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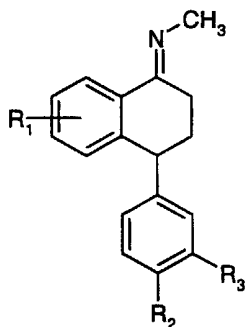
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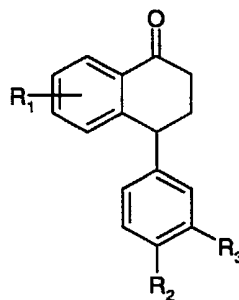
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(54) Title: PROCESS FOR THE PREPARATION OF KETIMINES



(1)



(2)

(57) Abstract: The present invention relates to a process for the preparation of compounds of formula (1), in which R₁, R₂ and R₃ independently of one another are hydrogen, halogen, trifluoromethyl or C₁-C₄alkoxy, wherein a compound of formula (2), in which R₁, R₂ and R₃ are as defined in formula (1), is reacted with methylamine in the presence of a non-alcoholic solvent and, if desired, in the presence of a sulfonic acid catalyst to give the compound of formula (2) and, if desired, is subjected to purification by recrystallization.



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Process for the preparation of ketimines

The present invention relates to a process for the preparation of ketimines, which are suitable as starting materials for the preparation of pharmaceutical active compounds having antidepressant properties, for example sertraline.

Processes for the preparation of ketimines are described, for example, in US-A-4,536,518 or US-A-4,855,500.

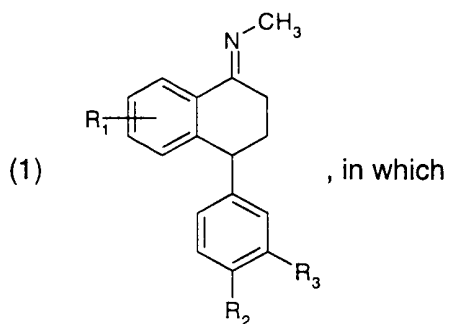
The process for the preparation of ketimines disclosed in US-A-4,536,518 (columns 9/10, Example 1(F)) is characterized in that the ketone is reacted with methylamine with cooling in the presence of titanium tetrachloride in an aprotic solvent, for example tetrahydrofuran. This process has the disadvantage that it has to be carried out using titanium tetrachloride, which is ecologically hazardous. The process procedure is additionally expensive, because the reaction is carried out with cooling. A further disadvantage of this process relates to the work-up. The product must be precipitated using additional hexane.

The process for the preparation of ketimines disclosed in US-A-4,855,500 (columns 5/6, claim 1) comprises reacting the ketone with anhydrous methylamine with cooling in an aprotic solvent, such as, for example, methylene chloride, toluene or tetrahydrofuran in the presence of a molecular sieve.

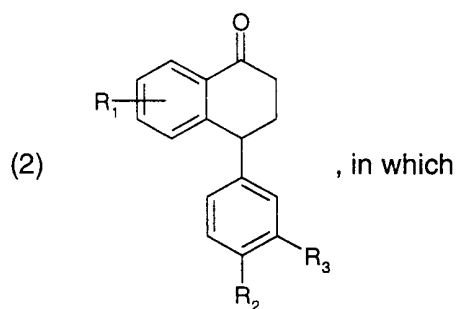
This process has the disadvantage that the molecular sieve employed is expensive and has to be recycled again in an additional step. A further disadvantage of this process is that the molecular sieve has to be separated off and the product precipitated using additional hexane.

There is therefore furthermore the need to find an efficient process for the preparation of ketimines, which does not have the abovementioned disadvantages.

The present invention therefore relates to a process for the preparation of compounds of the formula



R_1 , R_2 and R_3 independently of one another are hydrogen, halogen, trifluoromethyl or C_1 - C_4 alkoxy, wherein a compound of the formula



R_1 , R_2 and R_3 are as defined in formula (1)

is reacted with methylamine in the presence of a C_1 - C_{24} amine or C_1 - C_{12} nitrile as solvent to give the compound of the formula (1), or

is reacted with methylamine in the presence of a sulfonic acid catalyst and of a non-alcoholic solvent to give the compound of the formula (1).

Halogen is, for example, chlorine, bromine or iodine. Chlorine is preferred.

C_1 - C_4 alkoxy is a branched or unbranched hydrocarbon radical, for example methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy or tert-butoxy. Methoxy is preferred.

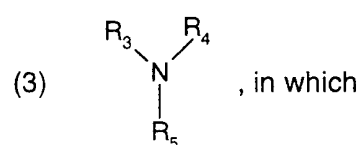
The non-alcoholic solvent preferred for the process according to the invention is preferably selected from

- (a) C_1 - C_{24} amines,
- (b) C_1 - C_{12} nitriles,
- (c) C_2 - C_{24} carboxylic acid esters,
- (d) C_3 - C_{24} orthoesters,
- (e) C_2 - C_{24} ethers,
- (f) C_6 - C_{24} alkanes,
- (g) aromatic solvents,

- (h) amides,
- (i) sulfoxides,
- (k) halogenated solvents, and
- (l) supercritical CO₂.

Particularly preferred solvents (a) are selected from aliphatic monoamines, in particular methylamine, nitrogen heterocycles, aliphatic di- and triamines, non-substituted or substituted aromatic monoamines or aromatic diamines.

Further preferred solvents (a) are those of the formula

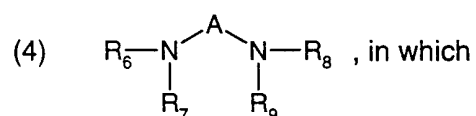


R₃ is hydrogen; C₁-C₅alkyl; hydroxy-C₁-C₅alkyl; C₅-C₇cycloalkyl; phenyl which is not substituted or is substituted by one or more C₁-C₅alkyl groups, halogen or nitro; phenyl-C₁-C₃alkyl which is not substituted or is substituted by one or more C₁-C₅alkyl groups, halogen or nitro;

R₄ and R₅, independently of one another, are C₁-C₅alkyl; hydroxy-C₁-C₅alkyl; C₅-C₇cycloalkyl; phenyl which is not substituted or is substituted by one or more C₁-C₅alkyl groups, halogen or nitro; phenyl-C₁-C₃alkyl which is not substituted or is substituted by one or more C₁-C₅alkyl groups, halogen or nitro; or

R₄ and R₅ together with the nitrogen atom form a three- to 6-membered heterocyclic radical.

