INSTRUCTIONS

(a) If Convention application insert "Convention"

619044

convention (a)
AUSTRALIA
Patents Act

APPLICATION FOR A (b) STANDARD/~~PETTY~~ PATENT

(b) Delete one

I/We (c) **MERRELL DOW PHARMACEUTICALS INC.**

(c) Insert FULL name(s) of applicant(s)

of (d) **2110 East Galbraith Road**
Cincinnati, Ohio 45215
United States of America

(d) Insert FULL address(es) of applicant(s)

hereby apply for the grant of a (e) Standard/~~Petty~~ Patent for an invention entitled (f)

(e) Delete one

ANTIEPILEPTIC PYRAZOLOPYRIDINES

(f) Insert TITLE of invention

which is described in the accompanying (g) **complete** specification.

(g) Insert "complete" or "provisional" or "petty patent"

(**Note:** *The folowing applies only to Convention applications*)

Details of basic application(s)

(h)

Application No.	Country	Filing Date
250,478	United States of America	September 28, 1988

(h) Insert number, country and filing date for the/or each basic application

Address for Service: PHILLIPS ORMONDE AND FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne, Australia 3000

M 012592 220989

Dated (i) **August 17, 1989**

(i) Insert date of signing

(j) **MERRELL DOW PHARMACEUTICALS INC.**

(j) Signature of applicant(s) (For body corporate see headnote*)

(k)

By _____
Gary D. Street
Managing Patent Counsel

(k) Corporate seal if any

Note: No legalization or other witness required

1339 AU

PHILLIPS ORMONDE & FITZPATRICK
Patent and Trademark Attorneys
367 Collins Street
Melbourne, Australia

AUSTRALIA

Patents Act

DECLARATION FOR A PATENT APPLICATION

INSTRUCTIONS

(a) Insert "Convention" if applicable

(b) Insert FULL name(s) of applicant(s)

(c) Insert "of addition" if applicable

(d) Insert TITLE of invention

(e) Insert FULL name(s) AND address(es) of declarant(s) (See headnote*)

(f) Insert FULL name(s) AND address(es) of actual inventor(s)

(g) Recite how applicant(s) derive(s) title from actual inventor(s) (See headnote**)

(h) Insert country, filing date, and basic applicant(s) for the/or EACH basic application

(k) Insert PLACE of signing

(l) Insert DATE of signing

(m) Signature(s) of declarant(s)

Note: No legalization or other witness required

In support of the (a) **convention** application made by
(b)

MERRELL DOW PHARMACEUTICALS INC.

(hereinafter called "applicant(s)" for a patent (c) for an invention entitled (d)

ANTIEPILEPTIC PYRAZOLOPYRIDINES

I/We (e) **Gary D. Street, Managing Patent Counsel**
MERRELL DOW PHARMACEUTICALS INC.
2110 East Galbraith Road
Cincinnati, Ohio 45215, United States of America

do solemnly and sincerely declare as follows:

~~1. I am/We are the applicant(s).~~

(or, in the case of an application by a body corporate)

1. I am/We are authorized to make this declaration on behalf of the applicant(s).

~~2. I am/We are the actual inventor(s) of the invention.~~

(or, where the applicant(s) is/are not the actual inventor(s))

2. (f) **Anis MIR, 6 Rue des Vosges, 78870 Bartenheim, France; Michael G. PALFREYMAN, 11515 Applejack Court, Cincinnati, Ohio 45249, United States of America; and Francis P. MILLER, 336 Broadway, Loveland, Ohio 45150, United States of America**

is/are the actual inventor(s) of the invention and the facts upon which the applicant(s) is/are entitled to make the application are as follows:

(g) **Applicant is the assignee of the above-entitled invention by virtue of a deed of Assignment from Anis Mir to Merrell Dow France et Cie dated September 16, 1988; from Merrell Dow France et Cie to Merrell Dow Pharmaceuticals Inc. dated September 21, 1988; and from Michael G. Palfreyman and Francis P. Miller to Merrell Dow Pharmaceuticals Inc. dated September 28, 1988.**

(Note: *Paragraphs 3 and 4 apply only to Convention applications)*

3. The basic application(s) for patent or similar protection on which the application is based is/are identified by **country, filing date, and basic applicant(s)** as follows:

(h) **United States of America - September 28, 1988**
By: Anis Mir, Michael G. Palfreyman and Francis P. Miller

4. The basic application(s) referred to in paragraph 3 hereof was/were the first application(s) made in a Convention country in respect of the invention the subject of the application.

