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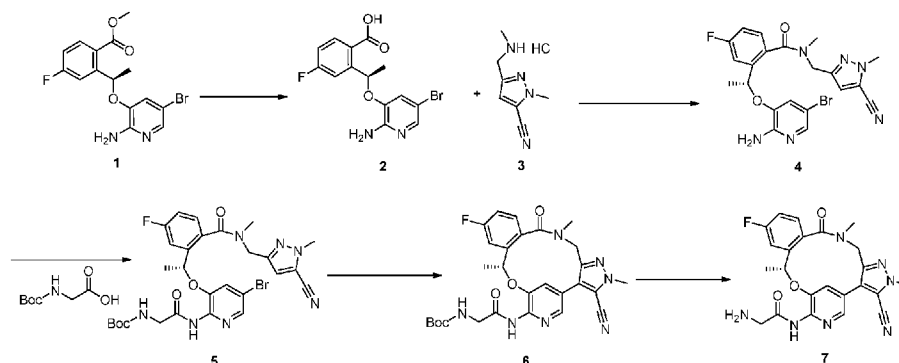
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(54) Title: Process for the Preparation of (10R) -7- (2-aminoacetyl) amino-12-fluoro-2, 10, 16-trimethyl-15-oxo-10, 15, 16, 17-tetrahydro-2H-8, 4- (metheno) pyrazolo [4, 3-h] [2, 5, 11] -benzoxadiazacyclotetradecine-3-carbonitrile



(57) Abstract: The present application disclosed a process for the preparing (10R) -7- (2-aminoacetyl) amino-12-fluoro-2, 10, 16-trimethyl-15-oxo-10, 15, 16, 17-tetrahydro-2H-8, 4- (metheno) pyrazolo [4, 3-h] [2, 5, 11] -benzoxadiazacyclotetradecine-3-carbonitrile, characterized by using Compound 5 with Boc protecting group, which is more suitable for industrial production.



Process for the Preparation of (10*R*)-7-(2-aminoacetyl)amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile

CROSS REFERENCE

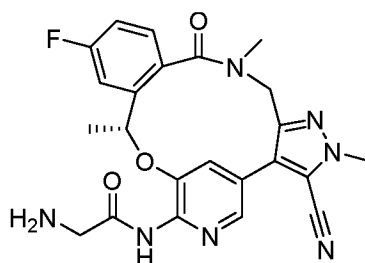
- 5 [0001] This invention claims the benefit of U.S. Provisional Patent Application No. 62/499,395, filed on January 25, 2017, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

- 10 [0002] The present invention relates to (10*R*)-7-(2-aminoacetyl)amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile, to processes for its preparation.

BACKGROUND OF THE INVENTION

- 15 [0003] Compound (10*R*)-7-(2-aminoacetyl)amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile is mentioned in WO2016/026423 and corresponds to the compound of the Formula (I):



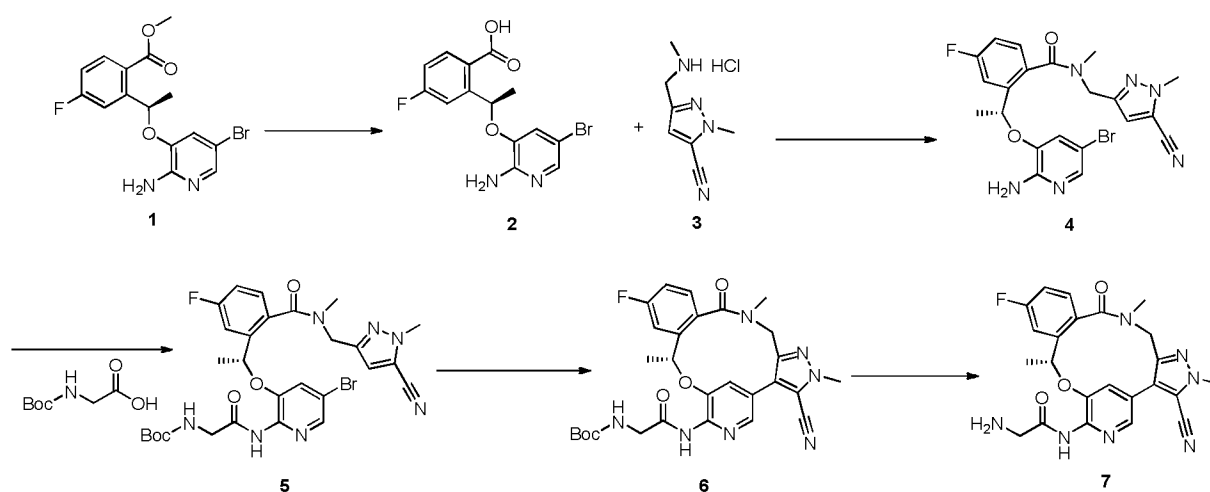
(I)

- 20 [0004] The synthetic procedure described in WO2016/026423, although suitable, regarded as disadvantageous for commercial production. There is a need for improved manufacturing methods of compound described in Formula (I). In

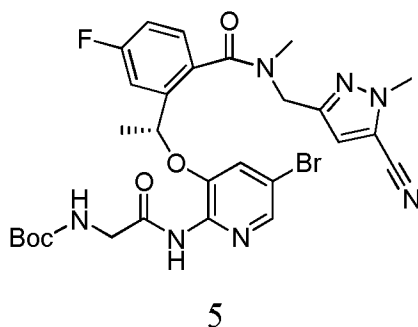
particular, there is a need to provide processes that fulfill one or more of the following criteria: scalable, safer, simpler, higher yielding and more economical when compared to known.

