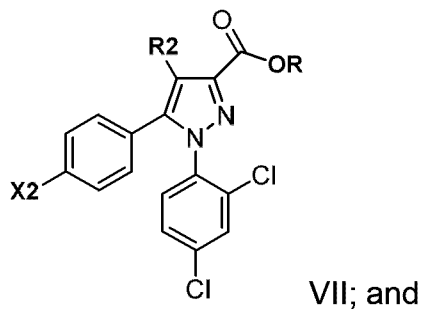
reacting a compound represented by Formula II:



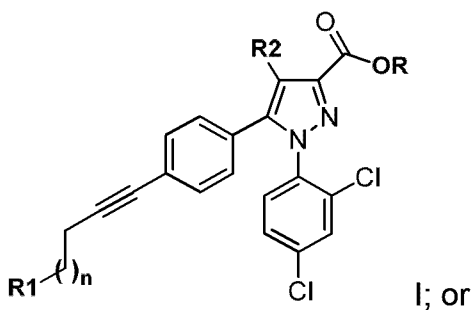
with a compound represented by Formula III:



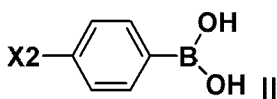
- 10 to provide a compound represented by Formula VII:



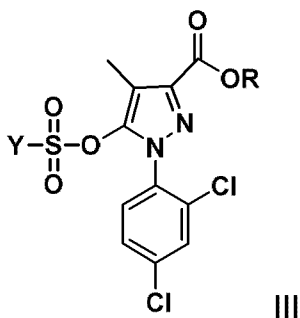
reacting the compound of Formula VII with an alkyne to provide a compound represented by formula I:



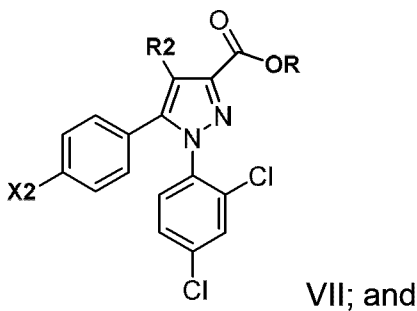
5 reacting a reacting a compound represented by Formula II:



with a compound represented by Formula III:

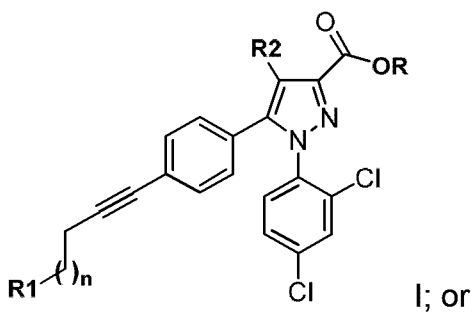


to provide a compound represented by Formula VII:

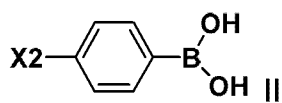


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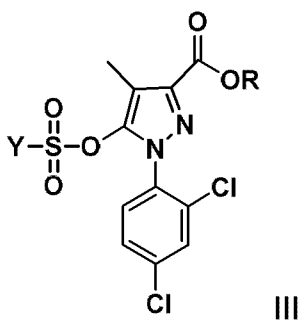
reacting the compound of Formula VII with an alkyne to provide a compound represented by Formula I:



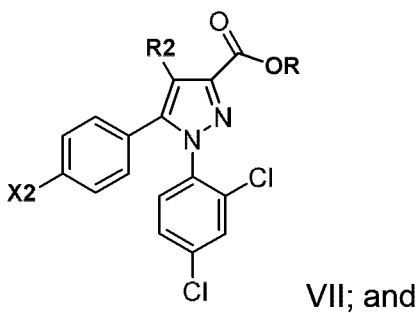
5 reacting a compound represented by Formula II:



with a compound represented by Formula III:

