Compounds of formula (I), or a pharmaceutically acceptable salt and/or N-oxide and/or a solvate, wherein: one of X and Y is CO and the other is NH; E is O, S or NR wherein R is hydrogen, C1-6 alkyl or a protecting group and A is C3-4 alkyne or C3-4 alkenylene or E and A together with the phenyl to which they are attached form a quinoline nucleus; R4 is groups, (II), (III), (IV), wherein: p and q each independently are 0 to 2; Z is O or S; n is 0 or 1; having dopamine antagonist activity, a process for their preparation and their use as pharmaceuticals.
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AZABICYCLOALKYL BENZAMIDE AND ANILIDE DERIVATIVES

This invention relates to novel compounds, to a process for their preparation and their use.

U.S. Patent No. 4273778 and published European Application No. 80304467.6 (corresponding to allowed U.S. Application No. 213237) disclose benzamides and anilides respectively having a bicyclic side chain. These compounds are described as having dopamine antagonist activity.

A novel class of benzamides and anilides have been discovered which compounds also have dopamine antagonist activity.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt and/or N-oxide and/or a solvate thereof:

\[
\begin{align*}
X-Y-R_4 \\
\overset{E}{\text{A}} \\
R_3 \\
\overset{R_1}{\text{A}} \\
\overset{R_2}{\text{A}} \\
(\text{I})
\end{align*}
\]
wherein:

one of X and Y is CO and the other is NH;

E is O, S or NR wherein R is hydrogen, C\textsubscript{1-6} alkyl
or a protecting group and A is C\textsubscript{2-4} alkylene or C\textsubscript{2-4}
alkenylene or E and A together with the phenyl to which they are attached form a quinoline nucleus;

R\textsubscript{4} is a group:

\[ (\text{CH}_2)_q \]

\[ \text{NR}_5 \]

\[ (\text{CH}_2)_p \]

(II)

(III)

or

(IV)

wherein:

p and q each independently are 0 to 2;
Z is 0 or S;
n is 0 or 1;
one of R\textsubscript{6} and R\textsubscript{7} when n=0 is C\textsubscript{1-4} alkoxy,
C₁-₄ alkoxy carbonyl, hydroxy or C₁-₄ alkyl optionally substituted by hydroxy, C₁-₄ alkoxy or C₁-₄ acyloxy, and the other is hydrogen or C₁-₄ alkyl or one of R₆, R₇ and R₈ when n=1 is C₁-₄ alkyl and the other two are the same or different and are hydrogen or C₁-₄ alkyl;

R₅ is C₁-₇ alkyl, -(CH₂)ₚR₁₀ₚ, p being 0 to 2 and R₁₀ being C₃-₈ cycloalkyl, -(CH₂)ₚR₁₁ₚ, p being 1 or 2 and R₁₁ being thienyl or phenyl optionally substituted by one or two substituents selected from C₁-₄ alkoxy, trifluoromethyl, halogen, nitro, carboxy, esterified carboxy and C₁-₄ alkyl optionally substituted by hydroxy, C₁-₄ alkoxy, carboxy, esterified carboxy or in vivo hydrolysable acyloxy;

R₁ is hydrogen or C₁-₆ alkyl; and

R₂ and R₃ are the same or different and are hydrogen, halogen, trifluoromethyl, C₁-₆ alkoxy, C₁-₆ alkylthio, carboxylic C₁-₇ acyl, carboxylic C₁-₇ acylamino, C₁-₆ alkylsulphonyl, C₁-₆ alkyl sulphenyl, nitro or NR₁₂R₁₃, NR₁₂R₁₃CO, NR₁₂ R₁₃SO₂, or C₁-₆ alkyl-SO₂NR₁₄, NR₁₂R₁₃SO₂NR₁₄ wherein R₁₂ and R₁₃ are the same or different and are hydrogen C₁-₆ alkyl, phenyl or phenyl C₁-₄ alkyl groups any of which phenyl moieties may be substituted by one or more halogen, trifluoromethyl, C₁-₆ alkoxy or nitro groups, or R₁₂ and R₁₃ together form C₄-₅ polymethylene, and R₁₄ is hydrogen or C₁-₆ alkyl.

Preferably, X is CO and Y is NH.

Suitable values for E-A include the following:

a) ![Diagram](image1)

b) ![Diagram](image2)
c) and d)

wherein \( E^1 \) is O, S or NR\(^-\) wherein \( R^- \) is hydrogen, methyl or acetyl;

or e)

Preferred values for E-A include a) wherein \( E^1 \) is O or NH, and c) wherein \( E^1 \) is O or NH.

A preferred value of \( R_4 \) is of formula (II).

When \( R_4 \) is a group of formula (II) as defined, \( p \) is suitably 0 or 1, and \( q \) is suitably 0 or 1.

Often the group \( Y \) and the heterobicycle nitrogen atom are separated by 2 or 3 carbon atoms preferably 3.

The X,Y moiety is preferably in an equatorial orientation to the heterobicycle ring.

When \( R_4 \) is a group of formula (III) as defined \( Z \) is O or S, preferably O.

When \( R_4 \) is a group of formula (IV) as defined, preferably each of \( R_6 \) and \( R_7 \) when \( n=0 \) and each of \( R_5 \), \( R_7 \) and \( R_8 \) when \( n=1 \) are in the exo-position.

Suitable examples for one of \( R_6 \) and \( R_7 \) when \( n=0 \) include methoxy, ethoxy, \( n \)-propoxy, methyl, ethyl,
n-propyl, methoxycarbonyl and ethoxycarbonyl, hydroxy, hydroxymethyl or hydroxethyl, methoxymethyl, methoxyethyl, ethoxymethyl, ethoxyethyl, acetylmethyl and acetylethyl. Methyl is preferred.

Suitable examples for one of R₆, R₇ and R₈ when n=1 include methyl, ethyl and n-propyl.

Suitable examples for the other of R₆ and R₇ when n=0 and for the other two of R₆, R₇ and R₈ when n=1 include hydrogen, methyl, ethyl and n- and iso-propyl.

Examples of R₅ when C₁-₇ alkyl include methyl, ethyl and n-and iso-propyl. Within C₁-₇ alkyl, C₄-₇ alkyl are of interest, especially those of the formula (CH₂)ₓR₁₆ wherein u is 1 or 2 and R₁₆ is a secondary or tertiary C₃-₆ alkyl group. Examples of C₄-₇ alkyl include n-, sec- and tert-butyl, n-pentyl, n-heptyl, and especially iso-butyl, 3-methylbutyl, 2,2-dimethylpropyl and 3,3-dimethylbutyl.

Preferred examples of R₅, when -(CH₂)ₛR₁₀ are those wherein s is 1 or 2, in particular those wherein R₁₀ is C₅-₈ cycloalkyl, such as cyclohexyl, and cyclopropyl.

Preferred examples of R₅, when -(CH₂)ₜR₁₁, are those wherein t is 1. R₁₁ may be 2- or 3-thienyl or preferably is phenyl optionally substituted by one of C₁-₄ alkoxy, trifluoromethyl, halogen, carboxy, esterified carboxy or C₁-₄ alkyl optionally substituted by hydroxy, C₁-₄ alkoxy, carboxy, esterified carboxy and in vitro hydrolysable acyloxy.

When phenyl is substituted by optionally substituted C₁-₄ alkyl, examples of C₁-₄ alkyl include
methyl, ethyl, n- and iso-propyl, and n-, iso-, sec- and tert- butyl; methyl however is preferred. Examples of substituents of such alkyl groups include hydroxy, methoxy, ethoxy, n- and iso- propoxy, carboxy, esterified carboxy and in vivo hydrolysable acyloxy. The substitution preferably occurs on the terminal carbon atom of the alkyl group.

