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(71) Applicant (for all designated States except US):
FERMION OY [FI/FI]; Koivu-Mankkaan tie 6 A,
FI-02200 Espoo (FI).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **GRUMANN, Arne**
[DE/FI]; Siestankuja 13 A, FI-02700 Kauniainen (FI).
HUHTA, Soini [FI/FI]; Nuotiotie 11, FI-02600 Espoo
(FI). **RUMMAKKO, Petteri** [FI/FI]; Hämäläistentie 11 C
7, FI-02780 Espoo (FI).

(74) Agent: **ORION CORPORATION ORION PHARMA**;
Legal Affairs and Intellectual Property Rights, P.O.Box 65,
FI-02101 Espoo (FI).

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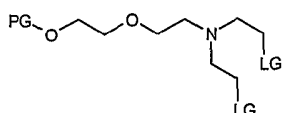
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(54) Title: PREPARATION OF QUETIAPINE



(II)

(57) Abstract: The present invention discloses a process for the preparation of quetiapine, which comprises the reaction of dibenzo[b,f][1,4]thiazepin-11-ylamine with a compound of the general formula (II) as well as novel intermediates in the process.

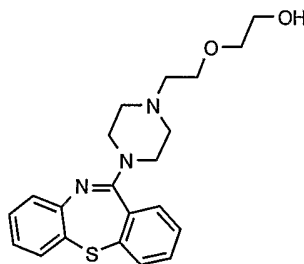
PREPARATION OF QUETIAPINE

Field of the invention

5 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)dibenzo[b,f]-1,4-thiazepine is a well established drug substance known under the INN name quetiapine. It is used as an antipsychotic or neuroleptic. The present invention provides an economical alternative method for the preparation of quetiapine in high yield and purity. Further objects of the invention are novel intermediates useful in the process according to
10 the invention.

Background of the invention

Several methods for the preparation of quetiapine I are known, as disclosed in e.g.
15 GB 8607684, GB 8705574, and WO 01/55125.

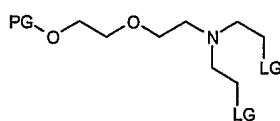


I

Known methods include reacting a halo derivative (e.g. iminochloride) of
dibenzo[b,f][1,4]-thiazepin-11(10-H)-one with 1-(hydroxyethoxyethyl)piperazine;
25 reacting the aforementioned halo derivative with piperazine and reacting the resulting intermediate with a haloethoxyethanol; and reacting a haloethylpiperazinylthiazepine derivative with ethylene glycol.

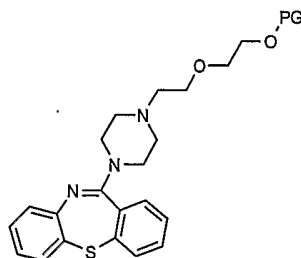
Summary of the invention

30 According to the present invention, the target compound I is prepared by reacting dibenzo[b,f][1,4]thiazepin-11-ylamine with a compound of the general formula II:



II

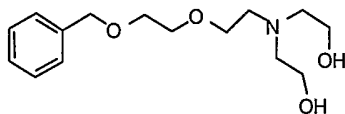
- 5 wherein PG is a hydroxyl protecting group selected from the group consisting of acetyl, benzoyl, pivaloyl, methoxymethyl, benzyl, 4-methoxybenzyl, allyl, tetrahydropyranyl, silyl, alkyl carbonate, aryl carbonate, aralkyl carbonate, benzyl carbonate, allylsulfonyl, benzylsulfonyl, toluenesulfonyl; preferably PG is methoxymethyl, benzyl, tetrahydropyranyl or acyl; LG is a suitable leaving group
10 selected from halogen, trifluoromethyl, O-p-toluenesulfonyl and O-methylsulfonyl, preferably halogen, most preferably chloro, to produce a compound of formula III



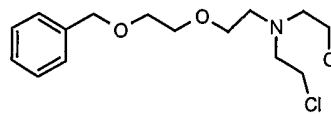
III

and subsequently removing the protecting group to produce quetiapine.

