COMMONWEALTH OF AUSTRALIA
Patents Act 1952
APPLICATION FOR A STANDARD PATENT

I/We A/S FERROSAN
of Sydmarken 5, DK-2860 Soborg, Denmark

hereby apply for the grant of a Standard Patent for an invention entitled:

"OXADIAZOLYL IMIDAZOBENZODIAZEPINE COMPOUND, PHARMACEUTICAL COMPOSITION CONTAINING SAID COMPOUND, METHOD OF PREPARING SAID COMPOUND AND METHOD OF TREATING A CENTRAL NERVOUS SYSTEM AILMENT"

which is described in the accompanying complete specification.

This application is made under the provisions of Section 51 of the Patents Act 1952 in respect of Australian Patent Application No.57429/86 made by A/S Ferrosan.

The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

DATED this 3rd day of August, 1989

To: THE COMMISSIONER OF PATENTS

(a member of the firm of Davies & Collison for and on behalf of the Applicant)

Davies & Collison, Melbourne and Canberra
COMMUNE OF AUSTRALIA

PATENTS ACT 1952

DECLARATION IN SUPPORT OF CONVENTION OR
NON-CONVENTION APPLICATION FOR A PATENT

In support of the Application made for a patent for an invention
entitled: "OXADIAZOLYL IMIDAZOBENZODIAZEPINE COMPOUND,
PHARMACEUTICAL COMPOSITION CONTAINING SAID COMPOUND, METHOD
OF PREPARING SAID COMPOUND AND METHOD OF TREATING A CENTRAL
NERVOUS SYSTEM AILMENT" by A/S FERROSAN, Sydmarken 5,
DK-2860 Sæborg, Denmark

Do solemnly and sincerely declare as follows:

(a) I am the applicant for the patent

or (b) I am authorized by

A/S FERROSAN

the applicant for the patent to make this declaration on its behalf

(a) I am the actual inventor of the invention

or (b)

Frank Watjen of Josteinsvej 27, DK-2880 Bagsaerd, Denmark;
Mogens Engelstoft of Mosegaard Park 121, DK-3500 Værløse, Denmark;
John Bondo Hansen of Havretoften 10, DK-2800 Lyngby, Denmark; and
Leif Helth Jensen of Bøjergårds Brygge 37, DK-2900 Hellerup, Denmark

are

the actual inventors of the invention and the facts upon which the applicant

is entitled to make the application are as follows:

The actual inventors have assigned the invention to the said applicant.

The basic application as defined by Section 141 of the Act was made

in

by

in

by

in

by

on the

on the

on the

on the

on the

4 The basic application referred to in paragraph 3 of this Declaration was

the first application made in a Convention country in respect of the invention the subject

of the application

Declared at Søborg this 30th day of August

DAVIS & COLLISON, MELBOURNE and CANBERRA
$R^4$ and $R^5$ each is H, halogen, CF$_3$ and n is 2 or 3.

The compounds disclosed in examples 2, 3, 16, 29, 32, 43, 44, 45, 49, 50, 51, 52, 53, and 56 of EP No. 150,049 are
Compounds are intermediates.

1. 5-Cyclopropyl-3-isocyanomethyl-1,2,4-oxadiazole having the formula

\[
\text{CN-CH}_2 \quad \text{N-O} \quad \text{N} 
\]
Name of Applicant: A/S FERROSAN

Address of Applicant: Sydmarken 5, DK-2860 Søborg, Denmark.

Actual Inventor(s): Frank WÄTJEN
Mogens ENGELSTOFT
John Bondo HANSEN
Leif Helth JENSEN

Address for Service: DAVIES & COLLISON, Patent Attorneys, 1 Little Collins Street, Melbourne, 3000.

Complete Specification for the invention entitled:
"OXADIAZOLYL IMIDAZOBENZODIAZEPINE COMPOUND, PHARMACEUTICAL COMPOSITION CONTAINING SAID COMPOUND, METHOD OF PREPARING SAID COMPOUND AND METHOD OF TREATING A CENTRAL NERVOUS SYSTEM AILMENT"

The following statement is a full description of this invention, including the best method of performing it known to us :-
This invention relates to a novel substituted 1,2,4-oxadiazole.

The novel compound is useful for the preparation of oxadiazolylimidazo-benzodiazepine compounds. The latter compounds are useful in psychopharmaceutical compositions, e.g. for the treatment of central nervous system ailments, such as anticonvulsants and anxiolytics.

It is well known (Squires, R.F. and Braestrup, C., Nature (London) 266, (1977) 732) 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.

