We, DR KARL THOMAE GmbH, a body corporate of Federal Republic of Germany, of D-7950 Biberach an der Riss, Federal Republic of Germany, hereby apply for the grant of a Patent for an invention entitled "USE OF CONDENSED DIAZEPINONES" which is described in the accompanying complete specification.

This application is a Convention application and is based on the Application Numbered P3919076.5 for a patent or similar protection made in West Germany on 10 June 1989.

Our address for service is care of CALLINAN LAWRIE, Patent Attorneys, of 278 High Street, Kew, 3101, Victoria, Australia.

DATED this 8 day of June 1990.

DR KARL THOMAE GmbH
By their Patent Attorneys:

CALLINAN LAWRIE

To: The Commissioner of Patents.
Declaration in Support of an Application for Patent

In support of the Convention application made for a patent for an invention entitled
"USE OF CONDENSED DIAZEPINONES".

I, Keith W. Callinan, of 278 High Street, Kew, 3101, Victoria, Australia, do solemnly and sincerely declare as follows:-

1. I am authorised by DR KARL THOMAE GmbH the applicant for the patent to make this declaration on its behalf.

2. The basic application as defined by Section 141 of the Act is -

   Filing Date  Country        Applicant
   10 June 1989  West Germany  DR KARL THOMAE GmbH

3. The basic application referred to in this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

   Wolfhard ENGEL, of Mozartstrasse 13, D-7950 Biberach 1, West Germany; Norbert MAYER, of Friedrich-Ebert-Strasse 66, D-7950 Biberach 1, West Germany; Henri DOODS, of Hornsteinweg 7, D-7951 Biberach 1, West Germany; Wolfgang EBERLEIN, of Obere Au 6, D-7950 Biberach 1, West Germany; Gerhard MIHM, of Nickeleshalde 5/1, D-7950 Biberach 1, West Germany; and Klaus RUDOLF, of Marktplatz 38, D-7950 Biberach 1, West Germany are the actual inventors of the invention and the facts upon which the applicant is entitled to make the application are as follows:-

   The applicant would, if a patent were to be granted upon an application made by the actual inventors, be entitled to have the patent assigned to it.

Declared at Kew, Victoria this 8th day of June 1990.

Signed: [Signature]

AUSTRALIA PATENTS ACT 1952


It has now surprisingly been found that the compounds described in the above-mentioned publications as vagal pacemakers for treating bradycardia and bradyarrhythmia also have completely different activities.
Condensed diazepinones of general formulae

![Formula 1a](image)

and

![Formula 1b](image)

can be used for treating diseases of the central nervous system, particularly Alzheimer's disease and Parkinson's disease. They increase cerebral blood flow and can therefore be used in geriatric medicine and for treating migraine as well, and furthermore they have an antiemetic effect.
TO BE COMPLETED BY APPLICANT

Name of Applicant: DR KARL THOMAE GmbH

Address of Applicant: a body corporate of Federal Republic of Germany, of D-7950 Biberach an der Riss, Federal Republic of Germany

Actual Inventors: Wolfhard ENGEL, Norbert MAYER, Henri DOODS, Wolfgang EBERLEIN, Gerhard MIHM and Klaus RUDOLF

Address for Service: CALLINAN LAWRIE, 278 High Street, Kew, 3101, Victoria, Australia

Complete Specification for the invention entitled: “USE OF CONDENSED DIAZEPINONES”

The following statement is a full description of this invention, including the best method of performing it known to me:-
USE OF CONDENSED DIAZEPINONES

The invention relates to the use of certain condensed diazepinones for treating diseases of the central nervous system and for promoting cerebral blood flow.


It has now surprisingly been found that the compounds described in the above-mentioned publications as vagal pacemakers for treating bradycardia and bradyarrhythmia also have completely different activities. In the light of their antiemetic properties some of these compounds are also suitable for preventing travel sickness and seasickness and in view of their
favourable effects on cerebral blood flow they are also suitable for use in geriatric medicine and for the treatment of migraine. However, in particular, a number of these compounds show good suitability for use against CNS disorders due to their highly lipophilic nature and can be used to treat diseases of the central nervous system, particularly Alzheimer's disease and Parkinson's disease.

Thus, according to one aspect, the invention provides the use of a compound of formula I

![Chemical Structure](image)

(\text{wherein} ~ B ~ \text{represents a divalent group (S), (T), (U), (V) or (W)})

R¹ represents a C₄₋₄ alkyl group or a chlorine or hydrogen atom,

R² represents a hydrogen atom or a methyl group,

R³ and R⁴ each independently represent a hydrogen, fluorine, chlorine or bromine atom or a C₄₋₄ alkyl group,

R⁵ represents a hydrogen or chlorine atom or a methyl group,
R^6 represents a hydrogen, chlorine, fluorine or bromine atom or a C_{1-4} alkyl group,

R^7 represents a hydrogen atom or a C_{1-4} alkyl group,

R^2 represents a hydrogen atom or a methyl group,

X^1 and X^2 independently represent nitrogen atoms or =CH-groups or \( \text{B} \) represents a group (S), (T), (U) or (V) X^2 may also represent a =CCl- group and E is defined as follows:

a) E represents a group of formula II

\[
\begin{align*}
A^1 & - N \\
& \quad Z \\
& \quad R^8 \\
A^2 & - N \\
& \quad R^9 \\
\end{align*}
\]

where

A^1 represents a C_{1-2} alkylene group,

A^2 represents a C_{1-2} alkylene group in a 2-position relative to the nitrogen of the saturated heterocyclic ring or a A^2 represents single bond or a methylene group in a 3- or 4-position relative to the nitrogen of said saturated heterocyclic ring,

Z represents a single bond, an oxygen atom or a methylene or 1,2-ethylene group,

R^8 represents a branched or unbranched C_{1-3} alkyl group, and
R\textsuperscript{9} represents a branched or unbranched C\textsubscript{1-7} alkyl group optionally substituted at a 2nd to 7th carbon atom by a hydroxy group, or R\textsuperscript{9} represents a C\textsubscript{2-7} cycloalkyl or (C\textsubscript{2-7}cycloalkyl)methyl group optionally substituted by a hydroxy group,

or R\textsuperscript{8} and R\textsuperscript{9} together with the intervening nitrogen atom form a 4- to 7-membered saturated, monocyclic heterocyclic ring optionally also be interrupted by an oxygen atom or by an \(\text{N-CH}_3\) group,

and where any one of R\textsuperscript{1}, R\textsuperscript{2}, R\textsuperscript{3} and R is other than hydrogen R\textsuperscript{8} and R\textsuperscript{9} independently represent C\textsubscript{1-6} alkyl groups and \(\text{A}\) and \(\text{X}^2\) respectively represent a methylene group and a nitrogen atom,

with the proviso that where E represents a group of formula II then R\textsuperscript{6} represents a hydrogen or chlorine atom or a C\textsubscript{1-4} alkyl group, \(\text{X}^1\) represents a \(=\text{CH-}\) group, and either \(\text{X}^2\) represents a \(=\text{CH-}\) group and \(\text{B}\) represents a group (S), (T) or (U) or \(\text{X}^2\) represents a nitrogen atom and \(\text{B}\) represents an ortho-phenylene group; or

b) E represents a group of formula III

![Illustration of formula III]

Wherein

\(\text{A}\) represents a straight-chained or branched, saturated C\textsubscript{3-7} alkylene group optionally interrupted by an oxygen or sulphur atom or by a group >NR\textsuperscript{12} where R\textsuperscript{12} represents a
C<sub>1-3</sub> alkyl group,

