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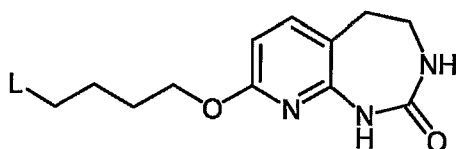
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(54) Title: PROCESS FOR MAKING A TETRAHYDRO-PYRIDOAZEPIN-8-ONE COMPOUND



(II)

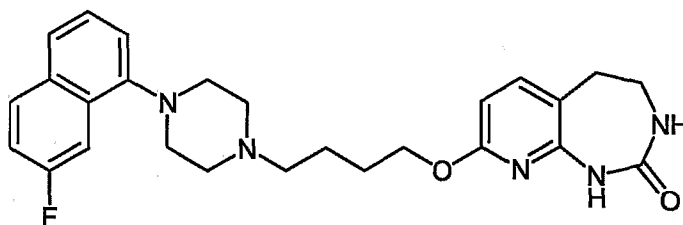
(57) Abstract: The present invention relates to a method of preparing 2-{4-[4-(7-fluoro-naphthalen-1-yl)-piperazin-1-yl]-butoxy}-5,6,7,9-tetrahydro-1,7,9-triaza-benzocyclohepten-8-one. The method comprises reacting 1-(7-fluoro-naphthalen-1-yl)-piperazine hydrochloride with a compound of formula (II) wherein L in formula (II) is a leaving group.

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PROCESS FOR MAKING A TETRAHYDRO-PYRIDOAZEPIN-8-ONE COMPOUND

BACKGROUND OF THE INVENTION

5 This invention relates to process for preparing 2-{4-[4-(7-fluoro-naphthalen-1-yl)-piperazin-1-yl]-butoxy}-5,6,7,9-tetrahydro-1,7,9-triaza-benzocyclohepten-8-one, which is represented by formula (I) below:

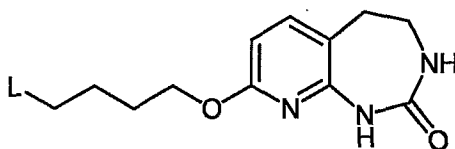


(I)

10 WO 2006/103559 discloses 2-{4-[4-(7-fluoro-naphthalen-1-yl)-piperazin-1-yl]-butoxy}-5,6,7,9-tetrahydro-1,7,9-triaza-benzocyclohepten-8-one, its property of binding to dopamine D2 receptors, a method of making this compound, and uses of this compound for treating certain central nervous system (CNS) disorders, such as schizophrenia.

SUMMARY OF THE INVENTION

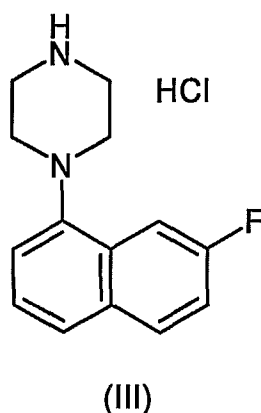
15 The present invention provides a process for preparing 2-{4-[4-(7-fluoro-naphthalen-1-yl)-piperazin-1-yl]-butoxy}-5,6,7,9-tetrahydro-1,7,9-triaza-benzocyclohepten-8-one, which comprises reacting a compound of formula (II)



(II)

with 1-(7-fluoro-naphthalen-1-yl)-piperazine hydrochloride of formula (III)

2



wherein L in formula (II) represents a leaving group.

As used herein, a "leaving group" refers to a group that can be replaced in a chemical reaction by a nucleophile such as an amine, an alkoxy (RO^-), or thio (RS^-) compound. Examples of specific leaving group that may be used in the process include chloro (Cl), bromo (Br), iodo (I), mesylate (MsO), and triflate (TfO).

DETAILED DESCRIPTION OF THE INVENTION

Compounds of formula (II) with various leaving groups and compound of formula (III) may be prepared by conventional methods known in the art, as well as according to the methods described in the Examples below.

The reaction of 1-(7-fluoro-naphthalen-1-yl)-piperazine hydrochloride with a compound of formula (II) is generally carried out in a solvent and in the presence of a base. One mole of 1-(7-fluoro-naphthalen-1-yl)-piperazine hydrochloride is theoretically needed based on one mole of the compound of formula (II), but the ratio may be slightly different.

