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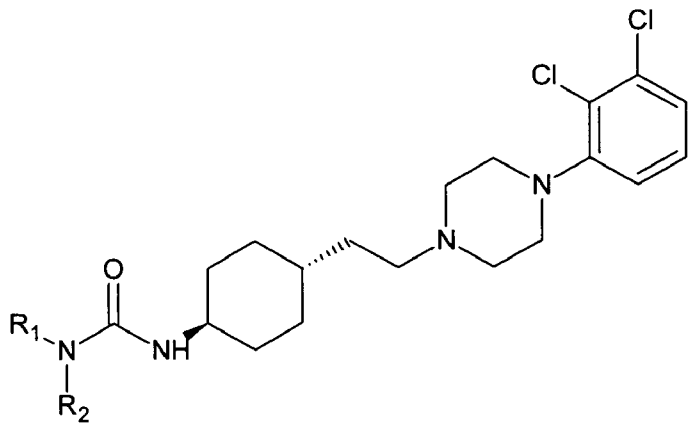
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(54) **Title**: PROCESS FOR THE PREPARATION OF PIPERAZINE COMPOUNDS AND HYDROCHLORIDE SALTS THEREOF



(I)

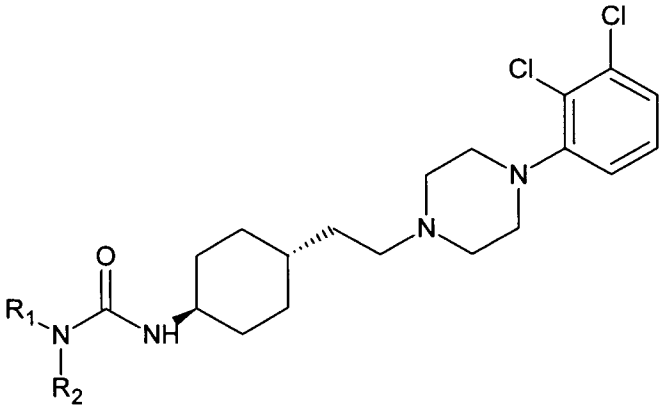
(57) **Abstract**: The invention relates to a new process for the preparation of compounds of general formula (I) and hydrochloric acid alts and/or hydrates and/or solvates thereof, by dissolving suspending trans 4-[2-[4-(2,3-dichlorophenyl)-piperazine1-il]-cyclohexylamine of formula (III) or a salt or a hydrate or a solvate thereof in an inert solvent in the presence base then adding a carbonic acid derivative of general formula (VI) wherein R is alkyl with C_{1-6} straight or branched chain or C_{1-2} fully halogenated alkyl, Z is -O-R or -X, wherein R is as described above, X is halogen, and reacting the compound of general formula (IV) obtained wherein R is as described above, in situ or, optionally in isolated state with an amine of general formula (V) wherein R_1 and R_2 are as described above to obtain the compound of general formula (I) and then optionally forming the hydrochloride salts and/or hydrates and/or solvates thereof.

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Process for the preparation of piperazine compounds and hydrochloride salts thereof

Technical field

The invention relates to a new process for the preparation of trans N-{4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl}-cyclohexyl}-carbamide compounds of general formula (I)



(I)

wherein R_1 and R_2 represent independently

- hydrogen or
- C_{1-6} alkyl with straight or branched chain optionally substituted with aryl group, or
- R_1 and R_2 together with the adjacent nitrogen atom may form an optionally substituted, saturated or unsaturated, monocyclic or bicyclic heterocyclic ring which may contain further heteroatoms selected from oxygen, nitrogen or sulphur atoms
- C_{2-7} alkenyl containing 1-3 double bonds, or
- monocyclic, bicyclic or tricyclic aril group optionally substituted with one or more C_{1-6}-alkoxy, trifluoro-C_{1-6}-alkoxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkanoyl, aryl, C_{1-6} alkylthio, cyano groups or halogen atom
- optionally substituted monocyclic, bicyclic, or tricyclic C_{3-14} cycloalkyl group

and hydrochloride salts and/or hydrates and/or solvates thereof.

