



(43) International Publication Date
18 May 2017 (18.05.2017)

(10) International Publication Number
WO 2017/081702 A2

(51) International Patent Classification:
C07D 233/86 (2006.01)

(21) International Application Number:
PCT/IN2016/050388

(22) International Filing Date:
8 November 2016 (08.11.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
4279/MUM/2015 9 November 2015 (09.11.2015) IN

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to the identity of the inventor (Rule 4.17(i))
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

- without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: A PROCESS FOR PREPARATION OF ENZALUTAMIDE

(57) Abstract: The present invention relates to an improved process for preparation of enzalutamide which involves direct condensation of 2-(4-alkoxycarbonyl-3-fluoro-anilino)-2-methyl-propanoic acid and 4-isothiocyanato-2-(trifluoromethyl)benzonitrile to obtain alkyl 4-[3-(4-cyano-3-methyl-phenyl)-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]-2-fluoro-benzoate, which is further converted to enzalutamide.



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A PROCESS FOR PREPARATION OF ENZALUTAMIDE

RELATED APPLICATIONS

- 5 This application claims the benefit of Indian Patent Application no. 4279/MUM/2015 filed on November 09, 2015 which is hereby incorporated by reference.

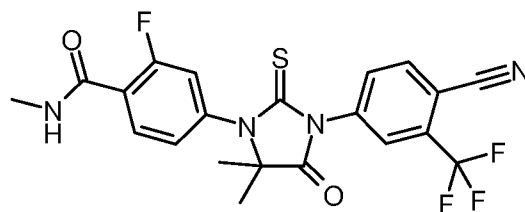
FIELD OF THE INVENTION

- 10 The present invention relates to an improved process for preparation of enzalutamide which involves direct condensation of 2-(4-alkoxycarbonyl-3-fluoro-anilino)-2-methyl-propanoic acid and 4-isothiocyanato-2-(trifluoromethyl)benzonitrile to obtain alkyl 4-[3-(4-cyano-3-methyl-phenyl)-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]-2-fluoro-benzoate, which is further converted to enzalutamide.

15

BACKGROUND OF THE INVENTION

- Enzalutamide is an androgen receptor inhibitor approved for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC). The chemical name is 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide depicted as Formula I
- 20



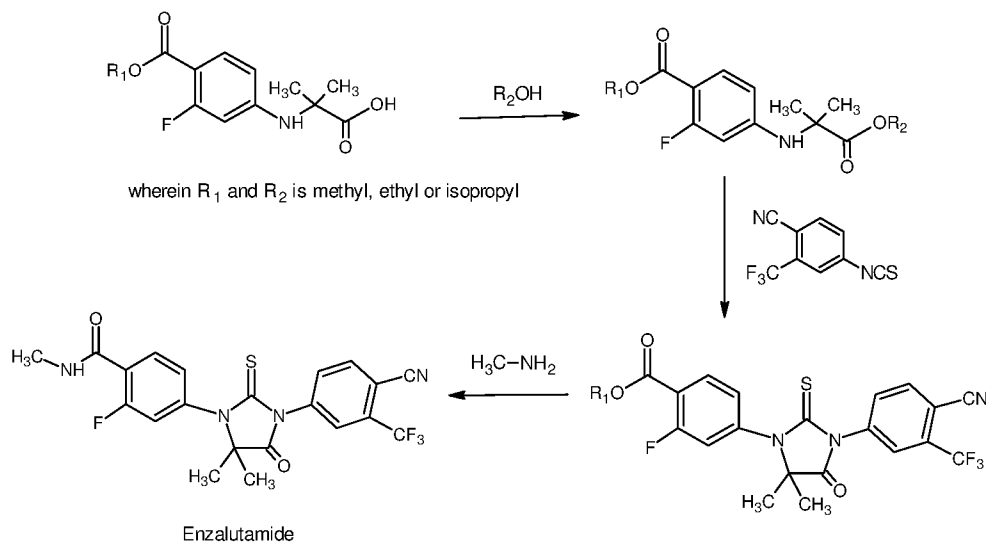
Formula I

- US patent number 7709517 (the '517 patent) discloses a process for preparation of enzalutamide which involves reacting *N*-Methyl-2-fluoro-4-aminobenzamide with acetone cyanohydrin to give *N*-methyl-2-fluoro-4-(1,1-dimethyl-cyanomethyl)-aminobenzamide which was further reacted with 4-isothiocyanato-2-trifluoromethylbenzonitrile to afford the compound of Formula I. The process involves the use of acetone cyanohydrin which is known to be toxic and hazardous and is not recommended for commercial manufacturing.
- 25

The process also requires elevated temperature which causes decomposition of 4-isothiocyanato-2-trifluoromethylbenzonitrile or the final product, enzalutamide.