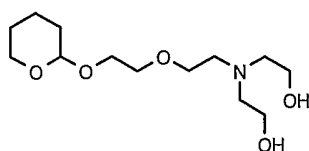
Further objects of the invention are the novel intermediates IV, V, VI, VII, VIII and IX:



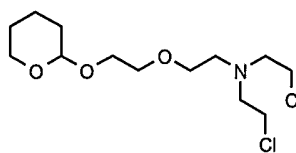
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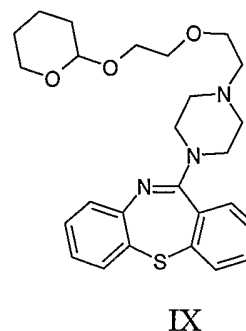
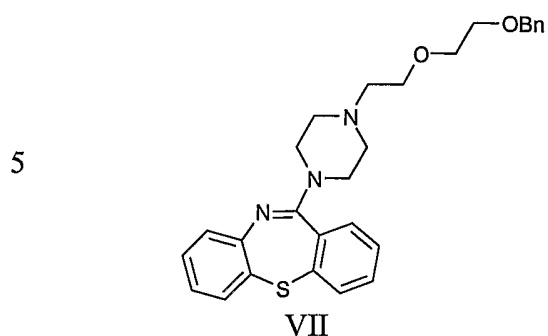
VI



VIII



IV

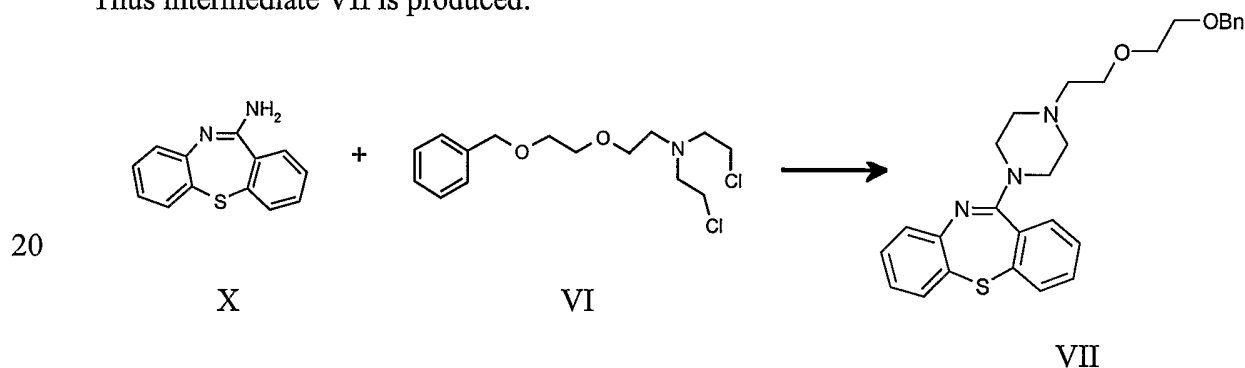


10 Disclosure of the invention

Dibenzo[b,f][1,4]thiazepin-11-ylamine may be prepared e.g. according to **J.Heterocyclic Chem.**, 34, 465 (1997) from 2-aminothiophenol and 2-chlorobenzonitrile.

15 According to one embodiment of the present invention, the compound of formula II is [2-(2-benzyloxy-ethoxy)-ethyl]bis-(2-chloroethyl)amine VI.

Thus intermediate VII is produced:



Preferably, the debenzylation step is carried out with a suitable Lewis acid, preferably boron trichloride, or alternatively using catalytic hydrogenation.

25

According to another embodiment of the invention, the compound according to formula II is bis(2-chloroethyl)-{2-[2-(tetrahydropyran-2-yloxy)ethoxy]ethyl}amine IV, whereby intermediate IX above, which can be deprotected to product I, is obtained.

30

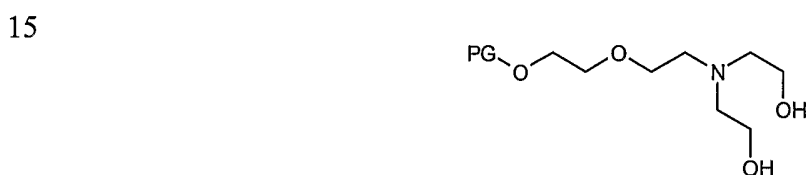
[2-(2-benzyloxy-ethoxy)-ethyl]bis-(2-chloroethyl)amine VI may be prepared starting from (2-chloro-ethoxymethylbenzene) by reacting it with triethanolamine to obtain a dihydroxy compound. Preferably, the reaction is carried out without a solvent at a temperature of 20 -160 °C. Instead of (2-chloro-ethoxymethylbenzene), derivatives with alternative leaving groups at the 2-site may be used, e.g. other halogens, O-p-toluenesulfonyl or O-methanesulfonyl.