Furthermore, solvents (a) are preferably used which are those of the formula



R₆ and R₈ independently of one another are hydrogen; C₁-C₅alkyl; or C₅-C₇cycloalkyl,

R₇ and R₉ independently of one another are C₁-C₅alkyl; or C₅-C₇cycloalkyl, phenyl which is not substituted or is substituted by one or more C₁-C₅alkyl groups, halogen or nitro; phenyl-C₁-C₃alkyl which is not substituted or is substituted by one or more C₁-C₅alkyl groups, halogen or nitro; or

R₆ and R₇, R₈ and R₉ or R₇ and R₉ form a three- to 6-membered heterocyclic radical; and

A₂ is C₁-C₅alkylene.

Exemplary representatives of solvents (a) used according to the invention which may be mentioned are:

as aliphatic monoamines, for example, methylamine, dimethylamine, triethylamine, diethylamine, triethylamine, di-n-propylamine, diisopropylamine, tri-n-propylamine, or triisopropylamine;

as nitrogen heterocycles ethyleneimine, pyrrolidine, piperidine or morpholine,

as aliphatic diamines, for example, N,N-dimethylethylenediamine or hexamethylenediamine;

as aromatic monoamines, for example, N-methylaniline or N,N-dimethylaniline;

as substituted aromatic monomamines, for example, o-, m- or p-toluidine, 2-, 3- or 4-chloroaniline, 2-, 3- or 4-nitroaniline;

as aromatic diamines, for example, o-, m- or p-phenylenediamine.

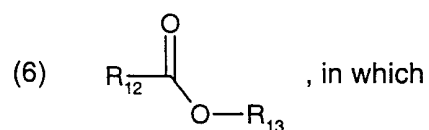
Solvents (b) preferably used are those of the formula



R_{10} is straight-chain or branched C_1 - C_{12} alkyl; C_5 - C_7 cycloalkyl; phenyl which is not substituted or is substituted by one or more C_1 - C_5 alkyl groups, halogen or nitro; phenyl- C_1 - C_3 alkyl which is not substituted or is substituted by one or more C_1 - C_5 alkyl groups, halogen or nitro.

Exemplary representatives of this group are benzonitrile or in particular acetonitrile.

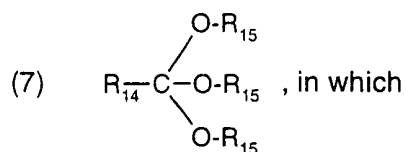
Solvents (c) which are preferably used are compounds of the formula



R_{12} and R_{13} independently of one another are straight-chain or branched C_1 - C_{12} alkyl; C_5 - C_7 cycloalkyl; or phenyl which is not substituted or is substituted by one or more C_1 - C_5 alkyl groups, halogen or nitro; phenyl- C_1 - C_3 alkyl which is not substituted or is substituted by one or more C_1 - C_5 alkyl groups, halogen or nitro.

Exemplary representatives of these solvents are acetates, such as, for example, methyl acetate or ethyl acetate.

Solvents (d) preferably employed according to the invention are those of the formula

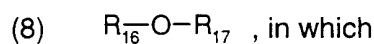


R_{14} is hydrogen; straight-chain or branched C_1 - C_5 alkyl; or C_5 - C_7 cycloalkyl; and

R_{15} is C_1 - C_5 alkyl.

Exemplary representatives of these solvents are C_1 - C_3 alkyl orthoformates, in particular methyl or ethyl orthoformate or C_1 - C_3 alkyl orthoacetates, in particular ethyl orthoacetate.

Solvents (e) preferably employed according to the invention are those of the formula



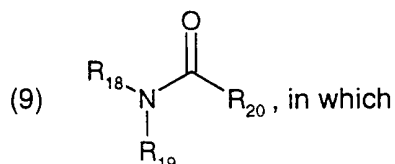
R_{16} and R_{17} independently of one another are hydrogen; straight-chain or branched C_1 - C_{12} alkyl; or C_5 - C_7 cycloalkyl; or R_{16} and R_{17} together with the oxygen atom form a 5- to 6-membered radical.

Exemplary representatives of these solvents are dimethyl ether, diethyl ether, methyl ethyl ether, methyl n-propyl ether, methyl i-propyl ether, diisopropyl ether, dibutyl ether or tert-butyl methyl ether. In addition, polyethers can also be employed.

Solvents (f) preferably employed according to the invention are saturated C_1 - C_{22} hydrocarbons, such as, for example, methane, ethane, propane, butane, pentane, hexane, neohexane, heptane, octane, i-octane, nonane, decane, undecane, dodecane, tridecane, tetradecane, pentadecane, hexadecane, heptadecane, octadecane, nonadecane, eicosane, heneicosane or docosane.

Solvents (g) preferably employed according to the invention are in particular benzene, toluene, xylene and xylene isomer mixtures.

Solvents (h) preferably employed according to the invention are in particular aliphatic and aromatic amides of the formula



R_{18} and R_{19} independently of one another are hydrogen; C_1 - C_5 alkyl; or C_5 - C_7 cycloalkyl, and

R₂₀ is C₁-C₅alkyl; C₅-C₇cycloalkyl; phenyl which is not substituted or is substituted by one or more C₁-C₅alkyl groups, halogen or nitro; or phenyl-C₁-C₃alkyl which is not substituted or is substituted by one or more C₁-C₅alkyl groups, halogen or nitro.

Exemplary solvents (i) are those of the formula

(10) R₂₁-(S=O)-R₂₂, in which

R₂₁ and R₂₂ independently of one another are C₁-C₅alkyl; C₅-C₇cycloalkyl; phenyl which is not substituted or which is substituted by one or more C₁-C₅alkyl groups, halogen or nitro; or phenyl-C₁-C₃alkyl which is not substituted or which is substituted by one or more C₁-C₅alkyl groups, halogen or nitro.

Exemplary solvents (k) are those of the formula

(11a) ClCR₂₃R₂₄R₂₅, (11b) Cl₂CR₂₆R₂₇ or (11c) Cl₃CR₂₈, in which

R₂₃, R₂₄, R₂₅, R₂₆, R₂₇ and R₂₈ independently of one another are C₁-C₅alkyl; C₅-C₇cycloalkyl; phenyl which is not substituted or which is substituted by one or more C₁-C₅alkyl groups, halogen or nitro; or phenyl-C₁-C₃alkyl which is not substituted or which is substituted by one or more C₁-C₅alkyl groups, halogen or nitro.

