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(54) Title: PROCESS FOR THE PREPARATION OF ANDROGEN RECEPTOR ANTAGONISTS AND INTERMEDIATES THEREOF

(57) Abstract: The present invention relates to an improved process for the preparation of carboxamide structured androgen receptor (AR) antagonists such as N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)-propan-2-yl)-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide (IA) and key intermediates thereof such as (S)-4-(1-(2-aminopropyl)-1H-pyrazol-3-yl)-2-chlorobenzonitrile (VII). AR antagonists are useful in the treatment of cancer, particularly prostate cancer and other diseases where AR antagonism is desired.



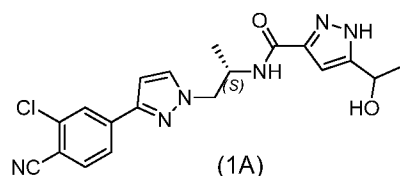
PROCESS FOR THE PREPARATION OF ANDROGEN RECEPTOR
ANTAGONISTS AND INTERMEDIATES THEREOF

5 Technical field

The present invention relates to an improved process for the preparation of carboxamide structured androgen receptor antagonists such as N-((*S*)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)-propan-2-yl)-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide (1A) and key intermediates thereof such as (S)-4-(1-(2-aminopropyl)-1H-pyrazol-3-yl)-2-chlorobenzonitrile (VII).

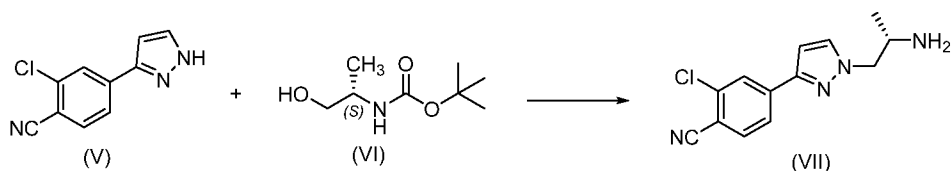
Background of the invention

15 The compound N-((*S*)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)-propan-2-yl)-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide of formula (1A) and derivatives thereof have been disclosed in WO 2011/051540. Compound of formula (1A) and its derivatives are potent androgen receptor (AR) antagonists that are useful in the treatment of cancer, particularly prostate cancer and other diseases where AR
20 antagonism is desired.



The compound of formula (1A) is currently known as darolutamide. It can be
25 prepared from the compound of formula (VII), for example, using the methods described in WO 2011/051540, WO 2012/143599 and WO 2016/162604.

WO 2011/051540 discloses a process for the preparation of the compound of formula (1A) via (S)-4-(1-(2-aminopropyl)-1H-pyrazol-3-yl)-2-chlorobenzonitrile intermediate of formula (VII). The intermediate of formula (VII) was prepared as
30 shown in Scheme I:



SCHEME 1.

This process comprises reacting 2-chloro-4-(1H-pyrazol-3-yl)benzonitrile (V) with (S)-tert-butyl-1-hydroxypropan-2-ylcarbamate (VI) in a Mitsunobu reaction in dry THF in the presense of triphenylphosphine and DIAD. The reaction mixture is evaporated to dryness. Boc deprotection of the formed compound is thereafter carried out by adding 10 % HCl/EtOH solution to the evaporation residue followed by evaporating to dryness. Water is added followed by washing the mixture several times with dichloromethane (DCM) to remove reactant residues. pH of the water phase is adjusted to 12 followed by extracting several times with DCM. The combined organic phase is dried, filtered and evaporated to give the compound of formula (VII).

A similar process for preparing the compound of formula (VII) is disclosed in WO 2012/143599. The Mitsunobu reaction is carried out in EtOAc solvent in the presense of triphenylphosphine and DIAD. Boc deprotection is carried out by adding concentrated HCl followed by water and DCM. Organic phase is washed twice with acidic water after which the combined water phases are washed twice with DCM. Then DCM is added to the water phase and pH adjusted to 11.5. After filtration the organic phase is washed with water and DCM distilled out. Heptanes is added followed by cooling the mixture to 10 °C. The precipitated compound of formula (VII) is recovered by filtering.

