(54) Title: 3,9-DIAZABICYCLO (3.3.1) NONAN-7-YL DERIVATIVES, PROCESS AND INTERMEDIATES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract

Compounds of formula (I) wherein X is a phenyl group or a monocyclic 5 or 6 membered heteroaryl group, either of which group is optionally fused to a saturated or unsaturated 5-7 membered carbocyclic or heterocyclic ring; A is linking moiety; Z is C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl, C<sub>3-8</sub> cycloalkyl C<sub>1-4</sub> alkyl, phenyl, naphthyl, phenyl C<sub>1-4</sub> alkyl or naphthyl C<sub>1-4</sub> alkyl wherein a phenyl or naphthyl moiety is optionally substituted by one or more of halo, C<sub>1-6</sub> alkoxy or C<sub>1-6</sub> alkyl; R is hydrogen or methyl having 5-HT<sub>3</sub> receptor antagonist activity.
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Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.
3,9-Diazabicyclo (3.3.1) nonan-7-yl derivatives, process and intermediates for their preparation and pharmaceutical compositions containing them.

This invention relates to novel compounds having pharmacological activity, to a process and intermediates for their preparation, and to their use as pharmaceuticals.


A class of novel compounds has now been discovered in which the saturated azabicyclic moiety is endo-3,9-diazabicyclo[3.3.1]nonan-7-yl. These compounds have 5-HT₃ receptor antagonist activity.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:
wherein

10 X is a phenyl group or a monocyclic 5 or 6 membered heteroaryl group, either of which group is optionally fused to a saturated or unsaturated 5-7 membered carbocyclic or heterocyclic ring;

A is a linking moiety;

15 Z is C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl C₁₋₄ alkyl, phenyl, naphthyl, phenyl C₁₋₄ alkyl or naphthyl C₁₋₄ alkyl wherein a phenyl or naphthyl moiety is optionally substituted by one or more of halo, C₁₋₆ alkoxy or C₁₋₆ alkyl;

20 R is hydrogen or methyl;

having 5-HT₃ receptor antagonist activity.

X may be unsubstituted or substituted, usually by one or more substituents selected from halogen, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkyl, hydroxy, amino, C₁₋₆ alkylamino, C₁₋₇ alkanoylamino, or two substituents on X (when fused), may be linked to form a saturated or unsaturated optionally substituted carbocyclic ring.

30 Heteroatoms for heteroaryl and heterocyclic groups within X are selected from oxygen, nitrogen and sulphur.

Halo includes bromo, chloro and fluoro.
X may be joined to A by an aromatic carbon atom, or (when X is fused), by a carbocyclic ring carbon atom, or by a heterocyclic ring carbon or nitrogen atom. When X is fused, and A is attached at an aromatic carbon atom, it is preferably attached at the aromatic carbon adjacent a 'fused' carbon atom, which is attached to the heteroatom of a heterocyclic ring in formula (I). The azagranatane side chain may be attached to A in a 'spiro' configuration.

X may also be further joined to A as defined in formula (IA) hereinafter, when Y-R₁₀ is N-B=N.

Suitable examples of X are as described in the aforementioned patent publications relating to 5-HT₃ receptor antagonists, the subject matter of which is incorporated herein by reference.

Suitable examples of A include CONH (amide), COO (ester), NHCONH (ureide), CONHCONH (extended ureide), or a group of structure (j):

\[
\begin{array}{c}
\text{G} \quad \text{H} \\
\text{I} \quad \text{E}
\end{array}
\]

wherein the dotted circle represents two double bonds in any position in the 5 membered ring; two of G, H and I are selected from oxygen, sulphur, nitrogen and carbon and the other is oxygen, sulphur or nitrogen; and E is a bond or C₁-₅ alkylene optionally substituted by phenyl or hydroxy; or E is absent and the heterocycle in structure (j) is joined to the azagranatane, in a 'spiro' configuration, when G is nitrogen, H is methylene and I is oxygen or sulphur.

For the avoidance of doubt, the suitable X values in formula (I) which are described in the referenced patent publications, are that part of the structure remaining when
the saturated azabicyclic moiety and A (where A is one of the suitable examples listed above), are disregarded.

Z is often benzyl, n- or iso-butyl, n- or iso-propyl, ethyl or methyl, preferably iso-propyl or ethyl.

R is preferably methyl.

There is a group of compounds within formula (I) wherein Z is C₁⁻⁶ alkyl, phenyl or phenyl C₁⁻⁴ alkyl optionally substituted as defined in formula (I).

In a particular aspect, the present invention provides a compound of formula (IA), or a pharmaceutically acceptable salt thereof:

```
X₁ - CO - Y
```

wherein

- Y is NH or O (or is joined to R₁₀ as defined below);
- X₁ is a group of formula (a), (b), (c), (d), (e), (f), or (g) or (h):

```
Ra
```

(a)
wherein

Rₐ to Rₖ and R₉ to Rₙ are selected from hydrogen, halogen or hydroxy;

R₁ is hydrogen and R₂ is hydrogen or C₁₋₄ alkyl; or

R₁ and R₂ together are a bond;

R₃ to R₇ are independently hydrogen or C₁₋₆ alkyl; and

R₄ together with R₂ may be C₂₋₇ polymethylene or C₂₋₆ polymethylene interrupted by an -O- linkage when R₁ is hydrogen;
$-7-$

$R_8$ and $R_9$ are independently selected from hydrogen or $C_{1-6}$ alkyl or $R_8$ and $R_9$ together are $C_{2-6}$ polymethylene or $C_{2-5}$ polymethylene interrupted by an $-O-$ linkage;

5 either $R_{10}$ is hydrogen, $C_{1-6}$ alkoxy, $C_{3-8}$ cycloalkyloxy or $C_{3-8}$ cycloalkyl $C_{1-4}$ alkyloxy; or $R_{10}$ is joined to $Y$ so that $Y-R_{10}$ is $N-B=N$ where $B$ is $N$ or CH; and $R_{11}$ is hydrogen, halo, $C_{1-6}$ alkoxy or $C_{1-6}$ alkyl; or $R_{10}$ and $R_{11}$ are joined to form $-OCH(R_{15}R_{16})-E-$ wherein $E$ is $(CH_2)_n$ or $NR_{17}CO(CH_2)_m$ wherein $n$ is 1 or 2 and $m$ is 0 or 1 and $R_{15}$, $R_{16}$ and $R_{17}$ are independently selected from hydrogen or $C_{1-6}$ alkyl;

10 $R_{12}$ is hydrogen, $C_{1-6}$ alkoxy or; amino optionally substituted by a $C_{1-6}$ alkyl group, or $R_{12}$ is alkanoylamino; and $R_{13}$ is halo, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy or $C_{1-6}$ alkylthio;

15 $R_{14}$ is hydrogen or $C_{1-6}$ alkyl;

in formula (h):

20 $CO-Y-$ is in the 1-position and either $R_{15}$ is in the 3-position and is hydrogen, $C_{1-6}$ alkyl or $C_{1-6}$ alkoxy, or $R_{15}$ is in the 4-position and is hydrogen, halogen, CF$_3$, $C_{1-6}$ alkyl, $C_{1-7}$ acyl, $C_{1-7}$ acylamino, phenyl optionally substituted by one or two $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy or halogen groups, or amino, aminocarbonyl or aminosulphonyl, optionally substituted by one or two $C_{1-6}$ alkyl or $C_{3-8}$ cycloalkyl groups or by $C_{4-5}$ polymethylene or by phenyl, $C_{1-6}$ alkylsulphonyl, $C_{1-6}$ alkylsulphinyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkylthio, hydroxy or nitro; or

30 $CO-Y-$ is in the 3-position and either $R_{15}$ is in the 1-position and is hydrogen, $C_{1-6}$ alkyl or $C_{1-6}$ alkoxy, or $R_{15}$ is in the 4-position and is hydrogen or $C_{1-6}$ alkoxy;

$L$ is $CH$ or $N$; and

35 $Z$ and $R$ are as defined in formula (I).
Examples of moieties in alkyl or alkyl containing groups in Z or in R₁ to R₁₅ include methyl, ethyl, n- and iso-propyl, n-, iso-, sec- and tert-butyl, preferably methyl. Cycloalkyl moieties include C₃, C₄, C₅, C₆, C₇ and C₈ cycloalkyl. Halo moieties include fluoro, chloro, bromo and iodo.

