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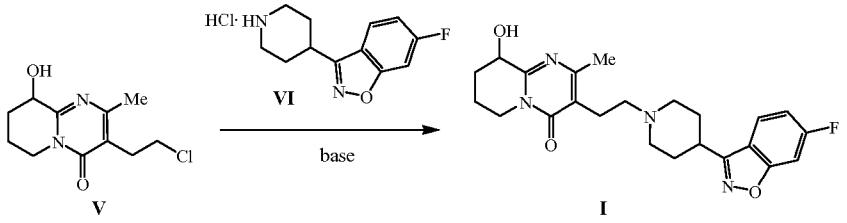
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(54) **Title**: PROCESS TO PREPARE PALIPERIDONE AND INTERMEDIATES THEREOF



(57) **Abstract**: The present invention relates to an improved process for obtaining Paliperidone, I, comprising alkylating compound VI, or a salt thereof, with compound V, or a salt thereof, using a base selected from triethylamine or diisopropylethylamine and, optionally, a solvent. Moreover, the invention relies on the preparation of intermediates used in such process.

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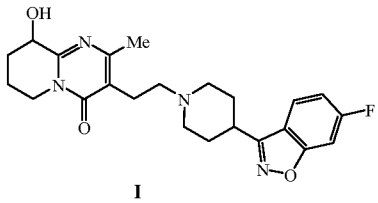
PROCESS TO PREPARE PALIPERIDONE AND INTERMEDIATES THEREOF

FIELD OF THE INVENTION

The invention relates to the synthesis of Paliperidone, a drug useful to treat schizophrenia, and processes to prepare intermediates thereof with improved yield and atomic economy.

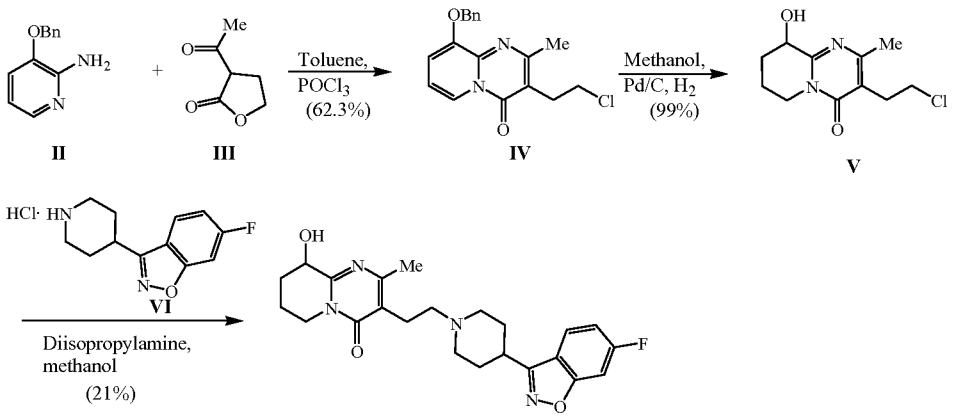
BACKGROUND

Paliperidone, **I**, is an orally active drug useful for the treating of schizophrenia. Its chemical name is (±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one and its chemical structure is depicted below:



I

Paliperidone was first disclosed in European patent application EP0368388. In said application Paliperidone is prepared as depicted in Scheme 1.



Scheme 1

In the synthesis exemplified in said document it is used a benzyl protecting group in the hydroxyl of pyridine **II**. Protected pyridine **II** is reacted with the lactone **III** where the protecting group in the hydroxyl avoids selectivity problems during the coupling step. Then, the phosphoryl chloride substitutes the resulting hydroxyl group with chlorine and compound **IV** is obtained in a 62.3% yield, again the benzyl group avoids selectivity problems. Compound **IV** is then hydrogenated in the presence of a palladium catalyst to remove the benzyl protecting group and to reduce the pyridine ring. Compound **V** is obtained quantitatively.

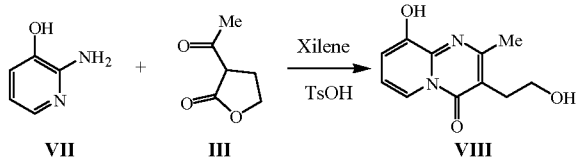
Said compound **V** is coupled with compound **VI** in the presence of diisopropylamine in methanol to yield the desired compound **I** in a 21% yield.

International patent applications WO2008021345A and WO2008024415A also relate to the synthesis of Paliperidone and use a similar approach, also using, a benzyl protecting group with low to moderate yields.

The use of protecting groups is widely present in the field of organic synthesis, and they are useful to differentiate two or more moieties with similar reactivity. Even that, its use reduces the atomic economy of the reaction and increases the waste by-products. All this increases the costs and the environmental problems of the reaction.

Not only that, but in this case the use of the benzyl protecting group increases the amount of hydrogen gas, which is a toxic and flammable gas, consumed during the synthesis process.

There are documents describing the synthesis of suitable intermediates, such as EP0730594 and EP0808313 that prepare compound **VIII** in xylene and *p*–toluenesulphonic acid (Scheme 2). The resulting hydroxyethyl moiety is activated with a mesyl group.

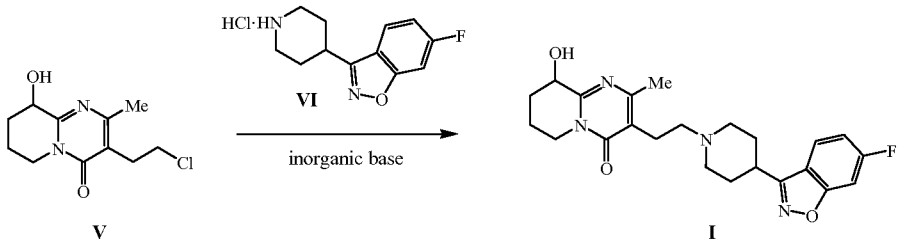


VII **III** **VIII**

Scheme 2

In EP1791839 it is also described the synthesis of compound **VIII** in similar conditions and it is said that in the conditions described in EP0730594 and EP0808313 compound **VIII** is poorly soluble and that renders a difficulty in the following reactions (not described in the document). In EP1791839 this problem is solved using chlorobenzene.

In WO2008021345 it is described the preparation of Paliperidone, **I**, via the coupling of compounds **V** and **VI** using an inorganic base (Scheme 3).