Declared at (k) **Cincinnati, Ohio, U.S.A.**

Date (l) **August 17, 1989**

(m) **MERRELL DOW PHARMACEUTICALS INC.**

By _____
Gary D. Street
Managing Patent Counsel

To: The Commissioner of Patents

1339 AU

PHILLIPS ORMONDE & FITZPATRICK
Patent and Trademark Attorneys
367 Collins Street
Melbourne, Australia

(12) PATENT ABRIDGMENT (11) Document No. AU-B-41692/89
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 619044

(54) Title
ANTIEPILEPTIC PYRAZOLOPYRIDINES

International Patent Classification(s)
(51)[4] A61K 031/44

(21) Application No. : 41692/89 (22) Application Date : 22.09.89

(30) Priority Data

(31) Number (32) Date (33) Country
250478 28.09.88 US UNITED STATES OF AMERICA

(43) Publication Date : 05.04.90

(44) Publication Date of Accepted Application : 16.01.92

(71) Applicant(s)
MERRELL DOW PHARMACEUTICALS INC.

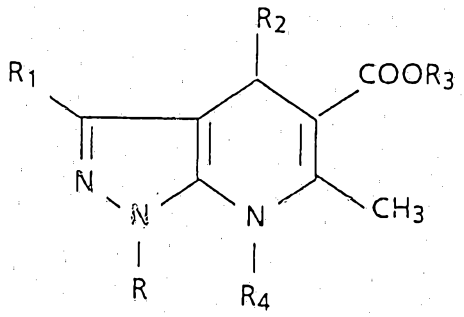
(72) Inventor(s)
ANIS MIR; MICHAEL G. PALFREYMAN; FRANCIS P. MILLER

(74) Attorney or Agent
PHILLIPS ORMONDE & FITZPATRICK , 367 Collins Street, MELBOURNE VIC 3000

(56) Prior Art Documents
EP 114273

(57) Claim

1. A method for treating epilepsy in a patient in need thereof which comprises administering to the patient an anticonvulsantly effective amount of a compound of the formula



I

wherein

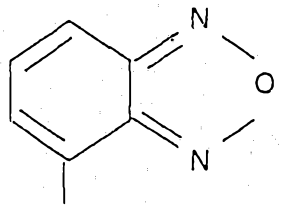
R represents hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_3-C_7)cycloalkyl, phenyl which is optionally substituted by 1, 2 or 3 substituents selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, chloro, fluoro, bromo, nitro, and (C_1-C_6) alkoxycarbonyl, or phenyl (C_1-C_4)alkyl, wherein the phenyl group is optionally substituted as above;

R_1 represents hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_3-C_7)cycloalkyl, (C_1-C_6)alkoxycarbonyl, phenyl

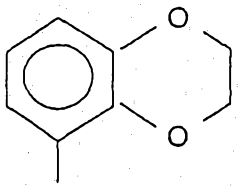
.../2

optionally substituted as above, or phenyl(C_1-C_4)alkyl, optionally substituted as above;

R_2 represents phenyl groups optionally substituted with 1, 2 or 3 substituents selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkyl, chloro, bromo, fluoro, nitro, cyano, (C_1-C_6)alkoxycarbonyl, and a group of formula S(O)n-(C_1-C_6)alkyl, wherein n represents zero or the integer 1 or 2, or R_2 represents a pentafluorophenyl group, an α- or β-naphthyl group, an aromatic 5-6 membered heterocycle ring, ~~such as furanyl or thienyl,~~ a group of formula

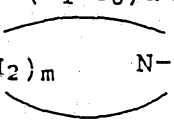


or a group of formula



wherein

R_3 represents (C_1-C_6)alkyl, (C_2-C_6)alkenyl, phenyl optionally substituted as above, and phenyl(C_1-C_4)alkyl optionally substituted as above, (C_1-C_4)alkoxy-(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, mono- or di-(C_1-C_4)alkylamino(C_1-C_6)alkyl,

or a group 

wherein m is an integer selected from 3, 4, and 5, and one of the $-CH_2-$ groups can be replaced by a heteroatom selected from O, S, and N;

R_4 represents hydrogen, (C_1-C_4)alkyl or benzyl;

or a physiologically acceptable salt thereof.