The process of WO 2016/162604 again discloses carrying out the Mitsunobu reaction in EtOAc solvent in the presense of triphenylphosphine and DIAD followed by Boc deprotection by adding concentrated HCl after which water and DCM are added. The organic phase is washed with water and the combined water phases are washed with DCM. Then DCM and 25 % ammonium solution are added to the water phase and pH adjusted to over 9. After filtration the organic phase is isolated and DCM is distilled out. 2-Propanol is added and the temperature of the mixture adjusted to about 50 °C. Thereafter N-heptane is added followed by cooling the

mixture to about 0 °C. The precipitated compound of formula (VII) is recovered by filtering.

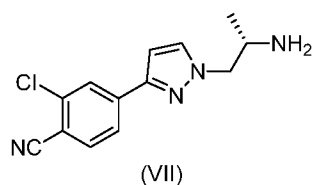
The above-mentioned processes have several drawbacks. The high number of
5 extraction steps necessary to remove Mitsunobu reaction side products make the
manufacture cumbersome. Also the required high amount of solvents limits the
available batch size. Thus, there is a need for a more practical and economical
process that is suitable for the manufacture of intermediate compound of formula
(VII) in a large scale.

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Summary of the invention

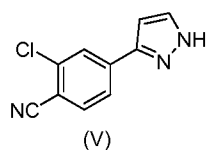
It has now been found that the compound of formula (VII) can be prepared
15 using a process which is more practical and economical and enabling use of larger
batch sizes. In particular, the extraction steps and solvent amounts can be
substantially reduced as the process enables removal of Mitsunobu reaction side
products without extraction steps.

20 Thus, the present invention provides a process for the preparation of (S)-4-(1-
(2-aminopropyl)-1H-pyrazol-3-yl)-2-chlorobenzonitrile of formula (VII)

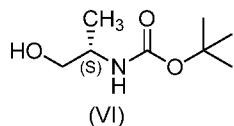


comprising the steps of

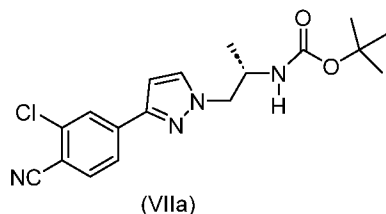
25 a) reacting 2-chloro-4-(1H-pyrazol-3-yl)benzonitrile of formula (V)



with (S)-*tert*-butyl-1-hydroxypropan-2-ylcarbamate of formula (VI)



to produce a compound of formula (VIIa);



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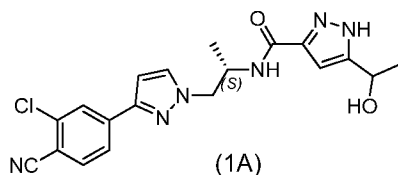
b) adding hydrobromic acid to the reaction mixture to produce a hydrobromic salt of compound of formula (VII);

c) adding Zn salt to the reaction mixture followed by filtering;

d) precipitating the hydrobromic salt of compound of formula (VII) from the filtrate by adding non-polar solvent; and

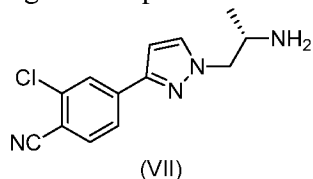
e) treating the isolated hydrobromic salt of compound of formula (VII) with a base to obtain compound of formula (VII).

In another aspect, the present invention provides a process for the preparation of the compound of formula (1A)



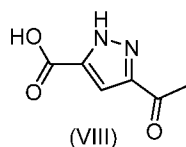
comprising the steps of

i) reacting the compound of formula (VII)

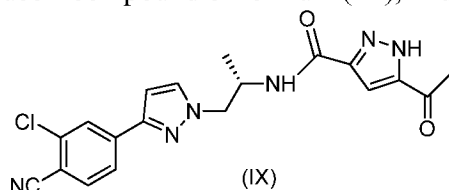


with a compound of formula (VIII)

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to produce a compound of formula (IX); and



- 5 ii) reducing the compound of formula (IX) to produce the compound of formula (1A);
 wherein the compound of formula (VII) is prepared according to steps (a) to (e) as defined above.