Description of the prior art

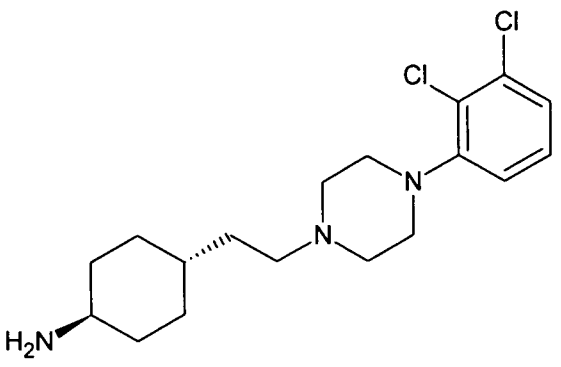
The base form of the compounds of general formula (I) was originally disclosed in the Hungarian Patent Specification No. P0302451. In the specification three reaction routes (A, B, C methods) are given for the preparation of the base form of compounds of formula (I). In the method „A" a suitable amine is reacted with a (thio)carbamoylchloride to give the end products of general formula (I). According to the A Method of P0302451 the "A" procedure gives the product with a yield of only 65% and with very long reaction time. According to Method B an iso(thio)cyanate is reacted with an amine compound. Drawback of the "B" process is that using this procedure only the compound of general formula (I) may be prepared wherein one of the R_1 and R_2 groups represents hydrogen. According to the "C" Method of P0302451 a suitable amine is transformed to an iso(thio)cyanate derivative then this iso(thio)cyanate derivative is reacted with an amine to give the desired end products of formula (I). The total yield of Method C is very low, only 52%.

Drawbacks of the "A" and "C" procedures are the long reaction times (48 and 20 hours) and poor yields (65% and 52%). Besides, in the "A" and "C" procedures the end product obtained should be purified in an additional purification (recrystallization) step to give the product in suitable quality.

Brief description of the invention

Our aim was to develop a process which provides both unsubstituted and mono- and disubstituted carbamide compounds of general formula (I) with excellent yield.

We have surprisingly found that by reacting trans 4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl}-cyclohexylamine of formula (III)



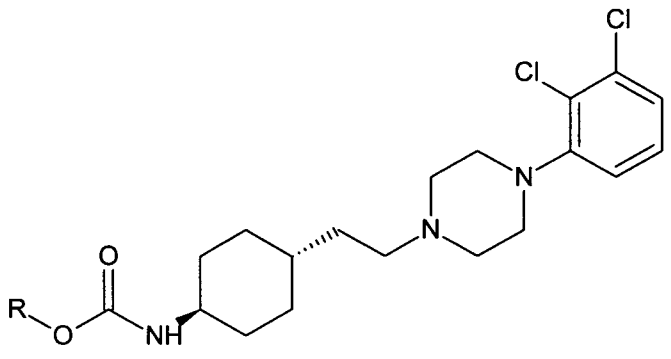
(III)

or a salt and/or a hydrate and/or a solvate thereof with a carbonic acid derivative of general formula (VI)

R–O–CO–Z (VI)

wherein R is C_{1-6} straight or branched alkyl or fully halogenated C_{1-2} alkyl, Z is –O–R or –X, wherein R is as described above, X is halogen,

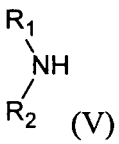
then reacting the compound of general formula (IV) obtained



(IV)

wherein R is as described above ,

with an amine derivative of general formula (V)



(V)