Examples of esterified carboxy groups include C_{1-4} alkoxy carbonyl, such as methoxy-, ethoxy-, n- and iso- propoxy carbonyl, phenoxy carbonyl or benzyloxycarbonyl, either being optionally substituted in the phenyl ring by one or two substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, halogen or nitro.

Examples of in vivo hydrolysable acyloxy groups include C_{1-6} alkanoyloxy, for example acetoxy, propionoxy, n- and iso- butyroxy, and 2,3- dimethylpropanoxy, benzyloxy or benzenesulphonyloxy either being optionally substituted in the phenyl ring by one or two substituents selected from C_{1-4} alkyl, C_{1-4} trifluoromethyl, halogen or nitro, or other sulphonyloxy groups, for example C_{1-6} alkanesulphonyloxy group, such as methanesulphonyloxy.

The most preferred examples of R_5, when -(CH_2)_tR_{11}, are those wherein t is 1 and R_{11} is unsubstituted phenyl or monosubstituted phenyl in particular mono-p-substituted phenyl. Examples of preferred p-substituents include methyl, trifluoromethyl, fluoro, chloro and bromo, especially fluoro. Unsubstituted benzyl, p-fluorobenzyl, p-chlorobenzyl and p-methylbenzyl are especially preferred examples of R_5.
Suitable examples of R₁ include hydrogen, methyl, ethyl, n- and iso-propyl. Preferably R₁ is hydrogen or methyl.

R₁ is preferably attached at the 2-position, i.e. at the carbon atom adjacent to E.

Suitable examples of R₂ and R₃ include the following groups: hydrogen, chloro, bromo, CF₃, methoxy, ethoxy, n- and iso-propoxy, methylthio, ethylthio, n- and iso-propylthio, nitro, amino, C₁-₄ alkanoylamino such as formylamino, acetylamino, propionylamino, n- and iso-butyrylamino, aminosulphonyl; and amino, aminosulphonyl and aminosulphonylamino N-substituted by one or two methyl, ethyl, n- or iso-propyl n-, sec-, or tert-butyl; cyclopropyl, cyclopentyl, cyclohexyl, phenyl or benzyl groups or N-disubstituted by C₄ or C₅ polymethylene; or aminosulphonylamino or methyl-, ethyl-, n- or iso-propylsulphonylamino.

Preferably R₂ and R₃ are independently hydrogen, chloro, amino or optionally substituted aminosulphonyl, as defined.

When R₂ and R₃ are other than C₁-₆ alkoxy or C₁-₆ alkylthio, R₂ is preferably in the 4-position with respect to X as the 1-position; R₃ is then preferably in the 5-position similarly defined.

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

Compounds of formula (I) include those containing the moiety of formula (V):

\[
\begin{align*}
\text{CO-NH-} & \\
\text{E}^1 & \\
\text{R}_1 & \\
\text{(CH}_2\text{)}_m & \\
\end{align*}
\]

(V)

wherein \( m \) is 1 or 2, \text{R}_3^1 \text{ is aminosulphonyl optionally substituted as defined and R}_1 \text{ and E}^1 \text{ are as hereinbefore defined.}

A group of compounds within those of formula (I) is therefore of formula (VI):

\[
\begin{align*}
\text{CO-NH-} & \\
\text{E}^1 & \\
\text{R}_1 & \\
\text{(CH}_2\text{)}_m & \\
\end{align*}
\]

(VI)

wherein the variable groups are as hereinbefore defined. Suitable values for \text{R}_3^1 \text{ N-substituents are as described under formula (I). Preferably R}_3^1 \text{ is aminosulphonyl optionally substituted by one or two methyl groups. Suitable and preferred values for R}_1 \text{ and E}^1 \text{ are as so described under formula (I).}
More suitably p is 0 or 1, it is believed preferably 0. Preferably q is 1 and the CONH moiety is then attached at the 3-position (conventional numbering) and in the β orientation.

A sub-group of compounds within those formula (VI) those of formula (VII):

![Chemical Structure](image)

(VII)

wherein:
- $R^{1}_{5}$ is $C_{4-7}$ alkyl or $-(CH_{2})_{s}R_{10}$ where s is 0 to 2 and $R_{10}$ is $C_{5-8}$ cycloalkyl; and the remaining variables are as defined in formula (V).

Suitable and preferred $R_{1}$ and $E^{1}$ are as so described under formula (I).

Suitable and preferred $R^{1}_{3}$ are as so described under formula (I) for corresponding $R_{3}$.

A group of compounds within those of formula (VII) is that wherein $R^{1}_{5}$ is $(CH_{2})_{u}R_{16}$ as defined or $(CH_{2})_{u}R_{10}$ where u and $R_{10}$ are as defined.

Examples of $R^{1}_{5}$ in these compounds include iso-butyl, 3-methylbutyl, 2,2-dimethylpropyl, 3,3-dimethylbutyl and cyclopropylethyl.

It is preferred that the CONH moiety is in the β-orientation to the nortropane ring.
A sub-group of compounds within those of formula (VI) is of the formula (VIII):

wherein:

$R^2_5$ is thiethylmethyl or $-(CH_2)_t R_{11}$, $t$ being 1 or 2, and $R_{11}$ being phenyl optionally substituted by one or two substituents selected from $C_1-4$ alkoxy, trifluoromethyl, halogen, carboxy, esterified carboxy, and $C_1-4$ alkyl optionally substituted by hydroxy, $C_1-4$ alkoxy, carboxy esterified carboxy or in vivo hydrolysable acyloxy.

Particularly preferred compounds are those wherein $R^2_5$ is benzyl optionally substituted in the phenyl ring by one or two substituents selected from $C_1-4$ alkoxy, trifluoromethyl, halogen and $C_1-4$ alkyl.

It is especially preferred that the phenyl ring is unsubstituted.

Suitable and preferred $R_1$ and $E_1$ are as so described under formula (I).

Suitable and preferred $R^{l3}$ are as so described under formula (V).
It is preferred that the CONH moiety is in the β-orientation to the nortropane moiety.

A third sub-group of compounds within those of formula (VI) is of formula (IX):

![Chemical Structure IX]

wherein \( R^{15} \) is as defined in formula (VII).

Suitable and preferred variables are as so described under formula (VII).

Another sub-group of compounds within those of the formula (VI) of interest are those of the formula (X):

![Chemical Structure X]

wherein \( R^{25} \) is as defined in formula (VIII).

Preferred compounds are those wherein \( R^{25} \) is optionally substituted benzyl as defined under formula (VIII).
It is especially preferred that the phenyl ring is mono-substituted and/or that the substitution is in the para-position and/or that the substituent is chloro, fluoro or methyl.

Suitable and preferred $R_{13}$ are as so described under formula (VIII).

A second group of compounds within those of formula (I) is of formula (XI):

\[
\begin{array}{c}
\text{CO-NH} \\
\text{NR}_{5} \\
\text{E}^1 \\
\text{R}_{1} \\
\text{(CH}_{2}\text{)}_{m} \\
\end{array}
\]

wherein the variables are as defined in formulae (I) and (III).

Suitable and preferred variables are as so described under formula (VI).

Preferably $Z$ is $0$, and the CONH moiety is in the $\beta$-orientation.