Examples of suitable base that may be used in the reaction include potassium or sodium *tert*-butoxides, potassium or sodium hydrides, lithium diisopropylamide (LDA), lithium, sodium or potassium bis(trimethylsilyl)amides, potassium or sodium carbonates, and potassium or sodium bicarbonates. The amount of the base is usually in the range of 0.1 to 10 moles, preferably one mole or more in the view of the reaction rate, based on one mole of the compound of formula (II) or (III).

Examples of suitable solvents that may be used in this reaction include tetrahydrofuran (THF), dioxane, diethylether, *tert*-butyl methylether, dimethylformamide (DMF), dimethyl phthalate (NMP), dimethylsulfoxide (DMSO), and acetonitrile (MeCN). A single solvent or a mixture of two or more solvents may be used in the reaction.

The reaction temperature is usually in the range of about 20 °C to 120 °C, typically at the range of about 25 °C to 100 °C, and more desirably at the range of about 60 °C to 80 °C. Depending on the reaction temperature and other conditions employed, the reaction time is usually in the range of about 1 hour to 5 hours. For example, the reaction may be run for about 4
5 hours at a temperature of about 70 °C in the presence of acetonitrile and potassium carbonate.

The end point of the reaction can be detected by sampling a part of the reaction mixture, analyzing the sample by conventional analytical means such as liquid chromatography, thin-layer chromatography, and so on, and measuring the remaining amount of one or both starting materials.

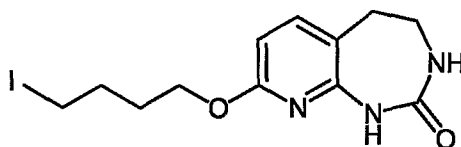
10 The obtained product 2-{4-[4-(7-Fluoro-naphthalen-1-yl)-piperazin-1-yl]-butoxy}-5,6,7,9-tetrahydro-1,7,9-triaza-benzocyclohepten-8-one (I) can be purified by a known procedure such as chromatography, recrystallization, and son on.

EXAMPLES

The following examples are provided for the sole purpose of illustrating one or more of
15 the embodiments of the invention and should be construed as limiting the scope of the invention.

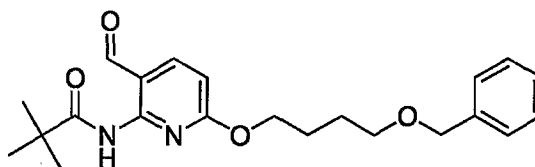
Example 1

Preparation of 2-(4-Iodo-butoxy)-5,6,7,9-tetrahydro-1,7,9-triaza-benzocyclohepten-8-one



Step 1. Preparation of N-[6-(4-Benzyloxy-butoxy)-3-formyl-pyridin-2-yl]-2,2-dimethyl-propionamide

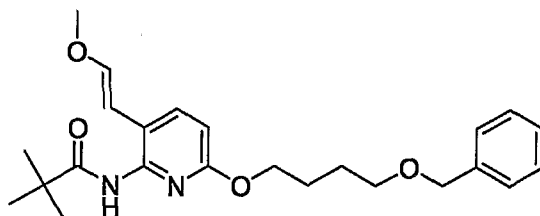
20



A solution of sodium t-butoxide (3eq., 3.41mmol/ml DMF) was prepared over a temperature range of 5 °C to 20 °C. To this solution at 5 °C was added a solution of 4-Benzyloxy-butan-1-ol (1eq., 2.39mmole/ml DMF) over 30minutes. After the mixture was stirred for 2
25 hours, a solution of N-(6-chloro-3-formyl-pyridin-2-yl)-2,2-dimethyl-propionamide (1.3eq., 2.29mmol/ml DMF) was added over 40 minutes, maintaining 10 °C with cooling of the mixture. After 2 hours the mixture at 20 °C was diluted with water and extracted with methyl-t-butyl ether. The organic phase was evaporated in vacuo and the residue was diluted with

