

617785

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

Merck Sharp & Dohme Limited, of Hertford Road, Hoddesdon, Hertfordshire, England, EN11 1BU, UNITED KINGDOM, hereby apply for the grant of a standard patent for an invention entitled:

Spirocyclic Compounds Incorporating Five-membered Rings
with two Heteroatoms

which is described in the accompanying complete specification.

Details of basic application(s):-

Basic Applic. No: Country: Application Date:

8808433.0 GB 11 April 1988

The address for service is:-

Spruson & Ferguson
Patent Attorneys
Level 33 St Martins Tower
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Sydney New South Wales Australia

DATED this TENTH day of APRIL 1989

Merck Sharp & Dohme Limited

By:

M. J. Anderson

Registered Patent Attorney

TO: THE COMMISSIONER OF PATENTS
OUR REF: 88019
S&F CODE: 58167

5006674 10/04/89

5845/2

COMMONWEALTH OF AUSTRALIA
THE PATENTS ACT 1952

DECLARATION IN SUPPORT OF A
CONVENTION APPLICATION FOR A PATENT

In support of the Convention Application made for a patent for an invention entitled:

Spirocyclic compounds incorporating five-membered rings with two heteroatoms

I ALAN HESKETH

of Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon,
Hertfordshire EN11 9BU,
England

do solemnly and sincerely declare as follows:

1. I am authorised by Merck Sharp & Dohme Limited the applicant for the patent to make this declaration on its behalf.
2. The basic application(s) as defined by Section 141 of the Act was/~~were~~ made
in Great Britain
on 11 April 1988
by Merck Sharp & Dohme Limited

3. Raymond BAKER

Clare O. KNEEN

John SAUNDERS

Christopher SWAIN

of

Bulls Cottage, Green Tye,
Much Hadham, Hertfordshire,
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Slade Cottage, Petts Lane,
Little Walden, Essex,
England.

13 The Ridings, Thorley Park,
Bishops Stortford, Hertfordshire,
England.

8 Mangers Lane,
Duxford, Cambridge,
England.

(respectively)

is/are the actual inventor(s) of the invention and the facts upon which the applicant is entitled to make the application are as follows:

Assignment dated 26 January 1989 to the said Applicant from the actual inventors.

4. The basic application(s) referred to in paragraph 2 of this Declaration was/~~were~~ the first application(s) made in a Convention country in respect of the invention(s) the subject of the application.

Declared at Harlow, Essex, England

this 14th day of February 1989

.....

Alan Hesketh
European Patent Counsel

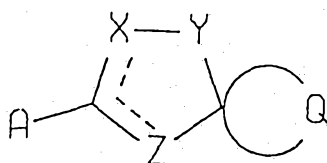
To: The Commissioner of Patents

FORMAU2

(12) PATENT ABRIDGMENT (11) Document No. AU-B-32632/89
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 617785

- (54) Title
SPIROCYCLIC COMPOUNDS INCORPORATING FIVE-MEMBERED RINGS WITH TWO HETEROATOMS
- International Patent Classification(s)
(51)⁴ **C07D 498/20 A61K 031/46 C07D 498/10 A61K 031/445**
- (21) Application No. : **32632/89** (22) Application Date : **10.04.89**
- (30) Priority Data
- (31) Number (32) Date (33) Country
8808433 11.04.88 GB UNITED KINGDOM
- (43) Publication Date : **12.10.89**
- (44) Publication Date of Accepted Application : **05.12.91**
- (71) Applicant(s)
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- (72) Inventor(s)
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- (74) Attorney or Agent
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- (56) Prior Art Documents
AU 28834/89 C07D 451/14
AU 81633/87 C07D 471/10
AU 19554/76 C07D 491/20
- (57) Claim

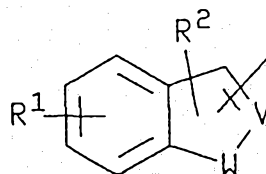
¹
as herein defined, A compound of formula I or a salt or
prodrug thereof:



(I)

wherein the dotted line represents an optional chemical bond in one of the two possible positions;

A represents a group of formula II:



(II)

(11) AU-B-32632/89
(10) 617785

-2-

in which R^1 represents hydrogen, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, benzyloxy, hydroxy(C_{1-6})alkyl, halogen, amino, cyano, nitro, $-\text{CONR}^6\text{R}^7$ or $-\text{SO}_2\text{NR}^6\text{R}^7$, in which R^6 and R^7 independently represent hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl;

R^2 represents hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkylcarbonyl;

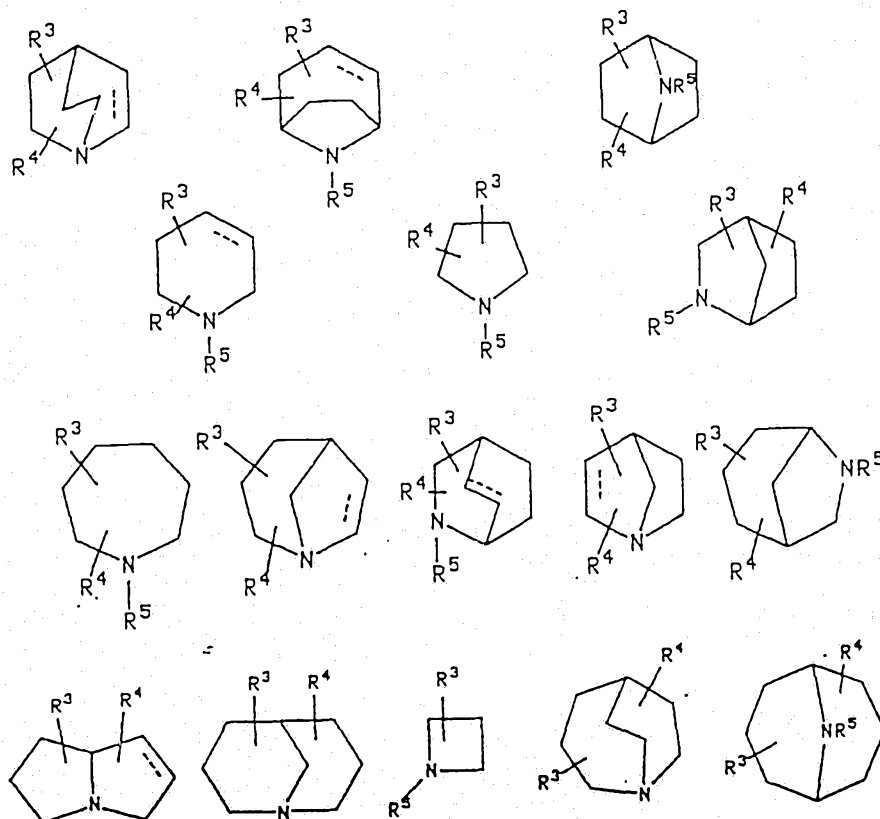
V represents nitrogen, $-\text{CH}-$ or $-\text{C}-$; and

W represents oxygen, sulphur or $-\text{NR}^8$, in

which R^8 represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl;

two of X, Y and Z are the same or different and each represents oxygen, sulphur or nitrogen; and the remaining group X, Y or Z is carbon, or Y is carbonyl ($\text{C}=\text{O}$); and

Q is the residue of an azacyclic or azabicyclic ring system selected from the group consisting of



(11) AU-B-32632/89
(10) 617785

-3-

wherein the broken line represents an optional chemical bond;

R^3 and R^4 independently represent hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halogen, C_{1-4} alkoxy, hydroxy, carboxy or C_{2-4} alkoxycarbonyl; or R^3 and R^4 together represent carbonyl; and

R^5 represents hydrogen, benzyl, C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl.

17. A method for the treatment or prophylaxis of psychotic disorders; anxiety; alcohol or drug withdrawal or dependence; pain; gastric stasis; gastric dysfunction; migraine, nausea and vomiting; movement disorders; and presenile and senile dementia in a patient requiring said treatment or prophylaxis, which method comprises administering to said patient an effective amount of at least one compound according to claim 13 or a composition as claimed in claim 15 or claim 16.

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S & F Ref: 88019

FORM 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE:

Class Int Class

Complete Specification Lodged:

Accepted:

Published:

Priority:

Related Art:

Name and Address
of Applicant:

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Hertford Road
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UNITED KINGDOM

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Complete Specification for the invention entitled:

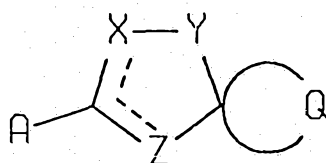
Spirocyclic Compounds Incorporating Five-membered Rings
with two Heteroatoms

The following statement is a full description of this invention, including the
best method of performing it known to me/us

ABSTRACT

5 SPIROCYCLIC COMPOUNDS INCORPORATING FIVE-MEMBERED
 RINGS WITH TWO HETEROATOMS

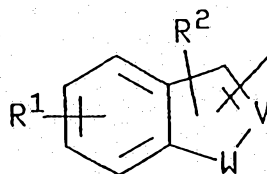
10 The present invention provides a compound of
 formula I or a salt or prodrug thereof:



(I)

20 wherein the dotted line represents an optional
 chemical bond in one of the two possible positions;

 A represents a group of formula II:



(II)

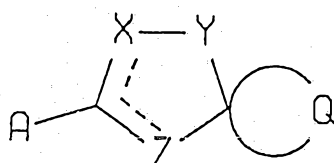
30 in which R¹ represents hydrogen, hydroxy, C₁₋₆ alkyl,

- C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, benzyloxy, hydroxy(C₁₋₆)alkyl, halogen, amino, cyano, nitro, -CONR⁶R⁷ or -SO₂NR⁶R⁷, in which R⁶ and R⁷
- 5 independently represent hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl;
R² represents hydrogen, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy or C₁₋₆ alkylcarbonyl;
V represents nitrogen, -CH or -C-; and
- 10 W represents oxygen, sulphur or -NR⁸, in which R⁸ represents hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl;
two of X, Y and Z are the same or different and each represents oxygen, sulphur or nitrogen; and
- 15 the remaining group X, Y or Z is carbon, or Y is carbonyl (C=O); and
Q is the residue of an azacyclic or azabicyclic ring system; which compounds are useful in the treatment of psychotic disorders (e.g.
- 20 schizophrenia and mania); anxiety; alcohol or drug withdrawal or dependence; pain; gastric stasis; gastric dysfunction (such as occurs with dyspepsia, peptic ulcer, reflux oesophagitis and flatulence); migraine, nausea and vomiting; movement disorders;
- 25 and presenile and senile dementia.

SPIROCYCLIC COMPOUNDS INCORPORATING FIVE-MEMBERED
RINGS WITH TWO HETEROATOMS

This invention relates to a class of spirocyclic compounds which are useful in the treatment of psychotic disorders (e.g. schizophrenia and mania); anxiety; alcohol or drug withdrawal or dependence; pain; gastric stasis; gastric dysfunction (such as occurs with dyspepsia, peptic ulcer, reflux oesophagitis and flatulence); migraine, nausea and vomiting; movement disorders; and presenile and senile dementia (also known as Alzheimer's disease and senile dementia of the Alzheimer type respectively).

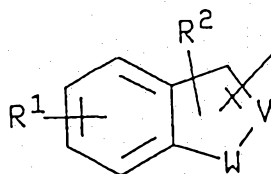
According to a broad format of this invention, there is provided a compound of formula I or a salt or prodrug thereof:



(I)

wherein the dotted line represents an optional chemical bond in one of the two possible positions;

A represents a group of formula II:



(II)

in which R^1 represents hydrogen, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, benzyloxy, hydroxy(C_{1-6})alkyl, halogen, amino, cyano, nitro, $-CONR^6R^7$ or $-SO_2NR^6R^7$, in which R^6 and R^7 independently represent hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl;
 R^2 represents hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkylcarbonyl;



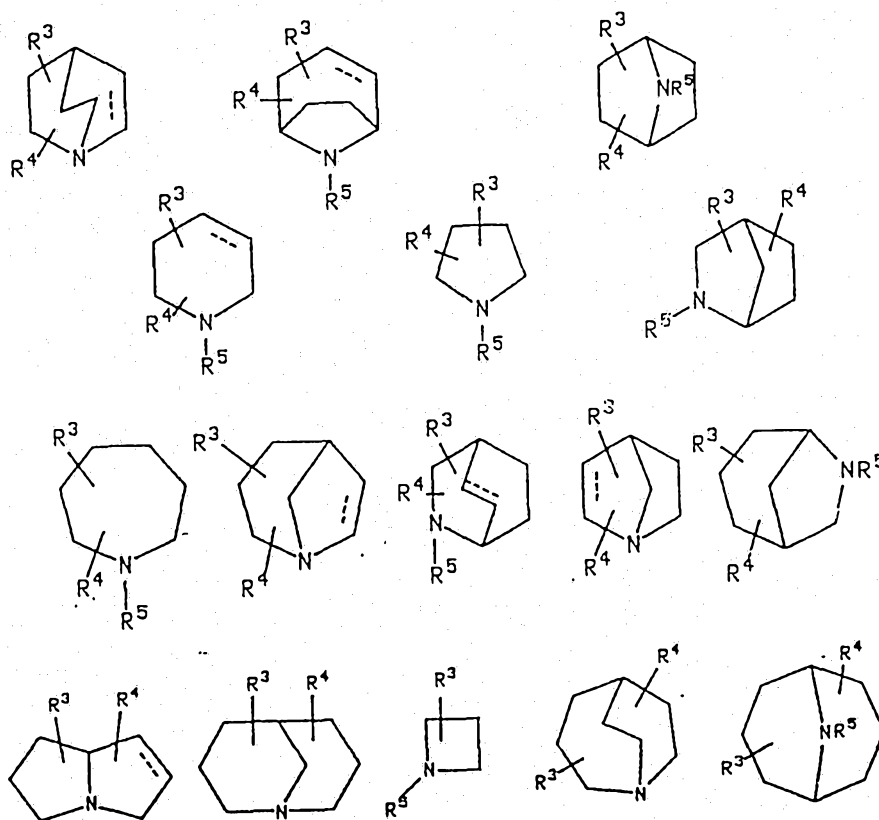
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V represents nitrogen, $\text{-}\overset{\text{||}}{\text{CH}}$ or $\text{-}\overset{\text{||}}{\text{C-}}$; and

W represents oxygen, sulphur or -NR^8 , in which R^8 represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl;

two of X, Y and Z are the same or different and each represents oxygen, sulphur or nitrogen; and the remaining group X, Y or Z is carbon, or Y is carbonyl (C=O); and

Q is the residue of an azacyclic or azabicyclic ring system selected from the group consisting of



10 wherein the broken line represents an optional chemical bond;

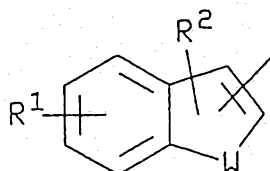
R^3 and R^4 independently represent hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halogen, C_{1-4} alkoxy, hydroxy, carboxy or C_{2-4} alkoxycarbonyl; or R^3 and R^4 together represent carbonyl; and

15 R^5 represents hydrogen, benzyl, C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl.

Throughout the specification and the claims the term prodrugs refers to protected derivatives which are deprotected in vivo.

The 5-membered ring containing X, Y and Z shown in formula I may, for example, be an oxazoline, isoxazoline, thiazoline, dioxolane, 5 oxathiolane or dithiolane ring. Preferably the ring is an oxazoline or dioxolane ring.

The group A is suitably an indole, benzofuran or benzthiophene, of formula IIA:

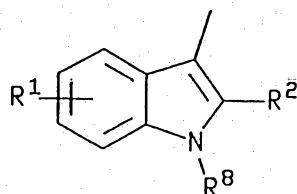


(IIA)

10 wherein R¹, R² and W are as defined above.



Preferably the group A represents an indole of structure IIB:

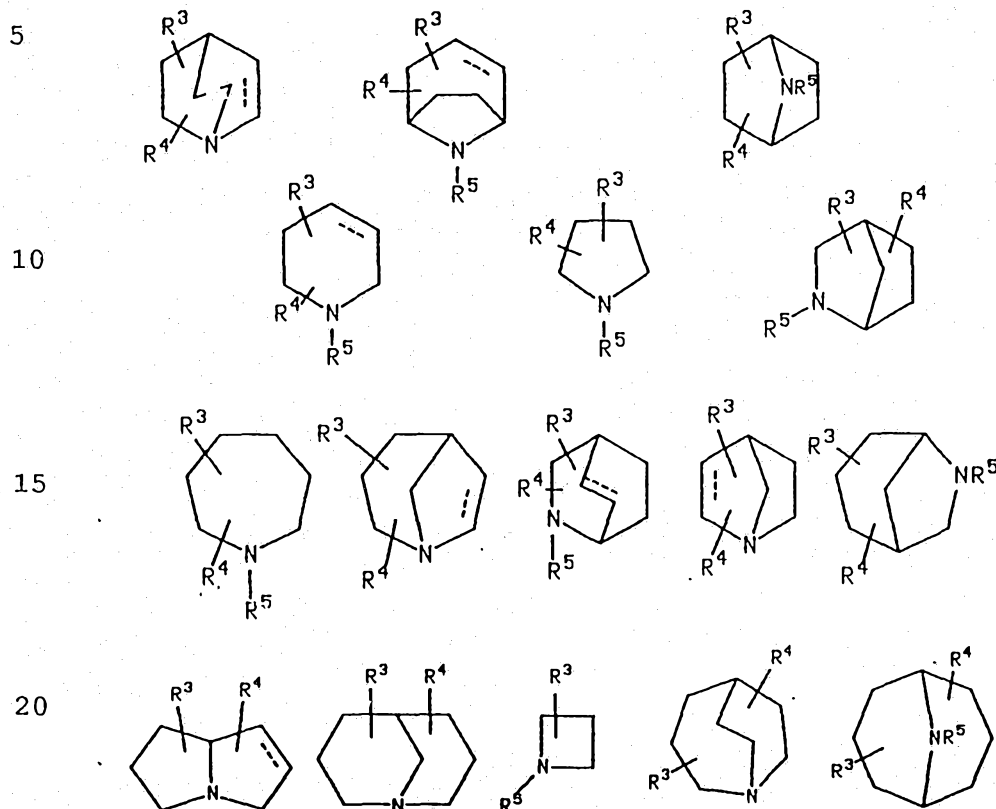


(IIB)

wherein R^1 , R^2 and R^8 are as defined above. Preferably R^1 and R^8 independently represent hydrogen or methyl, and R^2 is hydrogen.

The azacyclic or azabicyclic ring system of which Q is the residue is a non-aromatic ring system containing one nitrogen atom as the sole heteroatom. Suitably the ring system contains from 4 to 10 ring atoms, preferably from 5 to 9 ring atoms. The bicyclic systems may be fused, spiro or bridged.

Examples of suitable ring systems which Q completes include the following:



25 wherein the broken line represents an optional chemical bond;

R^3 and R^4 independently represent hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halogen, C_{1-4} alkoxy, hydroxy, carboxy or C_{2-4} alkoxy carbonyl; or R^3 and R^4 together represent carbonyl; and

30 R^5 represents hydrogen, benzyl, C_{1-4} alkyl, C_{2-4} alkenyl or C_{2-4} alkynyl.

It will be appreciated that the nitrogen atom in the azacyclic or azabicyclic ring will carry a lone pair of electrons.

