1605511-6 SDS

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[✓] Claim(s) : paged 44,45,50,51,53-55 to paged .....
[ ] Drawing(s) : paged ..... to paged .....
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Heterocyclic Compounds and Their Preparation and Use

The present invention relates to therapeutically active azacyclic compounds, a method of preparing the same and to pharmaceutical compositions comprising the compounds. The novel compounds are useful as stimulants of the cognitive function of the forebrain and hippocampus of mammals and especially in the treatment of Alzheimer's disease.

Due to the in general improved health situation in the western world, elderly-related diseases are much more common now than in the past and are likely to be even more common in the future.

One of the elderly-related symptoms is a reduction of the cognitive functions. This symptom is especially pronounced in the patophysiological disease known as Alzheimer's disease. This disease is combined with, and also most likely caused by, a up to 90% degeneration of the muscarinic cholinergic neurons in nucleus basalis, which is part of substantia innominata. These neurons project to the prefrontal cortex and hippocampus and have a general stimulatory effect on the cognitive functions of the forebrain as well as of hippocampus, namely learning, association, consolidation, and recognition.

It is a characteristic of Alzheimer's disease that although the cholinergic neurons degenerate, then the postsynaptic muscarinic receptors in the forebrain and hippocampus still exist. Therefore muscarinic choliner-

gic agonists are useful in the treatment of Alzheimer's disease and in improving the cognitive functions of elderly people.

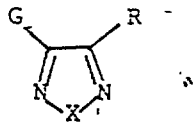
It is well known that arecoline (methyl 1-methyl-1,2,5,6- tetrahydropyridine-3-carboxylate) is such a cholinergic agonist.

Arecoline however has a very short biological half life and a small separation between central and peripheral muscarinic effects. Furthermore arecoline is a rather toxic compound.

EP-A-0307142 discloses a class of thiadiazoles, substituted on one of the ring carbon atoms with a non-aromatic azacyclic or azabicyclic ring system, and substituted on the other ring carbon atom with a substituent of low lipophilicity, or a hydrocarbon substituent, which are muscarinic agonists and therefore useful in the treatment of neurological and mental illnesses and severe painful conditions.

It is an object of the invention to provide new muscarinic cholinergic compounds.

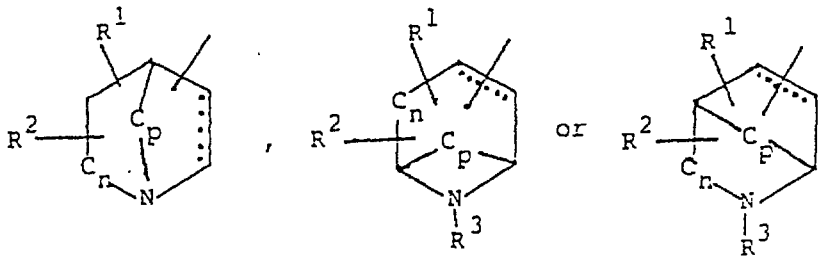
The novel compounds of the invention are heterocyclic compounds having the formula I



(I)

wherein X is oxygen or sulphur;

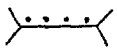
wherein G is selected from the group of azabicyclic ring systems consisting of

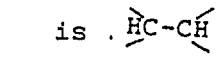
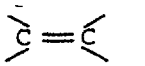


wherein the oxadiazole or thiadiazole ring can be attached at any position;

R^1 and R^2 may be present at any position, including the point of attachment of the oxadiazole or thiadiazole ring, and independently are hydrogen, -OH, halogen, $-NH_2$, carboxy, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl, straight or branched C_{2-5}-alkynyl, straight or branched C_{1-10}-alkoxy, or straight or branched C_{1-5}-alkyl substituted with -OH;

R^3 is hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl or straight or branched C_{2-5}-alkynyl;

n and p independently are 0, 1, 2, 3, or 4; 

is  or  ;

R is Y which represents hydrogen, halogen, -CN, -CHO, -OH, $-OR^4$, $-SR^4$, $-NH_2$, $-NHR^4$, $-NR^4R^5$, $-NO_2$, $-SOR^4$, $-SO_2R^4$, $-COR^4$, $-CO_2R^4$, $-CONH_2$, $-CONHR^4$, $-CONR^4R^5$, $-CH=NOR^4$, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen,

-CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R is a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturated, partly saturated or aromatic, R^4 substituted with Y or XR^4 substituted with Y wherein X has the meaning defined above; R^4 and R^5 independently are straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R^4 and R^5 independently are a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturated, partly saturated or aromatic; or a salt thereof with a pharmaceutically acceptable acid, or a prodrug thereof.

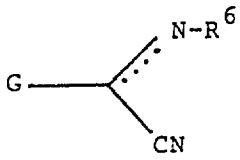
Examples of such salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate, or similar pharmaceutically- acceptable inorganic or organic acid addition salt.

The compounds of this invention are also useful analgesic agents and therefore useful in the treatment of severe painful conditions.

Furthermore, the compounds of this invention are useful in the treatment of glaucoma.

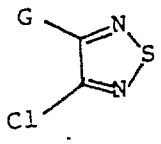
The invention also relates to methods of preparing the above mentioned compounds, comprising:

a) reacting a compound of formula II



(II)

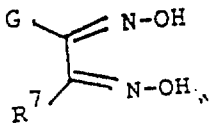
wherein G has the meaning defined above, >····N is >——NH or >═══N and R^6 is H, OH or O-alkyl, with S_2Cl_2 to form a compound of formula III



(III)

wherein G has the meaning defined above; subsequent displacement of Cl with an appropriate nucleophile gives a compound of formula I wherein X is S, or

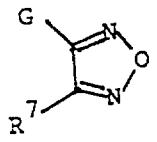
b) dehydrating a compound of formula IV



(IV)

wherein G has the meaning defined above and R^7 is alkyl, amino, halogen, alkoxy or alkylthio, to form a

compound of formula V



(V)

wherein G and R^7 have the meanings defined above, or

c) when R^7 in formula V is amino, the amino group can be substituted by chloro by known procedures, and subsequent displacement of Cl with an appropriate nucleophile gives a compound of formula I wherein X is O.

It is to be understood that the invention extends to each of the stereoisomeric forms of the compounds of formula I as well as the racemates.

The pharmacological properties of the compounds of the invention can be illustrated by determining their capability to inhibit the specific binding of ^{3}H-Oxotremorine-M (^{3}H-Oxo). Birdsdall N.J.M., Hulme E.C., and Burgen A.S.V. (1980). "The Character of Muscarinic Receptors in Different Regions of the Rat Brain". Proc. Roy. Soc. London (Series B) 207,1.

^{3}H-Oxo labels muscarinic receptor in the CNS (with a preference for agonist domaines of the receptors). Three different sites are labelled by ^{3}H-Oxo. These sites have affinity of 1.8, 20 and 3000 nM, respectively. Using the present experimental conditions only the high and medium affinity sites are determined.

The inhibitory effects of compounds on ^{3}H-Oxo binding

reflects the affinity for muscarinic acetylcholine receptors.

All preparations are performed at 0-4°C unless otherwise indicated. Fresh cortex (0.1-1 g) from male Wistar rats (150-250 g) is homogenized for 5-10 s in 10 ml 20 mM Hepes pH: 7.4, with an Ultra-Turrax homogenizer. The homogenizer is rinsed with 10 ml of buffer and the combined suspension centrifuged for 15 min at 40,000 × g. The pellet is washed three times with buffer. In each step the pellet is homogenized as before in 2×10 ml of buffer and centrifuged for 10 min at 40,000 × g.

The final pellet is homogenized in 20 mM Hepes pH: 7.4 (100 ml per g of original tissue) and used for binding assay. Aliquots of 0.5 ml is added 25 µl of test solution and 25 µl of ^{3}H-Oxotremorine (1.0 nM, final concentration) mixed and incubated for 30 min at 25°C. Non-specific binding is determined in triplicate using arecoline (1 µg/ml, final concentration) as the test substance. After incubation samples are added 5 ml of ice-cold buffer and poured directly onto Whatman GF/C glass fiber filters under suction and immediately washed 2 times with 5 ml of ice-cold buffer. The amount of radioactivity on the filters are determined by conventional liquid scintillation counting. Specific binding is total binding minus non specific binding.

Test substances are dissolved in 10 ml water (if necessary heated on a steambath for less than 5 minutes) at a concentration of 2.2 mg/ml. 25-75% inhibition of specific binding must be obtained before calculation of IC_{50}.

The test value will be given as IC_{50} (the concentration (ng/ml) of the test substance which inhibits the

specific binding of ^{3}H-Oxo by 50%).

IC_{50} = (applied test substance concentration)

$$x \frac{1}{\left(\frac{C_o}{C_x} - 1\right)} \text{ ng/ml}$$

where C_o is specific binding in control assays and C_x is the specific binding in the test assay. (The calculations assume normal mass-action kinetics).

Test results obtained by testing some compounds of the present invention will appear from the following table 1.

TABLE 1

Compound No.	Inhibition in vitro OXO BINDING (ng/ml)
1	156
2	270
3	208
4	21
5	18
6	>300
7	13
8	5.2
9	0.69
10	1.7
11	1.2
12	0.45

13	0.65
14	4.8
15	0.61
16	67
17	3.2
18	7.5
20	11
21	0.96
22	3.4
23	43
24	0.52
25	1.9
26	1.4
27	17
28	1.9
29	0.39
30	0.13
31	0.6
32	0.45
33	6.4
34	7.9
35	1.9
36	0.82
37	2.0
39	0.52
40	0.19
41	0.56
42	0.35
43	2.33
44	4.7
45	1.6
46	0.56
47	>300
48	0.43
49	0.33
50	1.0
51	0.89

52	0.61
53	0.3
54	3.1
55	0.43
56	0.14
57	4.6
62	1.9
63	8.2
64	8.2
65	9.6
67	0.43
68	0.69

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, and if desired in the form of a pharmaceutically-acceptable acid addition salt thereof, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids, such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective muscarinic cholinergic agonistic amount of the active ingredient commensurate with the intended daily dosage range to be employed. Tablets containing ten (10) milligrams of the active ingredient or, more broadly, one (1) to hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of this invention can thus be used for the formulation of pharmaceutical preparations, e.g. for oral and parenteral administration to mammals including humans, in accordance with conventional methods of galenic pharmacy.

Conventional excipients are such pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral or enteral application which do not deleteriously react with the active compounds.

Examples of such carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Ampoules are convenient unit dosage forms.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch, are particularly suitable for oral application. A syrup, elixir of the like can be used in cases where a sweetened vehicle can be employed.

Generally, the compounds of this invention are dispensed in unit form comprising 1-100 mg in a pharmaceutically-acceptable carrier per unit dosage.

The dosage of the compounds according to this invention is 1-100 mg/day, preferably 10-70 mg/day, when administered to patients, e.g. humans, as a drug.

