(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 January 2004 (29.01.2004)

PCT

(10) International Publication Number
WO 2004/009591 A1

(51) International Patent Classification[7]: C07D 471/04

(21) International Application Number:
PCT/IN2003/000207

(22) International Filing Date: 2 June 2003 (02.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
545/MAS/2002 22 July 2002 (22.07.2002) IN

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

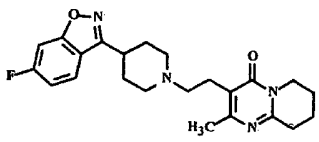
Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

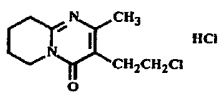
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU,*

[Continued on next page]

(54) **Title:** A PROCESS FOR THE PREPARATION OF ANTIPSYCHOTIC RISPERIDONE



(I)



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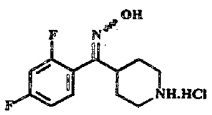

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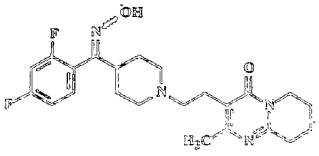

(IV)

(57) **Abstract:** This invention relates to a process for the preparation of antipsychotic risperidone (Formula I); which comprises reacting 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido-[1,2-a]pyrimidin-4-one (Formula II); with 4-(2,4-difluorobenzoyl)piperidine oxime (Formula III); to form oxime (Formula IV); and *in situ* cyclization of oxime (Formula IV) to form risperidone (Formula I) in a solvent selected from the group consisting of acetonitrile, *N,N*-dimetylformamide and methyl isobutyl ketone.

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SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*

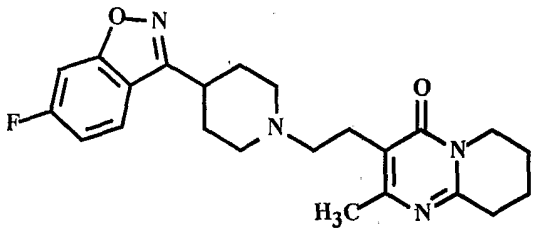
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

TITLE

A PROCESS FOR THE PREPARATION OF ANTIPSYCHOTIC RISPERIDONE

PRIOR ART

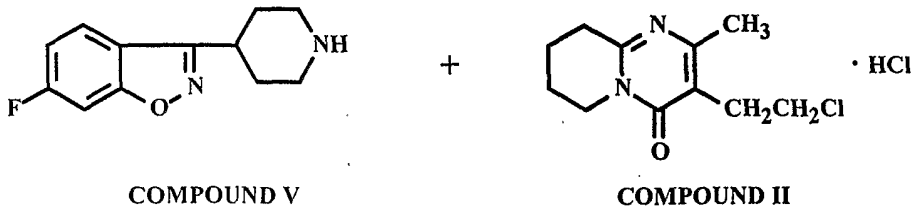
Risperidone (Compound I) is an antipsychotic agent belonging to 3-piperidinyl-1,2-benzisoxazole derivative reported by Janssen Pharmaceutica in US Patent 4,804,663.



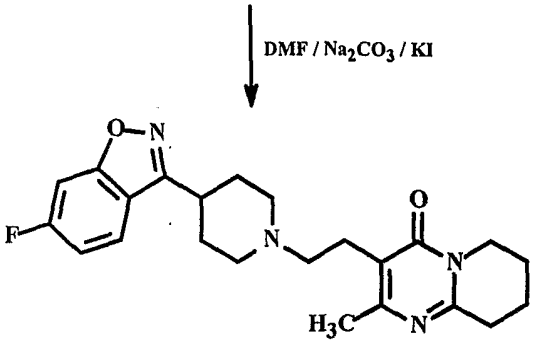
Compound I

It has chemical name 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.