European patent application No. 109,921 discloses compounds having the general formula I

\[
\text{la}
\]

\[ \text{Substituted 1,2,4-oxadiazole.} \]

\[
\text{This invention relates to a novel substituted 1,2,4-oxadiazole.}
\]

\[
\text{The novel compound is useful for the preparation of oxadiazolylimida-}
\]

\[
\text{zo-benzodiazepine compounds. The latter compounds are useful in}
\]

\[
\text{psychopharmaceutical compositions, e.g. for the treatment of central}
\]

\[
\text{nervous system ailments, such as anticonvulsants and anxiolytics.}
\]

\[
\text{It is well known (Squires, R.F. and Braestrup, C., Nature (London)
}
\]

\[
\text{266, (1977) 732) that specific sites in the central nervous systems of}
\]

\[
\text{vertebrates exhibit a high specific affinity for binding 1,4- and}
\]

\[
\text{1,5-benzodiazepines. These sites are called benzodiazepine receptors.}
\]

\[
\text{European patent application No. 109,921 discloses compounds having the}
\]

\[
\text{general formula I}
\]

\[
\text{(I)}
\]

\[
\text{wherein}
\]

\[
\text{R'} \text{ is hydrogen, chlorine, fluorine or nitro in the 7- or 8-position,}
\]

\[
\text{R}^1 \text{ is hydrogen or C}_1^3 \text{-alkyl,}
\]

\[
\text{R}^3 \text{ is an oxadiazoly1 group having the formula}
\]

\[
\text{R}'' \text{ is C}_1^3 \text{-alkyl,}
\]

\[
\text{A...B is a group having the formula}
\]
European patent application No. 109,921 further discloses that certain oxadiazolyl benzodiazepines and oxadiazolyl beta-carbolines exhibit stronger binding affinity for the benzodiazepine receptors than the alkyl esters of the corresponding acids.

European patent application No. 150,040 discloses 1,2,4-oxadiazolyl benzodiazpine compounds having the formulae II and III:

wherein

$R^5$ is hydrogen or methyl and
$R'''$ is hydrogen or chlorine.

wherein

$R^1$ is alkyl, cycloalkyl, methoxymethyl,
$R^3$ is H, CH$_3$ and
$R^4$ and $R^5$ each is H or halogen,
The compounds disclosed in examples 2, 3, 16, 29, 32, 43, 44, 45, 49, 50, 51, 52, 53 and 56 of EP No. 150.040 are 5,6-dihydro-6-oxo-4H-imidazo(1,5-a)(1,4)benzodiazepine compounds (having the above formula II), whereas the compounds disclosed in examples 1, 8, 9, 17, 18, 23 and 30 are 10,11,12,12a-tetrahydro-9-oxo-9H-imidazo-(1,5-a)azeto(2,1-c)(1,4)benzodiazepine compounds (having the above formula III) and the compounds disclosed in examples 4, 5, 6, 7, 10, 11, 12, 13, 14, 15, 19, 20, 21, 22, 24, 25, 26, 27, 28, 31, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 46, 48, 54, 55, 57, 58 and 59 are 11,12,13,13a-tetrahydro-9-oxo-9H-imidazo-(1,5-a)pyrrolo(2,1-c)(1,4)benzodiazepine compounds (also having the formula III).

Finally, the compound disclosed in example 47 of EP 150.040 is an 11,13a-dihydro-9-oxo-9H-imidazo(1,5-a)pyrrolo(2,1-c)(1,4)-benzodiazepine compound.

The compounds disclosed in examples 11, 15, 26 and 40 of EP 150.040 are compounds of formula III, in which X is 1,2,4-oxadiazol-3-yl group and in the compound disclosed in example 40 X is a 5-cyclopropyl-1,2,4-oxadiazol-3-yl group.

EP No. 150.040 also discloses a method of preparing compounds having the formulae II and III, said process comprising reacting a compound having the formula V and VI, respectively:

![Diagram](image)

wherein $R^4$, $R^5$ and n have the meanings defined above and Y is a leaving group, with a compound of the formula $CN-CH_2-CO_2R$ to form a compound of Formula II or III comprising a $-CO_2R$ substituent in the 3-position and converting in several steps this compound to the desired oxadiazole derivative.
The compound of the invention is 5-cyclopropyl-3-isocyanomethyl-1,2,4-oxadiazole having the formula:

\[
\begin{align*}
\text{CN} & \quad \text{CH}_2 \\
\end{align*}
\]

The compound of the invention is suitable for the preparation of 3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a] (1,4) benzodiazepine having the formula VII:

Thus the compound having the formula VII can be prepared by reacting the compound of the invention with a compound having the formula VIII

\[
\begin{align*}
\text{CH}_3 \\
\end{align*}
\]

wherein \( Y \) is a leaving group.