AUSTRALIA

Patents Act

COMPLETE SPECIFICATION
(ORIGINAL)

619044

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority

Related Art:

Applicant(s):

Merrell Dow Pharmaceuticals Inc.
2110 East Galbraith Road, Cincinnati, Ohio, 45215, UNITED STATES OF AMERICA

Address for Service is:

PHILLIPS ORMONDE & FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne 3000 AUSTRALIA

Complete Specification for the invention entitled:

ANTIEPILEPTIC PYRAZOLOPYRIDINES

Our Ref : 146652
POF Code: 1432/1432

The following statement is a full description of this invention, including the best method of performing it known to applicant(s):

6006

ANTIEPILEPTIC PYRAZOLOPYRIDINES

FIELD OF THE INVENTION

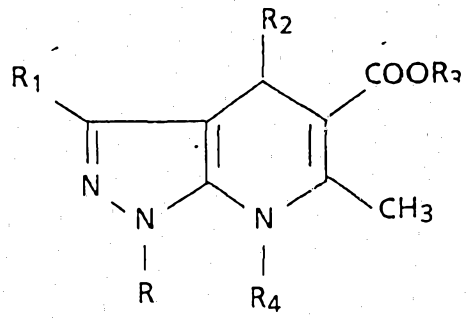
This invention relates to the use of certain pyrazolopyridine calcium channel blockers in the treatment of epilepsy by virtue of their anticonvulsant activity.

BACKGROUND OF THE INVENTION

Evidence suggests that blockers of calcium channels may have anticonvulsant activity. While this may be true, few calcium channel blockers pass the blood brain barrier. Anticonvulsant activity has been demonstrated for nifedipine, but its use as an antiepileptic has not been fully demonstrated. Applicants have now discovered a class of calcium channel blockers which are effective as anticonvulsants and would therefore be useful in the treatment of epilepsy.

SUMMARY OF THE INVENTION

The present invention is directed to the antiepileptic use of a class of pharmacologically active 4,7-dihydropyrazolo[3,4-b]pyridines of formula



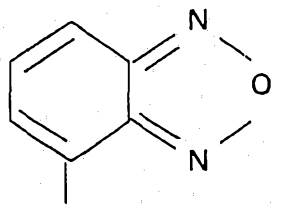
I

wherein

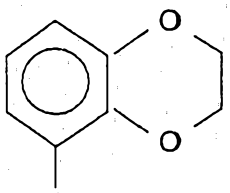
R represents hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_3-C_7)cycloalkyl, phenyl which is optionally substituted by 1, 2 or 3 substituents selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, chloro, fluoro, bromo, nitro, and (C_1-C_6) alkoxycarbonyl, or phenyl (C_1-C_4)alkyl, wherein the phenyl group is optionally substituted as above;

R_1 represents hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_3-C_7)cycloalkyl, (C_1-C_6)alkoxycarbonyl, phenyl optionally substituted as above, or phenyl(C_1-C_4)alkyl, optionally substituted as above;

R_2 represents phenyl groups optionally substituted with 1, 2 or 3 substituents selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkyl, chloro, bromo, fluoro, nitro, cyano, (C_1-C_6)alkoxycarbonyl, and a group of formula S(O)n-(C_1-C_6)alkyl, wherein n represents zero or the integer 1 or 2, or R_2 represents a pentafluorophenyl group, an α- or β-naphthyl group, an aromatic 5-6 membered heterocycle ring such as furanyl or thienyl, a group of formula

