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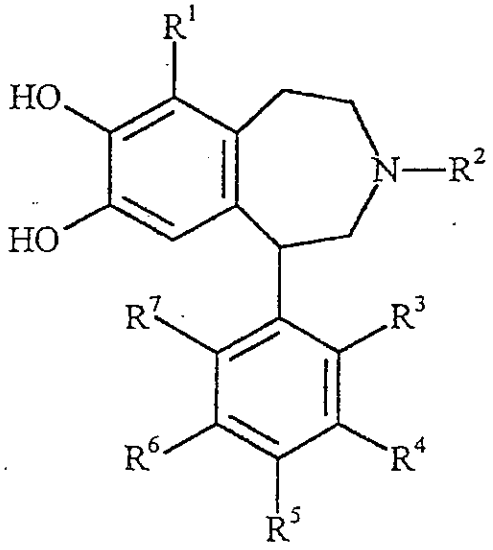
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(54) Title: DOPAMINE D1 RECEPTOR AGONIST COMPOUNDS



(I)

(57) Abstract

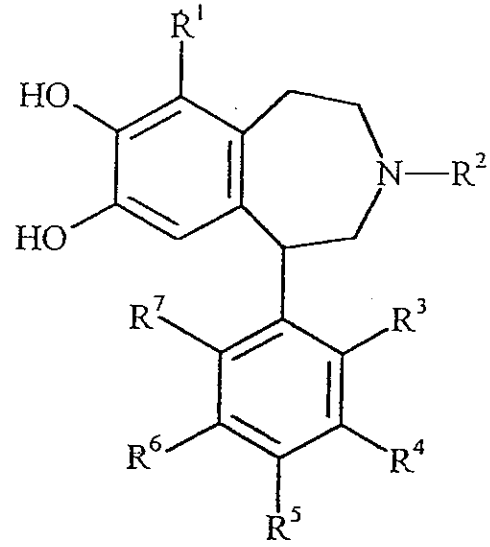
The invention provides 2,3,4,5–tetrahydro–1H–3–benzazepines of general formula (I) wherein: R^1 is hydrogen, halogen, C_1–C_4 alkyl, or CF_3; R^2 is hydrogen, methyl, or lower alkenyl of 3–5 carbon atoms; R^3 and R^4 together form a furan, dihydrofuran, thiophene, dihydrothiophene, cyclopentane or cyclohexane ring and R^5 is hydrogen or R^4 and R^5 together form a furan, dihydrofuran, thiophene, dihydrothiophene, cyclopentane or cyclohexane ring and R^3 is hydrogen; R^6 is hydrogen, halogen, CF_3, CN, NO_2 or NH_2; R^7 is hydrogen, halogen, CF_3, CN, NO_2 or NH_2. The specific combination of substituents: R_1 = H, R_2 = H and R_4 and R_5 together forming a cyclohexane ring is excluded, namely 1–(5,6,7,8–tetrahydronaphthalen–2–yl)–2,3,4,5–tetrahydro–1H–benzol[d]azepine–7,8–diol. The compounds of the invention provide therapeutic agents that selectively interact positively with postsynaptic dopamine D1 receptors in the striatum, directly or in–directly (termed dopamine D1 agonists) and are particularly valuable as anti–Parkinsonian agents.

Dopamine D1 Receptor Agonist Compounds

The present invention relates to Dopamine D1 receptor agonist compounds, to methods for preparing such compounds and to their use.

GB 1 599 705 discloses 1-thienyl and 1-furyl-2,3,4,5-tetrahydro-1H-3-benzazepines having utility as cardiovascular agents. Some benzazepines as Dopamine D1 receptor agonists have been described. For example, 1-phenyl-3-benzazepines are disclosed in EP 0 230 755-A and carbamates of 6-chloro-7,8-dihydroxy-1 (4'-hydroxyphenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine are disclosed in
EP 0 380 355-A.

