

8-P330/GD/MP/4233T.2

PATENT APPLICATION FORM

COMMONWEALTH OF AUSTRALIA

Patents Act 1952

Regulation 9

593694

We, SCHERING AKTIENGESELLSCHAFT

of Postfach 65 03 11, D-1000 Berlin 65, Germany

hereby apply for the grant of a Standard Patent for an invention
entitled USE OF 5-(SUBSTITUTED PHENYL)-OXAZOLIDINONE DERIVATIVES
FOR TREATMENT OF DEPRESSION

which is described in the accompanying complete specification.

For a Convention application - details of basic application-

<u>Number</u>	<u>Country</u>	<u>Date of Application</u>
P 36 39 225.1	Germany	14th November 1986

Our address for service is ARTHUR S. CAVE & CO., Patent and Trade
Mark Attorneys, 1 Alfred Street, Sydney, New South Wales,
Australia 2000.

Dated this 11th day of November, 1987.

SCHERING
AKTIENGESELLSCHAFT
By Its Patent Attorneys,
ARTHUR S. CAVE & CO.

APPLICATION ACCEPTED AND AMENDMENTS

ALLOWED

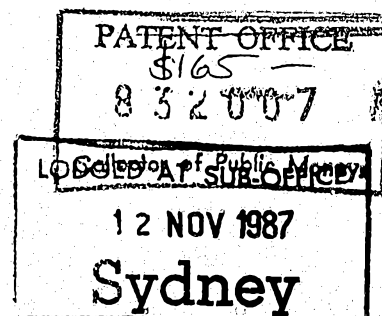
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for P.R. L.
HECTOR CUMMING, Solicitor

To:
Commissioner of Patents

ARTHUR S. CAVE & CO.
PATENT AND TRADE MARK ATTORNEYS
SYDNEY

ASC 1



254420:SLC

Regulation 12(2)

PATENT DECLARATION FORM (CONVENTION)
COMMONWEALTH OF AUSTRALIA

Patents Act 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION
FOR A PATENT

In support of the Convention application made for a patent for an invention entitled: USE OF 5-(SUBSTITUTED PHENYL)-OXAZOLIDINONE DERIVATIVES FOR TREATMENT OF DEPRESSION

I/We .Dr..Gerhard.Liedtke.and.Dr..Ute.Kirsch..... (full name of declarant)
of .SCHERING AKTIENGESELLSCHAFT,.Berlin.and.Bergkamen,.Müller... (full address)
strasse 170-178, D-1000 Berlin 65
do solemnly and sincerely declare as follows:-

1. I am/We are authorised by SCHERING AKTIENGESELLSCHAFT the applicant for the patent to make this declaration on its behalf.

2. The basic Application(s) as defined by Section 141 of the Act was/were made in the following country or countries on the following date namely:-
in GERMANY on 14th November 1986 by SCHERING AKTIENGESELLSCHAFT

3. 1. DR. HELMUT WACHTEL and 2. DR. HERBERT H. SCHNEIDER
of 1. Suarazestr. 22, D-1000 Berlin 19, Germany and 2. Duisburgerstr. 20,
D-1000 Berlin 15, Germany
are the actual inventors of the invention and the facts upon which the applicant(s) are entitled to make the application are as follows:

The Applicant is the Assignee of the said invention from the actual inventors.

4. The basic application(s) referred to in paragraph 2 of this Declaration was the first application(s) made in a Convention country in respect of the invention the subject of the application.

Declared at Berlin this 11th day of October, 1989.

SCHERING AKTIENGESELLSCHAFT
ppa. i.A.

To:
The Commissioner of Patents

Dr. Gerhard Liedtke Dr. Ute Kirsch

ARTHUR S. CAVE & CO.

Signature of Declarant(s)

PATENT AND TRADE MARK ATTORNEYS

SYDNEY

(12) PATENT ABRIDGMENT (11) Document No. AU-B-81143/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 593694

(54) Title
USING 5-(SUBSTITUTED PHENYL)-OXAZOLIDINONE DERIVATIVES FOR DEPRESSION TREATMENT

International Patent Classification(s)
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(71) Applicant(s)
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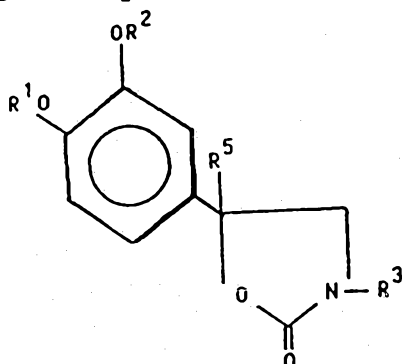
(72) Inventor(s)
Dr. HELMUT WACHTEL; Dr. HERBERT H. SCHNEIDER

(74) Attorney or Agent
ARTHUR S. CAVE & CO.