There are further compounds within formula (I) containing the moiety of formula (XII):

\[
\begin{array}{c}
\text{CO-NH} \\
\text{R}_{2} \\
\text{R}_{3} \\
\text{E}^1 \\
\text{R}_{1} \\
\text{(CH}_{2}\text{)}_{m} \\
\end{array}
\]
wherein R_{12} and R_{23} are the same or different and are hydrogen, halogen, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, trifluoromethyl, amino or C_{1-7} acylamino; and

R_1 and E are as hereinbefore defined.

Another group of compounds within formula (I) is therefore of formula (XIII):

![Chemical structure diagram](attachment:image.png)

wherein the variable groups are as hereinbefore defined.

Suitable and preferred values for R_{12} and R_{23} are as so described for the relevant R_2 and R_3 under formula (I).

Suitable values for R_1 and E are as so described under formula (I).

A sub-group of compounds within those of formula (XIII) are those of formula (XIV):
wherein the variable groups are as hereinbefore defined.

Suitable and preferred R₁ and E¹ are as so described under formula (I).

Suitable and preferred R₁² and R₂³ are as so described under formula (I) for corresponding R₂ and R₃. Often, R₁² and R₂³ are both hydrogen.

A group of compounds within those of formula (XIV) is that wherein R₁⁵ is (CH₂)ᵤR₁₀ where u and R₁₀ are as defined.

Examples of R₁⁵ in these compounds include iso-butyl, 3-methylbutyl, 2,2-dimethylpropyl and cyclopropylethyl.

It is preferred that the CONH moiety is in the β-orientation to the nortropane ring.

A sub-group of compounds within those of formula (XIII) is of formula (XV):

(XV)
wherein the variable groups are as hereinbefore defined.

Particularly preferred compounds are those wherein $R^2_5$ is benzyl optionally substituted in the phenyl ring by one or two substituents selected from $C_1-4$ alkoxy, trifluoromethyl, halogen and $C_1-4$ alkyl.

Suitable and preferred $R_1$ and $E^1$ are as so described under formula (I).

Suitable and preferred $R^1_2$ and $R^2_3$ are as so described under formula (XII).

It is preferred that the CONH moiety is in the $\beta$-orientation to the nortropane moiety.

A third sub-group of compounds within those of formula (XIII) is of formula (XVI):

![Chemical Structure](image)

wherein the variable groups are as hereinbefore defined under formula (XIV).

Another sub-group of compounds within those of the formula (XIII) of interest are those of formula (XVII):
wherein $R^2_5$ is as defined in formula (VIII).

Preferred compounds are those wherein $R^2_5$ is optionally substituted benzyl as defined under formula (VIII).

It is especially preferred that the phenyl ring is mono-substituted and/or that the substitution is in the para-position and/or that the substituent is chloro, fluoro or methyl.

Suitable and preferred $R^1_2$ and $R^2_3$ are as so described under formula (XII).

Within formulae (XIV) to (XVII) there are sub-groups wherein the benzamide moiety is of formula (XVIII):

wherein:

- $R^1_1$ is halogen or C$_1$-6 alkyl;
- $R^3_3$ is halogen; and
- $R^2_1$ is hydrogen or C$_1$-4 alkanoyl.
The invention also provides a process for the preparation of a compound of the formula (I), which process comprises reacting a compound of the formula (XIX):

![Chemical Structure](image)

with a compound of formula (XX):

![Chemical Structure](image)

wherein:

One of J and L is COQ, where Q is a leaving group, and the other is -NH₂; and the remaining variable groups are as defined in formula (I), with the proviso that when J is -NH₂, R₂ or R₃ is other than amino, and thereafter optionally converting R, R₁, R₂ or R₃ to another R, R₁, R₂ or R₃ respectively; as necessary converting R₅ to other R₅; and optionally forming a pharmaceutically acceptable salt of the resultant compound of the formula (I).

The leaving group Q is a group that is readily displaceable by a nucleophile. Examples of such groups are hydroxy, halogen such as chloro and bromo, acyloxy such as C₁₋₄ alkanoyloxy, C₁₋₄alkoxycarbonyloxy and activated hydrocarbyloxy such as pentachlorophenoxy. Another example of an acyloxy group Q is when Q is joined to E¹ to form -O-CO-N⁻⁻.
If the leaving group is hydroxy, then the reaction is preferably carried out in an inert non-hydroxylic solvent, such as benzene, toluene or diethyl ether in the presence of a dehydrating catalyst, such as a carbodiimide, for example dicyclohexylcarbodiimide. The reaction may be carried out at a non-extreme temperature such as -10 to 100°C, for example 0 to 80°C.

If the leaving group is a halide, then the reaction is preferably carried out at a non-extreme temperature in an inert non-hydroxylic solvent, such as benzene, toluene or diethyl ether. 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.

If the leaving group is acyloxy, then the reaction is preferably carried in substantially the same manner as if the leaving group were hydroxy. Suitable examples of acyloxy leaving groups include C₁-₄ alkanoyloxy, mesyloxy, tosylxy and triflate; and when E¹ is NH, and X-Y is CO-N⁻.

If the leaving group is C₁-₄ alkoxy carbonyloxy, then the reaction is preferably carried out in an inert solvent, such as methylene chloride, at a non-extreme temperature in the presence of an acid acceptor, such as triethylamine.

If the leaving group is activated hydrocarbyloxy then the reaction is preferably carried out in an inert polar solvent, such as dimethylformamide. It is also preferred that the activated hydrocarbyloxy group is a
pentachlorophenyl ester and that the reaction is

carried out at ambient temperature.

Preferably Q is halogen, such as chloro.

The compounds of formula (XIX) and (XX) are either
known compounds or can be prepared analogously to the
preparation of structurally similar known compounds.

Compounds of formula (XIX) wherein R₃ is
aminosulphonyl may be formed from the corresponding R₃
chlorosulphonyl derivatives of the compound of formula
(XIX) wherein R₃ is hydrogen, with a suitable amine or
ammonia.

The E-A moiety in compounds of the formula (XIX)
is generally prepared by a cyclisation reaction. For
example, when E-A is of sub-formula (a) or (c) and E₁
is O, the chroman/dihydrobenzofuran nucleus may be
prepared according to the following scheme:

**Scheme 1**

1) 48% HBr
2) 10% NaOH
Compounds of the formula (XIX) having E-A of sub-formula (d) wherein E₁ is NH may be prepared by a conventional Fischer indole synthesis. Compounds of formula (XIX) having E-A of sub-formula (c) wherein E₁ is NH may accordingly be prepared by reduction of the corresponding indole.

Compounds of the formula (XIX) having E-A of sub-formula (e) may be prepared by a conventional Skraup quinoline synthesis. Compounds of formula (XIX) having an E-A of sub-formula (a) wherein E₁ is NH may accordingly be prepared by reduction of the corresponding quinoline.

The skilled man will appreciate that the choice or necessity of conversion of groups R, R₁, R₂ and/or R₃ to other groups R, R₁, R₂ and/or R₃ will be dictated by the nature and/or position of substituents R, R₁, R₂ and R₃.