Z<sup>1</sup> represents a single bond, an oxygen or sulphur atom or a methylene or 1,2-ethylene group,

R<sub>10</sub> represents a branched or unbranched C<sub>1-7</sub> alkyl group, a cycloalkyl or (cycloalkyl)alkyl group with a total of up to 8 carbon atoms, an aralkyl group with up to 9 carbon atoms optionally substituted by a fluorine, chlorine or bromine atom and/or by a methyl, methoxy or trifluoromethyl group, an aliphatic acyl group with up to 7 carbon atoms or a benzoyl group optionally substituted by a fluorine, chlorine or bromine atom and/or by a methyl, methoxy or trifluoromethyl group,

R<sub>11</sub> represents a branched or unbranched C<sub>1-4</sub> alkyl group, and where R<sub>10</sub> represents an aliphatic acyl or optionally substituted benzoyl group R<sub>11</sub> may also represent a hydrogen atom, or

R<sub>10</sub> and R<sub>11</sub> together with the intervening nitrogen atom may form a saturated, monocyclic 5-, 6- or 7-membered ring optionally substituted by an aminocarbonyl, dimethylaminocarbonyl or diethylaminocarbonyl group and/or interrupted by an oxygen atom, or

R<sub>11</sub> is bonded to a carbon atom of the A<sup>2</sup>-chain and, together with the group >NR<sub>12</sub>, forms a saturated 5-, 6- or 7-membered heterocyclic ring,

with the proviso that where E represents a group of formula III then R<sup>2</sup> represents a hydrogen or chlorine atom or a C<sub>1-4</sub> alkyl group, X<sup>1</sup> represents a =CH- group, R<sup>1</sup> and R<sup>2</sup> represent hydrogen atoms, X<sup>2</sup> represents a nitrogen atom or a =CH- group and E represents a group (S), (T), (U) or (V); or
c) E represents a group of formula IV

\[-A^4 - CH_2 - C = C - CH_2 - A^5\]  

(IV)

wherein

A^4 represents a group H=Ca-R^{13}, \(N-R^{13}\) or -O-, and

A^5 represents a group

\[
\begin{array}{c}
\text{N}\text{-}\text{R}^{14} \\
\text{N}\text{-}\text{R}^{15} \\
\text{N} \text{-} \left(\text{CH}_2\right)_n \text{-} \text{N} \text{-}\text{R}^{16} \\
\text{N} \text{-}\text{R}^{17}
\end{array}
\]

R^{13} represents a hydrogen atom or a C_{1-3} alkyl group,

R^{14} and R^{15} which may be the same or different each represents a hydrogen atom, a C_{1-3} alkyl group, a phenylalkyl group with a total of 7 to 9 carbon atoms or a 5- to 7-membered cycloalkyl group optionally substituted by a hydroxy group,

n represents the number 0, 1 or 2,

R^{16} represents a hydrogen atom, a hydroxy group, a C_{1-3} alkyl group or a group of formula

\[
\begin{array}{c}
\text{R}^{18} \\
\text{R}^{19}
\end{array}
\]

(where n is as hereinbefore defined and R^{18} and R^{19} each independently represents a C_{1-3} alkyl group) and

R^{17} represents a straight-chained or branched C_{1-3} alkyl group or a phenylalkyl group with a total of 7 to 9
carbon atoms,

with the proviso that where E represents a group of
formula IV then \( X^1 \) represents a group \(-\text{CH-}\), \( X^2 \) represents
a nitrogen atom, \( \text{B} \) represents an orthophenylene group
and \( R^1, R^2, R^3 \) and \( R^4 \) represent hydrogen atoms; or

d) E represents a group of formula V

\[
\begin{align*}
\text{R}^{21} \\
\text{R}^{22}
\end{align*}
\]

wherein

\( \text{R}^{20} \) represents a hydrogen atom or a C\(_{1-3}\) alkyl group,

\( \text{R}^{21} \) represents a hydrogen atom or a C\(_{1-4}\) alkyl group,

\( \text{R}^{22} \) represents a C\(_{1-3}\) alkyl group optionally substituted
by a phenyl group or a 5- to 7-membered cycloalkyl group
optionally substituted by a hydroxy group, or

\( \text{R}^{21} \) and \( \text{R}^{22} \) together with the intervening nitrogen atom
represent a 5- to 7-membered saturated monocyclic ring
optionally substituted by a di(C\(_{1-3}\)alkyl)aminoC\(_{1-3}\)alkyl
group, a hydroxy group or a C\(_{1-3}\)alkyl group, or a 1-
piperazinyl group substituted in the 4-position by a
C\(_{1-3}\)alkyl, phenylC\(_{1-3}\)alkyl or phenyl group, and

\( m \) represents the number 1, 2 or 3,

with the proviso that where E represents a group of
formula V then \( X^1 \) and \( X^2 \) represent \(-\text{CH-}\) groups, \( R^1 \) and \( R^2 \)
represent hydrogen atoms and \( \text{B} \) represents a group
(U); or
e) E represents a group of formula VI

\[
\begin{align*}
\text{VII} \\
\text{wherein} \\
A^6 \text{ and } A^7 \text{ independently represent straight-chained} \\
saturated C_{1-4} \text{ alkylene groups, and} \\
R^{23} \text{ and } R^{24} \text{ represent hydrogen atoms or branched or} \\
unbranched C_{1-4} \text{ alkyl groups or } C_{4-7} \text{ cycloalkyl groups} \\
\text{which may optionally be further substituted by a hydroxy} \\
\text{group,} \\
\end{align*}
\]

with the provisos that where E represents a group of 
formula VI then X^1 represents a \(-\text{CH-} \) group, that where 
\{B\} represents a group (T) and R^5 represents a hydrogen 
atom then R^5 represents C_{1-4} alkyl group or a hydrogen atom 
and that where \{B\} represents a group (V) then X 
represents a \(-\text{CH-} \) group; or

f) E represents a group of formula VII

\[
\begin{align*}
\text{VII} \\
\text{wherein} \\
A^6 \text{ and } A^8 \text{ independently represent straight chained or} \\
branched saturated C_{1-4} \text{ alkylene groups,}
\end{align*}
\]
z' represents an oxygen atom or a C$_{1-3}$ alkylene chain,

R$_{26}$ represents a branched or unbranched C$_{1-7}$ alkyl group, a cycloalkyl or (cycloalkyl)alkyl group with a total of up to 8 carbon atoms or a hydrogen atom, and

R$_{27}$ represents a branched or unbranched C$_{1-6}$ alkyl group or a cycloalkyl group with up to 7 carbon atoms,

with the provisos that where E represents a group of formula VII then R$^1$ and R$^2$ represent hydrogen atoms, X$^1$ represents a =CH- group and [8] represents a group (S), (T), {U} or (V) and that where [8] represents a group (V) X$^2$ represents a =CH- or =CCl- group; or

g) E represents a group of formula VIII

\[
\begin{array}{c}
- N - A^{10} - D \\
\mid R_{28}
\end{array}
\]

(VIII)

wherein

R$_{28}$ represents a hydrogen atom or a methyl group,

A$^{10}$ represents a straight-chained or branched C$_{2-7}$ alkylene group,

D represents a group
in which $Z^1$ is as defined above,

$A^{11}$ represents a straight-chained or branched saturated C$_{1-5}$ alkylene group or if in the 3-position relative to the nitrogen of the saturated heterocyclic ring it may also represent a single bond,

