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(54) Title: PROCESSES TO PRODUCE ELAGOLIX

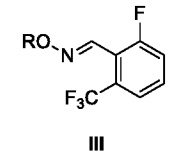
(57) Abstract: The present invention relates to a scalable process for the making of elagolix, its salts and the process of intermediate compounds.

PROCESSES TO PRODUCE ELAGOLIX

BACKGROUND OF THE INVENTION

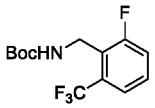
1. Field of the invention

The present invention relates to process for preparing the compound of formula **III**, compound of formula **IV**, compound of formula **V**, compound of formula **VI**, compound of formula **VIII**, compound of formula **IX**, compound of formula **XIV**, compound of formula **X**, compound of formula **XII**, compound of formula **XIII**, and elagolix sodium, a gonadotropin-releasing hormone (GnRH) receptor antagonist indicated for the management of moderate to severe pain associated with endometriosis.

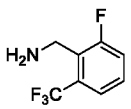


III

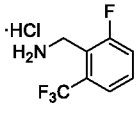
R=H, methyl or ethyl ,



IV ,



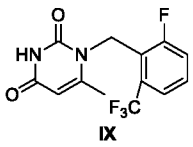
V ,



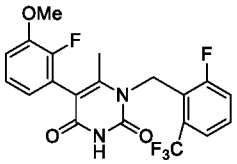
VI ,



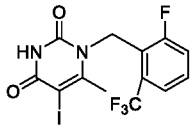
VIII ,



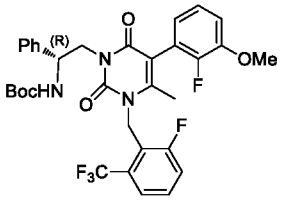
IX ,



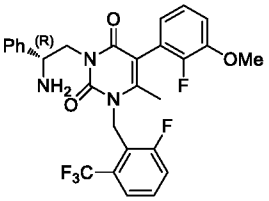
X ,



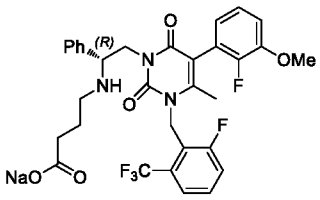
XIV



XII ,



XIII ,



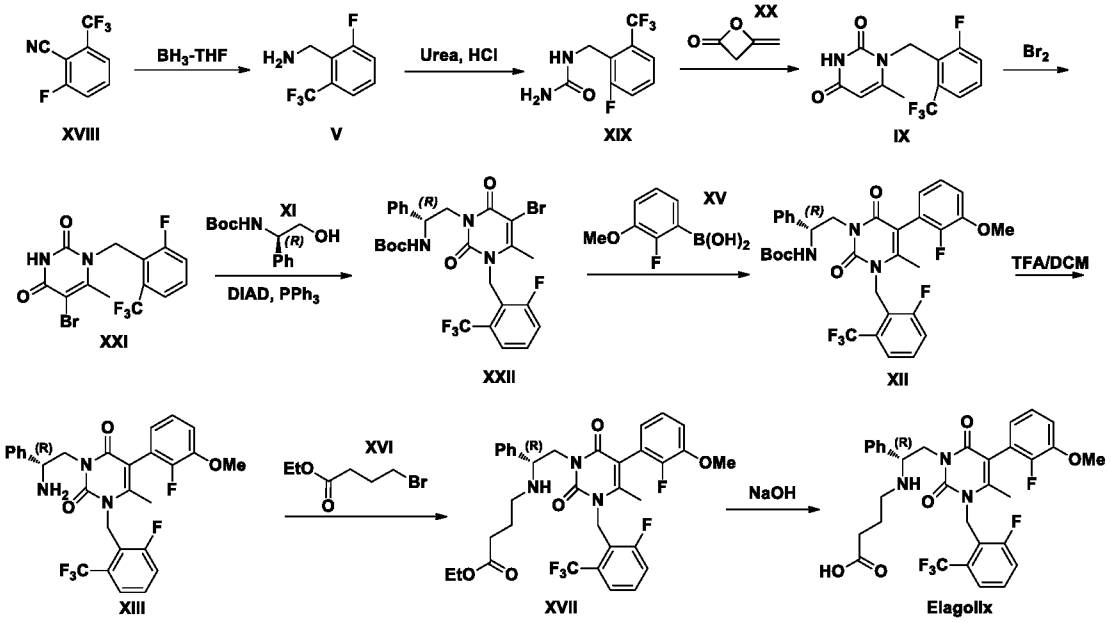
Elagolix sodium .

2. Description of the Related Art

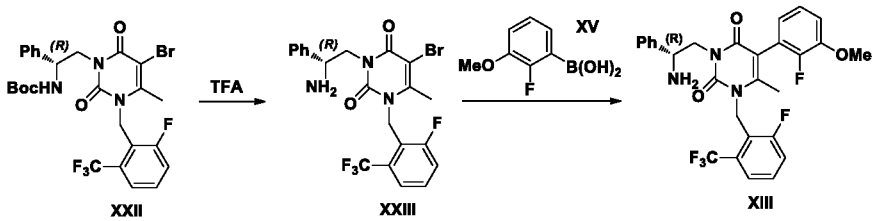
Orilissa (elagolix sodium; previously known as NBI-56418 or ABT-620) is a gonadotropin-releasing hormone antagonist (GnRH antagonist) medication which is used in the treatment of pain associated with endometriosis in women. Orilissa is also under development for the treatment of uterine fibroids in women.

Orilissa was approved by the FDA for the treatment of endometriosis-associated pain in the United States on 23 July 2018. It was the first new medication to be approved by the FDA for the treatment of endometriosis in more than a decade. Elagolix is the first and currently the only marketed member of a new class of GnRH modulators, which is described as "second-generation" due to their non-peptide and small-molecule nature and oral activity.

The preparation of elagolix was disclosed in International Patent Application WO2005/007165 A1:

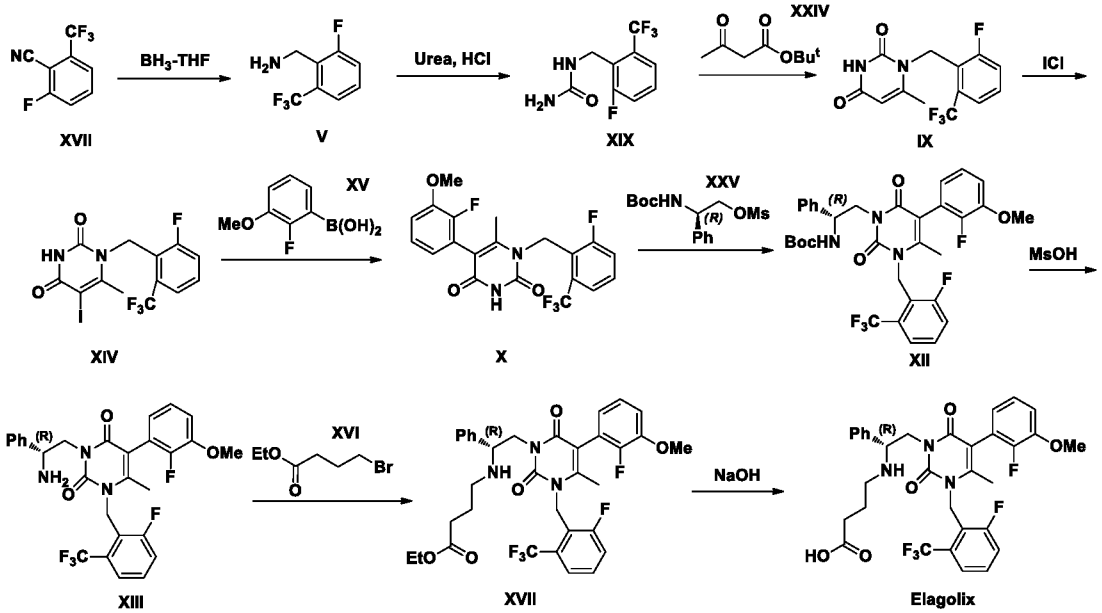


Compound **V**, **IX**, **XII** and **XIII** are key intermediates for the preparation of elagolix. Another synthetic route to the Compound **XIII** from the Compound **XXII** was also disclosed:



In WO2005/007165 A1, the technical solution for the preparation of compound **V** requires the use of the expensive starting material **XVIII**, as compound **XVIII** is not a commercially available bulk material. For the preparation of compound **IX**, compound **V** reacts with urea to produce compound **XIX**; compound **XIX** is treated with 15 equivalents of acetyl ketene, sodium iodide, and chlorotrimethylsilane; the yield of compound **IX** from compound **V** is 58%, resulting in an uneconomic synthetic process. For the preparation of compound **XIII**, two routes were disclosed. Both of the routes start from compound **XXII**, requiring a large amount of catalyst for the Suzuki coupling reaction.

Another route for the preparation of elagolix was disclosed in WO2009/062087 A1:
In WO2009/062087 A1, the preparation of compound **V** is same as the method in WO2005/007165 A1. For the preparation of compound **IX**, the compound **XIX** reacts with tert-butyl acetoacetate catalyzed by p-toluenesulfonic acid. The yield of compound **IX** from compound **V** is 46%, which is undesirably low. For the preparation of compound **XII**, compound **X** reacts with compound **XXV**, the byproduct of which is methanesulfonic acid. The residue of methanesulfonic acid may lead to the formation of methanesulfonic acid ester, which is a potential genotoxic impurity. For the preparation of compound **XIII**, methanesulfonic acid is also used, which may bring the same potential genotoxic impurity problem.



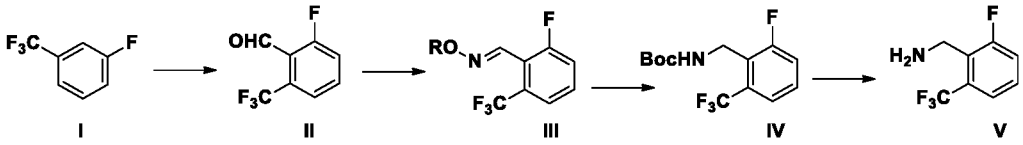
Technical Problem: The current processes to the intermediates of elagolix, compound **V** and compound **IX** require high raw material costs, and results in low yield. For compound **XII** and compound **XIII**, the process cost is high and there is the problem of a genotoxic impurity. A scalable preparation route is needed to overcome these problems for large-scale production.

SUMMARY OF THE INVENTION

It is the object of the present invention to provide a cost effective and scalable process for the preparation of elagolix and the seven intermediates: compound of formula **III**, compound of formula **IV**, compound of formula **V**, compound of formula **VIII**, compound of formula **IX**, compound of formula **XIV**, compound of formula **X**, compound of formula **XII**, and compound of formula **XIII**.

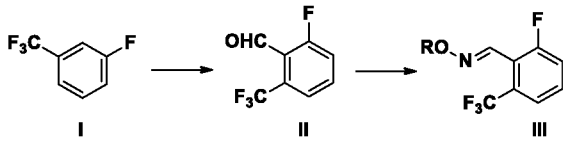
One purpose of the present application is to provide a preparation of compound **III**, compound **IV** and compound **V**.
A further purpose of the present application is to provide a method to prepare the compound **VIII** and compound **IX**.
A further purpose of the present application is to provide a method to prepare the compound **X**.
A further purpose of the present application is to provide a method to prepare the compound **XII** and compound **XIII**.
A further purpose of the present application is to provide a process to prepare of elagolix and elagolix sodium.

The present application provides a process for the preparation of compound **III**, compound **IV** and compound **V**:



wherein R is a substituent selected from the group consisting of H, methyl or ethyl.
In a specific embodiment, the reaction conditions for each reaction step are detailed below:

Synthesis of the compound of formula **III** from the compound of formula **I** and compound of formula **II**:



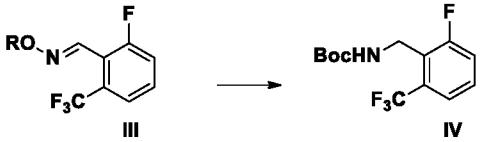
Compound **I** is a commercially available bulk material, and the compound **III** can be prepared efficiently by continuous reaction without separation of compound **II**.

The compound **I** reacts with DMF in an organic solvent in the presence of organolithium reagents and amine additives to prepare compound **II**. Preferably, the organic solvent is selected from tetrahydrofuran, methyl tetrahydrofuran, n-heptane, n-hexane, toluene, xylene and mixtures thereof. Preferably, the solvent is tetrahydrofuran. Preferably, the amine additive is one or more of tetramethylethylenediamine, diisopropylamine, diethylamine, di-sec-butylamine or pentamethyldiethylenetriamine. Preferably, the amine additives are tetramethylethylenediamine and diisopropylamine. Preferably, the organolithium reagent is one of n-butyl lithium, tert-butyl lithium, isobutyl lithium, lithium diisopropylamide, lithium bis (trimethylsilyl) amide. Preferably,

the organolithium reagent is n-butyl lithium. Preferably, the reaction temperature is -60~-80 °C. The compound **II** reacts with alkoxy amine or hydroxylamine hydrochloride at 10~50 °C in the presence of a base to prepare compound **III**. Preferably, the base is selected from sodium hydroxide, potassium hydroxide, triethylamine, N,N-diisopropylethylamine, sodium carbonate, potassium carbonate, and sodium bicarbonate. More preferably, the base is sodium bicarbonate.

Because of the low boiling point and volatility of compound **II**, it is used in the preparation of Compound **III** directly without separation from the solution.

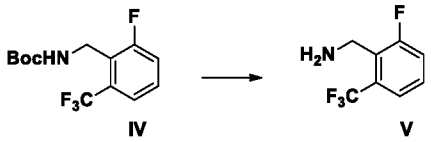
Synthesis the compound of formula **IV** from the compound of formula **III**:



III IV

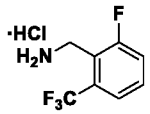
The compound **III** reacts with di-tert-butyl dicarbonate in an alcoholic solvent at 10~70 °C in the presence of a transition-metal catalyst under hydrogen atmosphere to prepare compound **IV**. Preferably, the alcoholic solvent is selected from methanol, ethanol, isopropanol and mixtures thereof. Preferably, the solvent is methanol. Preferably, the transition-metal catalyst is selected from Raney Ni or Pd/C. More preferably, the transition-metal catalyst is Raney nickel, and the hydrogen pressure is 0.1~5.0 MPa, more preferably, the hydrogen pressure is 0.2~0.5 MPa. Preferably, the reaction temperature is 20~40 °C.

