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(54) Title: PROCESS FOR THE RACEMISATION OF 1-BENZYL-4-(4-FLUOROPHENYL)-3-HYDROXYMETHYL-1,2,3,6-TETRAHYDROPYRIDINE TO BE USED AS INTERMEDIATE IN THE SYNTHESIS OF PAROXETINE

(57) Abstract: A process for the racemisation of enantiomerically enriched 1-benzyl-4-(4-fluorophenyl)-3-hydroxymethyl-1,2,3,6-tetrahydropyridine which is a useful intermediate in the preparation of paroxetine. Formula (A) means that the compound (I) has an enantiomeric excess of one enantiomer over the other enantiomer. R₁ and R₂ are defined as in claim 1.

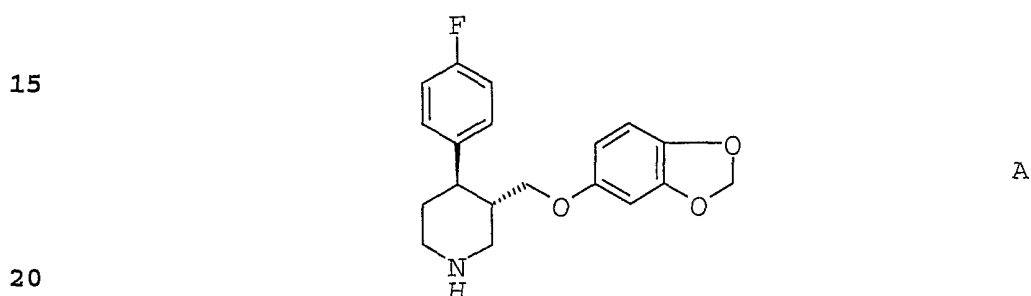


WO 02/18338 A1

PROCESS FOR THE RACEMISATION OF 1-BENZYL-4-(4-FLUOROPHENYL)-3-HYDROXYMETHYL-1,2,3,6-TETRAHYDROPYRIDINE TO BE USED AS INTERMEDIATE IN THE SYNTHESIS OF PAROXETINE

This invention relates to a process for the racemisation of
5 enantiomerically enriched 1-benzyl-4-(4-fluorophenyl)-3-hydroxymethyl-1,2,3,6-tetrahydropyridine which is a useful intermediate in the preparation of paroxetine.

US Patent No. 4,007,196 discloses compounds which possess anti-
10 depressant activity. One particular compound disclosed in this patent is known as paroxetine and has the structure A below:



This compound has been found to be especially useful in the treatment of depression and several processes have been described
25 to prepare this important compound. WO 96/36636 (which is incorporated herein by reference) discloses one such process. WO 98/52920 (which is incorporated herein by reference) discloses a process for preparing a useful intermediate in the preparation of paroxetine.

30 WO 98/01424 (which is incorporated herein by reference) discloses a process for the preparation of racemic trans-1-benzyl-3-hydroxymethyl-4-(4-fluorophenyl)piperidine in which 4-(4-fluorophenyl)-N-benzyl-1,2,5,6-tetrahydropyridine is reacted with
35 formaldehyde in acidic medium via the Prins reaction to give the desired product. One of the optional next stages for the process is the resolution of this compound with an optically active acid, preferably dibenzoyltartaric acid or di-p-toluyll-tartaric acid, to give the individual enantiomers of trans-1-
40 benzyl-3-hydroxymethyl-4-(4-fluorophenyl)piperidine. Clearly this process is wasteful in that 50% of the material is then discarded as only one enantiomer, the (+)-enantiomer, is further processed to give paroxetine. It would be desirable to be able to racemise the unwanted enantiomer and to then resolve the racemic mixture
45 to produce more of the desired enantiomer. However, many attempts by the present applicants to find a satisfactory racemisation process ended in failure.

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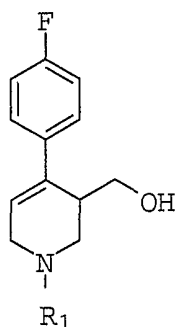
Surprisingly an efficient process for carrying out this racemisation has now been found.

The present invention provides a process for the racemisation of a compound of formula I comprising the steps of

- a) reacting an enantiomerically enriched compound of formula I

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I

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in which R_1 represents an amine protecting group, with a compound of formula II



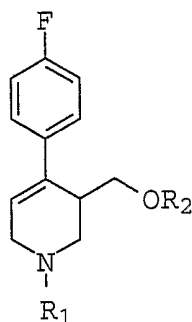
II

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in which R_2 represents a group of formula R_3SO_3 - in which R_3 represents optionally substituted phenyl, a C_{1-6} alkyl group or a trifluoromethyl group and X represents halo to give a compound of formula III

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III

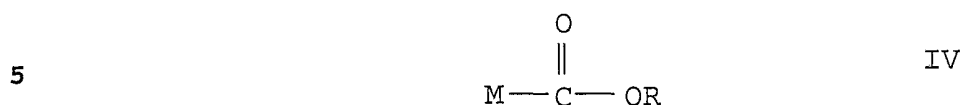
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in which i) R_2 represents a group of formula R_3SO_2 - in which R_3 represents optionally substituted phenyl, a C_{1-6} alkyl group or a trifluoromethyl group,