$R^{29}$ represents a branched or unbranched C$_{1-4}$ alkyl group,

$R^{30}$ represents a branched or unbranched C$_{1-7}$ alkyl group optionally substituted by a hydroxy group at a 2nd to 7th carbon atom, or $R^{30}$ represents a C$_{5-7}$cycloalkyl or (C$_{5-7}$cycloalkyl)methyl group optionally substituted in the cycloalkyl ring by a hydroxy group, or $R^{29}$ and $R^{30}$ together with the intervening nitrogen atom between them form a 4- to 7-membered saturated, monocyclic, heterocyclic ring optionally interrupted by an oxygen atom or by a group $>\text{N-CH}_3$, and

$R^{31}$ represents a branched or unbranched C$_{1-6}$ alkyl group,

with the proviso that where $E$ represents a group of formula VIII then either $X^1$ or $X^2$ both represent =CH-groups or $E$ represents a group (S), (U) or (W) and $X^1$ or $X^2$ each independently represents a =CH-group or a nitrogen atom; or

h) $E$ represents a group of formula IX
wherein

Z is as hereinbefore defined,

A represents a straight-chained or branched saturated C\textsubscript{2-7} alkylene group optionally interrupted by an oxygen or sulphur atom or by a methylimino or ethylimino group,

R\textsuperscript{29} represents a benzyl group or a group R\textsuperscript{29} as hereinbefore defined, and

R\textsuperscript{30} is as hereinbefore defined or R\textsuperscript{30} may bond to A via an alkylene bridge whereby, together with the group \textsuperscript{29}-NR\textsuperscript{29}, to form a saturated 5-, 6- or 7-membered heterocyclic ring,

with the proviso that where E represents a group of formula VIII then either \(X_1\) or \(X_2\) both represent =CH- groups or \(\overline{B}\) represents a group (S), (U) or (W) and \(X_1\) or \(X_2\) each independently represents a =CH- group or a nitrogen atom; or

i) E represents a group of formula X

\[
\begin{align*}
\text{R}\textsuperscript{30} & \quad \text{R}\textsuperscript{31} \\
\text{R}\textsuperscript{30} & \quad \text{R}\textsuperscript{31}
\end{align*}
\]

wherein

R\textsuperscript{30} represents a C\textsubscript{1-3} alkyl group,

R\textsuperscript{31} represents a straight-chained or branched C\textsubscript{1-3} alkyl
group optionally substituted from the 2nd carbon atom by a hydroxy group, a \(C_2\)cycloalkyl or \((C_1\)cycloalkyl)methyl group optionally substituted in the cycloalkyl moiety by a methyl or hydroxy group, a phenyl\(C_1\)alkyl group mono- or disubstituted in the phenyl moiety \(X\) by substituents selected from halogen atoms and methyl, methoxy and trifluoromethyl groups,

\[R^{39'}\text{ and } R^{31}\text{ together with the intervening nitrogen atom form a 6- to 8-membered saturated monocyclic ring wherein a methylene group, separated by at least two ring carbons from the } A^{13}\text{ attached ring nitrogen optionally is replaced by an oxygen atom or by an imino group itself optionally substituted by a } C_1\text{-alkyl, phenyl}C_1\text{-alkyl or phenyl group, the phenyl moiety of which is optionally mono- or disubstituted by substituents selected from halogen atoms methyl, methoxy and trifluoromethyl groups, and}

\[A^{13}\text{ represents a } C_5\text{, alkyne or alkenylene group with the provisos that there are at least 5 carbon atoms between the semicyclic carbonyl group and the nitrogen atom of the } R^{39'}\text{.}

\[R^{31}\text{ } N \text{ group,}

\[R^{31}\]

and with the proviso that where } E \text{ represents a group of formula VIII then either } X^1 \text{ or } X^2 \text{ both represent } =CH- \text{ groups or } (B) \text{ represents a group } (S), (U) \text{ or } (W) \text{ and } X^1 \text{ or } X^2 \text{ each independently represents a } =CH- \text{ group or a nitrogen atom; or}

\(j\) \(E\) represents a group of formula XI
wherein

$Z^1$ is as hereinbefore defined,

$A_{14}$ represents a straight-chained C$_{1-6}$ alkylene group,

$R^{32}$ and $R^{33}$ independently represent C$_{1-6}$alkyl groups or $R^{32}$ or $R^{33}$ together with the intervening nitrogen atom form a 4- to 7-membered saturated, monocyclic, heteroaliphatic ring optionally interrupted by an imino or methylimino group,

with the proviso that where $E$ represents a group of formula VIII then either $X^1$ or $X^2$ both represent =CH- groups or $\bigg]^{\text{R}}$ represents a group (S), (U) or (W) and $X^1$ or $X^2$ each independently represents a =CH- group or a nitrogen atom,

or an isomer or physiologically acceptable acid addition salt thereof for the manufacture of a therapeutic agent for the treatment of diseases of the central nervous system, migraine or emesis or for the promotion of cerebral blood flow.

Viewed from another aspect the invention also provides the use of a compound of formula I or an isomer or physiologically acceptable acid addition salt thereof for the treatment of diseases of the central nervous system, migraine or emesis or for the promotion of cerebral blood flow.

Viewed from a further aspect the invention provides a method of treatment of the human or non-human,
preferably mammalian, body to combat diseases of the central nervous system, migraine or emesis or to promote cerebral blood flow, said method comprising in need of such treatment administering to said body a compound of formula I or an isomer or physiologically acceptable acid addition salt thereof.


The compounds of formula I exhibit generally advantageous effects on cerebral blood flow and are therefore suitable for use in geriatric medicine and for the treatment of migraine.

The stimulation of muscarinic receptors in arteries which have suffered endothelial damage, e.g. coronary or basilar arteries, results in constriction. For example, vagally released acetylcholine reduces the coronary blood flow in isolated rat hearts, whilst methacholine brings about dosage-dependent contraction in coronary and basilar arteries in in vitro trials (K.J. van Charlordorp, Dissertation "Characterisation of Muscarinic Receptors in the Vascular System", Amsterdam 1988; K.J. van Charlordorp, D. Davidesko and P.A. van Zwieten, Eur. J. Pharmacol. 152, 197-199 (1988); K.J. van Charlordorp and P.A. van Zwieten, Naunyn Schmiedebergs Arch. Pharmacol. 339, 403-408 (1989)).

The above-mentioned investigations provide clear indications that the cholinergic stimulation of vascular muscarinic receptors is of pathophysiological importance, e.g. in patients suffering from Prinzmetal angina or those who have suffered cerebral sclerotic damage. Inhibition of the muscarinic receptors which can be detected in the blood vessels in the brain thus
results in the prevention of constriction and an improvement or normalisation in the arteriosclerotic induced disorders of cerebral blood flow. The compounds of the present application inhibit the muscarinic receptors which are detectable in cerebral blood vessels, for example in the pia mater, even at physiologically attainable concentrations or plasma levels and are suitable for developing drugs for treating arteriosclerotic produced blood flow disorders in the CNS.

Owing to their highly lipophilic nature, a number of compounds of formula I exhibit good CNS availability and are therefore additionally suitable for the treatment of diseases of the central nervous system, particularly Alzheimer's disease and Parkinson's disease. In Alzheimer's disease the compounds influence the autoregulatory function of presynaptic muscarinic receptors on the release of acetylcholine and consequently lead to a strengthening of the impulse pattern of the cholinergic fibres still present, whilst in Parkinson's disease the advantage of using the compounds of general formula I instead of the non-selective antimuscarinics which have hitherto been conventional is the absence of intolerable peripheral and central atropine-like side effects.

