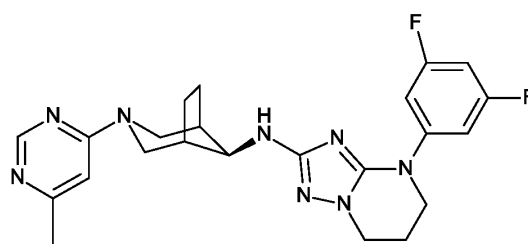


Process for the preparation 4-(3,5-difluorophenyl)-N-[3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine

5 The present invention relates to a process for the preparation of a compound (I),



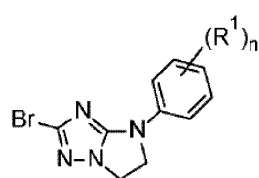
(I)

or pharmaceutically acceptable salt thereof, which is a modulator of γ -secretase and may be useful for prophylaxis and treatment of a disease associated with the deposition of β -amyloid in the brain, in particular Alzheimer's disease, and other diseases such as cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis, Dutch-type (HCHWA-D), multi-infarct dementia, dementia pugilistica and Down syndrome.

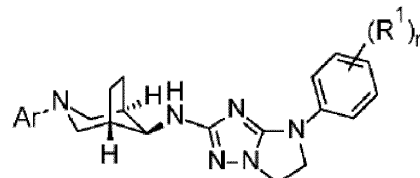
BACKGROUND OF THE INVENTION

The synthetic approach of compound (I) was disclosed in WO2018060300, and WO2018065340. However, the current processes are not suitable for large-scale production due to the following issues:

- (a) seven linear synthesis steps with very low yield, e.g., 19.8% for producing

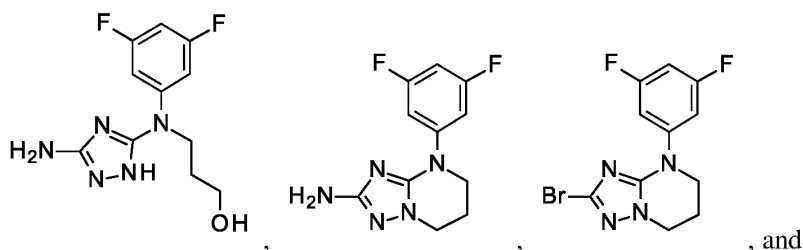


and 62% for making



-2-

- 5 (b) column purification with tedious work up process for all of the intermediates, such as:



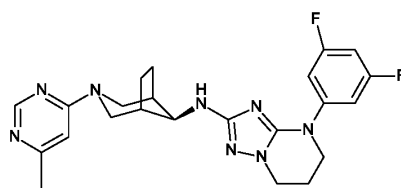
the final product.

- (c) safety concern with toxic reagent of hydrazine.
- (d) use of high loading of expensive catalyst Pd (20%) which could result higher cost for
- 10 large scale API production and complicated process to remove the catalyst.
- (e) high cost with HPLC separation.
- (f) safety, repeatability, and scalability concerns for the newly form tri-azole ring during large-scale production.

SUMMARY OF THE INVENTION

- 15 Based on the issues above, one object of this invention therefore is to find an efficient synthetic approach, which can address some or all of above issues and be applied on a technical scale.

One aspect of the present invention relates to a process for the preparation of compound (I),

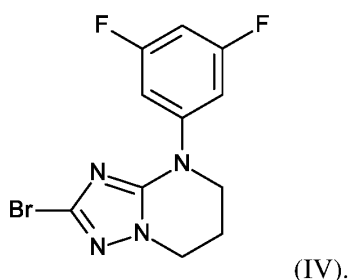
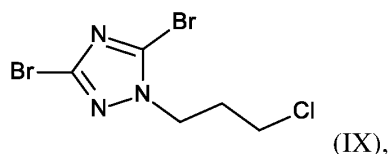


- 20 (I)

or pharmaceutically acceptable salt thereof.

Another aspect of the present invention relates to novel processes for the preparation of compound (III) and compound (IV):

-3-



The advantages of the process of the present invention include, but not limited to, one or more of the following:

- (a) Totally new process with less steps;
- (b) Safe and robust for scale up, no tri-azole ring formation step;
- (c) Practice work up process, no column purification.

In another embodiment, provided herein is a pharmaceutical composition comprising compound (I); and a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.

- 15 In another embodiment, provided herein is compound (I) for the treatment or prophylaxis of a disease associated with the deposition of β -amyloid in the brain, in particular Alzheimer's disease, or a disease selected from cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis, Dutch-type (HCHWA-D), multi-infarct dementia, dementia pugilistica and Down syndrome.

- 20 In another embodiment, provided herein is the use of compound (I) for the treatment or prophylaxis of a disease associated with the deposition of β -amyloid in the brain, in particular Alzheimer's disease, or a disease selected from cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis, Dutch-type (HCHWA-D), multi-infarct dementia, dementia pugilistica and Down syndrome.

- 25 In another embodiment, provided herein is the use of compound (I) or the pharmaceutical composition for the manufacture of a medicament for the treatment or prophylaxis of a disease associated with the deposition of β -amyloid in the brain, in particular Alzheimer's disease, or a disease selected from cerebral amyloid angiopathy, hereditary cerebral hemorrhage with

5 amyloidosis, Dutch-type (HCHWA-D), multi-infarct dementia, dementia pugilistica and Down syndrome.

In another embodiment, provided herein is a method for the treatment or prophylaxis of a disease associated with the deposition of β -amyloid in the brain, in particular Alzheimer's disease, or a disease selected from cerebral amyloid angiopathy, hereditary cerebral hemorrhage
10 with amyloidosis, Dutch-type (HCHWA-D), multi-infarct dementia, dementia pugilistica and Down syndrome, which method comprises administering a therapeutically effective amount of compound (I) or the pharmaceutical composition disclosed herein.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

15 The term "pharmaceutically acceptable salt" refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of formula I and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Acid-addition salts include for example those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric
20 acid and nitric acid, and those derived from organic acids such as *p*-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethyl ammonium hydroxide. The chemical modification of a pharmaceutical compound into a salt is a technique
25 well known to pharmaceutical chemists in order to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. It is for example described in Bastin R.J., *et al.*, Organic Process Research & Development 2000, 4, 427-435; or in Ansel, H., *et al.*, In: Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th ed. (1995), pp. 196 and 1456-1457.

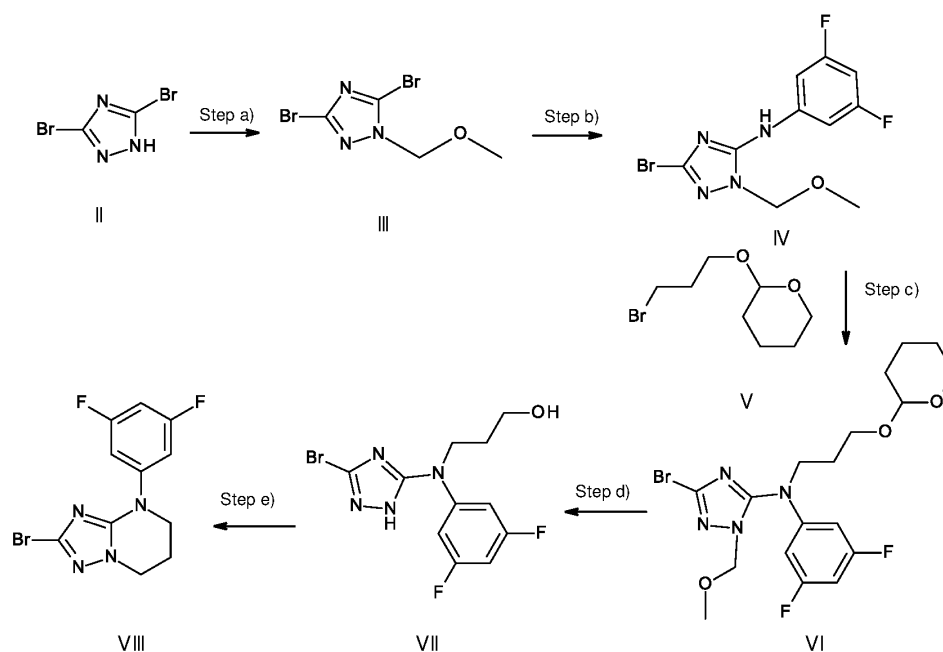
30 ABBREVIATION

API	Active Pharmaceutical Ingredient
(Boc) ₂ O	Di-tert-butyl dicarbonate
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate

5	DIPEA	N,N-Diisopropylethylamine
	DMF	Dimethylformamide
	DMSO	Dimethyl sulfoxide
	Eq.	Equivalent
	EtOAc or EA	Ethyl acetate
10	EtOH	Ethanol
	IPA	Isopropanol
	IPAc	Isopropyl acetate
	K ₂ CO ₃	Potassium carbonate
	KOAc	Potassium acetate
15	KOH	Potassium Hydroxide
	Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium(0)
	Pd(OAc) ₂	Palladium(II) acetate
	LiHMDS	Lithium bis(trimethylsilyl)amide
	2-MeTHF	2-Methyltetrahydrofuran
20	MeOH	Methanol
	MOM	Methoxymethyl
	MgSO ₄	Magnesium sulfate
	MTBE	Methyl tert-butyl ether
	NaH	Sodium hydrid
25	NaHMDS	Sodium bis(trimethylsilyl)amide
	NaOAc	Sodium acetate
	NaOtBu	Sodium tert-butanol
	NH ₄ Cl	Ammonium Chloride
	NMP	N-Methyl-2-pyrrolidone
30	PPh ₃	Triphenyl phosphine
	SEM	2-(Trimethylsilyl)ethoxymethyl
	tBuOH	tert-Butanol
	TEA	Triethylamine
	THF	Tetrohydrofuran
35	TFA	Trifluoroacetic acid
	v/v	Volume ratio
	wt. %	Weight percentage

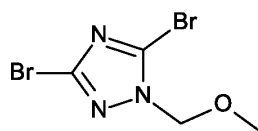
5 The present invention provides innovative processes as outlined in the **schemes 1 to 3**.