In US Patent 4,804,663, it is prepared by N-alkylation of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (Compound V) with 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (Compound II) in dimethylformamide solvent using sodium carbonate base and potassium iodide catalyst in 46% yield. The product prepared in this manner often requires extensive purification.

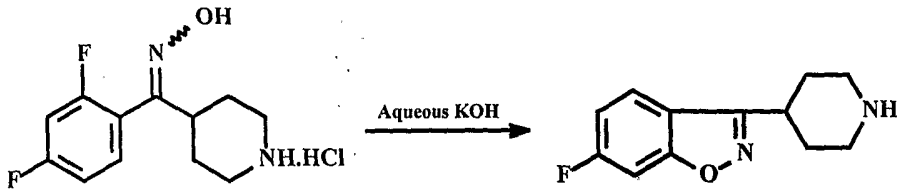


COMPOUND V COMPOUND II



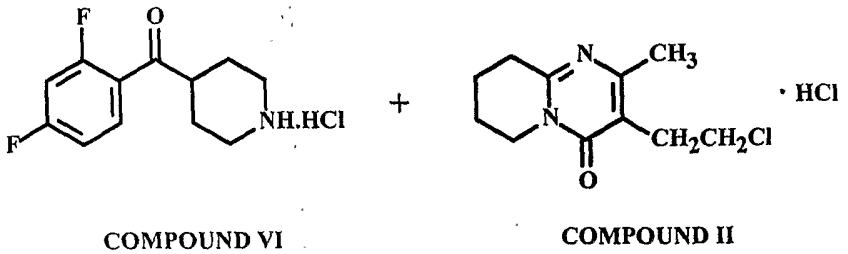
COMPOUND I

The benzisoxazole intermediate (Compound V) required in this route of risperidone synthesis has been prepared in US Patent 4,804,663 and US Patent 5,134,147 by cyclization of 4-(2,4-difluorobenzoyl)piperidine oxime (Compound III) in aqueous sodium hydroxide solution.

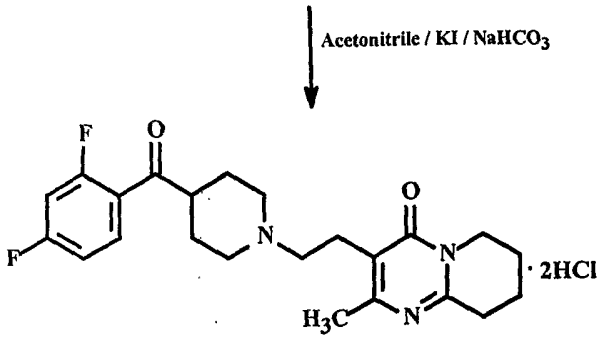


COMPOUND III COMPOUND V

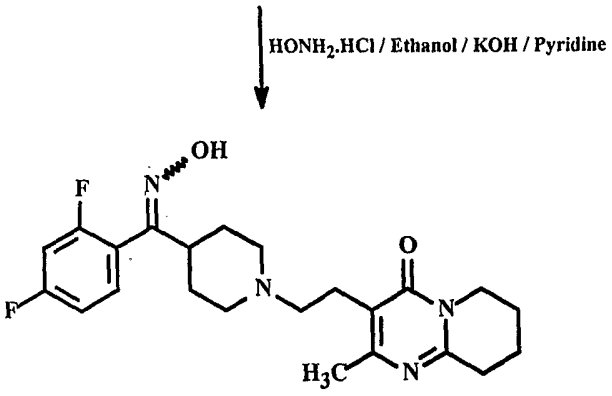
In Spanish Patent ES 2 050 069, an alternate synthesis of risperidone is disclosed where 4-(2,4-difluorobenzoyl)piperidine hydrochloride (Compound VI) is reacted with 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (Compound II) in presence of sodium bicarbonate and potassium iodide to obtain 3-[2-[4-(2,4-difluorobenzoyl)piperidino]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one dihydrochloride (Compound VII) which is then reacted with hydroxyl amine hydrochloride in ethanol in presence of pyridine and potassium hydroxide to obtain the oxime compound (Compound IV). The isolation of oxime and its purification from ethyl acetate is reported before cyclization to obtain risperidone (Compound I).