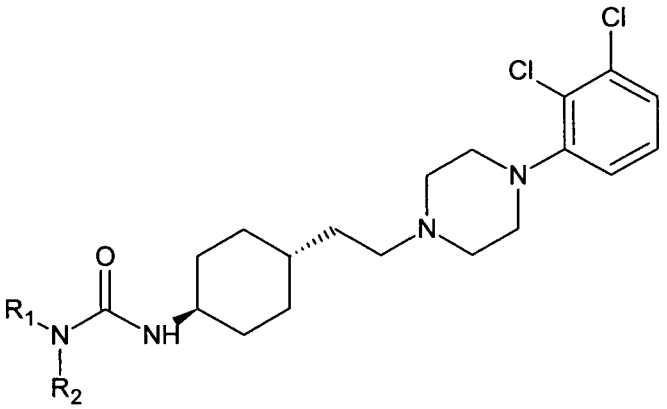
wherein

R_1 and R_2 represent independently

- hydrogen or
- C_{1-6} alkyl with straight or branched chain optionally substituted with aryl group, or
- C_{2-7} alkenyl containing 1-3 double bonds, or
- monocyclic, bicyclic or tricyclic aryl optionally substituted with one or more C_{1-6} alkoxy, trifluoro-C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, C_{1-6} alcanoyl, aryl, C_{1-6} alkyltio, halogen, or cyano groups, or
- optionally substituted monocyclic, bicyclic or tricyclic C_{3-14} cycloalkyl group, or

- R_1 and R_2 together with the adjacent nitrogen may form a saturated or unsaturated optionally substituted monocyclic or bicyclic heterocyclic ring which may contain further heteroatoms, selected from oxygen, nitrogen or sulphur atoms

we get the compounds of general formula (I)

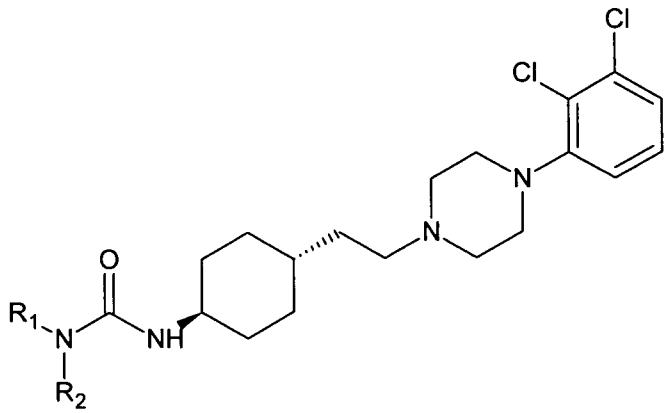


(I)

wherein R_1 and R_2 are as described above with very high yield.

Detailed description of the invention

The invention relates to a new process for the preparation of compounds of general formula (I)



(I)

wherein R_1 and R_2 represent independently

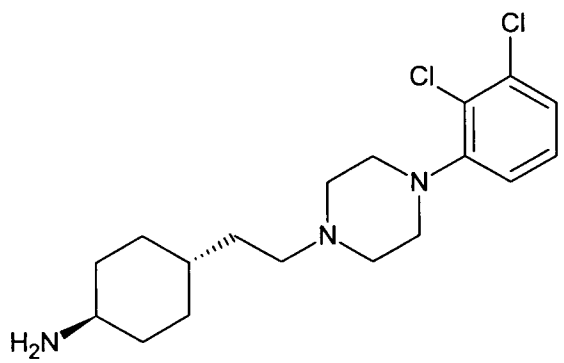
- hydrogen or
- C_{1-6} alkyl with straight or branched chain optionally substituted with aryl group, or
- C_{2-7} alkenyl containing 1-3 double bonds, or

- monocyclic, bicyclic or tricyclic aryl group optionally substituted with one or more C_{1-6} alkoxy, trifluoro-C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl, C_{1-6} alcanoyl, aryl, C_{1-6} alkyltio, halogen, or cyano groups, or
- optionally substituted monocyclic, bicyclic or tricyclic C_{3-14} cycloalkyl group, or
- R_1 and R_2 together with the adjacent nitrogen may form a saturated or unsaturated optionally substituted monocyclic or bicyclic heterocyclic ring which may contain further heteroatoms selected from oxygen, nitrogen or sulphur atoms

and hydrochloride salts, and/or hydrates and/or solvates thereof.

In the meanings of R_1 and R_2 the aryl group represents for example phenyl, tolyl, naphthyl or phenanthryl groups.

