

25684/88

FORM 1

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

602268

APPLICATION FOR A STANDARD PATENT

I\We, FARMITALIA CARLO ERBA s.r.l.

of VIA CARLO IMBONATI, 24  
20159 MILAN  
ITALY

hereby apply for the grant of a standard patent for an invention entitled:

ANTIPARKINSON ERGOLINE DERIVATIVES

which is described in the accompanying complete specification

Details of basic application(s):

Number of basic application	Name of Convention country in which basic application was filed	Date of basic application
8727236	GB	20 NOV 87
8822424.1	GB	23 SEP 88

My/our address for service is care of GRIFFITH HACK & CO., Patent Attorneys, 601 St. Kilda Road, Melbourne 3004, Victoria, Australia.

DATED this 17th day of November 1988

FARMITALIA CARLO ERBA s.r.l.

GRIFFITH HACK & CO.

TO: The Commissioner of Patents.

APPLICATION ACCEPTED AND AMENDMENTS

ALLOWED ..... 18-7-90 .....

Forms 7 and 8

AUSTRALIA

Patents Act 1952

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

Name(s) of Applicant(s)

In support of the application made by FARMITALIA CARLO ERBA S.r.l.

Title

for a patent for an invention entitled ANTIPARKINSON ERGOLINE DERIVATIVES

Name(s) and address(es) of person(s) making declaration

I/We, Giorgio Orlando, Director of Patent and Trademark Dept., Farmitalia Carlo Erba S.r.l., Via Carlo Imbonati, 24 - 20159, Milan, Italy

do solemnly and sincerely declare as follows:-

1. I am/we are the applicant(s) for the patent, or am/are authorised by the abovementioned applicant 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(s) by the following applicant(s) namely:-

Country, filing date and name of Applicant(s) for the or each basic application

in Great Britain on 20th November 1987  
 by Farmitalia Carlo Erba S.r.l.  
 in Great Britain on 23rd September 1988  
 by Farmitalia Carlo Erba S.r.l.

3. The said basic application(s) was/were the first application(s) made in a Convention country in respect of the invention the subject of the application.

Name(s) and address(es) of the or each actual inventor

4. The actual inventor(s) of the said invention is/are Metilde Buonamici, Via Canova n.33-PARABIAGO, (Milan), Italy  
Lorenzo Pegrassi, Via Giosue Carducci n.32, Milan, Italy  
Alessandro Rossi, Via Luigi Barzini n.7, Milan, Italy  
Sergio Mantegani, Via Carlo Pisacane n.57, Milan, Italy

See reverse side of this form for guidance in completing this part

5. The facts upon which the applicant(s) is/are entitled to make this application are as follows:-  
The said applicant is the assignee of the said inventors

DECLARED at Milan, Italy this 18th day of October 1988

FARMITALIA CARLO ERBA S.r.l.



(Giorgio Orlando Director of Patent and Trademark Deptm.)

**(12) PATENT ABRIDGMENT (11) Document No. AU-B-25684/88**  
**(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 602268**

(54) Title  
**METHOD OF TREATING EXTRAPYRAMIDAL SYNDROME**

International Patent Classification(s)  
(51)<sup>4</sup> **A61K 031/48**

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(71) Applicant(s)  
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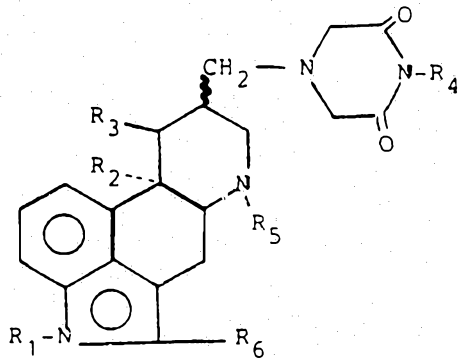
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(56) Prior Art Documents  
**US 4728649**

(57) Claim

1. A method of treating an extrapyramidal syndrome in a patient in need thereof which comprises administering to said patient an effective amount of a compound of the formula 1



(11) AU-B-25684/88  
(10) 602268

-2-

wherein  $R_1$  represents a hydrogen atom or methyl group, either  $R_2$  and  $R_3$  represent hydrogen atoms or together represent a chemical bond,  $R_4$  represents a hydrogen atom or a  $C_1$ - $C_4$  alkyl group,  $R_5$  represents a  $C_1$ - $C_4$  alkyl group or an allyl group and  $R_6$  represents a hydrogen or halogen atom; or a pharmaceutically acceptable salt thereof.