Scheme 1



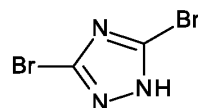
The synthesis comprises the following steps:

step a) the formation of compound **(III)**,



(III),

via the reaction of compound **(II)**

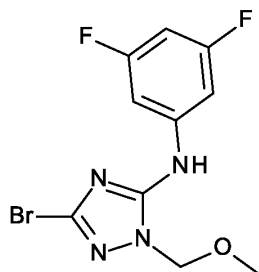


(II)

and MOMChloride;

-7-

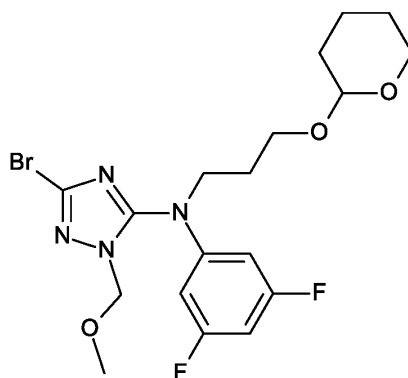
5 step b) the formation of compound (IV),



(IV),

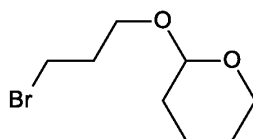
via alkylation reaction of compound (III) and 3,5-difluoroaniline;

step c) the formation of compound (VI),



(VI),

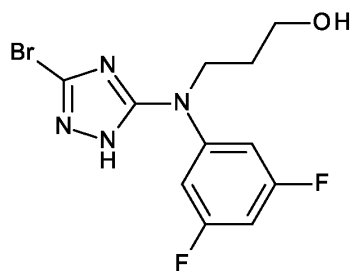
via the reaction of compound (IV) and compound (V)



(V);

15 step d) the formation of compound (VII),

-8-

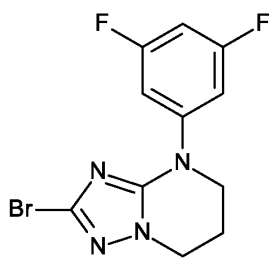


5

(VII),

via the de-protection reaction of compound (VI);

Step e) the formation of compound (VIII),



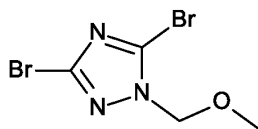
10

(VIII),

via the internal Mitsunobu cyclization reaction of compound (VII).

A detailed description of Steps a) to e) is as follows:

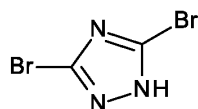
Step a) the formation of compound (III),



15

(III),

via the reaction of compound (II),



-9-

5

(II)

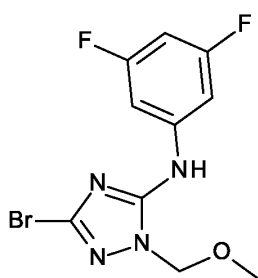
and MOMChloride.

Compound (III) is synthesized in the presence of a suitable solvent, and a suitable base.

The suitable solvent is selected from DCM and THF; preferably, the solvent is THF.

The suitable base is selected from KOAc, NaOAc and NaH; preferably, the suitable base is
10 NaH.

Step b) the formation of compound (IV),



(IV),

via alkylation reaction from compound (III) and 3,5-difluoroaniline;

15

Compound (IV) is synthesized in a suitable solvent with a suitable base.

The suitable solvent is selected from 2-MeTHF, DCM and THF; preferably, the solvent is THF.

The suitable base is selected from NaHMDS, K₂CO₃, KOH, NaOH, NaH and LiHMDS; preferably, the base is LiHMDS.

20

The suitable equivalent of the suitable base is from 1.0 eq. to 2.5 eq.; preferably, the equivalent is selected from about 1.0 eq., about 1.2 eq., about 1.5 eq., about 2.0 eq. and about 2.5 eq.; more preferably, the equivalent is about 2.0 eq.

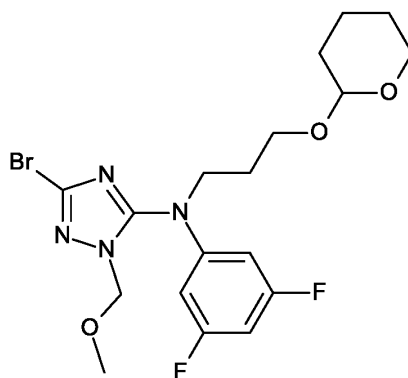
The suitable equivalent of 3,5-difluoroaniline is from 1.0 eq. to 2.5 eq.; preferably, the equivalent is selected from about 1.0 eq., about 1.2 eq., about 1.5 eq., about 2.0 eq. and about 2.5
25 eq.; more preferably, the equivalent is about 2.5 eq..

The reaction is performed at -20 ~ 70 °C, 10 ~ 70 °C, preferably at 25 ~ 30 °C.

-10-

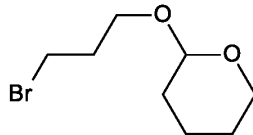
- 5 The temperature system designed in present invention gives high yield and good purge effect for impurities.

Step c) the formation of compound (VI),



(VI),

- 10 via the reaction of compound (IV) and compound (V)



(V);

Compound (VI) is synthesized in the presence of the compound (V) with a suitable amount of base.

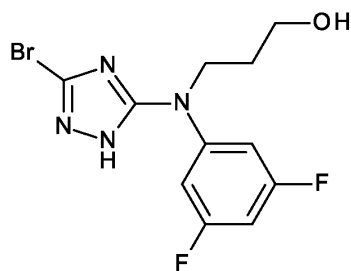
- 15 The suitable amount of compound (V) is 1.7 eq. ~ 2.26 eq.; preferably, the equivalent is about 1.7 equivalent.

The suitable base is selected from NaOH, Na₂CO₃, Cs₂CO₃ and potassium carbonate; preferably, the base is potassium carbonate.

- 20 The suitable amount of base is 2.0 eq. ~ 3.0 eq.; preferably, the amount is about 2.06 equivalent.

Step d) the formation of compound (VII),

-11-



5

(VII),

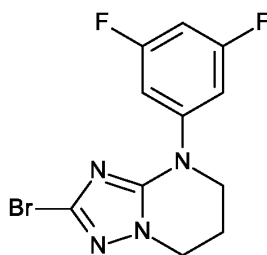
via the de-protection reaction of compound (VI);

Compound (VII) in this step is synthesized via de-protection reaction in the presence of a suitable volume of acid.

10 The suitable acid is selected from HBr, TFA and HCl; preferably, the acid is HCl; more preferably, the acid is HCl (36.5% wt.) in water.

The suitable volume of acid used in de-protection reaction is 1 V to 2 V; preferably, the volume is about 2 V.

Step e) the formation of compound (VIII),



15

(VIII),

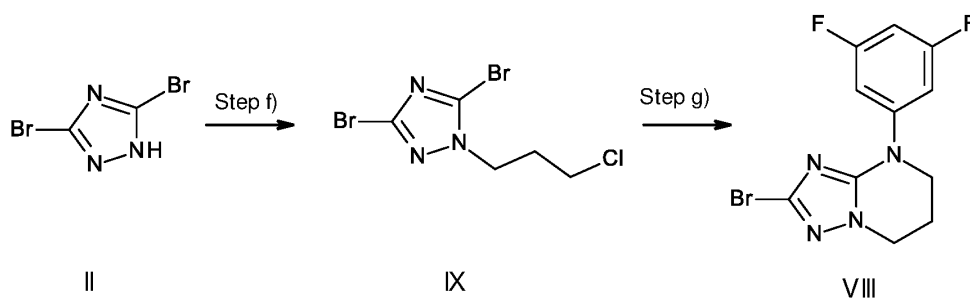
via the internal Mitsunobu cyclization reaction of compound (VII).

Compound (VIII) is cyclization in the presence of DEAD, PPh₃ with a suitable volume of solvent.

20 The suitable solvent is selected from DMSO, NMP, and DMF; preferably, the solvent is DMF.

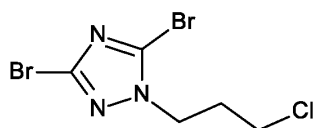
5 The suitable volume of solvent is from 5 V to 10 V; preferably the volume is about 5 V.