Performing the process according to the invention the trans 4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl}-cyclohexyl-amine compound of formula (III)

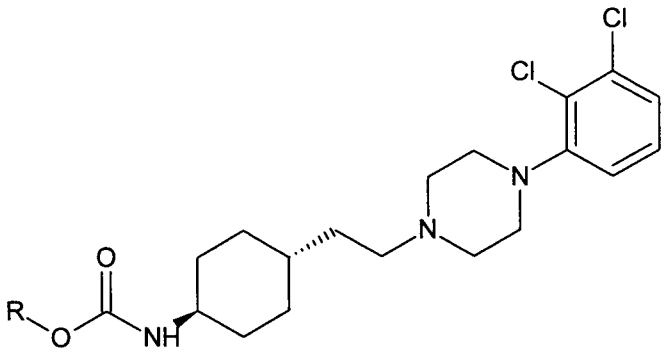


(III)

or a salt or a hydrate or a solvate thereof is dissolved or suspended in an inert solvent in the presence of a base and reacted with a carbonic acid derivative of general formula (VI)

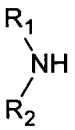
R–O–CO–Z (VI)

wherein R is C_{1-6} alkyl with straight or branched chain or C_{1-2} fully halogenated alkyl, Z is –O–R or –X, wherein R is as described above, X is halogen to give a compound of general formula (IV)



(IV)

wherein R is C_{1-6} alkyl or fully halogenated C_{1-2} alkyl group. Then the compound of general formula (IV) obtained is reacted with an amine of general formula (V)



wherein R_1 and R_2 are as described above to give a compound of general formula (I). The above reaction may be carried out in situ in an inert solvent or after the isolation of the compound of general formula (IV).

Suitable solvents, which can be used in the process according to the invention include inert, water immiscible solvents, for example toluene, dichloromethane, chlorobenzene or xylene. In a preferred embodiment of the invention the solvent is dichloromethane.

Suitable bases, which can be used in the process according to the invention include organic bases, preferably tertiary amines, for example triethylamine.

In the substituents meanings of the carbonic acid derivatives of general formula (VI) when R represents fully halogenated alkyl group, the alkyl group may be for example trichloromethyl or pentachloroethyl group. In a preferred embodiment of the invention the carbonic acid derivative is chloroformic acid ester or bis-trichloromethylcarbonate.

Performing the process according to the invention the reaction between the compounds of general formula (IV) and (V) may be carried out in such a manner, that after an isolation step the urethane compound of general formula (IV) is reacted with an amine of general formula (V). However, owing to the bad isolability of compounds of general formula (IV) the above reaction is preferably may be performed in situ in an inert solvent in such a

way that an appropriate amine of general formula (V) is added to the reaction mixture of formulas of (III) and (VI). In this latter case, starting from the compound of formula (III) via the non-isolated compound of general formula (IV) we get the compound of general formula (I) in high yield of over 90%.

In the light of the technical literature the advantages of the process according to the invention are as follows: the yield increases from 52-65% to 95%, and by using the procedure besides the N-monosubstituted compounds of formula (I) N-disubstituted compounds can be obtained too.

The invention relates to a process for the preparation the trans N-{4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl}-cyclohexyl}-carbamide base of general formula (I) and the hydrochloride salts thereof.

In an embodiment of the invention to give the trans N-{4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl}-cyclohexyl}-carbamide base of general formula (I) work-up of the reaction mixture is carried out in such a manner that after an aqueous dilution the reaction mixture is extracted with an organic solvent and the base compound of formula (I) may be isolated by a known manner preferably by removing the solvent.

In a preferred embodiment of the invention the base is not isolated but after an aqueous dilution the reaction mixture is acidified with hydrochloric acid to pH 2-4, then the reaction mixture is converted to an aqueous suspension by distillation and the hydrochloride salt of the compound of general formula (I) is isolated in high purity ad yield of over 90%.

Examples

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

Example 1

***Trans* N-(4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl}-cyclohexyl)-carbamic acid methylester**

6.45 g (0.015 mol) of dihydrochloride of compound of formula (III) was added to a mixture of 125 ml dichloromethane and 12.25 ml triethylamine and the thick suspension obtained was

stirred at a temperature between 20-25°C for one hour. The so obtained suspension was added to a solution of 2.3 ml (0.03 mol) methyl chloroformate in 25 ml of dichloromethane at a temperature between 5-10°C. The reaction mixture obtained was stirred at a temperature between 20-25°C for 3 hours then extracted with 3x150 ml (150 g) of distilled water. The organic phase was evaporated in vacuum and the residue was recrystallized from methanol.