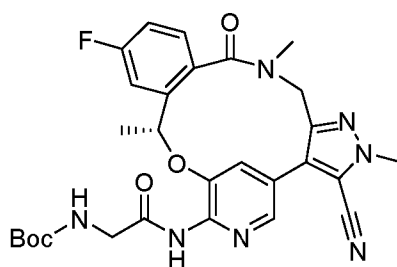
5 SUMMARY OF THE INVENTION

[0005] In the first aspect, the invention provides a process for the preparation of (10R)-7-(2-aminoacetyl)amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile (Compound 7 in Formula (I)), which is characterized by using Compound 5 with Boc protecting group as Scheme 1:



[0006] In the second aspect, the invention provides the key intermediates for the preparing Compound 7:



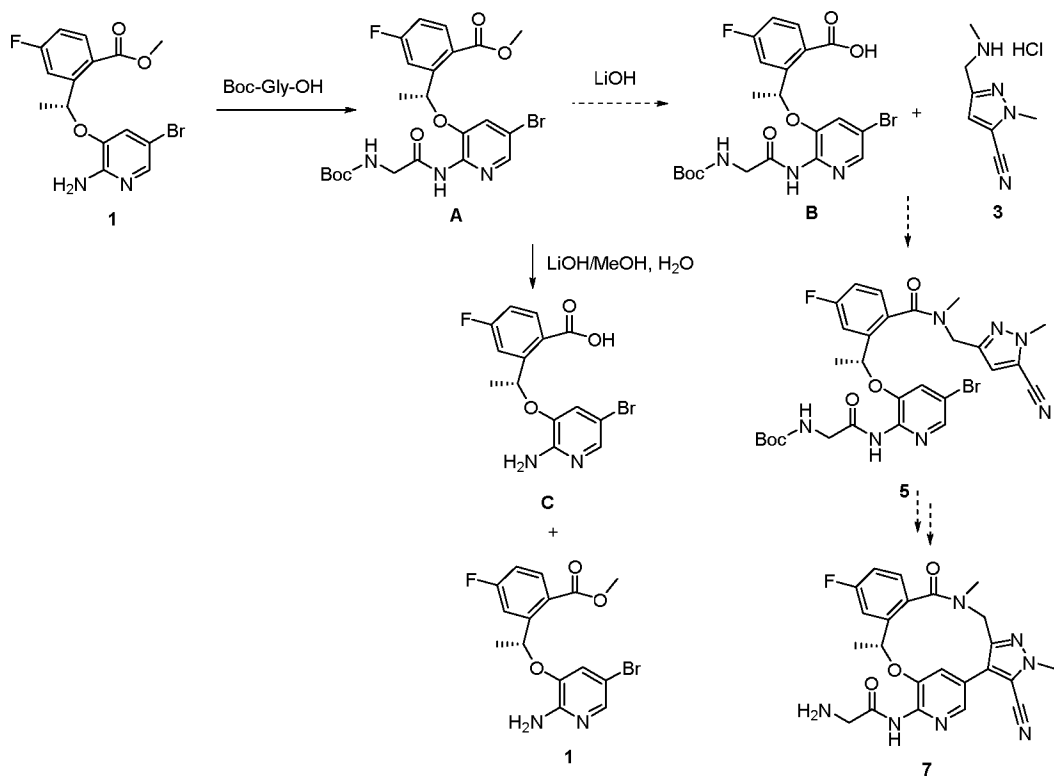


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DETAILED DESCRIPTION OF THE INVENTION

5 [0007] The initial designed synthesis of compound 7 in Formula (I) was described in Scheme 2. The protection of compound 1 with Boc-Glycine afforded compound A. The hydrolysis of compound A did not give the desire compound B, but generated compound C as the major product along with some compound 1. The protection of compound A with Fmoc-Glycine also afforded very low yield of
10 desired product. Most of the Fmoc group was cleaved under various reaction conditions.

