

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

(19) World Intellectual Property Organization

International Bureau



(43) International Publication Date

24 June 2010 (24.06.2010)

(10) International Publication Number

WO 2010/070369 A1

(51) International Patent Classification:

C07D 295/135 (2006.01)

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(21) International Application Number:

PCT/HU2009/000108

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(22) International Filing Date:

17 December 2009 (17.12.2009)

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

P08 00763 17 December 2008 (17.12.2008) HU

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

- with international search report (Art. 21(3))



WO 2010/070369 A1

(54) Title: PIPERAZINE SALT AND A PROCESS FOR THE PREPARATION THEREOF

(57) **Abstract:** The invention relates to novel trans N-[4-[2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl]- cyclohexylamine dihydrochloride monohydrate and a process for the preparation of the trans N-[4-[2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl]-cyclohexylamine dihydrochloride monohydrate, said process comprising the steps a) reacting trans 2-[1-[4-(N-tert-butoxycarbonyl)amino]-cyclohexyl]-acetic acid ester with sodium borohydride and aluminium trichloride to give trans 2-[1-[4-(N-tert-butoxycarbonyl)amino]-cyclohexyl]-ethanol; b) reacting trans 2-[1-[4-(N-tert-butoxycarbonyl)amino]-cyclohexyl]-ethanol obtained with methanesulfonic acid chloride in the presence of an acid binding agent to give trans 2-[1-[4-(N-tert-butoxycarbonyl)amino]-cyclohexyl]-ethyl methanesulfonate; c) reacting trans 2-[1-[4-(N-tert-butoxycarbonyl)amino]-cyclohexyl]-ethyl methanesulfonate obtained with 2,3-dichlorophenyl-piperazine in the presence of an acid binding agent to give trans 2-[1-[4-(N-tert-butoxycarbonyl)amino]-cyclohexyl]-carbamic acid tert-butylester; d) heating trans 2-[1-[4-(N-tert-butoxycarbonyl)amino]-cyclohexyl]-carbamic acid tert-butylester obtained to a temperature between 40-100°C in a mixture of aqueous hydrochloric acid/ methanol to give trans N-[4-[2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl]- cyclohexylamine dihydrochloride monohydrate.

## Piperazine salt and a process for the preparation thereof

### Field of the invention

The present invention relates to novel trans 5 {4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-il]-ethyl}-cyclohexylamine dihydrochloride monohydrate and to a process for the preparation thereof.

### Background of the invention

The trans {4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-il]-ethyl}-cyclohexylamine dihydrochloride monohydrate according to the invention is a key intermediate for the preparation of a number of compounds acting on D<sub>3</sub>/D<sub>2</sub> receptor. Similar compounds were described in the Hungarian Patent Specifications No. P0103988 and P0302451, and in Bioorg. Med. Chem. Lett. EN; 7; 18; 1997 2403-2408.

The Hungarian Patent Specification No. P0103988 discloses a reaction route for the preparation of trans {4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-il]-ethyl}-cyclohexylamine dihydrochloride. According to the preparation process described in Example 1, 2,3-dichlorophenyl-piperazine and trans 2-{1-[4-(N-terc-butoxycarbonyl)-amino]-cyclohexyl}-acetaldehyde are dissolved and coupled in dichloromethane in the presence of sodium triacetoxy borohydride to give trans N-{4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-il]-ethyl}-cyclohexyl}-carbamic acid tertiary butylester. Then the protective group is removed in ethyl acetate by hydrochloride acid according to a process described in Example 2. The yield data for trans N-{4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-il]-ethyl}-cyclohexyl}-carbamic acid tertiary butylester or for trans N-{4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-il]-ethyl}-cyclohexyl}-amine dihydrochloride are not described either.

The drawback of the above procedure is that when preparing trans 2-{1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl}-acetaldehyde from the corresponding trans 2-{1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl}-acetic acid ester the reaction can be carried out at a temperature below 70°C and with only 55% yield (Stemp et al. J. Med. Chem. 2000. Vol. 43, No. 9, p. 7878-7885). However, use of the above operating temperature and the very hazardous diisobutyl aluminium hydride mean technological problems in industrial scale therefore the reaction can be carried out only in extra equipments and at extreme conditions.

