APPLICATION FOR A (b) STANDARD/REGENCY PATENT

(We) MERRELL DOW PHARMACEUTICALS INC.

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

hereby apply for the grant of a (a) Standard/Regency Patent for an invention entitled

(f) 5-HETEROCYCLIC-2,4-DIALKYL-3H-1,2,4-TRIAZOLE-3-THIONES AND THEIR USE AS ANTIDEPRESSANTS

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

(Note: The following applies only to Convention applications)

Details of basic application(s)

<table>
<thead>
<tr>
<th>Application No.</th>
<th>Country</th>
<th>Filing Date</th>
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<tbody>
<tr>
<td>792,367</td>
<td>United States of America</td>
<td>October 29, 1985</td>
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</tbody>
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Address for Service:

LODGED AT SUB-OFFICE

27 OCT 1985

Melbourne

Dated (i) August 14, 1986

By

Gary D. Streub
Managing Patent Counsel

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367 Collins Street
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MERRELL DOW PHARMACEUTICALS INC.
AUSTRALIA

Patents Act

DECLARATION FOR A PATENT APPLICATION

In support of the (a) convention application made by

MERRELL DOW PHARMACEUTICALS INC.

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

5-HETEROCYCLIC-2,4-DIALKYL-3H-1,2,4-TRIAZOLE-3-THIONES AND THEIR USE AS ANTI-DEPRESSANTS

I/We (c)

Gary D. Street
of 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).

(1) 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. John M. Kane

6813 Dearwester Drive
Cincinnati, Ohio 45236
United States of America

Francis P. Miller

336 Broadway
Loveland, Ohio 45140
United States of America

(2) Where the applicant(s) is/are not the actual inventor(s)

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:

United States of America - October 29, 1985

By: John M. Kane 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
Dated (l) August 14, 1986

(m) MERRELL DOW PHARMACEUTICALS INC.

By

Gary D. Street
Managing Patent Counsel

To: The Commissioner of Patents

34653 AU

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5-HETEROCYCLIC-2,4-DIALKYLU-3H-1,2,4-TRIAZOLE-3-THIONES.

MERRELL DOW PHARMACEUTICALS INC

64408/86 (22) 27.10.86 (24) 29.10.85
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914 C07D 401/04 C07D 403/04 C07D 405/04 C07D 409/04
A61K 31/41 A61K 31/44

JOHN M. KANE, FRANCIS P. MILLER

PO

Claim

1. A compound of the formula

\[ R_n ^\text{HET} \]

and the tautomers thereof, and the pharmaceutically acceptable salts thereof wherein

R is halogeno, C1-6 lower alkyl, C1-6 lower alkoxy, hydroxy or trifluoromethyl.
n is zero, 1 or 2,
R2 and R4 independently represent C1-6 lower alkyl or hydrogen.

"Het" represents a heterocyclic moiety.

6. A method of treating a patient in need of an anti-depressant which comprises administering an effective amount of a compound of claim 1.
AUSTRALIAN

Patents Act

COMPLETE SPECIFICATION
(ORIGINAL)

Application Number: 64408824
Lodged: 

Complete Specification Lodged: 
Accepted: 
Published: 

Priority 

Related Art: 

Name(s) of Applicant(s): MERRELL DOW PHARMACEUTICALS INC 

Address(es) of Applicant(s): 2110 East Galbraith Road, Cincinnati, Ohio 45215, United States of America 

Actual Inventor(s): John M. Kane Francs P. Miller 

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Complete Specification for the invention entitled: 5-HETEROCYCLIC-2, 4-DIALKYL-3H-1, 2, 4-TRIZAOLE-3-THIONES AND THEIR USE AS ANTIDEPRESSANTS 

The following statement is a full description of this invention, including the best method of performing it known to applicant(s):
5-HETEROCYCLIC-2,4-DIALKYL-3H-1,2,4-TRIAZOLE-3-ThIONES
AND THEIR USE AS ANTIDEPRESSANTS

BACKGROUND OF THE INVENTION

This invention relates to 5-aryl-2,4-dialkyl-3H-1,2,4-triazole-3-thiones, to the intermediates and processes for their preparation, to their pharmacological properties, and to their use as antidepressants.

