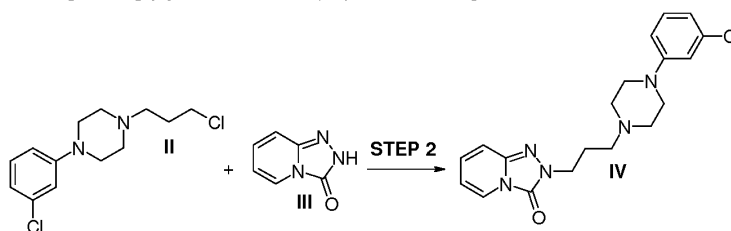


CLAIMS

1. A continuous process for the preparation of trazodone base (IV), starting from N-(3-chlorophenyl)-N'-(3-chloropropyl)-piperazine (II) and s-triazolo-[4,3-a]-pyridin-3-one (III), according to reaction scheme 2:



Scheme 2

comprising continuously mixing in a flow reactor an alkaline aqueous solution of s-triazolo-[4,3-a]-pyridin-3-one (III) and an organic solution of N-(3-chlorophenyl)-N'-(3-chloropropyl)-piperazine (II), and continuously recovering trazodone base (IV).

2. The continuous process according to claim 1, comprising the following steps:

- (i) continuously feeding a first channel of a flow reactor with an aqueous solution of s-triazolo-[4,3-a]-pyridin-3-one (III) and at least one basic compound;
- (ii) continuously feeding a second channel of said flow reactor with an organic solution of N-(3-chlorophenyl)-N'-(3-chloropropyl)-piperazine (II) in at least one organic solvent;
- (iii) continuously reacting said s-triazolo-[4,3-a]-pyridin-3-one (III) with said N-(3-chlorophenyl)-N'-(3-chloropropyl)-piperazine (II) by continuously mixing said alkaline aqueous solution and said organic solution in said flow reactor, at a temperature of at least 90 °C; and
- (iv) continuously collecting said reaction mixture from said flow reactor, and isolating the obtained product trazodone base (IV).

3. The process according to any one of claims 1-2, wherein trazodone base (IV) is obtained with a conversion yield of at least 70% by HPLC.

5 4. The process according to any one of claims 1-3, wherein trazodone base (IV) has a purity of at least 90% by HPLC.

5. The process according to any one of claims 2-4, wherein the residence time of the continuous reaction according to step iii) is of from 70 to 300 seconds.

10 6. The process according to any one of claims 2-5, wherein the temperature of the continuous reaction according to step iii) is of from 130 °C to 160 °C.

15 7. The process according to any one of claims 2-6, wherein the basic compound according to step i) is an inorganic base selected from the group comprising sodium hydroxide, potassium hydroxide, sodium hydride, sodium amide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium phosphate, potassium phosphate, ammonium hydroxide, magnesium oxide, and mixtures thereof.

20 8. The process according to claim 7, wherein the inorganic base is selected from the group comprising sodium hydroxide, potassium hydroxide, sodium carbonate, and mixtures thereof.

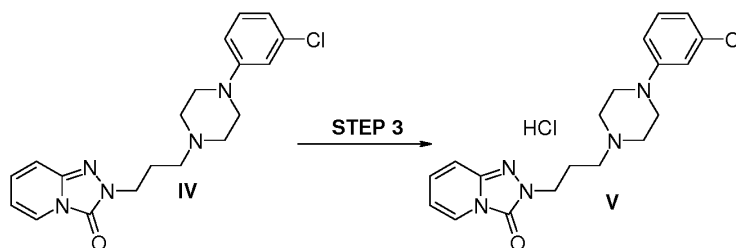
25 9. The process according to any one of claims 2-8, wherein the basic compound according to step i) is an organic base selected from the group comprising aliphatic and aromatic amines, and mixtures thereof.

10. The process according to claim 9, wherein said amines are selected in the group comprising: trimethylamine, triethylamine, N,N-diisopropylethylamine, triethanolamine, N,N-dimethylethanolamine, N-methylethanolamine, and mixtures thereof.

11. The process according to any one of claims 2-10 wherein the organic solvent according to step ii) is a polar aprotic solvent selected from the group comprising: dimethylformamide, dimethyl sulfoxide, acetone, tetrahydrofuran, acetonitrile, dioxane; or is an apolar solvent selected from the group comprising: toluene, diethyl ether; or is a polar protic solvent selected from the group comprising: methanol, ethanol, propanol, isopropanol, butyl alcohol, isobutyl alcohol, benzyl alcohol.

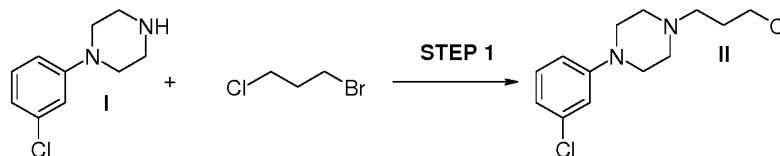
12. The process according to claim 11, wherein the organic solvent is selected from the group comprising: isobutyl alcohol, isopropanol, dioxane, and acetonitrile.

13. The process according to any one of claims 1-12, further comprising step v) wherein trazodone base (**IV**) is converted to trazodone hydrochloride (**V**) and isolated, according to reaction scheme 3:



Scheme 3

14. The continuous process according to any one of claims 1-13, further comprising a prior reaction of m-chlorophenyl-piperazine (**I**) and 1-bromo-3-chloropropane, to N-(3-chlorophenyl)-N'-(3-chloropropyl)-piperazine (**II**) according to reaction scheme 4:



Scheme 4

15. The process according to claim 14 wherein m-chlorophenyl-piperazine (I) and 1-bromo-3-chloropropane are reacted in a continuous mode.