An alternative route to intermediate II involves the reaction between a compound of the general formula XI



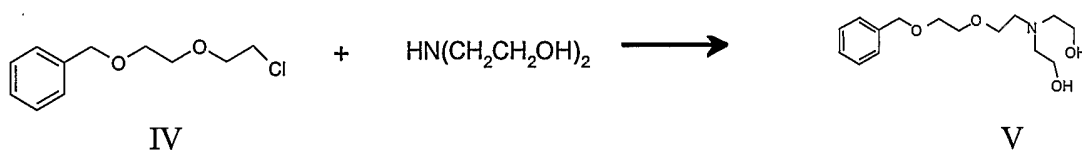
XI

wherein PG and LG are defined as above, and diethanolamine to yield an intermediate of formula XII:



XII

20 According to a preferable embodiment, this alternative route involves reacting [2-(2-chloro-ethoxy)-ethoxymethyl]benzene IV (obtained from bromomethylbenzene and 2-(2-chloro-ethoxy)-ethanol) with diethanolamine:



25

The resulting diol V may be converted to the dichloro derivative VI, preferably using thionyl chloride.

Coupling of dibenzo[b,f][1,4]thiazepin-11-ylamine with the relevant compound of formula II and removal of the protective group yields the target compound I.

30

Compounds VII and IX may be obtained by treating dibenzo[b,f][1,4]thiazepin-11-ylamine X with sodium hydride in DMF, adding the relevant substrate and isolating the reaction product. Debenzylation with boron trichloride or removal of the THP group in acid conditions, respectively, yields quetiapine I, which can be further
5 reacted to a pharmaceutically acceptable salt thereof.

Examples

Example 1. 2-[[[(2-benzyloxy-ethoxy)-ethyl]bis-(2-hydroxyethyl)amino]ethanol

10

Triethanolamine (150 ml, 1 mol) was charged into a reaction flask and warmed to 60 °C. 60% sodium hydride (16 g, 0.4 mol) was added in small portions at 60-100 °C. The mixture was stirred for 30 min. at 60-100 °C. (2-chloroethoxymethyl)-benzene (60 g, 0.35 mol) and potassium iodide (0.1 g) were added. The mixture was
15 warmed for 6 h at 140 °C. The mixture was cooled to 30 °C. 10% NaCl-water (300 ml) was added, and the obtained solution was washed with a mixture of 80 ml hexane and 20 ml toluene. The water phase was extracted twice with ethyl acetate (150 ml and 50 ml). The combined organic phase was washed twice with 10% NaCl-water (100 ml and 50 ml). The organic phase was dried with K₂CO₃ and
20 evaporated. The product 6 was a yellowish oil which was used without further purification. Yield of 2-[[[(2-benzyloxy-ethoxy)-ethyl]bis-(2-hydroxyethyl)-amino]ethanol: 62 g.

¹H NMR (CDCl₃) 2.7 (6H, m), 3.59 (10H, m), 4.55 (2H, s), 7.3 (5H, m).

¹³C NMR (CDCl₃) 53.9, 57.3, 59.8, 69.2, 69.8, 69.9, 73.3, 127.57, 127.65, 127.72,
25 127.87, 138.0.

Example 2. [2-(2-benzyloxy-ethoxy)-ethyl]bis-(2-chloroethyl)amine, hydrochloride

30 2-[[[(2-benzyloxy-ethoxy)-ethyl]bis-(2-hydroxyethyl)amino]ethanol (60 g, 0.21 mol), toluene (300 ml) and dimethylformamide (2 ml) were charged into a reaction flask. Thionyl chloride (100 ml) was added. The mixture was stirred at reflux for 4

h. 100 ml was distilled off. The reaction mixture was slowly added to water (200 ml) at 20-50°C. The toluene phase was separated.

The water phase was extracted twice with dichloromethane (150 ml and 30 ml). The solvent was evaporated and the residue (36 g) was dissolved in ethyl acetate (200 ml). The solution was cooled to 0 °C and the precipitated product was filtered, washed with cold ethyl acetate and dried. Yield of [2-(2-benzyloxy-ethoxy)-ethyl]bis-(2-chloroethyl)amine as hydrochloride 15.8 g .

¹H NMR (CDCl₃) 2.45-3.70 (10H, m), 4.0 (6H, m), 4.54 (2H, s), 7.30-7.38 (5H, m), 13.1 (1H, s).

¹³C NMR (CDCl₃) 36.7, 53.0, 55.2, 65.2, 69.2, 70.7, 73.4, 127.83, 127.93, 128.0, 128.46, 128.53, 137.82.

