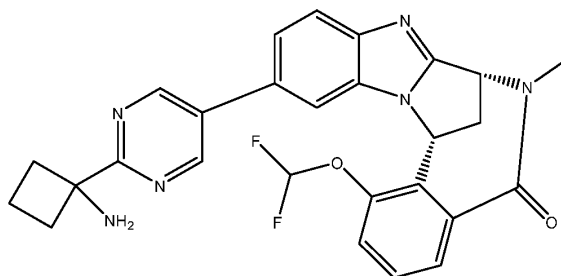


PREPARATION OF BRIDGED PENTACYCLIC IMIDAZOLE DERIVATIVES AS MODULATORS OF TNF ACTIVITY, INTERMEDITATES AND THEIR PREPARATION

Disclosed herein is a method of preparing a compound of Formula (I):



Formula (I)

i.e. (7R,14R)-11-[2-(1-aminocyclobutyl)pyrimidin-5-yl]-1-(difluoromethoxy)-6-methyl-6,7-dihydro-7,14-methanobenzimidazo[1,2-b][2,5]benzodiazocin-5(14H)-one. Also disclosed herein are intermediates, and methods of manufacturing intermediates.

Background

(7R,14R)-11-[2-(1-aminocyclobutyl)pyrimidin-5-yl]-1-(difluoromethoxy)-6-methyl-6,7-dihydro-7,14-methanobenzimidazo[1,2-b][2,5]benzodiazocin-5(14H)-one (the compound of Formula (I)) is a pharmacologically active substituted fused pentacyclic benzimidazole derivative which shows pharmacological activity on TNF α signalling. The compound of Formula (I) is described in patent publication WO 2018/197503.

TNF α is the prototypical member of the Tumour Necrosis Factor (TNF) superfamily of proteins that share a primary function of regulating cell survival and cell death. One structural feature common to all known members of the TNF superfamily is the formation of trimeric complexes that bind to, and activate, specific TNF superfamily receptors. By way of example, TNF α exists in soluble and transmembrane forms and signals through two receptors, known as TNFR1 and TNFR2, with distinct functional endpoints.

Various products capable of modulating TNF α activity are already commercially available. All are approved for the treatment of inflammatory and autoimmune disorders such as rheumatoid arthritis and Crohn's disease. All currently approved products are macromolecular and act by inhibiting the binding of human TNF α to its receptor. Typical macromolecular TNF α inhibitors include anti-TNF α antibodies and soluble TNF α receptor fusion proteins. Examples of commercially available anti-TNF α antibodies include fully

human antibodies such as adalimumab (Humira®) and golimumab (Simponi®), chimeric antibodies such as infliximab (Remicade®), and pegylated Fab' fragments such as certolizumab pegol (Cimzia®). An example of a commercially available soluble TNF α receptor fusion protein is etanercept (Enbrel®).

The compound of Formula (I) is a potent modulator of human TNF α activity and is therefore beneficial in the treatment and/or prevention of various human ailments. These include autoimmune and inflammatory disorders, neurological and neurodegenerative disorders, pain and nociceptive disorders, cardiovascular disorders, metabolic disorders, ocular disorders, and oncological disorders.

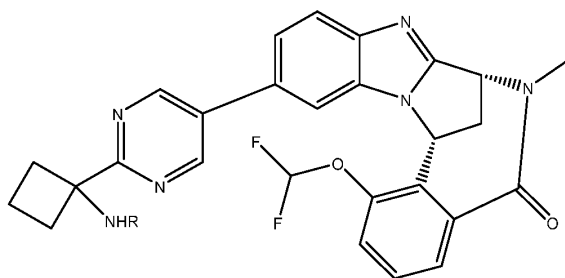
The compound of Formula (I) is described in Example 6 of WO 2018/197503 A1. The synthetic method used to produce the compound involves a step in which the pentacyclic moiety (7R,14R)-11-chloro-1-(difluoromethoxy)-6-methyl-6,7-dihydro-7,14-methano-benzimidazo[1,2-*b*][2,5]benzodiazocin-5(14*H*)-one is reacted with bis(pinacolato)diboron in the presence of a palladium catalyst. *tert*-Butyl *N*-[1-(5-bromopyrimidin-2-yl)cyclobutyl]carbamate is then added to the reaction mixture. The pyrimidine moiety is therefore added to the pentacyclic core by a Suzuki coupling in which a boronated derivative of the pentacyclic core is reacted with a brominated pyrimidine.

There is a desire to provide improved methods of manufacturing the compound of Formula (I), for example methods which are suitable for the large-scale manufacture of the compound of Formula (I). There is a particular desire to provide methods which do not involve the use of flash chromatography during purification steps.

Summary

The present disclosure is based on the unexpected finding of a synthetic pathway for the manufacture of the compound of Formula (I), which provides a high yield of Formula (I) and which is suitable for manufacturing the compound of Formula (I) at a large scale. The synthetic pathway is summarised in Fig. 1, Fig. 2, and Fig. 3.

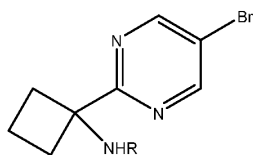
The present invention provides a method of preparing Intermediate 6:



Intermediate 6,

the method comprising:

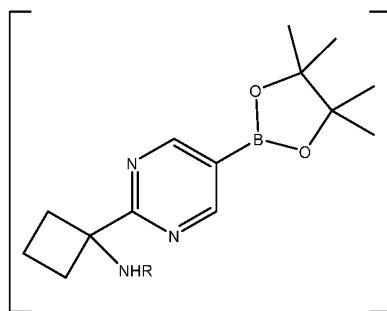
a) reacting Intermediate B:



Intermediate B

wherein R is an amine protecting group

with a reagent to provide Intermediate C:

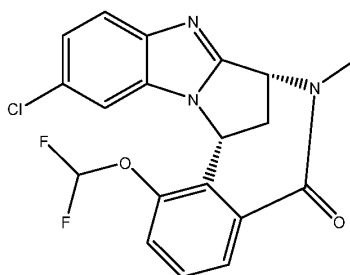


Intermediate C;

wherein R is an amine protecting group

and

b) reacting Intermediate C with Intermediate 5:



Intermediate 5

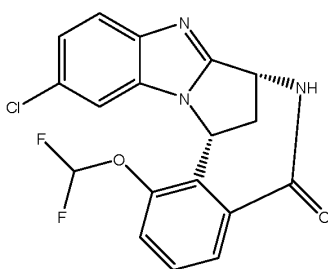
in the presence of a base and a palladium catalyst to provide Intermediate 6.

In one embodiment, the reagent in step a) comprises bis(pinacolato)diboron.

In another embodiment, step a) comprises contacting Intermediate B with a palladium catalyst. Typically, such a palladium catalyst is XPhos-PdG2.

In a further embodiment, the palladium catalyst used in step b) is XPhos-PdG2.

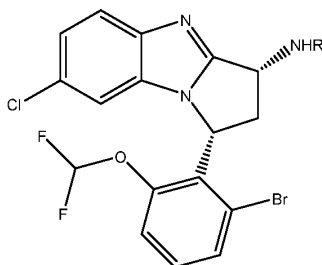
The present invention also provides a method for preparing Intermediate 4:



Intermediate 4,

the method comprising

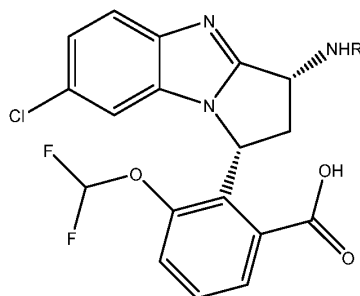
a) reacting Starting Material 1:



Starting Material 1

wherein R is an amine protecting group,

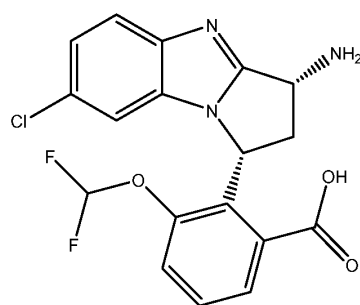
with a reagent to provide Intermediate 2,



Intermediate 2;

wherein R is an amine protecting group

b) reacting Intermediate 2 with a reagent to provide Intermediate 3



Intermediate 3; and

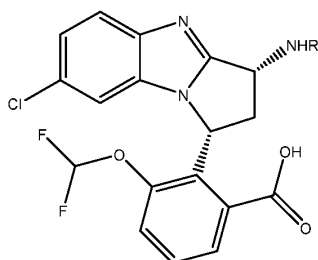
c) reacting Intermediate 3 with a reagent to provide Intermediate 4.

In one embodiment, in step a) the reagent comprises carbon monoxide.

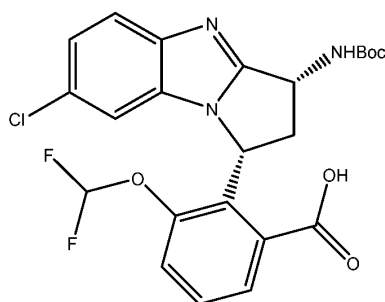
In another embodiment, in step b) the reagent comprises an acid.

In a further embodiment, in step c) the reagent comprises an amide coupling reagent, optionally wherein the reagent comprises COMU ((1-cyano-2-ethoxy-2-oxoethylideneaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate).

The invention further provides a compound selected from:



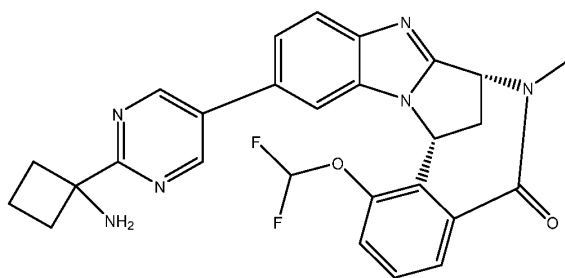
Intermediate 2; and



Intermediate 2a,

wherein R is an amine protecting group.

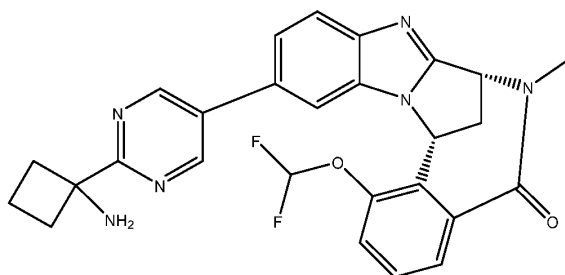
Also provided is a method of preparing a compound of Formula (I):



Formula (I),

which comprises a method of preparing a method of preparing Intermediate 6 in accordance with the invention.

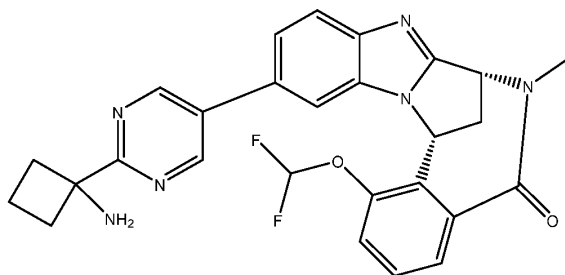
Further provided is a method of preparing a compound of Formula (I):



Formula (I),

which comprises a method of preparing Intermediate 4 in accordance with the invention.

Also provided is a method of preparing a compound of Formula (I):

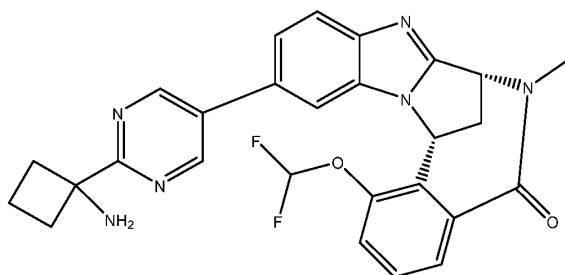


Formula (I),

which comprises a method of preparing Intermediate 4 in accordance with the invention and which further comprises a method of preparing Intermediate 6 in accordance with the invention.

Such methods of preparing a compound of Formula (I) can further comprises a step of preparing an Intermediate 7 by exposing Intermediate 6 to hydrochloric acid in accordance with the invention. Such a method can further comprise reacting Intermediate 7 with aqueous hydrochloric acid to provide the compound of Formula (I).

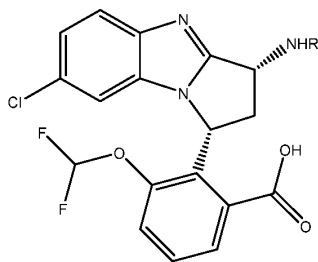
Additionally provided is a method of preparing a compound of Formula (I):



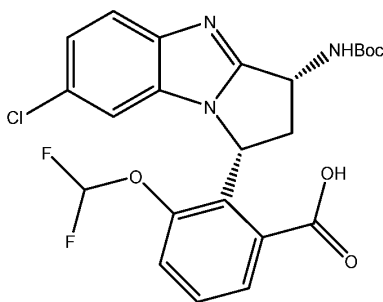
Formula (I),

the method comprising performing a synthesis scheme as shown in any one of Fig. 1, Fig. 2, or Fig. 3, wherein, in the scheme shown in Fig. 1, R is an amine protecting group.