In this manner 4.5 g of the title product was obtained.

Yield: 72 %.

Melting point: 143-147 °C

Example 2

Trans N-(4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl}-cyclohexyl)-carbamic acid isopropylester

6.45 g (0.015 mol) of dihydrochloride of compound of formula (III) was added to a mixture of 125 ml dichloromethane and 12.25 ml of triethylamine and the thick suspension obtained was stirred at a temperature between 20-25°C-on for one hour. The suspension was added to a solution of 3.7 g (0.03 mol) of isopropyl chloroformate in 30 ml of toluene at a temperature between 5-10°C. The reaction mixture was stirred at a temperature between 20-25°C for 3 hours and then extracted with 3x150 ml (150 g) of distilled water. The organic phase was evaporated in vacuum and the residue obtained was recrystallized from isopropanole.

In this manner 4,4 g of title compound was obtained.

Yield: 67 %.

Melting point: 128-131°C

Example 3

Trans 4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine

6.45 g (0.015 mol) of dihydrochloride of compound of formula (III) was added to a mixture of 125 ml of dichloromethane and 12.25 ml of triethylamine and the thick suspension obtained was stirred at a temperature between 20-25°C for one hour. The suspension was added to a

solution of 4.9 g of bis(trichloromethyl)carbonate in 50 ml of dichloromethane at a temperature between -5-(-10)°C for one hour. The reaction mixture obtained was added to a solution of 13 g dimethylamine in 100 ml isopropyl alcohol (IPA) (40 ml, 0.12 mol) cooled at a temperature between 0-(-10)°C during which the temperature of the reaction mixture was kept under 0°C. After stirring at a temperature between 0-(-5)°C for 30 minutes to the reaction mixture 100 ml of distilled water was added under stirring. Then the pH of the aqueous phase was adjusted to 7-8 by adding concentrated hydrochloric acid and volume of the reaction mixture was concentrated to 130 ml under vacuum. To the reaction mixture obtained additional 70 ml of distilled water was added and the mixture was concentrated to 170 ml under vacuum. The suspension was stirred at 20-25°C for one hour and the product obtained was isolated by filtration.

In this manner 6.6 g of title compound was obtained.

Yield: 95 %

Melting point: 208-211 °C

Example 4

Trans 4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl}-N,N-dimethylcarbamoyl-cyclohexylamine hydrochloride

6.45 g (0.015 mol) dihydrochloride of formula (III) was added to a mixture of 125 ml of dichloromethane and 12.25 ml of triethylamine and the thick suspension obtained was stirred at a temperature between 20-25°C for one hour. The suspension was added to the solution of 4.9 g of bis(trichloromethyl)carbonate in 50 ml of dichloromethane at a temperature between -5-(-10)°C for one hour. The reaction mixture obtained was added to a solution of 13 g dimethylamine in 100 ml isopropyl alcohol (IPA) (40 ml, 0.12 mol) cooled at a temperature between 0-(-10)°C during which the temperature of the reaction mixture was kept under 0°C. After stirring at a temperature between 0-(-5)°C for 30 minutes 100 ml of distilled water was added to the reaction mixture under stirring. Then the pH of the aqueous phase is adjusted to 2-3 by adding concentrated hydrochloric acid and the reaction mixture was concentrated to 130 ml, additional 70 ml of distilled water was added and the mixture was concentrated to

170 ml. The suspension was stirred at 20-25°C for one hour and the product obtained was isolated by filtration.

In this manner 6.7 g of title compound was obtained.

