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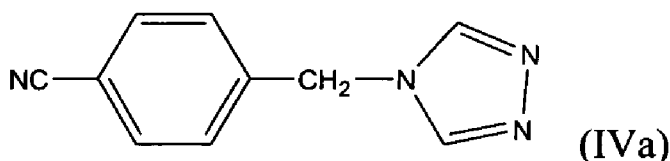
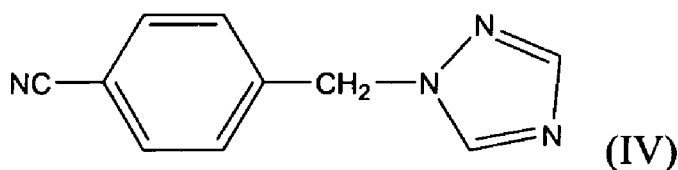
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CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO,
DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
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(54) Title: PURIFICATION OF LETROZOLE INTERMEDIATE

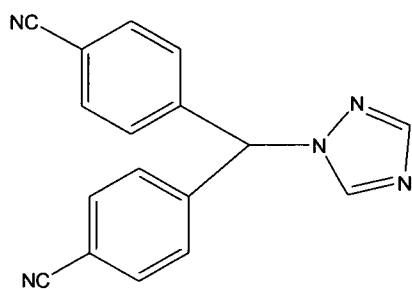


(57) Abstract: The present invention relates to a process for purification of a material comprising 4- [1-(1,2,4-triazolyl)methyl]benzonitrile of the formula (IV), comprising contacting the material comprising the compound of the formula (IV) (IV) and at least the compound (IVa) (IVa) with an aqueous acid, precipitation the solid state compound (IV) from the aqueous solution as a free base, and to the use of the purified compound of formula (IV) in preparing letrozole.



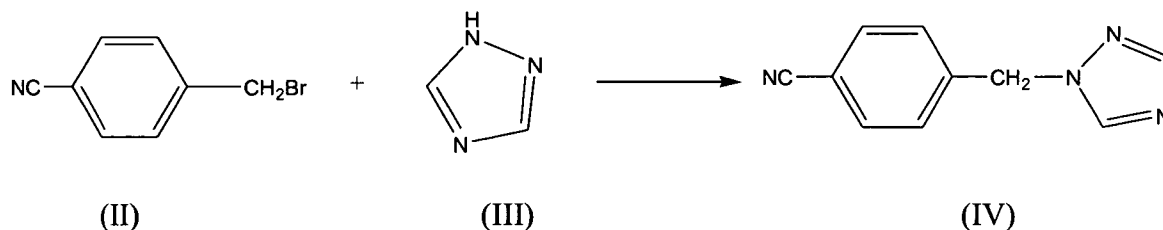
PURIFICATION OF LETROZOLE INTERMEDIATE

5 [0001] Letrozole, 4,4'-(1H-1,2,4-triazol-1-ylmethylene)dibenzonitrile of the formula (I)

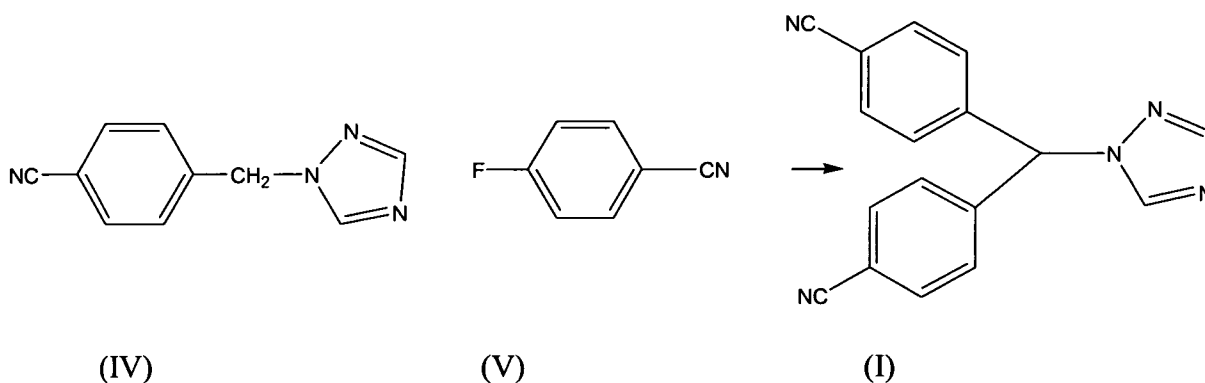


is a known compound used as a pharmaceutically active substance in the pharmaceutical industry. Letrozole is indicated for, inter alia, treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy. It is a non-steroidal competitive inhibitor of the aromatase enzyme system. Letrozole is marketed under the brand name FEMARA[®] by Novartis Pharmaceuticals as a film coated tablet containing 2.5 mg of letrozole as the free base.