Example 3. 11-{4-[2-(2-benzyloxy-ethoxy)ethyl]-piperazin-1-yl}-dibenzo[b,f][1,4]thiazepine

15

Dibenzo[b,f][1,4]thiazepin-11-ylamine (9.3 g, 0.041 mol) and dimethylformamide (40 ml) were charged into a reaction flask. 60% sodium hydride (5 g, 0.12 mol) was added in small portions. The mixture was stirred for 15 min. at 40 °C. The mixture was cooled to 20 °C and [2-(2-benzyloxy-ethoxy)-ethyl]bis-(2-chloroethyl)amine hydrochloride (15 g, 0.042 mol) was added. The mixture was warmed for 5 h at 80 °C. The solvent was distilled off under reduced pressure. The residue was dissolved into dichloromethane (80 ml) and water (100 ml). The water phase was separated. The organic phase was dried with K₂CO₃ and evaporated, the residue being 17.7 g (91,2%).

25 Purification: The residue (12 g) was chromatographed on silica gel eluting with ethyl acetate - triethylamine (96:4), yield 7.9 g (65.8%).

¹H NMR (CDCl₃) 2.51-2.67 (6H, m), 3.53-3.67 (10H, m), 4.55 (2H, s), 6.87-7.51 (13H, m)

¹³C NMR (CDCl₃) 46.1, 57.8, 69.0, 69.1, 69.5, 70.5, 73.2, 122.7, 125.3, 127.6, 128.0, 128.2, 128.3, 129.0, 129.1, 130.7, 131.6, 132.1, 132.2, 132.7, 134.2, 138.3, 139.9, 149.0, 160.7.

30

Example 4. Quetiapine

11-{4-[2-(2-benzyloxy-ethoxy)ethyl]-piperazin-1-yl}-dibenzo[b,f][1,4]thiazepine (0.2 g, 0.422 mmol) and toluene (5 ml) were charged into a reaction flask. The mixture was cooled to -5 °C. 1 M BCl₃ in xylene (1 ml) was added and the reaction mixture was allowed to warm to room temperature and stirred 2 h at ambient temperature. A mixture of triethylamine (2 ml) and methanol (5 ml) was added. After 10 min. of stirring, 1 M NaOH (1 ml) and saturated NaCl-water (2 ml) were added. The organic phase was separated and evaporated. Yield of quetiapine 0.15 g.

Using tetrahydropyran as OH-protective group:**Example 5. 2-((2-hydroxy-ethyl)-{2-[2-(tetrahydropyran-2-yloxy)-ethoxy]-ethyl}-amino)-ethanol**

2-(2-chloro-ethoxy)-ethanol (25 g, 0.2 mol), dichlorometane (50 ml) and Amberlyst H-15 (1 g) were charged into a reaction flask. 2,3-dihydropyran (25 ml, 0.3 mol) was added during 15 minutes. The mixture was stirred for 17 h at 25 °C. Amberlyst H-15 was filtered off and dichlorometane was evaporated *in vacuo*. To the residue were added diethanolamine (50 g), Na₂CO₃ (20 g), NaI (1 g), TBABr (0.1 g) and DMF (60 ml). The mixture was stirred for 5 h at 140 °C. DMF was evaporated *in vacuo*. Ethyl acetate (100 ml) and 10 % NaCl-water (100 ml) were added. The mixture was stirred for 5 min. and the water phase was separated. The organic phase was washed with 10 % NaCl-water (100 ml), dried with Na₂CO₃ and evaporated *in vacuo*. Yield 43.9 g.

The product was used without further purification.

Example 6. Bis-(2-chloro-ethyl)-{2-[2-(tetrahydropyran-2-yloxy)-ethyl]-amine

2-((2-hydroxy-ethyl)-{2-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-ethyl}-amino)-ethanol (9 g, 0.03 mol), dichlorometane (50 ml) and triphenylphosphine (18.4 g, 0.07 mol) were charged into a reaction flask. The mixture was cooled to 0 °C, and N-chlorosuccinimide (9.3 g (0.07 mol) was added in small portions at 0-20 °C. The

mixture was stirred for 17 h at 25 °C. Dichlorometane was evaporated *in vacuo*. To the residue was added hexane (100 ml) and 10 % K₂CO₃-water (20 ml). The mixture was stirred for 10 min. and the insoluble material was filtered off. The organic phase was evaporated *in vacuo*. Yield of **2** 7.7 g. ¹³C NMR (CDCl₃) 19.5, 26.4, 30.6, 42.0, 54.3, 57.2, 62.2, 66.7, 70.1, 70.2, 99.0.