Synthesis the compound of formula **V** from the compound of formula **IV**:



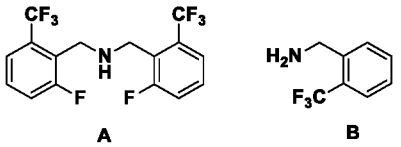
IV V

The compound **IV** reacts in the presence of an acid at 10~70 °C to prepare compound **V** or its salt compound **VI**. Preferably, the acid is hydrochloric acid. Preferably, the reaction temperature is 20~40 °C.



VI

The compound **III** can be reduced directly with Raney Ni and H_2 to prepare compound **V**. However, such a process leads to the formation of impurity **A**. It is found that the addition of di-tert-butyl dicarbonate can effectively control the formation of impurity **A**. Further, we unexpectedly found that this method can effectively control the formation of impurity **B**. Impurity **B** has similar structure with compound **V**, which has a greater adverse impact to the final product quality. This improved method can effectively improve the final product quality by reducing the presence of impurities A and B.



A B

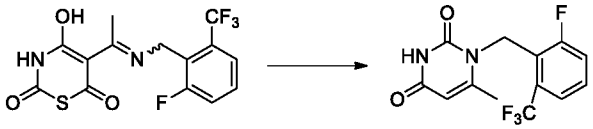
Compared with the prior art, the method has the following advantages:

1. The reaction conditions are mild. The explosive reagents such as boron hydride or Zn powder are not needed, so it is more environmentally-friendly and safe.
2. Continuous reaction reduces the loss of product resulting from product separation, and increases production efficiency.
3. Impurity formation is effectively reduced.
4. Inexpensive commercially available starting material is used in the process, resulting in reduced raw material cost.

The present application provides a process for the preparation of compound **IX** from compound **VIII**:

In a specific embodiment, the reaction conditions for each reaction step are detailed below:

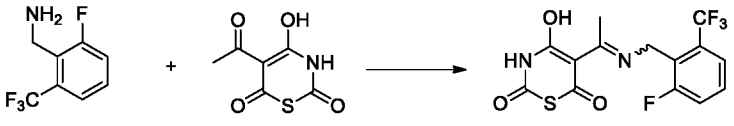
Synthesis the compound of formula **IX** from the compound of formula **VIII**:



VIII IX

The compound **VIII** reacts in an organic solvent at 50~200 °C to prepare compound **IX**. Preferably, the organic solvent is selected from dimethylformamide, dimethylacetamide, acetonitrile, n-butanol, tert-butanol, 1,4-dioxane, dimethyl sulfoxide, N-methylpyrrolidone, sulfolane and mixtures thereof. Preferably, the organic solvent is dimethylformamide, N-methylpyrrolidone. More preferably, the organic solvent is dimethylformamide. Preferably, the reaction temperature is 80~160 °C.

Synthesis of the compound of formula **VIII** from the compound of formula **V** and the compound of formula **VII**:

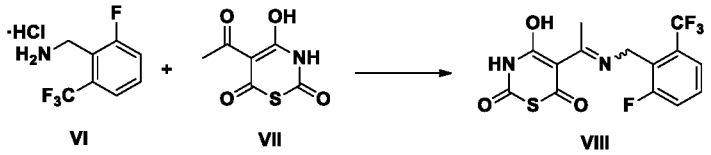


V VII VIII

Compound **VII** can be readily prepared from malonic acid and potassium thiocyanate in acetic acid and acetic anhydride.

The compound **V** reacts with compound **VII** in an organic solvent at 50~200 °C to prepare compound **VIII**. Preferably, the organic solvent is selected from dimethylformamide, dimethylacetamide, acetonitrile, tetrahydrofuran, methyl tetrahydrofuran, isopropanol, n-butanol, tert-butanol, dioxane, dimethyl sulfoxide, N-methyl pyrrolidone, cyclobutanone and mixtures thereof. More preferably, the organic solvent is isopropanol. Preferably, the molar equivalence of compound **VII** is between 0.8 and 5. Preferably, the molar equivalence of compound **VII** is between 1 and 3. Preferably, the reaction temperature is 80~160 °C.

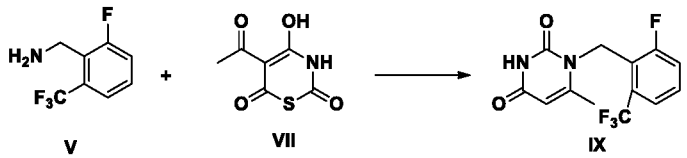
Synthesis of the compound of formula **VIII** from the compound of formula **VI** and the compound of formula **VII**:



VI VII VIII

The compound **VI** reacts with compound **VII** in an organic solvent at 50~200 °C in the presence of a base to prepare compound **VIII**. Preferably, the base is selected from sodium hydroxide, potassium hydroxide, triethylamine, N,N-diisopropylethylamine, sodium carbonate, potassium carbonate, and sodium bicarbonate. More preferably, the base is sodium hydroxide. Preferably, the organic solvent is selected from dimethylformamide, dimethylacetamide, acetonitrile, tetrahydrofuran, methyl tetrahydrofuran, isopropanol, n-butanol, tert-butanol, dioxane, dimethyl sulfoxide, N-methyl pyrrolidone and cyclobutanone. More preferably, the organic solvent is isopropanol. Preferably, the molar equivalence of compound **VII** is between 0.8 and 5. More preferably, the molar equivalence of compound **VII** is between 1 and 3. Preferably, the reaction temperature is 80~160 °C.

Synthesis of the compound of formula **IX** from the compound of formula **V** and the compound of formula **VII**:



V VII IX

The compound **V** reacts with compound **VII** in an organic solvent at 50~200 °C to prepare compound **IX**. Preferably, the organic solvent is selected from dimethylformamide, dimethylacetamide, acetonitrile, tetrahydrofuran, methyl tetrahydrofuran, isopropanol, n-butanol, tert-butanol, dioxane, dimethyl sulfoxide, N-methyl pyrrolidone and cyclobutanone. More preferably, the organic solvent is dimethylformamide,. Preferably, the molar equivalence of compound **VII** is between 1 and 10. Preferably, the molar equivalence of compound **VII** is between 1 and 3. Preferably, the reaction temperature is 100~150 °C.

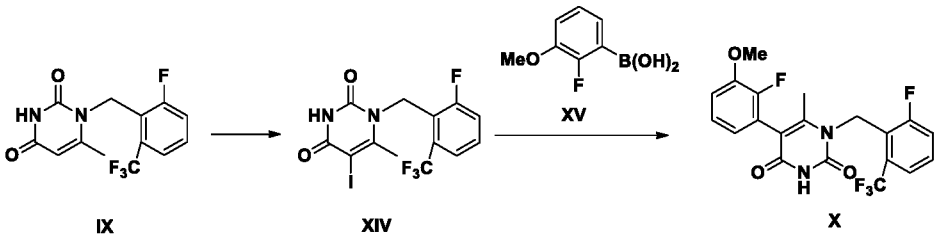
Compared with the prior art, the method has the following advantages:

1. The process is efficient and atom-economic.
2. The yield of the process is high. The cost of synthesizing elagolix and elagolix sodium is greatly reduced.
3. The workup of the process is simple, the impurity removal is facile, and the purity of the product is high.

