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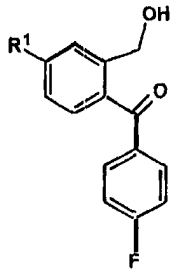

(IV)

(57) Abstract

A method for the preparation of citalopram is described comprising reduction of the oxo group of a compound of formula (IV), wherein R^1 is CN, C_{1-6} alkyloxycarbonyl or C_{1-6} alkylaminocarbonyl, ring closure of the resulting hydroxy compound thereby obtaining the corresponding 1–(4–fluorophenyl)–1,3–dihydroisobenzofuran, then if R^1 is cyano using it directly in the next step and if R^1 is C_{1-6} alkyloxycarbonyl or C_{1-6} alkylaminocarbonyl, conversion of the compound to the corresponding compound wherein R^1 is cyano; and alkylation of the resulting 5–cyano compound with 3–dimethyl–aminopropylhalogenid in basic conditions thereby obtaining citalopram.

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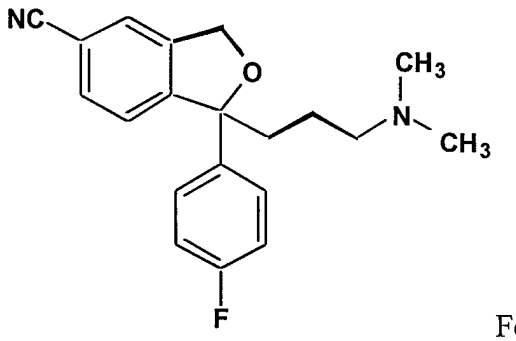
Method for the Preparation of Citalopram

The present invention relates to a method for the preparation of the well known anti-depressant drug citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile.

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:



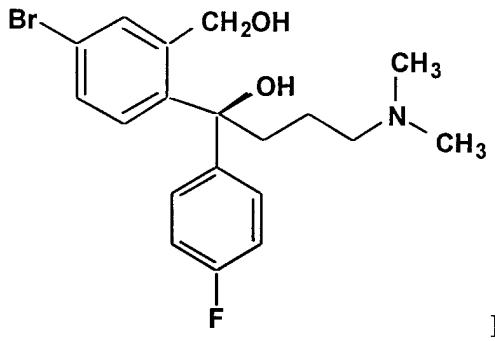
Formula **I**

It is a selective, centrally active serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities. The antidepressant activity of the compound has been reported in several publications, eg. J. Hyttel, *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.*, **1982,** *6*, 277-295 and A. Gravem, *Acta Psychiatr. Scand.*, **1987**, *75* , 478-486. The compound has further been disclosed to show effects in the treatment of dementia and cerebrovascular disorders, EP-A 474580.

Citalopram was first disclosed in DE 2,657,271 corresponding to US 4,136,193. This patent publication describes the preparation of citalopram by one method and outlines a further method which may be used for preparing citalopram.

According to the process described, the corresponding 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile is reacted with 3-(N,N-dimethylamino)propyl-chloride in the presence of methylsulfinylmethide as condensing agent. The starting material was prepared from the corresponding 5-bromo derivative by reaction with cuprous cyanide.

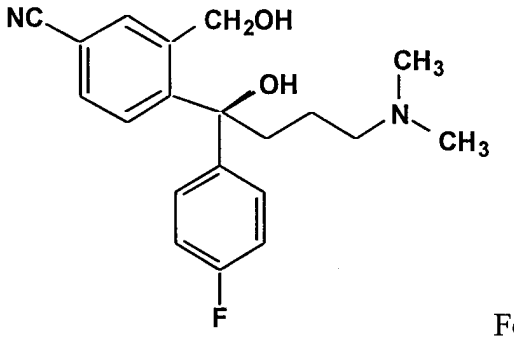
According to the method, which is only outlined in general terms, citalopram may be obtained by ring closure of the compound:



Formula **II**

in the presence of a dehydrating agent and subsequent exchange of the 5-bromo group with cuprous cyanide. The starting material of Formula **II** is obtained from 5-bromophthalide by two successive Grignard reactions, i.e. with 4-fluorophenyl magnesium chloride and N,N-dimethylaminopropyl magnesium chloride, respectively.