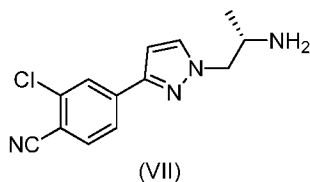
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Detailed description of the invention

Tautomerism: As the hydrogen atom of the pyrazole ring may exist in tautomeric equilibrium between the 1- and 2-position, it is recognized by the skilled person that the formulas and chemical names disclosed herein comprising a hydrogen atom in the pyrazole ring are inclusive of the tautomer of the compound in question. For example, the chemical name as “N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)-propan-2-yl)-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide” and the corresponding formula (1A) is inclusive of the tautomer of the compound, namely
 20 “N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)-propan-2-yl)-3-(1-hydroxyethyl)-1H-pyrazole-5-carboxamide”.

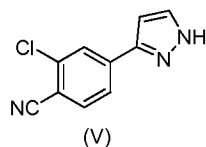
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In accordance with the present invention (S)-4-(1-(2-aminopropyl)-1H-pyrazol-3-yl)-2-chlorobenzonitrile of formula (VII)



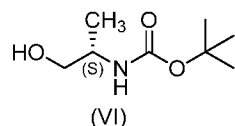
is prepared by a process comprising the steps of

a) reacting 2-chloro-4-(1H-pyrazol-3-yl)benzonitrile of formula (V)

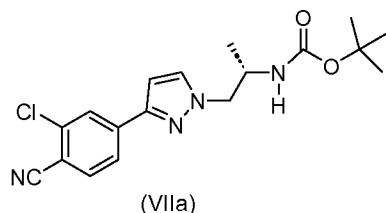


with (S)-tert-butyl-1-hydroxypropan-2-ylcarbamate of formula (VI)

5



to produce a compound of formula (VIIa);



10 b) adding hydrobromic acid to the reaction mixture to produce a hydrobromic salt of compound of formula (VII);

c) adding Zn salt to the reaction mixture followed by filtering;

d) precipitating the hydrobromic salt of compound of formula (VII) from the filtrate by adding non-polar solvent; and

15 e) treating the isolated hydrobromic salt of compound of formula (VII) with a base to obtain compound of formula (VII).

It was found that the use of hydrobromic acid for removing the Boc protection group from the compound of formula (VIIa) results in clear reaction mixture solution whereas the use of hydrochloric acid results in precipitation of various components including Mitsunobu reaction side products and salt of compound of formula (VII). Using hydrobromic acid a selective precipitation and removal of Mitsunobu reaction side products from the reaction mixture was possible by complexation with Zn salts, such as ZnCl₂. Therefore, the extraction steps needed for purification of salt of compound (VII) can be significantly reduced.

20

25

The compounds of formula (V) and (VI) are commercially available or they can be prepared according to methods known in the art.

The reaction between 2-chloro-4-(1H-pyrazol-3-yl)benzonitrile of formula (V) and (*S*)-tert-butyl-1-hydroxypropan-2-ylcarbamate of formula (VI) is suitably carried out under conditions of Mitsunobu reaction in the presence of a suitable redox system, such as a combination of a trisubstituted phosphine and an azodicarboxylate. Suitable trisubstituted phosphines include triphenylphosphine and suitable azodicarboxylates include diisopropyl azodicarboxylate (DIAD). For carrying out the reaction, the compound of formula (V) and the compound of formula (VI) are placed in a reaction vessel under nitrogen atmosphere together with triphenylphosphine in a suitable solvent such as ethyl acetate (EtOAc) or THF. DIAD is added to the reaction mixture gradually, for example under 4 hours, and under lowered temperature such as from about 0 °C to about 10 °C, for example at about 5 °C. The reaction mixture can then be stirred at room temperature until the reaction is completed, for example from about 3 to about 24 h, for example 16 h.