The present invention provides compounds which are potent and selective ligands for the Dopamine D1 receptor. Such compounds can be used in the treatment of neurodegenerative diseases especially, but not limited to, Parkinson's disease. Parkinson's disease is a progressive neurodegenerative disorder characterized by the progressive death of presynaptic dopamine nuerones in the substantia nigra that innervate postsynaptic striatal neurones and the resultant loss of striatal dopamine. The primary therapy for Parkinson's disease focuses upon compensation for this loss of dopamine in the striatum. The current main-stay for this replacement in the administrattion of the metabolic precursor of dopamine, namely, L-DOPA which is converted into dopmaine in the central nervous system. However, L-DOPA can cause severe adverse effects such as nausea, vomiting, cardiac arrythmias and hypotension. Additionally, long-term use of L-DOPA is associated with the development of abnormal involuntary movements (dyskinesias) and psychosis. Furthermore, the positive benefits associated with chronic L-DOPA therapy experienced by suffers is lessened, typically several years after treatment was first initiated. Therapeutic agents that selectively interact positively with postsynaptic dopamine D1 receptors in the striatum, directly or in-directly (hereafter termed dopamine D1 agonists) are particularly valuable as anti-Parkinsonian agents.



(I)

According to the present invention there are provided 2,3,4,5-tetrahydro-1H-3-benzazepines of the general formula I

wherein: R^1 is hydrogen, halogen, C_1-C_4 alkyl, or CF_3;
R^2 is hydrogen, methyl, or lower alkenyl of 3-5 carbon atoms;
R^3 and R^4 together form a furan, dihydrofuran, thiophene, dihydrothiophene, cyclopentane or cyclohexane ring and R^5 is hydrogen or R^4 and R^5 together form a furan, dihydrofuran, thiophene, dihydrothiophene, cyclopentane or cyclohexane ring and R^3 is hydrogen;
R^6 is hydrogen, halogen, CF_3, CN, NO_2 or NH_2;
R^7 is hydrogen, halogen, CF_3, CN, NO_2 or NH_2.

The specific combination of substituents: R_1 = H, R_2 = H and R_4 and R_5 together forming a cyclohexane ring is excluded, namely 1-(5,6,7,8-tetrahydronaphthalen-2-yl)-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7,8-diol.

K. S. Sugamori, et al., (Journal of Neurochemistry. 1998. 71,4,1685-93) describes the functional differentiation of multiple Dopamine D1 like receptors by compound NNC 01-0012. The compound disclosed which is closest to that of the invention (Compound NNC 01-0127), differs from that of the invention in that it has a hydrogen at the R^1 position.

US 4,265,889 discloses 6-lower alkyl-7,8-dihydroxy-1-phenyl 1,2,3,4,5-tetrahydro-1h-3-benzazepines. The compounds disclosed in this patent differ from that of the invention in that the substituents on the phenyl group at position 1, do not have a furan, dihydrofuran, thiopene, dihydrothiopene, cyclopentane, or cyclohexane ring.

DE 2629887 discloses medicaments with peripheral Dopamine receptor stimulation for kidney disorders, diuretics and anti-Parkinson syndrome defects. Preferred compounds have a hydrogen at the R^1 position and do not have a furan, dihydrofuran, thiopene, dihydrothiopene, cyclopentane, or cyclohexane ring structure on the phenyl group.

GB 1 599 705 discloses 1-thienyl and 1-furyl-2,3,4,5-tetrahydro,1H-3-benzazepines being medicinally active compounds especially as cardiovascular agents due to their peripheral Dopaminergic activity. These compounds do not have a phenyl group at position 1 on the benzazepine ring.

EP 0 380 355 discloses carbamates of 6-chloro-7,-dihydroxy-1-(4'-Hydroxyphenyl)-2,3,4,5-tetra-hydro-1H-3-benzazepines as prodrugs. The compounds disclosed do not have hydroxyl substituents at positions 7 and 8 on the benzazepine ring, and they do not have a ring substituent on the phenyl group at position 1.

EP 0 230 755 discloses 1-phenyl-3-benzazepines. These compounds have a hydrogen residue at position R^1 and do not a furan, dihydrofuran, thiopene, dihydrothiopene, cyclopentane, or cyclohexane ring structure on the phenyl group.

The compounds of formula I may be presented as a mixture of enantiomers, which may be resolved into the individual pure enantiomers. This resolution may conveniently be performed by fractional crystallisation, from various solvents, of the salts of compounds of the formula I with optically active acids or by other methods known from the literature e.g. chiral column chromatography. Therefore, this invention includes all isomers, whether resolved or mixtures thereof.

Particularly valuable embodiments of this invention are non-toxic, pharmaceutically acceptable acid addition salts of benzazepines of formula I. Such salts include those derived from inorganic and organic acids such as hydrochloric, hydrobromic, sulphuric, phosphoric, methanesulfonic, acetic, lactic, maleic, phthalic and tartaric acids.