The present invention provides a process for the preparation of compound **X**:

In a specific embodiment, the reaction conditions for each reaction step are detailed below:

Synthesis of the compound of formula **X** from the compound of formula **IX**:



The compound of formula **IX** reacts with N-iodosuccinimide to prepare the compound of formula **XIV**. The compound of formula **XIV** reacts with the compound of formula **XV** to produce the compound of formula **X** using methanesulfonato[tri(tert-butyl) phosphine (2'-amino-1,1'-biphenyl-2-yl)] palladium (II) as the catalyst.

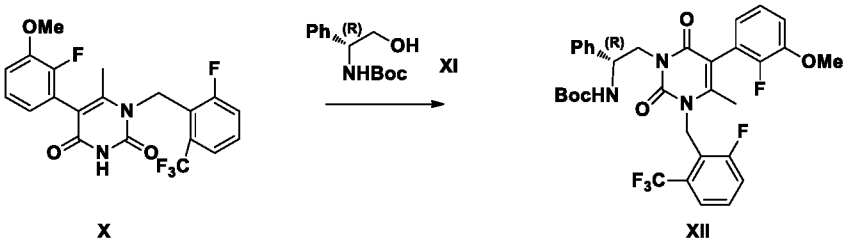
Compared with the prior art, the present method has the following advantages:

1. N-iodosuccinimide is easy to handle in production.
2. Methanesulfonato[tri (tert-butyl) phosphine (2'-amino-1,1'-biphenyl-2-yl)] palladium (II) that is used as the catalyst is less air and moisture sensitive than the combination of $Pd(OAc)_2$ and tri-tert-butylphosphine ligand, which makes the reaction more robust.

The present application provides a process for the preparation of compound **XII** and compound **XIII**:

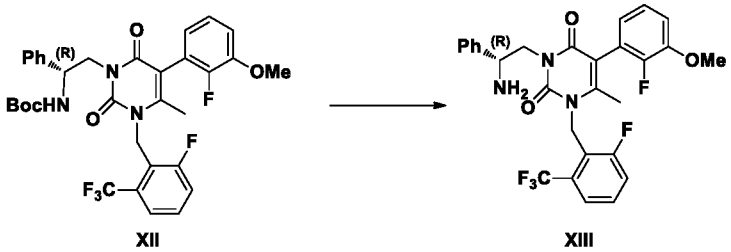
In a specific embodiment, the reaction conditions for each reaction step are detailed below:

Synthesis of the compound of formula **XII** from the compound of formula **X** and the compound of formula **XI**:



The compound of formula **X** reacts with the compound of formula **XI** under Mitsunobu reaction conditions in the presence of an organic solvent to prepare compound **XII**. Preferably, the organic solvent is selected from dichloromethane, toluene, 1,4-dioxane, tetrahydrofuran, methyl tetrahydrofuran and mixtures thereof. More preferably, the organic solvent is tetrahydrofuran.

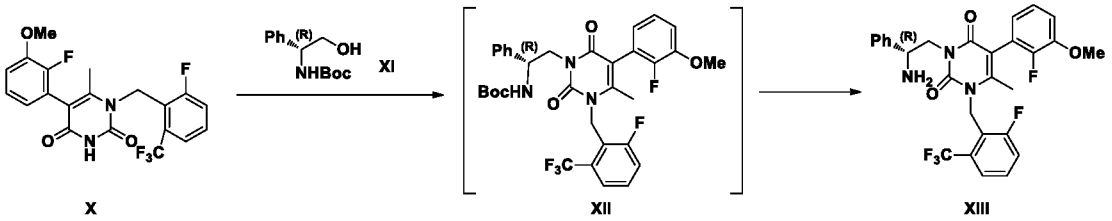
Synthesis of the compound of formula **XIII** from the compound of formula **XII**:



The compound of formula **XII** reacts under acidic conditions to prepare the compound of formula **XIII**. Preferably, the acid is selected from methanesulfonic acid, hydrochloric acid, sulfuric acid, trifluoroacetic acid and mixtures thereof. Preferably, the acid is hydrochloric acid. Preferably, the

reaction temperature is 50~60 °C.

Synthesis the compound of formula **XIII** from the compound of formula **X** and the compound of formula **XI**:



X XII XIII

The compound of formula **XIII** can be prepared from the compound of formula **X** and the compound of formula **XI** in telescope or continuous reaction without the separation of compound **XII**.

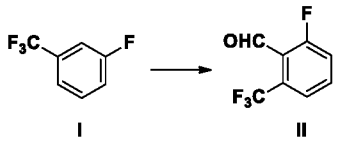
Compared with the prior art, the present method has the following advantages:

1. Simplified reaction process, suitable for large-scale continuous reaction.
2. Avoid the use of potential genotoxic substances in the reaction process, making the process environmentally greener and safer.

DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS

Example

Example 1: Synthesis of compound II

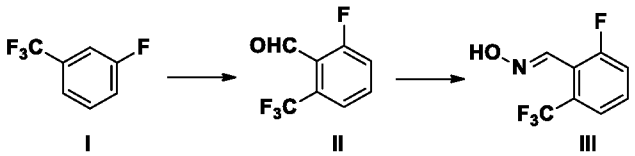


I II

To a round-bottom flask were added compound I (20 g), tetramethylethylenediamine (15.6 g), diisopropylamine (0.6 g) and THF (200 mL). The mixture was cooled to -60~-78 °C. n-BuLi solution in hexanes (53.5 mL, 2.5 M) was added at -60~-78 °C. The reaction mixture was stirred at -60~-78 °C for 1h. DMF (13.4 g) was added at -60~-78 °C. After completion of the reaction, the reaction mixture was quenched with saturated NH_4Cl solution (100 mL). The layers were separated. The organic phase was concentrated under vacuum. The crude material was purified by silica gel column chromatography eluting with hexane to get compound II as yellow oil (1.1 g, 4.5% yield, 99.0% purity).

^1H NMR (400 MHz, DMSO-d6) δ 10.46 (s, 1H) 7.71 (m, 1H), 7.64 (d, *J*=7.6Hz, H), 7.44 (t, *J*=9.2Hz, 1H).

Example 2: Synthesis of compound III



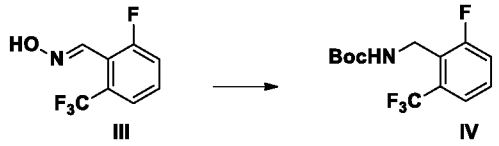
I II III

To a 100 L reactor were added THF (25 L), compound I (2.5 Kg), tetramethylethylenediamine (1.95 Kg) and diisopropylamine (77.5 g). The mixture was cooled to -60~-78 °C. n-BuLi solution in hexanes (4.55 Kg, 2.5 M) was added at -60~-78 °C. After the reaction mixture was stirred at -60~-78 °C for 1 h, DMF (1.68 Kg) was added at -60~-78 °C. After completion of the reaction, the reaction mixture was warmed to -40~-20°C. The reaction mixture was poured into 20% AcOH aqueous solution. The layers were separated. The organic layer was added hydroxylamine hydrochloride (1.27 Kg) and sodium bicarbonate (1.02 Kg). The reaction mixture was stirred at 15~25 °C for 1 h. After the completion of the reaction, the reaction mixture was added HCl solution. The layers were separated. The product was crystallized with $EtOH/H_2O$ to give the product as off-white solid (2.27 Kg, 72% yield, 99.3% purity).