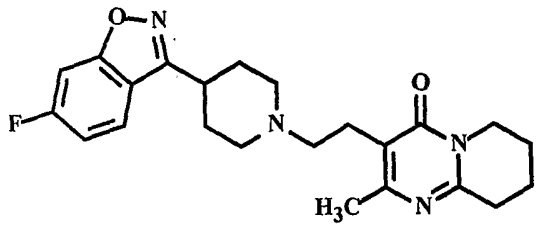
COMPOUND VI COMPOUND II



COMPOUND VII



COMPOUND IV



COMPOUND I

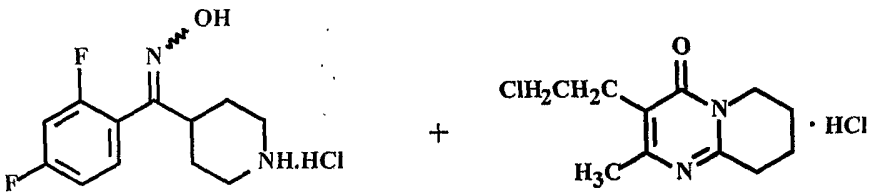
This approach of preparing risperidone involves number of chemical steps and results in an overall yield of 40%.

The aim of the present invention is to provide a method to obtain highly pure risperidone in high yield.

DESCRIPTION OF THE INVENTION

The instant invention relates to an industrially advantageous, economic and efficient method for the preparation of highly pure risperidone.

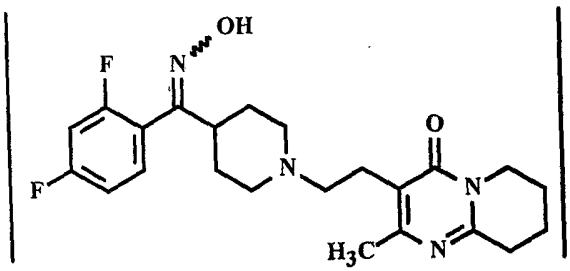
The process comprises reacting 4-(2,4-difluorobenzoyl)piperidine oxime hydrochloride (Compound III) with 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a] pyrimidin-4-one monochloride (Compound II) in a solvent such as acetonitrile, methyl isobutyl ketone, *N,N*-Dimethylformamide using potassium carbonate or sodium carbonate base in presence of catalytic amount of potassium iodide to obtain an intermediate oxime (Compound IV) that cyclizes *in situ* to produce risperidone. The product thus produced is crystallized from ethyl acetate to obtain highly pure risperidone in 81% yield.



COMPOUND III

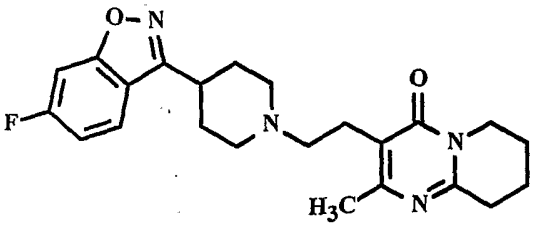
+

COMPOUND II



COMPOUND IV

Cyclization



COMPOUND I

In the instant process, single pot reaction of Compound III with Compound II results in risperidone. This eliminates one chemical step of subjecting Compound III to preparation of isoxazole Compound V prior to reaction with Compound II (US Patent 4,804,663). Further, this route advantageously does not require the isolation and purification of intermediate, 3-[2-[4-[1-(2,4-difluorophenyl)-1-(hydroxyimino)methyl]piperidino]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-4-one (Compound IV), which means fewer number of process operations resulting in safety and cost effectiveness. Using the process according to the invention, risperidone is isolated from the reaction mixture directly in highly pure form and high yield.