The compounds of the invention are useful because of their pharmacological activity. In particular, the compounds of the invention are potent (high affinity) and selective ligands for the central dopamine D1 receptor (Table 1) as measured by competitive radio-ligand displacement assays using rat striatal tissue homogenates as per the method described in *Psychopharmacology* 117:275-286 (1995).

Test Compound	Ki (nM) Dopamine D1 receptor affinity	Ki (nM) Dopamine D2 receptor affinity
Example 1	31	790
Example 4	6.7	2500

Table 1

The benzazepine compounds of Formula I possess anti-Parkinsonian activity due to central dopaminergic activity as demonstrated by employing the standard pharmacological test procedure as reported by Ungerstedt *et al.*, in Brain Research 24:485-493 (1970). This procedure is based on the drug-induced rotation (circling) of rats having extensive unilateral dopaminergic lesions of

the substantia nigra. Briefly, the test comprises the quantitative recording of rotational behaviour in rats in which 6-hydroxydopamine lesions of the nigrostriatal dopamine system have been produced. Unilateral brain lesioning of the substantia nigra in one hemisphere results in the dopamine receptor system in that region to become hypersensitive following the degeneration of the nigral cell bodies. Activation of these super-sensitive dopamine receptors by drugs induce asymmetrical movement of the animal, contralateral rotation (with respect to the lesioned side of the brain). The rate and duration of contralateral rotation induced upon drug administration is an index of central dopaminergic activity of the agent. Compounds which are known to be clinically effective in controlling Parkinsonism, e.g. L-DOPA and apomorphine, are also effective in this rat circling model. By way of example the compound 1-indan-5-yl-6-chloro-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7,8-diol produces robust circling in the unilateral lesioned 6-hydroxydopamine rat model in a dose-related fashion from 0.438 to 5.79 micromoles/kg when administered by subcutaneous injection. Cumulative rotations over a set time-period (190mins) were as follows: 0.438 micromoles/kg = 23, 0.965 micromole/kg = 397 rotations, 1.93 micromoles/kg = 867 rotations, 3.86 micromoles/kg = 1078 rotations, 5.79 micromoles/kg = 1388 rotations.

The invention is further described by way of example only.

Example 1

a) *1-(Benzofuran-7-yl)-2-[2-(2-chloro-3,4-dimethoxyphenyl)ethylamino]ethanol*

A solution of 2-chloro-3,4-dimethoxyphenylethylamine (6.35g, 0.0296mol) and (7-benzofuranyl)oxirane (4.29g, 0.0268mol) in 15ml acetonitrile was refluxed for 16 hours. The reaction mixture was cooled to 0°C (ice-bath), filtered and the crude product re-crystallised from hot acetonitrile to afford the title compound (3.52g, 35%) as a white crystalline solid. ^{1}H-NMR in $CDCl_3$ [δ, ppm]: 2.86-3.16 (m, 6H); 3.85 (s, 6H); 5.26 (dd, 1H); 6.73-6.77 (m, 2H); 6.91 (d, 1H); 7.21-7.26 (m, 1H); 7.39 (d, 1H),;7.51 (d, 1H); 7.61 (d, 1H).

b) *1-(Benzofuran-7-yl)-6-chloro-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine*

1-(Benzofuran-7-yl)-2-[2-(2-chloro-3,4-dimethoxyphenyl)ethylamino]ethanol (2.20g, 5.85mmol) in 70ml trifluoroacetic acid was treated with concentrated sulphuric acid (0.71ml, 0.0135mol) and stirred at ambient temperature for 90 minutes. The solution was evaporated in vacuo and the residue dissolved in 30ml 4M sodium hydroxide and extracted with dichloromethane (4 x 50ml). The organic fractions are combined, dried, filtered and evaporated to afford the crude product as a yellow/green glass. Subsequent purification by column chromatography on silica with dichloromethane/methanol (9:1) as eluant afforded the title compound as a sticky white solid (1.42g, 68%).

