650733

AUSTRALIA

PATENTS ACT 1990

NOTICE OF ENTITLEMENT

We, **Novo Nordisk A/S**, the applicant/Nominated Person in respect of Application No. 14148/92 state the following:-

The Nominated Person is entitled to the grant of the patent because the Nominated Person would, on the grant of a patent for the invention to the inventor, be entitled to have the patent assigned to the Nominated Person.

The Nominated Person is entitled to claim priority from the application listed in the declaration under Article 8 of the PCT because the Nominated Person made the application listed in the declaration under Article 8 of the PCT, and because that application was the first application made in a Convention country in respect of the invention.

DATED this TWENTY SEVENTH day of SEPTEMBER 1993

.....

a member of the firm of
DAVIES COLLISON
CAVE for and on behalf
of the applicant(s)

(DCC ref: 1612429)

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TETRACYCLIC IMIDAZOQUINAZOLINE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

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(56) Prior Art Documents
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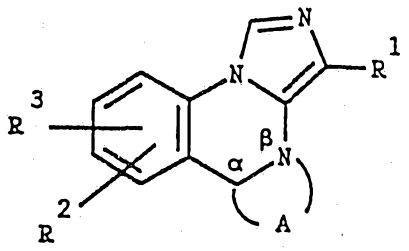
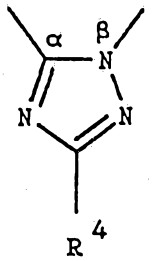
(57) Claim

1. Tetracyclic imidazotriazoloquinazoline compounds having the formula I:

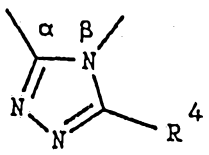


(I)

wherein A together with the α-marked carbon atom and the ß-marked nitrogen atom is one of the groups

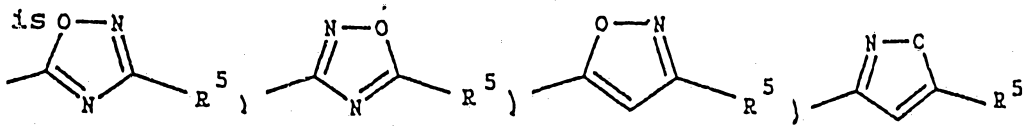


or



;

.../2

R^1 is  cyano or CO_2R^5,

wherein R^5 is hydrogen, C_{1-6}-alkyl, C_{3-7}-cycloalkyl, trifluoromethyl, or C_{1-6}-alkoxymethyl; and

R^2, R^3 and R^4 independently are hydrogen, hydroxy, halogen, CN, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, trifluoromethyl, C_{1-6}-alkoxy, dialkylaminoalkoxy, aralkoxy, aryloxy which may be substituted with halogen or alkoxy, a cyclic amino group, or NR^6R^7, wherein R^6 and R^7 independently are hydrogen or C_{1-6}-alkyl, and pharmaceutically acceptable acid addition salts thereof.

10. 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 according to any one of Claims 1-5 which is effective for the alleviation of such ailment in the form af a pharmaceutical composition thereof, in which it is present together with a pharmaceutically acceptable carrier or diluent.

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0411/91 7 March 1991 (07.03.91) DK

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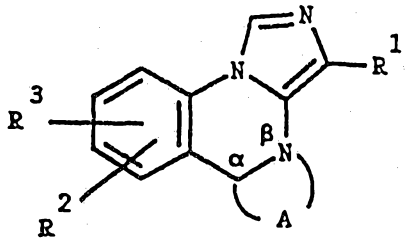
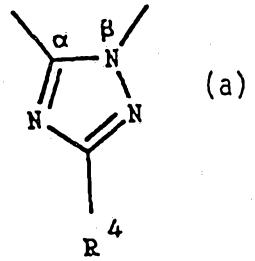
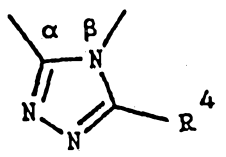
(54) Title: TETRACYCLIC IMIDAZOQUINAZOLINE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM



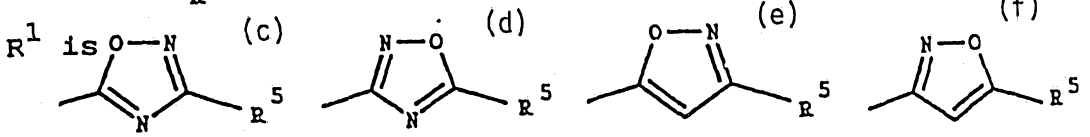
(I)



(a)



(b)



(c) (d) (e) (f)

(57) Abstract

Imidazotriazoloquinazoline compounds having general formula (I), wherein A together with the α-marked carbon atom and the β-marked nitrogen atom is one of the groups (a) or (b); R^1 is (c), (d), (e), (f), cyano or CO_2R^5, wherein R^5 is H, alkyl, cycloalkyl, trifluoromethyl or alkoxymethyl; and R^2, R^3 and R^4 independently are H, hydroxy, halogen, CN, alkyl, alkenyl, alkynyl, trifluoromethyl, alkoxy, dialkylaminoalkoxy, aralkoxy, aryloxy which may be substituted, a cyclic amino group, or NR^6R^7, wherein R^6 and R^7 independently are H or alkyl. The compounds are useful in psychopharmaceutical preparations as anticonvulsants, anxiolytics, hypnotics, antipsychotics, antiemetics, or in improving the cognitive function of the brain of mammals, or as benzodiazepine antagonists.

TETRACYCLIC IMIDAZOQUINAZOLINE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

The present invention relates to therapeutically active tetracyclic imidazotriazoloquinazoline 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, anxiolytics, hypnotics, antipsychotics, antiemetics, in improving the cognitive function of the brain of mammals, or as benzodiazepine antagonists.

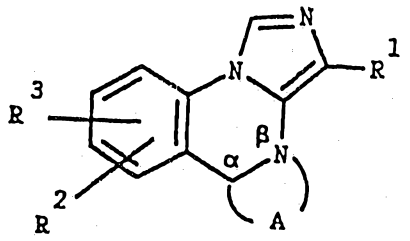
It is well known (Squires, R.F. and Braestrup, C. in Nature (London) 266 (1977) 732-734) that specific sites in the central nervous systems of vertebrates exhibit a high specific affinity for binding 1,4- and 1,5-benzodiazepines. These sites are called benzodiazepine receptors.

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

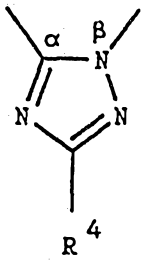
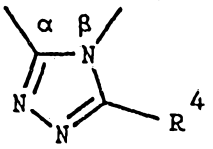
Accordingly, it is an object of the invention to provide such novel tetracyclic imidazotriazoloquinazoline compounds.

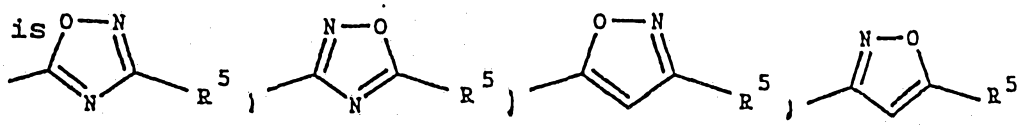
The compounds of the invention have the general formula I

(I)



and pharmaceutically acceptable acid addition salts thereof, wherein A together with the α-marked carbon atom and the ß- marked nitrogen atom is one of the groups

 or  ;

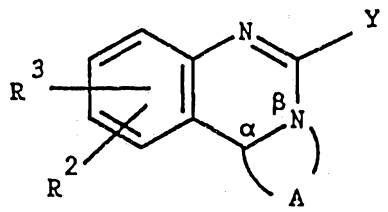
R^1 is 

cyano or CO_2R^5,
wherein R^5 is hydrogen, C_{1-6}-alkyl, C_{3-7}-cycloalkyl, trifluoromethyl or C_{1-6}-alkoxymethyl; and

R^2, R^3 and R^4 independently are hydrogen, hydroxy, halogen, CN, C_{1-6}- alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, trifluoromethyl, C_{1-6}-alkoxy, dialkylaminoalkoxy, aralkoxy, aryloxy which may be substituted with halogen or alkoxy, a cyclic amino group, or NR^6R^7, wherein R^6 and R^7 independently are hydrogen or C_{1-6}-alkyl.