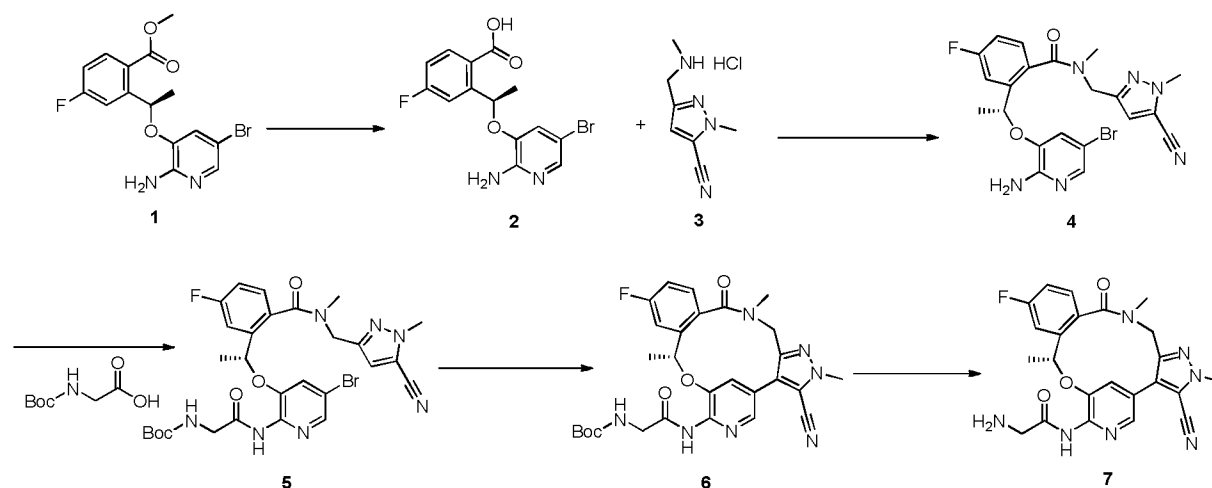
Scheme 2:



[0008] In one embodiment, the invention provides a process for the preparation of (10R)-7-(2-aminoacetyl)amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]-

5 benzoxadiazacyclotetradecine-3-carbonitrile (Compound 7 in Formula (I)), which is characterized by using Compound 5 with Boc protecting group shown in Scheme 1:

Scheme 1



in which includes the following steps:

- (1) the ester group of Compound 1 is hydrolyzed into Compound 2;
- (2) Compound 2 is coupled with Compound 3 to afford Compound 4;
- (3) Compound 4 is reacted with Boc-Glycine to generate Compound 5;
- (4) Compound 5 is intramolecularly cyclized into Compound 6;
- (5) Compound 6 is deprotected to afford Compound 7.

[0009] In one preferred embodiment, the invention provided a process of preparing Compound 7, the ester group of Compound 1 is hydrolyzed with NaOH in THF/Water or MeOH/Water or acetone/Water or acetonitrile/water or isopropanol/Water or EtOH/Water into Compound 2 in the Step (1), and more preferably, in THF/Water or MeOH/Water.

[0010] In one preferred embodiment, the invention provided a process of preparing Compound 7, the amide formation of Compound 2 and 3 optionally with a coupling reagent and in a non-reactive solvent, afforded Compound 4 in the Step (2); more preferably, the coupling reagent is selected from HATU, EDC, DCC, BOP, T₃P, or HOBt, and with DIEA or DIPEA; the non-reactive solvent is selected from DCM, DMF, or dioxane; most preferably, the coupling reagent is HATU,

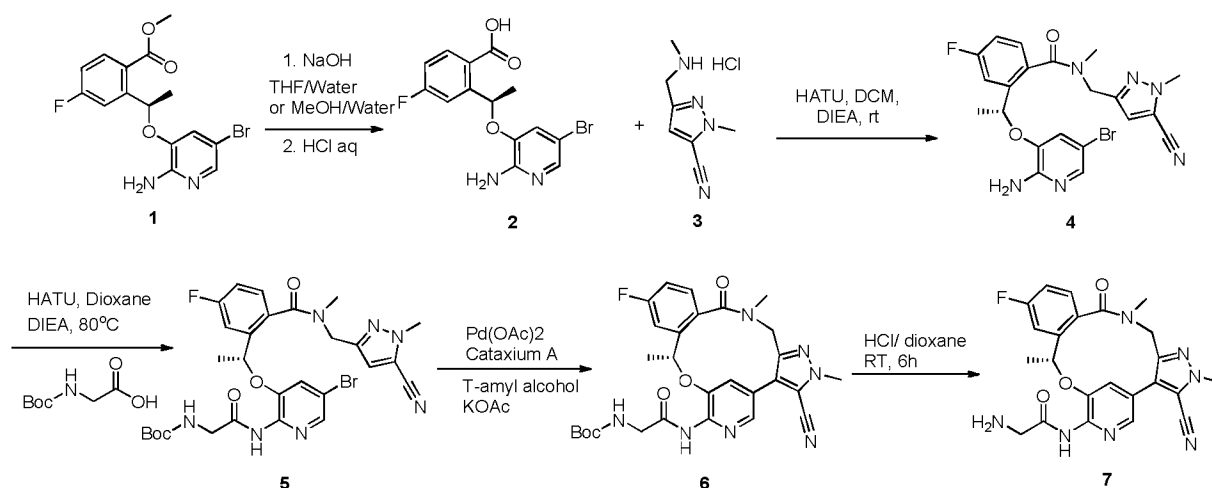
EDC, or DCC, and with DIEA or DIPEA; the non-reactive solvent is selected from DCM, DMF, or dioxane.

[0011] In one preferred embodiment, the invention provided a process of preparing Compound 7, Compound 4 is reacted with Boc-Glycine optionally in the present of a coupling reagent and in a non-reactive solvent to afford Compound 5 in the Step (3); more preferably, the coupling reagent is selected from HATU, EDC, DCC, BOP, T₃P, or HOBT, and with DIEA or DIPEA; the non-reactive solvent is selected from DCM, DMF, or dioxane; most preferably, the coupling reagent is HATU, EDC, or DCC, and with DIEA or DIPEA; the non-reactive solvent is selected from DCM, DMF, or dioxane.