^{1}H NMR (400 MHz, DMSO-d6) δ 11.94 (s, 1H), 8.22 (dd, ^{1}J = 4.0 Hz, ^{2}J = 2.0 Hz, 1H), 7.68-7.63 (m, 3H).

Mass: $[M+H]^+$: 208.1;

Example 3: Synthesis of compound IV

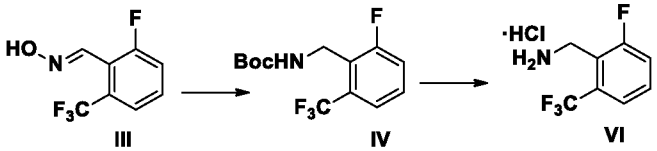


To a 20 L reactor were added MeOH (7.1 Kg), Raney Ni (100 g), di-tert-butyl dicarbonate (1.06 Kg) and compound III (500 g), the reactor was degassed three times and refilled with H_2 (0.3 MPa). The mixture was stirred at 20~40 °C under H_2 (0.1-0.3) MPa. After completion of the reaction, the reaction mixture was filtered to remove Raney Ni. 1/25 of the filtrate was concentrated to dryness. The crude product was purified by silica gel column chromatography eluting with heptane/EA to give the product as a white solid (19.01 g, 95.05% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.0 Hz, 1H), 7.43-7.38 (m, 1H), 7.32-7.29 (m, 1H), 4.56 (d, *J* = 6.8 Hz, 1H), 1.45 (s, 9H).

Mass: $[M-^t Bu+H]^+$: 238.1;

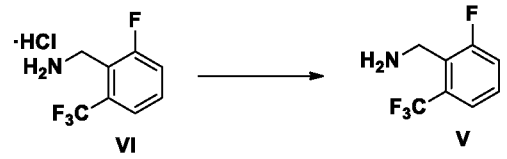
Example 4: Synthesis of compound VI



To a 20 L reactor were added MeOH (7.1 Kg), Raney Ni (100 g), di-tert-butyl dicarbonate (1.06 kg) and compound III (500 g). The reactor was degassed three times and refilled with H_2 (0.3 MPa). The mixture was stirred at 20~40 °C under H_2 (0.1~0.3 MPa). After completion of the reaction, the reaction mixture was filtered to remove Raney Ni. The filtrate was concentrated to 1.5 L, and then added 30% HCl in EtOH (535 g). The mixture was stirred at 30~40°C for 3 h. After the completion of the reaction, the solvent was exchanged to IPAC. The resulting suspension was filtered to give the product as a white solid (482 g, 87% yield). HPLC showed the ratio of compound VI, impurity A and impurity B was 99.9: 0.1: 0.

Mass: $[M+H]^+$: 194.1;

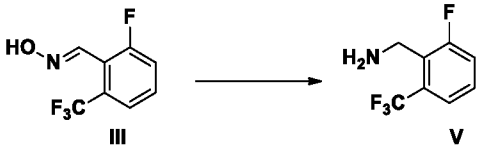
Example 5: Synthesis of compound V



To a mixture of H_2O (2 L), MTBE (1.5 L) and compound VI (475 gin a 5 L reactor was added 25% NaOH (331 g) dropwise. After the reaction complete, the layers were separated. The aqueous layer was extracted with MTBE (1.5 L). The combined organic phase was washed with H_2O and concentrated to dryness. The product was obtained by vacuum distillation as colorless oil (367.9 g, 92.1% yield).

Mass: $[M+H]^+$: 194.1;

Example 6: Synthesis of compound V



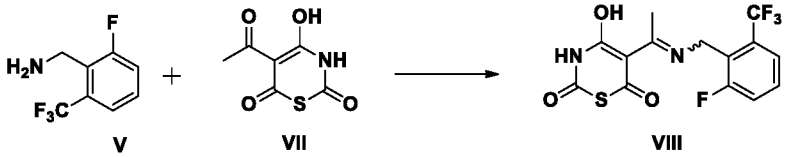
To a 2 L reactor was added MeOH (1 L), Raney Ni (40 g) and compound III (200 g). The reactor was degassed three times and refilled with H_2 (3.0~4.0 MPa). The mixture was stirred at 60~70 °C under H_2 (2.0-3.5 MPa). After completion of the reaction, the reaction mixture was filtered to remove Raney Ni. HPLC showed the ratio of compound V, impurity A and impurity B was 90.2: 0.9: 8.9.

Example 7: Synthesis of compound V



To a 250 mL reactor was added MeOH (100 mL), Pd/C (1 g), HCl (8 mL) and compound III (10 g). The reactor was degassed three times and refilled with H_2. The mixture was stirred at 60~70 °C under H_2 (2.0~3.0 MPa). After completion of the reaction, HPLC showed the ratio of compound V, impurity A and impurity B was 97.7: 0.1: 2.2.

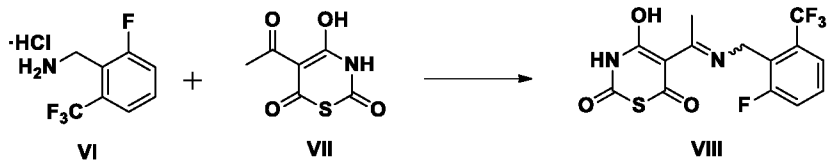
Example 8: Synthesis of compound VIII



To a 100 mL round bottom flask was added isopropanol (50 mL), compound V (5 g) and compound VII (5.33 g), the reaction mixture was heated to 80~90 °C for 3 h. After completion of the reaction, H_2O (100 mL) was added to the reaction mixture. The mixture was extract with DCM. The organic phase was concentrated. The crude product was purified by silica gel column chromatography to give the product as a yellow solid (9.2 g, 98% yield, 98.0% purity).

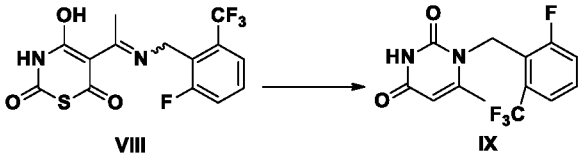
1H NMR (400 MHz, DMSO) δ 12.91 (s, 1H), 11.66 (s, 1H), 7.73 (dd, J = 7.4, 4.5 Hz, 3H), 4.94 (d, J = 5.0 Hz, 2H), 2.69 (s, 3H).

Example 9: Synthesis of compound VIII



To a 5 L reactor was added IPA (3.2 L), NaOH (70 g), compound VI (400 g) and compound VII (358.7 g). The reaction mixture was heated to 80~90 °C for 2 h. After completion of the reaction, the reaction mixture was cooled to 15~25 °C. The resulting suspension was filtered to give the product as a light yellow solid (650 g, 104.5% yield, 98.9% purity).

Example 10: Synthesis of compound IX

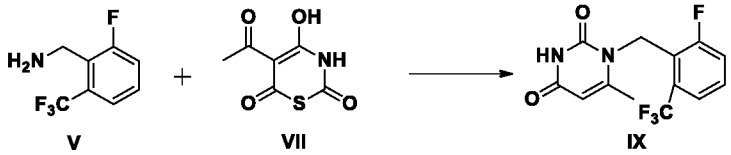


To a 100 mL round-bottom flask was added DMF (25 mL) and compound VIII (5 g). The reaction mixture was heated to 120~130 °C for 8 h. After completion of the reaction, H_2O (50 mL) was added to the reaction mixture. The resulting suspension was filtered to give the product as a light yellow solid (3.44 g, 82.5% yield, 98.0% purity).