The procedure disclosed in the above mentioned Bioorg. Med. Chem. Lett. EN; 7; 18; 1997 2403-2408 literature consists of eight reaction steps and the compounds are mentioned only in general without any characterizing features. The eight steps procedure seems to be complicated, expensive and hazardous particularly performing in industrial scale.

5 Our aim was to provide a safe and in industrial scale easy-to-manage process for the preparation of trans N-{4-[2-[4-(2,3-dichlorophenyl)-piperazine-1-il]-ethyl}-cyclohexylamine key intermediate by which it can be prepared in good yield via simple reaction steps without using extreme reaction conditions and extra equipments.

10 **Brief description of the invention**

In the course of our experiences, we have surprisingly found, that starting from trans 2-{1-(4-N-[tert-butoxycarbonyl]-amino)-cyclohexyl}-acetic acid ester and using the economical process according to the invention the trans 4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-il]-ethyl}-cyclohexylamine dihydrochloride monohydrate can be produced by 15 four easy-to-make and economical synthesis steps in high purity at industrial scale wherein all of the steps can be carried out with good yields.

In the first reaction step trans 2-{1-(4-[N-tert-butoxycarbonyl]-amino)-cyclohexyl}-acetic acid ester is converted to trans-2-{1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl}-ethyl alcohol quantitatively by using sodium borohydride and aluminium trichloride. In the 20 following reaction step the trans 2-{1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl}-ethyl alcohol obtained in step 1 is reacted with methanesulfonyl chloride to give mesylester, then the mesylester is reacted with 2,3-dichlorophenylpiperazine in the presence of an acid binding agent. In the last step the protecting group is removed under simple reaction conditions in a mixture of water/hydrochloric acid/methanol at a temperature of 40-100°C to give trans N- 25 {4-[2-[4-(2,3-dichlorophenyl)-piperazine-1-il]-ethyl]-cyclohexylamine dihydrochloride monohydrate in very high purity and good yield.

**Detailed description of the invention**

In the first reaction step trans 2-{1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl}-acetic acid ester is converted to trans 2-{1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl}-ethyl alcohol. It is well known to those skilled in the art that the above reaction may be carried out only at low (-40°C) temperature and in the presence of the very hazardous lithium

aluminium hydride. In our experiments we have surprisingly found that when the reaction is performed in an ether solvent, for example in THF at a temperature between 0-30°C, preferably between 5-25°C in the presence of sodium borohydride and aluminium trichloride, the trans 2-{1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl}-ethyl alcohol is obtained with almost quantitative yield.

In the second reaction step the trans 2-{1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl}-ethyl alcohol obtained in step 1 is treated with methanesulfonyl chloride in the presence of an acid binding agent to give mesylester. Optionally the reaction may be carried out without isolation of the starting trans 2-{1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl}-ethyl alcohol. Suitable acid binding agents, which can be used in this reaction step, include inert organic bases, preferably inert organic amines, more preferably triethylamine. Suitable solvents which can be used include inert water-immiscible solvents, for example toluene, dichloromethane, chlorobenzene or xylene, preferably dichloromethane. The efficiency of the reaction is almost quantitative.

In the following step trans 2-{1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl}-ethyl methanesulfonate is reacted with 2,3-dichlorophenyl-piperazine in the presence of an acid binding agent to obtain trans {4-[2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl]-cyclohexyl}-carbaminic acid tert-butyl ester. As an optional route, the reaction may be carried out without isolation of the starting trans 2-{1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl}-ethyl methanesulfonate. As acid binding agent alkali bases, for example alkali carbonates, preferably potassium carbonate is employed. Suitable solvents, which can be used in this reaction step, include inert water-immiscible solvents, for example toluene, dichloromethane, chlorobenzene or xylene, preferably dichloromethane. The yield is higher than 80%.

In a preferred embodiment of the invention the above three reaction steps are reduced to one step and the reaction is carried out in one reaction vessel without isolation of the intermediate compounds. In this case there is no need to clean the equipments in costly separate steps. In this manner the total yield is higher than 70% based on the starting material, hereby increasing the economical efficiency of the procedure.