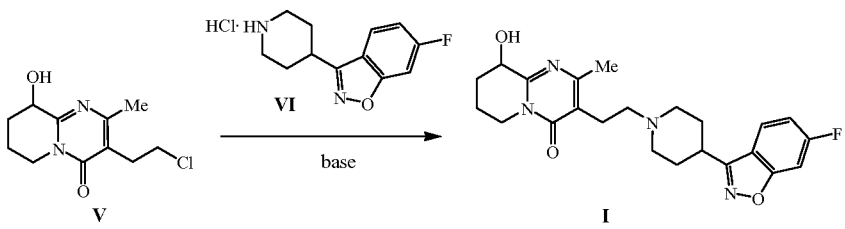
Scheme 3

Therefore, there is a need in the art to develop a new process to obtain Paliperidone with higher yield, increase atomic economy and less environmental drawbacks.

All the documents cited therein are enclosed in its entirety by reference.

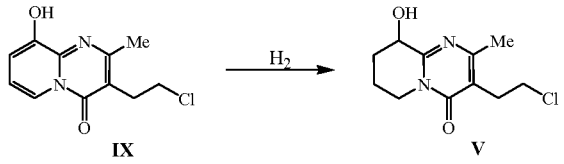
BRIEF DESCRIPTION OF THE INVENTION

The invention relates to a process for obtaining Paliperidone, **I**, comprising alkylating compound **VI**, or a salt thereof, with compound **V**, or a salt thereof, using a base selected from triethylamine or diisopropylethylamine and, optionally, a solvent (Scheme 4).



Scheme 4

Moreover, the invention relies on to a process for preparing compound **V** or a salt thereof by hydrogenation of compound **IX** or a salt thereof (Scheme 5).



IX **V**

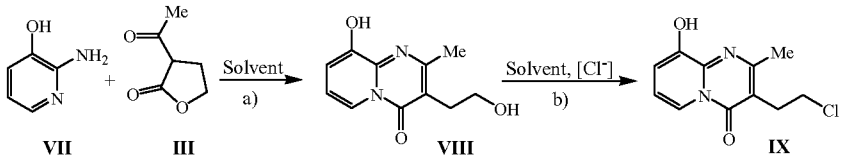
Scheme 5

The invention also relates to a process for obtaining 3-(2-chloroethyl)-2-methyl-9-hydroxy-4*H*-pyrido[1,2-a]pyrimidin-4-one, **IX**, or a salt thereof, comprising two steps (Scheme 6):

a) reaction of 2-amino-3-hydroxypyridine, **VII**, and 2-acetylbutyrolactone, **III**, in a solvent and a cosolvent to obtain the diol **VIII**,

b) diol **VIII** is reacted with a suitable chlorinating agent, [Cl^-], to selectively obtain compound **IX**, and

c) optionally, compound **IX** is converted into a salt thereof.



VII **III** **VIII** **IX**

Scheme 6

FIGURES

FIG.1 illustrates the X-ray powder diffraction pattern of **IX.HCl**;

FIG.2 illustrates the X-ray powder diffraction pattern of an embodiment of purified **IX.HCl**.

FIG.3 illustrates the Differential scanning calorimetry of a second embodiment of purified **IX.HCl**.

FIG.4 illustrates the X-ray powder diffraction pattern of a second embodiment of purified **IX.HCl**.

DETAILED DESCRIPTION OF THE INVENTION

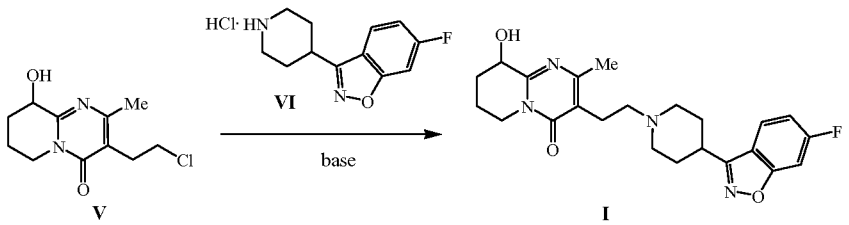
In the context of the present invention, the following terms have the meaning detailed below:

The term "one-pot reaction" means two or more reactions that take place without isolating intermediate compounds, wherein all the reactants are added at the beginning of the first reaction or adding the reactants sequentially during the course of the reaction.

The term "polar aprotic solvent" relates to a polar solvent that is not capable of exchanging protons with the reagents and that has no polarizable proton. Examples of polar aprotic solvents are dimethylformamide (DMF), dimethylsulphoxide (DMSO), N-methylpyrrolidone and dimethylacetamide (DMAc).

The FT-IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrophotometer in an ATR accessory, from 650 to 4000 cm^{-1}.

The present invention relates to a process for obtaining Paliperidone, **I**, comprising alkylating compound **VI**, or a salt thereof, with compound **V**, or a salt thereof, using a base selected from triethylamine or diisopropylethylamine and, optionally, a solvent.



It has been surprisingly found that the change from the diisopropylamine base used in the prior art (EP0368388) to triethylamine or diisopropylethylamine allows to obtain the desired product Paliperidone, **I**, not only with a great increase on the yield (93%) but also without requiring column chromatography. In fact, only one crystallization is needed. Therefore, the use of triethylamine or diisopropylethylamine allows increasing the yield of the process and avoids the use of column chromatographic solvents and other related materials. Moreover, another

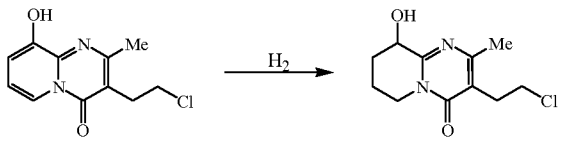
advantage of avoiding purification through column chromatography is the use of no special equipment which means that the process can be undertaken with common reactors.

The increase on the yield and the use of common reactors to perform the reaction reduces the costs of the overall process, and the reduction of the solvents and other materials reduces the environmental drawbacks of the reaction.

The solvent used in the process for obtaining Paliperidone of the present invention is selected from an alcohol such as methanol, ethanol or isopropanol or water or a mixture of said solvents. When the process is performed in the absence of a solvent, the base, triethylamine or diisopropylethylamine, is used as solvent.

The process of the present invention preferably takes place from room temperature to the reflux temperature of the solvent. The preferred temperature is from 50 °C to the reflux temperature of the solvent.

Compound **V**, or a salt thereof, used in the process of the present invention can be prepared by hydrogenation of compound **IX**, or a salt thereof.