Exemplary representatives of this solvent class are dichloroethane, dichloropropane, trichloroethane, furthermore haloaromatics, for example chlorobenzene or dichlorobenzene.

If supercritical CO₂ is used, the reaction is carried out at temperatures $T \geq T_{\text{crit}}$ and $p \geq p_{\text{crit}}$ in CO₂ as solvent. After the reaction, CO₂ is evaporated and the imine is discharged as solid.

The solvents employed according to the invention can be used as individual compounds or as mixtures of two or more individual compounds of identical or different solvent groups a) - (l).

In addition, there is the possibility of adding further solubilizing or solubility-inhibiting additives (e.g. toluene or cyclohexane).

If the preparation of the compound of the formula (1) is carried out with methylamine in the presence of a C₁-C₂₄amine or C₁-C₁₂nitrile as solvent (with or without catalyst), the conditions and preferences indicated above for the solvent (a) apply for the C₁-C₂₄amines and those indicated above for the solvent (b) apply for the C₁-C₁₂nitriles. The use of solvents (b) is preferred here.

Generally, the use of solvents (a) or (b), in particular (b), is preferred.

Suitable sulfonic acid catalysts are, for example, methanesulfonic acid, p-toluenesulfonic acid or camphor-10-sulfonic acid.

A process for the preparation of compounds of the formula (1) is especially preferred in which a sulfonic acid catalyst is used, in particular p-toluenesulfonic acid, methanesulfonic acid or camphor-10-sulfonic acid.

The molar quantitative ratio of the catalyst employed to the methylamine employed is expediently 0.001:1 to 1:1, in particular 0.01:1 to 0.5:1, e.g. 0.05:1 to 0.1:1.

The 1:1 molar quantitative ratio of the catalyst to the methylamine also means that the methylamine can also be employed in the process according to the invention in the form of a salt, for example of methylamine hydrochloride.

The process according to the invention is preferably carried out at a temperature from 20 to 120, in particular 30 to 100°C, if appropriate under slight pressure, and the isolation at a temperature from -20 to 40, in particular 0 to 30°C.

For the preparation of the compound of the formula (1) in the presence of a catalyst, a temperature range from 30 to 80°C, in particular 30 to 70°C and preferably 30 to 60°C, is preferred.

For the preparation of the compound of the formula (1) without the presence of a catalyst, a temperature range from 50 to 120°C, in particular 70 to 120°C and preferably 80 to 120°C, is preferred. The upper value of the temperature range preferred here is 110°C, in particular 100°C.

The proportion of sertralone in the reaction mixture is, for example, in the range from 5 to 70, preferably 30 to 60, % by weight.

The reaction is particularly preferably carried out using a large molar excess of methylamine.

A process for the preparation of compounds of the formula (1) is therefore particularly preferred in which the molar quantitative ratio of the compound of the formula (2) to methylamine is 1:1 to 1:1000, in particular 1:1.05 to 1:50, e.g. 1:1.5 to 1:15.

The methylamine can be employed in the form of methylamine gas or as a solution in a non-alcoholic solvent.

A process variant is of very particular interest in which the reaction can be carried out in pure methylamine, in particular under pressure, this compound being employed simultaneously as

a solvent and reagent. In this case, customarily no significant amounts of further solvent are employed.

Also of particular interest is a process for the preparation of compounds of the formula (1) in which the compound of the formula (1) is continuously crystallized from the reaction medium during the preparation and then filtered off.

Also of especial interest is a process for the preparation of compounds of the formula (1), in which the filtrate is employed for a further reaction for the preparation of compounds of the formula (1). In this case, the amounts of the compound of the formula (2) and methylamine used are replenished. 2 to 10 recyclings of the filtrate are preferred.

The present process according to the invention is accordingly also suitable as a continuous process for the preparation of the compounds of the formula (1).

The water formed during the process can be bound, if desired, using an additional chemical water-binding agent for example an orthoester, e.g. trimethyl orthoformate.

After reaction is complete, if desired, the compound of the formula (1) obtained can be subjected to purification by recrystallization.

Preferably, for this purification process a solvent is employed which is selected from

- (a) C₁-C₂₄amines,
- (b) C₁-C₁₂nitriles,
- (c) C₂-C₂₄carboxylic acid esters,
- (d) C₃-C₂₄orthoesters,
- (e) C₂-C₂₄ethers,
- (f) C₆-C₂₄alkanes,
- (g) aromatic solvents,
- (h) amides,
- (i) sulfoxides,
- (k) halogenated solvents,
- (l) supercritical CO₂,
- (m) protic solvents, and
- (n) C₂-C₂₄ketones.

The solvents (a) to (l) are the solvents which are also used for the reaction.

The protic solvent (m) is preferably an alcohol, which in particular is of the formula

(12) $X(OH)_b$

in which

b is 1, 2, 3 or 4, and

if b is 1,

X is C_1 - C_8 alkyl, C_5 - C_8 cycloalkyl or $-CH_2CH_2(OCH_2CH_2)_cR_{21}$,

c 0, 1 or 2, and

R_{21} is C_1 - C_4 alkoxy, or

if b is 2,

X is C_2 - C_8 alkylene or $-CH_2CH_2(OCH_2CH_2)_c-$, where c has the above meaning, or

if b is 3,

X is C_3 - C_8 alkanetriyl or $N(CH_2CH_2)_3$, or

if b is 4,

X is C_4 - C_8 alkanetetrayl.

In the abovementioned definitions of the radicals R_1 to R_{21} :

C_1 - C_{12} alkyl is a branched or unbranched hydrocarbon radical, for example methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, 2-ethylbutyl, n-pentyl, isopentyl, 1-methylpentyl, 1,3-dimethylbutyl, n-hexyl, 1-methylhexyl, n-heptyl, isoheptyl, 1,1,3,3-tetramethylbutyl, 1-methylheptyl, 3-methylheptyl, n-octyl, 2-ethylhexyl, isooctyl, nonyl, decyl, undecyl or dodecyl.

C_5 - C_8 cycloalkyl is, for example, cyclopentyl, cycloheptyl, cyclooctyl or preferably cyclohexyl.

