Abstract: The present invention relates to a novel process for the preparation of ioperidone (I) that comprises reactions of 1-[4-(3-halopropoxy)-3-methoxyphenyl] ethanone (Hla / lIlb) with 6-fluoro-3-(piperidine-4-yl)-1,2-benzisoxazole hydrochloride (II) under pressure in an autoclave.
PROCESS FOR THE PREPARATION OF ILOPERIDONE

Field of the Invention:
The invention relates to a novel process preparation of iloperidone (I).

Background of the Invention:
Iloperidone is chemically known as 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone (I) and it is used for the treatment of schizophrenia.

The method for preparation of iloperidone disclosed in the patent EP 0402644 and the publication Drugs of Future 2000, 25(1):29 involves condensation of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride (II) with 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (IIIa), in the presence of potassium carbonate in dimethylformamide as solvent.
The patent application IN 1980/MUM/2007 describes the preparation of iloperidone by condensation of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride (II) with 1-[4-(3-chloropropoxy)-3-methoxyphenyl] ethanone (IIia) in the presence of inorganic base using water as solvent.

Summary of the Invention:

The present invention relates to a novel process for the preparation of iloperidone that comprises reaction of 6-fluoro-3-(piperidine-4-yl)-1,2-benzisoxazole hydrochloride (II) with 1-[4-(3-chloro/bromopropoxy)-3-methoxyphenyl]ethanone (III) in the presence of base and phase transfer catalyst in an autoclave.

Detailed description of the invention:

The present invention relates to a novel process for the preparation of iloperidone that comprises:

i) reaction of 4-hydroxy-3-methoxy acetophenone (IV) with 1-bromo-3-chloropropane (V) in the presence of a base and phase transfer catalyst to obtain 1-[4-(3-chloro/bromo propoxy)-3-methoxyphenyl]ethanone (III a / III b);

ii) reaction of 6-fluoro-3-(piperidine-4-yl)-1,2-benzisoxazole hydrochloride (II) with 1-[4-(3-chloro/bromopropoxy)-3-methoxyphenyl]ethanone (III a / III b) in the presence of base and phase transfer catalyst in an autoclave;

iii) isolation of iloperidone.

The present invention provides novel process for the preparation of iloperidone (I) as shown below:
The base used is an inorganic base selected from carbonates such as sodium bicarbonate, potassium bicarbonate; bicarbonates such as sodium bicarbonate, potassium bicarbonate; hydroxides such as sodium hydroxide, potassium hydroxide, ammonium hydroxide; alkali amides such as sodium amide, potassium amide etc; the preferred inorganic base is potassium carbonate. Potassium iodide can be optionally used in the steps (i) and (ii).

The solvent used is selected from nitriles such as acetonitrile, alcohols such as methanol, ethanol, isopropanol; ketones such as diethyl ketone, dimethyl ketone, ethyl methyl ketone, methyl isobutyl ketone, esters such as ethyl acetate, methyl acetate; ethers such dioxane, hydrocarbons such as toluene, tetrahydrofuran and polar aprotic solvents such as dimethyl sulfoxide, sulfolanes, 2-pyrrolidinone etc and mixtures thereof.

The most preferred solvent for step (i) is acetonitrile and for step (ii) is methanol.

The phase transfer catalyst used is selected from group comprising of benzyltrimethylammonium chloride, hexadecyltributylphosphonium bromide, methyltributylammonium chloride, tertiary butyl ammonium bromide (TBAB). The most preferred catalyst is TBAB.
The pressure of the autoclave is maintained in the range of 0.1-4 Kg/cm$^2$; preferably 1-2 Kg/cm$^2$.

Purification of iloperidone can be carried by crystallization from solvents selected from the group comprising of nitriles such as acetonitrile, alcohols such as methanol, ethanol, isopropanol; ketones such as diethyl ketone, dimethyl ketone, ethyl methyl ketone, methyl isobutyl ketone, esters such as ethyl acetate, methyl acetate; ethers such as dioxane, hydrocarbons such as toluene or mixtures thereof. The most preferred solvents for crystallization are methanol or acetone.

The aforementioned process uses less toxic and less hazardous solvents such as dimethyl formamide thereby making ecofriendly process.

The principles, preferred embodiments, and modes of operation of the present invention have been described in the foregoing examples.

**Examples**

**Example 1: Preparation of l-[4-(3-chloro/bromo propoxy)-3-methoxyphenyl] ethanone (III)**

Acetonitrile (1L) was charged to 4-hydroxy-3-methoxy acetophenone (IV) (0.5 kg, 3.009 moles). l-Bromo-3-chloropropane (V) (1.89 Kg, 12.036 moles) was added to the reaction mixture and was stirred followed by addition of TBAB (0.030 Kg, 0.0903 moles). Potassium carbonate (0.78 Kg, 5.657 moles) was added to the reaction mixture and heated to 80°C. The mixture was cooled and filtered. The solid obtained was charged to dichloromethane (2 liters) and stirred. The reaction mixture was heated to 40-45°C and distilled. The reaction mixture was cooled and methanol (0.5 liters) was added followed by the addition of water (5 liters). The entire reaction mixture was added to chilled water and stirred. The reaction mixture was filtered and washed with water and dried.
Example 2: Preparation of iloperidone (I)

6-Fluoro-3-(piperidinyl-4-yl)-1,2-benzisoxazole hydrochloride (II) (0.60 kg, 2.34 moles) and 1-[4-(3-chloro/bromo propoxy)-3-methoxyphenyl]ethanone (0.68 kg, 2.81 moles) were added to methanol (6 liters) in autoclave. To the mixture potassium carbonate (0.39 kg, 2.81 moles) was added followed by the addition of TBAB (0.03 kg). The reaction was maintained in the autoclave at 60-65°C for 15-16 hours. The reaction was then cooled and methanol was distilled out for the mixture. Toluene was charged to the reaction mixture and heated to 50-55°C. The reaction mixture was maintained for half an hour. Toluene was distilled out and reaction mixture is cooled. The solid was filtered and washed with chilled toluene and dried.

