

temperature. Potassium carbonate (0.84 g) was added, and the mixture was stirred overnight and for a further 20 hr. The reaction mixture was poured into water (500 ml) and the resulting white solid was filtered off, and recrystallized from methanol to give 3-*t*-butyloxycarbonylamino-6-carboxamidomethyl-1,2,3,4-tetrahydrocarbazole (5.42 g).

The above product (500 mg) was dissolved in dry dioxane (30 ml), and HCl gas was bubbled through for 20 min. The resulting solution and deposited gum were evaporated to dryness, and treated with aqueous potassium carbonate solution. This was extracted with ethyl acetate, and the extracts were combined, dried (MgSO₄) and evaporated to dryness. The residue was dissolved in methanol and treated with excess oxalic acid. Addition of ether led to crystallization of the title compound (250 mg), mp 257°–260° C.

Example 24

3-Methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride

4-Cyanophenyl hydrazine hydrochloride (20.2 g) and 4-benzoyloxycyclohexanone (25.9 g) were dissolved in glacial acetic acid (400 ml) and the mixture was heated under reflux for 1.5 hr. After allowing to cool, the mixture was filtered, and the filtrate was evaporated to dryness, and neutralized with aqueous sodium bicarbonate solution to give a solid precipitate, which was purified by chromatography (SiO₂; hexane/ethyl acetate) to give 3-benzoyloxy-6-cyano-1,2,3,4-tetrahydrocarbazole (18 g). This product (11.6 g) was suspended in ethanol (230 ml) and treated with 2.5% aqueous potassium hydroxide solution (120 ml), and heated under reflux for 1 hr. The cooled mixture was neutralized with glacial acetic acid and evaporated to a solid residue, which was washed with water, and dried to give 3-hydroxy-6-cyano-1,2,3,4-tetrahydrocarbazole (6.6 g).

The above product (3.57 g) was dissolved in dry pyridine (35 ml) and treated with tosyl chloride (3.51 g) in dry pyridine (35 ml), and the mixture was stirred at 100° C. for 2 hr. After cooling, the solution was poured into water (500 ml), extracted with ethyl acetate, and the latter extract was washed with 2M HCl, dried (MgSO₄) and evaporated to dryness. Purification by chromatography (SiO₂; hexane/ethyl acetate) gave 3-tosyloxy-6-cyano-1,2,3,4-tetrahydrocarbazole (0.53 g).

This product (0.40 g) was dissolved in 33% methylamine in alcohol (25 ml) and heated at 100° C. in a sealed steel vessel for 1.5 hr. After cooling, the mixture was evaporated to dryness and purified by chromatography (SiO₂; chloroform/methanol) to give 3-methylamino-6-cyano-1,2,3,4-tetrahydrocarbazole (0.13 g).

The above product (0.12 g) was dissolved in THF (10 ml) and reacted with di-*tert*-butyl dicarbonate (0.36 g) in THF (3 ml) at room temperature overnight. The reaction mixture was evaporated to dryness, partitioned between 2M sodium bicarbonate solution and ethyl acetate, and the organic extract dried and evaporated to give a white solid. This was triturated with ether/hexane to give 3-*t*-butyloxycarbonylmethyl amino-6-cyano-1,2,3,4-tetrahydrocarbazole (0.14 g).

This product (0.14 g) was dissolved in methanol (15 ml) and treated with a mixture of 20% aqueous sodium hydroxide (0.20 ml) and 30% hydrogen peroxide (0.20 ml), and the whole mixture was stirred at room temperature overnight. Sodium metabisulphite (38 mg) was added, and the solution was evaporated to dryness, and chromatographed (SiO₂; chloroform/10% NH₄OH in methanol) to give 3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (0.12 g). The above compound (0.11 g) was dissolved in

methanol (10 ml), and treated with 3M hydrochloric acid at room temperature. The mixture was evaporated to dryness, azeotroping with ethanol to give a solid, which was recrystallized from methanol/ether to give the title compound, mp 327°–328° C. (80 mg).

¹H NMR [250 MHz, MeOH-*d*⁴] δ 1.98–2.20 (1H, m), 2.29–2.49 (1H, m), 2.75–2.90 (5H, s+m), 2.90–3.09 (2H, m), 3.52–3.69 (1H, m), 7.31 (1H, d), 7.63 (1H, d), 8.05 (1H, s).

Example 25

3-Ethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate

1,4-Cyclohexanedione mono-2',2'-dimethyl trimethylene ketal (2.00 g) was mixed with anhydrous ethylamine (10.0 g) and benzene (10 ml), and the mixture was cooled to 5° C. A solution of titanium tetrachloride (0.95 g) in benzene (10 ml) was added, dropwise, then the mixture was stirred at room temperature for 1 hr. The mixture was filtered, and evaporated to dryness to give an oil, which was dissolved in ethanol (30 ml). To this solution was added palladium-on-carbon catalyst (100 mg), and the mixture was hydrogenated at 50 psi pressure overnight. The catalyst was filtered off and the ethanol evaporated to leave 4-ethylaminocyclohexanone 2',2'-dimethyl trimethylene ketal as an oil (2.0 g).

This compound (0.80 g) was dissolved in formic acid (20 ml) and the solution was heated to 90° C. for 1 hr. Formic acid was evaporated, and the residue was partitioned between chloroform and 1M hydrochloric acid. The aqueous layer was evaporated to dryness to give 4-ethylaminocyclohexanone (0.40 g).

A mixture of the above product (0.40 g) and 4-carboxamidophenyl hydrazine hydrochloride (0.60 g) in glacial acetic acid (20 ml) was heated under reflux for 1 hr. The acid was evaporated in vacuo to an oil, which was purified by chromatography (SiO₂; CHCl₃/10% NH₃ in MeOH) to give an oil (0.50 g). Part of this product (150 mg) was dissolved in methanol and treated with oxalic acid. The solution was treated with ether to give the title compound as a crystalline solid, mp 165°–170° C. (100 mg).

¹H NMR [250 MHz, DMSO-*d*⁶] δ 1.25 (3H, t), 1.81–2.05 (1H, m), 2.20–2.38 (1H, m), 2.61–2.79 (1H, m), 2.79–2.94 (2H, m), 2.98–3.28 (3H, dd+s), 3.41–3.60 (1H, m), 7.08 (1H, brd. s), 7.28 (1H, d), 7.60 (1H, d), 7.82 (1H, brd. s), 8.00 (1H, s), 11.12 (1H, s).

Example 26

3-*n*-Propylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate

Propylamine (1.81 g) was dissolved in methanol (12.5 ml), and 1.5M HCl in methanol (6.6 ml) was added with cooling. After 1 min, 1,4-cyclohexanedione mono-2',2'-dimethyl trimethylene ketal (1.0 g) was added, followed after a further 10 min by sodium cyanoborohydride (0.23 g). The mixture was stirred at room temperature for 3 days. The resulting mixture was filtered, and the filtrate was evaporated and treated with 1M HCl (10 ml) with cooling. The residue was digested to form a solution, which was washed with ether, basified to pH 12 with aqueous sodium hydroxide, and extracted with dichloromethane. This extract was washed with saturated aqueous sodium bicarbonate solution, dried (MgSO₄), and evaporated to dryness. Chromatography (SiO₂; chloroform/methanol/ammonia) gave 4-*n*-propylamino cyclohexanone 2',2'-dimethyl trimethylene ketal (0.72 g).

This product (0.66 g) was hydrolyzed to the ketone, which was reacted with 4-carboxamidophenyl hydrazine hydro-

17

chloride and converted to the oxalate salt as described for Example 25, to give the title compound (0.44 g), mp >168° C. dec.

Example 27

3-i-Propylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of isopropylamine (9.54 g) with 1,4-cyclohexanedione mono-2',2'-dimethyl trimethylene ketal (2.0 g) by the method described for Example 25 gave 4-i-propylamino cyclohexanone 2',2'-dimethyl trimethylene ketal (2.38 g). This product (0.66 g) was hydrolyzed and reacted with 4-carboxamidophenyl hydrazine hydrochloride (0.45 g), and the mixture worked up as described above to give the title compound free base (0.34 g). This was converted to the oxalate, mp >235° C. dec.

Example 28

3-Dimethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate

Dimethylamine (10.0 g) was reacted with 1,4-cyclohexanedione mono-2',2'-dimethyl trimethylene ketal (2.0 g) by the method described for Example 25 to give 4-dimethylaminocyclohexanone-2',2'-dimethyl trimethylene ketal (0.72 g). This product (0.72 g) was hydrolyzed and reacted with 4-carboxamidophenyl hydrazine hydrochloride (0.47 g) and the product converted to the oxalate salt as described above to give the title compound (0.20 g), mp 99°-101° C.

¹H NMR [250 MHz, DMSO-d₆] δ 1.83-2.05 (1H, m), 2.27-2.40 (1H, m) 2.72-3.00 (9H, 2m+s), 3.07-3.22 (1H, dd), 3.50-3.68 (1H, m), 7.05 (1H, brd. s), 7.27 (1H, d), 7.60 (1H, d), 7.81 (1H, brd. s), 8.00 (1H, s), 11.11 (1H, s).

Example 29

3-Benzylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of benzylamine (0.59 g) with 1,4-cyclohexanedione mono-2',2'-dimethyl trimethylene ketal (1.0 g) and subsequent reduction of the imine with sodium cyanoborohydride by the method described for Example 26 gave 4-benzylaminocyclohexanone 2',2'-dimethyl trimethylene ketal (0.54 g). This product (0.52 g) was reacted with 4-carboxamidophenyl hydrazine hydrochloride (0.34 g) and the product treated with oxalic acid to give the title compound, mp >190° C. dec (0.11 g).

Example 30

3-Pyrrolidinyl-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of pyrrolidine (15.6 g) with 1,4-cyclohexanedione mono-2',2'-dimethyl trimethylene ketal (2.0 g) by the method described for Example 25 gave 4-pyrrolidinyl-cyclohexanone-2',2'-dimethyl trimethylene ketal (1.74 g). This product (1.70 g) was hydrolyzed and reacted with 4-carboxamidophenyl hydrazine hydrochloride (1.70 g) and the product treated with oxalic acid as described above to give the title compound (32 mg), mp >190° C. dec.

Example 31

3-(N-methyl ethylamino)-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of N-methyl ethylamine (13.0 g) with 1,4-cyclohexanedione mono-2',2'-dimethyl trimethylene ketal (2.0 g) by the method described for Example 25 gave

18

4-(N-methyl ethylamino)-cyclohexanone-2',2'-dimethyl trimethylene ketal (1.71 g). This product (0.86 g) was hydrolyzed and reacted with 4-carboxamidophenyl hydrazine hydrochloride (0.52 g) and worked up as described above to give the title compound (76 mg), mp >130° C. dec.

Example 32

3-Amino-6-(2-carboxamidoethyl)-1,2,3,4-tetrahydrocarbazole oxalate

A mixture of 4-nitrocinnamic acid (22.5 g) and thionyl chloride (20.8 g) in benzene (160 ml) was heated under reflux for 4 h. The resulting orange mixture was filtered and evaporated to give the acid chloride (22.9 g). This was dissolved in dichloromethane (1 l), and ammonia gas was bubbled through, with cooling to below 20° C. and stirring. Solvent was removed in vacuo, and the residue was dissolved in hot ethyl acetate and the solution was shaken with 1M sodium hydroxide solution. The resulting organic phase was dried, filtered and evaporated to leave a residue which was slurried with ethyl acetate to give 4-nitro cinnamamide as a crystalline solid (18.6 g). This product (18.6 g) was suspended in ethanol (1 l) and hydrogenated using Pd-C catalyst (6.6 g) at 50 psi for 1 h. The resulting mixture was filtered and evaporated to dryness, providing 4-aminophenyl propionamide (17.1 g).

Concentrated hydrochloric acid (4 ml) was added slowly, with cooling and stirring to 4-aminophenyl propionamide (0.80 g), maintaining the temperature below 5° C. To this slurry was added a solution of sodium nitrite (0.37 g) in water (2 ml), dropwise over 15 min, followed by stirring for a further 15 min. The turbid solution thus formed was added portionwise to a cooled, stirred solution of stannous chloride (2.19 g) in conclusion. HCl (4 ml), and the resulting mixture was stirred for 1 h. After filtering, the solution was reduced in volume until an inorganic precipitate formed. This was filtered off, and the filtrate was evaporated to dryness. The residual gum was crystallized from acetic acid to give crude 4-hydrazinophenyl propionamide hydrochloride (1.05 g).

A mixture of the above product (1.05 g) and 4-phthalimidocyclohexanone (1.18 g) in acetic acid (40 ml) was heated under reflux for 40 min. The solvent was removed in vacuo and the residue was partitioned between aqueous potassium carbonate solution and ethyl acetate. The organic phase was dried (MgSO₄) and evaporated to dryness, and the residue was chromatographed (SiO₂; CH₂Cl₂/MeOH) to give 3-phthalimido-6-carboxamidoethyl-1,2,3,4-tetrahydrocarbazole (0.70 g).

This product (0.70 g) was dissolved in methanol (50 ml), treated with hydrazine hydrate (1.0 ml), and heated under reflux for 30 min. The mixture was evaporated to dryness then partitioned between ethyl acetate and aqueous potassium carbonate solution. The organic phase was dried (MgSO₄) and evaporated to dryness, and the residue was dissolved in ethanol to dryness, and the residue was dissolved in ethanol and treated with oxalic acid (83 mg) in ethanol. A solid was formed, which was recrystallized from ethanol to give the title compound (110 mg), mp 232°-5° C.

Pharmaceutical formulations

Example A

A tablet for oral administration is prepared by combining

	Mg/Tablet
Compound of formula (I)	100
lactose	153

19

-continued

	Mg/Tablet
starch	33
crospovidone	12
microcrystalline cellulose	30
magnesium stearate	2
	330 mg

into a 9 mm tablet.

Example B

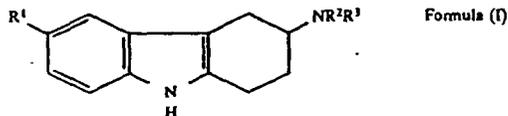
An injection for parenteral administration is prepared from the following

	% w/w
Compound of formula (I)	0.50% (w/v)
1M citric acid	30% (v/v)
sodium hydroxide (qs)	to pH 3.2
water for injection BP	to 100 ml

The compound of formula (I) is dissolved in the citric acid and the pH slowly adjusted to pH 3.2 with the sodium hydroxide solution. The solution is then made up to 100 ml with water, sterilised by filtration and sealed into appropriately sized ampoules and vials.

We claim:

1. A method of treatment of a condition wherein a 5-HT₁-like agonist is indicated, which comprises administering to a subject in need thereof an effective amount of a compound of general formula (I):



wherein

R¹ represents hydrogen, halogen, trifluoromethyl, nitro, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, arylC₁₋₆alkoxy, —CO₂R⁴, —(CH₂)_nCN, —(CH₂)_nCONR⁵R⁶, —(CH₂)_nSO₂NR⁵R⁶, C₁₋₆alkanoylamino(CH₂)_n, or C₁₋₆alkylsulphonylamino(CH₂)_n;

R² represents hydrogen, C₁₋₆alkyl or arylC₁₋₆alkyl;

R⁵ and R⁶ each independently represent hydrogen or C₁₋₆alkyl, or R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 5 to 7-membered saturated heterocyclic ring, which may optionally contain a further heteroatom selected from oxygen, sulphur or nitrogen;

n represents 0, 1 or 2; and

R² and R³ each independently represent hydrogen, C₁₋₆alkyl or benzyl or together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino or hexahydroazepino ring;

or a physiologically acceptable salt, solvate or hydrate thereof.

2. The method according to claim 1 wherein the condition is migraine.

3. The method according to claim 1 wherein in the compound of formula (I) R¹ represents halogen, CF₃, C₁₋₆alkoxy, —(CH₂)_nCN, —(CH₂)_nCONR⁵R⁶, —(CH₂)_nSO₂NR⁵R⁶ or C₁₋₆alkanoylamino, and R⁵ and R⁶ are as hereinbefore defined.

4. The method according to claim 1 wherein in the compound of formula (I) R¹ is a group —(CH₂)_nCONR⁵R⁶

20

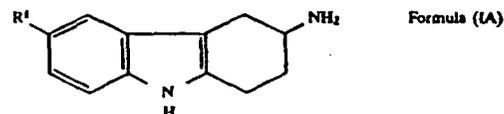
wherein n is zero and R⁵ and R⁶ each independently represent hydrogen, methyl, ethyl or propyl; and R⁵ and R⁶ each independently represent hydrogen, methyl or ethyl.

5. The method according to claim 2 wherein in the compound of formula (I) R¹ is a group —(CH₂)_nCONR⁵R⁶ wherein n is zero and R⁵ and R⁶ each independently represent hydrogen, methyl, ethyl or propyl; and R⁵ and R⁶ each independently represent hydrogen, methyl or ethyl.

6. The method according to claim 4 wherein in the compound of formula (I) R⁵ and R⁶ each independently represent hydrogen or methyl.

7. The method according to claim 5 wherein in the compound of formula (I) R⁵ and R⁶ each independently represent hydrogen or methyl.

8. A compound of formula (IA):



wherein

R¹ represents nitro, —CO₂R⁴, CN, —(CH₂)_nCONR⁵R⁶, —(CH₂)_nSO₂NR⁵R⁶, or C₁₋₆alkylsulphonylamino(CH₂)_n;

R⁴ represents arylC₁₋₆alkyl;

R⁵ and R⁶ each independently represent hydrogen or C₁₋₆alkyl, or R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 5 to 7-membered saturated heterocyclic ring, which may optionally contain a further heteroatom selected from oxygen, sulphur or nitrogen; and

n represents 0, 1 or 2;

or a physiologically acceptable salt, solvate or hydrate thereof.

9. A compound of formula (IA) according to claim 8 wherein R¹ represents —(CH₂)_nCONR⁵R⁶, wherein n represents 0 and R⁵ and R⁶ each independently represent hydrogen, methyl, ethyl or propyl.

10. A compound of formula (IA) according to claim 9 wherein R⁵ and R⁶ each independently represent hydrogen or methyl.

11. A compound of formula (I) according to claim 8, which is selected from:

3-Amino-6-cyano-1,2,3,4-tetrahydrocarbazole;

3-amino-6-(N-methylsulphonamidomethyl)-1,2,3,4-tetrahydrocarbazole;

3-amino-6-sulphonamido-1,2,3,4-tetrahydrocarbazole;

3-amino-6-nitro-1,2,3,4-tetrahydrocarbazole;

3-amino-6-(piperidin-1-ylcarbonyl)-1,2,3,4-tetrahydrocarbazole;

3-amino-6-(pyrrolidin-1-ylcarbonyl)-1,2,3,4-tetrahydrocarbazole;

3-amino-6-methanesulphonamido-1,2,3,4-tetrahydrocarbazole;

or a physiologically acceptable salt, solvate or hydrate thereof.

12. A compound of formula (I) according to claim 8, which is selected from:

3-amino-6-(N-methylcarboxamido)-1,2,3,4-tetrahydrocarbazole;

3-amino-6-(N,N-dimethylcarboxamido)-1,2,3,4-tetrahydrocarbazole;

3-amino-6-(N,N-diethylcarboxamido)-1,2,3,4-tetrahydrocarbazole;

or a physiologically acceptable salt, solvate or hydrate thereof.

21

13. A compound of formula (I) according to claim 8, which is selected from:

3-amino-6-carboxamidomethyl-1,2,3,4-tetrahydrocarbazole;

3-amino-6-(2-carboxamidoethyl)-1,2,3,4-tetrahydrocarbazole;

or a physiologically acceptable salt, solvate or hydrate thereof.

14. A compound of formula (I) according to claim 8, which is (+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole or a physiologically acceptable salt, solvate or hydrate thereof.

15. A compound of formula (I) according to claim 8, which is (-)-3-amino-6-carboxamido-1,2,3,4-

22

tetrahydrocarbazole or a physiologically acceptable salt, solvate or hydrate thereof.

16. A compound of formula (I) according to claim 8 wherein the said physiologically acceptable salt is formed from hydrochloric, sulphuric, phosphoric, succinic, maleic, acetic or fumaric acid.

17. A pharmaceutical composition comprising a compound of formula (I) according to claim 8, or a physiologically acceptable salt, solvate or hydrate thereof and a physiologically acceptable carrier.

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United States Patent [19]

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King et al.

[45] Date of Patent: Jun. 10, 1997

[54] MEDICAMENTS

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[21] Appl. No.: 442,719

[22] Filed: May 15, 1995

Related U.S. Application Data

[63] Continuation of Ser. No. 167,846, Dec. 23, 1993, Pat. No. 5,464,864.

[51] Int. Cl.⁶ C07D 209/82; A61K 31/40

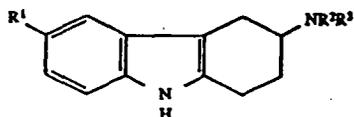
[52] U.S. Cl. 514/468; 548/439

[58] Field of Search 548/439; 514/468

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Attorney, Agent, or Firm—Nora Stein-Fernandez; William T. King; Edward T. Lentz

[57] ABSTRACT

Use of a compound of general formula (I):



Formula (I)

wherein:

R¹ represents hydrogen, halogen, trifluoromethyl, nitro, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, arylC₁₋₆alkoxy, —CO₂R⁴, —(CH₂)_nCN, —(CH₂)_nCONR⁵R⁶, —(CH₂)_nSO₂NR⁵R⁶, C₁₋₆alkanoylamino (CH₂)_n, or C₁₋₆alkylsulphonylamino (CH₂)_n;

R⁴ represents hydrogen, C₁₋₆alkyl or arylC₁₋₆alkyl;

R⁵ and R⁶ each independently represent hydrogen or C₁₋₆alkyl, or R⁵ and R⁶ together with the nitrogen atom to which they are attached form a ring;

n represents 0, 1 or 2; and

R² and R³ each independently represent hydrogen, C₁₋₆alkyl or benzyl or together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino or hexahydroazepino ring;

or a physiologically acceptable salt thereof, in the manufacture of a medicament for the treatment of a condition where a 5-HT₁-like agonist is indicated, for example migraine. Novel compounds of formula (I), processes for preparing them and pharmaceutical compositions containing them are also described.

11 Claims, No Drawings

1
MEDICAMENTS

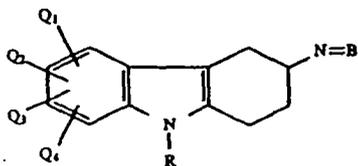
This is a continuation of application Ser. No. 08/167,846, filed Dec. 23, 1993, now U.S. Pat. No. 5,464,864.

The present invention relates to certain tetrahydrocarbazole derivatives for use in the treatment of disorders characterised by excessive vasodilatation, in particular the treatment of migraine.

Migraine is a non-lethal disease which has been reported to be suffered by one in ten individuals. The main symptom is headache; other symptoms include vomiting and photophobia. Currently, the most widely used treatment for migraine involves administration of ergotamine, dihydroergotamine or methysergide, which are also used prophylactically. These drugs are inter alia agonists of 5HT₁-like receptors but also have other actions; treatment with them is associated with a number of adverse side effects. In addition, some patients experience a "withdrawal headache" following the cessation of treatment with an ergot product, such as ergotamine, causing them to repeat the treatment and resulting in a form of addiction. More recently various tryptamine derivatives have been proposed for potential use in treating migraine.

In view of the foregoing, there is clearly a need for the provision of effective and safe medicaments for the treatment of migraine.

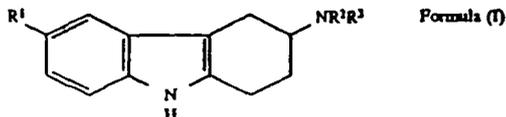
U.S. Pat. Nos. 4,257,952, 4,172,834, 4,062,864 and 3,959,309 disclose a broad class of tetrahydrocarbazoles of the formula:



wherein N=B is inter alia —NHR' or —NR'R" where R' and R" are lower alkyl, aryl-lower alkyl or together form a heterocyclic ring; R is inter alia hydrogen; Q₁ is inter alia hydrogen, halogen, lower alkoxy, cyano, —CO₂R₁ or —CONR₂R₃ (where R₁ may be hydrogen, lower alkyl or —CH₂Ar and R₂ and R₃ are hydrogen, lower alkyl or together form a heterocyclic ring); Q₂ is inter alia hydrogen, aryl-(lower alkoxy), hydroxy, trihalomethyl, nitro or alkanoylamino, and Q₃ and Q₄ may each be inter alia hydrogen. These compounds are said to have analgetic, psychotropic and antihistaminic activities.

It has now surprisingly been found that certain tetrahydrocarbazoles are agonists and partial agonists at 5HT₁-like receptors and are expected to have utility in the treatment of conditions wherein a 5-HT₁-like agonist or partial agonist is indicated, in particular conditions associated with cephalic pain such as migraine, cluster headache and headache associated with vascular disorders. In this specification the term '5-HT₁-like agonist' will hereinafter be used to include partial agonists at this receptor.

The present invention therefore provides the use of compounds of general formula (I):



wherein:

2

R¹ represents hydrogen, halogen, trifluoromethyl, nitro, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, arylC₁₋₆alkoxy, —CO₂R⁴, —(CH₂)_nCN, —(CH₂)_nCONR⁵R⁶, —(CH₂)_nSO₂NR⁵R⁶, C₁₋₆alkanoylamino (CH₂)_n, or C₁₋₆alkylsulphenylamino (CH₂)_n;

R⁴ represents hydrogen, C₁₋₆alkyl or arylC₁₋₆alkyl;

R⁵ and R⁶ each independently represent hydrogen or C₁₋₆alkyl, or R⁵ and R⁶ together with the nitrogen atom to which they are attached form a ring;

n represents 0, 1 or 2; and

R² and R³ each independently represent hydrogen, C₁₋₆alkyl or benzyl or together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino or hexahydroazepino ring;

and physiologically acceptable salts thereof, in the manufacture of a medicament for the treatment of a condition where a 5-HT₁-like agonist is indicated, in particular the treatment or prophylaxis of migraine.