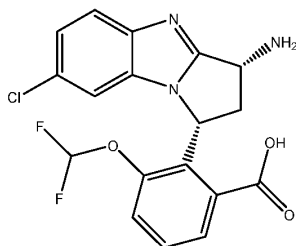
In one embodiment of the invention, as used herein R is a Boc protecting group. Herein is further provided a compound selected from:



Intermediate 2;



Intermediate 2a; and



Intermediate 3,

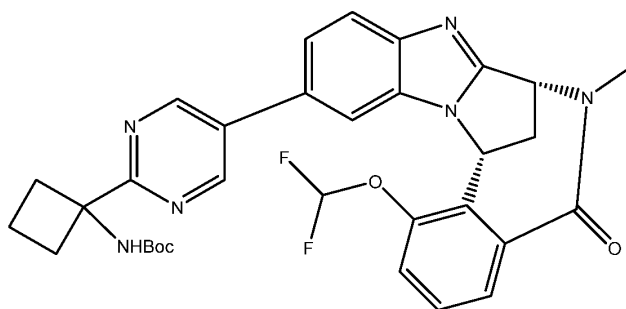
wherein R is an amine protecting group.

Also provided herein are methods of preparing each of the intermediates shown in Fig. 1 and Fig 2. These intermediates are referred to herein as Intermediates 2, 2a, 3, 4, 5, 6, 6a, 7, 7a, B, Ba, C and Ca.

Also provided herein is a method of preparing the compound of Formula (I) from Intermediate 7.

Also provided herein is a method of preparing a compound of Formula (I), the method comprising performing a synthesis scheme as shown in any one of Fig. 1, Fig. 2, or Fig. 3, wherein, in the scheme shown in Fig. 1, R is an amine protecting group.

Also provided herein is a crystalline form of Intermediate 6a:



Intermediate 6a;

having:

- a) an X-ray powder diffraction pattern comprising characteristic peaks at $6.36^\circ \pm 0.2^\circ 2\theta$, $11.34^\circ \pm 0.2^\circ 2\theta$, and $18.58^\circ \pm 0.2^\circ 2\theta$; and/or
- b) a DSC thermogram having a single peak at $229^\circ \text{C} \pm 2^\circ \text{C}$.

Brief Description of the Figures

Fig. 1 shows a reaction scheme for synthesising a compound of Formula (I), using starting materials and intermediates with an amine protecting group R.

Fig. 2 shows a reaction scheme for synthesising a compound of Formula (I), using starting materials and intermediates with a Boc protecting group.

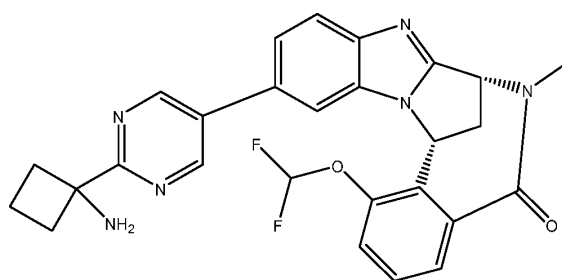
Fig. 3 shows a reaction scheme for synthesising a compound of Formula (I), including exemplary reagents and reaction conditions.

Fig. 4 shows the X-ray powder diffraction pattern of a crystalline form of Intermediate 6a.

Fig. 5 shows a differential scanning calorimetry (DSC) thermogram of a crystalline form of Intermediate 6a.

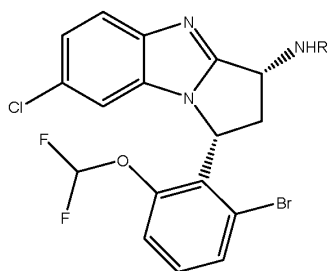
Detailed Description

Herein is provided a method of preparing a compound of Formula (I):

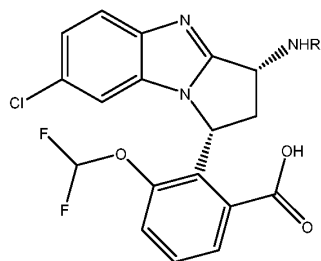


Formula (I).

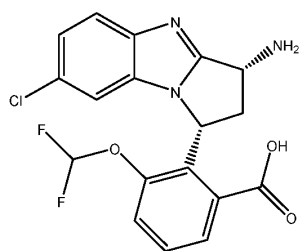
The synthetic pathway provided herein proceeds via a number starting materials and intermediates. Described herein are the following compounds:



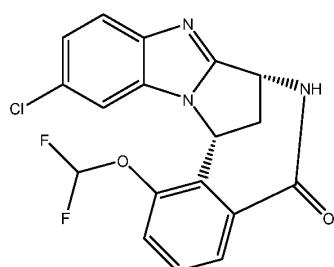
Starting Material 1;



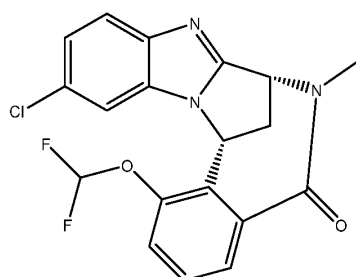
Intermediate 2;



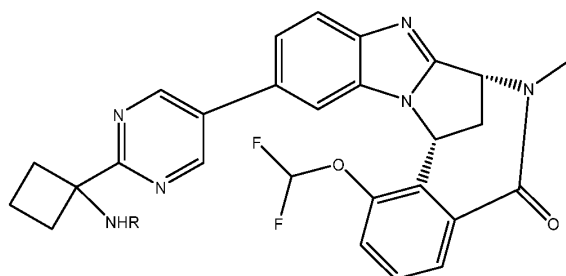
Intermediate 3;



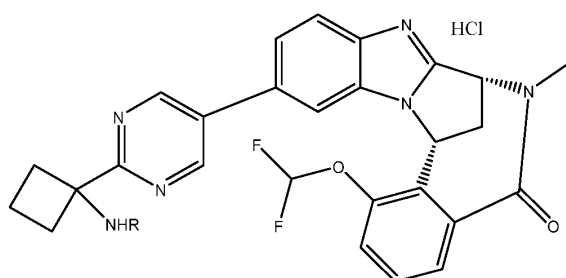
Intermediate 4;



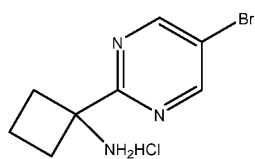
Intermediate 5;



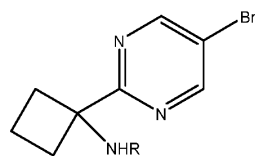
Intermediate 6;



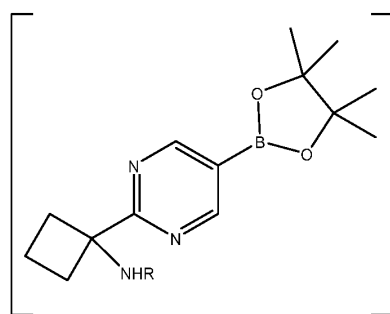
Intermediate 7;



Starting Material A;



Intermediate B; and



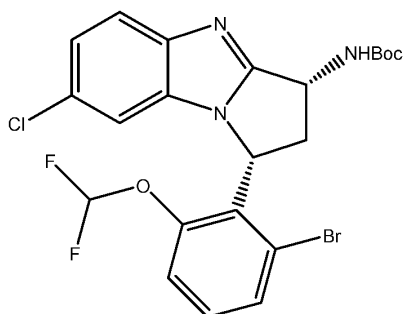
Intermediate C,

wherein R is an amine protecting group.

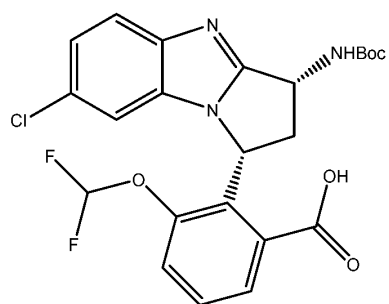
As used herein, R can be any amine protecting group known in the art. For example, R can be a tert-butyloxycarbonyl (Boc) group or a carbamate group.

In Intermediate B and Intermediate C described herein, the R protecting group may be the same as the R protecting group in Intermediate 2, or the R protecting group may be different to the R protecting group in Intermediate 2.

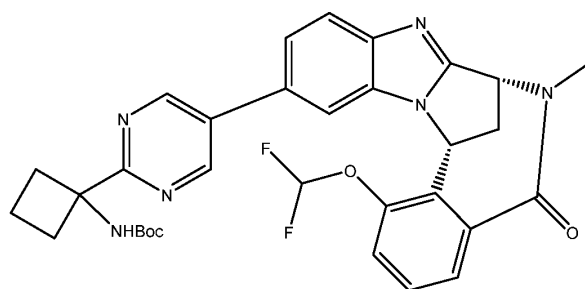
Typically, R is a tert-butyloxycarbonyl protecting group, also known and referred to herein as a Boc group. Described herein are the following compounds with a Boc protecting group:



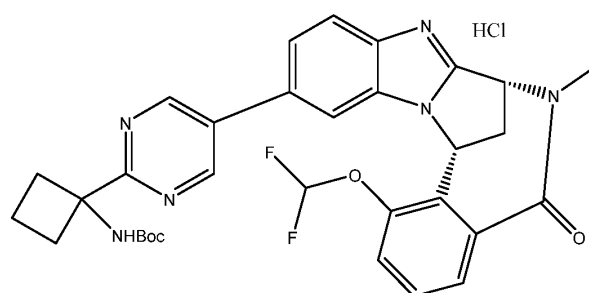
Starting Material 1a;



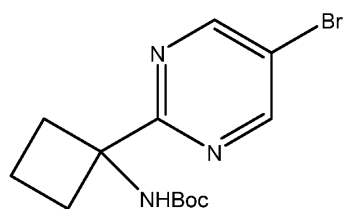
Intermediate 2a;



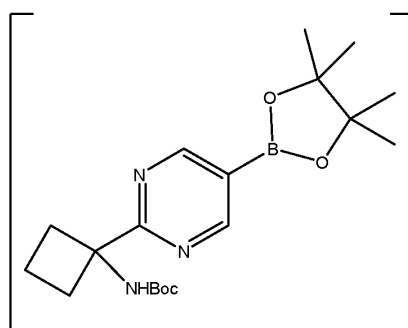
Intermediate 6a;



Intermediate 7a;



Intermediate Ba; and



Intermediate Ca.

These compounds are intermediates or starting materials in the synthetic pathway described herein.

Provided in particular are compounds selected from Intermediate 2, Intermediate 2a, and Intermediate 3.

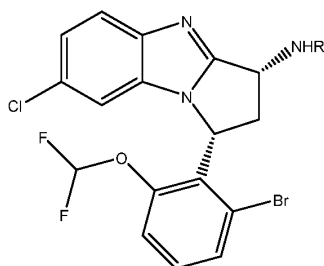
Starting from Starting Material 1/Starting Material 1a and Starting Material A, the method of preparing a compound of Formula (I) comprises nine reaction steps. The process provided herein relates to each of these steps in isolation, to combinations of two or more of these steps, and also to the complete method of synthesising the compound of Formula (I), starting from Starting Material 1 and Starting Material A and performing all nine reaction steps sequentially.

In the present invention, each of the nine reaction steps may be performed without performing flash chromatography purification.

The steps are discussed in turn below.

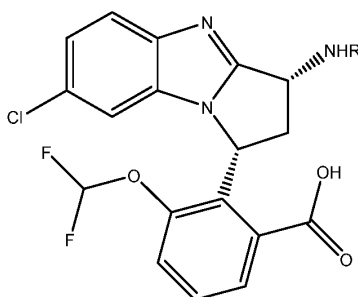
Step 1 – synthesis of Intermediate 2

In step 1, Starting Material 1:



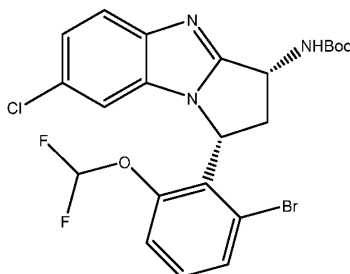
Starting Material 1

is reacted with a reagent to provide Intermediate 2:



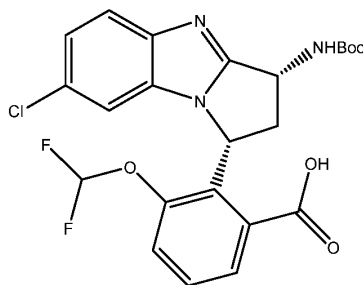
Intermediate 2.

R is an amine protecting group, for example a Boc group. When R is a Boc group, Starting Material 1 is referred to as Starting Material 1a:



Starting Material 1a

and Intermediate 2 is referred to as Intermediate 2a:



Intermediate 2a.

The reagent may comprise carbon monoxide.

The reaction may occur in a reaction mixture. The reaction mixture may comprise a catalyst, which may be a palladium catalyst, for example $\text{PdCl}_2(\text{dppb})$, also known as 1,4-bis(diphenylphosphino)butane-palladium(II) chloride. The reaction mixture may comprise K_2CO_3 . The reaction mixture may comprise KHCO_3 . The reaction mixture may comprise water *i.e.* the reaction mixture may be an aqueous solution. The reaction mixture may comprise DMSO. The reaction mixture may comprise DMAc (dimethylacetamide).

In one embodiment, the reaction mixture in step 1 is an aqueous solution which comprises $\text{PdCl}_2(\text{dppb})$, K_2CO_3 , and DMSO, and the reagent is carbon monoxide. In this embodiment, the $\text{PdCl}_2(\text{dppb})$ may be present in an amount of from about 0.01 eq to about 0.03 eq, for example from about 0.017 eq to about 0.022 eq. The K_2CO_3 may be present in an amount of from about 2 eq to about 4 eq, for example from about 2.88 eq to about 3.08 eq.

The DMSO may be present in an amount of from about 6 vol to about 8 vol, for example from about 6.8 vol to about 7.3 vol. The carbon monoxide may be present at a pressure of from about 1 bar to about 3 bar, for example from about 1.5 bar to about 2.0 bar.