The invention also relates to methods of preparing the above mentioned compounds. These methods comprise:

a) reacting a compound of formula II



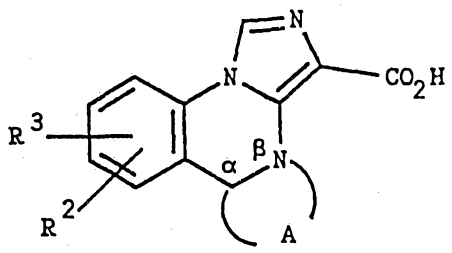
(II)

wherein A, R^2 and R^3 are as defined above and wherein Y is a leaving group, with a compound having the formula III

$$CN - CH_2 - R^1 \qquad (III)$$

wherein R^1 is as defined above, to form a compound of the invention, or

b) reacting a reactive derivative of a compound having the general formula IV



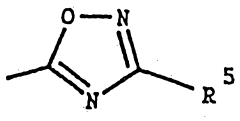
(IV)

wherein A, R^2 and R^3 are as defined above with a compound having the general formula V

$$R^5\text{-}C(=NOH)NH_2 \qquad (V)$$

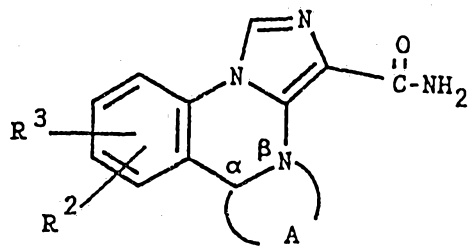
wherein R^5 is as defined above to form a compound of

the general formula I wherein R^1 is



wherein R^5 is as defined above, or

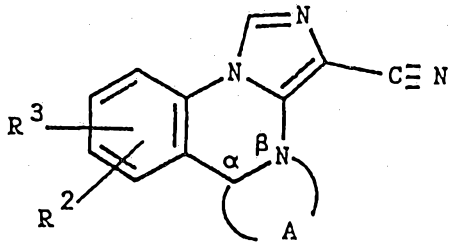
c) reacting a compound of the general formula VI



(VI)

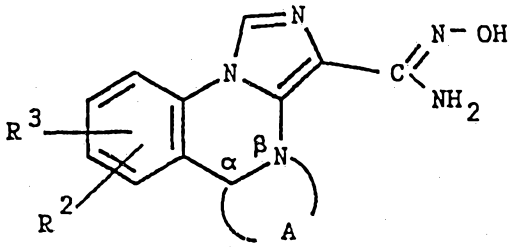
wherein -A-, R^2 and R^3 have the meanings set forth above, with a dehydrating agent to form a compound of formula I, wherein -A-, R^2 and R^3 have the meanings set forth above and wherein R^1 is cyano, or

d) reacting a compound of formula VII



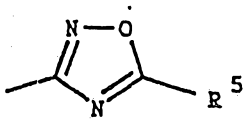
(VII)

wherein -A-, R^2 and R^3 have the meaning set forth above, with NH_2OH to form a compound of formula VIII



(VIII)

wherein -A-, R^2, and R^3 have the meanings set forth above, and reacting the compound of formula VIII with R^5-COCl or with $(R^5CO)_2O$, wherein R^5 is as defined above to form a compound of the general formula I wherein R^1 is



wherein R^5 is as defined 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), tetrahydrofuran (THF), 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 employed in the syntheses of the compounds of formula I are either known or may be prepared in conventional manner from commercially available materials, see e.g. J.E. Francis et al., J. Med. Chem. 34, 281 (1991) and references cited therein.

The isocyanomethyloxadiazoles of formula III may be prepared as described in the prior art, e.g. US 4,774,245. 3(5)-Alkyl-5(3)-halomethylisoxazoles, either known or prepared from appropriate starting materials according to known procedures (e.g. U.S. 3,290,301 and Ger. Offen. DE 25 49 962), may by conventional techniques be converted to 3(5)-alkyl-5(3)-aminomethylisoxazoles which in turn may be N-formylated and subsequently dehydrated to give isocyanomethylisoxazoles.