The Boc protection group of the obtained compound of formula (VIIa) can then be removed by treating the compound of formula (VIIa) with hydrobromic acid. This reaction is suitably synchronized with the previous step by heating the reaction mixture, for example to the temperature from about 50 °C to about 70 °C, for example to about 60 °C, and adding aqueous hydrobromic acid, for example 48 % aqueous hydrobromic acid, to the reaction mixture gradually, for example within 0.5 to 1 hour, followed by stirring at this temperature until the reaction is complete resulting typically in a clear reaction mixture. The amount of HBr used per amount of compound of formula (V) is from about 2 to about 4, preferably about 3 molar equivalents.

The above mixture is then suitably cooled to about 50 °C and Zn salt is added to precipitate the Mitsunobu reaction side products, particularly triphenylphosphine oxide (TPPO), as Zn complex. Zn salts include, for example ZnCl₂ and ZnBr₂, ZnCl₂ being particularly preferred. ZnCl₂ can be dissolved in suitable solvent such as ethanol. ZnCl₂ solution is suitably added gradually followed by cooling the reaction mixture to the temperature from about -5 °C to about 10 °C, for example to from about 0 °C to about 5 °C. The precipitated Zn complex can be removed from the reaction mixture, for example, by filtering. The amount of ZnCl₂ used per amount of

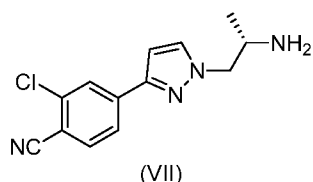
compound of formula (V) is from about 3 to about 5, preferably about 4 molar equivalents.

The hydrobromic salt of compound of formula (VII) can then be isolated from
5 the filtrate by adding non-polar solvent, for example toluene or heptane. Part of the
solvents can be distilled off, if desired, and the non-polar solvent, for example
toluene, is added followed by cooling the mixture, for example, to the temperature
from about -5 °C to about 10 °C, such as from about 0 °C to about 5 °C. The
precipitated hydrobromic salt of compound of formula (VII) can be isolated, for
10 example, by filtering.

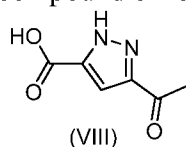
The obtained hydrobromic salt of compound of formula (VII) can be
transformed to the compound of formula (VII) by treatment with a base. This step
can be suitably carried out by partitioning the isolated hydrobromic salt of compound
15 of formula (VII) between water and DCM (water : DCM ratio for example of about
2:1). The mixture can be basified, for example, with aqueous ammonium hydroxide
and/or sodium hydroxide to pH > 11. The mixture can then be heated, for example,
to about 40 °C for about 1 hour. After filtering the layers are separated and part of
the organic phase can be distilled. 2-Propanol can be added to the organic phase and
20 the temperature of the mixture adjusted to about 50 °C. Thereafter *n*-heptane is
added slowly, optionally with seeding, and the compound of formula (VII) is
precipitated by cooling the mixture, for example to about 0 – 5 °C, and stirring at this
temperature for a period of time sufficient to complete the precipitation, suitably
from about 3 to about 16 h, for example from about 3 to about 8 h. The precipitated
25 product can be isolated, for example by filtering, washed with *n*-heptane and dried
under vacuum, for example at about 50 °C.