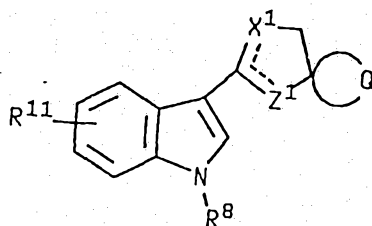
It will also be appreciated that the R^3 and R^4 substituents may be present at any position in the azacyclic or azabicyclic ring system; and it will further be appreciated that the point of attachment of the azacyclic or azabicyclic ring system to the five-membered ring in formula I may be at any position of the ring system.

Suitably the group R^3 is hydrogen or methyl; and R^4 is hydrogen, C_{1-4} alkoxy, C_{1-4} alkyl or hydroxy, preferably methoxy, methyl or hydroxy. Preferably one or both of R^3 and R^4 is hydrogen.

Suitably the azacyclic or azabicyclic ring system is pyrrolidine, piperidine, tetrahydropyridine, azanorbornane, quinuclidine, isoquinuclidine, azabicyclo[3.2.1]octane or azabicyclo[3.3.1]nonane, any of which may be optionally substituted with methyl or hydroxy.

The alkyl, alkenyl and alkynyl groups referred to with respect to any of the above formulae may represent straight, branched or cyclic groups. Thus, for example, suitable alkyl groups include methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and cycloalkyl-alkyl groups such as cyclopropylmethyl; suitable alkenyl groups include vinyl and allyl; and suitable alkynyl groups include propargyl.

One sub-class of compounds within the scope of the present invention is represented by formula III:



(III)

wherein R^8 , Q and the dotted line are as defined above; X^1 and Z^1 independently represent oxygen, sulphur or nitrogen; and R^{11} represents hydrogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, halogen, amino or nitro. In particular, Q may represent the residue of an optionally substituted piperidine, azanorbornane, quinuclidine, 8-azabicyclo[3.2.1]octane or 1-azabicyclo[3.3.1]nonane ring system, wherein the R^5 substituent as defined above, where present, suitably represents methyl or benzyl.

Most of the compounds of this invention have at least one asymmetric centre and often more than one; and can therefore exist both as enantiomers and as diastereoisomers. In particular, those compounds possessing an unsymmetrical azabicyclic ring system may exist as exo and endo diastereoisomers. It is to be understood that the invention covers all such isomers and mixtures thereof.

Also included within the scope of the present invention are salts of the novel compounds. It will be appreciated that salts of the compounds for use in medicine will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful for the preparation of the compounds of the invention or their non-toxic pharmaceutically acceptable salts. Acid addition salts, for example, may be formed by mixing a

solution of the compound with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Salts of amine groups may also comprise the quaternary ammonium salts in which the amino nitrogen atom carries an alkyl, alkenyl, alkynyl or aralkyl group. Where the novel compound carries a carboxylic acid group the invention also contemplates salts thereof, preferably non-toxic pharmaceutically acceptable salts thereof, such as the sodium, potassium and calcium salts thereof.

Specific compounds of this invention include:

- 15 [2'-(1-methyl-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]octane-3,5' (4'H)-oxazole);
[8-methyl-2'-(1-methyl-1H-indol-3-yl)]spiro(8-azabicyclo[3.2.1]octane-3,5' (4'H)-oxazole);
[8-benzyl-2'-(1-methyl-1H-indol-3-yl)]spiro(8-azabicyclo[3.2.1]octane-3,5' (4'H)-oxazole);
20 [2'-(5-fluoro-1-methyl-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]octane-3,5' (4'H)-oxazole);
[8-methyl-2'-(5-fluoro-1-methyl-1H-indol-3-yl)]spiro(8-azabicyclo[3.2.1]octane-3,5' (4'H)-oxazole);
25 [2'-(1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]octane-3,5' (4'H)-oxazole);
[2'-(1-methyl-1H-indol-3-yl)]spiro(1-azabicyclo[3.3.1]nonane-4,5' (4'H)-oxazole);
[2'-(1-cyclopropylmethyl-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]octane-3,5' (4'H)-oxazole);
30 [2'-(1-ethyl-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]octane-3,5' (4'H)-oxazole);

- [2'-(5-nitro-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]-octane-3,5' (4'H)-oxazole);
- [2'-(1-methyl-1H-indol-3-yl)]spiro(1-methylpiperidine-4,5' (4'H)-oxazole);
- 5 [2'-(1-methyl-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.1]-heptane-3,5' (4'H)-oxazole);
- [2'-(1-methyl-1H-indol-3-yl)]spiro(1-methyl-1-azoniabicyclo[2.2.2]octane-3,5' (4'H)-oxazole) iodide;
- [2'-(benzo(b)thiophen-3-yl)]spiro(1-azabicyclo[2.2.2]-octane-3,5' (4'H)-oxazole);
- 10 [2'-(1-propyn-2-yl-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]octane-3,5' (4'H)-oxazole);
- [2'-(1-propen-2-yl-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]octane-3,5' (4'H)-oxazole);
- 15 [2'-(5-amino-1-methyl-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]octane-3,5' (4'H)-oxazole);
- [2'-(2-iodo-1-methyl-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]octane-3,5' (4'H)-oxazole);
- [2'-(1H-indazol-3-yl)]spiro(1-azabicyclo[2.2.2]octane-3,5' (4'H)-oxazole);
- 20 [2'-(5-nitro-1-methyl-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]octane-3,5' (4'H)-oxazole);
- [2'-(5-methoxy-1-methyl-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]octane-3,5' (4'H)-oxazole);
- 25 [2'-(5-hydroxy-1-methyl-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]octane-3,5' (4'H)-oxazole);
- [2'-(1,5-dimethyl-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]octane-3,5' (4'H)-oxazole);
- [2'-(1,7-dimethyl-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]octane-3,5' (4'H)-oxazole);
- 30 [2'-(1-methyl-1H-indol-3-yl)]spiro(8-azabicyclo[3.2.1]octane-3,5' (4'H)-oxazole);
- [2'-(1-methyl-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]octane-3,4' (5'H)-oxazole);
- and salts and prodrugs thereof.

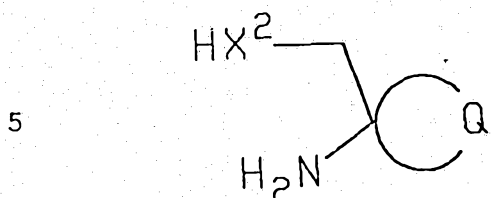
This invention also provides a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier.

- 5 The compounds of the invention can be administered orally, parenterally or rectally at a daily dose of about 0.01 to 10 mg/kg of body weight, preferably about 0.1 to 1 mg/kg, and may be administered on a regimen of 1 to 4 times a day.
- 10 The pharmaceutical formulations of this invention preferably are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, or suppositories for oral, parenteral or rectal administration. For
- 15 preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate,
- 20 dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When
- 25 referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets,
- 30 pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel

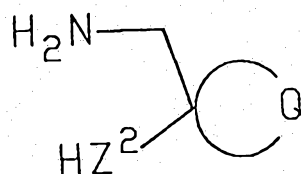
composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids or mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil and peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspension include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone and gelatin.

The oxazoline and thiazoline compounds of this invention may be prepared by a process which comprises reacting a reactive derivative of a carboxylic acid of formula $A-CO_2H$ with a compound either of formula IV or of formula V or a salt thereof:



(IV)



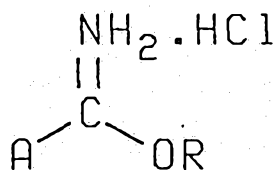
(V)

10 wherein X^2 and Z^2 are oxygen or sulphur; and A and Q are as defined above.

Suitable reactive derivatives of the acid $A-CO_2H$ include esters, for example C_{1-4} alkyl esters; thioesters, for example pyridylthioesters; acid anhydrides, for example $(ACO)_2O$; acid halides, for example acid chlorides; orthoesters; and primary, secondary and tertiary amides.

A preferred reactive derivative of the acid $A-CO_2H$ is the iminoether derivative of formula VI:

20



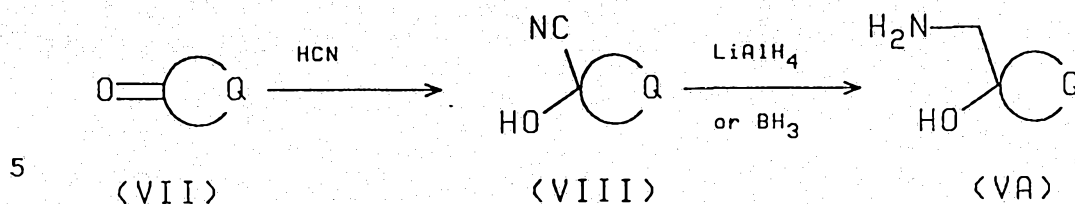
25

(VI)

where R is C_{1-4} alkyl.

The process is conveniently effected by condensation of the starting materials in the presence of thionyl chloride, phosphorus oxychloride or triphenylphosphine/diethyl azodicarboxylate.

The intermediate of formula V may be prepared by conventional methods, for example:



10 The oxazoline compounds according to the invention may alternatively be prepared by the silicon tetrafluoride-promoted reaction of a suitable oxirane with a nitrile A-CN, as described in Heterocycles, 1988, 27, 2527.

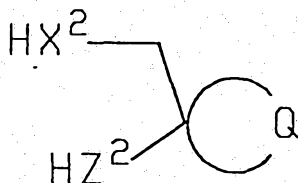
15 The isoxazolines according to the present invention may be prepared by reaction of a nitrile oxide of formula $\text{A}-\text{C}\equiv\text{N}^+-\text{O}^-$ with an alkene of formula IX:



25 wherein A and Q are as defined above. The nitrile oxide may itself be prepared by reacting the oxime of formula $\text{A}-\text{CH}(\text{=NOH})$ with N-chlorosuccinimide, followed by treatment with triethylamine.

30 The dioxolanes, oxathiolanes and dithiolanes of this invention may be prepared by either of two alternative methods, depending on the orientation of the heteroatoms relative to the groups A and Q. One method is to react an aldehyde of formula $\text{A}-\text{CHO}$ with a compound of formula X:

5

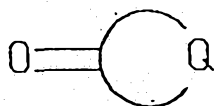


(X)

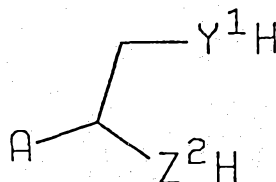
10

wherein x^2 and z^2 independently represent oxygen or sulphur; and A and Q are as defined above. An alternative method is to react an azacyclic or azabicyclic ketone of formula VII with a compound of formula XI:

15



(VII)



(XI)

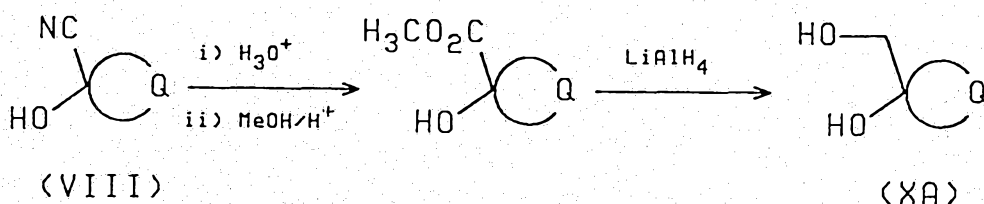
20

wherein y^1 and z^2 independently represent oxygen or sulphur; and A and Q are as defined above. Either reaction is suitably carried out in the presence of acid in an inert solvent such as benzene, toluene or dioxan.

25

The preparation of the intermediate of formula X from compound VIII is illustrated by the following sequence:

30



The azacyclic or azabicyclic derivatives VII and IX may be obtained by methods known from the art, in particular by methods analogous to those described in EP-A-0239309.

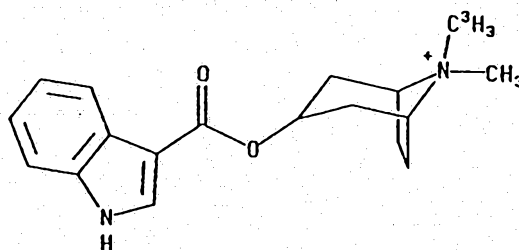
5 After any of the above described processes is complete, one substituent can be converted to another. For example an amino group may be converted to chloro, or hydrazo, $-NHNH_2$, via the intermediacy of diazonium, $-N_2$. Similarly, a chloro substituent
10 may be converted to methoxy by reaction with a nucleophile such as methoxide; alkoxycarbonyl groups may be converted, via carboxy, to an amino substituent, $-NH_2$; and methoxy may be converted to hydroxy by treatment with concentrated hydrobromic
15 acid.

 In any of the above reactions it may be necessary and/or desirable to protect any sensitive groups in the compounds. For example, if the substituents include amino, carboxy, keto, hydroxy or
20 thiol groups, these may be protected in conventional manner. Thus, suitable protecting groups for hydroxy groups include silyl groups such as trimethylsilyl or t-butyldimethylsilyl, and etherifying groups such as tetrahydropyranyl; and for amino groups include
25 benzyloxycarbonyl and t-butoxycarbonyl. Keto groups may be protected in the form of a ketal. Carboxy groups are preferably protected in a reduced form such as in the form of their corresponding protected alcohols, which may be subsequently oxidised to give
30 the desired carboxy group. Thiol groups may be protected by disulphide formation, either with the thiol itself or with another thiol to form a mixed disulphide. The protecting groups may be removed at any convenient stage in the synthesis of the desired compound according to conventional techniques.

The following Examples illustrate the preparation of compounds according to the invention.

The compounds according to the present invention may be evaluated for their anti-emetic activity in the von Bezold-Jarisch test (Nature, 1985, 316, 126), or in animal models of anxiety (see, for example, Br. J. Pharmac., 1988, 93, 985), schizophrenia (see, for example, Eur. J. Pharmac., 1987, 138, 303) or cognition (passive avoidance assay).

Certain of the compounds of the present invention act on 5-HT₃ receptors and this may account, in whole or in part, for the pharmacological activity of these compounds. The 5-HT₃ binding of the compounds of the invention was assayed using the protocol described in the literature (Nature, 1987, 330, 716) but instead of using the compound GR-65630 described therein, the ³H methylated quaternary derivative of formula XII was employed as a radioligand:

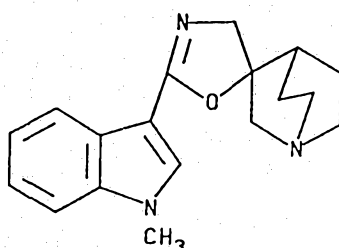


(XII)

The compounds of each of the Examples demonstrate an affinity for the 5-HT₃ receptor with a K_i (dissociation constant for the displacement of radioligand) better than 100 nM.

EXAMPLE 1

[2'-(1-Methyl-1H-indol-3-yl)-1spiro(1-azabicyclo
[2.2.2]octane-3,5'(4'H)-oxazole) dihydrochloride
 5 hydrate



15 (a) Methyl (1-methyl-1H-indol-3-yl)imidate
hydrochloride

Dry hydrogen chloride gas was bubbled through a solution of 1-methyl-1H-indole-3-nitrile (1.7 g) in dry methanol (30 mls). After standing at room temperature for 24 h addition of dry ether gave the title compound as colourless needles (1.8 g), m.p. 156-8°C (dec); δ_H (360 MHz, DMSO- d_6), 3.9 (3H, s, NCH₃), 4.3 (3H, s, OCH₃), 7.3 (1H, dt, J = 7.4 and 1.2Hz, CH), 7.4 (1H, dt, J = 8.2 and 1.6Hz, CH), 7.7 (1H, d, J = 7.8Hz, CH), 7.9 (1H, dd, J = 6.7 and 1.1Hz, CH), 9.0 (1H, s, CH); m/z 188 (M⁺).

30 (b) 3-Aminomethyl-3-hydroxy-1-azabicyclo
[2.2.2] octane dihydrochloride

A solution of lithium aluminium hydride (1.0 M solution in tetrahydrofuran, 10 mls,) in

tetrahydrofuran (20 mls) was heated at reflux under nitrogen and 3-cyano-3-hydroxy-1-azabicyclo[2.2.2]-octane (1.2 g.) was added portionwise. After heating at reflux for 30 min. the mixture was cooled and
 5 water (0.38 mls) was added followed by 15% sodium hydroxide solution (0.38 mls) and water (1.14 mls). The precipitate was filtered and the mother liquor evaporated in vacuo. The residue was dissolved in methanolic hydrogen chloride and, on standing, gave
 10 colourless needles (0.25 g), m.p. 318 - 320 °C;
 δ_H (360 MHz, D₂O), 1.9 - 2.0 (2H, m, CH₂), 2.0 - 2.1 (1H, m, CHH), 2.2 - 2.4 (2H, m, 4CH and CHH), 3.2 - 3.4 (8H, m, 4 x NCH₂); m/z 157 (M + H)⁺.

15

(c) [2'-(1-Methyl-1H-indol-3-yl)-]spiro(-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole), dihydrochloride hydrate

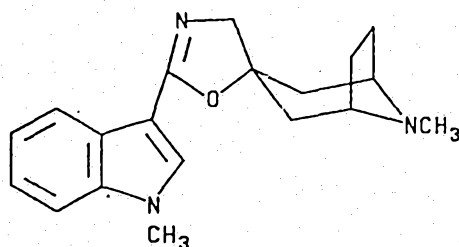
20

Methyl (1-methyl-1H-indol-3-yl)imidate hydrochloride (0.47 g.) and 3-aminomethyl-3-hydroxy-1-azabicyclo[2.2.2]octane (0.33 g, 2 mmol) were heated under nitrogen in refluxing methanol (25 mls) for 2 h and allowed to cool. After evaporation
 25 in vacuo the residue was dissolved in 2N hydrochloric acid. The solution was washed with dichloromethane basified with potassium carbonate and extracted with dichloromethane. The extract was washed (water), dried (MgSO₄) and solvents evaporated in vacuo.
 30 The residual solid was dissolved in methanol and methanolic hydrogen chloride added giving the title compound as colourless crystals (0.14 g), m.p. 262-3°C. Found: C, 55.94; H, 6.29; N, 10.76; Cl,

18.39; $C_{18}H_{21}N_3O \cdot 0.2HCl \cdot H_2O$ requires C, 55.96; H, 6.52; N, 10.88; Cl, 18.35%; δ_H (360 MHz, D_2O), 2.00 - 2.30 (3H, m, CH_2 + CHH) 2.46 - 2.56 (1H, m, CHH), 2.70 - 2.74 (1H, m, CH), 3.42 - 3.48 (2H, m, CH_2), 3.54 - 3.70 (2H, m, CH_2), 3.84 (1H, dd, J = 15.0 and 2.1Hz, CHH), 3.96 (3H, s, NCH_3), 4.09 (1H, d, J = 14.9Hz, CHH), 4.18 (1H, d, J = 12.3Hz, CHH), 4.46 (1H, d, J = 12.3Hz, CHH), 7.46 (1H, dt, J = 7.4 and 1.2Hz, CH), 7.51 (1H, dt, J = 7.2 and 1.3Hz, CH), 7.67 (1H, dd, J = 7.0 and 0.8Hz, CH), 7.93 (1H, dd, J = 7.2 and 1.6Hz, CH) 8.34 (1H, s, CH); m/z 295 (M^+).