A typical tablet which may be prepared by conventional tabletting techniques contains:

Active compound	5.0	mg
Lactosum	67.8	mg Ph.Eur.
Avicel®	31.4	mg
Amberlite®	1.0	mg
Magnesii stearas	0.25	mg Ph.Eur.

Due to the high muscarinic cholinergic receptor agonistic activity, the compounds of the invention are extremely useful in the treatment symptoms related to a reduction of the cognitive functions of the brain of mammals, when administered in an amount effective for stimulating the cognitive functions of the forebrain and hippocampus. The important stimulating activity of the compounds of the invention includes both activity against the patophysiological disease, Alzheimer's disease as well as against normal degeneration of brain function. The compounds of the invention may accordingly be administered to a subject, e.g., a living animal body, including a human, in need of stimulation of the cognitive functions of the forebrain and hippocampus, and if desired in the form of a pharmaceutically-acceptable acid addition salt thereof (such as the hydrobromide, hydrochloride, or sulfate, in any event prepared in the usual or conventional manner, e.g., evaporation to dryness of the free base in solution together with the acid), ordinarily concurrently, simultaneously, or together with a pharmaceutically-acceptable

carrier or diluent, especially and preferably in the form of a pharmaceutical composition thereof, whether by oral, rectal, or parenteral (including subcutaneous) route, in an effective forebrain and hippocampus stimulating amount, and in any event an amount which is effective for improving the cognitive function of mammals due to their muscarinic cholinergic receptor agonistic activity. Suitable dosage ranges are 1-100 milligrams daily, 10-100 milligrams daily, and especially 30-70 milligrams daily, depending as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and the preference and experience of the physician or veterinarian in charge.

The invention will now be described in further detail with reference to the following examples:

EXAMPLE 1

A. Ethyl (1-azabicyclo[2.2.2]octan-3-ylidine)cyanoacetate

A solution of 3-quinuclidone (75 g, 0.6 mol), ammonium acetate (2.3 g, 30 mmol), acetic acid (3.75 ml) and ethyl cyanoacetate (67.8 g, 0.6 mol) in toluene (400 ml) was refluxed with a water separator for 18 h. Water (100 ml) and NaOH was added, and the mixture extracted several times with ether. The organic phases were dried and evaporated. The residue was purified by column chromatography (eluent: EtOAc/MeOH (2:1)), yielding 73 g of the title compound.

B. Ethyl (1-azabicyclo[2.2.2]octan-3-yl)cyanoacetate

A solution of ethyl (1-azabicyclo[2.2.2]octan-3-ylidene)-cyanoacetate (73 g, 0.33 mol) in absolute ethanol (1 l) was treated with 10% palladium on charcoal (10 g) and hydrogen in a parr shaker at 20 psi for 5 h. Filtration and evaporation gave the wanted product in 68 g yield.

C. (1-Azabicyclo[2.2.2]octan-3-yl)hydroxyiminoacetonitrile

Ethyl (1-azabicyclo[2.2.2]octan-3-yl)cyanoacetate (10 g, 45 mmol) was added to a solution of sodium (1.04 g, 45 mmol) in absolute ethanol (60 ml). The mixture was stirred for 15 min. at room temperature and isoamylnitrite (7.9 ml, 60 mmol) was added. The reaction mixture was stirred for 18 h at 60°C. Evaporation of the reaction mixture gave crude title compound, which was used without further purification.

D. 3-Chloro-3-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]octane oxalate

To a solution of crude (1-azabicyclo[2.2.2]octan-3-yl)hydroxyiminoacetonitrile (max. 45 mmol) in DMF (60 ml) was slowly added a solution of S_2Cl_2 (10.85 ml, 135 mmol) in DMF (20 ml) at 0°C. After addition the reaction mixture was stirred at room temperature for 48 h. Water and 50% NaOH was added to the ice cooled reaction mixture and extracted with ether. The combined ether phases were dried and evaporated. The residue was purified by column chromatography (eluent: EtOAc/MeOH (2:1)) to give the free base of the title compound in 1.04 g yield. Crystallization with oxalic acid from acetone gave an analytical pu-

re product (Compound 1). M.p. 137-139°C.

EXAMPLE 2

3-(3-Chloro-1,2,5-thiadiazol-4-yl)-3-hydroxy-1-azabicyclo[2.2.2]octane oxalate

A solution of 3-chloro-3-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]octane (250 mg, 0.95 mmol) in ethanol (25 ml) was treated with formic acid (750 µl, 20 mmol), triethylamine (4.2 ml, 30 mmol) and 10% palladium on charcoal for 18 h at 60°C. After filtration and evaporation water and K_2CO_3 was added to the residue and extracted with ether. The dried ether phases were evaporated and purified by column chromatography (eluent: EtOAc/-MeOH (2:1)). Crystallization as the oxalate from acetone gave the title compound in 150 mg yield. (Compound 2). M.p. 241-242°C.

EXAMPLE 3

3-Methoxy-3-(3-methoxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]octane oxalate and 3-(3-Methoxy-1,2,5-thiadiazol- 3-yl)-1-azabicyclo[2.2.2]oct-2-ene oxalate

A solution of 3-chloro-3-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]octane (500 mg, 1.9 mmol) and sodiummethoxide (20 mmol) in methanol (20 ml) was stirred for 48 h at 60°C. Water was added to the reaction mixture and extracted with ether. The combined organic phases were dried and evaporated. The two products were separated by column chromatography (eluent: EtOAc/MeOH (2:1)). Crystallization of the dimethoxy product as the oxalate from acetone gave 200 mg. (Compound 3). M.p. 113-117°C. The monomethoxy oxalate was isolated in 60 mg yield (Com-

pound 4). M.p. 143-145°C.

EXAMPLE 4

3-(3-Hexyloxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]-oct-2-ene oxalate, 3-Hexyloxy-3-(3-hexyloxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]octane oxalate and 3-(3-Hexyloxy-1,2,5-thiadiazol-4-yl)-3-hydroxy-1-azabicyclo-[2.2.2]octane oxalate

A 50% sodiumhydride dispersion (960 mg, 20 mmol) was dissolved in 1-hexanol and 3-chloro-3-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]octane (500 mg, 1.9 mmol) was added. The reaction mixture was stirred at 90°C for 18 h and evaporated. The residue was dissolved in water and extracted with ether. The dried ether phases were evaporated and the products separated by column chromatography (eluent: EtOAc/MeOH (2:1)). The first fractions contained the eliminated product which, after crystallization with oxalic acid, was collected in 70 mg yield. (Compound 5). M.p. 135-137°C.

The next fractions contained the dihexyloxy analogue, which gave 70 mg as the oxalate salt. (Compound 6). M.p. 84-85°C.

The later fractions gave the hydroxy-hexyloxy compound in 100 mg yield as the oxalate salt. (Compound 7). M.p. 145-147°C.

EXAMPLE 5

3-(3-Chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]-octane oxalate

Hydrogenation for 48 h of 3-chloro-3-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]octane (15.2 g, 66 mmol) in ethanol (500 ml) at 30 psi in the presence of 10% palladium on charcoal (2.0 g) gave, after filtration and evaporation, the hydrochloride salt of the wanted product in quantitative yield. Crystallization of a sample with oxalic acid from methanol/acetone/ether produced the title compound. (Compound 8). M.p. 207-209°C.

EXAMPLE 6

3-(3-Ethoxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]-octane fumarate

Sodium (200 mg, 8.7 mmol) was dissolved in ethanol (30 ml) and 3-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.2]octane (300 mg, 1.3 mmol) was added. The reaction mixture was stirred at 60°C for 18 h. Water was added and the reaction mixture extracted with ether. The dried and filtrated ether extracts were evaporated to give the free base. Crystallization as the fumarate salt from isopropanol/ether gave the title compound in 210 mg yield. (Compound 9). M.p. 128-131°C.

EXAMPLE 7

The following compounds were made in exactly the same manner as described in example 6 using the appropriate alcohol:

3-(3-Propoxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]-octane fumarate. (Compound 10). M.p. 64-67°C.

3-(3-Butoxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]-octane oxalate. (Compound 46). M.p. 159-160°C.

EXAMPLE 8

3-(3-Hexyloxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]-octane fumarate

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A 50% dispersion of sodiumhydride (230 mg, 5 mmol) was dissolved in 1-hexanol (25 ml) and 3-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]octane (250 mg, 1.1 mmol) was added. The reaction was stirred at 80°C for 8 h and at room temperature for 18 h. After evaporation water was added to the residue and extracted with ether. The combined ether phases were dried and evaporated. Crystallization with fumaric acid from isopropanol/ether gave the title compound in 220 mg yield. (Compound 11). M.p. 108-109°C.

The following compounds were made in exactly the same manner using the appropriate alcohol instead of 1-hexanol:

3-(3-(6-Hexenyloxy)-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.2]octane fumarate, m.p. 107-110°C. (Compound 48)

3-(3-(3-Hexenyloxy)-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.2]octane fumarate, m.p. 135.5-137.5°C. (Compound 49)

3-(3-Pentyloxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.2]octane oxalate, m.p. 102-104°C. (Compound 50)

3-(3-Isopentyloxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.2]octane oxalate, m.p. 135.5-137.5°C. (Compound 51)

EXAMPLE 9

3-(3-Pentylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.2]octane fumarate

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A solution of 3-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]octane oxalate (500 mg, 1.56 mmol), sodiumhydrogen sulfide, monohydrate (463 mg, 6.25 mmol) and potassium carbonate (1.38 g, 10 mmol) in DMF (20 ml) was stirred at room temperature for 1 h. 1-Pentylbromide (755 mg, 5 mmol) was added, and the reaction mixture was stirred at room temperature for 18 h. 1N HCl was added, and the mixture extracted with ether once. 50% NaOH was added to the aqueous phase and extracted with ether. The ether phase was dried and evaporated. Crystallization of the residue with fumaric acid from isopropanol/ether gave the title compound in 380 mg yield. (Compound 12). M.p. 138-139°C.

EXAMPLE 10

The following compounds were made in exactly the same manner as described in example 9, using the appropriate alkyl bromide:

3-(3-Butylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.2]octane fumarate. (Compound 13). M.p. 85-87°C.

3-(3-Hexylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.2]octane fumarate. (Compound 14). M.p. 138-139°C.

3-(3-(3-Phenylpropylthio)-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]octane fumarate. (Compound 44). M.p. 123-

124°C.

3-(3-(4-Cyanobenzylthio)-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]octane oxalate. (Compound 45). M.p. 200°C. decomp.

3-(3-Ethylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.2]octane oxalate, m.p. 194-195°C (Compound 52)

3-(3-Propylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.2]octane oxalate, m.p. 206.5-208°C (Compound 53)

3-(3-Heptylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.2]octane fumarate, m.p. 130-132°C (Compound 54)

EXAMPLE 11

A. Ethyl (1-azabicyclo[3.2.1]octan-6-ylidene)cyano-acetate

A solution of 1-azabicyclo[3.2.1]octan-6-one (41.25 g, 0.33 mol), acetic acid (2 ml), ammonium acetate (1.25 g) and ethyl cyanoacetate (37 g, 0.33 mol) in toluene (500 ml) was refluxed with a Dean-Stark water separator for 40 h. The toluene phase was extracted with 3 x 200 ml 5 M HCl solution. The water phase was basified with 28% ammonium hydroxide solution and extracted with ether (4 x 200 ml). The organic phases were dried over magnesium sulfate and evaporated. The residue was purified by column chromatography (eluent CH_2Cl_2/MeOH (9:1), yield 41 g of the title compound.