A new and surprising method and an intermediate for the preparation of citalopram were described in US Patent No 4,650,884 according to which an intermediate of the formula



Formula **III**

is subjected to a ring closure reaction by dehydration with strong sulfuric acid in order to obtain citalopram. The intermediate of Formula **III** was prepared from 5-cyanophthalide by two successive Grignard reactions, *i.e.* with 4-fluorophenyl magnesium halogenide and N,N-dimethylaminopropyl magnesium halogenide, respectively.

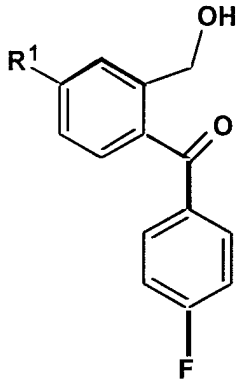
Finally, methods of preparing the individual enantiomers of citalopram are disclosed in US Patent No 4,943,590 from which it also appears that the ring closure of the intermediate of Formula **III** may be carried out via a labile ester with a base.

It has now, surprisingly, been found that citalopram may be manufactured by a novel favourable and safe procedure using convenient starting materials.

Summary of the invention

Accordingly, the present invention relates to a novel method for the preparation of citalopram comprising the steps of :

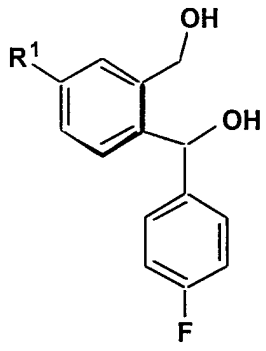
a) reduction of a compound of Formula **IV**



Formula **IV**

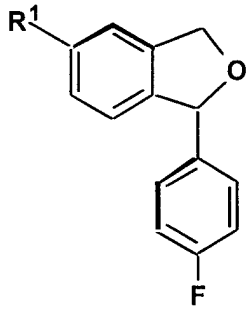
wherein R^1 is CN, C_{1-6} alkyloxycarbonyl or C_{1-6} alkylaminocarbonyl,

b) effecting ring closure of the resulting compound of Formula **V**



Formula **V**

wherein R^1 is as defined above thereby obtaining a compound of Formula **VI**

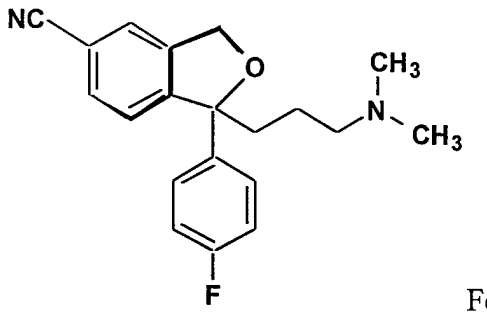


Formula **VI**

wherein R^1 is as defined above

c) then if R^1 is cyano using the compound of Formula VI directly in the next step and if R^1 is C_{1-6} alkyloxycarbonyl or C_{1-6} alkylaminocarbonyl, converting the compound of Formula **VI** to the corresponding compound wherein R^1 is cyano; and

d) alkylating the resulting 5-cyano compound of formula **VI** (R^1 = CN) with 3-dimethyl-aminopropylhalogenid in basic conditions thereby obtaining citalopram,



Formula **I**

which is isolated as the base or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides the novel intermediates of Formula **V**.

A further aspect of the invention relates to the novel intermediate for preparation of citalopram of Formula **VI** wherein R^1 is C_{1-6} alkyloxycarbonyl or C_{1-6} alkylaminocarbonyl.

In yet another aspect, the present invention relates to an antidepressant pharmaceutical composition comprising citalopram manufactured by the process of the invention.

Throughout the specification and claims, C_{1-6} alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, 2,2-dimethyl-1-ethyl and 2-methyl-1-propyl.

The 3-dimethylaminopropylhalogenide used may be the chloride, bromide or iodide, preferably the chloride.

The reduction of the compound of Formula **IV** may be performed with any convenient reducing agent, preferably by $NaBH_4$ in an alcohol, such as ethanol or methanol in basic conditions or with zink in aqueous acetic acid.

The ring closure of the compound of Formula **V** may be effected by an acid or via a labile ester with a base. Acidic ring closure is performed by an inorganic acid, such as a sulfuric or phosphoric acid, or an organic acid, such as methylsulfonic, p-toluenesulfonic or trifluoro-acetic acid. The basic ring closure may be performed via a labile ester, such as the methane sulfonyl, p-toluene sulfonyl, 10-camphorsulfonyl, trifluoroacetyl or trifluoromethanesulfonyl ester with addition of a base, such as triethyl amine, dimethylaniline, pyridine, etc. The reaction is performed in an inert solvent, preferably with cooling, in particular about 0 °C and is preferably carried out by a one-pot procedure, i.e. with esterification and simultaneous addition of the base.