The pharmaceutical properties of the compounds of the invention can be illustrated by determining their capability for displacing radioactive labelled flunitrazepam from benzodiazepine receptors.

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 ^{3}H-flunitrazepam to benzodiazepine receptors in a living brain to be reduced to 50% of the control value.

Such an in vivo test is carried out as described in US 4,774,245.

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

TABLE I.

Compound	ED_{50} (mg/kg)
3	0.16
5	0.30

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 tenth (0.1) milligram of active ingredient or, more broadly, one tenth (0.1) to hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

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.

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.

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.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxilliary 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.

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

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 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.

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

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

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 elimination thereof. The important CNS activity of the compounds of the invention includes both anticonvulsant, hypnotic, nootropic and anxiolytic activities along with a low toxicity, together presenting a most favorable therapeutic index. The compounds of the invention may accordingly be administered to a subject, e.g., a living mammal body, including a human, in need of the same for the treatment, alleviation, amelioration, or elimination of an indication, associated with the central nervous system and the socalled benzodiazepine receptors, which requires such psychopharmaceutical treatment, e.g., especially convulsion, insomnia, anxiety and/or dementia states, if desired in the form of a pharmaceuticallyacceptable 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, which may not be construed as limiting:

EXAMPLE 1

5-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-imidazo[1,5-a]-1,2,4-triazolo[4,3-c]quinazoline (compound 1)

To a stirred slurry of 5-chloro-1,2,4-triazolo[4,3-c]quinazoline (3.5 g, 17 mmol) in 40 ml of dry DMF at 10°C was first added 5-cyclopropyl-3-isocyanomethyl-1,2,4-oxadiazole (purity 80%, 3.4 g, 18 mmol) and then a solution of potassium tert-butoxide (2.55 g, 23 mmol) in 40 ml of DMF, allowing the temperature to rise to room temperature. After 1/2 h the mixture was filtered and the filter cake washed with water and finally with ether and dried, giving the title compound as colorless crystals, m.p. 308-314°C.

^{1}H-NMR ($CDCl_3$) δ: 10.50 (s, 1H, triazolo-) 8.52 (s, 1H, imidazo), 8.7-7.64 (m, 4H, benzo-), 2.45-2.34 (m, 1H, CH),

1.48-1.32 (m, 4H, CH_2). MS: m/e 317 (M^+), 250, 166, 129, 102, 69.

EXAMPLE 2

5-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-imidazo[1,5-a]-[1,2,4]triazolo[1,5-c]quinazoline (compound 2)

A stirred mixture of crude 5-chloro-[1,2,4]triazolo[1,5-c]quinazoline (1.0 g, 4.9 mmol) and 5-cyclopropyl-3-isocyanomethyl-1,2,4-oxadiazole (purity 80%, 1.16 g, 6.2 mmol) in 20 ml of dry dimethylformamide (DMF) was cooled to 0°C. Solid potassium tert-butoxide (1.15 g, 10 mmol) was added gradually, keeping the temperature below 5°C, whereafter the mixture was stirred at room temperature for 45 minutes. Then the mixture was stirred at 0°C for 1/2 h and the precipitated product was collected by filtration, rinsed on the filter with water and dried. Yield 0.64 g. An additional amount of product, 0.5 g, precipitated from the mother liqueour by addition of water. The combined crops of crystals was stirred with isopropyl alcohol at 60°C, cooled to room temperature and filtered. The filter cake was dried to give 0.73 g of the title compound m.p. 230-233°C.

^{1}H-NMR ($CDCl_3$) δ: 8.57 (s, 1H, imidazo-), 8.40 (s, 1H, triazolo-), 8.52-7.55 (m, 4H, benzo-), 2.46-2.26 (m, 1H, CH), 1.5-1.2 (m, 4H, CH_2); MS: m/e 317 (M^+), 250, 195, 166, 129, 102, 69.