WIPO publication number 2011106570A1 (the '570 application) also discloses processes for preparation of enzalutamide wherein one process involves activating 2-[3-fluoro-4-(methylcarbamoyl)anilino]-2-methyl-propanoic acid by converting it into its methyl ester and reacting the methyl ester with 4-isothiocyanato-2-trifluoromethylbenzonitrile. In another process reported in the WIPO '570 publication, 2-[3-fluoro-4-(methylcarbamoyl)anilino]-2-methyl-propanoic acid is condensed with 4-amino-2-(trifluoromethyl)benzonitrile to produce 4-(1-(4-cyano-3-(trifluoromethyl)phenylamino)-2-methyl-1-oxopropan-2-ylamino)-2-fluoro-N-methylbenzamide which in turn is converted to enzalutamide by reacting it with thiophosgene. The yields reported by the process are not viable for a commercial production.

CN104803919A and CN104803918A discloses a process for preparation of enzalutamide as depicted below-

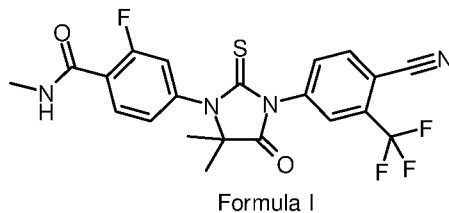


The various other processes for the preparation of enzalutamide are reported in US 20150210649A1, WO 2015154730A1, CN 103910679A, CN 103980141A, CN 104016924A.

The present invention provides a simple, scalable and economical process for the preparation of enzalutamide.

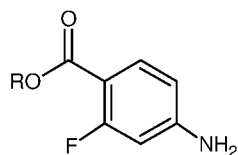
SUMMARY OF THE INVENTION

The present invention provides a process for preparation of a compound of Formula I

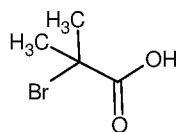


5 wherein the process comprises:

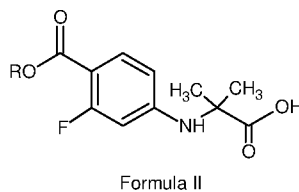
a) condensing a compound of Formula IIa



wherein R is C₁-C₄ alkyl, with a compound of Formula IIb

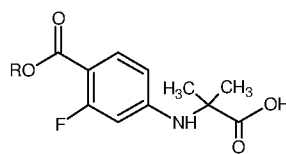


10 to obtain a compound of Formula II

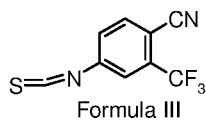


wherein R is C₁-C₄ alkyl,

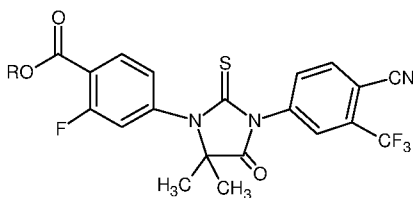
b) condensing the compound of Formula II



15 with a compound of Formula III



to obtain a compound of Formula IV



Formula IV

wherein R is C₁-C₄ alkyl, and

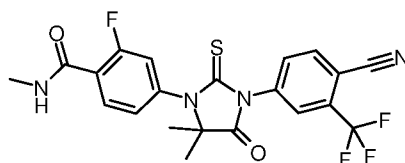
c) converting the compound of Formula IV to the compound of Formula I.

5 GLOSSARY

The term "C₁-C₄ alkyl" as used herein refers to a saturated hydrocarbon chain that includes carbon and hydrogen atoms in the backbone, either linear or branched, having from 1 to 4 carbon atoms. The non-limiting examples of C₁-C₄ alkyl includes methyl, ethyl, isopropyl, n-butyl or isobutyl.