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Form 10

COMPLETE SPECIFICATION

(ORIGINAL)

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Complete Specification-Lodged:

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Related Art:

This document contains the amendments made under section 47 and is entitled for filing.

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TO BE COMPLETED BY APPLICANT

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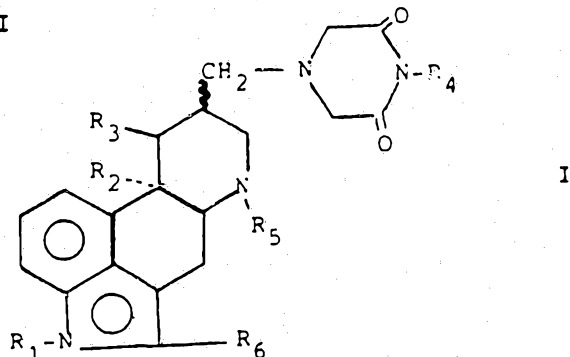
Complete Specification for the invention entitled:  
ANTIPARKINSON ERGOLINE DERIVATIVES

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

- 1A -

ANTIPARKINSON ERGOLINE DERIVATIVES

The present invention relates to a new therapeutic use of ergoline derivatives having the formula I



wherein  $R_1$  represents a hydrogen atom or methyl group, either  $R_2$  and  $R_3$  represent hydrogen atoms or together represent a chemical bond,  $R_4$  represents a hydrogen atom or a  $C_1-C_4$  alkyl group,  $R_5$  represents a  $C_1-C_4$  alkyl group or an allyl group and  $R_6$  represents a hydrogen or halogen atom; and the pharmaceutically acceptable salts thereof.

The compounds of the formula I and their preparation are described in EP-A-0197241. This shows their functional anti-dopaminergic activity in normal mice. The compounds are said to have moderate to good anti-hypertensive activity and to be useful as anxiolytic and antipsychotic agents.

It is known that bromocriptine, an ergot derivative with dopaminergic activity, is an effective antiparkinson agent, but severe side effects limit the clinical usefulness of this drug. Adverse effects of

bromocriptine include emesis, hypotension, cardiac arrhythmia, digital vasospasm in cold weather, conjunctival irritation, diplopia, nasal stuffiness, constipation and a syndrome of bilateral red, tender edema of the lower limbs and neuroendocrine alterations. These problems are due to the fact that bromocriptine exerts its agonist effect on both central and peripheral populations of dopamine receptors.

It has been found that the ergoline derivatives of the formula I may be unexpectedly used in the treatment of other diseases different from psychosis and anxiety. The compounds of formula I are surprisingly highly potent dopamine agonists when tested in animal experiments where central dopamine receptor supersensitivity had been induced by appropriate interventions.

Accordingly, the present invention provides the use of a compound of the formula I or a pharmaceutically acceptable salt thereof in the preparation of a pharmaceutical composition for treating extrapyramidal syndromes such as Parkinson's disease.

The ergoline derivatives of formula I and their salts induce less side effects than bromocriptine. They have a potent dopaminergic activity only on the central receptors when modified by extrapyramidal syndromes, such as in Parkinson's disease. They may be used alone or in association with other antiparkinson agents.

In formula I,  $R_4$  is preferably methyl or hydrogen.  $R_5$  may be methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, t-butyl, iso-butyl or allyl. Preferably  $R_5$  is methyl. When  $R_6$  is halogen, it may be fluorine, chlorine or bromine. Preferably  $R_6$  is chlorine or bromine or hydrogen.

The wavy line ( $\sim$ ) in formula I indicates that the substituent in the 8-position may be either in the  $\alpha$ -configuration, i.e. below the plane of the ring, or in the  $\beta$ -configuration, i.e. above the plane of the ring, or in both, i.e. a mixture thereof such as a racemic mixture. Preferably the substituent in the 8-position is in the  $\beta$ -configuration.

Preferred ergoline derivatives for use in the present invention are identified in Table I.