When R^1 is an alkylaminocarbonyl group, the conversion to cyano may be performed by conventional nitril synthesis. Thus, the amide of Formula **V** wherein R^1 is an alkylaminocarbonyl group is preferably converted to the cyano compound, i.e. citalopram, by reaction with a dehydrating agent, most preferably thionyl chloride or phosphor pentachloride.

When R^1 is an alkyloxycarbonyl group, the conversion to cyano is preferably performed via the corresponding amide group which is then converted to the cyano group in the same way as compounds of Formula **VI** wherein R^1 is an alkylaminocarbonyl group.

The reaction of alkyloxycarbonyl to amide is carried out by hydrolysis with an acid or a base and subsequent conversion to acid chloride and amidation by reaction with ammonia or an alkylamine, preferably t-butyl amine. Acid hydrolysis may be performed by use of any suitable acid, such as HBr, HCl, HBr/acetic acid. Basic hydrolysis may be performed with any suitable base, such as K_2CO_3, NaOH, KOH, etc. The conversion to amide may also be obtained by reaction of the ester (R^1 is an alkyloxycarbonyl group) with ammonia or an alkylamine under pressure and heating. The amide obtained is converted to the cyano group as described above.

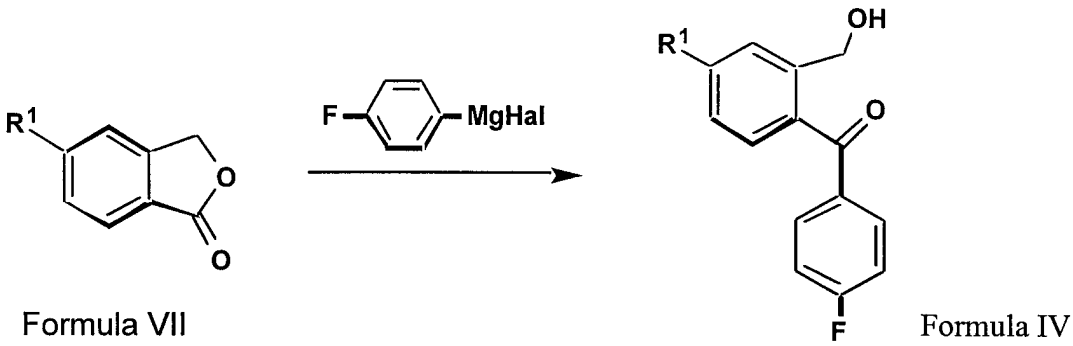
Alternatively, an ester, i.e. a compound of Formula **VI** wherein R^1 is an alkyloxycarbonyl group may be hydrolysed and then reacted with chlorosulfonyl isocyanate in order to form the nitrile.

The alkylation in step **d)** is carried out by addition of the 3-dimethylaminopropylhalogenide to the compound of formula **VI** (R^1 = CN) in a proper solvent, such as an ether, preferably 1,2-dimethoxyethane (DME), THF, diglyme or diethylether, in the presence of a base, preferably lithiumdiisopropylamine (LDA).

The process of the invention may be carried out with or without isolation of the intermediates.

Other reaction conditions, solvents, etc. are conventional conditions for such reactions and may easily be determined by a person skilled in the art.

The starting materials of formula **IV** may be prepared from the corresponding phthalide compound by reaction with a Grignard reagent of 4-halogen-fluorophenyl as exemplified with the magnesiumhalogenide in the following reaction scheme:



Formula VII Formula IV

wherein R^1 is as defined above.

When R^1 is a cyano group, the starting materials of formula **VII** may be prepared as described in Tirouflet, J.; Bull.Soc.Sci. Bretagne 26, 1959,35.

Other starting materials of formula **IV** may be prepared from 5-carboxyphtalide by reaction with thionyl chloride and then C_{1-6} alkanol or C_{1-6} alkylamine. 5-carboxyphtalide is commercially available and may be prepared by well known procedures (Tirouflet, J.; Bull.Soc.Sci. Bretagne 26, 1959,35).

In a preferred embodiment of the invention, R^1 is cyano.