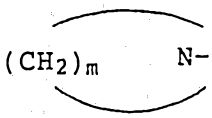


or a group of formula



wherein

R_3 represents (C_1-C_6)alkyl, (C_2-C_6)alkenyl, phenyl optionally substituted as above, and phenyl(C_1-C_4)alkyl optionally substituted as above, (C_1-C_4)alkoxy-(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, mono- or di-(C_1-C_4)alkylamino(C_1-C_6)alkyl,

or a group 

wherein m is an integer selected from 3, 4, and 5, and one of the $-CH_2-$ groups can be replaced by a heteroatom selected from O, S, and N;

R_4 represents hydrogen, (C_1-C_4)alkyl or benzyl;

and the physiologically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

(C_1-C_6)alkyl groups, as defined in the present application, include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, pentyl, hexyl, and the like.

(C_1-C_4)alkyl groups and (C_1-C_4)alkoxy groups are groups of 1 to 4 carbon atoms, inclusive, which are included in the above definition of (C_1-C_6)alkyl groups and (C_1-C_6)alkoxy groups, respectively.

(C_3-C_7)cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl groups.

(C_1-C_6)alkoxy groups include methoxy, ethoxy, propoxy, butoxy, pentoxy, and hexoxy groups.

The term "halo" represents halogen atoms selected from chloro, bromo, and fluoro, while halo(C_1-C_4)alkyl groups are halogenalkyl groups of 1 to 4 carbon atoms inclusive, wherein some or all the hydrogen atoms are replaced with halogen atoms. Representative examples of halo(C_1-C_4)alkyl groups are: trifluoromethyl, chlorodifluoromethyl, bromochlorofluoromethyl, trichloromethyl, 1,1-dichloroethyl, 1,2-dichloroethyl, 1-chloro-2,2,2-trifluorofluoroethyl, and the like.

"Physiologically acceptable salts" are pharmaceutically acceptable salts wherein the whole toxicity of the compound is not increased compared with the non-salt. These acid addition salts are obtained by treating compounds of the above formula I with pharmaceutically acceptable acids.

Representative examples of acids suitable for the formation of physiologically acceptable salts are: hydrohalide, sulfuric, phosphoric, and nitric acids; aliphatic, alicyclic, aromatic or heterocyclic carboxylic or sulfonic acids, such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, α-ketoglutaric, glutamic, aspartic, maleic, hydroxymaleic, pyruvic acid; phenylacetic, benzoic, para-aminobenzoic, anthranilic, para-hydroxybenzoic, salicylic, para-aminosalicylic or embonic acid, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenesulfonic acid; halobenzenesulfonic, toluenesulfonic, naphthalene-sulfonic acids or sulfanilic acid.

These or other salts of the new compounds may also be used for purifying the resulting compounds by converting them into salts, isolating the latter and liberating the free compound from them. When according to the above outlined procedures, compounds of formula I are obtained as the corresponding salts of pharmaceutically acceptable acids, they may be converted into the corresponding free base by treatment with an alkali agent.

The free base may in turn be transformed into the corresponding salts by reaction with predetermined pharmaceutically acceptable acids. In view of the close relationship between the new compounds in the free form and in the form of their salts what has been said above and hereinafter with reference to the free compounds concerns also the corresponding salts.

A preferred group of compounds of the present invention are those of formula I wherein R and R_1 independently are hydrogen, (C_1-C_6)alkyl or phenyl, unsubstituted or substituted as above, R_2 is a phenyl group substituted by 1 or 2 substituents, selected from nitro, (C_1-C_4)alkoxy, (C_1-C_4)alkyl, chloro or trifluoromethyl, R_3 is (C_1-C_6)alkyl or (C_1-C_4)alkoxy(C_1-C_4)alkyl, and R_4 is hydrogen, methyl or benzyl, or a corresponding physiologically acceptable acid addition salt.

Another preferred group of compounds are those compounds of formula I wherein R is hydrogen, methyl or phenyl, optionally substituted as above, R_1 is hydrogen, methyl, ethyl, isopropyl, sec-butyl, phenyl optionally substituted as above, R_2 is 2- or 3-nitrophenyl, 2- or 3-methylphenyl, or 2- or 3-trifluoromethylphenyl, R_3 is (C_1-C_6)alkyl, (C_1-C_4)alkoxy(C_1-C_6)alkyl, and R_4 is hydrogen, or a corresponding physiologically acceptable acid addition salt.

