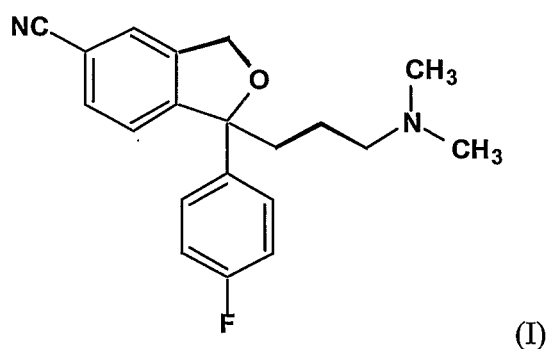


Escitalopram hydrobromide and a method for the preparation thereof

The present invention relates to escitalopram, which is the S-enantiomer of the well-known antidepressant drug citalopram, i.e. (S)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, in the form of its hydrobromide as well as a method for the preparation thereof.

Background of the Invention

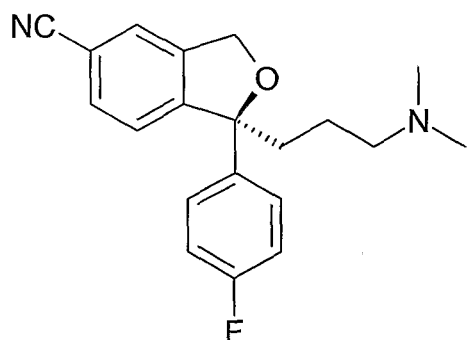
Citalopram is a well-known antidepressant drug that has now been on the market for some years and has the following structure:



It is a selective, centrally acting serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities. Citalopram was first disclosed in DE 2,657,013, corresponding to US 4,136,193.

The diol, 4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile, and its use as an intermediate in the preparation of citalopram has been disclosed in e.g. US patent No 4,650,884.

The S-enantiomer (escitalopram) of the formula



(II)

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and the antidepressant effect of said enantiomer is disclosed in US Patent No 4,943,590. EP patent application No. 1.200.081 describes the use of escitalopram for the treatment of neurotic disorders and WO 02/087566 describes the use of escitalopram for treating depressive patients who have failed to respond to
10 conventional SSRIs and for treating a number of other disorders.

Methods for the preparation of escitalopram are disclosed in US Patent No 4,943,590 and a number of other patent applications.

15 This application also describes the free base of escitalopram as an oil, the oxalic acid salt, the pamoic acid and the L-(+)-tartaric acid addition salt of escitalopram. Due to the toxicity of pamoic acid addition salts they are not suitable in pharmaceuticals.

Escitalopram has now been developed as an antidepressant and a need for alternative
20 salts of escitalopram has emerged.

In the search for salts suitable for a pharmaceutical composition more than 30 organic and inorganic acids were investigated in different solvent systems and under different conditions. These acids gave either oils or amorphous solids having moderate to high
25 hygroscopic properties. No non-hygroscopic crystalline solids were formed from monocarboxylic organic acids and these acids formed mostly oils. Di- and triphasic

organic acids gave amorphous solids. Interestingly, the salt formed with L-tartaric acid was an amorphous solid.

Thus, very few crystalline, stable, non-hygrosopic salts of escitalopram are known.

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Formation of crystalline salts with hydrochloric acid and hydrobromic acids have until now been unsuccessful.

It has now been found that crystalline escitalopram hydrobromide may be formed using gaseous hydrobromide under anhydrous conditions.

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Summary of the invention

The present invention relates to escitalopram (S-citalopram) in the form of its hydrobromide salt.

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In a particular embodiment the invention relates to escitalopram hydrobromide in solid form, such as amorphous or crystalline forms.

In a more particular embodiment the invention relates to escitalopram hydrobromide in crystalline form.

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The invention also relates to a pharmaceutical composition containing escitalopram hydrobromide and one or more pharmaceutically acceptable carriers or diluents.

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Finally the present invention relates to the use of escitalopram hydrobromide according to claims 1-2 for the manufacture of a pharmaceutical composition for the treatment of depression including treatment of patients which have failed to respond to initial treatment with conventional SSRIs, neurotic disorders (such as generalized anxiety disorder, social anxiety disorder, obsessive compulsive disorder, post traumatic stress disorder and panic attacks including panic disorder, social phobia, specific phobias and agoraphobia), acute stress disorder, eating disorders such as

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bulimia, anorexia and obesity, dysthymia, pre-menstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder and drug abuse.

5 Detailed description of the invention

It has been found that salt formation is very sensitive to the presence of water and salt formation should therefore be carried out under anhydrous conditions. Preferably salt formation is carried out by dissolving escitalopram in an anhydrous solvent, such as
10 acetone or a ketone with a larger molecule weight, such as methyl-isobutylketone. Preferably the anhydrous solvent is one that does not easily pick up water. The hydrobromic acid is suitably added as a gas.

Another method for making crystalline escitalopram hydrobromide comprises
15 preparing an anhydrous solution or almost anhydrous solution of hydrogen bromide in an organic solvent (such as *iso*-propyl alcohol) by bubbling anhydrous hydrogen bromide gas through the organic solvent. A suitable aliquot of this solution is then added to a solution of escitalopram base in an organic solvent.