(56) Prior Art Documents
US 4186129

(57) Claim

1. A method of treating depression comprising administering a compound of the formula



wherein

R¹ and R² each independently is a C₁₋₈ hydrocarbon group or C₃₋₇-cycloalkyl wherein a CH₂ group is replaced by oxa,

R³ is hydrogen, C₁₋₈-alkyl, C₆₋₈-aryl or C₆₋₈-aralkyl or an acyl group of a C₁₋₈-hydrocarbon carboxylic acid,

R⁵ is hydrogen or C₁₋₈-alkyl.

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

Application Number:

Lodged:

Complete Specification Lodged:

Accepted:

Published:

This document contains the
amendments made under
Section 49 and is correct for
printing

Priority:

Related Art:

TO BE COMPLETED BY APPLICANT

Name of Applicant:

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AUSTRALIA

Complete Specification for the invention entitled USE OF
5-(SUBSTITUTED PHENYL)-OXAZOLIDINONE DERIVATIVES FOR TREATMENT
OF DEPRESSION.

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

USE OF 5-(SUBSTITUTED PHENYL)-OXAZOLIDINONE
DERIVATIVES FOR TREATMENT OF DEPRESSION

Background of the Invention

The invention relates to the provision of medica-
ments useful in treating depression.

It is known from US patent 4 186 129 that 5-(sub-
stituted phenyl)-oxazolidinone derivatives have phospho-
diesterase-inhibiting properties and moreover have
central depressive, antidopaminergic, antinociceptive
and anticonvulsive effects. Further, in German patent
application No. 3438839 other 5-(substituted phenyl)-
oxazolidinones are described which have anti-inflam-
matory properties in topical application.

Summary of the Invention

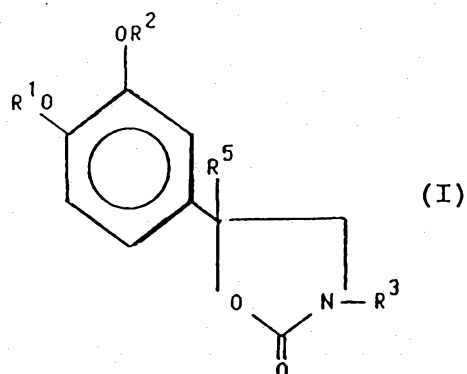
It is an object of this invention to provide medi-
caments which are valuable antidepressants.

Upon further study of the specification and
appended claims, further objects and advantages of this
invention will become apparent to those skilled in the
art.

It has now been found that the effect of the above-
described compounds is not centrally depressive but
centrally antidepressive. 5-(Substituted phenyl)-oxa-
zolidinones exhibit a very good neuropsychotropic effec-
tiveness.

According to this invention, there are preferred
racemic and optically active 5-(substituted phenyl)-

oxazolidinones of formula I



wherein

R¹ and R² each independently is a C₁₋₈ hydrocarbon radical,

R³ is hydrogen or a lower alkyl, aryl, aralkyl or acyl group and

R⁵ is hydrogen or lower alkyl.

The compounds of formula I have an asymmetric carbon atom and, therefore, can be used as racemates, or after resolution of the racemate by the usual methods, can be used as antipodes.

Substituents R¹ and R² can be the same or different.

Suitable lower alkyl groups throughout preferably contain 1-4 carbon atoms such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl and sec-butyl, but also all isomeric pentyl, hexyl, heptyl, octyl, etc., groups.

Saturated or unsaturated, straight-chain or branched, optionally substituted, acyclic aliphatic groups, of preferably 1-6 hydrocarbon atoms, and cycloalkyl and cycloalkylalkyl groups of preferably 3-7 carbon atoms, in the ring and, e.g., 1-4 C-atoms in the alkyl portion, as well as aryl and aralkyl groups of preferably 6-8 carbon atoms are all suitable as the hydrocarbon radicals R¹ and R².