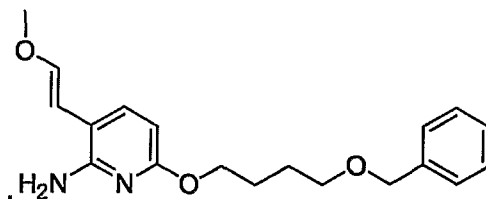
tetrahydrofuran and evaporated under vacuum to give a solution of crude product, sufficiently pure to be used in the following steps. $^1\text{H-NMR}$ (400 MHz, CDCl_3): 11.50 (s, 1H), 9.75 (s, 1H), 7.80 (d, 1H), 7.40 – 7.20 (m, 5H), 6.45 (d, 1H), 4.50 (m, 4H), 3.50 (t, 2H), 2.00 – 1.70 (m, 4H), 1.40 (s, 9H).

5 Step 2. Preparation of N-[6-(4-Benzyloxy-butoxy)-3-(2-methoxy-vinyl)-pyridin-2-yl]-2,2-dimethyl-propionamide



To a suspension of (methoxymethyl)-triphenylphosphonium chloride (1.5eq., 2.4mmol/ml THF) at -16°C was added a 1M solution of potassium t-butoxide in THF (2.60eq.) while temperature was maintained at near 0°C by external cooling. After stirring for 30 minutes, a solution of crude N-[6-(4-Benzyloxy-butoxy)-3-formyl-pyridin-2-yl]-2,2-dimethyl-propionamide obtained in Step 1 (1eq., 3.03mmol/ml THF), was added over 20 minutes, while maintaining 5°C . After 1 hour, the mixture was diluted with water and extracted with methyl-t-butylether. The organic extracts were washed with brine, and evaporated to a brown oil. The oil was purified by chromatography on silica gel, eluted with a 2:1 ratio of heptane/ethyl acetate. Azeotropic evaporation from toluene gave a yellow oil, (0.75 equivalents), crude N-[6-(4-Benzyloxy-butoxy)-3-(2-methoxy-vinyl)-pyridin-2-yl]-2,2-dimethyl-propionamide. $^1\text{HNMR}$: δ (CDCl_3 , 400 MHz): Major isomer 8.05 ((d, 1H), 7.65 (br s, 1H), 7.30-7.25 (m, 5H), 6.50 (d, 1H), 6.10 (d, 1H), 5.05 (d, 1H), 4.50 (s, 2H), 4.25 (m, 2H), 3.75 (s, 3H), 3.50 (t, 2H), 1.85-1.70 (m, 4H), 1.26 (s, 9H). Minor isomer 7.55 (d, 1H), 7.40 (br s, 1H), 7.30-7.25 (m, 5H), 6.80 (d, 1H), 6.50 (d, 1H), 5.60 (d, 1H), 4.50 (s, 2H), 4.25 (m, 2H), 3.65 (s, 3H), 3.50 (t, 2H), 1.85-1.70 (m, 4H), 1.28 (s, 9H). ESMS: 413.03, exact mass: 412.

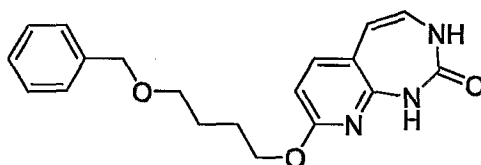
Step 3. Preparation of 6-(4-Benzyloxy-butoxy)-3-(2-methoxy-vinyl)-pyridin-2-ylamine



A solution of N-[6-(4-benzyloxy-butoxy)-3-(2-methoxy-vinyl)-pyridin-2-yl]-2,2-dimethyl-propionamide (1 eq., 0.711mmol/ml toluene) was diluted with 95% ethanol giving a solution of 0.227mmol/ml.. To this was added a solution of 50% NaOH in water (10eq) with