More specifically, this invention relates to compounds of the formula

\[
R_n \quad \text{(Het)} \quad \begin{array}{c}
\text{N} \\
\text{S} \\
\text{R}_4
\end{array}
\]

and the tautomers thereof, and the pharmaceutically acceptable salts thereof wherein

\( R \) represents halogeno, \( C_{1-6} \) lower alkyl, \( C_{1-6} \) lower alkoxy, hydroxy, or trifluoromethyl with \( n \) being zero, 1 or 2, each of \( R_2 \) and \( R_4 \) independently represent \( C_{1-6} \) lower alkyl or hydrogen, and "Het" represents a heterocyclic moiety.
Preferably halogeno represents chloro or fluoro, and methyl and ethyl represent the preferred lower alkyl moieties, although all the straight, branched and cyclic manifestations thereof such as n-propyl, cyclopentyl, cyclohexyl and cyclopropyl are herein included. Lower alkoxy radicals includes ethers having alkyl moieties paralelling the C_{1-6} alkyl group. Preferably n is one representing a mono-substituted heterocyclic moiety with the R-substituted being a group located on any of the carbon atoms of the heterocyclic moiety. When di-substituted (although not preferred) the two R substituents are also located on a carbon atom of the heterocyclic moiety. The tautomeric forms are included for each of the compounds embraced within formula I. Preferably \( R_2 \) and \( R_4 \) each represent an alkyl group, especially methyl or ethyl with those compounds wherein \( R_2 \) or \( R_4 \) is hydrogen predicted to be of nominal activity.

Representative of "Het" of formula I are such heterocyclic moieties as 2-, 3-, or 4-pyridyl, 2- or 3-furyl, 2- or 3-thienyl, pyrrol-2-yl, N-C_{1-6} alkylpyrrol-2-yl, 2-, 3- or 4-piperidinyl or their N-C_{1-6} alkyl substituted homologs, 6-isoquinolyl, 6-quinolyl and 3-quinolyl. Preferred is 4-pyridyl, with or without an R substituent, particularly when \( R_n \) is a monochloro or mono methyl. State of the art salts formed with the heterocyclic moieties are generally employed with the hydrochloride being one of convenience and general application; such salts being formed by standard techniques well known in the art.

The compounds of formula I may readily be prepared using processes and procedures analogously known in the art as seen by the following reaction scheme.
Reaction Scheme

(A) \( R_2\text{NHN}{\text{H}}_2 + R_4\text{NCS} \xrightarrow{\text{solvent}} R_4\text{NHC-NR}_2\text{-NH}_2 \)

(B) \( IV + R_n\text{-Het}+\text{COCl} \xrightarrow{\text{solvent}} R_n\text{-Het}+\text{C-NHR}_2\text{-CNHR}_4 \)

(C) \( VI + \text{NaHCO}_3 \rightarrow I \)

wherein \( R_2, R_4, R_n\text{-Het} \) are as previously defined.

In step A, the preparation of the thiosemicarbazides (IV) is readily effected by reacting a hydrazine (II) with an isothiocyanate (III) by contacting the reactants in a suitable solvent. The reaction is quite rapid and may be carried out at \( 0^\circ\text{C} \) to room temperature. Although the reaction proceeds rapidly, the mixture may be left for up to 24 hours without significant decrease in yields. Reflux conditions may be employed but are not preferred. Almost all solvents (with the exception of water and organic acids) may be used. Anhydrous alcohols (preferably ethanol or methanol) are preferred although DMF, CHCl\(_3\), CH\(_2\)Cl\(_2\), THF and Et\(_2\)O may also be used. The required hydrazines and isothiocyanates are readily available but may be prepared by known techniques quite obvious to one of ordinary skill in the art.