Scheme 2



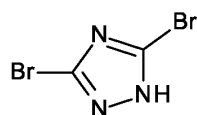
The synthesis comprises the following steps:

step f) the formation of compound (IX),



(IX),

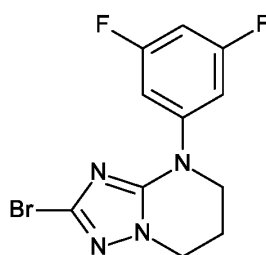
via the reaction of compound (II),



(II),

and 1-chloro-3-iodo-propane.

step g) the formation of compound (VIII),



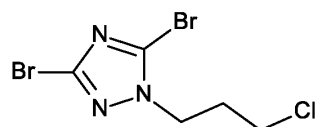
-13-

5 (VIII),

via telescope alkylation reaction from compound (IX) and 3,5-difluoroaniline.

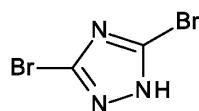
A detailed description of Steps f)-g) is as follows:

Step f) the formation of compound (IX),

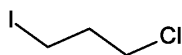


10 (IX),

via the reaction of compound (II),



(II),



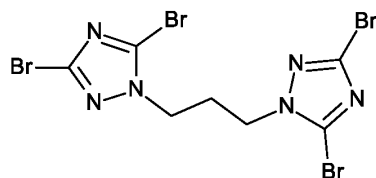
and 1-chloro-3-iodo-propane .

15 Compound of formula (IX) is synthesized in the presence of a suitable solvent with a suitable base.

The suitable solvent is selected from MeTHF and THF; preferably, the solvent is THF.

The suitable base is selected from KOAc, NaOAc, NaOH, KOH, K₂CO₃ and Na₂CO₃; preferably, the suitable base is K₂CO₃.

20 The reaction is performed at 0 °C ~ 70 °C, preferably at 20 °C ~ 30 °C, more preferably at 20 °C ~ 25 °C.

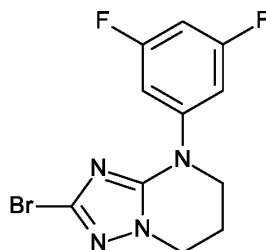


Dimer

was detected while dibromopropane or dichloropropane was employed as alkylation reagent, which are unsuitable for large scale

5 manufacture due to poor selectivity. In present invention, 1-chloro-3-iodo-propane was employed to provide compound (IX), which can be controlled well to avoid the dimer impurity in large-scale manufacture.

Step g) the formation of compound (VIII),



10 (VIII),

via telescope alkylation reaction from compound (IX) and 3,5-difluoroaniline.

Compound (VIII) is synthesized in a suitable solvent with a suitable base.

The suitable solvent is selected from 2-MeTHF, DCM and THF; preferably, the solvent is 2-MeTHF.

15 The suitable base is selected from NaHMDS, K₂CO₃, KOH, NaOH, NaH and LiHMDS; preferably, the base is LiHMDS.

The suitable equivalent of base is from 1.0 eq to 3.75 eq; preferably, the equivalent is 1.0 eq, 1.2 eq, 1.5 eq or 3.75 eq; more preferably, the equivalent is 3.75 eq.

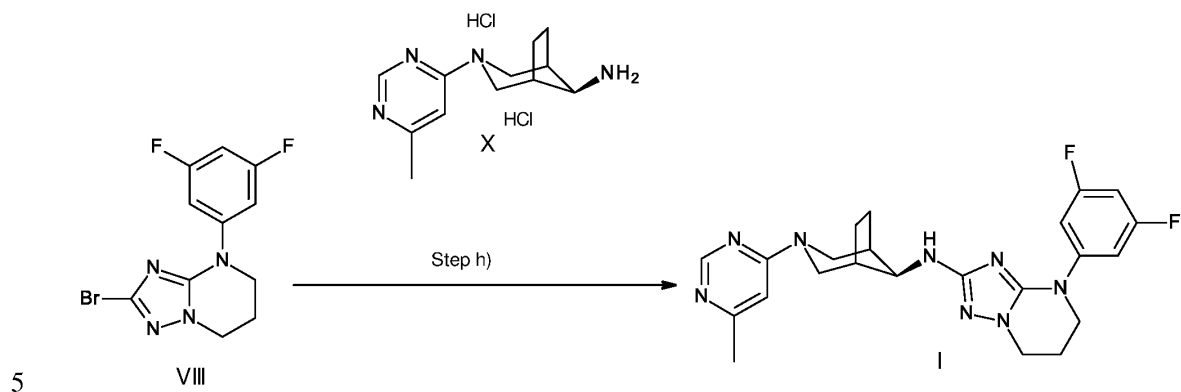
20 The suitable equivalent of 3,5-difluoroaniline is from 1.0 eq to 1.5 eq, preferably, the equivalent is selected from 1.0 eq, 1.2 eq and 1.5 eq; preferably, the equivalent is 1.2 eq.

The reaction is performed at - 20 °C ~ 70 °C, preferably at 0 °C ~ 25 °C, more preferably first at 0 °C ~ 5 °C, then at 20 °C ~ 25 °C.

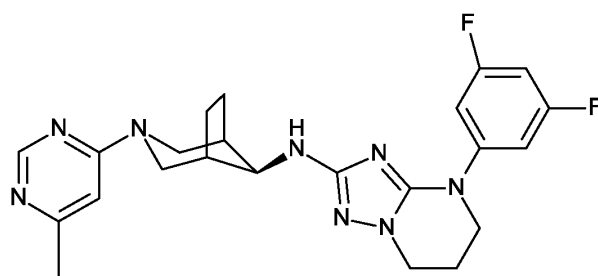
Temperature is critical for the whole process in terms of cyclization. In present invention, step g) can be run for 2 stages, which are telescoped without solid isolation. The temperature for
25 step g) of present invention gives high yield and good purge effect for impurities.

Scheme 3

-15-



Step h) the formation of compound (I),



10

(I),

via Buchwald cross coupling reaction of compound (VIII) and compound (X) (prepared according to the process described in WO 2019141832).

A detailed description of Step h) is as following:

15 Compound (I) in this step is synthesized via Buchwald cross coupling reaction in the presence of a suitable catalyst, base and ligand in a suitable solvent. The compound (I) is purified through recrystallization which was performed in a suitable solvent.

The suitable catalyst used in cross coupling reaction is selected from $\text{Pd}_2(\text{dba}_3) \cdot \text{CHCl}_3$, $\text{Pd}(\text{OAc})_2$; preferably, the catalyst is $\text{Pd}_2(\text{dba}_3) \cdot \text{CHCl}_3$.

20 The suitable base used in cross coupling reaction is selected from Na_2CO_3 , K_2CO_3 , NaHCO_3 , KHCO_3 , NaOH , KOH and NaOtBu ; preferably, the base is NaOtBu .

5 The suitable solvent used in cross coupling reaction is selected from IPAc, EtOAc, MTBE, toluene, THF and 2-MeTHF; preferably, the solvent is 2-MeTHF.

The cross coupling reaction is performed in a suitable solvent at 20 °C ~ 80 °C, preferably at 70 °C ~ 75 °C.

The ligand is selected from BrettPhos, AdCyBrettPhos, tBuBrettPhos, AdBrettPhos, 10 RocPhos, tBuXphos, BippyPhos, Me₄tBuXphos and Me₃MeOtBuXphos, preferably, the ligand is tBuXphos.

The recrystallization is performed in a suitable solvent at 20 °C ~ 80 °C, preferably at 70 °C ~ 75 °C; wherein the suitable solvent is selected from heptane, hexane and petroleum ether; preferably, the solvent is heptane; more preferably, the solvent is n-heptane.

15 For recrystallization, the pH of the solution was adjusted to 3 ~ 8; preferably, the pH of the solution was first adjusted to 3 ~ 4 to get a clear solution and then to 7 ~ 8.

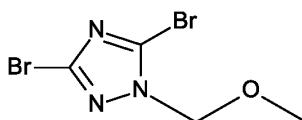
The recrystallization condition in this invention can produce high yield product with good purge effect for impurities and excess residual solvent.

EXAMPLES

20 The invention will be better understood by reference to the following examples. They
should not, however, be construed as limiting the scope of the invention.

Example 1

3,5-dibromo-1H-1,2,4-triazole (compound (III))



(III)

To a THF (3.5 L) solution of NaH (125 g, 3.11 mol, 1.1 eq.) in a 10 L glass-lined reactor was charged with 3, 5-dibromo-1H-1, 2,4-triazole (641 g, 2.83 mol) in portions slowly at 0 ~ 5 °C. After being stirred for 1 hours at 0 ~ 5 °C, the MOMchloride (275 g, 3.40 mol) was added dropwise to the mixture at 0 °C. The mixture was stirred at 20 ~ 25 °C for 16 hours. Ice water (6.5 kg, 10 v) was added dropwise to quench the reaction mixture at 0 ~ 5 °C and then extracted with

30 kg, 10 v) was added dropwise to quench the reaction mixture at 0 ~ 5 °C and then extracted with

- 5 EA (6.5 L) 3 times. The combined organic layer was washed with water (6.5 kg) and 20% wt NaCl aqueous solution (6.5 kg), then concentrated to afford compound (III) (613 kg, 80% yield, 99.4% purity).