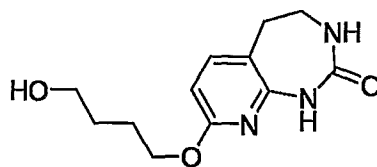
exotherm to 55 °C. The resulting dark brown mixture was heated to reflux for 1 hour, cooled to 25 °C, and extracted with toluene. The combined organic extracts were washed with water, saturated brine and dried over anhydrous magnesium sulfate. Following filtration, the solvent was removed to give a solution of crude 6-(4-Benzyloxy-butoxy)-3-(2-methoxy-vinyl)-pyridin-2-ylamine (assumed to be 1eq., 6.18mmol/ml toluene). ¹HNMR: δ (CDCl₃, 400 MHz): Major isomer 7.38-7.25 (m, 5H), 7.20 (d, 1H), 6.70 (d, 1H), 6.10 (d, 1H), 5.55 (d, 1H), 4.50 (s, 2H), 4.30 (br s, 1H), 4.20 (m, 2H), 3.65 (s, 3H), 3.50 (t, 2H), 1.90-1.80 (m, 4H). Minor isomer 7.60 (d, 1H), 7.38-7.20 (m, 6H), 6.10 (d, 1H), 5.05 (d, 1H), 4.50 (s, 3H), 3.70 (s, 3H), 3.50 (t, 3H), 1.90-1.80 (m, 4H). ESMS: 329.0, exact mass: 328.

Step 4. Preparation of 2-(4-Benzyloxy-butoxy)-7,9-dihydro-1,7,9-triaza-benzocyclohepten-8-one



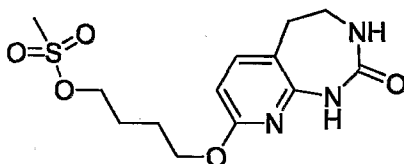
A solution of crude 6-(4-Benzyloxy-butoxy)-3-(2-methoxy-vinyl)-pyridin-2-ylamine obtained from Step 3 (assumed to be 1eq., 6.18mmol/ml toluene) was diluted with THF to a concentration of 0.28mmol/ml and cooled to 5 °C. Trichloroacetyl isocyanate (1.2eq.) was added neat while the temperature was maintained at 6 °C. The mixture was allowed to warm to 20 °C over 1 hour following the addition after which it was cooled to 7 °C. A solution of 4M HCl in methanol (5eq) was added with external cooling to maintain less than 10 °C. Following the addition, the mixture was stirred at 20 °C for 20 hours, then cooled to 10 °C and neutralized to pH 7 by addition of 1M NaOH solution. The resulting mixture was extracted with ethyl acetate, the combined extracts washed with brine, and the solvent removed under vacuum. The residue was crystallized by addition of water to a methanol solution, filtered, washed with a solution of 2:1 methanol/water. The solid was dried in a vacuum oven at 40 °C for 20 hours to give 2-(4-Benzyloxy-butoxy)-7,9-dihydro-1,7,9-triaza-benzocyclohepten-8-one as a light pink-orange solid (0.735eq.). ¹HNMR: δ (CDCl₃, 400 MHz) 9.15 (br s, 1H), 7.85 (d, 1H), 7.75 (d, 1H), 7.35-7.20 (m, 5H), 6.65 (d, 1H), 6.45 (d, 1H), 5.70 (br s, 1H), 4.50 (s, 2H), 4.30 (t, 2H), 3.55 (t, 2H), 1.95-1.80 (m, 4H). ESMS: 339.96, exact mass: 339.

Step 5. 2-(4-Hydroxy-butoxy)-5,6,7,9-tetrahydro-1,7,9-triaza-benzocyclohepten-8-one



To a solution of 2-(4-benzyloxy-butoxy)-7,9-dihydro-1,7,9-triaza-benzocyclohepten-8-one obtained in Step 4 (1eq, 0.297mmol/ml in methanol) was added Palladium on carbon (Johnson Matthey 1940 carbon, unreduced, 55%water;) in the amount 10% by weight of the 2-(4-
 5 Benzyloxy-butoxy)-7,9-dihydro-1,7,9-triaza-benzocyclohepten-8-one. The mixture was pressurized to 50 psig with hydrogen gas for 2.8 hours, after which the reaction was filtered to remove catalyst, , washed with methanol and the solvents combined and removed under vacuum to give a semi-solid residue. To the residue was added methyl t-butyl ether and the solid was then filtered. The solid was washed then washed with methyl t-butyl ether and dried in a vacuum
 10 oven for 1 hour to give 2-(4-Hydroxy-butoxy)-5,6,7,9-tetrahydro-1,7,9-triaza-benzocyclohepten-8-one as a pink solid, (0.905 eq.). ¹HNMR: δ (CD₃OD, 400 MHz) 7.45 (d, 1H), 6.30 (d, 1H), 4.25 (t, 2H), 4.00 (dd, 2H), 3.00 (t, 2H), 3.0 (t, 2H), 1.85 (m, 2H), 1.65 (m, 2H). ESMS: 252.08, exact mass: 251.