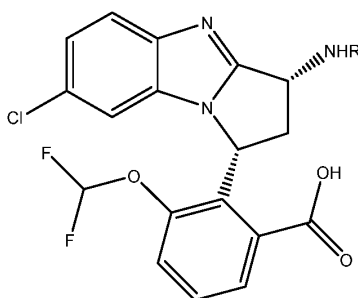
In another embodiment, the reaction mixture in step 1 is an aqueous which solution comprises $\text{PdCl}_2(\text{dppb})$, KHCO_3 , DMAc, and the reagent is carbon monoxide. In this embodiment, the $\text{PdCl}_2(\text{dppb})$ may be present in an amount of from about 0.01 eq to about 0.03 eq, for example from about 0.018 eq to about 0.022 eq. The KHCO_3 may be present in an amount of from about 2 eq to about 4 eq, for example from about 2.84 eq to about 3.16 eq. The DMAc may be present in an amount of from about 8 vol to about 12 vol, for example from about 9.5 vol to about 10.5 vol. The carbon monoxide may be present at a pressure of from about 1 bar to about 4 bar, for example from about 2.0 bar to about 2.7 bar.

The reaction may take place under any suitable conditions such as to effect the formation of Intermediate 2. The reaction may take place at a temperature of from about 70 to about 100 °C, or from about 75 to about 95 °C, or at a temperature of about 85 °C. The reaction may occur for a time of from about 5 to about 60 h, or from about 7 to about 55 h, or from about 10 to about 50 h.

Following the reaction in step 1, the product may be purified and/or washed. The purifying and/or washing may use one or more of water, AcOEt (ethyl acetate), citric acid solution in water, Na_2SO_4 (sulfate sodium) solution in water, and MTBE (methyl tert-butyl ether).

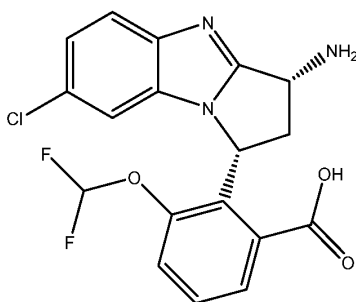
Step 2

In step 2, Intermediate 2:



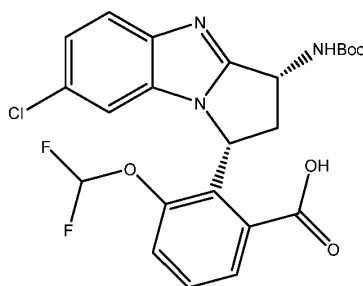
Intermediate 2

is reacted with a reagent to provide Intermediate 3:



Intermediate 3.

R is an amine protecting group, for example a Boc group. When R is a Boc group, Intermediate 2 is referred to as Intermediate 2a:



Intermediate 2a.

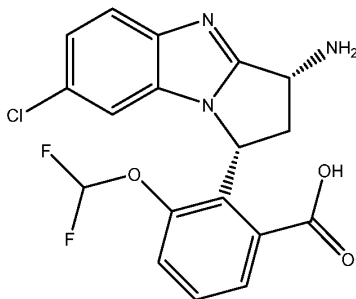
The reagent may comprise an acid, and preferably comprises HCl.

In step 2, the reaction may occur in a reaction mixture. The reaction mixture may comprise HCl. The reaction mixture may further comprise EtOH (ethanol). Said ethanol may be used at a ratio of 2 to 3 vol, such as 2.4 to 2.7 vol. The reaction mixture may be an aqueous solution.

The reaction may take place under any suitable conditions such as to effect the formation of Intermediate 3. The reaction may take place at a temperature of from about 40 to about 60 °C, or from about 45 to about 55 °C, or at a temperature of about 50 °C. The reaction may occur for a time of from about 10 to about 30 h, or from about 15 to about 25 h. For example, the reaction may occur for a time of about 20 h.

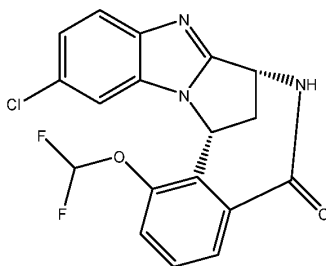
Step 3

In step 3, Intermediate 3:



Intermediate 3

is reacted with a reagent to provide Intermediate 4:



Intermediate 4.

The reagent may comprise an amide coupling reagent. The reagent may comprise COMU ((1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate).

In step 3, the reaction may occur in a reaction mixture. The reaction mixture may comprise NMM (N-methylmorpholine). The reaction mixture may further comprise ACN (acetonitrile). The reaction mixture may further comprise NaHCO₃ (sodium bicarbonate).

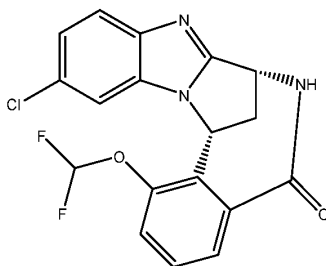
The reaction may take place under any suitable conditions such as to effect the formation of Intermediate 4. The reaction may take place at ambient temperature or at a temperature of from about 45 to about 55 °C. The reaction may occur for a time of from about 4 to about 20 h, or from about 6 to about 18 h, such as about 6 to about 10 h.

Taken in combination, steps 1 to 3 provide an efficient and high-yield route for the synthesis of Intermediate 4. Steps 1 to 3 provide Intermediate 4 at a high level of purity.

Thus, Intermediate 4 may be manufactured an industrial scale by performing steps 1 to 3 sequentially.

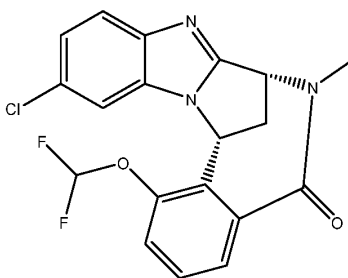
Step 4

In step 4, Intermediate 4:



Intermediate 4

is reacted with a reagent to provide Intermediate 5:



Intermediate 5.

The reagent may comprise a methylating agent. The reagent may comprise MeOTs (methyl p-toluenesulfonate).

In step 4, the reaction may occur in a reaction mixture. The reaction mixture may comprise tBuOK (potassium tert-butoxide). The reaction mixture may further comprise THF (tetrahydrofuran). The reaction mixture may further comprise DABCO (1,4-diazabicyclo[2.2.2]octane).

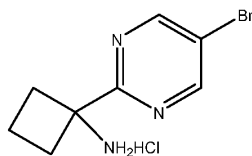
The reaction may take place under any suitable conditions such as to effect the formation of Intermediate 5. The reaction may take place at ambient temperature. The reaction may occur for a time of from about 12 to about 36 h, or from about 19 to about 27 h.

Step 4 provides an efficient and high-yield route for the synthesis of Intermediate 5. Step 4 provides Intermediate 5 at a high level of purity, without the need for cryogenic

conditions and/or purification steps involving flash chromatography. Thus, Intermediate 5 may be manufactured at an industrial scale by performing steps 1 to 4 sequentially.

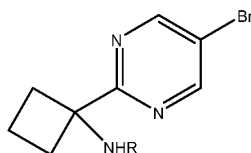
Step 5

In step 5, Starting Material A:



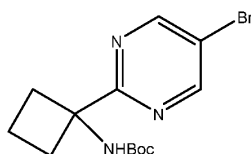
Starting Material A

is reacted with a reagent to provide Intermediate B:



Intermediate B.

R is an amine protecting group, for example a Boc group. When R is a Boc group, the Intermediate B is referred to as Intermediate Ba:



Intermediate Ba.

The reagent may comprise a compound which introduces a protecting group. The reagent may comprise Boc_2O (di-tert-butyl dicarbonate)

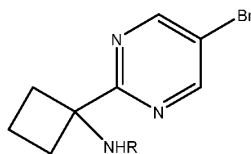
In step 5, the reaction may occur in a reaction mixture. The reaction mixture may comprise TEA (triethylamine). The reaction mixture may further comprise DCM (dichloromethane).

The reaction may take place under any suitable conditions such as to effect the formation of Intermediate B. The reaction may take place at a temperature of from about 15

to about 25 °C. The reaction may occur for a time of from about 12 to about 36 h, or from about 20 to about 28 h.

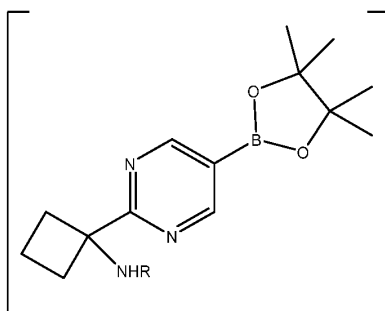
Step 6

In step 6, Intermediate B:



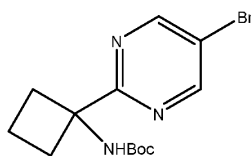
Intermediate B

is reacted with a reagent to provide Intermediate C:



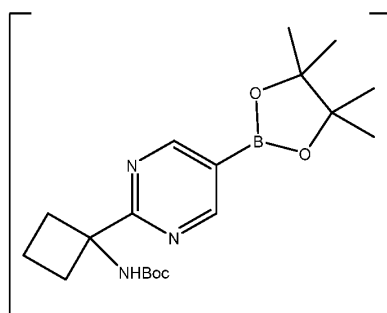
Intermediate C.

R is an amine protecting group, for example a Boc group. When R is a Boc group, Intermediate B is referred to as Intermediate Ba:



Intermediate Ba

and Intermediate C is referred to as Intermediate Ca:



Intermediate Ca.

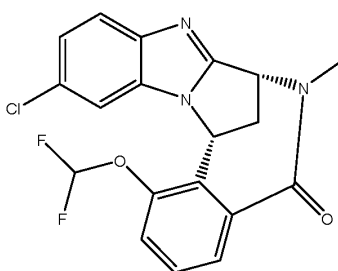
The reagent may comprise BisPin (bis(pinacolato)diboron).

In step 6, the reaction may occur in a reaction mixture. The reaction mixture may comprise a catalyst, which may be a palladium catalyst, for example XPhos-PdG2 (chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)). The reaction mixture may further comprise AcOK (potassium acetate). The reaction mixture may further comprise dioxane.

The reaction may take place under any suitable conditions such as to effect the formation of Intermediate C. The reaction may take place at a temperature of from about 70 to about 101 °C, or from about 85 to about 95 °C, or at a temperature of about 90 °C. The reaction may occur for a time of from about 30 min to about 7 h, or from about 2 to about 5 h, or for a time of about 3 h.

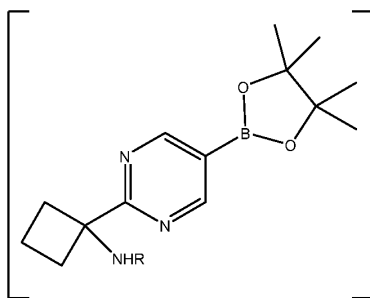
Step 7

In step 7, Intermediate 5:



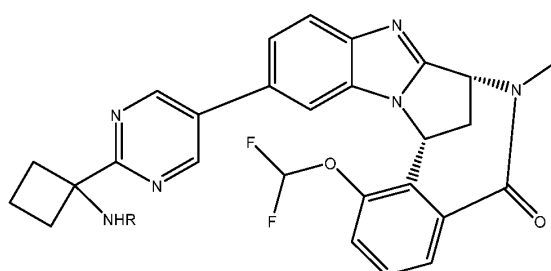
Intermediate 5

is reacted with Intermediate C:



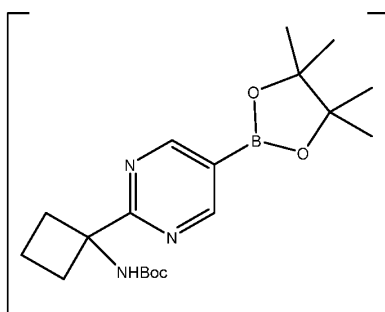
Intermediate C

to provide Intermediate 6:



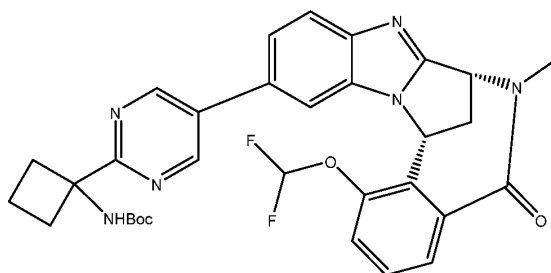
Intermediate 6.

R is an amine protecting group, for example a Boc group. When R is a Boc group, Intermediate C is referred to as Intermediate Ca:



Intermediate Ca

and Intermediate 6 is referred to as Intermediate 6a:



Intermediate 6a.

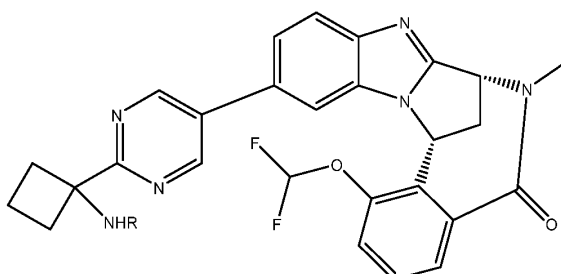
In step 7, the reaction may occur in a reaction mixture. The reaction mixture may comprise a catalyst, which may be a palladium catalyst, for example XPhos-PdG2 (chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)). The reaction mixture may comprise a base. For example, the reaction mixture may further comprise K_3PO_4 (potassium phosphate). The reaction mixture may further comprise dioxane. The reaction may be an aqueous solution.