In the same way the following compounds were prepared:

5-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-imidazo[1,5-a]-[1,2,4]triazolo[1,5-c]quinazoline, m.p. 267-269°C, ^{1}H-NMR (CF_3COOD) δ : 9.68 (s, 1H), 9.09 (s, 1H), 8.88-

8.02 (m, 4H), 2.50-2.28 (m, 1H), 163-1.2 (m, 4H); prepared from 5-chloro-[1,2,4]triazolo[1 c]quinazoline and 3-cyclopropyl-5-isocyanomethyl-1,2,4-oxadiazole. (compound 3)

5-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-2-methyl-imidazo[1,5-a][1,2,4]triazolo[1,5-c]quinazoline, m.p. 280-283°C, MS: m/e 332 (M^++1), 331, 264, 129, 102, 69; prepared from 5-chloro-2-methyl-[1,2,4]triazolo[1,5-c]quinazoline and 5-cyclopropyl-3-isocyanomethyl-1,2,4-oxadiazole. (compound 4)

12-chloro-5-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-imidazo[1,5-a][1,2,4]triazolo[1,5-c]quinazoline, m.p. 278-284°C, MS: m/e 351/353 (M^+/M^+ +2), 270/272, 268, 163; prepared from 5,10-dichloro-[1,2,4]triazolo[1,5-c]quinazoline and 3-cyclopropyl-5-isocyanomethyl-1,2,4-oxadiazole. (compound 5)

12-chloro-5-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-imidazo[1,5-a][1,2,4]triazolo[1,5-c]quinazoline, m.p. 262-263°C, MS: m/e 351/353 (M^+/M^+ +2), 268, 229, 200, 163, 136, 100, 69; prepared from 5,10-dichloro-[1,2,4]triazolo[1,5-c]quinazoline and 5-cyclopropyl-3-isocyanomethyl-1,2,4-oxadiazole. (compound 6)

5-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-11-methyl-imidazo[1,5-a][1,2,4]triazolo[1,5-c]quinazoline, m.p. 271-273°C, MS: m/e 331 (M^+), 250, 248, 222, 209, 143, 116, 89, 53; prepared from 5-chloro-9-methyl-[1,2,4]triazolo[1,5-c]quinazoline and 3-cyclopropyl-5-isocyanomethyl-1,2,4-oxadiazole. (compound 7)

5-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-11-methyl-imidazo[1,5-a][1,2,4]triazolo[1,5-c]quinazoline, m.p. 280-282°C, MS: m/e 331 (M^+), 264, 248, 209, 181, 143, 116, 89, 69; prepared from 5-chloro-9-methyl-

[1,2,4]triazolo[1,5-c]quinazoline and 5-cyclopropyl-3-isocyanomethyl-1,2,4-oxadiazole. (compound 8)

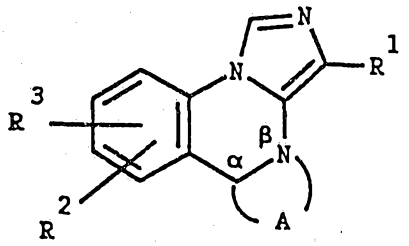
5-(5-methyl-1,2,4-oxadiazol-3-yl)-12-methyl-imidazo[1,5-a][1,2,4]triazolo[1,5-c]quinazoline, m.p. 265-269°C, MS: m/e 305 (m+), 263, 210, 184, 181, 157, 89, 43; prepared from 5-chloro-10-methyl-[1,2,4]triazolo[1,5-a]quinazoline and 3-isocyanomethyl-5-methyl-1,2,4-oxadiazole. (Compound 9)

5-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-12-methyl-imidazo[1,5-a][1,2,4]triazolo[1,5-c]quinazoline, m.p. 254-256°C, MS: m/e 331 (M+), 263, 69; prepared from 5-chloro-10-methyl-[1,2,4]triazolo[1,5-a]quinazoline and 5-cyclopropyl-3-isocyanomethyl-1,2,4-oxadiazole. (compound 10)