^{1}H-NMR in $CDCl_3$ [δ, ppm]: 2.95-3.80 (m, 6H); 3.57 (s, 3H); 3.85 (s, 3H); 4.76 (dd, 1H); 6.30 (s, 1H); 6.80 (d, 1H); 6.95 (d, 1H); 7.21 (t, 1H); 7.54 (d, 1H); 7.62 (d, 1H).

c) ***1-(Benzofuran-7-yl)-6-chloro-7,8-hydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide***

1-(Benzofuran-7-yl)-6-chloro-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (1.19g, 3.32mmol) dissolved in dry dichloromethane (20ml). The solution was cooled to -78°C and boron tribromide (133ml, 133mmol) added slowly via syringe. The reaction mixture was maintained at -78°C for 30 minutes, allowed to warm to 0°C and stirred for 2 hours. The reaction mixture was subsequently cooled to -78°C, methanol (25ml) added slowly and stirred for 30 minutes. After refluxing the reaction mixture for 1 hour the solvents were removed in vacuo to afford the crude product. Trituration with diethyl ether afforded the title compound as a off-white solid (1.26g, 92%).

^{1}H-NMR in CD_3OD [δ, ppm]: 3.15 (m, 1H); 3.30-3.99 (m, 5H); 5.00 (m, 1H); 6.10 (s, 1H); 6.93 (d, 1H); 7.07 (d, 1H); 7.30 (t, 1H); 7.64 (m, 1H); 7.79 (d, 1H).

Example 2

a) *1-(Benzo[b]thiophen-7-yl)-2-[2-(2-chloro-3,4-dimethoxyphenyl)ethylamino]ethanol*

A solution of 2-chloro-3,4-dimethoxyphenylethylamine (7.00g, 32.5mmol) and 7-benzo[b]thiophenyl oxirane (5.30g, 30.1mmol) in 20ml acetonitrile was refluxed for 72 hours. The reaction mixture was cooled to 0°C (ice-bath), filtered and the crude product re-crystallised from hot acetonitrile to afford the title compound (5.57g, 47%) as a white crystalline solid. ^{1}H-NMR in $CDCl_3$ [δ, ppm]: 2.83-3.08 (m, 6H); 3.84 (s, 3H); 3.85 (s, 3H); 5.06 (m, 1H); 6.73 (d, 1H); 6.88 (d, 1H); 7.35 (m, 3H); 7.43 (d, 1H); 7.73 (m, 1H).

b) ***1-(Benzo[b]thiophen-7-yl)-6-chloro-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine***

1-(Benzo[b]thiophen-7-yl)-2-[2-(2-chloro-3,4-dimethoxyphenyl)ethylamino]ethanol (3.90g, 10mmol) in 30ml trifluoroacetic acid was treated with methane sulphonic acid (0.7ml, 10.7mmol),under a nitrogen atmosphere, and the solution heated under reflux for 18 hours. The solution was evaporated in vacuo and the residue dissolved in dichloromethane (100ml) and the solution washed with concentrated aqueous ammonia (2x50ml, 0.880),water (100ml) and saturated aqueous sodium chloride solution (100ml), dried, filtered and evaporated to afford the crude product as a yellow/green glass. Subsequent purification by column chromatography on silica with dichloromethane/methanol (9:1) as eluant afforded the title compound as a pale brown gum (3.01g, 81%).

^{1}H-NMR in $CDCl_3$ [δ, ppm]: 2.82-2.92 (m, 2H); 3.13-3.23 (m, 2H); 3.41-3.55 (m, 2H); 3.49 (s 3H); 3.83 (s, 3H); 4.66 (d, 1H); 6.21 (s, 1H); 7.11 (d, 1H); 7.37-7.41 (m, 3H); 7.76 (d, 1H).

c) ***1-(Benzo[b]thiophen-7-yl)-6-chloro-7,8-hydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine***

1-(Benzo[b]thiophen-7-yl)-6-chloro-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (1.31g, 3.5mmol) dissolved in dry dichloromethane (20ml). The solution was cooled to -78°C and boron tribromide (14ml, 14mmol) added slowly via syringe. The reaction mixture was maintained at -78°C for 30 minutes, allowed to warm to 0°C and stirred for 2 hours. The reaction mixture was subsequently cooled to -78°C, methanol (10ml) added slowly and stirred for 30 minutes. After refluxing the reaction mixture for 1 hour the solvents were removed in vacuo to afford the crude product. Purification by recrystallisation from methanol afforded the title compound as an off-white solid (0.68g, 45%). Mpt 185-188°C. Anal. (Calc.)