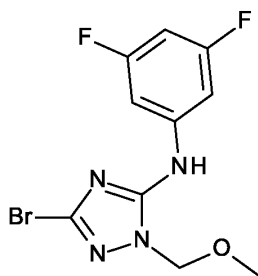
Compound (III): ^1H NMR (400 MHz, CDCl_3) δ = 5.44 (s, 2H), 3.47 (s, 3H).

$[\text{M}+\text{H}]^+ = 269.8$

10

Example 2

5-bromo-N-(3,5-difluorophenyl)-2-(methoxymethyl)-1,2,4-triazol-3-amine (compound (IV))



(IV)

- To an anhydrous THF (3 L) solution of compound (III) (613 g, 2.3 mol) in 10 L glass-lined
15 reactor was charged with 3,5-difluoroaniline (741 g, 5.75 mol, 2.5 eq.) at 20 ~ 25 °C. After being stirred for 30 min and cooled to 0 ~ 5 °C, LiHMDS (1M in THF, 4.6 L, 4.6 mol, 2.0 eq.) was added dropwise at 0 ~ 5 °C. The reaction mixture was allowed warm to 25 ~ 30 °C with stirring for another 16 hours. Saturated aqueous NH_4Cl solution (6.1 kg, 10 v) was added dropwise to the reaction mixture to quench the reaction at 0 ~ 5 °C and then extracted with EA (6.5 L) 3 times.
20 The combined organic layer was washed with water (6.5 kg) and 20 % wt NaCl aqueous solution (6.5 kg), then concentrated under vacuum. Petroleum (3.2 kg) was added to the reaction mixture, and then slurred for 1 h at 20 ~ 25 °C. The solid was separated via filtration and was washed with petroleum (1 kg). The filtrate was dried in vacuum oven (30 mmHg, 40 °C) for 32 hours to afford compound (IV) (541 g, 75% yield, 98.8% purity).

- 25 **Compound (IV):** ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 7.14 - 7.11 (t, 1H), 6.94 (s, 1H), 5.40 (s, 2H), 3.46 (s, 1H).

$[\text{M}+\text{H}]^+ = 320.8$

- A series of studies were carried out to demonstrate the impact of reaction temperature, which showed that 25 ~ 30 °C is the best condition for the alkylation reaction. In addition, 2.0
30 equivalent of LiHMDS and 2.5 equivalent of 3,5-difluoroaniline provide better result.

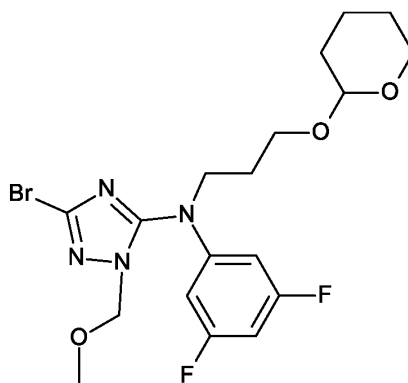
-18-

Test No.	LiHMDS	3,5-Difluoroaniline	temperature	Remaining Compound (III)
1	2.0 eq.	2.5 eq.	25 °C ~ 30°C	0.9%
2	1.5 eq.	1.5 eq.	5 °C ~ 10°C	13.6%
3	2.0 eq.	2.0 eq.	5 °C ~ 10°C	7.1%
4	2.0 eq.	2.0 eq.	25 °C ~ 30°C	5.2%

5

Example 3

5-bromo-N-(3, 5-difluorophenyl)-2-(methoxymethyl)-N-(3-tetrahydropyran-2-yloxypropyl)-1, 2, 4-triazol-3-amine (compound (VI))



(VI)

10

To a DMF (4000 mL) solution of compound (IV) (843 g, 2.64 mol) in 10 L glass-lined reactor was charged with K_2CO_3 (750 g, 5.43 mol, 2.06 eq.) and 2-(3-Bromopropoxy)tetrahydropyran (1000 g, 4.48 mol, 1.7 eq.) at 20 ~ 25 °C and stirred for 16 hours. The resulting reaction mixture was cooled to 0 ~ 5 °C. Water (3 kg) was added to the reaction mixture and then extracted with EA (6.5 L) 3 times. The combined organic layers were washed with water (6.5 kg) and 20% wt NaCl aqueous solution (6.5 kg), then concentrated to afford compound (VI) (1.51 kg, 100% yield, 94.0% purity) as brown oil, the oil was be used in the next step without further purification.

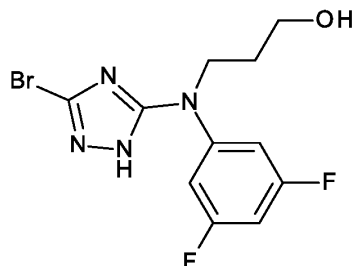
15

Compound (VI): 1H NMR (400 MHz, $DMSO-d_6$) δ = 6.54 – 6.47 (dd, 2H), 5.02 (s, 1H), 4.60-4.58 (d, 2H), 3.97-3.81 (m, 5H), 3.64-3.45 (m, 3H), 3.36 (s, 3H), 1.99 - 1.56 (m, 13H).

20

Example 4

5 **3-(N-(3-bromo-1H-1, 2, 4-triazol-5-yl)-3, 5-difluoro-anilino)propan-1-ocarbamate**
(compound (VII))



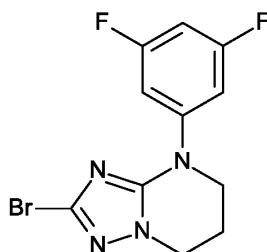
(VII)

To a 20 L glass-lined reactor was charged with compound (VI) (1510 g), methanol (6000 mL), hydrochloride acid (2.4 L) and water (2.4 L) at 20 ~ 25 °C, then the mixture was heated to 70 ~ 75 °C and stirred for 5 hours. The resulting reaction mixture was cooled to at 20 ~ 25 °C, concentrate to remove the methanol, and then adjusted the residue to pH = 8 ~ 9 with 4N aq. NaOH (6.9 L). The resulting reaction mixture was extracted with EA (15 L) twice. The combined organic layers was washed with brine with 20 % wt NaCl aqueous solution (20 L), dried through
15 Mg_2SO_4 , concentrated to remove the solvent. To the resulting reaction mixture was added EA (2 L), then heated to 50 ~ 55 °C, then heptane (6 L) was added dropwise to the reaction mixture, and then cooled to 20 ~ 25 °C during 6 h and stirred for another 1h. The solid was separated via filter and washed with EA/Heptane (1/3, 500 mL), and dried in vacuum (30 mmHg, 40 °C) for 16 hours to afford compound (VII) (621 g, 70% yield, 99.0% purity) as white solid.

20 **Compound (VII):** ^1H NMR: (400 MHz, CDCl_3) δ ppm: 12.17-10.22 (s, 1H), 6.90-6.88 (dd, 2H), 6.66-6.60 (t, 1H), 4.03-3.99 (t, 2H), 3.71-3.68 (d, 2H), 1.88-1.85 (t, 2H).

Example 5

25 **2-bromo-4-(3,5-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine**
(compound (I))



(VIII)

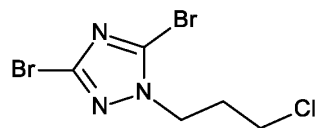
-20-

5 To a 10 L glass line reactor was charged with compound (VII) (621 g, 1.86 mol), DMF (4 L), PPh₃ (800 g, 3.05 mol, 1.64 eq.) at 20 ~ 25 °C. The resulting mixture was cooled to - 20 ~ 10 °C, then DEAD (500 g, 2.87 mol) was added dropwise into mixture at - 20 ~ - 10 °C and stirred for 3 hours. Water (6.21 kg, 10 v) was added dropwise to the reaction mixture to quench the reaction at 0 ~ 5 °C and then extracted with EA (6.5 L) 3 times. The combined organic layers
10 was washed with 20% wt NaCl aqueous solution (10 L), dried through Mg₂SO₄, concentrated to remove the solvent. The resulting residual was diluted with MeOH (6.2 L, 10 V) at 20 ~ 25 °C and stirred for 1 hours, then the solid was separated via filter and rinsed with MeOH (600 mL). The resulting residual was diluted with EA (6.2 L, 10 V) at 20 ~ 25 °C, then heated to 70 ~ 75 °C and stirred for 1 hours. The resulting mixture was cooled to 20 ~ 25 °C, then the solid was
15 separated via filter and rinsed with EA (600 mL). The resulting cake was dried in vacuum oven (30 mmHg, 40 °C) for 16 hours to afford compound (I) (287 g, 48.0% yield, 98.0% purity) as white solid.

Compound (VIII): ¹H NMR (400 MHz, DMSO-d₆) δ = 7.39-7.34 (m, 2H), 6.97-6.92 (m, 20 1H), 4.11-4.08 (m, 2H), 3.85-3.83 (m, 2H), 2.26-2.20 (m, 2H).