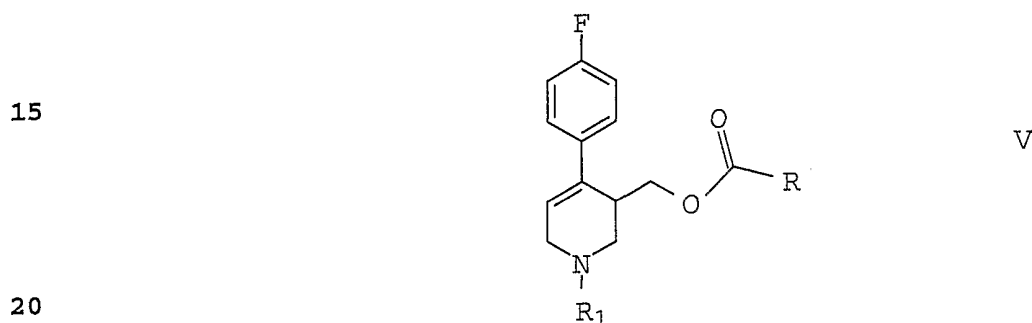
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- b) reacting the compound of formula III with a compound of formula IV



10 in which M represents an alkali metal and R represents H, a C₁₋₆alkyl group, optionally substituted phenyl or an (optionally substituted phenyl)hydroxyC₁₋₆alkyl group to give a substantially racemic compound of formula V

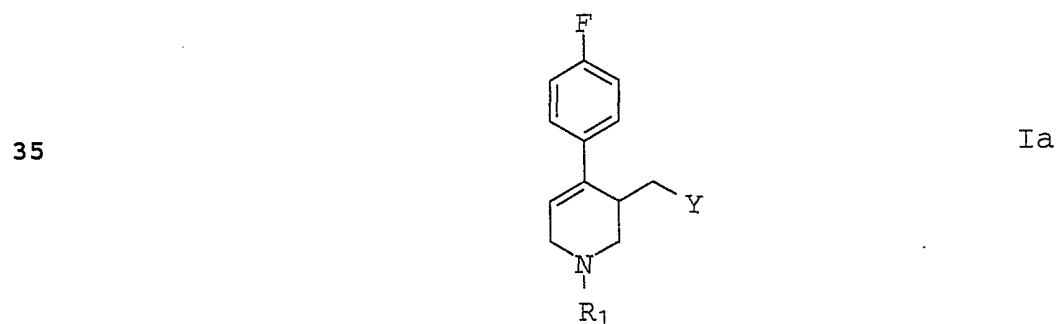


in which R₁ and R are as previously defined; and

- 25 c) reacting the compound of formula V with a hydrolysing agent to give a substantially racemic compound of formula I.

It will be appreciated by those skilled in the art that the compounds of formula III may also be prepared by reacting a compound of formula I with an halogenating agent to give a

30 compound of formula Ia



in which Y is halo. The compound of formula Ia may then be reacted with a salt of formula MOR₂ in which R₂ is as previously defined to give a compound of formula III. This alternative

45 process also forms part of the present invention.

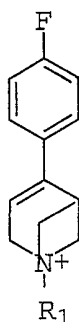
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Suitably halogenating agents include hydrogen bromide, hydrogen chloride, oxalyl chloride, phosphorus pentachloride, phosphorus trichloride, phosphorus pentabromide, phosphorus tribromide, bromine, phosphorus oxychloride, phosphorus oxybromide, thionyl chloride, thionyl bromide, a mixture of carbon tetrachloride and triphenylphosphine, a mixture of tetrabromomethane and triphenylphosphine, N-bromosuccinimide and N-chlorosuccinimide. Preferably the halogenating agent is thionyl chloride or thionyl bromide.

10 Whilst not bound by theory, it is believed that the mechanism of the above racemisation process involves an intermediate salt which is a compound of formula IIIa

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 R_2^-

IIIa

25 in which R_1 is as previously and R_2^- is an anion of formula $R_3SO_2^-$. The compound of formula IIIa in which R_2^- represents the anion $^-OSO_2CF_3$ and R_1 represents benzyl has been isolated from the reaction mixture and identified. In addition the product of formula IIIa where R_2^- represents $^-OSO_2-Ph$ has been identified in
30 the reaction solution by nuclear magnetic resonance spectroscopy.

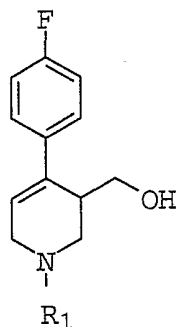
In a preferred aspect the present invention provides a process for the racemisation of a compound of formula I comprising the steps of

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a) reacting an enantiomerically enriched compound of formula I

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I

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in which R_1 represents an amine protecting group, with a compound of formula II

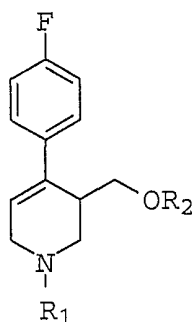
 R_2X

II

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in which R_2 represents a group of formula R_3SO_2 - in which R_3 represents optionally substituted phenyl, a C_{1-6} alkyl group or a trifluoromethyl group and X represents halo to give a compound of formula III