EXAMPLE 2

15 [8-Methyl-2'-(1-methyl-1H-indol-3-yl)-]spiro(8-azabicyclo[3.2.1]octane-3,5'-(4'H)oxazole).
dihydrochloride hydrate (isomer 1)



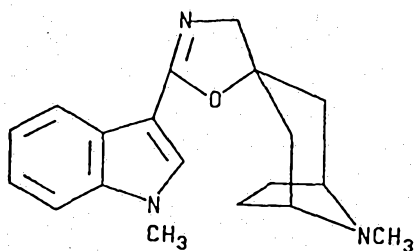
Following the method of Example 1c, methyl (1-methyl-1H-indol-3-yl)imidate hydrochloride (0.83 g, 3.7 mmol) and 3 α -aminomethyl-3 β -hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (0.63 g, 3.7 mmol) gave the title compound, (0.25 g), m.p. 252-3°C. Found: C, 57.21; H, 6.39; N, 10.53; Cl, 18.23; $C_{19}H_{23}N_3O \cdot 0.2HCl \cdot H_2O$ requires C, 57.00; H,

6.79; N, 10.50; Cl, 17.71%; δ_H (360 MHz, D_2O),
 2.18 - 2.28 (2H, m, CH_2), 2.44 - 2.50 (2H, m,
 CH_2), 2.71 (2H, d, $J = 13.5$ Hz, CH_2), 2.79 (2H,
 dd, $J = 15.3$ and 3.2 Hz, CH_2), 2.90 and 3.18 (3H, s,
 5 NCH_3), 3.96 (3H, s, NCH_3), 4.16 - 4.22 (2H, m, 2
 $\times CH$), 4.44 (2H, s, $-NCH_2-$), 7.46 (1H, dt, $J = 7.3$
 and 1.3 Hz, CH), 7.50 (1H, dt, $J = 7.7$ and 1.3 Hz, CH),
 7.66 (1H, d, $J = 7.4$, CH), 7.97 (1H, dd, $J = 8.3$ and
 1.3), 8.32 (1H, s, CH); m/z 309 (M^+ free base).

10

EXAMPLE 3

8-Methyl-[2'-(1-methyl-1H-indol-3-yl)]spiro(8-
azabicyclo[3.2.1]octane-3,5'(4'H)oxazole) dioxalate
 15 (isomer 2)



20

25

(a) 3 β -Aminomethyl-3 α -hydroxy-8-methyl-8-
azabicyclo[3.2.1]octane dihydrochloride

30

A mixture of 8-methyl-8-azabicyclo[3.2.1]octan-3-one (4.75 g.), trimethylsilylcyanide (5.63 mls.) and
 zinc iodide (0.3 g) was heated under nitrogen in dry
 dichloromethane (30 mls) at reflux for 24 h. After
 evaporation in vacuo, the residue was dissolved in
 dry tetrahydrofuran (20 mls) under nitrogen.

To this was added a 1.0 M solution of lithium aluminium hydride in tetrahydrofuran (34 mls,) and the reaction mixture was heated at reflux for 30 mins, and then chilled in ice/water. Water (1.3 mls) was added followed by 15% sodium hydroxide solution (1.3 mls) and water (3.9 mls). The precipitate was filtered and the mother liquor evaporated in vacuo. Methanolic hydrogen chloride and ether were added to give a 1:1 mixture of 3 α -aminomethyl-3 β -hydroxy-8-methyl-8-azabicyclo[3.2.1]octane dihydrochloride and 3 β -aminomethyl-3 α -hydroxy-8-methyl-8-azabicyclo[3.2.1]octane dihydrochloride (3.7g). Fractional crystallisation from methanol gave 3 β -aminomethyl-3 α -hydroxy-8-methyl-8-azabicyclo[3.2.1]octane dihydrochloride.

δ_H (360 MHz, D₂O), 2.13 - 2.24 (4H, m, 2 x CH₂), 2.26 - 2.32 (2H, m, CH₂), 2.36 - 2.46 (2H, m, CH₂), 2.81 (3H, s, NCH₃), 3.00 (2H, s, CH₂NH₂), 3.90 - 4.01 (2H, m, 2 x C-H).

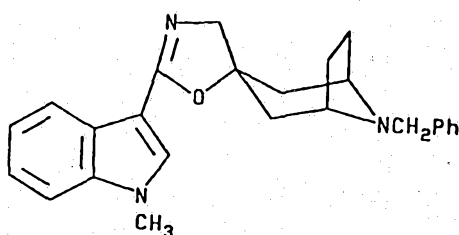
(b) [8-Methyl-2'-(1-methyl-1H-indol-3-yl)spiro (8-azabicyclo[3.2.1]octane-3,5'-(4'H)-oxazole) dioxalate

Following the method of Example 1c, 3 β -aminomethyl-3 α -hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (0.25 g) and methyl (1-methyl-1H-indol-3-yl) imidate hydrochloride (0.33 g) gave the title compound (0.25 g) as the free base. This was dissolved in methanol and treated with ethereal oxalic acid to give the title compound, m.p. 209 - 210°C. Found: C, 56.17; H, 5.62; N, 8.54;

$C_{19}H_{23}N_3O \cdot 2(CO_2H)_2$ requires C, 56.44; H, 5.56; N, 8.58%; δ_H (360 MHz, D_2O), 2.50 - 2.72 (6H, m, 3 x CH_2), 2.80 (2H, d, $J = 16.5$ Hz, CH_2), 2.91 and 3.05 (3H, s, NCH_3), 3.97 (3H, s, NCH_3), 4.08 (2H, s, $-NCH_2-$), 4.10 - 4.18 (2H, m, 2 x CH), 7.48 (1H, t, $J = 6.0$ Hz, CH), 7.52 (1H, t, $J = 7.2$, CH), 7.69 (1H, d, $J = 7.4$ Hz, CH), 7.92 (1H, dd, $J = 6.7$ and 1.6 Hz, CH), 8.37 (1H, s, CH); m/z 309 (M^+ , free base).

EXAMPLE 4

[8-Benzyl-2'-(1-methyl-1H-indol-3-yl)-]spiro
(8-azabicyclo[3.2.1]octane-3,5'(4'H)-oxazole)
dihydrochloride



(a) 3 α -Aminomethyl-3 β -hydroxy-8-benzyl-8-
azabicyclo[3.2.1]octane dihydrochloride

Following the method of Example 1b reduction of a 1:1 mixture of 3 α -cyano-3 β -hydroxy-8-benzyl-8-azabicyclo-[3.2.1]-octane and 3 β -cyano-3 α -hydroxy-8-benzyl-8-azabicyclo[3.2.1]octane (1.5g) gave a mixture of products. Purification by chromatography on silica eluting with

dichloromethane/MeOH/NH₄OH mixtures gave the required product (0.4g). Treatment of a methanolic solution of the amino alcohol with methanolic hydrogen chloride gave the title compound, m.p. 276 - 278°C. Found: C, 56.20; H, 7.44; N, 8.67; Cl, 22.10; C₁₅H₂₂N₂O.2HCl requires C, 56.43; H, 7.58; N, 8.77; Cl, 22.21%; δ_H (360 MHz, D₂O), 2.04 - 2.12 (2H, m, CH₂), 2.17 - 2.34 (4H, m, 2 x CH₂), 2.42 - 2.56 (2H, m, CH₂) 3.29 (2H, s, CH₂NH₂), 4.00 - 4.08 (2H, m, 2 x CH), 4.28 (2H, bs, CH₂Ph), 7.55 (5H, s, 5 x CH); m/z 247 (M + H)⁺.

(b) [8-Benzyl-2'-(1-methyl-1H-indol-3-yl)-] spiro(8-azabicyclo[3.2.1]octan-3,5'(4'H)-oxazole)dihydrochloride hydrate

Following the method of Example 1c, methyl (1-methyl-1H-indol-3-yl)imide hydrochloride (0.37 g, 1.65 mmol) and 3 α -aminomethyl-3 β -hydroxy-8-benzyl-8-azabicyclo[3.2.1]octane (0.40 g,) gave the title compound (0.15 g), m.p. 179 - 180°C (dec). Found: C, 61.11; H, 6.66; N, 8.45; Cl, 14.14; C₂₅H₂₇N₃O.2HCl.H₂O requires C, 60.73; H, 6.73; N, 8.50; Cl, 14.34%; δ_H (360 MHz, D₂O) 2.22 - 2.34 (2H, m, CH₂), 2.50 - 2.80 (6H, m, 3 x CH₂), 3.94 (3H, s, NCH₃), 4.18 - 4.25 (2H, m, 2 x CH), 4.30 - 4.37 (1.5H, bs, CH₂Ph), 4.43 (2H, s, -NCH₂-), 7.42 - 7.52 (2H, m, 2 x CH), 7.52 - 7.62 (5H, m, 5 x CH), 7.65 (1H, d, J = 7.6Hz, CH), 7.94 (1H, d, J = 7.6Hz, CH), 8.30 (1H, s, CH); m/z 386 (M + H)⁺.

EXAMPLE 5

[2'-(5-Fluoro-1-methyl-1H-indol-3-yl)-]spiro(1-azabicyclo[2.2.2]octane-3,5'-(4'H)oxazole) di-oxalate dihydrate

a) Methyl (5-fluoro-1-methyl-1H-indol-3-yl) imidate hydrochloride

Following the method described in Example 1a 5-fluoro-1-methyl-1H-indole-3-nitrile (0.9g) afforded the title compound (0.9g), m.p. 159-160°C. Found: C, 54.23; H, 5.04; N, 11.53. $C_{11}H_{11}FN_2O$ requires C, 54.44; H, 4.91; N, 11.54%; δ_H (360MHz, D_2O) 3.95 (3H, s, NMe), 4.3 (3H, s, OMe), 7.26 (1H, dt, J = 9.2Hz, 2.6Hz, CH), 7.69-7.75 (2H, m, 2 x CH), 8.93 (1H, s, CH); m/z 206 (M^+).

b) [2'-(5-Fluoro-1-methyl-1H-indol-3-yl)-]spiro(1-azabicyclo[2.2.2]octane-3,5'-(4'H)oxazole) di-oxalate dihydrate

Following the method described in Example 1c methyl (5-fluoro-1-methyl-1H-indol-3-yl)imidate hydrochloride (0.24g) and 3-aminomethyl-3-hydroxy-1-azabicyclo[2.2.2]octane (0.16g) in methanol (20ml) afforded the title compound (100mg); m.p. 175-178°C; Found: C, 50.18; H, 5.02; N, 7.81 $C_{18}H_{20}FN_3O_2$ (CO_2H) $\cdot 2H_2O$ requires C, 49.91; H, 5.33; N, 7.94%; δ_H (360MHz, D_2O) 2.0-2.6 (4H, m, 2 x CH_2), 2.76 (1H, m, CH), 3.4-3.68 (4H, m, 2 x CH_2N), 3.85 (1H, dd, J = 16.8Hz, 1.8Hz, $CHHN$), 3.96 (3H, s, NMe), 4.12 (1H, d, J = 16.8Hz, $CHHN$), 4.20

(1H, d, J = 12Hz, CHHN), 4.49 (1H, d, J = 12Hz, CHHN), 7.27 (1H, dt, J = 9.3Hz, 2.5Hz, CH), 7.59 (1H, dd, J = 9.3Hz, 2.5Hz, CH), 7.64 (1H, dd, J = 9.4Hz, 2.4Hz, CH), 8.41 (1H, s, CH); m/z 313 (M⁺, free base).

EXAMPLE 6

[8-Methyl-2'-(5-fluoro-1-methyl-1H-indol-3-yl)-1-spiro(8-azabicyclo[3.2.1]octane-3,5'(4'H)oxazole)dioxalate hemihydrate (isomer 1) and [8-methyl-2'-(5'-fluoro-1-methyl-1H-indol-3-yl)-1-spiro(8-azabicyclo[3.2.1]octane-3,5'(4'H)-oxazole) di-oxalate hemihydrate (isomer 2)]

Following the method described in Example 1c methyl (5-fluoro-1-methyl-1H-indol-3-yl)imidate hydrochloride (0.48g) and 3-aminomethyl-3-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (0.34g) in methanol (20ml) afforded the title compounds (isomer 1) (40mg), m.p. 125-128°C. Found: C, 53.09; H, 4.96; N, 8.04. C₂₁H₂₄FN₃O₉·0.5H₂O requires C, 53.49; H, 5.27; N, 8.14%; δ_H (360MHz, D₂O) 2.17-2.50 (4H, m, 2 x CH₂), 2.71 (2H, d, J = 15Hz, CH₂), 2.79 (2H, dd, J = 18Hz, 3.5Hz, CH₂), 2.89 (3H, s, NMe), 3.95 (3H, s, NMe), 4.14-4.22 (2H, m, 2 x CHN), 4.44 (2H, s, CH₂), 7.25 (1H, dt, J = 10Hz, 3Hz, CH), 7.6-7.65 (2H, m, 2 x CH), 8.36 (1H, s, CH); m/z 327 (M⁺, free base); and (isomer 2) (0.26g), m.p. 185-186°C. Found C, 53.18; H, 5.52; N, 7.83 C₂₁H₂₁FN₃O₉·0.5H₂O requires C, 53.48; H, 5.27; N, 8.14%; δ_H (360MHz, D₂O) 2.5-2.8 (8H, m, 4 x CH₂), 2.91 (3H, s, NCH₃), 3.96 (3H, s,

NMe), 4.08 (2H, s, CH₂), 4.10-4.18 (2H, m, 2 x CHN), 7.27 (1H, dt, J = 9.3Hz, 2.4, CH), 7.5-7.65 (2H, m, 2 x CH), 8.38 (1H, s, CH); m/z 327 (M⁺, free base).

5

EXAMPLE 7

[2'-(1H-Indol-3-yl)-]spiro(1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole) dihydrochloride
sesquihydrate

10

a) Methyl (1H-indol-3-yl)imidate hydrochloride

Following the procedure described in Example 1a
1H-indole-3-nitrile (2.0g) afforded the title
compound (1.8g), m.p. 165-167°C (dec), δ_H
(360MHz, DMSO-d₆), 4.30 (3H, s, OMe), 7.26-7.33
(2H, m, 2 x CH), 7.6 (1H, dd, J = 6.0Hz, 1.6Hz, CH),
7.93 (1H, dd, J = 8.4Hz, 2.0Hz, CH), 8.9 (1H, d, J =
20 2Hz, CH), 10.4, 11.4 (2H, 2 x bs, 2 x NH); m/z 174
(M⁺, free base), 143 (100, M⁺-OMe).

20

b) [2'-(1H-Indol-3-yl)-]spiro (1-azabicyclo
[2.2.2]octane-3,5'(4'H)-oxazole) dihydrochloride
sesquihydrate

25

Following the procedure described in Example 1c
methyl (1H-indol-3-yl)imidate (0.67g) and
3-aminomethyl-3-hydroxy-1-azabicyclo[2.2.2]octane
(0.5g) in methanol (70ml) gave the title compound
(1.0g); m.p. 220-222°C. Found: C, 52.72; H, 6.34; N,
10.91 C₁₇H₁₉N₃O.2HCl.1.5H₂O requires C,
53.04; H, 6.31; N, 10.92%; δ_H (360MHz, D₂O)

30

2.0-2.58 (4H, m, 2 x CH₂), 2.78 (1H, m, CH),
 3.4-3.5 (2H, m, CH₂N), 3.56-3.72 (2H, m, CH₂N),
 3.86 (1H, dd, J = 15Hz, 2Hz, CHHN), 4.13 (1H, d, J =
 15Hz, CHHN), 4.22 (1H, d, J = 12Hz, CHHN), 4.50 (1H,
 5 d, J = 12Hz, CHHN), 7.4-7.48 (2H, m, 2 x CH), 7.7
 (1H, m, CH), 7.95 (1H, m, CH), 8.48 (1H, s, CH); m/z
 281 (M⁺, free base).

EXAMPLE 8

10

[2'-(1-Methyl-1H-indol-3-yl)-]spiro(1-azabicyclo
[3.3.1]nonane-4,5'(4'H)-oxazole) dihydrochloride

15

a) 1-Carboethoxyethyl-3-carboethoxy
piperidine

20

Ethyl nipecotate (51g) in toluene (50ml) was added
 dropwise to a slurry of anhydrous potassium carbonate
 (89g) in toluene (200ml) and stirred for 15 minutes.

25

Ethyl 3-bromopropionate (58.6g) in toluene (50ml) was
 added dropwise and reaction mixture heated at reflux
 for 3 hours once addition was complete. The mixture
 was then cooled and toluene decanted. The residual
 toluene and inorganics were mixed with water (300ml)
 and extracted with dichloromethane (3 x 200ml). The
 combined organic layers were dried (MgSO₄),
 filtered and concentrated to a yellow oil (70g).