Suitable examples of R₂ and R₄ or R₈ and R₉ when joined include C₂, C₃, C₄, C₅ or C₆ polymethylene, preferably C₂, C₃, C₄ or C₅ polymethylene.

R₉ to Rₑ and R₉ to Rₙ are preferably selected from hydrogen, fluoro, chloro and hydroxy, most preferably hydrogen. R₉ may be 5-, 6- or 7-chloro or fluoro.

When X is of sub-formula (a), one of R₁ and R₃ is preferably hydrogen and one or both of R₂ and R₄ (most preferably both) are alkyl groups, such as methyl, or are joined to form C₂-7 polymethylene; or when one of R₂ and R₄ is hydrogen, the other is preferably ethyl or n- or iso-propyl.

When X is of sub-formula (b), R₅ is preferably hydrogen or a methyl or ethyl group.

When X is of sub-formula (c), one of CO-Y and R₆ is attached at the 1-position and the other is attached at the 3-position as depicted in sub-formula (c), and R₆ is preferably methyl or ethyl.

When X is of sub-formula (d), R₇ is preferably methyl.

When X is of sub-formula (e), R₈ and R₉ are preferably both methyl groups.
When X is of sub-formula (f), and R_{10} is C_{1-6} alkoxy or is joined to Y, R_{12} is preferably amino and R_{13} is preferably chloro or bromo, most preferably chloro. R_{10} is preferably methoxy when C_{1-6} alkoxy.

When X is of sub-formula (f), and R_{10} is hydrogen, R_9 and R_{11} are preferably chloro or methyl and R_{10} is preferably hydrogen.

Other values of X within sub-formula (f) of interest are those described in EP-A-307172 (Eli Lilly and Company) and EP-A-313393 (Yoshitomi Pharmaceutical Industries Limited).

When X is of sub-formula (g), R_{14} is preferably hydrogen or methyl.

When X is of sub-formula (h), and CO-Y- is in the 1-position suitable examples of R_{15} when in the 4-position, include the following: hydrogen, chloro, bromo, methyl, ethyl, amino, methylamino, dimethylamino, phenyl, C_{1-4} alkanoylamino such as formylamino, acetylamino, propionylamino, n- and iso-butyrylamino, aminosulphonyl, and amino and aminosulphonyl optionally substituted by one or two methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-buty1 or phenyl groups; nitro, n- and iso-propoxy, methylthio, ethylthio, n- and iso-propylthio, hydroxy, methysulphonyl and ethylsulphonyl or when R_{15} is in the 3-position suitable examples, include the following groups, hydrogen, methyl, ethyl, n- or iso-propyl, methoxy, and ethoxy.

When X is of sub-formula (h), and the CO-Y- is in the 3-position, suitable examples of R_{15} when in the 1-position, include hydrogen, methyl, ethyl, n- or iso-propyl, or when R_{15} is in the 4-position, suitable examples include the following: hydrogen, methoxy and ethoxy.
Preferred \( R_{15} \) groups, in any of the positions specified above, include hydrogen, methyl and methoxy. \( CO-Y \) is preferably in the 1-position.

5 \( Y \) is preferably NH.

The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, \( \alpha \)-keto glutaric, \( \alpha \)-glycerophosphoric, and glucose-1-phosphoric acids.

10 The pharmaceutically acceptable salts of the compounds of the formula (I) are usually acid addition salts with acids such as hydrochloric, hydrobromic, phosphoric, sulphuric, citric, tartaric, lactic and acetic acid.

15 Preferably the acid addition salt is the hydrochloride salt.

Examples of pharmaceutically acceptable salts include quaternary derivatives of the compounds of formula (I) such as the compounds quaternised by compounds \( R_x \cdot T \) wherein \( R_x \) is \( C_{1-6} \) alkyl, phenyl-\( C_{1-6} \) alkyl or \( C_{5-7} \) cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of \( R_x \) include methyl, ethyl and \( n- \) and \( iso \)-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

30 Examples of pharmaceutically acceptable salts also include internal salts such as N-oxides.
It will be appreciated that mono- or di- salts may be formed owing to the presence of two salifiable nitrogens in the azagranatane side chain.

The compounds of the formula (I), their pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever a compound of formula (I) or a salt thereof is herein referred to.

It will of course be realised that some of the compounds of the formula (I) have chiral or prochiral centres and thus are capable of existing in a number of stereoisomeric forms including enantiomers. The invention extends to each of these stereoisomeric forms (including enantiomers), and to mixtures thereof (including racemates). The different stereoisomeric forms may be separated one from the other by the usual methods.

The invention also provides a process for the preparation of a compound of formula (I) which process comprises reacting a compound $X'-A_1$ with a compound of formula (II):

$$
\begin{align*}
&\text{A}_2 \\
&\text{Z'N} \\
&\text{NR'}
\end{align*}
$$  

(II)

wherein $A_1$ and $A_2$ are moieties which react together, usually by an amide or ester coupling, or by condensation to form a
-12-

heterocycle \(^{(j)}\) as hereinbefore defined, to form A as defined; \(X'\) is \(X\) or a group convertible thereto and \(R'\) and \(Z'\) are \(R\) and \(Z\) as defined or a hydrogenolysable protecting group; and thereafter as desired or necessary, converting \(X'\) to \(X\), converting \(R'/Z'\), when other than \(R/Z\), to \(R/Z\), and optionally forming a pharmaceutically acceptable salt of the compound of formula (I).

Suitable values of \(A_1\) and \(A_2\) are as described in the aforementioned patent publications.

Intermediates of the formula \(X'-A_1\) are generally known from the aforementioned patent publications/references, or are prepared by analogous methods to those used for structurally related known compounds.

Intermediates of the formula (II) are generally prepared from the compound of formula (III):

\[
\begin{array}{c}
\text{O} \\
\text{NR'} \\
\text{Z'} \text{N}
\end{array}
\]

(III)

which is prepared by the condensation/cyclisation of as appropriate 2,6-disubstituted piperazine derivative, as described in the descriptions hereinafter.

In a particular aspect, the invention also provides a process for the preparation of a compound of formula (IA),
or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (IV):

\[ X_1'-\text{CO}Q_1 \]  (IV)

with a compound of formula (V):

\[ \begin{array}{c}
  \text{HY} \\
  \text{Z'}N \\
  \end{array} \]  (V)

or a reactive derivative thereof, when \( Y \) is 0;

wherein \( X_1' \) is \( X_1 \) or a group convertible thereto; \( Q_1 \) is a leaving group; \( R' \) is \( R \) as defined, or a hydrogenolysable protecting group; and the remaining variables are as hereinbefore defined; and thereafter optionally converting \( X_1' \) to \( X_1 \), including any \( R_a, R_b, R_c, R_d, R_e, R_g, R_h \) or \( R_{10}, R_{11}, R_{12}, R_{13}, R_{14} \) or \( R_{15} \) group to another such group, converting \( R'/Z' \), when other than \( R/Z \), to \( R/Z \); and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (IA).

Examples of leaving groups \( Q_1 \), displaceable by a nucleophile, include halogen such as chloro and bromo, \( C_{1-4} \) alkoxy, such as \( \text{CH}_3\text{O} \) and \( \text{C}_2\text{H}_5\text{O}^- \), \( \text{PhO}^- \), or activated hydrocarbonyloxy, such as \( \text{Cl}_5\text{C}_6\text{O}^- \) or \( \text{Cl}_3\text{CO}^- \).