Example 6

3,5-dibromo-1H-1,2,4-triazole (compound IX)

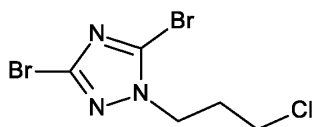


To a 250 mL reactor were charged 3,5-dibromo-1H-1,2,4-triazole (10 g, 44.1 mmol, Eq: 25 1); THF (88 g, 100 mL); potassium carbonate (12.2 g, 88.2 mmol, Eq: 2.0) and 1-chloro-3-iodopropane (11 g, 53.8 mmol, Eq: 1.22). The mixture was stirred for 16 hours at 20 °C ~ 25 °C. Water (100 mL) was added to the reaction mixture and then extracted with EA (100 mL). The combined organic layers were washed with 20 % wt NaCl aqueous solution (50 mL), dried through Mg₂SO₄, then concentrated to remove the solvent to afford compound (IX). The crude
30 will used for next step without further purification.

Example 7

3,5-dibromo-1H-1,2,4-triazole (compound IX)

-21-



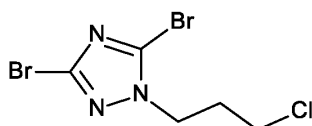
5

To a 250 mL reactor were charged 3,5-dibromo-1H-1,2,4-triazole (35 g, 154 mmol, Eq: 1); THF (88 g, 350 ml; potassium carbonate (42.6 g, 309 mmol, Eq: 2.0) and 1-chloro-3-iodopropane (31.5 g, 154 mmol, Eq: 1) at 20 °C ~ 25 °C and stirring for 48 hours. Water (300 mL) was added to the reaction mixture and then extracted with 2-MeTHF (150 mL). The combined organic layers were washed with 20 % wt NaCl aqueous solution (150 mL), dried through Mg₂SO₄, then concentrated to remove the solvent to afford compound (IX) (54.5 g, 78.94% purity GC-MS, 91.9% yield). The crude will used for next step without further purification.

10

Example 8

15 3,5-dibromo-1H-1,2,4-triazole (compound IX)

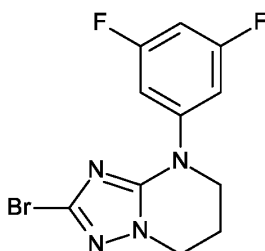


20

To a 2 L reactor were charged 3,5-dibromo-1H-1,2,4-triazole (110 g, 475 mmol, Eq: 1); THF (880 g, 1 L); potassium carbonate (134 g, 950 mmol, Eq: 2.0) and 1-chloro-3-iodopropane (129 g, 618 mmol, Eq: 1.3) at 20 °C ~ 25 °C and stirring for 48 hours. Water (550 mL) was added to the reaction mixture and then separated, then the organic layer was washed with 20 % wt NaCl aqueous solution (225 mL), dried through Mg₂SO₄, then concentrated to remove the solvent to afford compound (IX) (165 g, 81 % purity (GC-MS), 92.7 % yield). The crude will used for next step without further purification.

Example 9

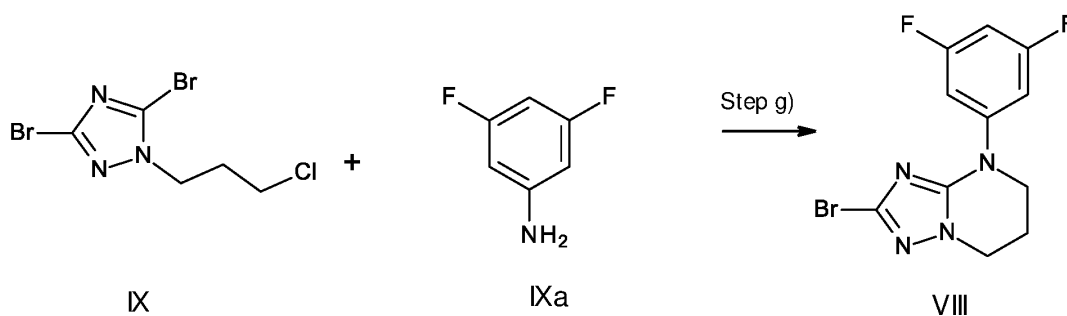
25 2-bromo-4-(3,5-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (compound (VIII))



5 To a 500 mL glass-lined reactor was charged with 3,5-difluoroaniline (5.79 g, 44.9 mmol, 1.2 eq.) , compound (IX) (14 g, 37.4 mmol, 1.0 eq.) and 2-MeTHF (140 mL) at 20 °C ~25 °C. After being stirred for 30 min and cooled to 0 ~ 5 °C, LiHMDS (1M in THF, 140 mL, 140 mmol, 3.75 eq.) was added dropwise at 0 °C ~ 5 °C. The reaction mixture was allowed warm to 20 °C ~ 25 °C with stirring for another 1 hours. Saturated aqueous NH₄Cl solution (200 mL, 10 v) was
10 added dropwise to the reaction mixture to quench the reaction at 20 ~ 25 °C and then 20 % wt NaCl aqueous solution (100 mL) was added to the reaction at 20 ~ 25 °C and stirred for 1 hours. The resulting mixture was extracted with EA (200 mL). The combined organic layer was washed with 20 % wt NaCl aqueous solution (100 mL), dried through Mg₂SO₄, then concentrated to remove the solvent. To the resulting reaction mixture was added EA (50 mL), then heated to
15 50 °C ~ 55 °C, then heptane (150 mL) was added dropwise to the reaction mixture, and then cooled to 20 °C ~ 25 °C during 6 h and stirred for another 1h. The solid was separated via filter and washed with EA/Heptane (1/3, 10 mL), and dried in vacuum oven (30 mmHg, 40 °C) for 32 hours to afford compound (IV) (8 g, 67.2 % yield, 99.0 % purity) as grey solid.

Compound (VIII): ¹H NMR (400 MHz, DMSO-d₆) δ =7.39-7.34 (m, 2H), 6.97-6.92 (m, 1H), 4.11-4.08 (m, 2H), 3.85-3.83 (m, 2H), 2.26-2.20 (m, 2H).
20

A series of studies were carried out to demonstrate the impact of reaction temperature and equivalent of aniline compound (IXa), which showed that 0 °C ~ 25 °C and 1.2 eq of compound (IXa) are the best condition for this cyclization reaction:



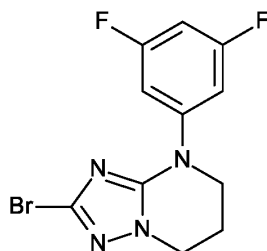
-23-

Test #	Aniline compound (IXa)	Base	Temperature	Result
1	1.0 eq.	LiHMDS (3 eq.)	0 °C ~ 5 °C	64% Conversion
2	1.2 eq.	LiHMDS (3 eq.)	0 °C ~ 5 °C, then 20 °C ~ 25 °C	81% Conversion
3	1.5 eq.	LiHMDS (3 eq.)	0 °C ~ 5 °C	100% Conversion, byproducts formed
4	1.2 eq.	LiHMDS (2.5 eq.)	0 °C ~ 5 °C	91% Conversion, byproducts formed
5	1.2 eq.	LiHMDS (4.0 eq.)	0 °C ~ 5 °C	100% Conversion, byproducts formed
7	1.2 eq.	NaHMDS (3.0 eq.)	- 20 °C ~ -10 °C	69% Conversion
8	1.2 eq.	NaHMDS (3.0 eq.)	0 °C ~ 5 °C	96% Conversion, byproducts formed
9	1.2 eq.	NaHMDS (3.0 eq.)	20 °C ~ 25 °C	100% Conversion, byproducts formed
10	1.2 eq.	NaHMDS (3.6 eq.)	0 °C ~ 5 °C then 20 °C ~ 25 °C	100% Conversion, byproducts formed

5

Example 10

2-bromo-4-(3,5-difluorophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidine (compound (VIII))



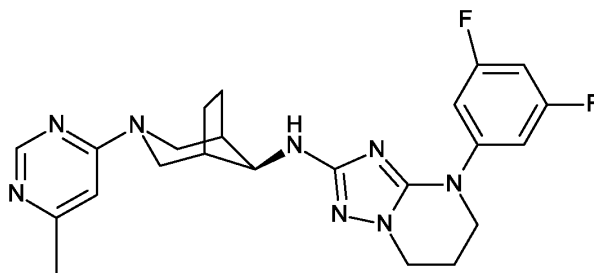
10

5 To a 3 L glass-lined reactor was charged with 3,5-difluoroaniline (69.6 g, 529 mmol, 1.2 eq.), compound (IX) (165 g, 441 mmol, 1.0 eq.) and 2-MeTHF (825 mL) at 20 °C ~ 25 °C. After being stirred for 30 min and cooled to 0-5 °C, LiHMDS (1.9 M in THF, 835 mL, 1.59 mol, 3.6 eq.) was added dropwise at 0 °C ~ 5 °C. The reaction mixture was allowed warm to 20 °C ~ 25 °C with stirring for another 1 hours. Saturated aqueous NH₄Cl solution (2 L, 10 v) was added
 10 dropwise to the reaction mixture to quench the reaction at 20-25 °C and then 20 % wt NaCl aqueous solution (1 L) was added to the reaction at 20-25 °C and stirred for 1 hours. The resulting mixture was extracted with EA (2000 mL). The combined organic layer was washed with 20 % wt NaCl aqueous solution (1 L), dried through Mg₂SO₄, then concentrated to remove the solvent. To the resulting reaction mixture was added EA (500 mL), then heated to 50 °C ~ 55
 15 °C, then heptane (1.5 L) was added dropwise to the reaction mixture, and then cooled to 20 °C ~ 25 °C during 6 h and stirred for another 1h. The solid was separated via filter and washed with EA/Heptane (1/1, 100 mL), and dried in vacuum oven (30 mmHg, 40 °C) for 32 hours to afford compound (IV) (94 g, 67.7 % yield, 98.8 % purity) as grey solid.