In senile dementia of the Alzheimer type, the degeneration of cholinergic neurones, particularly in hippocampal and cortical projections, leads to a reduced release of the neurotransmitter acetylcholine. The blockage of the presynaptic autoreceptors interrupts the negative feedback mechanism which the neurotransmitter exerts on the intact neurones, and therefore brings about an increased release of acetylcholine and, as a result, stimulation of the presynaptic receptors (D.C. Mash, D.L. Flynn and L.T. Potter, Science 228, 115-117 (1985); E.K. Perry et al., Can. J. Neurol. Sci. 13, 521-527 (1986); M. Sarter et al., TINS 11, 13-17
The following experiments were carried out in order to demonstrate the favourable effects on cerebral blood flow and the increased release of acetylcholine:

A. Binding of various muscarinic antagonists to receptors in the pia mater of the cerebral cortex

The pia blood vessels from cattle brains, obtained from the local abattoir, were dissected and cleaned to remove any residual blood. 0.5 g batches were stored at 8.0°C until required for use. In order to obtain a homogenised preparation, 0.5 g of pia blood vessels were comminuted using a tissue mincer, taken up in 60 ml of HEPES buffer (20 mM HEPES, 10 mM MgCl₂, 100 mM NaCl, pH 7.50), homogenised using an Ultra-Turrax and centrifuged for 20 minutes at 0°C at 48000 x g. The pellet was homogenised again using an Ultra-Turrax, filtered through muslin and diluted with HEPES buffer to a dilution of 1:140 based on the moist weight of the vessels.

0.3 nM [³H]NMS (³H-N-methylscopolamine) and increasing concentrations of the antagonist were incubated with the homogenised material in a total volume of 0.52 ml for 45 minutes at ambient temperature. The incubation mixture was filtered through glass fibre filter mats using a Scatron Cell Harvester and washed twice with ice-cold physiological saline solution. The filter-bound radioactivity was measured in a liquid scintillation counter. The bound radioactivity in the presence of 10⁻⁶M (-)-quinuclidinyl benzylate was defined as non-specific binding.

B. Transmitter release studies

The tests on in vitro release of acetylcholine from sections of hippocampal tissue were carried out.

Male rats of the Chbb:Thom strain, (weighing 200 to 300 g) were decapitated without any preliminary treatment; the whole brain was immediately removed and broken up while cooling with ice. Using the methods described above the hippocampus was cut into 0.4 mm thick slices using a McIlwain tissue cutter. The slices of tissue were pre-incubated for 30 minutes at 37°C in the presence of 0.05 mM \( ^3 \text{H} \)-choline in a Krebs-Henseleit buffer having the following composition: 120 mM NaCl, 4.8 mM KCl, 1.3 mM CaCl\(_2\), 1.2 mM KH\(_2\)PO\(_4\), 1.2 mM MgSO\(_4\) and 25 mM NaHCO\(_3\). The buffer additionally contained 2 g of glucose and 100 mg of EDTA. The buffer was adjusted to a pH of 7.4 at 20°C by means of sodium hydroxide solution. All the solutions were continuously saturated with 95\% O\(_2\) and 5\% CO\(_2\). The slices of tissue were then rinsed, and each slice of tissue was randomly distributed over 12 superfusion units and rinsed with the buffer at 37°C at a flow rate of 1 ml/min. The slices of tissue were held between two platinum electrodes by means of a polypropylene mesh. After 50 minutes' rinsing, 4 minute fractions of the superfused material were collected over a total period of 92 minutes. The slices of tissue were electrically stimulated twice, at 60 minutes (S1) and 100 minutes (S2) after the start of superfusion. Rectangular pulses lasting 2 ms with a frequency of 3 Hz were administered for 100 seconds at 5 V/cm and 24 mA using an HSE stimulator II made by Hugo Sachs Elektronik of Hugstetten, West Germany. The substances to be tested were added to the buffer starting 20 minutes before time S2 together with the agonist (Carbachol). At the end,
the tissue slices were removed from the chambers and solubilised in order to determine the quantity of tritium remaining.

The filter discs with the radioactivity bound to the receptors or to the membranes together with the synaptosomes were placed in minivials with the addition of 3 ml of a scintillation cocktail (Quickszint 2000, Zinsser Analytic, Frankfurt, West Germany) and slowly rotated for one hour. The extracts from the MAO activity measurement (4 ml) were transferred into standard vials with 10 ml of this cocktail. The radioactivity was then determined by conventional liquid scintillation measurement with external standardisation in Beckman LS 3800 or LS 7800 instruments. The results are shown in Table II.

C. Studies of binding to muscarinic receptors in the cortex

The organ donors were male Sprague-Dawley rats weighing 180-220 g. After removal of the cerebral cortex, all further steps were carried out in ice-cold HEPES HCl buffer (pH 7.4; 100 m molar NaCl, 10 m molar MgCl₂). The whole heart was cut up with scissors. All the organs were then homogenised in a Potter apparatus.

For the binding test the homogenised organ preparations were diluted as follows:

- Whole heart 1: 400 by volume
- Cerebral cortex 1:3000 by volume
- Submandibular gland 1: 400 by volume

The homogenised organ preparations were incubated at a specific concentration of the radioligand and at a series of concentrations of the non-radioactive test substances in Eppendorf centrifuge test-tubes at 30°C. Incubation was continued for 45 minutes. 0.3 N molar \( ^3\)H-
N-scopolamine (³H-NMS) was used as the radioligand. Incubation was ended by the addition of ice-cold buffer followed by vacuum filtration. The filters were rinsed with cold buffer and their radioactivity was determined. It represents the sum of specific and non-specific binding of ³H-NMS. The proportion of non-specific binding was defined as the radioactivity which was bound in the presence of 1 µ molar quinuclidinyl benzylate. Four-fold measurements were carried out in each case. The IC₅₀ values of the unlabelled test substances were determined graphically. They represent the concentration of test substance at which specific binding of ³H-NMS to the muscarinic receptors in the various organs was inhibited by 50%. The results are shown in Table II.

The following compounds were tested by way of example, using the methods described hereinbefore:

A (+)-11-[[2-[(diethylamino)methyl]-1-piperidinyl]-acetyl]-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one;

B 5,11-dihydro-11-[1-oxo-6-(1-piperidinyl)-4-hexyn-1-yl]-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one;

C (±)-9-chloro-11-[[2-[(diethylamino)methyl]-1-piperidinyl]-acetyl]-5,11-dihydro-6H-pyrido[2,3-b]-[1,4]benzodiazepin-6-one;


E 5,11-dihydro-11-[[3-[3-(1-piperidinyl)-1-propyl]-1-piperidinyl]carbonyl]-6H-pyrido[2,3-b][1,4]-benzodiazepin-6-one;
F 4,9-dihydro-3-methyl-4-[[4-[3-(1-piperidinyl)-1-propyl]-1-piperidinyl]acetyl]-10H-thieno[3,4-b]-[1,5]benzodiazepin-10-one;

G 5,11-dihydro-11-[1-oxo-6-(1-piperidinyl)-1-hexyl]-6H-pyrido[2,3-b][1,4]benzodiazepin-10-one;

H 4,9-dihydro-3-methyl-4-[[6-(hexahydro-1H-1-azepinyl)-1-oxo-4-hexyn-1-yl]-10H-thieno[3,4-b][1,5]benzodiazepin-10-one;

I 11-[4-[3-([diethylamino)methyl]-4-morpholinyl]-1-oxo-1-butyl]-5,11-dihydro-6H-pyrido[2,3-b]-[1,4]benzodiazepin-6-one;