The compound of formula (1A) can be prepared from the compound of
formula (VII), for example, using the methods described in WO 2011/051540, WO
30 2012/143599 and WO 2016/162604. For example, according to one embodiment, the
process for the preparation of the compound of formula (1A) comprises the steps of

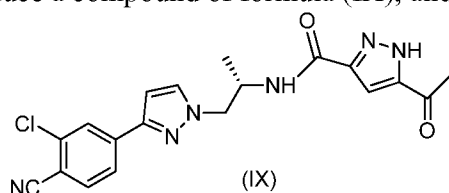
i) reacting the compound of formula (VII)



with a compound of formula (VIII)



to produce a compound of formula (IX); and



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ii) reducing the compound of formula (IX) to produce the compound of formula (1A);

10 The reaction step i) can be carried out at room temperature in the presence of suitable activating and coupling agent system such as a combination of DIPEA (*N,N*-diisopropylethylamine), EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) and anhydrous HOBt (1-hydroxy-benzotriazole) in a suitable solvent, for example DCM. As an alternative to HOBt, HBTU (O-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluroniumhexafluorophosphate) can be used. Alternatively, a combination of DIPEA and T3P (1-propanephosphonic acid cyclic anhydride) can be used as an activating and coupling agent system.

15

20 The reaction step ii) can be carried out at room temperature by treating the compound of formula (IX) with a reduction agent, for example sodium borohydride, in a suitable solvent, for example ethanol, followed by treating the mixture with aqueous HCl.

The invention is further illustrated by the following non-limiting examples.

25

Example 1. Preparation of (S)-4-(1-(2-aminopropyl)-1H-pyrazol-3-yl)-2-chlorobenzonitrile (VII)

10 g (49.1 mmol) of 2-Chloro-4-(1*H*-pyrazol-3-yl)benzonitrile, 17.6 g (101 mmol) of (*S*)-tert-butyl-1-hydroxypropan-2-ylcarbamate, triphenylphosphine (26.4 g, 101 mmol) and 57 mL of EtOAc were placed into a reaction vessel under nitrogen atmosphere. The mixture was cooled to 5 °C. DIAD (19.8 mL, 101 mmol) was added evenly during 4 h under stirring while keeping the temperature below 10 °C. The mixture was warmed to ambient temperature and stirred overnight. The mixture was heated to 60 °C and 48 % aqueous hydrobromic acid (18.3 mL, 162 mmol) was added dropwise over 45 minutes, and the mixture stirred at this temperature until the reaction was complete. The mixture was cooled to 50 °C and a solution of ZnCl₂ (27 g, 198 mmol) in 50 mL of ethanol was added dropwise. The mixture was cooled to 0-5 °C and filtered to remove the precipitated triphenylphosphine oxide zinc complex. Then 70 mL of solvents were distilled from the filtrate, and a corresponding volume of toluene added to the mixture at 50 °C to induce precipitation. The mixture was cooled to 0-5 °C and filtered. The solids were partitioned between water (100 mL) and DCM (50 mL) at 35 °C. The mixture was basified with ammonium hydroxide (25 %, 13.0 mL, 84 mmol) and sodium hydroxide to pH > 11, then heated to 40 °C for 1 hour. The solution was filtered through celite at 35 °C and the layers separated. The organic phase was distilled until 17 mL remained, then *i*-PrOH (3 mL) added. The mixture was heated to 50 °C and *n*-heptane (60 mL) was added over 1 hour, with seeding carried out when one third of the addition was complete. The mixture was cooled to 0-5 °C during 6 h and then stirred overnight. The precipitated product was isolated by filtering, washed with *n*-heptane (30 ml) and dried under vacuum at 50 °C. Yield 70.0 %.

25

Example 2. Preparation of 3-acetyl-1*H*-pyrazole-5-carboxylic acid (VIII)

3-Acetyl-1*H*-pyrazole-5-carboxylate (5 g, 29.7 mmol), water (30 ml) and sodium hydroxide 48 % (2.83 ml, 52.0 mmol) were carefully added into the reaction vessel. The mixture was warmed to 60-65 °C and stirred until the reaction was completed. The mixture was then cooled to 50 °C. 30 % HCl (2.83 ml, 26.8 mmol) was added at 50 °C during 1 h and the mixture was seeded at the end of the HCl addition. The mixture was stirred for 2 h. Further 30 % HCl (2.451 ml, 23.19 mmol) was added at 50 °C during 3 h followed by stirring at 50 °C for 30 min. The precipitated product was isolated by filtering, washed with water (5 ml) and then with methanol (2.5 ml) and dried under vacuum at 60 °C. Yield 92.8 %.

