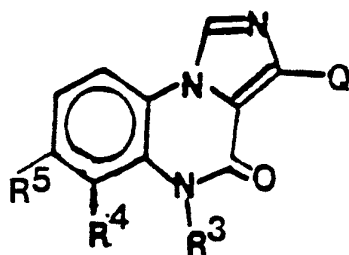




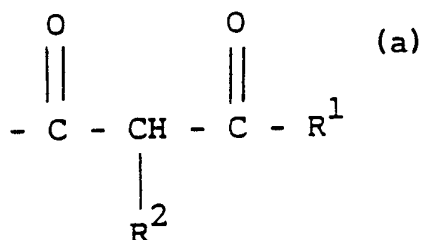
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/DK90/00303 (22) International Filing Date: 22 November 1990 (22.11.90) (30) Priority data: 5883/89 22 November 1989 (22.11.89) DK (71) Applicant: NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsværd (DK). (72) Inventors: WÄTJEN, Frank ; Ravnehusvej 27, DK-3500 Værløse (DK). HANSEN, Holger, Claus ; Bringe Krogen 9, DK-3500 Værløse (DK). (74) Agent: LEHMANN & REE; Frederiksberg Allé 26, DK- 1820 Frederiksberg C (DK).		(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent). Published <i>With international search report.</i>

(54) Title: IMIDAZOQUINOXALINE COMPOUNDS, THEIR PREPARATION AND USE



(I)



(a)

(57) Abstract

New imidazoquinoxaline compounds having general formula (I), wherein Q is (a), wherein R¹ and R² independently are hydrogen, straight or branched C₁₋₆-alkyl, or C₃₋₇-cycloalkyl; R³ is hydrogen, straight or branched C₁₋₆-alkyl, straight or branched C₂₋₆-alkenyl, or aralkyl or aroylalkyl which may optionally be substituted with halogen or C₁₋₆-alkoxy; R⁴ and R⁵ independently are hydrogen, halogen, C₁₋₆-alkyl or trifluoromethyl. The compounds are useful in psychopharmaceutical preparations as anticonvulsants, anxiolytics, hypnotics and in improving the cognitive function of the brain of mammals.

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IMIDAZOQUINOXALINE COMPOUNDS, THEIR PREPARATION AND USE

5

The present invention relates to therapeutically active imidazoquinoxaline compounds, a method of preparing the same, pharmaceutical compositions comprising the compounds, and to methods of treating therewith. The novel compounds are useful in psychopharmaceutical applications, e.g., in the treatment of central nervous system ailments, for example, as anticonvulsants or anxiolytics.

It is well known (Squires, R.F. and Braestrup, C. in Nature (London) 266 (1977) 732-734) that specific sites in the central nervous systems of vertebrates exhibit a high specific affinity for binding 1,4- and 1,5-benzodiazepines. These sites are called benzodiazepine receptors.

It has now been found that members of a novel group of imidazoquinoxaline compounds have strong affinity for the benzodiazepine receptors which make them useful in psychopharmaceutical preparations.

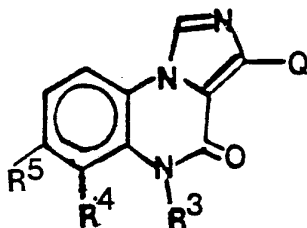
Accordingly, it is an object of the invention to provide such novel imidazoquinoxaline compounds.

The imidazoquinoxaline compounds having the general formula I

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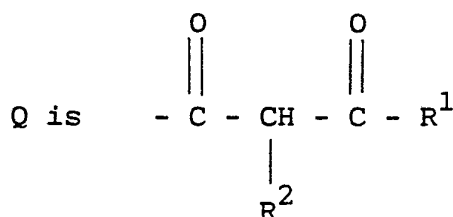
(I)

5



wherein

10



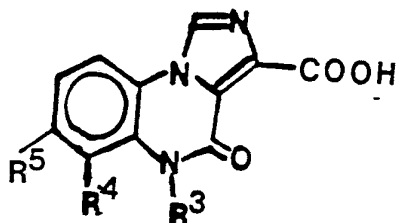
- 15 wherein R^1 and R^2 independently are hydrogen, straight or branched C_{1-6} -alkyl, or C_{3-7} -cycloalkyl; R^3 is hydrogen, straight or branched C_{1-6} -alkyl, straight or branched C_{2-6} -alkenyl, or aralkyl or aroylalkyl which may optionally be substituted with halogen or C_{1-6} -alkoxy; R^4 and R^5 independently are hydrogen, halogen, C_{1-6} -alkyl or trifluoromethyl.
- 20