The invention also provides a method of treatment of a condition wherein a 5-HT₁-like agonist is indicated, in particular migraine, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) or a physiologically acceptable salt thereof.

Suitably R¹ represents hydrogen, halogen, cyano, hydroxy, C₁₋₆alkoxy, arylC₁₋₆alkoxy, —CO₂R⁴, —(CH₂)_nCONR⁵R⁶ or —(CH₂)_nSO₂NR⁵R⁶; and R² and R³ each independently represent hydrogen or C₁₋₆alkyl.

It will be appreciated that compounds of formula (I) may contain one or more asymmetric centres, and such compounds will exist as optical isomers (enantiomers). The invention thus includes all such enantiomers and mixtures, including racemic mixtures, thereof.

In the compounds of formula (I) a halogen atom may be a fluorine, chlorine, bromine or iodine atom. An alkyl group or moiety may have a straight or branched chain. Suitable aryl groups include for example unsaturated monocyclic or bicyclic rings and partially saturated bicyclic rings of up to 12 carbon atoms, such as phenyl, naphthyl and tetrahydronaphthyl. When R⁵ and R⁶ together with the nitrogen atom form a ring, this is preferably a 5 to 7-membered saturated heterocyclic ring, which may optionally contain a further heteroatom selected from oxygen, sulphur or nitrogen. Suitable rings thus include pyrrolidino, piperidino, piperazino and morpholino.

In the above compounds R¹ preferably represents halogen (e.g. bromine), CF₃, C₁₋₆alkoxy (e.g. methoxy), (CH₂)_nCN, —(CH₂)_nCONR⁵R⁶, —(CH₂)_nSO₂NR⁵R⁶ or C₁₋₆alkanoylamino. Most preferably R¹ represents a group —(CH₂)_nCONR⁵R⁶ wherein n represents 0 and R⁵ and R⁶ each independently represent hydrogen, methyl, ethyl or propyl. Advantageously, R⁵ and R⁶ independently represent hydrogen or methyl.

When R¹ represents —CO₂R⁴, then R⁴ preferably represents C₁₋₆alkyl.

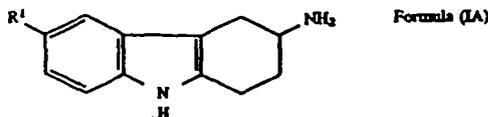
R² and R³ each preferably represent hydrogen, methyl or ethyl. Most preferably NR²R³ is —NH₂.

For use according to the present invention the compound of formula (I) is preferably a partial agonist.

Suitable physiologically acceptable salts will be apparent to those skilled in the art and include for example acid addition salts such as those formed with inorganic acids e.g. hydrochloric, sulphuric or phosphoric acids and organic acids e.g. succinic, maleic, acetic or fumaric acid. Other non-physiologically acceptable salts e.g. oxalates may be used for example in the isolation of compounds of formula (I), and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of compounds of formula (I).

3

It is believed that compounds of formula (I) wherein R^2 and R^3 both represent hydrogen are novel. Thus in a further aspect the present invention provides compounds of formula (IA):



wherein R^1 is as hereinbefore defined, and salts thereof.

The present invention further provides the following specific compounds which are also believed to be novel:

3-Amino-6-cyano-1,2,3,4-tetrahydrocarbazole hydrochloride,

(+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride,

(-)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride,

3-amino-6-methoxy-1,2,3,4-tetrahydrocarbazole 20 hydrochloride,

3-amino-6-bromo-1,2,3,4-tetrahydrocarbazole hydrochloride,

3-amino-6-methyl-1,2,3,4-tetrahydrocarbazole 25 oxalate,

3-amino-6-ethoxycarbonyl-1,2,3,4-tetrahydrocarbazole 25 oxalate,

3-amino-6-(N-methyl carboxamido)-1,2,3,4-tetrahydrocarbazole hemioxalate,

3-amino-6-cyanomethyl-1,2,3,4-tetrahydrocarbazole oxalate,

3-amino-6-(N-methylsulphonamidomethyl)-1,2,3,4-tetrahydrocarbazole oxalate,

3-amino-6-chloro-1,2,3,4-tetrahydrocarbazole oxalate,

3-amino-6-trifluoromethyl-1,2,3,4-tetrahydrocarbazole oxalate,

3-amino-6-n-butyl-1,2,3,4-tetrahydrocarbazole oxalate,

3-amino-6-sulphonamido-1,2,3,4-tetrahydrocarbazole oxalate,

3-amino-6-nitro-1,2,3,4-tetrahydrocarbazole oxalate,

3-amino-6-(N,N-dimethylcarboxamido)-1,2,3,4-tetrahydrocarbazole hemioxalate,

3-amino-6-(piperidin-1-ylcarbonyl)-1,2,3,4-tetrahydrocarbazole hydrochloride,

3-amino-6-(pyrrolidin-1-ylcarbonyl)-1,2,3,4-tetrahydrocarbazole hydrochloride,

3-amino-6-(N,N-diethylcarboxamido)-1,2,3,4-tetrahydrocarbazole hydrochloride,

3-Amino-6-(acetamido)-1,2,3,4-tetrahydrocarbazole oxalate,

3-amino-6-methanesulphonamido-1,2,3,4-tetrahydrocarbazole oxalate,

3-amino-6-carboxamidomethyl-1,2,3,4-tetrahydrocarbazole hydrochloride,

3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate,

3-ethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate,

3-n-propylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate,

3-i-propylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate,

3-dimethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate,

3-benzylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate,

3-pyrrolidinyl-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate, and

4

3-(N-(methyl)ethylamino)-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate,

3-amino-6-(2-carboxamidoethyl)-1,2,3,4-tetrahydrocarbazole oxalate.

In a further aspect the present invention provides a novel compound of formula (I) e.g. a compound of formula (IA) or any of the above-named compounds (in free base form or as a physiologically acceptable salt) for use as a therapeutic agent, in particular as a 5-HT₁-like agonist or partial agonist, for example for the treatment of migraine.

The invention also provides a process for the preparation of novel compounds of formula (I).

Compounds of formula (I) may be prepared by methods known in the art for the preparation of tetrahydrocarbazoles, for example:

A) Reaction of a compound of formula (II):

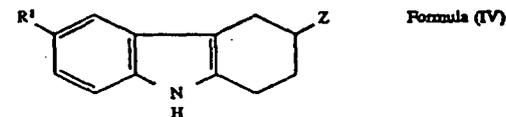


(wherein R^1 is as hereinbefore defined) or an acid addition salt thereof with a compound of formula (III):



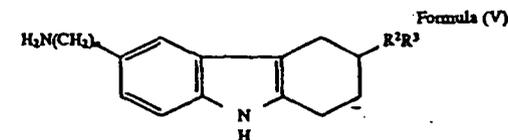
(wherein R^2 and R^3 are as hereinbefore defined) or an N-protected derivative thereof; or

B) Reaction of a compound of formula (IV):



(wherein R^1 is as defined for formula (I) and Z is a leaving group) with a compound of formula HNR^2R^3 ;

C) Reacting a compound of formula (V):



with an acylating or sulphonylating agent;

D) Conversion of one compound of formula (I) into another compound of formula (I) e.g.

(i) to prepare a compound of formula (I) wherein R^1 represents $-(CH_2)_nCONH_2$ or CO_2R^4 , hydrolysis of a compound of formula (I) wherein R^1 represents $-(CH_2)_nCN$, or an N-protected derivative thereof;

(ii) to prepare a compound of formula (I) wherein R^1 represents $-CONR^5R^6$, amination of a compound of formula (I) wherein R^1 represents $-CO_2H$, or an N-protected derivative thereof; or

(iii) to prepare a compound of formula (I) wherein one of R^2 and R^3 is hydrogen and the other is C_{1-6} alkyl, alkylation of a compound (I) in which R^2 and R^3 are both hydrogen;

(iv) to prepare a compound of formula (I) wherein R^1 represents hydroxy, cleavage of a compound wherein R^1 represents alkoxy or aralkoxy;

followed if necessary by deprotection of any protected nitrogen atoms and if desired by salt formation.

Process (A), which is a form of the Fischer indole synthesis, may be carried out using methods well known in

the art. Thus, the reaction may be effected in a solvent, for example an alcohol such as ethanol or butanol; or acetic acid, and at a temperature in the range 0° to 150° C.

Hydrazines of formula (II), which are usually employed as the hydrochloride salt, are known compounds, or may be prepared by conventional methods.

A cyclohexanone of formula (III) may be prepared by oxidation of the corresponding cyclic alcohol, using an oxidising agent such as pyridinium chlorochromate, pyridinium dichromate, dipyridine Cr (VI) oxide, sodium hypochlorite, calcium hypochlorite or manganese dioxide.

The leaving group Z in the compounds of formula (IV) may be for example a halogen atom, or a sulphonyloxy group e.g. p-toluenesulphonyloxy or methanesulphonyloxy. Process (B) may be effected in an inert organic solvent, such as an alcohol e.g. methanol or an ether e.g. tetrahydrofuran and at a temperature in the range 0° to 150° C. Compounds of formula (IV) may be obtained by reacting a hydrazine of formula (II) with an appropriately substituted cyclohexanone compound. When Z is acyloxy or sulphonyloxy this may be prepared from a compound (IV) wherein Z is hydroxy, using standard procedures.

Suitable acylating and sulphonylating agents which may be used in process (C) include carboxylic and sulphonic acid chlorides (e.g. acetyl chloride or methanesulphonylchloride) alkyl esters, activated esters and symmetrical and mixed anhydrides. The reaction may be carried out in an organic solvent such as a haloalkane (e.g. dichloromethane), an amide (e.g. N,N-dimethylformamide; an ether (e.g. tetrahydrofuran) or a tertiary amine such as pyridine. In general a base will also be used, e.g. triethylamine, dimethylaminopyridine, or an alkali metal carbonate or bicarbonate. The reaction may be effected at a temperature in the range of -10° to 100° C.

Compounds of formula (V) may be prepared by methods analogous to processes (A) and (B) hereinbefore described. Alternatively a compound of formula (V) may be obtained by subjecting a compound of formula (I) wherein R¹ is nitro to reduction, e.g. by catalytic hydrogenation.

It is well known in the chemical art that hydrolysis of a nitrile initially results in an amide, which can be further hydrolysed to an acid. It will therefore be appreciated that the precise product of process (Di) will depend upon the reaction conditions chosen for the hydrolysis. To obtain a compound wherein R¹ represents H₂NCO— the hydrolysis is preferably effected using hydrogen peroxide in the presence of an alkali hydroxide e.g. sodium hydroxide, in a solvent such as an alcohol e.g. methanol. Other suitable means of hydrolysis include acetic acid and BF₃; or formic acid and hydrobromic or hydrochloric acid. To prepare a compound wherein R¹ represents —COOH acid or base catalysed hydrolysis may be used.

Process (Dii) may be effected by reacting a compound of formula (I) wherein R¹ is —CO₂H with an amine HNR²R³, in the presence of a coupling agent e.g. dicyclohexylcarbodiimide or N,N'-carbonyldiimidazole. Alternatively the carboxylic acid starting material may first be reacted to form an activated derivative of the carboxyl group, for example an acid chloride, acid anhydride or activated ester, which is then reacted directly with an amine HNR²R³. The carboxylic acid may also be activated in situ for example by treating with hexamethylphosphorotriamide.

Alkylation according to process (Diii) may be effected by reacting an amine of formula (I) with an acylating agent, for example an anhydride, such as acetic or propionic anhydride, to form an intermediate in which one of R² or R³ is —C(O)C₁₋₆alkyl, followed by reduction of said interme-

diate to give the desired product. Other reagents and conditions will be apparent to those skilled in the art.

Cleavage according to process (Div) may be effected by reduction, using methods well known in the art.

It will be appreciated that in many of the above reactions it will be necessary to protect the group —NR²R³ when one or both of the groups R² and R³ represent hydrogen. Suitable N-protecting groups are well-known in the art and include for example acyl groups such as acetyl, trifluoroacetyl, benzoyl, methoxycarbonyl, t-butoxycarbonyl, benzyloxycarbonyl or phthaloyl; and aralkyl groups such as benzyl, diphenylmethyl or triphenylmethyl. When R² and R³ both represent hydrogen the nitrogen atom is preferably protected as the phthalimide. The protecting groups should be easily removable at the end of the reaction sequence. N-deprotection may be effected by conventional methods, for example a phthaloyl group may be removed by reaction with hydrazine; an acyl group such as benzoyl may be cleaved by hydrolysis and an aralkyl group such as benzyl may be cleaved by hydrogenolysis.

When a compound of formula (I) is obtained as a mixture of enantiomers these may be separated by conventional methods, for example by reaction of the mixture with a suitable optically active acid such as d-tartaric acid, l-malic acid, l-mandelic acid, l-gulonic acid or 2,3:4,6-di-O-isopropylidene-keto-L-gulonic acid to give two diastereoisomeric salts which may be separated e.g. by crystallisation.

Alternatively mixtures of enantiomers may be separated by chromatography, for example on a chiral HPLC column.

Compounds of formula (I) have been found to be agonists and partial agonists at 5HT₁-like receptors and are expected to have utility in the treatment and/or prophylaxis of migraine, and other conditions associated with cephalic pain.

For use in medicine, the compounds of the present invention are usually administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a novel compound of formula (I) or a physiologically acceptable salt thereof and a physiologically acceptable carrier.

The compounds of formula (I) may be administered by any convenient method, for example by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) and their physiologically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or physiologically acceptable salt in a suitable liquid carrier(s) for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example

aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or physiologically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or a physiologically acceptable salt thereof calculated as the free base.

The physiologically acceptable compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 500 mg, preferably between 10 mg and 400 mg, e.g. between 10 and 250 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of the compound of the formula (I) or a physiologically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

BIOLOGICAL DATA

5-HT₁-like Receptor Screen

Dog Saphenous Vein

Helicoids of dog saphenous vein were set up at 37° C. in modified Krebs solution at a resting force of 10 mN. The solution also contained 1 μmol/l each of ketanserin prazosin, atropine and mepyramine, 6 μmol/l cocaine and 200 μmol/l ascorbate. Nearly isometric contractions were measured with force transducers on a polygraph. The tissues were exposed twice to 5-hydroxytryptamine (5-HT) 2 μmol/l followed by washes. A cumulative concentration-effect curve was

determined, followed by a curve to 5-HT in the presence of the highest used concentration of test compound. Contractions caused by the test compound were compared with those caused by 5-HT. The intrinsic activity of the test compound was calculated as the ratio of the maximum test compound-induced effect over the effect caused by 2 μmol/l 5-HT. The EC₅₀ of the test compound was estimated from the corresponding effect curve. When appropriate equilibrium dissociation constants K_D were estimated by the method of Marano & Kaumann (1976, *J. Pharmacol. Exp. Ther.* 193, 518-525).

In this screen the compounds of Examples 2, 4, 5, 6, 9, 10, 11, 13, 17, 18, 21 and 24 had EC₅₀'s in the range 0.1 to 15 μmol.

RABBIT BASILAR ARTERY

Methods

Experiments were performed in intracranial arteries from rabbit isolated basilar artery in a similar method to one described previously (Parsons and Whalley, 1989, *Eur J Pharmacol* 174, 189-196).

In brief, rabbits were killed by overdose with anaesthetic (sodium pentobarbitone). The whole brain was quickly removed and immersed in ice cold modified Krebs's solution and the basilar artery removed with the aid of a dissecting microscope. The Krebs solution was of the following composition (mM) Na⁺ (120); K⁺ (5); Ca²⁺ (2.25); Mg²⁺ (0.5); Cl⁻ (98.5); SO₄²⁻ (1); EDTA (0.04), equilibrated with 95% O₂/5% CO₂. The endothelium was removed by a gentle rubbing of the lumen with a fine metal wire. Arteries were then cut into ring segments (ca 4-5 mm wide) and set up for recording of isometric tension in 50 ml tissue baths in modified Krebs solution with the additional supplement of (mM): Na²⁺ (20); fumarate (10); pyruvate (5); L-glutamate (5) and glucose (10). The arteries were then placed under a resting force of 3-4 mN maintained at 37° C. and the solution bubbled with 95% O₂/5% CO₂.

After tests for initial reactivity with 90 mM KCl depolarising solution and for lack of acetylcholine-induced relaxation of 5-HT (10 mM) precontraction, cumulative concentration-effect curves (2 nM-60 mM) to 5-HT were constructed in the presence of ascorbate 200 mM, cocaine 6 mM, indomethacin 2.8 mM, ketanserin 1 μM and prazosin 1 mM.

Following a 45-60 min wash period, cumulative concentration-effect curves to the test compounds or 5-HT (as a time match control) were constructed in the presence of ascorbate, indomethacin, cocaine, ketanserin and prazosin.

In this screen the compounds of Example 2, 5, 6, 15, 17, 24, 25, 26, 28 and 29 had EC₅₀'s in the range 0.04 to 15.

EXAMPLE 1

3-Amino-6-cyano-1,2,3,4-tetrahydrocarbazole hydrochloride

A solution of 4-aminocyclohexanol hydrochloride (6.08 g, 0.04 mole) in water (60 ml) was brought to pH 8 with aqueous sodium bicarbonate solution. N-carbethoxyphthalimide (8.76 g, 0.04 mole) was added followed by tetrahydrofuran (until homogenous solution was obtained). The clear solution was stirred at room temperature overnight. During this time a white solid was precipitated. The tetrahydrofuran was removed in vacuo and the remaining aqueous solution was extracted with ethyl acetate until the

solution was clear. The ethyl acetate extracts were combined, washed with water, dried ($MgSO_4$) and concentrated to give 4-phthalimido cyclohexanol as a white solid (7.1 g).

A solution of 4-phthalimido cyclohexanol (7.1 g, 0.029 mole) in dichloromethane (250 ml) was treated with pyridinium chlorochromate (8.6 g, 0.04 mole) and the resulting dark mixture was stirred at room temperature overnight. Diethyl ether (50 ml) was added and the mixture filtered through kieselguhr. The filtrate was concentrated in vacuo and the residue purified by column chromatography (SiO_2 ; $CHCl_3/EtOAc$) to give 4-phthalimido cyclohexanone as a white solid (6.4 g).

4-Cyanophenyl hydrazine hydrochloride (4.41 g, 0.026 mole) was dissolved in acetic acid (100 ml) and sodium acetate (2 g) was added. 4-Phthalimido cyclohexanone (6.4 g, 0.026 mole) was added and the mixture heated under reflux overnight. The solvent was removed in vacuo and the residue triturated with methanol to give 3-phthalimido-6-cyano-1,2,3,4-tetrahydrocarbazole as a beige solid, (5.3 g).

A suspension of the above product (1 g) in ethanol (40 ml) was treated with hydrazine in water (10 ml). The reaction mixture was stirred at room temperature overnight during which time the reactants dissolved. The solvent was removed in vacuo and the residue partitioned between aqueous potassium carbonate and ethyl acetate. The ethyl acetate solution was washed with water, dried and concentrated in vacuo to give 3-amino-6-cyano-1,2,3,4-tetrahydrocarbazole as a beige solid (500 mg). This product was converted into the hydrochloride salt to give the title compound, mp 289° C. (dec).

1H NMR [250 MHz, CD_3OD] δ 1.98–2.18 (1H, m), 2.25–2.40 (1H, m), 2.77 (1H, dd), 2.98 (2H, m), 3.22 (1H, dd), 3.68 (1H, m), 7.34 (1H, d), 7.43 (1H, d), 7.82 (1H, s).

EXAMPLE 2

3-Amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride

The product of Example 1 (400 mg) was dissolved in tetrahydrofuran, and di-*t*-butyl dicarbonate (500 mg) was added. The mixture was stirred at room temperature overnight. The solvent was removed in vacuo and the residue purified by column chromatography (SiO_2 ; $CHCl_3/EtOAc$) to give 3-*t*-butyloxycarbonylamino-6-cyano-1,2,3,4-tetrahydrocarbazole (40 mg).

A mixture of the above product nitrile (440 mg), aqueous hydrogen peroxide (30%, 0.5 ml) and sodium hydroxide (aq) (20%, 0.5 ml) in methanol (25 ml) was stirred at room temperature overnight. Sodium metabisulphite (100 mg) was added and the solvent removed in vacuo. The residue was dissolved in ethyl acetate and the ethyl acetate layer was separated, dried and concentrated in vacuo to give a gummy solid which was purified by column chromatography (SiO_2 ; $CHCl_3/EtOAc$) to give 3-*t*-butyloxycarbonylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole as a white solid (400 mg), mp 270° C. (dec).

The above product (400 mg, 0.0012 mole) was dissolved in dioxan (100 ml) and HCl gas was bubbled through the solution for 20 minutes. During this time a white solid was precipitated. Excess hydrogen chloride was swept from the solution by bubbling through N_2 , and the solid product, 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride was collected by filtration, washed with diethyl ether and dried to give the title compound as a white solid (300 mg), m.p. 270 (dec).

1H NMR [250 MHz, $DMSO-d_6$] δ 1.96 (1H, m), 2.16–2.30 (1H, m), 2.74 (1H, dd), 2.85 (2H, m), 3.12 (1H,

dd), 1 signal obscured by H_2O at ca. 3.6, 7.08 (1H, brd.s), 7.27 (1H, d), 7.61 (1H, d), 7.87 (1H, brd.s), 7.99 (1H, s), 8.39 (3H, brd.s).

EXAMPLE 3

3-Amino-6-methoxy-1,2,3,4-tetrahydrocarbazole hydrochloride

Reaction of 4-methoxyphenyl hydrazine hydrochloride (0.87 g, 5.0 mmol) with 4-phthalimido-cyclohexanone (1.22 g, 5.0 mmol) in ethanol (20 ml) heated under reflux for 2 hr, followed by cooling and removal of the precipitated solid by filtration gave 3-phthalimido-6-methoxy-1,2,3,4-tetrahydrocarbazole (1.62 g).

The above product (1.57 g, 4.5 mmol) was suspended in ethanol (100 ml) and treated with hydrazine hydrate (23 ml) while stirring at room temperature. After 30 min, the solvent was removed in vacuo and the residue was partitioned between K_2CO_3 (aq) and $EtOAc$. The latter layer was separated, washed with water, dried ($MgSO_4$) and evaporated to dryness. This residue was dissolved in ethanol and treated with ethereal HCl until cloudy, then left to stand overnight to yield the title compound (0.95 g) mp >250° C. 1H NMR [250 MHz, $DMSO-d_6$] δ 1.81–2.02 (1H, m), 2.10–2.28 (1H, m), 2.65 (1H, dd), 2.82 (2H, m), 3.02 (1H, dd), 1 signal obscured by H_2O at ca. 3.5, 3.74 (3H, s), 6.66 (1H, d), 6.84 (1H, d), 7.14 (1H, d), 8.16 (3H, brd.s).

EXAMPLE 4

3-Amino-6-bromo-1,2,3,4-tetrahydrocarbazole hydrochloride

Reaction of 4-bromophenylhydrazine hydrochloride (4.0 g, 18.1 mmol) with 4-phthalimido-cyclohexanone (4.39 g, 18.1 mmol) in refluxing *n*-butanol for 20 min, followed by cooling, filtration, and evaporation of the filtrate to dryness yielded 3-phthalimido-6-bromo-1,2,3,4-tetrahydrocarbazole as an orange solid (7.45 g).

This product (0.33 g, 0.83 mmol) was suspended in ethanol (13 ml) and treated with hydrazine hydrate (3 ml), then left to stir at room temperature overnight. The solid precipitate was filtered off, and the filtrate was evaporated to dryness and partitioned between K_2CO_3 (aq) and ethylacetate. After separation of the organic layer, washing with water, drying ($MgSO_4$) and evaporation to dryness, the residue was dissolved in $MeOH$ and treated with HCl gas. Solvent was removed in vacuo and the residue was crystallized from ethanol/ethyl acetate to yield the title compound as a cream-coloured solid (0.15 g), mp 308°–310° C. 1H NMR [250 MHz, $DMSO-d_6$] δ 1.91 (1H, m), 2.10–2.26 (1H, m), 2.63 (1H, dd), 2.84 (2H, m), 3.04 (1H, dd), 3.50 (1H, m), 7.12 (1H, d), 7.24 (1H, d), 7.55 (1H, s), 8.15 (2H, brd.s), 11.12 (1H, s).

EXAMPLE 5

3-Amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole

4-Carboxamidophenylhydrazine hydrochloride (2.87 g) and 4-phthalimidocyclohexanone (3.00 g) were mixed in acetic acid and the mixture was heated under reflux for 2 hr. After cooling, the mixture was neutralized using aq. potassium carbonate solution, and the yellow solid thus obtained was filtered, washed with water, and dried. Purification by column chromatography (SiO_2 ; $CHCl_3/CH_3OH$) gave 3-phthalimido-6-carboxamido-1,2,3,4-tetrahydrocarbazole (2.8 g).

The above product (1.0 g) was suspended in ethanol (10 ml) and hydrazine hydrate (5 ml) was added. A clear solution

was obtained, and the mixture was left to stir overnight, to yield a precipitate. The whole mixture was evaporated to dryness, washed with aq. K_2CO_3 solution, and water, to leave the title compound 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (0.44 g), as the monohydrate, mp. 146°-148° C.