IX **V**

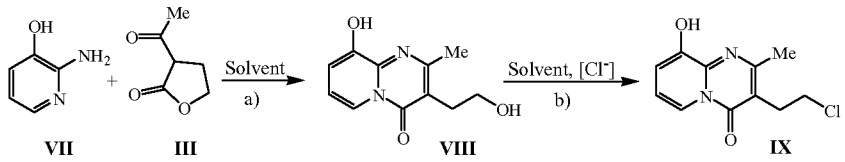
The hydrogenation of compound **IX** can be performed using a palladium hydrogenation catalyst in an alcoholic solution. The alcohol is preferably methanol, ethanol or isopropanol. According to one embodiment of the present invention, the alcoholic solution consists of an alcohol of commercial purity (see Example 3). According to another embodiment of the present invention, the alcoholic solution consists of a mixture of the alcohol with water, from 1:0.01 to a ratio of 1:1 (v/v) (i.e. from 99% alcohol up to 50% by volume of alcohol in the mixture), preferably from 99% to 80% of alcohol to water (see Example 4).

The preparation of intermediate 3-(2-chloroethyl)-2-methyl-9-hydroxy-4*H*-pyrido[1,2-a]pyrimidin-4-one, **IX**, or a salt thereof, can comprise the following steps:

a) reaction of 2-amino-3-hydroxypyridine, **VII**, and 2-acetylbutyrolactone, **III**, in a solvent and a cosolvent to obtain the diol **VIII**,

b) diol **VIII** is reacted with a suitable chlorinating agent, [Cl^-], to selectively obtain compound **IX**, and

c) optionally, compound **IX** is converted into a salt thereof.



VII III VIII IX

The solvent used in the aforementioned step a) is an aromatic hydrocarbon or a mixture thereof such as benzene, toluene or xylenes. The cosolvent used in step a) is a polar aprotic solvent such as *N*-methylpyrrolidone, DMSO, DMAc or DMF.

The use of a cosolvent facilitates the solubility of the starting and final products resulting in an easier and faster reaction.

To facilitate this step a) of the process, an acidic catalyst such as methanesulphonic acid, *p*–toluensulphonic acid, sulphuric acid or acetic acid is added. Preferably, the catalyst is methanesulphonic acid.

Step a) of the process of the present invention to prepare compound **IX**, can be performed from 80 °C to the reflux temperature of the solvent or mixture of solvents, preferably it is performed at reflux temperature.

The suitable chlorinating agent, [Cl^-], of the aforementioned step b) is selected from $POCl_3$, PCl_3, PCl_5, *N*–chlorosuccinimide, cyanuric chloride or the like.

Step b) of the process of the present invention to prepare compound **IX**, can be performed from room temperature to the reflux temperature of the solvent or mixture of solvents. Preferably the temperature is 80-120 °C, more preferably 90-100 °C.

The process of the present invention to prepare compound **IX** is performed with means to remove the evolved water, such as a Dean-Stark receiver or molecular sieves.

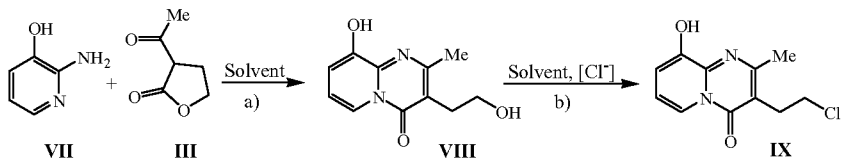
The process of the present invention to prepare compound **IX** can be performed as a one pot reaction, or the intermediate alcohol **VIII** can be isolated. Preferably, compound **IX** is prepared as a one pot reaction without isolation of **VIII**.

Since a chlorinating agent is used in step b), compound **IX** is likely to be obtained in the form of the hydrochloride salt. Other salts such as sulphate, hydrogensulphate, oxalate or acetate can also be formed from the free base and used for the purposes of the present invention.

The following non-limiting examples will further illustrate specific embodiments of the invention. They are, however, not intended to be limiting the scope of the present invention in any way.

EXAMPLES

Example 1: 3-(2-chloroethyl)-2-methyl-9-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride, IX·HCl



VII III VIII IX

5.0 g (45.41 mmol) of 2-amino-3-hydroxypyridine, **VII**, are suspended in xylene (35 ml) and *N*-methylpyrrolidone (5 ml). Next, methanesulphonic acid (0.021 ml; 0.31 mmol) and 2-acetylbutyrolactone, **III**, (2.9 ml, 26.93 mmol) were added. The resulting suspension is refluxed collecting the water evolved in a Dean-Stark receiver during two hours. Then a second portion of the 2-acetylbutyrolactone, **III**, (2.4 ml, 22.29 mmol) is added to the reaction mixture and the reflux is maintained until disappearance of the reactants.

The mixture is allowed to cooled down to 70-75 ºC and $POCl_3$ (12.5 ml, 136.55 mmol) is added, then the mixture is heated to 90-95 ºC and maintained until disappearance of the reactants. Then the mixture is allowed to cool to room temperature and water is added and the mixture cooled to 10 ºC and a off-white solid precipitates that is filtered and washed with water. 9.4 g (34.4 mmol, 75% yield) of **IX·HCl** were obtained.

Analytical data:

RMN ^{1}H (D_2O) δ (ppm): 2.70 (*s*, CH_3); 3.21 (*t*,CH_2); 3.87 (*t*,CH_2Cl); 7.58 (*t*, *ar*CH); 7.75 (*d*, *ar*CH); 8.71(*d*, *ar*CH).

m.p.: 213 - 218 °C

DSC: m.p. = 212.9 °C

K.F. = 5.6 % of H_2O

IR: 2844.8, 1703.5, 1641.4, 1584.10, 1515,9, 1406.8, 1297.7, 1227.0, 1162.2, 1142.3, 999.8, 877.2, 815.6, 778; 756.6; 722; 686 cm^{-1}

XRD Peak list: 8.68, 12.25, 13.71, 16.01, 16.58, 19.39, 20.67, 23.67, 25.58, 25.99, 28.02, 28.21, 31.02,

Purification of IX.HCl

The product **IX·HCl** (3-(2-chloroethyl)-2-methyl-9-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one monohydrochloride) thus obtained (9.4 g; 34.15 mmol), is placed in a round bottom flask and isopropyl alcohol 47ml is added. The suspension is taken to 60 °C and water is added until a clear solution is obtained. The solution is then allowed to cool and taken to 0 °C. The off-white precipitate was filtered and washed with isopropyl alcohol and dried.7.01 g (75% yield of a 99% HPLC purity pure product) of compound **IX** are obtained.