More preferred compounds of this invention are those compounds of formula 1 wherein R is methyl, R_1 is isopropyl or sec-butyl, R_2 is 2-methylphenyl, R_3 is methyl, and R_4 is hydrogen. The most preferred compound of this invention is the compound of formula 1 wherein R is methyl, R_1 is sec-butyl, R_2 is 2-methylphenyl, R_3 is methyl, and R_4 is hydrogen, that is the compound methyl 4,7-dihydro-1,6-dimethyl-4-(2-methylphenyl)-3-(2-methylpropyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate.

The compounds used in the present invention are known and can be prepared as described in, for example, European Patent Application Number 0114273, published August 1, 1984.

The ability of the compounds of this invention to act as calcium channel blockers can be demonstrated by their ability to antagonize calcium-induced contractions in K^+-depolarized taenia of the Guinea pig caecum. Strips of taenia (1-2 mm diameter, 2-2.5 cm relaxed length), were dissected from the caecum of male guinea pigs (250-350 g) and set up in 20 ml isolated-organ baths containing K^+-depolarizing Tyrode solution maintained at 35°C and gassed with 95% O_2 and 5% CO_2. The composition of the K^+-Tyrode solution was (mmol/l): NaCl 97; KCl 40; $NaHCO_3$ 11.9; NaH_2PO_4 0.4; glucose 5.5; pH 7.1. Contractile responses were measured under isotonic conditions (1g load) using a Harvard isotonic transducer connected to a Rikadenki potentiometric recorder.

Cumulative concentration response curves were obtained to $CaCl_2$ (30-3,000 µmol/l) by increasing the Ca^{2+} concentration at 3 minute intervals in logarithmic increments, (Van Rossum, Arch. Int. Pharmacodyn., 143, 299-330, 1963)). A 20 minute washout period (6 changes of bathing fluid) was allowed between curves. The 100% response was taken as the maximum contractile response of the tissue during the second concentration response curve, and all subsequent contractions were calculated as a percentage of this value. Dose ratios were calculated as the ratio of the concentration of Ca^{2+} which produced a 50% maximal response (EC_{50}) in the presence and absence of the antagonist. Apparent pA_2 values were calculated by the method of Arunlakshana and Schild, Br. J. Pharmac. Chemother., 14, 48-58, (1959), by plotting log (dose ratio-1) against negative log (molar concentration antagonist). Student's test was used for comparison of mean values. Values are expressed as mean ±SEM. All concentrations are the final concentration of drug in the bathing solution.

The compounds are initially tested at a fixed concentration (10 µg/ml). In these conditions the compounds of the invention show antagonism of Ca^{2+} induced contractions in K^+-depolarized taenia. More particularly, the compounds:

methyl 4,7-dihydro-1,3,6-trimethyl-4-(2-nitrophenyl)-1H-pyrazolo[3,4-b]pyridin-5-carboxylate;

ethyl 4,7-dihydro-1,3,6-trimethyl-4-(2-nitrophenyl)-1H-pyrazolo[3,4-b]pyridin-5-carboxylate;

ethyl 4,7-dihydro-1,6-dimethyl-3-phenyl-4-(2-methylphenyl)-1H-pyrazolo[3,4-b]pyridin-5-carboxylate;

ethyl 4,7-dihydro-1,6-dimethyl-3-phenyl-4-(2-nitrophenyl)-1H-pyrazolo[3,4-b]pyridin-5-carboxylate;

mechyl 4,7-dihydro-1,6-dimethyl-4-(2-nitrophenyl)-3-phenyl-1H-pyrazolo[3,4-b]pyridin-5-carboxylate;

ethyl 4,7-dihydro-1,6-dimethyl-3-(1-methylethyl)-4-(2-nitrophenyl)-1H-pyrazolo[3,4-b]pyridin-5-carboxylate;