30

δ_H (360MHz, CDCl₃), 1.25 (6H, 2 x t, J = 7.2Hz
 and J = 7.2Hz, 2 x CH₃), 1.4-1.9 (4H, m, 2 x
 CH₂), 2.0-2.1 (1H, m, CH), 2.2 (1H, m, NCHH), 2.5
 (2H, t, J = 7.4Hz, CH₂CO), 2.55 (1H, m, NCHH), 2.70
 (2H, t, J = 7.3Hz, NCH₂), 2.75 (1H, m, NCHH), 2.95
 (1H, br d, NCHH), 4.1 (4H, 2 x q, J = 7.1Hz and J =

7.1Hz, 2 x OCH₂); m/z 258 (M⁺+H, 40%).

b) 1-Azabicyclo[3.3.1]nonan-4-one

5 Anhydrous potassium t-butoxide (45.8g) in
anhydrous toluene (1.0dm³) was heated at reflux and
1-carboethoxyethyl-3-carboethoxypiperidine
(35.0g) in toluene (250ml) was added over 2 hours.
Reflux was maintained for a further 4 hours before
10 cooling to room temperature and concentrated
hydrochloric acid (300ml) was added. The mixture was
stirred for 1 hour, then the organic layer was
separated and extracted with concentrated
hydrochloric acid (225ml x 4). The combined acid
15 extracts were heated at reflux for 16 hours, then
basified to pH 10 with potassium carbonate and
extracted with chloroform (300ml x 6). The combined
organic extracts were dried (MgSO₄) and
concentrated in vacuo to an orange semi-solid
20 (9.7g). This was purified by chromatography (Alumina
grade III) by gradient elution in 3-10% methanol in
ethyl acetate. The title compound was isolated as
light orange semi-solid (3.5g). δ_H (360MHz,
CDCl₃), 1.55 (1H, m, CHH), 1.7-1.8 (1H, m, CHH),
25 1.95 (2H, m, CH₂), 2.4 (1H, s, CH), 2.55 (2H, m,
CH₂CO), 3.1-3.4 (6H, m, 3 x CH₂N); m/z 139 (M⁺)
(100%).

c) 4-Aminomethyl-4-hydroxy-1-azabicyclo[3.3.1]
30 nonane

Trimethylsilyl cyanide (3ml) was added dropwise
to a stirred solution of 1-azabicyclo[3.3.1]nonan-

4-one (2.5g) and zinc iodide (0.15g) in dry dichloromethane (20ml) and the resulting mixture was heated at reflux for 4 hours. The mixture was cooled and the solvent removed at reduced pressure; the residue was dissolved in dry tetrahydrofuran (20ml) and cooled to 0°C. A solution of lithium aluminium hydride in tetrahydrofuran (18ml of 1.0M soln) was then added and the resulting solution stirred overnight at room temperature. Water (0.7ml), followed by 15% sodium hydroxide (aq) (0.7ml) and water (2.1ml) were then added and the precipitate removed by filtration. Evaporation of the filtrate yielded the title compound (2.2g); δ_H (360MHz, $CDCl_3$) 1.2-1.3 (2H, m, CH_2), 1.34 (1H, m, CHH), 1.41 (1H, m, CHH), 1.6 (2H, m, CH_2), 1.7-1.74 (1H, m, CHH), 1.76-1.91 (2H, m, CH_2), 2.11-2.16 (1H, m, CHH), 2.67-3.18 (8H, m); m/z 170 (M^+).

d) [2'-(1-Methyl-1H-indol-3-yl)-]spiro(1-azabicyclo[3.3.1]nonane-4,5'-(4'H)-oxazole dihydrochloride

Following the method described in Example 1c methyl (1-methylindol-3-yl)imidate (2.65g) and 4-aminomethyl-4-hydroxy-1-azabicyclo[3.3.1]nonane (2.0g) in methanol (150ml) yielded the title compound (0.7g), m.p. 257-259°C. Found: C, 59.17; H, 6.55; N, 10.84. $C_{19}H_{23}N_3O \cdot 0.25 H_2O$ requires C, 58.99; H, 6.64; N, 10.86%; δ_H (360MHz, D_2O) 2.02-2.16 (2H, m, CH_2), 2.42-2.58 (2H, m, CH_2), 2.72 (1H, m, CH), 3.02 (1H, dt, $J = 14Hz$, 7.4Hz, CHH), 3.48 (1H, d, $J = 14Hz$, CHH), 3.6-3.8 (5H, m), 3.98 (3H, s, NMe), 4.19 (1H, d, $J = 11.3Hz$, CHH).

4.29 (1H, d, J = 11.3Hz, CHH), 7.4-7.5 (2H, m, H-5, H-6), 7.68 (1H, d, J = 7Hz, H - 7), 7.99 (1H, d, J = 7Hz, H-4), 8.39 (1H, s; H-2); m/z 309 (M⁺, free base).

5

EXAMPLE 9

10 [2'-(1-Cyclopropylmethyl-1H-indol-3-yl)spiro(1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole) dihydro-chloride hydrate

a) 1-Cyclopropylmethyl-1H-indole-3-carboxylic acid

15 Powdered sodium hydroxide (10g) was added cautiously to a stirred solution of indole-3-carboxylic acid (5g) and (bromomethyl)cyclopropane (10g) in dry acetone (50ml). The mixture was stirred for 24 hours at room temperature then diluted with
20 water (250ml) and washed with dichloromethane (2 x 100ml). The aqueous phase acidified to pH 2 and the precipitate isolated and dried (6.3g), m.p. 157°C; δ_H (360MHz, CDCl₃) 0.02-0.04 (2H, m, CH₂), 0.18-0.28 (2H, m, CH₂), 0.83-0.89 (1H, m, CH), 3.57 (2H, d, J = 7Hz, NCH₂), 6.7-6.8 (2H, m, H-5, H-6),
25 6.9 (1H; d, J = 7Hz, H-7), 7.55 (1H, s, H-2), 7.72 (1H, d, J = 7Hz, H-4); m/z 215 (M⁺, 100%), 174 (60), 144 (40).

30 b) 1-Cyclopropylmethyl-1H-indole-3-carboxamide

Oxalyl chloride (3.7g) was added slowly to a stirred solution of the carboxylic acid (6.3g) in dry

tetrahydrofuran (50ml) at 0°C. The resulting red solution was then stirred overnight at room temperature. The solvent was evaporated at reduced pressure and the residue dissolved in dry

5 dichloroethane (50ml); ammonia was bubbled through the solution for 1hr and the mixture stirred at room temperature for 12hrs. The solvent was evaporated at reduced pressure and the residue triturated with water, then ether and dried, (5.2g), m.p. 170°C; δ_H (60Mz, CDCl₃) 0.38-0.42 (2H, m, CH₂), 0.53-0.58 (2H, m, CH₂), 0.85-0.89 (1H, m, CH), 4.05 (2H, d, J = 7Hz, NCH₂), 7.09-7.20 (2H, m, H-5, H-6), 7.54 (1H, d, J = 7Hz, H-7), 8.11 (1H, s, H-2), 8.14 (2H, d, J = 6, H-4); m/z 214 (M⁺, 100%), 143 (50), 161 (30).

15 c) 1-Cyclopropylmethyl-1H-indole-3-nitrile

Trifluoroacetic anhydride (19.5g) was added dropwise to a cooled (0°C), stirred solution of 20 1-cyclopropylmethyl-1H-indole-3-carboxamide (5g) in dioxane (100ml) and triethylamine (18g). After the addition the mixture was stirred at room temperature for two hours, the mixture was diluted with dichloromethane (200ml) and washed with water (3 x 100ml), 25 dried (Na₂SO₄) and evaporated at reduced pressure. The residue was purified by column chromatography on silica eluting with dichloromethane to afford a colourless oil, (5g); δ_H (CDCl₃, 60MHz) 0.3-0.6 (4H, m, 2 x CH₂), 0.9 (1H, m, CH), 30 4.0 (2H, d, J = 7, CH₂), 7.0-7.7 (5H, m); ν_{max} 2210 (C≡N).

d) Methyl (1-cyclopropylmethyl-1H-indole-3-yl)
imide

Following the procedure described in Example 1a 1-
5 cyclopropylmethyl-1H-indole-3-nitrile (1g) afforded
the title compound (0.8g), m.p. 131°C; δ (360MHz,
DMSO- d_6) 0.4-0.6 (4H, m, 2 x CH_2) 1.29-1.34 (1H,
m, CH), 4.15 (2H, d, J = 7Hz, NCH_2), 4.30 (3H, s,
OMe), 7.32-7.38 (2H, m, H-5, H-6), 7.74 (1H, d, J =
10 7Hz, H-4), 7.96 (1H, d, J = 7, H-7), 9.17 (1H, s,
H-2); m/z 264 (M^+).

e) [2'-(1-Cyclopropylmethyl-1H-indol-3-yl)]spiro
(1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole) dihydro-
15 chloride dihydrate

Following the procedure described in Example 1c
methyl (1-cyclopropylmethyl-1H-indol-3-yl)imide
hydrochloride (0.5g) and 3-aminomethyl-3-hydroxy-1-
20 azabicyclo[2.2.2]octane (0.5g) was reacted in
methanol (20ml) and afforded the title compound
(0.5g); m.p. 199°C; Found C, 57.02; H, 7.01; N,
9.35. $C_{21}H_{31}N_3O_3Cl_2$ requires C, 56.76; H,
7.03; N, 9.46%; δ_H (360MHz, $CDCl_3$) 0.44-0.48
25 (2H, m, CH_2), 0.66-0.71 (2H, m, CH_2), 1.39-1.43
(1H, m, CH), 2.08-2.26 (3H, m, CH_2 CHH), 2.53 (1H,
m, CHH), 2.77 (1H, bs, CH), 3.43 (2H, m, CH_2N),
3.63 (2H, m, CH_2N), 3.87 (1H, d, J = 12Hz, CHHN),
4.13 (1H, d, J = 12Hz, CHHN), 4.20-4.24 (4H, m,
30 NCH_2 , CHH), 4.50 (1H, d, J = 10Hz, CHH), 7.4-7.53
(2H, m, H-5, H-6), 7.75 (1H, d, J = 6Hz, H-7), 7.96
(1H, d, J = 6Hz, H-7), 8.65 (1H, s, H-2); m/z 335
(M^+ , free base).

EXAMPLE 10

[2'-(1-Ethyl-1H-indol-3-yl)-]spiro(1-azabicyclo
[2.2.2]octane-3,5'(4'H)-oxazole) dihydrochloride
5 dihydrate

a) Methyl (1-ethyl-1H-indol-3-yl) imidate
hydrochloride

10 Following the procedure described in Example 1a
1-ethyl-1H-indole-3-nitrile (0.6g) afforded the title
compound (0.3g), m.p. 144-145°C; δ_H (360MHz,
D₂O) 1.44 (3H, t, J = 7Hz, CH₃), 3.3 (2H, brs,
NH₂), 4.30-4.37 (5H, m, NCH₂, OMe), 7.30-7.39
15 (2H, m, H-5, H-6), 7.72 (1H, d, J = 7Hz, H-7), 7.93
(1H, d, J = 6Hz, H-4), 9.10 (1H, s, H-2); m/z 202
(M⁺, free base), 171 (85), 155 (100).

b) [2'-(1-Ethyl-1H-indol-3-yl)-]spiro(1-
20 azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole
hydrochloride dihydrate

Following the procedure described in Example 1c
methyl (1-ethyl-1H-indol-3-yl)imidate hydrochloride
25 (0.3g) and 3-aminomethyl-3-hydroxy-1-azabicyclo[2.2.2]
octane (0.2g), in methanol (20ml) afforded the title
compound (0.2g); m.p. 194-196°C

EXAMPLE 11

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[2'-(1-Methyl-1H-indol-3-yl)-]spiro(1-azabicyclo
[2.2.2]octane-3,5'(4'H)-oxazole) dihydrochloride

a) 3-Cyano-3-hydroxyquinuclidine

To a cooled (ice bath), stirred solution of 3-quinuclidinone hydrochloride (300g) in water (400ml) was added dropwise a solution of sodium cyanide (90.97g) in water (400ml). After stirring at ice bath temperature for three hours the precipitate was collected by filtration, washed with water and dried under vacuum to afford the title compound (282g); m.p. 153-157°C (lit m.p. 152-155°C; Helv. Chim. Acta., 1954, 37, 1689).

b) 3-Aminomethyl-3-hydroxy-1-azabicyclo[2.2.2]octane borane complex

A solution of borane in tetrahydrofuran (266ml), of a 1.0M solution, was added to a stirred solution of 3-cyano-3-hydroxyquinuclidine (40g) in tetrahydrofuran (400ml) under nitrogen. When the borane complex had formed (tlc monitor) two further equivalents of borane in tetrahydrofuran were added (534ml), and the reaction heated at reflux for 12hr. The mixture was cooled to room temperature and ethanol (500ml) added slowly; the resulting solution was stirred at room temperature for 12hr. The solvent was then removed at reduced pressure and the residue recrystallised from ethanol to afford the title compound as a white crystalline solid (32g), m.p. 163°C; δ_H (360MHz, $CDCl_3$) 1.16-1.61 (3H, m, CH, CHH), 1.86 (1H, m, CHH), 2.05 (1H, m, CH), 2.4-2.97 (8H, m, 4 x CH_2N); m/z 157 (M^+).

c) [2'-(1-Methyl-1H-indol-3-yl)]-spiro(1-

azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole)
dihydrochloride

A solution of methyl (1-methyl-1H-indol-3-yl)
5 imidate hydrochloride (22.45g) in anhydrous methanol
(350ml) was added to a stirred solution of
3-aminomethyl-3-hydroxy-1-azabicyclo[2.2.2]octane
borane complex (20.4g) in methanol (350ml) under
nitrogen over 75 mins. The resulting solution was
10 then heated at reflux for 12hr and allowed to cool to
room temperature. Saturated methanolic hydrogen
chloride was added (100ml) and the mixture heated at
reflux for 12hr. The solvent was removed under
reduced pressure and the residue dissolved in 2N
15 hydrochloric acid (50ml) and water (200ml). The
solution was washed with dichloromethane (250ml),
basified with ammonium hydroxide and extracted with
dichloromethane (3 x 100ml). The combined extracts
were dried (Na_2SO_4) and the solvent removed at
20 reduced pressure. The residue was purified on silica
eluting with dichloromethane/methanol/ NH_4OH
(90:10:1) to afford the title compound as a viscous
oil (19.5g, 66%); δ_{H} (CDCl_3) 1.5-1.58 (3H, m,
 CH_2 , CHH), 2.01 (1H, m, CHH), 2.17 (1H, m, CH),
25 2.82 (2H, m, CH_2N), 2.97 (1H, d, J = 15, CHHN), 3.0
(2H, m, CH_2N), 3.31 (1H, d, J = 15, CHHN), 3.76
(1H, d, J = 12, CHN), 3.82 (3H, s, NMe), 4.19 (1H, d,
J = 12, CHHN), 7.22-7.35 (3H, m, Ar), 7.63 (1H, s,
H-2), 8.16 (1H, m, Ar); m/z 295 (M^+).

30

EXAMPLE 12

(+)[2'-(1-Methyl-1H-indol-3-yl)-]spiro(1-

azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole) and (-)[2'-(1-Methyl-1H-indol-3-yl)-]spiro(1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole)

- 5 To a solution of [2'-(1-methyl-1H-indol-3-yl)-]spiro(1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole (6.40g, 21.7mmol) in a minimum of ethanol was added a solution of (+)-O,O'-dibenzoyl-D-tartaric acid (1.93g, 5.4mmol). The salt which crystallised was
- 10 filtered and recrystallised from ethanol to constant rotation $[\alpha]_D^{20} +11.6^\circ$ (c=0.5, MeOH). The mother liquors from the original crystallisation were evaporated to dryness, taken up in dichloromethane (200ml) and washed with aqueous sodium bicarbonate (3
- 15 x 100ml). The organic phase was dried (MgSO₄) and evaporated. The residue was dissolved in ethanol (20ml) and treated with a solution of (-)-O,O'-dibenzoyl-L-tartaric acid (1.93g, 5.4mmol) in a minimum of ethanol. The salt which crystallised was
- 20 recrystallised to constant rotation (four recrystallisations from ethanol). $[\alpha]_D^{20} -12.4^\circ$ (c=0.5, MeOH). The (+)-salt was dissolved in dichloromethane (100ml) and washed with dilute aqueous ammonia solution (3 x 100ml). The organic
- 25 phase was dried (MgSO₄) and evaporated to dryness. The residue was dissolved in methanol and treated with ether/HCl to give the dihydrochloride salt which was crystallised from ethanol/ether to give the title compound m.p. 261-261°C. $[\alpha]_D^{20} -43.3^\circ$ (c=0.5
- 30 MeOH. The (-)-salt was treated similarly to give colourless crystals m.p. 261-262°C. $[\alpha]_D^{20} +43.3^\circ$ (c=0.5, MeOH).

EXAMPLE 13

[2'-(5-Nitro-1H-indol-3-yl)-]spiro(1-azabicyclo
[2.2.2]octane-3,5'(4H)-oxazole) dihydrochloride

5

a) 5-Nitro-1H-indole-3-carboxylic acid

Trifluoroacetic anhydride (21.37g) was added dropwise to a chilled solution of 5-nitro-1H-indole (15.0g) in dry dimethylformamide (150ml) under a dry N₂ atmosphere. The solution was allowed to warm to room temperature, and was then heated at reflux for 24 hours. The reaction mixture was cooled and poured into water (500ml) and the resulting dark brown precipitate was filtered, suspended in water (200ml) containing sodium hydroxide (50.0g), and heated at reflux for 3 hours. The dark brown solution was cooled to room temperature, extracted with ether (4 x 100ml), acidified to pH2 and the title compound filtered and dried (19g), m.p. 256-258°C δ_H (360MHz, DMSO-d₆) 7.71 (1H, d, J = 7.2Hz, H-7), 8.9 (1H, dd, J = 7.2, 1.0Hz), 8.27 (1H, s, H-2), 8.89 (1H, d, J = 1.0Hz, H-4); m/z 206 (M⁺, 70), 163 (10), 138 (20), 123 (100, 106 (15), 81 (10%).

25

b) 5-Nitro-1H-indole-3-carboxamide

Oxalyl chloride (1.87g) was added to a solution of 5-nitro-1H-indole-3-carboxylic acid (3.06g) in dry tetrahydrofuran (80ml). The solution was stirred at room temperature for 24 hours and then evaporated to dryness. The residue was taken up in 1,2-dichloroethane (50ml) and anhydrous NH₃ gas passed

30

through the solution for one hour, to afford the title compound as a bright yellow precipitate which was filtered and dried (3.2g), m.p. 284-288°C δ_H (360MHz, DMSO- d_6) 7.62 (1H, d, J = 7.0Hz, H-7), 8.04 (1H, dd, J = 7, 1.0Hz, H-6), 8.29 (1H, s, H-2), 9.08 (1H, d, J = 1.0Hz, H-4); m/z 205 (M^+ , 90), 189 (100), 159 (10), 143 (80), 142 (80), 130 (10), 114 (40), 87 (40), 76 (20).

10 c) 5-Nitro-1H-indole-3-carbonitrile

5-Nitro-1H-indole-3-carboxamide (2.0g) was suspended in dry dioxane (100ml) containing triethylamine (7.8g). Trifluoroacetic anhydride (8.2g) was added dropwise with the temperature of the solution maintained at less than 5°C, the reaction was then allowed to warm to room temperature overnight. The reaction mixture was diluted with dichloromethane (200ml), washed with water (3 x 100ml), dried ($MgSO_4$) and the solvent removed. Recrystallisation of the residue from ethyl acetate/hexane afforded the title compound (840mg), m.p. 186-190°C. δ_H (360MHz, $CDCl_3$) 7.58 (1H, d, J = 7.2Hz, H-7), 7.94 (1H, d, J = 1.0Hz, H-4), 8.16 (1H, dd, J = 7.2, 1.0Hz, H-6), 8.63 (1H, s, H-2); m/z 187 (M^+ , 100), 157 (45), 141 (95), 129 (30), 114 (55), 102 (10), 87 (20).

