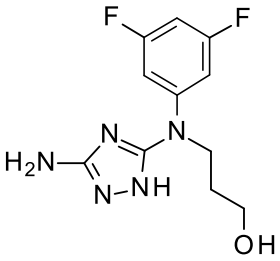
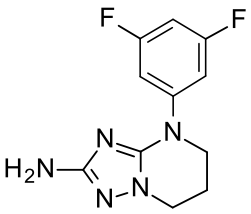
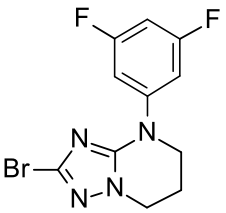
(b) column purification with tedious work up process for all of the intermediates, such as: intermediates , , , and the final product.

(c) safety concern with toxic reagent of hydrazine.

(d) use of high loading of expensive catalyst Pd (20%) which could result higher cost for large scale API production and complicated process to remove the catalyst.

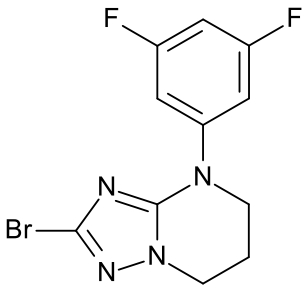
(e) high cost with HPLC separation.

(f) safety, repeatability, and scalability concerns for the newly form tri-azole ring during large-scale production.

SUMMARY

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

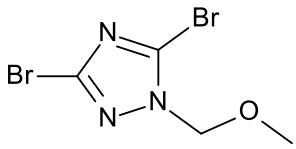
In one aspect, the present disclosure relates to a process for the preparation of a compound **(VIII)**,



(VIII),

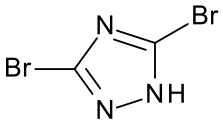
or pharmaceutically acceptable salt thereof, comprising the following steps:

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



(III),

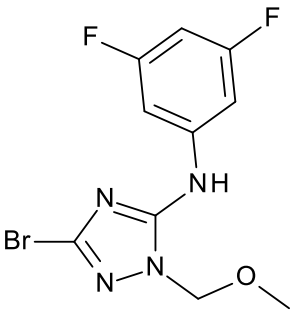
via the reaction of compound **(II)**



(**II**)

and MOMChloride;

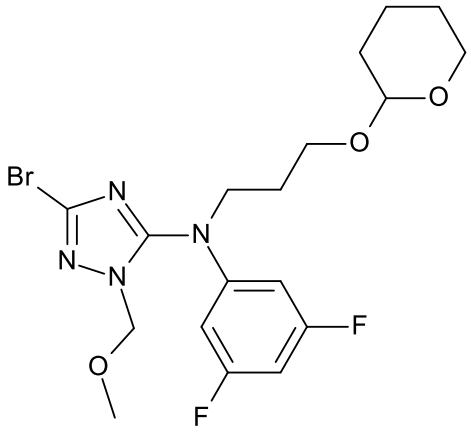
step b) the formation of compound **(IV),**



(IV),

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

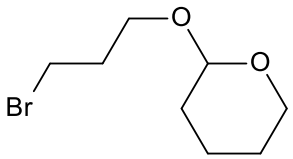
step c) the formation of compound **(VI),**



VI

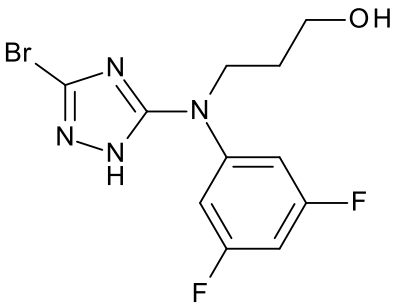
(VI),

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



(**V**);

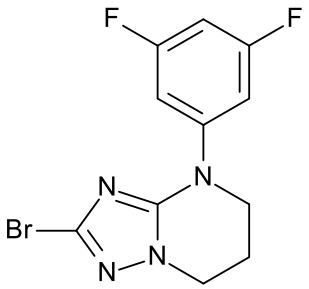
step d) the formation of compound **(VII)**,