DETAILED DESCRIPTION OF THE INVENTION

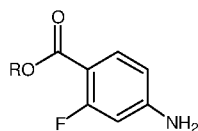
In one aspect, the present invention provides a process for preparation of enzalutamide, a compound of Formula I



Formula I

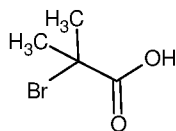
wherein the process comprises:

a) condensing a compound of Formula IIa



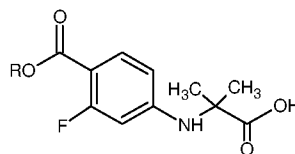
Formula IIa

wherein R is C₁-C₄ alkyl, with a compound of Formula IIb



Formula IIb

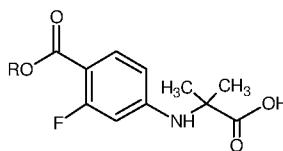
to obtain a compound of Formula II,



Formula II

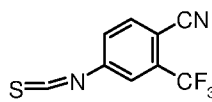
wherein R is C₁-C₄ alkyl,

b) condensing the compound of Formula II



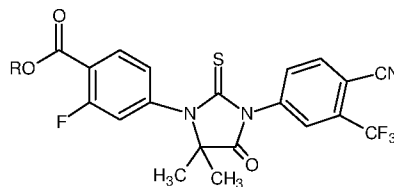
Formula II

with a compound of Formula III



Formula III

to obtain a compound of Formula IV



Formula IV

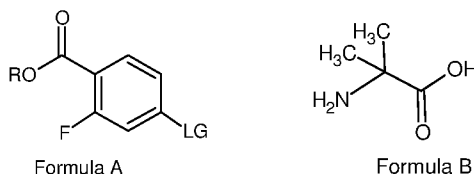
wherein R is C₁-C₄ alkyl, and

c) converting the compound of Formula IV to the compound of Formula I.

In one embodiment of the present invention, the condensation of the compound of Formula IIa and IIb as per step a is carried out in the presence of a suitable solvent and a base. The suitable solvent for the purpose can be selected from halogenated solvents such as dichloromethane; ethers such as tetrahydrofuran; esters such as ethyl acetate; *N,N*-dimethylformamide (DMF), dimethylsulfoxide, dimethylacetamide or a mixture thereof. The preferred solvent is dichloromethane. A base for the reaction may be selected from any suitable organic or inorganic bases, preferably weak bases such as triethylamine or diisopropylethylamine. The condensation of the compound of Formula IIa and IIb as per step a can be carried out at a temperature range of 25 °C to 80 °C. Preferably, the temperature is about 25 °C to about 40 °C. The reaction can be maintained at the given condition for a time

suitable for completion of the reaction, for example for about 5 to 20 hours, more preferably 10 to 15 hours. The compound of Formula IIb is used in a molar equivalent of about 1 to 1.5 equivalent with respect to the compound of Formula IIa.

- 5 CN104803919A (the CN '919 application) discloses a process for preparation of compound of Formula II by condensation of the compound of Formula A and B



wherein R in the compound of Formula A is methyl, ethyl or isopropyl and LG is a leaving group. However the process disclosed in the CN '919 application requires high temperature and use of metallic catalyst like copper. The use of the metallic catalyst for the preparation of the pharmaceutical compounds is not preferred as it leads to some problems with respect to impurities and other regulatory complexity.

In another embodiment of the present invention, the condensation of the compound of Formula II and III as per step b is carried out in the presence of a suitable solvent and a base. A suitable solvent for the purpose can be selected from but not limited to halogenated solvents such as dichloromethane; ethers such as tetrahydrofuran; esters such as ethyl acetate; *N,N*-dimethylformamide (DMF), dimethylsulfoxide, dimethylacetamide or a mixture thereof. More preferred solvents are ethyl acetate and dichloromethane. A base for the reaction may be selected from any suitable organic or inorganic bases, preferably weak bases, such as triethylamine and diisopropylethylamine. The condensation of the compound of Formula II and III is carried out at a temperature range of about 40 °C to 80 °C, more preferably about 60 °C. The reaction can be carried out for a time suitable for completion of the reaction for instance 2 to 10 hours, preferably, 5 to 8 hours. The compound of Formula III is used in a molar equivalent of about 1 to 3 equivalent with respect to the compound of Formula II, more preferably 1.7 molar equivalents.