In the last reaction step the N-tert-butoxycarbonyl protecting group is removed in a mixture of aqueous hydrochloric acid and methanol at a temperature between 40-400°C, preferably between 45-50°C to give a crystalline product, which proves the new

dihydrochloride monohydrate form of trans N-[4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl}-cyclohexyl]-amine. We have surprisingly found, that performing the reaction in the presence of water, the trans N-[4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl}-cyclohexyl]-amine dihydrochloride monohydrate is obtained almost quantitatively in high

5 purity and the yield is higher than 99%.

The invention is illustrated by the following non-limiting Examples.

**Example 1.**

10 **Preparation of trans 2-[1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl]-acetic acid ester**

An 500 ml four-necked flask is charged with 40 g (0,18 mol) of trans 2-[1-(4-amino)-cyclohexyl]-acetic acid ethyl ester and 160 ml of dichloromethane, then 18,2 g (0,18 mol) of triethylamine is added. The reaction mixture obtained is cooled to a temperature between 5-15 10°C then a solution of 40,0 g (0,18 mol) of di(tert-butyl)dicarbonate in 100 ml of dichloromethane is added for 1 hour with stirring under nitrogen. Then the reaction mixture is allowed to warm to room temperature and stirred until the reaction proceeds. After completion of the reaction 100 g of 5% aqueous sodium carbonate is added and the phases are separated. The organic layer is washed with 50 ml of water and after separation the organic 20 layer is dried under  $\text{Na}_2\text{SO}_4$  and the filtrate is concentrated to 40 ml in vacuum. The thick crystalline suspension obtained is poured into a platter and dried under infra-red lamp at up to 35°C.

In this manner 47,9 g of title compound was obtained.

Yield: 93%

25 Melting point: 73-74°C.

**Example 2**

**Preparation of trans 2-[1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl]ethanol**

30 An 500 ml four-necked flask is charged with 40 g (0,18 mol) of trans 2-[1-(4-amino)-cyclohexyl]-acetic acid ethyl ester hydrochloride and 160 ml of dichloromethane. To the resulting suspension 18,2 g (0,18 mol) of triethylamine is added. The reaction mixture is

cooled to a temperature between 8-10°C and a solution of 40,0 g (0,185 mol) of di(tert-butyl)dicarbonate in 100 ml of dichloromethane is added for 1 hour with stirring under nitrogen. Then the reaction mixture is allowed to warm to a temperature between 22-25°C and stirred until the reaction proceeds. After completion of the reaction 100 g of 5% aqueous 5 sodium carbonate is added and the phases are separated. The organic layer is extracted with 50 ml of water and after separation the organic layer is dried under Na<sub>2</sub>SO<sub>4</sub> and the filtrate is concentrated in vacuum. The trans 2-{1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl}-acetic acid ethyl ester obtained is dissolved in 460 ml of tetrahydrofuran then 13,68 g (0,36 mol) of sodium borohydride is added at 25°C under nitrogen. With stirring, to the reaction 10 mixture a solution of 24,0 g (0,18 mol) of aluminium chloride in 250 ml abs. tetrahydrofuran is added dropwise at a temperature between 18-22°C for 1 hour under nitrogen then the mixture is stirred for additional 2 hours. After completion of the reaction the mixture is cooled to a temperature between 5-10°C and 650 ml of water and 600 ml of toluene are added. Then the pH was adjusted to 3-4 by adding 40-45 ml of concentrated hydrochloric acid and 15 the stirring was continued at a temperature between 20-25°C for 1 hour. The phases are separated, the aqueous layer is extracted with 50 ml of toluene and the combined organic layers are washed with 3x150 ml of water and dried in vacuum.

In this manner 41,1 g of title compound was obtained.

Yield: 94%

20 Melting point: 101-103°C.

### Example 3

#### **Preparation of trans 2-{1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl}-ethyl methanesulfonate**

25 With stirring 37 g (0,15 mol) of trans 2-{1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl}-ethanol is dissolved in 360 ml of dichloromethane at a temperature between 20-25°C and 19,6 g (0,19 mol) of triethylamine is added. The solution obtained is cooled to a temperature between 0-5°C and a solution of 40,0 g (0,185 mol) of di(tert-butyl)dicarbonate in 100 ml of 30 dichloromethane is added dropwise for 1 hour. Then the stirring is continued for further 1 hour while the temperature is maintained between 0-5°C and the pH is kept at 8-9 by adding triethylamine. After completion of the reaction 450 ml water is added and after stirring for 15

minutes the phases are separated. The aqueous phase is extracted with 30 ml of dichloromethane then the combined organic phases are washed with 3x300 ml of water and the dichloromethane solution is concentrated in vacuum.