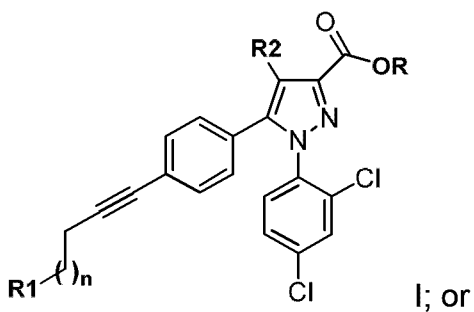


to provide a compound represented by Formula VII:

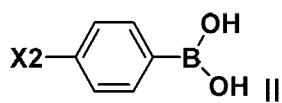


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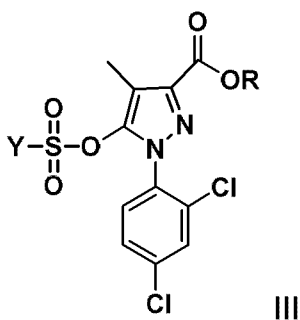
reacting the compound of Formula VII with an alkyne to provide a compound represented by Formula I:



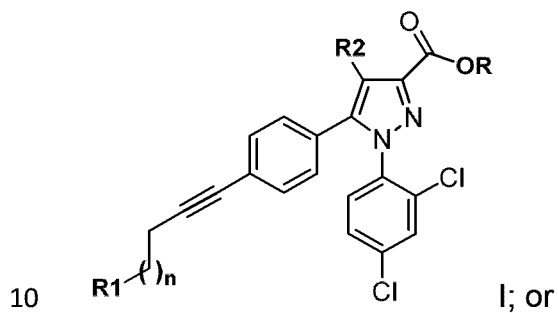
5 reacting a compound represented by Formula II:



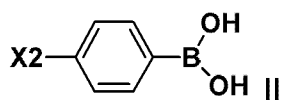
with a compound represented by Formula III:



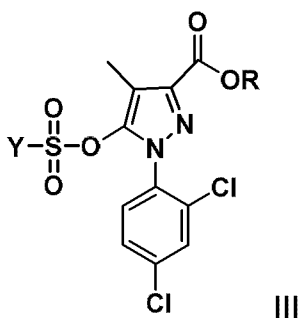
to provide a compound represented by Formula I:



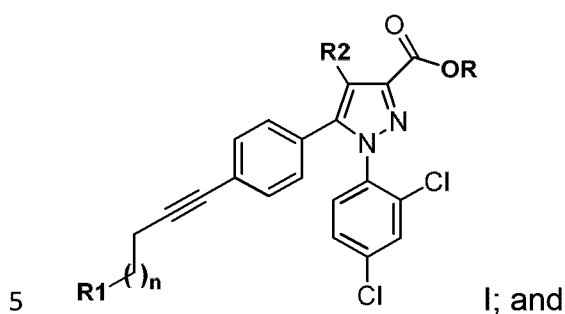
reacting a compound represented by Formula II:



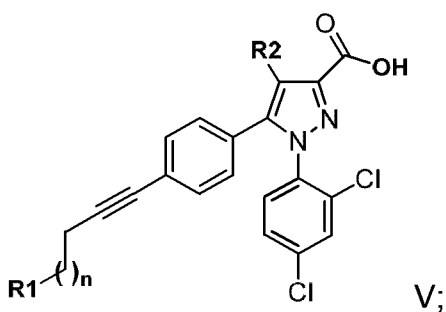
with a compound represented by Formula III:



to provide a compound represented by Formula I:

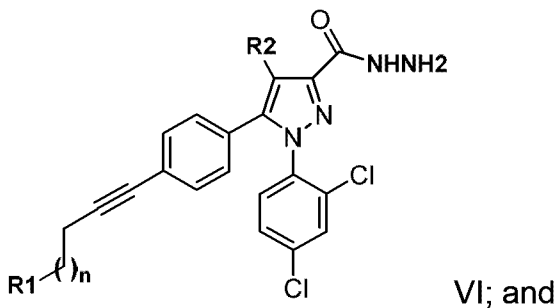


reacting the compound of Formula I with an alkali metal hydroxide to provide a compound represented by Formula V:



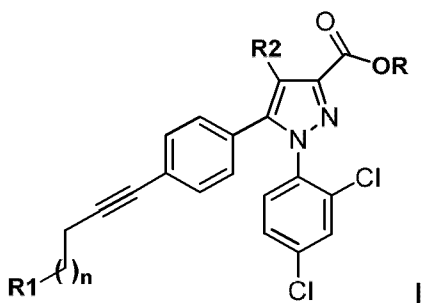
10 reacting the compound of Formula V with a substituted hydrazine to provide a compound represented by the Formula IA; or

reacting the compound of Formula I with a substituted hydrazine to provide a compound represented by Formula VI:

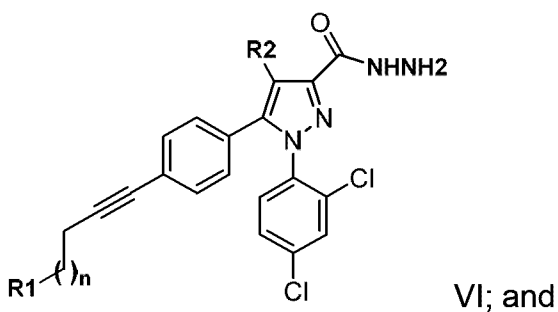


reacting the compound of Formula VI with a divinyl derivative to provide a compound represented by the Formula IA.

- 5 2. The process of claim 1, comprising reacting a compound represent by Formula I:

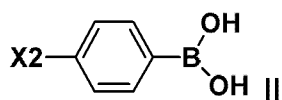


with a substituted hydrazine to provide a compound represented by Formula VI:

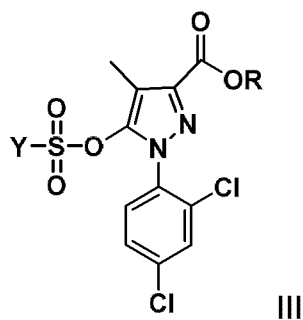


- 10 reacting the compound of Formula VI with a divinyl derivative to provide a compound represented by the Formula IA.

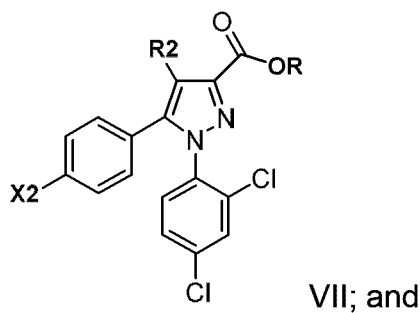
3. The process of claim 1, comprising reacting a compound represented by Formula II:



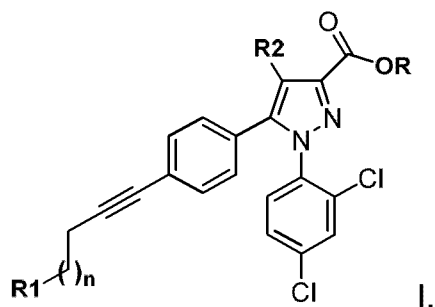
with a compound represented by Formula III:



to provide a compound represented by Formula VII:

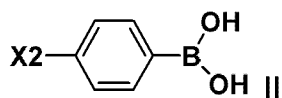


reacting the compound of Formula VII with an alkyne to provide a compound represented by Formula I:

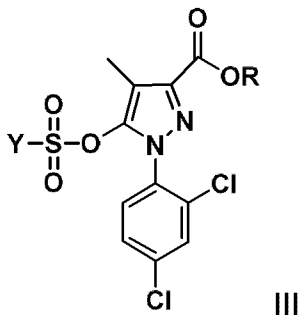


4. The process of claim 2, comprising:

reacting a compound represented by Formula II:

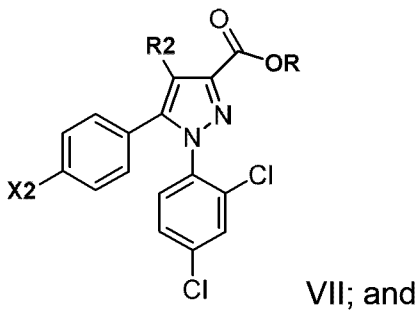


with a compound represented by Formula III:



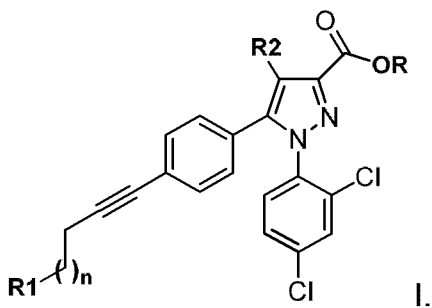
5

to provide a compound represented by Formula VII:



VII; and

reacting the compound of Formula VII with an alkyne to provide a compound represented by Formula I:

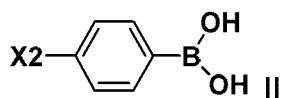


I.

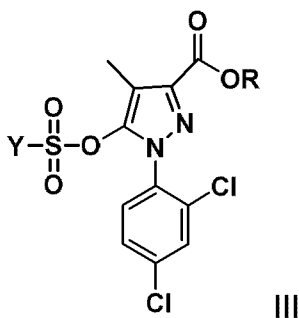
10

5. The process of claim 1, comprising:

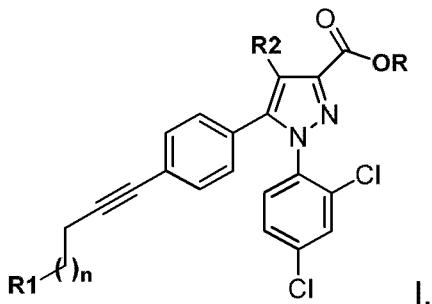
reacting a compound represented by Formula II:



5 with a compound represented by Formula III:

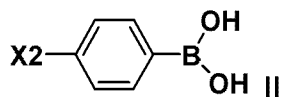


to provide a compound represented by Formula I:

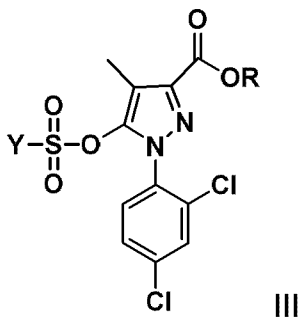


10 6. The process of claim 2, comprising:

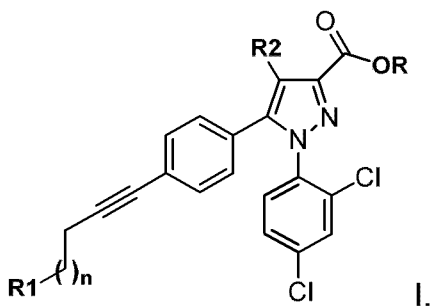
reacting a compound represented by Formula II:



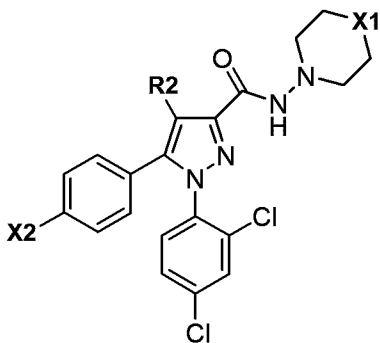
with a compound represented by Formula III:



to provide a compound represented by Formula I:

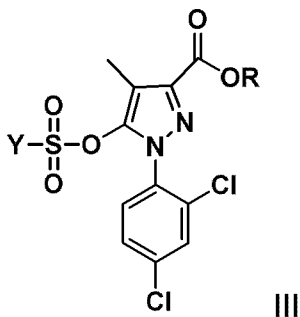


- 5 7. A process for preparing a compound represented by Formula ID, its solvates, polymorphs and isotopic variations thereof

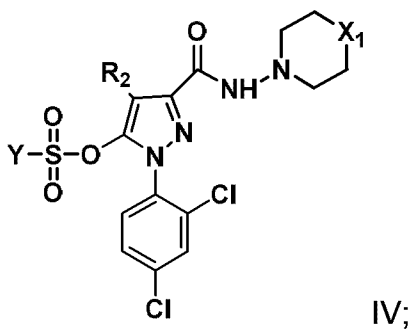


ID, comprising:

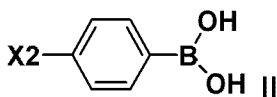
reacting a compound represented by Formula III:



with substituted hydrazide to provide a compound represented by Formula IV:



reacting the compound of Formula IV with a compound represented by
 5 Formula II:



to provide a compound represented by the Formula ID.