methyl 4,7-dihydro-1,6-dimethyl-3-(1-methylethyl)-4-(2-nitrophenyl)-1H-pyrazolo[3,4-b]pyridin-5-carboxylate;

methyl 4,7-dihydro-1,6-dimethyl-3-(1-methylethyl)-4-(3-nitrophenyl)-1H-pyrazolo[3,4-b]pyridin-5-carboxylate;

methyl 4,7-dihydro-1,6-dimethyl-3-(2-methylpropyl)-4-(2-nitrophenyl)-1H-pyrazolo[3,4-b]pyridin-5-carboxylate;

methyl 4,7-dihydro-1,6-dimethyl-3-(2-methylpropyl)-4-(3-nitrophenyl)-1H-pyrazolo[3,4-b]pyridin-5-carboxylate; and

2-methoxyethyl 4,7-dihydro-1,6-dimethyl-3-(2-methylpropyl)-4-(2-nitrophenyl)-1H-pyrazolo[3,4-b]pyridin-5-carboxylate

show a pA_2 value in the range 8.2 - 9, cause concentration-dependent displacement to the right of cumulative concentration-response curves to Ca^{2+}, have a rapid onset of action, and cause a rapid relaxation of Ca^{2+} (300 µM)-induced contractions at low concentrations (0.01-0.1 µM).

The anticonvulsive effect of the compound methyl 4,7-dihydro-1,6-dimethyl-4-(2-methylphenyl)-3-(2-methylpropyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (Methyl Ester) has been demonstrated in the following manner.

For controls, the convulsant ED_{50} of pentylenetetrazol (PTZ)was determined 30' after vehicle administration by dosing groups of 10 or more mice with various iv doses of PTZ. For drug studies, groups of mice were given methyl ester or flunarizine, 8 or 16 mg/kg ip. Thirty minutes later, dose-response curves for PTZ were determined as described for controls. Convulsant ED_{50} values (clonic and tonic) for PTZ for controls and each drug condition, as well as the significance of differences from control, were calculated with an appropriate computer program. Results are shown below.

TREATMENT (mg/kg ip)	PTZ ED_{50} mg/kg iv (95% C.L.)	
	clonic	tonic
Control	26.9 (24.4-29.2)	37.5 (34.8-40.7)
Methyl ester (8)	38.4 (33.9-42.7)**	47.1 (42.8-52.2)*
(16)	42.5 (37.7-46.8)**	48.9 (43.3-54.5)*
Flunarizine (8)	~34.6 (***)	43.8 (40.2-47.8)*
(16)	36.8 (31.4-41.9)*	44.4 (38.7-49.7)*

* $p<.05$ vs control
** dose-response functions not parallel to control
*** no 95% C.L.; dose-response function too steep

These data show the anticonvulsant activity for the methyl ester, a representative compound of this invention. Applicants believe the pyrazolopyridines of this invention will be of particular significance in the treatment of petit mal seizures.

Generally the compounds of the invention possess prolonged duration of action. In fact, representative examples possess a duration in animals of 8 to 12 hours or more at doses equal to the ED_{50} value.

The compounds may be administered in various manners to achieve the desired effect. The compounds may be administered alone or in the form of pharmaceutical preparations to the patient being treated either orally or parenterally, such as, intravenously or intramuscularly. The formulation of suitable pharmaceutical compositions can be carried out by one skilled in the art according to the general common knowledge in the art, and referring to reference books, such as the "Remington's Pharmaceutical Sciences Handbook", Mack Publishing Company, U.S.A. The amount of compound administered will vary with the severity of the convulsant condition and the mode of administration. For oral administration the anticonvulsantly effective amount of compound is from about 0.01 mg/kg (milligrams per kilograms) of patient body weight per day to about 10 mg/kg of patient body weight per day and preferably from about 0.05 mg/kg of patient body weight per day to about 5 mg/kg of patient body weight per day.

For parenteral administration the anticonvulsantly effective amount of compound is from about 0.001 mg/kg of patient body weight per day up to about 5 mg/kg of patient body weight per day and preferably from about 0.01 mg/kg of patient body weight per day up to about 2 mg/kg of patient body weight per day.