Example 3. Preparation of (S)-5-acetyl-N-(1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-1H-pyrazole-3-carboxamide (IX)

5 6.80 g (44.1 mmol) of 3-acetyl-1H-pyrazole-5-carboxylic acid (VIII), DCM (76 ml), 10.33 g (38.3 mmol) of (S)-4-(1-(2-aminopropyl)-1H-pyrazol-3-yl)-2-chlorobenzonitrile (VII) and DIPEA (18.04 ml, 104 mmol) were placed in to the reaction flask under nitrogen atmosphere at about 20 °C. The mixture was cooled to 5 °C. Thereafter 28.2 ml (49.9 mmol) of T3P (1-propanephosphonic acid cyclic
10 anhydride) in EtOAc (50 %) was added during 2 h under vigorous stirring at about 10 °C. The mixture was stirred at 10 ± 3 °C overnight. Thereafter ethanol (30 ml) was added to the mixture. About 70 ml of DCM was then distilled off at about 60 °C and the mixture was seeded at about 60 °C followed by stirring for 30 min at this temperature. A mixture of water (40 ml), 0.75 ml of 30 % HCl in water and ethanol
15 (10 ml) was then added during about 2 h followed by stirring at 60 ± 5 °C for about 2 h. The mixture was cooled to 5 -10 °C during 4 h followed by stirring at this temperature overnight. The precipitated product was isolated by filtering, washed with 2 x 30 ml of water and 1 x 20 ml of ethanol, and dried under vacuum at 60°C overnight. Yield 87.5 %.

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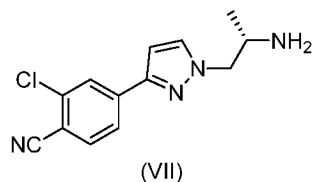
Example 4. Preparation of N-((S)-1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)-propan-2-yl)-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide (IA)

25 100 mg (0.25 mmol) of (S)-5-acetyl-N-(1-(3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl)propan-2-yl)-1H-pyrazole-3-carboxamide (IX) and 5ml of EtOH were put to reaction flask and 19 mg (0.5 mmol) of sodium borohydride was added slowly as EtOH suspension. The reaction was stirred overnight to completion. 0.5 ml of water and 1ml of 0.5 M HCl were added dropwise. The solution was evaporated to dryness and 20 ml of DCM was added. The mixture was washed with 10 ml of 1 M
30 NaHCO₃ and 10 ml of water followed with drying over Na₂SO₄. After filtration and evaporation 76 mg of the product was obtained. Yield 76 %.

Claims

1. A process for the preparation of (S)-4-(1-(2-aminopropyl)-1H-pyrazol-3-yl)-2-chlorobenzonitrile of formula (VII)

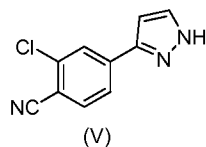
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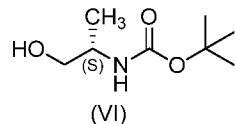
comprising the steps of

a) reacting 2-chloro-4-(1H-pyrazol-3-yl)benzonitrile of formula (V)

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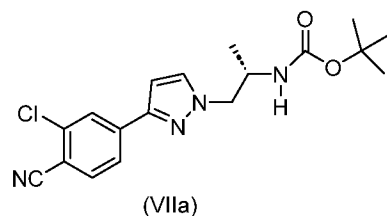


with (S)-*tert*-butyl-1-hydroxypropan-2-ylcarbamate of formula (VI)



to produce a compound of formula (VIIa);

15



b) adding hydrobromic acid to the reaction mixture to produce a hydrobromic salt of compound of formula (VII);

c) adding Zn salt to the reaction mixture followed by filtering;

20

d) precipitating the hydrobromic salt of compound of formula (VII) from the filtrate by adding non-polar solvent; and

e) treating the isolated hydrobromic salt of compound of formula (VII) with a base to obtain compound of formula (VII).