(VII),

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

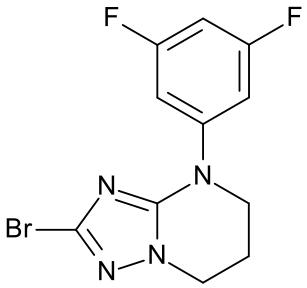
Step e) the formation of compound **(VIII),**



(VIII),

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

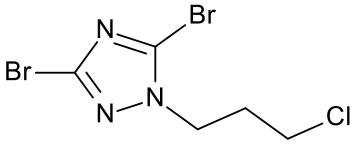
In another aspect, the present disclosure relates to a process for the preparation of a compound **(VIII)**,



(VIII),

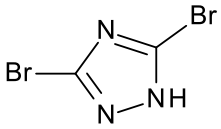
or pharmaceutically acceptable salt thereof, comprising the following steps:

step f) the formation of compound **(IX)**,



(IX),

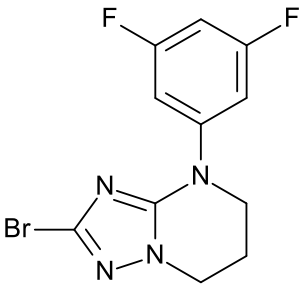
via the reaction of compound **(II)**,



(II),

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

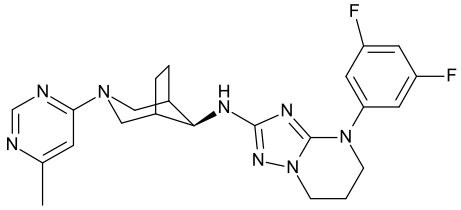
step g) the formation of compound **(VIII)**,



(VIII),

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

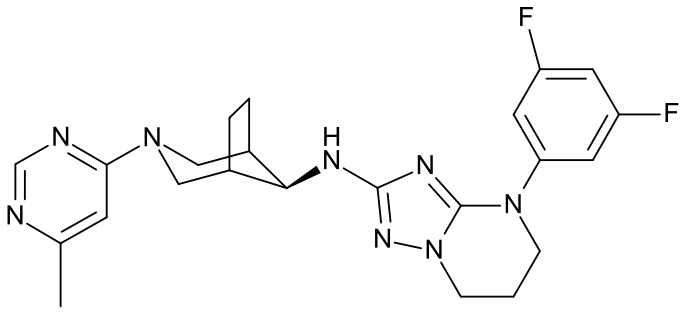
The present disclosure relates to a process for the preparation of compound **(I)**,



(I)

or pharmaceutically acceptable salt thereof.

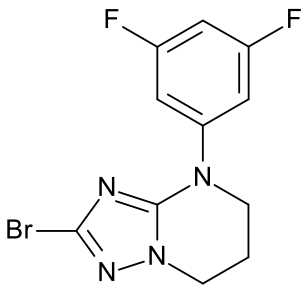
In another aspect, the present disclosure relates to a process for the preparation of a compound **(I)**,



(I),

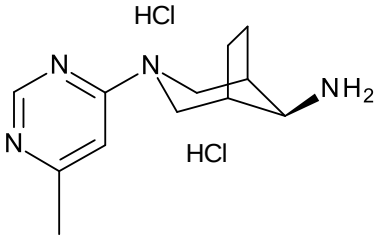
or pharmaceutically acceptable salt thereof, comprising the following step:

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



(VIII)

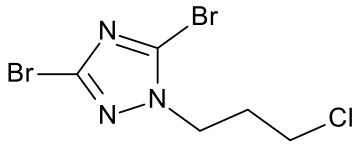
and compound **(X)**



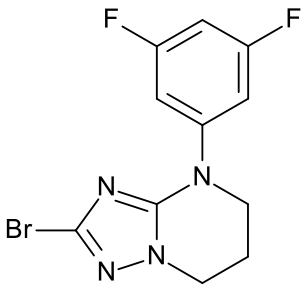
(X).

In another aspect, the present disclosure relates to compound (I) when manufactured according to the process as described herein.

The present disclosure relates to novel processes for the preparation of compound (III) and compound (IV):



(IX),



(IV).