The reaction may take place under any suitable conditions such as to effect the formation of Intermediate 6. The reaction may take place at a temperature of from about 50 to about 100 °C, or from about 70 to about 80 °C, or at a temperature of about 75 °C. The reaction may occur for a time of from about 30 min to about 7 h, or from about 2 to about 5 h, or for a time of about 3 h.

Taken in combination, steps 6 and 7 provide an efficient and high-yield route for the synthesis of Intermediate 6. Steps 6 and 7 provide Intermediate 6 at a high level of purity, without needing to use flash chromatography to purify the product. Thus, Intermediate 6 may be manufactured an industrial scale by performing steps 1 to 7 sequentially.

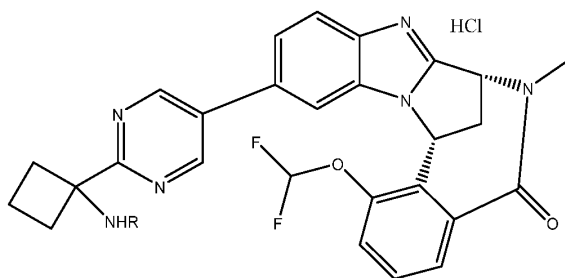
Step 8

In step 8, Intermediate 6:



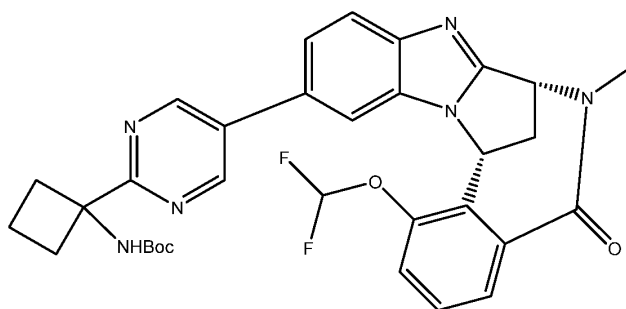
Intermediate 6

is reacted with a reagent to provide Intermediate 7:



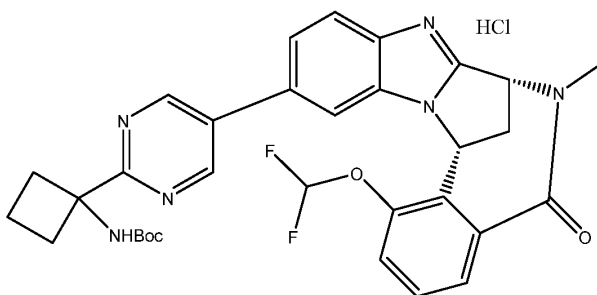
Intermediate 7.

R is an amine protecting group, for example a Boc group. When R is a Boc group, Intermediate 6 is referred to as Intermediate 6a:



Intermediate 6a;

and Intermediate 7 is referred to as Intermediate 7a



Intermediate 7a.

The reagent may comprise HCl.

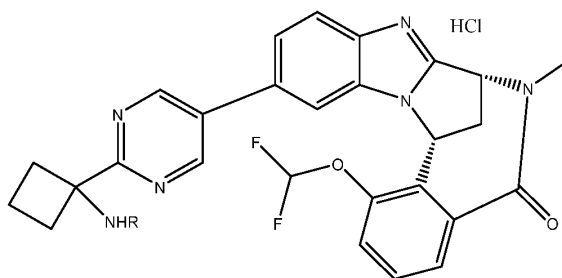
In step 8, the reaction may occur in a reaction mixture. The reaction mixture may comprise IPA (isopropyl alcohol).

The reaction may take place under any suitable conditions such as to effect the formation of Intermediate 7. The reaction may take place at a temperature of from about 40 to about 60 °C, or at a temperature of about 50 °C. The reaction may occur for a time of from about 30 min to about 4 h, or from about 30 min to about 1 h.

Salification Step 8 provides an efficient and high-yield route for the synthesis of Intermediate 7. In particular, step 8 ensures that any residual catalyst (which may be a palladium catalyst) is removed following Steps 6 and 7. Step 8 provides Intermediate 7 at a high level of purity. Thus, Intermediate 7 may be manufactured an industrial scale by performing Steps 1 to 8 sequentially.

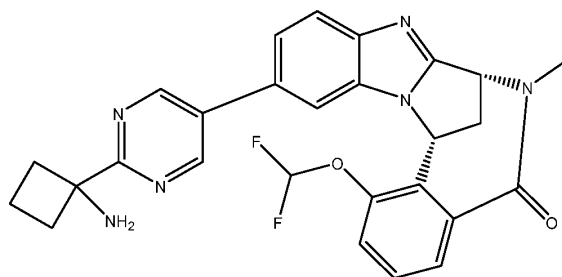
Step 9

In step 9, Intermediate 7:



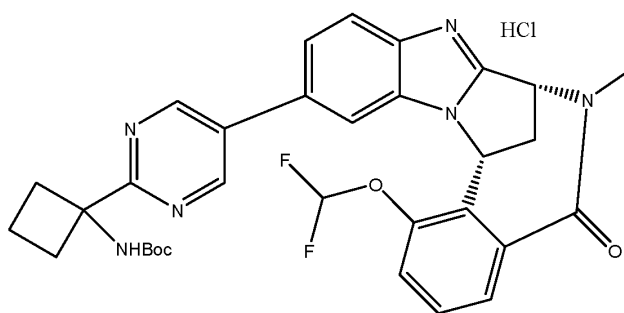
Intermediate 7

is reacted with a reagent to provide the compound of Formula (I):



Formula (I).

R is an amine protecting group, for example a Boc group. When R is a Boc group, Intermediate 7 is referred to as Intermediate 7a:



Intermediate 7a.

In step 9, the reaction may occur in a reaction mixture. The reaction mixture may be an aqueous solution. The reaction mixture may comprise IPA (isopropyl alcohol). The reaction mixture may comprise HCl. The reaction mixture may comprise DCM (dichloromethane). The reaction mixture may comprise 2-MeTHF (2-methyltetrahydrofuran). The reaction mixture may comprise K_3PO_4 (potassium phosphate), as an aqueous solution.

The reaction may take place under any suitable conditions such as to effect the formation of compound of Formula (I). The reaction may take place at a temperature of from about 60 to about 100 °C, or from about 70 to about 90 °C, or from about 75 to about 85 °C. The reaction may occur for a time of from about 2 to about 12 h, or from about 2 to about 4 h.

Step 9 provides an efficient and high-yield route for the synthesis of the compound of Formula (I). Thus, the compound of Formula (I) may be manufactured on an industrial scale by performing Steps 1 to 9 sequentially. Typically, none of Step 1 to 9 involve flash chromatography purification.

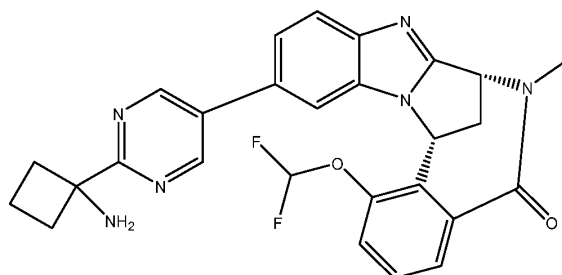
Overall synthesis scheme

Provided herein are methods of performing any one of stages 1 to 9 discussed herein individually.

Also provided herein is a method of preparing a compound of Formula (I), the method comprising performing all of steps 1 to 9 discussed herein sequentially. Thus, provided herein is a method of preparing a compound of Formula (I), the method comprising all of the steps shown in Fig. 1, wherein R is an amine protecting group. Also provided herein is a method of preparing a compound of Formula (I), the method comprising all of the steps shown in Fig. 2. Also provided herein is a method of preparing a compound of Formula (I),

the method comprising all of the steps shown in Fig. 3. Typically, the method of preparing a compound of Formula (I) does not involve purification by flash chromatography.

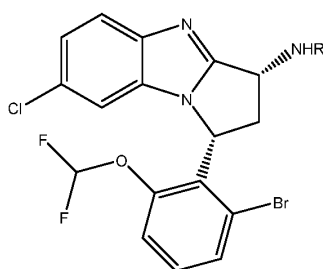
In one embodiment, provided herein is a method of preparing a compound of Formula (I):



Formula (I)

the method comprising

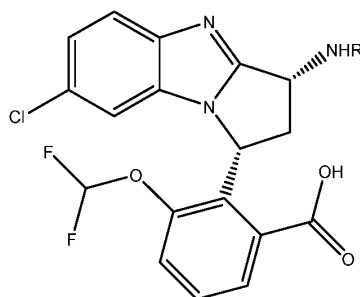
a) reacting Starting Material 1:



Starting Material 1

wherein R is an amine protecting group,

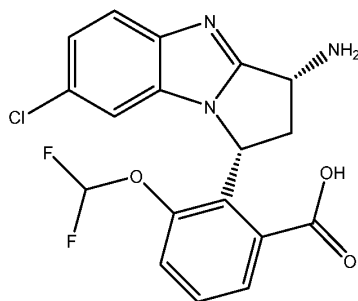
with a reagent to provide Intermediate 2,



Intermediate 2

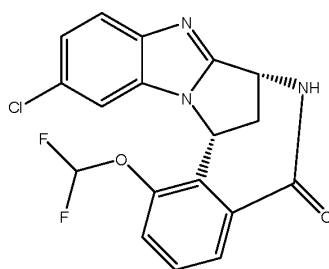
wherein R is an amine protecting group;

- b) reacting Intermediate 2 with a reagent to provide Intermediate 3



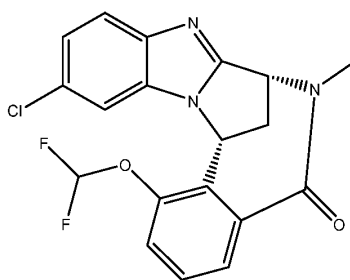
Intermediate 3;

- c) reacting Intermediate 3 with a reagent to provide Intermediate 4



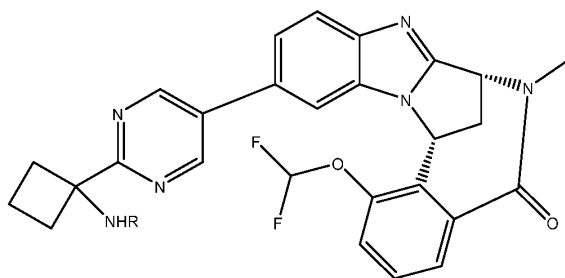
Intermediate 4;

- d) reacting Intermediate 4 with a reagent to provide Intermediate 5:



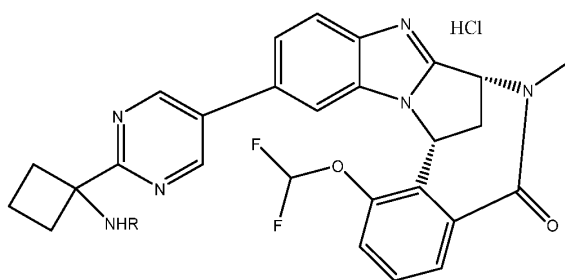
Intermediate 5;

- e) reacting Intermediate 5 with a reagent to provide Intermediate 6:



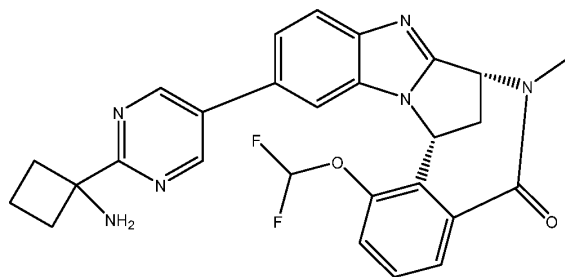
Intermediate 6;

f) reacting Intermediate 6 with a reagent to provide Intermediate 7



Intermediate 7; and

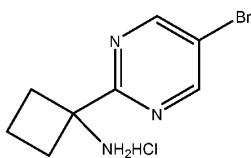
g) reacting Intermediate 7 with a reagent to provide the compound of Formula (I):



Formula (I).

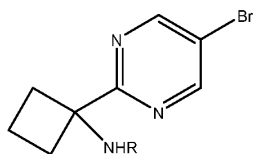
In one embodiment, the above-depicted method further comprises the steps of:

i) reacting Starting Material A:



Starting Material A

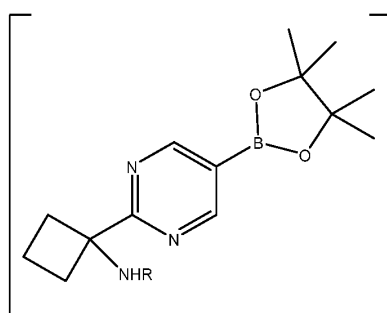
with a reagent to provide Intermediate B:



Intermediate B

wherein R is an amine protecting group; and

ii) reacting Intermediate B with a reagent to provide Intermediate C:



Intermediate C

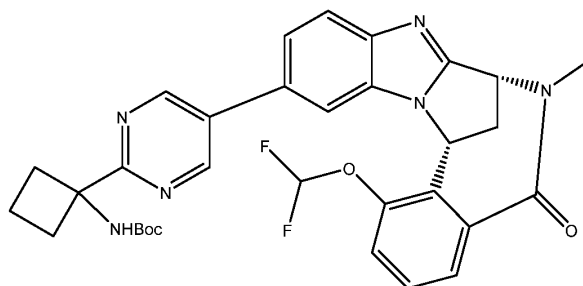
wherein R is an amine protecting group,

and wherein Intermediate C is the reagent which is reacted with Intermediate 5 to produce Intermediate 6.

In one embodiment of the above-depicted methods, R is a Boc group.