Yield: 96 %

Melting point: 221-224 °C

Example 5

Trans 4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl}-N,N-dimethylcarbamoil-cyclohexylamine hydrochloride

6.72 g (0.015 mol) dihydrochloride monohydrate of compound of formula (III) was added to a mixture of 125 ml of dichloromethane and 12.25 ml of triethylamine and the thick suspension obtained was stirred at a temperature between 20-25 °C for one hour. The suspension was added to the solution of 4.9 g of bis(trichloromethyl)carbonate in 50 ml of dichloromethane at a temperature between -5-(-10)°C for one hour. The reaction mixture obtained was added to a solution of 13 g dimethylamine in 100 ml isopropyl alcohol (IPA) (40 ml, 0,12 mol) cooled at a temperature between 0-(-10)°C during which the temperature of the reaction mixture was kept under 0°C. After stirring at a temperature between 0-(-5)°C for 30 minutes to the reaction mixture 100 ml of distilled water was added and the pH of the aqueous phase was adjusted to 2-3 by adding concentrated hydrochloric acid. The reaction mixture was concentrated to 130 ml under vacuum then additional 70 ml of water was added and the mixture was concentrated to 170 ml. The suspension was stirred at a temperature between 20-25°C for one hour and the product obtained was isolated by filtration.

In this manner 6.7 g of title compound was obtained.

Yield: 96 %.

Melting point: 221-224 °C

Example 6

1-Trans {4-[2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl]-cyclohexyl}carbamide

6.45 g (0.015 mol) dihydrochloride of compound of formula (III) was added to a mixture of 160 ml of dichloromethane and 12.8 ml of triethylamine and the thick suspension obtained was stirred at a temperature between 20-25°C for one hour. The suspension was added to the solution of 4.9 g of bis(trichloromethyl)carbonate in 75 ml of dichloromethane at a temperature between -5-(-10)°C for one hour. The reaction mixture obtained was added to a solution of ammonia in methanol (110 ml, 17g/100ml) cooled at a temperature between 0-(-10)°C during which the temperature of the reaction mixture was kept under 0°C. After stirring at a temperature between 0-(-5)°C for 30 minutes the reaction mixture was concentrated to 100 ml in vacuum then 800 ml of distilled water was added. The suspension was stirred at 20-25°C for one hour and the product obtained was isolated by filtration.

In this manner 5.6 g of title compound was obtained.

Yield: 94 %.

Melting point: 221-224 °C

Example 7

Trans N-{4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl}-cyclohexyl}-N'-methylcarbamide hydrochloride

6.45 g (0.015 mol) dihydrochloride of compound of formula (III) was added to a mixture of 125 ml of dichloromethane and 12.25 ml of triethylamine and the thick suspension obtained was stirred at a temperature between 20-25°C for one hour. The suspension was added to the solution of 4.9 g of bis(trichloromethyl)carbonate in 50 ml of dichloromethane at a temperature between -5-(-10)°C for one hour. The reaction mixture obtained was added to a solution of methylamine in isopropyl alcohol (IPA) (60 ml, 12.5 g/100 ml) cooled at a temperature between 0-(-10)°C during which the temperature of the reaction mixture was kept under 0°C. After stirring at a temperature between 0-(-5)°C for 30 minutes to the reaction mixture 130 ml of distilled water was added then the pH of the aqueous phase was adjusted to 2-3 by adding concentrated hydrochloric acid. The reaction mixture was concentrated to 120

ml in vacuum and additional 70 ml of distilled water was added. The suspension was stirred at a temperature between 20-25°C for one hour and the product obtained was isolated by filtration.

In this manner 6.6 g of title compound was obtained.

Yield: 95 %.

Melting point: 230-255 °C.

Example 8

Trans N-{4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl}-cyclohexylcarbamide hydrochloride

6.45 g (0.015 mol) dihydrochloride of compound of formula (III) was added to a mixture of 160 ml of dichloromethane and 12.8 ml of triethylamine and the thick suspension obtained was stirred at a temperature between 20-25°C for one hour. The suspension was added to a solution of 4.9 g of bis(trichloromethyl)carbonate in 75 ml of dichloromethane at a temperature between -5-(-10)°C for one hour. The raction mixture obtained was added to a solution of ammonia in methanol (110 ml, 17 g/100 ml) cooled at a temperature between 0-(-10)°C during which the temperature of the reaction mixture was kept under 0°C. After stirring at 0-10°C for 30 minutes the reaction mixture was concentrated to 20 ml in vacuum then 140 ml of distilled water was added. The pH of the aqueous phase was adjusted to 2-3 by adding concentrated hydrochloric acid. The suspension was stirred at a temperature between 20-25°C for one hour and the product obtained was isolated by filtration. In this manner 5.86 g of title compound was obtained.