K 5,11-dihydro-11-[[2-(1-methyl-2-pyrrolidinyl)-ethyl]methylamino]acetyl]-6H-pyrido[2,3-b][1,4]-benzodiazepin-6-one; and

The results are set forth in the following Tables:

**Table I:**

Inhibition of $^3$H-NMS binding to muscarinic receptors in the pia mater of cattle

<table>
<thead>
<tr>
<th>Substance</th>
<th>$-\log IC_{50}$ (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>7.1</td>
</tr>
<tr>
<td>B</td>
<td>6.9</td>
</tr>
<tr>
<td>C</td>
<td>7.5</td>
</tr>
<tr>
<td>D</td>
<td>7.9</td>
</tr>
<tr>
<td>E</td>
<td>8.8</td>
</tr>
<tr>
<td>F</td>
<td>8.6</td>
</tr>
<tr>
<td>H</td>
<td>8.0</td>
</tr>
<tr>
<td>I</td>
<td>7.7</td>
</tr>
<tr>
<td>K</td>
<td>8.2</td>
</tr>
<tr>
<td>L</td>
<td>8.4</td>
</tr>
</tbody>
</table>
Table II:

Influence on the release of transmitter by comparison with the affinity for muscarinic receptors of the M₁ subtype

<table>
<thead>
<tr>
<th>Substance</th>
<th>ACh release in hippocampus tissue (pA₂)</th>
<th>Receptor binding tests cortex -log IC₅₀ (M)</th>
<th>Ratio of IC₅₀ (cortex) to pA₂ (ACh release)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>7.15</td>
<td>6.00</td>
<td>14</td>
</tr>
<tr>
<td>B</td>
<td>7.2</td>
<td>5.92</td>
<td>19</td>
</tr>
<tr>
<td>C</td>
<td>7.3</td>
<td>6.30</td>
<td>10</td>
</tr>
<tr>
<td>D</td>
<td>8.35</td>
<td>7.05</td>
<td>20</td>
</tr>
<tr>
<td>E</td>
<td>9.55</td>
<td>8.00</td>
<td>35</td>
</tr>
<tr>
<td>F</td>
<td>7.7</td>
<td>7.22</td>
<td>3</td>
</tr>
<tr>
<td>G</td>
<td>8.45</td>
<td>7.22</td>
<td>17</td>
</tr>
<tr>
<td>H</td>
<td>8.0</td>
<td>7.15</td>
<td>7</td>
</tr>
<tr>
<td>I</td>
<td>7.5</td>
<td>7.0</td>
<td>3</td>
</tr>
<tr>
<td>K</td>
<td>8.5</td>
<td>7.52</td>
<td>10</td>
</tr>
<tr>
<td>L</td>
<td>8.45</td>
<td>7.40</td>
<td>11</td>
</tr>
</tbody>
</table>

Table I above shows that the compounds used according to the invention are capable of inhibiting muscarinic receptors of the cerebral blood vessels (those of the pia mater being used by way of example) even at physiologically attainable concentrations or plasma levels.

Table II above shows that the compounds used according to the invention not only block the inhibitory autoreceptors in hippocampal tissue at very low concentrations and thus increase the acetylcholine release, but are also selective, since they inhibit
postsynaptic receptors of the M₁ subtype only at appreciably higher concentrations. The compounds thus make it possible to compensate for the cholinergic deficits characteristic of senile dementia of the Alzheimer type and are suitable for use as drugs for treating Alzheimer's disease.

The invention relates in particular to the use of pharmaceutical compositions containing one or more condensed diazepinones of formula I or isomers or physiologically acceptable salts thereof for combating Alzheimer's disease and Parkinson's disease.

The compounds used according to the invention can be incorporated for this purpose in conventional pharmaceutical preparations, e.g. solutions, suppositories, plain or coated tablets, capsules or infusions. The daily dose is generally between 0.02 and 5 mg/kg, preferably between 0.02 and 2.5 mg/kg, more particularly 0.05 and 1.0 mg/kg of body weight, optionally administered in the form of several, preferably 1 to 3, individual doses, to achieve the desired results.
The preparation of some pharmaceutical forms will now be described by the following, non-limiting of Examples:

Example I

Tablets containing 5 mg of 11-[[2-[(diethylamino)methyl]-1-piperidinyl]acetyl]-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one

<table>
<thead>
<tr>
<th>Composition:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 tablet contains:</td>
</tr>
<tr>
<td>Active substance</td>
</tr>
<tr>
<td>Lactose</td>
</tr>
<tr>
<td>Potato starch</td>
</tr>
<tr>
<td>Magnesium stearate</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

A 10% mucilage is prepared from potato starch by heating. The active substance, lactose and remaining potato starch are mixed together and granulated with the above mucilage through a 1.5 mm mesh screen. The granules are dried at 45°C, rubbed through the same screen again, mixed with magnesium stearate and compressed into tablets.

Weight of tablet: 220 mg
Punch: 9 mm

Example II

Coated tablets containing 5 mg of 11-[[2-[(diethylamino)methyl]-1-piperidinyl]acetyl]-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one

The tablets prepared according to Example I are
coated by known methods with a coating consisting essentially of sugar and talc. The finished coated tablets are polished with beeswax. Weight of coated tablet: 300 mg

Example III

Ampoules containing 1 mg of 5,11-dihydro-11-[1-oxo-6-(1-piperidinyl)-4-hexynyl]-6H-pyrido[2,3-b][1,4]-benzodiazepin-6-one

Composition:
1 ampoule contains:
Active substance 10.0 mg
Sodium chloride 8.0 mg
Distilled water ad 1 ml

The active substance and sodium chloride are dissolved in distilled water and then made up to the volume specified. The solution is sterile filtered and transferred into 1 ml ampoules.
Sterilisation: 20 minutes at 120°C.

Example IV

Suppositories containing 20.0 mg of 9-chloro-11-[[2-[(diethylamino)methyl]-1-piperidinyl]acetyl]-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one

Composition:
1 suppository contains:
Active substance 20.0 mg
Suppository mass (e.g. Witepsol W 45°) 1680.0 mg
1700.0 mg
The finely powdered active substance is suspended in the suppository mass which has been melted and cooled to 40°C. At 37°C the mass is poured into slightly chilled moulds. Weight of suppository: 1.7 g.

Example V

Drops containing 5,11-dihydro-11-[[2-[[2-[(dipropylamino)methyl]-1-piperidinyl]ethyl]amino]-carbonyl]-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one-methanesulphonate

Composition:

100 ml of drops solution contain:
Methyl p-hydroxybenzoate 0.035 g
Propyl p-hydroxybenzoate 0.015 g
Aniseed oil 0.05 g
Menthol 0.06 g
Pure ethanol 10.0 g
Active substance 0.5 g
Sodium cyclamate 1.0 g
Glycerol 15.0 g
Distilled water ad 100.0 ml

The active substance and sodium cyclamate are dissolved in about 70 ml of water and glycerol is added. The p-hydroxybenzoates, aniseed oil and menthol are dissolved in ethanol and this solution is added to the aqueous solution with stirring. Finally the solution is made up to 100 ml with water and filtered to remove any suspended particles.

