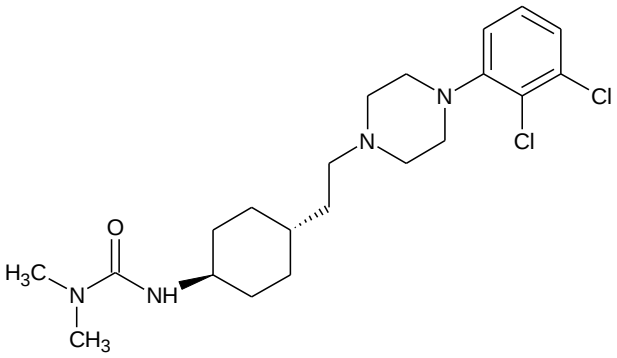
Claims

1. Process for the preparation of cariprazine or a salt thereof



(1)

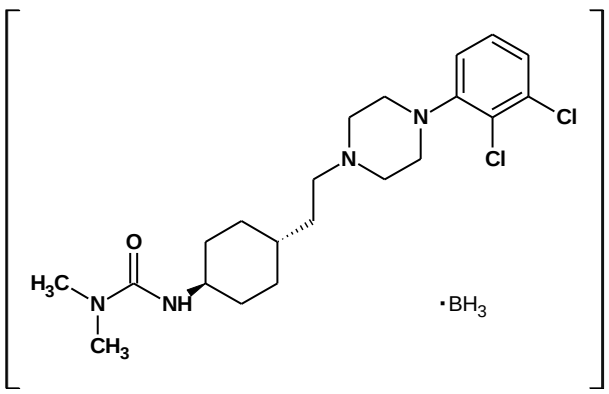
wherein

a) (trans-4-amino-cyclohexyl)-acetic acid ethyl ester hydrochloride is converted to trans-4-aminocyclohexyl) acetic acid or its hydrochloride by hydrolysis,

b) from the obtained product with addition of a dicarbamoyl derivative selected from a halide, imidazolide, anhydride or active ester as a suitable reagent in presence of alkaline reagent (trans-4-{[(dimethylamino)carbonyl]amino} cyclohexyl) acetic acid is formed,

c) then the obtained compound is linked to 1-(2,3-dichlorophenyl)-piperazine in the presence of carboxylic acid activating coupling reagent, and so 1,1-dimethyl-3-[trans-4-(2-oxo-2-(4-(2,3-dichlorophenyl)piperazin-1-yl-ethyl)cyclohexyl] urea is formed,

d) which is converted to cariprazine borane adduct of formula (2),



(2)

in the presence of a borohydride compound, borane or a borane complex as a reducing agent,

e) and the final product itself is eliminated directly or is obtained from its salt.

2. Process according to claim 1 characterized by carrying out the hydrolysis of (trans-4-amino-cyclohexyl)-acetic acid ethyl ester hydrochloride by basic or acidic hydrolysis.

3. Process according to claims 1 or 2 characterized in that (trans-4-{[(dimethylamino)carbonyl]amino}cyclohexyl)-acetic acid is formed with dimethyl-carbamoyl chloride as reagent.

4. Process according to any of the claims 1 to 3 characterized in that the carboxylic acid activating coupling reagent for coupling of 1-(2,3-dichlorophenyl)-piperazine is a dehydrating agent.

5. Process according to any of the claims 1 to 3 characterized in that for coupling reaction with 1-(2,3-dichlorophenyl)-piperazine carbonyldiimidazole or thionyl chloride is used.

6. Process according to any of the claims 1 to 5 characterized in that the reducing agent is borane which is formed “in situ” from a suitable precursor.

7. Process according to any of the claims 1 to 6 characterized in that borohydrides or boranes or complexes thereof having the corresponding counter ion are used as reducing agent.

8. Process according to claim 7 characterized in that borane complex refers to the complexes of boranes formed with Lewis bases, such as complexes formed with ethers, thioethers, amines, preferably a complex formed with tetrahydrofuran.

9. Process according to claim 7 characterized in that suitable counter ion for borohydrides are positive ions of metallic elements such as alkali metals, alkaline earth metals, earth metals, preferably aluminum.

10. Process according to any of the claims 1 to 9 characterized in that after isolation of cariprazine borane adduct, carprazine salts are obtained by decomposition with Brönsted acids in conventional solvents.

11. A process according to claim 10 characterized in that after isolation of cariprazine borane adduct, Brönsted acid used for decomposition in conventional solvents is hydrogen chloride.

12. Process according to any of the claims 1 to 11 characterized in that the resulting cariprazine hydrochloride salts are converted into base final product.

13. Process according to any of the claims 1 to 9 characterized in that from the isolated cariprazine borane adduct in conventional solvents by thermal decomposition carprazine base final product is obtained.