C_1 - C_4 alkoxy is a branched or unbranched hydrocarbon radical, for example methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy or tert-butoxy. Methoxy is preferred.

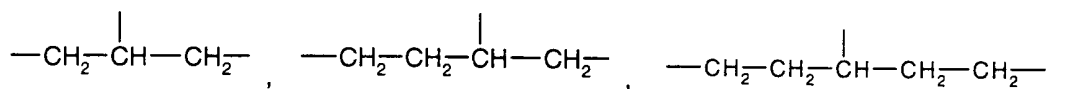
C_2 - C_{12} alkenyl is, for example, allyl, methallyl, isopropenyl, 2-butenyl, 3-butenyl, isobutenyl, n-penta-2,4-dienyl, 3-methylbut-2-enyl, n-oct-2-enyl, n-dodec-2-enyl, isododecenyl, n-dodec-2-enyl or n-octadec-4-enyl.

C_3 - C_{12} alkynyl is C_3 - C_{12} alkyl or C_3 - C_{12} alkenyl, which is mono- or polydiunsaturated, where the triple bonds can, if desired, be isolated or conjugated with one another or with double bonds, for example 1-propyn-3-yl, 1-butyne-4-yl, 1-pentyn-5-yl, 2-methyl-3-buten-2-yl,

1,4-pentadiyn-3-yl, 1,3-pentadiyn-5-yl, 1-hexyn-6-yl, cis-3-methyl-2-penten-4-yn-1-yl, trans-3-methyl-2-pentyn-4-yn-1-yl, 1,3-hexadiyn-5-yl, 1-octyn-8-yl, 1-nonyn-9-yl or 1-decyn-10-yl.

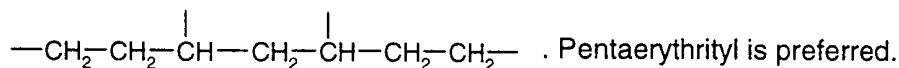
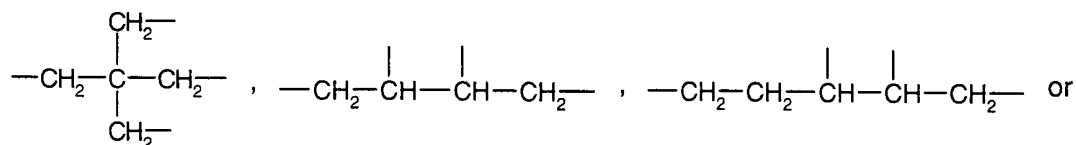
C₂-C₈alkylene is a branched or unbranched radical, for example ethylene, propylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene or octamethylene.

Alkanetriyl having 3 to 8 carbon atoms is derived, for example, from an alkane having 3 to 8 carbon atoms, in which 3 hydrogen atoms are absent and is, for example



or $\begin{array}{c} | \\ -\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}_2- \end{array}$. Glyceryl is preferred.

Alkanetetrayl having 4 to 8 carbon atoms is derived, for example, from an alkane having 4 to 8 carbon atoms, in which 4 hydrogen atoms are absent, and is, for example



A preferred meaning of X (for b = 1) is, for example, C₁-C₈alkyl, in particular C₁-C₄alkyl, e.g. ethyl or isopropyl.

A preferred meaning of X (for b = 2) is, for example, C₂-C₆alkylene, in particular C₂-C₄alkylene, e.g. ethylene.

Of particular interest is a process for the preparation of compounds of the formula (1), in which the protic solvent is a compound of the formula (12), in which

b is 1 or 2, and

if b is 1,

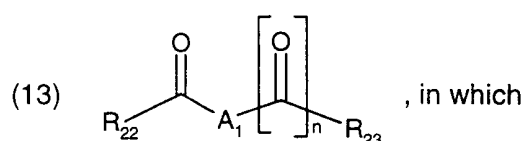
X is C₁-C₄alkyl or C₅-C₆cycloalkyl, or

if b is 2,

X is C₂-C₄alkylene.

Practically relevant alcohols for the purification step are methanol, ethanol, isopropanol, n-butanol, ethylene glycol, methylcellosolve, cyclohexanol, diethylene glycol or triethanolamine.

Solvents employed for the purification process are furthermore C₂-C₂₄ketones (=component (n)), which in particular are those of the formula



R₂₂ and R₂₃ independently of one another are branched or unbranched C₁-C₁₂alkyl; C₅-C₇cycloalkyl; C₂-C₁₂alkenyl; C₃-C₁₂alkynyl; phenyl or phenyl-C₁-C₃alkyl, which is not substituted or is substituted by one or more C₁-C₅alkyl groups;

A₁ is a direct bond; or C₁-C₅alkylene; and

n is 0 or 1.

Exemplary representatives of this group are, for example, aliphatically saturated ketones, such as, for example, propanone (acetone), butanone (methyl ethyl ketone) or 2-pentanone (methyl propyl ketone); cycloaliphatically saturated ketones, for example cyclopentanone, cyclohexanone or cycloheptanone (suberone); aliphatically unsaturated ketones, for example 3-buten-2-one, 1,4-pentadien-3-one, 3-pentyn-2-one; aromatic ketones, for example benzophenone; aromatic/aliphatic ketones, for example methyl phenyl ketone (acetophenone) or propiophenone; diketones, for example 2,3-butanedione, 2,4-pentanedione or 2,5-hexanedione; or aromatic diketones, for example diphenylethanedione (benzil).

In a particularly preferred embodiment, the purification is carried out in the same solvent as the reaction.

In a preferred process variant, the purification is carried out by recrystallization of sertraline (compound of the formula (1)) under reflux. For this, the isomerically pure sertraline is introduced in a suitable solvent into a suitable reaction vessel having a stirrer and reflux condenser. The reaction mass is heated to reflux temperature in an inert gas atmosphere with stirring until a clear solution is present. The solution is cooled to the appropriate isolation temperature, the product slowly crystallizing. The suspension is filtered, and the filter cake is washed with the solvent and dried. The imine yield is from 80 to 99%, with a sertralone

content of 0.1 to 5.0% (HPLC), a catalyst contamination of ≤ 0.01 and up to 0.3% water content.