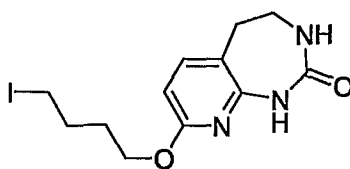
Step 6. Preparation of Methanesulfonic acid 4-(8-oxo-6,7,8,9-tetrahydro-5H-1,7,9-triaza-benzocyclohepten-2-yloxy)-butyl ester



To a suspension of 2-(4-Hydroxy-butoxy)-5,6,7,9-tetrahydro-1,7,9-triaza-benzocyclohepten-8-one (1eq., 0.1mmol/ml in THF) was added triethyl amine (3eq.) giving a solution. Over 4 hours, methanesulfonyl chloride (1.5eq.) was added with an exotherm from
 20 21°C to 33 °C and precipitation of solids. Water (5eq.) was added with stirring over 5 minutes, followed by concentration of the mixture under vacuum to remove tetrahydrofuran. The residue was further diluted with water, stirred, filtered and washed with water. The solid was dried in a vacuum oven at 40 °C for 20 hours to give methanesulfonic acid 4-(8-oxo-6,7,8,9-tetrahydro-5H-1,7,9-triaza-benzocyclohepten-2-yloxy)-butyl ester as a white solid (0.88eq.).

Step 7. Preparation of 2-(4-Iodo-butoxy)-5,6,7,9-tetrahydro-1,7,9-triaza-benzocyclohepten-8-one

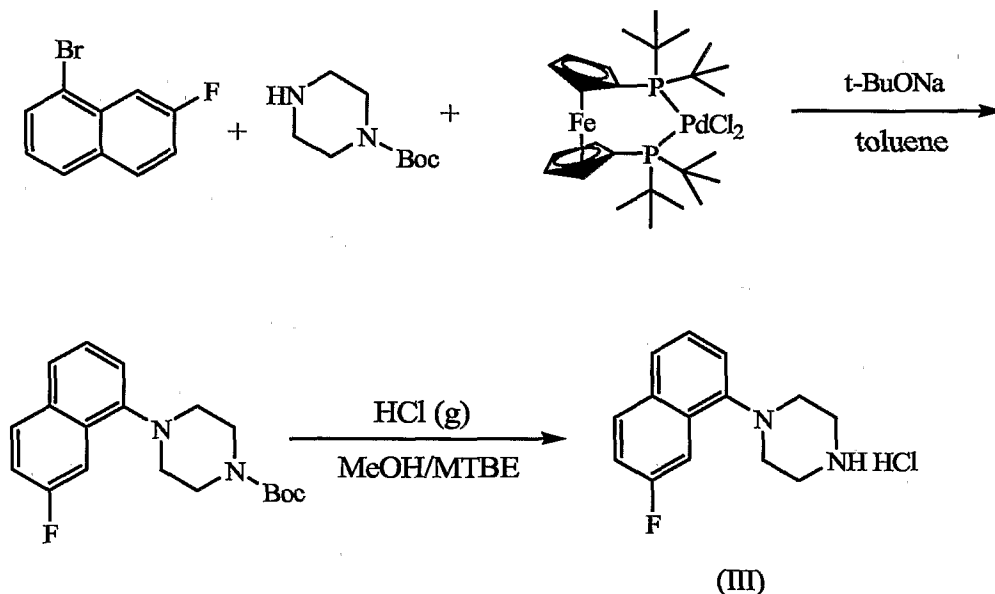
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To a suspension of methanesulfonic acid 4-(8-oxo-6,7,8,9-tetrahydro-5H-1,7,9-triaza-benzocyclohepten-2-yloxy)-butyl ester (1eq., 0.155mmol/ml in acetone) was added sodium iodide (3eq.), followed by heating to reflux for 2 hours. The mixture was then quenched by addition of water and ethyl acetate and the mixture was cooled to 40°C. The solvent was concentrated under vacuum to reduce the amount of the organic solvents. Further addition of water gave a crystalline solid which was cooled to 20 °C, filtered, washed with water and dried in a vacuum oven at 40 °C for 18 hours to give a white solid, 2-(4-iodo-butoxy)-5,6,7,9-tetrahydro-1,7,9-triaza-benzocyclohepten-8-one (0.96eq).