[0012] In one preferred embodiment, the invention provided a process of preparing Compound 7, Compound 5 is intramolecularly cyclized into Compound 6 under palladium catalyzed condition in the Step (4), more preferably, in the present of Pd(OAc)₂, cataxiuma and KOAc, and in t-AmOH.

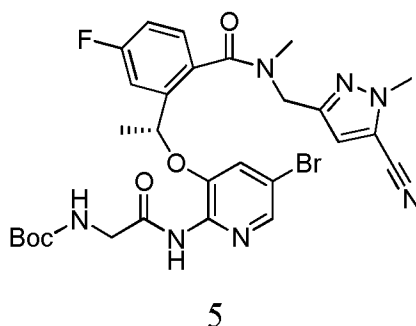
[0013] In one preferred embodiment, the invention provided a process of preparing Compound 7, Compound 6 is deprotected under acidic condition such as HCl in MeOH or dioxane in the Step (5).

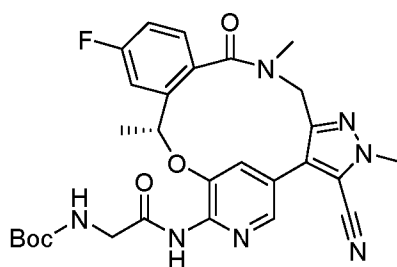
[0014] In specific embodiment, the invention provided a process of preparing Compound 7 in the Scheme 3:



[0015] The ester group of Compound 1 was hydrolyzed with NaOH in THF/Water or MeOH/Water to give Compound 2. The amide formation of Compound 2 and 3 with HATU in DCM afforded Compound 4, which reacted with Boc-Glycine to generate Compound 5. The intramolecular cyclization of Compound 5 under palladium catalyzed condition afforded Compound 6. Deprotection of Boc group of Compound 6 led to the synthesis of Compound 7.

[0016] In another embodiment, the invention provides the key intermediates for the preparing Compound 7:





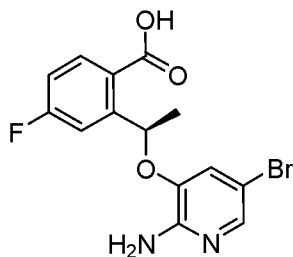
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Abbreviations

- 5 DMF means N,N-dimethylformamide.
 DCM means dichloromethane.
 HATU means 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
 DIPEA or DIEA means diisopropyl ethylamine.
- 10 DCC means Dicyclohexylcarbodiimide.
 EDC means N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride.
 THF means tetrahydrofuran.
 EA means ethyl acetate.
 HOBt means hydroxybenzotriazole.
- 15 m-CPBA means *meta*-Chloroperoxybenzoic acid.
 Boc-Gly-OH means *N*-(*tert*-Butoxycarbonyl)glycine.
 BOP means (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate.
 Pd(dppf)Cl₂ means [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium.
- 20 T₃P means n-propylphosphonic anhydride
 Et₃N means triethyl amine
 Fmoc means Fluorenylmethyloxycarbonyl
 cataXium A means Di(1-adamantyl)-*n*-butylphosphine

$\text{Pd}(\text{OAc})_2$ means palladium acetate

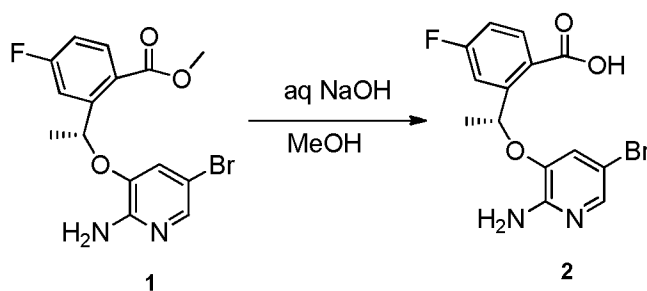
Example 1 (Compound 2)



- 5 To a solution of Compound 1 (500 mg) in methanol and water was added 5 equivalents of NaOH and the reaction was stirred at room temperature overnight. The reaction solution was heated to 45°C for another 4 hours and cooled down to room temperature. The reaction then was worked out to give Compound 2 (400 mg). MS m/z 355 $[\text{M}+1]$.

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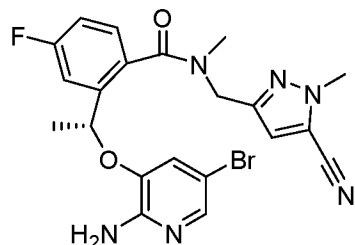
Example 2 Synthesis of (R)-2-(1-((2-amino-5-bromopyridin-3-yl)oxy)ethyl)-4-fluorobenzoic acid (Compound 2)



- 15 To a solution of compound 1 (10 g, 27 mmol) in MeOH (150 mL) were added a solution of NaOH (5.42 g, 13.55 mmol) in water (40 mL). The mixture was heated at 40 °C for 10 h. Then cooled and evaporated under reduced pressure. The residue was added water (150 mL) and extracted with EA (50 mL). The aqueous phase was adjusted to pH about 7 and extracted with EA (50 mL*3). The combined organic phase was washed with brine, dried with Na_2SO_4 and