Crystalline form of Intermediate 6a

Herein is disclosed a specific crystalline form of Intermediate 6a:



Intermediate 6a.

The crystalline form of Intermediate 6a may be characterised by powder X-ray diffraction. The crystalline form of Intermediate 6a may have an X-ray powder diffraction pattern comprising characteristic peaks at $6.36^\circ \pm 0.2^\circ$, $11.34^\circ \pm 0.2^\circ$ 2θ , and $18.58^\circ \pm 0.2^\circ$ 2θ . The X-ray powder diffraction pattern may further comprise a peak at $13.42^\circ \pm 0.2^\circ$ 2θ . The X-ray powder diffraction pattern may further comprise a peak at $19.79^\circ \pm 0.2^\circ$ 2θ . Thus, the X-ray powder diffraction pattern may comprise 3, 4, 5, or more characteristic peaks. Typically, the X-ray powder diffraction pattern is measured using CuK α radiation with a wavelength of about 1.54 Å. Typically, the X-ray powder diffraction pattern is measured at room temperature.

The X-ray powder diffraction pattern of the crystalline form of Intermediate 6a may therefore comprise peaks at 6.36, 11.34, 18.58, 13.42 and 19.79, with each peak measured to $\pm 0.2^\circ$ 2θ .

The X-ray powder diffraction pattern of the crystalline form of Intermediate 6a may comprise peak positions corresponding to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26 or all of the peak positions listed in Table 1 below, which is generated from experimental powder diffraction data:

Angle (2-theta °) (± 0.2)	Relative Intensity (%)
6.36	94
7.90	16
9.37	27
9.90	56
10.65	12
11.34	100
13.42	91
13.61	34
15.24	13
17.19	18
18.58	94
18.83	30
19.07	28
19.79	75
21.07	37
21.38	57
21.79	40
22.06	11
22.84	16

Angle (2-theta °) (± 0.2)	Relative Intensity (%)
23.83	14
24.40	26
25.15	20
26.19	30
26.94	20
28.45	15
28.56	11
29.48	13

Table 1

The X-ray powder diffraction pattern of the crystalline form of Intermediate 6a may be substantially as illustrated in Fig. 4.

The crystalline form of Intermediate 6a may be characterised by differential scanning calorimetry (DSC). A DSC thermogram of the crystalline form of Intermediate 6a may have a single peak at about $229^{\circ}\text{C} \pm 2^{\circ}\text{C}$. The enthalpy change of the endothermic peak may be about 55 J/g. The DSC thermogram of the crystalline form of Intermediate 6a may be substantially as illustrated in Fig. 5.

EXAMPLES

Having been generally described herein, the follow non-limiting examples are provided to further illustrate the disclosure.

Unless otherwise specified, parameters disclosed herein are measured as set out in the Examples below.

Analytical methods

All NMRs were obtained either at 400 MHz or 500 MHz.

Compound LCMS data was determined by using the methods below:

For Intermediate 1:

Instrument	Agilent 1290 UPLC with UV detector		
Column	Acquity UPLC BEH C8, 2.1 × 100 mm, 1.7 μm		
Wavelength	210 nm		
Reference Wavelength	Off (This parameter is only applicable to Agilent and Thermo instruments)		
Column Temperature	30°C		
Flow Rate	0.4 mL/min		
Injector Volume	2 μL		
Needle Wash	ACN		
Mobile Phase A	<u>5 mM Ammonium acetate (NH₄Ac) in H₂O (pH 9.0)</u> For example, approximately weigh 0.39 g NH ₄ Ac and transfer to 1000 mL of pure water, mix well and degas by ultrasonic. Then adjust pH to 9.0 with ammonium hydroxide.		
Mobile Phase B	ACN		
Gradient Program	Time (min)	A%	B%
	Initial	86	14
	0.40	86	14
	12.00	40	60
	13.00	40	60
	14.00	5	95
	15.00	5	95
	15.40	86	14
	18.00	86	14
Run Time	18 min		
Data Acquisition Time	18 min		

For Intermediate 3:

Column	Waters XSelect CSH C18, 4.6 × 150 mm, 3.5 µm		
Wavelength	210 nm		
Reference Wavelength	Off (This parameter is only applicable to Agilent and Thermo instruments)		
Column Temperature	40°C		
Sampler Temperature	10°C		
Flow Rate	1.0 mL/min		
Injector Volume	1 µL		
Needle Wash	0.05% NH ₃ .H ₂ O in ACN:Water = 50:50 (v/v) For example, accurately transfer 0.5 mL NH ₃ .H ₂ O to 500 mL ACN and 500 mL pure water, mix well and degas by ultrasonic.		
Mobile Phase A	<u>0.08% NH₃.H₂O in water, v/v</u> For example, accurately transfer 0.8 mL NH ₃ .H ₂ O to 1000 mL pure water, mix well and degas by ultrasonic.		
Mobile Phase B	ACN		
Gradient Program	Time (min)	A%	B%
	Initial	95	5
	10.00	50	50
	12.00	10	90
	14.00	10	90
	15.00	95	5
	18.00	95	5
Run Time	18 min		
Data Acquisition Time	18 min		

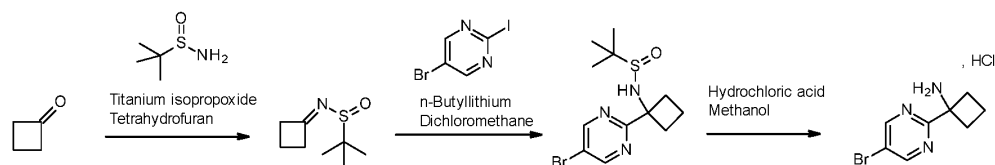
For Intermediate 7:

Instrument	Agilent 1290 HPLC with UV detector or equivalent		
Column	Acquity UPLC CSH C18, 2.1 × 100 mm, 1.7 µm, PN: 186005297		
Wavelength	210 nm		
Reference Wavelength	Off (This parameter is only applicable to Agilent and Thermo instruments)		
Column Temperature	50°C		
Flow Rate	0.6 mL/min		
Injector Volume	1 µL		
Needle Wash	MeOH		
Mobile Phase A	0.01% TFA in water, v/v For example, transfer 0.1 mL TFA to 1000 mL pure water, mix well and degas by ultrasonic.		
Mobile Phase B	0.01% TFA in ACN, v/v For example, transfer 0.1 mL TFA to 1000 mL acetonitrile, mix well and degas by ultrasonic.		
Gradient Program	Time (min)	A%	B%
	Initial	95	5
	1.00	95	5
	9.50	10	90
	11.00	10	90
	12.00	95	5
	14.00	95	5
Run Time	14 min		
Data Acquisition Time	14 min		

Starting materials

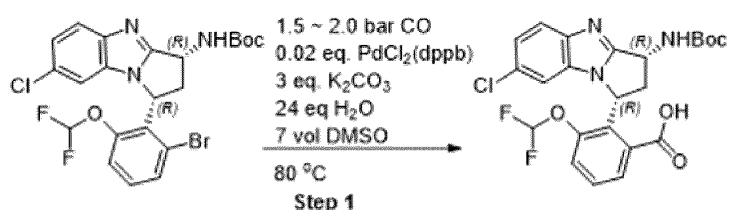
Starting Material 1a was prepared as set out in WO 2016/050975, where Starting Material 1 is referred to as INTERMEDIATE 42.

Starting Material A was synthesised according to the following reaction scheme:



Step 1 – synthesis of Intermediate 2aFirst batch

Intermediate 2a was synthesised according to the following reaction scheme:

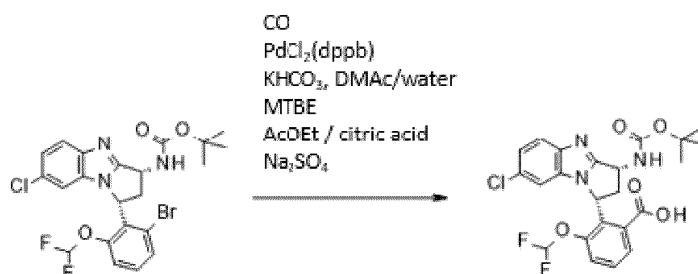


A suspension of Starting Material 1a (29.4 kg; 55.6 mol), palladium(II) chloride-1,4-bis(disphenylphosphine)butane (0.74 kg; 2% mol), potassium carbonate (22.9 kg; 165.7 mol; 3.0 eq), 0.82 vol (24 eq) of water and 7.0 vol of dimethyl sulfoxide was heated to 75-85 °C and maintained under monoxide carbon pressure (1.5-2.0 Bar) for 24-48 h. 7.0 vol of water were added at 20-30 °C and the mixture was filtered on diatomite. The cake was washed with 3.0 vol of water and the combined aqueous mother liquors were washed with 5.5 vol of tert-butylmethylether.

To the aqueous layer, 7.8 vol ethyl acetate were added and the pH was adjusted to 4-6 with a 2.5 M citric acid solution in water under stirring at 20-30 °C. Finally, the organic layer was washed with 4.4 vol of a 5% sulfate sodium solution in water. Intermediate 2a was isolated in ethyl acetate solution with 60% yield (16.26 kg; 96.1% LC Purity).

Second batch

Intermediate 2a was synthesised according to the following reaction scheme:



A suspension of Starting Material 1a (49.9 kg; 94.36 mol), palladium(II) chloride-1,4-bis(disphenylphosphine)butane (1.14 kg; 2% mol), potassium bicarbonate (28.31 kg; 283.09 mol; 3.0 eq), 4 vol of water and 10 vol of dimethylacetamide (DMAc) was heated to 75-85 °C and maintained under monoxide carbon pressure (2.0 Bar) for 10-48 h. 6.5 vol water were added at 20-30 °C and the mixture was filtered on diatomite. The cake was washed with 2.0 vol water and the combined aqueous mother liquors were washed with 6.0 vol tert-butylmethylether (MTBE) and 4.0 vol ethyl acetate (AcOEt).

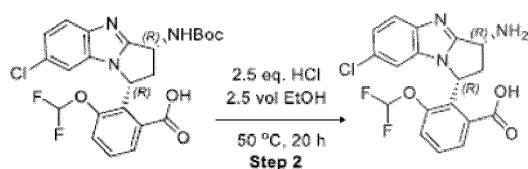
To the aqueous layer, 6.1 vol ethyl acetate were added and the pH was adjusted to 4-6 with a 2.5 M citric acid solution in water under stirring at 20-30 °C. Finally, the organic layer was washed with 4.5 vol of a 5% sulfate sodium solution in water. Intermediate 2a was isolated in ethyl acetate solution with 78% yield (35.5 kg; 99.8% LC Purity).

¹H NMR (400 MHz, CDCl₃), δ (ppm): 1.27 (s, 9H), 3.09 (m, 1H), 3.61 (ddd, J=12.6, 8.3, 8.1 Hz, 1H), 5.50 (q, J=8.3 Hz, 1H), 6.14 (t, J=8.1 Hz, 1H), 6.54 (d, J=1.9 Hz, 1H), 6.67 (d, J=8.6 Hz, 1H), 6.71 (t, JHF=72.6 Hz, 1H), 7.00 (br d, J=8.0 Hz, 1H), 7.04 (dd, J=8.7, 1.9 Hz, 1H), 7.46 (d, J=8.0 Hz, 1H), 7.54 (t, J=8.0 Hz, 1H), 7.82 (d, J=8.0 Hz, 1H)

LC/MS (ES⁺) [M+H]⁺ 494.4, RT 6.171 min

Step 2 – synthesis of Intermediate 3

Intermediate 3 was synthesised according to the following reaction scheme:



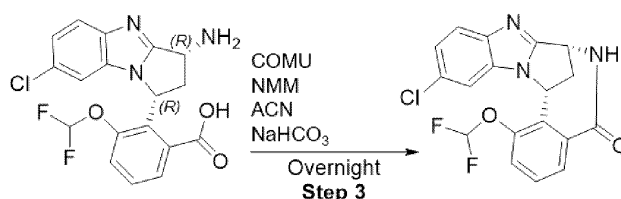
Intermediate 2a in ethyl acetate solution (26.2 kg; 39.9 mol) was concentrated below 40 °C under vacuo to 2-3 vol and then ethyl acetate was removed with 2 x 8 vol ethanol (EtOH) by distillation. 2.5 vol ethanol and 7% hydrogen chloride solution in water (99.8 mol; 2.5 eq) were added at 15-25 °C. The mixture was heated to 45-55 °C for 15-20 h and then added on 0.7-0.76 vol of N-methylmorpholine in 2.6 vol ethanol under stirring at 20-30 °C. After cooling at 5-15 °C, the mixture was stirred during 2.5 h and filtered. The cake was washed with 2.5 vol of water and dried under vacuo at 40-50 °C for 16-20 h to yield 19.7 kg of Intermediate 3 (93.6%; 99.7% LC Purity).

