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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| (51) International Patent Classification 3 : | | (11) International Publication Number: WO 83/ 00863 |
|---|---|---|
| C07D237/14 | A1 | (43) International Publication Date: 17 March 1983 (17.03.83) |

(21) International Application Number: PCT/US82/01118

(22) International Filing Date: 18 August 1982 (18.08.82)

(31) Priority Application Number: 301,328

(32) Priority Date: 11 September 1981 (11.09.81)

(33) Priority Country: US

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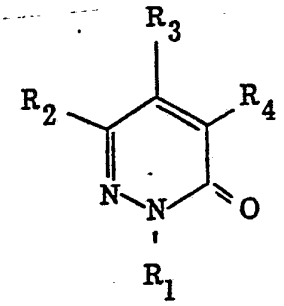
(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), JP, KP, LU (European patent), NL (European patent), SE (European patent).

**Published**
*With international search report.*

(54) Title: ANTIINFLAMMATORY AND ANALGETIC 4-PYRIDYLPYRIDAZIN(2H)-3-ONES

(57) Abstract

Novel 4-pyridylpyridazinones of the formula:




have been discovered to be useful antiinflammatory and analgesic agents.

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# ANTIINFLAMMATORY AND ANALGETIC 4-PYRIDYLPYRIDAZIN(2H)-3-ONES

## BACKGROUND OF THE INVENTION

(1) Field of the Invention

This invention relates generally to 4-pyridylpyridazinone derivatives which exhibit valuable antiinflammatory and analgesic activity in warm-blooded animals. The invention also relates to novel pharmaceutical compositions containing active 4-pyridylpyridazinone compounds and their use for inducing or obtaining antiphlogistic and/or analgesic effects in mammals.

(2) State of the Art

Substituted pyridazinone compounds having various substituents thereon have heretofore been prepared and proposed for use in a wide range of different ultimate applications.

For example, U.S. Patent No. 3,689,652 discloses 6-(substituted-phenyl)-4,5-dihydro-3(2H)-pyridazinones as hypotensive agents. More specifically, 6-halomethylphenyl-5-methyl (or unsubstituted)-4,5-dihydro-3(2H)-pyridazinone compounds are disclosed. In related U.S. Patent Nos. 3,746,712, 3,812,256, 3,822,260, 3,876,786 and 3,876,787, the patentees further disclose corresponding 6-substituted phenyl-4,5-dihydro-pyridazinone compounds wherein the additional phenyl substituents include lower alkanoyl, nitro, amino, lower alkanoylamino and cyano wherein the 2- position of the pyridazinone ring may be optionally substituted by lower alkyl.

U.S. Patent No. 3,657,242 discloses a series of 4,5-dihydro-pyridazin-(2H)-3-one and hexahydropyridazines and, more specifically, certain 2-hydroxy-alkyl-6-aryl or heterocyclic substituted-4,5-dihydro-pyridazinones and hexa-hydropyridazines useful as antiinflammatories.

In U.S. Patent No. 3,931,177, the patentees disclose a series of 6-(3-substituted amino-2-hydroxy propoxyaryl)-4,5-dihydro-3(2H)-pyridazinones active as β -adrenergic-blocking agents and antihypertensives.

The patentees in U.S. Patent No. 3,975,388 disclose 6-alkoxy-, alkyl-, hydroxymethyl-, cycloalkylamino-, alkylamino- and heterocyclic-substituted-phenyl-4,5-dihydro-3(2H)-pyridazinone compounds having antihypertensive activity.

The foregoing compounds are representative of 4,5-dihydro-pyridazinone compounds previously suggested as pharmacologically active compounds. As a chemical class, the foregoing compounds comprise dihydro (saturated) ketopyridazines.

Representative of another class of related compounds are the pyridaz-3-one compounds disclosed in U.S. Patent No. 2,839,532. The aforesaid patent is directed to 4,5-unsaturated pyridaz-3-one (or 3-ketopyridazine) compounds having a cyano, acetyl, carboxyl, carbethoxy or benzoyl group in the 4- position optionally substituted in the 5,6- positions by lower alkyl, phenyl or substituted phenyl residues. These compounds are disclosed as being useful as medicaments, particularly, analgesics, anesthetics, antibacterials or disinfectants.

U.S. Patent No. 3,491,096 and British Patent No. 840,522 are directed to other previously investigated pyridazone compounds. The aforementioned British patent pertains to 2-hydroxymethyl-6-phenyl-3-pyridazone and the analgesic utility thereof. U.S. Patent No. 3,491,096 describes 2-pyridylalkylated-6-phenyl-pyridaz-3-one compounds possessing sedative, analgesic and antispasmodic properties, with occasional hypotensive effects being observed.