The advantages of the process of the present disclosure 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 aspect, provided herein is a pharmaceutical composition comprising the compound (I) as described herein and a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.

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.

In another aspect, provided herein is compound (I) as described herein or the pharmaceutical composition as described herein for use in 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.

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.

In another aspect, provided herein is the use of the compound (I) as described herein or the pharmaceutical composition as described herein in 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.

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 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

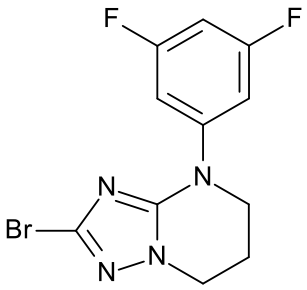
The term "pharmaceutically acceptable salt" refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of formula I and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Acid-addition salts include for example those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric 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 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.

ABBREVIATION

API	Active Pharmaceutical Ingredient
$(Boc)_2O$	Di-tert-butyl dicarbonate
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate

Claims

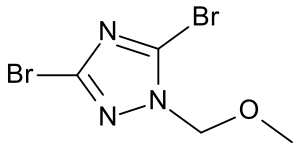
1. A process for the preparation of a compound **(VIII)**,



(VIII),

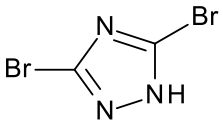
or pharmaceutically acceptable salt thereof, comprising the following steps:

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



(III),

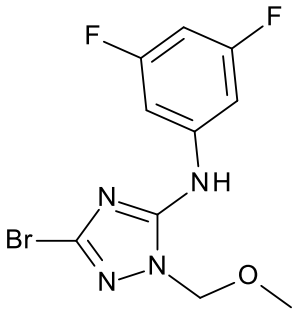
via the reaction of compound **(II)**



(**II**)

and MOMChloride;

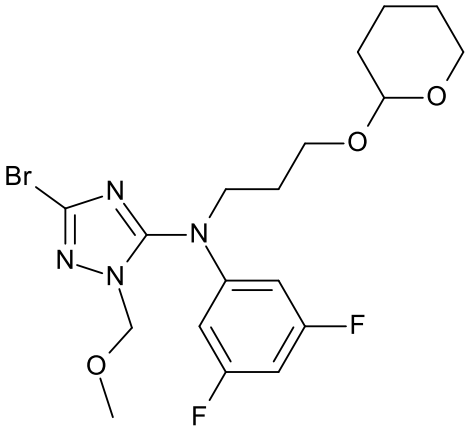
step b) the formation of compound **(IV),**



(IV),

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

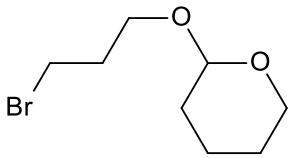
step c) the formation of compound **(VI),**



VI

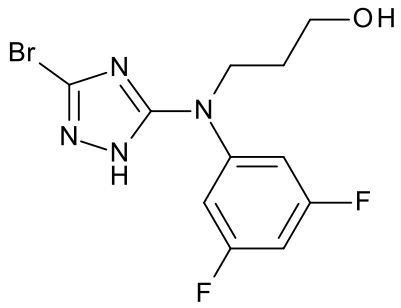
(VI),

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



(**V**);

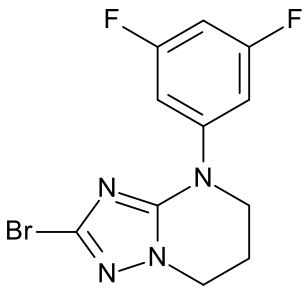
step d) the formation of compound **(VII)**,



(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. 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, K_2CO_3, 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 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.

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 from NaOH, Na_2CO_3, Cs_2CO_3 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 compound **(V)** is from 1.7 eq. to 2.26 eq.; preferably, the equivalent is 1.7 equivalent.