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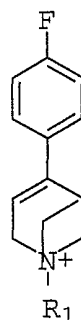
III

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in which i) R_2 represents a group of formula R_3SO_2 - in which R_3 represents optionally substituted phenyl, a C_{1-6} alkyl group or a trifluoromethyl group, wherein the compound of formula III is in equilibrium with a compound of formula IIIa

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IIIa

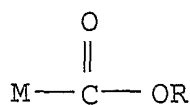
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 R_2^-

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in which R_1 represents an amine protecting group and R_2^- is an anion of R_2

40 b) reacting the compound of formula IIIa with a compound of formula IV



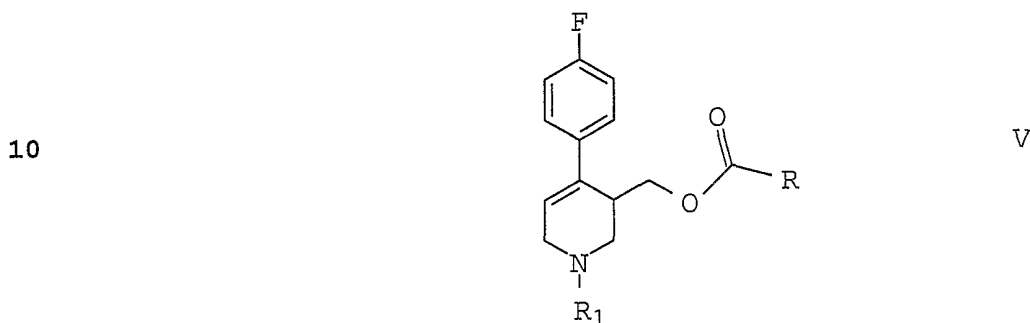
IV

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in which M represents an alkali metal and R represents H, a C₁₋₆alkyl group, optionally substituted phenyl or an (optionally substituted phenyl)hydroxyC₁₋₆alkyl group to give a substantially racemic compound of formula V

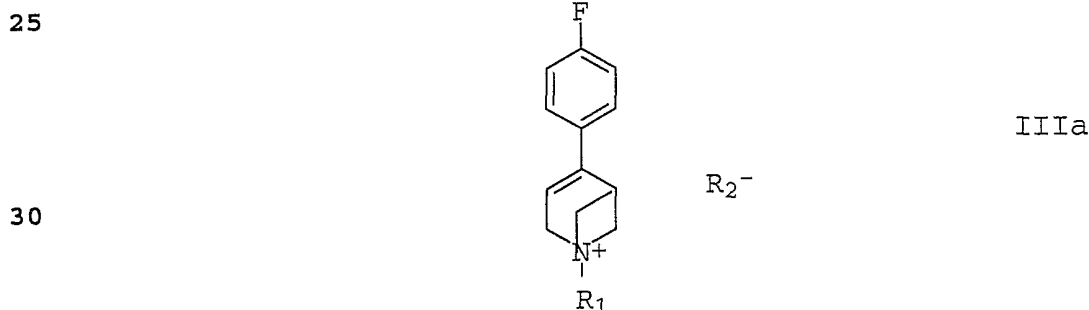
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in which R₁ and R are as previously defined; and

- 20 c) reacting the compound of formula V with a hydrolysing agent to give a substantially racemic compound of formula I.

In a further aspect the present invention provides compounds of formula IIIa



- 35 in which R₁ represents an amine protecting group and R₂ is a previously stated. Preferably R₁ represents benzyl or a C₁₋₆-alkyl group. More preferably R₁ represents benzyl, methyl or ethyl. Most preferably R₁ represents benzyl. Preferably R₂⁻ is a benzene-sulphonate anion, a methanesulphonate anion or a trifluoro-
- 40 methanesulphonate anion.

- Preferably the amino protecting group is one which is inert to reduction by a metal hydride. More preferably the amine protecting group is selected from a) allyl, b) benzhydryl,
- 45 c) methoxymethyl, d) benzyloxymethyl, e) tetrahydropyranyl, f) an optionally substituted benzyl group, g) di(p-methoxyphenyl)methyl, h) triphenylmethyl, i) (p-methoxyphenyl)diphenyl-

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methyl, j) diphenyl-4-pyridylmethyl, k) a C₁₋₆alkyl group, for example methyl or ethyl, l) a trifluoro C₁₋₄alkyl group, m) an alkynyl group or n) p-methoxybenzyl. Most preferably the amine protecting group is a benzyl group which is optionally substituted on the phenyl ring by one or more of the following groups: a C₁₋₄alkyl group, a C₁₋₄alkoxy group, halo or nitro. Especially preferably R₁ represents benzyl.

The term optionally substituted phenyl means phenyl substituted by one or more of the following: a) a C₁₋₆alkyl group, b) nitro or c) halo.

The term enantiomerically enriched should be understood to mean that the compound of formula I has an enantiomeric excess of one enantiomer over the other enantiomer in the range of 1 to 100%, preferably an enantiomeric excess in the range of 50 to 100%, and more preferably an enantiomeric excess in the range of 70 to 100%.

Suitably either enantiomer may predominate in the enantiomerically enriched compound. Preferably the predominant enantiomer is the (+) enantiomer. More preferably the predominant enantiomer is the (-) enantiomer.