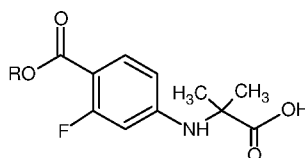
In another embodiment of the present invention, the conversion according to step c, can be done by any possible way as one of the skilled person of the art can perform, such as by direct coupling of the compound of Formula IV with methylamine to afford compound of Formula I. In another way, the compound of Formula IV can be first hydrolyzed to its

corresponding acid, then reacted with methylamine to afford compound of Formula I. In yet another way, the free acid of the compound of Formula IV is first activated by a suitable activating agent and subsequently reacted with methylamine to afford compound of Formula I. Thus the compound of Formula IV may be converted to compound of Formula I by any of the processes under the purview of a person skilled in the art.

In another embodiment of the present invention, R in the compound of Formula IIa, compound of Formula II and compound of Formula IV is C₁-C₄ alkyl selected from methyl, ethyl, isopropyl, n-butyl or isobutyl; more preferably ethyl.

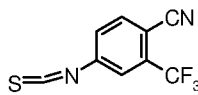
In another embodiment, the present invention provides a process for the preparation of enzalutamide, comprising:

(aa) condensing a compound of Formula II



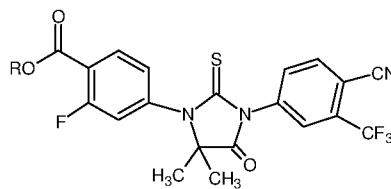
Formula II

wherein R is C₁-C₄ alkyl,
with a compound of Formula III



Formula III

to obtain a compound of Formula IV



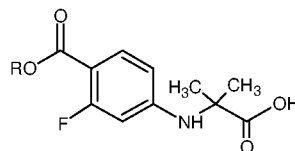
Formula IV

wherein R is C₁-C₄ alkyl, and

(ab) converting the compound of Formula IV to the compound of Formula I.

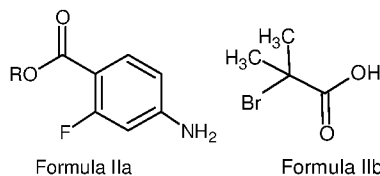
In another embodiment, the steps “aa” and “ab” can be performed as per the process disclosed for the steps b and step c earlier in the specification.

In yet another embodiment, the present invention provides a process for preparation of a compound of Formula II



Formula II

wherein R is C₁-C₄ alkyl, comprising condensing the compound of Formula IIa with a compound of Formula IIb



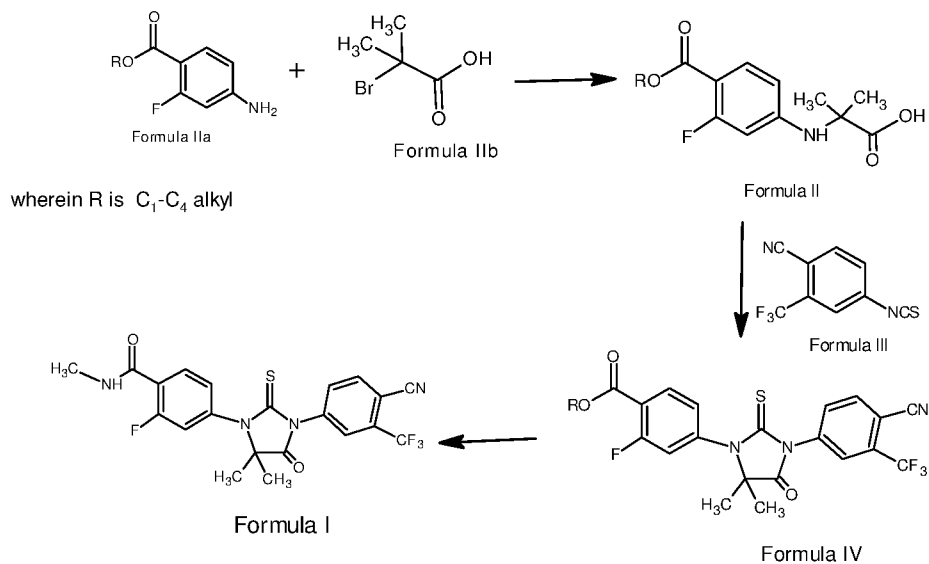
Formula IIa

Formula IIb

wherein R in the compound of Formula IIa is C₁-C₄ alkyl.

In another embodiment, the condensation of compound of Formula IIa and IIb can be carried out as per the process described earlier in the specification.