Compound (VIII): ¹H NMR (400 MHz, DMSO-d₆) δ = 7.39-7.34 (m, 2H), 6.97-6.92 (m, 1H), 4.11-4.08 (m, 2H), 3.85-3.83 (m, 2H), 2.26-2.20 (m, 2H).

Example 11

4-(3,5-difluorophenyl)-N-[3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine (compound (I))



25

To a 50 mL One-neck flask was charged with NaOtBu (1.2 g, 12.4 mmol, Eq: 4), 2-MeTHF (10.2 g, 120 ml, 10 V), (1R,5S,8S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-amine dihydrochloride (1.06 mg, 3.42 mmol, Eq: 1.1) in one portion under N₂ at 20 °C ~ 25 °C. And then, to the resulting mixture were charged compound (VIII) (1 g, 3.11 mmol, Eq: 1); Pd₂dba₃·CHCl₃ (32.2 mg, 31 μmol, Eq: 0.01) and tBuXphos (26.4 mg, 62.2 μmol, Eq: 0.02) at 20 °C ~ 25 °C. The resulting mixture was heated to ~75 °C and stirred for 2
 30 hours. The resulting mixture was cooled to 20 °C ~ 25 °C, water (10 mL) and MeOH (10 mL)

-25-

5 was added, and then extracted with 2-MeTHF (25 mL) twice. The combined organic layer was filter through MCC pad, then concentrated to remove solvents. To the residual was added 2-MeTHF (5 mL), and then the reaction mixture was heated to 20 °C ~ 25 °C. Hpetane (15 mL) was added dropwise to the reaction mixture, then cooled to 20 °C ~ 25 °C and stirred for another 10 hours. The product was collected via filter and washed with heptane (2 ml), and dried in vacuum oven (30 mmHg, 40 °C) for 16 hours to afford compound (IV) (1.1 g, 77.5 % yield, 98.8 % purity).

Compound (VI): ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.35 (s, 1 H), 7.45 (dd, J = 10.6, 2.0 Hz, 2 H), 6.78 - 6.86 (m, 1 H), 6.63 (s, 1 H), 5.84 (d, J = 4.1 Hz, 1 H), 3.96 - 4.41 (m, 2 H), 3.93 (t, J = 6.0 Hz, 2 H), 3.75 - 3.81 (m, 2 H), 3.54 (d, J = 4.1 Hz, 1 H), 2.96 (br d, J = 12.1 Hz, 2 H), 2.44 (br s, 2 H), 2.25 (s, 3 H), 2.19 (quin, J = 5.8 Hz, 2 H), 1.83 - 1.88 (m, 2 H), 1.27 - 1.33 (m, 2 H).

¹³C NMR (101 MHz, DMSO-d₆) δ ppm 21.85 (s, 1 C), 24.20 (s, 1 C), 25.74 (s, 2 C), 38.73 (s, 2 C), 43.86 (s, 1 C), 45.64 (s, 1 C), 50.63 (s, 2 C), 62.08 (s, 1 C), 97.20 (t, J = 26.41 Hz, 1 C), 101.92 (s, 1 C), 102.81 (d, J = 29.34 Hz, 2 C), 145.80 (t, J = 13.94 Hz, 1 C), 149.51 (s, 1 C), 157.61 (s, 1 C), 160.39 (s, 1 C), 162.79 (dd, J = 242.09, 16.14 Hz, 2 C), 163.20 (s, 1 C), 164.75 (s, 1 C)

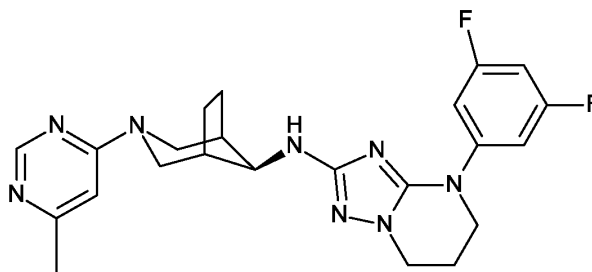
¹⁹F NMR (376 MHz, DMSO-d₆) δ = -110.00-1110.13 (m, 2F)

[α]_D²⁵ = 0.199 °

HRMS: calculated 453.225 [C₂₃H₂₆F₂N₈+H]⁺, found 453.2354 [M+H]⁺

Example 12

4-(3, 5-difluorophenyl)-N-[3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3. 2. 1]octan-8-yl]-6, 7-dihydro-5H-[1, 2, 4]triazolo[1, 5-a]pyrimidin-2-amine (compound (I))



5 To a 250 mL One-neck flask was charged with NaOtBu (12 g, 124 mmol, Eq: 4), 2-MeTHF (102 g, 120 ml, 10 V), (1R,5S,8S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-amine dihydrochloride (10.7 g, 34.2 mmol, Eq: 1.1) in one portion under N₂ at 20 °C ~ 25 °C. And then, to the resulting mixture were charged compound (VIII) (10 g, 31.1 mmol, Eq: 1); Pd₂dba₃·CHCl₃ (322 mg, 311 μmol, Eq: 0.01) and tBuXphos (264 mg, 622 μmol, Eq: 0.02) at
10 20 °C ~ 25 °C. The resulting mixture was heated to 75 °C and stirred for 2 hours. The resulting mixture was cooled to 20 °C ~ 25 °C, water (100 mL) and MeOH (100 mL) was added, and then extracted with 2-MeTHF (250 mL) twice. The combined organic layer was filter through MCC (Microcrystalline Cellulose) pad, then concentrated to remove solvents. To the residual was added 2-MeTHF (50 mL), and then the reaction mixture was heated to 20 °C ~ 25 °C. Heptane
15 (150 mL) was added dropwise to the reaction mixture, then cooled to 20 °C ~ 25 °C and stirred for another 10 hours. The product was collected via filter and washed with heptane (20), and dried in vacuum oven (30 mmHg, 40 °C) for 16 hours to afford compound (I) (12 g, 85 % yield, 98.1 % purity).

20 **Compound (I):** ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.35 (s, 1 H), 7.45 (dd, J = 10.6, 2.0 Hz, 2 H), 6.78 - 6.86 (m, 1 H), 6.63 (s, 1 H), 5.84 (d, J = 4.1 Hz, 1 H), 3.96 - 4.41 (m, 2 H), 3.93 (t, J = 6.0 Hz, 2 H), 3.75 - 3.81 (m, 2 H), 3.54 (d, J = 4.1 Hz, 1 H), 2.96 (br d, J = 12.1 Hz, 2 H), 2.44 (br s, 2 H), 2.25 (s, 3 H), 2.19 (quin, J = 5.8 Hz, 2 H), 1.83 - 1.88 (m, 2 H), 1.27 - 1.33 (m, 2 H).

25 ¹³C NMR (101 MHz, DMSO-d₆) δ ppm 21.85 (s, 1 C), 24.20 (s, 1 C), 25.74 (s, 2 C), 38.73 (s, 2 C), 43.86 (s, 1 C), 45.64 (s, 1 C), 50.63 (s, 2 C), 62.08 (s, 1 C), 97.20 (t, J = 26.41 Hz, 1 C), 101.92 (s, 1 C), 102.81 (d, J = 29.34 Hz, 2 C), 145.80 (t, J = 13.94 Hz, 1 C), 149.51 (s, 1 C), 157.61 (s, 1 C), 160.39 (s, 1 C), 162.79 (dd, J = 242.09, 16.14 Hz, 2 C), 163.20 (s, 1 C), 164.75 (s, 1 C)

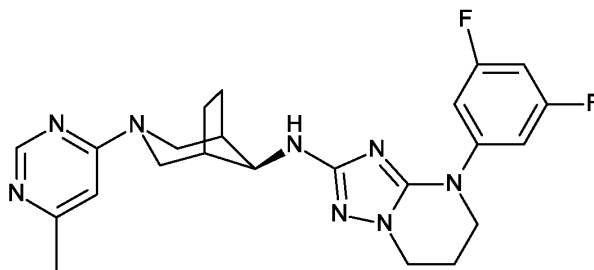
30 ¹⁹F NMR (376 MHz, DMSO-d₆) δ = -110.00-1110.13 (m, 2F)
[α]_D²⁵ = 0.199°

HRMS: calculated 453.225 [C₂₃H₂₆F₂N₈+H]⁺, found 453.2354 [M+H]⁺

35

Example 13

5 **4-(3,5-difluorophenyl)-N-[3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-yl]-6,7-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine (compound (I))**