In another embodiment of the invention, R^1 is C_{1-6} alkyloxycarbonyl, the C_{1-6} alkyl group being preferably ethyl, propyl, or butyl, preferably ethyl, 2-propyl or t-butyl.

In yet another embodiment of the invention, R^1 is C_{1-6} alkylaminocarbonyl, the C_{1-6} alkyl group being preferably ethyl, propyl, or butyl, preferably ethyl, 2-propyl or t-butyl, most preferably t-butyl.

The compound of general Formula **I** may be used as the free base or as a pharmaceutically acceptable acid addition salt thereof. As acid addition salts, such salts formed with organic or inorganic acids may be used. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene sulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

The acid addition salts of the compounds may be prepared by methods known in the art. The base is reacted with either the calculated amount of acid in a water miscible solvent, such as

acetone or ethanol, with subsequent isolation of the salt by concentration and cooling, or with an excess of the acid in a water immiscible solvent, such as ethylether, ethylacetate or dichloromethane, with the salt separating spontaneously.

The pharmaceutical compositions of the invention may be administered in any suitable way and in any suitable form, for example orally in the form of tablets, capsules, powders or syrups, or parenterally in the form of usual sterile solutions for injection.

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art. For example, tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting maschine. Examples of adjuvants or diluents comprise: Corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive colourings, aroma, preservatives etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by solving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to the desired volume, sterilization of the solution and filling in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

Examples

The invention is further illustrated by the following examples.

Example 1

(4-Cyano-2-hydroxymethylphenyl)(4-fluorophenyl)methanol.

A solution of 4-fluorophenylmagnesium bromide, prepared from 4-fluorobromobenzene (605 g, 3.45 mole) and magnesium turnings (107 g, 4.4 mole) in dry THF (1200 mL), is added dropwise to a suspension of 5-cyanophthalid (500 g, 3.14 mole) in dry THF (3000 mL). The temperature is kept below 5 °C. After the addition is complete, the reaction mixture is stirred the night over at room temperature.

Ethanol (4500 mL) is added to the reaction mixture and $NaBH_4$ (238 g, 6.30 mole) is added to the mixture in portions of 50 grams and is stirred the night over at room temperature.

About 2/3 of the solvents is removed *in vacuo* and water (4000 mL) is added to the reaction mixture. The resulting solution is extracted with EtOAc (2x500 mL). Evaporation of the solvents leaves a crude title compound (780 g) as an oil which is deemed pure enough for further reaction.

A pure sample is obtained after column chromatography on silica gel using EtOAc/n-Heptane (1/1) as eluent. The title compound is obtained as crystals after evaporation of the eluent. DSC onset: 116.5 °C.

^{1}H NMR (DMSO-d_6, 500 MHz): 4.42 (1H, dd J=13 Hz, J=5 Hz), 4.53 (1H, dd J=13 Hz, J=5 Hz), 5.45 (1H, t J=5 Hz), 5.98 (1H, d J=3 Hz), 6.14 (1H, d J=3 Hz), 7.15 (2H, t J=10 Hz), 7.35 (2H, m), 7.74 (1H, d J=8.5 Hz), 7.77 (1H, d J=8.5 Hz), 7.83 (1H, s).

Anal. calcd. for $C_{15}H_{12}N_1F_1O_2$; C, 70.02; H, 4.71; N, 5.45. Found C, 70.01; H, 4.71; N, 5.51.

1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile.

Crude (4-cyano-2-hydroxymethylphenyl)(4-fluorophenyl)methanol (700 g) is disolved in H_3PO_4 (60%, 3000 mL) and the solution is heated to 80 °C for 3 hours. Toluene (1000 mL) is added and the phases are separated. The aqueous phase is further extracted with toluene (1000 mL). The toluene phases are joined and the solvents are removed *in vacuo*. The remaining crystals are recrystallized from EtOH (99%). Yield 219 g (29%). DSC onset: 97 °C.

^{1}H NMR (DMSO-d_6, 500 MHz): 5.15 (1H, d J=12.5 Hz), 5.32 (1H, d J=12.5 Hz), 6.27 (1H, s), 7.21 (2H, t J=10 Hz), 7.25 (1H, d J=8.5 Hz), 7.40 (2H, m), 7.71 (1H, d J=8.5 Hz), 7.90 (1H, s).

Anal. calcd. for $C_{15}H_{10}N_1F_1O_1$; C, 75.30; H, 4.22; N, 5.86. Found C, 75.01; H, 4.22; N, 5.83.