Table I

Laboratory Code	Chemical Name	Reference
FCE 23884	6-Methyl-9,10-didehydro-8 $\beta$ -(3,5-dioxo-piperazin-1-yl-methyl)-ergoline (I: $R_1=R_4=R_6=H$ , $R_5=CH_3$ , $R_2+R_3=bond$ )	EP-A-197241 Example 5
FCE 23952	1,6-Dimethyl-8 $\beta$ -(3,5-dioxo-piperazin-1-yl-methyl)-ergoline (I: $R_2=R_3=R_4=R_6=H$ , $R_1=R_5=CH_3$ )	EP-A-197241 Example 2



FCE 23710      6-Methyl-8 $\beta$ -(3,5-dioxo-4-methyl-piperazin-1-yl-methyl)-ergoline  
(I:R<sub>1</sub>=R<sub>2</sub>=R<sub>3</sub>=R<sub>6</sub>=H, R<sub>4</sub>=R<sub>5</sub>=CH<sub>3</sub>)      EP-A-197241  
Example 3

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6-Methyl-8 $\beta$ -(3,5-dioxo-piperazin-1-yl-methyl)-ergoline (I:R<sub>1</sub>=R<sub>2</sub>=R<sub>3</sub>=R<sub>4</sub>=R<sub>6</sub>=H, R<sub>5</sub>=CH<sub>3</sub>)      EP-A-197241  
Example 1

6-Methyl-9,10-didehydro-8 $\alpha$ -(3,5-dioxopiperazin-1-yl-methyl)-ergoline (I:R<sub>1</sub>=R<sub>4</sub>=R<sub>6</sub>=H, R<sub>5</sub>=CH<sub>3</sub>, R<sub>2</sub>+R<sub>3</sub>=bond)

6-Allyl-9,10-didehydro-8 $\beta$ -(3,5-dioxopiperazin-1-yl-methyl)-ergoline (I:R<sub>1</sub>=R<sub>4</sub>=R<sub>6</sub>=H, R<sub>5</sub>=allyl, R<sub>2</sub>+R<sub>3</sub>=bond)

6-Propyl-9,10-didehydro-8 $\beta$ -(3,5-dioxopiperazin-1-yl-methyl)-ergoline (I:R<sub>1</sub>=R<sub>4</sub>=R<sub>6</sub>=H, R<sub>5</sub>=propyl, R<sub>2</sub>+R<sub>3</sub>=bond)

6-Propyl-9,10-didehydro-8 $\alpha$ -(3,5-dioxopiperazin-1-yl-methyl)-ergoline (I:R<sub>1</sub>=R<sub>4</sub>=R<sub>6</sub>=H, R<sub>5</sub>=propyl, R<sub>2</sub>+R<sub>3</sub>=bond)

2-Chloro-6-methyl-9,10-didehydro-8 $\beta$ -(3,5-dioxopiperazin-1-yl-methyl)-ergoline (I:R<sub>1</sub>=R<sub>4</sub>=H, R<sub>5</sub>=CH<sub>3</sub>, R<sub>6</sub>=Cl, R<sub>2</sub>+R<sub>3</sub>=bond)

2-Bromo-9,10-didehydro-8 $\beta$ -(3,5-dioxopiperazin-1-yl-methyl)-ergoline (I:R<sub>1</sub>=R<sub>4</sub>=H, R<sub>5</sub>=CH<sub>3</sub>, R<sub>6</sub>=Br, R<sub>2</sub>+R<sub>3</sub>=bond)

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The ergoline derivatives of formula I and their pharmaceutically acceptable salts are useful in the therapy of extrapyramidal syndromes such as Parkinson's disease.

Thus, they may be used for the preparation of medicaments effective against Parkinson's disease and for the improvement of effectiveness with control of side-effects when used in association with other antiparkinson agents.

Accordingly, the compounds of formula I and their pharmaceutically acceptable salts can be used to treat extrapyramidal syndromes such as Parkinsonism by administering to a patient in need of said treatment a therapeutically effective amount of a said compound or salt. Morbus Parkinson can therefore be treated by use of a compound of formula I or a pharmaceutically acceptable salt thereof.