*Analytical data of **IX·HCl:***

RMN ^{1}H (D_2O) δ (ppm): 2.70 (*s*, CH_3); 3.21 (*t*,CH_2); 3.87 (*t*,CH_2Cl); 7.57 (*t*, *ar*CH); 7.74 (*d*, *ar*CH); 8.70(*d*, *ar*CH).

DSC: m.p.= 228 °C

K.F: 4.7 % of H_2O

IR: 3493; 3290; 1692.3; 1644.5; 1619.1; 1589.4; 1511.6, 1411,7; 1304,02; 1230.6; 1174.4; 1146.7; 1075.1; 914.1, 874.7, 811.1, 781.7, 760.9; 739.7; 721; 686.

XRD Peak list: 10.49, 11.08, 11.91, 16.54, 22.47, 23.23, 23.94, 26.08, 26.77, 27.00, 28.01, 35.07.

The product obtained as described above can be further dried in the vacuum oven at 60 °C for 24 hours.

Analytical data:

K.F: 0.1 % of H_2O

DSC: m.p.= 227 °C

IR: 2650, 2603, 2523, 1701, 1636, 1616, 1580, 1508, 1441, 1403, 1358, 1334, 1302, 1229, 1189, 1172, 1160, 1138, 1101, 1074, 1039, 1014, 998, 938, 918, 888, 874, 825, 800, 789, 755, 708, 678;

XRD Peak list: 7.85, 10.51, 13.25, 14.60, 16.65, 17.20, 19.50, 21.04, 22.63, 23.13, 23.29, 24.00, 24.97, 25.91, 26.30, 26.68, 27.09, 29.21, 29.72, 30.51, 32.74, 33.39.

Alternative purification method of IX.HCl

3-(2-chloroethyl)-2-methyl-9-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one monohydrochloride, **IX.HCl**, (15.0g; 54.5mmol) was placed in a round bottom flask and isopropyl alcohol was added. The suspension was taken to reflux and it was kept for 30 minutes. The reaction mixture was then allowed to cool and taken to 0 °C. The off-white precipitate was filtered and washed with isopropyl alcohol and dried. 13.3g (88.7% yield of a 98% HPLC purity pure product) of compound **IX.HCl** were obtained.

Analytical data:

K.F= 0.1% of H_2O

DSC: m.p.= 227.6 °C.

RMN ^{1}H (D_2O) δ (ppm): 2.70 (*s*, CH_3); 3.22 (*t*,CH_2); 3.88 (*t*,CH_2Cl); 7.59 (*t*, *ar*CH); 7.75 (*d*, *ar*CH); 8.71(*d*, *ar*CH).

IR: 1709.7; 1642.6; 1620.4; 1583.2; 1514.2; 1410.73; 1303.02; 1228.6; 1171.1; 1144.7; 1076.7; 919.1; 876.6; 815.2 ; 781.65; 736.7; 719.9; 679.9 cm^{-1}.

XRD Peak list: 7.94, 10.57, 13.37, 14.64, 16.45, 17.28, 19.55, 21.11, 22.26, 22.70, 23.54, 24.08, 25.03, 26.00, 26.20, 26.39, 26.83, 27.21, 28.85, 29.43, 30.59,

32.67. The obtained XRD pattern was the same as that obtained in the previous embodiment.

The product obtained as described above can be further dried in the vacuum oven at 60 °C for 24 hours. The product was characterised by IR and DSC:

DSC: m.p.= 222.7-230.74 °C

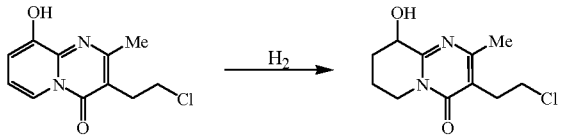
IR: 2439.4; 1712.5; 1640.6; 1618.3; 1578.9; 1522.4; 1442.6; 1410.4; 1356; 1333.3; 1300.9; 1270.1; 1228.33; 1189.4; 1169; 1140.8; 1076.1; 1039.5; 1020.9; 921.47; 876.6; 849.9; 789.9; 755.9; 736.0; 705.73; 676.8 cm^{-1}.

Example 2: 3-(2-chloroethyl)-2-methyl-9-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one monohydrochloride, IX.

5.0 g (45.41 mmol) of 2-amino-3-hydroxypyridine, **VII**, are suspended in xylene (35 ml) and *N*-methylpyrrolidone (5 ml). Next, methanesulphonic acid (0.021ml; 0.31mmol) and 2-acetylbutyrolactone, **III**, (2.9 ml, 26.93 mmol) are added to the suspension. The resulting suspension is refluxed collecting the water evolved in a Dean-Stark receiver during two hours. Then a second portion of the 2-acetylbutyrolactone, **III**, (2.4 ml, 22.29 mmol) is added to the reaction mixture and the reflux is maintained until disappearance of the reactants.

The mixture is allowed to cooled down to 70-75 °C and $POCl_3$ (12.5 ml, 136.55 mmol) is added, then the mixture is heated to 90-95 °C and maintained until disappearance of the reactants. Then, the reaction mixture is allowed to cool to room temperature and water is added. The mixture is neutralised with NH_3aq and the product is extracted with DCM (3x 100ml). The solvent is evaporated under reduced pressure and an oily residue is obtained. Next, IPA is added and HClaq is added until pH 2-3. An off-white solid precipitates during the addition. The suspension is allowed to cool and the solid is filtered and washed with IPA. 9.4 g (34.4 mmol, 75% yield of a 98% HPLC pure product) of **IX** are obtained.

Example 3: 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-9-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one, V



IX V

25.0 g (90.86 mmol) of compound **IX** hydrochloride are dissolved in methanol (225ml) and the solution is then treated with carbon and Celite during 1h at 40 °C. The mixture was then filtered and the cake was washed with hot methanol. The solution is placed in a hydrogenation reactor and 3.75 mg of Pd/C are added to the mixture. The reactor is then purged with nitrogen once and three times with H_2. The reaction mixture was heated to 50 °C and the reaction was controlled until disappearance of the reactants at atmospheric pressure.

When the reaction is over the catalyst is filtered and the solvent is evaporated until an oily residue is obtained. Then, water is added and a solution of potassium acetate in water is added dropwise to the above solution. The compound precipitates and is filtered and washed with water. 19.7 g. (81.17 mmol; 89.5% yield) of the desired product **V** are obtained.