The term substantially racemic means that there is an enantiomeric excess of less than 20% preferably less than 10% and most preferably less than 5%.

Preferably R₃ represents methyl or phenyl optionally substituted by a methyl group, a nitro group or halo. More preferably R₃ represents methyl, 4-tolyl, 4-nitrophenyl, or 4-bromophenyl.

Suitably the hydrolysing agent includes a basic or acidic hydrolysing agent. Preferred basic hydrolysing agents include aqueous sodium hydroxide, aqueous ammonia, aqueous potassium carbonate, aqueous potassium bicarbonate, aqueous sodium bicarbonate, aqueous sodium carbonate, potassium hydroxide, aqueous potassium hydroxide and aqueous lithium hydroxide. Preferred acidic hydrolysing agents include hydrochloric acid, hydrobromic acid and sulphuric acid. Most preferably the hydrolysing agent is aqueous hydrochloric acid or aqueous sodium hydroxide solution.

In another aspect the present invention provides novel compounds of formula III and V in which R₁ and R are as previously defined which are useful as intermediates in the preparation of paroxetine. Preferably R₁ is benzyl. Preferably R is methyl. Preferably M is potassium.

- In yet another aspect the present invention provides a process for the preparation of paroxetine from a compound of formula I according to the methods described in WO 96/36636, and WO 98/01424 characterised in that the compound of formula I
- 5 was prepared by racemisation of an enantiomerically enriched compound of formula I by the process of the present invention. The paroxetine may be obtained as the hydrochloride salt as the anhydrous form or the hemihydrate or other solvate. The process of the present invention may also be used in conjunction with
- 10 the process described in WO 98/52920 to prepare an intermediate which may be further processed as described below to produce paroxetine. These combination processes also form part of the present invention.
- 15 The process of the present invention is advantageous because it provides a pure precursor to paroxetine. Paroxetine may be obtained in a pure form from compounds of formula I by a) conversion of the hydroxy group into a leaving group, for example halo or tosyloxy, b) reaction with sesamol or a salt
- 20 thereof, c) removal of the protecting group R_1 by conventional means for example by hydrogenolysis when R_1 is benzyl and optionally d) salt formation, for example the hydrochloride salt as the anhydrous form or the hemihydrate.
- 25 The invention is illustrated by the following Examples which are given by way of example only. The final product of each of these Examples was characterised by one or more of the following procedures: gas-liquid chromatography; high performance liquid chromatography; elemental analysis; nuclear magnetic resonance
- 30 spectroscopy and infrared spectroscopy.

EXAMPLES

Example 1

- 35 Triethylamine (16.1 ml) was added to a solution of (+)-1-benzyl-3-hydroxymethyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine (21.7 g) in dichlormethane (87 ml) at ambient temperature and then benzenesulphonyl chloride (11.3 ml) was added to the
- 40 solution with stirring. The mixture was stirred at ambient temperature for 18 hours. Water (74 ml) was added and the mixture was stirred for 10 minutes. The organic layer was separated off, washed with water (74 ml), then dried, filtered and evaporated to give (+)-1-benzyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine-
- 45 3-methyl benzenesulphonate.

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Example 2

Potassium acetate (1.23 g) was added to a stirred solution of (+)-1-benzyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine-3-methyl benzenesulphonate (5.0 g) in acetonitrile (50 ml). 18-Crown-6 (0.3 g) was added to this mixture and the mixture was stirred at ambient temperature for 18 hours and then stirred and boiled under reflux for 6 hours. The mixture was allowed to cool to ambient temperature and then allowed to stand at this temperature for 64 hours. Water (50 ml) was added, followed by ethyl acetate (50 ml). The mixture was stirred for around 5 minutes. The organic layer was separated, washed with water (50 ml), dried, filtered and evaporated to give (+,-)-1-benzyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine-3-methyl acetate.

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Example 3

Aqueous sodium hydroxide solution (1.84 ml of a 4M solution) was added to a solution of (+,-)-1-benzyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine-3-methyl acetate (0.5 g) in industrial methylated spirits (5 ml). The mixture was boiled under reflux for 4.25 hours. The mixture was evaporated under reduced pressure and then water (10 ml) and toluene (10 ml) were added to the residue. The organic layer was separated, washed with water (10 ml) then dried, filtered and evaporated to give (+,-)-1-benzyl-3-hydroxymethyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine (ee 11.6%).

Example 4

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Triethylamine (3.2 ml) was added to a solution of (+)-1-benzyl-3-hydroxymethyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine (5.65 g) in toluene (44.35 g) and the mixture was stirred at ambient temperature. The solution was cooled to 5°C in an ice/water bath and the methanesulphonyl chloride (1.6 ml) was added dropwise over a minute. The temperature rose to 11°C over 5 minutes and then dropped to 5°C over 5 minutes. The mixture was stirred at 0 - 5°C for 75 minutes. The mixture was allowed to warm to 10°C and water (10 ml) was added. The mixture was stirred for 5 minutes and then the organic layer was separated, washed with water (20 ml), and then dried, filtered and evaporated to give (+)-1-benzyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine-3-methyl methanesulphonate as an oil which solidified on standing. $[\alpha]_D^{21.5^\circ\text{C}} = + 78.2 \pm 1.4$ concentration 1.0735 g per 100 ml of chloroform.