For oral administration a unit dosage may contain, for example, from 0.50 to 100 mg of the active ingredient. For parenteral administration a unit dosage may contain, for example, from 0.05 to 70 mg of the active ingredient. Since the compounds of the invention generally possess a long lasting duration of action they might be conveniently administered once or twice a day, however, repetitive daily administrations may be, at least in some instances, desirable and will vary with the conditions of the patient and the mode of administration. As used herein, the term "patient" is taken to mean a warm blooded animal, humans included.

For oral administration the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, troches, powders, solutions, suspensions or emulsions. The solid unit dosage form can be a capsule which can be of the ordinary gelatin type, either hard or soft, containing, for example, lubricants and inert fillers such as lactose, sucrose and cornstarch.

In another embodiment the compounds of the invention can be tabletted with conventional tablet bases such as lactose, sucrose and cornstarch in combination with binders such as acacia, cornstarch or gelatin, disintegrating agents such as potato starch or alginic acid, and a lubricant such as stearic acid or magnesium stearate.

For parenteral administration the compounds may be administered as injectable dosages of a solution or suspension of the compound in a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid such as water and oils with or without the addition of a surfactant and other pharmaceutically acceptable adjuvants. Illustrative of oils which can be employed in these preparations are those of mineral petroleum, animal, vegetable or synthetic origin. For example, peanut oil, soybean oil and mineral oil. In general, water, saline, aqueous dextrose and related sugar solutions, ethanol and glycols such as propylene glycol or polyethylene glycol can be used as liquid carriers for injectable solutions.

For rectal administration the compounds are administered in the form of suppositories, admixed with conventional vehicles such as, for example, cocoa butter, wax, spermaceti, polyvinylpyrrolidone, or polyoxyethyleneglycols and their derivatives.

The compounds can be administered in the form of a depot injection or implant preparation which may be formulated in

such a manner as to permit a sustained release of the active ingredient. The active ingredient can be compressed into pellets or small cylinders and implanted subcutaneously or intramuscularly as depot injections or implants. Implants may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic®, a silicone rubber manufactured by the Dow-Corning Corporation. The oral route is generally the preferred route of administration of the compounds of the invention, while the capsule is generally the preferred pharmaceutical formulation.

The following are illustrative pharmaceutical formulations which may be employed in practicing the present invention:

A capsule is prepared with:

4,7-Dihydro-1,6-dimethyl-4-(2-methylphenyl)-1H-pyrazolo[3,4-b]pyridin-5-carboxylic acid methyl ester	50	mg
Saccharose	10	mg
Polyvinylpyrrolidone	2	mg
Sodium dioctylsulfosuccinate	0.5	mg
Magnesium stearate	2.5	mg
Corn starch	q.s. to 150	mg

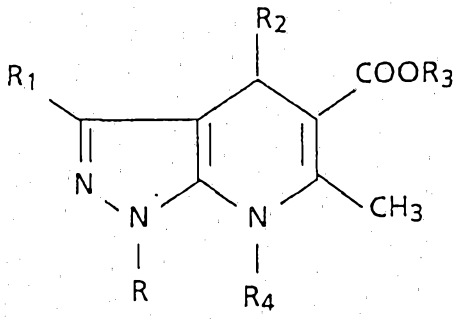
A tablet is prepared with:

4,7-Dihydro-1,6-dimethyl-4-(2-methylphenyl)-1H-pyrazolo[3,4-b]pyridin-5-carboxylic acid methyl ester	50	mg
Polyvinylpyrrolidone	2	mg
Sodium carboxymethylcellulose	1.5	mg
Avicel®	5	mg
Titanium dioxide	2	mg
Magnesium stearate	2.5	mg
Cornstarch	8	mg
Gum arabic	5	mg
Talc	10	mg
Kaolin	2	mg
Saccharose	q.s. to 150	mg

CLAIMS

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for treating epilepsy in a patient in need thereof which comprises administering to the patient an anticonvulsantly effective amount of a compound of the formula