1H NMR [250 MHz, DMSO-d₆] δ 1.49-1.77 (1H,m), 1.83-2.03 (1H,m), 2.17-2.40 (1H,m), 2.62-2.80 (2H,m), 2.90 (1H, dd), 1 signal obscured by H_2O at ca. 3.1, 7.03 (1H, brd.s), 7.18 (1H,d), 7.58 (1H, d), 7.83 (1H,brd.s), 7.98 (1H, s).

EXAMPLE 6

(+)- and (-)-3-Amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride

Method 1

(+)-3-t-Butyloxycarbonylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole was separated into its enantiomers using chiral HPLC: (chiralcel OD 4.6 mm column, eluting with hexane/ethanol 85:15). The (+)-enantiomer was collected first and had mp=150°-152° C. and $[\alpha]_D^{25}=+70.1$ (in methanol, 0.41% w/v). The (-)-enantiomer had mp=150°-152° C. and $[\alpha]_D^{25}=-79.4$ (in methanol, 0.40% w/v). The (+)-enantiomer was converted to the parent amine hydrochloride by treating with HCl gas in dioxane, to furnish the (+)-enantiomer of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride, mp=248°-251° C., $[\alpha]_D^{25}=+26.2$ (in methanol, 0.50% w/v). The (-)-enantiomer of 3-t-butyloxycarbonylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole was similarly converted into the (-)-enantiomer of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride, mp=248°-251° C., $[\alpha]_D^{25}=-28.6$ (in methanol, 0.50% w/v).

Method 2

(±)-6-carboxamido-3-amino-1,2,3,4-tetrahydrocarbazole was treated with one equivalent of 2,3,4,6-di-O-isopropylidene-2-keto-L-gulonic acid in methanol to give the salt of the (+)-enantiomer, in 38% yield (with respect to racemate) and 84% enantiomeric excess (ee). This material was recrystallized twice from methanol to give the salt of the (+)-enantiomer in 25% overall yield (with respect to racemate), and >98% ee. This product was converted to the hydrochloride salt first by treatment with aqueous alkali, and the precipitated free base treated with 2M aq. HCl in ethanol, to give (+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride.

EXAMPLE 7

3-Amino-6-methyl-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (2.16 g) with 4-tolylhydrazine hydrochloride (1.41 g), and subsequent deprotection of the product by the method described in example 3, gave the title compound free base, which was converted to the oxalate salt (0.23 g), mp 272°-5° C.

EXAMPLE 8

3-Amino-6-ethoxycarbonyl-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (0.37 g) with 4-ethoxycarbonylphenylhydrazine hydrochloride (0.33 g), and subsequent deprotection by the method described in example 3, gave the title compound free base. This was converted to the oxalate salt (0.11 g), mp 230°-240° C. dec.

EXAMPLE 9

3-Amino-6-(N-methyl carboxamido)-1,2,3,4-tetrahydrocarbazole hemioxalate

Reaction of 4-phthalimidocyclohexanone (1.20 g) with 4-(N-methylcarboxamido)-phenylhydrazine hydrochloride (1.00 g), and subsequent deprotection by the method described in example 3, gave the title compound free base. This was converted to the hemioxalate salt (0.22 g), mp 227° C. dec.

EXAMPLE 10

3-Amino-6-cyanomethyl-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (1.05 g) with 4-cyanomethylphenylhydrazine hydrochloride (0.79 g), and subsequent deprotection by the method described in example 3, gave the title compound free base, which was treated with oxalic acid to give the oxalate salt (0.49 g), mp 219°-224° C. dec.

EXAMPLE 11

3-Amino-6-(N-methylsulphonamidomethyl)-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (0.42 g) with 4-(N-methylsulphonamidomethyl) phenyl hydrazine hydrochloride (0.44 g), and subsequent deprotection by the method described in example 3, gave the title compound free base. This was treated with oxalic acid to give the oxalate salt (0.15 g), mp 218°-222° C. dec.

EXAMPLE 12

3-Amino-6-chloro-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (6.7 g) with 4-chlorophenyl hydrazine hydrochloride (4.93 g), and subsequent deprotection by the method described in example 3, gave the title compound free base, which was treated with oxalic acid to give the oxalate salt (2.77 g), dec >220° C.

EXAMPLE 13

3-Amino-6-trifluoromethyl-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (1.14 g) with 4-trifluoromethyl phenyl hydrazine hydrochloride (1.00 g), and subsequent deprotection by the method described in example 3, gave the title compound free base (0.40 g). This was treated with oxalic acid to give the oxalate salt, mp 212°-213° C.

EXAMPLE 14

3-Amino-6-n-butyloxy-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (1.12 g) with 4-n-butyloxyphenyl hydrazine hydrochloride (1.00 g) and subsequent deprotection by the method described in example 3, gave the title compound free base. This was treated with oxalic acid to give the oxalate salt (0.47 g), mp 227°-229° C.

EXAMPLE 15

3-Amino-6-sulphonamido-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (1.00 g) with 4-sulphonamido phenyl hydrazine hydrochloride (1.08 g).

13

and subsequent deprotection by the method described in example 3, gave the title compound free base. This was converted to the oxalate salt (0.090 g), dec >200° C.

EXAMPLE 16

3-Amino-6-Nitro-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimidocyclohexanone (1.28 g) with 4-nitrophenyl hydrazine hydrochloride (1.00 g), and subsequent deprotection by the method described in example 3, gave the title compound free base, which was converted to the oxalate salt (0.25 g), mp 275°-277° C.

EXAMPLE 17

3-Amino-6-(N,N-dimethyl carboxamido)-1,2,3,4-tetrahydrocarbazole hemioxalate

3-Amino-6-ethoxycarbonyl-1,2,3,4-tetrahydrocarbazole (260 mg, 1.0 mmol) was suspended in dry THF (5 ml), and di-tert butyl dicarbonate (320 mg, 1.5 mmol) was added. A clear solution was obtained after 10 min. The mixture was left to stir for 20 hr, then the solvent was removed, and the residue was dissolved in ethyl acetate, washed with aqueous sodium bicarbonate solution, and dried (MgSO₄). After removal of ethyl acetate, the residue was triturated with ether and hexane to give 3-t-butylloxycarbonylamino-6-ethoxycarbonyl-1,2,3,4-tetrahydrocarbazole (310 mg).

The above product (556 mg, 1.55 mmol) was suspended in ethanol (5 ml) and 2M NaOH (3 ml) was added. The mixture was heated under reflux for 1 hr and evaporated to dryness. The residue was dissolved in water and neutralized with acetic acid, when 3-t-butylloxycarbonylamino-6-carboxy-1,2,3,4-tetrahydrocarbazole precipitated out as a white solid (425 mg). A solution of the above product (400 mg, 1.2 mmol) in dry DMF (8 ml) was treated with hexamethyl phosphorous triamide (198 mg, 1.2 mmol), and cooled to -10° C. Dimethylamine gas was bubbled into the mixture for 10 min at this temperature, then carbon tetrachloride (185 mg, 1.2 mmol) was added dropwise, under an atmosphere of nitrogen. The mixture was left to stir at room temperature for 1 hr, then the DMF was removed in vacuo. The residue was partitioned between ethyl acetate and water, and the organic layer was washed with saturated aqueous sodium bicarbonate solution, then brine, and dried (MgSO₄). The solvent was removed in vacuo, and the residual oil was triturated with ether and hexane and the solid recrystallized from toluene to give 3-t-butylloxycarbonylamino-6-(N,N-dimethyl carboxamido)-1,2,3,4-tetrahydrocarbazole (198 mg).

This product (180 mg, 0.53 mmol) was dissolved in dioxane (5 ml) and HCl gas was bubbled through, to precipitate an oil. The solvent was removed in vacuo, and the oil was dissolved in water, and treated with K₂CO₃ solution to bring the pH to 12. The amine free base was then extracted with ethyl acetate, dried (MgSO₄) and evaporated to dryness. The resulting oil was dissolved in methanol and treated with oxalic acid to provide the title compound as a pale pink solid (140 mg) mp=190°-195° C.

EXAMPLE 18

3-Amino-6-(piperidin-1-yl carbonyl)-1,2,3,4-tetrahydrocarbazole hydrochloride

Reaction of 3-t-butylloxycarbonylamino-6-carboxy-1,2,3,4-tetrahydrocarbazole (175 mg) with piperidine and the product subsequently deprotected by the method described for Example 17, gave the title compound, mp=246°-249° C. (55 mg).

14

EXAMPLE 19

3-Amino-6-(pyrrolidin-1-yl carbonyl)-1,2,3,4-tetrahydrocarbazole hydrochloride

Reaction of 3-t-butylloxycarbonylamino-6-carboxy-1,2,3,4-tetrahydrocarbazole (140 mg) with pyrrolidine, and the product subsequently deprotected as described for Example 17, gave the title compound, mp=201°-212° C. (81 mg).

EXAMPLE 20

3-Amino-6-(N,N-diethyl carboxamido)-1,2,3,4-tetrahydrocarbazole hydrochloride

Reaction of 3-t-butylloxycarbonylamino-6-carboxy-1,2,3,4-tetrahydrocarbazole (105 mg) with diethylamine, and deprotection of the product, as described for Example 17, gave the title compound, mp 200°-205° C. (50 mg).

EXAMPLE 21

3-Amino-6-(acetamido)-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of 4-phthalimido cyclohexanone (1.2 g) with 4-(acetamido)-phenyl hydrazine hydrochloride (1.0 g), and subsequent deprotection of the product by the method described in example 3, gave the title compound free base (570 mg). A portion of this product (50 mg) was treated with oxalic acid in methanol to give the oxalate salt, which softens >170° C. (38 mg).

EXAMPLE 22

3-Amino-6-methanesulphonamido-1,2,3,4-tetrahydrocarbazole oxalate

3-phthalimido-6-nitro-1,2,3,4-tetrahydrocarbazole (4.00 g) was dissolved in hot ethyl acetate (130 ml). To the cooled solution was added raney nickel, and the mixture was hydrogenated at an initial pressure of 39 psi at room temperature for 4 hr. After filtering off the insoluble materials, the filtrate was evaporated to dryness, and extracted twice into 20% aqueous methanol and the extracts combined and reduced in volume to give 3-phthalimido-6-amino-1,2,3,4-tetrahydrocarbazole (0.31 g).

The above product (0.50 g) was dissolved in freshly distilled pyridine (30 ml), and methanesulphonyl chloride (0.28 g) and 4-dimethylaminopyridine (46 mg) were added. The mixture was heated with stirring at 50° C. for 5 hr, and then evaporated to dryness. The residue was dissolved in chloroform, washed with water, brine and aqueous sodium bicarbonate, then dried (MgSO₄), and evaporated to dryness to give a pale yellow solid, which was recrystallized from aqueous ethanol to give 3-phthalimido-6-methanesulphonamido-1,2,3,4-tetrahydrocarbazole (0.27 g).

The above compound was suspended in ethanol (15 ml) and hydrazine hydrate (2.72 g) was added. After stirring for 25 min at room temperature, the mixture was evaporated to dryness, partitioned between water and ethyl acetate, and the aqueous layer re-extracted with ethyl acetate. The organic extracts were combined, washed with water, dried (MgSO₄) and evaporated to give a pale yellow solid. This was dissolved in methanol and treated with oxalic acid (89 mg). Addition of ether resulted in crystallization of the title compound (50 mg), mp 230°-233° C.

EXAMPLE 23

3-Amino-6-carboxamidomethyl-1,2,3,4-tetrahydrocarbazole hydrochloride

3-Amino-6-cyanomethyl-1,2,3,4-tetrahydrocarbazole (2.5 g) and di-t-butyl dicarbonate (3.63 g) were stirred in

THF (56 ml) for 2 hr. The THF was evaporated, and the residue was partitioned between aqueous sodium bicarbonate solution and ethyl acetate. The aqueous phase was re-extracted with ethyl acetate, and the combined organic extracts were washed with water, dried (MgSO₄), and evaporated to dryness to leave a solid which was triturated with ether/hexane (20%) to give 3-t-butylloxycarbonylamino-6-cyanomethyl-1,2,3,4-tetrahydrocarbazole as an off-white solid (3.44 g).

The above product (7.0 g) was dissolved in DMSO (70 ml), and hydrogen peroxide (100 volume, 3.5 ml) was added. After stirring for an hour, further peroxide (8.5 ml) was added, and the mixture was stirred for 2 hr at room temperature. Potassium carbonate (0.84 g) was added, and the mixture was stirred overnight and for a further 20 hr. The reaction mixture was poured into water (500 ml) and the resulting white solid was filtered off, and recrystallized from methanol to give 3-t-butylloxycarbonylamino-6-carboxamidomethyl-1,2,3,4-tetrahydrocarbazole (5.42 g).

The above product (500 mg) was dissolved in dry dioxane (30 ml), and HCl gas was bubbled through for 20 min. The resulting solution and deposited gum were evaporated to dryness, and treated with aqueous potassium carbonate solution. This was extracted with ethyl acetate, and the extracts were combined, dried (MgSO₄) and evaporated to dryness. The residue was dissolved in methanol and treated with excess oxalic acid. Addition of ether led to crystallization of the title compound (250 mg), mp 257°-260° C.

EXAMPLE 24

3-Methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride

4-Cyanophenyl hydrazine hydrochloride (20.2 g) and 4-benzoyloxycyclohexanone (25.9 g) were dissolved in glacial acetic acid (400 ml) and the mixture was heated under reflux for 1.5 hr. After allowing to cool, the mixture was filtered, and the filtrate was evaporated to dryness, and neutralized with aqueous sodium bicarbonate solution to give a solid precipitate, which was purified by chromatography (SiO₂; hexane/ethyl acetate) to give 3-benzoyloxy-6-cyano-1,2,3,4-tetrahydrocarbazole (18 g). This product (11.6 g) was suspended in ethanol (230 ml) and treated with 2.5% aqueous potassium hydroxide solution (120 ml), and heated under reflux for 1 hr. The cooled mixture was neutralized with glacial acetic acid and evaporated to a solid residue, which was washed with water, and dried to give 3-hydroxy-6-cyano-1,2,3,4-tetrahydrocarbazole (6.6 g).

The above product (3.57 g) was dissolved in dry pyridine (35 ml) and treated with tosyl chloride (3.51 g) in dry pyridine (35 ml), and the mixture was stirred at 100° C. for 2 hr. After cooling, the solution was poured into water (500 ml), extracted with ethyl acetate, and the latter extract was washed with 2M HCl, dried (MgSO₄) and evaporated to dryness. Purification by chromatography (SiO₂; hexane/ethyl acetate) gave 3-tosyloxy-6-cyano-1,2,3,4-tetrahydrocarbazole (0.53 g).

This product (0.40 g) was dissolved in 33% methylamine in alcohol (25 ml) and heated at 100° C. in a sealed steel vessel for 1.5 hr. After cooling, the mixture was evaporated to dryness and purified by chromatography (SiO₂; chloroform/methanol) to give 3-methylamino-6-cyano-1,2,3,4-tetrahydrocarbazole (0.13 g).

The above product (0.12 g) was dissolved in THF (10 ml) and reacted with di-tert-butyl dicarbonate (0.36 g) in THF (3 ml) at room temperature overnight. The reaction mixture was evaporated to dryness, partitioned between 2M sodium

bicarbonate solution and ethyl acetate, and the organic extract dried and evaporated to give a white solid. This was triturated with ether/hexane to give 3-t-butylloxycarbonylmethyl amino-6-cyano-1,2,3,4-tetrahydrocarbazole (0.14 g).

This product (0.14 g) was dissolved in methanol (15 ml) and treated with a mixture of 20% aqueous sodium hydroxide (0.20 ml) and 30% hydrogen peroxide (0.20 ml), and the whole mixture was stirred at room temperature overnight. Sodium metabisulphite (38 mg) was added, and the solution was evaporated to dryness, and chromatographed (SiO₂; chloroform/10% NH₄OH in methanol) to give 3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (0.12 g). The above compound (0.11 g) was dissolved in methanol (10 ml), and treated with 3M hydrochloric acid at room temperature. The mixture was evaporated to dryness, azeotroping with ethanol to give a solid, which was recrystallized from methanol/ether to give the title compound, mp 327°-328° C. (80 mg).

¹H NMR [250 MHz, MeOH-d⁴] δ 1.98-2.20 (1H, m), 2.29-2.49 (1H, m), 2.75-2.90 (5H, s+m), 2.90-3.09 (2H, m), 3.52-3.69 (1H, m), 7.31 (1H, d), 7.63 (1H, d), 8.05 (1H, s).

EXAMPLE 25

3-Ethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate

1,4-Cyclohexanedione mono-2,2'-dimethyl trimethylene ketal (2.00 g) was mixed with anhydrous ethylamine (10.0 g) and benzene (10 ml), and the mixture was cooled to 5° C. A solution of titanium tetrachloride (0.95 g) in benzene (10 ml) was added, dropwise, then the mixture was stirred at room temperature for 1 hr. The mixture was filtered, and evaporated to dryness to give an oil, which was dissolved in ethanol (30 ml). To this solution was added palladium-on-carbon catalyst (100 mg), and the mixture was hydrogenated at 50 psi pressure overnight. The catalyst was filtered off and the ethanol evaporated to leave 4-ethylaminocyclohexanone 2,2'-dimethyl trimethylene ketal as an oil (2.0 g).

This compound (0.80 g) was dissolved in formic acid (20 ml) and the solution was heated to 90° C. for 1 hr. Formic acid was evaporated, and the residue was partitioned between chloroform and 1M hydrochloric acid. The aqueous layer was evaporated to dryness to give 4-ethylaminocyclohexanone (0.40 g).

A mixture of the above product (0.40 g) and 4-carboxamidophenyl hydrazine hydrochloride (0.60 g) in glacial acetic acid (20 ml) was heated under reflux for 1 hr. The acid was evaporated in vacuo to an oil, which was purified by chromatography (SiO₂; CHCl₃/10% NH₃ in MeOH) to give an oil (0.50 g). Part of this product (150 mg) was dissolved in methanol and treated with oxalic acid. The solution was treated with ether to give the title compound as a crystalline solid, mp 165°-170° C. (100 mg).

¹H NMR [250 MHz, DMSO-d⁶] δ 1.25 (3H, t), 1.81-2.05 (1H, m), 2.20-2.38 (1H, m), 2.61-2.79 (1H, m), 2.79-2.94 (2H, m), 2.98-3.28 (3H, dd+s), 3.41-3.60 (1H, m), 7.08 (1H, brd. s), 7.28 (1H, d), 7.60 (1H, d), 7.82 (1H, brd. s), 8.00 (1H, s), 11.12 (1H, s).

EXAMPLE 26

3-n-Propylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate

Propylamine (1.81 g) was dissolved in methanol (12.5 ml), and 1.5M HCl in methanol (6.6 ml) was added with

17

cooling. After 1 min, 1,4-cyclohexanedione mono-2',2'-dimethyl trimethylene ketal (1.0 g) was added, followed after a further 10 min by sodium cyanoborohydride (0.23 g). The mixture was stirred at room temperature for 3 days. The resulting mixture was filtered, and the filtrate was evaporated and treated with 1M HCl (10 ml) with cooling. The residue was digested to form a solution, which was washed with ether, basified to pH 12 with aqueous sodium hydroxide, and extracted with dichloromethane. This extract was washed with saturated aqueous sodium bicarbonate solution, dried (MgSO₄), and evaporated to dryness. Chromatography (SiO₂; chloroform/methanol/ammonia) gave 4-n-propylamino cyclohexanone 2',2'-dimethyl trimethylene ketal (0.72 g).

This product (0.66 g) was hydrolyzed to the ketone, which was reacted with 4-carboxamidophenyl hydrazine hydrochloride and converted to the oxalate salt as described for Example 25, to give the title compound (0.44 g), mp >168° C. dec.

EXAMPLE 27

3-i-Propylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of isopropylamine (9.54 g) with 1,4-cyclohexanedione mono-2',2'-dimethyl trimethylene ketal (2.0 g) by the method described for Example 25 gave 4-i-propylamino cyclohexanone 2',2'-dimethyl trimethylene ketal (2.38 g). This product (0.66 g) was hydrolyzed and reacted with 4-carboxamidophenyl hydrazine hydrochloride (0.45 g), and the mixture worked up as described above to give the title compound free base (0.34 g). This was converted to the oxalate, mp >235° C. dec.

EXAMPLE 28

3-Dimethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate

Dimethylamine (10.0 g) was reacted with 1,4-cyclohexanedione mono-2',2'-dimethyl trimethylene ketal (2.0 g) by the method described for Example 25 to give 4-dimethylaminocyclohexanone-2',2'-dimethyl trimethylene ketal (0.72 g). This product (0.72 g) was hydrolyzed and reacted with 4-carboxamidophenyl hydrazine hydrochloride (0.47 g) and the product converted to the oxalate salt as described above to give the title compound (0.20 g), mp 99°-101° C.

¹H NMR [250 MHz, DMSO-d₆] δ 1.83-2.05 (1H, m), 2.27-2.40 (1H, m), 2.72-3.00 (9H, 2m+s), 3.07-3.22 (1H, dd), 3.50-3.68 (1H, m), 7.05 (1H, brd. s), 7.27 (1H, d), 7.60 (1H, d), 7.81 (1H, brd. s), 8.00 (1H, s), 11.11 (1H, s).

EXAMPLE 29

3-Benzylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of benzylamine (0.59 g) with 1,4-cyclohexanedione mono-2',2'-dimethyl trimethylene ketal (1.0 g) and subsequent reduction of the imine with sodium cyanoborohydride by the method described for Example 26 gave 4-benzylaminocyclohexanone 2',2'-dimethyl trimethylene ketal (0.54 g). This product (0.52 g) was reacted with 4-carboxamidophenyl hydrazine hydrochloride (0.34 g) and the product treated with oxalic acid to give the title compound, mp >190° C. dec (0.11 g).

18

EXAMPLE 30

3-Pyrrolidinyl-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of pyrrolidine (15.6 g) with 1,4-cyclohexanedione mono-2',2'-dimethyl trimethylene ketal (2.0 g) by the method described for Example 25 gave 4-pyrrolidinyl-cyclohexanone-2',2'-dimethyl trimethylene ketal (1.74 g). This product (1.70 g) was hydrolyzed and reacted with 4-carboxamidophenyl hydrazine hydrochloride (1.70 g) and the product treated with oxalic acid as described above to give the title compound (32 mg), mp >190° C. dec.

EXAMPLE 31

3-(N-methyl ethylamino)-6-carboxamido-1,2,3,4-tetrahydrocarbazole oxalate

Reaction of N-methyl ethylamine (13.0 g) with 1,4-cyclohexanedione mono-2',2'-dimethyl trimethylene ketal (2.0 g) by the method described for Example 25 gave 4-(N-methyl ethylamino)-cyclohexanone-2',2'-dimethyl trimethylene ketal (1.71 g). This product (0.86 g) was hydrolyzed and reacted with 4-carboxamidophenyl hydrazine hydrochloride (0.52 g) and worked up as described above to give the title compound (76 mg), mp >130° C. dec.

EXAMPLE 32

3-Amino-6-(2-carboxamidoethyl)-1,2,3,4-tetrahydrocarbazole oxalate

A mixture of 4-nitrocinnamic acid (22.5 g) and thionyl chloride (20.8 g) in benzene (160 ml) was heated under reflux for 4 h. The resulting orange mixture was filtered and evaporated to give the acid chloride (22.9 g). This was dissolved in dichloromethane (1 l), and ammonia gas was bubbled through, with cooling to below 20° C. and stirring. Solvent was removed in vacuo, and the residue was dissolved in hot ethyl acetate and the solution was shaken with 1M sodium hydroxide solution. The resulting organic phase was dried, filtered and evaporated to leave a residue which was slurried with ethyl acetate to give 4-nitro cinnamide as a crystalline solid (18.6 g). This product (18.6 g) was suspended in ethanol (1 l) and hydrogenated using Pd-C catalyst (6.6 g) at 50 psi for 1 h. The resulting mixture was filtered and evaporated to dryness, providing 4-aminophenyl propionamide (17.1 g).

Concentrated hydrochloric acid (4 ml) was added slowly, with cooling and stirring to 4-aminophenyl propionamide (0.80 g), maintaining the temperature below 5° C. To this slurry was added a solution of sodium nitrite (0.37 g) in water (2 ml), dropwise over 15 min, followed by stirring for a further 15 min. The turbid solution thus formed was added portionwise to a cooled, stirred solution of stannous chloride (2.19 g) in conclusion. HCl (4 ml), and the resulting mixture was stirred for 1 h. After filtering, the solution was reduced in volume until an inorganic precipitate formed. This was filtered off, and the filtrate was evaporated to dryness. The residual gum was crystallized from acetic acid to give crude 4-hydrazinophenyl propionamide hydrochloride (1.05 g).

A mixture of the above product (1.05 g) and 4-phthalimido-cyclohexanone (1.18 g) in acetic acid (40 ml) was heated under reflux for 40 min. The solvent was removed in vacuo and the residue was partitioned between aqueous potassium carbonate solution and ethyl acetate. The organic phase was dried (MgSO₄) and evaporated to dryness, and the residue was chromatographed (SiO₂; CH₂Cl₂/MeOH) to give 3-phthalimido-6-carboxamidoethyl-1,2,3,4-tetrahydrocarbazole (0.70 g).

This product (0.70 g) was dissolved in methanol (50 ml), treated with hydrazine hydrate (1.0 ml), and heated under reflux for 30 min. The mixture was evaporated to dryness then partitioned between ethyl acetate and aqueous potassium carbonate solution. The organic phase was dried (MgSO₄) and evaporated to dryness, and the residue was dissolved in ethanol to dryness, and the residue was dissolved in ethanol and treated with oxalic acid (83 mg) in ethanol. A solid was formed, which was recrystallized from ethanol to give the title compound (110 mg). mp 232°-5° C.