1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile.

n-BuLi (1.6 N in hexane, 320 mL) is added to diisopropylamine (55 g, 0.5 mole) dissolved in DME (150 mL) at - 50 °C over a nitrogen atmosphere. 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (62 g, 0.26 mole) is dissolved in DME (500 mL) and added dropwise while the temperature is kept below - 40° C. After addition (45 min), the dark red solution is stirred for an additional period of 20 min. 3-Dimethylpropylchloride (100 g, 0.82 mole) is added in one portion at - 50 °C and the cooling is removed. After 60 min, the solution is warmed to 50 °C for 120 min. The reaction mixture is poured onto ice water (1 L) and extracted with toluene (2x500 mL). The organic phase is extracted with HCl (4 N, 500 mL). The acid solution is made alkaline (pH = 10) with NaOH (10 N) and extracted with toluene (500 mL) which is washed with water (3x200 ml). The toluene phase is dried anhydrous Na_2SO_4 (50 g), treated with active carbon and the solvents are removed *in vacuo*. The title compound (64-71 g, 76-84%) is obtained as an oil.

^{1}H NMR (DMSO-d_6,, 500 MHz): 1.20 (1H, m), 1.30 (1 H, m), 2.00 (6H, s), 2.10-2.20 (4H, m), 5.12 (1H, d, J=13.5 Hz), 5.20 (1H, d, J=13.5 Hz), 7.13 (2H, t, J=8.5 Hz), 7.58 (2H, dt, J=1.2 Hz J=8.5 Hz), 7.70-7.78 (3H, m).

The oxalic acid salt is crystallized from acetone. DSC onset: 156 °C. Anal. calcd. for $C_{22}H_{23}N_2F_1O_5$; C, 63.75: H, 5.60: N, 6.76. Found C, 61.60: H, 5.62: N, 6.63.

Eksample 2

(4-Ethoxycarbonyl-2-hydroxymethylphenyl)(4-fluorophenyl)methanol.

A solution of 4-fluorophenylmagnesium bromide, prepared from 4-fluorobromobenzene (21 g, 0.12 mole) and magnesium turnings (3.4 g, 0.14 mole) in dry THF (150 ml), is added dropwise to a suspension of 5-ethoxycarbonylphthalide (20.6 g, 0.1 mole) in dry THF (150 ml). The temperature is kept below 5 °C. After the addition is complete, the reaction mixture is stirred the night over at room temperature.

Ethanol (300 ml) is added to the reaction mixture and $NaBH_4$ (7.6 g, 0.2 mole) is added to the mixture in portions of about 1 gram and is stirred for 4 hours at room temperature. The solvents are removed *in vacuo* and ammonium chloride (sat. aq, 300 ml) is added to the remaining oil. The pH of the resulting solution is adjusted to 7.2 with aqueous 4 N HCl and extracted with EtOAc (2x100 ml). Evaporation of the solvents leaves a crude title compound as an oil (30 g) which is deemed pure enough for further reaction.

^{1}H NMR (DMSO-d_6, 500 MHz): 1.3 (3H, t J=7 Hz), 4.3 (2H, d J=7Hz), 4.35-4.5 (2H, m), 4.55-4.65 (2H, m) 5.35 (1H, t J=3Hz) 5.95 (1H, d J=3 Hz), 6.05 (1H, d J=3 Hz), 7.13 (2H, t J=10Hz), 7.33 (2H, m), 7.64 (1H, d J=8.5 Hz),), 7.90 (1H, d J=8.5 Hz), 8.10 (1H, s).

Ethyl 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carboxylat.

Crude (4-ethoxycarbonyl-2-hydroxymethylphenyl)(4-fluorophenyl)methanol (30 g) is dissolved in H_3PO_4 (60%, 250 ml) and the solution is heated to 80°C for 1.5 hours. Water (300 ml) and EtOAc (100 ml) is added and the phases are separated. The aqueous phase is further extracted with EtOAc (100 ml). The organic phases are joined and the solvents are removed *in vacuo*. The yield of the remaining somewhat impure oil is 30 g.

^{1}H NMR (DMSO-d_6, 500 MHz): 1.3 (3H, t J=7 Hz), 4.3 (2H, d J=7Hz), 5.17 (1H, d J=13 Hz), 5.35 (1H, d J=13 Hz), 6.25 (1H, s) 7.20 (3H, d+t J=8.5Hz J=10 Hz), 7.41 (2H, m), 7.86 (1H, d J=8.5 Hz), 7.97 (1H, s).