Examples of suitable leaving groups for use in the above reactions are halogen, alkylthio, e.g., methylthio, aralkylthio, N-nitrosoalkylaminoo, alkoxy, mercapto, \(-\text{OP}(\text{OR})_2\) wherein \( R \) is lower-alkyl or \(-\text{OP}(\text{NR}R')\) wherein \( R' \) and \( R'' \) each represents lower-alkyl, or phenyl, or together with the adjacent nitrogen atom form 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. Preferred bases are alkali metal, e.g., potassium or sodium, alkoxides or hydrides. The reaction is preferably effected in the presence of an organic solvent which does
not react with the reactants and products of reaction under the prevailing reaction conditions. Suitable solvents are anhydrous solvents and preferably anhydrous aprotic solvents such as dimethylformamide (DMF) or the like. The reaction temperature should be sufficiently high to allow the reaction to proceed at a reasonable rate and without undue delay or decomposition and a range from -40°C to about 30°C is ordinarily suitable.

The invention will now be described in further detail with reference to the following non-limiting example.

**Example**

a. **Formylaminomethyl-carboxamide oxime**

0.55 Mole of freshly liberated hydroxylamine dissolved in 370 ml methanol was added to 53.6 g (0.638 mole) of N-formylamino-acetonitrile. An ice bath was used to keep the temperature below 20°C during the addition. The solution was allowed to stand at room temperature overnight, whereafter it was evaporated to give the title compound as pale crystals.

Decomp. 104-110°C.

b. **3-Formylaminomethyl-5-cyclopropyl-1,2,4-oxadiazole**

A mixture of 35 ml ethylcyclopropyl carboxylate, 30 g formylaminomethyl-carboxamide oxime, 1 g sodium, and 30 g crushed molecular sieves (4Å) was refluxed in 300 ml abs. EtOH for 8 hours, whereafter a further 1 g sodium was added. The reaction mixture was filtered and the filtrate was evaporated. A dark oily residue was formed and it was suspended in 300 ml CHCl₃, filtered and the filtrate was evaporated to give the title compound as an oil.

H-NMR (60 MHz, CDCl₃) δ (ppm): 1.2 (4 H, m), 2.8 (1 H, m), 4.5 (2 H, d, j=6 Hz), 7.8 (1 H, broad-NH), 8.2 (1 H, s).

c. **5-Cyclopropyl-3-isocyanomethyl-1,2,4-oxadiazole**

A stirred solution of 5-cyclopropyl-3-formylamino-methyl-1,2,4-oxadia-
zole (60 mmol) and triethylamine (176 mmol) in CH₂Cl₂ (100 ml) was charged dropwise with POCl₃ (60 mmol) at 0°C, whereafter a solution of Na₂CO₃ (60 mmol) in H₂O (50 ml) was added. The mixture was heated to room temperature, whereafter the organic phase was separated, dried and evaporated in vacuo. The residue was treated with ether, decanted and the solution was evaporated to give the title compound as an oil.

The oil was processed without any further purification.

IR: cm⁻¹: 2160.

d. 3-(5-cyclopropyl-1,2,4-oxadiazole-3-yl)-5,6-dihydro-5-methyl-6-oxo-4H-imidazo(1,5-a)(1,4)benzodiazepine.

3,4-dihydro-4-methyl-2H-1,4-benzodiazepine-2,5(1H)-dione (16.5 mmol) was dissolved in dry DMF (25 ml) and charged with K-t-butylate (18 mmol). The resulting solution was cooled under N₂ to -20°C, whereafter chlorodiethylphosphate (20 mmol) was added.

The reaction mixture was kept under N₂ with stirring at -20°C and charged with a -30°C cold solution of 5-cyclopropyl-3-isocyanomethyl-1,2,4 oxadiazole (20 mmol) and K-t-butylate (20 mmol) in dry DMF (20 ml).

The resulting reaction mixture was allowed to heat to room temperature, whereafter it was evaporated to dryness in vacuo. An oily residue thus obtained and containing the crude product was purified on SiO₂ with ethyl acetate as eluent. This gave the title compound as white crystals.

M.p. 179-180°C.
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. 5-Cyclopropyl-3-isocyanomethyl-1,2,4-oxadiazole having the formula

\[
\begin{array}{c}
\text{CN-CH}_2 \\
\text{N} \\
\text{O} \\
\end{array}
\]

2. A compound according to claim 1, or a method of preparation or use thereof, substantially as hereinbefore described with reference to the Examples.

3. The steps, features, compositions and compounds referred to or indicated in the specification and/or claims of this application, individually or collectively, and any and all combinations of any two or more of said steps or features.

DATED THIS 3rd August, 1989

DAVIES & COLLISON
Patent Attorneys for the Applicant