In Nannini et al Eur. J. Med. Chem.-Chim. Thera., 14 (1), pp. 53-60 (1979), 5,6-diphenyl-pyridazines are disclosed which exhibit pharmacological activity and more specifically antiinflammatory and analgesic activity. However, no 4-pyridylpyridazinones are disclosed. U.S. Patent No. 4,238,490 also discloses 5,6-diphenylpyridazinones which are useful antihypertensive agents. There is no disclosure, however, to 4-pyridylpyridazinones nor is there any disclosure relating to the use of the patented compounds as antiinflammatory or analgesic agents.

## SUMMARY OF THE INVENTION

It has now been discovered, in accordance with the present invention, novel 4-pyridylpyridazinone compounds which evidence effective antiinflammatory and analgesic activity in warm-blooded animals.

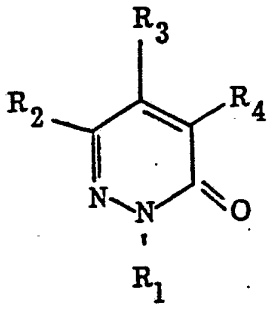
Further in accordance with the invention, a method is provided for the treatment of inflammation, swelling, fever and the like conditions in mammals by the administration of preselected dosages of active 4-pyridylpyridazinone compounds or pharmaceutically acceptable salts thereof in suitable nontoxic pharmaceutical dosage unit forms or compositions.

Still further in accordance with the present invention, novel, stable nontoxic pharmaceutical compositions and/or formulations adaptable for, e.g., oral, rectal, parenteral, etc., administration, are provided.

These and other aspects and advantages of the invention will be appreciated by those skilled in the art upon the reading and understanding of the specification.

## DESCRIPTION OF THE PREFERRED EMBODIMENTS

The novel class of compounds of the present invention are various 4-pyridylpyridazinone compounds of the general formula I below:



I

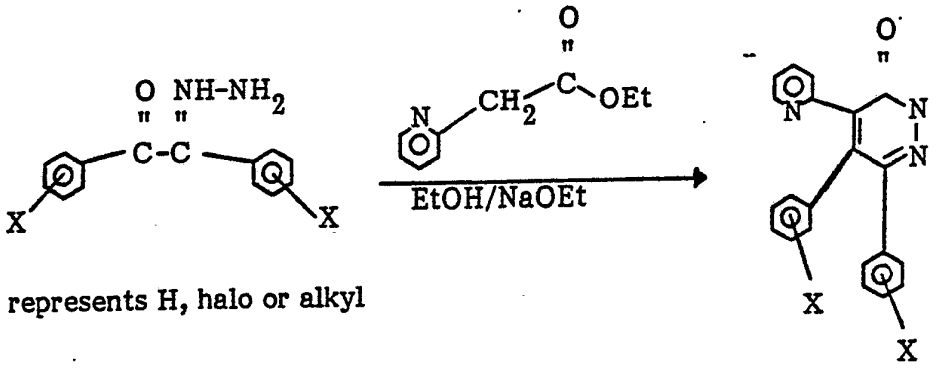
or a pharmaceutically acceptable nontoxic salt thereof wherein $R_1$ is hydrogen, hydroxyalkyl or alkoxycarbonylalkyl; $R_4$ is 2-pyridyl, 3-pyridyl or 4-pyridyl; and $R_2$ and $R_3$ are the same and represent phenyl, halophenyl or alkylphenyl.

As used throughout the instant specification and claims, the expressions "alkyl" and "alkoxy" are inclusive of straight and branched chain carbon-carbon linkages, e.g., methyl, ethyl, N-propyl, isopropyl, N-butyl, tert-butyl, etc., and represent 1 to 5 carbon atoms. The expression "pharmaceutically acceptable nontoxic salts" as used herein is intended to include those salts

capable of being formed with the instant compounds and substituted derivatives thereof in accordance with the invention without materially altering the chemical structure or pharmacological properties of the parent compounds. Representative of acids for reaction with sufficiently basic pyridazinone derivatives include hydrochloric, hydrobromic, hydroiodic, nitric, phosphoric, citric, etc. Alkali metal salts of carboxylic acid derivatives of the invention may be obtained by reaction with suitable bases, e.g., sodium hydroxide, potassium hydroxide, etc. Alkaline earth metal salts may be similarly obtained.