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Example 5

Potassium acetate (1.23 g) and 18-crown-6 (0.3 g) were added to a stirred solution of (+)-1-benzyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine-3-methyl methanesulphonate (4.27 g) in acetonitrile (50 ml) with stirring. The mixture was stirred at ambient temperature for 1.5 hours and then boiled under reflux with stirring for 5 hours. The mixture was allowed to stand at ambient temperature for 64 hours and then boiling under reflux was continued for a further 5 hours. The mixture was cooled to ambient temperature and then ethyl acetate (50 ml) and water (50 ml) were added. The mixture was stirred for approximately 5 minutes and then brine (20 ml) was added to the mixture followed by dry ethyl acetate (10 ml). The organic layer was separated, washed with brine (50 ml), dried, filtered and evaporated to give (+,-)-1-benzyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine-3-methyl acetate.

Example 6

Aqueous sodium hydroxide solution (9.6 ml of a 4M solution) was added to a solution of (+,-)-1-benzyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine-3-methyl acetate (2.6 g) in industrial methylated spirits (26 ml) with stirring. The mixture was boiled under reflux for 1.5 hours. The mixture was evaporated under reduced pressure and then toluene (40 ml) and water (20 ml) were added. The organic layer was removed, washed with water, and then dried, filtered and evaporated to give (+,-)-1-benzyl-3-hydroxymethyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine (ee 16.3%).

30

Example 7

A solution of (-)-enriched)-1-benzyl-3-hydroxymethyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine (19.8 g) in toluene (100 g) which had been previously dried by azeotropic distillation, was stirred at ambient temperature whilst triethylamine (13.9 ml) and benzenesulphonyl chloride (9.9 ml) were added. The mixture was stirred at ambient temperature for 64 hours. Water (64 ml) was added and the mixture was stirred for approximately 15 minutes. The organic layer was separated off, washed with water and a sample (10 ml) was removed for analysis. The remaining toluene solution was boiled under reflux with azeotropic removal of the water using a Dean & Stark apparatus for approximately 15 minutes. The mixture was cooled to ambient temperature and potassium acetate (7.18 g) and propan-2-ol (97.2 ml) were added. The mixture was boiled under reflux for 19 hours, then cooled to 45°C and an aqueous solution of sodium hydroxide (66.6 ml of a

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4M solution) and water (33 ml) were added. The resulting 2-phase mixture was boiled and stirred under reflux for 1.75 hours. Solvent (60 ml) was removed by distillation and the mixture was allowed to cool to ambient temperature. The organic layer
5 was separated, washed with water then evaporated under reduced pressure to give (+,-)-1-benzyl-3-hydroxymethyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine as an oil (ee 5.4%)

Example 8

10

Triethylamine (1.39 ml) and benzenesulphonyl chloride (9.9 ml) were added to a solution of (-)-1-benzyl-3-hydroxymethyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine (19.8 g) made up to 100 g with toluene, with stirring under nitrogen. The mixture was
15 stirred at ambient temperature for 72 hours. Water (64 ml) was added and the mixture was stirred for 15 minutes. The organic layer was separated, washed with water and a small sample of the solution (5 ml) was removed. The remaining toluene solution was stirred while potassium acetate (7.18 g) and 4-methyl-2-pentanol
20 (71 ml) were added. The mixture was then boiled and stirred under reflux with removal of water via a Dean & Stark apparatus for 5.5 hours. The mixture was allowed to cool to ambient temperature and stood at this temperature for 18 hours. Water (64 ml) was added and the mixture was stirred for 5 minutes. The aqueous
25 layer was separated off. The organic layer was returned to the reaction flask and stirred while water (51.2 ml) followed by concentrated hydrochloric acid (28.6 ml) were added. This mixture was boiled under reflux for 1.5 hours. The reaction mixture was cooled to around 40°C and the concentrated aqueous ammonia
30 (22.1 ml) was added dropwise keeping the temperature below 45°C. More concentrated aqueous ammonia solution (6 ml) was added to give a final pH of 8 - 9. The reaction mixture was stirred for around 15 minutes and then cooled to ambient temperature. The organic layer was separated, washed with water, dried and
35 evaporated to give (+,-)-1-benzyl-3-hydroxymethyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine (ee 4.47%).

Example 9

40 Triethylamine (12.9 ml) was added to a solution of (-)-1-benzyl-3-hydroxymethyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine (25.0 g) made up to 137 g with toluene, with stirring under nitrogen. The solution was cooled to 5°C in an ice/water bath and methanesulphonyl chloride (6.6 ml) was added dropwise over
45 20 minutes keeping the temperature below 10°C. The mixture was stirred at 0 - 10°C for 45 minutes. 4-Methyl-2-pentanol (6.5 ml) was added and the mixture stirred for a further 15 minutes. The