*Analytical data of **V**:*

NMR ^1H ($CDCl_3$) δ (ppm): 1.72-2.33 (*m*, CH_2-CH_2); 2.37 (*s*, CH_3); 3.01 (*t*,CH_2); 3.77 (*t*, CH_2Cl); 3.94 (d*t*, CH_2); 4.52 (*t*, CH-OH).

m.p.: 102-106 °C

IR: 1651.6, 1597.0, 153.9, 1486.4, 1447.2, 1326.0, 1270.4, 1182.1, 1118.8, 1074.2, 1020.7, 981.0, 951.1, 907.6, 802.1, 736.0, 706.5, 659.7.

*Preparation of **V·HCl***

0.500 g (2.06mmol) of compound **V**, obtained according to the process described above, are dissolved in 2-butanone (3.5 ml) and concentrated hydrochloric acid is added to the solution until pH 2 is obtained. The solvent was then removed

under vacuum till an oily residue is obtained. 2-Butanone is added to the residue and evaporated under vacuum. This procedure is repeated three times.

2-Butanone is added to the oily residue and the product is allowed to precipitate. Then, the suspension is cooled to 0 °C. The precipitated product is filtered and washed with 2-butanone. 0.263 g. (0.942 mmol; 46% yield) of the desired product **V.HCl** are obtained.

Analytical data of V·HCl:

NMR ^{1}H (D2O) δ (ppm): 1.91-2.37 (*m*, CH_2-CH_2); 2.53 (*s*, CH_3); 3.07 (*t*,CH_2); 3.80 (*t*, CH_2Cl); 4.01 (d*t*, CH_2); 4.97 (*t*, CH-OH).

m.p.: 118-121 °C

IR: 1691.5, 1661.8, 1591.8, 1548.8, 1454.4, 1432.4, 1388.5, 1329.8, 1188.3, 1113.0, 1058.0, 1025.6, 906.1, 832.3, 789.5, 728.8.

Example 4: 3-(2-chloroethyl)6,7,8,9-tetrhydro-2-methyl-9-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one, V

2.75 g (10 mmol) of IX.HCl, 40 ml of IPA/H_2O (19:1 v/v, 0.25 M) and 404 mg of Pd/C catalyst (5% w/w (dry), containing 66.20% water) are placed in a reaction vessel and purged with nitrogen (~40 psi) five times at room temperature. Afterwards, the reaction vessel is purged an extra five times with hydrogen (50-60 psi) and heated up to 55°C under hydrogen (at atmospheric pressure) over 20 minutes. After that, the vessel is pressurized with hydrogen (15 psi) and mechanical stirring supplied (1500 rpm) at 55°C for 3 hours. The reaction vessel is then cooled to room temperature and carefully vented.

Analysis of the supernatant by HPLC showed that high conversions are achieved, over 98 %, and less than 1% of the de-chlorinated by-product is produced.

The reaction solution is filtered over celite, the filtered cake washed with MeOH and the combined filtrates evaporated to dryness to give V.HCl, as an off-white solid. A solution of potassium acetate in water is added drop wise, until complete

precipitation of compound V is achieved. The obtained precipitate is filtered and washed with water, yielding 2.23g (92% yield) of compound V.

Analytical data of V.HCl:

RMN ^{1}H (D_2O) δ (ppm): 1.91-2.37 (*m*, CH_2-CH_2), 2.53 (*s*, CH_3); 3.07 (*t*, CH_2); 3.80 (*t*, CH_2Cl); 4.01 (d*t*, CH_2); 4.97 (*t*, CH-OH).

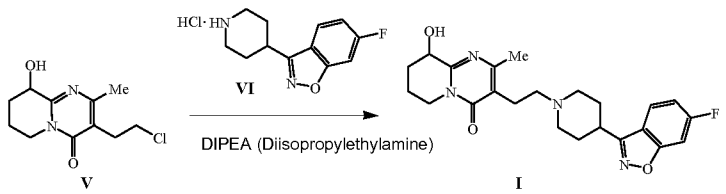
Analytical data of V:

RMN ^{1}H ($CDCl_3$) δ (ppm): 1.72-2.33 (*m*, CH_2-CH_2), 2.37 (*s*, CH_3); 3.01 (*t*, CH_2); 3.77 (*t*, CH_2Cl); 3.94 (d*t*, CH_2); 4.52 (*t*, CH-OH).

Example 5: **Preparation of Paliperidone, I**

5.7 g (23.49 mmol) of compound **V** are placed in a reaction vessel and methanol is added (29 ml). To this suspension 6.0 g (23.41 mmol) of compound **VI** are added and then Et_3N (9.8 ml; 70.41 mmol) is added. The resulting reaction mixture is then taken to reflux and maintained at this temperature overnight. The reaction mixture is then cooled down to 0 ºC and the solid precipitated is filtered and washed with MeOH. 7.4 g (17.35 mmol, 74%) of Paliperidone **I** are obtained.

Example 6: Preparation of Paliperidone, **I**.

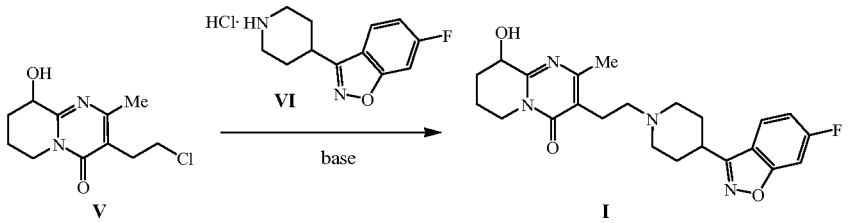


10.0 g (41.20 mmol) of compound **V** and 50 ml of methanol are placed in a reaction vessel. Afterwards, 10.6 g (41.33 mmol) of compound **VI** and 17.6 ml of DIPEA (102.81 mmol) are added. The resulting suspension is heated under reflux overnight. The reaction mixture is then cooled down to 0 ºC and the solid precipitate

filtered and washed firstly with MeOH and then with water. 16.3 g (38.22 mmol, 93% yield) of Paliperidone **I** are obtained.

CLAIMS

1. A process for obtaining Paliperidone, **I**, comprising alkylating compound **VI**, or a salt thereof, with **V**, or a salt thereof, using a base selected from triethylamine or diisopropylethylamine and, optionally, a solvent.