$C_{18}H_{16}ClNO_2S.HBr.H_2O$ C 48.61 (48.61), H 4.27 (4.30), N 2.98 (3.15). ^{1}H-NMR in CD_3OD [δ, ppm]: 3.02 (t, 1H); 3.30-3.38 (m, 1H); 3.60-3.74 (m, 3H); 3.89 (d, 1H); 4.91 (d, 1*H); 5.97 (s, 1H); 7.23 (d, 1H); 7.41 (d, 1H); 7.45-7.52 (m, 2H); 7.84 (d, 1H).

Example 3

a) ***2-(2-Chloro-3,4-dimethoxyphenyl)ethylamino]-1-indan-5-yl-ethanol***

To the solution of 2-indan-5-yl oxirane (3.38 g, 21.1 mmol) in anhydrous acetonitrile (20 ml) was added 2-(2-chloro-3,4-dimethoxyphenyl)ethylamine (2.0 g, 23.2 mmol) and the solution refluxed for 20h. Upon cooling a white precipitate formed and was collected by filtration and washed with diethyl ether, giving the title compound as a white solid (2.85 g, 36%). ^{1}H NMR (400 MHz, DMSO-d6): δ (ppm) 1.96-2.03 (2H, m, CH_2-CH_2-CH_2), 2.50-2.84 (10H, m, 5×CH_2), 3.72 (3H, s, CH_3O), 3.80 (3H, s, CH_3O), 4.56 (1H, t, *J* 6.04, *H*-1), 5.14 (1H, broad, N*H*) and 6.94-7.14 (5H, m, Ar-*H*). This material was used for the next step without further purification.

b) ***1-Indan-5-yl-6-chloro-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine***

2-(2-Chloro-3,4-dimethoxyphenyl)ethylamino]-1-indan-5-yl-ethanol (2.7 g, 7.18 mmol) was dissolved in trifluoroacetic acid (50 ml), to which was added methane sulfonic acid (0.76 g, 7.90 mmol). The reaction mixture was stirred under reflux for 20 h, and was then allowed cooling to rt. Removal of the solvent afforded an oily residue, which was dissolved in dichloromethane (200 ml) and washed with ammonia solution (0.88 M, 150 ml), water (2×150 ml), brine (100 ml) and dried. Removal of the solvent gave the crude product as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.04-3.52 (12H, m, 6×CH_2), 2.55 (1H, broad, N*H*), 3.70 (3H, s, CH_3O), 3.86 (3H, s, CH_3O), 4.27 (1H, d, *H*-1), 6.43 (1H, s, *H*-9), 6.88-7.20 (3H, m, other Ar-*H*). This material was used for the next step without further purification.

c) *1-Indan-5-yl-6-chloro-7,8-dimethoxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine*

1-Indan-5-yl-6-chloro-7,8-dimethoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (1.3 g, 3.63 mmol) was dissolved in methanol (20 ml), to which was added dropwise formaldehyde solution (37%, 1.87 ml, 23.2 mmol). White precipitate formed with the addition. Sodium cyanoborohydride (97%, 0.92 g, 14.9 mmol) was added, bringing most of the solid into solution. The reaction mixture was then stirred at r.t for 3 h. Removal of the solvent gave a residue containing a colorless oil and a white solid (3.8 g). This residue was purified by column chromatography (Petroleum ether/ethyl acetate, 1:1, R_f 0.25), giving the desired product as colourless oil (1.16 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.08 (2H, t, *J* 7.5, 1×CH_2), 2.37 (3H, s, *N*-CH_3), 2.86-3.54 (10H, m, other 5×CH_2), 3.61 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.32 (1H, d, 1-*H*), 6.26 (1H, s, 9-*H*), 6.92-7.22 (3H, m, other Ar-*H*).

d) ***1-Indan-5-yl-6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7,8-diol***