If a group \( Q_1 \) is a halide, then the reaction is preferably carried out at non-extreme temperatures in an inert non-hydroxylic solvent, such as benzene, dichloromethane, toluene, diethyl ether, tetrahydrofuran (THF) or
dimethylformamide (DMF). It is also preferably carried out in the presence of an acid acceptor, such as an organic base, in particular a tertiary amine, such as triethylamine, trimethylamine, pyridine or picoline, some of which can also function as the solvent. Alternatively, the acid acceptor can be inorganic, such as calcium carbonate, sodium carbonate or potassium carbonate. Temperatures of 0°C-100°C, in particular 10-80°C are suitable.

If a group Q₁ is C₁₋₄ alkoxy, phenoxy or activated hydrocarbyloxy then the reaction is preferably carried out in an inert polar solvent, such as toluene ordimethylformamide. It is also preferred that the group Q₁ is Cl₃CO⁻ and that the reaction is carried out in toluene at reflux temperature.

When Y is 0 the compound of formula (V) may be in the form of a reactive derivative thereof, which is often a salt, such as the lithium, sodium or potassium salt.

Usually, X₁' will be X₁, but when R₁₀ is joined to Y, in formula (IA), X₁' is of sub-formula (f) wherein R₁₀ is nitro or amino, which may be subsequently be linked to Y as described in EP-A-315390.

It will be apparent that compounds of the formula (IA) containing an R₈ to Rₑ, R₉, R₇ or R₁₀ to R₁₅ group which is convertible to another such group are useful novel intermediates. i.e. a hydrogen substituent is convertible to a halogen substituent by halogenation using conventional halogenating agents; or a C₁₋₇ alkanoylamino substituent is convertible to amino by conventional hydrolysis.

R'/Z' when other than R/Z may be a hydrogenolysable protecting group which is benzyl optionally substituted by one or two groups selected from halo, C₁₋₄ alkoxy and C₁₋₄
alkyl. Such benzyl groups may, for example, be removed, when $R_2$ to $R_6$, $R_7$, $R_8$ to $R_9$ is not halogen, by conventional transition metal catalysed hydrogenolysis to give the corresponding compound wherein $R'/Z'$ is hydrogen.

A further process for the preparation of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, therefore comprises N-alkylating a compound of formula (I), wherein R/Z is hydrogen and optionally forming a pharmaceutically acceptable salt of the resulting compound of the formula (I). In this further process of the invention 'N-alkylation' comprises the substitution of the azabicyclic N-atoms by a group R/Z as hereinbefore defined. This may be achieved by reaction with a compound RQ3 or ZQ3 wherein R and Z are as hereinbefore defined and Q3 is a leaving group. Suitable values for Q3 include groups displaced by nucleophiles such as Cl, Br, I, OSO$_2$CH$_3$ or OSO$_2$C$_6$H$_4$PCH$_3$. Favoured values for Q3 include Cl, Br and I. The reaction may be carried out under conventional alkylation conditions for example in an inert solvent such as dimethylformamide in the presence of an acid acceptor such as potassium carbonate. Generally the reaction is carried out at non-extreme temperature such as at ambient or slightly above. Alternatively, 'N-alkylation' may be effected under conventional reductive alkylation conditions.

Interconverting R or Z in the compound of the formula (V) before coupling with the compound of the formula (IV) is also possible. Such interconversions are effected conveniently under the above conditions. It is desirable to protect any amine function with a group readily removable by acidolysis such as a C$_2$-7 alkanoyl group, before R/Z interconversion.

It is often convenient in the preparation of such a compound of formula (V) to prepare the corresponding compound wherein
the methylene group is replaced by -CO-, or for R or Z is methyl, where the methyl group is replaced by alkoxy carbonyl. Such compounds may then be reduced using a strong reductant such as lithium aluminium hydride to the corresponding compound of formula (IV).

The compounds of formula (IV) are known or are preparable analogously to, or routinely from, known compounds.

Compounds of the formula (V) wherein R' is R and Z' is Z as defined, are novel and form an aspect of the invention.

Compounds of the formula (I) may also be prepared by the processes analogous to those described in the aforementioned European Patent Publications.

It will be realised that in the compound of the formula (I) the -A- linkage has an endo orientation with respect to the ring of the bicyclic moiety to which it is attached. A mixture of endo and exo isomers of the compound of the formula (I) may be synthesised non-stereospecifically and the desired isomer separated conventionally therefrom e.g. by chromatography; or alternatively the endo isomer may if desired be synthesised from the corresponding endo form of the compound of the formula (II).

Pharmaceutically acceptable salts of the compounds of this invention may be formed conventionally.

The salts may be formed for example by reaction of the base compound of formula (I) with a pharmaceutically acceptable organic or inorganic acid.

The compounds of the present invention are 5-HT₃ receptor antagonists and it is thus believed may generally be used in
the treatment or prophylaxis of pain, emesis, CNS disorders and gastrointestinal disorders. Pain includes migraine, cluster headache, trigeminal neuralgia and visceral pain; emesis includes, in particular, that of preventing vomiting and nausea associated with cancer therapy, post-operative emesis, and nausea associated with migraine. Examples of such cancer therapy include that using cytotoxic agents, such as platinum complexes including cisplatin, and also doxorubicin and cyclophosphamide, particularly cisplatin; and also radiation treatment. CNS disorders include anxiety, psychosis, cognitive disorders such as senile dementia and age associated memory impairment (AAMI), and drug dependence. Gastrointestinal disorders include irritable bowel syndrome and diarrohea.

5-HT₃ receptor antagonists may also be of potential use in the treatment of obesity and/or arrhythmia.

Some of the compounds of the invention may also have gastric prokinetic activity, useful in the treatment of gastrointestinal disorders, for example when R₁₄ is C₁₋₆ alkyl.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are usually adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusible solutions or suspensions or suppositories. Orally administrable compositions are preferred, since they are more convenient for general use.
Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such
liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing.

Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

The invention further provides a method of treatment or prophylaxis of pain, emesis, CNS disorders and/or gastrointestinal disorders in mammals, such as humans, which
comprises the administration of an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

An amount effective to treat the disorders hereinbefore described depends on the relative efficacies of the compounds of the invention, the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70kg adult will normally contain 0.05 to 1000mg for example 0.5 to 500mg, of the compound of the invention. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.0001 to 50mg/kg/day, more usually 0.0002 to 25 mg/kg/day.

No adverse toxicological effects are indicated at any of the aforementioned dosage ranges.

The invention also provides a pharmaceutical composition for use in the treatment and/or prophylaxis of pain, emesis, CNS disorders and/or gastrointestinal disorders which composition comprises an effect non-toxic amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof and pharmaceutically acceptable carrier.

The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use in the treatment of pain, emesis, CNS disorders and/or gastrointestinal disorders.

The following Examples illustrate the preparation of compounds of formula (I); the following descriptions illustrate the preparation of intermediates.
Intermediates of formulae (III)' and (V)'

D1c/d*  \text{CH}_2\text{Ph}
D2c/d  \text{CH}_2\text{Ph}
D3c/d  \text{iPr}
D4c/d  \text{nPr}
D5c/d  \text{iBu}
D6c/d  \text{nBu}
D7c/d  \text{Ph}
D8c/d  \text{Nm}
D9c/d  \text{Me}
D10c/d  \text{Et}
D11c/d  \text{Pe}
D12c/d  \text{Cm}

Nm = 1-naphthylmethyl;
Cm = cyclohexylmethyl;
Pe = phenethyl

* mixture of \textit{endo} and \textit{exo} isomers
Description 1

3-Benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine

5 a) Ethyl 4-bromocrotonate (25g) in Et₂O (200 ml) was stirred, cooled to 0°C and benzylamine (12.6ml) in Et₂O (50ml) was added dropwise. The reaction was stirred at room temperature for 2 days, filtered and the filtrate washed with H₂O, dried (Na₂SO₄) and concentrated. Column chromatography of the residue on silica, eluting with 1:3 Et₂O:petrol gave diethyl-4,4₁-benzylimino di-trans-2-butenoate (15g).

b) The above diester (29g) dissolved in MeOH (300ml) at 0°C was treated with solution of 33% MeNH₂ in IMS (5.7ml). The reaction mixture was stirred at room temperature overnight, the solvent removed and the residue filtered through silica, eluting with 1:1 Et₂O:petrol to give dimethyl-4-benzyl-1-methyl-piperazinyl-2,6-diacetate (D1b) (13.9g).