In this manner 46,2 g of title compound was obtained.

5 Yield: 90%

Melting point: 112-113°C.

**Example 4**

**Preparation of trans N-tert-butoxycarbonyl-4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl}-cyclohexylamine**

48 g (0,15 mol) of trans 2-{1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl}-ethyl methanesulfonate is suspended in 800 ml of acetonitrile. To the suspension obtained 75 g (0,28 mol) of 1-2,3-dichlorophenyl)-piperazine hydrochloride and 71,8 g (0,56 mol) of 15 potassium carbonate are added and the reaction mixture is heated to reflux and stirred for 15-17 hours. After completion of the reaction the mixture is cooled to a temperature between 45-50°C and 900 ml of water is added. With stirring the temperature is brought to room temperature and the stirring is continued for further 1,5 hours. The product separated is filtered and washed with water until pH neutral. Then a solution of 400 ml of water and 7 ml 20 of concentrated hydrochloric acid is added and the mixture is stirred for 2 hours at a temperature between 20-25°C and filtered then washed with 15-20 ml of water. To the crude product obtained 540 ml of acetonitrile is added and the reaction mixture is heated to reflux and stirred for 15 minutes. The mixture is cooled to a temperature between 0-5°C and the stirring is continued for 1 hour while the temperature is maintained at this level. The 25 precipitated product is filtered, washed with 10 ml of cold acetonitrile and dried.

In this manner 54,7 g of title compound was obtained.

Yield: 80%

Melting point: 150-154°C.

**Example 5****Preparation of trans N-tert-butoxycarbonyl-4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl}-cyclohexylamine**

5 An 1 l four-necked round bottom flask is charged with 42,9 g (0,15 mol) of trans 2-{1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl}-acetic acid ethyl ester and 400 ml of tetrahydrofuran and to the solution obtained 11,4 g (0,3 mol) of sodium borohydride is added at 25°C temperature under nitrogen. To the stirred reaction mixture a solution of 20,0 g (0,15 mol) of aluminium chloride in 225 ml abs. tetrahydrofuran is added dropwise at a  
10 temperature between 18-22°C for 1 hour under nitrogen, then the stirring is continued for additional 2 hours. After ending the reaction the mixture is cooled to a temperature between 5-10°C and 650 ml of water then 450 ml of toluene are added and the pH is adjusted to 3-4 by adding 30-40 ml of concentrated hydrochloric acid. Stirring is continued for 1 hour at a temperature between 20-25°C. The phases are separated, the aqueous layer is extracted with  
15 50 ml of toluene, and the combined organic layers are washed with 3x150 ml of water and concentrated to about 50 ml volume in vacuum. To the concentrated stirred solution 360 ml of dichloromethane and 19,6 g (0,19 mol) of triethylamine are added at a temperature between 20-20°C. The solution is then cooled to a temperature between 0-5°C and a solution of 19,7 g (0,17 mol) of methanesulfonyl chloride in 90 ml of dichloromethane is added dropwise over 1  
20 hour and the reaction mixture is stirred for further 1 hour. The pH is maintained at 8-9 by adding triethylamine. After completion of the reaction 450 ml of water is added and the mixture is stirred for 15 minutes then the phases are separated. The aqueous layer is extracted with 30 ml of dichloromethane then the combined organic layers are washed with 3x300 ml of water. The dichloromethane solution is concentrated to about 70 ml volume under vacuum  
25 then 900 ml of acetonitrile is added and about 80-100 ml solvent is distilled off under vacuum. The residue obtained is cooled to a temperature between 20-25°C and 75 g (0,28 mol) of 1-(2,3-dichlorophenyl)-piperazine hydrochloride and 71,8 g (0,56 mol) of potassium carbonate are added then the mixture is heated to reflux and stirred for 15-16 hours. After  
30 ending the reaction the mixture is cooled to a temperature between 45-50°C and 900 ml of water is added then the stirred mixture is cooled to room temperature. The stirring is continued for further 1.5 hours during which the temperature is kept at this level. The product obtained is filtered off and washed with water until pH neutral then a solution of 400 ml of