In step B, the desired caroyl-substituted thiosemicarbazides (VI) may be prepared by reacting the thiosemicarbazides (IV) with an R-substituted-caroyl chloride (V) in an aprotic solvent such as pyridine, CHCl\(_3\), THF and the like. The acylation proceeds rather easily at temperatures ranging from \( 0^\circ\text{C} \) to room temperature over periods of 3 to 24 hours although elevated temperatures (e.g. reflux temperatures) may
be employed. Again, the acid halides (V) generally are commercially available but may also be prepared from the corresponding acids which are available from obvious starting materials.

In Step C, the caroyl thiosemicarbazides (VI) are subjected to a cyclization reaction which is effected by heating the compounds (VI) in an aqueous base, preferably using a molar equivalent of the base (e.g. sodium bicarbonate or sodium hydroxide). Alcoholic bases may be utilized but generally are less desirable. The reaction is conducted at about the reflux temperature of the solvent, preferably at about 65°-100°C. In practice, the thiosemicarbazides (VI) need not be purified for use in Step C so that even 1:1 mixtures with pyridine hydrochloride may be used.

The following specific examples are given to illustrate the preparation of the compounds of this invention although the scope of compounds exemplified is not meant to be limiting, this being so in view of the ease by which the compounds of formula I may be prepared. Interchange, or modification, and employment of the necessary intermediates and solvents are quite obvious to a chemist of ordinary skill.

Preparation of $\text{R}_2\text{R}_4$-Substituted-Thiosemicarbazides

**EXAMPLE 1**

**2,4-DIMETHYLTHIOSEMICARBAZIDE**

To a stirred solution of methyl hydrazine (16.0 ml, $3.00 \times 10^{-1}$ mole) and sieve dry ethanol (50 ml) was added dropwise a solution of methyl isothiocyanate (22.0 g, $3.00 \times 10^{-1}$ mole) and sieve dry ethanol (30 ml). The reaction is exothermic and gently refluxes as the isothiocyanate is added. A precipitate soon forms. After stirring overnight, the reaction was cooled in an ice bath. The precipitate was
then collected by filtration, washed with a little cold isopropanol, and dried by suction affording a pale yellow powder: 26.7 g (75%). This material was crystallized two times from water and two times from isopropanol affording small colorless needles: 14.7 g (41%), mp = 135-137°C.

**Preparation of R₁,1-Benzoyl-R₂, R₄-Thiosemicarbazides**

**EXAMPLE 2**

**2,4-DIMETHYL-1-(4-PYRIDOYL)-THIOSEMICARBAZIDE**

To a stirred solution of 2,4-dimethylthiosemicarbazide (6.7 g, 5.6 × 10⁻² mole) and pyridine (150 ml) was added dropwise 4-pyridoyl chloride. (HCl 10.0 g, 5.62 × 10⁻² mole). After stirring for 17 hours the solvent was evaporated to dryness affording a mixture of the desired 1-(4-pyridoyl)-2,4-dimethylthiosemicarbazide and pyridine hydrochloride. In general this mixture was used without further purification in the subsequent cyclization step. If pure 1-(4-pyridoyl)-2,4-dimethylthiosemicarbazide is desired, the above mixture is treated with water and that which does not dissolve is collected by filtration. After drying by suction this material is crystallized.

**Preparation of Final Products**

**EXAMPLE 3**

**5-(4-PYRIDYL-2,4-DIMETHYL-3H-1,2,4-TRIAZOLE-3-THIONE**

The 1:1 mixture from Example 2 and 1 molar aqueous NaHCO₃ (100 ml, 1.00 × 10⁻¹ mole) were stirred and warmed to reflux. After refluxing for 15 hours the reaction was allowed to cool in an ice bath. The resulting precipitate was collected by filtration, and was dried by suction. The desired product was crystallized from ethyl acetate/hexane to yield large colorless plates: 4.1 g (35%) mp. 150-152°C.

In a similar manner by substituting the reactants of examples 1-3 with appropriate R₂, R₄-substituted reactants,
and by substantially following the techniques therein, there is produced the 2,4-dimethyl-5-heterocyclic-3H-1,2,4-triazole-3-thione of formula I wherein the heterocyclic is as stated above when "Rn-Het-" was defined.