Pharmaceutical Formulations

EXAMPLE A

A tablet for oral administration is prepared by combining

	Mg/Tablet
Compound of formula (I)	100
lactose	153
starch	33
crospovidone	12
microcrystalline cellulose	30
magnesium stearate	2
	330 mg

into a 9 mm tablet.

EXAMPLE B

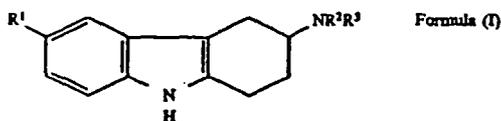
An injection for parenteral administration is prepared from the following

	% w/v
Compound of formula (I)	0.50% (w/v)
1M citric acid	30% (v/v)
sodium hydroxide (qs)	to pH 3.2
water for injection BP	to 100 ml

The compound of formula (I) is dissolved in the citric acid and the pH slowly adjusted to pH 3.2 with the sodium hydroxide solution. The solution is then made up to 100 ml with water, sterilised by filtration and sealed into appropriately sized ampoules and vials.

We claim:

I. A compound of the general formula (I):



wherein:

R¹ is a group $-(CH_2)_nCONR^2R^3$;

n is zero;

R⁵ and R⁶ each independently represent hydrogen, methyl, ethyl or propyl; and

R² and R³ each independently represent hydrogen or C₁₋₆alkyl provided both are not hydrogen;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 wherein R² and R³ each independently represent hydrogen, methyl or ethyl.

3. A compound of claim 2 wherein R⁵ and R⁶ each independently represent hydrogen or methyl.

4. A compound of claim 1, which is selected from

3-n-propylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole;

3-i-propylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole, or a salt thereof.

5. A compound of claim 1, which is selected from

3-(N-(methyl)ethylamino)-6-carboxamido-1,2,3,4-tetrahydrocarbazole;

3-dimethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole;

3-ethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole;

or a pharmaceutically acceptable salt thereof.

6. 3-Benzylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole; or salt thereof.

7. 3-Pyrrolidinyl-6-carboxamido-1,2,3,4-tetrahydrocarbazole, or salt thereof.

8. A pharmaceutical composition comprising a compound of claim 1 or a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier.

9. A pharmaceutical composition comprising a compound of claim 3 or a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier.

10. A method of treatment of a condition wherein a 5-HT₁-like agonist is indicated, which comprises administering to a subject in need thereof an effective amount of a compound of claim 1.

11. A method of claim 10 wherein in a compound of formula (I) R⁵ and R⁶ each independently represent hydrogen and methyl and R¹ and R² each represent hydrogen, methyl or ethyl provided R¹ and R² are not both hydrogen.

* * * * *

United States Patent [19]

Borrett et al.

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[54] PROCESS OF PREPARING ENANTIOMERS OF CARBAZOLE DERIVATIVES

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[56] References Cited

U.S. PATENT DOCUMENTS

4,257,952 3/1981 Mooradian 548/448

FOREIGN PATENT DOCUMENTS

WO93/00086 1/1993 WIPO.

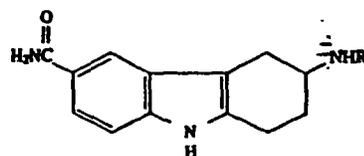
OTHER PUBLICATIONS

Hackzell et al., "Chirality in drug research and design", *Trends in Biotechnology*, vol. 11, pp. 73-74 (1993).

Arianda, "Nonchiral, homochiral and composite chiral drugs", *Trends in Pharmacological Sciences*, vol. 14, pp. 68-75 (1993).

Primary Examiner—Robert W. Ramsuer
Attorney, Agent, or Firm—Nora Stein-Fernandez, William T. King, Edward T. Lentz

[57] ABSTRACT



A (+) or (-) enantiomer of a compound of formula (I) wherein R⁴ is methyl or ethyl, or a salt, solvate or hydrate thereof, processes for preparing said compounds and pharmaceutical compositions containing them. Compounds of formula (+) are 5-HT₁-like agonists.

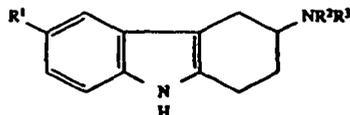
5 Claims, No Drawings

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PROCESS OF PREPARING ENANTIOMERS
OF CARBAZOLE DERIVATIVES

The present invention relates to certain tetrahydrocarbazole derivatives, in particular their enantiomeric forms, processes for preparing them, pharmaceutical compositions containing them and their use in therapy, in particular the treatment of migraine.

International Patent Application WO93/00086 describes compounds of the formula:

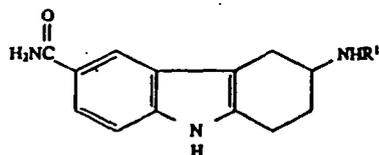


and salts thereof for use in the treatment of conditions wherein a 5-HT₁-like agonist is indicated, in particular migraine.

In the above compounds R¹ represents hydrogen, halogen, trifluoromethyl, nitro, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, arylC₁₋₆alkoxy, -CO₂R⁴, (CH₂)_nCN, (CH₂)_nCONR⁵R⁶, C₁₋₆alkanoylamino(CH₂)_n, or C₁₋₆alkylsulphonylamino(CH₂)_n; R⁴ represents hydrogen, C₁₋₆alkyl or arylC₁₋₆alkyl; R⁵ and R⁶ each independently represent hydrogen, or C₁₋₆alkyl, or R⁵ and R⁶ together with the nitrogen atom to which they are attached form a ring; n represents 0, 1 or 2; and R² and R³ each independently represent hydrogen, C₁₋₆alkyl or benzyl or together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino or hexahydroazepino ring. The carbon atom to which the group NR²R³ is attached (i.e. at position 3 of the tetrahydrocarbazole ring) is an asymmetric carbon atom and hence the compounds exist as optically active enantiomers.

WO93/00086 describes inter alia the preparation of the above compounds wherein R¹ is -C(O)NH₂, one of R² and R³ is hydrogen and the other is methyl or ethyl, viz: 6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (as the hydrochloride salt) and 6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole (as the oxalate salt). Both compounds were obtained only as mixtures of enantiomers.

We have now isolated the individual isomers of the above compounds. Thus, in a first aspect the present invention provides the (+) and (-) enantiomers of a compound of formula (I):



Formula (I)

wherein R¹ is methyl or ethyl, or a salt thereof.

In accordance with convention the (+) and (-) designations indicate the direction of rotation of plane-polarised light by the compounds. The prefix (+) indicates that the isomer is dextrorotatory (also designated d) and the prefix (-) indicates the levorotatory isomer (also designated l). The R and S designations denote the absolute configuration as determined by X-ray crystallography.

The individual compounds of formula (I) provided by the invention may be named as:

R-(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole; (compound A)

2

S-(-)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole; (compound B)

R-(+)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole; (compound C)

S-(-)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole. (compound D)

Salts, solvates and hydrates of the above named compounds are also within the scope of the present invention.

It will be appreciated that for use in medicine a physiologically acceptable salt should be employed. Suitable physiologically acceptable salts will be apparent to those skilled in the art and include for example acid addition salts such as those formed with inorganic acids e.g. hydrochloric, hydrobromic, sulphuric or phosphoric acids and organic acids e.g. succinic, tartaric, malonic, citric, maleic, acetic, fumaric or methanesulphonic acid. Other non-physiologically acceptable salts e.g. oxalates may be used for example in the isolation of enantiomers of formula (I), and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of enantiomers of formula (I) and their salts.

Acids which have more than one carboxyl group e.g. succinic, tartaric, malonic or citric acids may correspondingly react with more than one molecule of an enantiomer (I), for example succinic acid may react with either one or two molecules of (I) to form either a 1:1 salt (succinate) or a 2:1 salt (hemi-succinate). All such salt forms are encompassed by the present invention; in general the 1:1 salt form is preferred.

Specific salts according to the present invention include:

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole L (+)-tartrate salt (1:1),

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole D (-)-tartrate salt (1:1),

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hemisuccinate (2:1),

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole methanesulphonate,

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole succinate (1:1),

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hydrochloride,

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hydrobromide,

(+)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole succinate (1:1),

(+)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole hydrochloride, and

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole camphorsulphonate.

It will be appreciated that an enantiomer according to the present invention for example a (+)-enantiomer, will be substantially free from the corresponding (-) enantiomer, and vice versa. Preferably, a specific enantiomer of the invention will contain less than 10%, e.g. less than 5% and advantageously less than 1% e.g. less than 0.5% of its opposite enantiomer.

In vitro testing (rabbit basilar artery) indicates that for both the methyl and ethyl derivatives of formula (I) the (+) enantiomer is more active than the corresponding (-) enantiomer. The above-named (+)-enantiomers are therefore preferred compounds of the invention.

Enantiomers of formula (I) may be prepared by standard methods, for example:

(a) Separation of an enantiomeric mixture of a compound of formula (I) or a derivative thereof by chromatography e.g. on a chiral HPLC column.

(b) Separation of diastereoisomers of a chiral derivative (e.g. a chiral salt) of a compound of formula (I) e.g. by crystallisation, or by chromatography.

(c) Alkylation of a (+) or (-) enantiomer of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole or a salt thereof, followed if necessary or desired by converting a derivative of compound (I) so obtained into a compound of formula (I) itself or a different derivative thereof e.g. by removal of any N-protecting group or facilitating group, conversion of a salt into the free base, and/or salt formation.

Separation according to process (a) is generally facilitated by first introducing a readily removable group into the alkylamino moiety of the compound of formula (I). Suitable removable facilitating groups include those commonly used as N-protecting groups e.g. an alkoxycarbonyl group such as t-butyloxycarbonyl or an aralkoxycarbonyl group such as benzyloxycarbonyl, which groups may be introduced by reaction with for example a di-alkyl-dicarbonate such as di-t-butyl-dicarbonate or a chloroformate such as benzylchloroformate. The resulting enantiomeric mixture can be applied to a chiral HPLC column and fractions containing the individual isomers collected. A facilitating group may be removed by standard methods such as acid hydrolysis or catalytic hydrogenation.

A chiral derivative according to process (b) is a derivative containing at least two chiral centres, such that an enantiomeric mixture of a compound (I) is converted into a pair of diastereoisomers. Such derivatives include chiral salts wherein the anion contains a chiral centre and derivatives of formula (I) in which the alkylamino moiety is substituted by a group containing a chiral centre.

A chiral salt may be prepared for example by reaction of an enantiomeric mixture, such as a 1:1 racemate, of a compound (I) with an optically active acid such as (1S)-(+)-camphorsulphonic acid, d-tartaric acid, l-malic acid, l-mandelic acid, l-gulonic acid, 2,3:4,6-di-O-isopropylidene-2-keto-L-gulonic acid or R-2-pyrrolidone-5-carboxylic acid (also known as D-pyrroglutamic acid) to give two diastereoisomeric salts which may be separated e.g. by crystallisation. The free base form of the desired enantiomer may be obtained by neutralisation with a base such as sodium hydroxide or an ion exchange resin. Preferred optically active acids for use in this process include (1S)-(+)-camphorsulphonic acid and especially R-2-pyrrolidone-5-carboxylic acid.

Alternatively, an optically active reagent such as R- α -methylbenzoyloxysuccinimide may be reacted with an enantiomeric mixture of formula (I), to give a mixture of diastereoisomers which can be separated by chromatography, followed by hydrogenolysis to give the desired enantiomer of formula (I).

A chiral derivative may also be prepared by employing a chiral auxiliary at an earlier stage in the synthesis as described hereinafter. This may advantageously result in a mixture enriched with one diastereoisomer of a compound (I), and most preferably a single diastereoisomer, thus providing a stereoselective synthesis of an enantiomer according to the invention.

Alkylation of an enantiomer of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole according to process (c) may be carried out by standard methods well known in the art. For example alkylation may be achieved indirectly by formation of a group which can be reduced to the desired alkylamino function (reductive alkylation). Thus for example the 3-amino compound can be reacted with an appropriate aldehyde or ketone e.g. formaldehyde, acetaldehyde or acetone, in the presence of a suitable reducing agent such as

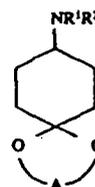
an alkali metal borohydride or cyanoborohydride e.g. sodium cyanoborohydride. Alternatively formylation may be effected using p-nitrophenol formate in aqueous tetrahydrofuran, using similar reducing conditions. Preferably, the 3-amino compound is first reacted with benzaldehyde, also in the presence of a reducing agent such as a cyanoborohydride, to form 3-N-benzylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole, prior to introduction of the methyl or ethyl group. The benzyl group may subsequently be cleaved by standard methods such as catalytic hydrogenation.

In a further alkylation method, an N-methyl substituent may be introduced by formation of a 3-isothiocyanato derivative e.g. by reaction of the 3-amino compound with carbon disulphide and dicyclohexylcarbodiimide; followed by reduction for example with a borohydride.

It will be appreciated by those skilled in the art that other standard means of alkylation may also be employed.

The starting compounds for use in the above processes may be prepared by methods known in the art for the preparation of tetrahydrocarbazoles, such as the methods described in International Application WO93/00086. Thus for example an enantiomeric mixture of formula (I) may be prepared by reductive alkylation of the corresponding 3-amino compound, as described for process (c) above.

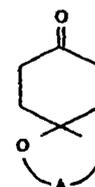
An enantiomeric mixture of formula (I) may also be prepared by reaction of 4-carboxamido-phenylhydrazine, or a salt thereof e.g. the hydrochloride, with 4-(methyl or ethyl)-aminocyclohexanone. In a particular embodiment of this method a protected derivative of the 4-alkylaminocyclohexanone is advantageously employed, e.g. a ketal of formula (II):



Formula (II)

wherein R¹ is as defined for formula (I), R² is hydrogen or an N-protecting group and A is an alkylene moiety, such as ethylene or neopentylene ($-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2-$).

Compounds of formula (II) may themselves be prepared from a protected 1,4-cyclohexane-dione of formula (III):



Formula (III)

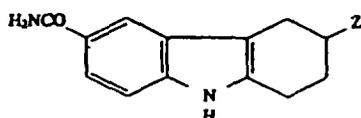
by reaction with the appropriate alkylamine compound. This reaction may be effected in a suitable solvent, for example a hydrocarbon such as benzene or toluene in the presence of titanium tetrachloride or suitable molecular sieves e.g. 4 Å molecular sieves, to give the corresponding iminoketal derivative which may then be converted to an alkylamino compound of formula (II) by catalytic hydrogenation using for example palladium on carbon. Alternatively the reaction may be effected in a solvent such as an alcohol e.g. ethanol and the mixture hydrogenated directly, using e.g. palladium on charcoal, to give a compound of formula (II).

The alkylamino group in the resulting compound of formula (II) may if desired be protected using standard methods. Suitable N-protecting groups are well-known in

the an and include for example acyl groups such as acetyl, trifluoroacetyl, or benzoyl; an alkyl- or aralkyloxycarbonyl group such as methoxycarbonyl, t-butoxycarbonyl, benzyloxycarbonyl or phthaloyl; and aralkyl groups such as benzyl, diphenylmethyl or triphenylmethyl. The protecting groups should be easily removable at the end of the reaction sequence. N-deprotection may be effected by conventional methods, for example an alkoxycarbonyl group such as t-butoxycarbonyl may be cleaved by hydrolysis and an aralkyloxycarbonyl group such as benzyloxycarbonyl or an aralkyl group such as benzyl may be cleaved by hydrogenolysis.

Cyclisation with 4-carboxamidophenylhydrazine or a salt thereof is preferably carried out with a ketal of formula (II); however if desired the ketal may be converted to the corresponding ketone prior to this reaction.

Yet a further method for preparing an enantiomeric mixture of formula (I) comprises reacting a compound of formula (IV):



Formula (IV)

wherein Z is a leaving group, such as a halogen atom or a sulphonyloxy (e.g. p-toluenesulphonyloxy or methanesulphonyloxy) group with an amine H_2NR^1 or a derivative thereof. Said derivative may optionally contain a chiral centre, as in for example R- α -methylbenzylamine, resulting in a diastereoisomeric mixture of the corresponding derivative of formula (I). The diastereoisomers may be separated by chromatography, followed by hydrogenolysis to give the desired enantiomer of formula (I).

An enantiomeric mixture of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole may be prepared in an analogous manner to formula (I), using 4-aminocyclohexanone, optionally protected as a ketal derivative, or an N-protected (e.g. phthalimido) derivative thereof. The enantiomers of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole may be resolved by chiral HPLC as described for process (a) above, using a derivative such as of 3-t-butyloxycarbonylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole; or by formation of a chiral salt of the 3-amino compound in a similar manner to process (b) above, using for example 2,3,4,6-di-O-isopropylidene-2-keto-L-gulonic acid, followed by selective crystallisation. Such methods are described in International Application WO93/00086.

Enantiomers of formula (I) have been found to be agonists and partial agonists at 5-HT₁-like receptors. Nomenclature of 5-HT receptors is constantly evolving. At least four subtypes of the 5-HT₁ receptor family have been described, namely 5-HT_{1a}, 5-HT_{1b}, 5-HT_{1c} and 5-HT_{1d}. Functional contractile 5-HT₁-like receptors have been identified in the dog saphenous vein and in cerebral (basilar) arteries of various species including rabbit and human. It is now believed that the functional 5-HT₁-like receptor correlates with the 5-HT_{1d} binding site (A. A Parsons, TIPS, Aug 1991, Vol 12).

Enantiomers of formula (I) are expected to have utility in the treatment and/or prophylaxis of migraine, with and without aura, tension headache, cluster headache and other forms of cephalic pain and trigeminal neuralgias.

The invention therefore further provides the use of an enantiomer of formula (I) or a physiologically acceptable salt thereof in the manufacture of a medicament for the treatment of a condition where a 5-HT₁-like agonist is indicated, in particular the treatment or prophylaxis of migraine.

The invention also provides a method of treatment of a condition wherein a 5-HT₁-like agonist is indicated, in particular migraine, which comprises administering to a subject in need thereof an effective amount of an enantiomer of formula (I) or a physiologically acceptable salt thereof.

For use in medicine, a compound of the present invention will usually be administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising an enantiomer of formula (I) or a physiologically acceptable salt thereof and a physiologically acceptable carrier.

The compounds of formula (I) may be administered by any convenient method, for example by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) and their physiologically acceptable salts which are active when given orally can be formulated as liquids or solids, for example syrups; suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or physiologically acceptable salt in a suitable liquid carrier(s) for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or physiologically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or nonaqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

7

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (1) or a physiologically acceptable salt thereof calculated as the free base.

The physiologically acceptable compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 500 mg, preferably between 10 mg and 400 mg, e.g. between 10 and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of the compound of the formula (1) or a physiologically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

BIOLOGICAL TEST METHODS

5-HT₁-like Receptor Screen

RABBIT BASILAR ARTERY

Experiments were performed in intracranial arteries from rabbit isolated basilar artery in a similar method to that described previously (Parsons and Whalley, 1989. Eur J Pharmacol 174, 189-196.).

In brief, rabbits were killed by overdose with anaesthetic (sodium pentobarbitone). The whole brain was quickly removed and immersed in ice cold modified Krebs's solution and the basilar artery removed with the aid of a dissecting microscope. The Krebs solution was of the following composition (mM) Na⁺ (120); K⁺ (5); Ca²⁺ (2.25); Mg²⁺ (0.5); Cl⁻ (98.5); SO₄²⁻ (1); EDTA (0.04), equilibrated with 95% O₂/5% CO₂. The endothelium was removed by a gentle rubbing of the lumen with a fine metal wire. Arteries were then cut into ring segments (ca 4-5 mm wide) and set up for recording of isometric tension in 50 ml tissue baths in modified Krebs solution with the additional supplement of (mM); Na²⁺ (20); fumarate (10); pyruvate (5); L-glutamate (5) and glucose (10). The arteries were then placed under a resting force of 3-4 mN maintained at 37° C. and the solution bubbled with 95% O₂/5% CO₂.

After tests for initial reactivity with 90 mM KCl depolarising solution and for lack of acetylcholine-induced relaxation of 5-HT (10 mM) precontraction, cumulative concentration-effect curves (2 nM-60 mM) to 5-HT were constructed in the presence of ascorbate 200 mM, cocaine 6 mM, indomethacin 2.8 mM, ketanserin 1 mM and prazosin 1 mM.

Following a 45'60 min wash period, cumulative concentration-effect curves to the test compounds or 5-HT (as a time match control) were constructed in the presence of ascorbate, indomethacin, cocaine, ketanserin and prazosin. Test Compounds:

R-(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole; (compound A)

8

S-(-)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole; (compound B)

R-(+)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole; (compound C)

S-(-)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole. (compound D)

Results	EC ₅₀
Compound A	0.03 μM
Compound B	>2 μM
Compound C	0.16 μM
Compound D	2.1 μM

Pharmaceutical Formulations

The following represent typical pharmaceutical formulations according to the present invention, which may be prepared using standard methods.

IV Infusion	
Compound of formula (1)	1-40 mg
Buffer	to pH ca 7
Solvent/complexing agent	to 100 ml
Bolus Injection	
Compound of formula (1)	1-40 mg
Buffer	to pH ca 7
Co-Solvent	to 5 ml

Buffer: Suitable buffers include titrate, phosphate, sodium hydroxide/hydrochloric acid.

Solvent: Typically water but may also include cyclodextrins (1-100 mg) and co-solvents such as propylene glycol, polyethylene glycol and alcohol.

Tablet	
Compound	1-40 mg
Diluent/Filler*	50-250 mg
Binder	5-25 mg
Disintegrant*	5-50 mg
Lubricant	1-5 mg
Cyclodextrin	1-100 mg

*may also include cyclodextrins

Diluent: e.g. Microcrystalline cellulose, lactose, starch
Binder: e.g. Polyvinylpyrrolidone, hydroxypropylmethylcellulose

Disintegrant: e.g. Sodium starch glycolate, crospovidone
Lubricant: e.g. Magnesium stearate, sodium stearyl fumarate.

Oral Suspension	
Compound	1-40 mg
Suspending Agent	0.1-10 mg
Diluent	20-60 mg
Preservative	0.01-1.0 mg
Buffer	to pH ca 5-8
Co-solvent	0-40 mg
Flavour	0.01-1.0 mg
Colourant	0.001-0.1 mg

Suspending agent: e.g. Xanthan gum, microcrystalline cellulose

Diluent: e.g. sorbitol solution, typically water

Preservative: e.g. sodium benzoate

Buffer: e.g. citrate

Co-solvent: e.g. alcohol, propylene glycol, polyethylene glycol, cyclodextrin

Preparation 1

 (\pm) -3-Amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole

4-Carboxamidophenylhydrazine hydrochloride (2.87 g) and 4-phthalimidocyclohexanone (3.00 g) were mixed in acetic acid and the mixture was heated under reflux for 2 hr. After cooling, the mixture was neutralized using aq. potassium carbonate solution, and the yellow solid thus obtained was filtered, washed with water, and dried. Purification by column chromatography (SiO_2 ; $\text{CHCl}_3/\text{CH}_3\text{OH}$) gave 6-carboxamido-3-phthalimido-1,2,3,4-tetrahydrocarbazole (2.8 g).

The above product (1.0 g) was suspended in ethanol (10 ml) and hydrazine hydrate (5 ml) was added. A clear solution was obtained, and the mixture was left to stir overnight, to yield a precipitate. The whole mixture was evaporated to dryness, washed with aq. K_2CO_3 solution, and water, to leave the title compound 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (0.44 g), as the monohydrate, mp. $146^\circ\text{--}148^\circ\text{C}$.

$^1\text{H NMR}$ [250 MHz, $\text{DMSO-}d_6$] δ 1.49–1.77 (1H,m), 1.83–2.03 (1H,m), 2.17–2.40 (1H,m), 2.62–2.80 (2H,m), 2.90 (1H,dd), 1 signal obscured by H_2O at ca. 3.1, 7.03 (1H,brd.s), 7.18 (1H,d), 7.58 (1H,d), 7.83 (1H,brd.s), 7.98 (1H,s).

Preparation 2

(+)- and (-)-

3-Amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride

Method 1

(\pm) -3-t-Butyloxycarbonylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole was separated into its enantiomers using chiral HPLC: (chiralcel OD 4.6 mm column, eluting with hexane/ethanol 85:15). The (+)-enantiomer was collected first and had mp= $150^\circ\text{--}152^\circ\text{C}$. and $[\alpha]_D^{25} = +70.1$ (in methanol, 0.41% w/v). The (-)-enantiomer had mp= $150^\circ\text{--}152^\circ\text{C}$. and $[\alpha]_D^{25} = -79.4$ (in methanol, 0.40% w/v). The (+)-enantiomer was converted to the parent amine hydrochloride by treating with HCl gas in dioxane, to furnish the (+)-enantiomer of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride, mp= $248^\circ\text{--}251^\circ\text{C}$. $[\alpha]_D^{25} = +26.2$ (in methanol, 0.50% w/v). The (-)-enantiomer of 3-t-butyloxycarbonylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole was similarly converted into the (-)-enantiomer of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride, mp= $248^\circ\text{--}251^\circ\text{C}$. $[\alpha]_D^{25} = -28.6$ (in methanol, 0.50% w/v).

Method 2

(\pm) -3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole was treated with one equivalent of 2,3,4,6-di-O-isopropylidene-2-keto-L-gulonic acid in methanol to give the salt of the (+)-enantiomer, in 38% yield (with respect to racemate) and 84% enantiomeric excess (ee). This material was recrystallized twice from methanol to give the salt of the (+)-enantiomer in 25% overall yield (with respect to racemate), and >98% ee. This product was converted to the hydrochloride salt first by treatment with aqueous alkali, and the precipitated free base treated with 2 M aq. HCl in ethanol, to give (+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride.