The invention also relates to a method of preparing the above mentioned compounds. This method comprises:

25

- a) reacting a reactive derivative of a compound having the general formula II

30

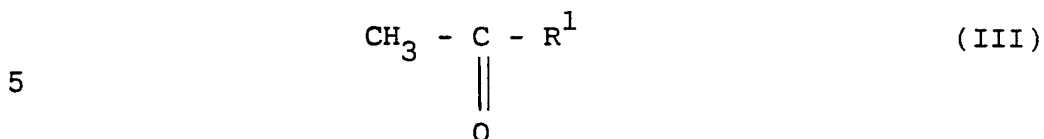


(II)

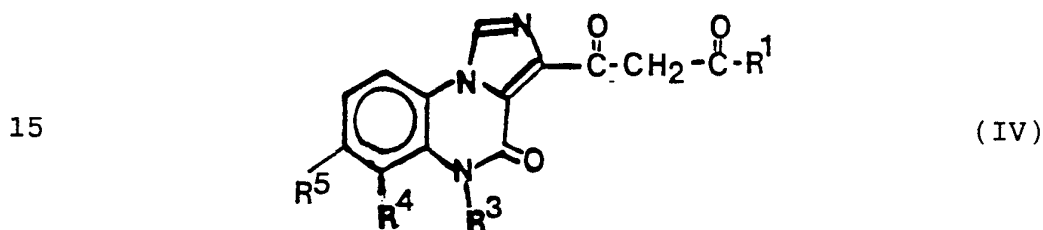
35

wherein R^3 , R^4 and R^5 have the meanings set forth

above, with a compound having the general formula III

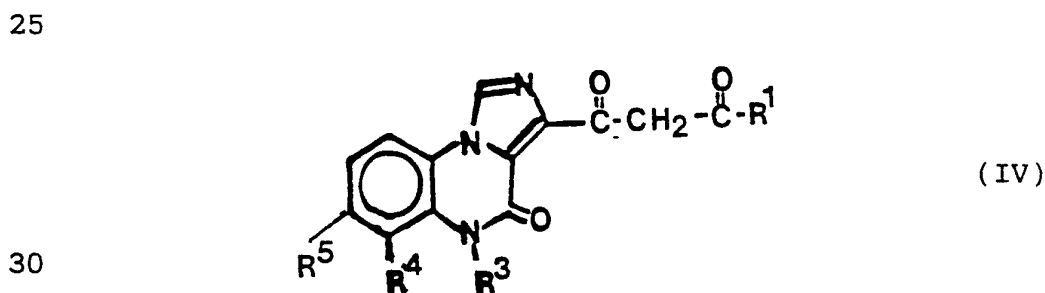


wherein R^1 has the meaning set forth above, to form a
10 compound of the general formula IV



20 wherein R^1 , R^3 , R^4 and R^5 have the meanings set forth above, or

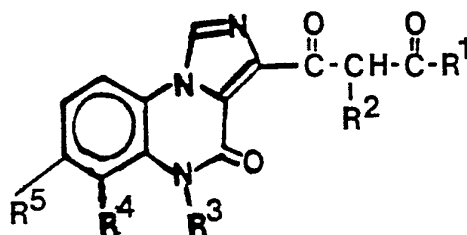
b) alkylating a compound having the general formula IV



wherein R^1 , R^3 , R^4 and R^5 have the meanings set forth
above, with an alkyl halide to form a compound of the
35 general formula I

(I)

5



10 wherein R^1 , R^2 , R^3 , R^4 and R^5 have the meanings set forth above.