Other compounds embraced within formula I may similarly be prepared by using the procedures of Example 1-3.

Using standard laboratory methodology, the pharmacological properties, and their relative potencies, may readily be determined. When compared with other agents clinically known to be useful as antidepressants, the dosage regimen may readily be ascertained by those of ordinary skill in the art.

For example, the assay testing for prevention of reserpine-induced ptosis in mice and in rats is a standard assay. In those test groups, weighed mice or rats are housed individually in wire mesh stick cages and administered test compound or vehicle. At a selected time thereafter, reserpine, prepared as a 4 mg/ml solution in dilute acetic acid, is given to rats at a dose of 4 mg/kg subcutaneously, and to mice as a 0.2 mg/ml solution in dilute acetic acid at a dose of 2 mg/kg intravenously into a tail vein. In each assay the animals are examined individually in a plexiglass cylinder 90 minutes later. Prevention or delay in ptosis is considered significant if the average closure of both eyes is less than 50% after observing for 30 seconds. The ED50 for prevention of ptosis is defined as the dose of test compound that significantly prevents ptosis in 50% of the test animals.

In these tests imipramine has an ED50 of 2.6 mg/kg (using a 30 minute pre-treatment time) in rats. In mice, imipramine, at a 60 minute pre-treatment time, has as ED50 of 4.1 mg/kg.
Another assay utilized to evaluate antidepressant activity is testing for the antagonism to RO-4-1284*-induced hypothermia. (*Niemegeers, Carlos, J.E. "Antagonism of Reserpine - Like Activity", edited by S. Fielding and Lal, published by Futura, pg. 73-98.) In this test, groups of male mice are weighed and housed individually in wire mesh stick cages. The rectal temperature of each mouse is recorded and the test compound or vehicle is then administered. At a selected time thereafter, RO-4-1284, prepared as a 2 mg/ml solution in distilled water, is administered at a dose of 20 mg/kg i.p. Mice are then placed in a cold room (36°F) for 30 minutes, and then returned to room temperature for 30 minutes. At this time (60 minutes after RO-4-1284 administration) the rectal temperature of each mouse is again recorded. Under these conditions, RO-4-1284 causes a fall in rectal temperature of 10 to 12°C. The final temperatures of control groups of ten RO-4-1284-treated mice from a number of experiments are combined to form an "historic control" of 100 mice. This control is updated periodically by replacement of the oldest data. Any drug-treated animal which has a final temperature (after RO-4-1284) which is greater than the mean + 2 S.D. of the RO-4-1284 historic control is considered to exhibit significant antagonism to the hypothermic effect of RO-4-1284. The ED50 for antagonism is defined as that dose of test compound which significantly antagonizes RO-4-1284 hypothermia in 50% of the test animals.

Using a 60 minute pre-treatment time and these criteria for evaluation of effects, desipramine was found to have an ED50 of 0.1 mg/kg i.p.; imipramine, an ED50 of 1.8 mg/kg i.p., Catron*, an ED50 of 0.7 mg/kg i.p.

It is expected that based upon standard laboratory methodology, as well as comparative studies with known agents, the compounds of this invention have pharmacological
effects generally attributed to anti-depressants and thus the compounds of this invention will elevate mood in patients suffering from depression and therefore will have an end-use application of treating patients suffering from endogenous depression, a term used interchangeably with psychotic or involutinal depression. In this use, the compound (I) will exert a relatively quick onset of action and have a prolonged duration of activity. In general, the compounds are expected to exert their anti-depressant effects at dose levels of about 0.25-25 mg/kg of body weight per day although, of course, the degree of severity of the disease state, age of the patient and such other factors determined by the attending diagnostician will influence the exact course and dosage regimen suitable for each patient. In general the parenterally administered doses are about ¼ to ¼ that of the orally administered dose.