30 d) Methyl (5-nitro-1H-indole-3-yl)imidate hydrochloride

Dry hydrogen chloride gas was passed through a solution of 5-nitro-1H-indole-3-carbonitrile (2.6g)

in dry methanol (100ml) for one hour. The solution was then allowed to stand at room temperature under a dry N₂ atmosphere for 24 hours, during which time a purple precipitate formed. The precipitate was
 5 filtered and recrystallised from acetone to give the title compound as pink needles (2.09g), m.p. 220°C dec. δ_H (360MHz, DMSO) 3.07 (3H, s, -OCH₃), 7.63 (1H, d, J = 10.0Hz, H-7), 8.06 (1H, dd, J = 10.0, 2.5Hz, H-6), 8.29 (1H, d, J = 5.0Hz, H-2), 4.13
 10 (1H, d, J = 2.5Hz, H-4); m/z 219 (M⁺, 55), 205 (10), 188 (85), 174 (20), 158 (30), 142 (100), 129 (35), 114 (60), 87 (25), 76 (15).

e) [2'-(5-Nitro-1H-indol-3-yl)-]spiro(1-azabicyclo[2.2.2]octane-3,5'-(4'H)-oxazole) borane complex

Methyl (5-nitro-1H-indol-3-yl)imidate hydrochloride (930mg) and 3-hydroxy-3-aminomethyl-1-azabicyclo[2.2.2]octane borane complex (742mg) were
 20 dissolved in dry methanol (80ml) and the resulting solution heated at reflux for 12 hours, cooled to room temperature and the solvent removed. The residue was chromatographed on silica gel using
 25 dichloromethane/methanol/ammonium hydroxide as eluant to afford the title compound as a yellow solid, m.p. 290°C (dec) δ_H (360MHz, CDCl₃) 1.78 (3H, bm, CH₂CH₂N), 2.08 (1H, bm, CH-CH₂CH₂N), 2.1 (1H, bm, CH₂CH₂N), 2.91-3.2 (6H, bm, CH₂CH₂N),
 30 3.89 (1H, d, (C=N-CH₂), 4.11 (1H, d, J = 15.0Hz, C=N-CH₂), 7.65 (1H, d, J = 10.0Hz, H-7), 8.09 (1H, dd, J = 10.0, 2.5Hz, H-6), 8.18 (1H, s, H-2), 10.37 (1H, d, J = 2.5Hz, H-4); m/z (C₁₇H₂₁N₄O₃B =

340) 326 (M^+ -14, 10%), 189 (60), 142 (60), 114 (40), 96 (100), 82 (60).

f) [2'-(5-Nitro-1H-indol-3-yl)-]spiro(1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole hydrochloride

The aforementioned borane complex (300mg) was dissolved in methanol (50ml) previously saturated with hydrogen chloride gas. The solution was heated at reflux for 12 hours, then cooled and the solvent removed. The residue was dissolved in water (50ml), washed with dichloromethane (4 x 50ml), basified to pH12 with ammonium hydroxide, extracted with dichloromethane (4 x 50ml), and dried ($MgSO_4$). Filtration and removal of solvent afforded a yellow solid. Purification by flash chromatography on silica gel using dichloromethane/methanol/ammonium hydroxide as eluant afforded the free base which was further purified by treatment with a solution of ethereal hydrogen chloride and crystallisation from ethanol to afford the title compound (100mg), m.p. 260°C (dec); Found: C, 51.43; H, 5.21; N, 13.97 $C_{17}H_{20}N_4O_3Cl_2$ requires C, 51.3; H, 5.04; N, 14.03%; δ_H (360Mz, D_2O) 2.1-2.52 (4H, bm, $\underline{CH_2CH_2N}$), 2.79 (1H, bm, $\underline{CHCH_2CH_2N}$), 3.2-4.1 (6H, bm, $\underline{CH_2CH_2N}$), 4.27 (1H, d, $J = 14.4Hz$, $C=N-\underline{CH_2}$), 4.55 (1H, d, $J = 14.4Hz$, $C=N-\underline{CH_2}$), 7.65 (1H, d, $J = 10.8Hz$, H-7), 7.98 (1H, dd, $J = 10.8, 3.6Hz$, H-6), 8.51 (1H, s, H-2), 8.8 (1H, d, $J = 3.6Hz$, H-4); m/z 326 (M^+ , 40), 250 (20), 224 (100), 183 (30), 157 (50), 139 (50), 87 (40).

EXAMPLE 14

2'-(1-Methyl-1H-indol-3-yl)spiro[1-methyl
piperidine-4,5'-(4'H)-oxazole] dihydrochloride 2.25
5 hydrate

To a chilled solution of 4-cyano-4-hydroxy-1-methylpiperidine (1.4g.) in tetrahydrofuran (20ml) under nitrogen was added borane-tetrahydro-
10 furan complex (1.0M in tetrahydrofuran, 12ml). After stirring at room temperature for 15 minutes a further 24ml of borane-tetrahydrofuran complex was added. After heating at reflux for 1.5 hours the reaction mixture was cooled and ethanol (25ml) added. After
15 stirring for 30 minutes the mixture was evaporated to dryness. The residue was dissolved in methanol (20ml) and added dropwise to a solution of methyl (1-methyl-1H-indol-3-yl)imidate (0.43g, 1.9mmol) in methanol (30ml) stirred under nitrogen. After
20 refluxing for 24 hours the reaction mixture was evaporated to dryness and the residue purified by column chromatography on silica eluting with dichloromethane/methanol/ammonium hydroxide mixtures to give a colourless oil. This oil was dissolved in
25 methanol and treated with ethereal hydrogen chloride to give the title compound as a colourless crystalline solid (0.26g), m.p. 238-240°C; Found: C, 51.12; H, 6.96; N, 10.47; Cl, 18.09;
C₁₇H₂₁N₃O.2HCl. 2.25H₂O requires C, 51.45; H, 6.99; N, 10.59; Cl, 17.97%; δ_H (360MHz, D₂O) 2.28-2.44 (2H, m) and 2.44-2.58 (2H, m, two CH₂), 3.06 (3H, s, N-CH₃), 3.44-3.56 (2H, m) and 3.64-3.76 (2H, m, two N-CH₂), 3.96 (3H, s,
30

N-CH₃), 4.03 (2H, s, CH₂), 7.44-7.54
(2H, m, two CH), 7.67 (1H, d, J = 7.6Hz, CH), 7.98
(1H, d, J = 8.3, CH), 8.29 (1H, s, CH); m/z 283
(M⁺).

5

EXAMPLE 15

2'-(1-Methyl-1H-indol-3-yl)spiro (3(R*), 4(R*)-1-
azabicyclo[2.2.1]heptane-3,5'(4'H)-oxazole)
10 dihydrochloride hydrate

a) 3(R*), 4(R*)-3-amino methyl-3-hydroxy-1-
azabicyclo[2.2.1]heptane borane complex

15 To a solution of 1-azabicyclo[2.2.1]heptan-3-one
(E.P. 0239309, Example 24) (3.15g,) in water (1.0ml)
was added, without cooling, hydrochloric acid (2N,
14ml.) followed by a solution of sodium cyanide
(1.40g,) in water (4.0ml). After stirring at room
20 temperature for 30 minutes the precipitate was
filtered and dried in vacuo to give the cyanohydrin
(3.15g). To a chilled suspension of this cyanohydrin
(3.15g,) in dry tetrahydrofuran (50ml) under nitrogen
was added borane tetrahydrofuran complex (1.0M in
25 tetrahydrofuran, 25ml,) dropwise. After stirring at
room temperature for 1 hour borane-tetrahydrofuran
complex (1.0M in tetrahydrofuran, 50 ml, 50mmol) was
added. After heating at reflux for 1.5 hours, the
reaction mixture was cooled and ethanol (50 ml) was
30 added. Evaporation to dryness and trituration with
ether gave a colourless crystalline solid (3.47g).
Recrystallisation from ethanol gave the title
compound, m.p. 130-132°C. Found: C, 53.58; H, 10.87;

N, 17.97; $C_7H_{14}N_2O \cdot BH_3$ requires C, 53.88; H, 10.98; N, 17.95%. δ_H (360MHz, DMSO- d_6), 1.56-1.66 (1H, m, CHH), 1.74-1.84 (1H, m, CHH), 1.0-2.0 (3H, bs, BH_3), 2.39 (1H, d, J = 4.4, CH), 2.59 (1H, d, J = 8.5) and 2.65 (2H, d, J = 8.7) and 2.68-2.76 (3H, m) and 2.77-2.86 (1H, m) and 3.10 (1H, d, J = 8.9, four of CH_2N), 4.87 (1H, bs, OH). m/z 155 ($M^+ - H$).

- 10 b) 2'-(1-Methyl-1H-indol-3-yl)spiro(3(R*), 4(R*)-1-azabicyclo[2.2.1]heptane-3,5'(4'H)-oxazole) dihydrochloride hydrate

Following the method of Example 11(c), 3(R*), 4(R*)-3-aminomethyl-3-hydroxy-1-azabicyclo[2.2.1]heptane borane complex (1.0g, 6.4mmol) was reacted with methyl (1-methyl-1H-indol-3-yl)imidate hydrochloride (1.2g, 5.3mmol), to give the title compound (1.25g) m.p. 258-260°C. Found: C, 54.97; H, 6.27; N, 11.30; Cl, 19.03; $C_{17}H_{19}N_3O \cdot 2HCl \cdot H_2O$ requires C, 54.85; H, 6.23; N, 11.29; Cl, 19.05%. δ_H (360MHz, D_2O) 1.94-2.04 (1H, m, CHH), 2.32-2.44 (1H, m, CHH), 3.34-3.44 (2H, m + d, J = 5.0Hz, CHHN + CH), 3.52-3.62 (2H, m + d, J = 10.1, 2 x CHHN + CHH), 3.75 (1H, d, J = 13.8, CHH), 3.91 (1H, d, J = 9.8, CHHN), 3.95 (3H, s, NCH_3), 4.14 (1H, d, J = 13.7, CHHN), 4.29 (1H, d, J = 12.9) and 4.47 (1H, d, J = 12.9, CH_2N), 7.43 (1H, dt, J = 7.5 and 1.5, CH), 7.49 (1H, dt, J = 7.2 and 1.2, CH), 7.66 (1H, d, J = 7.8, CH), 7.98 (1H, d, J = 7.2, CH) and 8.26 (1H, s, CH). m/z 281 (M^+).

EXAMPLE 16

2'-(1-Methyl-1H-indol-3-yl)spiro(3(S*), 4(R*)-1-azabicyclo[2.2.1]heptane-3,5'(4'H)-oxazole) 2.1 hydrochloride dihydrate

a) 3(S*), 4(R*)-3-aminomethyl-3-hydroxy-1-azabicyclo[2.2.1]heptane borane complex

10 To a chilled solution of 1-azabicyclo[2.2.1]heptan-3-one (E.P. 0239309, Example 24) (2.0g, 18mmol) in water was added hydrochloric acid (2N, 9ml, 18mmol) followed by sodium cyanide (0.88g, 18mmol) in water. The precipitated cyanohydrin was
15 filtered and dried in vacuo (1.04g). To a suspension of the cyanohydrin in tetrahydrofuran (40ml), under nitrogen was added borane (1.0M in tetrahydrofuran, 7.5ml,) with ice chilling, followed after 1 hour by additional borane (1.0M in tetrahydrofuran, 15ml, 15mmol). After 16 hours reflux the reaction mixture
20 was cooled, and ethanol (15ml) added. Evaporation to dryness, and crystallisation from ethanol gave the title compound (0.85g), m.p. 147-9°C. δ_H (360MHz, DMSO-d₆) 1.60 (3H, bs, BH₃), 1.66-1.76 (1H, m, CHH), 2.13-2.22 (1H, m, CHH), 2.40 (2H, dd, J = 11.4 and 3.4, CH₂), 2.53 (1H, d, J = 13.0) and
25 2.65 (1H, d, J = 13.3, CH₂), 2.61 (1H, dd, J = 9.8 and 3.4, CHHN), 2.76-2.86 (3H, m, CHHN and CH₂N), 2.86-2.96 (1H, m, CHHN), 4.85 (1H, bs, OH).

30 b) 2'-(1-Methyl-1H-indol-3-yl)spiro(3(S*), 4(R*)-1-azabicyclo[2.2.1]heptane-3,5'(4'H)-oxazole) 2.1 hydrochloride hydrate

Following the method of Example 11(c), 3(S*), 4(R*)-3-aminomethyl-3-hydroxy-1-azabicyclo[2.2.1]heptane borane complex (0.35g, 2.24mmol) was reacted with methyl (1-methyl-1H-indol-3-yl)imidate hydrochloride to give the title compound (0.47g), m.p. 215-7°C. Found: C, 51.51; H, 6.36; N, 10.59; Cl, 18.98; $C_{17}H_{19}N_3O \cdot 2.1HCl \cdot H_2O$ requires C, 51.83; H, 6.42; N, 10.67; Cl, 18.90%; δ_H (360MHz, D_2O) 2.20-2.32 (1H, m) and 2.54-2.64 (1H, m, CH_2), 3.34 (1H, d, $J = 4.0$, CH), 3.48-3.76 and 3.84-3.94 (6H, each m, three of CH_2N), 3.95 (3H, s, NCH_3), 4.17 (1H, d, $J = 12.8$) and 4.40 (1H, d, $J = 12.8$, CH_2N), 7.45 (1H, t, $J = 6.6$, CH), 7.49 (1H, t, $J = 5.9$, CH), 7.66 (1H, d, $J = 8.2$, CH), 7.98 (1H, d, $J = 7.1$, CH), 8.26 (1H, s, CH). m/z 281 (M^+).

EXAMPLE 17

2'-(1-Methyl-1H-indol-3-yl)spiro[1-azabicyclo[2.2.2]octane-3,5'-(4'H)-oxazole]1-methyl iodide hydrate

Methyl iodide (35 μ l.) was added to a solution of 2'-(1-methyl-1H-indol-3-yl) spiro[1-azabicyclo[2.2.2]octane-3,5'-(4'H)-oxazole], (0.15g,) in acetone, and stirred for 30 minutes at room temperature. Evaporation to dryness gave the title compound as a colourless solid (0.15g) m.p. 198-200°C (dec). Found: C, 49.99; H, 5.74; N, 9.07; $C_{19}H_{24}N_3OI \cdot H_2O$ requires C, 50.11; H, 5.75; N, 9.23%; δ_H (360MHz, D_2O), 2.02-2.26 (3H, m, $CHH + CH_2$), 2.40-2.46 (1H, m, CH), 2.46-2.58 (1H, m, CHH), 3.11 (3H, s, $N-CH_3$), 3.38-3.48 (1H, m, $CHHN$).

3.48-3.62 (1H, m, CHHN), 3.62-3.72 (2H, m, CH₂),
3.80 (1H, d, J = 14.5, CHHN), 3.89 (3H, s, NCH₃),
3.92 (1H, d, J = 14.5, CHH), 3.95 (1H, d, J = 14.4,
CHHN), 4.23 (1H, d, J = 14.6, CHHN), 7.36 (1H, t, J =
5 6.9, CH), 7.43 (1H, t, J = 6.8, CH), 7.60 (1H, d, J =
8.2, CH), 7.96 (1H, s, CH), 8.0 (1H, d, J = 7.9, CH).
m/z 310 (M⁺).

EXAMPLE 18

10

[2'-(Benzo[b]thiophen-3-yl)-]spiro(1-azabicyclo
[2.2.2]octane-3,5'(4'H)-oxazole) dihydrochloride
hydrate

15

a) Methyl(benzo[b]thiophen-3-yl)imidate
hydrochloride

20

Benzo[b]thiophen-3-carbonitrile (700mg) was
dissolved in dry methanol (25ml), and the resulting
solution cooled to 10°C under a dry nitrogen
atmosphere. Dry hydrogen chloride gas was passed
through the chilled solution for 40 minutes, and the
resulting red solution allowed to stand at room
temperature overnight. Removal of solvent under
25 reduced pressure and recrystallisation from
methanol/ether afforded the title compound as white
needles (810mg), m.p. 197-200°C. δ_H (360MHz,
DMSO-d₆) 4.35 (3H, s, OCH₃), 7.53 (2H, m, H-5,6),
8.19 (2H, m, H-4, 7) 8.41 (1H, s, H-2); m/z 191(M⁺,
30 70%) 160(100), 133(30), 89(40).

b) [2'-(Benzo[b]thiophen-3-yl)-]spiro(1-azabicycl
o[2.2.2]octane)-3,5'(4'H)-oxazole) hydrochloride

3-Aminomethyl-3-hydroxy-1-azabicyclo[2.2.2]octane (420mg) in dry methanol (50ml) was added to a solution of methyl (benzo[b]thiophen-3-yl)imidate hydrochloride (500mg) in dry methanol (50ml) stirring at room temperature under a dry nitrogen atmosphere. The mixture was heated at reflux overnight, cooled to room temperature and the solvent removed under reduced pressure. The residue was taken up in 2N hydrochloric acid (50ml), extracted with dichloromethane (6 x 50ml), basified to pH 12 (0.88M NH_4OH), extracted with dichloromethane (6 x 50ml), and the final organic extract dried (MgSO_4). Removal of solvent under reduced pressure and chromatography on silica gel (ether/hexane 1:4) afforded a colourless oil (400mg). Treatment with saturated ethereal hydrogen chloride and recrystallisation from methanol afforded the title compound as white needles (270mg), m.p. 167-70°C. Found: C, 49.62; H, 5.96; N, 6.80; $\text{C}_{17}\text{H}_{24.2}\text{N}_2\text{O}_{3.1}\text{Cl}_2\text{S}$ requires C, 49.90; H, 5.96; N, 6.84%; δ_{H} (360MHz, DMSO-d_6) 1.93 (3H, brm, $\text{CH}_2\text{CH}_2\text{N}$), 2.26 (1H, brm, $\text{CH}_2\text{CH}_2\text{N}$), 2.36 (1H, brm, $\text{CHCH}_2\text{CH}_2\text{N}$) 3.16-3.49 (2H, brm, $\text{CH}_2\text{CH}_2\text{N}$), 4.12 (2H, d, $J = 15.0\text{Hz}$, $\text{C} = \text{N} - \text{CH}_2$), 4.29 (2H, d, $J = 15.0\text{Hz}$, $\text{C} = \text{N} - \text{CH}_2$), 7.52 (2H, m, H-5,6), 8.12 (1H, dd, $J = 7.0, 1.0\text{Hz}$, H-4), 8.59 (1H, dd, $J = 7.0, 1.0\text{Hz}$, H-7), 8.91 (1H, s, H-2); m/z 298(M^+ , 25), 157(40), 139(30), 96(100), 82(60), 69(35).

EXAMPLE 19

2'-(1-Propyn-2-yl-1H-indol-3-yl)spiro[1-azabicyclo

[2.2.2]octane-3,5'(4'H)-oxazole] dihydrochloride
sesquihydrate

5 a) 2'-(1H-Indol-3-yl)spiro[1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole]-borane complex

To a solution of 3-aminomethyl-3-hydroxy-1-azabicyclo[2.2.2]octane-borane complex (10.0g,) in methanol (220ml) was added dropwise a solution of methyl (1H-indol-3-yl)imide hydrochloride (10.9g,) in methanol (1000ml). The reaction mixture was stirred at room temperature for 24 hours under nitrogen, then stirred at 50°C for a further 12 hours. The mixture was allowed to cool and basified with .88M ammonium hydroxide solution. The mixture was evaporated to dryness. The residue was purified by column chromatography on silica, eluting with dichloromethane/methanol 9:1, to give (14.2g), m.p. 262-264°C. δ_H (360MHz, DMSO- d_6) 1.1-1.7 (3H, s, BH_3), 1.69-1.75 (3H, m) and 2.04 (1H, s, two CH_2), 2.14-2.16 (1H, m, CH), 2.86-2.95 (2H, m) and 3.00-3.05 (2H, t, two $N-CH_2$), 3.08-3.11 (1H, d, J = 14.2) and 3.12-3.17 (1H, d, J = 14.2, $N-CH_2$), 3.80-3.84 (1H, d, J = 14.8) and 4.03-4.07 (1H, d, J = 14.7, CH_2), 7.18-7.25 (2H, m, two CH), 7.44 (1H, dd) and 7.9 (1H, d, two CH), 8.04 (1H, d, CH), 11.69 (1H, s, NH); m/z 281(M^+ free base, 20), 271(100%).