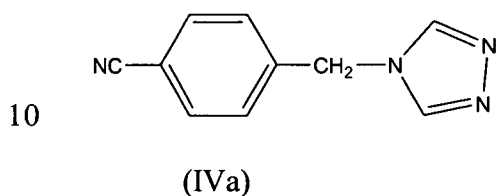
[0002] US patent 4,978,672 (EP 236,940) describes the synthesis of letrozole by reacting 4-(bromomethyl)benzonitrile of the formula (II) and 1H-1,2,4-triazole of the formula (III) in a presence of a base to provide 4-[1-(1,2,4-triazolyl)methyl]benzonitrile of the formula (IV),



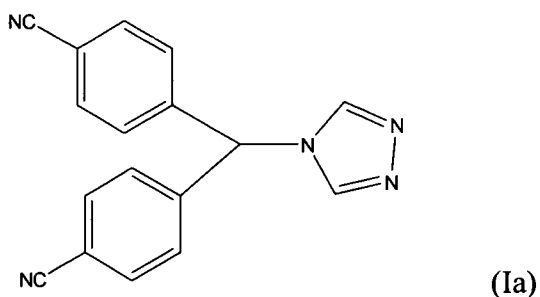
which is then purified by column chromatography and subsequently converted to letrozole of the formula (I) by the reaction with 4-fluorobenzonitrile of the formula (V) in a presence of a strong base.



[0003] According to WO 2004/076409, the purification of the compound (IV) by column chromatography is necessary as the raw product is contaminated with approx. 20 to 40% of the side product of the reaction of (II) and (III), which is 4-[1-(1,3,4-triazolyl)methyl]benzonitrile (IVa).



If not removed, this side product reacts with the compound (V) in the letrozole synthesis pathway to yield 4,4'-(1H-1,3,4-triazol-1-ylmethylene)bisbenzonitrile (Ia),



15 which is a site isomer of letrozole (and is called hereinunder as isoletrozole), the presence of which in the final product of pharmaceutical grade is undesirable. US Pharmacopoeia

monograph restricts the maximum allowable amount of isoletrozole in the letrozole to max. 0.3 %.

[0004] The need of chromatographic purification makes the process economically unattractive.

5 **[0005]** WO 2004-076409 describes an alternative process avoiding the formation of the iso-compound (IVa), by using an amino-substituted triazole. However, this process requires an additional step of removing the amino-substituent, which may involve a formation of dangerous diazo-intermediates.

[0006] US 5,280,035 describes a process for making compound (IV) by converting
10 1,2,4-triazole into sodium salt (by sodium hydride in DMF), followed by the reaction of this salt with (II). However, the compound (IV) must still be purified by column chromatography for to obtain the desired purity. In an improvement, US appl. 2005/0209294 isolates the compound (IV) by extraction/crystallization, however allowing for obtaining the product only with 96% purity.

15 **[0007]** WO 2007-100346 improves the reaction between the 1,2,4-triazole salt and (II) by using dimethylacetamide, N-methyl-2-pyrrolidone or combinations thereof as the solvent. In such a case, the compound (IV) needs not to be purified in some cases and the whole process leading to letrozole may be arranged in a one-pot process. Similar process is disclosed in WO 2007-039912.

20 **[0008]** WO 2007-107733 discloses a process of making the compound (IV) employing the reaction of (II) and (III) in a presence of cesium carbonate. Under such process, the amounts of the formed undesired isomer (IVa) are lower.