Yield: 90%.

Melting point: 250-253 °C (decomp.).

Example 9

Trans N-{4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl}-cyclohexyl}-morpholine-4-carbonic amide

6.45 g (0.015 mol) dihydrochloride of compound of formula (III) was added to a mixture of 125 ml of dichloromethane and 12.25 ml of triethylamine and the thick suspension obtained was stirred at a temperature between 20-25°C for one hour. The suspension was added to a solution of 4.9 g of bis(trichloromethyl)carbonate in 50 ml of dichloromethane at a temperature between -5-(-10) °C for one hour. The so obtained reaction mixture was added to the solution of 10.44 g (0.12 mol) morpholine in 70 ml of isopropyl alcohol (IPA) cooled at a temperature between 0-(-10)°C during which the temperature of the reaction mixture was kept under 0°C. After stirring at 0-10°C for 30 minutes to the reaction mixture 100 ml of distilled water was added under stirring and the pH of the aqueous phase was adjusted to 7-8 by adding concentrated hydrochloric acid. The reaction mixture was concentrated to 130 ml under vacuum and additional 100 ml of distilled water was added. Volume of the reaction mixture was decreased to 150 ml in vacuum. The suspension was stirred at a temperature between 20-25°C for one hour and the product obtained was isolated by filtration.

In this manner 6.55 g of title compound was obtained.

Yield: 93 %.

Melting point: 204-206°C (decomp).

Example 10

Trans N-{4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-yl]-ethyl}-cyclohexyl}-morpholine-4-carbonic amide hydrochloride

6.45 g (0.015 mol) dihydrochloride of compound of formula (III) was added to a mixture of 125 ml dichloromethane and 12.25 ml of triethylamine and the thick suspension obtained was stirred at a temperature between 20-25°C for one hour. The suspension was added to a solution of 4.9 g of bis(trichloromethyl)carbonate in 50 ml of dichloromethane ata temperature between -5-(-10)°C for one hour. The reaction mixture obtained was added to a solution of 10.44 g of (0.12 mol) morpholine in 70 ml of isopropyl alcohol (IPA) cooled to a

temperature between 0-(-10)°C during which the temperature of the reaction mixture was kept under 0°C. After stirring at 0-10°C for 30 minutes to the reaction mixture 100 ml of distilled water was added under stirring then the pH of the aqueous phase was adjusted to 2-3. The reaction mixture was concentrated to 130 ml under vacuum and further 100 ml of distilled water was added. Then the volume of the reaction mixture was decreased to 150 ml under vacuum. The suspension was stirred at a temperature between 20-25°C for one hour and the product obtained was isolated by filtration.

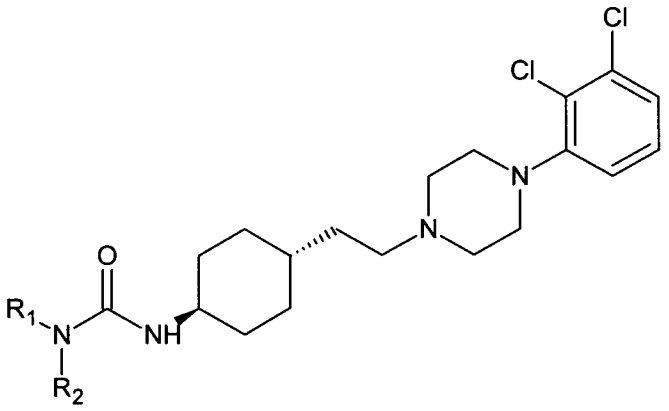
In this manner 7.1 g of title product was obtained.

Yield: 94 %.

Melting point: 197 °C (decomp.).