30 b) 2'(1-Propyn-2-yl-1H-indol-3-yl)spiro[1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole] dihydrochloride sesquihydrate

To a solution of the aforementioned borane

complex (0.5g.) in tetrahydrofuran (40ml) under nitrogen was added sodium hydride (0.09g.). After stirring at room temperature for 30 minutes propargyl bromide (0.16ml.) was added. After stirring at room temperature for 12 hours the mixture was evaporated to dryness. The residue was dissolved in methanol and treated with methanolic hydrogen chloride. After heating at 60°C for 24 hours the mixture was evaporated to dryness. The residue was dissolved in water and washed with dichloromethane. The aqueous solution was basified with .88M ammonium hydroxide solution. This solution was then extracted with dichloromethane (3 x 100ml). The organic extracts were dried (MgSO₄) and evaporated at reduced pressure. The residue was dissolved in methanol and treated with ethereal hydrogen chloride to give the title compound as a colourless crystalline solid (0.22g), m.p. 200-220°C. Found: C, 57.26; H, 6.21; N, 10.05; C₂₀H₂₁N₃O.2HCl.1.5H₂O requires C, 57.27; H, 6.21; N, 10.02%; δ_H (360MHz, D₂O) 2.09-2.28 (3H, m), 2.50-2.52 (1H, m, two CH₂), 2.74 (1H, m, CH), 2.97-2.99 (1H, t, CH), 3.38-3.46 (2H, m), 3.55-3.66 (2H, m, two N-CH₂), 3.83-3.87 (1H, dd), 4.09-4.13 (1H, d, N-CH₂), 4.19-4.23 (1H, d), 4.48-4.51 (1H, d, CH₂), 5.18-5.19 (2H, d, N-CH₂), 7.45-7.55 (2H, m, two CH), 7.76-7.78 (1H, dd), 7.94-7.97 (1H, dd, two CH) and 8.54 (1H, s, CH); m/z 319 (M⁺, 15), 225 (100).

30

EXAMPLE 20

2'-(1-Propen-2-yl-1H-indol-3-yl)spiro[1-azabicyclo [2.2.2]octane-3,5'-(4'H)-oxazole] dihydrochloride dihydrate

To a solution of 2'-(1H-indol-3-yl)spiro[1-azabicyclo[2.2.2]-octane-3,5'-(4'H)-oxazole] borane complex (0.5g,) in tetrahydrofuran (40ml) under nitrogen was added sodium hydride (55% suspension in oil, 0.09g,). After stirring at room temperature for 30 minutes, allyl bromide (0.24g,) was added. After stirring at room temperature for 24 hours the mixture was evaporated to dryness. The residue was dissolved in methanol and treated with methanolic hydrogen chloride. After heating at 60°C for 36 hours the mixture was evaporated to dryness. The residue was dissolved in water and washed with dichloromethane. The aqueous solution was basified with .88M ammonium hydroxide solution. This solution was extracted with dichloromethane (3 x 100ml). The organic extracts were dried (MgSO₄) and evaporated. The residue was purified by column chromatography on silica, eluting with dichloromethane/methanol 9:1. The product was dissolved in methanol and treated with ethereal hydrogen chloride, and evaporated. Recrystallisation from propan-2-ol gave the title compound as a white crystalline solid (0.2g), m.p. 215-217°C. Found: C, 55.70; H, 6.54; N, 9.67; C₂₀H₂₃N₃O.2HCl.2H₂O requires C, 55.87; H, 6.79; N, 9.76%; δ_H (360MHz, D₂O) 2.00-2.30 (3H, m), 2.46-2.54 (1H, m, two CH₂), 2.63 (1H, s, CH), 3.38-3.44 (2H, m), 3.54-3.62 (2H, m, two CH₂), 3.75-3.79 (1H, d), 4.00-4.04 (1H, d, CH₂), 4.10-4.14 (1H, d, J = 13), 4.39-4.43 (1H, d, J = 13, CH₂), 4.95-4.96 (2H, d, CH₂), 5.04-5.09 (1H, d), 5.26-5.29 (1H, d, CH₂), 6.00-6.18 (1H, m, CH), 7.42-7.46 (2H, m, two CH), 7.64-7.66 (1H, d), 7.97-7.99 (1H, d, two CH) and 8.31 (1H, s, CH); m/z 329 (M⁺, 10%), 96 (100).

EXAMPLE 21

5 [2'-(5-Amino-1-methyl-1H-indol-3-yl)-]spiro(1-
azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole)
hydrochloride

10 a) [2'-(5-Amino-1-methyl-1H-indol-3-yl)-]spiro(1-
azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole)-borane
complex

15 [2'-(5-Nitro-1-methyl-1H-indol-3-yl)-]spiro(1-
azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole) borane
complex (500mg) was suspended in ethyl acetate (50ml)
and hydrogenated over 10% Pd/C (50mg) for six hours
at atmospheric pressure. The catalyst was filtered
and the solvent removed under reduced pressure. The
residue was chromatographed on silica gel using
dichloromethane/ammonium hydroxide 90/10/1 as eluant
to afford the title compound (140mg), m.p. 225-230°C;
20 δ_H (360MHz, $CDCl_3$) 1.81 (3H, brm, $\underline{CH_2CH_2N}$),
2.14 (1H, brm, $\underline{CHCH_2CH_2N}$), 2.29 (1H, brm,
 $\underline{CH_2CH_2N}$), 2.95-3.2 (6H, brm, $\underline{CH_2CH_2N}$), 3.76
(3H, s, N- $\underline{CH_3}$), 3.81 (1H, d, J = 14.4Hz,
C=N- $\underline{CH_2}$), 4.16 (1H, d, J = 14.4Hz, C=N- $\underline{CH_2}$), 6.73
25 (1H, dd, J = 10.8Hz, H-6), 7.13 (1H, d, J = 10.8Hz,
H-7), 7.41 (1H, d, J = 1.0Hz, H-4), 7.50 (1H, s,
H-2); m/z 325 (M^+ , 10), 311 (25), 185 (40), 93
(100), 75 (40).

30 b) [2'-(5-Amino-1-methyl-1H-indol-3-yl)-]spiro
(1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole)
trihydrochloride hydrate

2'-(5-Amino-1-methyl-1H-indole-3-yl) spiro(1-azabicyclo[2.2.2]octane-3,5'-(4'H)-oxazole) borane complex (140mg) was dissolved in methanol (50ml) previously saturated with hydrogen chloride gas. The resulting solution was heated at reflux for one hour, cooled to room temperature and the solvent removed. The residue was recrystallised from isopropanol to give the title compound (140mg), m.p. 260°C (dec); Found: C, 48.30; H, 6.26; N, 12.36;

$C_{18}H_{28}N_4O_{2.5}Cl_3$ requires C, 48.38; H, 6.31; N, 12.54%; δ_H (360MHz, D_2O) 2.17 (3H, bm, $\underline{CH_2CH_2N}$), 2.50 (1H, bm, $\underline{CH_2CH_2N}$), 2.73 (1H, bm, $\underline{CHCH_2CH_2N}$), 3.45 (2H, bt, $J = 9.5Hz$, $\underline{CH_2CH_2N}$), 3.64 (2H, bt, $J = 9.5Hz$, $\underline{CH_2CH_2N}$), 3.85 (1H, d, $J = 12.0Hz$, $\underline{CH_2CH_2N}$), 3.98 (3H, s, $\underline{N-CH_3}$), 4. (1H, d, $J = 12.0Hz$, $\underline{CH_2CH_2N}$), 4.20 (1H, d, $J = 10.0Hz$, $\underline{C=N-CH_2}$), 4.50 (1H, d, $J = 10.0Hz$, $\underline{C=N-CH_2}$), 7.40 (1H, dd, $J = 11.0, 1.0Hz$, H-6), 7.75 (1H, d, $J = 11.0Hz$, H-7), 7.90 (1H, d, $J = 1.0Hz$, H-4), 8.41 (1H, s, H-2); m/z 310 (M^+ , 100) 171 (30), 139 (50), 111 (10), 96 (80), 82 (35), 69 (20).

EXAMPLE 22

[2'-(2-Iodo-1-methyl-1H-indol-3-yl)-]spiro(1-azabicyclo[2.2.2]octane-3,5'-(4'H)-oxazole) dihydrochloride

t-Butyllithium (2ml of a 1.7M soln in hexane) was added dropwise to a stirred solution of [2'-(1-methyl-1H-indol-3-yl)-]spiro(1-azabicyclo[2.2.2]octane-3,5'-(4'H)-oxazole) (0.5g, 1.7mmol) in

tetrahydrofuran (20ml) at -78°C under a nitrogen atmosphere. After stirring for 1hr at -78°C a solution of iodine (0.5g in 10ml THF) was added dropwise until the colour persisted. The mixture was then allowed to warm to room temperature, diluted with water (100ml), extracted with chloroform (2 x 100ml), and dried (Na_2SO_4). The solvent was removed at reduced pressure to afford an off-white solid (0.6g). This was further purified by treatment with a solution of hydrogen chloride in methanol (excess) and evaporation. Recrystallisation from methanol afforded a white crystalline solid (0.5g); m.p. 188°C (dec). Found: C, 40.77; H, 4.94; N, 7.92; $\text{C}_{18}\text{H}_{20}\text{N}_3\text{OI}$ requires C, 40.50; H, 5.17; N, 7.72%; δ_{H} (360MHz, D_2O) 2.1-2.3 (3H, m, CH_2CHH), 2.6 (1H, m, CHH), 2.76 (1H, m, CH), 3.46-3.72 (4H, m, 2 x CH_2N), 3.84 (3H, s, NMe), 3.93 (1H, d, $J = 12\text{Hz}$, CHHN), 4.12 (1H, a, $J = 12\text{Hz}$, CHHN) 4.25 (1H, d, $J = 13\text{Hz}$, CHHN), 4.52 (1H, d, $J = 13\text{Hz}$, CHHN), 7.4-7.47 (2H, m, H-5, H-6), 7.61 (1H, d, $J = 7\text{Hz}$, H-7), 7.81 (1H, d, $J = 7\text{Hz}$, H-4); m/z (M^+ , free base, 30%), 295(20), 139(75), 96(100).

EXAMPLE 23

[2'-(1H-Indazole-3-yl)]-spiro(1-azabicyclo[2.2.2]octane-3,5'-(4'H)-oxazole) hydrochloride

Anhydrous hydrogen chloride was passed through a solution of indazole-3-carbonitrile (2.3g) in anhydrous methanol (50ml) for one hour. The solvent was then removed under reduced pressure and the residue redissolved in anhydrous methanol (50ml). A

solution of 3-aminomethyl-3-hydroxy-1-azabicyclo
 [2.2.2]octane (3.51g) in anhydrous methanol (50ml)
 was added over a period of one hour. The solution
 was then heated at reflux for 18 hours, cooled to
 5 room temperature and evaporated to dryness. The
 residue was taken up in 2N hydrochloric acid (100ml),
 extracted with dichloromethane (4 x 100ml), basified
 to pH 12 with 0.88 ammonium hydroxide solution, and
 extracted with dichloromethane (6 x 100ml). The
 10 final organic extracts were washed with ether (100ml)
 dried (MgSO_4) and the solvent removed to give a
 white solid. Treatment with excess ethereal hydrogen
 chloride and recrystallisation from ethanol gave the
 title compound (950mg), m.p. 187-189°C. Found: C,
 15 52.73; H, 6.04; N, 14.86; $\text{C}_{16}\text{H}_{20}\text{N}_4\text{OCl}_2 \cdot$
 $2\frac{1}{2}\text{H}_2\text{O}$. requires C, 52.72; H, 6.16; N, 14.63%;
 δ_{H} (360MHz, DMSO) 1.95 (3H, bm, $\text{CH}_2\text{CH}_2\text{N}$),
 2.36 (1H, bm, $\text{CH}_2\text{CH}_2\text{N}$), 2.54 (1H, bm,
 $\text{CHCH}_2\text{CH}_2\text{N}$), 3.24 (3H, bm, $\text{CH}_2\text{CH}_2\text{N}$), 3.41 (3H,
 20 bm, $\text{CH}_2\text{CH}_2\text{N}$), 4.22 (1H, d, $J = 14.4\text{Hz}$,
 $\text{C}=\text{N}-\text{CH}_2$), 4.39 (1H, d, $J = 14.4\text{Hz}$, $\text{C}=\text{N}-\text{CH}_2$),
 7.40 (1H, d, $J = 7.2\text{Hz}$, H-6), 7.52 (1H, t, $J = 7.2\text{Hz}$,
 H-5), 7.71 (1H, d, $J = 7.2\text{Hz}$, H-6), 8.15 (1H, d, $J =$
 7.2Hz , H-7), 8.85 (1H, bs, H-1); m/z 282 (M^+ , 40),
 25 145 (20), 121 (15), 108 (10), 97 (80), 96 (100), 82
 (50), 69 (30).

EXAMPLE 24

30 2'-(1-Ethyl-1H-indol-3-yl)-spiro[1-azabicyclo
[2.2.2]octane- 3,5'(4'H)-oxazole] dihydrochloride
dihydrate

To a solution of 2'-(1H-indol-3-yl)spiro[1-azabicyclo[2.2.2]-octane-3,5'-(4'H)-oxazole] borane complex (1.0g, 3.4mmol) in tetrahydrofuran (40ml) under nitrogen was added sodium hydride (55% suspension in oil, 0.18g,). After stirring at room temperature for 45 minutes, ethyl iodide (0.64g,) was added. After stirring at room temperature for 8 hours the mixture was evaporated to dryness. The residue was dissolved in methanol and treated with methanolic hydrogen chloride. After heating at 60°C for 3 hours the mixture was evaporated. The residue was dissolved in water and washed with dichloromethane. The aqueous solution was basified with .88M ammonium hydroxide. This solution was then extracted with dichloromethane (3 x 100ml). The organic extracts were dried (MgSO₄) and evaporated. The residue was dissolved in methanol and treated with ethereal hydrogen chloride and ether to give a brown solid. The solid was dissolved in the minimum of hot propan-2-ol and stirred with charcoal. The solution was filtered and allowed to cool to give the title compound as a cream crystalline solid (0.24g), m.p. 194-196°C; δ_H (360MHz, D₂O) 1.51-1.55 (3H, t, J = 7.3, CH₃), 2.08-2.27 (3H, m), 2.78 (1H, s, two CH₂), 2.53 (1H, m, CH), 3.44-3.46 (2H, t), 3.61-3.66 (2H, m, two CH₂), 3.86-3.90 (1H, d, J = 15.1Hz), 4.12-4.16 (1H, d, J = 15.1Hz, CH₂), 4.21-4.25 (1H, d, J = 11.9Hz), 4.50-4.53 (1H, d, J = 11.9Hz, CH₂), 4.36-4.42 (2H, q, J = 7.3Hz, CH₂); m/z 309 (M⁺).

EXAMPLE 25

a) 2'-(5-Nitro-1-methyl-1H-indol-3-yl)-]spiro(1-azabicyclo[2.2.2]octane-3,5'-(4'H)-oxazole)-borane complex

5

2'-(5-Nitro-1H-indol-3-yl)-]spiro(1-azabicyclo
[2.2.2]octane-3,5'-(4'H)-oxazole) borane complex (3g)
was suspended in dry tetrahydrofuran (80ml) under a
dry nitrogen atmosphere. Sodium hydride (211mg of
10 55% dispersion in oil) was added and the solution
stirred until the evolution of hydrogen ceased.
Methyl iodide (1.25g) was added dropwise over a
period of ten minutes, and the resulting mixture
stirred for four hours at room temperature. The
15 bright yellow precipitate was filtered and
recrystallised from absolute ethanol to afford the
title compound (2.7g), m.p. 195-200°C; δ_H
(360MHz, DMSO- d_6) 1.76 (4H, brm, $\underline{CH_2CH_2N}$), 2.07
(1H, brm, $\underline{CHCH_2CH_2N}$), 2.9-3.1 (4H, brm
20 $\underline{CH_2CH_2}$), 3.6 (2H, brm, $\underline{CH_2CH_2N}$), 3.89 (1H, d,
J = 15.4Hz, $\underline{CH_2-C-O}$), 3.92 (3H, s, N-CH₃), 4.10
(1H, d, J = 15.4Hz, $\underline{CH_2-C-O}$), 7.76 (1H, d, J =
11.6Hz, H-7), 8.14 (1H, dd, J = 11.6, 1.0Hz, H-6),
8.21 (1H, s, H-2), 8.96 (1H, d, J = 1.0Hz, H-4); m/z
25 (M^+ , 80% free base), 340 (80), 310 (30), 250 (15),
191 (30), 154 (95), 132 (20), 96 (100), 82 (40).

b) 2-(5-Nitro-1-methyl-1H-indol-3-yl)-]spiro(1-azabicyclo[2.2.2]octane-3,5'-(4'H)-oxazole)
30 tetrahydrochloride

2'-(5-Nitro-1-methyl-1H-indol-3-yl)-]spiro(1-azabicyclo[2.2.2]octane-3,5'-(4'H)-oxazole) borane

complex (250mg) was suspended in absolute methanol saturated with HCl gas with vigorous stirring. The solution was warmed to 55°C for three hours, cooled to room temperature and the solvent removed under reduced pressure. The residue was recrystallised from absolute ethanol to give the title compound (100mg), m.p. 245-250°C. Found: C, 44.76; H, 5.16; N, 11.54; $C_{18}H_{24}N_4O_3Cl_4$ requires C, 44.46; H, 4.98; N, 11.52%; δ_H (360MHz, D_2O) 2.10 (3H, brm, $\underline{CH_2CH_2N}$), 2.51 (1H, brm, $\underline{CH_2CH_2N}$), 2.75 (1H, brm, $\underline{CHCH_2CH_2N}$), 3.46 (2H, brm, $\underline{CH_2CH_2N}$), 3.64 (2H, brm, $\underline{CH_2CH_2N}$), 3.85 (2H, d, $J = 14.4Hz$, $R_2C\underline{CH_2N}$), 3.97 (3H, s, $N-CH_3$), 4.12 (2H, d, $J = 14.4Hz$, $R_2C-\underline{CH_2}-N$), 4.23 (2H, d, $J = 10.8Hz$, $C=N-\underline{CH_2}$), 4.78 (2H, d, $J = 10.8Hz$, $C=N-\underline{CH_2}$), 7.63 (1H, d, $J = 7.2Hz$, H-7), 8.16 (1H, dd, $J = 7.2, 1.0Hz$, H-6), 8.44 (1H, s, H-2), 8.6 (1H, d, $J = 1.0Hz$, H-4); m/z (M^+ , 50%, free base) 340 (50), 310 (10), 203 (10), 157 (15), 139 (50), 96 (100), 82 (45).