BIOLOGICAL TESTS

The anti-dopaminergic activity in normal mice of the ergoline derivatives according to the invention was assessed by the antagonism to apomorphine-induced climbing (Protais, P et al., Psychopharmacology, 50, 1, 1976).

The obtained results are reported in Table II.

T A B L E II

Compound	Apomorphine antagonism (ED <sub>50</sub> , mg/kg p.o.)
FCE 23884	0.5
FCE 23952	0.9
FCE 23710	2.2
Eromocriptine	Inactive at 10 mg/kg

EFFECT ON TURNING BEHAVIOUR IN 6-OHDA LESIONED RATS

The profile of dopamine agonists of the compound of the formula I was preliminary discovered by an induction of contralateral turning in rats with unilateral 6-hydroxy dopamine-induced lesions of the dopaminergic nigrostriatal pathway (according to the principles of U. Ungerstedt et al., Brain Research 24 (1970); p.485).

Methods

Male (ICR) Wistar rats (290-310 g) anaesthetized i.p. with 50 mg/kg pentobarbital sodium were placed in a Stoelting stereotaxis frame and unilaterally injected with 6-hydroxy-dopamine (6-OHDA) in substantia nigra, pars compacta (8 µg of free base in 4 µl of saline kept ice cold with 0.2% ascorbic acid at the rate of 1 µl/min.).

The neurotoxin was injected via a 10  $\mu$ l Hamilton syringe under following coordinates : A, 3.7 mm anterior to interaural line; V, 2.2 mm dorsal to interaural line; L, 2.2 mm from midline, according to Paxinos and Watson (The rat brain in stereotaxic coordinates. Academic Press, Sidney, Australia, 1982).

The needle was left in place a further 5 minutes before being slowly withdrawn.

Following recovery from anaesthesia, rats were housed in a cage and given ad libitum access to food and water.

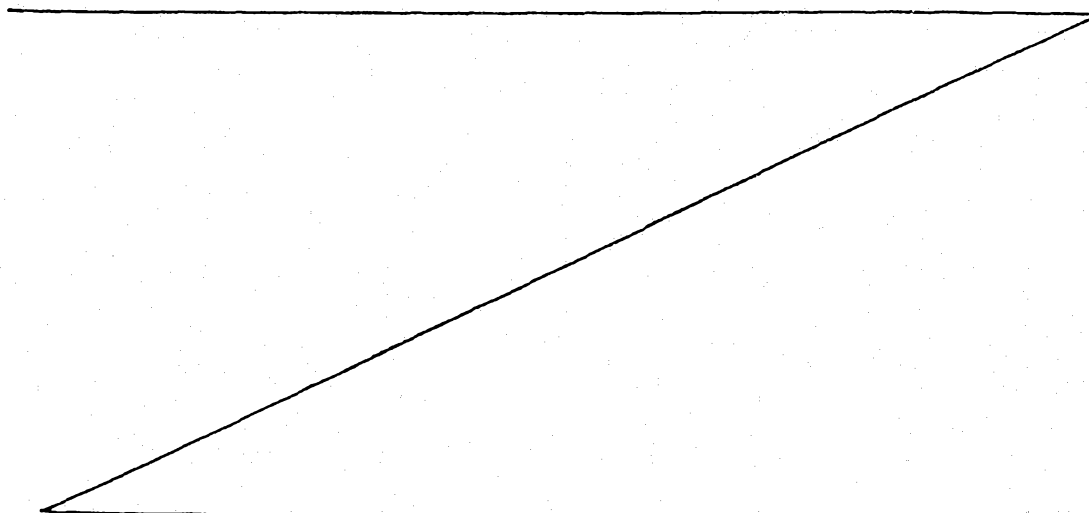
After a 3 weeks recovery, rats were injected with apomorphine (0.5 mg/kg s.c.) and immediately put in automated rotometer bowls with printing unit for 3 hours.

Only rats showing contralateral turning behaviour totalling at least 250 complete turns within the control time, were used for the test with the compounds.

The test compounds were injected subcutaneously and rotational behaviour scored each time for six hours.

All tested compounds were administered in a fixed volume (2 ml/kg body weight).

The obtained results are reported in Table III.