Example VI

Suppositories containing 20 mg of 5,11-dihydro-11-[[3-...
[3-(1-piperidinyl)propyl]-1-piperidinyl]carbonyl]-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one

Composition:
1 suppository contains:
Active substance 20.0 mg
Suppository mass (e.g. Witepsol W 45°) 1 680.0 mg
1 700.0 mg

The finely powdered active substance is suspended in the suppository mass which has been melted and cooled to 40°C. At 37°C the mass is poured into slightly chilled moulds.
Weight of suppository 1.7 g

Example VII

Tablets containing 5 mg of 4,9-dihydro-3-methyl-4-[[4-[3-(1-piperidinyl)propyl]-1-piperidinyl]acetyl]-10H-thieno[3,4-b][1,5]benzodiazepin-10-one

Composition:
1 tablet contains:
Active substance 5.0 mg
Lactose 148.0 mg
Potato starch 65.0 mg
Magnesium stearate 2.0 mg
220.0 mg

A 10% mucilage is prepared from potato starch by heating. The active substance, lactose and remaining potato starch are mixed together and granulated with the above mucilage through a 1.5 mm mesh screen. The granules are dried at 45°C, rubbed through the same screen again, mixed with magnesium stearate and...
compressed into tablets.
Weight of tablet: 220 mg
Punch: 9 mm

Example VIII

Drops containing 5,11-dihydro-11-[6-(1-piperidinyl)-1-oxo-hexyl]-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one

Composition:
100 ml of drops solution contain:
Methyl p-hydroxybenzoate 0.035 g
Propyl p-hydroxybenzoate 0.015 g
Aniseed oil 0.05 g
Menthol 0.06 g
Pure ethanol 10.0 g
Active substance 0.5 g
Sodium cyclamate 1.0 g
Glycerol 15.0 g
Distilled water ad 100.0 ml

The active substance and sodium cyclamate are dissolved in about 70 ml of water and glycerol is added. The p-hydroxybenzoates, aniseed oil and menthol are dissolved in ethanol and this solution is added to the aqueous solution with stirring. Finally the solution is made up to 100 ml with water and filtered to remove any suspended particles.

in which Z is as defined above
Example IX

Suppositories containing 50 mg of 4,9-dihydro-3-methyl-4-[1-oxo-6-(hexahydro-1H-1-azepinyl)-4-hexynyl]-10H-thieno[3,4-b][1,5]benzodiazepin-10-one

Composition:
1 suppository contains:
Active substance 50.0 mg
Suppository mass (e.g. Witepsol W 45°) 1 695.0 mg
1 745.0 mg

The finely powdered active substance is suspended in the suppository mass which has been melted and cooled to 40°C. At 37°C the mass is poured into slightly chilled moulds.
Weight of suppository: 1.745 g

Example X

Tablets containing 5 mg of 11-[4-[(diethylamino)methyl]-4-morpholinyl]-1-oxobutyl]-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one

Composition:
1 tablet contains:
Active substance 5.0 mg
Lactose 148.0 mg
Potato starch 65.0 mg
Magnesium stearate 2.0 mg
220.0 mg

A 10% mucilage is prepared from potato starch by heating. The active substance, lactose and remaining...
potato starch are mixed together and granulated with the above mucilage through a 1.5 mm mesh screen. The granules are dried at 45°C, rubbed through the same screen again, mixed with magnesium stearate and compressed into tablets.
Weight of tablet: 220 mg
Punch: 9 mm

Example XI

Drops containing 5,11-dihydro-11-[[[2-(1-methyl-2-pyrrolidinyl)ethyl]methylamino]acetyl]-6H-pyrido-[2,3-b][1,4]benzodiazepin-6-one

Composition:
100 ml of drops solution contain:
- Methyl p-hydroxybenzoate: 0.035 g
- Propyl p-hydroxybenzoate: 0.015 g
- Aniseed oil: 0.05 g
- Menthol: 0.06 g
- Pure ethanol: 10.0 g
- Active substance: 0.5 g
- Sodium cyclamate: 1.0 g
- Glycerol: 15.0 g
- Distilled water: ad 100.0 ml

The active substance and sodium cyclamate are dissolved in about 70 ml of water and glycerol is added. The p-hydroxybenzoates, aniseed oil and menthol are dissolved in ethanol and this solution is added to the aqueous solution with stirring. Finally the solution is made up to 100 ml with water and filtered to remove any suspended particles.

Example XII

form a 6- to 8-membered saturated monocyclic ring
Tablets containing 5 mg of 5,11-dihydro-11-[[2-(1-methyl-hexahydro-1H-2-azepinyl)ethyl]methylamino]-acetyl]-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one

Composition:
1 tablet contains:
- Active substance: 5.0 mg
- Lactose: 148.0 mg
- Potato starch: 65.0 mg
- Magnesium stearate: 2.0 mg

A 10% mucilage is prepared from potato starch by heating. The active substance, lactose and remaining potato starch are mixed together and granulated with the above mucilage through a 1.5 mm mesh screen. The granules are dried at 45°C, rubbed through the same screen again, mixed with magnesium stearate and compressed into tablets.

Weight of tablet: 220 mg
Punch: 9 mm

Example XIII

Tablets containing 5 mg of 11-[[4-[4-(diethylamino)-butyl]-1-piperidinyl]acetyl]-5,11-dihydro-6H-pyrido-[2,3-b][1,4]benzodiazepin-6-one

A^4 represents a straight-chained C₄₈ alkylene group.
Composition:
1 tablet contains:
Active substance  5.0 mg
Lactose          148.0 mg
Potato starch    65.0 mg
Magnesium stearate 2.0 mg

A 10% mucilage is prepared from potato starch by heating. The active substance, lactose and remaining potato starch are mixed together and granulated with the above mucilage through a 1.5 mm mesh screen. The granules are dried at 45°C, rubbed through the same screen again, mixed with magnesium stearate and compressed into tablets.
Weight of tablet: 220 mg
Punch: 9 mm
The claims defining the invention are as follows:

1. A method of treatment of the human or non-human animal body to combat diseases of the central nervous system, migraine or emesis or to promote cerebral blood flow, said method comprising administering to a body in need of such treatment a compound of formula I

\[
R^1 \text{ represents a } C_{1-4} \text{ alkyl group or a chlorine or hydrogen atom,}
\]

\[
R^2 \text{ represents a hydrogen atom or a methyl group,}
\]

\[
R^3 \text{ and } R^4 \text{ each independently represent a hydrogen, fluorine, chlorine or bromine atom or a } C_{1-4} \text{ alkyl group,}
\]

\[
R^5 \text{ represents a hydrogen or chlorine atom or a methyl group,}
\]
R6 represents a hydrogen, chlorine, fluorine or bromine atom or a C1-4 alkyl group,

R7 represents a hydrogen atom or a C1-4 alkyl group,

R25 represents a hydrogen atom or a methyl group,

X1 and X2 independently represent nitrogen atoms or =CH-groups or , where \( \text{B} \) represents a group (S), (T), (U) or (V) X8 may also represent a =CCl-group and E is defined as follows:

a) E represents a group of formula II

![Chemical structure](image)

where

A1 represents a C1-2 alkylene group,

A2 represents a C1-2 alkylene group in a 2-position relative to the nitrogen of the saturated heterocyclic ring or a A2 represents single bond or a methylene group in a 3- or 4-position relative to the nitrogen of said saturated heterocyclic ring,