As will be apparent to those skilled in the art, the keto compounds of the above formula wherein $R_1$ is hydrogen may be present in the enol tautomeric form. It is also noted that the other possible $R_1$ substituents, i.e., hydroxyalkyl and alkoxycarbonylalkyl, constitute possible enolic derivatives and/or metabolites of compounds within the scope of the present invention.

The 4-pyridylpyridazinone, i.e., substituted keto-pyridazine, compounds of the present invention, may be prepared by various alternative methods heretofore employed in the synthesis of other pyridazinone compounds or modifications thereof to obtain the $R_1$, $R_2$, $R_3$ or $R_4$ substituents thereon as defined above. In general, one method for the preparation of the 4-pyridylpyridazinone compounds of the present invention comprises reacting an appropriately substituted monohydrazone, with pyridyl acetic acid ethyl ester or reacting the appropriately substituted benzil and pyridyl substituted hydrazide under cyclization conditions, e.g., in the presence of suitable solvents, such as xylene, acetonitrile, methanol, benzene, etc., and alkaline condensing agents, such as hydroxides, alcoholates, hydrides, alkali or alkaline earth metals, tertiary amines, etc., to effect ring closure. The foregoing general scheme may be depicted as follows:




X represents H, halo or alkyl

The monohydrazone reactants may be prepared by the reaction of an appropriately substituted benzil with hydrazine hydrate. Suitable benzil starting materials may be obtained commercially or prepared by known methods, for example, cyanide ion catalyzed benzoin condensation followed by oxidation. The pyridazin(2H)-3-one compounds thus prepared may be utilized following recrystallization/purification as an intermediate for the preparation of further 2-substituted derivatives in accordance with the above $R_1$ definition as illustrated more particularly in the specific examples of preferred embodiments of the invention hereinafter.

As previously indicated, the compounds of the present invention evidence antiinflammatory and analgesic effects in warm-blooded animals. It will be appreciated, however, that the specific response elicited upon administration of the compounds of the present invention to an animal species in need thereof will vary depending upon the specific structure of the administered compound, the unit dose, dosage regimen and mode of administration, as well as the particular mammalian species involved. Accordingly, as detailed hereinbelow, certain of the compounds of the invention are preferred over others relative to a predetermined pharmacological activity. Thus, as preferred compounds for use in the antiinflammatory compositions and methods of the present invention are 2-hydroxyethyl-4-(3'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one; 2-hydroxyethyl-4-(4'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one; 2-acetic acid-4-(4'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one, ethyl ester; 4-(3'-pyridyl)-5,6-bis(4'-methylphenyl)pyridazin(2H)-3-one hydrochloride; and 2-hydroxyethyl-4-(2'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one hydrochloride. As specifically preferred compounds, there may be mentioned 2-acetic acid-4-(4'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one, ethyl ester; 2-hydroxyethyl-4-(2'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one hydrochloride; and 2-hydroxyethyl-4-(4'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one.

Representative of preferred compounds of formula I for use in the analgesic compositions and methods of the present invention are 2-acetic acid-4-(4'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one, ethyl ester; 4-(3'-pyridyl)-5,6-bis(4'-methylphenyl)pyridazin(2H)-3-one hydrochloride; 2-hydroxyethyl-4-(2'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one hydrochloride; 4-(3'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one; and 4-(3'-pyridyl)-5,6-bis(4'-chlorophenyl)pyridazin(2H)-3-one. Based upon presently defineable dose response relationships, especially preferred compounds falling within the aforesaid general formula I are 2-acetic acid-4-(4'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one, ethyl ester; 2-hydroxyethyl-4-(2'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one hydrochloride; and 4-(3'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one.

In accordance with the practices of the present invention, the active compounds of the invention may be administered alone or in combination with each other or administered in admixture with pharmaceutical diluents, carriers, excipients or adjuvants suitably selected with respect to the intended route of administration and conventional pharmaceutical practices. For instance, for oral administration in the form of tablets or capsules, the active compound or compounds of the invention may be combined with such excipients as starch, lactose, sucrose, cellulose, magnesium stearate, and the like. Similarly, injectable dosage unit forms may be utilized to accomplish intraveneous, intramuscular or subcutaneous administration and, for such parenteral administration, suitable sterile aqueous or nonaqueous solutions or suspensions, optionally containing appropriate solutes to effectuate isotonicity, will be employed. Other suitable adjuvants and dosage forms will be apparent to those skilled in the art.