2. A process according to claim 1, wherein step a) is carried out in the presence of a trisubstituted phosphine and an azodicarboxylate.

3. A process according to claim 2, wherein the trisubstituted phosphine is triphenylphosphine and the azodicarboxylate is diisopropyl azodicarboxylate (DIAD).

4. A process according to any of the preceding claims, wherein the solvent used in step a) comprises ethyl acetate (EtOAc).

5. A process according to any of the preceding claims, wherein hydrobromic acid is step b) is added as aqueous hydrobromic acid.

6. A process according to any of the preceding claims, wherein the Zn salt in step c) is ZnCl_2 .

7. A process according to claim 6, wherein ZnCl_2 is added as ZnCl_2 in ethanol.

8. A process according to any of the preceding claims, wherein the non-polar solvent in step d) is toluene.

9. A process according to claim 8, wherein the precipitation is carried out in a temperature ranging from about $-5\text{ }^{\circ}\text{C}$ to about $10\text{ }^{\circ}\text{C}$.

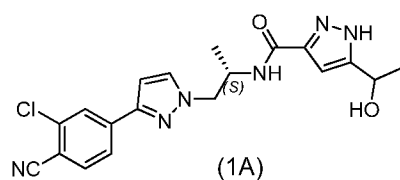
10. A process according to any of the preceding claims, wherein the base in step e) comprises ammonium hydroxide and/or sodium hydroxide.

11. A process according to any of the preceding claims, wherein step e) is carried out in the mixture of water and DCM.

12. A process according to any of the preceding claims, wherein the compound of formula (VII) is precipitated after step e) by addition of *n*-heptane.

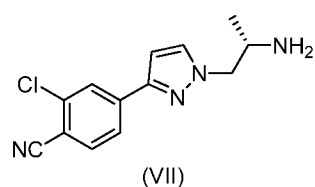
13. A process for the preparation of the compound of formula (1A)

14

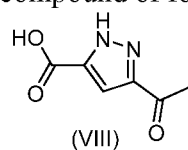


comprising the steps of

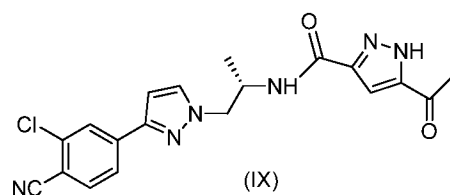
- 5 i) reacting the compound of formula (VII)



with a compound of formula (VIII)



- 10 to produce a compound of formula (IX); and



- 15 ii) reducing the compound of formula (IX) to produce the compound of formula (1A);

wherein the compound of formula (VII) is prepared according to any of claims 1-13.

INTERNATIONAL SEARCH REPORT

International application No
PCT/FI2024/050423

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D231/12 C07D403/12 ADD.		
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) C07D 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) EPO-Internal, CHEM ABS Data, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2018/099938 A1 (LAITINEN ILPO [FI] ET AL) 12 April 2018 (2018-04-12) cited in the application page 7, line 84 - line 85; example 4 ----- - / - -	1 - 13
☒ 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 15 October 2024		Date of mailing of the international search report 24/10/2024
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Bissmire, Stewart

INTERNATIONAL SEARCH REPORT

International application No

PCT/FI2024/050423

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BATESKY DONALD C. ET AL: "Removal of Triphenylphosphine Oxide by Precipitation with Zinc Chloride in Polar Solvents", THE JOURNAL OF ORGANIC CHEMISTRY, vol. 82, no. 19, 28 September 2017 (2017-09-28), pages 9931-9936, XP093131789, United States ISSN: 0022-3263, DOI: 10.1021/acs.joc.7b00459 Retrieved from the Internet: URL: http://pubs.acs.org/doi/pdf/10.1021/acs.joc.7b00459> abstract Scheme I; page 9932 page 9933; table 2 and 3 Scheme 2 and Scheme 3; page 9934 -----	1 - 13

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International application No

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