To a 5 L 3-neck flask was charged with NaOtBu (191 g, 1.99 mol, Eq: 4), 2-MeTHF (1.6 L,
10 10 V), (1R,5S,8S)-3-(6-methylpyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-8-amine
dihydrochloride (171 g, 547 mmol, Eq: 1.1) in one portion under N₂ at 20 °C ~ 25 °C. And then,
to the resulting mixture were charged compound (VIII) (160 g, 498 mmol, Eq: 1);
Pd₂(dba)₃·CHCl₃ (4.56 g, 4.98 mmol, Eq: 0.01) and tBuXphos (4.23 g, 9.95 mmol, Eq: 0.02) at
20 °C ~ 25 °C. The resulting mixture was heated to 70 °C ~ 75 °C and stirred for 2 hours. To the
15 resulting mixture was added heptane (1.6 L) and then cooled to 20 °C ~ 25 °C. The crude solid
was collected via filter and rinsed with Hep/2-MeTHF (1:1, 150 mL). The resulting cake was
slurried with water and stirred for 2 hours at 20 °C ~ 25 °C. The crude solid was collected via
filter and rinsed with water (200 mL). The resulting cake was diluted with MeOH (400 mL) and
DCM (1L) in a 2 L reactor. Charcoal (20 g) was added to the suspension and was heated to 60 °C
20 ~ 65 °C with stirring for 2 hours, then cooled to 20 °C ~ 25 °C. The suspension was filtered
through celite, rinsed with MeOH/DCM (4:10, 100 mL). The filtrate was concentrated and the
residual was diluted with 2-MeTHF (500 mL), heated to 60 °C ~ 65 °C and stirred for 30 min.
Heptane (1500 mL) was added dropwise to the resulting mixture at 60 °C ~ 65 °C, then allowed
cooled to 60 °C ~ 65 °C and stirred for 10 hours. The crude was collected via filter and rinsed
25 with heptane (200 mL), then the cake was diluted with water (160 ml) and adjust pH to 3-4 with
HCl (36.5% wt., 129 mL). To the resulting reaction mixture was added NaOH (1M, 568 mL),
adjust pH back to 7-8, the resulting mixture was stirred at 1 hours at 20 °C ~ 25 °C. The product
was collected via filter and washed with heptane (20), and dried in vacuum oven (30 mmHg, 40
°C) for 16 hours to afford compound (I) (200 g, 87.9 % yield, 98.98 % purity).

30

Compound (I): ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.35 (s, 1 H), 7.45 (dd, J = 10.6, 2.0 Hz, 2 H), 6.78 - 6.86 (m, 1 H), 6.63 (s, 1 H), 5.84 (d, J = 4.1 Hz, 1 H), 3.96 - 4.41 (m, 2 H), 3.93 (t, J

-28-

5 = 6.0 Hz, 2 H), 3.75 - 3.81 (m, 2 H), 3.54 (d, J = 4.1 Hz, 1 H), 2.96 (br d, J = 12.1 Hz, 2 H), 2.44 (br s, 2 H), 2.25 (s, 3 H), 2.19 (quin, J = 5.8 Hz, 2 H), 1.83 - 1.88 (m, 2 H), 1.27 - 1.33 (m, 2 H).

¹³C NMR (101 MHz, DMSO-d₆) δ ppm 21.85 (s, 1 C), 24.20 (s, 1 C), 25.74 (s, 2 C), 38.73 (s, 2 C), 43.86 (s, 1 C), 45.64 (s, 1 C), 50.63 (s, 2 C), 62.08 (s, 1 C), 97.20 (t, J = 26.41 Hz, 1 C),
10 101.92 (s, 1 C), 102.81 (d, J = 29.34 Hz, 2 C), 145.80 (t, J = 13.94 Hz, 1 C), 149.51 (s, 1 C), 157.61 (s, 1 C), 160.39 (s, 1 C), 162.79 (dd, J = 242.09, 16.14 Hz, 2 C), 163.20 (s, 1 C), 164.75 (s, 1 C)

¹⁹F NMR (376 MHz, DMSO-d₆) δ = -110.00-1110.13 (m, 2F)

15

[α]_D²⁵ = 0.199 °

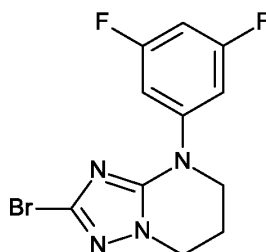
HRMS: calculated 453.225 [C₂₃H₂₆F₂N₈+H]⁺, found 453.2354 [M+H]⁺

20

5

Claims

1. A process for the preparation of a compound **(VIII)**,

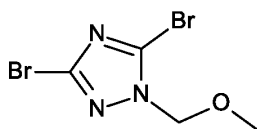


(VIII),

or pharmaceutically acceptable salt thereof, comprising the following steps:

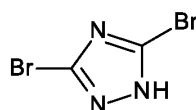
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step a) the formation of compound **(III)**,



(III),

via the reaction of compound **(II)**



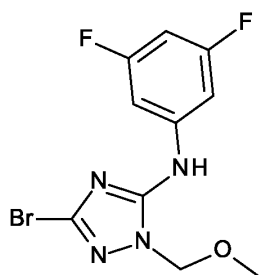
(II)

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and MOMChloride;

step b) the formation of compound **(IV)**,

-30-

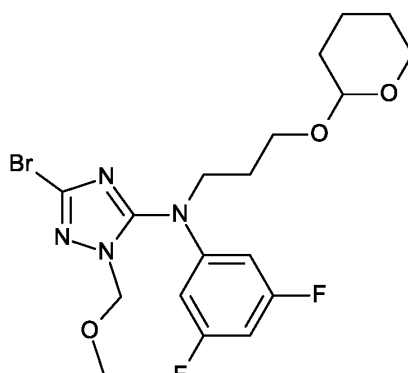


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(IV),

via alkylation reaction of compound (III) and 3,5-difluoroaniline;

step c) the formation of compound (VI),

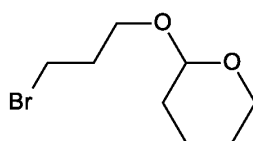


VI

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(VI),

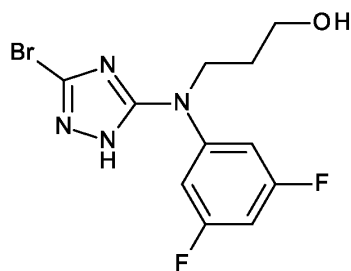
via the reaction of compound (IV) and compound (V)



(V);

step d) the formation of compound (VII),

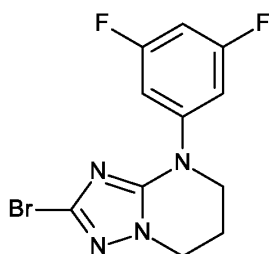
-31-



(VII),

via the de-protection reaction of compound (VI);

Step e) the formation of compound (VIII),



(VIII),

via the internal Mitsunobu cyclization reaction of compound (VII).

2. The process according to claim 1, characterized in that the formation of compound (III) in step a) is performed in the presence of a solvent, wherein the solvent is selected from DCM and THF; preferably, the solvent is THF.

3. The process according to claim 1 or claim 2, characterized in that the formation of compound (III) in step a) is performed in the presence of a base, wherein the base is selected from KOAc, NaOAc and NaH; preferably, the base is NaH.

4. The process according to any one of claims 1 to 3, characterized in that the formation of compound (IV) in step b) is performed in the presence of a solvent, wherein the solvent is selected from 2-MeTHF, DCM and THF; preferably, the solvent is THF.

5 5. The process according to any one of claims 1 to 4, characterized in that the formation of compound (IV) in step b) is performed in the presence of a base, wherein the base is selected from NaHMDS, K₂CO₃, KOH, NaOH, NaH and LiHMDS; preferably, the base is LiHMDS.

 6. The process according to claim 5, characterized in that the equivalent of the base is from 1.0 eq. to 2.5 eq.; preferably, the equivalent is selected from about 1.0 eq., about 1.2 eq., about
10 1.5 eq., about 2.0 eq. and about 2.5 eq.; more preferably, the equivalent is about 2.0 eq.

 7. The process according to any one of claims 1 to 6, characterized in that equivalent of 3,5-difluoroaniline is from 1.0 eq. to 2.5 eq.; preferably, the equivalent is selected from about 1.0 eq., about 1.2 eq., about 1.5 eq., about 2.0 eq. and about 2.5 eq.; more preferably, the equivalent is about 2.5 eq.

15 8. The process according to any one of claims 1 to 7, characterized in that the formation of compound (IV) in step b) is performed at -20 ~ 70 °C, preferably at 10 ~ 70 °C, more preferably at 25 ~ 30 °C.

 9. The process according to any one of claims 1 to 8, characterized in that the formation of compound (VI) in step c) is performed in the presence of a base, wherein the base is selected
20 from NaOH, Na₂CO₃, Cs₂CO₃ and potassium carbonate; preferably the base is potassium carbonate.

 10. The process according to claim 9, characterized in that the amount of base is from 2.0 eq. to 3.0 eq.; preferably, the amount is about 2.06 equivalent.

 11. The process according to any one of claims 1 to 10, characterized in that equivalent of
25 compound (V) is from 1.7 eq. to 2.26 eq.; preferably, the equivalent is 1.7 equivalent.

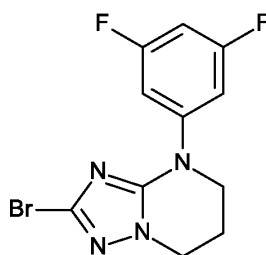
 12. The process according to any one of claims 1 to 11, characterized in that the formation of compound (VII) in step d) is performed in the presence of an acid, wherein the acid is selected from HBr, TFA and HCl; preferably the acid is HCl; more preferably the acid is HCl (36.5% wt.).