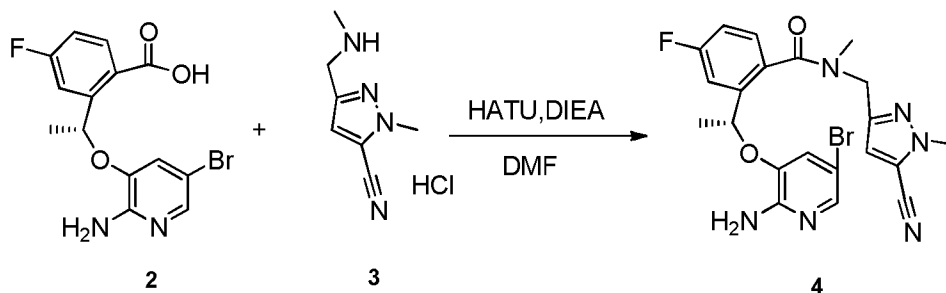
evaporated under reduced pressure to provide compound **2** (9.5 g, 98.7% yield) as a light yellow solid. ¹H-NMR (CD₃OD, 300 MHz): δ 8.07-8.12 (m, 1H), 7.50 (s, 1H), 7.38-7.34 (m, 1H), 7.15-7.09 (m, 1H), 6.88 (s, 1H), 6.49 (t, *J*=6.0 Hz, 1H), 1.66 (dd, *J*=6.3 Hz, 3H). MS *m/z* 355 [M+1].

Example 2 (Compound **4**)



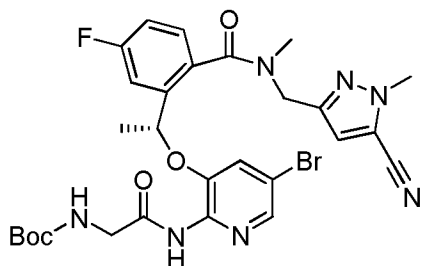
[0017] To a solution of Compound **2** (100 mg) in DCM was added Compound **3**, HATU, and DIEPA, the reaction was stirred overnight and worked out to give desired product Compound **4** (100 mg). MS *m/z* 487 [M+1].

Example 3 Synthesis of (R)-2-(1-((2-amino-5-bromopyridin-3-yl)oxy)ethyl)-N-((5-cyano-1-methyl-1H-pyrazol-3-yl)methyl)-4-fluoro-N-methylbenzamide (Compound **4**)



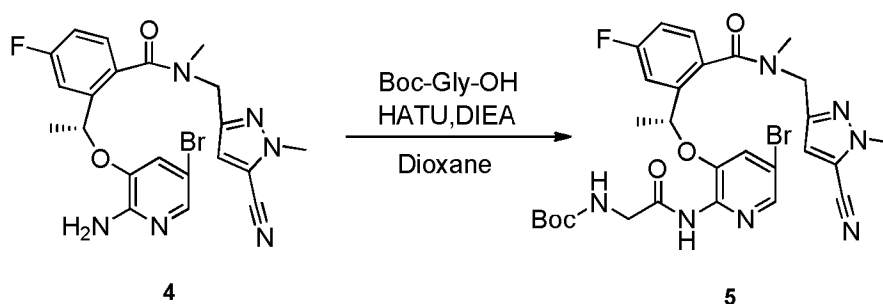
To a solution of compound **3** (8.4 g, 45.07 mmol), HATU (17.12 g, 45.07 mmol) and DIEA (14.53 g, 112.68 mmol) in DMF (200 mL) was added compound **2** (10.0 g, 28.17 mmol) under N₂ with ice-water bath. The mixture was stirred overnight at room temperature. Water (500 mL) was added and extracted with EA (100 mL*3). The combined organic phase was washed with brine, dried with Na₂SO₄ and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (PE:EA = 2:1 to 1:1, v:v) to provide compound **4** (10.0 g, 73% yield) as an off-white solid. ¹H-NMR (DMSO, 300 MHz): δ= 7.35-7.54 (m, 3H), 6.99-7.23 (m, 3H), 6.09-6.29 (m, 2H), 5.48-5.52 (m, 1H), 4.66-4.75 (m, 1H), 4.45-4.66 (m, 1H), 3.92-3.95 (m, 3H), 2.97 (s, 1H), 2.76 (s, 1H). MS: 488 [M+1]⁺. MS *m/z* 487 [M+1].

Example 4 (Compound 5)



[0018] To a solution of Compound 4 in dioxane were added Boc-Glycine, HATU
 5 and DIEA. The reaction was heated at 80°C and followed by TLC until the
 completion. Worked out to give the desire product Compound 5. MS m/z 644
 [M+1].