1-Indan-5-yl-6-chloro-7,8-dimethoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (1.03 g, 2.77 mmol) was dissolved in anhydrous dichloromethane (15 ml), which was cooled to -78°C. To this solution was added dropwise BBr_3 (1.0 M solution in dichloromethane, 13.8 ml, 13.8 mmol) over 25 min. The reaction mixture was stirred at -78°C for 1 h, at 0°C for 3 h and at r.t for further 1 h. The reaction mixture was cooled to -78°C again and treated with methanol (20 ml) and was then stirred at r.t overnight. Removal of the solvent afforded a brown residue. Methanol (10 ml) was added and removed under reduced pressure. This process was repeated four times, giving the crude product as a brown residue, which was recrystallised from methanol/ether to give a pale solid (0.87 g, 74%). The material was recrystallised again from methanol/ether to give the title compound as a pale solid (0.53 g, 45%), mp. 255-257°C (decomp.); Found: %C, 56.42; %H, 5.58; %N, 3.14. $C_{20}H_{23}BrClNO_2$ requires %C, 56.55; %H, 5.46; %N, 3.30. Mass 354 (m-81). ^{1}H NMR (400 MHz, DMSO-d6): δ (ppm) 2.05-3.79 (m, 6×CH_2), 4.60 (1H, d, *H*-1), 6.16 (1H, broad, *H*-9), 6.97-7.28 (3H, m, other Ar-*H*).

Example 4

a) *1-(Benzo[b]thiophen-5-yl)-2-[2-(2-chloro-3,4-dimethoxyphenyl)ethylamino]ethanol*

A solution of 2-chloro-3,4-dimethoxyphenylethylamine (7.00g, 32.5mmol) and (5-benzo[b]thiophenyl oxirane (5.30g, 30mmol) in 30ml acetonitrile was refluxed for 48 hours. The reaction mixture was cooled to 0°C (ice-bath), filtered and the crude product re-crystallised from hot acetonitrile to afford the title compound (4.40g, 37%) as a white crystalline solid. Mpt 137-9 °C. ^{1}H-NMR in $CDCl_3$ [δ, ppm]: 2.75 (m, 6H); 3.72 (s, 3H); 3.79 (s, 3H); 4.76 (m, 1H); 6.90 (d, 1H); 6.99 (d, 1H); 7.35 (d, 1H); 7.43 (d, 1H); 7.73 (d, 1H); 7.83 (s, 1H); 7.91 (d, 1H).

b) *1-(Benzo[b]thiophen-5-yl)- 3- methyl-6-chloro-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine*

1-(Benzo[b]thiophen-5-yl)-2-[2-(2-chloro-3,4-dimethoxyphenyl)ethylamino]ethanol (2.00g, 5.1mmol) in 40ml trifluoroacetic acid was treated with methane sulphonic acid (0.36ml, 5.5mmol), under a nitrogen atmosphere, and heated under reflux for 18 hours. The solution was evaporated in vacuo and the residue taken up in dichloromethane (100ml) and washed with concentrated aqueous ammonia (100ml,0.880), water (2x 100ml) and saturated aqueous sodium chloride solution (100ml), dried, filtered and evaporated to afford the crude product as a yellow/green glass. The crude amine was taken up in methanol (40ml) and aqueous formaldehyde (2.8ml, 37% wt, 37 mmol) was added followed by sodium cyanoborohydride (1.35g, 21mmol) and the resulting solution stirred for 18 hours. The solvents were removed in vacuo, and the residue taken up in hydrochloric acid (100ml, 1M). The solution was washed with diethyl ether (2x 100ml) and basified with concentrated aqueous ammonia (100ml, 0.880), the mixture was extracted with dichloromethane (2x 100ml). The combined extracts were washed with water (2x 100ml) and saturated aqueous sodium chloride solution (150ml), dried, filtered and concentrated in vacuo. Subsequent purification by column chromatography on silica with diethyl ether as eluant afforded the title compound as a white solid (640mg, 34%).

^{1}H-NMR in $CDCl_3$ [δ, ppm]: 2.35 (m, 1H); 2.39 (s, 3H) ;2.85-2.98 (m, 2H); 3.13 (m, 2H); 3.31 (m, 1H); 3.56 (s 3H); 3.83 (s, 3H); 4.47 (d, 1H); 6.25 (s, 1H); 7.11 (d, 1H); 7.37-7.41 (m, 3H); 7.76 (d, 1H).

c) ***1-(Benzo[b]thiophen-5-yl)-3-methyl-6-chloro-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine***

1-(Benzo[b]thiophen-5-yl)-3-methyl-6-chloro-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine

(470mg, 1.2mmol) dissolved in dry dichloromethane (15ml). The solution was cooled to -78°C and boron tribromide (6ml, 6mmol) added slowly via syringe. The reaction mixture was maintained at -78°C for 60 minutes, allowed to warm to 0°C and stirred for 2 hours. The reaction mixture was subsequently cooled to -78°C, methanol (40ml) added slowly and stirred for 30 minutes. After the solvents were removed in vacuo purification by column chromatography on silica using methanol/dichloromethane (1:9) as eluant afforded the title compound as a yellow solid (127mg, 30%). ^{1}H-NMR in $(CD_3)_2SO$ [δ, ppm]: 2.29 (s, 3H); 2.4 (m, 1H); 2.95-3.12 (m, 4H); 3.30-3.4 (m, 3H); 3.89 (d, 1H); 4.38 (d, 1*H); 6.09 (s, 1H); 7.21 (dd, 1H); 7.44 (d, 1H); 7.68 (s, 1H); 7.74 (d, 1H); 7.96 (d, 1H).

d) ***1-(Benzo[b]thiophen-5-yl)-3-methyl-6-chloro-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine. monohydrochloride***

1-(Benzo[b]thiophen-5-yl)-3-methyl-6-chloro-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine

(111mg, 0.31mmol) was dissolved in a mixture of dry diethylether (30ml) and dry chloroform (6ml). The solution was treated with 2N hydrochloric acid in dry diethylether (12ml, 24mml) and stirred for 5 hours. The reaction mixture was filtered and the crude product re-crystallised from methanol/diethylether to afford the title compound as a pale yellow solid (95mg, 78%). Mpt >220C (decomp), ^{1}H-NMR in $(CD_3)_2SO$ [δ, ppm]: 2.82 (s, 3H); 2.9-3.0 (m, 2H); 3.5-3.6 (m, 2H); 3.7 (m, 1H); 3.84 (d, 1H); 4.87 (d, 1H); 5.89 (s, 1H); 7.23 (dd, 1H); 7.52 (d, 1H); 7.77 (s, 1H); 7.84 (d, 1H); 8.10 (d, 1H); 9.04 (s, OH); 9.40 (s, OH); 11.15 (broad s, HCl).

Calculated for C19H18NO2ClS.HCl: C, 57.71; H, 4.85; N, 3.54; Cl, 17.70. Found: C, 55.51; H, 5.18; N, 3.08; Cl, 17.66.

Example 5

a) *1-(Benzo[b]furan-7-yl)-3-methyl-6-chloro-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine*

1-(Benzo[b]furan-7-yl)-6-chloro-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (0.96g, 2.7mmol) was taken up in methanol (25ml) and aqueous formaldehyde (1.6ml, 37%wt, 21mmol) was added, followed by sodium cyanoborohydride (0.75g, 12mmol) and the resulting solution stirred for 24 hours. The solution was concentrated in vacuo and the residue was taken up in dichloromethane (100ml), the solution was washed with water (2x 100ml) and saturated sodium chloride solution (100ml), dried, filtered and concentrated in vacuo. After purification by column chromatography on silica using dichloromethane/ methanol (9:1) as eluant the title compound was obtained as a pale orange gum (0.88g, 88%). ^{1}H-NMR in $CDCl_3$ [δ, ppm]: 2.34 (m, 1H); 2.37 (s, 3H); 2.96 (m, 1H); 3.07 (m, 1H); 3.18 (m, 1H); 3.45 (s, 3H); 3.81 (s, 3H); 4.84 (d, 1*H); 6.10 (s, 1H); 6.78 (d, 1H); 7.06 (d, 1H); 7.23 (m, 1H); 7.53 (dd, 1H) 7.58 (d, 1H).

b) *1-(Benzo[b]furan-7-yl)-3-methyl-6-chloro-7,8-hydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine*

1-(Benzo[b]furan-7-yl)-3-methyl-6-chloro-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (0.52g, 1.4mmol) dissolved in dry dichloromethane (15ml). The solution was cooled to -78°C and boron tribromide (6ml, 6mmol) added slowly via syringe. The reaction mixture was maintained at -78°C for 1 hour, allowed to warm to 0°C and stirred for 2 hours. The reaction mixture was subsequently cooled to -78°C, methanol (10ml) added slowly and stirred for 1 hour, and for 18 hours at ambient temperature. The solvents were removed in vacuo to afford the crude product. Purification by column chromatography on silica using dichloromethane/ methanol (9:1) as eluant and re-crystallisation from propan-2-ol/ diethyl ether afforded the title compound as a