T A B L E III

EFFECT OF THE TESTED COMPOUNDS ON TURNING BEHAVIOUR IN 6-OHDA LESIONED RATS

Compounds	mg/kg s.c.	Turning rats/ Treated rats	No. of contralateral turns (X) in turning rats
FCE 23884	1.0	5/5	2146
	0.5	10/10	2591.7
	0.1	9/10	1317.5
FCE 23952	1.0	4/4	710.5
FCE 23710	1.0	4/4	1829.2
Bromocriptine 1		6/9	1922.3

The orientative acute toxicity of the compounds I in rats is higher than 300 mg/kg p.o..

The compounds are therefore indicated for use as antiparkinson agents:

The amount of active compound for this indication will, of course, be dependent on the subject being treated, the severity of the application, the manner of administration and the judgment of the prescribing physician.

However, an effective dosage is in the range of about 0.01 to about 5 mg, conveniently given in divided doses 1 to 5 times a day in unit dosage form containing from about 0.01 to about 2 mg of the compound or in sustained release form.

ADMINISTRATION AND COMPOSITIONS

Administration of the active compound and salts described herein can be via any of the accepted modes of administration for antiparkinson agents.

The routes of administration include parenteral, oral, buccal, peroral, transdermal, intranasal or other suitable routes. Depending on the intended route of administration, such compositions may be formulated in conventional manner or other pharmaceutical systems for delivery of the drug in a rate and extent needed for the intended therapeutical use.

The composition will include a conventional pharmaceutical carrier or excipient and an active compound of formula I or the pharmaceutically acceptable salts thereof and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc.

For solid composition, conventional non toxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate and the like may be used. Liquid pharmaceutically administerable compositions can, for example, be prepared by dissolving, dispersing, etc., an active compound as defined above and optional pharmaceutical adjuvant in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension.

The compound coded FCE 23884 is the preferred compound.

The following examples still further illustrate the invention without limiting it.

EXAMPLE 1

LOCOMOTOR ACTIVITY IN RESERPINE-TREATED MICE

Method

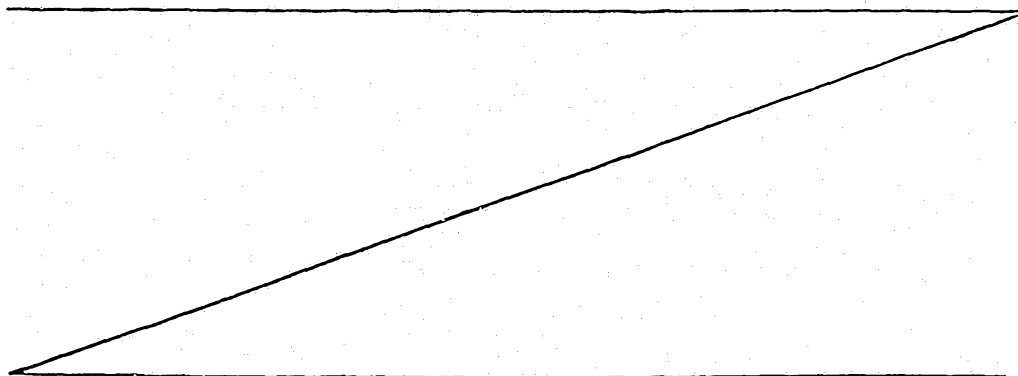
Male mice, (22-25 g) of the Crl:CD<sup>R</sup>-1 (ICR) BR strain, were used. Injection volume for drugs was 0.5 ml/100 g body weight. Locomotor activity in mice was examined from 5 up to 90 min. by use of two "Columbus activity Meters" placing 5 animals per cage after each treatment. Comparison was made with reserpine treated animals (5 mg/kg i.p.) receiving saline (controls).

Groups of five mice were used each time. Eighteen hours reserpine pretreated mice were subcutaneously injected with the test compound or apomorphine or saline.

Five minutes later, the animals were tested for locomotor activity according D. Hinzen et al., European Journal of Pharmacology 131 (1986) 75-86.

Results (see Table IV)

As shown in Table IV, FCE 23884 at the dose of 1 mg/kg s.c. elicits locomotor activity as does apomorphine - the classical dopaminergic agonist - in akinetic reserpinized mice.



T A B L E IV

LOCOMOTOR ACTIVITY IN RESERPINE-TREATED MICE (5mg/kg i.p.)