The leaving group, Y, may be any suitable leaving group and, for example, those disclosed in U.S. Patents 4,031,079 or 4,359,420, for example, halogen, alkylthio, e.g., methylthio, aralkylthio, N-nitrosoalkylamino, alkoxy, mercapto, $-OP(O)(OR)_2$ wherein R is lower-alkyl or $-OP(O)(NR'R'')_2$ wherein R' and R'' each represents lower-alkyl or phenyl, or together with the nitrogen atom to which they are attached represent a heterocyclic radical such as morpholino, pyrrolidino, piperidino, or methylpiperazino. The reaction is preferably carried out under alkaline conditions, i.e., in the presence of a base, and among bases alkali metal, e.g., potassium or sodium, alkoxides or hydrides are preferred. The reaction is preferably conducted in the presence of an organic solvent which is nonreactive with the reactants and products of reaction under the conditions of reaction, especially an anhydrous solvent and preferably an anhydrous aprotic solvent such as dimethylformamide (DMF) or the like. The temperature range employed may be any range suitable for the reaction to proceed at a reasonable rate and without undue delay or decomposition and a range from a minus forty (-40) degrees Celsius to about room temperature is accordingly usually particularly suitable.

The starting materials may be prepared from commercially available organic compounds and by using well known synthetic methods.

- 5 The pharmaceutical properties of the compounds of the invention can be illustrated by determining their capability for displacing radioactive labelled flunitrazepam from benzodiazepine receptors.
- 10 The displacement activity of the compounds of the invention may be found by determining the ED_{50} value. The ED_{50} value represents the dose (mg/kg) of a test substance which causes the specific binding of flunitrazepam to benzodiazepine receptors in a living brain
- 15 to be reduced to 50% of the control value.

Such an in vivo test is carried out as follows:

- Principle. Twenty minutes after a dose of ^3H -flunitrazepam (^3H -FNM) (200 μ Ci/kg, i.v.) the amount of specific
- 20 ^3H -FNM binding to brain benzodiazepine receptors has reached its maximal value. This specific binding of ^3H -FNM can be partly or completely prevented by simultaneous or prior administration of pharmacologically
- 25 active benzodiazepines and by some benzodiazepine-like agents (Chang and Snyder, Eur.J. Pharmacol. 48, 212-218 (1978)).

- Test procedure. Suspensions of test substances (2 mg/-
- 30 ml) are prepared in 5% Duphasol-X (TM Duphar, castor oil- ethylene oxide derivative for emulsifying and solubilizing oil and other water-insoluble substances) by sonification for 10 min using a Branson B15 microtip ultrasonifier (setting 7). Groups of three mice (female,
- 35 NMR, 18-22 grams) are injected with the test substance at 100 mg/kg intraperitoneally. Fifteen minutes after test substance administration the mice are challenged

with 4 μ Ci intravenously of ^3H -FNM (70-90 Ci/mole) in 200 μ l physiological saline. Twenty minutes after ^3H -FNM administration mice are sacrificed by decapitation, the forebrains rapidly excised (within 30 sec) and homogenized in 12 ml of icecold 25 mM KH_2PO_4 , pH 7.1, using an Ultra-Turrax homogenizer fitted with an N 10 shaft. Two aliquots of 1 ml are immediately filtered through Whatman GF/C glassfibre filters and washed with 2 x 5 ml of the above mentioned buffer. The amounts of radioactivity on the filters are determined by conventional scintillation counting. One group of untreated mice serves as control. One to three mice are injected with 25 μ g/kg clonazepam i.p. 30 minutes before ^3H -FNM to determine the amount of non-specific ^3H -FNM binding, which should be between 8-15% of total binding. When doses of 100 mg/kg inhibit more than 50% of specific ^3H -flunitrazepam binding; test substances are administered in doses, which are factors of 3.16 times lower than 100 mg/kg. The ED_{50} for a test substance is defined as that dose which inhibits 50% of specific ^3H -FNM binding. Specific binding is the amount of binding in controls minus the amount binding in clonazepam- treated mice.

Results. The ED_{50} value is determined from dose response curves. If only one dose of test substance is administered the ED_{50} value is calculated as follows, provided that the inhibition of specific binding is within the range of 25-75%:

$$\text{ED}_{50} = (\text{administered dose}) \times \frac{1}{\left[\frac{C_o}{C_x} - 1 \right]} \text{ mg/kg}$$

where C_o is specific binding in controls and C_x is specific binding in mice treated with test substance.

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

TABLE 1.

Compound	ED ₅₀ (mg/kg)
Compound 2	1.5
Compound 4	1.4
Compound 6	2.5

The compound of the invention, together with a conventional adjuvant, carrier, or diluent, and if desired in the form of a pharmaceutically-acceptable acid addition salt thereof, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids, such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective central nervous system ailment alleviating amount of the active ingredient commensurate with the intended daily dosage range to be employed. Tablets containing

one (1) milligram of active ingredient or, more broadly, one (1) to thirty (30) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

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

10

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

15

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

20

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

25

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

35

Ampoules are convenient unit dosage forms.