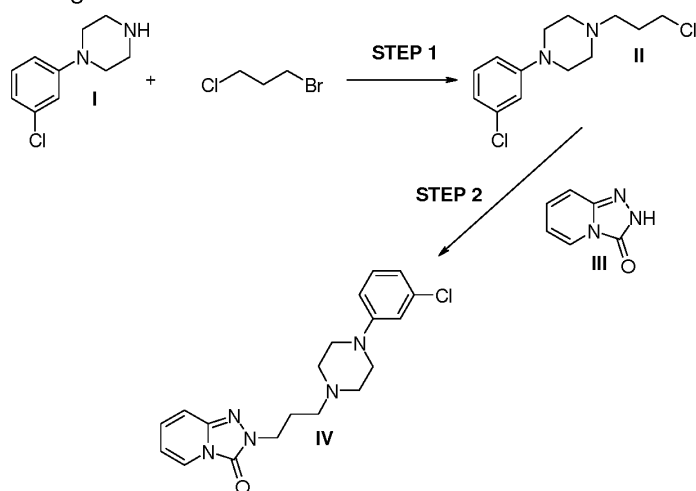
5 16. The process according to claim 14 wherein m-chlorophenyl-piperazine (I) and 1-bromo-3-chloropropane are reacted in a batch mode.

17. The process according to claim 15, comprising the following steps:

- 10 (a) continuously feeding a first channel of a flow reactor with m-chlorophenyl-piperazine (I) and an aqueous solution of at least one basic compound, to provide an alkaline aqueous phase;
- (b) continuously feeding a second channel of said flow reactor with an organic phase of 1-bromo-3-chloropropane optionally in combination with at least one organic solvent;
- 15 (c) continuously reacting said m-chlorophenyl-piperazine (I) with said 1-bromo-3-chloropropane by continuously mixing said alkaline aqueous phase and said organic phase in said flow reactor, at a temperature of at least 70 °C; and
- 20 (d) continuously removing said reaction mixture from said flow reactor and isolating the obtained product N-(3-chlorophenyl)-N'-(3-chloropropyl)-piperazine (II) which is further admixed with at least one organic solvent;
- (i) continuously feeding a first channel of a flow reactor with an aqueous solution of s-triazolo-[4,3-a]-pyridin-3-one (III) and at least one basic compound;
- 25 (ii) continuously feeding a second channel of said flow reactor with an organic solution of N-(3-chlorophenyl)-N'-(3-chloropropyl)-piperazine (II) and at least one organic solvent;
- (iii) continuously reacting said s-triazolo-[4,3-a]-pyridin-3-one (III) with said N-(3-chlorophenyl)-N'-(3-chloropropyl)-piperazine (II) by
- 30

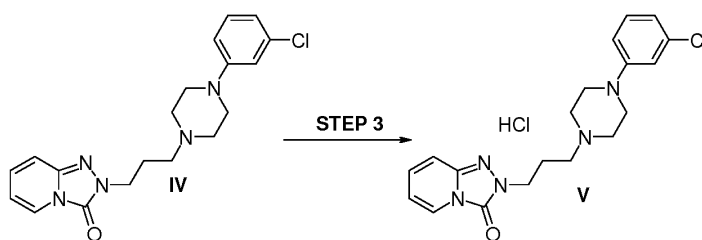
continuously mixing said alkaline aqueous solution and said organic solution in said flow reactor, at a temperature of at least 90 °C; and

- 5 (iv) continuously removing said reaction mixture from said flow reactor and isolating the obtained product trazodone base (IV), according to reaction scheme 5:



Scheme 5

18. The process according to any one of claims 14-17, further comprising step v) wherein trazodone base (IV) is converted to trazodone hydrochloride (V) and isolated, according to reaction scheme 3:
- 10 3:



Scheme 3

19. The process according to any one of claims 17-18, wherein the temperature of the continuous reaction according to step c) is of from 80 °C to 100 °C.

5 20. The process according to any one of claims 17-19, wherein the basic compound in step a) is an inorganic base selected from the group comprising sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium phosphate, potassium phosphate, ammonium hydroxide, magnesium oxide, hydrazine, hydroxylamine, and mixtures thereof.

10 21. The process according to any one of claims 17-20 wherein the basic compound in step a) is an organic base selected from the group comprising: trimethylamine, triethylamine, N,N-diisopropylethylamine, triethanolamine, N,N-dimethylethanolamine, quinoline, pyridine, morpholine, N-methylmorpholine, and mixtures thereof.

15 22. The process according to any one of claims 17-21, wherein the organic solvent according to step b) is a polar aprotic solvent selected from the group comprising: N-methylpyrrolidone, dimethylformamide, dimethyl sulfoxide, acetone, ethyl acetate, tetrahydrofuran and acetonitrile; or is an apolar solvent selected from the group comprising: 20 toluene, benzene, and diethyl ether.

23. The process according to claim 22 wherein the solvent is N-methylpyrrolidone.

24. The process according to any one of claims 1-23 wherein the flow reactor is a micro-scale, mesoscale or large scale flow reactor 25 selected from the group comprising: microchip flow reactors, microfluidic flow reactors, coil-type flow reactors, tubular flow reactors, plate reactors, packed-bed reactors, fluidized bed reactors, fixed-bed reactors and their combinations.

25. The process according to claim 24 wherein the reactor is 30 selected from the group comprising: microfluidic flow reactors, chip

mesoscale flow reactors, coil-type mesoscale flow reactors, and large scale flow reactors.