Compounds of the invention or compositions thereof may be administered to warm-blooded animals, i.e., mammals, including, for instance, mice, rats, guinea pigs, dogs and other domesticated animals, or humans. Dosages sufficient to elicit the above-identified antiinflammatory and/or analgesic response will generally range between about 1 to about 500 mg/kg/day in laboratory mice based upon body weight, and preferably between about 10 to about 200 mg/kg/day. The foregoing dosages will normally be administered in 3 or 4 divided doses, depending upon the desired dosage regimen. Of course, the actual effective dosage to be administered will vary, depending upon the specific compound involved, as well as the age, weight and responsiveness of the particular species.

The compounds of the invention exhibit relatively low toxicities and the acute oral $LD_{50}$ (lethal dose to 50 percent of mice) will generally be greater than 300 mg/kg.

The following non-limiting examples are afforded in order that those skilled in the art may more readily understand the present invention and specific preferred embodiments thereof with respect to the preparation of starting materials, intermediates and compounds in accordance with the foregoing description.

## EXAMPLE 1

4-(4'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one

Sodium (1.4 g.) was allowed to react with ethanol in a dry atmosphere. When the addition was complete, benzil monohydrazone (11.2 g.) and ethyl-4-pyridylacetate (10 g.) were added as a slurry in ethanol. The reaction mixture was heated at reflux for 2 hours, poured into 500 mL. of water to give a solution. Solid $CO_2$ was added to the solution to lower the pH. The resulting precipitate was separated by filtration and recrystallized from acetonitrile. Yield 10 g. M.P. 277-279° C.

## EXAMPLE 2

4-(2'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one

Sodium (1.4 g.) was allowed to react with ethanol in a dry atmosphere. When the addition was complete, benzil monohydrazone (11.2 g.) and ethyl-2-pyridylacetate (10 g.) were added as a slurry in EtOH. The reaction mixture was heated at reflux for 2 hours and poured into 500 mL. of water to give a solution. Solid $CO_2$ was added to the solution to lower the pH. The resulting precipitate was separated by filtration and recrystallized from acetonitrile. Yield 12 g. M.P. 277-278° C.

## EXAMPLE 3

4-(3'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one

1 g. sodium metal was dissolved in 100 mL. absolute EtOH with stirring under a nitrogen atmosphere. 10 g. (0.044 m.) of benzil monohydrazone and 7.26 g. (0.044 m.) of ethyl-3-pyridylacetate were added to the sodium ethoxide along with 100 mL. additional EtOH. The reaction was heated to reflux for 3 hours. The hot solution was added to an equal volume of $H_2O$, causing a

milky dispersion. Upon addition of $CO_2$ (dry ice), a white precipitate formed which was filtered. Impurities were extracted from the solid with boiling acetonitrile, leaving 6.7 g. of white solid. M.P. 275-277° C.

## EXAMPLE 4

2-acetic acid-4-(4'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one, ethyl ester

10.5 g. (0.032 m.) of the compound of Example 1 and 4.4 g. (0.032 m.) of potassium carbonate were charged to a reaction flask in 200 mL. DMF. With stirring at room temperature, 3.75 g. (0.032 m.) of ethyl chloroacetate were added to the reaction mixture. The milky dispersion transformed into a brown slurry upon stirring at room temperature overnight. The reaction mixture was quenched in 300 mL. $H_2O$. The product oiled out, an aqueous layer was decanted off and product extracted with ethyl acetate. The solvent was stripped to yield a brown oil which crystallized. this product was recrystallized from hexane/chloroform with charcoal filtering. The product yielded a light brown solid upon drying for 48 hrs. at 105° C in an oven. A final yield of 3.8 g. was obtained. M.P. 150-153° C.

## EXAMPLE 5

2-hydroxyethyl-4(4'-pyridyl)-5,6-diphenylpyridazin-3-one

3.0 g. (0.0092 m.) of the compound of Example 1 and 1.0 g. (0.011 m.) of ethylene carbonate were charged to a flask in 100 mL. DMF. Three powderized KOH pellets were added to the mixture and the flask was placed in a oil bath preheated to 115° C. The reaction was heated for 4 hrs. The cooled solution was quenched in an equal volume of water and made less basic by adding $CO_2$ (dry ice) until a pH 9 was obtained. A precipitate formed upon cooling. The precipitate was filtered and recrystallized from ethyl acetate. Dried over IPA for approximately 6 hrs. M.P. 198-201° C.