For oral application, particularly suitable are

tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch. A syrup, elixir or like can be used when
5 a sweetened vehicle can be employed. Generally, as to broader ranges, the compounds of the invention are dispensed in unit dosage form comprising 0.05-100 mg in a pharmaceutically-acceptable carrier per unit dosage.

10

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

	Active compound	1.0 mg
15	Lactosum	67.8 mg Ph.Eur.
	Avicel®	31.4 mg
	Amberlite® IRP 88	1.0 mg
	Magnesii stearas	0.25 mg Ph.Eur.

20 Due to their high degree of affinity for the benzodiazepin receptors, the compounds of the invention are extremely useful in the treatment of central nervous system ailments or disorders, when administered in an amount effective for the alleviation, amelioration, or
25 elimination thereof. The important CNS activity of the compounds of the invention includes both anticonvulsant and anxiolytic activities along with a low toxicity, together presenting a most favorable therapeutic index. The compounds of the invention may accordingly be ad-
30 ministered to a subject, e.g., a living animal or a human body, in need of the same for the treatment, alleviation, amelioration, or elimination of an indication, associated with the central nervous system and the so-called benzodiazepin receptors, which requires
35 such psychopharmaceutical treatment, e.g., especially convulsion and/or anxiety states, if desired in the form of a pharmaceutically acceptable acid addition salt

thereof (such as the hydrobromide, hydrochloride, or sulfate, in any event prepared in the usual or conventional manner, e.g., evaporation to dryness of the free base in solution together with the acid), ordinarily concurrently, simultaneously, or together with a pharmaceutically-acceptable carrier or diluent, especially and preferably in the form of a pharmaceutical composition thereof, whether by oral, rectal, or parenteral (including subcutaneous) route, in an effective psychopharmaceutical central nervous system ailment alleviating amount, e.g., an anticonvulsant and/or anxiolytic amount, and in any event an amount which is effective for the alleviation of such a central nervous system ailment due to their benzodiazepine receptor affinity. Suitable dosage ranges are 1-200 milligrams daily, 1-100 milligrams daily, and especially 1-30 milligrams daily, depending as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and the preference and experience of the physician or veterinarian in charge.

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

EXAMPLE 1

5-tert-butyl-4,5-dihydro-3-(4,4-dimethyl-1,3-dioxopentyl)-4-oxo-imidazo[1,5-a]quinoxaline

To a stirred mixture of ethyl 5-tert-butyl-4,5-dihydro-4-oxo-imidazo[1,5-a]quinoxaline-3-carboxylate (1.6 g, 5 mmol) and pinacolone (1.25 ml, 10 mmol) in dry tetrahydrofuran (THF) (30 ml) was added sodium hydride (200 mg, 80% in mineral oil, 6.9 mmol). The mixture was

brought to reflux for 2 h, then cooled to room temperature and neutralized with acetic acid. After evaporation of the solvent the residue was partitioned between sat. aqueous NaHCO_3 (10 ml) and methylene chloride
5 (30 ml). The organic phase was dried over Na_2SO_4 and evaporated to give the title compound as yellow crystals. M.p. 190-191 °C. (Compound 1).

From the appropriate methyl ketones and ethyl imidazo-
10 quinoxalinecarboxylates the following 1,3-diketones were prepared:

3-(3-cyclopropyl-1,3-dioxopropyl)-4,5-dihydro-5-isopropyl-4-oxo-imidazo[1,5-a]quinoxaline, m.p. 210-212 °C
15 from reaction between cyclopropyl methyl ketone and ethyl 4,5-dihydro-5-isopropyl-4-oxo-imidazo[1,5-a]quinoxaline-3-carboxylate. (Compound 2).

6-chloro-3-(3-cyclopropyl-1,3-dioxopropyl)-4,5-dihydro-
20 5-methyl-4-oxo-imidazo[1,5-a]quinoxaline. M.p. 189-190 °C from reaction between cyclopropyl methyl ketone and ethyl 6-chloro-4,5-dihydro-5-methyl-4-oxo-imidazo[1,5-a]quinoxaline-3-carboxylate. (Compound 3).