Yield: 0.779 Kg.
Purity: 99.35%

Example 3: Purification of iloperidone

Iloperidone (0.750 kg) was charged to methanol (1.688 liters). The mixture was heated to reflux temperature. The solution was gradually cooled to 0°C. The reaction mixture was maintained for 2 hours and the solid was filtered. The wet solid was washed with chilled methanol at 0-5°C and dried.

Yield: 0.71 kg
Purity: 99.25%

Example 4: Purification of iloperidone

Iloperidone obtained in example 3 (2.12 kg) was charged to acetone (10.6 liters) and charge charcoal (0.11 Kg). The mixture was heated to reflux temperature at 55-60°C and maintained for an hour. The solution was filtered through hyflo bed and washed with acetone. The filtrate was heated between 55-60°C to get a clear solution. The reaction was maintained for
an hour and cooled to 0-5°C. The solid was filtered and washed with chilled acetone. The solid was dried for 5-6 hours.

Yield: 1.735 kg
Purity: 99.90%
CLAIMS

1) A novel process for the preparation of iloperidone that comprises:
   (i) reaction of 4-hydroxy-3-methoxy acetophenone (IV) with 1-bromo-3-chloropropane (V) in the presence of a base and phase transfer catalyst to obtain 1-[4-(3-chloro/bromo propoxy)-3-methoxyphenyl]ethanone (IIa / IIb);
   (ii) reaction of 6-fluoro-3-(piperidine-4-yl)-1,2-benzisooxazole hydrochloride (II) with 1-[4-(3-chloro/bromopropoxy)-3-methoxyphenyl]ethanone (IIa / IIb) in the presence of base and phase transfer catalyst in an autoclave;
   (iii) isolation of iloperidone.

2) Process according to claim 1 wherein, the base is selected from carbonates such as sodium carbonate, potassium carbonate; bicarbonates such as sodium bicarbonate, potassium bicarbonate; hydroxides such as sodium hydroxide, potassium hydroxide, ammonium hydroxide; alkali amides such as sodium amide, potassium amide.

3) A process of claim 2 wherein, most preferred base is potassium carbonate.

4) Process according to claim 1 wherein, the phase transfer catalyst is selected from benzyl trimethylammonium chloride, hexadecyltributylphosphonium bromide, methyl trioctylammonium chloride, tertiary butyl ammonium bromide.

5) Process according to claim 4 wherein, the most preferred phase transfer catalyst used is tertiary butyl ammonium bromide.

6) Process according to claim 1 wherein, step (i) and step (ii) are optionally carried out in the presence of potassium iodide.

7) A process according to claim 1 wherein, the solvent in step (i) and (ii) is selected from nitriles such as acetonitrile; alcohols such as methanol, ethanol, isopropanol;
ketones such as diethyl ketone, dimethyl ketone, ethyl methyl ketone, methyl isobutyl ketone; esters such as ethyl acetate, methyl acetate; ethers such as dioxane, tetrahydrofuran; hydrocarbons such as toluene; and polar aprotic solvents such as dimethylformamide, dimethyl sulfoxide, sulfolanes, 2-pyrrolidinone etc and mixtures thereof.

8) Process according to claim 7 wherein, the most preferred solvent for step (i) is acetonitrile.

9) Process according to claim 7 wherein, the most preferred solvent for step (ii) is methanol.

10) Process according to claim 1 wherein the pressure in step (ii) is maintained at 1-2 kg/cm².

11) The process for the preparation of iloperidone as described by foregoing examples.
INTERNATIONAL SEARCH REPORT

According to International Patent Classification (IPC) or to both national classification and IPC:

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D413/04
ADD.

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, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>X</td>
<td>WO 2011/055188 A1 (ORCHID CHEMICALS &amp; PHARM LTD [IN]; REGURI BUCHI REDDY [IN]; ARUNAGI RI) 12 May 2011 (2011-05-12) examples 1,4</td>
<td>1-11</td>
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<td>A</td>
<td>REINHOLZ, E. ET AL: &quot;Selectivity in alkylation of phenols with l-bromo-3-chloropropane using phase-transfer catalysis&quot;, SYNTHESIS, (11), 1069-71 CODEN: SYNTBF; ISSN: 0039-7881, 1990, XP002680937, the whole document</td>
<td>1-5,7</td>
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<td>A, P</td>
<td>WO 2011/154860 A1 (ALEMBIC PHARMACEUTICALS LTD [IN]; RAMAN JAYARAMAN VENKAT [IN]; RANE DN) 15 December 2011 (2011-12-15) examples 1,2</td>
<td>1-11</td>
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* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent but published on or after the international filing date

"C" document on which the priority claim(s) are based

"D" document concerning the same invention as the claimed invention

"E" document concerning the same invention as another document cited in this report

“A” 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 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

"S" document member of the same patent family

Date of the actual completion of the international search: 29 August 2012

Date of mailing of the international search report: 12/09/2012

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Von Daacke, Axel
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