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mixture was allowed to warm to 20°C and water (40 ml) was added. The mixture was stirred for 15 minutes and then the organic layer was separated, and washed with water (40 ml). The remaining toluene solution was stirred while potassium acetate (9.5 g) and
5 4-methyl-2-pentanol (19.5 ml) were added. The mixture was then boiled and stirred under reflux with removal of water via a Dean & Stark apparatus for 15 to 20 hours. The mixture was allowed to cool to 50°C. Water (40 ml) was added and the mixture was stirred for 15 minutes. The aqueous layer was separated off. The organic
10 layer was returned to the reaction flask and stirred while water (12.8 ml) followed by concentrated hydrochloric acid (10.2 ml) were added. This mixture was boiled under reflux for 3 hours. The reaction mixture was cooled to around 40°C and then concentrated aqueous ammonia (23 ml) was added dropwise keeping the
15 temperature below 45°C to give a final pH of 8 - 9. The reaction mixture was stirred for around 15 minutes and then cooled to ambient temperature. The organic layer was separated, washed with water (2 x 40 ml) and evaporated to give (+,-)-1-benzyl-3-hydroxymethyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine
20 (ee 9.0%).

Example 10

Triethylamine (1.5 ml) was added to a solution of (+)-1-benzyl-
25 3-hydroxymethyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine (2.82 g) in toluene (22.18 g) and the mixture was stirred at ambient temperature. The solution was cooled to 5°C in an ice/water bath and the trifluoromethanesulphonic anhydride (1.8 ml) was added dropwise over 5 minutes. The mixture was stirred at 0°C
30 to room temperature for 4 hours, then stood for 48 hours. Water (25 ml) was added. The mixture was stirred for 2 minutes and then ethyl acetate and 4M-NaOH were added to dissolve an insoluble oil. The organic layer was separated, washed with water (25 ml), and then dried, filtered and evaporated to give 1-benzyl-4-
35 (4-fluorophenyl)-1-azoniabicyclo[3.1.1]hept-3-ene trifluoromethanesulphonate as an oil. The oil was triturated with 60 - 80°C petrol to give a solid.

Example 11

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Potassium acetate (0.14 g) was added to a stirred solution of 1-benzyl-4-(4-fluorophenyl)-1-azoniabicyclo[3.1.1]hept-3-ene trifluoromethanesulphonate (0.5 g) in toluene (2.5 ml) and
propan-2-ol (2.5 ml). The mixture was then boiled and stirred
45 under reflux for 24 hours. The mixture was cooled to room temperature and toluene (10 ml) and water (5 ml) were added. The organic layer was separated, dried and evaporated to leave

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an oil. A solution of the oil in propan-2-ol (2 ml) and toluene (2 ml) was treated with 4M-NaOH (0.4 ml). The mixture was boiled under reflux for 2 hours then cooled to room temperature. Water (5 ml) and toluene 95 ml) were added. The organic layer was
5 separated, washed with water (2 x 5 ml) and evaporated to give (+, -)-1-benzyl-3-hydroxymethyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine (ee 5.48%).

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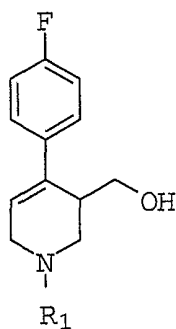
Claims

1. A process for the racemisation of a compound of formula I comprising the steps of

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- a) reacting an enantiomerically enriched compound of formula I

10



I

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in which R_1 represents an amine protecting group, with a compound of formula II

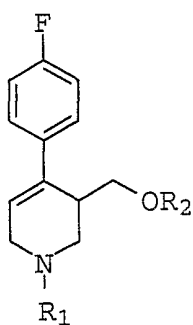
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II

in which R_2 represents a group of formula R_3SO_x - in which R_3 represents optionally substituted phenyl, a C_{1-6} alkyl group or a trifluoromethyl group and X represents halo to give a compound of formula III

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III

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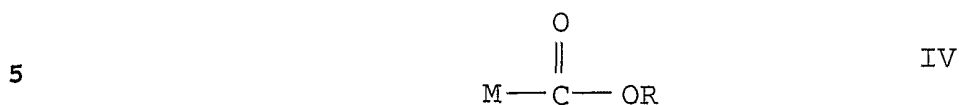
in which i) R_2 represents a group of formula R_3SO_2 - in which R_3 represents optionally substituted phenyl, a C_{1-6} alkyl group or a trifluoromethyl group,

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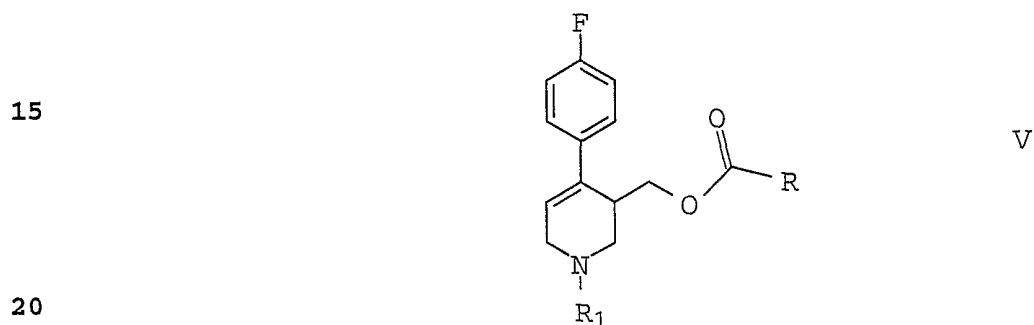
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- b) reacting the compound of formula III with a compound of formula IV