In a further process variant, the recrystallization of sertraline is carried out under pressure. For this, the crude sertraline and the solvent are introduced into a suitable pressure reactor having a stirrer. The reactor is sealed under a nitrogen atmosphere. The stirrer is started and the reaction mixture is heated to the desired reaction temperature until a clear solution is present. The solution is cooled to the appropriate isolation temperature, the product slowly precipitating. The suspension is filtered, and the filter cake is washed with the solvent and dried.

The solution temperatures in the selected solvents are in the range from 30 to 150, preferably 70 to 120, °C.

According to the boiling points of the solvents indicated, the purification process can be carried out at normal pressure under reflux or at elevated pressure, normally in the range from 0 to 10, preferably from 0 to 3, bar.

The cooling gradients are in the range from 0.05 to 10, preferably 0.1 to 1, °C/min.

The isolation temperatures are in the range from -20 to 40, preferably 0 to 25, °C.

The concentrations of crude sertraline in the clear solution are in the range from 5 to 40, preferably 15 to 20, % by weight.

During the process, adsorbents, for example active carbon or adsorber resins, can be added for the removal of colouring impurities. These adsorbents are added to the clear solution in amounts from 1 to 10% and removed hot by filtration before the crystallization process.

By means of the purification step, both the product purity can be improved and impurities interfering in the further reaction, for example water or catalyst residues, can be separated off.

In a very particularly preferred embodiment, the reaction according to claim 1 is carried out in the presence of a sulfonic acid catalyst and the compound of the formula (1) obtained is subjected to a purification step.

The present invention also relates to a process for the preparation of optically pure (cis)- and/or (trans)-sertraline or enantiomerically enriched mixtures of (cis)- and (trans)-sertraline. The process is characterized by the following reaction steps (I)-(III):

- (I) reaction of pure sertralone of the formula (2) to give the sertraline of the formula (1) corresponding to the process according to claim 1,
- (II) subsequent cis-selective hydrogenation with noble metal catalysts or other catalysts based on copper or nickel to give cis-sertraline-enriched mixtures of racemic cis- and trans-sertraline,
- (III) subsequent mandelic acid-based resolution for the selective preparation of the desired enantiomerically pure cis isomer.

Starting from pure sertralone, sertraline is prepared according to the process described in claim 1. The imine is converted to cis-sertraline-enriched mixtures of racemic cis- and trans-sertraline in a subsequent cis-selective hydrogenation with noble metal catalysts or other catalysts based on copper or nickel on very different supports, such as, for example, carbon, alumina, silica, calcium carbonate, barium carbonate, barium sulfate etc.

In a subsequent mandelic acid-based resolution, the desired enantiomerically pure cis isomers can be crystallized.

The optically pure amine is liberated using sodium hydroxide solution and converted into the desired polymorphic form as the hydrochloride in suitable solvents.

The following examples illustrate the invention further. Details in parts or percentages relate to the weight.

Example 1 : Preparation of sertraline in acetonitrile with acid catalysis

240 g of pure sertralone (> 99%) and 650 ml of acetonitrile are introduced into a suitable reaction vessel having a stirrer and gas inlet. The stirrer is started, the suspension is cooled to 0°C and 55 g of methylamine are passed in. After addition of 10 ml of methanesulfonic acid (catalyst), the reaction mass is heated, stirred at 50°C until the reaction stops and then cooled to 0°C. The suspension is filtered, washed with cold acetonitrile and dried in vacuo.

Yield: 231.4 g (corresponds to 92.5% of theory) of crude sertraline having the following composition:

96.6% sertraline;
2.9% sertralone;
0.5% water.

The product additionally contains traces of methanesulfonic acid derivatives and salts.

Example 2 : Preparation of sertraline in amines with acid catalysis at 50°C

10 g of pure sertralone (> 99%) and 23 g of amine are introduced into a suitable reaction vessel having a stirrer and gas inlet. The stirrer is started, the suspension is cooled to 0°C and 3 g of methylamine are passed in. After addition of 0.65 g (0.1 eq) of para-toluene-sulfonic acid (catalyst), the reaction mass is heated to 50°C, stirred until the reaction stops and then cooled to 10°C. The suspension is filtered, washed with cold ethanol and dried in vacuo.

The following yields for various amines as solvents are obtained:

N-Benzyl dimethylamine: 9.3 g of sertraline (corresponds to 90% of theory)

Content:

96% imine,

3.8% sertralone,

0.2% water.

The product additionally contains traces of para-toluenesulfonic acid derivatives.

Triethylamine: 8.8 g of sertraline (corresponds to 85% of theory)

Content:

95% imine,

4.8% sertralone,

0.2% water.

The product additionally contains traces of para-toluenesulfonic acid derivatives.

Diethylamine: 8.9 g of sertraline (corresponds to 86% of theory)

Content:

94% imine,

5.9% sertralone,

0.1% water.

The product additionally contains traces of para-toluenesulfonic acid derivatives.

Diisopropylamine: 7.4 g of sertraline (corresponds to 71% of theory)

Content:

93% imine,

6.9% sertralone,
0.1% water.

The product additionally contains traces of para-toluenesulfonic acid derivatives.

Ethyldiisopropylamine: 85 g of sertraline (corresponds to 82% of theory)

Content:

93% imine,
6.9% sertralone,
0.1% water.

The product additionally contains traces of para-toluenesulfonic acid derivatives.

Example 3 : Preparation of sertraline without acid catalysis at 90°C

10 g of pure sertralone (> 99%) and 23 g of amine are introduced into a suitable reaction vessel having a stirrer and gas inlet. The stirrer is started, the suspension is cooled to 0°C and 3 g of methylamine are passed in. The reaction mass is heated, stirred at 90°C until the reaction stops and then cooled to 10°C. The suspension is filtered, washed with cold ethanol and dried in vacuo.

The following results emerge for various amines as solvents:

N-Benzyltrimethylamine: 8.5 g of sertraline (corresponds to 81% of theory)

Content:

95% imine,
4.8% sertralone,
0.2% water

Triethylamine: 9.2 g of sertraline (corresponds to 88% of theory)

Content:

96% imine,
3.8% sertralone,
0.2% water.

N-Methylpiperazine: 6.4 g of sertraline (corresponds to 61% of theory)

Content:

97% imine,
2.8% sertralone,

0.2% water.