[0009] It is apparent from the above that obtaining the compound (IV) in a proper quality is a key issue in any process of making letrozole by the above reaction sequence. The
25 formation of the certain amount of the iso-product (IVa) may never be excluded, particularly

in an industrial scale, and purification processes should be readily available. If a purification process is efficient and cheap, then the need to use extreme reaction conditions and expensive reagents may be avoided.

[0010] The process of purification of (IV) based on column chromatography
5 disclosed above is not useful, particularly in an industrial scale due to its low capacity, time consumption and high cost.

[0011] WO 2005-047269 provides a crystallization process for purification of the mixtures of compounds (IV) and (IVa) comprising dissolving the isomeric mixture in dichloromethane, adding an isopropanolic solution of hydrogen chloride thereto, and adding
10 isopropyl ether to the mixture to precipitate the undesired isomer (i.e. the compound (IVa)) in its hydrochloride form. The desired compound (IV) is then obtained from the filtrate by the precipitation as the hydrochloride salt and is then converted into a base.

[0012] WO 2007-100346 suggests a purification process based on an extraction involving an aqueous phase and water immiscible phase, which preferably contains C5-C12
15 hydrocarbon such as toluene, benzene and hexane. In a preferred arrangement comprising salted water as the aqueous phase and warmed toluene as the organic phase, the content of the iso-product (IVa) may be decreased to 1.5 %. This process is more effective than the extraction /crystallization process of US appl. 2005/0209294 shown above.

[0013] WO 2007-100346 also suggests that the raw intermediate (IV) may be
20 further purified as its acid salt, e.g., the hydrochloride, hydrobromide or methane sulfonate. In the only disclosed example, the raw intermediate (IV) is dissolved in acetone, and the hydrochloride of (IV) is precipitated by adding concentrated aqueous HCl to this acetonetic solution. The hydrochloride of the iso-product (IVa) remains in the solution.

[0014] WO 2007-054964 provides a purification of the reaction mixture comprising
25 the (IV) and (IVa) compounds, comprising quenching the reaction mixture by water,

adjusting the pH to acidic by slow addition of the sufficient amount of HCl, extracting of the acidic solution by a suitable organic solvent, e.g. a hydrocarbon, then basifying the organic phase to pH 7.5-10, saturating with NaCl and extracting again with the same solvent. The undesired regioisomer (IVa) remains in the aqueous phase.

5 **[0015]** While the above purification processes are available for making the compound (IV) essentially free from the compound (IVa), there is still a need of an improvement in the matter. In particular, purification processes, which do not employ organic solvents, are desirable from safety, economy and ecology aspects.

10 BRIEF DESCRIPTION OF THE PRESENT INVENTION

[0016] The present invention is based on the discovery that 4-[1-(1,2,4-triazolyl)methyl]benzonitrile of the formula (IV) can be precipitated from an aqueous solution of an acid in a form of a free base and that such precipitation can dramatically
15 increase the purity of the product. Furthermore, no organic solvent is used in the precipitation process.

[0017] Accordingly, a first aspect of the invention provides a process for purification of 4-[1-(1,2,4-triazolyl)methyl]benzonitrile of the formula (IV), comprising contacting the material comprising the compound (IV) and impurities, reaction side products
20 and starting materials, such as the compound (IVa), with an aqueous acid, preferably hydrochloric acid, and precipitating the solid state compound (IV) from the mixture. This precipitation comprises preferably adjusting the pH to less acidic value.

[0018] The aqueous acid is preferably diluted hydrochloric acid, which preferably has a concentration of between 5 to 20 % (w/v).

[0019] In a particular aspect, 1 weight part of the material comprising the compound (IV) admixed with / impurified by the compound (IVa) is contacted with 2.5- 10 volume parts of the aqueous solution of the acid, preferably the hydrochloric acid.

[0020] In yet another particular aspect, the relative molar amount of the acid in respect to the molar amount of the compound (IV) is 1.5:1 to 2.5 :1.

[0021] In another particular aspect, the pH at the precipitation is adjusted to a value of at least 3.0 , preferably between 3.0 - 11.0, more preferably 6 – 10.

[0022] In a second aspect, the invention relates to a process for making a pharmaceutical grade letrozole of the formula (I) comprising the steps of

- providing a purified compound of the formula (IV) by the above process and
- reacting the purified compound (IV) with the compound (V) to form letrozole of the formula (I).