1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carboxylic acid.

Crude ethyl 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carboxylat (30 g) is disolved in EtOH (96%, 150 ml) and aqueous 2N NaOH (150 ml). The solution is refluxed for 1 hour. 1/2 of the volume is removed *in vacuo*. The aqueous phase is extracted with EtOAc (2x100 ml). The aqueous phase is made acidic (pH=1, conc. HCl) and after cooling to 5 °C the white crystals are filtered off. Yield 16g. Overall yield is 66% starting from 5-ethoxycarbonyl-phthalid. Mp 187-190 °C.

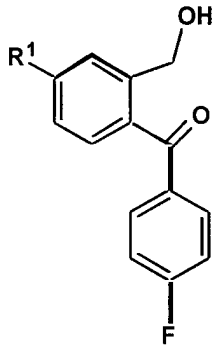
^{1}H NMR (DMSO-d_6, 500 MHz) 5.15 (1H, d J=13 Hz), 5.33 (1H, d J=13 Hz), 6.23 (1H, s) 7.18 (3H, d+t J=8.5Hz J=10 Hz), 7.40 (2H, m), 7.84 (1H, d J=8.5 Hz), 7.94 (1H, s) 12.95 (1H, bs).

The compound obtained is then converted to the corresponding cyano compound which again is alkylated as described in Example **1**.

CLAIMS

1. A method for the preparation of citalopram comprising the steps of

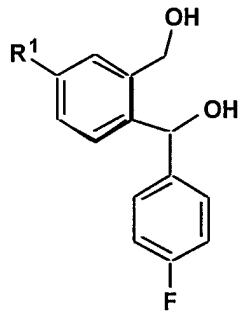
a) reduction of a compound of Formula **IV**



Formula **IV**

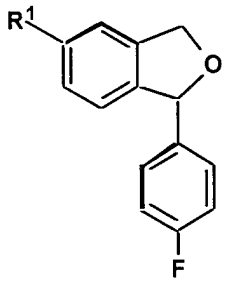
wherein R^1 is CN, C_{1-6} alkyloxycarbonyl or C_{1-6} alkylaminocarbonyl,

b) effecting ring closure of the resulting compound of Formula **V**



Formula **V**

wherein R^1 is as defined above thereby obtaining a compound of Formula **VI**

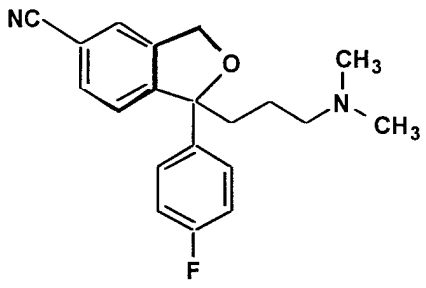


Formula **VI**

wherein R^1 is as defined above;

c) then if R^1 is cyano using the compound of Formula VI directly in the next step and if R^1 is C_{1-6} alkyloxycarbonyl or C_{1-6} alkylaminocarbonyl, converting the compound of Formula **VI** to the corresponding compound wherein R^1 is cyano; and

d) alkylating the resulting 5-cyano compound of formula **VI** (R^1 = CN) with 3-dimethyl-aminopropylhalogenid in basic conditions thereby obtaining citalopram,



Formula **I**

which is isolated as the base or a pharmaceutically acceptable salt thereof.

2. The method of Claim **1** wherein R^1 is CN.

3. The method of Claim **1** wherein R^1 is C_{1-6} alkyloxycarbonyl.

4. The method of Claim **1** wherein R^1 is C_{1-6} alkylaminocarbonyl.

5. The method of Claim **3** or **4** wherein C_{1-6} alkyl is ethyl-, propyl-, or butyl, preferably ethyl, 2-propyl or t-butyl, most preferably t-butyl.

6. The method of any of Claims **1 - 5** wherein the reduction of the compound of Formula **IV** is performed by use of $NaBH_4$ in an alcohol, such as ethanol or methanol in basic conditions.

7. The method of any of Claims **1-6** wherein the ring closure of the compound of Formula **V** is effected by acidic ring closure performed by an inorganic acid, such as a sulfuric or phosphoric acid, or an organic acid, such as methylsulfonic, p-toluenesulfonic or trifluoroacetic acid.