Example 4 : Preparation of sertraline in methylamine using a catalyst at 60°C

6 g of pure sertralone (> 99%) and 0.5 g of para-toluenesulfonic acid are introduced into a suitable pressure reaction vessel (autoclave) having a stirrer and gas inlet. 24 g of methylamine are then injected. The stirrer is started. The reaction mass is heated, kept at 60°C and then cooled to room temperature. The methylamine is released in a controlled manner and the residual, solid product dried in vacuo.

Yield: 6.9 g of sertraline (corresponds to 99% of theory)

Content:

89% imine,

1% sertralone,

3% water,

7% para-toluenesulfonic acid derivatives.

Example 5 : Preparation of sertraline in methylamine without a catalyst at 90°C

6 g of pure sertralone (> 99%) are introduced into a suitable pressure reaction vessel (autoclave) having a stirrer and gas inlet. 24 g of methylamine are then injected. The stirrer is started. The reaction mass is heated, kept at 90°C and then cooled to room temperature. The methylamine is released in a controlled manner and the residual, solid product is dried in vacuo.

Result: 6.4 g of sertraline (corresponds to 99% of theory)

Content:

96% imine,

1% sertralone,

3% water.

Example 6 : Purification of sertraline in acetonitrile

200 g of crude sertraline (cf. Example 1) and 3.5 l of acetonitrile are initially introduced into a suitable reaction vessel having a stirrer, nitrogen inlet and reflux condenser. The nitrogen flushing and the stirrer are started and the reaction mixture is heated to reflux temperature until a clear solution is present. The solution is slowly cooled to 20°C, the product

precipitating. The suspension is filtered, and the filter cake is washed with the solvent and dried.

Yield: 178 g of sertraline having the following composition (GC analysis):

99.4% sertraline (corresponds to 88.0% of theory),

0.6% sertralone.

Methanesulfonic acid derivatives and salts are no longer detectable.

Example 7 : Purification of sertraline in ethyl acetate

200 g (0.637 mol) of crude dry sertraline (96.9% purity) are suspended in 1000 ml of ethyl acetate and 8.0 g of active carbon in a suitable reaction container, equipped with a stirrer and reflux condenser. The mixture is stirred under reflux for 1 h. The active carbon is filtered off hot and the clear filtrate is cooled to 0°C.

The crystalline suspension is filtered off. The filter cake is dried overnight in vacuo and yields 174 g (89%) of sertraline.

Purity: 99.5%; 0.3% sertralone.

Methanesulfonic acid derivatives and salts are no longer detectable.

Example 8 : Purification of sertraline in other solvents analogously to the previous examples:

Other solvents and mixtures can also be used for the purification of crude sertraline (same conditions as above) and produce a similar product purity and yield (cf. Table 1).

The reaction is carried out by heating under reflux.

<u>Table 1</u>			
<u>Solvent used</u>	<u>Yield [%]</u>	<u>Purity [%]</u>	<u>Sertralone content [%]</u> 1
2-Butanone (MEK)	88	99.4	0.4
Mixture of ethanol/toluene (7:3 vol.)	90	99.6	0.4
2-Propanol (IP)	90	99.6	0.4

Pure ethanol or ethanol denatured with 2% toluene can also be used for the recrystallization of crude sertraline.

The ratio to be employed is: 2 g of crude sertralone in 30 ml of ethanol.

Yield with 86% and 99.4% purity; 0.5% sertralone.

By adjusting the solubility using solubility-inhibiting compounds such as alkanes and/or low isolation temperatures, N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAC) and dimethyl sulfoxide (DMSO) can also be used, which can also be employed pure or in mixtures for the imine formation.

In all solvents used, the catalyst residues are no longer detectable after the recrystallization.

Example 9: Recrystallization of sertraline above the boiling point of the solvent (under pressure)

5 g of crude sertraline (product from Example 2) and 15 to 20 ml of ethanol are introduced into a suitable pressure reaction vessel having a stirrer. The reactor is sealed under a nitrogen atmosphere and the stirrer is started. The reaction mixture is heated to about 110°C until a clear solution is present. The solution is cooled to 25°C, the product slowly precipitating. The suspension is filtered, and the filter cake is washed with cold ethanol and dried.

Yield: 4.55 g (91%) of sertraline having the following composition:

99.4% sertraline

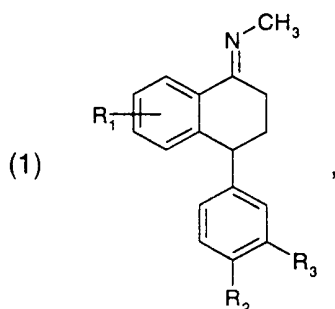
0.6% sertralone.

Water and traces of catalyst are no longer detectable.

If ethyl acetate is used instead of ethanol, a yield of 4.35 g (87%) is obtained.

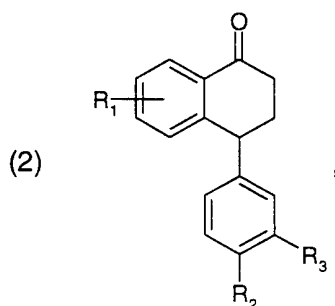
WHAT IS CLAIMED IS:

1. A process for the preparation of compounds of the formula



in which R_1 , R_2 and R_3 independently of one another are hydrogen, halogen, trifluoromethyl or C_1 - C_4 alkoxy,

wherein a compound of the formula



in which R_1 , R_2 and R_3 are as defined in formula (1),

is reacted with methylamine in the presence of a C_1 - C_{24} amine or C_1 - C_{12} nitrile as solvent to give the compound of the formula (1), or

is reacted with methylamine in the presence of a sulfonic acid catalyst and of a non-alcoholic solvent to give the compound of the formula (1).

2. A process according to claim 1, wherein a compound of the formula (2) is reacted with methylamine in the presence of a sulfonic acid catalyst and of a non-alcoholic solvent to give the compound of the formula (1).

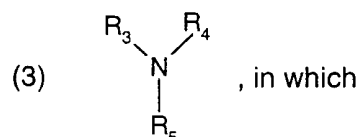
3. A process according to claim 1, wherein a compound of the formula (2) is reacted with methylamine in the presence of a C_1 - C_{24} amine or C_1 - C_{12} nitrile as solvent to give the compound of the formula (1).