12-chloro-5-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-2-methyl-imidazo[1,5-a][1,2,4]triazolo[1,5-c]quinazoline, m.p. 210-213, MS: m/e 365, 298, 69; prepared from 5,10-dichloro-2-methyl-[1,2,4]triazolo[1,5-c]quinazoline and 5-cyclopropyl-3-isocyanomethyl-1,2,4-oxadiazole. (Compound 11)

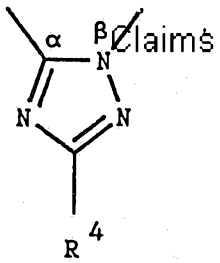
CLAIMS

1. Tetracyclic imidazotriazoloquinazoline compounds having the formula I:

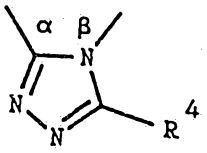


(I)

wherein A together with the α-marked carbon atom and the ß-marked nitrogen atom is one of the groups

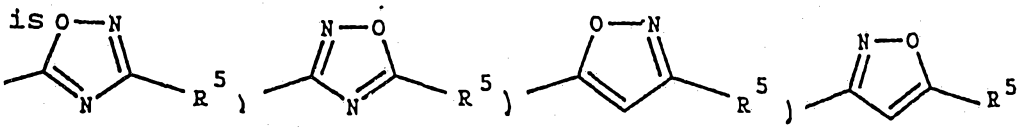


or



;

R^1 is



cyano or CO_2R^5,

wherein R^5 is hydrogen, C_{1-6}-alkyl, C_{3-7}-cycloalkyl, trifluoromethyl, or C_{1-6}-alkoxymethyl; and

R^2, R^3 and R^4 independently are hydrogen, hydroxy, halogen, CN, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, trifluoromethyl, C_{1-6}-alkoxy, dialkylaminoalkoxy, aralkoxy, aryloxy which may be substituted with halogen or alkoxy, a cyclic amino group, or NR^6R^7, wherein R^6 and R^7 independently are hydrogen or C_{1-6}-alkyl, and pharma-

ceutically acceptable acid addition salts thereof.

2. A compound which is 5-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-imidazo[1,5-a][1,2,4]triazolo[1,5-c]quinazoline.

3. A compound which is 5-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-imidazo[1,5-a][1,2,4]triazolo[1,5-c]quinazoline.

4. A compound which is 12-chloro-5-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-imidazo[1,5-a][1,2,4]triazolo-[1,5-c]quinazoline.

5. A compound which is 12-chloro-5-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-imidazo[1,5-a][1,2,4]triazolo-[1,5-c]quinazoline.

6. A pharmaceutical composition comprising as active component an imidazotriazoloquinazoline compound according to any one of claims 1-5 or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically-acceptable carrier or diluent.

7. A pharmaceutical composition suitable for use in the treatment of a central nervous system ailment comprising an amount of a compound according to any one of claims 1-5 which is effective for the alleviation of such disorder together with a pharmaceutically-acceptable carrier or diluent.

8. A pharmaceutical composition according to claim 6 or 7 wherein it is in the form af an oral dosage unit containing 0.1-100 mg of the active compound.

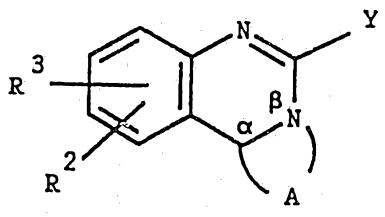
9. A method of treating a central nervous system ailment in a subject in need of such treatment com-

prising the step of administering to said subject an amount of a compound according to any one of Claims 1-5 which is effective for the alleviation of such ailment.

10. 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 according to any one of Claims 1-5 which is effective for the alleviation of such ailment in the form af a pharmaceutical composition thereof, in which it is present together with a pharmaceutically acceptable carrier or diluent.