^1H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.46-7.41 (m, 1H), 7.30-7.25 (m, 1H), 5.61 (s, 1H), 5.38 (s, 2H), 2.17 (s, 3H).

Mass: $[M+H]^+$: 303.1;

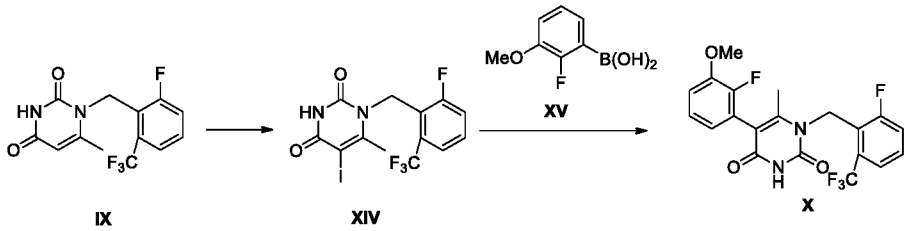
Example 11: Synthesis of compound IX



V VII IX

To a 50 mL round bottom flask was added DMF (5 mL), compound V (1 g) and compound VII (1.07 g). The reaction mixture was heated to 140 °C for 0.5 h. After completion of the reaction, H_2O (15 mL) was added to the reaction mixture at 50~60°C. The resulting suspension was filtered. The cake was washed with EtOH (1 mL) to give the product as a white solid (1.05 g, 67% yield, 98.6% purity).

Example 12: Synthesis of compound **X**



IX XIV XV X

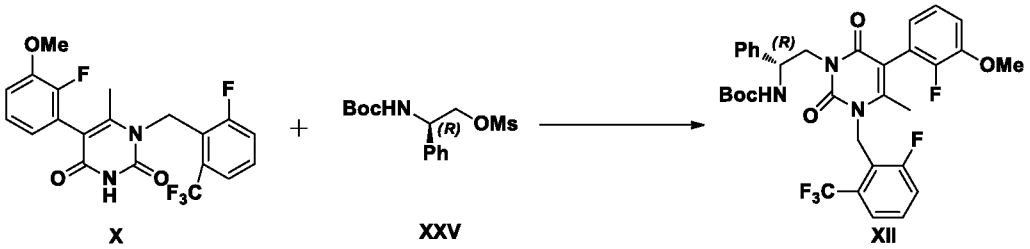
To a 50 mL round bottom flask was added AcOH (20 mL), compound IX (2 g) and N-Iodosuccinimide (1.5 g). The reaction mixture was heated to 50 °C for 1h. After completion of the reaction, H_2O (10 mL) was added to the reaction mixture. The resulting suspension was filtered. The cake was washed with MeOH (4 mL). The solid was slurried with MeOH (20 mL) to give the product as a white solid (2.3 g, 82% yield, 96.1% purity).

^{1}H NMR (400 MHz, DMSO-d6) δ 11.75 (s, 1H), 77.67-7.61 (m, 1H), 7.59-7.50 (m, 2H), 5.39 (s, 1H), 2.56 (s, 3H).

To a 1.0 L reactor was added compound XIV (30 g), compound XV (13.1 g), acetone (90 mL) and 14.4% KOH solution (113 g). The reaction mixture was degassed with N_2 for 1h. Methanesulfonato tri(tert-butyl)phosphine (2'-amino-1, 1'-biphenyl-2-yl) palladium (II) (200 mg) was added. The reaction mixture was stirred at 50 °C. After completion of the reaction, AcOH (8.4 g) was added. The resulting suspension was filtered. The cake was washed with H_2O (60 mL) and MeOH (120 mL) to give the product as an off-white solid (21.6 g, 72.3% yield, 98% purity).

^{1}H NMR (400 MHz, DMSO-d6) δ 11.59 (s, 1H), 7.67-7.65 (m, 1H), 7.59-7.56 (m, 2H), 7.17-7.13 (m, 2H), 6.76-6.72 (m, 1H), 5.34 (s, 2H), 3.85 (s, 3H), 2.05(s, 3H).

Example 13: Synthesis of compound **XII**

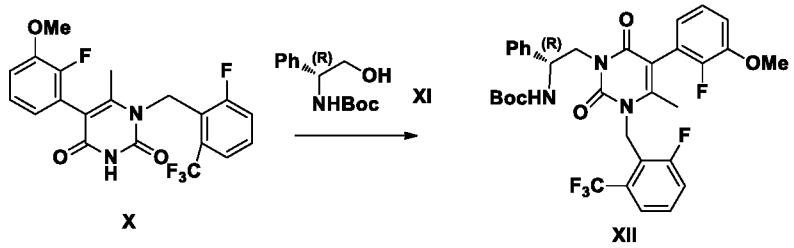


To a 50 mL round bottom flask was added DMF (9 mL), compound X (1.5 g), potassium carbonate (1.22 g) and compound XXV (1.44 g). The reaction mixture was stirred at 55 °C for 16 h. After completion of the reaction, H_2O was added to the reaction mixture. The mixture was extracted with IPAC. The organic phase was concentrated to dryness. The crude product was purified by silica gel column chromatography eluting with IPAC/heptane to give the product (1.65 g, 86% yield, 92% purity).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 7.9 Hz, 1H), 7.43 (m, 3H), 7.34 (t, J = 7.4 Hz, 2H), 7.31-7.23 (m, 2H), 7.16 (t, J = 8.0 Hz, 1H), 7.01 (t, J = 8.1 Hz, 1H), 6.86 (t, J = 6.9 Hz, 1H), 5.78 (t, J = 8.4 Hz, 1H), 5.62 (m, 1H), 5.45 (m, 1H), 5.13 (m, 1H), 4.37 (m, 1H), 4.13 (m, 1H), 3.92 (s, 3H), 2.10 (s, 3H), 1.37-1.17 (m, 9H).

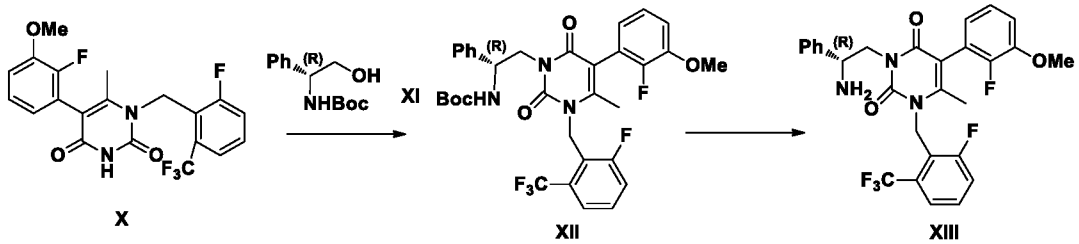
Mass: $[M+H\text{-}Boc]^+$ 546.1

Example 14: Synthesis of compound XII



To a mixture of THF (150 mL), compound X (10.0 g), compound XI (6.97 g), and PPh_3 (9.23 g) in a 250 mL round-bottom flask, diisopropyl azodicarboxylate (7.12 g) was added dropwise at 20~30 °C. After completion of the reaction, HPLC showed the desired product XII formed.