25 4,5-dihydro-5-isopropyl-4-oxo-3-(1,3-dioxobutyl)-imidazo[1,5-a]quinoxaline, m.p. 216-218 °C from reaction between acetone and ethyl 4,5-dihydro-5-isopropyl-4-oxo-imidazo[1,5-a]quinoxaline-3-carboxylate. (Compound 4).

30 5-tert-butyl-4,5-dihydro-4-oxo-3-(1,3-dioxobutyl)-imidazo[1,5-a]quinoxaline, m.p. 175-177 °C from reaction between acetone and ethyl 5-tert-butyl-4,5-dihydro-4-oxo-imidazo[1,5-a]quinoxaline-3-carboxylate.
35 (Compound 5).

5-tert-butyl-3-(3-cyclopropyl-1,3-dioxopropyl)-4,5-

dihydro-4-oxo-imidazo[1,5-a]quinoxaline, m.p. 175-178°C from reaction between cyclopropyl methyl ketone and ethyl 5-tert-butyl-4,5-dihydro-4-oxo-imidazo[1,5-a]quinoxaline-3-carboxylate. (Compound 6).

5

EXAMPLE 2

3-(3-cyclopropyl-2-methyl-1,3-dioxopropyl)-4,5-dihydro-5-isopropyl-4-oxo-imidazo[1,5-a]quinoxaline

10

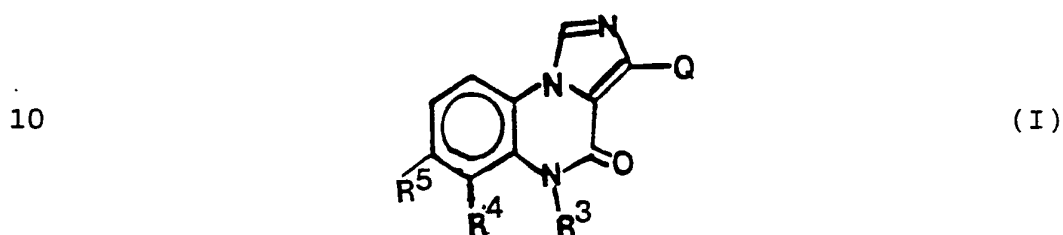
Sodium hydride (0.8 g, 60% in mineral oil) was added to a stirred solution of cyclopropyl methyl ketone (1.12 ml, 12 mmol) in dry THF (40 ml). Then ethyl 4,5-dihydro-5-isopropyl-4-oxo-imidazo[1,5-a]quinoxaline-3-carboxylate (3 g, 10 mmol) was added and the mixture was heated at reflux for 30 min. The resulting solution was cooled to room temperature and an excess of methyl iodide (1.4 ml) was added. After stirring overnight the mixture was neutralized with acetic acid and the solvent was evaporated. The residue was triturated with a mixture of ether and water and the precipitate was collected by filtration, rinsed with saturated aqueous NaHCO₃, recrystallized from isopropyl alcohol and finally purified by column chromatography (SiO₂/dichloromethane-acetone 4:1), m.p. 167- 169°C. (Compound 7).

30

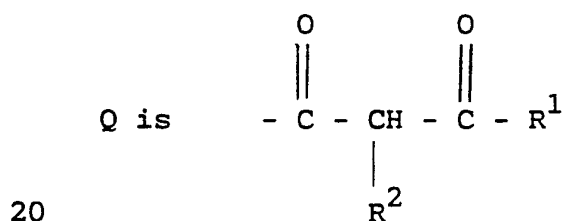
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CLAIMS

1. Imidazoquinoxaline compounds having the general
 5 formula I



15 wherein



wherein R¹ and R² independently are hydrogen, straight or branched C₁₋₆-alkyl, or C₃₋₇-cycloalkyl; R³ is hydrogen, straight or branched C₁₋₆-alkyl, straight or
 25 branched C₂₋₆-alkenyl, or aralkyl or aroylalkyl which may optionally be substituted with halogen or C₁₋₆-alkoxy; R⁴ and R⁵ independently are hydrogen, halogen, C₁₋₆-alkyl or trifluoromethyl

30 2. A compound which is 4,5-dihydro-5-isopropyl-4-oxo-3-(1,3-dioxobutyl)-imidazo[1,5-a]quinoxaline