Example 7. 11-(4-{2-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-ethyl}-piperazin-1-yl)-dibenzo[b,f][1,4]thiazepine

Dibenzo[b,f][1,4]thiazepin-11-ylamine (0.11 g, 0.5 mmol), bis-(2-chloro-ethyl)-{2-[2-(tetrahydropyran-2-yloxy)-ethyl]-amine (0.3 g) and dimethylformamide (1 ml) were charged into a reaction flask. 60% sodium hydride (0.1 g) was added in small portions. The mixture was stirred for 30 min. at 50 °C. The mixture was warmed for 3.5 h at 105 °C. The mixture was cooled to 20 °C and water (3 ml) was added. The water phase was decanted, and the precipitated product was dissolved into ethyl acetate (5 ml). The solution was washed with water (2 ml). The solvent was distilled under reduced pressure. The residue was used further without purification. Yield 0.24 g.

¹³C NMR (CDCl₃) 19.5, 25.4, 30.6, 45.6, 45.7, 57.7, 62.2, 66.6, 68.8, 70.4, 98.9, 122.8, 125.3, 126.9, 129.0, 129.1, 130.7, 131.9, 131.95, 133.6, 134.2, 140.0, 149.0, 160.7

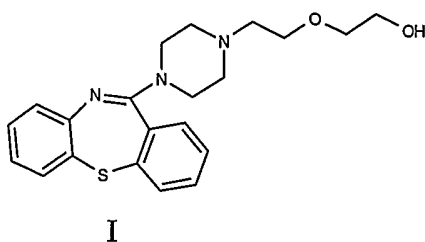
Example 8. Quetiapine

11-(4-{2-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-ethyl}-piperazin-1-yl)-dibenzo[b,f][1,4]thiazepine (0.24 g, 0.5 mmol), methanol (2 ml) and 30% HCl (1 ml) were charged into a reaction flask. The mixture was stirred 2 h at 50°C and the methanol was evaporated. The residue was dissolved in water (3 ml). The solution was washed with ethyl acetate (3 ml). To the water phase was added 50% NaOH (1 ml) and the product was extracted with ethyl acetate (5 ml). The ethyl acetate phase was washed with saturated NaCl-water (3 ml), and the organic phase was evaporated. Yield 0.16 g.

What is claimed is:

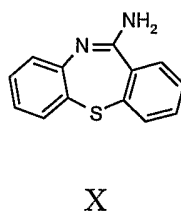
1. A method for the preparation of the compound of formula I

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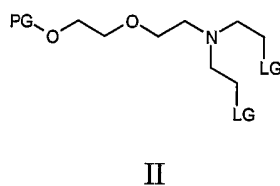


by reacting the compound of formula X

10



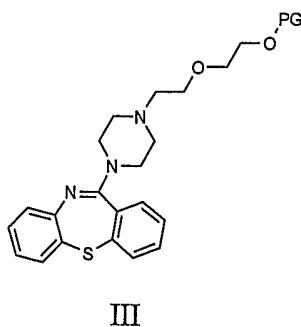
15 with a compound of the general formula II



20

wherein PG is a suitable protective group, and LG is a leaving group selected from the group consisting of halo, trifluoromethyl, O-p-toluenesulfonyl and O-methylsulfonyl, to yield a compound of the general formula III

25



30

and removing the protective group PG.

2. The method of claim 1, wherein LG is chloro.
3. The method of claim 1, wherein PG is selected from the group consisting of
5 benzyl, tetrahydropyryl, methoxymethyl and acyl.
4. The method of claim 1, wherein PG is benzyl.
5. The method of claim 4, wherein the benzyl group is removed using boron
10 trichloride.
6. The method of claim 1, wherein PG is tetrahydropyryl.
7. 2-[[2-benzyloxy-ethoxy]-ethyl]bis-(2-hydroxyethyl)amino]ethanol.
15
8. [2-(2-benzyloxy-ethoxy)-ethyl]bis-(2-chloroethyl)amine.
9. 11-{4-[2-(2-benzyloxy-ethoxy)ethyl]-piperazin-1-yl}-dibenzo[b,f][1,4]
thiazepine.
20
10. 2-((2-hydroxy-ethyl)-{2-[2-(tetrahydropyran-2-yloxy)-ethoxy]-ethyl}-amino)-
ethanol.
11. Bis-(2-chloro-ethyl)-{2-[2-(tetrahydropyran-2-yloxy)-ethyl]-amine.
25
12. 11-{4-[2-(2-tetrahydropyran-2-yloxy)-ethoxy]ethyl]-piperazin-1-yl}-
dibenzo[b,f][1,4]thiazepine.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/FI2004/000559

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D281/16 C07C219/28 C07D309/12 C07D417/12

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 C07C

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, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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| Y | EP 0 711 763 A (SANTEN PHARMACEUTICAL CO., LTD) 15 May 1996 (1996-05-15) page 3, line 27 - page 4, line 25; examples 1,2 ----- -/-- | 1-12 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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