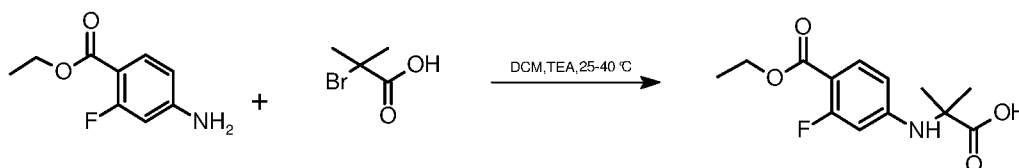
The process of the present invention can be depicted as in following scheme:



The present invention is further illustrated in detail with reference to the following examples.

It is desired that the examples be considered in all respect as illustrative and are not intended to limit the scope of the claimed invention.

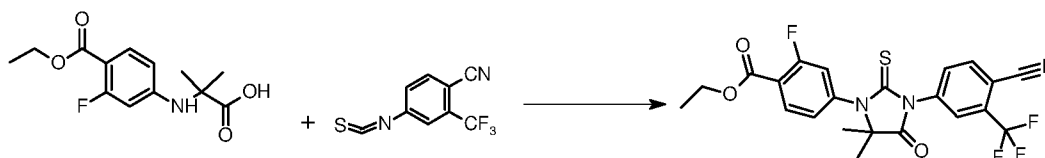
EXAMPLES

Example 1: Preparation of 2-(4-ethoxycarbonyl-3-fluoro-anilino)-2-methyl-propanoic acid

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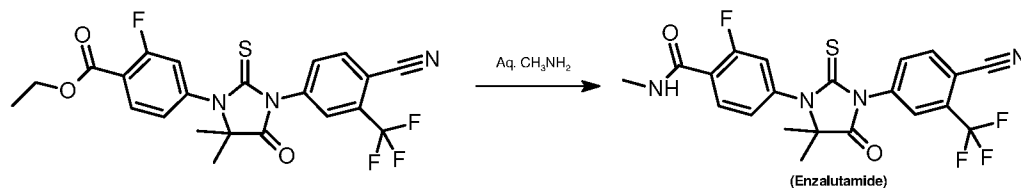
In a round bottomed flask equipped with nitrogen atmosphere facility, 2-fluoro-4-aminobenzoic acid ethyl ester (10 g), bromoisobutyric acid (16 g) and dichloromethane (100 mL) were added at room temperature followed by the addition of triethylamine (25 mL) and the reaction mixture was stirred for 15 hours at 25 °C to 40 °C. After completion of the reaction, the reaction mixture was concentrated under reduced pressure at 40 °C, water was added and stirred for 1 hour. Aqueous layer was acidified with hydrochloric acid (7.5 mL) and stirred for another 60 minutes. Then the reaction mixture was cooled to 0 °C to 5 °C and stirred for additional 3 hour. The product was filtered and washed with 25 mL water and dried under vacuum at 40 °C for 6 hours to give the title compound. Yield: 14 g.

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Example 2: Preparation of ethyl 4-[3-(4-cyano-3-methyl-phenyl)-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]-2-fluoro-benzoate

In a 500 mL round bottomed flask equipped with nitrogen atmosphere facility, 4-isothiocyanato-2-(trifluoromethyl)benzonitrile (14 g) and ethylacetate (150 mL) were added. The reaction mixture was stirred for 15 minutes and triethylamine (5 mL) was added at 20 °C to 30 °C. The reaction mixture was heated to reflux for 15 minutes and then 2-(4-ethoxycarbonyl-3-fluoro-anilino)-2-methyl-propanoic acid (10 g) was added. The reaction was refluxed for 4-6 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure at 50 °C. Ethyl alcohol (25 mL) was added to the residue and stirred for 1 hour, at 0 °C to 5 °C. The product was filtered, washed with ethyl alcohol and dried under vacuum at 40 °C for 6 hours to give the title compound. Yield: 9.2 g

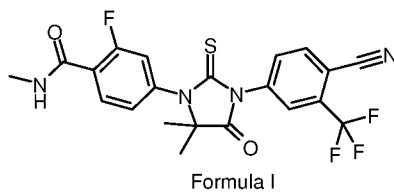
Example 3- Preparation of 4-[3-(4-cyano-3-methyl-phenyl)-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]-2-fluoro-N-methyl-benzamide (Enzalutamide)



5 A mixture of ethyl 4-[3-(4-cyano-3-methyl-phenyl)-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]-2-fluoro-benzoate (10 g) and aqueous methylamine (40 % solution, 150 mL) was stirred at 20 °C to 30 °C for 5 to 7 hours. Completion of reaction mixture was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated to a volume of 100 mL under reduced pressure at 30 °C to 35 °C. The product was extracted
10 with ethyl acetate (100 mL). The organic layer was concentrated under reduced pressure to obtain enzalutamide. Yield: 7 g.