EXAMPLE 26

[2'-(5-Methoxy-1-methyl-1H-indole-3-yl)-]spiro(1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole)
trihydrochloride

a) 5-Methoxy-1H-indole-3-carboxylate

Trifluoroacetic anhydride (15ml) was added to a chilled (0°C) solution of 5-methoxy-1H-indole (10g) in dry dimethylformamide (200ml) under a dry N_2 atmosphere. The solution was allowed to warm to room

temperature overnight, poured into water (500ml), and the pink solid was filtered. This was re-suspended in water (300ml), sodium hydroxide (30g) was added and the solution heated at reflux for three hours.

- 5 The solution was then cooled to 10°C, neutralised to pH2 with conc HCl, solid isolated by filtration and dried in vacuo to afford the title compound (4.4g), m.p. 215-220°C; δ_H (360 MHz, DMSO- d_6) 3.78 (3H, s, OCH_3), 6.81 (1H, dd, J = 5.0, 1.0Hz, H-6), 7.35 (1H, d, J = 5.0Hz, H-7), 7.49 (1H, d, J = 1.0Hz, H-4), 7.93 (1H, s, H-2); m/z 191 (M^+ , 70), 147 (80), 104 (100), 77 (40).

b) 5-Methoxy-1H-indole-3-carboxamide

15

Oxalyl chloride (3.0g) was added dropwise to a stirred solution of 5-methoxy-1H-indole-3-carboxylate (4.4g) in tetrahydrofuran under a dry N_2 atmosphere. The solution was stirred at room temperature overnight, the solvent removed under reduced pressure, and the residue redissolved in dry 1,2-dichloroethane. Anhydrous ammonia was passed through the solution for 1.5 hours, and the solution stirred for a further three hours at room

25

temperature. The solution was then filtered to afford the title compound as a pale red powder (6.1g), m.p. 260°C (dec); δ_H (360MHz, DMSO- d_6) 3.76 (3H, s, OCH_3), 6.75 (1H, dd, J = 6.5, 1.0Hz, H-6), 7.30 (1H, d, J = 6.5Hz, H-7), 7.49 (1H, d, J = 1.0Hz, H-4), 8.15 (1H, s, H-2) m/z 190 (M^+ , 100), 147(30), 91(55).

30

c) 5-Methoxy-1H-indole-3-carbonitrile

5-Methoxy-1H-indole-3-carboxamide (6.1g) was treated with refluxing POCl_3 (65ml) for ten minutes. Excess POCl_3 was removed under high vacuum (0.1mmHg) and the residue quenched with water/0.88 NH_4OH 1:1 (100ml). The resulting solution was extracted with CHCl_3 (4 x 100ml), treated with charcoal (10g), dried (MgSO_4), filtered and the solvent removed to afford a brown solid. Recrystallisation from hexane afforded the title compound as pale brown needles (3.3g), m.p. 147°C ; δ_{H} (360MHz, CDCl_3) 3.86 (3H, s, OCH_3), 6.90 (1H, dd, $J = 7.5, 1.0\text{Hz}$, H-6), 7.13 (1H, d, $J = 1.0\text{Hz}$, H-4), 7.36 (1H, d, $J = 7.5\text{Hz}$, H-7), 7.67 (1H, s, H-2).

d) 5-Methoxy-1-methyl-1H-indole-3-carbonitrile

A solution of 5-methoxy-1H-indole-3-carbonitrile (550mg) in dry tetrahydrofuran (50ml) was treated with NaH (152mg of a 55% dispersion in oil). The solution was stirred under a dry nitrogen atmosphere until the evolution of hydrogen ceased. Methyl iodide (0.45mg) was then added and the reaction allowed to stir at room temperature for one hour. The solvent was then removed under reduced pressure and the residue taken up in dichloromethane (50ml), washed with water (2 x 25ml), dried (MgSO_4), filtered, and evaporated to dryness under reduced pressure. The residue was recrystallised from absolute ethanol to afford the title compound as white prisms (480mg); m.p. $105-108^\circ\text{C}$; δ_{H} (360MHz, CDCl_3) 3.84 (3H, s, OCH_3), 3.87 (3H, s, NCH_3), 6.98 (1H, dd, $J = 7.5, 1.0\text{Hz}$, H-6), 7.12 (1H, d, $J =$

1.0Hz, H-4), 7.31 (1H, d, J = 7.5Hz, H-7), 7.61 (1H, s, H-2); m/z 186 (M^+ 100), 171 (90), 143 (80), 116 (20), 101 (15), 89 (15).

5 e) Methyl(5-methoxy-1-methyl-1H-indol-3-yl)imide hydrochloride

Anhydrous hydrogen chloride gas was passed through a solution of 5-methoxy-1-methyl-1H-indole-3-carbonitrile (100mg) in dry methanol (50ml) for 1.5 hours. The solution was cooled to 0°C and filtered to afford the title compound as pink needles (260mg), m.p. 220°C (dec); δ_H (360MHz, $CDCl_3$) 3.79 (3H, s, NCH_3), 3.89 (6H, s, 2 x OCH_3), 6.93 (1H, dd, J = 7.5, 1.0Hz, H-6), 7.22 (1H, d, J = 7.5Hz, H-7), 7.65 (1H, d, J = 1.0Hz, H-4), 7.70 (1H, s, H-2); m/z 219 (M^+ 100), 188 (60), 145 (20), 117 (10).

20 f) [2'-(5-Methoxy-1-methyl-1H-indol-3-yl)-]spiro (1-azabicyclo[2.2.2]octane-3,5'-(4'H)-oxazole borane complex

3-Aminomethyl-3-hydroxy-1-azabicyclo[2.2.2]octane borane complex (262mg) in dry methanol (50ml) was added over thirty minutes to a stirred solution of methyl (5-methoxy-1-methyl-1H-indol-3-yl)imide hydrochloride (260mg) in dry methanol (100ml) under a dry nitrogen atmosphere. The mixture was warmed at reflux for six hours, cooled to room temperature, solvent removed under reduced pressure, and the residue chromatographed on silica gel using 4% methanol/dichloromethane to afford the title compound as a white solid (260mg), m.p. 198°C; δ_H

(CDCl₃) 1.77 (3H, brm, $\text{CH}_2\text{CH}_2\text{N}$), 2.15 (1H, brm, $\text{CHCH}_2\text{CH}_2\text{N}$), 2.26 (1H, brm, $\text{CH}_2\text{CH}_2\text{N}$), 2.98 (2H, brm, $\text{CH}_2\text{CH}_2\text{N}$), 3.08 (1H, d, J = 14.0Hz, $\text{CH-C-CH}_2\text{N}$), 3.13 (2H, brm, $\text{CH}_2\text{CH}_2\text{N}$), 3.39 (1H, d, J = 14.0Hz, $\text{CH-C-CH}_2\text{N}$), 3.81 (3H, s, OCH_3), 3.85 (1H, d, J = 13.5Hz, C=N-CH_2), 3.89 (3H, s, NCH_3), 4.17 (1H, d, J = 13.5Hz, C=N-CH_2), 6.95 (1H, dd, J = 7.0, 1.0Hz, H-6), 7.24 (1H, d, J = 7.0Hz, H-7), 7.55 (1H, s, H-2), 7.61 (1H, d, J = 1.0Hz, H-4); m/z (M^+ free base, 25%); 325 (20), 205 (30), 139 (15), 83 (100).

g) [2'-(5-Methoxy-1-methyl-1H-indol-3-yl)-]spiro(1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole)
15 trihydrochloride

[2'-(5-Methoxy-1-methyl-1H-indol-3-yl)-]spiro(1-azabicyclo[2.2.2]octane-3',5'(4'H)-oxazole) borane complex (260mg) was dissolved in methanol (50ml) previously saturated with HCl gas. The solution was warmed to 55°C for four hours, cooled to room temperature and the solvent removed under reduced pressure. The residue was recrystallised from dry ethanol to afford the title compound as white needles
20 (210mg), m.p. 210-214°C. Found C, 49.67; H, 6.46; N, 9.39; C₁₉H₂₆N₃O₂Cl₃·2.5H₂O requires C, 49.46; H, 6.22; N, 9.12%; δ_{H} (360MHz, D₂O) 2.09 (4H, brm, $\text{CHCH}_2\text{CH}_2\text{N}$), 2.71 (1H, brm, $\text{CHCH}_2\text{CH}_2\text{N}$), 3.58 (4H, brm, $\text{CH}_2\text{CH}_2\text{N}$), 3.87 (1H, d, J = 11.0Hz, $\text{CH-C-CH}_2\text{N}$), 3.91 (6H, s, OCH_3 , NCH_3), 4.06 (1H, d, J = 11.0Hz, $\text{CH-C-CH}_2\text{N}$), 4.15 (1H, d, J = 13.0Hz, C=N-CH_2), 4.45 (1H, d, J = 13.0Hz, C=N-CH_2), 7.14 (1H, dd, J

= 7.0, 1.0Hz, H-6), 7.35 (1H, d, J = 1.0Hz, H-4),
7.56 (1H, d, J = 7.0Hz, H-7), 8.26 (1H, s, H-2); m/z
325 (M^+ , 40), 188 (30), 139 (40), 96 (100).

5

EXAMPLE 27

[2'-(5-Hydroxy-1-methyl-1H-indol-3-yl)]spiro
(1-azabicyclo[2.2.2]octane-1H-3,5'(4'H)-oxazole)
hydrochloride

10

a) [2'-(5-Methoxy-1-methyl-1H-indol-3-yl)]spiro
(1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole)

15

[2'-(5-Methoxy-1-methyl-1H-indol-3-yl)]spiro
(1-azabicyclo [2.2.2]octane)-3,5'(4'H)-oxazole
borane complex (1.9g) was dissolved in methanol
(100ml) previously saturated with hydrogen chloride
gas. The solution was warmed to 55°C for three
hours, cooled to room temperature, and the residue
taken up in water (50ml). The aqueous solution was
basified with 0.88 NH_4OH to pH 11, extracted with
dichloromethane (4x50ml), and dried ($MgSO_4$); the
solvent was then removed under reduced pressure.

20

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30

Purification by chromatography on silica gel using
dichloromethane/methanol (99:1) as eluant afforded
the title compound as a colourless oil (1.1g); δ_H
(360MHz, $CDCl_3$) 1.54 (1H brm, CH_2CH_2N), 1.60
(2H brm, CH_2CH_2N) 1.68 (1H, brm, $CHCH_2CH_2N$),
2.21 (1H, brm, CH_2CH_2N) 2.84 (2H, brm,
 CH_2CH_2N), 2.84 (1H, d, J = 10.8Hz $CH-C-CH_2N$),
3.1 (2H, brm, CH_2CH_2N), 3.3 (1H, d, J = 10.8Hz
 $CH-C-CH_2N$) 3.70 (1H, d, J = 14.5Hz $C = N CH_2$),
3.79 (3H, s, OCH_3), 3.89 (3H, s, NCH_3) 4.17 (1H,

d, $J = 14.5\text{Hz}$ C = N CH_2), 6.92 (1H, dd, $J = 10$, 10Hz, H-6), 7.21 (1H, d, $J = 10\text{Hz}$, H-7), 7.57 (1H, s, H-2), 7.66 (1H, d, $J = 10\text{Hz}$ H-4); m/z 325 (M^+ , 60%), 188(25), 139(60), 96(100), 82(50).

5

b) [2'-(5-Hydroxy-1-methyl-1H-indol-3-yl)-]spiro(1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole)
10 trihydrochloride hydrate

[2'-(5-Methoxy-1-methyl-1H-indol-3-yl)-]spiro
(1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole) (160mg)
was dissolved in dry dichloromethane (50ml) and
cooled to -78°C under a dry nitrogen atmosphere.
15 Boron tribromide (0.63g) was added and the resulting
solution allowed to warm to room temperature over
three hours. The reaction was then quenched with
crushed ice (10g), basified to pH 7.5 with 0.88
20 NH_4OH , extracted with dichloromethane (2x100ml) and
the organic extracts dried (MgSO_4). Filtration and
removal of solvent under reduced pressure afforded a
yellow gum. Treatment with excess ethereal hydrogen
chloride, filtration and recrystallisation of the
25 recovered solid afforded the title compound as white
needles (120mg); m.p. $215-220^\circ\text{C}$ (dec). Found: C,
50.99; H, 6.06; N, 9.50; $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_2 \cdot 3\text{HCl}$
 $0.3\text{H}_2\text{O}$ requires C, 50.73; H, 5.81; N, 9.86 δH
(360MHz, D_2O) 2.21 (3H, brm, $\text{CH}_2\text{CH}_2\text{N}$), 2.48
30 (1H, brm, $\text{CH}_2\text{CH}_2\text{N}$), 2.72 (brm $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$)
3.45 (2H, brm, $\text{CH}_2\text{CH}_2\text{N}$), 3.65 (2H, brm,
 $\text{CH}_2\text{CH}_2\text{N}$), 3.84 (1H, $J = 14.0\text{Hz}$, $\text{CH}-\text{C}-\text{CH}_2\text{N}$),
3.90 (3H, s, NCH_3), 4.10 (1H, d, $J = 14.0\text{Hz}$,

CH-C-CH₂N) 4.18 (1H, d, J = 14.5Hz, C = N-CH₂),
 4.45 (1H, d, J = 14.5Hz, C = N-CH₂) 7.02 (1H, dd, J
 = 10, 10Hz, H-6), 7.29 (1H, d, J = 10Hz H-4), 7.50
 (1H, d, J = 10Hz, H-7), 8.24 (1H, s, H-2); m/z
 5 311(M⁺, free base, 40%), 174(20), 156(25), 139(40),
 96(100), 82(60).

EXAMPLE 28

10 [2'-(1,5-Dimethyl-1H-indol-3-yl)-]spiro(1-
azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole) 2.1
hydrochloride hydrate

15 a) Methyl (1,5-Dimethyl-1H-indol-3-yl) imidate
hydrochloride

Dry hydrogen chloride gas was bubbled through a
 water cooled solution of 1,5-dimethyl-1H-indole-3-
 nitrile (0.3g, 1.8mmol) in methanol (30ml) until the
 20 solution was saturated. After standing for 3 days,
 evaporation to dryness and trituration with ether,
 the title compound was obtained as colourless
 crystals (0.38g); m.p. 128-130°C; δ_H (360MHz,
 DMSO-d₆), 2.45 (3H, s, CH₃), 3.91 (3H, s,
 25 N-CH₃), 4.30 (3H, s, OCH₃), 7.21 (1H, d, J = 8.4,
 CH), 7.55 (1H, d, J = 8.4, CH), 7.74 (1H, s, CH),
 8.76 (1H, s, CH), 10.28 (1H, s, NH), 11.16 (1H, s,
 NH); m/z 202 M⁺.

30 b) [2'-(1,5-Dimethyl-1H-indol-3-yl)-]spiro(1-
azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole) 2.1
hydrochloride hydrate

A solution of methyl (1,5-dimethyl-1H-indole-3-yl) imidate hydrochloride (0.37g, 1.55mmol) in methanol (30ml) was added to a solution of 3-aminomethyl-3-hydroxy-1-azabicyclo[2.2.2]octane borane complex (0.29g, 1.70mmol) in methanol (15ml). After heating at reflux for 24 hours, methanolic hydrogen chloride (30ml) was added and the reaction mixture was heated under reflux for 3 hours. After evaporation the residue was dissolved in water and washed with dichloromethane. The aqueous phase was basified with ammonium hydroxide and extracted with dichloromethane (3x100ml). The combined extracts were washed (H₂O), dried (MgSO₄) and solvents evaporated. The residue was dissolved in ethanol and treated with ethereal hydrogen chloride to give the title compound (0.35g) m.p. 242-3°C. Found: C, 56.47; H, 6.68; N, 10.35; Cl, 18.53; C₁₉H₂₃N₃O.2.1HCl.H₂O requires C, 56.49; H, 6.76; N, 10.40; Cl, 18.53%; δ_H (360MHz, D₂O) 2.02-2.32 (3H, m, 1 of CH₂ and CH₂), 2.44-2.58 (4H, m, CHH and CH₃), 2.72-2.78 (1H, m, CH), 3.42-3.52 (2H, m, CH₂), 3.56-3.74 (2H, m, CH₂), 3.87 (1H, d, J = 15.1, CHHN), 3.94 (3H, s, NCH₃), 4.11 (1H, d, J = 15.1, CHHN), 4.21 (1H, d, J = 12, CHHN), 4.50 (1H, d, J = 12, CHHN), 7.36 (1H, d, J = 8.4, CH), 7.57 (1H, d, J = 8.5, CH), 7.68 (1H, s, CH), 8.35 (1H, s, CH); m/z 309 M⁺.

EXAMPLE 29

[2'-(1,7-Dimethyl-1H-indol-3-yl)-]spiro(1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole) 2.1 hydrochloride 1.5 hydrate

a) Methyl (1,7-dimethyl-1H-indol-3-yl) imidate hydrochloride

Following the method of 28a 1,7-dimethyl-1H-indole-3-nitrile (0.75g, 4.4mmol) was reacted to give the title compound (0.76g), m.p. 205-7°C; δ_H (360MHz, DMSO- d_6), 2.76 (3H, s, CH_3), 4.17 (3H, s, NCH_3), 4.27 (3H, s, OCH_3), 7.07 (1H, d, J = 7.2, CH), 7.17 (1H, t, J = 7.5, CH), 7.77 (1H, d, J = 8.1, CH), 8.66 (1H, s, CH); m/z 202 M^+ .

b) [2'(1,7-Dimethyl-1H-indol-3-yl)-]spiro(1-azabicyclo[2.2.2]octane-3,5'(4'H) oxazole 2.1) hydrochloride 1.5 hydrate

Following the method of 28b methyl (1,7-dimethyl-1H-indole-3-yl) imidate hydrochloride (0.24g, 1.0mmol) and 3-aminomethyl-3-hydroxy-1-azabicyclo[2.2.2]octane borane complex (0.19g, 1.1mmol) were reacted to give the title compound (0.18g), m.p. 204-6°C. Found: C, 55.33; H, 6.81; N, 10.20; CL 17.88; $C_{19}H_{23}N_3O \cdot 2.1 HCl \cdot 1.5 H_2O$ requires C, 55.26; H, 6.86; N, 10.17; Cl, 18.03; δ_H (360MHz, D_2O) 1.98-2.28 (3H, m, CHH and CH_2), 2.44-2.54 (1H, m, CHH), 2.66-2.72 (1H, m, CH), 2.78 (3H, s, CH_3), 3.38-3.46 (2H, m, CH_2N), 3.52-3.68 (2H, m, CH_2N), 3.81 (1H, d, J = 15, $CHHN$), 4.06 (1H, d, J = 15, $CHHN$), 4.15 (1H, d, J = 12.4, $CHHN$), 4.18 (3H, s, NCH_3), 4.43 (1H, d, J = 12.4, $CHHN$), 7.19 (1H, d, J = 7.3, CH), 7.29 (1H, t, J = 7.8, CH), 7.76 (1H, d, J = 7.9, CH), 8.22 (1H, s, CH); m/z 309 (M^+ , free base).