## EXAMPLE 6

2-hydroxyethyl-4-(2'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one hydrochloride

The compound of Example 2 (9.0 g.) and ethylene carbonate 2.7 g. were slurried in DMF (100 mL.) and 3 powdered KOH pellets added. The reactants were stirred at 110-120° for 2 hrs. The mixture was poured into water and the suspension extracted with benzene. The organic layer was washed with water and dried over $Na_2SO_4$. HCl gas was bubbled through the solution to give a gummy precipitate which solidified on addition of ether. The solid was

separated and recrystallized from MeOH-EtOAc. Yield 7.2 g., M.P. 237-247° C, decomposition with effervescence.

## EXAMPLE 7

2-hydroxyethyl-4-(3'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one

4.0 g. (0.012 m.) of the compound of Example 3 and 1.15 g. (0.013 m.) of ethylene carbonate were charged to a flask in 125 mL. of DMF. A few powderized KOH pellets were added, and the flask was placed in an oil bath at 110° C. The reaction was heated for about 8 hrs. During the course of the reaction, a second equivalent of ethylene carbonate was added. The hot solution was added to an equal volume of water, then made basic by addition of $CO_2$ (dry ice). Refrigeration produced a white solid which was filtered and recrystallized from benzene/carbon tetrachloride. Approx. 4.0 g. of product were recovered. M.P. 187-189° C.

## EXAMPLE 8

4-(3'-pyridyl)-5,6-bis(4'-chlorophenyl)pyridazin(2H)-3-one

21.98 g. (0.075 m.) of 4,4'-dichlorobenzilmonohydrazone and 13.1 g. (0.08 m.) of ethyl 3-pyridylacetate were charged to a dry flask in approx. 400 mL. absolute ethanol. To the stirred mixture, 5.44 g. (0.08 m.) of sodium ethoxide were added portionwise. After addition, the reaction was heated to reflux for 6 hrs. Hot solution quenched in equal volume of water, and pH adjusted to approx. 9 by addition of $CO_2$ (dry ice), thereby precipitating a white solid. Solid filtered from cooled solution and recrystallized from benzene/acetonitrile. Dried over IPA overnight. M.P. 269-272° C.

## EXAMPLE 9

2-hydroxyethyl-4-(3'-pyridyl)-5,6-bis(4'-chlorophenyl)pyridazin(2H)-3-one

3.0 g. (0.0075 m.) of the compound of Example 8 and 1.3 g. (0.015 m.) of ethylene carbonate were charged to a flask in 125 mL. DMF. Four powderized KOH pellets were added to the flask which was then placed in a preheated oil bath at 115° C. The reaction was heated for 3 hrs. The slightly cooled solution was then added to an equal volume of water and the pH adjusted to approx. 9 by addition of $CO_2$ (dry ice). A solid precipitated out of the cooled solution, was filtered and recrystallized from ethyl acetate. Solid dried over IPA overnight. M.P. 190-193° C.

The following compounds were prepared utilizing synthesis methods analogous to the foregoing.

EXAMPLE 10

2-acetic acid-4-(3'-pyridyl)-5,6-bis(4'-chlorophenyl)pyridazin(2H)-3-one, methyl ester, melting point 173-175° C.

EXAMPLE 11

4-(2'-pyridyl)-5,6-bis(4'-methylphenyl)pyridazin(2H)-3-one, melting point is greater than 305° C.

EXAMPLE 12

2-hydroxyethyl-4-(2'-pyridyl)-5,6-bis(4'-methylphenyl)pyridazin(2H)-3-one, melting point 209-211° C.

EXAMPLE 13

4-(3'-pyridyl)-5,6-bis(4'-methylphenyl)pyridazin(2H)-3-one hydrochloride, melting point 290-295° C.

EXAMPLE 14

2-hydroxyethyl-4-(3'-pyridyl)-5,6-bis(4'-methylphenyl)pyridazin(2H)-3-one hydrochloride, melting point 243-245° C.

PHARMACOLOGICAL ACTIVITY

The results of studies demonstrating the indicated antiinflammatory and analgesic effects observed upon administration of effective dosages of typical preferred compounds in accordance with the present invention and the procedures utilized to evaluate pharmacological activity are set forth below.

A. Antiinflammatory Assay

Antiinflammatory activity, i.e., effectiveness in the prevention and inhibition of granuloma tissue formation, is demonstrated by relative inhibition of carrageenin-induced edema as determined by the diminution of experimental edema induced in the hind paw of a rat by the injection of carrageenin. The procedure employed is a modification of the method of Winter et al, Proc. Soc. Exptl. Biol. Med., 111:544 (1962). The device used for measurement of the paw volume is an adaptation of the water displacement procedure described by

Adamkiewicz et al, Can. J. Biochem. Physiol., 33:332 (1955). Test compounds were administered orally, one hour prior to the intraplanter injection of 0.05 mL. of sterile 1.0% solution of carrageenin into the left hind paw of male rats (Long Evans strain) weighing between about 130-200 g. At peak swelling time (3 hrs.) the volume of edema was calculated by differential paw volumes.