¹H NMR (500 MHz, DMSO-d₆), δ (ppm): 2.87 (ddd, J=14.1, 4.9, 4.0 Hz, 1H), 3.56 (m, 1H), 4.85 (dd, 9.8, 4.0 Hz, 1H), 6.03 (dd, J=9.8, 4.9 Hz, 1H), 6.78 (d, J=2.0 Hz, 1H), 7.12-7.19 (m, 2H), 7.26 (d, J=8.0 Hz, 1H), 7.39 (t, JHF=73.5 Hz, 1H), 7.40 (t, J=8.0 Hz, 1H), 7.61 (d, J=8.6 Hz, 1H)

LC/MS (ES+) [M+H]⁺ 394.1, RT 4.958 min

Step 3 – synthesis of Intermediate 4

Intermediate 4 was synthesised according to the following reaction scheme:



Intermediate 3 (35.2 kg; 89.39 mol) in 5.5 vol acetonitrile (ACN) was stirred at 15-25 °C. To the solution was added 1-cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbeniumhexafluorophosphate (COMU; 44.8 kg; 104.61 mol; 1.17 eq) and 0.6 vol acetonitrile. The mixture was stirred at 15-25 °C for 0.5-1 h and then heated to 45-55 °C for 0.5-1 h. N-methylmorpholine (NMM, 39.55 mol; 0.44 eq) was added followed by 0.07 vol acetonitrile and the mixture was stirred at 45-55 °C for 6-10 h. After completion, the mixture was cooled to 15-25 °C and 9.2 vol of a 7% aqueous sodium bicarbonate solution was added. The mixture was stirred at 20-30 °C for 0.5-1 h and then at -5/5 °C for 3-5 h. The suspension was filtered and the cake was washed in 5.5 vol water at 20-30 °C for 0.5-2 h. The suspension was filtered and then the cake was finally washed with 2.2 vol of water. The wet cake was dried at 40-50 °C under vacuo for 18-24 h to yield 31.15 kg (90% yield; 100% LC Purity).

Overall, by performing Steps 1 to 3, Intermediate 4 may be synthesized at an overall yield of 65%, with excellent purity control.

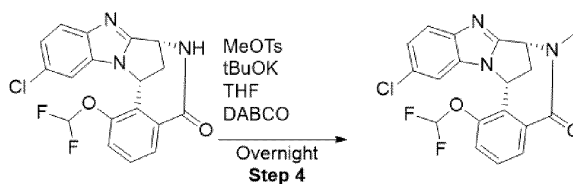
The above combination of Steps 1 to 3 can be compared to the synthetic route described in Example 11 of WO 2016/050975 A1 which describes a reaction in which (1R,3R)-1-[2-bromo-6-(difluoromethoxyphenyl)-7-chloro-2,3-dihydro-1H-pyrrolo[1,2-a]benzodiazol-3-amine is converted to Intermediate 4 using potassium carbonate and

dichloro[9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene]palladium (II). The reaction in WO 2016/050975 A1 takes place in one step and has a yield of 33.1%. In contrast, the combined yield of Steps 1 to 3 is up to 65% showing that such a synthetic route is associated with a significant improvement in yield. The improved yield of the present invention as compared to WO 2016/050975 A1 is also evident when taking into account the preliminary step of obtaining the protected Starting Material 1a (starting material in Step 1), which is described in WO 2016/050975 A1. In particular, Starting Material 1a is obtained with a 70% yield from Intermediate 40 in WO 2016/050975 A1. Thus, overall, the preliminary protection step followed by Steps 1 to 3 described herein provides Intermediate 4 in a yield of up to 46%.

In addition, Steps 1 to 3 herein provide Intermediate 4 with excellent purity without using flash chromatography as described in WO 2016/050975, which cannot be used at an industrial scale.

Step 4 – synthesis of Intermediate 5

Intermediate 5 was synthesised according to the following reaction scheme:



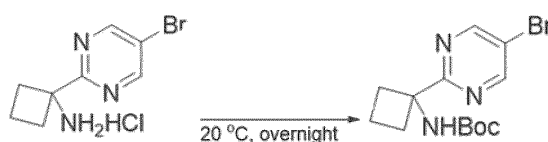
Intermediate 4 (31 kg; 82.50 mol) was solubilized in 5.5 vol tetrahydrofuran and the solution was concentrated below 45 °C under vacuo to 2-3 vol. 4.5 vol tetrahydrofuran (THF) was added.

The operation was repeated three times. The mixture was cooled to -5/5 °C and 4.5 vol tetrahydrofuran was added. At -5/5 °C under stirring, a solution of methyl p-toluenesulfonate in tetrahydrofuran (MeOTs, 52 kg; 47%; 1.6 eq) was first added, followed by a solution of potassium tert-butoxide (tBuOK) in tetrahydrofuran (11-15%; 54.2 kg; 1.02 eq). The mixture was stirred to completion at -5/5 °C for 1-3 h and then at 15-25 °C for 18-24 h. 1,4-diazabicyclo(2,2,2)octane (DABCO, 5.4 kg; 0.58 eq) was then added at 15-25 °C and the mixture was stirred for 0.5-2 h. A 5% solution of sulfate sodium in water (212 kg;

6.6 vol) and 10.5 vol of 2-methyltetrahydrofuran were added and the mixture was stirred for 0.5-2 h. The aqueous layer was washed with 5.25 vol 2-methyltetrahydrofuran and the combined organic layers were washed with a 5% aqueous solution of sulfate sodium (100 kg; 3.1 vol) and with a lithium hydroxide solution. The mixture was stirred for 0.5-1 h and the organic layer was concentrated below 50 °C under vacuo to 3-4 vol. The solvent was replaced with methanol by distillation below 50 °C under vacuo. The volume was adjusted to 8-10 vol and 4.5 vol of water was added at 45-55 °C. The mixture was stirred for 1-2 h at 45-55 °C, then at 5-15 °C for 3-5 h and finally filtered at 5-15 °C. The cake was washed with a mixture of 1.6 vol methanol and 0.58 vol water and then dried under vacuo at 25-35 °C for 18-24 h and at 45-55 °C for 18-24 h to yield 28.15 kg (86% yield; 99.7% LC Purity).

Step 5 – synthesis of Intermediate Ba

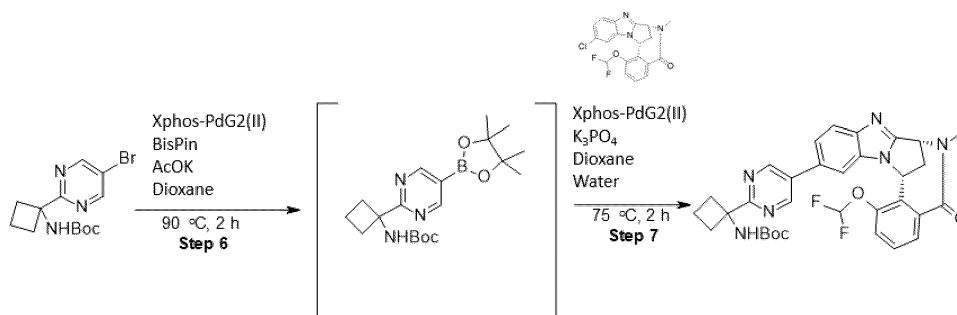
Intermediate Ba was synthesised according to the following reaction scheme:



To a suspension of Starting Material A (35.0 kg; 132.3 mol) in 6.0 vol of 2-methyltetrahydrofuran, triethylamine (17.4 kg; 1.3 eq; 172.0 mol) was added at 15-25 °C. A solution of di-tert-butyl dicarbamate (41.4 kg; 1.4 eq; 189.7 mol) in 2-methyltetrahydrofuran (1.3 vol; 40 l) was added in 0.5 h to 2 h at 15-25 °C. The mixture was stirred at 15-25 °C for 18-24 h to completion. Water (2.34 vol) was added and the mixture was stirred at 15-25 °C for 1-2 h. The organic layer was then washed with an 8.4% aqueous citric acid solution (2.3 vol) and then with water (2 vol). The combined aqueous layers were extracted with 2-methyltetrahydrofuran (2.2 vol). Combined organic phases were concentrated below 50 °C to 1-3 vol under vacuum and 2-methyltetrahydrofuran was replaced by acetonitrile. Temperature was adjusted to 55-70 °C and water (10 vol) was added. The mixture was stirred for 0.5-1 h and then cooled to 10-20 °C, to be maintained for 2-6 h. The suspension was filtered, and the cake was washed with water (2.3 vol) and then dried under vacuo at 45-55 °C for 18-24 h to yield 41.0 kg of Intermediate Ba (91% yield; 99.4% LC Purity).

Steps 6 and 7 – synthesis of Intermediate 6a

Intermediate 6a was synthesised according to the following reaction schemes:



A suspension of Intermediate Ba (30.6 kg; 93.2 mol), potassium acetate (AcOK, 1.72 kg; 1.88 eq), bis(pinacolato)diboron (BisPin, 27.5 kg; 1.16 eq) in 0.015 vol of water and 9.8 vol of 1,4-dioxane was formed. To this suspension was added a suspension of Xphos-PdG2(II) (0.75 kg; 1% mol) and 0.16 vol 1,4-dioxane. The mixture was heated to 85-95 °C and stirred for 2-5 h.

After completion, the temperature was adjusted to 70-80 °C and a solution of Intermediate 5 (27.4 kg; 0.75 eq) in 9.8 vol of 1,4-dioxane, then a solution of potassium phosphate (99.5 kg; 5.0 eq) in 7.0 vol of water and finally a suspension of XPhos-PdG2(II) (0.75 kg; 1% mol) 0.19 vol in 1,4-dioxane were added. The mixture was stirred at 70-80 °C for 2-5 h and then filtered on diatomite at 15-25 °C. The cake was washed with 10.9 vol of ethyl acetate. The combined filtrates were washed twice with a 5% sodium chloride aqueous solution (2 x 9.4 vol) at 20-30 °C. The combined aqueous layers were washed with 3.3 vol of ethyl acetate at 20-30 °C.

The combined organic layers were treated by activated carbon at 15-25 °C for 3-10 h. The cartridge filter was washed with 6.5 vol ethyl acetate and the combined organic solutions were concentrated to 2-3 vol at below 50 °C under vacuo. 4.9 vol of 1,4-dioxane was added and the mixture was concentrated to 2-3 vol at below 50 °C under vacuo. The operation was repeated twice and the final volume was adjusted to 3-6 vol. To the heated solution, 19.0 vol n-heptane was added at 45-55 °C and the temperature was cooled to 15-25 °C. The suspension was stirred for 1-3 h and filtered. A second crop was obtained by adding filtrate on a mixture of 2.6 vol 1,4-dioxane and 17 vol n-heptane at 50-65 °C. The mixture was stirred for 1-3 h, cooled to 15-25 °C, stirred for 3-4 h and filtered. The combined cake was washed with 3.6 vol of n-heptane and then dried under vacuo at 45-55 °C for 10-20 h to yield 42.15 kg (74% yield; 99.6% LC purity).

X-ray analysis was carried out on the resulting crystalline form of Intermediate 6a. Analysis was performed at room temperature on a D8 Advance from Bruker, configured in PHI-SPINNER with a sealed copper anode X-ray tube (λ CuK α average = 1.54178 Å) (45kV and 40mA). An acquisition time of 0.2s per step in an angular range from few 2-Theta degrees to 40° degrees with a 0.02° step size in 2θ was used. Table 2 summarises the key peak positions recorded.

Angle (2-theta °) ($\pm$ 0.2)	Relative Intensity (%)
6.36	94
7.90	16
9.37	27
9.90	56
10.65	12
11.34	100
13.42	91
13.61	34
15.24	13
17.19	18
18.58	94
18.83	30
19.07	28
19.79	75
21.07	37
21.38	57
21.79	40
22.06	11
22.84	16
23.83	14
24.40	26
25.15	20
26.19	30
26.94	20
28.45	15
28.56	11
29.48	13

Table 2

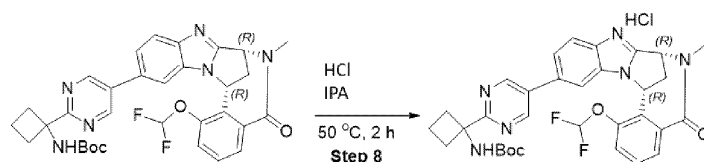
The powder X-ray diffraction pattern for the crystalline form of Intermediate 6a is shown in Fig. 4.

Differential scanning calorimetry (DSC) analysis was carried out on a Diamond apparatus from Perkin Elmer. Samples were prepared in Aluminum 50 µl crucibles with perforated lids crimped not tightly. Analyses were carried out with a scanning rate of 5 °C/min up to 256°C. Results are shown in Fig. 5. The melting temperature of the crystalline form of Intermediate 6a was found to be approximately 229.4°C, and the melting enthalpy was found to be 55 J/g.

TGA analysis was performed and showed no significant loss weight, indicating that the crystalline form of Intermediate 6a is an anhydrate crystalline form.

Step 8 – synthesis of Intermediate 7a

Intermediate 7a was synthesised according to the following reaction schemes:



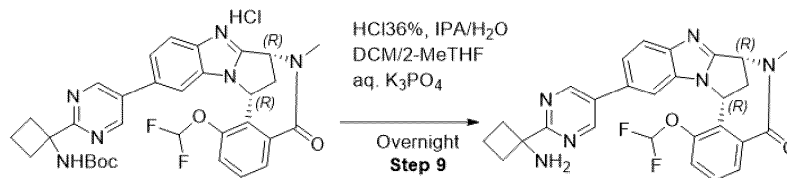
A suspension of Intermediate 6a (42 kg; 3.94 mol) in 9.5 vol isopropyl alcohol was heated to 65-75 °C to clear. The solution was concentrated to remove water below 50 °C under vacuo to 4-6 vol and the temperature was adjusted to 45-55 °C. A 5 M hydrogen chloride in isopropyl alcohol solution (IPA, 21.90%; 105.48 mol; 1.5 eq) was added and the mixture was stirred for 0.5-1 h. The temperature was adjusted to 10-20 °C within 2-4 h and the suspension was filtered. The cake was washed twice with isopropyl alcohol (2.4 vol and 1.3 vol) and then dried at 45-55 °C under vacuo to yield 41.75 kg (90% yield; 98.7% LC Purity).