Suitable such alkyl groups, besides the lower alkyl groups mentioned above, are, for example, pentyl, 2-methylbutyl, 2,2-dimethylpropyl, hexyl, etc. As alkenyl and alkynyl groups there can be mentioned, for example:

2-propenyl, 3-methyl-2-propenyl, 2-propinyl, etc.

5 Halogens, especially fluorine, chlorine and bromine (but also iodine), hydroxy, lower alkoxy (e.g., of 1-4 C-atoms) and amino groups which optionally can be mono-substituted or disubstituted by lower alkyl groups (e.g., of 1-4 C-atoms each), are suitable as substituents. Typically, there are 1 or 2 such substituents but more are possible.

10 If the hydrocarbon radical represents a cycloalkyl group, a CH₂ group of the cycloalkyl radical can optionally be replaced by an oxygen atom. As a cyclic ether radical there can be mentioned, for example, 3-tetrahydrofuranyl and 3-tetrahydropyranyl and as cycloalkyl radical there can be mentioned, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. 15 If the hydrocarbon radical represents a cycloalkylalkyl group, cyclopropylmethyl, cyclopropylethyl and cyclopentylmethyl are preferred.

20 Suitable aryl and aralkyl groups R¹, R² and R³ preferably have 6-8 carbon atoms, for example, phenyl, benzyl and phenethyl.

25 All organic acids can be used as the basis for the acyl radicals R³, preferably those of hydrocarbon acids. Carbamic acid and carboxylic acid radicals of up to 8 carbon atoms are preferred. These can be saturated or unsaturated, aliphatic, cycloaliphatic, araliphatic and aromatic. Lower such acyl groups with up to 4 carbon atoms such as, for example, acetyl, propionyl and butyryl are most suitable. Further typical such acyl 30 groups are those disclosed in USP 4,186,129 whose disclosure is entirely incorporated by reference herein.

Lower alkyl and acyl groups are especially suitable as substituents R³.

35 Especially preferred compounds of formula I are those in which R³ represents a hydrogen atom, R¹ represents a lower alkyl group and R² represents a C₁₋₆ alkyl

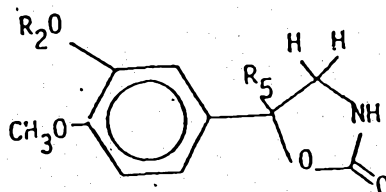
or a cycloalkyl radical, optionally interrupted by an oxygen atom. These are particularly suitable for treatment of neuropsychotropic disorders. Most especially preferred are compounds of general formula I, in which R^1 represents a methyl group.

The production of the compounds of formula I can be accomplished routinely according to the processes described in German patent application No. 3,438,839 and US patent 4,186,129.

The effect of the compounds of general formula I on the central nervous system was determined by measuring the antagonism of the compounds on reserpine-induced lowering of the body temperature. The determination of the antagonism of the reserpine-induced lowering of body temperature was performed conventionally on male NMRI mice weighing 20-25 g. The test substances were administered i.p. as a function of their effectiveness in doses between 0.00625 and 25 mg/kg to experimental animals treated with reserpine (10 mg/kg, i.p.) 4 hours before and the rectal temperature was measured with an electric thermometer (ellab TE3, Thermosonde RM 6). Control animals were treated i.p. with 0.1 ml/10 g of body weight of the solvent (physiological NaCl solution with addition of 100 g/l of Cremophor EL^R). The different treatment groups each comprised 6-8 mice.

The significance of the difference between the average values of the different groups treated with the test substances and the control group was determined by analysis of variance in combination with the Dunnett test. The minimal effective dose (MED), i.e., the lowest statistically significant antihypothermally effective dose is indicated.

The following table shows the results obtained in this test.



	No.	R ²	R ⁵	Reserpine Antag. MED (mg/kg)
5	1	Cyclopentyl	H	0.39
	2	Tetrahydro- furanyl	H	0.1
	3	C ₂ H ₅	CH ₃	0.39
	4	C ₃ H ₇	CH ₃	0.10
	5	C ₄ H ₉	CH ₃	1.56
10	6	Cyclopentyl	CH ₃	0.39

Therefore the compounds of general formula I are suitable for the production of antidepressant agents, marked by having few side effects, for symptomatic treatment of depression in general, e.g., in mammals including humans. They can be used especially in acute and chronic disorders of the depressive formenkreis, of endogenous depression and of senile depression. Their use for these purposes is analogous to the corresponding use of the known antidepressant Imipramine.