4. A process according to claim 1 or 2, wherein the non-alcoholic solvent is selected from

- (a) C₁-C₂₄amines,
- (b) C₁-C₁₂nitriles,
- (c) C₂-C₂₄carboxylic acid esters,
- (d) C₃-C₂₄orthoesters,
- (e) C₂-C₂₄ethers,
- (f) C₆-C₂₄alkanes,
- (g) aromatic solvents,
- (h) C₁-C₂₄amides,
- (i) sulfoxides,
- (k) halogenated solvents, and
- (l) supercritical CO₂.

5. A process according to one of claims 1, 3 and 4, wherein the C₁-C₂₄amines used as solvents are methylamine, nitrogen heterocycles, or aliphatic or aromatic non-substituted or substituted secondary or tertiary mono-, di- or triamines.

6. A process according to claim 5, wherein the C₁-C₂₄amines used are compounds of the formula

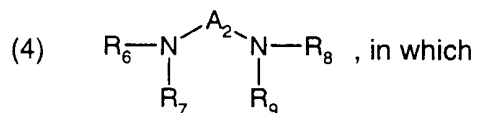


R₃ is hydrogen; C₁-C₅alkyl; hydroxy-C₁-C₅alkyl; C₅-C₇cycloalkyl; phenyl which is not substituted or is substituted by one or more C₁-C₅alkyl groups, halogen or nitro; phenyl-C₁-C₃alkyl which is not substituted or is substituted by one or more C₁-C₅alkyl groups, halogen or nitro;

R₄ and R₅, independently of one another, are C₁-C₅alkyl; C₅-C₇cycloalkyl; hydroxy-C₁-C₅alkyl; phenyl which is not substituted or is substituted by one or more C₁-C₅alkyl groups, halogen or nitro; phenyl-C₁-C₃alkyl which is not substituted or is substituted by one or more C₁-C₅alkyl groups, halogen or nitro; or

R₄ and R₅ together with the nitrogen atom form a 3- to 6-membered heterocyclic radical.

7. A process according to claim 5, wherein the C₁-C₂₄amines used are compounds of the formula



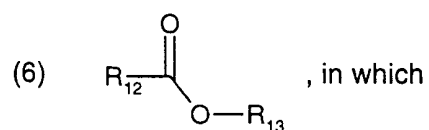
R₆ and R₈ independently of one another are hydrogen; C₁-C₅alkyl; or C₅-C₇cycloalkyl, R₇ and R₉ independently of one another are C₁-C₅alkyl; or C₅-C₇cycloalkyl, phenyl which is not substituted or is substituted by one or more C₁-C₅alkyl groups, halogen or nitro; phenyl-C₁-C₃alkyl which is not substituted or is substituted by one or more C₁-C₅alkyl groups, halogen or nitro; or R₆ and R₇, R₈ and R₉ or R₇ and R₉ form a 3- to 6-membered heterocyclic radical; and A₂ is C₁-C₅alkylene.

8. A process according to one of claims 1, 3 and 4, wherein the C₁-C₁₂nitriles used as solvents are compounds of the formula



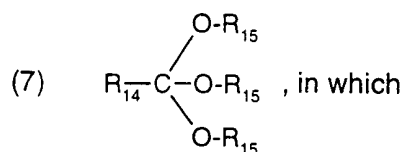
R₁₀ is straight-chain or branched C₁-C₁₂alkyl; C₅-C₇cycloalkyl; phenyl which is not substituted or is substituted by one or more C₁-C₅alkyl groups, halogen or nitro; phenyl-C₁-C₃alkyl which is not substituted or is substituted by one or more C₁-C₅alkyl groups, halogen or nitro.

9. A process according to claim 4, wherein the solvents (c) used are compounds of the formula



R₁₂ and R₁₃ independently of one another are straight-chain or branched C₁-C₁₂alkyl; C₅-C₇cycloalkyl; or phenyl which is not substituted or is substituted by one or more C₁-C₅alkyl groups, halogen or nitro; phenyl-C₁-C₃alkyl which is not substituted or is substituted by one or more C₁-C₅alkyl groups, halogen or nitro.

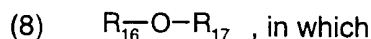
10. A process according to claim 4, wherein the solvents (d) used are compounds of the formula



R_{14} is hydrogen; straight-chain or branched C_1 - C_5 alkyl; or C_5 - C_7 cycloalkyl; and

R_{15} is C_1 - C_5 alkyl.

11. A process according to claim 4, wherein the solvents (e) used are compounds of the formula



R_{16} and R_{17} independently of one another are hydrogen; straight-chain or branched C_1 - C_{12} alkyl; or C_5 - C_7 cycloalkyl; or R_{16} and R_{17} together with the oxygen atom form a 5- to 6-membered radical.

12. A process according to claim 4, wherein the solvents (f) used are saturated C_1 - C_{22} hydrocarbons.

13. A process according to claim 4, wherein the solvents (g) are selected from benzene, toluene, xylene and xylene isomer mixtures.

14. A process according to any one of claims 1 to 13, wherein the compound of the formula (1) is recrystallized from the reaction medium continuously during the preparation and then filtered off.

15. A process according to claim 14, wherein the filtrate is employed for a further reaction for the preparation of the compound of the formula (1).

16. A process according to any one of claims 1 to 15, wherein the molar quantitative ratio of the compound of the formula (2) to methylamine is 1:1 to 1:1000.

17. A process according to any one of claims 1 to 16, wherein the reaction is carried out at a temperature from 20 to 120°C and the isolation is carried out at a temperature from -20°C to

40°C.

18. A process according to any one of claims 1 to 17, wherein the reaction is carried out at elevated pressure.

19. A process according to claim 1 or 2, wherein the sulfonic acid catalyst is p-toluene-sulfonic acid, methanesulfonic acid or camphor-10-sulfonic acid.

20. A process according to any one of claims 1 to 19, wherein the compound of the formula (1) obtained is subjected to purification by recrystallization using a solvent.

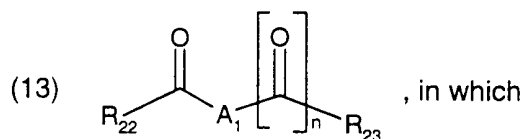
21. A process according to claim 20, wherein the solvent is selected from

- (a) C₁-C₂₄amines,
- (b) C₁-C₁₂nitriles,
- (c) C₂-C₂₄carboxylic acid esters,
- (d) C₃-C₂₄orthoesters,
- (e) C₂-C₂₄ethers,
- (f) C₆-C₂₄alkanes,
- (g) aromatic solvents,
- (h) amides,
- (i) sulfoxides,
- (k) halogenated solvents,
- (l) supercritical CO₂,
- (m) protic solvents, and
- (n) C₂-C₂₄ketones.