11. A method of preparing a compound according to any one of claims 1-5, CHARACTERIZED in

a) reacting a compound of formula II



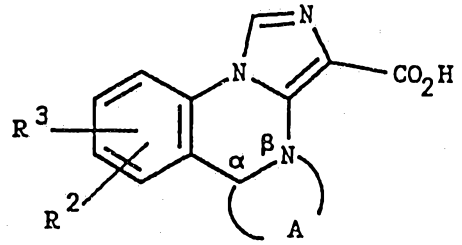
(II)

wherein A, R^2 and R^3 are as defined above and wherein Y is a leaving group, with a compound having the formula III

$$CN - CH_2 - R^1 \qquad (III)$$

wherein R^1 is as defined above, to form a compound of the general formula I, or

b) reacting a reactive derivative of a compound having the general formula IV

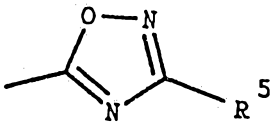


(IV)

wherein A, R^2 and R^3 are as defined above with a compound having the general formula V

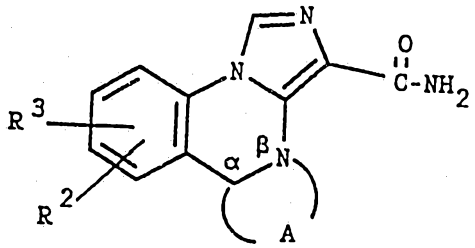
$$R^5\text{-}C(=NOH)NH_2 \qquad (V)$$

wherein R^5 is as defined above to form a compound of the general formula I wherein R^1 is



wherein R^5 is as defined above, or

c) reacting a compound of the general formula VI

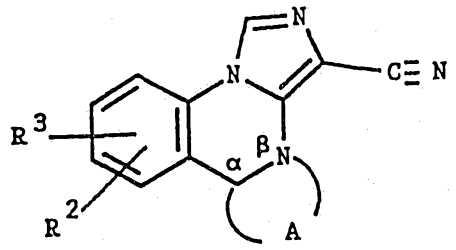


(VI)

wherein -A-, R^2 and R^3 have the meanings set forth above, with a dehydrating agent to form a compound of

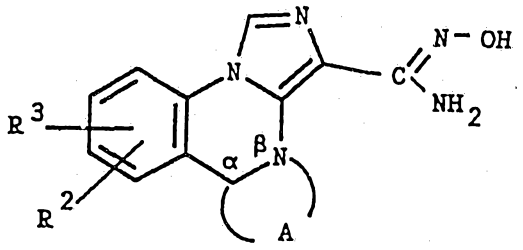
formula I, wherein -A-, R^2 and R^3 have the meanings set forth above and wherein R^1 is cyano, or

d) reacting a compound of formula VII



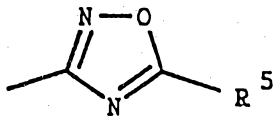
(VII)

wherein -A-, R^2, and R^3 have the meaning set forth above, with NH_2OH to form a compound of formula VIII



(VIII)

wherein -A-, R^2, and R^3 have the meanings set forth above, and reacting the compound of formula VIII with R^5-COCl or with $(R^5CO)_2O$, wherein R^5 is as defined above to form a compound of the general formula I wherein R^1 is



wherein R^5 is as defined above.

12. Use of a compound according to any one of claims 1-5 for producing a pharmaceutical composition for the treatment of an indication related to a central nervous system ailment.

INTERNATIONAL SEARCH REPORT

International Application No PCT/DK 92/00050

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 487/14, A 61 K 31/505

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 RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
P,X	EP, A1, 0417027 (A/S FERROSAN) 13 March 1991, see the whole document --	1-8,11-12
A	US, A, 4774245 (FRANK WÄTJEN ET AL) 27 September 1988, see the whole document --	1-8,11-12

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* 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
9th June 1992	1992 -06- 15
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Carolina Gómez Lagerlöf Carolina Gómez Lagerlöf

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] 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. [X] Claim numbers 9, 10 because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

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 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 additonal fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional seach fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/DK 92/00050

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 30/04/92
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0417027	91-03-13	AU-D- 6429790	91-04-08
		WO-A- 91/03478	91-03-21
US-A- 4774245	88-09-27	AU-B- 586043	89-06-29
		AU-B- 591937	89-12-21
		AU-D- 6417886	87-04-30
		AU-D- 6417986	87-04-30
		AU-D- 6418086	87-04-30
		CA-A- 1275411	90-10-23
		CA-A- 1293723	91-12-31
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