It will be apparent that compounds of the formula (I) containing an R₂, R₃ or R₅ group which is convertible to another R₂ and R₃ group or to an R₅ group are useful novel intermediates. A number of such conversions is possible not only for the end compounds of formula (I), but also for their intermediates as follows:

(a) an hydrogen substituent is convertible to a nitro substituent by nitration;

(b) a nitro substituent is convertible to an amino substituent by reduction;

(c) a C₁-₄ acylamino substituent is convertible to an amino substituent by deacylation;
(d) an amino substituent is convertible to a C\textsubscript{1-4} acylamino substituent by acylation;

(e) a hydrogen substituent is convertible to a halogen substituent by halogenation;

(f) a C\textsubscript{1-6} alkythio or C\textsubscript{1-6} alkylsulphinyl substituent is convertible to a C\textsubscript{1-6} alkylsulphinyl or a C\textsubscript{1-6} alkylsulphonyl substituent respectivelly by oxidation; and

(g) an amino substituent is convertible to a C\textsubscript{1-6} alkyl SO\textsubscript{2}NR\textsubscript{14} or NR\textsubscript{12}R\textsubscript{13} SO\textsubscript{2}NR\textsubscript{14} substituent by reaction with C\textsubscript{1-6} alkyl SO\textsubscript{2}NQ\textsubscript{2} or NR\textsubscript{12}R\textsubscript{13}SO\textsubscript{2}Q\textsubscript{2} where Q\textsubscript{2} is leaving group.

(h) a fluoro or chloro substituent is convertible to an optionally substituted amino substituent by reaction with a suitable amine or ammonia.

Conversions (a) to (h) are only exemplary and are not exhaustive of the possibilities.

In regard to (a), nitration is carried out in accordance with known procedures.

In regard to (b), the reduction is carried out with a reagent suitable for reducing nitroanisole to aminoanisole.

In regard to (c), deacylation is carried out by treatment with a base, such as an alkali metal hydroxide.

In regard to (d), the acylation is carried out with an acylating agent, such as the corresponding acid.
or acid chloride. Formylation is carried out with the free acid.

In regard to (e), halogenation is carried out with conventional halogenating agents.

In regard to (f), oxidation is carried out at below ambient temperatures in a non-aqueous solvent, such as a chlorinated hydrocarbon, in the presence of an organic peracid, such as 3-chloroperbenzoic acid, or in water in the presence of a soluble strong inorganic oxidant, such as an alkali metal permanganate or in aqueous hydrogen peroxide.

In regard to (g), O₂ is often halide, for example chloride or bromide, or hydroxy. When halide is the leaving group, the reaction is generally carried out in the presence of a base. When hydroxy is the leaving group, the reaction is generally carried out in the presence of a dehydrating agent, such as dicyclohexylcarbodiimide, in an inert solvent at non-extreme temperature, such as ambient temperature.

In regard to (h), the amination is carried out under conventional conditions using an inert solvent such as CH₂Cl₂ or an excess of amine also functioning as the solvent.

Depending on steric and/or electronic factors and/or reaction conditions mono- or di-acylation may occur. If diacylation takes place, subsequent selective monodeacylation of the resultant compound is necessary to form the desired alkyl- or aminosulphonymino group.

Treatment with a base such as methanolic sodium hydroxide at ambient or slightly elevated temperatures is apt.
It is sometimes most convenient to effect the coupling of compounds (XIX) and (XX) using a compound of formula (XIX) wherein one of R₂ and R₃ is amino and to convert to alkyl- or aminosulphonylamino.

It will be appreciated that, R₅ when optionally substituted benzyl as hereinbefore defined, may be replaced by another group R₅.

Such R₅ benzyl groups may be removed for example when R₁, R₂ or R₃ is not halogen by conventional transition metal catalysed hydrogenolysis to give compounds of the formula (XXI):

\[ X - Y - R₄^1 \]

\[ R₁ \]

\[ \text{R}^3 \] (CH₂)m

wherein R₄ is R₄ wherein the R₅ substituent is replaced by hydrogen and the remaining variable groups are as defined in formula (I).

This invention also provides an optional process step in the preparation of a compound of the formula (I) which comprises the reaction of a corresponding compound of the formula (XXI) as hereinbefore defined with a compound Q₃R₅ wherein R₅ is as defined in formula (I) and Q₃ is a leaving group, and optionally forming a pharmaceutically acceptable salt of the resulting compound of the formula (I).

Suitable values for Q₃ include groups readily displaced by nucleophiles such as Cl, Br, I, OSO₂CH₃ or OSO₂C₆H₄PCH₃.
Favoured values for Q3 include Cl, Br and I.

Particularly suitably the compound Q3R5 is a benzyl halide, such as the bromide or chloride.

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 at a slightly elevated temperature.

Converting R5 to another R5 in the compound of the formula (XX) before coupling with the compound of the formula (XIX) or its derivative is preferred. Such interconversions are effected conveniently under the above conditions. It is desirable to protect the amine function with a group readily removable by hydrolysis such as a C2-7 alkanoyl group before R5 interconversion.

The substituents in the phenyl ring in an R5 benzyl group in a compound of formula (I), in particular the substituted C1-4 alkyl substituents, are interconvertible. A number of such interconversions are possible not only for the end compounds of formula (I), but also for their intermediates as follows:

(i) a carboxy C1-4 alkyl substituent is convertible to an esterified carboxy C1-4 alkyl substituent by esterification:

(ii) an esterified carboxy C1-4 alkyl substituent is convertible to a carboxy C1-4 alkyl substituent by deesterification;
(iii) C\textsubscript{1–4} alkoxy C\textsubscript{1–4} alkyl substituent or an \textit{in vivo} hydrolysable C\textsubscript{2–4} acyloxy C\textsubscript{1–4} alkyl substituent is convertible to an hydroxy C\textsubscript{1–4} alkyl substituent;

(iv) an optionally esterified carboxy or carboxy C\textsubscript{1–3} alkyl substituent is convertible to an hydroxymethyl or hydroxy C\textsubscript{2–4} alkyl substituent by reduction; and

(v) a hydroxy C\textsubscript{1–4} alkyl is convertible to C\textsubscript{1–4} alkyl by O-alkylation or \textit{in vivo} hydrolysable C\textsubscript{2–4} acyloxy C\textsubscript{1–4} alkyl by O-acylation.

Conversions (i) to (iv) are only exemplary and are not exhaustive of the possibilities.

In regard to (i) and (ii), the esterification and de-esterification reactions are carried out in conventional manner.

In regard to (iii), a C\textsubscript{1–4} alkoxy C\textsubscript{1–4} alkyl substituent is convertible to an hydroxy C\textsubscript{1–4} alkyl substituent by conventional methods, such as warming with aqueous hydrobromic acid or by treatment with pyridine hydrochloride, boron tribromide, boron triiodide or iodo(trimethyl)silane.

As \textit{in vivo} hydrolysable C\textsubscript{2–4} acyloxy C\textsubscript{1–4} alkyl substituent is convertible to an hydroxy C\textsubscript{1–4} alkyl substituent by acid or base hydrolysis.

In regard to (iv), the reduction is carried out with a selective metal complex hydride, for example lithium aluminium hydride, under conventional conditions.
In regard to (v), O-alkylation is carried out under conventional conditions in an inert solvent at a non-extreme temperature such as ambient temperature or slightly above or at reflux temperature. The C1-4 alkylating agent has a leaving group that is readily displaceable by a nucleophile. Examples of leaving groups include halide, such as chloride, bromide or iodide, or labile acyloxy groups, such as mesyl or tosyl.

O-acylation is carried out under conventional conditions with an acylating agent which has an acyl group capable of forming an in vivo hydrolysable acyloxy group and a leaving group, such as halide, for example chloride and bromide, and hydrogen. When halide is the leaving group, the reaction is generally carried out in the presence of a base. When hydroxy is the leaving group, the reaction is generally carried out in the presence of a dehydrating agent, such as dicyclohexylcarbodiimide, in an inert solvent at non-extreme temperature, such as ambient temperature or slightly above, or reflux temperature.