Preparation 3

 (\pm) -6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hydrochloride

4-Cyanophenyl hydrazine hydrochloride (20.2 g) and 4-benzoyloxycyclohexanone (25.9 g) were dissolved in glacial acetic (400 ml) and the mixture was heated under reflux for 1.5 hr. After allowing to cool, the mixture was filtered, and the filtrate was evaporated to dryness, and neutralized with aqueous sodium bicarbonate solution to give a solid precipitate, which was purified by chromatography (SiO_2 ; hexane/ethyl acetate) to give 3-benzoyloxy-6-cyano-1,2,3,4-tetrahydrocarbazole (18 g). This product (11.6 g) was suspended in ethanol (230 ml) and treated with 2.5% aqueous potassium hydroxide solution (120 ml), and heated under reflux for 1 hr. The cooled mixture was neutralized with glacial acetic acid and evaporated to a solid residue, which was washed with water, and dried to give 3-hydroxy-6-cyano-1,2,3,4-tetrahydrocarbazole (6.6 g).

The above product (3.57 g) was dissolved in dry pyridine (35 ml) and treated with tosyl chloride (3.51 g) in dry pyridine (35 ml), and the mixture was stirred at 100°C . for 2 hr. After cooling, the solution was poured into water (500 ml), extracted with ethyl acetate, and the latter extract was washed with 2 M HCl, dried (MgSO_4) and evaporated to dryness. Purification by chromatography (SiO_2 ; hexane/ethyl acetate) gave 3-tosyloxy-6-cyano-1,2,3,4-tetrahydrocarbazole (0.53 g).

This product (0.40 g) was dissolved in 33% methylamine in alcohol (25 ml) and heated at 100°C . in a sealed steel vessel for 1.5 hr. After cooling, the mixture was evaporated to dryness and purified by chromatography (SiO_2 ; chloroform/methanol) to give 3-methylamino-6-cyano-1,2,3,4-tetrahydrocarbazole (0.13 g).

The above product (0.12 g) was dissolved in THF (10 ml) and reacted with di-*tert*-butyl dicarbonate (0.36 g) in THF (3 ml) at room temperature overnight. The reaction mixture was evaporated to dryness, partitioned between 2 M sodium bicarbonate solution and ethyl acetate, and the organic extract dried and evaporated to give a white solid. This was triturated with ether/hexane to give 3-t-butyloxycarbonylmethylamino-6-cyano-1,2,3,4-tetrahydrocarbazole (0.14 g).

This product (0.14 g) was dissolved in methanol (15 ml) and treated with a mixture of 20% aqueous sodium hydroxide (0.20 ml) and 30% hydrogen peroxide (0.20 ml), and the whole mixture was stirred at room temperature overnight. Sodium metabisulphite (38 mg) was added, and the solution was evaporated to dryness, and chromatographed (SiO_2 ; chloroform/10% NH_4OH in methanol) to give 3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (0.12 g). The above compound (0.11 g) was dissolved in methanol (10 ml), and treated with 3 M hydrochloric acid at room temperature. The mixture was evaporated to dryness, azeotroping with ethanol to give a solid, which was recrystallized from methanol/ether to give the title compound, mp $327^\circ\text{--}328^\circ\text{C}$. (80 mg).

$^1\text{H NMR}$ [250 MHz, $\text{MeOH-}d_4$] δ 1.98–2.20 (1H, m), 2.29–2.49 (1H, m), 2.75–2.90 (5H, s+m), 2.90–3.09 (2H, m), 3.52–3.69 (1H, m), 7.31 (1H, d), 7.63 (1H, d), 8.05 (1H, s).

Preparation 4

(+)-6-Carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole oxalate

1,4-Cyclohexanedione mono-2',2'-dimethyl trimethylene ketal (2.00 g) was mixed with anhydrous ethylamine (10.0

g) and benzene (10 ml), and the mixture was cooled to 5° C. A solution of titanium tetrachloride (0.95 g) in benzene (10 ml) was added, dropwise, then the mixture was stirred at room temperature for 1 hr. The mixture was filtered, and evaporated to dryness to give an oil, which was dissolved in ethanol (30 ml). To this solution was added palladium-on-carbon catalyst (100 mg), and the mixture was hydrogenated at 50 psi pressure overnight. The catalyst was filtered off and the ethanol evaporated to leave 4-ethylamino-cyclohexanone 2',2'-dimethyl trimethylene ketal as an oil (2.0 g).

This compound (0.80 g) was dissolved in formic acid (20 ml) and the solution was heated to 90° C. for 1 hr. Formic acid was evaporated, and the residue was partitioned between chloroform and 1 M hydrochloric acid. The aqueous layer was evaporated to dryness to give 4-ethylaminocyclohexanone (0.40 g).

A mixture of the above product (0.40 g) and 4-carboxamidophenyl hydrazine hydrochloride (0.60 g) in glacial acetic acid (20 ml) was heated under reflux for 1 hr. The acid was evaporated in vacuo to an oil, which was purified by chromatography (SiO₂; CHCl₃/10% NH₃ in MeOH) to give an oil (0.50 g). Part of this product (150 mg) was dissolved in methanol and treated with oxalic acid. The solution was treated with ether to give the title compound as a crystalline solid, mp 165°-170° C. (100 mg).

¹H NMR [250 MHz, DMSO-d₆]δ 1.25 (3H, t), 1.81-2.05 (1H, m), 2.20-2.38 (1H, m), 2.61-2.79 (1H, m), 2.79-2.94 (2H, m), 2.98-3.28 (3H, dd+s), 3.41-3.60 (1H, m), 7.08 (1H, brd. s), 7.28 (1H, d), 7.60 (1H, d), 7.82 (1H, brd. s), 8.00 (1H, s), 11.12 (1H, s).

Preparation 5

(±)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole

A solution of (±)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hydrochloride salt (6.0 g) in water (60 ml) at 68° C. was basified to pH 10.5 with 5 M aqueous sodium hydroxide. The resultant mixture was extracted with butan-1-ol (30 ml, 15 ml). These extracts were combined and evaporated to give the title compound as a dark oil (6.96 g) containing ca. 46% w/w butan-1-ol.

¹H NMR [400 MHz, d⁶-DMSO]δ 1.40-2.00 (1H, br), 1.62 (1H, m), 2.06 (1H, m), 2.33 (1H, m), 2.39 (3H, s), 2.77 (3H, m), 2.97 (1H, dd), 7.02 (1H, s), 7.24 (1H, d), 7.59 (1H, dd), 7.80 (1H, s), 7.99 (1H, d), 10.93 (1H, s)+peaks due to butan-1-ol.

Preparation 6

4-Methylaminocyclohexanone (2',2'-dimethyltrimethylene) ketal hydrochloride

1,4-Cyclohexanedione (mono-2',2'-dimethyltrimethylene) ketal (50 g) was dissolved in dry toluene (500 ml) in a flask fitted with a dry ice trap and flushed with nitrogen with stirring. Methylamine (47.0 g) was then added dropwise to the reaction mixture, at 20° C. slowly to allow dissolution in the toluene. Molecular sieves (32.0 g) were then added and the reaction mixture stirred at 20° C. under an air lock. The reaction was complete after ca. 4 h (>97%). The sieves were then filtered off and the clear amber filtrate evaporated to a volume of 160 ml. The concentrated solution of iminoketal was diluted with ethanol (340 ml) and degassed with argon. Palladium catalyst (palladium on charcoal, 3.55 g) was added and the mixture hydrogenated at atmospheric pressure

and 20° C. for 24 h. When hydrogen uptake was complete the reaction mixture was filtered through Celite and the Celite bed washed with a little ethanol (2x25ml). The solvent was then removed under reduced pressure to give the ketal amine as an amber oil. (49.12 g, 92%).

The ketal amine (80 g, 0.375 Mol) was dissolved in isopropyl ether with stirring. A solution of HCl in isopropyl ether (prepared by bubbling a known weight of gas into a known volume of solvent) was added dropwise causing the formation of an immediate white precipitate, which became very thick as the addition was completed. The thick suspension was stirred for a further 30 minutes, filtered off, and the product washed with a little fresh isopropyl ether and then dried under vacuum to give the title compound as a white, free flowing powder (84.01 g).

¹H NMR: -[1270 MHz, CDCl₃]δ 9.51 (2H, br), 3.48 (4H, d), 3.00 (1H, m), 2.73 (3H, s), 2.32 (2H, d), 2.15 (2H, d), 1.85, (2H, dq), 1.41 (2H, dt), 0.96 (6H, s).

Preparation 7

(+)-6-Carboxamide-3-methylamino-1,2,3,4-tetrahydrocarbazole hydrochloride

4-Aminobenzamide (3.0 g) was dissolved in 5N HCl (20 ml) cooled to -5° to 0° C. with stirring and the mixture further cooled to around -15° C. Sodium nitrite (1.98 g) in water (4.4 ml) was added dropwise with stirring at such a rate that the temperature was maintained at between -10° to -15° C. The mixture was then stirred at around -8° C. for 30 min. Ice cold water (40 ml) was then added followed by solid sodium dithionite (7.7 g) in a single portion, the means of cooling removed and the mixture stirred at around 15° C. for 30 min. To the resulting yellow suspension was added conc. HCl (30 ml) followed by 4-methylaminocyclohexanone (2',2'-dimethyltrimethylene) ketal hydrochloride (5.488 g) and the mixture heated to around 70° C., not allowing the reaction temperature to rise above 75° C. After ca. 2 h, the reaction mixture was cooled to 20° C. and the dark solution then carefully neutralised with caustic (aq., 40%) to pH 10 maintaining the temperature between 15°-20° C., whereupon a thick precipitate formed to give the title compound. The reaction mixture was then left to stir overnight and the precipitate filtered off and dried (3.88 g, 63%).

¹H nmr [250 MHz, d₆-DMSO]δ=11.21 (1H, s), 8.06 (1H, s), 7.89 (1H, bs), 7.63 (1H, d), 7.28 (1H, d), 7.10 (1H, bs), 3.50-3.15 (2H, m), 2.95-2.70 (3H, m), 2.62 (3H, s), 2.33 (1H, m), 1.97 (1H, m).

Preparation 8

4-Methylaminocyclohexanone (2',2'-dimethyltrimethylene) ketal hydrochloride

1,4-Cyclohexanedione mono-2,2-dimethyltrimethylene ketal (20.0 g, 0.101 mol) was dissolved in ethanol (200 ml) containing methylamine (8.0 g, 0.258 mol). The resultant solution was hydrogenated at 30 psi over 10% Pd/C catalyst (2.0 g) for 4 hrs at room temperature. The reaction mixture was filtered through a celite pad and the filtrate evaporated under reduced pressure to give an oil (21.4 g).

The oil was dissolved in tetrahydrofuran (210 ml) and the resultant solution cooled in an ice/water bath while conc. HCl (10.5 ml) was added to the stirred solution in two portions such that the temperature did not rise above 15° C. and then filtered. The solid was washed with THF (50 ml)

13

and air dried overnight to give the title compound (22.80 g). mp 245.1° C. (EtOH).

¹H nmr (250 MHz, d₆DMSO) δ 0.9 (s, 6H), 1.3 (q, 2H), 1.45 (q, 2H), 1.9 (brd, 2H), 2.25 (brd, 2H), 2.5 (s, 3H), 3.0 (m, 1H), 3.5 (d, 4H).

Example 1

(+) and (-)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hydrochloride

(a) To a stirred solution of (±)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hydrochloride (0.3 g) in propan-2-ol/saturated aqueous potassium hydrogen carbonate (20:1 21 ml), di-tert-butyl dicarbonate (0.425 g) was added and stirring continued for 1 hour. The mixture was diluted with ethyl acetate (50 ml) washed with water (2×20ml), dried (MgSO₄) and solvent removed at reduced pressure to give (±) 3-N-tert-butoxycarbonyl-N-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (0.36 g).

¹H NMR (d₆-DMSO) δ 1.47 (s, 9H), 1.84–2.08 (m, 2H), 2.71–2.94 (m, 4H), 2.80 (s, 3H), 4.26 (m, 1H), 7.02 (br.s, 1H), 7.25 (d, 1H), 7.57 (d, 1H), 7.76 (br.s, 1H), 7.97 (s, 1H) and 10.96 (s, 1H).

(b) The (+) and the (-) enantiomers of (±)-3-N-tert-butoxycarbonyl-N-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (0.3 g) were separated by chiral HPLC: (chiralpak AD 20 mm column, hexane:ethanol 9:1 eluant).

Treatment of the first eluting enantiomer (0.02 g) with 3N aqueous hydrochloric acid/methanol 1:1 (4 ml) for 16 hours, filtration and removal of solvent gave, after recrystallisation from methanol/diethyl ether, the (+) enantiomer of the title compound (0.009 g) m.p. 219°–225° C., [α]_D²⁵ = +25.4 methanol 0.063% w/v.

Treatment of the second eluting enantiomer (0.03 g) under similar conditions gave the (-) enantiomer of the title compound (0.02 g), m.p. 219°–225° C., [α]_D²⁵ = -23.3 (methanol 0.116% w/v).

Example 2

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole

(a) To a solution of (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.77 g) in dimethylformamide (70 ml), methylamine (0.62 g) and benzyl chloroformate (0.47 g) were added. The solution was stirred overnight, further triethylamine (0.27 g) and benzyl chloroformate (0.26 g) added and the mixture stirred for 4 hours. The reaction mixture was poured into water (500 ml), and extracted with ethyl acetate (2×50 ml). The combined extracts were dried (MgSO₄) and solvent was removed at reduced pressure. The residue was recrystallised from methanol/water to give (+)-3-N-benzyloxycarbonyl-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.62 g) m.p. 103°–110° C.

(b) The (+) and (-) enantiomers of (+)-3-N-benzyloxycarbonyl-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole were separated by chiral HPLC (OD column, eluant hexane/ethanol 4:1).

The first eluting enantiomer (0.23 g) m.p. 105°–106° C., [α]_D²⁵ = +157.2 (ethanol, 0.39% w/v).

The second eluting enantiomer (0.23g) m.p. 105°–106° C., [α]_D²⁵ = -163.1 (ethanol, 0.23% w/v).

14

(c) A solution of (+)-3-N-benzyloxycarbonyl-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.23 g) in ethanol (20 ml) containing 10% palladium/charcoal (0.23 g) was shaken under a hydrogen atmosphere (50 psi) for 3 hours. Catalyst was removed by filtration and solvent removed at reduced pressure to give the (+) enantiomer of the title compound (free base) as a foam m.p. 98°–102° C., [α]_D²⁵ = +61.2.

Example 3

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole camphorsulphonate

To a solution of (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (3 g) in methanol (20 ml), a solution of (1S)-(+)-10-camphorsulphonic acid (2.86 g) in methanol was added. Solvent was removed at reduced pressure and the residue recrystallised ten times to give the (+) enantiomer of the title compound as the camphorsulphonate salt m.p. 177°–180° C. This was treated with 2 equivalents of methylamine and 10 equivalents of 2,3,4,6-tetra-O-acetyl-beta-D-glucopyranosylisothiocyanate in dimethylformamide at room temperature for 90 minutes. Aliquots of the reaction mixture were removed from the mixture for HPLC analysis. Analytical HPLC of the 2,3,4,6-tetra-O-acetyl-beta-D-glucopyranosylthiourea derivative (C18 Novapak, eluant methanol/50 mMNaH₂PO₄ pH 2.9) gave the same retention time as the same derivative prepared from the (+) enantiomer of Example 1 and showed the material was 99% ee.

Example 4

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole succinate (1:1)

(a) Benzaldehyde (10.6 g) was added to a suspension of (+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (12.35 g) in methanol (100 ml). The mixture was stirred for 1 hour, sodium cyanoborohydride (9.3 g) added over 1 hour and the clear solution stirred for 24 hours. The solution was cooled (ice bath) and formaldehyde (37% aqueous methanolic, 9:1 solution, 5.5 ml) added. After 30 minutes stirring at room temperature water (100 ml) was added, stirring continued for 30 minutes followed by extraction with dichloromethane (3×150 ml). The combined organic extracts were washed with water (2×200 ml), dried (Na₂SO₄), filtered and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, dichloromethane-10% ethanol/dichloromethane) to give 3-N-benzyl-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (9.4 g) as a foam. The succinate salt (1:1) was recrystallised from methanol m.p. 175°–182° C.

¹H NMR (d₆-DMSO) δ 1.81–1.96 (m, 1H), 2.09–2.21 (m, 1H), 2.29 (s, 3H), 2.44 (s, 4H), 2.66–3.11 (m, 5H), 3.76 (q, 2H), 7.05 (br. s, 1H), 7.22–7.43 (m, 6H), 7.59 (d, 1H), 7.79 (br. s, 1H), 8.03 (s, 1H), and 10.94 (s, 1H).

(b) To a solution of 3-N-benzyl-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (1.0 g) in ethanol (100 ml) containing succinic acid (0.39 g), Pearlman's catalyst (1.0 g) was added and the mixture shaken under an atmosphere of hydrogen at 45 psi and 50° C. for 2 hours. The mixture was filtered (celite pad) and the pad washed thoroughly with ethanol. The combined filtrate and washings were evaporated to dryness, co-evaporated with ethanol (3×100 ml) and recrystallised from methanol to give the title compound [(1:1) succinate salt]. m.p. 148°–155° C.

15

¹H NMR (d₆-DMSO) δ 1.84(m, 1H), 2.15-2.34 (m, 1H), 2.28 (s,4H), 2.57 (m, 1H), 2.61 (s,3H), 2.83 (m,2H), 3.13 (dd, 1H), 3.29 (m, 1H), 7.08 (br s, 1H), 7.26 (d, 1H), 7.60 (dd, 1H), 7.82 (br s,1H), 8.01 (d,1H) and 11.08 (s, 1H).

Example 5

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole

(a) To a solution of (+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (5 g) in pyridine (150 ml), dicyclohexylcarbodiimide (4.13 g) was added followed by carbon disulphide (1.67 g). The solution was stirred for 1 hour, solvent removed at reduced pressure and the residue co-evaporated with toluene (3x100 ml). The residue was recrystallised from methanol to give 6-carboxamido-3-isothiocyanato-1,2,3,4-tetrahydrocarbazole (5.06 g) m.p.245°-248° C.

(b) A solution of 6-carboxamido-3-isothiocyanato-1,2,3,4-tetrahydrocarbazole (0.25 g) in ethanol (40 ml) was treated with sodium borohydride (0.17 g) in one portion and stirred for 18 hours. Acetone (5 ml) was added the mixture stirred for a further 1 hour and solvent removed at reduced pressure. The residue was column chromatographed (basic alumina, 5% methanol/dichloromethane eluant) to give the title compound (0.11 g) having the same physico chemical characteristics as the product of Example 2.

Example 6

(+)- and (-)-6-Carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole hydrochloride

(a) From (±)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole (0.26 g), (±)-3-N-tert butoxycarbonyl-N-ethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (0.27 g) isolated as an oil was prepared according to the procedure of Example 1.

¹H NMR (d₆-DMSO) δ 1.1 (t,3H), 1.23 (s,9H), 1.92 (m, 1H), 2.09 (m, 1H), 2.78-2.92 (m,4H), 3.21-3.62 (m,2H), 4.21 (m, 1H), 7.04 (br.s, 1H), 7.24 (d, 1H), 7.58 (d, 1H), 7.76 (br.s, 1H), 7.99 (s, 1H) and 10.99 (s, 1H).

(b) From (±)-3-N-tert butoxycarbonyl-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole (0.25 g), the (+)- and the (-)-enantiomers of 3-N-tert butoxycarbonyl-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole were prepared by chiral HPLC (chiralcel OD 4.67 mm, eluant hexane/ethanol 92/8).

Treatment of the enantiomer eluting first, (0.06 g) [α]_D²⁵ c=+108.2 (ethanol 0.9% w/v) with hydrochloric acid/methanol according to the method of Example 1 gave (+)-6-carboxamido-N-ethylamino-1,2,3,4-tetrahydrocarbazole hydrochloride (0.04 g) m.p. 211°-221° C. [α]_D²⁵ c=+37.2 (methanol, 0.12% w/v).

Treatment of the second eluting enantiomer (80 mg) [α]_D²⁵ c=-103.5 (ethanol, 0.19% w/v) with hydrochloric acid/methanol according to the method of Example 1 gave (-)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole hydrochloride (0.05 g) m.p. 211°-221° C. after recrystallisation from methanol/diethyl ether [α]_D²⁵ c=-33.6 (methanol, 0.11% w/v).

Example 7

(+)-6-Carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole succinate (1:1)

(a) From (+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (1.15 g), (+)-3-N-benzyl-N-ethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (1.26 g) was

16

obtained according to the procedure of Example 4 replacing formaldehyde with acetaldehyde (0.44 g). The succinate salt (1:1) was prepared by addition of succinic acid (0.4 g) to the free base (1.08 g) and recrystallisation from propan-2-ol m.p. 130°-140° C.

¹H NMR (d₆-DMSO) δ 1.05 (t,3H), 1.85 (m, 1H), 2.10 (m, 1H), 2.40 (s,4H), 2.58-2.91 (m,5H), 3.06 (m, 1H), 3.77 (q,2H), 7.03 (br.s, 1H), 7.17-7.47 (m,5H), 7.58 (d, 1H), 7.78 (br.s, 1H), 8.00 (s, 1H), 10.90 (s, 1H) and 12.28 (br. s,2H).

(b) Recrystallisation of (+)-3-N-benzyl-N-ethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole succinate (1.36 g), from methanol, according to the procedure of Example 4 gave the title compound (1.04 g) m.p. 165°-167° C.

¹H NMR (d₆-DMSO) δ 1.19 (t,3H), 1.86 (m, 1H), 2.23 (m,1H), 2.30 (s,4H), 2.62 (m,1H), 2.85 (m,2H), 3.02 (q,2H), 3.14 (m, 1H), 3.38 (m, 1H), 7.08 (br.s, 1H), 7.26 (d, 1H), 7.59(d, 1H), 7.80 (br.s, 1H), 8.00 (s,1H) and 11.08 (s, 1H).

Example 8

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole L (+)-tartrate salt (1:1)

To a hot solution of (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.25 g) in methanol/water (11:1, 24 ml) L (+)-tartaric acid (0.15 g) was added and the solution allowed to stand for 3 hours. The crystalline title compound (0.30 g) was isolated by filtration. m.p. 195°-197° C.

¹H NMR (d₆-DMSO) δ 1.92 (m, 1H), 2.25 (m, 1H), 2.67 (s,3H), 2.68 (m, 1H), 2.84 (m,2H), 3.17 (dd, 1H), 3.43 (m, 1H), 3.87 (s,2H), 7.07 (br.s, 1H), 7.27 (d, 1H), 7.61 (d, 1H), 7.82 (br.s,1H), 8.01 (s,1H) and 11.1 (s, 1H).

Example 9

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole D (-)-tartrate salt (1:1)

To a hot solution of (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.25 g) in methanol (9 ml) D (-)-tartaric acid (0.15 g) was added and the solution allowed to stand for 3 hours. The crystalline title compound (0.32 g) was isolated by filtration m.p. softens above 147° C.

¹H NMR (d₆-DMSO) δ 1.92 (m, 1H), 2.25 (m,1H), 2.67 (s,3H), 2.68 (m, 1H), 2.84 (m,2H), 3.17 (dd, 1H), 3.43 (m, 1H), 3.87 (s,2H), 7.07(br.s, 1H), 7.27 (d, 1H), 7.61(d, 1H), 7.82 (br.s, 1H), 8.02 (s, 1H) and 11.09 (s, 1H).

Example 10

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hemisuccinate (2:1)

To a hot solution of (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.30 g) in propan-2-ol was added succinic acid (0.07 g) and the solution allowed to stand for 3 hours. The title compound (0.21 g) was isolated by filtration. m.p. 220°-235° C.

¹H NMR (d₆-DMSO) δ 1.77 (m, 1H), 2.14 (m,1H), 2.26 (s,2H), 2.54 (s,3H), 2.55 (m, 1H), 2.79 (m,2H), 3.10 (dd, 1H), 3.43 (m, 1H), 7.06 (br.s, 1H), 7.25 (d, 1H), 7.59(d, 1H), 7.82 (br.s,1H), 7.99 (s,1H) and 11.01 (s, 1H).

Example 11

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole methanesulphonate

To a hot solution of (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.30 g) in propan-2-ol/ethyl acetate methanesulphonic acid (0.12 g) was added and the solution allowed to stand for 3 hours. The title compound (0.33 g) was isolated as a gum.

¹H NMR (d₆-DMSO) δ 1.93 (m, 1H), 2.25 (m, 1H), 2.35 (s, 3H), 2.70 (m, 4H), 2.86 (m, 2H), 3.10 (dd, 1H), 3.50 (m, 1H), 7.11 (br.s, 1H), 7.27 (d, 1H), 7.61 (d, 1H), 7.82 (br.s, 1H), 8.02 (s, 1H), 8.65 (br.s, 2H) and 11.12 (s, 1H).

Example 12

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hydrobromide

Hydrogen bromide gas was passed through a solution of (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.30 g) in ethanol (50 ml) for 15 seconds. After 30 minutes the title compound (0.03 g) m.p. 205°-208° C. was separated by filtration and washed with ethanol.

¹H NMR (d₆-DMSO) δ 1.94 (m, 1H), 2.25 (m, 1H), 2.26 (s, 2H), 2.70 (m, 4H), 2.85 (m, 2H), 3.17 (dd, 1H), 7.10 (br.s, 1H), 7.27 (d, 1H), 7.61 (d, 1H), 7.82 (br.s, 1H), 8.02 (s, 1H) 8.67 (br.s, 2H) and 11.01 (s, 1H).