I

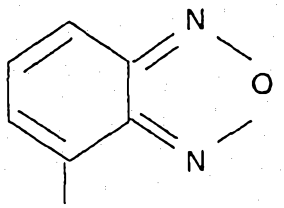
wherein

R represents hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_3-C_7)cycloalkyl, phenyl which is optionally substituted by 1, 2 or 3 substituents selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, chloro, fluoro, bromo, nitro, and (C_1-C_6) alkoxycarbonyl, or phenyl (C_1-C_4)alkyl, wherein the phenyl group is optionally substituted as above;

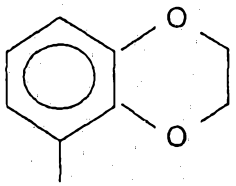
R_1 represents hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_3-C_7)cycloalkyl, (C_1-C_6)alkoxycarbonyl, phenyl optionally substituted as above, or phenyl(C_1-C_4)alkyl, optionally substituted as above;

R_2 represents phenyl groups optionally substituted with 1, 2 or 3 substituents selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkyl, chloro, bromo,

fluoro, nitro, cyano, (C_1-C_6)alkoxycarbonyl, and a group of formula S(O)n-(C_1-C_6)alkyl, wherein n represents zero or the integer 1 or 2, or R_2 represents a pentafluorophenyl group, an α- or β-naphthyl group, an aromatic 5-6 membered heterocycle ring, ~~such as furanyl or thienyl,~~ a group of formula

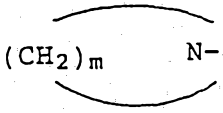


or a group of formula



wherein

R_3 represents (C_1-C_6)alkyl, (C_2-C_6)alkenyl, phenyl optionally substituted as above, and phenyl(C_1-C_4)alkyl optionally substituted as above, (C_1-C_4)alkoxy-
(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, mono- or di-(C_1-C_4)alkylamino(C_1-C_6)alkyl,

or a group 

wherein m is an integer selected from 3, 4, and 5, and one of the -CH_2- groups can be replaced by a heteroatom selected from O, S, and N;

R_4 represents hydrogen, (C_1-C_4)alkyl or benzyl;

or a physiologically acceptable salt thereof.

2. A method of claim 1 wherein R and R_1 independently are hydrogen, (C_1-C_6)alkyl or phenyl, unsubstituted or substituted as in claim 1; R_2 is a phenyl group substituted

by 1 or 2 substituents, selected from nitro, (C_1-C_4) alkoxy, (C_1-C_4)alkyl, chloro or trifluoromethyl; R_3 is (C_1-C_6)alkyl or (C_1-C_4)alkoxy(C_1-C_4)alkyl; and R_4 is hydrogen, methyl or benzyl; or a corresponding physiologically acceptable acid addition salt thereof.

3. A method of claim 1 wherein R is hydrogen, methyl or phenyl optionally substituted as in claim 1; R_1 is hydrogen, methyl, ethyl isopropyl, sec-butyl, or phenyl optionally substituted as in claim 1; R_2 is 2- or 3-nitrophenyl, 2- or 3-methylphenyl, or 2- or 3-trifluoromethylphenyl; R_3 is (C_1-C_6)alkyl, (C_1-C_4) alkoxy(C_1-C_6)alkyl, or R_4 is hydrogen, or a corresponding physiologically acceptable acid addition salt thereof.

4. A method of claim 3 wherein R is methyl; R_1 is isopropyl or sec-butyl; R_2 is 2-methylphenyl; R_3 is methyl; and R_4 is hydrogen; or a corresponding physiologically acceptable acid addition salt thereof.

5. A method of claim 4 wherein R is methyl; R_1 is sec-butyl; R_2 is 2-methylphenyl; R_3 is methyl; and R_4 is hydrogen; that is the compound methyl 4,7-dihydro-1,6-dimethyl-4-(2-methylphenyl)-3-(2-methylpropyl)-1H-pyrazolo [3,4-b]pyridine-5-carboxylate; or a corresponding physiologically acceptable acid addition salt thereof.

6. A method according to claim 1 wherein R_2 is furanyl or thienyl.

7. A method according to any one of the previous claims wherein the patient is treated with a composition substantially as herein described with reference to any one of the Examples.

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