Example 5 Synthesis of (R)-tert-butyl (2-((5-bromo-3-(1-(2-(((5-cyano-1-methyl-1H- pyrazol-3-
 10 oxoethyl)carbamate (Compound 5)

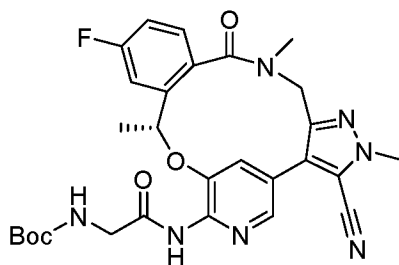


A solution of compound 4 (10.5 g, 21.56 mmol), Boc-Gly-OH (13.2 g, 75.46 mmol),
 HATU (32.77 g, 96.24 mmol) and DIEA (16.68 g, 129 mmol) in dioxane (300 ml) was heated to
 15 80 °C for 8 h under N₂. The solvent was removed under reduced pressure. Water (150 mL) was
 added and extracted with EA (100 ml*3), the combined organic phase was washed with brine,
 dried with Na₂SO₄ and evaporated under reduced pressure. The residue was purified by silica gel
 column chromatography (PE:EA =2:1, v:v) to provide compound 5 (9.0 g, 64.7% yield) as a
 yellow solid. ¹H-NMR (DMSO, 400 MHz): δ = 9.87-9.88 (d, J =1.6 Hz, 1H), 7.65-7.69 (m, 1H),

7.42-7.46 (m, 1H), 7.14-7.25 (m, 1H), 5.56-5.57(m, 1H), 4.36-4.75(m, 2H) , 3.96-4.046(m, 3H), 3.96-4.06(m, 2H), 3.01 (s, 1H) , 2.84 (s, 2H) , 1.55 (d, $J=4.4$ Hz, 3H) , 1.40 (s, 1H) . MS m/z 644 $[M+1]$.

Example 6 (Compound 6)

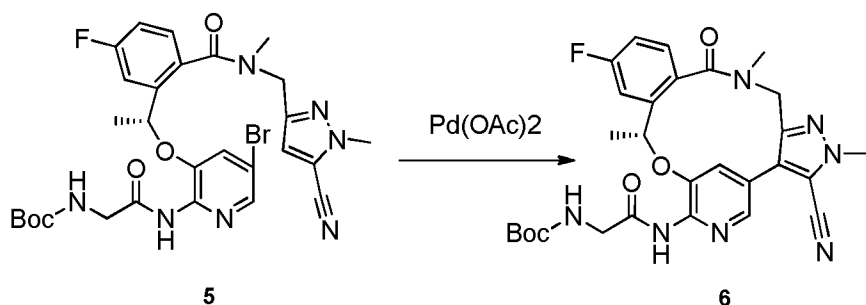
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[0019] To a solution of Compound 5 in t-AmOH were added $Pd(OAc)_2$, catax1 and KOAc. The reaction was heated to reflux for overnight to give desired product Compound 6. MS m/z 564 $[M+1]$.

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Example 7 Synthesis of compound (6)

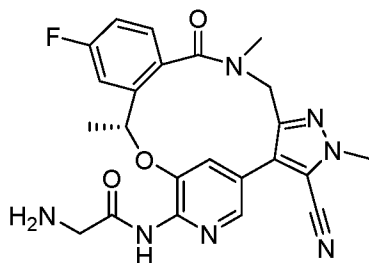


To a solution of compound **5** (7.0g, 10.87 mmol) in t-AmOH (200 mL) was added $Pd(OAc)_2$ (650 mg, 2.90 mmol), cataxiuma (2.08 g, 5.80 mmol) and KOAc (5.35 g, 54.35 mmol). The mixture was heated at 120 °C overnight under N_2 . After cooled and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (DCM:MeOH =100:1, v:v) to provide the yellow solid, then the solid was again purified by silica gel column chromatography (EA) to provide compound **6** (1.5g, 24.5% yield) as a yellow solid. ^1H -NMR (CD $_3$ OD, 400 MHz): δ = 7.96 (s, 1H), 7.54-7.57 (m, 1H), 7.40-7.43

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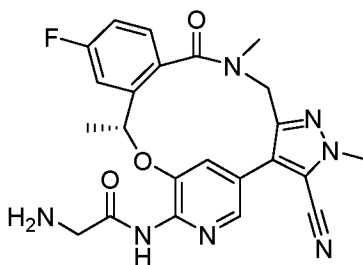
(m, 1H), 7.21 (s, 1H), 7.10-7.13(m, 1H), 5.77 (t, $J=6.0$ Hz, 1H), 4.39-4.51(m, 2H), 4.07-4.12(m, 5H), 3.12 (s, 3H), 1.81 (dd, $J=6.0$ Hz, 3H), 1.50 (s, 9H). MS m/z 564 $[M+1]$.

Example 8 (Compound 7)



- 5 [0020] To compound **6** in DCM was added HCl (4N in dioxane, 2ml) at 0°C, the mixture was stirred at 0°C for another 6 hr, stop the reaction and evaporated to be dry, to the residue was added water (10ml), the mixture was extracted with DCM (2ml x2), the DCM layer was discarded, the water layer was adjusted pH to 8-9 by NaOH (1N) and then filtered, the solid was washed by water (2ml) and dried to
- 10 give the crude product, the crude product was purified by silica gel column chromatography (DCM:MeOH / 30:1 to 15:1) to give the desired product as an off-white solid. MS m/z 464 $[M+1]$.