The following specific examples illustrate the process of this invention.

Example-1

A mixture of 5.58 g of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido [1,2-a]pyrimidin-4-one hydrochloride, 5.1 g of 4-(2,4-difluorobenzoyl)piperidine oxime hydrochloride, 0.46 g of potassium iodide, 6.76 g of anhydrous powdered potassium carbonate and 40 ml of acetonitrile was stirred and refluxed for 30 hours. Reaction monitoring by HPLC analysis indicated the formation of N-alkylated product, oxime, which subsequently slowly cyclized *in situ* to give risperidone. Thereafter, the reaction mixture was cooled and filtered. Residue was washed with cold water (50 ml) to remove the inorganics. Further washed with chilled ethyl acetate (5 ml). The product was crystallized from ethyl acetate yielding 6 g (81%) of 3-[2-[4-(6-fluoro-1,2-benzisoxazole-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a] pyrimidin-4-one.

Example-2

A mixture of 4.75 g of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido [1,2-a]pyrimidin-4-one hydrochloride, 5.1 g of 4-(2,4-difluorobenzoyl)piperidine oxime hydrochloride, 0.46 g of potassium iodide, 6.5 g of anhydrous powdered potassium carbonate and 30 ml of acetonitrile was stirred and refluxed for 30 hours. Reaction monitoring by HPLC analysis indicated *in situ* formation of risperidone. After the completion of reaction, the reaction mixture was cooled and water (120 ml) was added under stirring. Separated

solid stirred at 5°C for 1 hour, filtered, washed with water and crystallized from ethyl acetate yielding 6 g (81%) of 3-[2-[4-(6-fluoro-1,2-benzisoxazole-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a] pyrimidin-4-one.

Example-3

A mixture of 4.75 g of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido [1,2-a]pyrimidin-4-one hydrochloride, 5.1 g of 4-(2,4-difluorobenzoyl)piperidine oxime hydrochloride, 0.46 g of potassium iodide, 6.5 g of anhydrous powdered potassium carbonate and 30 ml of *N,N*-dimethylformamide was stirred at 95-100°C for 18 hours. The reaction mixture was cooled and water (120 ml) was added under stirring. Separated solid stirred at 5°C for 1 hour, filtered, washed with water and crystallized from ethyl acetate yielding 5.7 g (77%) of 3-[2-[4-(6-fluoro-1,2-benzisoxazole-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.

Example-4

A mixture of 4.75 g of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido [1,2-a]pyrimidin-4-one hydrochloride, 5.1 g of 4-(2,4-difluorobenzoyl)piperidine oxime hydrochloride, 0.46 g of potassium iodide, 6.5 g of anhydrous powdered potassium carbonate and 30 ml of MIBK was stirred at 100-105°C for 30 hours. The reaction mixture was cooled and water (150 ml) was added under stirring. Separated solid stirred at 5°C for 1 hour, filtered, washed with water and crystallized from ethyl acetate yielding 5.4 g (73%) of 3-[2-[4-(6-fluoro-1,2-benzisoxazole-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.

Example-5

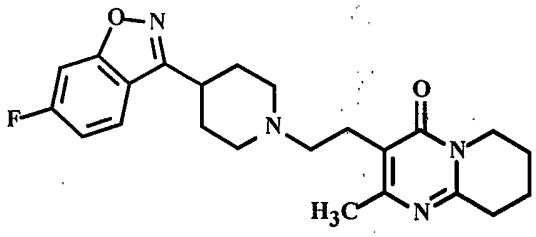
A mixture of 4.75 g of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido [1,2-a]pyrimidin-4-one, 6.0 g of 4-(2,4-difluorobenzoyl)piperidine oxime hydrochloride, 0.46 g of potassium iodide, 6.1 g of anhydrous powdered potassium carbonate and 40 ml of acetonitrile was stirred and refluxed for 30 hours. The reaction mixture was cooled and water (120 ml) was added under stirring. Separated solid stirred at 5°C for 1 hour, filtered, washed with water. Crude product was purified by crystallization in ethyl acetate to afford 6.8 g (79%) of 3-[2-[4-(6-fluoro-1,2-benzisoxazole-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a] pyrimidin-4-one.