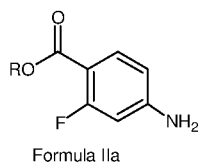
CLAIMS:

1. A process for preparation of a compound of Formula I

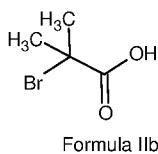


wherein the process comprises:

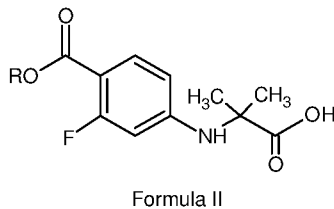
- 5 a) condensing a compound of Formula IIa



wherein R is C₁-C₄ alkyl, with a compound of Formula IIb



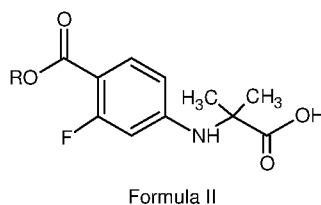
to obtain a compound of Formula II



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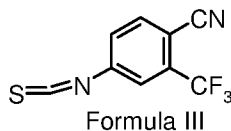
wherein R is C₁-C₄ alkyl,

- b) condensing the compound of Formula II

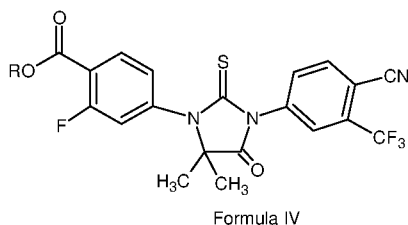


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with a compound of Formula III



to obtain a compound of Formula IV

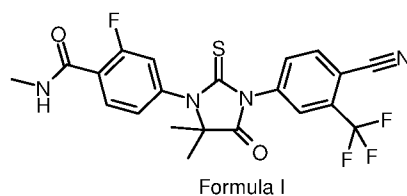


wherein R is C₁-C₄ alkyl, and

c) converting the compound of Formula IV to the compound of Formula I.

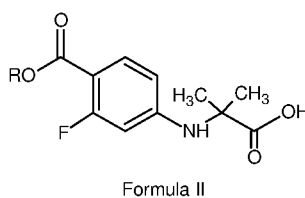
- 5 2. The process as in claim 1, wherein the step a is conducted in presence of a solvent selected from a group consisting of halogenated solvents, ethers, *N,N*-dimethylformamide, dimethylsulfoxide, dimethylacetamide and a base selected from inorganic base or organic base.
- 10 3. The process as in claim 2, wherein the solvent is selected from dichloromethane and a base selected from triethylamine or diisopropylethylamine.
- 15 4. The process as in claim 1, wherein the step b is conducted in presence of a solvent selected from a group consisting of halogenated solvents, ethers, *N,N*-dimethylformamide, dimethylsulfoxide, dimethylacetamide and a base selected from inorganic base or organic base.
- 20 5. The process as in claim 4, wherein the solvent is ethyl acetate and a base is selected from triethylamine or diisopropylethylamine.
- 25 6. The process as in claim 1, wherein the compound of Formula IV is converted into the compound of Formula I by condensing the compound of Formula IV with methylamine.
7. The process as in claim 1, wherein R in the compound of Formula IIa, Formula II and Formula IV is ethyl.

8. A process for preparation of Formula I



wherein the process comprises:

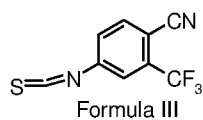
(aa) condensing a compound of Formula II



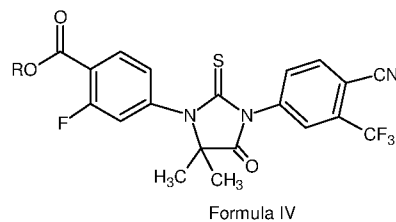
5

wherein R is C₁-C₄ alkyl,

with a compound of Formula III



to obtain compound of Formula IV



10

wherein R is C₁-C₄ alkyl, and

(ab) converting the compound of Formula IV to the compound of Formula

I.

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