c) The diester (13.9g) in toluene (150 ml) was added dropwise during 1h to a stirred suspension of Bu₅OK (12.9g) in toluene (600ml) being heated to reflux. After heating for a further 30 min., no starting material remained as determined by TLC. On cooling, the intermediate β-keto ester was extracted into 5N HCl (200ml) and the acidic extract heated to vigorous reflux for 5h. The reaction mixture was concentrated and the residue neutralised, then saturated with K₂CO₃ and the product extracted into CHCl₃. The concentrated organic extracts were purified by column chromatography on silica, eluting with 5% MeOH/CHCl₃ to give 3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one (D1c) (3.7g).

d) The ketone (D1c) (2g) in EtOH (50ml) was heated to reflux with H₂NOH.HCl (0.65g) for 1h. The reaction mixture
was cooled, concentrated to approx. 1/3rd volume, treated with a little ether and the hydrochloride salt of the oxime collected and dried (1.7g). The oxime hydrochloride (0.9g) was reduced with sodium (1.2g) in amyl alcohol (50ml) at reflux. After all the sodium had dissolved, the mixture was cooled to 90°C, water (4ml) was carefully added, then allowed to re-cool to room temperature. The aqueous layer was separated and the amyl alcohol extracted with an excess of 5N HCl. Concentration of the acidic extract, neutralisation then saturation with K₂CO₃ and extraction of the product into CHCl₃ gave, on concentration, the title compounds (D1d) (0.64g) as a crude mixture of endo and exo isomers.

Description 2

**endo-3-Benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine**

a) To methyl-4-bromocrotonate (50g) in diethyl ether (500ml) was added, dropwise benzylation (22ml) in diethyl ether (20ml) at 0°C. The reaction mixture was stirred at room temperature for 72h. The precipitate was removed by filtration and the filtrate washed with water (75 ml). The organic phase was dried (MgSO₄), the solvent evaporated under reduced pressure and the residue purified using flash chromatography on silica eluting with light petrol and diethyl ether to afford dimethyl-4,4₁-benzyliminodi-trans-2-butenoate (17.1g).

b) To dimethyl-4,4₁-benzyliminodi-trans-2-butenoate (17.1g) in methanol (250 ml) was added dropwise methylamine (7.5 ml, 33% w/w in IMS) at 0°C. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure and the residue chromatographed on silica using light petrol and diethyl ether as the eluant to afford dimethyl-1-benzyl-4-methyl
piperazinyl-3,5-diacetate as a mixture of cis and trans isomers (9.29g).

c) To potassium tert-butoxide (9.67g) in toluene (350 ml) was added dimethyl-4-benzyl-1-methyl piperazinyl-2,6-diacetate (9.26g) in toluene (150 ml) at room temperature under a nitrogen atmosphere. The reaction mixture was heated to reflux for 3h. The reaction mixture was cooled and washed with 5N HCl (4x75ml). The combined aqueous extracts were heated to reflux for 13h. The reaction mixture was cooled, the solvent concentrated under reduced pressure and the residue saturated with solid potassium carbonate. The product was extracted into chloroform (4x75ml), the organic phase dried (MgSO₄) and the solvent evaporated under reduced pressure. Flash chromatography on silica using chloroform with increasing volumes of ethanol (up to 10%) eluant gave 3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one (D2c) (1.8g).

d) To a stirred solution of the above ketone (1.80g) in ethanol (50ml) was added hydroxylamine hydrochloride (0.54g). The reaction mixture was then heated to reflux for 2h. The reaction mixture was cooled and the solvent evaporated under reduced pressure. The residue was triturated with diethyl ether to give 3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one oxime hydrochloride (1.87g).

To a stirred solution of alane [generated by the action of conc. H₂SO₄ (0.93ml) on lithium aluminium hydride (0.88g) in dry THF (30ml)] was added 3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one oxime [generated by the treatment of 3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one oxime hydrochloride with potassium carbonate]. The reaction mixture was then heated to reflux overnight under a nitrogen atmosphere. The reaction mixture was cooled and 40% aqueous NaOH solution (2ml) and water (1ml) were added dropwise. Diethyl ether (5ml) was added and the mixture
stirred for 1h. The resultant precipitate was removed by filtration through keiselguhr and the filtrate concentrated under reduced pressure to afford the crude title compound (D2d) (0.90g).

Following the procedures outlined in Descriptions 1 and 2, parts a) to c) the following intermediates were obtained:

3-isopropyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one (D3c);

3-n-propyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one (D4c);

3-isobutyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one (D5c);

3-n-butyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one (D6c);

9-methyl-3-phenyl-3,9-diazabicyclo[3.3.1]nonan-7-one (D7c);

9-methyl-3-(1-naphthylmethyl)-3,9-diazabicyclo[3.3.1]nonan-7-one (D8c);

3,9-dimethyl-3,9-diazabicyclo[3.3.1]nonan-7-one (D9c);

3-ethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one (D10c);

9-methyl-3-(2-phenethyl)-3,9-diazabicyclo[3.3.1]nonan-7-one (D11c);

3-cyclohexylmethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one (D12c).
Following the procedures outlined in descriptions 1d) and 2d) the following intermediates were obtained:

**endo-3-isopropyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-5 amine (D3d);**

**endo-3-n-propyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine (D4d);**

10 **endo-3-isobutyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine (D5d);**

**endo-3-n-butyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine (D6d);**

15 **endo-9-methyl-3-phenyl-3,9-diazabicyclo[3.3.1]nonan-7-amine (D7d);**

**endo-9-methyl-3-(1-naphthylmethyl)-3,9-diazabicyclo[3.3.1]-20 nonan-7-amine (D8d);**

**exo/endo-3,9-dimethyl-3,9-diazabicyclo[3.3.1]nonan-7-amine (D9d);**

25 **endo-3-ethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine (D10d);**

**endo-9-methyl-3-(2-phenethyl)-3,9-diazabicyclo[3.3.1]-nonan-7-amine (D11d);**

30 **endo-3-cyclohexylmethyl-9-methyl-3,9-diazabicyclo[3.3.1]-nonan-7-amine (D12d);**
Examples

\[ X_1 \]

\( X_1 = (f) : \)

\( R_{10} = \text{OCH}_3, \)

\( R_{11} = \text{H}, \)

\( R_{12} = \text{NHCOCH}_3, \)

\( \text{NH}_2, \)

\( R_{13} = \text{Cl}. \)

\( \)

E2 (as E1b)  \( \text{Me} \)

E3  \( X_1 = (b) : \)

\( L = \text{N}, \)

\( R_5 = \text{CH}_3, \)

\( R_b = \text{H}. \)

E4 (as E3)  \( \text{iPr} \)

E5 (as E3)  \( \text{nPr} \)

E6 (as E3)  \( \text{iBu} \)

E7 (as E3)  \( \text{nBu} \)

E8 (as E3)  \( \text{Ph} \)
\[ X_1 \quad \text{z} \]

E9 (as E3) \quad \text{Nm}

5 E10 (as E3) \quad \text{Et}

E11 (as E3) \quad \text{Pe}

E12 (as E3) \quad \text{Cm}

10 E13 \quad X_1 = (a): \quad \text{CH}_2\text{Ph}

R_1 = \text{H},
R_2 = \text{Me},
R_3 = \text{H},
R_4 = \text{Me},
R_a = \text{H}.