Table I sets forth results obtained at the indicated dosages with representative compounds of the present invention.

TABLE I

Carrageenin Assay

| Compd. Example No. | Dose (mg/kg) | % Reduction of Edema |
|---|---|---|
| 4 | 200 | 24 |
| 4 | 100 | 14 |
| 5 | 200 | 37 |
| 6 | 160 | 45 |
| 7 | 200 | 39 |
| 8 | 200 | 15 |
| 10 | 10 | 8 |
| 13 | 100 | 27 |

B. Analgesic Assay

Phenylquinone writhing test was employed to evaluate analgesic activity for selected compounds for the present invention according to the following procedure:

Phenylquinone (phenyl-p-benzoquinone, No. 7104, Eastman Organic Chemicals) is made up as a 0.02% aquequs solution and 5% ethyl alcohol. Phenylquinone solutions are made up fresh twice daily. Standard reference agents and the test compounds are dissolved or suspended in a 0.25% methyl-cellulose solution. A control group consisting of 10 mice (Carworth $CF_1$ male mice) are administered the 0.02% phenylquinone solution at a dose of 0.25 mL./mouse. The mice are housed individually and observed closely for 10 min. for exhibition of writhing. The onset of writhing occurs within 3 min. and 100% of the mice must writh within 10 min. Test compounds are administered orally to groups of 10 mice. The volume given is 0.01 mL. per gram of body weight. Activity can be studied at 15, 30, 60 and 120 min. after oral administration. After the designated time interval of a dose group has elapsed, the mice are challenged with phenylquinone intraperitoneally. Complete blocking of the

writhing syndrome for the 10-min. observation period in any one mouse is considered a positive analgesic response for that mouse. Conversely, if any mouse wriths definitely once, it is considered not to be protected. The number of mice not writhing in a group multiplied by 10 equals percent analgesia for that dose at that time interval.

The compounds tested, dose administered, and analgesic response are summarized in Table II.

TABLE II

Phenylquinone Writhing Assay (% Control)

| Compd. Example No. | Dose (mg/kg) | % at 30 min. |
|---|---|---|
| 3 | 100 | 50 |
| 4 | 100 | 70 |
| 6 | 100 | 40 |
| 8 | 100 | 30 |
| 13 | 100 | 30 |

C. Neurotoxicity-$NTD_{50}$

The compounds of the present invention were further tested to determined if they exhibited adverse neurotoxic effects. A standard testing procedure was employed to determine the mean neurotoxic dose in 50% of test mice.

The mean neurotoxic dose (expressed as $NTD_{50}$ value in mg/kg) is defined as that dose of the drug administered orally or intraperitoneally (i.p.) to test mice that causes minimal recognizable neurotoxicity in 50% of the animals tested. The procedure followed is described by Swinyard et al, J. Pharmac. Exp. Therap., 106, 319-330 (1952).

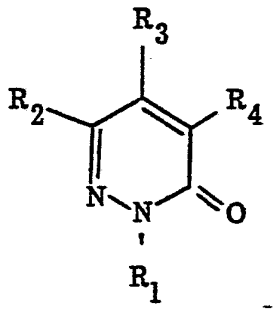
The results of this test showed that the compounds of the present invention all demonostrated $NTD_{50}$ values of greater than 300 mg/kg and the compound of Example 4 gave an $NTD_{50}$ value of greater than 1000 mg/kg.

While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit of the invention. For example, effective dosages other than the preferred ranges set forth hereinabove may be applicable as a consequence of variations in the responsiveness of the mammal treated,

severity of the particular condition, dosage related adverse effects, if any, observed and analogous considerations. Likewise, the specific pharmacological responses observed may vary depending upon the particular active compounds selected or where different active compounds are used in combination or in the presence of suitable pharmaceutical carriers, as well as the type of formulation and mode of adminisration employed, in such expected variations or differences in results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow.