B. Ethyl (1-azabicyclo[3.2.1]octan-6-yl)cyanoacetate

A solution of ethyl (1-azabicyclo[3.2.1]octan-6-ylidene)-

cyanoacetate (41 g, 0.19 mol) in abs. ethanol (500 ml) was treated with 10% palladium on carbon (5 g) and hydrogen in a Parr shaker at 30 psi for 5 h. Filtration and evaporation gave the title compound in 36 g yield.

C. (1-azabicyclo[3.2.1]octan-6-yl)hydroxyiminoacetonitrile

Ethyl (1-azabicyclo[3.2.1]octan-6-yl)cyanoacetate (36 g, 0.16 mol) in abs. ethanol (100 ml) was added to a solution of sodium (4 g, 0.21 mol) in abs. ethanol (100 ml). Isoamylnitrite (25 ml, 0.19 mol) was added over 0.5 h, and the mixture was heated at 50°C for 4 h. Evaporation of the reaction mixture gave crude sodium salt of the title compound, which was used without further purification.

D. 6-Chloro-6-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane

A solution of crude (1-azabicyclo[3.2.1]octan-6-yl)hydroxy- iminoacetonitrile (max. 0.16 mol) in DMF (150 ml) was added to a solution of S_2Cl_2 (50 ml, 0.68 mol) in DMF (100 ml) at 0°C over 1 h. The reaction mixture was stirred over night and icewater (500 ml) was added. The mixture was filtered and the filter cake washed with 1 m HCl (3 x 100 ml). The water solution was extracted with ether (2 x 200 ml), then basified with a 28% ammonium hydroxide solution and extracted with ether (4 x 200 ml). The combined ether extracts from the last extraction were dried and evaporated. The residue was purified by column chromatography (eluent: CH_2Cl_2/MeOH (9:1)) to give the title compound in 11 g yield as a mixture of the endo and exo forms.

EXAMPLE 12

The following compound was made in exactly the same manner as described in example 11, starting from 1-azabicyclo[2.2.1]heptan-3-one:

3-Chloro-3-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.1]heptane.

EXAMPLE 13

Exo-6-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane and Endo-6-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane-oxalate

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A solution of Endo/Exo-6-chloro-6-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane (1.3 g, 5 mmol) in abs. ethanol (100 ml) was treated with 10% palladium on carbon (300 mg) in a Parr shaker at 20 psi for 4 h. The solution was filtered and evaporated. The residue was purified by column chromatography with CH_2Cl_2/MeOH/TEA (9:1:0.25). The first fraction contained the exo compound, which after crystallization with oxalic acid in acetone, was collected in 150 mg yield. (Compound 15). M.p. 148- 149°C. The next fractions contained the endo compound, which after crystallization with oxalic acid from acetone was collected in 600 mg yield. (Compound 16). M.p. 195- 197°C.

EXAMPLE 14

Endo-6-(3-hexylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane oxalate

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To a solution of endo-6-(3-chloro-1,2,5-thiadiazol-4-yl)-

1-azabicyclo[3.2.1]octane (229 mg, 1.0 mmol) in DMF (10 ml) was added sodiumhydrogen sulfide monohydrate (230 mg, 3.1 mmol). The reaction mixture was stirred at room temperature for 1 h. Potassium carbonate (1.38 g, 10 mmol) and 1-hexylbromide (335 mg, 2.5 mmol) was added and the mixture was stirred for 1 h. 1N HCl solution was added and the mixture extracted with ether (2 x 50 ml). The aqueous solution was basified with a 28% NH_3 solution and extracted with methylene chloride (3 x 100 ml). The methylene chloride phase was dried and evaporated. The residue was purified by column chromatography (eluent CH_2Cl_2/MeOH (9:1)). Crystallization of the pure base with oxalic acid from acetone gave the title compound in 100 mg yield. (Compound 17). M.p. 137-139°C.

EXAMPLE 15

The following compounds were made in exactly the same manner as described in Example 14, using the appropriate alkyl bromide:

Endo-6-(3-(5-hexenylthio)-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane oxalate. (Compound 18). M.p. 113-114°C.

Endo-6-(3-butylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane oxalate. (Compound 24). M.p. 123-124°C.

Endo-6-(3-ethylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane oxalate. (Compound 25). M.p. 150-151°C.

Endo-6-(3-pentylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane oxalate. (Compound 26). M.p. 137-138°C.

Endo-6-(3-(3-phenylpropylthio)-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane oxalate. (Compound 27). M.p. 127-129°C.

Endo-6-(3-(4-cyanobenzylthio)-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane oxalate (Compound 28). M.p. 159-161°C.

Endo-6-(3-propylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane oxalate (Compound 57) m.p. 132-134°C.

EXAMPLE 16

Exo-6-(3-ethoxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane oxalate and Endo-6-(3-ethoxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane oxalate

To a solution of sodium (230 mg, 10 mmol) in abs. ethanol (20 ml) was added endo-6-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane (229 mg, 1 mmol). The reaction mixture was heated at 50°C for 12 h and evaporated. Water (100 ml) was added, and the mixture was extracted with methylene chloride (4 x 50 ml). The organic phases were dried and evaporated. The residue was purified by column chromatography eluent (CH_2Cl_2/MeOH/TEA, 9:1:0.25). The first fractions contained the exo compound, which after crystallization with oxalic acid in acetone was collected in 50 mg yield. (Compound 19). M.p. 110-112°C. The next fractions contained the endo compound, which after crystallization with oxalic acid in acetone was collected in 20 mg yield. (Compound 20). M.p. 127-129°C.

EXAMPLE 17

Exo-3-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.1] heptane oxalate and Endo-3-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.1]heptane oxalate

A solution of endo/exo-3-chloro-3-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.1]heptane (0.5 g, 2 mmol) in abs. ethanol (100 ml) was treated with 10% palladium on carbon in a Parr shaker at 20 psi for 4 h. The solution was filtered and evaporated. The residue was purified by column chromatography, eluent CH_2Cl_2/MeOH (9:1). The first fractions contained the exo compound, which after crystallization with oxalic acid from acetone/ether was collected in 50 mg yield. (Compound 21). M.p. 138-140°C. The next fractions contained the endo compound, which after crystallization with oxalic acid from acetone, was collected in 450 mg yield. (Compound 22). M.p. 118-121°C.

EXAMPLE 18

Endo-3-(3-methoxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.1]heptane oxalate

To a solution of sodium (110 mg, 5 mmol) in methanol (20 ml) was added endo-3-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.1]heptane (110 mg, 0.5 mmol). The reaction mixture was heated at reflux for 60 h and evaporated. Water (50 ml) was added, and the mixture was extracted with methylene chloride (4 x 50 ml). The organic phases were dried and evaporated. The residue was purified by column chromatography eluent (CH_2Cl_2/MeOH, 9:1). Crystallization of the free base with oxalic acid from acetone/ether gave the title compound in 40 mg yield. (Compound 23). M.p. 104-106°C.

EXAMPLE 19

Exo-6-(3-Hexylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane oxalate

To a solution of exo-6-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane (229 mg, 1.0 mmol) in DMF (20 ml) was added sodiumhydrogen sulfide monohydrate (230 mg, 3.0 mmol). The reaction mixture was stirred at room temperature for 1 h. Potassium carbonate (1.38 g, 10 mmol) and 1-hexylbromide (335 mg, 2.5 mmol) was added and the mixture was stirred for 1 h. 1N HCl solution was added and the mixture extracted with ether (2 x 50 ml). The aqueous solution was basified with a 28% NH_3 solution and extracted with ether (2 x 50 ml). The ether phase was dried and evaporated. The residue was crystallized as the oxalate salt from acetone/ether in 200 mg yield. (Compound 29. M.p. 118-119°C.

EXAMPLE 20

The following compounds were made in exactly the same manner as described in example 19, using the appropriate alkylbromide:

Exo-6-(3-butylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane oxalate. (Compound 30). M.p. 143-145°C.

Exo-6-(3-pentylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane oxalate. (Compound 31). M.p. 117-118°C.

Exo-6-(3-ethylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane oxalate. (Compound 32). M.p. 159-160°C.

Exo-6-(3-propylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane oxalate (Compound 58), m.p. 173-174°C.

EXAMPLE 21

Endo-3-(3-pentylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.1]heptane fumarate

To a solution of endo-3-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.1]heptane (215 mg, 1.0 mmol) in DMF (20 ml) was added sodium hydrogensulfide monohydrate (230 mg, 3.0 mmol). The reaction mixture was stirred at room temperature for 1 h. Potassium carbonate (1.38 g, 10 mmol) and 1-pentylbromide (0.45 g, 3 mmol) was added and the mixture was stirred for 1 h. 1 M hydrochloric acid solution (100 ml) was added and the mixture extracted with ether (2 x 50 ml). The aqueous solution was basified with a 28% NH_3-solution and extracted with ether (3 x 75 ml). The ether phase was dried and evaporated. The residue was crystallized as the fumarate salt from MeOH/ether in 250 mg yield. (Compound 33). M.p. 120-122°C.

EXAMPLE 22

The following compounds were made in exactly the same manner as described in example 21 using the appropriate alkylbromide:

Endo-3-(3-hexylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.1]heptane fumarate. (Compound 34). M.p. 127-129°C.

Endo-3-(3-(3-phenylpropylthio)-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.1]heptane oxalate. (Compound 35). M.p. 119-120°C.

Endo-3-(3-butylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.1]heptane fumarate. (Compound 36). M.p. 106-108°C.

Endo-3-(3-propylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.1]heptane oxalate. (Compound 37). M.p. 169-170°C.

EXAMPLE 23

Exo-3-(3-pentylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.1]heptane oxalate

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To a solution of exo-3-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.1]heptane (215 mg, 1.0 mmol) in DMF (20 ml) was added sodium hydrogensulfide monohydrate (230 mg, 3.0 mmol). The reaction mixture was stirred at room temperature for 1 h. Potassium carbonate (1.38 g, 10 mmol) and 1-pentylbromide (0.45 g, 3 mmol) was added and the mixture was stirred for 1 h. 1 M hydrochloric acid solution (100 ml) was added and the mixture extracted with ether (2 x 50 ml). The aqueous solution was basified with a 28% NH_3-solution and extracted with ether (3 x 75 ml). The ether phase was dried and evaporated. The residue was crystallized as the oxalate salt from MeOH/ether in 250 mg yield. (Compound 38). M.p. 120-122°C.

EXAMPLE 24

The following compounds were made in exactly the same manner as described in example 23, using the appropriate alkylbromide:

Exo-3-(3-hexylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.1]heptane oxalate. (Compound 39). M.p. 102-103°C.