8. The method of any of Claims **1-6** wherein the ring closure of the compound of Formula **V** is performed by a basic ring closure via a labile ester preferably with simultaneous esterification and addition of base.

9. The method of Claim **8** wherein the labile ester is the methane sulfonyl, p-toluene sulfonyl, 10-camphorsulfonyl, trifluoroacetyl or trifluoromethanesulfonyl ester and the base is triethyl amine, dimethylaniline or pyridine.

10. The method of Claim **3** wherein the conversion of the C_{1-6} alkyloxycarbonyl to cyano is performed via the corresponding amide group.

11. The method of Claim **10** wherein the reaction of C_{1-6} alkyloxycarbonyl to amide is carried out by hydrolysis with an acid or a base, subsequent conversion to acid chloride and amidation by reaction with ammonia or an alkylamine, preferably t-butyl amine.

12. The method of Claim **11** wherein the hydrolysis is performed by use of a suitable acid, such as HBr, HCl, HBr/acetic acid.

13. The method of Claim **11** wherein the hydrolysis is performed by use of a suitable base, preferably K_2CO_3, NaOH or KOH.

14. The method of Claim **8** wherein the reaction of C_{1-6} alkyloxycarbonyl to amide is carried out by reaction of the ester with ammonia or an alkylamine under pressure and heating.

15. The method of any of Claims **4** and **9-14** wherein the amide is converted to the cyano group by reaction with a dehydrating agent, preferably thionyl chloride or phosphor pentachloride.

16. The method of any of Claims **1 - 15** wherein the 3-dimethylaminopropylhalogenide used as alkylation agent in step **d)** is the chloride, bromide or iodide, preferably the chloride.

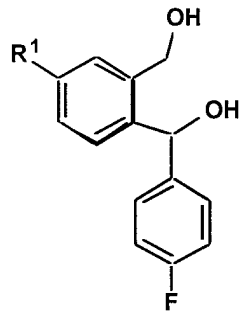
17. The method of any of Claims **1 - 16** wherein the alkylation in step **d)** is carried out in an ether, preferably 1,2-dimethoxyethane, THF, Diglyme or diethylether.

18. The method of any of Claims **1 - 17** wherein the alkylation in step **d)** is carried out in the presence of a base, preferably lithiumdiisopropylamine.

19. The method of any of Claims **1 - 18** wherein the starting material of formula **IV** is prepared from the corresponding phthalide compound by reaction with a Grignard reagent of 4-halogen-fluorophenyl, preferably a 4-fluorophenylmagnesiumhalogenide, most preferably the magnesiumbromide.

20. The method of Claim **1** wherein R^1 is cyano, the starting material of formula **IV** is prepared from the corresponding phthalide compound by reaction with a 4-fluorophenyl-magnesiumhalogenide, the reduction in **a)** is performed by $NaBH_4$ in an alcohol, the ring closure in **b)** is effected by an inorganic acid and the alkylation in **d)** is carried out by use of dimethylaminopropylchloride in an ether in the presence of lithiumdiisopropylamine

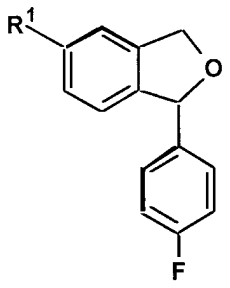
21. A compound of Formula **V**



Formula **V**

wherein R^1 is CN, C_{1-6} alkyloxycarbonyl or C_{1-6} alkylaminocarbonyl.

22. A compound of Formula **VI**

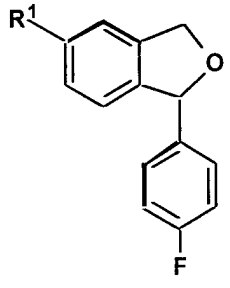


Formula **VI**

wherein R^1 is C_{1-6} alkyloxycarbonyl or C_{1-6} alkylaminocarbonyl.

23. An antidepressant pharmaceutical composition comprising citalopram manufactured by the process of any of Claims **1 - 20**.

24. A method for the preparation of citalopram comprising alkylating a compound of formula **VI**



Formula **VI**

wherein R^1 is with 3-dimethyl-aminopropylhalogenid in basic conditions in which the reaction is carried out in an ether, preferably 1,2-dimethoxyethane, THF, diglyme or diethylether, in the presence of lithiumdiisopropylamine.