DETAILED DESCRIPTION OF THE INVENTION

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[0023] The present invention can purify the letrozole intermediate of the formula (IV) without the need to convert crude compound (IV) into an isolated acid addition salt thereof and/or to employ extraction steps using organic solvents. Instead, a simple process comprising precipitation of the compound (IV) as a free base from a solution thereof in a diluted aqueous acid may be employed, whereby the process allows to decrease not only the content of the iso- impurity of formula (IVa) but also other impurities arisen from the synthesis. As a result, a reagent grade compound of the formula (IV), i.e. a product having the content of the title compound of at least 99.7% and the content of any single structurally related impurity of less than 0.2 %, may be obtained in a simple and reliable process on an industrial scale.

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[0024] The purification process of the present invention is based on the finding that compounds (IV) and (IVa) have different solubility in the solvent comprising the diluted aqueous acid, particularly diluted aqueous hydrochloric acid, at different values of pH. If a mixture of compounds (IV) and (IVa), which typically arises from the synthesis comprising a condensation of the compound (II) and (III) and isolation of the reaction product from the reaction mixture, is dissolved in a diluted aqueous acid, particularly hydrochloric acid, and the pH of the mixture is adjusted to a less acidic value, typically to a pH higher than 3.0, the compound (IV) preferably precipitates from the solution as a free base, while the compound (IVa) stays dissolved in the solvent. The main advantage of the process is in that no organic solvent is employed therein, which has serious safety, economy and ecology impacts.

[0025] The first step of the purification process comprises contacting the crude compound (IV), i.e. the material comprising an admixture of the compound (IV) with the compound (IVa), herein referred to as the material, with a diluted aqueous acid. The crude material is typically obtained by a synthesis comprising a condensation of the compound (II) and (III), the conditions of which are well known in the art, eventually followed by pre-purification steps. In general, more than 0.5 %, sometimes even up to 5-10 %, of the iso-impurity (IVa) may be present in the material. The material may also comprise other impurities arising from the synthesis, particularly the unreacted 1,2,4-triazol and colour-forming impurities. The amount of the compound of formula (IV) in the starting material may be determined by routine analytical methods, e.g. by HPLC.

[0026] In particular, the amount of the acid in the diluted aqueous acid is usually from 0.1 to 3 molar equivalents, more typically 1.5 to 2.5 molar equivalents, in respect to the compound of formula (IV). In terms of concentration, the acid is normally less than 20%, preferably between 5 and 20%, based on the amount of water present. In terms of volume, the amount of the diluted aqueous acid is typically within the range of 2.5- 10 volume parts per 1

weight part of the crude material to be purified. The preferred acid is hydrochloric acid.

However, it should be understood that hydrochloric acid is only an example of a suitable acid useful in the inventive process and the invention is by no way limited to using this acid only.

[0027] The mixture of the material and diluted aqueous acid is preferably heated to
5 an enhanced temperature, preferably at a temperature of between 30 and 60 °C and allowed to stir for certain time.

[0028] In a second optional step, the formed mixture is filtered to remove the solids and to form a clear filtrate. The solids are particularly represented by structurally related impurities present in the material. Advantageously, a small amount of a surface active
10 material, such as activated carbon or kieselguhr is added prior to the filtration to the mixture, which not only enhances the speed of the filtration, but adsorbs also other impurities present in the starting material.

[0029] In a third step, the clear filtrate is treated with a base, preferably the inorganic base such as sodium or potassium hydroxide or carbonate, more preferably with an
15 aqueous solution thereof, to adjust the pH of the solution to less acidic values. Typically, the pH is adjusted to a pH of 3.0 and more, more particularly to pH between 3.0 and 11.0, such as 6 - 10. At this pH range, the compound (IV) precipitates from the solution as a free base, not as a salt with the acid. The pH adjustment and precipitation is normally performed at ambient temperature. It is however possible to cool the reaction mixture before or after the pH
20 adjustment to temperatures less than ambient, typically to 5- 15 °C. It is also possible to dilute the reaction mixture with another portion of water subsequently.

[0030] In the last step, the solid product is isolated from the mixture, typically by filtration or centrifugation, and optionally washed and dried. A second crop of the solid product may be obtained from the filtrate, particularly by salting the solution with NaCl
25 and/or by further increasing the pH of the filtrate.