Exo-3-(3-propylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.1]heptane oxalate. (Compound 40). M.p. 132-133°C.

Exo-3-(3-(3-phenylpropylthio)-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.1]heptane oxalate. (Compound 41). M.p. 126-127°C.

Exo-3-(3-butylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.1]heptane oxalate. (Compound 42). M.p. 188-189°C.

EXAMPLE 25

A. 8-Ethoxycarbonyl-3-chloro-2-formyl-8-azabicyclo-[3.2.1]oct-2-ene

To a solution of dry DMF (45 g, 0.6 mol) in dry CH_2Cl_2 (150 ml) was added $POCl_3$ (75 g, 0.5 mol) at 0-10°C. 8-Ethoxycarbonyl-8-azabicyclo[3.2.1]octane-3-one (57 g, 0.29 mol) dissolved in dry CH_2Cl_2 (60 mol) was added. The reaction mixturre was stirred over night at room temperature, then added to ice water (1.000 ml). The phases were separated and the water phase extracted with CH_2Cl_2 (2 x 200 ml). The combined CH_2Cl_2 extracts were washed with a saturated $NaHCO_3$ solution and water, dried and evaporated to give 70 g of the title compound, which was used in the next step without further purification.

B. 8-Ethoxycarbonyl-3-chloro-2-(3-chloro-1,2,5-thiadiazol-4-yl)-8-azabicyclo[3.2.1]oct-2-ene

Potassium cyanide (8.5 g, 0.13 mol) and ammonium chloride (6.4 g, 0.12 mol) was dissolved in a min. amount of water. 8-Ethoxycarbonyl-3-chloro-2-formyl-8-azabicyclo[3.2.1]-oct-2-ene (23 g, 0.1 mol) dissolved in DMF (25 ml) was added. The reaction mixture was stirred at room temperature for 3 days, then added to a 5 N hydrochloric acid solution (200 ml). The aqueous phase was extracted with ether (3 x 75 ml), then basified with a 28% NH_3 solution and extracted with ether (4 x 100 ml). The ether phases from the last extraction were dried, evaporated and dissolved in DMF (50 ml). This solution was added to sulphur monochloride (16.8 g, 0.12 mol) in DMF (50 ml). The reac-

tion mixture was stirred over night at room temperature and poured into ice-water. The water phase was extracted with ether (3 x 100 ml). The combined ether phases were dried and evaporated. The residue was purified by column chromatography (eluent: CH_2Cl_2). Yield 3.2 g as an oil.

EXAMPLE 26

3-Chloro-2-(3-ethoxy-1,2,5-thiadiazol-4-yl)-8-azabicyclo-[3.2.1]oct-2-ene oxalate

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To a solution of sodium (230 mg, 10 mmol) in abs., ethanol (50 ml) was added 8-ethoxycarbonyl-3-chloro-2-(3-chloro-1,2,5-thiadiazol-4-yl)-8-azabicyclo[3.2.1]oct-2-ene (670 mg, 2 mmol). The reaction mixture was heated at reflux overnight, evaporated and conc. HCl (40 ml) was added. The reaction mixture was heated at reflux for 4 days, evaporated and basified with a 28% NH_3 solution. The aqueous solution was extracted with ether (3 x 75 ml). The combined ether extracats were dried and evaporated. The residue was purified by column chromatography (eluent CH_2Cl_2/MeOH; 9:1). Crystallization of the free base with oxalic acid in acetone gave the title compound in 110 mg yield. (Compound 43). M.p. 178-180°C.

EXAMPLE 27

3-Chloro-2-(3-chloro-1,2,5-thiadiazol-4-yl)-8-azabicyclo-[3.2.1]oct-2-ene oxalate

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To a solution of 8-Ethoxycarbonyl-3-chloro-2-(3-chloro-1,2,5-thiadiazol-4-yl)-8-azabicyclo[3.2.1]oct-2-ene (1.7 g, 5 mmol) in dry toluene (50 ml) was added $AlCl_3$ (2.6 g, 20 mmol). The reaction mixture was slowly heated to 80°C and kept at this temperature for 10 min. After cooling to

room temperature the reaction mixture was poured on ice and basified with a 50% NaOH solution. The aqueous phase was extracted with CH_2Cl_2 (3 x 100 ml). The combined organic extracts were dried over $MgSO_4$ and evaporated. The residue was crystallized as the oxalate salt from acetone to give the title compound. Yield 1.6 g (Compound 47), m.p. 194-195°C.

EXAMPLE 28

The following compounds were made in exactly the same manner as described in Example 16 using the appropriate alcohol:

Exo-6-(3-pentyloxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane oxalate (Compound 59), m.p. 122-123°C.

Endo-6-(3-pentyloxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane oxalate (Compound 60), m.p. 124-125°C.

EXAMPLE 29

A. 4-Chloro-3-formyl-1-azabicyclo[3.3.1]non-2-ene

To DMF (50 ml, 0.68 mol) was slowly added $POCl_3$ (50 ml, 0.54 mol) at 0°C over 1 h. 1-Azabicyclo[3.3.1]nonane-4-one hydrochloride (17.5 g, 0.1 mol) was added in one portion and the reaction mixture heated at 100°C for 1 h. After cooling the reaction mixture was poured on ice (1000 g) and the reaction mixture neutralized with potassium carbonate. The water phase was extracted with ether (5 x 200 ml). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography (eluent: CH_2Cl_2/CH_3OH (9:1), yielding 17 g of the title compound.

B. 4-Chloro-3-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.3.1]non-3-ene oxalate

To a solution of oxalic acid (9.0 g, 100 mmol) in water (100 ml) was added 4-chloro-3-formyl-1-azabicyclo[3.3.1]-non-2-ene (17.0 g, 95 mmol). Potassium cyanide (6.8 g, 10 mmol) dissolved in a min. amount of water was added dropwise. The reaction mixture was stirred at room temperature for 2 h. The precipitated crystals were filtered and suspended in water/EtOH (4:1, 120 ml). Ammonium chloride (6.0 g, 100 mmol) and ammonium hydroxide (28% in water 10 ml) was added and the reaction mixture was stirred at room temperature overnight. The water phase was extracted with methylene chloride (5 x 100 ml). The organic phases were dried over magnesium sulphate and evaporated. The residue was dissolved in DMF (50 ml) and added dropwise to a solution of sulfurmonochloride (20 ml, 250 mmol) in DMF (30 ml) at 0°C. The reaction mixture was stirred at room temperature for 4 h, then crushed ice ((500 g) was added. The precipitated sulfur was filtered off and the filtrate washed with 1 M hydrochloric acid solution (2 x 100 ml) the combined water phases was basified with ammonia (28% in water) and extracted with ether (4 x 200 ml). The combined organic phases were dried and evaporated. The residue was crystallized as the oxalate salt from acetone/ether to give the title compound. Yield 10.8 g (Compound 61) m.p. 149-150°C.

EXAMPLE 30

4-Chloro-3-(3-propyloxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.3.1]non-3-ene oxalate

To a solution of sodium (0.23 g, 10 mmol) in n-propanol (10 ml) was added 4-chloro-3-(3-chloro-1,2,5-thiadiazol-

4-yl)-1-azabicyclo[3.3.1]non-3-ene (0.274 g, 1 mmol). The reaction mixture was heated at 60°C for 2 h. Hydrochloric acid (1 M, 100 ml) was added, and the water phase extracted with ether (2 x 50 ml). The water phase was basified with solid potassium carbonate and extracted with ether (3 x 75 ml). The combined ether extracts were dried over magnesium sulfate and evaporated. The residue was crystallized as the oxalate salt from acetone/ether to give the title compound. Yield 180 mg (Compound 62) m.p. 122-123°C.

EXAMPLE 31

The following compounds were made in exactly the same manner as described in example 30 using the appropriate alcohol:

4-Chloro-3-(3-pentyloxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.3.1]non-3-ene oxalate (Compound 63) m.p. 114-115°C

4-Chloro-3-(3-methoxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.3.1]non-3-ene oxalate (Compound 64) m.p. 103-104°C.

EXAMPLE 32

4-Chloro-3-(1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.3.1]-non-3-ene oxalate

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To a solution of sodium (0.092 g, 4 mmol) in isopropanol (40 ml) was added n-butylmercaptan (270 ml, 3 mmol). 4-chloro-3-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.3.1]non-3-ene (0.82 g, 3 mmol) dissolved in isopropanol (10 ml) was added and the reaction mixture was stirred overnight at room temperature. The reaction mixture was evaporated and hydrochloric acid (1 M, 100 ml) was

added. The water phase was extracted with ether (2 x 50 ml) basified with solid potassium carbonate and extracted with ether (3 x 75 ml). The organic phase was dried and evaporated. The residue was purified by column chromatography (eluent: ethyl acetate) and the free base was crystallized with oxalic acid from acetone to give the title compound. Yield 250 mg (Compound 65) m.p. 175-77°C.

EXAMPLE 33

(-) 3-(3-Butylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.2]octane (+) L-tartrate

To a solution of (±) 3-butylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]octane (free base of compound 13, example 10) (5.5 g, 19.43 mmol) in ethanol (50 ml) was added a solution of (+)L-tartaric acid (2.9 g, 19.4 mmol) in water (10 ml). Ether (approx. 200 ml) was added to the solution to give a slightly unclear solution. The title compound was precipitated overnight and the crystals collected by filtration (3.05 g). Recrystallization twice from ethanol (20 ml) and ether gave the pure (-) enantiomer (1.90g) (Compound 55), m.p. 106-108°C. $[\alpha]_{(\text{free base})} = -15.80^{\circ}$ (C = 4.05 MeOH).

EXAMPLE 34

(+) 3-(3-Butylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.2]octane (-)D-tartrate

The motherliquour from the crystallization with (+)L-tartaric acid (example 33) was evaporated and the residue treated with 50% NaOH in water and extracted with ether. The combined ether phase were dried and evaporated to give crude free base of the title compound (2.9 g, 10.2

mmol). The residue was dissolved in ethanol (15 ml) and a solution of (-) D-tartaric acid (1.54 g, 10.2 mmol) in water (4 ml) was added. Ether was added to the solution and the title compound precipitated overnight. The crystals were collected by filtration and recrystallization twice from ethanol/ether gave the pure (+) enantiomer (1.90 g) (Compound 56), m.p. 106-108°C. $[\alpha]_{(\text{free base})}$ = + 14.94°. (C = 4.09 in MeOH).