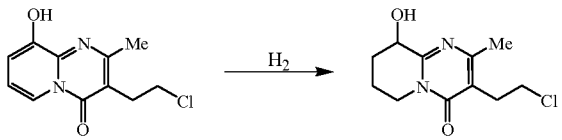


V I

2. The process according to claim 1 wherein the solvent is an alcohol such as methanol, ethanol, isopropanol, water or a mixture thereof.

3. The process according to claim 1 which takes place from room temperature to the reflux temperature of the solvent, preferably from 50 °C to the reflux temperature of the solvent.

4. The process according to claim 1 wherein compound **V**, or a salt thereof, is prepared by hydrogenation of compound **IX**, or a salt thereof.



IX V

5. The process according to claim 4 wherein compound **IX** is hydrogenated using a palladium hydrogenation catalyst.

6. The process according to claim 4 wherein compound **IX** is hydrogenated in an alcoholic solution.

7. The process according to claim 6 wherein the alcohol in the alcoholic solution is selected from methanol, ethanol or isopropanol.

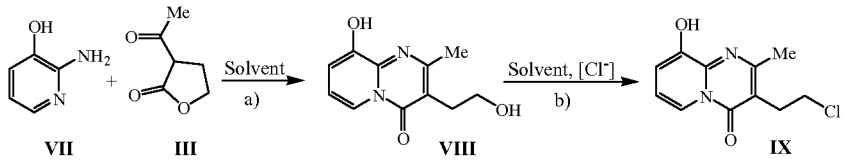
8. The process according to claim 6 wherein the alcoholic solution consist of a mixture of an alcohol with water from 1:0.01 to a ratio of 1:1 (v/v).

9. The process according to claim 4 wherein the preparation of compound **IX** or a salt thereof comprises the following steps:

a) reaction of 2-amino-3-hydroxypyridine, **VII**, and 2-acetylbutyrolactone, **III**, in a solvent and a cosolvent to obtain the diol **VIII**,

b) diol **VIII** is reacted with a chlorinating agent, [Cl^-], to selectively obtain compound **IX**, and

c) optionally, compound **IX** is converted into a salt thereof.



VII III VIII IX

10. The process according to claim 9 wherein the solvent is an aromatic hydrocarbon or a mixture thereof such as benzene, toluene or xylenes.

11. The process according to claim 9 wherein the cosolvent is a polar aprotic solvent such as *N*-methylpyrrolidone, DMSO or DMF.

12. The process according to claim 9 wherein an acidic catalysis is used in step a), being the preferred acid methanesulphonic acid.

13. The process according to claim 9 wherein step a) is performed at reflux temperature.

14. The process according to claim 9 wherein the chlorinating agent, [Cl^-], in step b) is $POCl_3$.

15. The process according to claim 9 wherein step b) is performed at 80-120 °C, preferably at 90-100 °C.

16. The process according to claim 9 which is performed with means to remove the evolved water, such as a Dean-Stark receiver or molecular sieves.