8. The process of claim 1, wherein X1 is -SO2-, -O- or -CH2- .

10

9. The process of claim 7, wherein X1 is -SO2-, -O- or -CH2- .

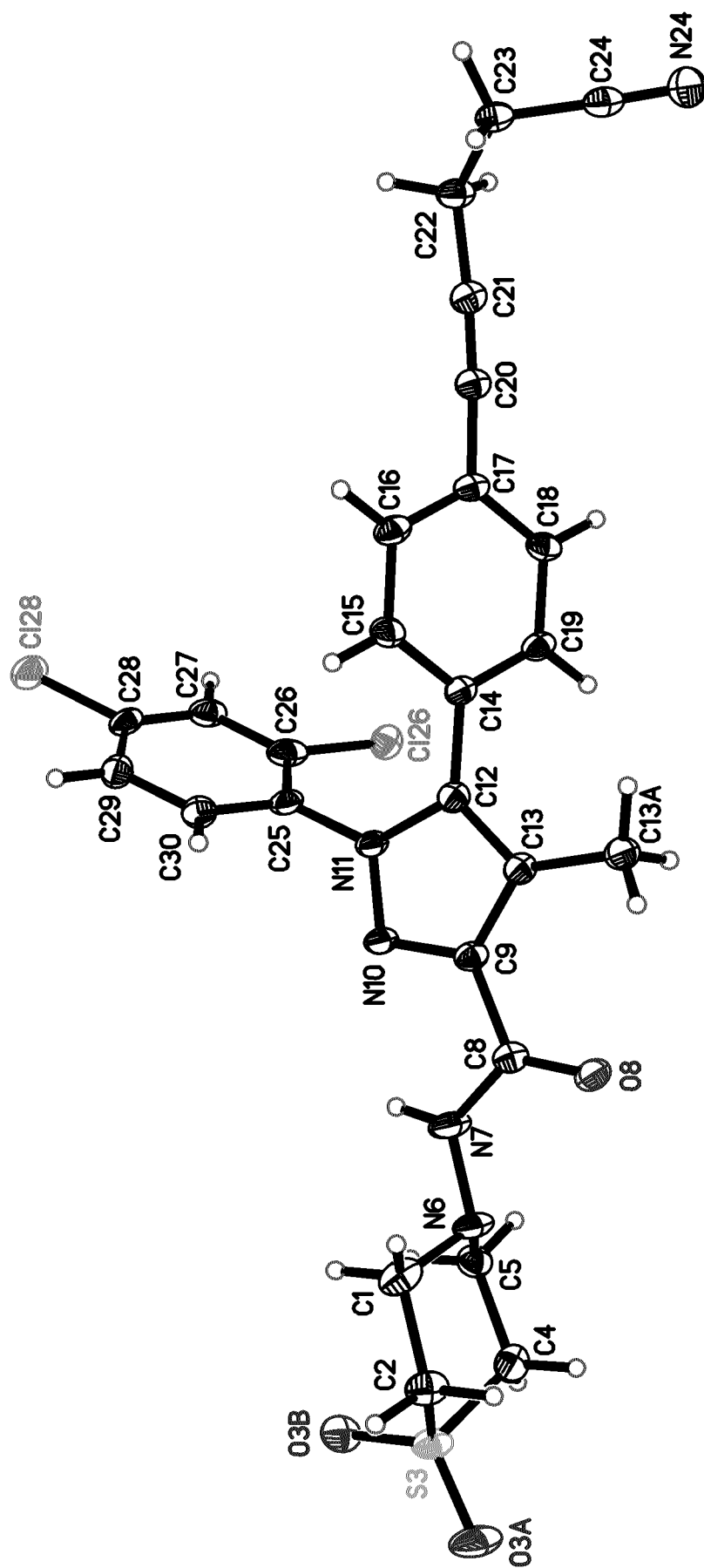


Fig. 1