Example 2

Preparation of 1-(7-Fluoro-naphthalen-1-yl)piperazine Hydrochloride



To a 2-L, 3-necked round-bottomed flask, equipped with a reflux condenser, with a N₂ inlet adapter at the top of the condenser, a thermal couple and a mechanical stirrer, was added 1-bromo-7-fluoronaphthalene (100.0 g, 444.3 mmol), Boc-piperazine, (107.6, g, 577.6 mmol, 1.30 equiv.), *t*-BuONa (55.5 g, 577.6 mmol, 1.30 equiv), and catalyst 1,1'-bis(di-*t*-butylphosphino)ferrocene palladium dichloride (5.79 g, 8.89 mmol, 0.02 equiv.). Toluene (883.38 g, 1000 mL, 10 mL/g) was added to the reaction mixture. The system was filled with N₂ (Note 1). The dark solution was heated to 105 °C (internal temperature) from 20.5 °C in 45 minutes with a heating mantle with mechanical stirring. After 2 h at 105 °C, HPLC analysis showed the product peak (86.6%) and no starting material 1-bromo-7-fluoronaphthalene. The

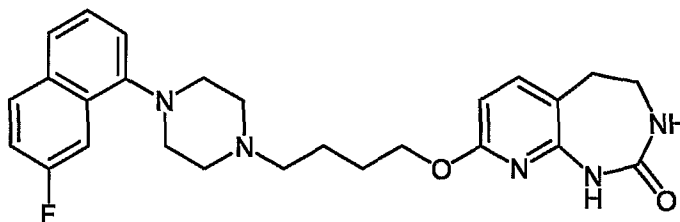
heating mantle was removed and the reaction mixture was cooled to 25 °C with a cold water bath with stirring. The dark reaction mixture was filtered through celite (1 inch thick, packed with water and sucked dry), washed with MTBE (500 g) (Note 2). The filtrate was washed with H₂O (2 X 500 g), NaCl brine (300 g), saturated NaHCO₃ solution (300 g). The dark brown solution (1486.2g) was concentrated under reduced pressure to 172 g to give a thick dark brown solution.

To a 2-L, 3-necked round-bottomed flask equipped with a teflon tubing with one end connected to an HCl tank, and the other end through a teflon adapter in one neck of the flask, a glass adapter with a Tygon tubing in the 2nd side neck, connected to a flask with 1 N NaOH solution (150 mL), and a mechanical stirrer, was added the dark brown solution from the above run and MeOH (405 g, 500 mL) + MTBE (218 g, 300 mL) were added. The dark solution was cooled in ice-water bath to 5 – 10 °C. HCl gas (105.5 g) was introduced to the reaction via the Teflon tube to the top surface of the solution for 1 h. Solid formed after 20 min. The mixture was stirred at ambient temperature over night (18 h) after HCl was stopped. HPLC analysis showed no starting material Boc-piperazine. The solid was filtered, washed with MTBE (200 g), and dried at 45 °C vacuum oven for 20 h, to give a light brown solid 117.24 g, (98.9%). The solid was suspended in MeOH (300 g) + MTBE (150 g) and stirred for 2 h. The solid was filtered, washed with MTBE (200 g), dried at 55 °C vacuum oven for 20 h to give an off-white solid 109.83 g (92.7%). mp > 230 °C; HPLC: 99.4% (A Akin, ARD); Elemental analysis: calculated (C₁₄H₁₅F₁N₂ HCl): C, 63.04; H, 6.05; N, 10.50, F, 7.12; found: C, 62.98; H, 6.10; N, 10.46, F, 6.85;

¹H NMR (DMSO): 20060607; MS: MU0665044

Example 3

Preparation of 2-{4-[4-(7-Fluoro-naphthalen-1-yl)-piperazin-1-yl]-butoxy}-5,6,7,9-tetrahydro-1,7,9-triaza-benzocyclohepten-8-one