Example 13

a) **(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole-R-2-pyrrolidone-5-carboxylic acid salt**

To a solution of (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (6.96 g containing ca. 46% w/w butan-1-ol, prepared as in Preparation 5) in ethanol (50 ml), stirred at ambient temperature, was added a solution of R-2-pyrrolidone-5-carboxylic acid (1.00 g, e.e. >99%) in hot ethanol (33 ml). The resultant mixture was stirred at ambient temperature for 40 h. The crystalline product was filtered off under nitrogen, washed with a small volume of ethanol, then dried in vacuo at 60° C. (Yield = 2.63 g).

This product was dissolved in water (2.6 ml), and the solution was then diluted with ethanol (130 ml) and stirred at ambient temperature for 40 h. The crystalline product was filtered off, washed and dried as before. (Yield = 1.72 g).

This product was recrystallised from ethanol (90 ml)/water (1.8 ml) as described above to give the title compound (1.44 g; e.e. = >99%).

¹H NMR [250 MHz, d₆-DMSO] δ 1.90 (2H, m), 2.06 (2H, m), 2.19 (2H, m), 2.57 (3H, s), 2.62 (1H, m), 2.82 (2H, m), 3.15 (2H, m), 3.80 (1H, dd), 7.07 (1H, s), 7.26 (1H, d), 7.59 (1H, s), 7.62 (1H, s), 7.84 (1H, s), 8.00 (1H, s), 11.10 (1H, s) + peaks due to ethanol.

b) **(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole succinate salt, monohydrate**

A solution of (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole R-2-pyrrolidone-5-carboxylic acid salt (1.34 g) in water (5.4 ml) was basified to pH 13.2 with 5 M aqueous sodium hydroxide. The resultant mixture was extracted with butan-1-ol (5.4 ml). This extract was evaporated to give (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole as an oil/solid (735 mg) containing ca. 2% w/w butan-1-ol.

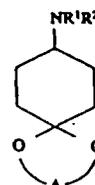
A portion of this product (232 mg) was dissolved in ethanol (1.45 ml). This solution was filtered, and added dropwise to a stirred solution of succinic acid (110 mg) in ethanol (1.45 ml)/water (0.48 ml). The mixture was seeded before the addition was complete. Stirring was continued for 30 min at ambient temperature, then 30 min at 0° C. The crystalline product was filtered off, washed with a small volume of ethanol, then dried in vacuo at 60° C. Yield = 233 mg.

¹H NMR [250 MHz, d₆-DMSO] δ 1.87 (1H, m), 2.25 (1H, m), 2.29 (4H, s), 2.62 (3H, s), 2.65 (1H, m), 2.83 (2H, m), 3.15 (1H, dd), 3.34 (1H, m), 7.09 (1H, s), 7.27 (1H, d), 7.61 (1H, dd), 7.84 (1H, s), 8.02 (1H, s), 11.10 (1H, s).

We claim:

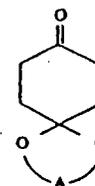
1. A process for preparing (+)-6-carboxamido-3-methylamino-1,2,3,4-tetrahydrocarbazole or a salt, solvate or hydrate thereof which comprises:

(a) Separation of an enantiomeric mixture of (±)-6-carboxamido-3-methylamino-1,2,3,4-tetrahydrocarbazole or a derivative thereof by chromatography, wherein said enantiomeric mixture is prepared by reaction of 4-carboxamido-phenylhydrazine, or a salt thereof, with a ketal of formula (II):



Formula (II)

wherein R¹ is methyl, R² is hydrogen or an N-protecting group and A is an alkylene moiety, said compound of formula (II) being prepared from a protected 1,4-cyclohexane-dione of formula (III):



Formula (III)

by reaction with an appropriate alkylamine compound.

2. A process according to claim 1 wherein the reaction between a compound of formula (II) and an alkylamine is effected in the presence of suitable molecular sieves to give the corresponding iminoketal derivative which is then converted to an alkylamine compound of formula (II) by catalytic hydrogenation.

3. A process according to claim 2 wherein reaction of a compound of formula (III) with an alkylamine is effected in a hydrocarbon solvent.

4. A process according to claim 3 wherein ethanol is added to the reaction mixture prior to catalytic hydrogenation.

5. A process according to claim 1 wherein reaction between a compound of formula (III) and an alkylamine is effected in ethanol and the mixture hydrogenated directly to give a compound of formula (II), followed if necessary or desired by removal of any N-protecting group, and conversion of a salt into a free base and/or salt formation.

United States Patent [19]

Borrett et al.

[11] Patent Number: 5,618,948

[45] Date of Patent: Apr. 8, 1997

[54] **PROCESS FOR PREPARING AN ENANTIOMER OF A CARBAZOLE DERIVATIVE**

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[21] **Appl. No.:** 451,846

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[51] **Int. Cl.⁶** C07D 209/88

[52] **U.S. Cl.** 548/448

[58] **Field of Search** 548/448

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,257,952 3/1981 Mooradian 548/448

FOREIGN PATENT DOCUMENTS

WO93/00086 1/1993 WIPO .

OTHER PUBLICATIONS

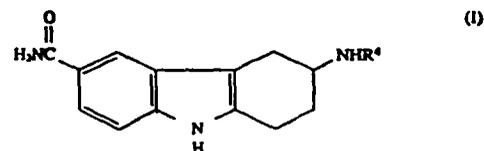
Hacksell et al., "Chirality in drug research and design", *Trends in Biotechnology*, vol. 11, pp. 73-74 (1993).

Ariens, "Nonchiral homochiral and composite chiral drugs", *Trends in Pharmacological Sciences*, vol. 14, pp. 68-75 (1993).

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Attorney, Agent, or Firm—Nora Stein-Fernandez; William T. King; Edward T. Leatz

[57] **ABSTRACT**

A (+) or (-) enantiomer of a compound of formula (I) wherein R⁴ is methyl or ethyl, or a salt, solvate or hydrate thereof, processes for preparing said compounds and pharmaceutical compositions containing them. Compounds of formula (+) are 5-HT₁-like agonists.



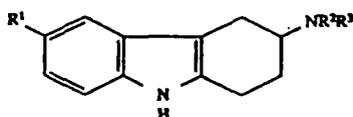
1 Claim, No Drawings

1
PROCESS FOR PREPARING AN
ENANTIOMER OF A CARBAZOLE
DERIVATIVE

This is a continuation of PCT application Ser. No. PCT/EP93/03627, filed Dec. 16, 1993, which claimed priority from GB 9226530.5, filed on Dec. 21, 1992.

The present invention relates to certain tetrahydrocarbazole derivatives, in particular their enantiomeric forms, processes for preparing them, pharmaceutical compositions containing them and their use in therapy, in particular the treatment of migraine.

International Patent Application WO93/00086 describes compounds of the formula:

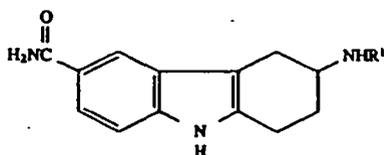


and salts thereof for use in the treatment of conditions wherein a 5-HT₁-like agonist is indicated, in particular migraine.

In the above compounds R¹ represents hydrogen, halogen trifluoromethyl, nitro, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, aryl, C₁₋₆alkoxy, —(CH₂)_nCN, —(CH₂)_nCONR⁵R⁶, —(CH₂)_nSO₂R⁵R⁶, C₁₋₆alkanoylamino(CH₂)_n, or C₁₋₆alkylsulphonylamino(CH₂)_n; R⁴ represents hydrogen, C₁₋₆alkyl or aryl, C₁₋₆alkyl; R⁵ and R⁶ each independently represent hydrogen, or C₁₋₆alkyl, or R⁵ and R⁶ together with the nitrogen atom to which they are attached form a ring; n represents 0, 1 or 2; and R² and R³ each independently represent hydrogen, C₁₋₆alkyl or benzyl or together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino or hexahydroazepino ring. The carbon atom to which the group NR²R³ is attached (i.e. at position 3 of the tetrahydrocarbazole ring) is an asymmetric carbon atom and hence the compounds exist as optically active enantiomers.

WO93/00086 describes inter alia the preparation of the above compounds wherein R¹ is —C(O)NH₂, one of R² and R³ is hydrogen and the other is methyl or ethyl, viz: 6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (as the hydrochloride salt) and 6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole (as the oxalate salt). Both compounds were obtained only as mixtures of enantiomers.

We have now isolated the individual isomers of the above compounds. Thus, in a first aspect the present invention provides the (+) and (–) enantiomers of a compound of formula (I):



Formula (I)

wherein R¹ is methyl or ethyl, or a salt thereof.

In accordance with convention the (+) and (–) designations indicate the direction of rotation of plane-polarised light by the compounds. The prefix (+) indicates that the isomer is dextrorotatory (also designated d) and the prefix (–) indicates the levorotatory isomer (also designated l). The R and S designations denote the absolute configuration as determined by X-ray crystallography.

2

The individual compounds of formula (I) provided by the invention may be named as:

R-(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole; (compound A)

S-(–)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole; (compound B)

R-(+)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole; (compound C)

S-(–)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole. (compound D)

Salts, solvates and hydrates of the above named compounds are also within the scope of the present invention.

It will be appreciated that for use in medicine a physiologically acceptable salt should be employed. Suitable physiologically acceptable salts will be apparent to those skilled in the art and include for example acid addition salts such as those formed with inorganic acids e.g. hydrochloric, hydrobromic, sulphuric or phosphoric acids and organic acids e.g. succinic, tartaric, malonic, citric, malic, acetic, fumaric or methanesulphonic acid. Other non-physiologically acceptable salts e.g. oxalates may be used for example in the isolation of enantiomers of formula (I), and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of enantiomers of formula (I) and their salts.

Acids which have more than one carboxyl group e.g. succinic, tartaric, malonic or citric acids may correspondingly react with more than one molecule of an enantiomer (I), for example succinic acid may react with either one or two molecules of (I) to form either a 1:1 salt (succinate) or a 2:1 salt (hemi-succinate). All such salt forms are encompassed by the present invention; in general the 1:1 salt form is preferred.

Specific salts according to the present invention include:

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole L (+)-tartrate salt (1:1),

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole D (–)-tartrate salt (1:1),

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hemisuccinate (2:1),

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole methanesulphonate,

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole succinate (1:1),

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hydrochloride,

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hydrobromide,

(+)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole succinate (1:1),

(+)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole hydrochloride, and

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole camphorsulphonate.

It will be appreciated that an enantiomer according to the present invention for example a (+) enantiomer, will be substantially free from the corresponding (–) enantiomer, and vice versa. Preferably, a specific enantiomer of the invention will contain less than 10%, e.g. less than 5% and advantageously less than 1% e.g. less than 0.5% of its opposite enantiomer.

In vitro testing (rabbit basilar artery) indicates that for both the methyl and ethyl derivatives of formula (I) the (+) enantiomer is more active than the corresponding (–) enantiomer. The above-named (+)-enantiomers are therefore preferred compounds of the invention.

Enantiomers of formula (I) may be prepared by standard methods, for example:

- (a) Separation of an enantiomeric mixture of a compound of formula (I) or a derivative thereof by chromatography e.g. on a chiral HPLC column.
- (b) Separation of diastereoisomers of a chiral derivative (e.g. a chiral salt) of a compound of formula (I) e.g. by crystallisation, or by chromatography.
- (c) Alkylation of a (+) or (-) enantiomer of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole or a salt thereof,

followed if necessary or desired by converting a derivative of compound (I) so obtained into a compound of formula (I) itself or a different derivative thereof e.g. by removal of any N-protecting group or facilitating group, conversion of a salt into the free base, and/or salt formation.

Separation according to process (a) is generally facilitated by first introducing a readily removable group into the alkylamino moiety of the compound of formula (I). Suitable removable facilitating groups include those commonly used as N-protecting groups e.g. an alkoxycarbonyl group such as t-butyloxycarbonyl or an aralkoxycarbonyl group such as benzoyloxycarbonyl, which groups may be introduced by reaction with for example a di-alkyl-dicarbonate such as di-t-butyl-dicarbonate or a chloroformate such as benzylchloroformate. The resulting enantiomeric mixture can be applied to a chiral HPLC column and fractions containing the individual isomers collected. A facilitating group may be removed by standard methods such as acid hydrolysis or catalytic hydrogenation.

A chiral derivative according to process (b) is a derivative containing at least two chiral centres, such that an enantiomeric mixture of a compound (I) is converted into a pair of diastereoisomers. Such derivatives include chiral salts wherein the anion contains a chiral centre and derivatives of formula (I) in which the alkylamino moiety is substituted by a group containing a chiral centre.

A chiral salt may be prepared for example by reaction of an enantiomeric mixture, such as a 1:1 racemate, of a compound (I) with an optically active acid such as (1S)-(+)-camphorsulphonic acid, d-tartaric acid, l-malic acid, l-mandelic acid, l-gulonic acid, 2,3,4,6-di-O-isopropylidene-2-keto-L-gulonic acid or R-2-pyrrolidone-5-carboxylic acid (also known as D-pyrroglutamic acid) to give two diastereoisomeric salts which may be separated e.g. by crystallisation. The free base form of the desired enantiomer may be obtained by neutralisation with a base such as sodium hydroxide or an ion exchange resin. Preferred optically active acids for use in this process include (1S)-(+)-camphorsulphonic acid and especially R-2-pyrrolidone-5-carboxylic acid.

Alternatively, an optically active reagent such as R- α -methylbenzyloxysuccinimidate may be reacted with an enantiomeric mixture of formula (I), to give a mixture of diastereoisomers which can be separated by chromatography, followed by hydrogenolysis to give the desired enantiomer of formula (I).

A chiral derivative may also be prepared by employing a chiral auxiliary at an earlier stage in the synthesis as described hereinafter. This may advantageously result in a mixture enriched with one diastereoisomer of a compound (I), and most preferably a single diastereoisomer, thus providing a stereoselective synthesis of an enantiomer according to the invention.

Alkylation of an enantiomer of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole according to process (c) may be carried out by standard methods well known in the art. For example alkylation may be achieved indirectly by formation of a group which can be reduced to the desired alkylamino

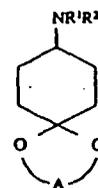
function (reductive alkylation). Thus for example the 3-amino compound can be reacted with an appropriate aldehyde or ketone e.g. formaldehyde, acetaldehyde or acetone, in the presence of a suitable reducing agent such as an alkali metal borohydride or cyanoborohydride e.g. sodium cyanoborohydride. Alternatively formylation may be effected using p-nitrophenol formate in aqueous tetrahydrofuran, using similar reducing conditions. Preferably, the 3-amino compound is first reacted with benzaldehyde, also in the presence of a reducing agent such as a cyanoborohydride, to form 3-N-benzylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole, prior to introduction of the methyl or ethyl group. The benzyl group may subsequently be cleaved by standard methods such as catalytic hydrogenation.

In a further alkylation method, an N-methyl substituent may be introduced by formation of a 3-isothiocyanato derivative e.g. by reaction of the 3-amino compound with carbon disulphide and dicyclohexylcarbodiimide; followed by reduction for example with a borohydride.

It will be appreciated by those skilled in the art that other standard means of alkylation may also be employed.

The starting compounds for use in the above processes may be prepared by methods known in the art for the preparation of tetrahydrocarbazoles, such as the methods described in International Application WO93/00086. Thus for example an enantiomeric mixture of formula (I) may be prepared by reductive alkylation of the corresponding 3-amino compound, as described for process (c) above.

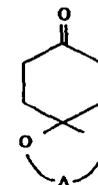
An enantiomeric mixture of formula (I) may also be prepared by reaction of 4-carboxamido-phenylhydrazine, or a salt thereof e.g. the hydrochloride, with 4-(methyl or ethyl)-aminocyclohexanone. In a particular embodiment of this method a protected derivative of the 4-alkylaminocyclohexanone is advantageously employed, e.g. a ketal of formula (II):



Formula (II)

wherein R¹ is as defined for formula (I), R² is hydrogen or an N-protecting group and A is an alkylene moiety, such as ethylene or neopentylene ($-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2-$).

Compounds of formula (II) may themselves be prepared from a protected 1,4-cyclohexane-dione of formula (III):



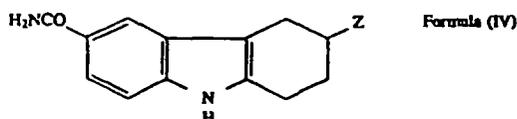
Formula (III)

by reaction with the appropriate alkylamine compound. This reaction may be effected in a suitable solvent, for example a hydrocarbon such as benzene or toluene in the presence of titanium tetrachloride or suitable molecular sieves e.g. 4Å molecular sieves, to give the corresponding iminoketal derivative which may then be converted to an alkylamino compound of formula (II) by catalytic hydrogenation using for example palladium on carbon. Alternatively the reaction may be effected in a solvent such as an alcohol e.g. ethanol and the mixture hydrogenated directly, using e.g. palladium on charcoal, to give a compound of formula (II).

The alkylamino group in the resulting compound of formula (II) may if desired be protected using standard methods. Suitable N-protecting groups are well-known in the art and include for example acyl groups such as acetyl, trifluoroacetyl, or benzoyl; an alkyl- or aralkyloxycarbonyl group such as methoxycarbonyl, t-butoxycarbonyl, benzoyloxycarbonyl or phthaloyl; and aralkyl groups such as benzyl, diphenylmethyl or triphenylmethyl. The protecting groups should be easily removable at the end of the reaction sequence. N-deprotection may be effected by conventional methods, for example an alkoxycarbonyl group such as t-butoxycarbonyl may be cleaved by hydrolysis and an aralkyloxycarbonyl group such as benzoyloxycarbonyl or an aralkyl group such as benzyl may be cleaved by hydrogenolysis.

Cyclisation with 4-carboxamidophenylhydrazine or a salt thereof is preferably carried out with a ketal of formula (II); however if desired the ketal may be converted to the corresponding ketone prior to this reaction.

Yet a further method for preparing an enantiomeric mixture of formula (I) comprises reacting a compound of formula (IV):



wherein Z is a leaving group, such as a halogen atom or a sulphonyloxy (e.g. p-toluenesulphonyloxy or methane-sulphonyloxy) group with an amine H_2NR^1 or a derivative thereof. Said derivative may optionally contain a chiral centre, as in for example R- α -methylbenzylamine, resulting in a diastereoisomeric mixture of the corresponding derivative of formula (I). The diastereoisomers may be separated by chromatography, followed by hydrogenolysis to give the desired enantiomer of formula (I).

An enantiomeric mixture of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole may be prepared in an analogous manner to formula (I), using 4-aminocyclohexanone, optionally protected as a ketal derivative, or an N-protected (e.g. phthalimido) derivative thereof. The enantiomers of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole may be resolved by chiral HPLC as described for process (a) above, using a derivative such as of 3-t-butyloxycarbonylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole; or by formation of a chiral salt of the 3-amino compound in a similar manner to process (b) above, using for example 2,3,4,6-O-isopropylidene-2-keto-L-gulonic acid, followed by selective crystallisation. Such methods are described in International Application WO93/00086.

Enantiomers of formula (I) have been found to be agonists and partial agonists at 5-HT₁-like receptors. Nomenclature of 5-HT receptors is constantly evolving. At least four subtypes of the 5-HT₁ receptor family have been described, namely 5-HT_{1a}, 5-HT_{1b}, 5-HT_{1c} and 5-HT_{1d}. Functional contractile 5-HT₁-like receptors have been identified in the dog saphenous vein and in cerebral (basilar) arteries of various species including rabbit and human. It is now believed that the functional 5-HT₁-like receptor correlates with the 5-HT_{1d} binding site (A. A. Parsons, TIPS, Aug. 1991, Vol 12).

Enantiomers of formula (I) are expected to have utility in the treatment and/or prophylaxis of migraine, with and without aura, tension headache, cluster headache and other forms of cephalic pain and trigeminal neuralgias.

The invention therefore further provides the use of an enantiomer of formula (I) or a physiologically acceptable

salt thereof in the manufacture of a medicament for the treatment of a condition where a 5-HT₁-like agonist is indicated, in particular the treatment or prophylaxis of migraine.

The invention also provides a method of treatment of a condition wherein a 5-HT₁-like agonist is indicated, in particular migraine, which comprises administering to a subject in need thereof an effective amount of an enantiomer of formula (I) or a physiologically acceptable salt thereof.

For use in medicine, a compound of the present invention will usually be administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising an enantiomer of formula (I) or a physiologically acceptable salt thereof and a physiologically acceptable carrier.

The compounds of formula (I) may be administered by any convenient method, for example by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) and their physiologically acceptable salts which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or physiologically acceptable salt in a suitable liquid carrier(s) for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or physiologically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively, the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or a physiologically acceptable salt thereof calculated as the free base.

The physiologically acceptable compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 500 mg, preferably between 10 mg and 400 mg, e.g. between 10 and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of the compound of the formula (I) or a physiologically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

BIOLOGICAL TEST METHODS

5-HT₁-like Receptor Screen

RABBIT BASILAR ARTERY

Experiments were performed in intracranial arteries from rabbit isolated basilar artery in a similar method to that described previously (Parsons and Whalley, 1989, Eur J Pharmacol 174, 189-196.)

In brief, rabbits were killed by overdose with anaesthetic (sodium pentobarbitone). The whole brain was quickly removed and immersed in ice cold modified Krebs's solution and the basilar artery removed with the aid of a dissecting microscope. The Krebs solution was of the following composition (mM) Na⁺ (120); K⁺ (5); Ca²⁺ (2.25)Mg²⁺ (0.5); Cl⁻ (98.5); SO₄²⁻ (1); EDTA (0.04), equilibrated with 95% O₂/5% CO₂. The endothelium was removed by a gentle rubbing of the lumen with a fine metal wire. Arteries were then cut into ring segments (ca 4-5 mm wide) and set up for recording of isometric tension in 50 ml tissue baths in modified Krebs solution with the additional supplement of (mM); Na²⁺ (20); fumarate (10); pyruvate (5); L-glutamate (5) and glucose (10). The arteries were then placed under a resting force of 3-4 mN maintained at 37° C. and the solution bubbled with 95% O₂/5% CO₂.

After tests for initial reactivity with 90 mM KCl depolarising solution and for lack of acetylcholine-induced relaxation of 5-HT (10 mM) precontraction, cumulative concentration-effect curves (2 nM-60 mM) to 5-HT were constructed in the presence of ascorbate 200 mM, cocaine 6 mM, indomethacin 2.8 mM, ketanserin 1 mM and prazosin 1 mM.

Following a 45-60 min wash period, cumulative concentration-effect curves to the test compounds or 5-HT (as a time match control) were constructed in the presence of ascorbate, indomethacin, cocaine, ketanserin and prazosin.

Test Compounds:

R-(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole; (compound A)

S-(-)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole; (compound B)

R-(+)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole; (compound C)

S-(-)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole. (compound D)

Results	EC ₅₀
Compound A	0.03 μM
Compound B	>2 μM
Compound C	0.16 μM
Compound D	2.1 μM

Pharmaceutical Formulations

The following represent typical pharmaceutical formulations according to the present invention, which may be prepared using standard methods.

IV Infusion	
Compound of formula (I)	1-40 mg
Buffer	to pH ca 7
Solvent/complexing agent	to 100 ml
Bolus Injection	
Compound of formula (I)	1-40 mg
Buffer	to pH ca 7
Co-Solvent	to 5 ml
Buffer: Suitable buffers include citrate, phosphate, sodium hydroxide/hydrochloric acid.	
Solvent: Typically water but may also include cyclodextrins (1-100 mg) and co-solvents such as propylene glycol, polyethylene glycol and alcohol.	
Tablet	
Compound	1-40 mg
Diluent/Filler*	50-250 mg
Binder	5-25 mg
Disintegrant*	5-50 mg
Lubricant	1-5 mg
Cyclodextrin	1-100 mg
*may also include cyclodextrins	
Diluent: e.g. Microcrystalline cellulose, lactose, starch	
Binder: e.g. Polyvinylpyrrolidone, hydroxypropylmethylcellulose	
Disintegrant: e.g. Sodium starch glycolate, croscopolone	
Lubricant: e.g. Magnesium stearate, sodium stearyl fumarate.	
Oral Suspension	
Compound	1-40 mg
Suspending Agent	0.1-10 mg
Diluent	20-60 mg
Preservative	0.01-1.0 mg
Buffer	to pH ca 5-8
Co-solvent	0-40 mg
Flavour	0.01-1.0 mg
Colourant	0.001-0.1 mg
Suspending agent: e.g. Xanthan gum, microcrystalline cellulose	
Diluent: e.g. sorbitol solution, typically water	
Preservative: e.g. sodium benzoate	
Buffer: e.g. citrate	
Co-solvent: e.g. alcohol, propylene glycol, polyethylene glycol, cyclodextrin	

PREPARATION I

(±)-3-Amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole

4-Carboxamidophenylhydrazine hydrochloride (2.87 g) and 4-phthalimidocyclohexanone (3.00 g) were mixed in acetic acid and the mixture was heated under reflux for 2 hr.

After cooling, the mixture was neutralized using aq. potassium carbonate solution, and the yellow solid thus obtained was filtered, washed with water, and dried. Purification by column chromatography (SiO_2 ; $\text{CHCl}_3/\text{CH}_2\text{OH}$) gave 6-carboxamido-3-phthalimido-1,2,3,4-tetrahydrocarbazole (2.8 g).