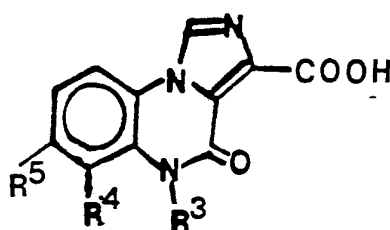
3. A compound which is 3-(3-cyclopropyl-1,3-dioxopropyl)-4,5-dihydro-5-isopropyl-4-oxo-imidazo[1,5-a]qui-
 35 noxaline

4. A compound which is 5-tert-butyl-3-(3-cyclopropyl-

1,3-dioxopropyl)-4,5-dihydro-4-oxo-imidazo[1,5-a]quinoxaline

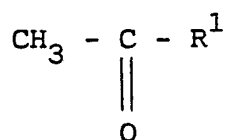
5. A method of preparing a compound according to claim 1, CHARACTERIZED in

a) reacting a reactive derivative of a compound having the general formula II



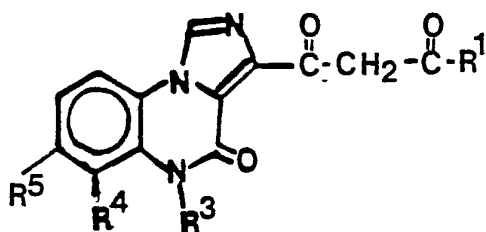
(II)

wherein R^3 , R^4 , and R^5 have the meanings set forth above, with a compound having the general formula III



(III)

wherein R^1 has the meaning set forth above, to form a compound of the general formula IV



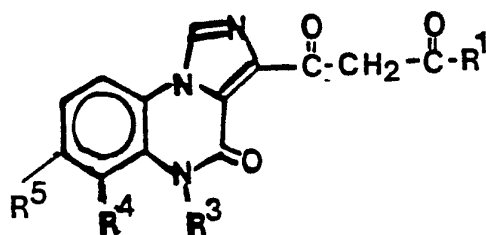
(IV)

wherein R^1 , R^3 , R^4 and R^5 have the meanings set forth above, or

b) alkylating a compound having the general formula IV

5

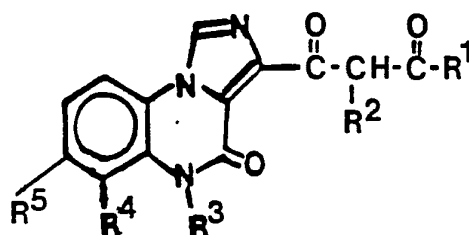
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(IV)

wherein R^1 , R^3 , R^4 and R^5 have the meanings set forth above, with an alkyl halide to form a compound of the general formula I

20



(I)

25

wherein R^1 , R^2 , R^3 , R^4 and R^5 have the meanings set forth above.

6. A pharmaceutical composition suitable for use in the treatment of a central nervous system ailment comprising an amount of a compound of claim 1 which is effective for the alleviation of such disorder together with a pharmaceutically-acceptable carrier or diluent.

35

7. A pharmaceutical composition according to claim 6 wherein it is in the form of an oral dosage unit con-

taining 1-100 mg of the active compound.

5 8. A method of treating a central nervous system ailment in a subject in need of such treatment comprising the step of administering to said subject an amount of a compound of Claim 1 which is effective for the alleviation of such ailment.

10 9. A method of treating a central nervous system ailment in a subject in need of such treatment comprising the step of administering to said subject an amount of a compound of Claim 1 which is effective for the alleviation of such ailment in the form of a pharmaceutical composition thereof, in which it is present together
15 with a pharmaceutically acceptable carrier or diluent.

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INTERNATIONAL SEARCH REPORT

International Application No PCT/DK 90/00303

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC5: C 07 D 487/04, A 61 K 31/495		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC5	C 07 D; A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched ⁸		
SE,DK,FI,NO classes as above		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP, A2, 0283162 (A/S FERROSAN) 21 September 1988, see pages 1-7 --	1-7
A	EP, A2, 0320136 (A/S FERROSAN) 14 June 1989, see pages 1-7 --	1-7
A	EP, A1, 0225013 (A/S FERROSAN) 10 June 1987, see pages 1-9 -- -----	1-7
* Special categories of cited documents: ¹⁰ "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
21st February 1991		1991 -03- 05
International Searching Authority		Signature of Authorized Officer
SWEDISH PATENT OFFICE		Göran Karlsson

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET**V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹**

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 8, 9 because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy,
see rule 39.

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

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

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.PCT/DK 90/00303

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 Swedish Patent Office EDP file on 91-01-31. The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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