In medical practice these oxazolidinone derivative drugs can be administered parenterally, subcutaneously, intramuscularly, intravenously and especially orally. The daily dose typically is 0.1-10 mg but preferably 0.5-5 mg. The dose can be administered once or in divided doses as usual. The agents according to the invention are suitable for a long-term treatment.

The production of the drug specialties takes place in a way known in the art, by processing the active substance with vehicles, diluents, taste corrigents, etc. customary in galenic pharmacy, e.g., as disclosed in the mentioned disclosures. Aqueous but also oily solutions and suspensions are especially suitable for

injections. For the production of intramuscular depot forms the active substances can be suspended or dissolved in fatty oils according to current conventional methods. Such depot forms typically contain about 1-10 mg of active substance per application unit; the active substance is released over a period of 1 to 10 days.

The drugs according to the invention in the form of tablets, capsules, dragees, pills, suspensions or solutions are especially suitable for oral application. The amount of active substance per oral application unit typically is 0.1-5 mg, preferably 0.1-1 mg.

Also suitable are slow-release oral forms, which are obtained in the usual way; i.e., by addition of hydrogenated fats and processing with resin formers and varnishes. Drops for oral application can be produced by aqueous solutions or suspensions of the active substance in oils with addition of taste corrigents and/or solubilizers. For example, 0.5-5 mg can be contained in a daily dose of 3-10 drops.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description; utilize the present invention to its fullest extent. The preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The entire text of all applications, patents and publications, if any, cited above are hereby incorporated by reference.

The preceding can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding.

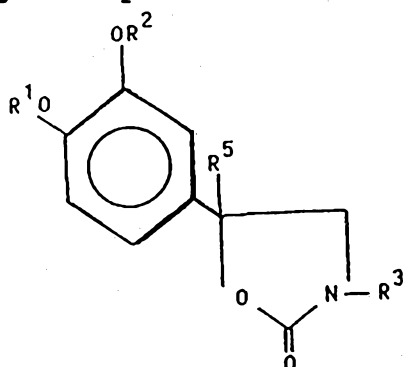
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From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

10

The claims defining the invention are as follows:

1. A method of treating depression comprising administering a compound of the formula



wherein

- R^1 and R^2 each independently is a C_{1-8} hydrocarbon group or C_{3-7} -cycloalkyl wherein a CH_2 group is replaced by oxa,
 R^3 is hydrogen, C_{1-8} -alkyl, C_{6-8} -aryl or C_{6-8} -aralkyl or an acyl group of a C_{1-8} -hydrocarbon carboxylic acid,
 R^5 is hydrogen or C_{1-8} -alkyl.

2. A method of claim 1, wherein R^1 is CH_3 .
3. A method of claim 1, wherein R^3 is H.
4. A method of claim 1, wherein said compound is in the form of a racemate.
5. A method of claim 1, wherein said compound is in the form of an antipode.

6. A method of claim 1, wherein all alkyl groups are of 1-4 C-atoms.

7. A method of claim 1, wherein R^2 is cycloalkyl, cycloalkyl wherein a CH_2 group is replaced by oxa, C_{2-4} -alkenyl, C_{2-4} -alkynyl, phenyl, benzyl or phenethyl.

8. A method of claim 1, wherein R^2 is acyclic aliphatic and is substituted by halo, OH, C_{1-4} -alkoxy or amino.

9. A method of claim 1, wherein R^3 is H, C_{1-4} -alkyl, phenyl, phenethyl, benzyl or C_{1-4} -alkanoyl.

10. A method of claim 1, wherein R^5 is H or C_{1-4} -alkyl.

11. A method of claim 1, wherein said compound is 5-methyl-5-(3-propoxy-4-methoxyphenyl)-2-oxazolidinone.

12. A method of claim 1, wherein said compound is 5-(3-cyclopentyloxy-4-methoxyphenyl)-2-oxazolidinone.

13. A method of claim 1, wherein the administration is oral.

14. A method of claim 1, wherein the dose administered is 0.1-10 mg.

15. A method of claim 1, wherein R^3 is H, R^1 is CH_3 , R^2 is cyclopentyl, tetrahydrofuranyl, C_2H_5 , C_3H_7 or C_4H_9 , and R^5 is H or CH_3 .

DATED this 25th day of October, 1989.

SCHERING AKTIENGESELLSCHAFT
By Its Patent Attorneys
ARTHUR S. CAVE & CO.

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