EXAMPLE 35

3-(3-Amino-1,2,5-oxadiazol-4-yl)-1-azabicyclo[2.2.2]-octane fumarate

To a solution of crude (1-azabicyclo[2.2.2]octan-3-yl)-hydroxyiminoacetonitrile (10 g, max. 29 mmol) (example 1C) in methanol (50 ml) was added a methanol solution of hydroxylamine (prepared from NH_2OH, HCl (4.2 g, 60 mmol) in methanol (60 ml) and sodium (1.38 g, 60 mmol) in methanol (60 ml)). The reaction mixture was stirred at 40°C for 18 h and evaporated to give the crude amide oxime derivative. The residue was treated with excess of $POCl_3$ at 45°C for 18 h. Water and sodium hydroxide was added to obtain alkaline pH and the aqueous mixture extracted with chloroform. The combined organic phases were dried and evaporated to give the free base of the title compound as a solid (yield 570 mg). MS: M^+: 194. Crystallization as the fumarate salt from isopropanol gave the title compound (110 mg) (Compound 66), m.p. 60-75°C.

EXAMPLE 36

A. 5-Carboxaldehyde-1-azabicyclo[3.2.1]octane

To a solution of 1-azabicyclo[3.2.1]oct-5-yl-N-methyl-N-

methoxycarboxamide (4.0 g, 17.4 mmol) in tetrahydrofuran (100 ml) was added dropwise a 1 Molar solution of DIBAL (26 ml, 26 mmol) at -65°C. The temperature of the reaction mixture was allowed to raise to 0°C over 30 min. and then cooled to -65°C. Aqueous hydrochloric acid (75 ml, 5N) was added to the cold reaction mixture and the tetrahydrofuran was evaporated in vacuo. The aqueous residue was stirred overnight at room temperature and then evaporated. Water and potassium carbonate was added to the residue and extracted with methylene chloride (3 x 300 ml). The combined methylene chloride phases were dried and evaporated to give the title compound as an oil. Yield 2.75 g.

B. 2-Amino-2-(1-azabicyclo[3.2.1]oct-5-yl)acetonitrile

To a solution of potassium cyanide (1.43 g, 22 mmol) in water (20 ml) 5-carboxaldehyde-1-azabicyclo[3.2.1]octane (2.75 g, 19.8 mmol) was added over 30 min. at 0-10°C. Acetic acid (1.26 ml, 22 mmol) was added to the reaction mixture over 30 min. at 5-10°C. The reaction mixture was stirred at room temperature for further 18 h and cooled to 5°C. Aqueous sodium hydroxide was added to obtain alkaline pH and then extracted with methylene chloride (3 x 200 ml). The combined organic phases were evaporated and the residue was treated with a solution of ammonium chloride (3.8 g, 72 mmol) in water (10 ml) and 25% aqueous ammonia (5 ml). The reaction mixture was stirred at room temperature for 18 h and then extracted with methylene chloride. The combined organic phases were dried and evaporated to give the title compound. Yield. 1.67 g.

C. 5-(3-Chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane oxalate

2-Amino-2-(1-azabicyclo[3.2.1]oct-5-yl)acetonitrile (1.67 g, 10 mmol) was dissolved in DMF (10 ml) and a solution of sulfur monochloride (2.57 ml, 30 mmol) in DMF (10 ml) was added dropwise at 0°C. The reaction mixture was stirred at room temperature for 18 h and cooled to 0°C whereupon water (40 ml) and aqueous potassium hydroxide was added slowly. The alkaline reaction mixture was extracted with ether (3 x 300 ml) and the combined ether phases were dried and evaporated. The residue (850 mg) was crystallized with oxalic acid from acetone/ methanol to give the title compound. Yield 710 mg (Compound 67), m.p. 137.5- 139.5°C.

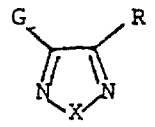
EXAMPLE 37

5-(3-Hexylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane oxalate

Sodium hydrosulfide monohydrate (326 mg, 4.4 mmol) was added to a solution of 5-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane oxalate (350 mg, 1.1 mmol) in DMF (20 ml) at room temperature and the reaction mixture was stirred for 30 min. Potassium carbonate (1.24 g, 9 mmol) and 1-bromohexan (561 µl, 4 mmol) were added and the reaction mixture was stirred for 3 h. Water (50 ml) was added to the reaction mixture and the aqueous phase extracted with ether (3 x 200 ml). The combined ether phases were dried and evaporated to give the crude free base of the title compound (220 mg). The residue was crystallized as the oxalate salt from acaetone to give the title compound. Yield 200 mg (Compound 68), m.p. 67-69°C.

CLAIMS

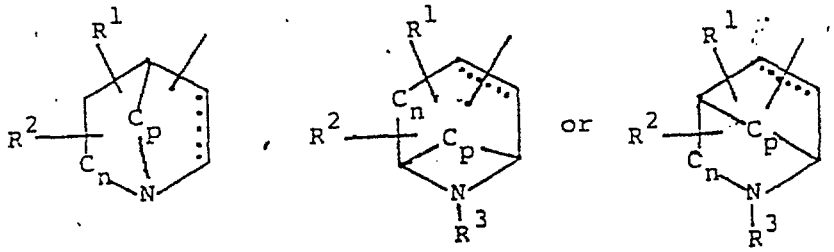
1. A compound of formula I



(I)

wherein X is oxygen or sulphur;

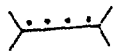
wherein G is selected from the group of azabicyclic ring systems consisting of

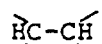
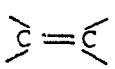


wherein the oxadiazole or thiadiazole ring can be attached at any position;

R^1 and R^2 may be present at any position, including the point of attachment of the oxadiazole or thiadiazole ring, and independently are hydrogen, -OH, halogen, $-NH_2$, carboxy, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl, straight or branched C_{2-5}-alkynyl, straight or branched C_{1-10}-alkoxy, or straight or branched C_{1-5}-alkyl substituted with -OH;

R^3 is hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl or straight or branched C_{2-5}-alkynyl;

n and p independently are 0, 1, 2, 3, or 4; 

is  or  ;

R is Y which represents hydrogen, halogen, -CN, -CHO, -OH, $-OR^4$, $-SR^4$, $-NH_2$, $-NHR^4$, $-NR^4R^5$, $-NO_2$, $-SOR^4$, $-SO_2R^4$, $-COR^4$, $-CO_2R^4$, $-CONH_2$, $-CONHR^4$, $-CONR^4R^5$, $-CH=NOR^4$, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R is a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturated, partly saturated or aromatic, R^4 substituted with Y or XR^4 substituted with Y wherein X has the meaning defined above; R^4 and R^5 independently are straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R^4 and R^5 independently are a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturated, partly saturated or aromatic; or a salt thereof with a pharmaceutically acceptable acid, or a prodrug thereof.

2. A compound according to claim 1 selected from the following:

3-Chloro-3-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.2]octane

3-(3-Chloro-1,2,5-thiadiazol-4-yl)-3-hydroxy-1-azabicyclo-[2.2.2]octane

3-Methoxy-3-(3-methoxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]octane

3-(3-Methoxy-1,2,5-thiadiazol-3-yl)- 1-azabicyclo[2.2.2]oct-2-ene

3-(3-Hexyloxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]-oct-2-ene

3-Hexyloxy-3-(3-hexyloxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]octane

3-(3-Hexyloxy-1,2,5-thiadiazol-4-yl)-3-hydroxy-1-azabicyclo[2.2.2]octane

3-(3-Chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]-octane

3-(3-Ethoxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]-octane

3-(3-Propoxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]-octane

3-(3-Butoxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]-octane

3-(3-Pentylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]-octane

3-(3-Butylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]-octane

3-(3-Hexylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]-octane

3-(3-(3-Pentylpropylthio)-1,2,5-thiadiazol-4-yl)-1-aza-bicyclo[2.2.2]octane

3-(3-(4-Cyanobenzylthio)-1,2,5-thiadiazol-4-yl)-1-azabi-cyclo[2.2.2]octane

Exo-6-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]-octane

Endo-6-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]-octane

Endo-6-(3-hexylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane

Endo-6-(3-(5-hexenylthio)-1,2,5-thiadiazol-4-yl)-1-aza-bicyclo[3.2.1]octane

Endo-6-(3-butylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane

Endo-6-(3-ethylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane

Endo-6-(3-pentylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane

Endo-6-(3-(3-phenylpropylthio)-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane

Endo-6-(3-(4-cyanobenzylthio)-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane

Exo-6-(3-ethoxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane

Endo-6-(3-ethoxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane

Exo-3-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.1]heptane

Endo-3-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.1]heptane

Endo-3-(3-methoxy-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.1]heptane

Exo-6-(3-Hexylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane

Exo-6-(3-butylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane

Exo-6-(3-pentylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane

Exo-6-(3-ethylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[3.2.1]octane

Endo-3-(3-pentylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.1]heptane

Endo-3-(3-(3-phenylpropylthio)-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.1]heptane

Endo-3-(3-butylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.1]heptane

* C L M S *

Endo-3-(3-propylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.1]heptane

Exo-3-(3-pentylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.1]heptane

Exo-3-(3-hexylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.1]heptane

Exo-3-(3-propylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.1]heptane

Exo-3-(3-(3-phenylpropylthio)-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.1]heptane

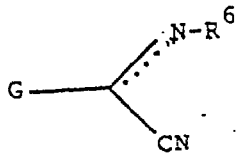
Exo-3-(3-butylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo-[2.2.1]heptane

3-Chloro-2-(3-ethoxy-1,2,5-thiadiazol-4-yl)-8-azabicyclo-[3.2.1]oct-2-ene

or salts thereof with pharmaceutically-acceptable acids or prodrugs thereof.

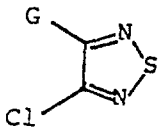
3. A method of preparing a compound according to claim 1, comprising

a) reacting a compound of formula II



(II)

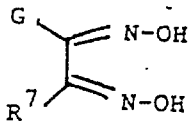
wherein G has the meaning defined above, >····N is >—NH or >═N and R^6 is H, OH or O-alkyl, with S_2Cl_2 to form a compound of formula III



(III)

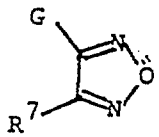
wherein G has the meaning defined above; subsequent displacement of Cl with an appropriate nucleophile gives a compound of formula I wherein X is S, or

b) dehydrating a compound of formula IV



(IV)

wherein G has the meaning defined above and R^7 is alkyl, amino, halogen, alkoxy or alkylthio, to form a compound of formula V



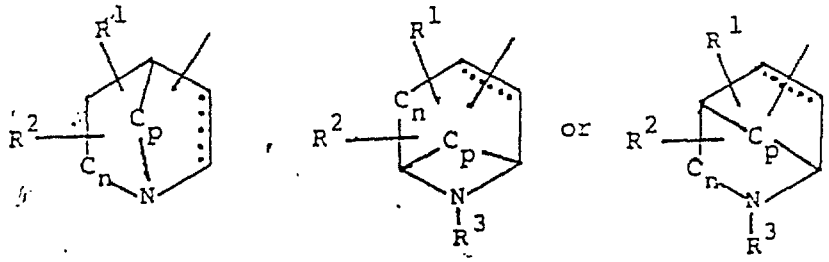
(V)

wherein G and R^7 have the meanings defined above, or

c) when R^7 in formula V is amino, the amino group can be substituted by chloro by known procedures, and subsequent displacement of Cl with an appropriate nucleophile gives a compound of formula I wherein X is O.