water and 7 ml of concentrated hydrochloric acid is added. After stirring at a temperature between 20-25°C for 2 hours the product obtained is filtered and washed with water. To the resulting crude product 540 ml of acetonitrile is added and the mixture obtained is heated to reflux and stirred for 15 minutes, then cooled to a temperature between 0-5°C. The stirring is continued for another 1 hour maintaining temperature between 0-5°C. The product precipitated is filtered off and washed with 10 ml of cold acetonitrile then dried.

In this manner 51,3 g of title compound was obtained.

**Yield: 75%**

**Melting point: 150-154°C.**

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#### **Example 6**

#### **Preparation of trans N-tert-butoxycarbonyl-4-[2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl]-cyclohexylamine**

15 A 500 ml four-necked round bottom flask is charged with 40 g (0.18 mol) of trans 2-[1-(4-aminocyclohexyl)-acetic ethyl ester hydrochloride and 160 ml of dichloromethane and to the resulting suspension 18.2 g (0,18 mol) of triethylamine is added. The mixture obtained is cooled to a temperature between 0-10°C and with stirring a solution of 40.0 g (0.185 mol) of di(tert-butyl dicarbonate) in 100 ml of dichloromethane is added for one hour under nitrogen.

20 The reaction mixture is then allowed to warm to a temperature between 20-25°C and the stirring is continued until the reaction proceeds. After completion of the reaction 100 g of 5% aqueous sodium carbonate solution is added then the phases are separated. The organic layer is extracted with 50 ml of water and after separating the organic layer is dried on  $\text{Na}_2\text{SO}_4$  and the solvent is removed under vacuum.

25 The trans 2-[1-[N-tert-butoxycarbonyl]-amino]-cyclohexyl]-acetic ethyl ester obtained is dissolved in 468 ml of tetrahydrofuran then 13.68 g (0,36 mol) of sodium borohydride is added at 25°C temperature under nitrogen. To the stirred reaction mixture a solution of 24.0 g (0.18 mol) of aluminium chloride in 270 ml of absolute tetrahydrofuran is added dropwise over 1 hour at a temperature between 18-22°C and the stirring is continued for about 2 hours.

30 The reaction mixture is then cooled to a temperature between 5-10°C and 650 ml of water and 600 ml of toluene are added and the pH is adjusted to 3-4 by adding concentrated hydrochloric acid. After stirring at a temperature between 20-25°C for 1 hour, the phases are

separated and the aqueous layer is extracted with 50 ml of toluene. The combined organic extracts are washed with 3x150 ml of water and the mixture is concentrated to 60 ml volume under vacuum. To the stirred concentrated solution 430 ml of dichloromethane and 23.5 g (0.23 mol) of triethylamine are added at a temperature between 20-25°C. The solution 5 obtained is cooled to 0-5°C temperature and a solution of 23.6 g (0.2 mol) of methanesulfonic chloride in 110 ml of dichloromethane is added dropwise over 1 hour. The reaction mixture is stirred for 1 hour maintaining the temperature at 0-5°C. The pH is maintained at 8-9 by adding triethylamine. After ending the reaction 500 ml of water is added and after stirring for 15 minutes the phases are separated. The aqueous layer is extracted with 50 ml of water and 10 the combined organic layers are washed with 3x300 ml of water. The dichloromethane solution is concentrated to about 80 ml volumes under vacuum and 1 l of acetonitrile is added, then about 80-100 ml of solvent are distilled off under vacuum. The mixture obtained is cooled to a temperature between 20-25°C and 80 g (0.3 mol) of 1-(2,3-dichlorophenyl)-piperazine and 82.8 g (0.6 mol) of potassium carbonate are added. The reaction mixture is heated to 15 reflux and stirred for 15-17 hours. The mixture is then cooled to 45-50°C and 1 l of water is added with stirring and the mixture is cooled to room temperature and the stirring is continued for further 1.5 hours. The product precipitated is filtered and washed with water until pH neutral and a solution of 400 ml of water and 7 ml of concentrated hydrochloric acid is added. The mixture obtained is stirred for 2 hours at a temperature between 20-25°C and the product 20 is filtered and washed with water. To the crude product obtained 600 ml of acetonitrile is added and the mixture is stirred under reflux for 15 minutes, then cooled to 0-5°C and the stirring was continued for further 1 hour. The product precipitated is filtered, washed with 10 ml of cold acetonitrile and dried.