Compound	Dosage mg/kg s.c.	Number of animals	No. of counts in 85 min.
Reserpine + saline	-	10	15
Reserpine + apomor- phine	0.05	10	413
Reserpine + FCE 23884	1.0	15	625

EXAMPLE 2

MPTP-INDUCED PARKINSONISM IN MONKEY MODEL

In non human primates the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) selectively destroys dopaminergic neurons in the substantia nigra pars compacta as has been shown in different primate species (1) (2) including common marmoset and cynomolgus.

Repeated administration of MPTP produces varying degrees of akinesia or bradykinesia accompanied by rigidity of limbs, loss of vocalization and postural tremor.

The early motor deficits produced by MPTP mimic the major symptoms occurring in human Parkinson's disease and all these behavioural effects can be reversed by L-DOPA plus carbidopa or by some other dopaminergic drugs.



Marmoset and cynomolgus were employed in our experiments and we administered a variable dosage regime for each animal showing them an individual susceptibility to MPTP according to Jenner et al. (3).

For marmoset the cumulative dose was between 11-29 mg/kg i.p. over time courses of 4-10 days for three marmosets and 10-12 mg/kg i.p. for two cynomolgus in 4 days.

All the monkeys were severely affected, completely akinetic and rigid with loss of vocalization, and blink reflex, with some postural tremor and unable to eat by themselves.

After two or three days of wash-out to avoid the acute effect of MPTP administration, we injected subcutaneously our compound FCE 23884 once a day starting from the dose 0.1 mg/kg up to 2 mg/kg and we observed the reversal of akinesia dose-dependently.

We alternated saline every three treatments to avoid the normal described improvement after the suspension of MPTP administration.

Depending from the dose we observed the reversal of akinesia starting from 30 minutes for the lowest dose (0.1 mg/kg s.c.) to 5 minutes for the highest dose (2 mg/kg s.c.).

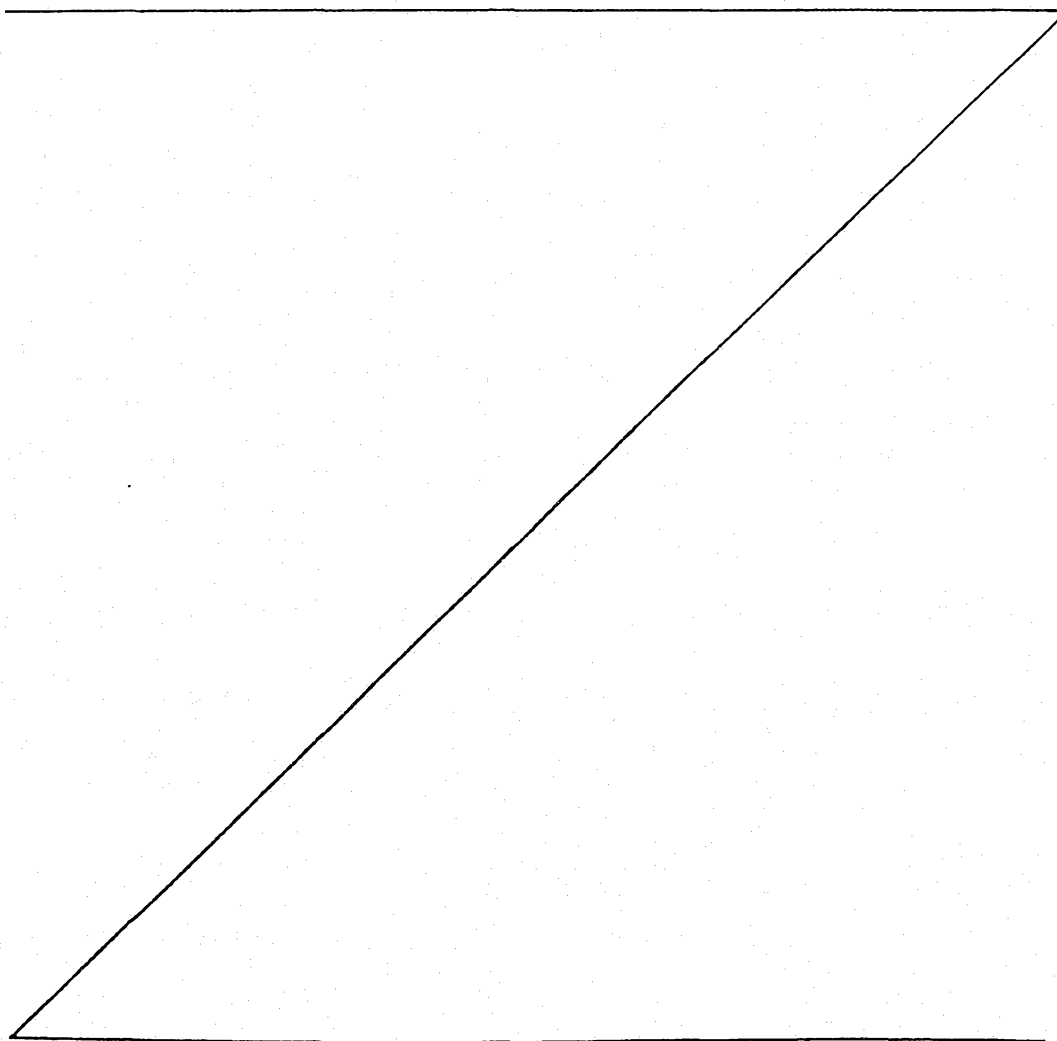
On the contrary our compound, injected subcutaneously to MPTP non-treated monkeys, dose dependently showed a sedative effect like an antidopaminergic compound reproducing the same behavioural patterns already seen in normal rats, while it shows a dopaminergic effect in lesioned animals.