4. A pharmaceutical composition comprising a compound of formula I wherein X is oxygen or sulphur;

wherein G is selected from the group of azabicyclic ring systems consisting of

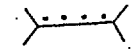


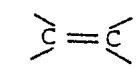
wherein the oxadiazole or thiadiazole ring can be attached at any position;

R^1 and R^2 may be present at any position, including the point of attachment of the oxadiazole or thiadiazole ring, and independently are hydrogen, -OH, halogen, $-NH_2$, carboxy, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl, straight or branched C_{2-5}-alkynyl, straight or branched C_{1-10}-alkoxy, or straight or branched C_{1-5}-alkyl substituted with -OH;

R^3 is hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl or straight or branched C_{2-5}-alkynyl;

* C L M S *

n and p independently are 0, 1, 2, 3, or 4; 

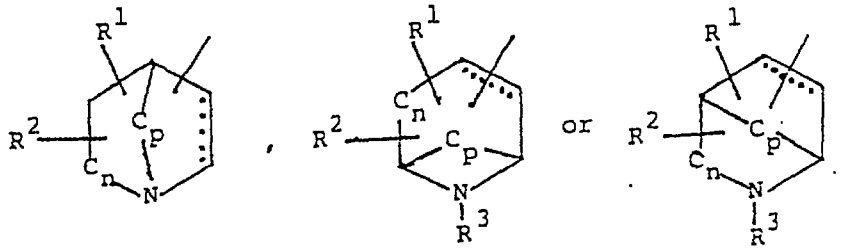
is  or  ;

R is Y which represents hydrogen, halogen, -CN, -CHO, -OH, $-OR^4$, $-SR^4$, $-NH_2$, $-NHR^4$, $-NR^4R^5$, $-NO_2$, $-SOR^4$, $-SO_2R^4$, $-COR^4$, $-CO_2R^4$, $-CONH_2$, $-CONHR^4$, $-CONR^4R^5$, $-CH=NOR^4$, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R is a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturated, partly saturated or aromatic, R^4 substituted with Y or XR^4 substituted with Y wherein X has the meaning defined above; R^4 and R^5 independently are straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R^4 and R^5 independently are a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturated, partly saturated or aromatic; or a salt thereof with a pharmaceutically acceptable acid together with a pharmaceutically acceptable carrier or diluent.

5. A pharmaceutical composition suitable for use in stimulating the cognitive functions of the forebrain and hippocampus of mammals, including humans, and in treating Alzheimer's disease, glaucoma or providing an analgesic effect, comprising an amount of a compound of formu ·· I wherein X is oxygen or sulphur;

wherein G is selected from the group of azabicyclic ring systems consisting of

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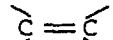


wherein the oxadiazole or thiadiazole ring can be attached at any position;

R^1 and R^2 may be present at any position, including the point of attachment of the oxadiazole or thiadiazole ring, and independently are hydrogen, -OH, halogen, $-NH_2$, carboxy, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl, straight or branched C_{2-5}-alkynyl, straight or branched C_{1-10}-alkoxy, or straight or branched C_{1-5}-alkyl substituted with -OH;

R^3 is hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl or straight or branched C_{2-5}-alkynyl;

n and p independently are 0, 1, 2, 3, or 4;

is  or  ;

R is Y which represents hydrogen, halogen, -CN, -CHO, -OH, $-OR^4$, $-SR^4$, $-NH_2$, $-NHR^4$, $-NR^4R^5$, $-NO_2$, $-SOR^4$, $-SO_2R^4$, $-COR^4$, $-CO_2R^4$, $-CONH_2$, $-CONHR^4$, $-CONR^4R^5$, $-CH=NOR^4$, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R is a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturated, partly saturated or aromatic, R^4 substituted with Y or

* C L M S *

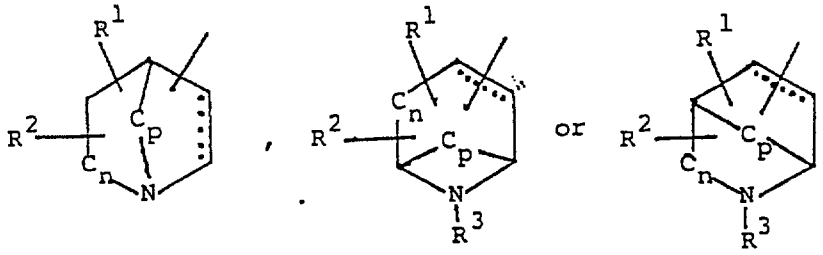
XR^4 substituted with Y wherein X has the meaning defined above; R^4 and R^5 independently are straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R^4 and R^5 independently are a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturated, partly saturated or aromatic; or a salt thereof with a pharmaceutically acceptable acid together with a pharmaceutically acceptable carrier or diluent.

6. A pharmaceutical composition according to claim 4 or 5 in the form of an oral dosage unit, or an parenteral dosage unit.

7. A pharmaceutical composition according to claim 4, 5 or 6, wherein said dosage unit comprises about 1 to about 100 mg of a compound of formula I or a salt thereof with a pharmaceutically acceptable acid together with a pharmaceutically acceptable carrier or diluent.

8. A method of stimulating the cognitive functions of the forebrain and hippocampus comprising providing to a subject in need of such stimulation an effective amount of a compound of formula I wherein X is oxygen or sulphur;

wherein G is selected from the group of azabicyclic ring systems consisting of

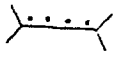


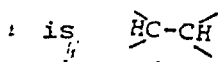
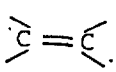
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wherein the oxadiazole or thiadiazole ring can be attached at any position;

R^1 and R^2 may be present at any position, including the point of attachment of the oxadiazole or thiadiazole ring, and independently are hydrogen, -OH, halogen, $-NH_2$, carboxy, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl, straight or branched C_{2-5}-alkynyl, straight or branched C_{1-10}-alkoxy, or straight or branched C_{1-5}-alkyl substituted with -OH;

R^3 is hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl or straight or branched C_{2-5}-alkynyl;

n and p independently are 0, 1, 2, 3, or 4; 

is  or ;

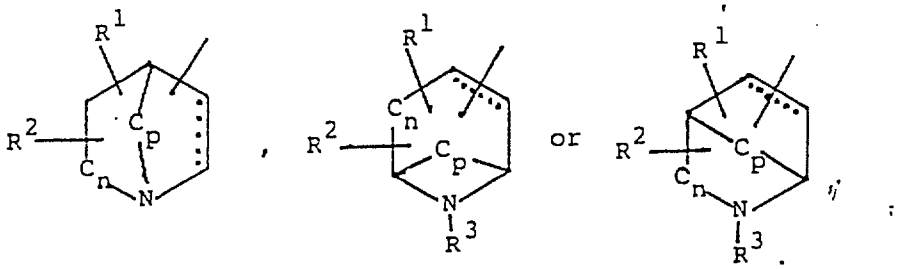
R is Y which represents hydrogen, halogen, -CN, -CHO, -OH, $-OR^4$, $-SR^4$, $-NH_2$, $-NHR^4$, $-NR^4R^5$, $-NO_2$, $-SOR^4$, $-SO_2R^4$, $-COR^4$, $-CO_2R^4$, $-CONH_2$, $-CONHR^4$, $-CONR^4R^5$, $-CH=NOR^4$; phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R is a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturated, partly saturated or aromatic, R^4 substituted with Y or XR^4 substituted with Y wherein X has the meaning defined above; R^4 and R^5 independently are straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R^4 and R^5 independently are a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturat-

* C L M S *

ed, partly saturated or aromatic; or a salt thereof with a pharmaceutically acceptable acid together with a pharmaceutically acceptable carrier or diluent.

9. A method of treating Alzheimer's disease in a subject in need of such treatment, comprising providing to said subject an effective amount of a compound of formula I wherein X is oxygen or sulphur;

wherein G is selected from the group of azabicyclic ring systems consisting of

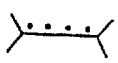


wherein the oxadiazole or thiadiazole ring can be attached at any position;

R^1 and R^2 may be present at any position, including the point of attachment of the oxadiazole or thiadiazole ring, and independently are hydrogen, -OH, halogen, $-NH_2$, carboxy, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl, straight or branched C_{2-5}-alkynyl, straight or branched C_{1-10}-alkoxy, or straight or branched C_{1-5}-alkyl substituted with -OH;

R^3 is hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl or straight or branched C_{2-5}-alkynyl;

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n and p independently are 0, 1, 2, 3, or 4; 

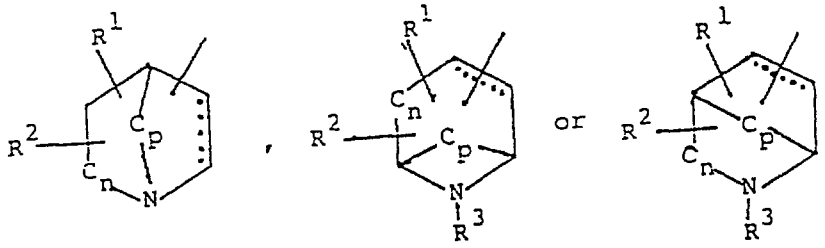
is or  ;

R is Y which represents hydrogen, halogen, -CN, -CHO, -OH, $-OR^4$, $-SR^4$, $-NH_2$, $-NHR^4$, $-NR^4R^5$, $-NO_2$, $-SOR^4$, $-SO_2R^4$, $-COR^4$, $-CO_2R^4$, $-CONH_2$, $-CONHR^4$, $-CONR^4R^5$, $-CH=NOR^4$, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R is a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturated, partly saturated or aromatic, R^4 substituted with Y or XR^4 substituted with Y wherein X has the meaning defined above; R^4 and R^5 independently are straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R^4 and R^5 independently are a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturated, partly saturated or aromatic; or a salt thereof with a pharmaceutically acceptable acid together with a pharmaceutically acceptable carrier or diluent.