Example-6

A mixture of 4.75 g of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido [1,2-a]pyrimidin-4-one hydrochloride, 5.1 g of 4-(2,4-difluorobenzoyl)piperidine oxime hydrochloride, 0.46 g of potassium iodide, 5 g of anhydrous sodium carbonate and 30 ml of acetonitrile was stirred and refluxed for 32 hours. The reaction mixture was cooled and water (120 ml) was added under stirring. Separated solid stirred at 5° for 1 hour, filtered, washed with water and crystallized from ethyl acetate yielding 6 g (81%) of 3-[2-[4-(6-fluoro-1,2-benzisoxazole-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a] pyrimidin-4-one.

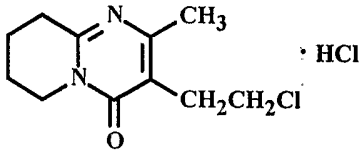
CLAIMS:

(1) A method of preparing risperidone (Compound I)



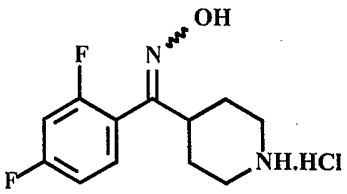
Compound I

which comprises reacting 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido-[1,2-a]pyrimidin-4-one (Compound II)



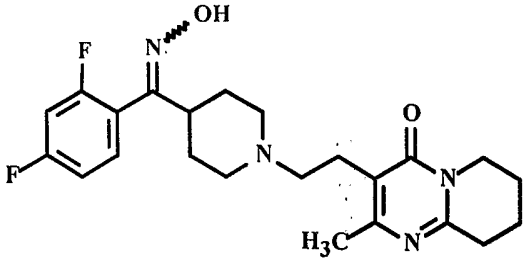
Compound II

with 4-(2,4-difluorobenzoyl)piperidine oxime (Compound III)



Compound III

to form oxime (Compound IV)



Compound IV

and *in situ* cyclization of oxime (Compound IV) to form risperidone (Compound I) in a solvent selected from the group consisting of acetonitrile, *N,N*-dimetylformamide and methyl isobutyl ketone.

(2) A method according to Claim 1 wherein the reaction is carried out with a base such as anhydrous powdered potassium carbonate or sodium carbonate in presence of potassium iodide as catalyst.

(3) A method according to Claim 1 wherein the reaction is carried out at a temperature in the range of 75°C to 110°C.

(4) A method according to Claim 1 wherein risperidone produced is purified by crystallization from an organic solvent preferably ethyl acetate.

(5) A method for preparing risperidone substantially as herein described with reference to the examples.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN 03/00207

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 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)
IPC 7 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, WPI Data, PAJ, 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.
P,X	WO 03 042212 A (CLEMENTIS GYOERGY ;EGYT GYOGYSZERVEGYESZETI GYAR (HU); KOERTVELYES) 22 May 2003 (2003-05-22) claim 1; examples	1-5
Y	WO 95 14691 A (JANSSEN PHARMACEUTICA NV ;VANDENBERK JAN (BE); KENNIS LUDO EDMOND) 1 June 1995 (1995-06-01) page 5 -page 6	1-5
Y	ES 2 050 069 A (VITA INVEST SA) 1 May 1994 (1994-05-01) cited in the application column 2 -column 3	1-5
Y	EP 0 453 042 A (JANSSEN PHARMACEUTICA NV) 23 October 1991 (1991-10-23) page 4 -page 5	1-5

-/--

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

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
22 September 2003	13/10/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Fazzi, R

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