The above product (1.0 g) was suspended in ethanol (10 ml) and hydrazine hydrate (5 ml) was added. A clear solution was obtained, and the mixture was left to stir overnight, to yield a precipitate. The whole mixture was evaporated to dryness, washed with aq. K_2CO_3 solution, and water, to leave the title compound 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (0.44 g), as the monohydrate, mp. $146^\circ\text{--}148^\circ\text{C}$.

^1H NMR [250 MHz, $\text{DMSO}-d_6$] δ 1.49–1.77 (1H,m), 1.83–2.03 (1H,m), 2.17–2.40 (1H,m), 2.62–2.80 (2H,m), 2.90 (1H,dd), 1 signal obscured by H_2O at ca. 3.1, 7.03 (1H,brd.s), 7.18 (1H,d), 7.58 (1H,d), 7.83 (1H,brd.s), 7.98 (1H,s).

PREPARATION 2

(+) and

(-)-2-Amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride

Method 1

(\pm)-3-*t*-Butyloxycarbonylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole was separated into its enantiomers using chiral HPLC: (chiralcel OD 4.6 mm column, eluting with hexane/ethanol 85:15). The (+)-enantiomer was collected first and had mp= $150^\circ\text{--}152^\circ\text{C}$. and $[\alpha]_D^{25} = +70.1$ (in methanol, 0.41% w/v). The (-)-enantiomer had mp= $150^\circ\text{--}152^\circ\text{C}$. and $[\alpha]_D^{25} = -79.4$ (in methanol, 0.40% w/v). The (+)-enantiomer was converted to the parent amine hydrochloride by treating with HCl gas in dioxane, to furnish the (+)-enantiomer of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride, mp= $248^\circ\text{--}251^\circ\text{C}$., $[\alpha]_D^{25} = +26.2$ (in methanol, 0.50% w/v). The (-)-enantiomer of 3-*t*-butyloxycarbonylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole was similarly converted into the (-)-enantiomer of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride, mp= $248^\circ\text{--}251^\circ\text{C}$., $[\alpha]_D^{25} = -28.6$ (in methanol, 0.50% w/v).

Method 2

(\pm)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole was treated with one equivalent of 2,3:4,6-di-*O*-isopropylidene-2-keto-*L*-gulonic acid in methanol to give the salt of the (+)-enantiomer, in 38% yield (with respect to racemate) and 84% enantiomeric excess (ee). This material was recrystallized twice from methanol to give the salt of the (+)-enantiomer in 25% overall yield (with respect to racemate), and >98% ee. This product was converted to the hydrochloride salt first by treatment with aqueous alkali, and the precipitated free base treated with 2M aq. HCl in ethanol, to give (+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride.

PREPARATION 3

(\pm)-6-Carboxamido-3-*N*-methylamino-1,2,3,4-tetrahydrocarbazole hydrochloride

4-Cyanophenyl hydrazine hydrochloride (20.2 g) and 4-benzoyloxycyclohexanone (25.9 g) were dissolved in glacial acetic acid (400 ml) and the mixture was heated under reflux for 1.5 hr. After allowing to cool, the mixture was

filtered, and the filtrate was evaporated to dryness, and neutralized with aqueous sodium bicarbonate solution to give a solid precipitate, which was purified by chromatography (SiO_2 ; hexane/ethyl acetate) to give 3-benzoyloxy-6-cyano-1,2,3,4-tetrahydrocarbazole (18 g). This product (11.6 g) was suspended in ethanol (230 ml) and treated with 2.5% aqueous potassium hydroxide solution (120 ml), and heated under reflux for 1 hr. The cooled mixture was neutralized with glacial acetic acid and evaporated to a solid residue, which was washed with water, and dried to give 3-hydroxy-6-cyano-1,2,3,4-tetrahydrocarbazole (6.6 g).

The above product (3.57 g) was dissolved in dry pyridine (35 ml) and treated with tosyl chloride (3.51 g) in dry pyridine (35 ml), and the mixture was stirred at 100°C . for 2 hr. After cooling, the solution was poured into water (500 ml), extracted with ethyl acetate, and the latter extract was washed with 2M HCl, dried (MgSO_4) and evaporated to dryness. Purification by chromatography (SiO_2 ; hexane/ethyl acetate) gave 3-tosyloxy-6-cyano-1,2,3,4-tetrahydrocarbazole (0.53 g).

This product (0.40 g) was dissolved in 33% methylamine in alcohol (25 ml) and heated at 100°C . in a sealed steel vessel for 1.5 hr. After cooling, the mixture was evaporated to dryness and purified by chromatography (SiO_2 ; chloroform/methanol) to give 3-methylamino-6-cyano-1,2,3,4-tetrahydrocarbazole (0.13 g).

The above product (0.12 g) was dissolved in THF (10 ml) and reacted with di-*tert*-butyl dicarbonate (0.36 g) in THF (3 ml) at room temperature overnight. The reaction mixture was evaporated to dryness, partitioned between 2M sodium bicarbonate solution and ethyl acetate, and the organic extract dried and evaporated to give a white solid. This was triturated with ether/hexane to give 3-*t*-butyloxycarbonylmethylamino-6-cyano-1,2,3,4-tetrahydrocarbazole (0.14 g).

This product (0.14 g) was dissolved in methanol (15 ml) and treated with a mixture of 20% aqueous sodium hydroxide (0.20 ml) and 30% hydrogen peroxide (0.20 ml), and the whole mixture was stirred at room temperature overnight. Sodium metabisulphite (38 mg) was added, and the solution was evaporated to dryness, and chromatographed (SiO_2 ; chloroform/10% NH_4OH in methanol) to give 3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (0.12 g). The above compound (0.11 g) was dissolved in methanol (10 ml), and treated with 3M hydrochloric acid at room temperature. The mixture was evaporated to dryness, azeotroping with ethanol to give a solid, which was recrystallized from methanol/ether to give the title compound, mp $327^\circ\text{--}328^\circ\text{C}$. (80 mg).

^1H NMR [250 MHz, $\text{MeOH}-d_4$] δ 1.98–2.20 (1H,m), 2.29–2.49 (1H,m), 2.75–2.90 (5H, s+m), 2.90–3.09 (2H, m), 3.52–3.69 (1H, m), 7.31 (1H, d), 7.63 (1H, d), 8.05 (1H, s).

PREPARATION 4

(\pm)-6-Carboxamido-3-*N*-ethylamino-1,2,3,4-tetrahydrocarbazole oxalate

1,4-Cyclohexanedione mono-2,2'-dimethyl trimethylene ketal (2.00 g) was mixed with anhydrous ethylamine (10.0 g) and benzene (10 ml), and the mixture was cooled to 5°C . A solution of titanium tetrachloride (0.95 g) in benzene (10 ml) was added, dropwise, then the mixture was stirred at room temperature for 1 hr. The mixture was filtered, and evaporated to dryness to give an oil, which was dissolved in ethanol (30 ml). To this solution was added palladium-on-carbon catalyst (100 mg), and the mixture was hydrogenated

11

at 50 psi pressure overnight. The catalyst was filtered off and the ethanol evaporated to leave 4-ethylamino-cyclohexanone 2,2'-dimethyl trimethylene ketal as an oil (2.0 g).

This compound (0.80 g) was dissolved in formic acid (20 ml) and the solution was heated to 90° C. for 1 hr. Formic acid was evaporated, and the residue was partitioned between chloroform and 1M hydrochloric acid. The aqueous layer was evaporated to dryness to give 4-ethylaminocyclohexanone (0.40 g).

A mixture of the above product (0.40 g) and 4-carboxamidophenyl hydrazine hydrochloride (0.60 g) in glacial acetic acid (20 ml) was heated under reflux for 1 hr. The acid was evaporated in vacuo to an oil, which was purified by chromatography (SiO₂; CHCl₃/10% NH₃ in MeOH) to give an oil (0.50 g). Part of this product (150 mg) was dissolved in methanol and treated with oxalic acid. The solution was treated with ether to give the title compound as a crystalline solid, mp 165°-170° C. (100 mg).

¹H NMR (250 MHz, DMSO-d₆) δ 1.25 (3H, t), 1.81-2.05 (1H, m), 2.20-2.38 (1H, m), 2.61-2.79 (1H, m), 2.79-2.94 (2H, m), 2.98-3.28 (3H, dd+ts), 3.41-3.60 (1H, m), 7.08 (1H, brd. s), 7.28 (1H, d), 7.60 (1H, d), 7.82 (1H, brd. s), 8.00 (1H, s), 11.12 (1H, s).

PREPARATION 5

(±)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole

A solution of (±)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hydrochloride salt (6.0 g) in water (60 ml) at 68° C. was basified to pH 10.5 with 5M aqueous sodium hydroxide. The resultant mixture was extracted with butan-1-ol (30 ml, 15 ml). These extracts were combined and evaporated to give the title compound as a dark oil (6.96 g) containing ca. 46% w/w butan-1-ol.

¹H NMR (400 MHz, d₆-DMSO) δ 1.40-2.00 (1H, br), 1.62 (1H, m), 2.06 (1H, m), 2.33 (1H, m), 2.39 (3H, s), 2.77 (3H, m), 2.97 (1H, dd), 7.02 (1H, s), 7.24 (1H, d), 7.59 (1H, dd), 7.80 (1H, s), 7.99 (1H, d), 10.93 (1H, s)+peaks due to butan-1-ol.

PREPARATION 6

4-Methylaminocyclohexanone (2,2'-dimethyltrimethylene) ketal hydrochloride

1,4-Cyclohexanedione (mono-2,2'-dimethyltrimethylene) ketal (50 g) was dissolved in dry toluene (500 ml) in a flask fitted with a dry ice trap and flushed with nitrogen with stirring. Methylamine (47.0 g) was then added dropwise to the reaction mixture, at 20° C. slowly to allow dissolution in the toluene. Molecular sieves (32.0 g) were then added and the reaction mixture stirred at 20° C. under an air lock. The reaction was complete after ca. 4 h (>97%). The sieves were then filtered off and the clear amber filtrate evaporated to a volume of 160 ml. The concentrated solution of iminoketal was diluted with ethanol (340 ml) and degassed with argon. Palladium catalyst (palladium on charcoal, 3.55 g) was added and the mixture hydrogenated at atmospheric pressure and 20° C. for 24 h. When hydrogen uptake was complete the reaction mixture was filtered through Celite and the Celite bed washed with a little ethanol (2x25 ml). The solvent was then removed under reduced pressure to give the ketal amine as an amber oil, (49.12 g, 92%).

The ketal amine (80 g, 0.375 Mol) was dissolved in isopropyl ether with stirring. A solution of HCl in isopropyl ether (prepared by bubbling a known weight of gas into a

12

known volume of solvent) was added dropwise causing the formation of an immediate white precipitate, which became very thick as the addition was completed. The thick suspension was stirred for a further 30 minutes, filtered off, and the product washed with a little fresh isopropyl ether and then dried under vacuum to give the title compound as a white, free flowing powder (84.01 g).

¹H NMR: [270 MHz, CDCl₃] δ 9.51 (2H, bs), 3.48 (4H, d), 3.00 (1H, m), 2.73 (3H, t), 2.32 (2H, d), 2.15 (2H, d), 1.85, (2H, dq), 1.41 (2H, d), 0.96 (6H, s).

PREPARATION 7

(±)-6-Carboxamide-3-methylamino-1,2,3,4-tetrahydrocarbazole hydrochloride

4-Aminobenzamide (3.0 g) was dissolved in 5N HCl (20 ml) cooled to -5° to 0° C. with stirring and the mixture further cooled to around -15° C. Sodium nitrite (1.98 g) in water (4.4 ml) was added dropwise with stirring at such a rate that the temperature was maintained at between -10° to -15° C. The mixture was then stirred at around -8° C. for 30 min. Ice cold water (40 ml) was then added followed by solid sodium dithionite (7.7 g) in a single portion, the means of cooling removed and the mixture stirred at around 15° C. for 30 min. To the resulting yellow suspension was added conc. HCl (30 ml) followed by 4-methylaminocyclohexanone (2,2'-dimethyltrimethylene) ketal hydrochloride (5.488 g) and the mixture heated to around 70° C., not allowing the reaction temperature to rise above 75° C. After ca. 2 h, the reaction mixture was cooled to 20° C. and the dark solution then carefully neutralised with caustic (aq., 40%) to pH 10 maintaining the temperature between 15°-20° C., whereupon a thick precipitate formed to give the title compound. The reaction mixture was then left to stir overnight and the precipitate filtered off and dried (3.88 g, 63%).

¹H nmr [250 MHz, d₆-DMSO] δ=11.21 (1H, s), 8.06 (1H, s), 7.89 (1H, bs), 7.63 (1H, d), 7.28 (1H, d), 7.10 (1H, bs), 3.50-3.15 (2H, m), 2.95-2.70 (3H, m), 2.62 (3H, s), 2.33 (1H, m), 1.97 (1H, m).

PREPARATION 8

4-Methylaminocyclohexanone (2,2'-dimethyltrimethylene) ketal hydrochloride

1,4-Cyclohexanedione mono-2,2'-dimethyltrimethylene ketal (20.0 g, 0.101 mol) was dissolved in ethanol (200 ml) containing methylamine (8.0 g, 0.258 mol). The resultant solution was hydrogenated at 30 psi over 10% Pd/C catalyst (2.0 g) for 4 hrs at room temperature. The reaction mixture was filtered through a celite pad and the filtrate evaporated under reduced pressure to give an oil (21.4 g).

The oil was dissolved in tetrahydrofuran (210 ml) and the resultant solution cooled in an ice/water bath while conc. HCl (10.5 ml) was added to the stirred solution in two portions such that the temperature did not rise above 15° C. and then filtered. The solid was washed with THF (50 ml) and air dried overnight to give the title compound (22.80 g), mp 245.1° C. (EtOH).

¹H nmr (250 MHz, d₆-DMSO) δ 0.9 (s, 6H), 1.3 (q, 2H), 1.45 (q, 2H), 1.9 (brd, 2H), 2.25 (brd, 2H), 2.5 (s, 3H), 3.0 (m, 1H), 3.5 (d, 4H).

EXAMPLE 1

(+) and (-)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hydrochloride

(a) To a stirred solution of (\pm)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hydrochloride (0.3 g) in propan-2-ol/saturated aqueous potassium hydrogen carbonate (20:1 21 ml), di-tert-butyl dicarbonate (0.425 g) was added and stirring continued for 1 hour. The mixture was diluted with ethyl acetate (50 ml) washed with water (2x20 ml), dried ($MgSO_4$) and solvent removed at reduced pressure to give (\pm)-3-N-tert-butoxycarbonyl-N-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (0.36 g).

1H NMR (d_6 -DMSO) δ 1.47(s,9H), 1.84-2.08(m,2H), 2.71-2.94(m,4H), 2.80(s,3H), 4.26(m,1H), 7.02(br.s,1H), 7.25(d,1H), 7.57(d,1H), 7.76(br.s,1H), 7.97(s,1H) and 10.96(s,1H).

(b) The (+) and the (-) enantiomers (\pm)-3-N-tert-butoxycarbonyl-N-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (0.3 g) were separated by chiral HPLC: (chiralpak AD 20 mm column, hexane:ethanol 9:1 eluant).

Treatment of the first eluting enantiomer (0.02 g) with 3N aqueous hydrochloric acid/methanol 1:1 (4 ml) for 16 hours, filtration and removal of solvent gave, after recrystallisation from methanol/diethyl ether, the (+) enantiomer of the title compound (0.009 g) m.p. 219°-225° C., $[\alpha]_D^{25} C = +25.4$ (methanol 0.063% w/v).

Treatment of the second eluting enantiomer (0.03 g) under similar conditions gave the (-) enantiomer of the title compound (0.02 g), m.p. 219°-225° C. $[\alpha]_D^{25} C = -23.3$ (methanol 0.116% w/v).

EXAMPLE 2

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole

(a) To a solution of (\pm)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.77 g) in dimethylformamide (70 ml), triethylamine (0.62 g) and benzyl chloroformate (0.47 g) were added. The solution was stirred overnight, further triethylamine (0.27 g) and benzyl chloroformate (0.26 g) added and the mixture stirred for 4 hours. The reaction mixture was poured into water (500 ml), and extracted with ethyl acetate (2x50 ml). The combined extracts were dried ($MgSO_4$) and solvent was removed at reduced pressure. The residue was recrystallised from methanol/water to give (\pm)-3-N-benzyloxycarbonyl-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.62 g) m.p. 103°-110° C.

(b) The (+) and (-) enantiomers of (\pm)-3-N-benzyloxycarbonyl-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole were separated by chiral HPLC (OD column, eluant hexane/ethanol 4:1).

The first eluting enantiomer (0.23 g) m.p. 105°-106° C., $[\alpha]_D^{25} C = +157.2$ (ethanol, 0.39% w/v).

The second eluting enantiomer (0.23 g) m.p. 105°-106° C., $[\alpha]_D^{25} C = -163.1$ (ethanol, 0.23% w/v).

(c) A solution of (+)-3-N-benzyloxycarbonyl-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.23 g) in ethanol (20 ml) containing 10% palladium/charcoal (0.23 g) was shaken under a hydrogen atmo-

sphere (50 psi) for 3 hours. Catalyst was removed by filtration and solvent removed at reduced pressure to give the (+) enantiomer of the title compound (free base) as a foam m.p. 98°-102° C., $[\alpha]_D^{25} C = +61.2$.

EXAMPLE 3

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole camphorsulphonate

To a solution of (\pm)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (3 g) in methanol (20 ml), a solution of (1S)-(+)-10-camphorsulphonic acid (2.86 g) in methanol was added. Solvent was removed at reduced pressure and the residue recrystallised ten times to give the (+) enantiomer of the title compound as the camphorsulphonate salt m.p. 177°-180° C. This was treated with 2 equivalents of triethylamine and 10 equivalents of 2,3,4,6-tetra-O-acetyl-beta-D-glucopyranosylisothiocyanate in dimethylformamide at room temperature for 30 minutes. Aliquots of the reaction mixture were removed from the mixture for HPLC analysis. Analytical HPLC of the 2,3,4,6-tetra-O-acetyl-beta-D-glucopyranosylthiourea derivative (C18 Novapak, eluant methanol/50 mM NaH_2PO_4 pH 2.9) gave the same retention time as the same derivative prepared from the (+) enantiomer of Example 1 and showed the material was 99% ee.

EXAMPLE 4

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole succinate (1:1)

(a) Benzaldehyde (10.6 g) was added to a suspension of (+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (12.35 g) in methanol (100 ml). The mixture was stirred for 1 hour, sodium cyanoborohydride (9.3 g) added over 1 hour and the clear solution stirred for 24 hours. The solution was cooled (ice bath) and formaldehyde (37% aqueous methanolic, 9:1 solution, 5.5 ml) added. After 30 minutes stirring at room temperature water (100 ml) was added, stirring continued for 30 minutes followed by extraction with dichloromethane (3x150 ml). The combined organic extracts were washed with water (2x200 ml), dried (Na_2SO_4), filtered and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, dichloromethane-10% ethanol/dichloromethane) to give 3-N-benzyl-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (9.4 g) as a foam. The succinate salt (1:1) was recrystallised from methanol m.p. 175°-182° C.

1H NMR (d_6 -DMSO) δ 1.81-1.96(m,1H), 2.09-2.21(m,1H), 2.29(s,3H), 2.44(s,4H), 2.66-3.11(m,5H), 3.76(q,2H), 7.05(br.s,1H), 7.22-7.43(m,6H), 7.59(d,1H), 7.79(br. s,1H), 8.03(s,1H), and 10.94(s,1H).

(b) To a solution of 3-N-benzyl-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (1.0 g) in ethanol (100 ml) containing succinic acid (0.39 g), Pearlman's catalyst (1.0 g) was added and the mixture shaken under an atmosphere of hydrogen at 45 psi and 50° C. for 2 hours. The mixture was filtered (celite pad) and the pad washed thoroughly with ethanol. The combined filtrate and washings were evaporated to dryness, co-evaporated with ethanol (3x100 ml) and recrystallised from methanol to give the title compound [(1:1) succinate salt] m.p. 148°-155° C.

15

¹H NMR (d₆-DMSO) δ 1.84(m,1H), 2.15-2.34(m,1H), 2.28(s,4H), 2.57(m,1H), 2.61(s,3H), 2.83(m,2H), 3.13(dd,1H), 3.29(m,1H), 7.08(br s,1H), 7.26(d,1H), 7.60(dd,1H), 7.82(br s,1H), 8.01(d,1H) and 11.08(s,1H).

EXAMPLE 5

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole

- (a) To a solution of (+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (5 g) in pyridine (150 ml), dicyclohexylcarbodiimide (4.13 g) was added followed by carbon disulphide (1.67 g). The solution was stirred for 1 hour, solvent removed at reduced pressure and the residue co-evaporated with toluene (3×100 ml). The residue was recrystallised from methanol to give 6-carboxamido-3-isothiocyanato-1,2,3,4-tetrahydrocarbazole (5.06 g) m.p. 245°-248° C.
- (b) A solution of 6-carboxamido-3-isothiocyanato-1,2,3,4-tetrahydrocarbazole (0.25 g) in ethanol (40 ml) was treated with sodium borohydride (0.17 g) in one portion and stirred for 18 hours. Acetone (5 ml) was added the mixture stirred for a further 1 hour and solvent removed at reduced pressure. The residue was column chromatographed (basic alumina, 5% methanol/dichloromethane eluant) to give the title compound (0.11 g) having the same physico chemical characteristics as the product of Example 2.

EXAMPLE 6

(+)- and (-)-6-Carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole hydrochloride

- (a) From (±)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole (0.26 g), (±)-3-N-tert butoxycarbonyl-N-ethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (0.27 g) isolated as an oil was prepared according to the procedure of Example 1.
- ¹H NMR (d₆-DMSO) δ 1.1(t,3H), 1.23(s,9H) 1.92(m,1H), 2.09(m,1H), 2.78-2.92(m,4H), 3.21-3.62(m,2H), 4.21(m,1H), 7.04(br.s,1H), 7.24(d,1H), 7.58(d,1H), 7.76(br.s,1H), 7.99(s,1H) and 10.99(s,1H).
- (b) From (±)-3-N-tert butoxycarbonyl-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole (0.25 g), the (+)- and the (-)-enantiomers of 3-N-tert butoxycarbonyl-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole were prepared by chiral HPLC (chiralcel OD 4.67 mm, eluant hexane/ethanol 92/8).
- Treatment of the enantiomer eluting first, (0.06 g) [α]_D²⁵ C = +108.2 (ethanol 0.9% w/v) with hydrochloric acid/methanol according to the method of Example 1 gave (+)-6-carboxamido-N-ethylamino-1,2,3,4-tetrahydrocarbazole hydrochloride (0.04 g) m.p. 211°-221° C. [α]_D²⁵ C = +37.2 (methanol, 0.12% w/v).
- Treatment of the second eluting enantiomer (80 mg) [α]_D²⁵ C = -103.5 (ethanol, 0.19% w/v) with hydrochloric acid/methanol according to the method of Example 1 gave (-)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole hydrochloride (0.05 g) m.p. 211°-221° C. after recrystallisation from methanol/diethyl ether [α]_D²⁵ C = -33.6 (methanol, 0.11% w/v).

16

EXAMPLE 7

(+)-6-Carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole succinate (1:1)

- (a) From (+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (1.15 g), (+)-3-benzyl-N-ethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (1.26 g) was obtained according to the procedure of Example 4 replacing formaldehyde with acetaldehyde (0.44 g). The succinate salt (1:1) was prepared by addition of succinic acid (0.4 g) to the free base (1.08 g) and recrystallisation from propan-2-ol m.p. 130°-140° C.
- ¹H NMR (d₆-DMSO) δ 1.05(t,3H), 1.85(m,1H), 2.10(m,1H), 2.40(s,4H), 2.58-2.91(m,5H), 3.06(m,1H), 3.77(q,2H), 7.03(br.s,1H), 7.17-7.47(m,5H), 7.58(d,1H), 7.78(br.s,1H), 8.00(s,1H), 10.90(s,1H) and 12.28(br.s,2H).
- (b) Recrystallisation of (+)-3-N-benzyl-N-ethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole succinate (1.36 g), from methanol, according to the procedure of Example 4 gave the title compound (1.04 g) m.p. 165°-167° C.
- ¹H NMR (d₆-DMSO) δ 1.19(t,3H), 1.86(m,1H), 2.23(m,1H), 2.30(s,4H), 2.62(m,1H), 2.85(m,2H), 3.02(q,2H), 3.14(m,1H), 3.38(m,1H), 7.08(br.s,1H), 7.26(d,1H), 7.59(d,1H), 7.80(br.s,1H), 8.00(s,1H) and 11.08(s,1H).

EXAMPLE 8

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole L (+)-tartrate salt (1:1)

- To a hot solution of (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.25 g) in methanol/water (11:1, 24 ml) L (+)-tartaric acid (0.15 g) was added and the solution allowed to stand for 3 hours. The crystalline title compound (0.30 g) was isolated by filtration. m.p. 195°-197° C.
- ¹H NMR (d₆-DMSO) δ 1.92(m,1H), 2.25(m,1H), 2.67(s,3H), 2.68(m,1H), 2.84(m,2H), 3.17(dd,1H), 3.43(m,1H), 3.87(s,2H), 7.07(br.s,1H), 7.27(d,1H), 7.61(d,1H), 7.82(br.s,1H), 8.01(s,1H) and 11.11(s,1H).

EXAMPLE 9

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole D (-)-tartrate salt (1:1)

- To a hot solution of (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.25 g) in methanol (9 ml) D (-)-tartaric acid (0.15 g) was added and the solution allowed to stand for 3 hours. The crystalline title compound (0.32 g) was isolated by filtration m.p. softens above 147° C.
- ¹H NMR (d₆-DMSO) δ 1.92(m,1H), 2.25(m,1H), 2.67(s,3H), 2.68(m,1H), 2.84(m,2H), 3.17(dd,1H), 3.43(m,1H), 3.87(s,2H), 7.07(br.s,1H), 7.27(d,1H), 7.61(d,1H), 7.82(br.s,1H), 8.02(s,1H) and 11.09(s,1H).