20 E14 (as E13) \quad \text{iPr}

E15 (as E13) \quad \text{Me}

E16 (as E13) \quad \text{Et}

E17 (as E13) \quad \text{nPr}

25 E18 (as E13) \quad \text{nBu}

E19 (as E13) \quad \text{iBu}

30 E20 (as E13) \quad \text{Cm}

E21 (as E13) \quad \text{H}
Example 1

**endo-4-Acetylamino-5-chloro-2-methoxy-N-(3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)benzamide (ElA)**

A solution of the crude amine (D1d) (0.64g) and Et$_3$N (0.4ml) in CH$_2$Cl$_2$ (20ml) was added to a stirred solution of 4-acetylamino-5-chloro-2-methoxybenzoyl chloride (0.75g) in CH$_2$Cl$_2$ (50ml) at 0°C. After stirring overnight the reaction mixture was washed with aqueous NaHCO$_3$, dried, filtered and concentrated. The residue was purified by column chromatography on alumina, eluting with 1:1 CHCl$_3$:petrol to give three fractions;

- Fraction 1: 0.24g exo isomer
- Fraction 2: 0.46g mixture of endo/exo isomers
- Fraction 3: 0.23g endo isomer (mainly) compound El.

**endo-4-Amino-5-chloro-2-methoxy-N-(3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)benzamide (ElB)**

The mainly endo isomer (ElA), (fraction 3) (0.23g) was hydrolysed with 10% NaOH solution (1.0ml) in EtOH (20ml) and H$_2$O (5ml) heated for 2 hours. The solvent was removed and the residue extracted into CHCl$_3$. The organic extract was dried and concentrated. The residue was filtered through alumina, eluting with CHCl$_3$ to give the desired product E2 (0.12g) mp 145-162°C which contained ca. 20% of the exo isomer.

**MS M$^+$ 428, 430**

$^1$H NMR (CDCl$_3$); δ: 9.8 (brd 1H), 8.15 (s, 0.2H), 7.7 (s, 0.8H), 7.5-6.8 (m, 5H), 6.29 (s, 0.2H), 6.21 (s, 0.8H), 5.7-5.5 (m, 0.2H), 4.65-4.55 (m, 0.8H), 4.35 (brs, 0.4H), 4.24 (brs, 1.6H), .86 (s, 0.6H), 3.78 (s 2.4H), 3.5 (s, 2H), 3.0-2.3 (m 9H including 2.5, s, 3H), 1.42 (3, 1.6H).
Example 2

**endo-4-Amino-5-chloro-2-methoxy-N-(3,9-dimethyl-3,9-
diazabicyclo[3.3.1]nonan-7-yl)benzamide (E2)**

The title compound was prepared in a similar manner to that described in Example 1, from 3,9-dimethyl-3,9-
diazabicyclo[3.3.1]nonan-7-amine (D9d).

Example 3

**endo-N-1-Methyl-3-indazolyl-(3-benzyl-9-methyl-3,9-
diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E3)**

To a stirred suspension of 1-methyl-1H-indazole-3-carboxylic acid (0.50g) in CH₂Cl₂ (40ml) was added oxalyl chloride (0.25ml) and 3 drops of DMF. The reaction mixture was stirred at room temperature for 2h. The solvent was evaporated under reduced pressure to afford crude 1-methyl-1H-indazole-3-carboxyl chloride.

To a solution of 1-methyl-1H-indazole-3-carboxyl chloride (127 mg) in CH₂Cl₂ (20ml) was added a solution of **endo-3-
benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine (D2d)** (160 mg) and triethylamine (90µl) in CH₂Cl₂ (5ml). The reaction mixture was stirred overnight at room temperature. The resulting solution was washed with saturated NaHCO₃ solution, dried (MgSO₄) and the solvent removed under reduced pressure to afford crude product. Flash chromatography on silica using chloroform and ethanol as the eluant gave the title compound (E3) (33mg) mp 173-176°.

$^1$H NMR (CD₃OD) 400 MHz; δ: 1.51 (d, 2H), 2.48 (s, 3H), 2.51-
2.60 (m, 2H), 2.63 (dd, 2H), 2.80 (d, 2H), 2.87-2.92 (m,
2H), 3.92 (s, 5H), 4.50-4.59 (m, 1H), 7.09-7.18 (m, 3H), 7.29 (t, 1H), 7.35 (d, 2H), 7.47 (t, 1H), 7.57 (d, 2H), 8.22 (d, 1H).

5 M+ 403

Examples 4-12

Following the general procedure outlined in Example 3, the following compounds were obtained:

**endo-N-1-Methyl-3-indazolyl-(3-isopropyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-vl)carboxamide (E4)**

mp 180-184°C

1H NMR (CDCl₃) 250 MHz; δ: 1.27 (d, 6H), 1.49 (d, 2H), 2.45-2.59 (m, 5H), 2.65-2.81 (m, 3H), 2.85 (d, 2H), 4.08 (s, 3H), 4.63-4.77 (m, 1H), 7.22-7.30 (m, 1H), 7.36-7.47 (m, 2H), 8.42 (d, 1H), 10.62 (d, 1H).

M+ 355

**endo-N-1-Methyl-3-indazolyl-(9-methyl-3-npropyl-3,9-diazabicyclo[3.3.1]nonan-7-vl)carboxamide (E5)**

mp 147-149°C

1H NMR (CDCl₃) 250MHz; δ: 0.97 (t, 3H), 1.50 (d, 2H), 1.70-1.88 (m, 2H), 2.43-2.63 (m, 2H), 2.81-2.96 (m, 4H), 4.07 (s, 3H), 4.63-4.77 (m, 1H), 7.23-7.31 (m, 1H), 7.35-7.48 (m, 2H), 8.41 (d, 1H), 10.70 (d, 1H).

M+ 355
endo-N-1-Methyl-3-indazolyl-(3-isobutyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E6)

mp 107-109°C

$^1$H NMR (CDCl$_3$) 250 MHz; $\delta$: 0.89 (d, 6H), 1.58 (d, 2H), 1.95-2.10 (m, 1H), 2.40-2.74 (m, 9H), 2.87 (d, 2H), 2.92-3.05 (m, 2H), 4.09 (s, 3H), 4.68-4.81 (m, 1H), 7.23-7.31 (m, 1H), 7.38-7.48 (m, 2H), 8.34 (d, 1H), 10.25 (d, 1H).

MH$^+$ 370

endo-N-1-Methyl-3-indazolyl-(3-$^n$butyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E7)

mp 91-93°C

$^1$H NMR (CDCl$_3$) 250 MHz; $\delta$: 0.93 (t, 3H), 1.30-1.44 (m, 2H), 1.52 (d, 2H), 1.62-1.78 (m, 2H), 2.47-2.68 (m, 9H), 2.88 (d, 2H), 2.91-2.99 (m, 2H), 4.06 (s, 3H), 4.65-4.78 (m, 1H), 7.22-7.30 (m, 1H), 35-7.47 (m, 2H), 8.41 (d, 1H), 10.67 (d, 1H).

MH$^+$ 370

endo-N-1-Methyl-3-indazolyl-(9-methyl-3-phenyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E8)

mp 131-134°C

$^1$H NMR (CDCl$_3$) 250 Hz; $\delta$: 1.69 (d, 2H), 2.61 (s, 3H), 3.11-3.21 (m, 2H), 3.23-3.34 (m, 2H), 3.39 (s, 3H), 3.43-3.60 (m, 4H), 4.69-4.72 (m, 1H), 6.98 (t, 1H), 7.08 (d, 2H), 7.15-7.41 (m, 5H), 8.31 (d, 1H), 9.45 (d, 1H).

M$^+$ 389
endo-N-1-Methyl-3-indazolyl-(3-(1-naphthylmethyl)-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E9)

MP 89-92°C

$^1$H NMR (CDCl$_3$) 250 MHz; δ: 1.55 (d, 2H), 2.44-2.61 (m, 5H), 2.71-2.82 (m, 2H), 2.83-3.00 (m, 4H), 3.68 (s, 3H), 4.45 (s, 2H), 4.68-4.79 (m, 1H), 7.17 (t, 1H), 7.24-7.53 (m, 5H), 7.64 (d, 1H), 7.71 (d, 1H), 7.82-7.91 (m, 1H), 8.20-8.28 (m, 1H), 8.43 (d, 1H), 10.87 (d, 1H).