buff solid (100mg, 17%).Anal. (Calc.) $C_{19}H_{18}ClNO_3.HBr.1.5H_2O$ C 50.58 (50.51) H 4.78 (4.90) N 2.78 (3.10). ^{1}H-NMR in $(CD_3)_2SO$ [δ, ppm]: 2.51(s, 3H) 3.02 (t, 1H); 3.30-3.38(m, 1H); 3.60-3.74 (m, 3H); 3.89 (d, 1H); 5.03 (d, 1*H); 5.82 (s, 1H); 7.05 (d, 1H); 7.20 (d, 1H); 7.36 (m, 1H); 7.72 (m, 1H); 8.00 (d, 1H).

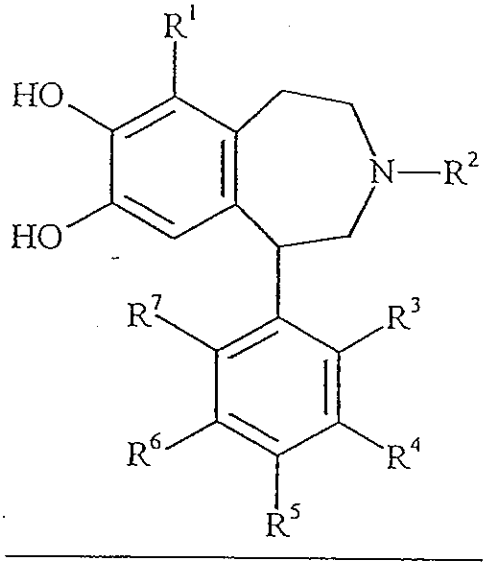
Example 6

a) ***1-(Benzo[b]thiophen-7-yl)-3-methyl-6-chloro-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine***

1-(Benzo[b]thiophen-7-yl)-6-chloro-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide. (180mg, 0.4mmol) was suspended in dry methanol (5ml) and aqueous formaldehyde (0.2ml, 37% wt., 2.7 mmol) was added followed by sodium cyanoborohydride (0.10g, 1.6 mmol) to give a clear colourless solution. The solution was stirred for 18 hours to give a white suspension. The suspension was cooled to 0°C and hydrobromic acid (1ml, 48% wt) was added to give a clear solution stirred for 90 minutes. The solution was evaporated in vacuo and the residue purified by column chromatography on silica with chloroform/ methanol (9/1) as eluant gave the title compound as a yellow solid (170mg, 94%). ^{1}H-NMR in $(CD_3)_2SO$ [δ, ppm]: 2.11 (t, 1H); 2.29 (s, 3H); 2.80 (dd, 1H); 2.95 (m, 2H); 3.18 (d, 1H); 3.35 (m, 3H): 4.53 (d, 1*H); 5.88 (s, 1H); 7.23 (d, 1H); 7.46 (m, 2H); 7.66 (d, 2H); 7.83 (d, 1H).

Claims

1. A Dopamine D1 receptor agonist compound of general formula I:



(I)

wherein: R^1 from hydrogen, halogen, C_1-C_4 alkyl, or CF_3;

R^2 is hydrogen, methyl, or lower alkenyl of 3-5 carbon atoms;

R^3 and R^4 together form a furan, dihydrofuran, thiophene, dihydrothiophene, cyclopentane or cyclohexane ring and R^5 is hydrogen or R^4 and R^5 together form a furan, dihydrofuran, thiophene, dihydrothiophene, cyclopentane or cyclohexane ring and R^3 is hydrogen;

R^6 is hydrogen, halogen, CF_3, CN, NO_2 or NH_2;

R^7 is hydrogen, halogen, CF_3, CN, NO_2 or NH_2;

2. A compound according to claim 1 wherein R^1 is halogen.

3. A compound according to claim 2 wherein R^1 is chlorine.

4. A pharmaceutical composition containing as an active ingredient a compound according to any of claims 1-3 or a salt thereof, optionally together with a physiologically acceptable carrier, excipient or diluent.

5. A compound according to any of claims 1-3 for use in the treatment or prevention of neurodegenerative disease.

6. Use of a compound according to any of claims 1-3 in the manufacture of a medicament for the treatment of neurodegenerative disease.

7. A method of treatment of neurodegenerative disease which includes administering to a patient suffering from said disease an effective amount of a composition according to claim 4.