(I)

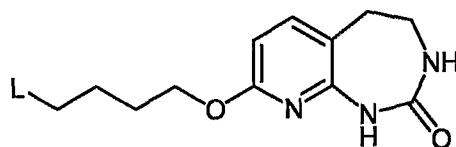
A combined suspension in acetonitrile of 1-(7-fluoro-naphthalen-1-yl)-piperazine hydrochloride, 2-(4-Iodo-butoxy)-5,6,7,9-tetrahydro-1,7,9-triaza-benzocyclohepten-8-one (1.0eq., 0.23mmol/ml) and potassium carbonate (3.0eq., 0.68mmol/ml) was heated to 70°C for 4 hours. The mixture was allowed to cool during the addition of water which gave a thick

suspension. The mixture was further cooled to 20 °C, filtered, washed with a 1:1 mixture of water/acetonitrile and dried in a vacuum oven at 50 °C for 18 hours to give a white solid, (0.95eq.). Further improvement in purity was obtained by recrystallization from chloroform at elevated temperature. ¹H-NMR δ (CDCl₃, 400 MHz): 8.50 (br s, 1H), 7.80 (m, 2H), 7.55 (d, 1H),
5 7.35 (m, 2H), 7.21 (m, 1H), 7.10 (d, 1H), 6.25 (d, 1H), 5.60 (br s, 1H), 4.25 (t, 2H), 4.05 (t, 2H), 3.20 (br s, 4H), 3.00 (t, 2H), 2.80 (br s, 4H), 2.50 (t, 2H), 1.90-1.65 (m, 4H). HPLC: 90.72%. MS: 464.18, exact mass: 463.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of preparing 2-{4-[4-(7-fluoro-naphthalen-1-yl)-piperazin-1-yl]-butoxy}-5,6,7,9-tetrahydro-1,7,9-triaza-benzocyclohepten-8-one, comprising reacting 1-(7-fluoro-



(II)

wherein L in formula (II) is a leaving group.

2. The method of claim 1, wherein the reaction is carried out in the presence of a solvent or a mixture of two or more solvents.
3. The method of claim 2, wherein the reaction is carried out in the presence of a base.
4. The method of claim 3, wherein the base is selected from potassium *tert*-butoxide, sodium *tert*-butoxide, potassium hydride, sodium hydride, lithium diisopropylamide, lithium, sodium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, potassium carbonate, sodium carbonate, potassium bicarbonate, or sodium bicarbonate.
5. The method of claim 5, wherein the base is potassium carbonate or sodium carbonate.
6. The method of claim 3, wherein the solvent is selected from tetrahydrofuran, dioxane, diethylether, *tert*-butyl methylether, DMF, NMP, DMSO, or acetonitrile.
7. The method of claim 6, wherein the solvent is acetonitrile.
8. The method of claim 3, wherein the reaction is carried out at a temperature between about 20 °C to 120 °C.
9. The method of claim 8, wherein the reaction is carried out at a temperature between about 60 °C and 80 °C.
10. The method of claim 3, wherein the leaving group is selected from chloro, bromo, iodo, mesylate, and triflate.
11. The method of claim 10, wherein the leaving group is iodo.

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2007/000762

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, WPI Data, BEILSTEIN 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 2006/103559 A (WARNER LAMBERT CO [US]; FAVOR DAVID ALAN [US]; JOHNSON DOUGLAS SCOTT []) 5 October 2006 (2006-10-05) Scheme B and D; example 18 -----	1-11
A	WO 2005/019215 A (WARNER LAMBERT CO [US]; CLARK JERRY [US]; DAVIS JAMIE [US]; FAVOR DAVI) 3 March 2005 (2005-03-03) pages 6,51; claim 1 -----	1-11
A	JP 57 193461 A (OTSUKA PHARMA CO LTD) 27 November 1982 (1982-11-27) the whole document -----	1-11

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Further documents are listed in the continuation of Box C.

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See patent family annex.

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Date of the actual completion of the international search

16 August 2007

Date of mailing of the international search report

28/08/2007

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2007/000762

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