Before carrying out any of these conversions, the effect, if any, on other substituents should be considered, and such reagents as are appropriate should be selected together with the adoption of such precautionary measures as are necessary. For example, O-alkylation and O-acylation may also produce N-alkylated and N-acylated products respectively unless the nitrogen atom(s) is (are) previously protected. This may be conveniently achieved by carrying out the alkylation or acylation reaction in a strong acid, such as trifluoroacetic acid, which protonates, and thereby protects, the nitrogen atom(s).
Compounds of the formula (XXI) are novel intermediates and thus form an aspect of the present invention.

It will be realised that in the compound of the formula (I) the -X-Y-linkage may have an \( \alpha \) or \( \beta \) orientation with respect to the ring of the bicyclic moiety to which it is attached. A mixture of \( \alpha \) and \( \beta \) isomers of the compound of the formula (I) may be synthesised non-stereospecifically and the desired isomer separated conventionally therefrom eg by chromatography; or alternatively the \( \alpha \) and \( \beta \) isomer may if desired by synthesised from the corresponding \( \alpha \) or \( \beta \) form of the compound of the formula (XX).

Synthesis from the corresponding \( \alpha \) or \( \beta \) isomer of the compound of the formula (XX) is in general preferred.

It will be appreciated that, when \( X \) is NH, \( Y \) is CO in the compounds of the formulae (I) or (XX), epimerisation of the CO-ring linkage to the energetically more favourable orientation often takes place readily in the presence of acid or base. In such cases if the less favoured isomer is desired, it is preferred to stereospecifically synthesise the isomer of the compound of the formula (XX) and to convert it to the required compound of the formula (I) under such conditions to avoid epimersation.

The \( \alpha \) or \( \beta \) form of the compound of the formula (XX) may if desired be prepared by known stereospecific processes, such as those leading to the \( \alpha \) or \( \beta \) isomers of the compound of the formula (XX) depicted in the Scheme and described in the Descriptions hereinafter.
Compounds of the formula (XX) are known from or are preparable by the methods disclosed in published European Patent Applications and U.S. Patents hereinbefore referred to.

Pharmaceutically acceptable salts, hydrates and N-oxides 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.

N-oxides of the nitrogen atom of the bicyclic ring system are produced by reaction of a compound of formula (I) with an organic peracid, such as m-chloroperbenzoic acid in, for example, a chlorinated hydrocarbon solvent at below ambient temperature.

Quaternary ammonium salts may be prepared by reaction of a compound of the present invention with the appropriate alkyl, aryl, aralkyl chloride, bromide or iodide. This reaction may be carried out in a solvent, such as acetone, methanol, ethanol, dimethylformamide at ambient or elevated temperature with or without pressure.

The compounds of the present invention are dopamine antagonists and may generally be used in the treatment of emesis. Depending on their balance between peripheral and central action on the nervous system, they may also be used in the treatment of disorders relating to impaired gastro-intestinal motility, such as retarded gastric emptying, dyspepsia, flatulence, oesophageal reflux and peptic ulcer and/or in the treatment of disorders of the central nervous system, such as psychosis.
Certain of the compounds of formula have blood pressure lowering activity and may also be useful in the treatment of hypertension.

Those compounds of the present invention which are of interest for their beneficial effect on gastric motility are the compounds of formula (I) and (VI) the quaternary ammonium salts of the compounds of formula (I).

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

Such compositions are prepared by admixture and are suitably 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 administerable compositions are preferred.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, tabletting agents, lubricants, disintegrants, and wetting agents. The tablets may be coated according to well known methods in the art. 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 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.

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 the vehicle and filter sterilizing 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.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilized by exposure to 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 of 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, or an hydrate or N-oxide thereof, or a pharmaceutical composition, as hereinbefore defined to the sufferer.

An amount effective to treat the disorders hereinbefore described depends on the relative efficiencies 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 will normally contain 0.1 to 20 mg, for example 0.5 to 10 mg, of the compound of the invention. Unit doses will normally be administered more than once a day, for example 2, 3, 4, 5 or 6 times a day such that the total daily dose is normally in the range 0.01 to 10 mg/kg per day. The compounds of the present invention have the ability to potentiate the effect of conventional analgesics in migraine treatment when administered concurrently with the analgesic.

Accordingly, the present invention also provides a pharmaceutical compositions comprising a compound of the formula (I) and an analgesic.

The compound of the formula (I) and the analgesic, such as aspirin or paracetamol, are present in the composition in amounts generally similar to their usual effective dose.

The composition can be a combination product, for example a tablet or capsule containing both a compound of the invention and an analgesic for oral administration, or a twin pack comprising the two active ingredients made up for separate administration.

The invention accordingly provides a method of treatment of migraine comprising the administration of an effective amount of a compound of the formula (I) and an analgesic.

The invention also provides a compound of formula (I), for use in the treatment of emesis, disorders relating to impaired gastro-intestinal motility and of disorders of the central nervous system.
The following examples illustrate the preparation of compounds of the invention and the following descriptions illustrate the preparation of intermediates.
Description 1

**Ethyl 2-(propen-3-oxy)benzoate (D1)**

![Chemical Structure](image)

80% sodium hydride (1.8g 60m. mole) was added in portions to ethyl salicylate (10g, 60m. mole) in dimethylformamide (150 mls).

The temperature of the mixture was maintained at 50°C for 6 hours, after the dropwise addition of allyl bromide (5.4 mls, 60m. mole).

Water was then added to the solution and the resulting mixture was extracted with ether. Concentration of the dried organic extract gave an oil which was distilled to give the title compound (D1) (12g), 95% yield, (b.pt 95-100°C/1mm.Hg)

Description 2

**Ethyl 2-hydroxy-3-propenylbenzoate (D2)**

![Chemical Structure](image)

Ethyl 2-(propen-3-oxy)benzoate (11.0g) was heated at 230°C for 1 hour. Distillation of the reaction mixture gave the title compound (D2) (10g), 83% yield, (b.pt. 100°C/1mmHg)
Description 3

Ethyl 2-acetoxy-3-propenyl benzoate (D3)

\[
\begin{align*}
&\text{CO}_2\text{C}_2\text{H}_5 \\
&\text{OAc} \\
&(\text{D3})
\end{align*}
\]

A mixture of ethyl 2-hydroxy-3-propenylbenzoate (8.0g), acetic anhydride (35mls) and pyridine (35mls) was stirred at room temperature overnight. After pouring into water, the mixture was extracted with methylene chloride. The organic extract was dried and evaporated to give the title compound (D3) (9.45g), 98% yield.

Description 4

Ethyl 2-acetoxy-3-bromopropylbenzoate (D4)

\[
\begin{align*}
&\text{CO}_2\text{C}_2\text{H}_5 \\
&\text{OAc} \\
&\text{Br} \\
&(\text{D4})
\end{align*}
\]

A solution of ethyl 2-acetoxy-3-propenylbenzoate (8.5g) and 2,2'-azobis-(2-methylpropionitrile) (0.2g) in carbon tetrachloride (30mls) was cooled to -5°C and saturated with hydrogen bromide. The reaction mixture was then left at 0°C in a pressure vessel overnight.

The product was poured into water and the organic layer was washed with dilute sodium hydrogen carbonate solution. Evaporation of the solvent in vacuo gave the title compound (D4) (11g) which was used immediately.
Description 5

Chroman-8-carboxylic acid (D5)

A solution of ethyl 2-acetoxy-3-bromopropylbenzoate (11g) in ethanol (65mls) and 10% sodium hydroxide solution (140mls) was heated under reflux for 4 hours.