Example 15: Synthesis of compound XIII



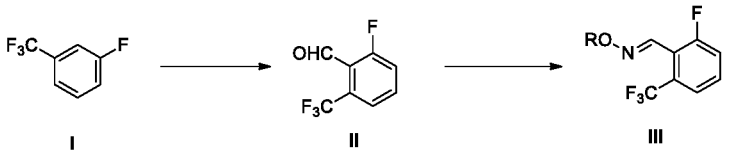
To a mixture of THF (3.0 L), compound X (200.0 g), compound XI (139.1 g), and PPh_3 (184 g) in a 5 L reactor was added diisopropyl azodicarboxylate (142 g) dropwise at 20~30 °C. After 1 h, conc. HCl (187.6 g) was added. The reaction mixture was heated and stirred at 50~60 °C. After completion of the reaction, the mixture was concentrated to 1 L. IPAC and potassium carbonate aqueous solution was added. The layers were separated. The organic layer was added H_3PO_4 solution. The layers were separated. The aqueous phase was washed with IPAC for 3 times. The pH of the aqueous phase was adjusted to 8~9 with potassium carbonate aqueous solution. The mixture was extracted with IPAC. The organic phase was concentrated. The crude product was recrystallized with IPAC/heptane to give the product as a white solid (210 g, 82.1% yield, 99.8% purity)

^{1}H NMR (400 MHz, DMSO-d6) δ 7.67-7.65 (m, 1H), 7.59-7.53 (m, 2H), 7.29-7.25 (m, 4H), 7.20-7.14 (m, 3H), 6.76-6.61 (m, 1H), 5.35-5.33 (m, 2H), 4.12-4.10 (m, 1H), 3.96-3.89 (m, 2H), 3.86 (s, 3H), 2.10 (s, 3H).

Mass: $[M+H]^+$ 546.2。

We claim:

1. A telescope process for the preparation of the compound of formula III from the compound of formula I,



I II III

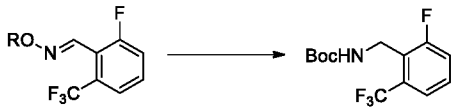
R=H, methyl or ethyl

comprising the steps of formylation of the compound of formula I in the presence of one or more amines and an organolithium reagent to produce the compound of formula II, and reacting the compound of formula II with hydroxylamine, O-methylhydroxylamine, O-ethylhydroxylamine or their salts to produce the compound of formula III, wherein R is H, methyl or ethyl.

2. The process of claim 1, wherein the amine is selected from the group consisting of tetramethylethylenediamine, diisopropylamine, diethylamine, di-sec-butylamine, pentamethyldiethylenetriamine and the combination thereof.

3. The process of claim 2, wherein the amines are tetramethylethylenediamine and diisopropylamine.

4. A process for the preparation of the compound IV from the compound of formula III,



III IV

R=H, methyl or ethyl

wherein the compound of formula III is hydrogenated in the presence of a transition-metal catalyst and di-tert-butyl dicarbonate under H_2 atmosphere to produce the compound of formula IV, wherein R is H, methyl or ethyl.

5. The process of claim 4, wherein the transition-metal catalyst is Pd/C or Raney nickel.

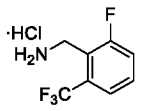
6. A process for the preparation of the compound of formula V or its salt form from the reaction of the compound of formula IV with an acid,



IV V

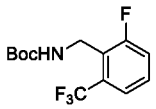
7. The process of claim 6, wherein the acid is hydrochloric acid.

8. The process of claim 6, wherein the salt form is formula VI having the structure:



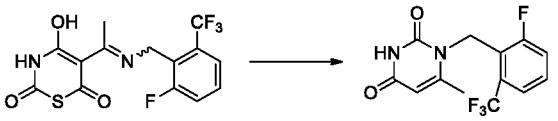
VI

9. A compound of formula IV having the structure:



IV

10. A process for the preparation of the compound of formula IX from the compound of formula VIII in an organic solvent

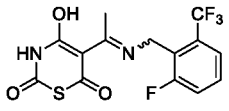


VIII IX

11. The process of claim 10, wherein the organic solvent is selected from the group consisting of dimethylformamide, dimethylacetamide, acetonitrile, n-butanol, tert-butanol, 1,4-dioxane, dimethyl sulfoxide, N-methylpyrrolidone, sulfolane and mixtures thereof.

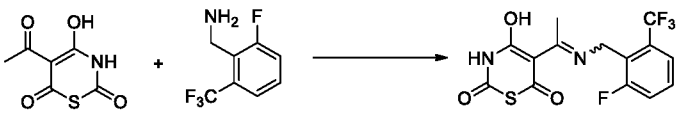
12. The process of claim 11, wherein the organic solvent is dimethylformamide or N-methylpyrrolidone.

13. A compound of formula VIII having the *Z*- or *E*- configuration or mixture of them:



VIII

14. A process for the preparation of the compound of formula VIII by reacting the compound of formula VII with the compound of formula V or its salts in a solvent

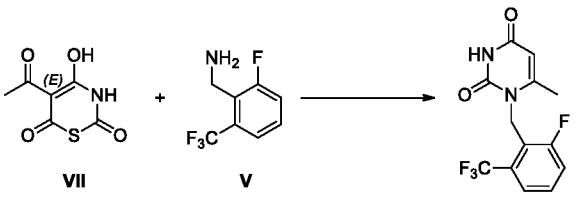


VII V VIII

15. The process of claim 14, wherein the solvent was selected from the group consisting of dimethylformamide, dimethylacetamide, acetonitrile, tetrahydrofuran, methyltetrahydrofuran, isopropanol, n-butanol, tert-butanol, 1,4-dioxane, dimethyl sulfoxide, N-methylpyrrolidone, sulfolane and mixtures thereof.

16. The process of claim 15, wherein the solvent is isopropanol.

17. A one-pot process for the preparation of the compound of formula IX by reacting the compound of formula VII with the compound of formula V in a solvent

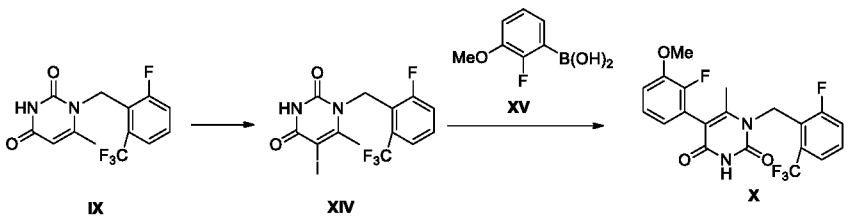


VII V IX

18. The process of claim 17, wherein the solvent is selected from the group consisting of dimethylformamide, dimethylacetamide, acetonitrile, tetrahydrofuran, methyltetrahydrofuran, isopropanol, n-butanol, tert-butanol, 1,4-dioxane, dimethyl sulfoxide, N-methylpyrrolidone, sulfolane, dichloromethane and mixtures thereof.