Z represents a single bond, an oxygen atom or a methylene or 1,2-ethylene group,

R8 represents a branched or unbranched C1-3 alkyl group, and
R^9 represents a branched or unbranched C_1 to C_7 alkyl group optionally substituted at a 2nd to 7th carbon atom by a hydroxy group, or R^9 represents a C_3 to C_7 cycloalkyl or (C_3 to C_7 cycloalkyl)methyl group optionally substituted by a hydroxy group,

or R^8 and R^9 together with the intervening nitrogen atom form a 4- to 7-membered saturated, monocyclic heterocyclic ring optionally also be interrupted by an oxygen atom or by an N-CH_3 group,

and where any one of R^1, R^2, R^3 and R^4 is other than hydrogen R^8 and R^9 independently represent C_1 to C_6 alkyl groups and A^1 and X^2 respectively represent a methylene group and a nitrogen atom,

with the proviso that where E represents a group of formula II then R^6 represents a hydrogen or chlorine atom or a C_1 to C_4 alkyl group, X^1 represents a =CH- group, and either X^2 represents a =CH- group and B represents a group (S), (T) or (U) or X^2 represents a nitrogen atom and B represents an ortho-phenylene group; or

b) E represents a group of formula III

\[ \text{III} \]

wherein

A^3 represents a straight-chained or branched, saturated C_3 to C_7 alkylene group optionally interrupted by an oxygen or sulphur atom or by a group >NR^12 where R^12 represents a
C₁₃ alkyl group,

Z¹ represents a single bond, an oxygen or sulphur atom or a methylene or 1,2-ethylene group,

R⁰ represents a branched or unbranched C₁₇ alkyl group, a cycloalkyl or (cycloalkyl)alkyl group with a total of up to 8 carbon atoms, an aralkyl group with up to 9 carbon atoms optionally substituted by a fluorine, chlorine or bromine atom and/or by a methyl, methoxy or trifluoromethyl group, an aliphatic acyl group with up to 7 carbon atoms or a benzoyl group optionally substituted by a fluorine, chlorine or bromine atom and/or by a methyl, methoxy or trifluoromethyl group,

R¹ represents a branched or unbranched C₁₆ alkyl group, and where R⁰ represents an aliphatic acyl or optionally substituted benzoyl group R¹ may also represent a hydrogen atom or

R⁰ and R¹ together with the intervening nitrogen atom may form a saturated, monocyclic 5-, 6- or 7-membered ring optionally substituted by an aminocarbonyl, dimethylaminocarbonyl or diethylaminocarbonyl group and/or interrupted by an oxygen atom, or

R¹ is bonded to a carbon atom of the A³-chain and together with the group >NR², forms a saturated 5-, 6- or 7-membered heterocyclic ring,

with the proviso that where E represents a group of formula III then R⁶ represents a hydrogen or chlorine atom or a C₁₄ alkyl group, X¹ represents a =CH- group, R¹ and R³ represent hydrogen atoms, X² represents a nitrogen atom or a =CH- group and J( beetle) represents a group (S), (T), (U) or (V); or
c) E represents a group of formula IV

\[ -A^4 - \text{CH}_2 - \text{C} = \text{C} - \text{CH}_2 - A^5 \]  

(IV)

wherein

A^4 represents a group H-C-R^{13}, >N-R^{13} or -O-, and

A^5 represents a group

\[ \begin{array}{c}
\text{N} \\
R^{14} \\
\text{N} \\
R^{15} \\
\text{N} \\
R^{16} \\
\text{N} \\
R^{17}
\end{array} \text{ or } \begin{array}{c}
\text{N} \\
R^{14} \\
\text{N} \\
R^{15} \\
\text{N} \\
R^{16} \\
\text{N} \\
R^{17}
\end{array} \]

R^{13} represents a hydrogen atom or a C_{1-3} alkyl group,

R^{14} and R^{15} which may be the same or different each represents a hydrogen atom, a C_{1-3} alkyl group, a phenylalkyl group with a total of 7 to 9 carbon atoms or a 5- to 7-membered cycloalkyl group optionally substituted by a hydroxy group,

n represents the number 0, 1 or 2,

R^{16} represents a hydrogen atom, a hydroxy group, a C_{1-3} alkyl group or a group of formula

\[ - (\text{CH}_2)_n - \text{N} \]

\[ \begin{array}{c}
\text{R}^{18} \\
\text{R}^{19}
\end{array} \]

(where n is as hereinbefore defined and R^{18} and R^{19} each independently represents a C_{1-3} alkyl group) and

R^{17} represents a straight-chained or branched C_{1-3} alkyl group or a phenylalkyl group with a total of 7 to 9 carbon atoms,
with the proviso that where \( E \) represents a group of formula IV then \( X' \) represents a group \( =\text{CH}- \), \( X^2 \) represents a nitrogen atom, \( \text{[B]} \) represents an orthophenylene group and \( R^1, R^2, R^3 \) and \( R^4 \) represent hydrogen atoms; or

d) \( E \) represents a group of formula V

\[
\begin{align*}
-\text{CH} - (\text{CH}_2)_m - \text{C} &= \text{C} - \text{CH}_2 - N \\
\text{R}^2_2 & \\
\text{R}^2_0
\end{align*}
\]

(V)

wherein

\( \text{R}^2_0 \) represents a hydrogen atom or a \( \text{C}_{1-3} \) alkyl group,

\( \text{R}^2_1 \) represents a hydrogen atom or a \( \text{C}_{4-9} \) alkyl group,

\( \text{R}^2_2 \) represents a \( \text{C}_{1-3} \) alkyl group optionally substituted by a phenyl group or a 5- to 7-membered cycloalkyl group optionally substituted by a hydroxy group, or

\( \text{R}^2_1 \) and \( \text{R}^2_2 \) together with the intervening nitrogen atom represent a 5- to 7-membered saturated monocyclic ring optionally substituted by a \( \text{di(C}_{1-3}\text{alkyl})\text{aminoc}_{1-3}\text{alkyl} \) group, a hydroxy group or a \( \text{C}_{1-3}\text{alkyl} \) group, or a 1-piperazinyl group substituted in the 4-position by a \( \text{C}_{1-3}\text{alkyl} \), \( \text{phenylC}_{1-3}\text{alkyl} \) or phenyl group, and

\( m \) represents the number 1, 2 or 3,

with the proviso that where \( E \) represents a group of formula V then \( X' \) and \( X^2 \) represent \( =\text{CH}- \) groups, \( \text{R}^1 \) and \( \text{R}^2 \) represent hydrogen atoms and \( \text{[B]} \) represents a group (U); or

e) \( E \) represents a group of formula VI
wherein

$A^6$ and $A^7$ independently represent straight-chained saturated $C_{1-4}$ alkylene groups, and

$R^{23}$ and $R^{24}$ represent hydrogen atoms or branched or unbranched $C_{1-4}$ alkyl groups or $C_{4-7}$ cycloalkyl groups which may optionally be further substituted by a hydroxy group,

with the provisos that where $E$ represents a group of formula VI then $X^1$ represents a $=CH -$ group, that where $E$ represents a group (T) and $R^5$ represents a hydrogen atom then $R^1$ represents $C_{1-4}$ alkyl group or a hydrogen atom and that where $E$ represents a group (V) then $X$ represents a $=CH -$ group; or

f) $E$ represents a group of formula VII

wherein

$A^8$ and $A^9$ independently represent straight chained or branched saturated $C_{1-4}$ alkylene groups,

$Z^{11}$ represents an oxygen atom or a $C_{1-3}$ alkylene chain,
$R^2_6$ represents a branched or unbranched C$_1$-$7$ alkyl group, a cycloalkyl or (cycloalkyl)alkyl group with a total of up to 8 carbon atoms or a hydrogen atom, and

$R^2_7$ represents a branched or unbranched C$_1$-$6$ alkyl group or a cycloalkyl group with up to 7 carbon atoms,

with the provisos that where E represents a group of formula VII then $R^1$ and $R^2$ represent hydrogen atoms, $\chi^1$ represents a =CH- group and $\gamma$ represents a group (S), (T), (U) or (V) and that where $\delta$ represents a group (V) $\chi^2$ represents a =CH- or =CCl- group; or

g) E represents a group of formula VIII

$$\begin{array}{c}
-N-A^{10}-D \\
R^{28}
\end{array}$$ (VIII)

wherein

$R^{28}$ represents a hydrogen atom or a methyl group,

$A^{10}$ represents a straight-chained or branched C$_2$-$7$ alkylene group,

D represents a group
in which \( Z^1 \) is as defined above.