The ethanol was then removed in vacuo and the residue was acidified with 5N hydrochloric acid to give chroman-8-carboxylic acid (D5) (4.6g), 74% yield m.p. 84-86°C (Lit. m.p. 1 85-88°C).

Ref. 1 Chem. Abs. 55 16535c

Description 6

6-Chlorosulphonylchroman-8-carboxylic acid (D6)

Chroman-8-carboxylic acid (1.0g) was added portionwise to chlorosulphonic acid (15mls) while keeping the temperature of the mixture below 5°C. The reaction mixture was then warmed to 55°C and maintained at this temperature for 2 hours before being cooled and poured into ice-water. The precipitated white solid was filtered and dried in vacuo to give the title compound (D6) (1.3g), 84% yield which was used immediately.
Description 7

6-Dimethylaminosulphonylchroman-8-carboxylic acid (D7)

\[
\text{CO}_2\text{H} \\
(\text{CH}_3)_2\text{N} \text{ SO}_2
\]

6-Chlorosulphonylchromon-8-carboxylic acid (1.3g) was added in small portions to a cooled solution of 33% dimethylamine (25mls) and the resulting solution was allowed to stand overnight.

Acidification with 5N hydrochloric acid gave a precipitate which was filtered, washed with water and dried over potassium hydroxide in vacuo to give the title compound (D7) (1.36g), 99% yield.

Description 8

2-Methyl-2,3-dihydrobenzofuran-7-carboxylic acid (D8)

\[
\text{CO}_2\text{H} \\
-\text{CH}_3
\]

A solution of ethyl 2-hydroxy-3-(propenyl)benzoate (1g) in acetic acid (5mls) was heated under reflux with a 48% solution of hydrobromic acid (2.5mls) for 30 minutes. The solvent was then removed in vacuo and the residue was heated with 10% sodium hydroxide solution (10mls) for a further 30 minutes.

Cooling of the solution followed by acidification, extraction with ether and evaporation of the solvent gave the title compound (D8) (0.9g) 98% yield.
Example 1

\[
N-3\beta(8\text{-benzyl-8\text{-azabicyclo (3,2,1) octyl})-chroman-8-carboxamide hydrochloride (1)}
\]

Chroman-8-carboxylic acid (1.5g) was suspended in dry dichloromethane (50mls) with oxalyl chloride (0.76ml), and dry dimethylformamide (0.5ml) was added. The mixture was stirred at room temperature until it became homogeneous.

The solution was cooled to 0°C and kept below this temperature during the dropwise addition of triethylamine (3.46ml) in dry dichloromethane (10mls), followed by the dropwise addition of 3β-amino-8-benzyl-8-azabicyclo (3,2,1) octane (1.8g) in dry dichloromethane (10mls).

The reaction mixture was allowed to warm to room temperature before being shaken with 10% sodium hydroxide solution (10ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed in vacuo to give an oil (4.5g) which was purified by column chromatography (silica, chloroform as eluant) to give the title compound as the free base (3.25g, 77%).

This was converted into its hydrochloride salt (1) nmr (D₂O) 2.4-2.85 (6H, m,-NCH₂Ph and ortho H), 3.02 (1H, d, para H), 3.32 (1H, t, meta H), 5.55-6.1 (5H, m,-NCH₂Ph, 3 H and Ar-O-CH₂), 6.25 (2H, m,
bridgehead H's), 7125-8.6 (12H, m, methylene H's).

C_{24}H_{29}N_{2}O_{2}Cl requires C, 70.12; H, 7.05; N, 6.69%.

Found C, 69.8; H, 7.0; N, 6.79%.

Mass spec. Observed mass = 376.2139. C_{24}H_{28}N_{2}O_{2}

requires 376.2140.
Example 2

6-Dimethylamino sulphonyl-N-[3\(\beta\)(8-benzyl-8-azabicyclo (3,2,1) octyl)]

chroman-8-carboxamide hydrochloride (2)

\[
\begin{align*}
\text{CO} & \quad \text{NH} \quad \text{NH}_2\text{Ph} \\
\text{(CH}_3\text{)}_2\text{N} & \quad \text{SO}_2
\end{align*}
\]

(2)

6-Dimethylaminosulphonylethrom-8-carboxylic acid (0.8g) was dissolved in dry dimethylformamide (15mls), and triethylamine (0.5ml) was added before cooling to 0°C. Ethyl chloroformate (0.22ml) was added dropwise to the reaction mixture whilst keeping the temperature at 0°C and the mixture was stirred at this temperature for 15 minutes.

3-Amino-8-benzyl-8-azabicyclo 3.2.1 octane (0.6g) in dry dimethylformamide (2mls) was added in one portion to the reaction mixture at 0°C before stirring at room temperature for 15 hours.

The solvent was removed in vacuo to leave a residue which was treated with ammonia solution and extracted with dichloromethane. The organic extract was dried and evaporated to give an oil which on purification by column chromatography (silica, chloroform to 5% methanol in chloroform as eluant) gave the title compound as its free base (1.3g, 96%). This was used to prepare the hydrochloride salt (2) m.p. 253-255°C. n.m.r. (D\(_2\)O) 2.25 (1H, d, aromatic H), 2.45 (1H, d, aromatic H), 2.52 (5H, m, \(-\text{NCH}_2\text{Ph}\)), 5.25-5.8 (5H, m,
3 H, -NCH₂Ph and Ar-O-CH₂-), 6.0 (2H, m, bridgehead H's), 7.2 (2H, t, Ar-CH₂-CH₂-), 7.42 (6H, s, -SO₂N(CH₃)₂), 7.55-8.4 (10H, m, methylene H's).

C₂₆H₂₆N₂SCl₄ requires C, 59.4; H, 6.7; N, 7.93%.

Found C, 59.37; H, 6.47; N, 7.19%.

Mass spec. Observed mass = 483.2156.

C₂₆H₂₆N₂SCl₄ requires 483.2192.

The above mentioned method was used to prepare 2-methyl-2,3-dihydrobenzofuryl-7(N-38(3-benzyl-8-azabicyclo (3.2.1) octyl) carboxamide hydrochloride (3) m.pt.240-241°C n.m.r. (D₂O) 2.4-2.5 (7H, m, -NCH₂Ph, ortho H and para H), 3.2 (1H, t, meta H), 5.1 (1H, m, Ar-O-CHCH₃-), 5.15-6.02 (3H, m, 3 H and -NCH₂Ph), 6.15 (2H, m, bridgehead H's), 6.6-8.5 (10H, m, methylene H's), 8.7 (3H, d, Ar-O-CHCH₃-).

C₂₄H₂₉N₂O₂Cl requires C, 69.8; H, 7.03; N, 6.79%.

Found C, 69.6; H, 7.19; N, 6.76%.

Mass spec. Observed mass = 376.2147

C₂₄H₂₈N₂O₂ requires 376.2149
EXAMPLE 3

N-[3β-(8-benzyl-8-azabicyclo[3.2.1]octyl)]-8-[1,2,3,4-tetrahydroquinolinyl]carboxamide (4)

6,7-Dihydro-1H,3H-5H-pyrido[3,2,1,i,j][3,1]benzoxazine-1,3-dione (as prepared by G.M. Coppola, J. Med. Chem., 15, 645, 1978) (2.25g) was dissolved in anhydrous dimethylformamide (50ml) and treated with 3-β-amino-8-benzylnor tropane (2.4g). The solution was warmed to 50° for one hour then left to cool to room temperature overnight: (17 hrs). The mixture was evaporated in vacuo, and the residue was chromatographed on Kieselgel 7734 via chloroform with 1-3% methanol. The isolated product was recrystallised from methylene chloride/ether to yield the title compound (2.19g) as colourless microcrystals mp. 142°.