¹H NMR CDCl₃, δ (ppm): 1.43 (br s, 9H), 2.17 (m, 2H), 2.62 (m, 2H), 2.81 (m, 2H), 3.06 (d, J=13.9 Hz, 1H), 3.68-3.79 (m, 4H), 5.61 (d, J=7.2 Hz, 1H), 5.82 (br, 1H), 6.53 (d, J=7.2 Hz, 1H), 6.90 (t, J_{HF}=72.5 Hz, 1H), 7.39 (dd, J=8.3, 1.0 Hz, 1H), 7.53 (t, J=8.3 Hz, 1H), 7.69 (dd, J=8.7, 1.6 Hz, 1H), 7.87 (d, J=1.6 Hz, 1H), 8.02 (d, J=8.7 Hz, 1H), 8.55 (dd, J=8.3, 1.0 Hz, 1H), 8.95 (s, 2H)

LC/MS (ES⁺) [M+H]⁺ 603.1, RT 7.461 min

Step 9 – synthesis of compound of Formula (I):

Compound of Formula (I) was synthesized according to the following reaction scheme:



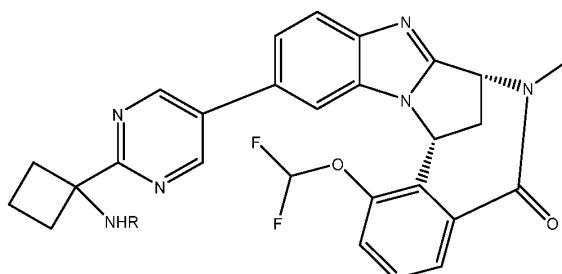
A mixture Intermediate 7a (39.8 kg; 62.28 mol) in 4.0 vol water and 4.15 vol isopropyl alcohol (IPA) was heated to 75-85 °C until clear and diluted hydrogen chloride solution in water (7.5%; 4.3 eq; 268.5 mol) was added. The mixture was stirred to completion for 2-4 h and concentrated below 50 °C under vacuo to 4-6 vol. The aqueous layer obtained was washed at 20-30 °C three times with 3.8 vol of dichloromethane (DCM) and finally with 4.0 vol of 2-methyltetrahydrofuran. To the aqueous layer, 19 vol of 2-methyltetrahydrofuran and a potassium phosphate solution in water (27%; 4.5 eq; 278.4 mol) were added at 20-30 °C. The mixture was stirred for 6-10 h and the organic layer was washed three times with 3.9 vol of water and with a lithium hydroxide solution. The organic layer was treated on activated carbon at 15-25 °C for 1-4 h, the cartridge filter was washed with 6.4 vol of 2-methyltetrahydrofuran. 28.8 kg of compound of Formula (I) was obtained in solution (92% yield; 98% LC purity).

Conclusion on the obtention of the compound of Formula (I):

Overall, Steps 1 to 9 described herein allow the compound of Formula (I) to be obtained in a yield of up to 35%. Including the preliminary step of producing Starting Material 1a from Intermediate 40 of patent application WO 2016/050975, the overall yield of Formula (I) obtained by the present invention is approximately 25%. This is improved as compared to the yield of compound of Formula (I) described in WO 2018/197503 (21%, starting from Intermediate 40 of WO 2016/050975). Further advantageously, the process described herein is scalable at an industrial production level, as it produces the end-product with excellent purity without performing purification steps involving flash chromatography, which is carried out at three points in the process described in WO 2018/197503.

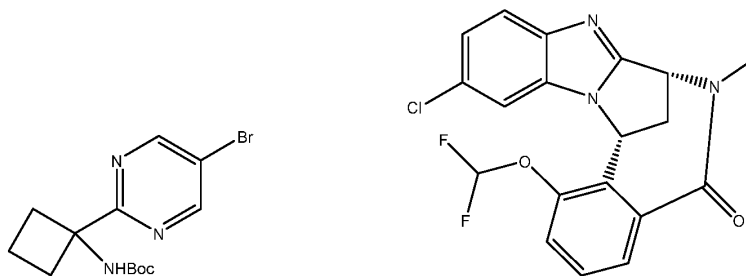
Comparison of the Formation of Intermediate 6 by Different Methods

Experiments were performed to investigate the efficacy of different methods for the formation of Intermediate 6:



Intermediate 6

The experiments involved the coupling of Intermediate Ba and Intermediate 5:



Intermediate Ba

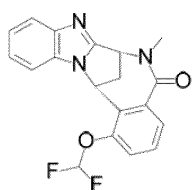
Intermediate 5

In a first experiment, the pentacycle was reacted with bis(pinacolato)diboron to form a boronated complex. This was then reacted with Intermediate Ba to produce Intermediate 6.

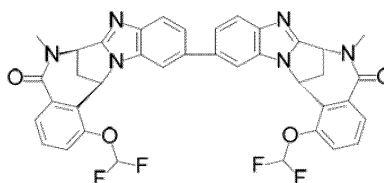
In a second experiment, Intermediate Ba was reacted with bis(pinacolato)diboron to form a boronated complex. This was then reacted with Intermediate 5 to produce Intermediate 6.

A number of differences were observed between the two experiments:

- in the first experiment it was found that the boronated pentacycle was unstable and led to impurities identified as the H-pentacycle (due to protodeboronation) and a pentacycle dimer (due to homocoupling of boronated pentacycle), see formulae below:



H-pentacycle



Dimer

The H-pentacycle was formed in an amount of 39% and the pentacycle dimer in an amount of 7%. The overall yield of the reaction for the desired end-product (Intermediate 6) was 38%.

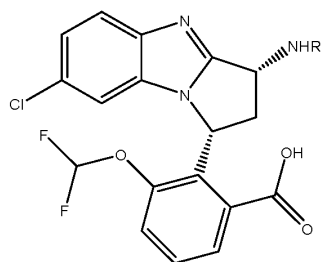
- In the second experiment, no such impurities were observed (no pyrimidine homocoupling by-product and below 0.50% of deboronated pyrimidine reactant detected), and the target product was obtained with a yield of 89%.

It can therefore be concluded that the pentacycle Intermediate 5 and the pyrimidine Intermediate B can be coupled by using a Suzuki reaction to produce Intermediate 6. However, performing the Suzuki reaction in such a manner that the pyrimidine is boronated is a more efficient reaction, leading to a higher yield compared to the reaction in which the pentacycle Intermediate 5 is boronated.

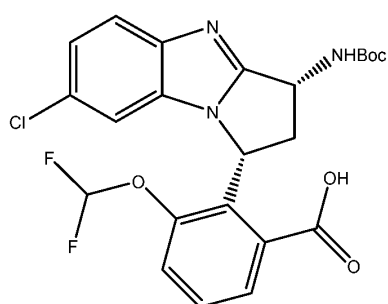
In addition, this high reaction yield for the Suzuki coupling reaction is afforded herein without performing a purification by flash chromatography, which is not scalable for an industrial production but was needed in the coupling step described in the previously published patent application WO 2018/197503.

The following represent aspects of the invention.

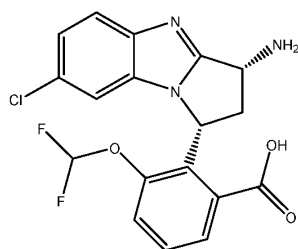
1. A compound selected from:



Intermediate 2;



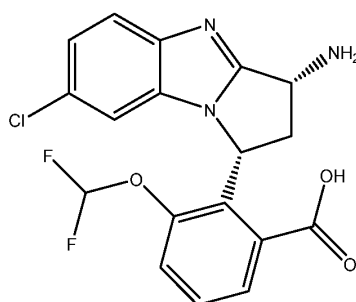
Intermediate 2a; and



Intermediate 3,

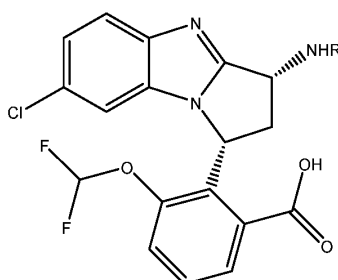
wherein R is an amine protecting group.

2. A method for preparing Intermediate 3:



Intermediate 3,

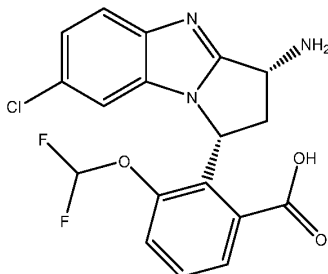
the method comprising reacting Intermediate 2:



Intermediate 2

Intermediate 4,

the method comprising reacting Intermediate 3:

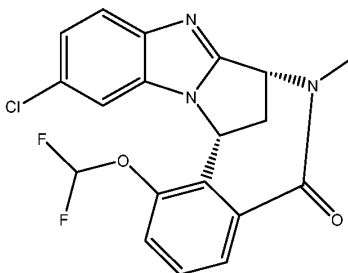


Intermediate 3

with a reagent to provide Intermediate 4.

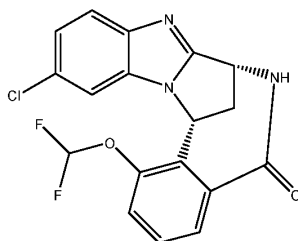
7. The method of aspect 6, wherein the reagent comprises an amide coupling reagent, optionally wherein the reagent comprises COMU ((1-cyano-2-ethoxy-2-oxoethylideneaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate).

8. A method of preparing Intermediate 5:



Intermediate 5,

the method comprising reacting Intermediate 4:



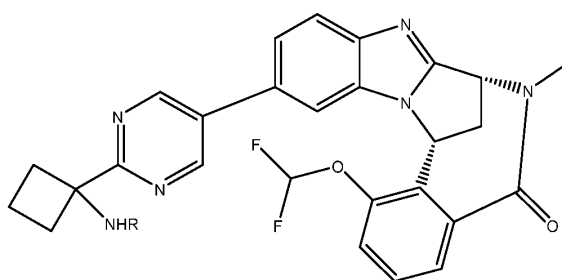
Intermediate 4

with a reagent to provide Intermediate 5;

wherein the reagent comprises MeOTs.

9. The method of aspect 8, wherein the reaction between Intermediate 4 and MeOTs occurs in THF solution, wherein the solution further comprises tBuOK (potassium tert-butoxide) and DABCO (1,4-diazabicyclo[2.2.2]octane).

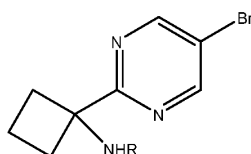
10. A method of preparing Intermediate 6:



Intermediate 6,

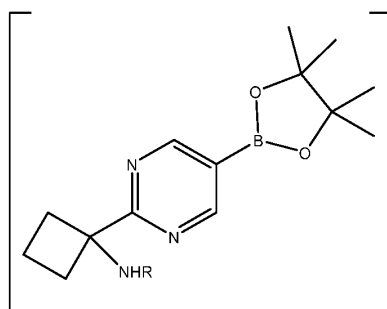
the method comprising:

a) reacting Intermediate B:



Intermediate B

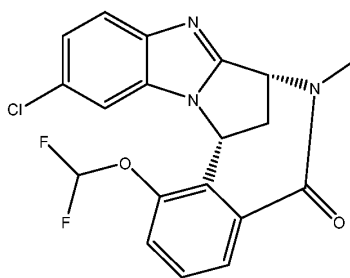
with a reagent to provide Intermediate C:



Intermediate C;

and

b) reacting Intermediate C with Intermediate 5:



Intermediate 5

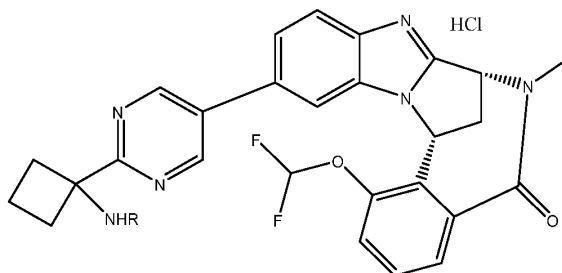
in the presence of a base and a palladium catalyst, such as XPhos-PdG2, to provide Intermediate 6;

wherein R is an amine protecting group.

11. The method of aspect 10, wherein the reagent in step a) comprises bis(pinacolato)diboron.

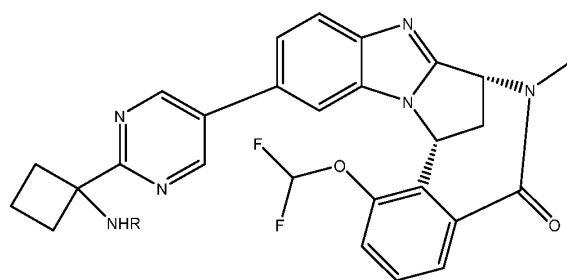
12. The method of aspect 10 or aspect 11, wherein step a) comprises contacting Intermediate B with a palladium catalyst, optionally wherein the palladium catalyst is XPhos-PdG2.

13. A method of preparing Intermediate 7:



Intermediate 7,

the method comprising exposing Intermediate 6:

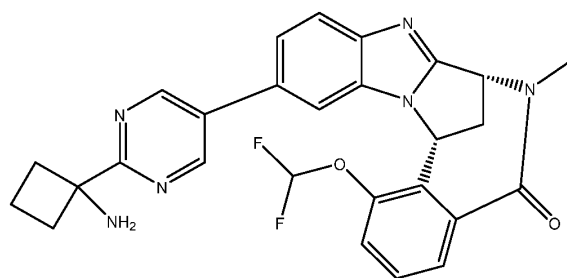


Intermediate 6

to hydrochloric acid to provide Intermediate 7;

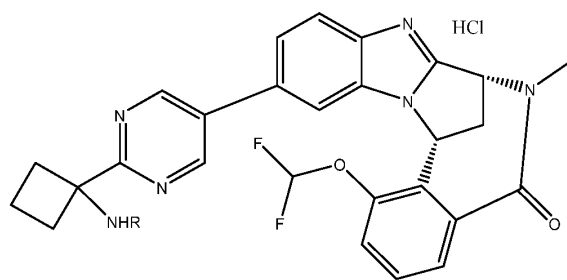
wherein R is an amine protecting group.