[0031] The process may provide a product, i.e. the purified compound (IV), which generally comprises less than 0.2% , sometimes even less than 0.1 %, of the iso-impurity of the formula (IVa). If the desired limit is not reached, it is advantageous to repeat the purification process until the limit is reached. In average, no repetition is generally needed.

5 [0032] In general, the yield of the overall process, calculated on the amount of the starting material, is around 60 to 70%. The purification process does not require any extraction step and no organic solvent. It may be easily performed in multi-kilogram scale on single equipment.

[0033] The compound (IV) purified by the above process, particularly of the reagent
10 grade specified above, is useful in a process for making letrozole. Accordingly, the above purification process steps may be followed by a subsequent step of converting the purified compound (IV) to letrozole, particularly by a condensation with the 4-fluorobenzonitrile of the formula (V). The conditions of the condensation as well as of the isolation of letrozole from the reaction mixture are known in the art.

15 [0034] Because of a low content of the iso-compound of the formula (IVa) in the starting compound (IV), the letrozole may be produced with a low content of the isoletrozole of the formula (Ia), which is desirable from the pharmaceutical perspective. In particular, a pharmaceutical grade letrozole, i.e. a product having the content of the title compound of at least 99.7% and the content of any single structurally related impurity of less than 0.1 %, may
20 be obtained in a simple and reliable process on an industrial scale.

[0035] The invention is further illustrated by the following examples.

Example 1

2 grams of the crude 4-[1-(1,2,4-triazolyl)methyl]benzonitrile , containing 0.5% of the
25 compound of formula (IVa), was added to 10 ml of 12.5 % (w/v) aqueous HCl at ambient

temperature and heated under stirring to 50°C. 0.1 g of activated charcoal was added and the mixture was stirred for 15 minutes. The mixture was filtered through a paper filter and washed with 5 ml of HCl (12.5 %) at 50°C. The filtrate was cooled to 10-15° C and 2M aqueous NaOH was added at this temperature until the pH 3.0. Crystalline suspension was allowed to stand overnight at 5-7 °C. The solid was filtered and dried at an ambient temperature to constant mass (1st crop).

The mother liquors were alkalinized by 2M aqueous NaOH at 10-15 °C to pH 8.0, 2 g of NaCl were added and the mixture was stirred at ambient temperature for 0.5 hours. Allowed to stand overnight at 5-7 °C. The solid was filtered and dried at an ambient temperature to constant mass (2nd crop).

Yield : 1.20 g (60.0 %) - 1st crop

0.33 g (16.5 %) - 2nd crop

Content of the compound (IVa) (HPLC) : less than 0.05%

Example 2

The experiment of the example 1 was repeated with the proviso that the pH of the first filtrate was adjusted by 2M Na OH to 6.0 .

Yield : 1.27 g (63.5 %) - 1st crop

0.14 g (7.0%) - 2nd crop

Content of the compound (IVa) (HPLC) : less than 0.05%

Example 3

3 grams of the crude 4-[1-(1,2,4-triazolyl)methyl]benzonitrile, containing 0.5% of the compound of formula (IVa), was mixed with 10 ml of 12.5 % (w/v) aqueous HCl at ambient

temperature and heated under stirring at 50 °C. 0.1 g of activated charcoal was added and the

mixture was stirred for 15 minutes at 50 °C. The mixture was filtered through a paper filter and washed with 3 ml of HCl (12.5 %) at 50 °C. The filtrate was cooled to 7-10 °C and 2M aqueous NaOH was added at 10-15 °C under stirring until the pH 10.0. Crystalline suspension was stirred at 7-10 °C for 1 hour. The solid was filtered and dried at an ambient temperature to constant mass (1st crop).

The mother liquors were mixed with 2.2 g of NaCl and the mixture was stirred at ambient temperature for 0.5 hours. Allowed to stand overnight at 5-7 °C. The solid was filtered and dried at an ambient temperature to constant mass (2nd crop).

Yield : 2.41 g (80.3 %) of the 1st crop

0.11 g (3.7%) of the 2nd crop

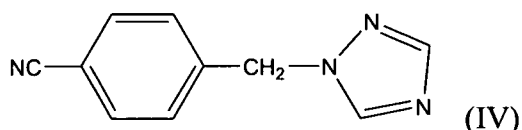
Content of the compound (IVa) : less than 0.05 % (HPLC)

The invention having been described it will be obvious that the same may be varied in many ways and all such modifications are contemplated as being within the scope of the invention as defined by the following claims.