MH$^+$ 454

endo-N-1-Methyl-3-indazolyl-(3-ethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E10)

mp 140-143°C

$^1$H NMR (CDCl$_3$) 250 MHz; δ: 1.30 (t, 3H), 1.52 (d, 2H), 2.45-20 2.70 (m, 9H), 2.85 (d, 2H), 2.95 (brs, 2H), 4.08 (s, 3H), 4.60-4.75 (m, H), 7.20-7.30 (m, H), 7.35-7.46 (m, 2H), 8.42 (d, H), 10.85 (d, H).

MS M$^+$ = 341

endo-N-1-Methyl-3-indazolyl-(9-methyl-3-phenethyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E11)

mp 129-131°C

$^1$H NMR (CDCl$_3$) 250 MHz; δ: 1.57 (d, 2H), 2.50-2.68 (m, 5H), 2.70-2.84 (m, 2H), 2.85-3.05 (m, 6H), 3.06-3.18 (m, 2H), 3.80 (s, 3H), 4.68-4.80 (m, H), 7.15-7.48 (m, 8H), 8.40 (d, H), 10.56 (d, H).

MS M$^+$ = 417
endo-N-1-Methyl-3-indazolyl-(3-cyclohexylmethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E12)

 mp 82-85°C

1H NMR (CDCl3) 250 MHz; δ: 0.75-1.15 (m, 4H), 1.40-1.72 (m, 8H), 2.45 (d, 2H), 2.48-2.72 (m, 7H), 2.80 (d, 2H), 2.94 (brs, 2H), 4.10 (s, 3H), 4.62-4.79 (m, H), 7.20-7.32 (m, 2H), 7.35-7.48 (m, 2H), 8.32 (d, H), 10.21 (d, H).

MS (EI) M⁺ = 409

Example 13

endo-N,3,3-Dimethylindolin-1-yl(3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E13)

A solution of 3,3-dimethylindoline (1.5g) and triethylamine (1.42ml) in CH₂Cl₂ (15ml) was added dropwise to a cooled stirred solution of phosgene (9ml, 12.5% w/w in toluene) in CH₂Cl₂ (15ml). The reaction mixture was stirred for 1h at 0°C and then poured into pentane (100ml), washed with 5N sulphuric acid (5ml) and brine (5ml). The organic phase was dried (MgSO₄) and the solvent evaporated under reduced pressure to give crude 1-(2,3-dihydro-3,3-dimethyl)indolylcarbonyl chloride (1.7g).

To a stirred solution of 1-(2,3-dihydro-3,3-dimethyl)indolylcarbonyl chloride (771mg) in CH₂Cl₂ (15ml) at ambient temperature was added endo-3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine (D2d) (902mg) and triethylamine (512μl) in CH₂Cl₂ (15ml). The reaction mixture was stirred at room temperature overnight. The resulting solution was washed with aqueous NaHCO₃ solution, dried (MgSO₄) and the solvent removed by rotary evaporation.
Flash chromatography on silica using chloroform and ethanol as the eluant gave the title compound (E13) (360mg) mp 188-191°C.

$^1$H NMR (CDCl$_3$) 250MHz; $\delta$: 1.29 (s, 6H), 1.48 (d, 2H), 2.40-2.57 (m, 5H), 2.62-2.78 (m, 4H), 2.83-2.90 (m, 2H), 3.53 (s, 2H), 3.70 (s, 2H), 4.39-4.42 (m, 1H), 6.90 (t, 1H), 7.05-7.46 (m, 8H), 7.81 (d, 1H), 8.78 (d, 1H).

10 Examples 14-20

Following the general procedure outlined in Example 13, the following compounds were obtained; in the case of hydrochloride salts, by treatment of the free base with ethereal HCl.

**endo-N-3,3-Dimethylindolin-1-yl(3-isopropyl-9-methyl-3,9-diaza
carbocycle[3.3.1]nonan-7-yl)carboxamide (E14)**

mp 109-111°C

$^1$H NMR (CDCl$_3$) 250MHz; $\delta$: 1.05 (d, 6H), 1.33 (s, 6H), 1.47 (d, 2H), 2.41-2.75 (m, 10H), 2.88-2.96 (m, 2H), 3.65 (s, 2H), 4.24-4.38 (m, 1H), 6.90 (t, 1H), 7.06-7.19 (m, 2H), 7.80 (d, 1H), 8.58 (d, 1H).

MH$^+$ 371

**endo-N-3,3-Dimethylindolin-1-yl(3,9-dimethyl-3,9-diaza
carbocycle[3.3.1]nonan-7-yl)carboxamide (E15)**

mp 173-175°C

$^1$H NMR (CDCl$_3$) 400 MHz; $\delta$: 1.34 (s, 6H), 1.45 (d, 2H), 2.31 (s, 3H), 2.40-2.50 (m, 2H), 2.52 (s, 3H), 2.55-2.65 (m, 2H), 2.69 (d, 2H), 2.88 (bri, 2H), 3.54 (s, 2H), 4.25-4.36 (m,
H), 6.90 (t, H), 7.07 (d, H), 7.15 (t, H), 7.93 (d, H), 9.15 (d, H).

MS M^+ = 342

**endo-N-3,3-Dimethylindolin-1-yl(3-ethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E16)**

mp 150°

$^1$H NMR (CDCl$_3$) 250 MHz; δ: 1.05 (t, 3H), 1.35 (s, 6H), 1.46 (d, 2H), 2.40-2.60 (m, 9H), 2.75 (d, 2H), 2.90 (brs, 2H), 3.60 (s, 2H), 4.25-4.40 (m, H), 6.90 (t, H), 7.05-7.20 (m, 2H), 7.85 (d, H), 8.95 (d, H).

MS MH^+ = 357

**endo-N-3,3-Dimethylindolin-1-yl(3-$^n$propyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide hydrochloride (E17)**

mp 139-142°C

$^1$HNMR (CDCl$_3$) 250 MHz - Free base; δ: 0.80 (t, 3H), 1.32 (s, 6H), 1.45 (d, 2H), 1.62-1.79 (m, 2H), 2.26-2.46 (m, 2H), 2.47-2.57 (m, 7H), 2.74 (d, 2H), 2.82-2.89 (m, 2H), 3.58 (s, 2H), 4.21-4.33 (m, 1H), 6.89 (t, 1H), 7.01-7.19 (m, 2H), 7.89 (d, 1H), 9.02 (d, 1H).

MH+ 371 (Free base)
-37-

endole-N-3,3-Dimethylindolin-1-yl(3-nbutyl-9-methyl-3,9-
diazebicyclo[3.3.1]nonan-7-yl)carboxamide hydrochloride
(E18)

mp 135-138°C

$^1$H NMR (CDCl$_3$) 250 MHz - Free base; δ: 0.85 (t, 3H), 1.15-
1.52 (m, 12H), 2.30-2.56 (m, 9H), 2.76 (d, 2H), 2.83-2.92
(m, 2H), 3.59 (s, 2H), 4.23-4.37 (m, 1H), 6.60 (t, 1H),
7.06-7.20 (m, 2H), 7.80 (d, 1H), 9.00 (d, 1H).

MH$^+$ 385 (Free base)

endole-N-3,3-Dimethylindolin-1-yl(3-isobutyl-9-methyl-3,9-
diazebicyclo[3.3.1]nonan-7-yl)carboxamide hydrochloride
(E19)

mp 141-144°C

$^1$H NMR (CDCl$_3$) 250MHz (Free base); δ: 0.69 (d, 6H), 1.30 (s,
6H), 1.49 (d, 2H), 2.17 (d, 2H), 2.39-2.55 (m, 8H), 2.65-
2.78 (m, 2H), 2.81-2.90 (m, 2H), 3.64 (s, 2H), 4.25-4.37 (m,
1H), 6.88 (t, 1H), 6.98-7.15 (d, 1H), 7.51 (d, 1H), 8.69 (d,
1H).