10. A method of treating glaucoma comprising providing to a subject in need of such treatment an effective amount of a compound of formula I wherein X is oxygen or sulphur;

wherein G is selected from the group of azabicyclic ring systems consisting of

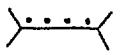
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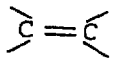


wherein the oxadiazole or thiadiazole ring can be attached at any position;

R^1 and R^2 may be present at any position, including the point of attachment of the oxadiazole or thiadiazole ring, and independently are hydrogen, -OH, halogen, $-NH_2$, carboxy, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl, straight or branched C_{2-5}-alkynyl, straight or branched C_{1-10}-alkoxy, or straight or branched C_{1-5}-alkyl substituted with -OH;

R^3 is hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl or straight or branched C_{2-5}-alkynyl;

n and p independently are 0, 1, 2, 3, or 4; 

is  or  ;

R is Y which represents hydrogen, halogen, -CN, -CHO, -OH, $-OR^4$, $-SR^4$, $-NH_2$, $-NHR^4$, $-NR^4R^5$, $-NO_2$, $-SOR^4$, $-SO_2R^4$, $-COR^4$, $-CO_2R^4$, $-CONH_2$, $-CONHR^4$, $-CONR^4R^5$, $-CH=NOR^4$, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R is a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturated, partly saturated or aromatic, R^4 substituted with Y or

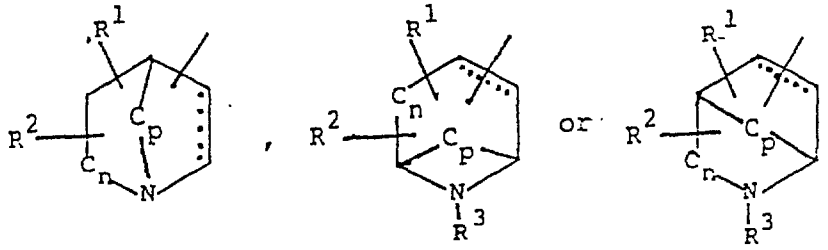
* C L M S *

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XR^4 substituted with Y wherein X has the meaning defined above; R^4 and R^5 independently are straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R^4 and R^5 independently are a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturated, partly saturated or aromatic; or a salt thereof with a pharmaceutically acceptable acid together with a pharmaceutically acceptable carrier or diluent.

11. A method of providing an analgesic effect comprising providing to a subject in need of such treatment an effective amount of a compound of formula I wherein X is oxygen or sulphur;

wherein G is selected from the group of azabicyclic ring systems consisting of



wherein the oxadiazole or thiadiazole ring can be attached at any position;

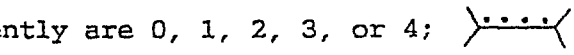
R^1 and R^2 may be present at any position, including the point of attachment of the oxadiazole or thiadiazole ring, and independently are hydrogen, -OH, halogen, $-NH_2$, carboxy, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl, straight or branch-

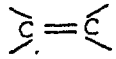
* C L M S *

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ed C_{2-5}-alkynyl, straight or branched C_{1-10}-alkoxy, or straight or branched C_{1-5}-alkyl substituted with -OH;

R^3 is hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl or straight or branched C_{2-5}-alkynyl;

n and p independently are 0, 1, 2, 3, or 4; 

is  or  ;

R is Y which represents hydrogen, halogen, -CN, -CHO, -OH, $-OR^4$, $-SR^4$, $-NH_2$, $-NHR^4$, $-NR^4R^5$, $-NO_2$, $-SOR^4$, $-SO_2R^4$, $-COR^4$, $-CO_2R^4$, $-CONH_2$, $-CONHR^4$, $-CONR^4R^5$, $-CH=NOR^4$, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R is a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturated, partly saturated or aromatic, R^4 substituted with Y or XR^4 substituted with Y wherein X has the meaning defined above; R^4 and R^5 independently are straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R^4 and R^5 independently are a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturated, partly saturated or aromatic; or a salt thereof with a pharmaceutically acceptable acid together with a pharmaceutically acceptable carrier or diluent.

12. A method of claim 8, 9, 10 or 11, wherein said compound is administered in the form of a pharmaceutical composition together with a pharmaceutically-acceptable carrier or diluent.

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13. A method of claim 8, 9, 10, 11 wherein said compound together with a pharmaceutically-acceptable carrier or diluent is administered in the form of an oral pharmaceutical dosage form.

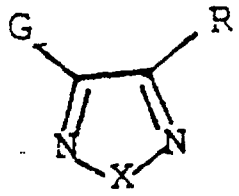
14. A method of claim 8, 9, 10 or 11 wherein said compound together with a pharmaceutically-acceptable carrier or diluent is administered in the form of a parenteral pharmaceutical dosage form.

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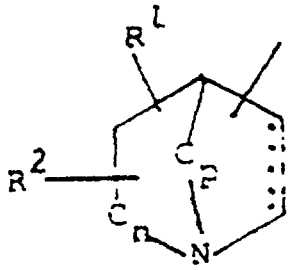
HETEROCYCLIC COMPOUNDS AND THEIR PREPARATION AND USE

ABSTRACT

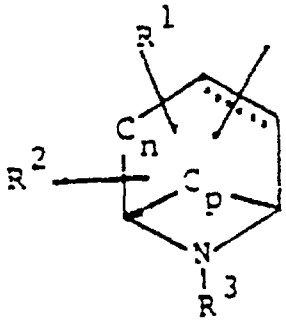
The present invention relates to therapeutically active piperidine compounds, a method of preparing the same and to pharmaceutical compositions comprising the compounds of formula (I), wherein X is oxygen or sulphur; wherein G is selected from the group of azabicyclic ring systems consisting of (1), (2), or (3) wherein the oxadiazole or thiadiazole ring can be attached at any position. The novel compounds are useful as stimulants of the cognitive function of the forebrain and hippocampus of mammals and especially in the treatment of Alzheimer's disease, severe painful conditions and glaucoma.



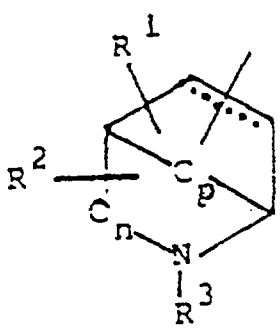
(I)



(1)

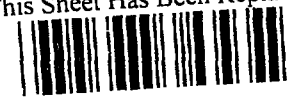


(2)



(3)

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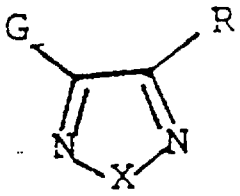
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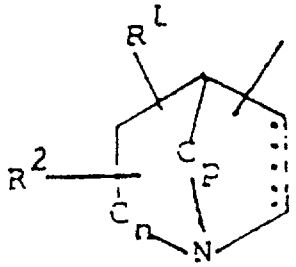
HETEROCYCLIC COMPOUNDS AND THEIR PREPARATION AND USE

ABSTRACT

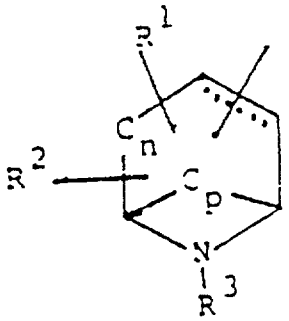
The present invention relates to therapeutically active piperidine compounds, a method of preparing the same and to pharmaceutical compositions comprising the compounds of formula (I), wherein X is oxygen or sulphur; wherein G is selected from the group of azabicyclic ring systems consisting of (1), (2), or (3) wherein the oxadiazole or thiadiazole ring can be attached at any position. The novel compounds are useful as stimulants of the cognitive function of the forebrain and hippocampus of mammals and especially in the treatment of Alzheimer's disease, severe painful conditions and glaucoma.



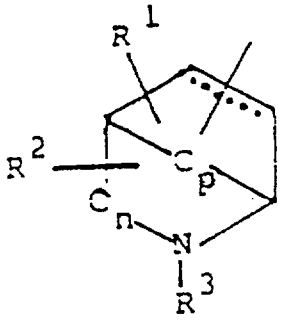
(I)



(1)



(2)



(3)

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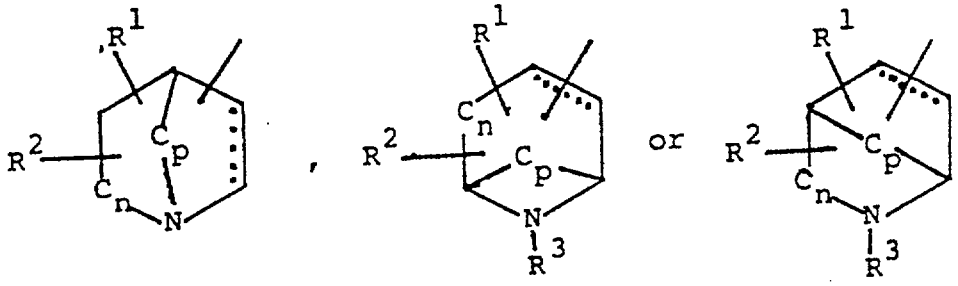
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XR^4 substituted with Y wherein X has the meaning defined above; R^4 and R^5 independently are straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R^4 and R^5 independently are a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturated, partly saturated or aromatic; or a salt thereof with a pharmaceutically acceptable acid together with a pharmaceutically acceptable carrier or diluent.

11. A method of providing an analgesic effect comprising providing to a subject in need of such treatment an effective amount of a compound of formula I wherein X is oxygen or sulphur;

wherein G is selected from the group of azabicyclic ring systems consisting of



wherein the oxadiazole or thiadiazole ring can be attached at any position;

R^1 and R^2 may be present at any position, including the point of attachment of the oxadiazole or thiadiazole ring, and independently are hydrogen, -OH, halogen, $-NH_2$, carboxy, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl, straight or branch-

PATENT COOPERATION TREATY
INTERNATIONAL SEARCH REPORT

COPY

IDENTIFICATION OF INTERNATIONAL APPLICATION	Applicant's or Agent's File Reference
	42157/ML/ki
International Application No. PCT/DK 91/00236	**International Filing Date** 20th August 1991
Receiving Office RO/DK	**Priority Date Claimed** 21st August 1990

Applicant
Novo Nordisk A/S

I. [X] CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1] (Observations on supplemental sheet (2))

II. [ ] UNITY OF INVENTION LACKING [2] (Observations on supplemental sheet (2))

III. TITLE, ABSTRACT AND FIGURE OF DRAWING

1. The following indicated items are approved as submitted by the applicant: [3]

[X] Title. [ ] Abstract.

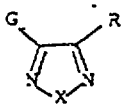
2. The texts established by this International Searching Authority of the following indicated items are set forth below:

[ ] Title.

[X] Abstract.

Abstract

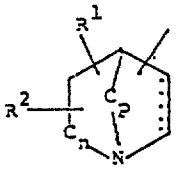
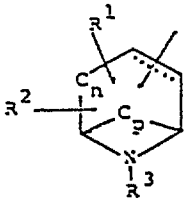
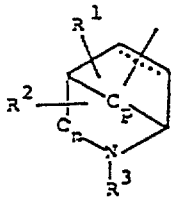
The present invention relates to therapeutically active piperidine compounds, a method of preparing the same and to pharmaceutical compositions comprising the compounds.



(I)

wherein X is oxygen or sulphur;

wherein G is selected from the group of azabicyclic ring systems consisting of

wherein the oxadiazole or thiadiazole ring can be attached at any position;

The novel compounds are useful as stimulants of the cognitive function of the forebrain and hippocampus of mammals and especially in the treatment of Alzheimer's disease, severe painful conditions and glaucoma.