EXAMPLE 30

[2'-(1-Methyl-1H-indol-3-yl)-]spiro(8-azabicyclo
[3.2.1]octane-3,5'-(4'H)oxazole) dihydrochloride
5 hydrate

[8-Benzyl-2'-(1-methyl-1H-indol-3-yl)-]spiro(8-
azabicyclo[3.2.1]octane-3,5'-(4'H)oxazole)
dihydrochloride dihydrate (0.095g, 0.2mmol) in
10 methanol was shaken with 10% palladium on carbon
under hydrogen at 45 psi for 6 hours. The catalyst
was filtered and methanol evaporated. The residue
was crystallised from methanol/ether to give the
title compound (0.035g) m.p. 196-8°C; δ_H (360MHz,
15 D_2O), 2.16-2.30 (4H, m, two of CH_2), 2.60 (2H, d,
 $J = 12.5$, CH_2), 2.68 (2H, dd, $J = 15.1$, 3.3,
 CH_2), 3.95 (1H, s, NCH_3), 4.34-4.40 (4H, m, 2x CH
and CH_2N), 7.44 (1H, dt, $J = 7.2$, 1.1, CH), 7.49
(1H, dt, $J = 7.2$, 1.3, CH), 7.66 (1H, dd, $J = 7.5$,
20 1.4, CH), 7.98 (1H, dd, $J = 7.1$, 1.5, CH), 8.26 (1H,
s, CH); m/z 295 (M^+ , free base).

EXAMPLE 31

25

Tablet Preparation

Tablets containing 1.0, 2.0, 25.0, 26.0, 50.0 and
100.0 mg, respectively, of the following compounds
are prepared as illustrated below:

30

[2'-(1-Methyl-1H-indol-3-yl)-]spiro(1-azabicyclo[2.2.2]
octane-3,5'-(4'H)-oxazole)

[8-Methyl-2'-(1-methyl-1H-indol-3-yl)-]spiro(8-azabicyclo[3.2.1]octane-3,5'(4'H)-oxazole)

5 [2'-(5-Fluoro-1-methyl-1H-indol-3-yl)-]spiro(1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole)

[2'-(1H-Indol-3-yl)-]spiro(1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole)

10 [2'-(1-Methyl-1H-indol-3-yl)-]spiro(1-azabicyclo[3.3.1]nonane-4,5'(4'H)-oxazole)

[2'-(1-Cyclopropylmethyl-1H-indol-3-yl)-]spiro(1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole)

15 [2'-(1-Methyl-1H-indol-3-yl)-]spiro(1-azabicyclo[2.2.1]heptane-3,5'(4'H)-oxazole)

TABLE FOR DOSES CONTAINING FROM

1-25 MG OF THE ACTIVE COMPOUND

Amount-mg

25	Active Compound	1.0	2.0	25.0
	Microcrystalline cellulose	49.25	48.75	37.25
	Modified food corn starch	49.25	48.75	37.25
	Magnesium stearate	0.50	0.50	0.50

30 TABLE FOR DOSES CONTAINING FROM

26-100 MG OF THE ACTIVE COMPOUND

		Amount-mg		
	Active Compound	26.0	50.0	100.0
5	Microcrystalline cellulose	52.0	100.0	200.0
	Modified food corn starch	2.21	4.25	8.5
	Magnesium stearate	0.39	0.75	1.5

10 All of the active compound, lactose, and a
 portion of the corn starch are mixed and granulated
 to a 10% corn starch paste. The resulting
 granulation is sieved, dried and blended with the
 remainder of the corn starch and the magnesium
 stearate. The resulting granulation is then
 15 compressed into tablets containing 1.0mg, 2.0mg,
 25.0mg, 26.0mg, 50.0mg and 100.0mg of active
 ingredient per tablet.

20

25

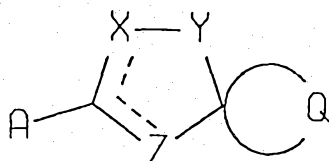
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~~CLAIMS:~~

The claims defining the invention are as follows:

- 5 ¹ as herein defined, A compound of formula I or a salt or
prodrug thereof:

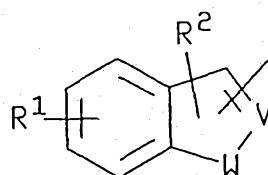
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(I)

- 15 wherein the dotted line represents an optional
chemical bond in one of the two possible positions;
A represents a group of formula II:

20



(II)

25

in which R¹ represents hydrogen, hydroxy, C₁₋₆ alkyl,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, benzyloxy,
hydroxy(C₁₋₆)alkyl, halogen, amino, cyano, nitro,
-CONR⁶R⁷ or -SO₂NR⁶R⁷, in which R⁶ and R⁷

- 30 independently represent hydrogen, C₁₋₆ alkyl, C₂₋₆
alkenyl or C₂₋₆ alkynyl;

R² represents hydrogen, halogen, C₁₋₆ alkyl,
C₁₋₆ alkoxy or C₁₋₆ alkylcarbonyl;

V represents nitrogen, -CH or -C=; and

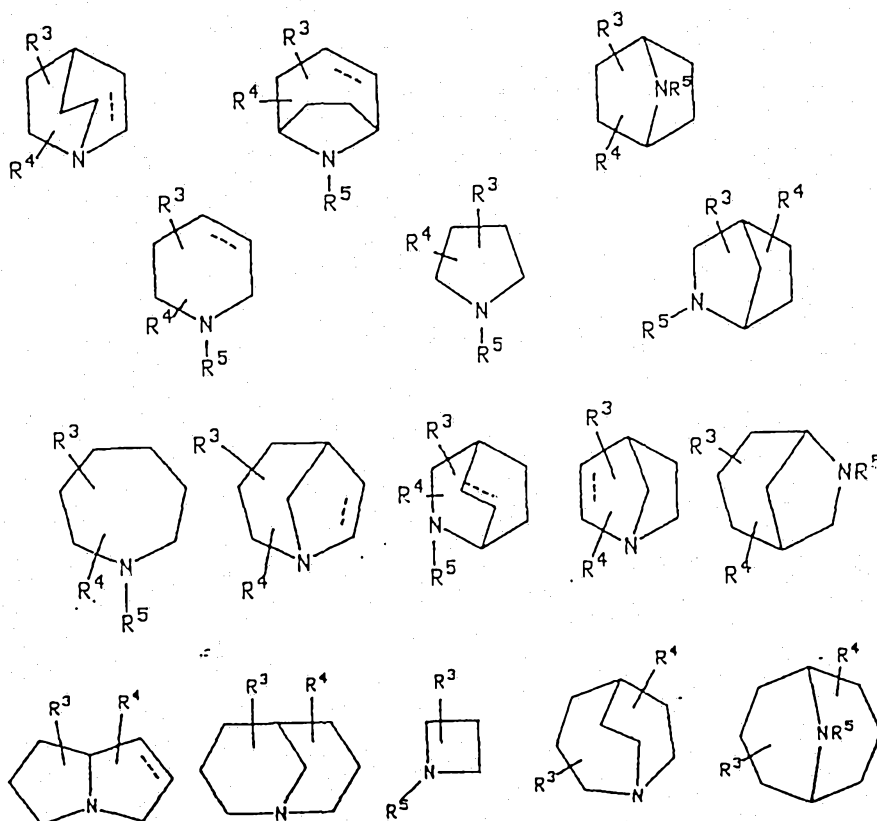
W represents oxygen, sulphur or -NR⁸, in



which R^8 represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl;

two of X, Y and Z are the same or different and each represents oxygen, sulphur or nitrogen; and the remaining group X, Y or Z is carbon, or Y is carbonyl ($C=O$); and

Q is the residue of an azacyclic or azabicyclic ring system selected from the group consisting of

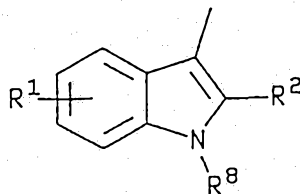


wherein the broken line represents an optional chemical bond;

10 R^3 and R^4 independently represent hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, halogen, C_{1-4} alkoxy, hydroxy, carboxy or C_{2-4} alkoxy carbonyl; or R^3 and R^4 together represent carbonyl; and

R^5 represents hydrogen, benzyl, C_{1-4} alkyl, C_{2-4} alkenyl or
15 C_{2-4} alkynyl.

2. A compound as claimed in claim 1 wherein A represents an indole of structure IIB:



(IIB)

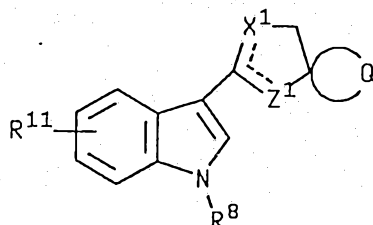
wherein R¹, R² and R⁸ are as defined in claim 1.

5 3. A compound as claimed in claim 1 or claim 2 wherein the azacyclic or azabicyclic ring system of which Q is the residue is pyrrolidine, piperidine, tetrahydropyridine, azanorbornane, quinuclidine, isoquinuclidine, azabicyclo[3.2.1]octane or azabicyclo[3.3.1]nonane, any of which may be optionally substituted with methyl or hydroxy.

10 4. A compound as claimed in claim 1 represented by formula III:



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(III)

10 wherein R^8 , Q and the dotted line are as defined in claim 1; X^1 and Z^1 independently represent oxygen, sulphur or nitrogen; and R^{11} represents hydrogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, halogen, amino or nitro.

15

5. A compound as claimed in claim 4 wherein Q represents the residue of an optionally substituted piperidine, azanorbornane, quinuclidine, 8-azabicyclo[3.2.1]octane or 1-azabicyclo[3.3.1]nonane ring system.

20

6. A compound as claimed in claim 1 selected from:

- 25 [2'-(1-methyl-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]octane-3,5' (4'H)-oxazole);
[8-methyl-2'-(1-methyl-1H-indol-3-yl)]spiro(8-azabicyclo[3.2.1]octane-3,5' (4'H)-oxazole);
[8-benzyl-2'-(1-methyl-1H-indol-3-yl)]spiro(8-azabicyclo[3.2.1]octane-3,5' (4'H)-oxazole);
30 [2'-(5-fluoro-1-methyl-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]octane-3,5' (4'H)-oxazole);
[8-methyl-2'-(5-fluoro-1-methyl-1H-indol-3-yl)]spiro(8-azabicyclo[3.2.1]octane-3,5' (4'H)-oxazole);
[2'-(1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]octane-3,5' (4'H)-oxazole);

- [2'-(1-methyl-1H-indol-3-yl)]spiro(1-azabicyclo[3.3.1]-
nonane-4,5' (4'H)-oxazole);
- 5 [2'-(1-cyclopropylmethyl-1H-indol-3-yl)]spiro(1-azabi-
cyclo[2.2.2]octane-3,5' (4'H)-oxazole);
- [2'-(1-ethyl-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]-
octane-3,5' (4'H)-oxazole);
- [2'-(5-nitro-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]-
octane-3,5' (4'H)-oxazole);
- 10 [2'-(1-methyl-1H-indol-3-yl)]spiro(1-methylpiperidine-
4,5' (4'H)-oxazole);
- [2'-(1-methyl-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.1]-
heptane-3,5' (4'H)-oxazole);
- 15 [2'-(1-methyl-1H-indol-3-yl)]spiro(1-methyl-1-azoniabi-
cyclo[2.2.2]octane-3,5' (4'H)-oxazole) iodide;
- [2'-(benzo(b)thiophen-3-yl)]spiro(1-azabicyclo[2.2.2]-
octane-3,5' (4'H)-oxazole);
- [2'-(1-propyn-2-yl-1H-indol-3-yl)]spiro(1-azabicyclo-
[2.2.2]octane-3,5' (4'H)-oxazole);
- 20 [2'-(1-propen-2-yl-1H-indol-3-yl)]spiro(1-azabicyclo-
[2.2.2]octane-3,5' (4'H)-oxazole);
- [2'-(5-amino-1-methyl-1H-indol-3-yl)]spiro(1-azabicyc-
lo[2.2.2]octane-3,5' (4'H)-oxazole);
- [2'-(2-iodo-1-methyl-1H-indol-3-yl)]spiro(1-azabicyclo-
[2.2.2]octane-3,5' (4'H)-oxazole);
- 25 [2'-(1H-indazol-3-yl)]spiro(1-azabicyclo[2.2.2]octane-
3,5' (4'H)-oxazole);
- [2'-(5-nitro-1-methyl-1H-indol-3-yl)]spiro(1-azabicy-
clo[2.2.2]octane-3,5' (4'H)-oxazole);
- 30 [2'-(5-methoxy-1-methyl-1H-indol-3-yl)]spiro(1-azabicy-
clo[2.2.2]octane-3,5' (4'H)-oxazole);
- [2'-(5-hydroxy-1-methyl-1H-indol-3-yl)]spiro(1-azabicy-
clo[2.2.2]octane-3,5' (4'H)-oxazole);
- [2'-(1,5-dimethyl-1H-indol-3-yl)]spiro(1-azabicyclo-
[2.2.2]octane-3,5' (4'H)-oxazole);

[2'-(1,7-dimethyl-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]octane-3,5'(4'H)-oxazole);

[2'-(1-methyl-1H-indol-3-yl)]spiro(8-azabicyclo[3.2.1]-octane-3,5'(4'H)-oxazole);

- 5 [2'-(1-methyl-1H-indol-3-yl)]spiro(1-azabicyclo[2.2.2]-octane-3,4'(5'H)-oxazole);
and salts and prodrugs thereof.

7. A pharmaceutical composition for the treatment of psychotic disorders; anxiety, alcohol or drug withdrawal or dependence; pain;
10 gastric stasis; gastric dysfunction; migraine, nausea and vomiting; movement disorders; and presenile and senile dementia comprising a compound as claimed in any one of the preceding claims in association with a pharmaceutically acceptable carrier or excipient.

8. A compound as claimed in any one of claims 1 to 6 when used as
15 a therapeutic agent.

9. A process for the preparation of a pharmaceutical composition for the treatment of psychotic disorders; anxiety, alcohol or drug withdrawal or dependence; pain; gastric stasis; gastric dysfunction;
migraine, nausea and vomiting; movement disorders; and presenile and
20 senile dementia comprising mixing a compound of any one of claims 1 to 6 with a pharmaceutically acceptable carrier, excipient, adjuvant and/or diluent.

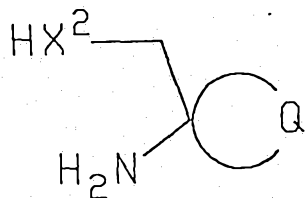
10. A process for the preparation of a compound as claimed in any one of claims 1 to 6 which comprises:

- 25 (A) reacting a reactive derivative of a carboxylic acid of formula A-CO₂H with a compound either of formula IV or of formula V or a salt thereof:

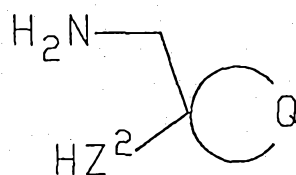
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(IV)

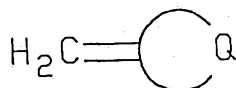


(V)

10 wherein x² and z² are oxygen or sulphur; and A and Q are as defined in claim 1; or

15

(B) reacting a nitrile oxide of formula A-C≡N⁺-O⁻ with an alkene of formula IX:



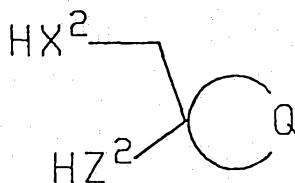
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(IX)

wherein A and Q are as defined in claim 1; or

25

(C) reacting an aldehyde of formula A-CHO with a compound of formula X:

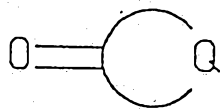


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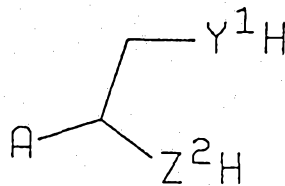
(X)

wherein x² and z² independently represent oxygen or sulphur; and A and Q are as defined in claim 1; or

(D) reacting an azacyclic or azabicyclic ketone of formula VII with a compound of formula XI:



(VII)



(XI)

wherein Y^1 and Z^2 independently represent oxygen or sulphur; and A and Q are as defined in claim 1.

11. A spirocyclic compound incorporating a 5-membered ring with two heteroatoms whenever prepared by the process of claim 10.

12. A method for the treatment or prophylaxis of psychotic disorders; anxiety; alcohol or drug withdrawal or dependence; pain; gastric stasis; gastric dysfunction; migraine, nausea and vomiting; movement disorders; and presenile and senile dementia in a patient requiring said treatment or prophylaxis, which method comprises administering to said patient an effective amount of at least one compound according to any one of claims 1 to 6, or of a composition according to claim 7.

13. A spirocyclic compound incorporating a 5-membered ring with two heteroatoms, substantially as hereinbefore described with reference to any one of Examples 1c, 2, 3b, 4b, 5b, 6, 7b, 8d, 9e, 10b, 11c, 12, 13f, 14, 15b, 16b, 17, 18b, 19b, 20, 21b, 22 to 24, 25b, 26g, 27b, 28b, 29b or 30.

14. A process for the preparation of spirocyclic compounds incorporating 5-membered rings with two heteroatoms, substantially as hereinbefore described with reference to any one of Examples 1 to 30.

15. A pharmaceutical composition for the treatment of psychotic disorders; anxiety, alcohol or drug withdrawal or dependence; pain; gastric stasis; gastric dysfunction; migraine, nausea and vomiting;

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movement disorders; and presenile and senile dementia, substantially as herein described with reference to Example 34.

16. A pharmaceutical composition for the treatment of psychotic disorders; anxiety, alcohol or drug withdrawal or dependence; pain;
5 gastric stasis; gastric dysfunction; migraine, nausea and vomiting; movement disorders; and presenile and senile dementia, comprising a composition comprising a compound of claim 13 together with a pharmaceutically acceptable carrier, adjuvant, excipient and/or diluent.

17. A method for the treatment or prophylaxis of psychotic
20 disorders; anxiety; alcohol or drug withdrawal or dependence; pain; gastric stasis; gastric dysfunction; migraine, nausea and vomiting; movement disorders; and presenile and senile dementia in a patient requiring said treatment or prophylaxis, which method comprises administering to said patient an effective amount of at least one
25 compound according to claim 13 or a composition as claimed in claim 15 or claim 16.

18. The invention substantially as herein described.

DATED this TWENTY-FIRST day of MAY 1991

Merck Sharp & Dohme Limited

Patent Attorneys for the Applicant
SPRUSON & FERGUSON