 13. The process according to claim 12, characterized in that the volume of acid is from 1 V
30 to 2 V; preferably, the volume is about 2 V.

5 14. The process according to any one of claims 1 to 13, characterized in that the formation of compound (VIII) in step e) is performed in the presence of DEAD, PPh₃ with a solvent, wherein the solvent is selected from DMSO, NMP, and DMF; preferably the solvent is DMF.

 15. The process according to claim 14, characterized in that the volume of solvent is from 5 V to 10 V; preferably the volume is about 5 V.

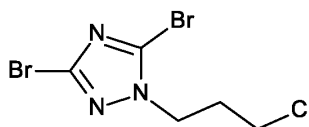
10 16. A process for the preparation of a compound (VIII),



(VIII),

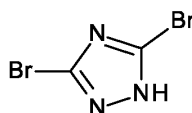
or pharmaceutically acceptable salt thereof, comprising the following steps:

step f) the formation of compound (IX),



(IX),

via the reaction of compound (II),

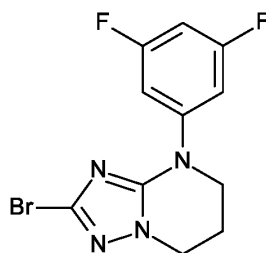


(II),

20 and 1-chloro-3-iodo-propane, and

step g) the formation of compound (VIII),

-34-



(VIII),

via telescope alkylation reaction from compound (IX) and 3,5-difluoroaniline.

17. The process according to claim 16, characterized in that the formation of compound (IX) in step f) is performed in the presence of a solvent, wherein the solvent is selected from MeTHF and THF; preferably, the solvent is THF.

18. The process according to claim 17 or claim 18, characterized in that the formation of compound (IX) in step f) is performed in the presence of a base, wherein the base is selected from KOAc, NaOAc, NaOH, KOH, K₂CO₃ and Na₂CO₃; preferably, the base is K₂CO₃.

19. The process according to any one of claims 16 to 18, characterized in that the formation of compound (IX) in step f) is performed at 0 ~ 70 °C, preferably at 20 ~ 30 °C, more preferably at 20 ~ 25 °C.

20. The process according to any one of claims 16 to 19, characterized in that the formation of compound (VIII) in step g) is performed in the presence of a solvent, wherein the solvent is selected from 2-MeTHF, DCM and THF; preferably, the solvent is 2-MeTHF.

21. The process according to any one of claims 16 to 20, characterized in that the formation of compound (VIII) in step g) is performed in the presence of a base, wherein the base is selected from NaHMDS, K₂CO₃, KOH, NaOH, NaH and LiHMDS; preferably, the base is LiHMDS.

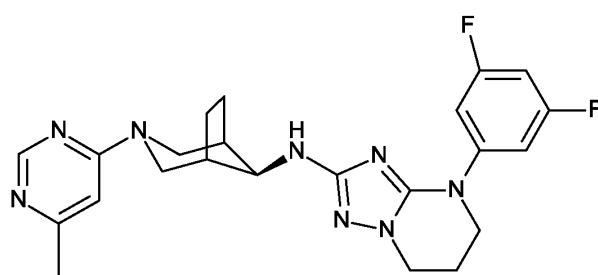
22. The process according to claim 21, characterized in that the amount of base is from 1.0 eq to 3.75 eq; preferably, the equivalent is 1.0 eq, 1.2 eq, 1.5 eq or 3.75 eq; more preferably, the equivalent is 3.75 eq.

-35-

- 5 23. The process according to any one of claims 16 to 22, characterized in that equivalent of 3,5-difluoroaniline is from 1.0 eq to 1.5 eq, preferably, the equivalent is selected from 1.0 eq, 1.2 eq and 1.5 eq; preferably, the equivalent is 1.2 eq.

24. The process according to any one of claims 16 to 23, characterized in that the formation of compound (VIII) in step g) is performed at -20 ~ 70 °C, preferably at 0 ~ 25 °C, more
10 preferably first at 0 °C ~ 5 °C, then at 20 °C ~ 25 °C.

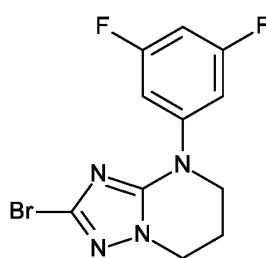
25. A process for the preparation of a compound (I),



(I),

or pharmaceutically acceptable salt thereof, comprising the following step:

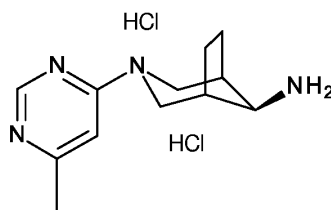
- 15 Step h) the formation of compound (I) via Buchwald cross coupling reaction of compound (VIII)



(VIII)

and compound (X)

-36-



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(X).

26. The process according to claim 25, characterized in that the formation of compound (I) in step h) is performed in the presence of a solvent, wherein the solvent is selected from IPAc, EtOAc, MTBE, toluene, THF and 2-MeTHF; preferably, the solvent is 2-MeTHF.

10 27. The process according to claim 25 or claim 26, characterized in that the formation of compound (I) in step h) is performed in the presence of a base, wherein the base is selected from Na_2CO_3 , K_2CO_3 , NaHCO_3 , KHCO_3 , NaOH , KOH and NaOtBu ; preferably, the base is NaOtBu .

15 28. The process according to any one of claim 25 to 27, characterized in that the formation of compound (I) in step h) is performed in the presence of a catalyst, wherein the catalyst is selected from $\text{Pd}_2(\text{dba}_3) \cdot \text{CHCl}_3$ and $\text{Pd}(\text{OAc})_2$; preferably, the catalyst is $\text{Pd}_2(\text{dba}_3) \cdot \text{CHCl}_3$.

29. The process according to any one of claims 25 to 28, characterized in that the formation of compound (I) in step h) is performed at $20\text{ }^\circ\text{C} \sim 80\text{ }^\circ\text{C}$, preferably at $70\text{ }^\circ\text{C} \sim 75\text{ }^\circ\text{C}$.

20 30. The process according to any one of claims 25 to claim 29, characterized in that the formation of compound (I) in step h) is performed in the presence of a ligand, wherein the ligand is selected from BrettPhos, AdCyBrettPhos, tBuBrettPhos, AdBrettPhos, RocPhos, tBuXphos, BippyPhos, $\text{Me}_4\text{tBuXphos}$ and $\text{Me}_3\text{MeOtBuXphos}$, preferably, the ligand is tBuXphos.

25 31. The process according to any one of claims 25 to 30, characterized in that the formation of compound (I) in step h) further comprising recrystallization in a solvent, wherein the solvent is selected from heptane, hexane and petroleum ether; preferably, the solvent is heptane; more preferably, the solvent is n-heptane.

32. The process according to claim 31, characterized in that the recrystallization is performed at $20\text{ }^\circ\text{C} \sim 80\text{ }^\circ\text{C}$, preferably at $70\text{ }^\circ\text{C} \sim 75\text{ }^\circ\text{C}$.

5 33. The process according to claim 31 or claim 32, characterized in that the pH of the solution was adjusted to 3 ~ 8, preferably the pH of the solution was first adjusted to 3 ~ 4, and then to 7 ~ 8.

 34. The process according to any one of claims 25 to 33, further comprising preparing compound (VIII) according to the process of any one of claims 1 to 15 or the process of any one
10 of claims 16 to 24.

 35. Compound (I) when manufactured according to the process of any one of claims 25 to 34.

 36. A pharmaceutical composition comprising the compound (I) of claim 35 and a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.

15 37. Compound (I) of claim 35 for the treatment or prophylaxis of a disease associated with the deposition of β -amyloid in the brain, in particular Alzheimer's disease, or a disease selected from cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis, Dutch-type (HCHWA-D), multi-infarct dementia, dementia pugilistica and Down syndrome.

 38. The use of compound (I) of claim 35 for the treatment or prophylaxis of a disease
20 associated with the deposition of β -amyloid in the brain, in particular Alzheimer's disease, or a disease selected from cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis, Dutch-type (HCHWA-D), multi-infarct dementia, dementia pugilistica and Down syndrome.

 39. The use of the compound (I) of claim 35 or the pharmaceutical composition of claim 36
25 for the manufacture of a medicament for the treatment or prophylaxis of a disease associated with the deposition of β -amyloid in the brain, in particular Alzheimer's disease, or a disease selected from cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis, Dutch-type (HCHWA-D), multi-infarct dementia, dementia pugilistica and Down syndrome.

 40. A method for the treatment or prophylaxis of a disease associated with the deposition of
30 β -amyloid in the brain, in particular Alzheimer's disease, or a disease selected from cerebral amyloid angiopathy, hereditary cerebral hemorrhage with amyloidosis, Dutch-type (HCHWA-D), multi-infarct dementia, dementia pugilistica and Down syndrome, which method comprises

-38-

- 5 administering a therapeutically effective amount of the compound (I) of claim 35 or the pharmaceutical composition of claim 36.