C_{24}H_{29}N_{3}O_{2} \cdot \frac{1}{2}H_{2}O requires C, 75.00; H, 7.81; N, 10.93%

Found C, 74.89; H, 7.514; N, 7.67, 7.69; N, 10.88, 10.82%

The above method was used to prepare 6-dimethylaminosulphonyl-N-[3β-8-benzyl-8-azabicyclo[3.2.1]octyl]-8-[1,2,3,4-tetrahydroquinolinyl]carboxamide 65% m.pt. 193-194°C. (Compound 5)

C_{26}H_{34}N_{4}O_{3}S required C, 64.73; H, 7.05; N, 11.62%

found C, 64.56; H, 7.13; N, 11.55%

Mass Spec. Observed mass = 482.2351

C_{26}H_{34}N_{4}O_{3}S requires 482.2352
2-Methyl-5-dimethylamino-sulphonyl-2,3-dihydrobenzofuryl-7(N-[8-benzyl-8-azabicyclo[3.2.1]octyl])carboxamide (Compound 6)

nmr (CDCl₃) δ 1.65 (1H, d, aromatic H), 2.3 (1H, d, aromatic H), 2.45-2.95 (6H, m, -NCH₂Ph and -CONH-), 4.5-5.05 (1H, m, C-2 H), 5.35-5.95 (1H, m, 3aH), 6.45 (2H, s, -NCH₂Ph), 6.7 (2H, m, bridgehead H's), 7.3 (6H, s, -N(CH₃)₂), 8.45 (3H, d, C-2 CH₃).

C₂₆H₃₃N₃SO₄ requires C, 64.59; H, 6.83; N, 8.69%
found C, 64.45; H, 6.87; N, 8.67%

Mass spec. Observed mass = 483.2182
C₂₆H₃₃N₃SO₄ requires 483.2192

6-Cyclopentylaminosulphonyl-N-[8-benzyl-8-azabicyclo[3.2.1]octyl]-8-chromancarboxamide (Compound 7)

nmr (CDCl₃) 1.45 (1H, d, aromatic H), 2.05-2.95 (7H, d and m, aromatic H, -CONH- and -NCH₂Ph), 4.75 (1H, d, -NHSO₂-), 5.6 (3H, m, Ar -O-CH₂- and (CH-NH-), 6.4 (2H, s, -NCH₂Ph), 6.75 (2H, m, bridgehead H's)

C₂₉H₃₇N₃SO₄ requires C, 66.5; H, 7.07; N, 8.03%
found C, 66.42; H, 7.12; N, 8.01%

Mass spec. Observed mass = 523.2509
C₂₉H₃₇N₃SO₄ requires 523.2505
Pharmacological Data

Increase in intragastric pressure

Intragastric pressure changes were recorded from previously starved conscious but restrained rats using a saline filled catheter inserted into the lumen of the stomach via a permanent gastric fistula. The catheter was connected to a physiological pressure transducer and pressure changes recorded on a hot wire pen recorder. In each animal a pre-dose period of 40 minutes was allowed to obtain a measure of spontaneous activity. An index of activity was obtained by measuring the average height of pressure waves during 10 minute periods. Values for 4 such periods were obtained during assessment of spontaneous activity and for 40 minute period after administration of compound. Student's 't' test was applied to the difference in average values obtained for spontaneous and post compound activity.

Compounds 1, 3, 6 and 7 significantly increased index of activity post administration at a dose of 1.0 mg/kg s.c. Compound 2 significantly increased index of activity post administration at a dose of 0.5 mg/kg s.c.

Anti-emetic activity in the dog

Compounds were administered subcutaneously 30 minutes prior to administration of a standard dose of
apomorphine HCl (0.1 mg/kg subcutaneously) and the vomiting response compared to that obtained when the same animals were dosed with apomorphine HCl and vehicle only. Compound 2 was active at a dose of 0.1 mg/kg s.c. Compound 3 had an ED50 value of 0.01 mg/kg s.c. and Compound 4 had an ED50 value of 0.5 mg/kg.

**Dopamine Receptor Blocking Activity in the Central nervous System**

Compounds were tested for inhibition of apomorphine induced climbing in the mouse. The test is based on that described by Protais, P., Constantin, J. and Schwartz J.C. (1976), Psychopharmacology, 50, 1.6.

Apomorphine 1 mg/kg s.c. induces mice to climb the wall of a wire cage (inverted food hopper - 11 x 7.5 x 18 cm high). Mice acclimatised in their home cages in groups of 5 are placed under the hoppers immediately after the injection of apomorphine 1mg/kg s.c. At 10.20 and 30 minutes after injection climbing behaviour is scored. The mice are observed for 30 seconds and scored according to the position they spend the majority of time in, score 0 - four paws on floor of cage; score 1 - four paws only on walls; score 2 - all paws on wall of cage. The scores at all 3 times and for each mouse are summed and mice drug treated orally compared to mice receiving apomorphine only. A saline only treated group is also included and any score >55% of maximum taken into account.
Compounds 1, 3, 4 and 7 had ED₅₀ values of 1.7, 0.2, 3.8 and 7 mg/kg s.c. respectively.

**Anti-hypertensive Activity**

Systolic blood pressures were recorded by a modification of the tail cuff method described by J.M. Claxton, M.G. Palfreyman, R.H. Poyser and R.L. Whiting, European Journal of Pharmacology, 37, 179, (1976). An oscilloscope of W+W BP recorder, model 8002, was used to display pulses. Prior to all measurements rats were placed in a heated environment (33.5 ± 0.5°C) before transfer to a restraining cage. Each determination of blood pressure was the mean of at least 6 readings. Spontaneously hypertensive rats (aged 12-18 weeks) with systolic blood pressures 170 mmHg were considered hypertensive.

Compound 2 gave a 41% reduction in blood pressure at 4 hours post dose at a dose of 10 mg/kg p.o.

**Toxicity**

No toxic effects were observed in the above tests.
1. A compound of formula (I), or a pharmaceutically acceptable salt and/or N-oxide and/or a solvate thereof:

![Chemical Structure](image)

wherein:

one of X and Y is CO and the other is NH;

E is O, S or NR wherein R is hydrogen, C<sub>1</sub>–6 alkyl or a protecting group and A is C<sub>2</sub>–4 alkyne or C<sub>2</sub>–4 alkenylene or E and A together with the phenyl to which they are attached form a quinoline nucleus;
R₄ is a group:

\[(\text{CH}_2)^q\]  
\[\text{NR}_5\]  
\[(\text{CH}_2)^p\]  

(II)

\[\text{N-R}_5\]  
\[\text{Z}\]  
\[\text{or}\]  

(III)

\[\text{CHR}_6\]  
\[\text{CHR}_7\]  
\[(\text{CHR}_8)^n\]  

(IV)

wherein:

p and q each independently are 0 to 2;
Z is O or S;
n is 0 or 1;
one of R₆ and R₇ when n=0 is C₁-₄ alkoxy, C₁-₄ alkoxy carbonyl, hydroxy or C₁-₄ alkyl optionally substituted by hydroxy, C₁-₄ alkoxy or C₁-₄ acyloxy, and the other is hydrogen or C₁-₄ alkyl or one of R₆,
R7 and R8 when n=1 is C1-4 alkyl and the other two are the same or different and are hydrogen or C1-4 alkyl;