EXAMPLE 10

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hemisuccinate (2:1)

- To a hot solution of (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.30 g) in propan-2-ol was added succinic acid (0.07 g) and the solution allowed to stand for 3 hours. The title compound (0.21 g) was isolated by filtration. m.p. 220°-235° C.

17

¹H NMR (d₆-DMSO)δ 1.77(m,1H), 2.14(m,1H), 2.26(s, 2H), 2.54(s,3H), 2.55(m,1H), 2.79(m,2H), 3.10(dd,1H), 3.43(m,1H), 7.06(br.s,1H), 7.25(d,1H), 7.59(d,1H), 7.82(br.s,1H), 7.99(s,1H) and 11.01(s,1H).

EXAMPLE 11

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole methanesulphonate

To a hot solution of (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.30 g) in propan-2-ol/ethyl acetate methanesulphonic acid (0.12 g) was added and the solution allowed to stand for 3 hours. The title compound (0.33 g) was isolated as a gum.

¹H NMR (d₆-DMSO)δ 1.93(m,1H), 2.25(m,1H), 2.35(s, 3H), 2.70(m,4H), 2.86(m,2H), 3.10(dd,1H), 3.50(m,1H), 7.11(br.s,1H), 7.27(d,1H), 7.61(d,1H), 7.82(br.s,1H), 8.02(s, 1H), 8.65(br.s,2H) and 11.12(s,1H).

EXAMPLE 12

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hydrobromide

Hydrogen bromide gas was passed through a solution of (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.30 g) in ethanol (50 ml) for 15 seconds. After 30 minutes the title compound (0.03 g) m.p. 205°-208° C. was separated by filtration and washed with ethanol.

¹H NMR (d₆-DMSO) δ 1.94(m,1H), 2.25(m,1H), 2.26(s, 2H), 2.70(m,4H), 2.85(m,2H), 3.17(dd,1H), 7.10(br.s,1H), 7.27(d,1H), 7.61(d,1H), 7.82(br.s,1H), 8.02(s,1H) 8.67(br.s, 2H) and 11.01(s,1H).

EXAMPLE 13

a) (+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole-R-2-pyrrolidone-5-carboxylic acid salt

To a solution of (±)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (6.96 g containing ca. 46% w/w butan-1-ol, prepared as in Preparation 5) in ethanol (50 ml), stirred at ambient temperature, was added a solution of R-2-pyrrolidone-5-carboxylic acid (1.00 g, e.e.>99%) in hot ethanol (33 ml). The resultant mixture was stirred at ambient temperature for 40 h. The crystalline product was filtered off under nitrogen, washed with a small volume of ethanol, then dried in vacuo at 60° C. (Yield=2.63 g).

18

This product was dissolved in water (2.6 ml), and the solution was then diluted with ethanol (130 ml) and stirred at ambient temperature for 40 h. The crystalline product was filtered off, washed and dried as before. (Yield=1.72 g).

⁵ This product was recrystallised from ethanol (90 ml)/water (1.8 ml) as described above to give the title compound (1.44 g; e.e.⇒99%).

¹⁰ ¹H NMR [250 MHz, d₆-DMSO]δ 1.90 (2H,m), 2.06 (2H,m), 2.19 (2H, m), 2.57 (3H,s), 2.62 (1H,m), 2.82 (2H,m), 3.15 (2H,m), 3.80 (1H,dd), 7.07 (1H,s), 7.26 (1H,d), 7.59 (1H,s), 7.62 (1H,s), 7.84 (1H,s), 8.00 (1H,s), 11.10 (1H,s)+peaks due to ethanol.

¹⁵ b) (+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole succinate salt, monohydrate

²⁰ A solution of (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole R-2-pyrrolidone-5-carboxylic acid salt (1.34 g) in water (5.4 ml) was basified to pH 1.32 with 5M aqueous sodium hydroxide. The resultant mixture was extracted with butan-1-ol (5.4 ml). This extract was evaporated to give (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole as an oil/solid (735 mg) containing ca. 2% w/w butan-1-ol.

A portion of this product (232 mg) was dissolved in ethanol (1.45 ml). This solution was filtered, and added dropwise to a stirred solution of succinic acid (110 mg) in ethanol (1.45 ml)/water (0.48 ml). The mixture was seeded before the addition was complete. Stirring was continued for 30 min at ambient temperature, then 30 min at 0° C. The crystalline product was filtered off, washed with a small volume of ethanol, then dried in vacuo at 60° C. Yield=233 mg.

³⁰ ³⁵ ¹H NMR [250 MHz, d₆-DMSO]δ 1.87 (1H,m), 2.25 (1H,m), 2.29 (4H,s), 2.62 (3H,s), 2.65 (1H,m), 2.83 (2H,m), 3.15 (1H,dd), 3.34 (1H,m), 7.09 (1H,s), 7.27 (1H,d), 7.61 (1H,dd), 7.84 (1H,s), 8.02 (1H,s), 11.10 (1H,s).

We claim:

⁴⁰ 1. A process for preparing (+)-6-carboxamido-3-methylamino-1,2,3,4-tetrahydrocarbazole or a salt, solvate or hydrate thereof which comprises separation of diastereoisomers of a chiral derivative formed by reaction of (±)-6-carboxamido-3-methylamino-1,2,3,4-tetrahydrocarbazole with R-2-pyrrolidone-5-carboxylic acid, by crystallization, or by chromatography.

* * * * *



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[54] ENANTIOMERS OF CARBAZOLE
DERIVATIVES AS 5-HT₁-LIKE AGONISTS

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- [52] U.S. Cl. 514/411; 548/448
- [58] Field of Search 548/448; 514/411

[56] References Cited

U.S. PATENT DOCUMENTS

4,257,952 3/1981 Mooradian 548/448

FOREIGN PATENT DOCUMENTS

WO93/00086 1/1993 WIPO .

OTHER PUBLICATIONS

Hacksell et al., "Chirality in drug research and design",
Trends in Biotechnology, vol. 11, pp. 73-74 (1993).

Ariens, "Nonchiral, homochiral and composite chiral
drugs", *Trends in Pharmacological Sciences*, vol. 14, pp.
68-75 (1993).

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[57] ABSTRACT

A (+)or (-) enantiomer of a compound of formula (I)
wherein R^o is methyl or ethyl, or a salt, solvate or hydrate
thereof, processes for preparing said compounds and phar-
maceutical compositions containing them. Compounds of
formula (+) are 5-HT₁-like agonists.

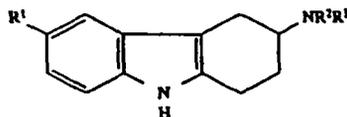
12 Claims, No Drawings

1
ENANTIOMERS OF CARBAZOLE
DERIVATIVES AS 5-HT₁-LIKE AGONISTS

This is a continuation of PCT application Ser. No. PCT/EP93/03627 filed Dec. 16, 1993 which claimed priority from GB 9226530.5 filed on Dec. 21, 1992.

The present invention relates to certain tetrahydrocarbazole derivatives, in particular their enantiomeric forms, processes for preparing them, pharmaceutical compositions containing them and their use in therapy, in particular the treatment of migraine.

International Patent Application WO93/00086 describes compounds of the formula:



and salts thereof for use in the treatment of conditions wherein a 5-HT₁-like agonist is indicated, in particular migraine.

In the above compounds R¹ represents hydrogen, halogen, trifluoromethyl, nitro, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, arylC₁₋₆alkoxy, —CO₂R⁴, —(CH₂)_nCN, —(CH₂)_nCONR²R⁶, —(CH₂)_nSO₂NR²R⁶, C₁₋₆alkanoylamino(CH₂)_n, or C₁₋₆alkylsulphonylamino(CH₂)_n; R⁴ represents hydrogen, C₁₋₆alkyl or arylC₁₋₆alkyl; R² and R⁶ each independently represent hydrogen, or C₁₋₆alkyl, or R² and R⁶ together with the nitrogen atom to which they are attached form a ring; n represents 0, 1 or 2; and R² and R³ each independently represent hydrogen, C₁₋₆alkyl or benzyl or together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino or hexahydroazepino ring. The carbon atom to which the group NR²R³ is attached (i.e. at position 3 of the tetrahydrocarbazole ring) is an asymmetric carbon atom and hence the compounds exist as optically active enantiomers.

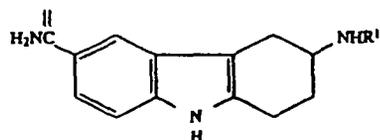
WO93/00086 describes inter alia the preparation of the above compounds wherein

R¹ is —C(O)NH₂, one of R² and R³ is hydrogen and the other is methyl or ethyl, viz:

6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (as the hydrochloride salt) and

6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole (as the oxalate salt). Both compounds were obtained only as mixtures of enantiomers.

We have now isolated the individual isomers of the above compounds. Thus, in a first aspect the present invention provides the (+) and (–) enantiomers of a compound of formula (I):



Formula (I)

wherein R¹ is methyl or ethyl, or a salt thereof.

In accordance with convention the (+) and (–) designations indicate the direction of rotation of plane-polarised light by the compounds. The prefix (+) indicates that the isomer is dextrorotatory (also designated d) and the prefix (–) indicates the levorotatory isomer (also designated l). The R and S designations denote the absolute configuration as determined by X-ray crystallography.

2

The individual compounds of formula (I) provided by the invention may be named as:

R-(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole; (compound A)

S-(–)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole; (compound B)

R-(+)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole; (compound C)

S-(–)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole. (compound D)

Salts, solvates and hydrates of the above named compounds are also within the scope of the present invention.

It will be appreciated that for use in medicine a physiologically acceptable salt should be employed. Suitable physiologically acceptable salts will be apparent to those skilled in the art and include for example acid addition salts such as those formed with inorganic acids e.g. hydrochloric, hydrobromic, sulphuric or phosphoric acids and organic acids e.g. succinic, tartaric, malonic, citric, maleic, acetic, fumaric or methanesulphonic acid. Other non-physiologically acceptable salts e.g. oxalates may be used for example in the isolation of enantiomers of formula (I), and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of enantiomers of formula (I) and their salts.

Acids which have more than one carboxyl group e.g. succinic, tartaric, malonic or citric acids may correspondingly react with more than one molecule of an enantiomer (I), for example succinic acid may react with either one or two molecules of (I) to form either a 1:1 salt (succinate) or a 2:1 salt (hemi-succinate). All such salt forms are encompassed by the present invention; in general the 1:1 salt form is preferred.

Specific salts according to the present invention include:

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole L (+)-tartrate salt (1:1),

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole D (–)-tartrate salt (1:1),

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hemisuccinate (2:1),

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole methanesulphonate,

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole succinate (1:1),

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hydrochloride,

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hydrobromide,

(+)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole succinate (1:1),

(+)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole hydrochloride, and

(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole camphorsulphonate.

It will be appreciated that an enantiomer according to the present invention for example a (+) enantiomer, will be substantially free from the corresponding (–) enantiomer, and vice versa. Preferably, a specific enantiomer of the invention will contain less than 10%, e.g. less than 5% and advantageously less than 1% e.g. less than 0.5% of its opposite enantiomer.

In vitro testing (rabbit basilar artery) indicates that for both the methyl and ethyl derivatives of formula (I) the (+) enantiomer is more active than the corresponding (–) enantiomer. The above-named (+)-enantiomers are therefore preferred compounds of the invention.

Enantiomers of formula (I) may be prepared by standard methods, for example:

- (a) Separation of an enantiomeric mixture of a compound of formula (I) or a derivative thereof by chromatography e.g. on a chiral HPLC column.
- (b) Separation of diastereoisomers of a chiral derivative (e.g. a chiral salt) of a compound of formula (I) e.g. by crystallisation, or by chromatography.
- (c) Alkylation of a (+) or (-) enantiomer of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole or a salt thereof, followed if necessary or desired by converting a derivative of compound (I) so obtained into a compound of formula (I) itself or a different derivative thereof e.g. by removal of any N-protecting group or facilitating group, conversion of a salt into the free base, and/or salt formation.

Separation according to process (a) is generally facilitated by first introducing a readily removable group into the alkylamino moiety of the compound of formula (I). Suitable removable facilitating groups include those commonly used as N-protecting groups e.g. an alkoxy-carbonyl group such as t-butyloxycarbonyl or an aralkoxycarbonyl group such as benzoyloxycarbonyl, which groups may be introduced by reaction with for example a di-alkyl-dicarbonate such as di-t-butyl-dicarbonate or a chloroformate such as benzylchloroformate. The resulting enantiomeric mixture can be applied to a chiral HPLC column and fractions containing the individual isomers collected. A facilitating group may be removed by standard methods such as acid hydrolysis or catalytic hydrogenation.

A chiral derivative according to process (b) is a derivative containing at least two chiral centres, such that an enantiomeric mixture of a compound (I) is converted into a pair of diastereoisomers. Such derivatives include chiral salts wherein the anion contains a chiral centre and derivatives of formula (I) in which the alkylamino moiety is substituted by a group containing a chiral centre.

A chiral salt may be prepared for example by reaction of an enantiomeric mixture, such as a 1:1 racemate, of a compound (I) with an optically active acid such as (1S)-(+)-camphorsulphonic acid, d-tartaric acid, l-malic acid, l-mandelic acid, l-gulonic acid, 2,3:4,6-di-O-isopropylidene-2-keto-L-gulonic acid or R-2-pyrrolidone-5-carboxylic acid (also known as D-pyrroglutamic acid) to give two diastereoisomeric salts which may be separated e.g. by crystallisation. The free base form of the desired enantiomer may be obtained by neutralisation with a base such as sodium hydroxide or an ion exchange resin. Preferred optically active acids for use in this process include (1S)-(+)-camphorsulphonic acid and especially R-2-pyrrolidone-5-carboxylic acid.

Alternatively, an optically active reagent such as R- α -methylbenzyloxy-succinimidate may be reacted with an enantiomeric mixture of formula (I), to give a mixture of diastereoisomers which can be separated by chromatography, followed by hydrogenolysis to give the desired enantiomer of formula (I).

A chiral derivative may also be prepared by employing a chiral auxiliary at an earlier stage in the synthesis as described hereinafter. This may advantageously result in a mixture enriched with one diastereoisomer of a compound (I), and most preferably a single diastereoisomer, thus providing a stereoselective synthesis of an enantiomer according to the invention.

Alkylation of an enantiomer of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole according to process (c) may be carried out by standard methods well known in the art. For example alkylation may be achieved indirectly by formation of a group which can be reduced to the desired alkylamino

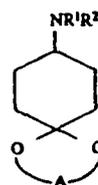
function (reductive alkylation). Thus for example the 3-amino compound can be reacted with an appropriate aldehyde or ketone e.g. formaldehyde, acetaldehyde or acetone, in the presence of a suitable reducing agent such as an alkali metal borohydride or cyanoborohydride e.g. sodium cyanoborohydride. Alternatively formylation may be effected using p-nitrophenol formate in aqueous tetrahydrofuran, using similar reducing conditions. Preferably, the 3-amino compound is first reacted with benzaldehyde, also in the presence of a reducing agent such as a cyanoborohydride, to form 3-N-benzylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole, prior to introduction of the methyl or ethyl group. The benzyl group may subsequently be cleaved by standard methods such as catalytic hydrogenation.

In a further alkylation method, an N-methyl substituent may be introduced by formation of a 3-isothiocyanato derivative e.g. by reaction of the 3-amino compound with carbon disulphide and dicyclohexylcarbodiimide; followed by reduction for example with a borohydride.

It will be appreciated by those skilled in the art that other standard means of alkylation may also be employed.

The starting compounds for use in the above processes may be prepared by methods known in the art for the preparation of tetrahydrocarbazoles, such as the methods described in International Application WO93/00086. Thus for example an enantiomeric mixture of formula (I) may be prepared by reductive alkylation of the corresponding 3-amino compound, as described for process (c) above.

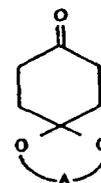
An enantiomeric mixture of formula (I) may also be prepared by reaction of 4-carboxamido-phenylhydrazine, or a salt thereof e.g. the hydrochloride, with 4-(methyl or ethyl)-aminocyclohexanone. In a particular embodiment of this method a protected derivative of the 4-alkylaminocyclohexanone is advantageously employed, e.g. a ketal of formula (II):



Formula (II)

wherein R¹ is as defined for formula (I), R² is hydrogen or an N-protecting group and A is an alkylene moiety, such as ethylene or neopentylene (-CH₂C(CH₃)₂CH₂-).

Compounds of formula (II) may themselves be prepared from a protected 1,4-cyclohexane-dione of formula (III):



Formula (III)

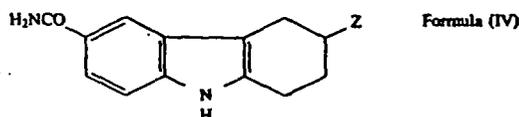
by reaction with the appropriate alkylamine compound. This reaction may be effected in a suitable solvent, for example a hydrocarbon such as benzene or toluene in the presence of titanium tetrachloride or suitable molecular sieves e.g. 4Å molecular sieves, to give the corresponding iminoketal derivative which may then be converted to an alkylamino compound of formula (II) by catalytic hydrogenation using for example palladium on carbon. Alternatively the reaction may be effected in a solvent such as an alcohol e.g. ethanol and the mixture hydrogenated directly, using e.g. palladium

on charcoal, to give a compound of formula (II).

The alkylamino group in the resulting compound of formula (II) may if desired be protected using standard methods. Suitable N-protecting groups are well-known in the art and include for example acyl groups such as acetyl, trifluoroacetyl, or benzoyl; an alkyl- or aralkyloxycarbonyl group such as methoxycarbonyl, t-butoxycarbonyl, benzyloxycarbonyl or phthaloyl; and aralkyl groups such as benzyl, diphenylmethyl or triphenylmethyl. The protecting groups should be easily removable at the end of the reaction sequence. N-deprotection may be effected by conventional methods, for example an alkoxy carbonyl group such as t-butoxycarbonyl may be cleaved by hydrolysis and an aralkyloxycarbonyl group such as benzyloxycarbonyl or an aralkyl group such as benzyl may be cleaved by hydrogenolysis.

Cyclisation with 4-carboxamidophenylhydrazine or a salt thereof is preferably carried out with a ketal of formula (II); however if desired the ketal may be converted to the corresponding ketone prior to this reaction.

Yet a further method for preparing an enantiomeric mixture of formula (I) comprises reacting a compound of formula (IV):



wherein Z is a leaving group, such as a halogen atom or a sulphonyloxy (e.g. p-toluenesulphonyloxy or methanesulphonyloxy) group with an amine H_2NR^1 or a derivative thereof. Said derivative may optionally contain a chiral centre, as in for example R- α -methylbenzylamine, resulting in a diastereoisomeric mixture of the corresponding derivative of formula (I). The diastereoisomers may be separated by chromatography, followed by hydrogenolysis to give the desired enantiomer of formula (I).

An enantiomeric mixture of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole may be prepared in an analogous manner to formula (I), using 4-aminocyclohexanone, optionally protected as a ketal derivative, or an N-protected (e.g. phthalimido) derivative thereof. The enantiomers of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole may be resolved by chiral HPLC as described for process (a) above, using a derivative such as 3-t-butyloxycarbonylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole; or by formation of a chiral salt of the 3-amino compound in a similar manner to process (b) above, using for example 2,3,4,6-di-O-isopropylidene-2-keto-L-gulonic acid, followed by selective crystallisation. Such methods are described in International Application WO93/00086.

Enantiomers of formula (I) have been found to be agonists and partial agonists at 5-HT₁-like receptors. Nomenclature of 5-HT receptors is constantly evolving. At least four subtypes of the 5-HT₁ receptor family have been described, namely 5-HT_{1a}, 5-HT_{1b}, 5-HT_{1c} and 5-HT_{1d}. Functional contractile 5-HT₁-like receptors have been identified in the dog saphenous vein and in cerebral (basilar) arteries of various species including rabbit and human. It is now believed that the functional 5-HT₁-like receptor correlates with the 5-HT_{1d} binding site (A. A. Parsons, TIPS, Aug. 1991, Vol 12).

Enantiomers of formula (I) are expected to have utility in the treatment and/or prophylaxis of migraine, with and without aura, tension headache, cluster headache and other forms of cephalic pain and trigeminal neuralgias.

The invention therefore provides the use of an enantiomer of formula (I) or a physiologically acceptable

salt thereof in the manufacture of a medicament for the treatment of a condition where a 5-HT₁-like agonist is indicated, in particular the treatment or prophylaxis of migraine.

The invention also provides a method of treatment of a condition wherein a 5-HT₁-like agonist is indicated, in particular migraine, which comprises administering to a subject in need thereof an effective amount of an enantiomer of formula (I) or a physiologically acceptable salt thereof.

For use in medicine, a compound of the present invention will usually be administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising an enantiomer of formula (I) or a physiologically acceptable salt thereof and a physiologically acceptable carrier.

The compounds of formula (I) may be administered by any convenient method, for example by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) and their physiologically acceptable salts which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or physiologically acceptable salt in a suitable liquid carrier(s) for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or physiologically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or nonaqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or a physiologically acceptable salt thereof calculated as the free base.

The physiologically acceptable compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 500 mg, preferably between 10 mg and 400 mg, e.g. between 10 and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of the compound of the formula (I) or a physiologically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

BIOLOGICAL TEST METHODS

5-HT₁-like Receptor Screen

Rabbit Basilar Artery

Experiments were performed in intracranial arteries from rabbit isolated basilar artery in a similar method to that described previously (Parsons and Whalley, 1989. Eur J Pharmacol 174, 189-196.).

In brief, rabbits were killed by overdose with anaesthetic (sodium pentobarbitone). The whole brain was quickly removed and immersed in ice cold modified Krebs's solution and the basilar artery removed with the aid of a dissecting microscope. The Krebs solution was of the following composition (mM) Na⁺ (120); K⁺ (5); Ca²⁺ (2.25); Mg²⁺ (0.5); Cl⁻ (98.5); SO₄²⁻ (1); EDTA (0.04) equilibrated with 95% O₂/5% CO₂. The endothelium was removed by a gentle rubbing of the lumen with a fine metal wire. Arteries were then cut into ring segments (ca 4-5 mm wide) and set up for recording of isometric tension in 50 ml tissue baths in modified Krebs solution with the additional supplement of (mM); Na²⁺ (20); fumarate (10); pyruvate (5); L-glutamate (5) and glucose (10). The arteries were then placed under a resting force of 3-4 mN maintained at 37° C. and the solution bubbled with 95% O₂/5% CO₂.

After tests for initial reactivity with 90 mM KCl depolarising solution and for lack of acetylcholine-induced relaxation of 5-HT (10 mM) precontraction, cumulative concentration-effect curves (2 nM-60 mM) to 5-HT were constructed in the presence of ascorbate 200 mM, cocaine 6 mM, indomethacin 2.8 mM, ketanserin 1 mM and prazosin 1 mM.

Following a 45-60 min wash period, cumulative concentration-effect curves to the test compounds or 5-HT (as a time match control) were constructed in the presence of ascorbate, indomethacin, cocaine, ketanserin and prazosin. Test Compounds

- R-(+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole; (compound A)
 S-(-)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole; (compound B)
 R-(+)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole; (compound C)
 S-(-)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole. (compound D)

Results	EC ₅₀
Compound A	0.03 μM
Compound B	>2 μM
Compound C	0.16 μM
Compound D	2.1 μM

Pharmaceutical Formulations

The following represent typical pharmaceutical formulations according to the present invention, which may be prepared using standard methods.

IV Infusion

Compound of formula (I)	1-40 mg
Buffer	to pH ca 7
Solvent/complexing agent	to 100 ml
Bolus Injection	

Compound of formula (I)	1-40 mg
Buffer	to pH ca 7
Co-Solvent	to 5 ml

Buffer: Suitable buffers include citrate, phosphate, sodium hydroxide/hydrochloric acid.
 Solvent: Typically water but may also include cyclodextrins (1-100 mg) and co-solvents such as propylene glycol, polyethylene glycol and alcohol.

Tablet

Compound	1-40 mg
Diluent/Filler*	50-250 mg
Binder	5-25 mg
Disintegrant*	5-50 mg
Lubricant	1-5 mg
Cyclodextrin	1-100 mg
Diluent:	e.g. Microcrystalline cellulose, lactose, starch
Binder:	e.g. Polyvinylpyrrolidone, hydroxypropylmethylcellulose
Disintegrant:	e.g. Sodium starch glycolate, croscopolidone
Lubricant:	e.g. Magnesium stearate, sodium stearyl fumarate.

Oral Suspension

Compound	1-40 mg
Suspending Agent	0.1-10 mg
Diluent	20-60 mg
Preservative	0.01-1.0 mg
Buffer	to pH ca 5-8
Co-solvent	0-40 mg
Flavour	0.01-1.0 mg
Colourant	0.001-0.1 mg
Suspending agent:	e.g. Xanthan gum, microcrystalline cellulose
Diluent:	e.g. sorbitol solution, typically water
Preservative:	e.g. sodium benzoate
Buffer:	e.g. citrate
Co-solvent:	e.g. alcohol, propylene glycol, polyethylene glycol, cyclodextrin

*may also include cyclodextrins

Preparation 1

(±)-3-Amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole 4-Carboxamidophenylhydrazine hydrochloride (2.87 g) and 4-phthalimidocyclohexanone (3.00 g) were mixed in