20 A third method for making crystalline escitalopram hydrobromide comprises adding an aqueous solution of hydrobromic acid to escitalopram free base to form the salt, with the water being removed subsequently by means known to the skilled chemist (for example drying by azeotropic distillation using for example toluene or *iso*-propyl alcohol, or drying using a solid drying agent). The escitalopram free base may be in
25 solid form, an oil or a solution.

Examples

A) Experiment with HCl gas: A 250 ml round bottom flask was charged with 5.7
30 g escitalopram free base and 120 ml isopropanol. The mixture was stirred until a homogenous solution was obtained. The mixture was cooled to 5 °C and HCL gas was bubbled in for 20 minutes with cooling. The mixture was placed in the

refrigerator overnight. No solid material was formed. The mixture was then concentrated in vacuo to an oil and the oily residue was dissolved in acetone by heating to 45 °C (the solution was a 0.5 molar solution in acetone). The flask was scratched to initiate nucleation and the solution became cloudy. The solution was cooled to 5 °C overnight. The fluffy material was collected by filtration and transferred to an amber bottle for drying (50 °C HI-VAC) to a powder. A sample of this powder was exposed to air and as it picked up water from the air it became an oil. Attempts were made to recrystallise the oil using a variety of different solvents. None of these trials resulted in a solid product.

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B) Experiment with HBr gas: This experiment was run exactly as the experiment above except HBr gas was bubbled into the solution in *iso*-propanol. No solid material was formed in *iso*-propanol but on solvent change to acetone (a 0.5 molar solution) an off-white solid formed. The solid was collected, washed with cold acetone to give a crystalline material. The crystalline escitalopram hydrobromide was found by melting point, HPLC, and proton NMR to have a good purity. A sample of the material was exposed to air and it was found to be non-hygroscopic.

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C) Experiments with different solvents: These experiments were performed as follows: To a solution of the escitalopram free base (approx. 20 % w/w) in dry 2-propanol was added dropwise 0.9-1.0 eq. of HBr (g) dissolved in dry 2-propanol. Precipitation of a solid normally occurred within 30 minutes. Where the precipitation was performed in a solvent other than 2-propanol, the resulting mixture was evaporated under reduced pressure and the appropriate solvent was added, evaporated again and the appropriate solvent given one more time to the mixture before final crystallisation.

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Below is a table showing results from different solvents:

Precipitation of escitalopram hydrobromide from different solvents

Solvent	Yield	Purity (HPLC)	Melting Point
Toluene	81 %	99,1 %	131 °C
MTBE/IPA (200:55)	72 %	98,3 %	132 °C
IPA	67 %	99,4 %	133 °C
MTBE	93,4 %	99,2 %	131,6 °C
THF	54,5 %	99,95 %	133,9 °C
Butanone	30 %	100 %	133-134 °C
<i>n</i> -Butanol	67 %	99,9 %	133-134 °C
<i>iso</i> -Butanol	66 %	99,6 %	133-134 °C
<i>tert</i> - Butanol/IPA (4:1)	82 %	99,9 %	133-134 °C
2-Butanol	85 %	100 %	133-134 °C
MIBK	75 %	100 %	-
2-methyl-THF	84 %	100 %	-
1,4-Dioxane	65 %	100 %	-
Ether	91 %	100 %	-
EtOAc	88 %	100 %	-

MTBE = methyl *t*-butyl ether; IPA = *iso*-propanol; MIBK = methyl *iso*-butyl ketone;

THF = tetrahydrofuran; EtOAc = ethyl acetate.

Other solvents, such as acetonitrile, methanol, ethanol and propylencarbonate, were tried, but gave no crystallisation:

- 5 Another approach is to dissolve the base in 2-propanol, add 0,9 – 1,0 eq. of aqueous hydrobromic acid, distil off the solvent and remove the water by repeated azeotropic distillations (e.g. 2-propanol and toluene). This procedure seems to give somewhat lower yields.

Claims

1. Escitalopram (S-citalopram) in the form of its hydrobromide.
- 5 2. Escitalopram according to claim 1 in solid form.
3. Escitalopram hydrobromide according to claim 2 in crystalline form.
4. A pharmaceutical composition containing escitalopram hydrobromide according
10 to any of claims 1-3 and pharmaceutically acceptable carriers and diluents.
5. The use of escitalopram hydrobromide according to any of claims 1-3 for the
manufacture of a pharmaceutical composition for the treatment of
depressionincluding treatment of patients which have failed to respond to initial
15 treatment with conventional SSRIs, neurotic disorders (such as generalized
anxiety disorder, social anxiety disorder, obsessive compulsive disorder, post
traumatic stress disorder and panic attacks including panic disorder, social phobia,
specific phobias and angoraphobia), acute stress disorder, eating disorders such as
bulimia, anorexia and obesity, dysthymia, pre-menstrual syndrome, cognitive
20 disorders, impulse control disorders, attention deficit hyperactivity disorder and
drug abuse.