In this manner 57,5 g of title compound was obtained.

25 Yield: 70%

Melting point: 150-154°C.

#### Example 7

Preparation of **trans 4-{2-[-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl}-cyclohexylamine dihydrochloride monohydrate**

A 500 ml 3-necked round bottom flask is charged with 22 g (0,05 mol) of trans N-tert-butoxycarbonyl-4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl}-cyclohexylamine and

150 ml of ethanol. To the stirred mixture a solution of 37,2 ml concentrated hydrochloric acid in 113 ml of water is added and the mixture is heated to a temperature between 45-50°C and the stirring is continued for 2 hours maintaining the same temperature. After ending the reaction 120-140 ml of aqueous methanol is distilled off and the resulting mixture is cooled to

5 room temperature and further to a temperature between 5-10°C with stirring and the stirring is continued for 1 hour at the same temperature. The product precipitated is filtered and dried.

In this manner 21,5 g of title compound was obtained.

Yield: 94%

Melting point: over 310°C (destroy).

## Claims

1. Trans N-{4-[2-[4-(2,3-dichlorophenyl)-piperazine-1-il]-ethyl}-cyclohexylamine dihydrochloride monohydrate.

2. Process for the preparation of trans N-{4-[2-[4-(2,3-dichlorophenyl)-piperazine-1-il]-ethyl}-cyclohexylamine dihydrochloride monohydrate characterized in that

- reacting trans 2-{1-[4-(N-tert-butoxycarbonyl)amino]-cyclohexyl}-acetic acid ester with sodium borohydride and aluminium trichloride to give trans 2-{1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl}-ethanol;
- reacting trans 2-{1-[4-(N-tert-butoxycarbonyl)-amino]cyclohexyl}-ethanol obtained with methanesulfonic acid chloride in the presence of an acid binding agent to give trans 2-{1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl}-ethyl methanesulfonate;
- reacting trans 2-{1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl}-ethyl methanesulfonate obtained with 2,3-dichlorophenyl-piperazine in the presence of an acid binding agent to give trans 2-{1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl}-carbamic acid tert-butylester;
- heating trans 2-{1-[4-(N-tert-butoxycarbonyl)-amino]-cyclohexyl}-carbamic acid tert-butylester obtained to a temperature between 40-100°C in a mixture of aqueous hydrochloric acid/methanol to give trans N-{4-[2-[4-(2,3-dichlorophenyl)piperazine-1-il]-ethyl}-cyclohexylamine dihydrochloride monohydrate.

3. A process according to claim 2 characterized in that the steps a) and b) are carried out without isolation of the intermediate compounds obtained.

4. A process according to claim 2 characterized in that in step b) organic amines are employed as acid binding agent.

5. A process according to claim 4 characterized in that in step b) triethylamine is employed as acid binding agent.

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**6.** A process according to claim 2 characterized in that in step c) an alkali carbonate is employed as acid binding agent.

**7.** A process according to claim 2 characterized in that in step d) heating is made at a

5 temperature between 45-50°C.

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/HU2009/000108

**A. CLASSIFICATION OF SUBJECT MATTER**  
INV. C07D295/135

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, WPI Data, 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.
A	WO 2005/012266 A1 (RICHTER GEDEON VEGYESZET [HU]; AGAINE CSONGOR EVA [HU]; GALAMBOS JANOS) 10 February 2005 (2005-02-10) cited in the application page 9, line 26 – page 9, line 27 -----	1-7
X	WO 03/029233 A1 (RICHTER GEDEON VEGYESZET [HU]; GALAMBOS JANOS [HU]; NOGRADI KATALIN [H]) 10 April 2003 (2003-04-10) cited in the application page 9, line 12 – page 9, line 13 ----- -/-	1

Further documents are listed in the continuation of Box C.

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11 March 2010	17/03/2010
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer  Menegaki, Fotini

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/HU2009/000108

## C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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