Example 9 (Compound 7)



- 15 A solution of compound **6** (2.2 g, 3.91 mmol) in DCM (10 mL) was added TFA (2 ml), then the solution was stirred for 2 h at room temperature. The solution was evaporated under reduced pressure. Water (20 mL) was added and extracted with DCM (20 ml), the aqueous phase was adjusted to pH about 8~9 and extracted with DCM (20*5). The combined organic phase was

dried over anhydrous Na_2SO_4 . The solvent was evaporated under reduced pressure and the residue was purified by pre-HPLC to provide Compound 7 (340 mg, 18.9% yield) as a white solid. $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ = 8.03 (d, J =1.6 Hz, 1H), 7.52-7.55(m, 1H), 7.41-7.44 (m, 1H), 7.23 (d, J =1.2 Hz, 1H), 7.10-7.14(m, 1H), 5.78(t, J =5.6 Hz, 1H), 4.40-4.52(m, 2H), 4.10(s, 3H), 3.63 (s, 2H) , 3.13 (s, 3H) 1.80 (dd, J =6.0 Hz, 3H) . MS m/z 464 $[\text{M}+1]$.

CLAIMS

What is claimed is:

1. A process for preparing of Compound 7, in which includes the following steps:

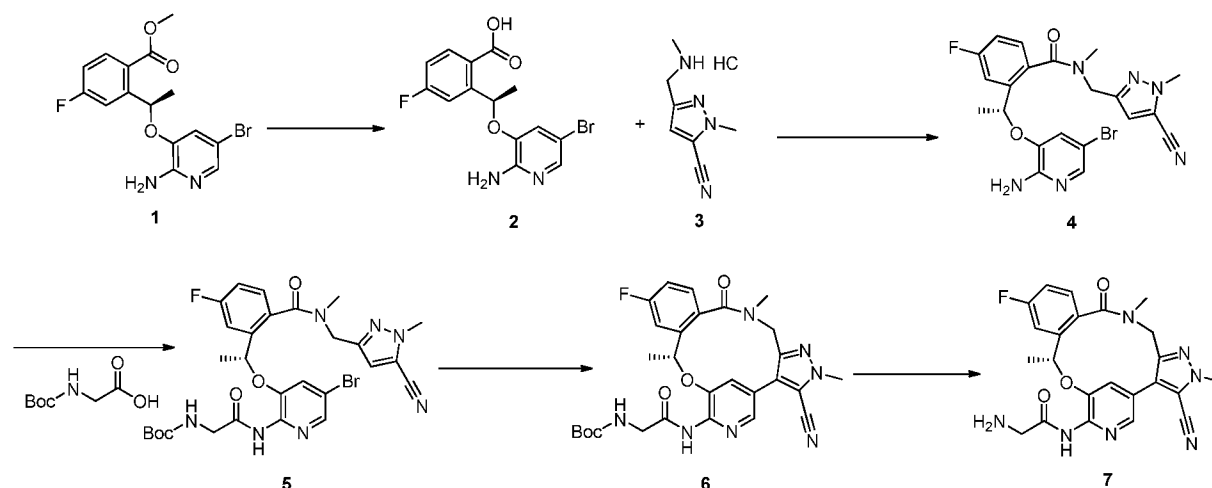
(1) the ester group of Compound 1 is hydrolyzed into Compound 2;

5 (2) Compound 2 is coupled with Compound 3 to afford Compound 4;

(3) Compound 4 is reacted with Boc-Glycine to generate Compound 5;

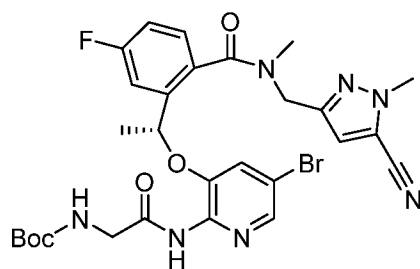
(4) Compound 5 is intramolecularly cyclized into Compound 6;

(5) Compound 6 is deprotected to afford Compound 7:



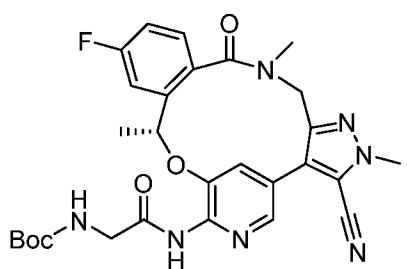
10 2. The process of Claim1, wherein Compound 1 is hydrolyzed with NaOH in THF/Water or MeOH/Water or acetone/Water or acetonitrile/water or isopropanol/Water or EtOH/Water into Compound 2 in the Step (1), and more preferably, in THF/Water or MeOH/Water.