WHAT IS CLAIMED IS:

1. A compound of the formula:



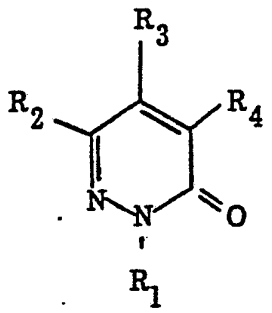
or a pharmaceutically acceptable nontoxic salt thereof wherein $R_1$ is hydrogen, hydroxyalkyl or alkoxycarbonylalkyl; $R_2$ and $R_3$ are the same and represent phenyl, halophenyl or alkylphenyl; and $R_4$ is 2-pyridyl, 3-pyridyl or 4-pyridyl.

2. The compound as defined in Claim 1 wherein said compound is selected from the group consisting of 2-acetic acid-4-(4'-pyridyl)-5,6-diphenyl-pyridazin(2H)-3-one, ethyl ester; 4-(3'-pyridyl)-5,6-bis(4'-methylphenyl)pyridazin-(2H)-3-one hydrochloride; 2-hydroxyethyl-4-(2'-pyridyl)-5,6-diphenylpyridazin-(2H)-3-one hydrochloride; 2-hydroxyethyl-4-(3'-pyridyl)-5,6-diphenylpyridazin-(2H)-3-one; 2-hydroxyethyl-4-(4'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one; 4-(3'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one; and 4-(3'-pyridyl)-5,6-bis(4'-chloro-phenyl)pyridazin(2H)-3-one.

3. The compound of Claim 2 wherein said compound is 2-acetic acid-4-(4'-pyridyl)-5,6-diphenylpyrdazin(2H)-3-one, ethyl ester.

4. The compound of Claim 3 wherein said compound is 2-hydroxyethyl-4-(2'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one hydrochloride.

5. A pharmaceutical antiinflammatory preparation in dosage unit form comprised of a pharmaceutical carrier and an active ingredient, the active ingredient of which consists of a nontoxic antiinflammatory amount of a compound of the formula:



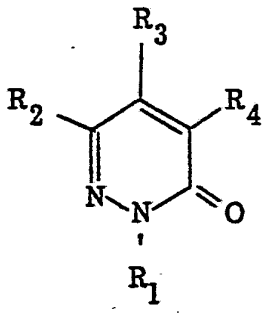
or a pharmaceutically acceptable nontoxic salt thereof wherein $R_1$ is hydrogen, hydroxyalkyl or alkoxycarbonylalkyl; $R_2$ and $R_3$ are the same and represent phenyl, halophenyl or alkylphenyl; and $R_4$ is 2-pyridyl, 3-pyridyl or 4-pyridyl.

6. A preparation as defined in Claim 5 wherein the compound is selected from the group consisting of 2-hydroxyethyl-4-(3'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one; 2-hydroxyethyl-4-(4'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one; 2-acetic acid-4-(4'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one, ethyl ester; 4-(3'-pyridyl)-5,6-bis(4'-methylphenyl)pyridazin(2H)-3-one hydrochloride; and 2-hydroxyethyl-4-(2'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one hydrochloride.

7. A preparation as defined in Claim 5 wherein the compound is selected from the group consisting of 2-acetic acid-4-(4'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one, ethyl ester; 2-hydroxy-4-(2'-pyridyl)-5,6-diphenylpyridazin-(2H)-3-one hydrochloride; and 2-hydroxyethyl-4-(4'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one.

8. A preparation as defined in Claims 5, 6 or 7 wherein the antiinflammatory amount is within the range of 10 to 500 mg/kg/day.

9. A method of obtaining an antiinflammatory effect in an animal in need thereof comprising administering thereto an antiinflammatory effective amount of a compound of the formula:



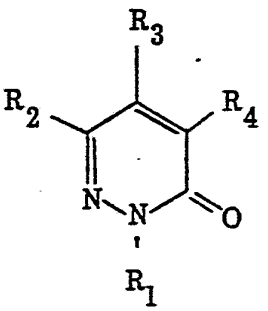
or a pharmaceutically acceptable nontoxic salt thereof wherein $R_1$ is hydrogen, hydroxyalkyl or alkoxycarbonylalkyl; $R_2$ and $R_3$ are the same and represent phenyl, halophenyl or alkylphenyl; and $R_4$ is 2-pyridyl, 3-pyridyl or 4-pyridyl.

10. The method of Claim 9 wherein said compound is selected from the group consisting of 2-hydroxyethyl-4-(3'-pyridyl)-5,6-diphenylpyridazin-(2H)-3-one; 2-hydroxyethyl-4-(4'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one; 2-acetic acid-4-(4'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one, ethyl ester; 4-(3'-pyridyl)-5,6-bis(4'-methylphenyl)pyridazin(2H)-3-one hydrochloride; and 2-hydroxyethyl-4-(2'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one hydrochloride.