22. A process according to claim 21, wherein the protic solvent (m) is an alcohol.

23. A process according to claim 21 or 22, wherein the protic solvent (m) is selected from methanol, ethanol, isopropanol, n-butanol, ethylene glycol, methylcellosolve, cyclohexanol, diethylene glycol, triethanolamine and polyethylene glycol.

24. A process according to claim 21, wherein the solvent(s) are selected from compounds of the formula



R_{22} and R_{23} independently of one another are branched or unbranched C_1 - C_{12} alkyl; C_5 - C_7 cycloalkyl; C_2 - C_{12} alkenyl; C_3 - C_{12} alkynyl; phenyl or phenyl- C_1 - C_3 alkyl, which is not substituted or is substituted by one or more C_1 - C_5 alkyl groups; A_1 is a direct bond; or C_1 - C_5 alkylene; and n is 0 or 1.

25. A process according to any one of claims 20 to 24, wherein the purification is carried out in the same solvent as the reaction itself.

26. A process according to any one of claims 20 to 25, wherein the purification is carried out under reflux.

27. A process according to any one of claims 20 to 25, wherein the purification is carried out at elevated pressure.

28. A process according to any one of claims 20 to 27, wherein the purification is carried out at a temperature of $< 150^{\circ}\text{C}$.

29. A process according to any one of claims 20 to 28, wherein the cooling gradient is in the range from 0.05 to $10^{\circ}\text{C}/\text{min}$.

30. A process according to any one of claims 20 to 29, wherein the isolation temperature is in the range from -20 to 40°C .

31. A process according to any one of claims 20 to 30, wherein the recrystallization is carried out at elevated pressure.

32. A process according to claim 1, wherein the reaction is carried out in the presence of a sulfonic acid catalyst and the compound of the formula (1) obtained is subjected to a

purification step.

33. A process according to any one of claims 1 to 32, wherein the starting compound of the formula (2) employed for the reaction has a purity of > 99%.

34. A process for the preparation of optically pure (cis)- and/or (trans)-sertraline or enantiomerically enriched mixtures of (cis)- and (trans)-sertraline, which comprises the following reaction steps (I)-(III):

- (I) reaction of pure sertralone of the formula (2) to give the sertraline of the formula (1) corresponding to the process according to claim 1,
- (II) subsequent cis-selective hydrogenation with noble metal catalysts or other catalysts based on copper or nickel to give cis-sertraline-enriched mixtures of racemic cis- and trans-sertraline, and
- (III) subsequent mandelic acid-based resolution for the selective preparation of the desired enantiomerically pure cis isomer.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/10971

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C249/02 C07C251/20

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)

IPC 7 C07C

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)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 855 500 A (SPAVINS JAMES C) 8 August 1989 (1989-08-08) cited in the application column 2; claims; example 1 column 3, line 1 - line 7 ---	1, 2, 34
X	US 4 536 518 A (WELCH JR WILLARD M ET AL) 20 August 1985 (1985-08-20) cited in the application column 6, line 17 - line 24 column 12; example 7E ---	1, 2, 34
A	WO 99 36394 A (COLBERG JUAN CARLOS ;PFISTERER DAVID MICHAEL (US); PFIZER PROD INC) 22 July 1999 (1999-07-22) example 3 --- -/--	1, 34



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

9 February 2001

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/10971

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 47486 A (JALET HANS PETER ; BENZ MARKUS (CH); STEINER HEINZ (CH); THOMMEN M) 23 September 1999 (1999-09-23) example 2 -----	1,34
A	"HOUBEN-WEYL METHODEN DER ORGANISCHEN CHEMIE. Band E14b. Teil 1", GEORG THIEME VERLAG, STUTTGART XP002138906 page 239 -page 242 -----	1,34

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/EP 00/10971

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4855500 A	08-08-1989	CA 1320499 A DK 218089 A EP 0341015 A FI 892129 A JP 2015053 A PT 90435 A, B	20-07-1993 05-11-1989 08-11-1989 05-11-1989 18-01-1990 30-11-1989
US 4536518 A	20-08-1985	AT 2668 T AU 517357 B AU 6389780 A BA 97149 B BA 97150 B BG 60333 B CA 1130815 A CS 9103542 A CS 238609 B CS 238617 B CS 238618 B DD 155615 A DD 203045 A DE 3062225 D DK 395280 A, B, EG 15527 A EP 0030081 A ES 496443 D ES 8201949 A ES 506892 D ES 8207123 A FI 803398 A, B, GR 70781 A HK 82284 A HR 930199 B HR 931527 B HU 182224 B IE 50395 B IL 61374 A IN 159644 A IN 159643 A JP 1287061 C JP 56086137 A JP 60005584 B KR 8402001 B KR 8402000 B LU 88330 A LV 5456 A LV 5457 A MX 5980 E MY 32685 A NO 803258 A, B, NZ 195407 A PH 17319 A PT 72004 A, B SG 56584 G SI 8012798 A SI 8310672 A SU 1014467 A SU 1034602 A	15-03-1986 23-07-1981 07-05-1981 28-12-1998 28-12-1998 27-05-1994 31-08-1982 16-12-1992 16-12-1985 16-12-1985 16-12-1985 23-06-1982 12-10-1983 07-04-1983 02-05-1981 30-04-1987 10-06-1981 16-01-1982 01-04-1982 01-09-1982 01-12-1982 02-05-1981 23-03-1983 09-11-1984 29-02-1996 30-04-1996 28-12-1983 16-04-1986 31-10-1983 30-05-1987 30-05-1987 31-10-1985 13-07-1981 12-02-1985 27-10-1984 27-10-1984 04-05-1994 10-03-1994 10-03-1994 12-09-1984 31-12-1985 04-05-1981 31-05-1984 20-07-1984 01-11-1980 08-03-1985 31-12-1994 30-04-1996 23-04-1983 07-08-1983

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/EP 00/10971

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9936394 A	22-07-1999	AU 9278698 A BR 9814248 A EP 1047666 A NO 20003625 A	02-08-1999 10-10-2000 02-11-2000 13-09-2000
WO 9947486 A	23-09-1999	AU 3412899 A EP 1064250 A	11-10-1999 03-01-2001