10 in which M represents an alkali metal and R represents H, a C₁₋₆alkyl group, optionally substituted phenyl or an (optionally substituted phenyl)hydroxyC₁₋₆alkyl group to give a substantially racemic compound of formula V

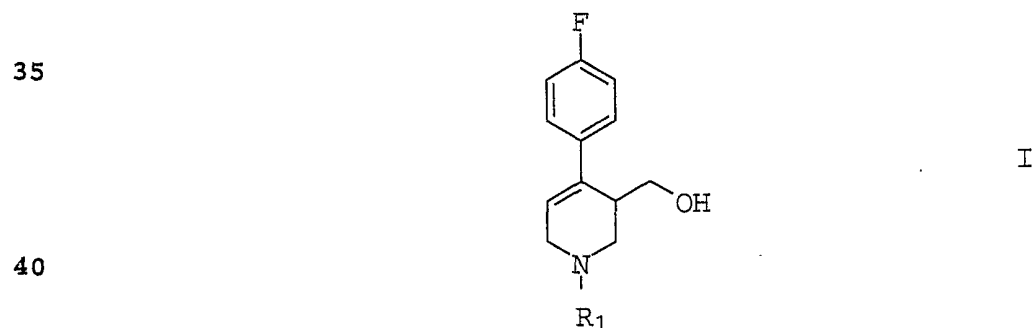


in which R₁ and R are as previously defined; and

- 25 c) reacting the compound of formula V with a hydrolysing agent to give a substantially racemic compound of formula I.

2. A process for the racemisation of a compound of formula I comprising the steps of

- 30 a) reacting an enantiomerically enriched compound of formula I



in which R₁ represents an amine protecting group, with a compound of formula II

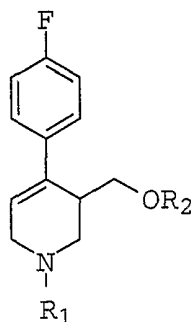


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in which R_2 represents a group of formula R_3SO_x - in which R_3 represents optionally substituted phenyl, a C_{1-6} alkyl group or a trifluoromethyl group and x represents halo to give a compound of formula III

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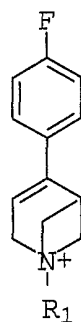
III

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in which i) R_2 represents a group of formula R_3SO_2 - in which R_3 represents optionally substituted phenyl, a C_{1-6} alkyl group or a trifluoromethyl group, wherein the compound of formula III is in equilibrium with a compound of formula IIIa

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IIIa

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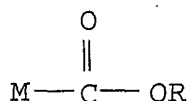
 R_2^-

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in which R_1 represents an amine protecting group and R_2^- is an anion of R_2

b) reacting the compound of formula IIIa with a compound of formula IV

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IV

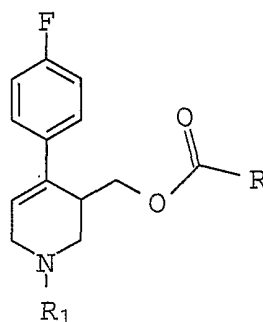
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in which M represents an alkali metal and R represents H, a C₁₋₆alkyl group, optionally substituted phenyl or an (optionally substituted phenyl)hydroxyC₁₋₆alkyl group to give a substantially racemic compound of formula V

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V

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in which R₁ and R are as previously defined; and

c) reacting the compound of formula V with a hydrolysing agent to give a substantially racemic compound of formula I.

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3. A process according to either claim 1 or claim 2 in which the amine protecting group is selected from a) allyl, b) benzhydryl, c) methoxymethyl, d) benzyloxymethyl, e) tetrahydropyranyl, f) an optionally substituted benzyl group, g) di(p-methoxyphenyl)methyl, h) triphenylmethyl, i) (p-methoxyphenyl)diphenylmethyl, j) diphenyl-4-pyridylmethyl, k) a C₁₋₆alkyl group, for example methyl or ethyl, l) a trifluoro C₁₋₄alkyl group, m) an alkynyl group or n) p-methoxybenzyl.

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4. A process according to any previous claim in which R₃ represents methyl or phenyl optionally substituted by a methyl, group, a nitro group or halo.

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5. A process according to any previous claim in which the hydrolysing agent is selected from one or more of the following: aqueous sodium hydroxide, aqueous ammonia, aqueous potassium carbonate, aqueous potassium bicarbonate, aqueous sodium bicarbonate, aqueous sodium carbonate, potassium hydroxide, aqueous potassium hydroxide and aqueous lithium hydroxide.

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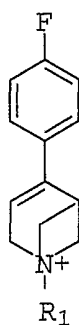
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6. A process according to any previous claim in which the hydrolysing agent is selected from one or more of the following: hydrochloride acid, hydrobromic acid and sulphuric acid.

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7. A compound of formula IIIa

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IIIa

 R_2^-

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 R_1

- in which R_1 represents an amine protecting group and R_2 is as previously stated. Preferably R_1 represents benzyl or a C_{1-6} alkyl group.

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8. A compound according to claim 7 in which R_1 represents benzyl, methyl or ethyl.

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9. A compound according to claim 7 or claim 8 in which R_2^- is a benzenesulphonate anion, a methanesulphonate anion or a trifluoromethanesulphonate anion.