\( A^{11} \) represents a straight-chained or branched saturated C\(_{1-5}\) alkylene group or if in the 3-position relative to the nitrogen of the saturated heterocyclic ring it may also represent a single bond,

\( R^{29} \) represents a branched or unbranched C\(_{1-4}\) alkyl group,

\( R^{30} \) represents a branched or unbranched C\(_{1-7}\) alkyl group optionally substituted by a hydroxy group at a 2nd to 7th carbon atom, or \( R^{30} \) represents a C\(_{3-7}\)cycloalkyl or (C\(_3\), \( \gamma \)-cycloalkyl)methyl group optionally substituted in the cycloalkyl ring by a hydroxy group, or \( R^{29} \) and \( R^{30} \) together with the intervening nitrogen atom between them form a 4- to 7-membered saturated, monocyclic, heterocyclic ring optionally interrupted by an oxygen atom or by a group >N-CH\(_3\), and

\( R^{31} \) represents a branched or unbranched C\(_{1-6}\) alkyl group,

with the proviso that where \( E \) represents a group of formula VIII then either \( X^1 \) or \( X^2 \) both represent =CH- groups or \( \{B\} \) represents a group (S), (U) or (W) and \( X^1 \) or \( X^2 \) each independently represents a =CH- group or a nitrogen atom; or

h) \( E \) represents a group of formula IX

\[
\text{(IX)}
\]

wherein

\( Z^1 \) is as hereinbefore defined,
A^{12} represents a straight-chained or branched saturated C_{2,7} alkylene group optionally interrupted by an oxygen or sulphur atom or by a methylimino or ethylimino group,

R^{29'} represents a benzyl group or a group R^{29} as hereinbefore defined,

R^{30} is as hereinbefore defined or R^{30} may bond to A^{12} via an alkylene bridge whereby, together with the group -NR^{29'}, to form a saturated 5-, 6- or 7-membered heterocyclic ring,

with the proviso that where E represents a group of formula VIII then either X^1 or X^2 both represent =CH- groups or E) represents a group (S), (U) or (W) and X^1 or X^2 each independently represents a =CH- group or a nitrogen atom; or

i) E represents a group of formula X

\[
\begin{array}{c}
{\text{R}}^{30'} \\
\text{R}^{31}
\end{array}
\]

\begin{equation}
\text{R}^{30'} \quad \text{N} \quad \text{R}^{31}
\end{equation}

wherein

R^{30'} represents a C_{1,3} alkyl group,

R^{31} represents a straight-chained or branched C_{1,8} alkyl group optionally substituted from the 2nd carbon atom by a hydroxy group, a C_{1,8}cycloalkyl or (C_{1,8}cycloalkyl)methyl group optionally substituted in the cycloalkyl moiety by a methyl or hydroxy group, a phenylC_{1,8}alkyl group mono- or disubstituted in the phenyl moiety X by substituents selected from halogen atoms and methyl, methoxy and trifluoromethyl groups,

R^{30'} and R^{31} together with the intervening nitrogen atom
form a 6- to 8-membered saturated monocyclic ring wherein a methylene group, separated by at least two ring carbons from the $A^{13}$ attached ring nitrogen optionally is replaced by an oxygen atom or by an imino group itself optionally substituted by a $C_{1-3}$alkyl, phenyl$C_{1-3}$alkyl or phenyl group, the phenyl moiety of which is optionally mono- or disubstituted by substituents selected from halogen atoms methyl, methoxy and trifluoromethyl groups, and

$A^{13}$ represents a $C_{5-8}$ alkylene or alkenylene group with the provisos that there are at least 5 carbon atoms between the semicyclic carbonyl group and the nitrogen atom of the

$$\begin{align*}
R^{30'} & \rightarrow N \text{ group,} \\
R^{31'} & 
\end{align*}$$

with the proviso that where $E$ represents a group of formula VIII then either $X^1$ or $X^2$ both represent $=CH-$ groups or $E$ represents a group (S), (U) or (W) and $X^1$ or $X^2$ each independently represents a $=CH-$ group or a nitrogen atom; or

j) $E$ represents a group of formula XI

$$\begin{align*}
\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH} \rightarrow N \\
A'_{14} \\
\text{wherein}
\end{align*}$$

wherein

$Z'$ is as hereinbefore defined,
A³ represents a straight-chained C₁-₆ alkylene group,

R₃² and R₃³ independently represent C₁-₆ alkyl groups or R₃² or R₃³ together with the intervening nitrogen atom form a 4- to 7-membered saturated, monocyclic, heteroaliphatic ring optionally interrupted by an imino or methylimino group,

with the proviso that where E represents a group of formula VIII then either X¹ or X² both represent =CH-groups or (B) represents a group (S), (U) or (W) and X¹ or X² each independently represents a =CH-group or a nitrogen atom.

or an isomer or physiologically acceptable acid addition salt thereof


3. A method of treatment as claimed in claim 1 for combatting Parkinson's disease.

4. A method of treatment as claimed in claim 1 for combatting emesis.

5. A method of treatment as claimed in claim 1 for combatting migraine.

6. A method of treatment as claimed in claim 1 for promoting cerebral blood flow in geriatric patients.

7. A method of treatment as claimed in any one of claims 1 to 6 comprising administering a compound selected from:

(+)-11-[[2-[(diethylamino)methyl]-1-piperidinyl]-
acetyl]-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one;

5,11-dihydro-11-[1-oxo-6-(1-piperidinyl)-4-hexyn-1-yl]-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one;

(±)-9-chloro-11-[[2-[(diethylamino)methyl]-1-piperidinyl]-acetyl]-5,11-dihydro-6H-pyrido[2,3-b]-[1,4]benzodiazepin-6-one;


5,11-dihydro-11-[[3-[3-(1-piperidinyl)-1-propyl]-1-piperidinyl]carbonyl]-6H-pyrido[2,3-b][1,4]-benzodiazepin-6-one;

4,9-dihydro-3-methyl-4-[[4-[3-(1-piperidinyl)-1-propyl]-1-piperidinyl]acetyl]-10H-thieno[3,4-b]-[1,5]benzodiazepin-10-one;

5,11-dihydro-11-[1-oxo-6-(1-piperidinyl)-1-hexyl]-6H-pyrido[2,3-b][1,4]benzodiazepin-10-one;

4,9-dihydro-3-methyl-4-[6-(hexahydro-1H-1-azepinyl)-1-oxo-4-hexyn-1-yl]-10H-thieno[3,4-b][1,5]benzodiazepin-10-one;

11-[4-[3-[(diethylamino)methyl]-4-morpholinyl]-1-oxo-1-butyl]-5,11-dihydro-6H-pyrido[2,3-b]-[1,4]benzodiazepin-6-one;

5,11-dihydro-11-[[2-(1-methyl-2-pyrrolidinyl)-ethyl]methylamino]acetyl]-6H-pyrido[2,3-b][1,4]-...
benzodiazepin-6-one; and


or an isomer or physiologically acceptable acid addition salt thereof.

8. A method of treatment as claimed in claim 1 comprising administering to said body a pharmaceutical composition substantially as herein described in any one of the Examples.

DATED this 26th day of February 1992

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