19. The process of claim 18, wherein the solvent is dimethylformamide.

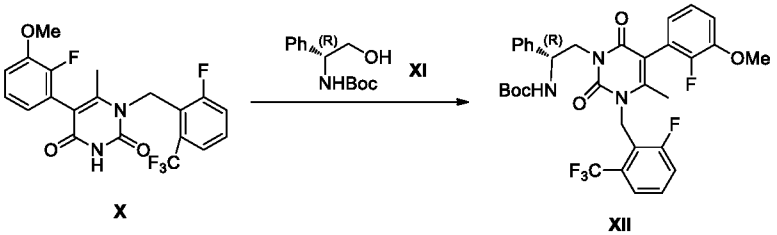
20. A process for the preparation of the compound of formula X from the compound of formula IX,



IX XIV XV X

comprising preparing the compound of formula XIV by reacting the compound of formula IX with N-iodosuccinimide in the presence of acetic acid, and preparing the compound of formula X by reacting the compound of formula XIV with the compound of formula XV using methanesulfonato[tri (tert-butyl) phosphine (2'-amino-1,1'-biphenyl-2-yl)] palladium (II) as the catalyst.

21. A process for the preparation of the compound of formula XII by reacting the compound of formula X with the compound of formula XI in a solvent,



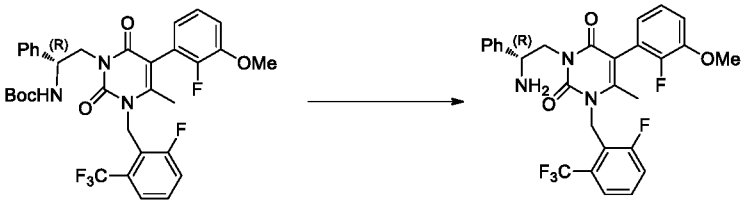
X XI XII

22. The process of claim 21, wherein the solvent is selected from the group consisting of

dichloromethane, toluene, 1, 4-dioxane, tetrahydrofuran, methyltetrahydrofuran and mixtures thereof.

23. The process of claim 22, wherein the solvent is tetrahydrofuran.

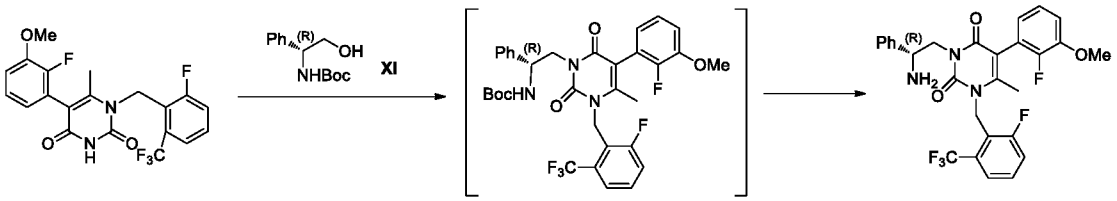
24. A process for the preparation of the compound of formula XIII by reacting the compound of formula XII with an acid



XII XIII

25. The process of claim 24, wherein the acid is hydrochloric acid.

26. A one-pot process for the preparation of the compound of formula XIII from the compound of formula X,



X XII XIII

comprising the Mitsunobu reaction of the compound of formula X and the compound of formula XI to produce the compound of formula XII, and an acidic deprotection of the Boc group to produce the compound of formula XIII.

27. The process of claim 26, wherein the acidic deprotection is conducted with hydrochloric acid.

28. The process of making the compound elagolix or elagolix sodium comprising the steps of claim 1, 4, 6, 10, 14, 17, 20, 21, 24 or 26.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/63682

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 239/54; C07D 239/00 (2019.01)
CPC - C07D 239/54; C07D 239/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,977,414 A (Okabe et al.) 02 November 1999 (02.11.1999); col 5, ln 35-45, 48-52, col 7, ln 30-40	1-3, 28/1
A	US 2005/0131032 A1 (Sit et al.) 16 June 2005 (16.06.2005); para [0276]	1-3, 28/1
A	WO 2008/152089 A1 (GLAXO GROUP LIMITED) 18 December 2008 (18.12.2008); pg. 21, Table, pg. 24, ln 15-20	1-3, 28/1
A	US 7,419,983 B2 (Guo et al.) 02 September 2008 (02.09.2008); entire document	1-3, 28/1
A	US 2017/0320836 A1 (Neurocrine Biosciences, Inc) 09 November 2017 (09.11.2017); entire document	1-3, 28/1
A	US 2012/0059179 A1 (Yu) 08 March 2012 (08.03.2012); entire document	1-3, 28/1

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05 March 2019	27 MAR 2019

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/63682

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
(see supplemental page)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3 and 28/1

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

--continued from Box No. III--

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I: Claims 1-3 and 28/1, directed to a process for the preparation of the compound of formula III.

Group II: Claims 4-5, 9, and 28/4 directed to a process for the preparation of the compound of formula IV and said compound.

Group III: Claims 6-8 and 28/6 directed to a process for the preparation of the compound of formula V.

Group IV: Claims 10-19 and 28/(10, 14, 17) directed to a process for the preparation of the compound of formula IX/VIII.

Group V: Claims 20 and 28/20 directed to a process for the preparation of the compound of formula X.

Group VI: Claims 21-27 and 28/(21, 24, 26) directed to a process for the preparation of the compound of formula XII/XIII.

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I includes the technical feature of a process for the preparation of the compound of formula III, which is not required by any other invention of Group II-VI.

Group II includes the technical feature of a process for the preparation of the compound of formula IV, which is not required by any other invention of Group I or III-VI.

Group III includes the technical feature of a process for the preparation of the compound of formula V, which is not required by any other invention of Group I-II or IV-VI.

Group IV includes the technical feature of a process for the preparation of the compound of formula IX/VIII, which is not required by any other invention of Group I-III or V-VI.

Group V includes the technical feature of a process for the preparation of the compound of formula X, which is not required by any other invention of Group I-IV or VI.

Group VI includes the technical feature of a process for the preparation of the compound of formula XII, which is not required by any other invention of Group I-V.

Common technical features:

The inventions of Groups I and II share the technical feature of a compound of formula III.

The inventions of Groups II and III share the technical feature of a compound of formula IV.

The inventions of Groups III and IV share the technical feature of a compound of formula V.

The inventions of Groups IV and V share the technical feature of a compound of formula IX.

The inventions of Groups V and VI share the technical feature of a compound of formula X.

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by US 2005/0131032 A1 to Sit et al. (hereinafter Sit). Sit discloses a compound of formula III wherein R is H (para [0276]: intermediate 31).

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by US 7,419,983 B2 to Guo et al. (hereinafter Guo). Guo discloses a compound of formula V (col. 18, ln 18: 2-fluoro-6-(trifluoromethyl)benzylamine).

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by US 2017/0320836 A1 to Neurocrine Biosciences, Inc (hereinafter Neurocrine). Neurocrine discloses a compound of formula IX (para [0039]: compound 1a) and formula X (para [0039]: compound 1c).

These shared technical features, however, do not provide a contribution over the prior art, as being obvious over US 2012/0059179 A1 to Yu. Yu discloses a compound similar to a compound of formula IV (para [0209]: compound 2f), but does not disclose a Boc protection group. However, Yu further discloses wherein the disclosed compounds may utilize various amine protection groups, including Boc (para [0050]), in order to provide sufficient yield of the desired reaction. It would have been obvious to one with skill in the art to prepare derivatives of the disclosed compound wherein the Tf protecting group is replaced with similar amine protecting groups, such as Boc, giving a compound of formula IV; while optimizing the yield of the desired compound.

As said compound was known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I-VI. The inventions of Group I-VI thus lack unity under PCT Rule 13.