For the results obtained we have to consider our compound FCE 23884 as a dopaminergic agent in the MPTP treated monkeys and an antidopaminergic in non MPTP-treated monkeys.

(1) Langston J.W. et al., Brain Res. 292:390-394, 1984.

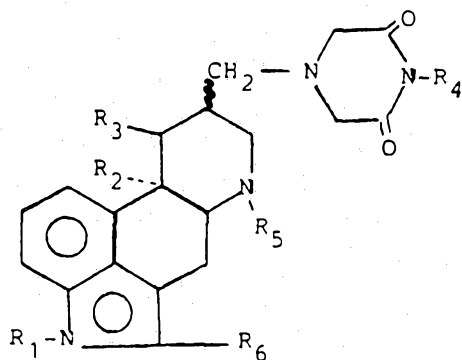
(2) Burns R.S. et al., Pro.Natl.Acad.Sci.USA 80. : 4546  
-4550, 1983.

(3) Jenner P. et al., J.Neuronal Trans. Suppl.20:11-39,  
1986.



THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of treating an extrapyramidal syndrome in a patient in need thereof which comprises administering to said patient an effective amount of a compound of the formula 1



wherein  $R_1$  represents a hydrogen atom or methyl group, either  $R_2$  and  $R_3$  represent hydrogen atoms or together represent a chemical bond,  $R_4$  represents a hydrogen atom or a  $C_1-C_4$  alkyl group,  $R_5$  represents a  $C_1-C_4$  alkyl group or an allyl group and  $R_6$  represents a hydrogen or halogen atom; or a pharmaceutically acceptable salt thereof.

2. The method according to claim 1, wherein said extrapyramidal syndrome is Parkinson's disease.
3. The method according to claim 1, wherein  $R_4$  is methyl.
4. The method according to claim 1, wherein  $R_5$  is methyl.
5. The method according to claim 1, wherein the substituent in the 8-position is in the  $\beta$ -configuration.



6. The method according to claim 1, wherein R<sub>6</sub> is chlorine, bromine or hydrogen.

7. The method according to claim 1, wherein the compound of formula I is 6-methyl-9,10-didehydro-8β-(3,5-dioxo-piperazin-1-yl-methyl)ergoline.

8. The method according to claim 1, wherein said effective amount is in the range of about 0.01 to about 5 mg, per dose.

9. The method according to claim 1, wherein said compound is administered to said patient 1 to 5 times per day in unit dosage form containing from about 0.01 to about 2 mg of said compound.

DATED THIS 5TH DAY OF JULY 1990

FARMITALIA CARLO ERBA SRL

By its Patent Attorneys:

GRIFFITH HACK & CO.

Fellows Institute of Patent  
Attorneys of Australia.