[ ] Text of the abstract continued on supplemental sheet (1)

3. a. [ ] The definitive contents of the abstract are established by this International Searching Authority as proposed in form PCT/ISA/204 previously sent to the applicant.

b. [X] This report is incomplete as far as the abstract is concerned as the time limit for comments by the applicant on the draft prepared by this International Searching Authority has not expired. [4]

4. Figure to be published with abstract [5]

Figure No. - -

[ ] None of the figures

[ ] as suggested by the applicant

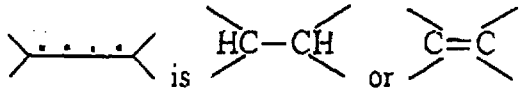
[ ] because the applicant failed to suggest a figure

[ ] because this figure better characterizes the invention

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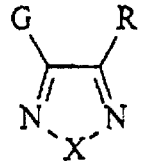
24 DEC 1991

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n and p independently are 0, 1, 2, 3, or 4;  is or ;

R is Y which represents hydrogen, halogen, -CN, -CHO, -OH, -OR^4, -SR^4, -NH_2, -NHR^4, -NR^4R^5, -NO_2, -SOR^4, -SO_2R^4, -COR^4, -CO_2R^4, -$CONH_2$, -$CONHR^4$, -$CONR^4R^5$, -CH=NOR^4, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R is a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturated, partly saturated or aromatic, R^4 substituted with Y or XR^4 substituted with Y wherein X has the meaning defined above; R^4 and R^5 independently are straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R^4 and R^5 independently are a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturated, partly saturated or aromatic; or a salt thereof with a pharmaceutically acceptable acid together with a pharmaceutically acceptable carrier or diluent.

5 A pharmaceutical composition suitable for use in stimulating the cognitive functions of the forebrain and hippocampus of mammals, including humans, and in treating Alzheimer's disease, glaucoma or providing an analgesic effect, comprising an amount of a compound of formula I



(I)

wherein X is oxygen or sulphur;

wherein G is selected from the group of azabicyclic ring systems consisting of

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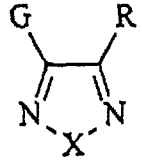
* C L M S *

XR^4 substituted with Y wherein X has the meaning defined above; R^4 and R^5 independently are straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R^4 and R^5 independently are a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturated, partly saturated or aromatic; or a salt thereof with a pharmaceutically acceptable acid together with a pharmaceutically acceptable carrier or diluent.

6. A pharmaceutical composition according to claim 4 or 5 in the form of an oral dosage unit, or an parenteral dosage unit.

7. A pharmaceutical composition according to claim 4, 5 or 6, wherein said dosage unit comprises about 1 to about 100 mg of a compound of formula I or a salt thereof with a pharmaceutically acceptable acid together with a pharmaceutically acceptable carrier or diluent.

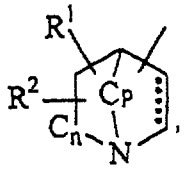
8. The use of a compound of formula I

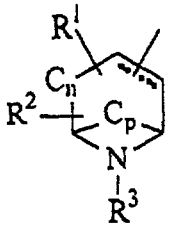


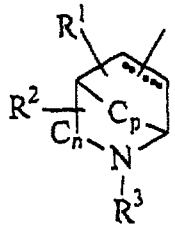
(I)

wherein X is oxygen or sulphur;

wherein G is selected from the group of azabicyclic ring systems consisting of







or

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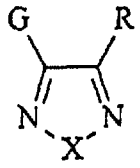
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* C L M S *

ed, partly saturated or aromatic; or a salt thereof with a pharmaceutically acceptable acid together, for the manufacture of a medicament for stimulating the cognitive functions of the forebrain and hippocampus in a subject in need of such stimulation.

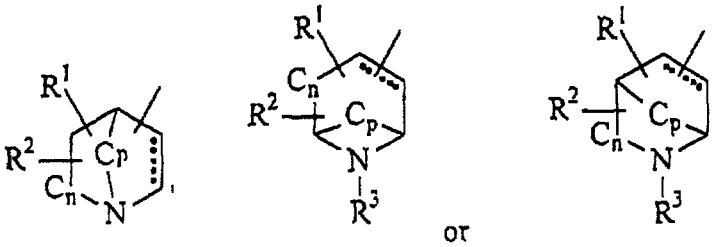
9. The use of a compound of formula I



(I)

wherein X is oxygen or sulphur;

wherein G is selected from the group of azabicyclic ring systems consisting of

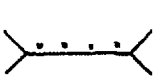
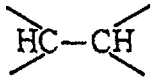
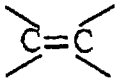


or

wherein the oxadiazole or thiadiazole ring can be attached at any position;

R^1 and R^2 may be present at any position, including the point of attachment of the oxadiazole or thiadiazole ring, and independently are hydrogen, -OH, halogen, $-NH_2$, carboxy, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl, straight or branched C_{2-5}-alkynyl, straight or branched C_{1-10}-alkoxy, or straight or branched C_{1-5}-alkyl substituted with –OH;

R^3 is hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl or straight or branched C_{2-5}-alkynyl;

n and p independently are 0, 1, 2, 3, or 4;  is  or ;

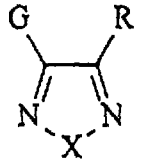
R is Y which represents hydrogen, halogen, -CN, -CHO, -OH, $-OR^4$, $-SR^4$, $-NH_2$, $-NHR^4$, $-NR^4R^5$, $-NO_2$, $-SOR^4$, $-SO_2R^4$, $-COR^4$, $-CO_2R^4$, $-CONH_2$, $-CONHR^4$, $-CONR^4R^5$, $-CH=NOR^4$, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R is a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturated, partly saturated or aromatic, R^4 substituted with Y or XR^4 substituted with Y wherein X has the meaning defined above; R^4 and R^5 independently are straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R^4 and R^5 independently are a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a

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combination thereof being saturated, partly saturated or aromatic; or a salt thereof with a pharmaceutically acceptable acid together, for the manufacture of a medicament for treating Alzheimer's disease in a subject in need of such treatment.

10. The use of a compound of formula I



(I)

wherein X is oxygen or sulphur;

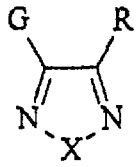
wherein G is selected from the group of azabicyclic ring systems consisting of

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XR^4 substituted with Y wherein X has the meaning defined above; R^4 and R^5 independently are straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R^4 and R^5 independently are a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturated, partly saturated or aromatic; or a salt thereof with a pharmaceutically acceptable acid together, for the manufacture of a medicament for treating glaucoma in a subject in need of such treatment.

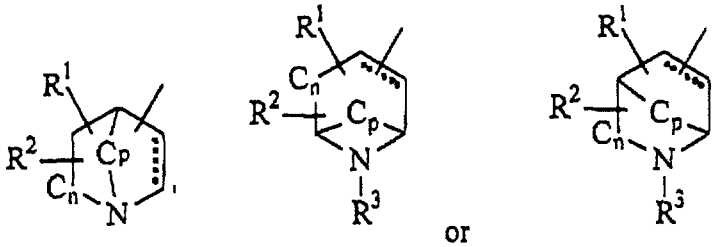
11. The use of a compound of formula I



(I)

wherein X is oxygen or sulphur;

wherein G is selected from the group of azabicyclic ring systems consisting of

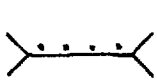
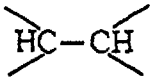
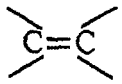


or

wherein the oxadiazole or thiadiazole ring can be attached at any position;

R^1 and R^2 may be present at any position, including the point of attachment of the oxadiazole or thiadiazole ring, and independently are hydrogen, -OH, halogen, $-NH_2$, carboxy, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl, straight or branched C_{2-5}-alkynyl, straight or branched C_{1-10}-alkoxy, or straight or branched C_{1-5}-alkyl substituted with –OH;

R^3 is hydrogen, straight or branched C_{1-5}-alkyl, straight or branched C_{2-5}-alkenyl or straight or branched C_{2-5}-alkynyl;

n and p independently are 0, 1, 2, 3, or 4;  is  or ;

R is Y which represents hydrogen, halogen, -CN, -CHO, -OH, $-OR^4$, $-SR^4$, $-NH_2$, $-NHR^4$, $-NR^4R^5$, $-NO_2$, $-SOR^4$, $-SO_2R^4$, $-COR^4$, $-CO_2R^4$, $-CONH_2$, $-CONHR^4$, $-CONR^4R^5$, $-CH{=}NOR^4$, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R is a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof

being saturated, partly saturated or aromatic, R^4 substituted with Y or XR^4 substituted with Y wherein X has the meaning defined above; R^4 and R^5 independently are straight or branched C_{1-15}-alkyl, straight or branched C_{2-15}-alkenyl, straight or branched C_{2-15}-alkynyl, phenyl, phenoxy, benzoyl, benzyl or benzyloxycarbonyl groups optionally substituted with halogen, -CN, C_{1-4}-alkyl or C_{1-4}-alkoxy; or R^4 and R^5 independently are a 5 or 6 membered heterocyclic group containing one to three N, O or S atom(s) or a combination thereof being saturated, partly saturated or aromatic; or a salt thereof with a pharmaceutically acceptable acid together, for the manufacture of a medicament for the providing an analgesic effect in a subject in need of such treatment.

12. The use of any one of claims 8 to 11, wherein said medicament is in the form of a pharmaceutical composition together with a pharmaceutically-acceptable carrier or diluent.

13. The use of any one of claims 8 to 12 wherein said medicament is in the form of an oral pharmaceutical dosage form.

14. The use of any one of claims 8 to 12 wherein said medicament is in the form of a parenteral pharmaceutical dosage form.

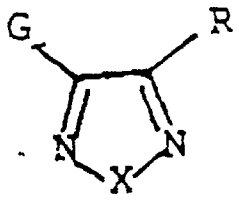
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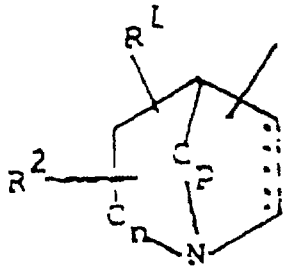
HETEROCYCLIC COMPOUNDS AND THEIR PREPARATION AND USE

ABSTRACT

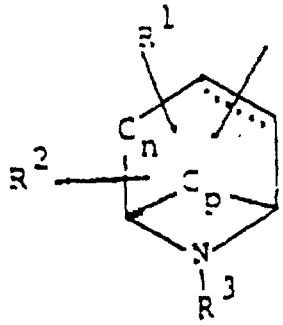
The present invention relates to therapeutically active piperidine compounds, a method of preparing the same and to pharmaceutical compositions comprising the compounds of formula (I), wherein X is oxygen or sulphur; wherein G is selected from the group of azabicyclic ring systems consisting of (1), (2), or (3) wherein the oxadiazole or thiadiazole ring can be attached at any position. The novel compounds are useful as stimulants of the cognitive function of the forebrain and hippocampus of mammals and especially in the treatment of Alzheimer's disease, severe painful conditions and glaucoma.



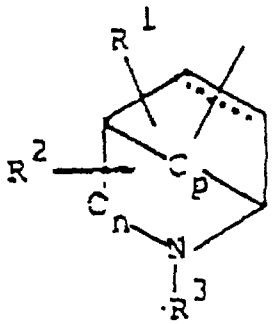
(I)



(1)



(2)



(3)

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