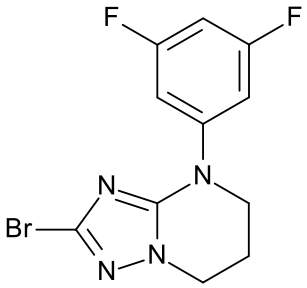
12. The process according to any one of claims 1 to 11, characterized in that the formation of compound **(VII)** in step d) is performed in the presence of an acid, wherein the acid is selected from HBr, TFA and HCl; preferably the acid is HCl; more preferably the acid is HCl (36.5% wt.).

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

14. The process according to any one of claims 1 to 13, characterized in that the formation of compound (**VII**I) in step e) is performed in the presence of DEAD, PPh_3 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.

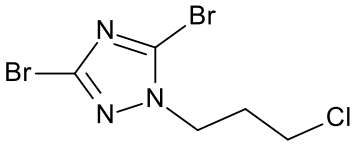
16. A process for the preparation of a compound **(VIII)**,



(VIII),

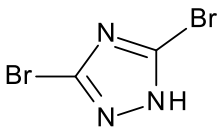
or pharmaceutically acceptable salt thereof, comprising the following steps:

step f) the formation of compound **(IX)**,



(IX),

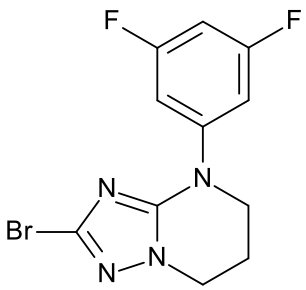
via the reaction of compound **(II)**,



(II),

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

step g) the formation of compound **(VIII)**,



(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, K_2CO_3 and Na_2CO_3; preferably, the base is K_2CO_3.

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.

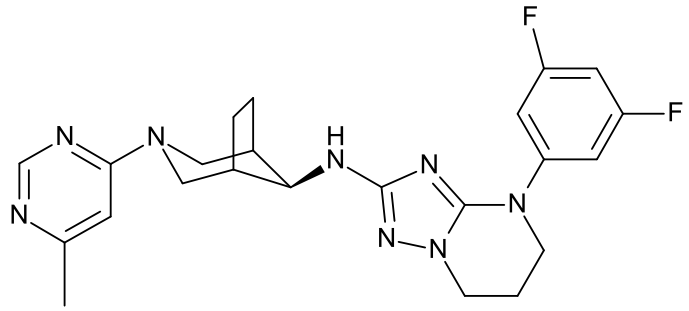
21. The process according to any one of claims 16 to 20, characterized in that the formation of compound **(VIII)** in step g) is performed in the presence of a base, wherein the base is selected from NaHMDS, K_2CO_3, KOH, NaOH, NaH and LiHMDS; preferably, the base is LiHMDS.

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.

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 preferably first at 0 °C ~ 5 °C, then at 20 °C ~ 25 °C.

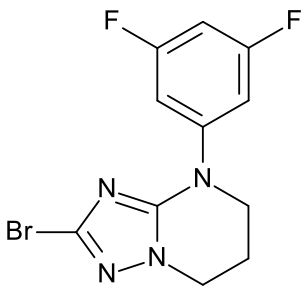
25. A process for the preparation of a compound **(I)**,



(I),

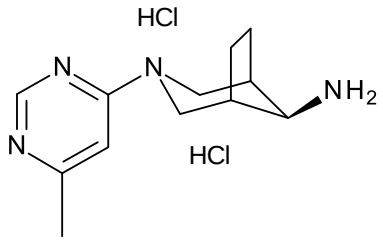
or pharmaceutically acceptable salt thereof, comprising the following step:

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



(VIII)

and compound **(X)**



(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.

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.

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 $Pd_2(dba_3)\cdot CHCl_3$ and $Pd(OAc)_2$; preferably, the catalyst is $Pd_2(dba_3)\cdot CHCl_3$.

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 °C ~ 80 °C, preferably at 70 °C ~ 75 °C.

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, Me_4tBuXphos and Me_3MeOtBuXphos, preferably, the ligand is tBuXphos.

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 °C ~ 80 °C, preferably at 70 °C ~ 75 °C.

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 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.

37. Compound (I) of claim 35 or the pharmaceutical composition of claim 36 for use in 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 the compound (I) of claim 35 or the pharmaceutical composition of claim 36 in 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.