3. The process of Claim1, wherein the amide formation of Compound 2 and 3 optionally with a coupling reagent and in a non-reactive solvent, afforded Compound 4 in the Step (2); more preferably, the coupling reagent is selected from HATU, EDC, DCC, BOP, T₃P, or HOBt, and with DIEA or DIPEA; the non-
5 reactive solvent is selected from DCM, DMF, or dioxane; most preferably, the coupling reagent is HATU, EDC, or DCC, and with DIEA or DIPEA; the non-reactive solvent is selected from DCM, DMF, or dioxane.
4. The process of Claim1, wherein Compound 4 is reacted with Boc-Glycine optionally in the present of a coupling reagent and in a non-reactive solvent to
10 afford Compound 5 in the Step (3); more preferably, the coupling reagent is selected from HATU, EDC, DCC, BOP, T₃P, or HOBt, and with DIEA or DIPEA; the non-reactive solvent is selected from DCM, DMF, or dioxane; most preferably, the coupling reagent is HATU, EDC, or DCC, and with DIEA or DIPEA; the non-reactive solvent is selected from DCM, DMF, or dioxane.
- 15 5. The process of Claim1, wherein Compound 5 is intramolecularly cyclized into Compound 6 under palladium catalyzed condition in the Step (4), more preferably, in the present of Pd(OAc)₂, cataxiuma and KOAc, and in t-AmOH.
6. The process of Claim1, wherein Compound 6 is deprotected under acidic condition such as HCl in MeOH or dioxane in the Step (5).
- 20 7. Compound 5 as a key intermediate for the process of Claim 1



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8 Compound 6 as a key intermediate for the process of Claim 1



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2018/074097

A. CLASSIFICATION OF SUBJECT MATTER

C07D 498/18(2006.01)i; C07D 401/10(2006.01)i; C07D 401/12(2006.01)i

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)

C07D498, C07D401, A61K31, A61P35

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

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

CNABS;CNKI;VEN:GLYCINE, BOC, DEPROTECT+, BUTOXYCARBONYL; CASREACT (STN system):searching based on the reaction formula of claim 1; REGISTRY,CAPLUS (STN system):searching based on the formulas of claims 7 and 8

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2016026423 A1 (TELIGENE LTD) 25 February 2016 (2016-02-25) the descriptionn, page 11, Scheme 2	1-8
Y	US 2014135339 A1 (PFIZER INC.) 15 May 2014 (2014-05-15) the description, page 107, paragraph [1184]; pages 110-111, paragraph [1198]; and page 135	1-8
Y	CN 106146614 A (SHENYANG KEHAI MEDICINE TECHNOLOGY CO. LTD.) 23 November 2016 (2016-11-23) the whole document, especially the description, paragraph [0006]	1-8
Y	CN 101654473 A (SHANGHAI ACHIEVER BIOCHEM. CO. LTD.) 24 February 2010 (2010-02-24) the whole document, especially the description, page 1, line 5	1-8

☐ 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

12 February 2018

Date of mailing of the international search report

12 April 2018

Name and mailing address of the ISA/CN

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2018/074097

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	2016026423	A1	25 February 2016	CN	107207528	A	26 September 2017
				JP	2017525716	A	07 September 2017
				US	2017216264	A1	03 August 2017
				EP	3183256	A1	28 June 2017
US	2014135339	A1	15 May 2014	ES	2621220	T9	23 November 2017
				US	9133215	B2	15 September 2015
				AU	2013229173	A1	21 August 2014
				RS	55814	B1	31 August 2017
				CA	2863892	C	30 August 2016
				CR	20140370	A	21 August 2014
				AR	090230	A1	29 October 2014
				AP	201407881	D0	31 August 2014
				ZA	201406244	B	27 May 2015
				GE	P201606560	B	25 October 2016
				WO	2013132376	A1	12 September 2013
				CO	7061081	A2	19 September 2014
				EP	2822953	B9	21 June 2017
				LT	2822953	T	10 April 2017
				JP	2016041709	A	31 March 2016
				SI	2822953	T1	26 April 2017
				EA	026155	B1	31 March 2017
				CA	2863892	A1	12 September 2013
				CL	2014002084	A1	03 November 2014
				PH	12014501992	B1	24 November 2014
				DK	2822953	T3	03 April 2017
				KR	101692600	B1	03 January 2017
				JP	6002825	B2	05 October 2016
				KR	20140137414	A	02 December 2014
				HK	1199247	A1	26 June 2015
				ES	2621220	T3	03 July 2017
				EP	2822953	A1	14 January 2015
				JP	5823066	B2	25 November 2015
				DO	P2014000188	A	16 November 2014
				DK	2822953	T5	11 September 2017
				PT	2822953	T	06 April 2017
				EA	201491394	A1	29 May 2015
				TW	201350484	A	16 December 2013
				PE	23392014	A1	15 January 2015
				PL	2822953	T3	31 July 2017
				EA	026155	B9	30 June 2017
				AU	2013229173	B2	01 June 2017
				HR	P20170287	T1	21 April 2017
				CN	104169286	B	08 June 2016
				SG	11201404451T	A	26 September 2014
				MX	2014010716	A	22 September 2014
				SI	EP2822953	T1	26 April 2017
				CN	104169286	A	26 November 2014
				US	2013252961	A1	26 September 2013
				TW	I476199	B	11 March 2015
				PH	12014501992	A1	24 November 2014

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2018/074097

Patent document cited in search report			Publication date (day/month/year)		Patent family member(s)			Publication date (day/month/year)	
					UY	34657	A	31 October 2013	
					MD	20140086	A2	31 January 2015	
					AP	201407881	A0	31 August 2014	
CN	106146614	A	23 November 2016		None				
CN	101654473	A	24 February 2010		None				