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 forms can be a capsule which can be of the ordinary gelatin type containing, for example, lubricants and inert filler, such as lactose, sucrose or cornstarch. In another embodiment the compounds of general formula I can be tableted 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, alcohols, oils an other acceptable organic solvents 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 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 or 2-pyrrolidone are preferred liquid carriers, particularly for injectable solutions.

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.

As is true in many classes of compounds generally suitable for any particular pharmacological activity having a therapeutic end-use application, certain subgeneric groups and certain specific members of the class, because of their overall therapeutic index, biochemical and pharmacological profile, are preferred. In this instance the preferred compounds are those wherein both \( R_2 \) and \( R_4 \) groups are methyl or ethyl, those wherein the \( R \) substituent is chloro or fluoro, those wherein the \( R_n \) heterocyclic is a 4-, 3- or 2-pyridyl, and each heterocycle having chloro or fluoro attached thereto.
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula

\[
\begin{array}{c}
\text{R}_n - \text{(Het)} - \text{N} \quad \text{N} - \text{R}_2 \\
\text{S} \\
\text{R}_4
\end{array}
\]

and the tautomers thereof, and the pharmaceutically acceptable salts thereof wherein

- \( \text{R} \) is halogeno, \( \text{C}_{1-6} \) lower alkyl, \( \text{C}_{1-6} \) lower alkoxy, hydroxy or trifluoromethyl.
- \( n \) is zero, 1 or 2,
- \( \text{R}_2 \) and \( \text{R}_4 \) independently represent \( \text{C}_{1-6} \) lower alkyl or hydrogen.
- "Het" represents a heterocyclic moiety.

2. A compound of claim 1 wherein \( \text{R}_n \text{(Het)} \) is 4-pyridyl.

3. A compound of claim 2 wherein each of \( \text{R}_2 \) and \( \text{R}_4 \) are methyl.

4. A compound of claim 2 wherein \( n \) is one.
5. A compound of claim 1, said compound being 5-(4-pyridyl)-2,4-dimethyl-3H-1,2,4-triazole-3-thione.

6. A method of treating a patient in need of an anti-depressant which comprises administering an effective amount of a compound of claim 1.

7. A process for preparing a compound of the formula

\[
\begin{align*}
\text{R}_n \text{(Het)} & \text{N} \rightarrow \text{N} \rightarrow \text{R}_2 \\
& \text{N} \rightarrow \text{S} \\
& \text{R}_4
\end{align*}
\]

and the tautomers thereof, wherein \( R \) represents halogeno, \( C_{1-6} \) lower alkyl, \( C_{1-6} \) lower alkoxy, hydroxy, or trifluoromethyl with \( n \) being zero, 1 or 2, each of \( R_2 \) and \( R_4 \) independently represent \( C_{1-6} \) lower alkyl or hydrogen, and "Het" represents a heterocyclic moiety which comprises effecting a cyclization of a Thiosemicarbazide of the formula

\[
\begin{align*}
\text{R}_n \text{(Het)} & \text{C} \rightarrow \text{NH} \rightarrow \text{R}_2 \rightarrow \text{CNHR}_4 \\
& \text{O} \\
& \text{S}
\end{align*}
\]

by contacting said reactant with an aqueous base.

8. A process according to claim 7 wherein the cyclization is effected by heating the intermediate (II) in a suitable solvent in the presence of a base.

9. A process of claim 8 wherein the base is an aqueous base.

10. A process of claim 9 wherein the heating is effected at about the reflux temperature of the reaction mixture.

11. A process of preparing 5-(4-pyridyl)-2,4-dimethyl-3H-1,2,4-triazole-3-thione according to any one of claims 7 to 9 wherein the intermediate is 2,4-dimethyl-1-(4-pyridyl) -
thiosemicarbazide.

12. A compound substantially as hereinbefore described with reference to any one of the examples.

13. A process substantially as hereinbefore described with reference to any one of the examples.

DATED: 8 October 1986

PHILLIPS ORMONDE & FITZPATRICK
Attorneys for: MERRELL DOW PHARMACEUTICALS INC. David B. Fitzpatrick