MH$^+$ 385 (Free base)

endole-N-3,3-Dimethylindolin-1-yl(3-cyclohexylmethyl-9-methyl-
3,9-diazebicyclo[3.3.1]nonan-7-yl carboxamide hydrochloride
(E20)

mp 130°C

$^1$H NMR (CDCl$_3$) 250 MHz; δ: 0.55-0.80 (m, 2H), 0.85-1.38 (m,
8H, including 1.33 (s, 6H), 1.40-1.90 (m, 10H), 2.22 (d,
2H), 2.40-2.59 (m, 7H including 2.50 (s, 3H)), 2.74 (d, 2H),
2.85 (brs, 2H), 3.65 (s, 2H), 4.29-4.43 (m, H), 6.90 (t, H),
7.05-7.19 (m, 2H), 7.62 (d, H).

MS M⁺ = 425

Example 21

endo-N-3,3-Dimethylindolin-1-yl-(9-methyl-3,9-
diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E21)

endo-N-3,3-Dimethylindolin-1-yl(3-benzyl-9-methyl-3,9-
diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E13) (350 mg) was
hydrogenated at atmospheric pressure in methanol (50ml) over
5% Pd/C catalyst for 4h. The catalyst was removed by
filtration and the filtrate evaporated to give the title
compound (E21) (149mg).

mp 248-251°C

¹H NMR (CDCl₃) 250 MHz; δ: 1.35 (s, 6H), 1.68 (d, 2H), 2.50-
2.67 (m, 3H), 2.75 (s, 3H), 2.99 (d, 2H), 3.17-3.26 (m, 2H),
3.58 (s, 2H), 3.61-3.71 (m, 2H), 4.37-4.49 (m, 1H), 6.89-
6.97 (m, 1H), 7.06-7.20 (m, 2H), 7.88 (m, 1H).

M⁺ 329
5-HT₃ Receptor Antagonist Activity

Compounds are evaluated for antagonism of the von Bezold-Jarisch reflex evoked by 5-HT in the anaesthetised rat according to the following method:

Male rats 250-350g, are anaesthetised with urethane (1.25g/kg intraperitoneally) and blood pressure and heart rate are recorded as described by Fozard J.R. et al., J. Cardiovasc. Pharmacol. 2, 229-245 (1980). A submaximal dose of 5-HT (usually 6μg/kg) is given repeatedly by the intravenous route and changes in heart rate quantified. Compounds are given intravenously and the concentration required to reduce the 5-HT-evoked response to 50% of the control response (ED₅₀) is then determined.
Claims

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:

\[
\begin{array}{c}
\text{NR} \\
\text{X} - \text{A} \\
\text{ZN}
\end{array}
\]

(I)

wherein

X is a phenyl group or a monocyclic 5 or 6 membered heteroaryl group, either of which group is optionally fused to a saturated or unsaturated 5-7 membered carbocyclic or heterocyclic ring;

A is a linking moiety;

Z is C\(_1\)-6 alkyl, C\(_3\)-8 cycloalkyl, C\(_3\)-8 cycloalkyl C\(_1\)-4 alkyl, phenyl, naphthyl, phenyl C\(_1\)-4 alkyl or naphthyl C\(_1\)-4 alkyl wherein a phenyl or naphthyl moiety is optionally substituted by one or more of halo, C\(_1\)-6 alkoxy or C\(_1\)-6 alkyl;

R is hydrogen or methyl;

having 5-HT\(_3\) receptor antagonist activity.

2. A compound according to claim 1 wherein A is CONH, NHCONH, CONHCONH or a group of structure (j):

\[
\begin{array}{c}
\text{G} \\
\text{H} \\
\text{I} \\
\text{E}
\end{array}
\]

(j)
wherein the dotted circle represents two double bonds in any position in the 5 membered ring; two of G, H and I are selected from oxygen, sulphur, nitrogen and carbon and the other is oxygen, sulphur or nitrogen; and E is a bond or 5 C₁₋₅ alkylene optionally substituted by phenyl or hydroxy.

3. A compound according to claim 1, of formula (IA), or a pharmaceutically acceptable salt thereof:

\[
\begin{align*}
\text{X}_1 & \text{ CO } \text{ Y} \\
\end{align*}
\]

wherein

Y is NH or O (or is joined to R₁₀ as defined below);

20 X₁ is a group of formula (a), (b), (c), (d), (e), (f), or (g) or (h):

\[
\begin{align*}
\text{R}_a & \text{ N} \\
\text{R}_1 & \text{ R}_2 \\
\text{R}_3 & \text{ R}_4 \\
\end{align*}
\]
25 wherein

$R_a$ to $R_e$ and $R_g$ to $R_h$ are selected from hydrogen, halogen or hydroxy;

$R_1$ is hydrogen and $R_2$ is hydrogen or $C_{1-4}$ alkyl; or
$R_1$ and $R_2$ together are a bond;

30 $R_3$ to $R_7$ are independently hydrogen or $C_{1-6}$ alkyl; and
$R_4$ together with $R_2$ may be $C_{2-7}$ polymethylene or $C_{2-6}$ polymethylene interrupted by an $-O-$ linkage when $R_1$ is hydrogen;

$R_8$ and $R_9$ are independently selected from hydrogen or
C_{1-6} alkyl or R_{8} and R_{9} together are C_{2-6} polymethylene or C_{2-5} polymethylene interrupted by an -O- linkage;

either R_{10} is hydrogen, C_{1-6} alkoxy, C_{3-8} cycloalkyloxy or C_{3-8} cycloalkyl C_{1-4} alkoxy; or R_{10} is joined to Y so that Y-R_{10} is N-B=N where B is N or CH; and R_{11} is hydrogen, halo, C_{1-6} alkoxy or C_{1-6} alkyl; or R_{10} and R_{11} are joined to form -OCH(R_{15}R_{16})-E- wherein E is (CH_{2})_{n} or NR_{17}CO(CH_{2})_{m} wherein n is 1 or 2 and m is 0 or 1 and R_{15}, R_{16} and R_{17} are independently selected from hydrogen or C_{1-6} alkyl;

R_{12} is hydrogen, C_{1-6} alkoxy or; amino optionally substituted by a C_{1-6} alkyl group, or R_{12} is alkanoylamino; and

R_{13} is halo, C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkylthio;

R_{14} is hydrogen or C_{1-6} alkyl;

in formula (h):

CO-Y- is in the 1-position and either R_{15} is in the 3-position and is hydrogen, C_{1-6} alkyl or C_{1-6} alkoxy, or R_{15} is in the 4-position and is hydrogen, halogen, CF_{3}, C_{1-6} alkyl, C_{1-7} acyl, C_{1-7} acylamino, phenyl optionally substituted by one or two C_{1-6} alkyl, C_{1-6} alkoxy or halogen groups, or amino, aminocarbonyl or aminosulphonyl, optionally substituted by one or two C_{1-6} alkyl or C_{3-8} cycloalkyl groups or by C_{4-5} polymethylene or by phenyl, C_{1-6} alkysulphonyl, C_{1-6} alkylsulphinyl, C_{1-6} alkoxy, C_{1-6} alkylthio, hydroxy or nitro; or

CO-Y- is in the 3-position and either R_{15} is in the 1-position and is hydrogen, C_{1-6} alkyl or C_{1-6} alkoxy, or R_{15} is in the 4-position and is hydrogen or C_{1-6} alkoxy;

L is CH or N; and
Z and R are as defined in claim 1.

4. A compound according to claim 3 wherein X is of sub-formula (a), one of R_{1} and R_{3} is hydrogen and R_{2} and R_{4}
are both C₁₋₆ alkyl groups or are joined to form C₂₋₇ polymethylene.

5. A compound according to claim 3 wherein X is of sub-formula (b), and R₅ is hydrogen or a methyl or ethyl group.

6. A compound according to claim 3 wherein X is of sub-formula (d) and R₇ is methyl.

7. A compound according to claim 3 wherein X is of sub-formula (f) wherein R₁₀ is methoxy, R₁₂ is amino and R₁₃ is chloro or bromo.

8. A compound according to any one of claims 1 to 7, wherein Z is benzyl, n- or iso-butyl, n- or iso-propyl, ethyl or methyl.


10. endo-4-Amino-5-chloro-2-methoxy-N-(3,9-dimethyl-3,9-diazabicyclo-[3.3.1]nonan-7-yl)benzamide.

11. endo-N-1-Methyl-3-indazolyl-(3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.