- 30 10. A compound selected from:

1-benzyl-4-(4-fluorophenyl)-1-azoniabicyclo[3.1.1]hept-3-ene trifluoromethanesulphonate

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1-benzyl-4-(4-fluorophenyl)-1-azoniabicyclo[3.1.1]hept-3-ene methanesulphonate

1-benzyl-4-(4-fluorophenyl)-1-azoniabicyclo[3.1.1]hept-3-ene benzenesulphonate

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 01/09998

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D211/70 C07D471/08 A61K31/44 A61P25/24

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 C07D

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)

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	ENGELSTOFT M ET AL: "SYNTHESIS AND RHT MODULATING ACTIVITY OF STEREOISOMERS OF 3-PHOXYMETHYL-4-PHENYLPYPERIDINES" ACTA CHEMICA SCANDINAVICA, MUNKSGAARD, COPENHAGEN, DK, vol. 50, no. 2, 1 February 1996 (1996-02-01), pages 164-169, XP000645441 ISSN: 0904-213X scheme 3 p.165; schemes 5 and 6, p.166 --- -/-	1-10

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

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E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

11 December 2001

Date of mailing of the international search report

21/12/2001

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INTERNATIONAL SEARCH REPORT

Int. Patent Application No.

PCT/EP 01/09998

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WILLOCKS K ET AL: "THE SYNTHESIS OF U14C-3S, 4R-4-(4-FLUOROPHENYL)-3-(3,4-METHYLENEDIOXYPHENOXYMETHYL)PIPERIDINE HYDROCHLORIDE (BRL 29060A), AND MECHANISTIC STUDIES USING CARBON-13 LABELLING" JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS, SUSSEX, GB, vol. 33, no. 8, 1993, pages 783-794, XP000645839 ISSN: 0362-4803 Scheme 2, p.787 the whole document	2
Y	WO 97 24323 A (CHIROSCIENCE LTD ;ADGER BRIAN MICHAEL (GB); POTTER GERARD ANDREW) 10 July 1997 (1997-07-10) Scheme 1, p.7	2
A	DE 199 00 576 A (MERCK PATENT GMBH) 13 July 2000 (2000-07-13) page 13, line 5-19; claim 7	7-10
A	US 4 007 196 A (CHRISTENSEN JORGEN ANDERS ET AL) 8 February 1977 (1977-02-08) cited in the application the whole document	1-6
A	WO 96 36636 A (NOVONORDISK AS ;HANSEN JOHN BONDO (DK); TREPPENDAHL SVEND (DK); EN) 21 November 1996 (1996-11-21) cited in the application the whole document	1-6
A	WO 98 01424 A (BORZA ISTVAN ;CZIBULA LASZLO (HU); DOBAY LASZLO (HU); HARSANYI KAL) 15 January 1998 (1998-01-15) cited in the application page 8; example 2	1-6

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 01/09998

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9724323	A	10-07-1997	AU 1204797 A	28-07-1997
			EP 0874820 A1	04-11-1998
			WO 9724323 A1	10-07-1997
			JP 2001504081 T	27-03-2001
			US 6066737 A	23-05-2000
DE 19900576	A	13-07-2000	DE 19900576 A1	13-07-2000
US 4007196	A	08-02-1977	GB 1422263 A	21-01-1976
			BE 893095 A7	30-08-1982
			AT 333759 B	10-12-1976
			AT 69674 A	15-04-1976
			BE 810310 A1	16-05-1974
			CA 1038390 A1	12-09-1978
			CH 592059 A5	14-10-1977
			DE 2404113 A1	08-08-1974
			DK 149843 B	13-10-1986
			ES 422734 A1	01-04-1976
			ES 8707224 A3	01-10-1987
			FI 57932 B	31-07-1980
			FR 2215233 A1	23-08-1974
			HK 13081 A	10-04-1981
			IE 38801 B1	07-06-1978
			IT 1054157 B	10-11-1981
			JP 1268487 C	10-06-1985
			JP 49101385 A	25-09-1974
			JP 59046216 B	10-11-1984
			JP 1272362 C	11-07-1985
			JP 58174363 A	13-10-1983
			JP 59048826 B	29-11-1984
			LU 88398 A9	04-05-1994
			LU 69264 A1	10-04-1974
			NL 7401189 A ,B,	01-08-1974
			NO 144568 B	15-06-1981
			PH 10383 A	02-03-1977
			SE 401827 B	29-05-1978
			US 3912743 A	14-10-1975
WO 9636636	A	21-11-1996	AU 721257 B2	29-06-2000
			AU 5684596 A	29-11-1996
			BR 9608471 A	29-12-1998
			CA 2220963 A1	21-11-1996
			CN 1184476 A ,B	10-06-1998
			WO 9636636 A1	21-11-1996
			EP 0828735 A1	18-03-1998
			HU 9900318 A2	28-09-1999
			JP 11505229 T	18-05-1999
			NZ 307479 A	30-08-1999
			ZA 9603951 A	21-01-1997
WO 9801424	A	15-01-1998	HU 9601857 A2	28-05-1998
			AU 3631197 A	02-02-1998
			EP 0923554 A1	23-06-1999
			WO 9801424 A1	15-01-1998