17. The process according to claim 9 which is performed as a one pot reaction.

18. The process according to claim 9 wherein compound **IX** is obtained in the form of a hydrochloride salt.

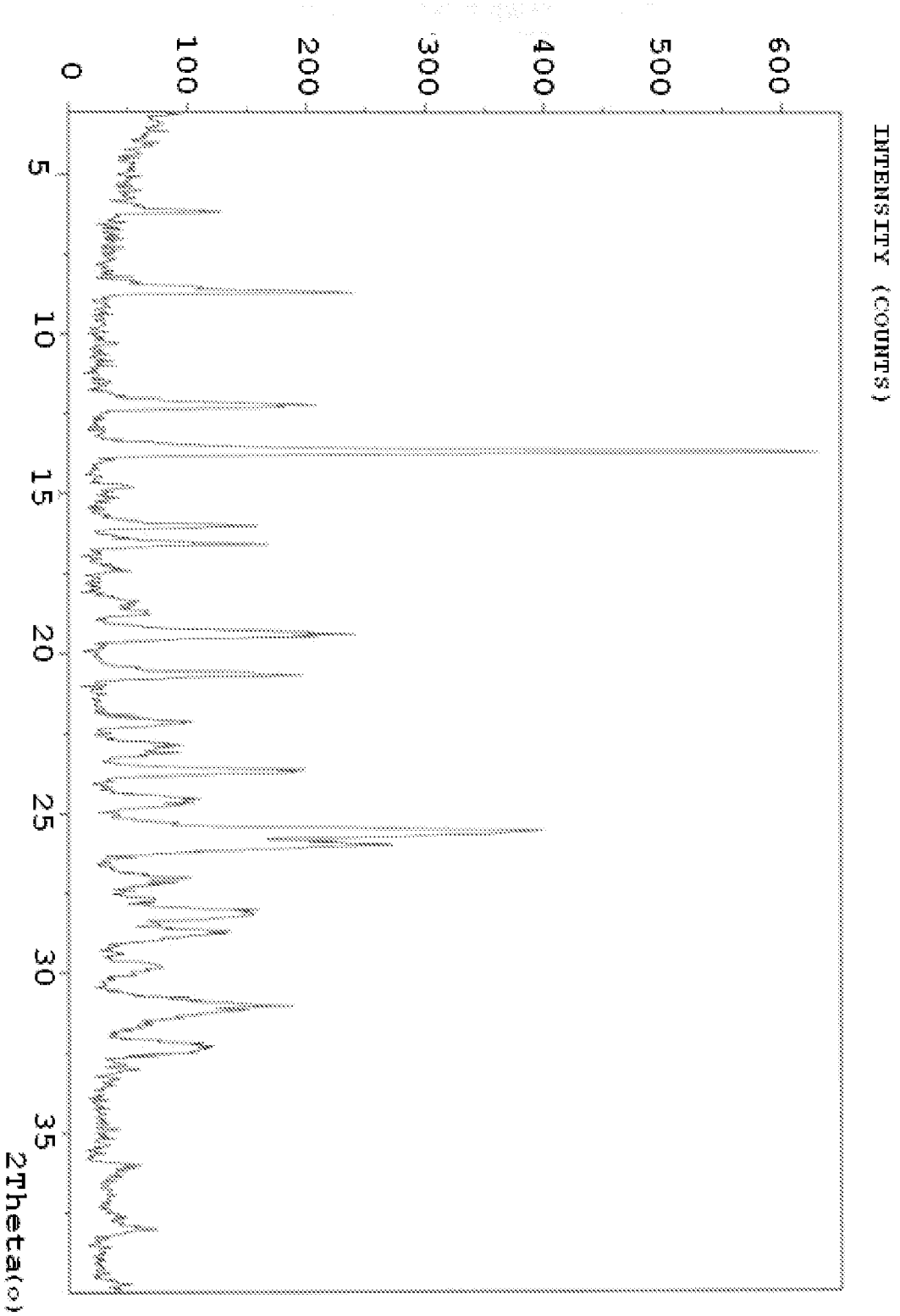

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FIG.1

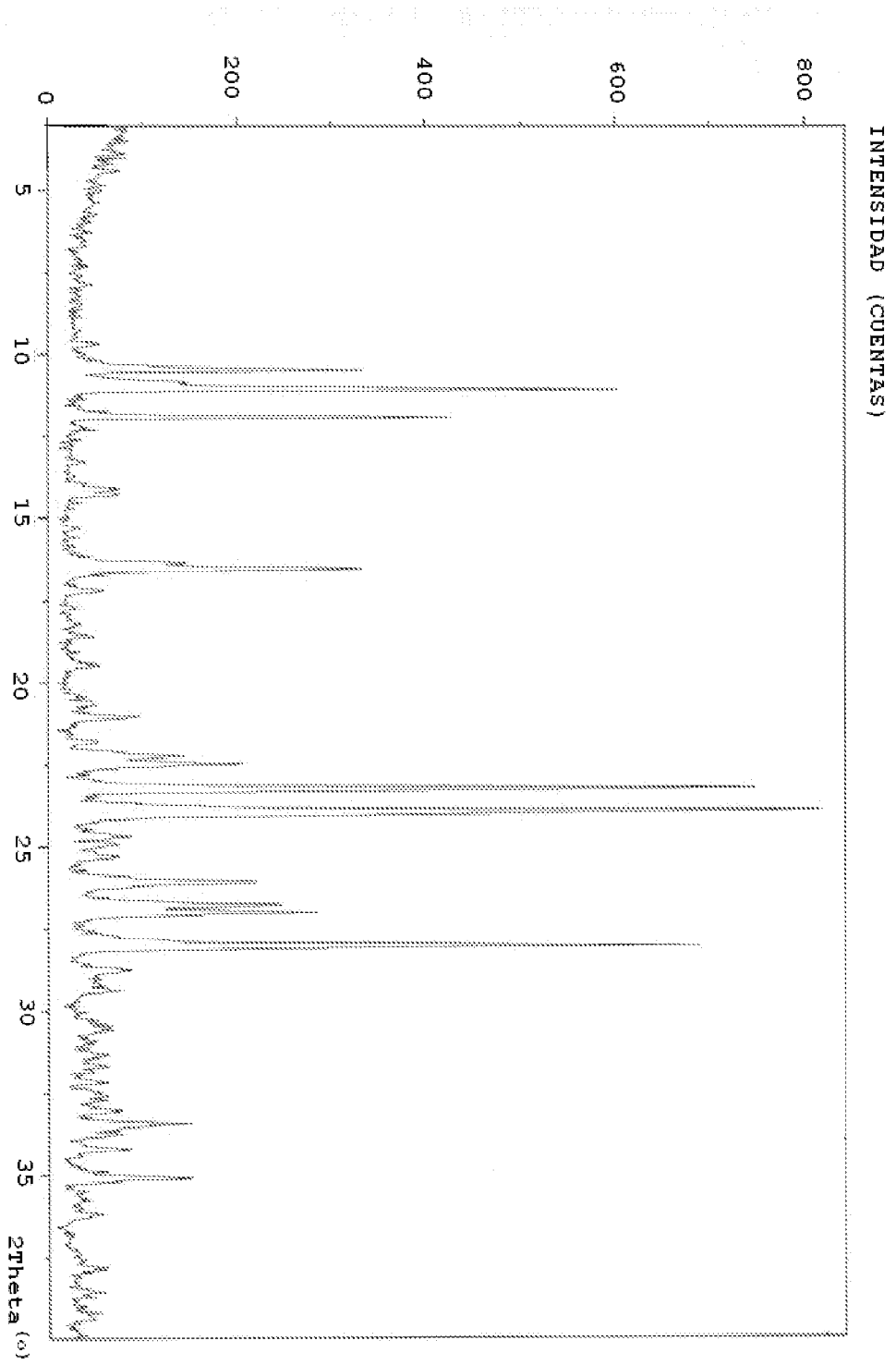

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FIG.2

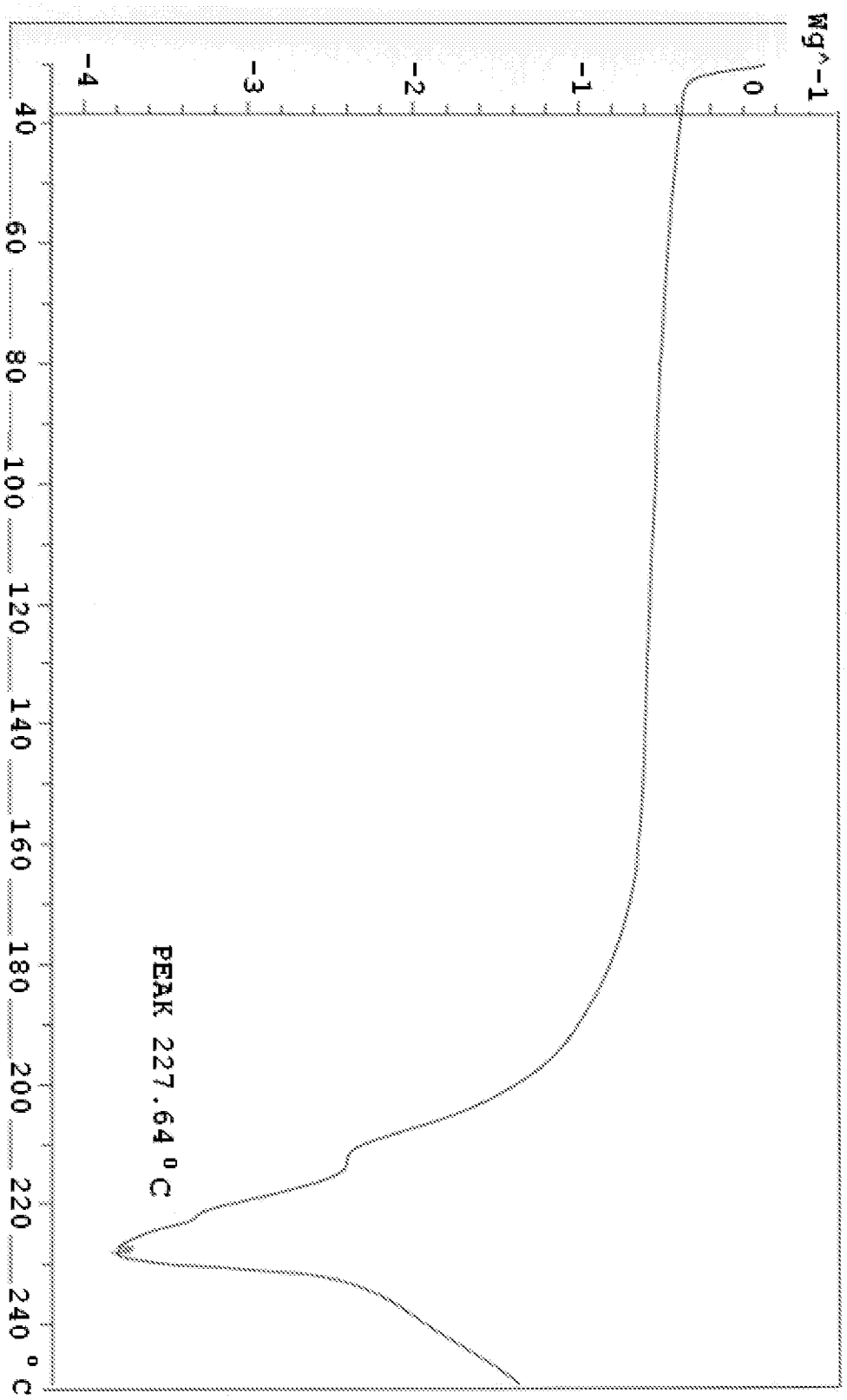


FIG.3

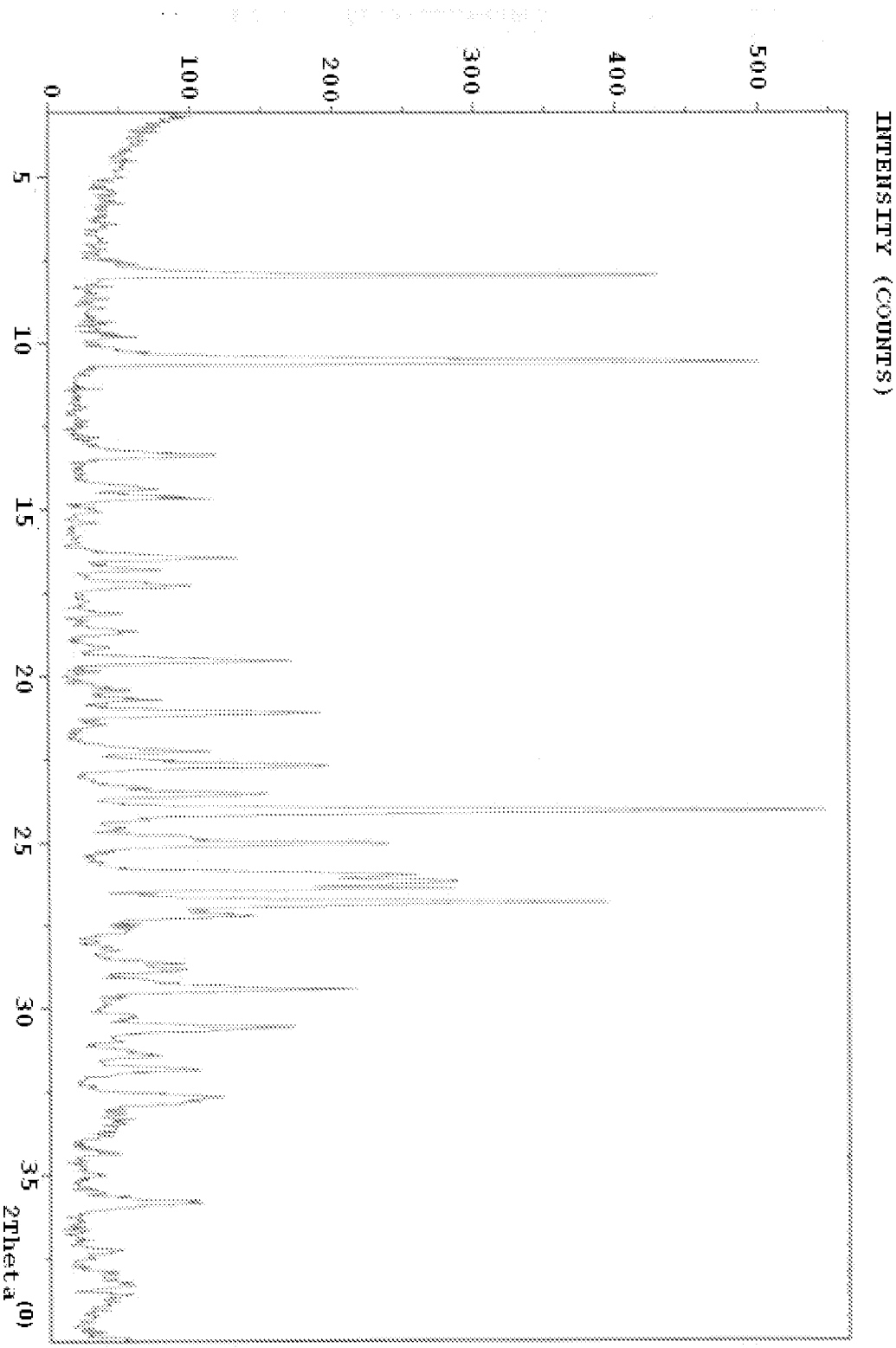

INTENSITY (COUNTS)
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FIG.4

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/056578

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04

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, 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.
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P,Y	WO 2009/015828 A (SYNTHON B. V.) 5 February 2009 (2009-02-05) page 13, line 4 - page 14, line 10; claims 1-19	1-18
Y	US 5 254 556 A (JANSSEN PHARMACEUTICA N. V.) 19 October 1993 (1993-10-19) column 2, line 29 - column 3, line 25	1-18

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 August 2009	21/08/2009

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/056578

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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US 2009048272	A1	19-02-2009	NONE		
WO 2009044413	A	09-04-2009	NONE		