12. endo-N-1-Methyl-3-indazolyl-(3-isopropyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.

13. endo-N-1-Methyl-3-indazolyl-(9-methyl-3-npropyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.

15. **endo-N-1-Methyl-3-indazolyl-(3-\text{R}butyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.**

16. **endo-N-1-Methyl-3-indazolyl-(3-(1-naphthylmethyl)-9-5 methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.**

17. **endo-N-1-Methyl-3-indazolyl-(3-ethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.**

10 18. **endo-N-1-Methyl-3-indazolyl-(9-methyl-3-phenethyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.**

19. **endo-N-1-Methyl-3-indazolyl-(3-cyclohexylmethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.**

15 20. **endo-N-3,3-Dimethylindolin-1-yl-(3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.**

21. **endo-N-3,3-Dimethylindolin-1-yl-(3-isopropyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.**

22. **endo-N-3,3-Dimethylindolin-1-yl-(3,9-dimethyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.**

25 23. **endo-N-3,3-Dimethylindolin-1-yl-(3-ethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.**

24. **endo-N-3,3-Dimethylindolin-1-yl-(3-\text{R}propyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.**

30 25. **endo-N-3,3-Dimethylindolin-1-yl-(3-\text{R}butyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.**
26. **endo-N-3,3-Dimethylindolin-1-yl-(3-isobutyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.**

27. **endo-N-3,3-Dimethylindolin-1-yl-(3-cyclohexylmethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl carboxamide hydrochloride.**

28. **endo-N-3,3-Dimethylindolin-1-yl-(9-methyl-3,9-10 diazabicyclo[3.3.1]nonan-7-yl)carboxamide.**

29. A pharmaceutically acceptable salt of a compound according to any one of claims 9 to 28.

30. A compound according to claim 1, substantially as described herein with reference to any one of the Examples.

31. A process for the preparation of a compound according to claim 1 which process comprises reacting a compound $X'-A_1$ with a compound of formula (II):

![Chemical Structure](image)

wherein $A_1$ and $A_2$ are moieties which react together, usually by an amide or ester coupling, or by condensation to form a heterocycle ($j$) as defined in claim 2, to form A as defined in claim 1; $X'$ is $X$ or a group convertible thereto and $R'$
and \( Z' \) are \( R \) and \( Z \) as defined in claim 1 or a hydrogenolysable protecting group; and thereafter as desired or necessary, converting \( X' \) to \( X \), converting \( R'/Z' \), when other than \( R/Z \), to \( R/Z \), and optionally forming a pharmaceutically acceptable salt of the compound of formula (I).

32. A process for the preparation of a compound according to claim 3, which process comprises reacting a compound of formula (IV):

\[
X'_1' - \text{COO} \ 1
\]

(IV)

with a compound of formula (V):

\[
\text{HY} \quad \text{NR'}
\]

(V)

or a reactive derivative thereof, when \( Y \) is 0;

wherein \( X'_1' \) is \( X_1 \) or a group convertible thereto; \( Q_1 \) is a leaving group; \( R' \) is \( R \) as defined, or a hydrogenolysable protecting group; and the remaining variables are as hereinbefore defined; and thereafter optionally converting \( X'_1 \) to \( X_1 \), including any \( R_a, R_b, R_c, R_d, R_e, R_g, R_h \) or \( R_{10} \), \( R_{11}, R_{12}, R_{13}, R_{14} \) or \( R_{15} \) group to another such group, converting \( R'/Z' \), when other than \( R/Z \), to \( R/Z \); and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (IA).

33. An intermediate of formula (V) wherein \( R' \) is \( R \) and \( Z' \) is \( Z \), as defined in claim 32.
34. endo-3-Benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine.

35. endo-3-Isopropyl-9-methyl-3,9-diazabicyclo[3.3.1]-5 nonan-7-amine.

36. endo-3-Propyl-9-methyl-3,9-diazabicyclo[3.3.1]-nonan-7-amine.

37. endo-3-Isobutyl-9-methyl-3,9-diazabicyclo[3.3.1]-nonan-7-amine.

38. endo-3-Butyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine.

39. endo-9-Methyl-3-phenyl-3,9-diazabicyclo[3.3.1]nonan-7-amine.

40. endo-9-Methyl-3-(1-naphthylmethyl)-3,9-diazabicyclo[3.3.1]nonan-7-amine.

41. exo/endo-3,9-Dimethyl-3,9-diazabicyclo[3.3.1]nonan-7-amine.

42. endo-3-Ethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine.

43. endo-9-Methyl-3-(2-phenethyl)-3,9-diazabicyclo-[3.3.1]nonan-7-amine.

44. endo-3-Cyclohexylmethyl-9-methyl-3,9-diazabicyclo-[3.3.1]nonan-7-amine.

45. A compound of formula (III)'
wherein Z and R are as defined in claim 1.

46. 3-Benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one.

47. 3-Isopropyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one.

48. 3-Propyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one.

49. 3-Isobutyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one.

50. 3-Butyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one.

51. 9-Methyl-3-phenyl-3,9-diazabicyclo[3.3.1]nonan-7-one.

52. 9-Methyl-3-(1-naphthylmethyl)-3,9-diazabicyclo[3.3.1]nonan-7-one.

53. 3,9-Dimethyl-3,9-diazabicyclo[3.3.1]nonan-7-one.

54. 3-Ethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one.

55. 9-Methyl-3-(2-phenethyl)-3,9-diazabicyclo[3.3.1]nonan-7-one.

56. 3-Cyclohexylmethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one.
57. A pharmaceutical composition comprising a compound according to any one of claims 1 to 30, and a pharmaceutically acceptable carrier.

58. A pharmaceutical composition for use in the treatment of pain, emesis, CNS disorders or gastrointestinal disorders comprising an effective amount of a compound according to claim 1, and a pharmaceutically acceptable carrier.

59. A compound according to any one of claims 1 to 30, for use as an active therapeutic substance.

60. A compound according to any one of claims 1 to 30, for use in the treatment of pain, emesis, CNS disorders or gastrointestinal disorders.

61. Use of a compound according to any one of claims 1 to 30, in the manufacture of a medicament for the treatment of pain, emesis, CNS disorders or gastrointestinal disorders.

62. A method of treatment of pain, emesis, CNS disorders or gastrointestinal disorders in mammals, which comprises the administration of an effective amount of a compound according to claim 1.
**INTERNATIONAL SEARCH REPORT**

**International Application No.** PCT/GB 91/01629

### I. CLASSIFICATION OF SUBJECT MATTER

If several classification symbols apply, indicate all.

According to International Patent Classification (IPC) or to both National Classification and IPC:

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<th>Classification Symbols</th>
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### II. FIELDS SEARCHED

#### Minimum Documentation Searched

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Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched.

### III. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of Document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to Claim No.</th>
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<tr>
<td>A</td>
<td>GB,A,2193633 (SANDOZ) 17 February 1988, see claims</td>
<td>1,57</td>
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* Special categories of cited documents:
  - "A" document defining the general state of the art which is not considered to be of particular relevance
  - "E" earlier document published on or after the international filing date
  - "I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  - "O" document referring to an oral disclosure, use, exhibition or other means
  - "T" document published prior to the international filing date but later than the priority date claimed
  - "X" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  - "Y" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
  - "Z" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
  - "&" document member of the same patent family

### IV. CERTIFICATION

Date of the Actual Completion of the International Search

09-12-1991

Date of Mailing of this International Search Report

23.01.92

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

[Signature]

Danielle van der Haas
**V. X OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE**

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** claim numbers Authority, namely:

   Remark: Although claim 62 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. □ Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically.

3. □ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

**VI. □ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING**

This International Searching Authority found multiple inventions in this international application as follows:

1. □ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the international application.

2. □ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. □ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. □ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

**Remark on Protest**

- □ The additional search fees were accompanied by applicant's protest.
- □ No protest accompanied the payment of additional search fees.
ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. GB 9101629
SA 51590

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EIP file on 13/01/92. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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For more details about this annex: see Official Journal of the European Patent Office, No. 12/82