Claims

1. Process for the preparation of compounds of general formula (I)

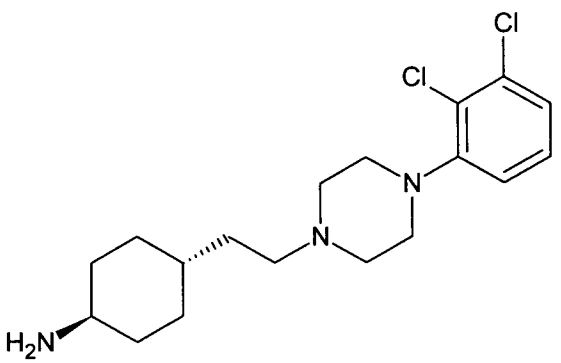


(I)

wherein R_1 and R_2 represent independently

- hydrogen or
- C_{1-6} alkyl with straight or branched chain optionally substituted with aryl group, or
- C_{2-7} alkenyl containing 1-3 double bonds, or
- monocyclic, bicyclic or tricyclic aryl optionally substituted with one or more C1-6 alkoxy, trifluoro-C_{1-6} alkoxy, C_{1-6}-alkoxycarbonil, C_{1-6}alkanoyl, aryl, C_{1-6} alkylthio, halogen or cyano, or
- optionally substituted monocyclic, bicyclic or tricyclic C_{3-14} cycloalkyl group,
- R_1 and R_2 together with the adjacent nitrogen form a saturated or unsaturated optionally substituted monocyclic or bicyclic heterocyclic ring which may contain further heteroatoms selected from oxygen, nitrogen, or sulphur atoms

and hydrochloric acid alts and/or hydrates and/or solvates thereof characterized in that dissolving or suspending trans 4-{2-[4-(2,3-dichlorophenyl)-piperazine-1-il]-ethyl}-cyclohexylamine of formula (III)



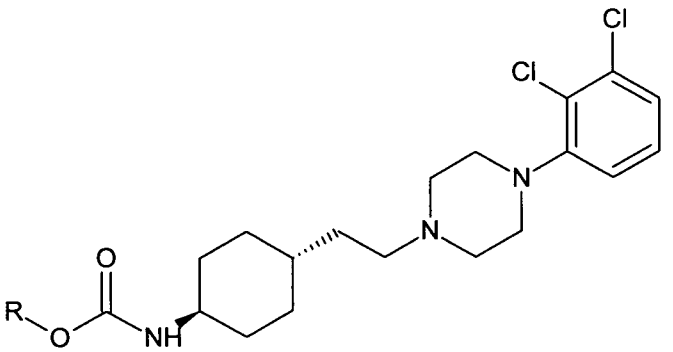
(III)

or a salt or a hydrate or a solvate thereof in an inert solvent in the presence a base then adding a carbonic acid derivative of general formula (VI)

R–O–CO–Z (VI)

wherein R is alkyl with C $_{1-6}$ straight or branched chain or C_{1-2} fully halogenated alkyl, Z is –O–R or –X, wherein R is as described above, X is halogen, and

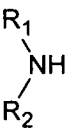
reacting the compound of general formula (IV) obtained



(IV)

wherein R is as described above,

in situ or, optionally in isolated state with an amine of general formula (V)



wherein R_1 and R_2 are as described above to obtain the compound of general formula (I) and then optionally

forming the hydrochloride salts and/or hydrates and/or solvates thereof.

2. A process according to claim 1 characterized in that the carbonic acid derivative of general formula (VI) is a chloroformate ester or bis(trichloromethyl)carbonate.

3. A process according to claim 1 characterized in that the reaction of compounds of general formula (IV) and (V) is carried out in situ without isolation of the compound of general formula (IV).

INTERNATIONAL SEARCH REPORT

International application No
PCT/HU2009/000109

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, BEILSTEIN 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 claim 9; example 3	1-3
A	WO 2008/142461 A1 (RICHTER GEDEON NYRT [HU]; AGAINE CSONGOR EVA [HU]; KIRSCHNER NORBERT A) 27 November 2008 (2008-11-27) example 3	1-3

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" 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 novel or 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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 March 2010	11/03/2010

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/HU2009/000109

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		EP 2155707 A1	24-02-2010