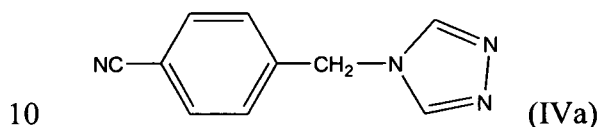
CLAIMS

5 1. A process for purification of a material comprising 4-[1-(1,2,4-triazolyl)methyl]benzonitrile of the formula (IV), comprising

- contacting the material comprising the compound of the formula (IV)



and at least the compound (IVa)



with an aqueous acid,

- precipitation the solid state compound (IV) from the aqueous solution as a free base.

2. The process of claim 1, wherein the precipitation comprises adjusting the pH of the solution to a less acidic pH value, preferably to a less acidic pH value in the range of 3.0 –
15 11.0.

3. The process of claim 2, wherein the pH is adjusted to a pH value in the range of 6 –
10.

4. The process according to claims 1- 3, wherein the aqueous acid is the hydrochloric acid .

20 5. The process according to claims 1 - 4, wherein the aqueous acid has a concentration of between 5 to 20 % (w/v) .

6. The process according to claims 1- 5 , wherein 1 weight part of the material is contacted with 2.5- 10 volume parts of the aqueous acid, preferably the hydrochloric acid.

7. The process according to claims 1-6 , wherein the relative molar amount of the acid, preferably the hydrochloric acid, is 1.5 : 1 to 2.5 : 1 in respect to the molar amount of the compound (IV)

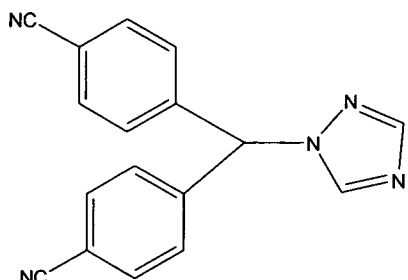
8. The process according to claims 1-7, wherein the solution is filtered before
5 precipitation. preferably in the presence of a surface active material .

9. The process according to claims 1 – 8, wherein the precipitated compound (IV) is isolated.

10. The process of claim 1 9, wherein the material originates from a reaction mixture of the reaction of 4-(bromomethyl)benzonitrile of the formula (II) and 1H-1,2,4-triazole of
10 the formula (III).

11. The process according to claims 1-10, further comprising the step of converting the isolated compound (IV) to letrozole .

12. A process for making a pharmaceutical grade letrozole of the formula (I)



(I)

15 comprising the steps of

- providing a purified compound of the formula (IV) by the process according to any of the claims 1-11; and

- reacting the purified compound (IV) with 4-fluorobenzonitrile of the formula (V) to form letrozole of the formula (I).

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/004959

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D249/08

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 practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 1 754 876 A (BEIJING D VENTURE PHARM T CORP [CN]) 5 April 2006 (2006-04-05) claims 1-3	1
Y	claims 1-3	2-12
X	WO 2007/134846 A (SYNTHON BV [NL]; PIS JAROSLAV [CZ]; SMRZ RUDOLF [CZ]) 29 November 2007 (2007-11-29) Experimental Example1 pages 6-7, paragraphs 20,21; example 1	1
Y	Experimental Example1 pages 6-7, paragraphs 20,21; example 1	2-12
Y	WO 2007/054964 A (CADILA HEALTHCARE LTD [IN]; HAIDER HUSSAIN [IN]; SOLANKI KIRTIPALSINH) 18 May 2007 (2007-05-18) cited in the application claims 1-12	2-12
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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search

4 September 2009

Date of mailing of the international search report

02/10/2009

Name and mailing address of the ISA/
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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2009/004959

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/100346 A (SICOR INC [US]; MACDONALD PETER LINDSEY [CH]; BIGATTI ETTORE [CH]; ROS) 7 September 2007 (2007-09-07) cited in the application claims 15-23; example 13 -----	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2009/004959

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
CN 1754876	A	05-04-2006	NONE	
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