14. A method of preparing a compound of Formula (I):



Formula (I),

the method comprising reacting Intermediate 7:



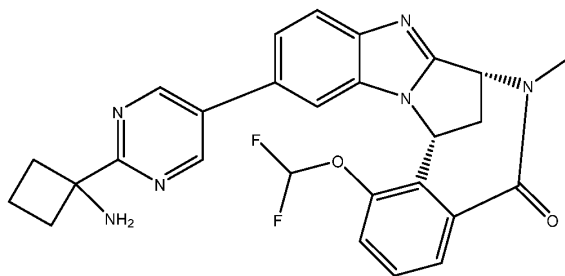
Intermediate 7

with a reagent to provide the compound of Formula (I);

wherein the reagent comprises aqueous hydrochloric acid; and

wherein R is an amine protecting group.

15. A method of preparing a compound of Formula (I):



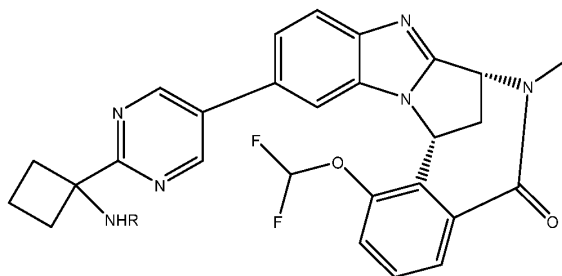
Formula (I),

the method comprising performing a synthesis scheme as shown in any one of Fig. 1, Fig. 2, or Fig. 3, wherein, in the scheme shown in Fig. 1, R is an amine protecting group.

16. The method of any one of aspects 2, 4, 10, 13, 14, or 15, wherein R is a Boc protecting group.

CLAIMS

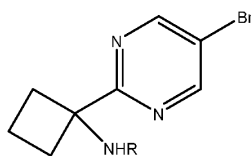
1. A method of preparing Intermediate 6:



Intermediate 6,

the method comprising:

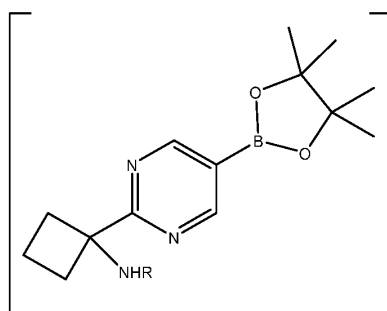
- a) reacting Intermediate B:



Intermediate B

wherein R is an amine protecting group

with a reagent to provide Intermediate C:

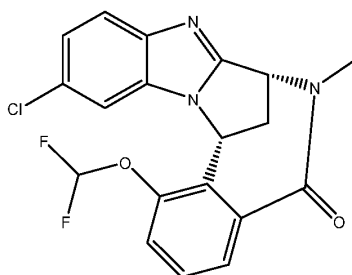


Intermediate C;

wherein R is an amine protecting group

and

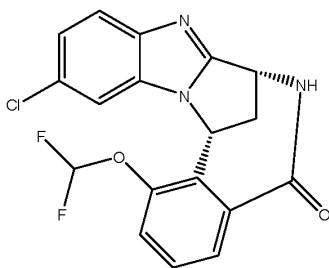
- b) reacting Intermediate C with Intermediate 5:



Intermediate 5

in the presence of a base and a palladium catalyst to provide Intermediate 6.

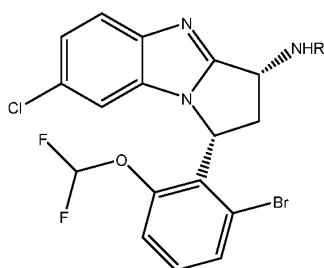
2. The method of claim 1, wherein the reagent in step a) comprises bis(pinacolato)diboron.
3. The method of claim 1 or claim 2, wherein step a) comprises contacting Intermediate B with a palladium catalyst.
4. The method of claim 3, wherein the palladium catalyst is XPhos-PdG2.
5. The method of any one of claims 1 to 4, wherein the palladium catalyst used in step b) is XPhos-PdG2.
6. A method for preparing Intermediate 4:



Intermediate 4,

the method comprising

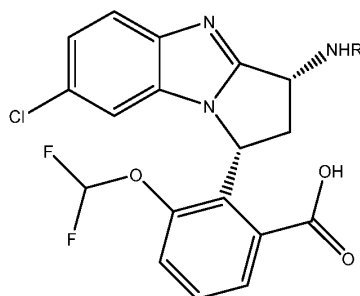
- a) reacting Starting Material 1:



Starting Material 1

wherein R is an amine protecting group,

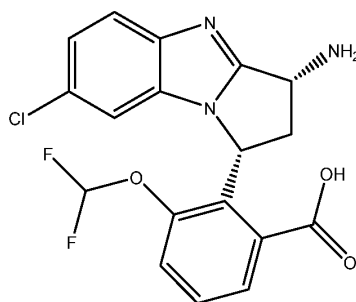
with a reagent to provide Intermediate 2,



Intermediate 2;

wherein R is an amine protecting group

b) reacting Intermediate 2 with a reagent to provide Intermediate 3

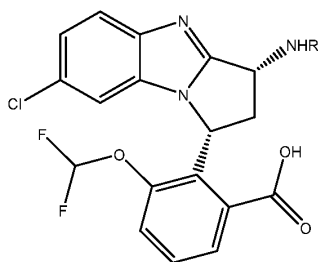


Intermediate 3; and

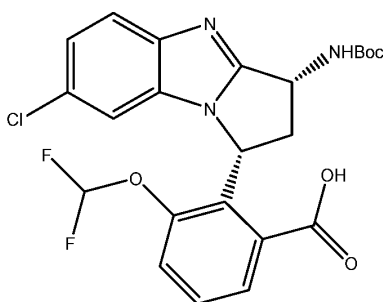
c) reacting Intermediate 3 with a reagent to provide Intermediate 4.

7. The method of claim 6, wherein in step a) the reagent comprises carbon monoxide.

8. The method of claim 6 or claim 7, wherein in step b) the reagent comprises an acid.
9. The method of any one of claims 6 to 8, wherein in step c) the reagent comprises an amide coupling reagent, optionally wherein the reagent comprises COMU ((1-cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate).
10. A compound selected from:



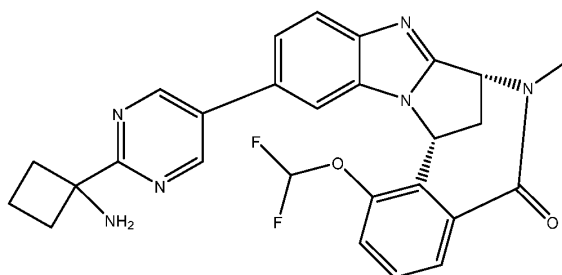
Intermediate 2; and



Intermediate 2a,

wherein R is an amine protecting group.

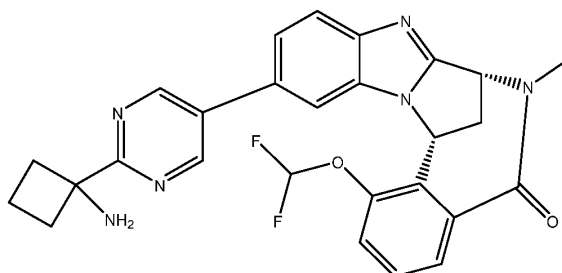
11. A method of preparing a compound of Formula (I):



Formula (I),

which comprises a method according to any one of claims 1 to 5.

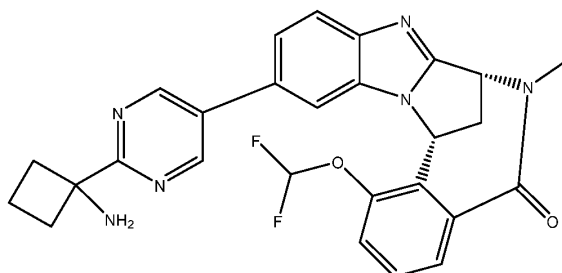
12. A method of preparing a compound of Formula (I):



Formula (I),

which comprises a method according to any one of claims 6 to 9.

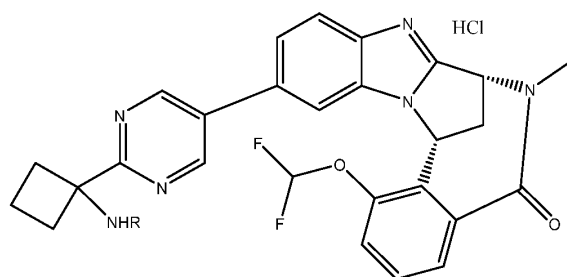
13. A method of preparing a compound of Formula (I):



Formula (I),

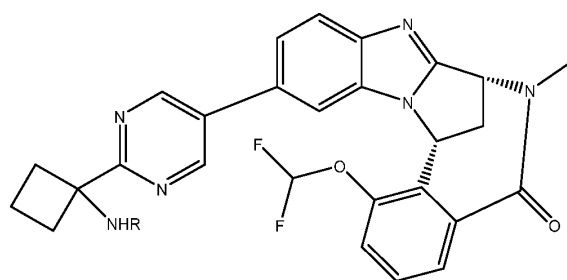
which comprises a method according to any one of claims 1 to 5 and which further comprises a method according to any one of claims 6 to 9.

14. A method of preparing a compound of Formula (I) according to any of claims 11 to 13, which method further comprises a step of preparing an Intermediate 7:



Intermediate 7,

the method comprising exposing Intermediate 6:

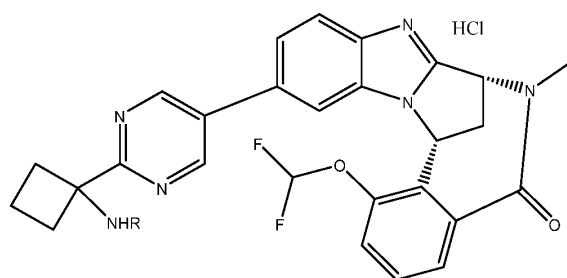


Intermediate 6

to hydrochloric acid to provide Intermediate 7;

wherein R is an amine protecting group.

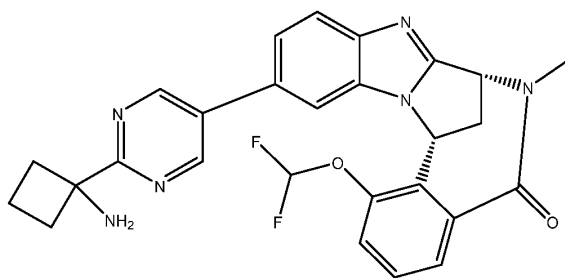
15. A method of preparing a compound of Formula (I) according to claim 14, which method further comprises a step of reacting Intermediate 7, wherein R is an amine protecting group:



Intermediate 7

with aqueous hydrochloric acid to provide the compound of Formula (I).

16. A method of preparing a compound of Formula (I):



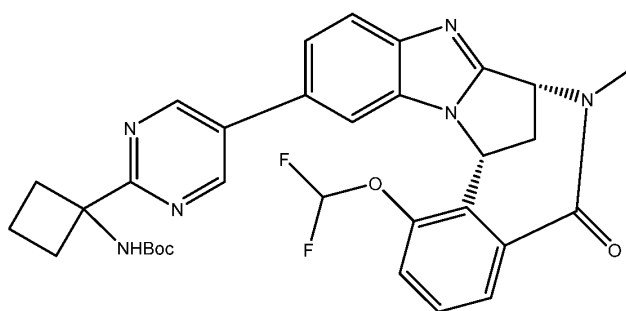
Formula (I),

the method comprising performing a synthesis scheme as shown in any one of Fig. 1, Fig. 2, or Fig. 3, wherein, in the scheme shown in Fig. 1, R is an amine protecting group.

17. The method of any one of claims 1 to 9 or 11 to 14 or the compound according to claim 10, wherein R is a Boc protecting group.

18. The method of any one of claims 1 to 9 or 11 to 17, wherein flash chromatography purification is not performed.

19. A crystalline form of Intermediate 6a:



Intermediate 6a;

having:

a) an X-ray powder diffraction pattern comprising characteristic peaks at $6.36^\circ \pm 0.2^\circ 2\theta$, $11.34^\circ \pm 0.2^\circ 2\theta$, and $18.58^\circ \pm 0.2^\circ 2\theta$; and/or

b) a DSC thermogram having a single peak at $229^\circ\text{C} \pm 2^\circ\text{C}$.

20. The crystalline form according to claim 19, having:

a) an X-ray powder diffraction pattern comprising characteristic peaks at $6.36^{\circ} \pm 0.2^{\circ} 2\theta$, $11.34^{\circ} \pm 0.2^{\circ} 2\theta$, and $18.58^{\circ} \pm 0.2^{\circ} 2\theta$; and

b) a DSC thermogram having a single peak at $229^{\circ}\text{C} \pm 2^{\circ}\text{C}$.

21. The crystalline form according to claim 19 or claim 20, wherein the X-ray powder diffraction pattern further comprises a peak at $13.42^{\circ} \pm 0.2^{\circ} 2\theta$ and/or $19.79^{\circ} \pm 0.2^{\circ} 2\theta$.