R5 is C1-7 alkyl, -(CH2)sR10, s being 0 to 2 and R10 being C3-8 cycloalkyl, -(CH2)tR11, t being 1 or 2 and R11 being thiyl or phenyl optionally substituted by one or two substituents selected from C1-4 alkoxy, trifluoromethyl, halogen, nitro, carboxy, esterified carboxy and C1-4 alkyl optionally substituted by hydroxy, C1-4 alkoxy, carboxy, esterified carboxy or in vivo hydrolysable acyloxy;

R1 is hydrogen or C1-6 alkyl; and

R2 and R3 are the same or different and are hydrogen, halogen, trifluoromethyl, C1-6 alkoxy, C1-6 alkylthio, carboxylic C1-7 acyl, carboxylic C1-7 acylamino, C1-6 alkylsulphonyl, C1-6 alkylsulphinyl, nitro or NR12R13, NR12R13CO, NR12 R13SO2, or C1-6 alkyl-SO2NR14, NR12R13SO2NR14 wherein R12 and R13 are the same or different and are hydrogen C1-6 alkyl, phenyl or phenyl C1-4 alkyl groups any of which phenyl moieties may be substituted by one or more halogen, trifluoromethyl, C1-6 alkoxy or nitro groups, or R12 and R13 together form C4-5 polymethylene, and R14 is hydrogen or C1-6 alkyl.
2. A compound according to claim 1 of formula (VI):

\[
\begin{align*}
\text{CO-NH} & \quad (\text{CH}_2)_q \\
\text{N-R}_5 & \quad (\text{CH}_2)_p \\
\end{align*}
\]

wherein \( E^1 \) is 0, S or NR\(^1 \) wherein \( R^1 \) is hydrogen, methyl or acetyl, \( m \) is 1 or 2, \( R^1_3 \) is aminosulphonyl optionally substituted as defined for \( R_3 \) in claim 1 and the remaining variables are as defined in claim 1.

3. A compound according to claim 2 of formula (VIII):

\[
\begin{align*}
\text{CO-NH} & \quad N-R^2_5 \\
\end{align*}
\]

wherein

\( R^2_5 \) is thienylmethyl or \(-(\text{CH}_2)_tR_{11}\), \( t \) being 1 or 2, and \( R_{11} \) being phenyl optionally substituted by one or two substituents selected from Cl-4 alkoxy,
trifluoromethyl, halogen, carboxy, esterified carboxy,
and C<sub>1</sub>-4 alkyl optionally substituted by hydroxy, C<sub>1</sub>-4
alkoxy, carboxy esterified carboxy or in vivo
hydrolysable acyloxy, and the remaining variables are
as defined in claim 2.

4. A compound according to claim 1 of formula (XIII):

\[
\text{CO-NH} \quad \begin{array}{c}
\text{(CH}_2\text{)}_q \\
\text{NR}_5 \\
\text{(CH}_2\text{)}_p
\end{array}
\]

\[
\text{(XIII)}
\]

\[
\begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{(CH}_2\text{)}_m
\end{array}
\]

wherein \( R^1 \) and \( R^2 \) are the same or different and are
hydrogen, halogen, hydroxy, C<sub>1</sub>-6 alkoxy, C<sub>1</sub>-6
alkythio, trifluoromethyl, amino or C<sub>1</sub>-7 acylamino;
and the remaining variables are as defined in claim 2.
5. A compound according to claim 4 of formula (XV):

wherein the variable groups are as defined in claims 3 and 4.

6. A compound according to any one of claims 2 to 5 wherein $E^1$ is oxygen.

7. A compound according to any one of claims 2 to 6 wherein $m$ is 1 and $R_1$ is 2-methyl.

8. A compound according to any one of claims 2 to 6 wherein $m$ is 2 and $R_1$ is hydrogen.

9. A compound according to anyone of claims 1 to 8 wherein $R_5$ (or $R^{25}$) is benzyl.

10. $N$-[3β(8-benzyl-8-azabicyclo (3,2,1)octyl)]-chroman-8-carboxamide,
6-Dimethylaminosulphonyl-N-[3β(8-benzyl-8-azabicyclo
8-(3,2,1)octyl)]chroman-8-carboxamide,

2-methyl-2,3-dihydrobenzofuryl-7(N-3β(8-benzyl
8-azabicyclo(3,2,1)octyl)]carboxamide,

N-(3β-(8-benzyl-8-azabicyclo(3,2,1)octyl)]-8-[1,2,3,4-
tetrahydroquinolinyl]carboxamide,

6-dimethylaminosulphonyl-N-[3β-8-benzyl-8-azabicyclo-
[3.2.1]]-8-[1,2,3,4-tetrahydroquinolinyl]carboxamide,

2-Methyl-5-dimethylaminosulphonyl-2,3-dihydrobenzo-
furyl-7(N[3β(8-benzyl-8-azabicyclo[3,2,1]octyl)])
carboxamide,

6-Cyclopentylaminosulphonyl-N[3β(8-benzyl-8-azabicyclo-
[3.2.1]octyl)]-8-chromancarboxamide, or a
pharmacologically acceptable salt thereof.

11. A process for the preparation of a compound
according to any one of claims 1 to 10, which process
comprises reacting a compound of the formula (XIX):

![Diagram](XIX)
with a compound of formula (XX):

\[ L-R_4 \] (XX)

wherein:
One of \( J \) and \( L \) is COQ, where \( Q \) is a leaving group, and the other is \(-\text{NH}_2\); and the remaining variable groups are as defined in claim I, with the proviso that when \( J \) is \(-\text{NH}_2\), \( R_2 \) or \( R_3 \) is other than amino, and thereafter optionally converting \( R, R_1, R_2 \) or \( R_3 \) to another \( R, R_1, R_2 \) or \( R_3 \) respectively; as necessary converting \( R_5 \) to other \( R_5 \); and optionally forming a pharmaceutically acceptable salt of the resultant compound of the formula (I).

12. A pharmaceutical composition comprising a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

13. A method of treatment of disorders related to impaired gastric motility, emesis and/or disorders of the central nervous system in mammals, which comprises the administration to the sufferer of an effective amount of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof.
**INTERNATIONAL SEARCH REPORT**

**INTERNATIONAL CLASSIFICATION OF SUBJECT MATTER**

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

- **IPC**: C 07 D 451/04, 451/14; A 61 K 31/46, 31/435; C 07 D 311/74, 307/79; C 07 C 69/92; C 07 C 69/84, 69/90

**FIELDS SEARCHED**

**Classification System**

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**DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>A</td>
<td>EP, A, 0068700 (BEECHAM) 5 January 1983</td>
<td>see examples 1-3, 8-9, 12-13; claims</td>
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<td>EP, A, 0095262 (BEECHAM) 30 November 1983</td>
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<td>X</td>
<td>WO, A, 8400166 (BEECHAM) 29 January 1984</td>
<td>see examples 31B, 32B, C4, C5; claims</td>
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**CERTIFICATION**

Date of Actual Completion of the International Search: 16th May 1984

Date of Mailing of this International Search Report: 02 Jui 1984

International Searching Authority: EUROPEAN PATENT OFFICE

Signature of Authorized Officer: [Signature]

Form PCT/ISA/210 (second sheet) (October 1981)
FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

VII. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE 10

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

1. × Claim numbers... because they relate to subject matter not required to be searched by this Authority, namely:

   Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods

   (PCT Rule 39.1(iv))

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:

VIII. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 11

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.
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 EDP file on 26/06/84.

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