11. The method of Claim 10 wherein said compound is selected from the group consisting of 2-acetic acid-4-(4'-pyridyl)-5,6-diphenylpyridazin-(2H)-3-one, ethyl ester; 2-hydroxy-4-(2'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one hydrochloride; and 2-hydroxyethyl-4-(4'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one.

12. The method of Claims 9, 10 or 11 wherein the antiinflammatory effective amount is within the range of 10 to 500 mg/kg/day.

13. A pharmaceutical analgesic preparation in dosage unit form comprised of a pharmaceutical carrier and an active ingredient, the active ingredient of which consists of a nontoxic analgesic amount of a compound of the formula:



or a pharmaceutically acceptable nontoxic salt thereof

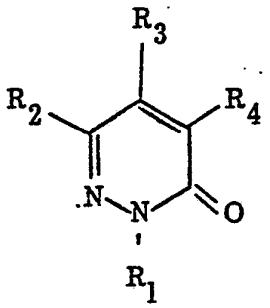
wherein $R_1$ is hydrogen, hydroxyalkyl or alkoxycarbonylalkyl; $R_2$ and $R_3$ are the same and represent phenyl, halophenyl or alkylphenyl; and $R_4$ is 2-pyridyl, 3-pyridyl or 4-pyridyl.

14. The preparation as defined in Claim 13 wherein said compound is selected from the group consisting of 2-acetic acid-4-(4'-pyridyl)-5,6-diphenyl-pyridazin(2H)-3-one, ethyl ester; 4-(3'-pyridyl)-5,6-bis(4'-methylphenyl)pyridazin-(2H)-3-one hydrochloride; 2-hydroxyethyl-4-(2'-pyridyl)-5,6-diphenylpyridazin-(2H)-3-one hydrochloride; 4-(3'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one; and 4-(3'-pyridyl)-5,6-bis(4'-chlorophenyl)pyridazin(2H)-3-one.

15. The preparation as defined in Claim 13 wherein said compound is selected from the group consisting of 2-acetic acid-4-(4'-pyridyl)-5,6-diphenyl-pyridazin(2H)-3-one, ethyl ester; 2-hydroxyethyl-4-(2'-pyridyl)-5,6-diphenyl-pyridazin(2H)-3-one hydrochloride; and 4-(3'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one.

16. The preparation as defined in Claims 13, 14 or 15 wherein the antiinflammatory amount is within the range of 10 to 500 mg/kg/day.

17. A method of obtaining an analgesic effect in an animal in need thereof comprising administering thereto an analgesically effective amount of a compound of the formula:




or a pharmaceutically acceptable nontoxic salt thereof

wherein $R_1$ is hydrogen, hydroxyalkyl or alkoxycarbonylalkyl; $R_2$ and $R_3$ are the same and represent phenyl, halophenyl or alkylphenyl; and $R_4$ is 2-pyridyl, 3-pyridyl or 4-pyridyl.

18. The method of Claim 17 wherein said compound is selected from the group consisting of 2-acetic acid-4-(4'-pyridyl)-5,6-diphenylpyridazin-(2H)-3-one, ethyl ester; 4-(3'-pyridyl)-5,6-bis(4'-methylphenyl)pyridazin(2H)-3-one hydrochloride; 2-hydroxyethyl-4-(2'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one hydrochloride; 4-(3'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one; and 4-(3'-pyridyl)-5,6-bis(4'-chlorophenyl)pyridazin(2H)-3-one.

19. The method of Claim 18 wherein said compound is selected from the group consisting of 2-acetic acid-4-(4'-pyridyl)-5,6-diphenylpyridazin-(2H)-3-one, ethyl ester; 2-hydroxyethyl-4-(2'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one hydrochloride; and 4-(3'-pyridyl)-5,6-diphenylpyridazin(2H)-3-one.

20. The method of Claims 17, 18 or 19 wherein said antiinflammatory effective amount is within the range of about 10 to about 500 mg/kg/day.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/US82/01118

## I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.[3] C07D 237/14

## II. FIELDS SEARCHED

Minimum Documentation Searched [4]

| Classification System | Classification Symbols |
|---|---|
| U.S. | 544/238<br>544/239<br>424/250 |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

| Category * | Citation of Document, [16] with indication, where appropriate, of the relevant passages [17] | Relevant to Claim No. [18] |
|---|---|---|
| X | U.S., A, 3,658,814, Published 25 April 1972 | 1-5, 13-19 |
| X | U.S., A, 3,920,646, Published 18 November 1975 | 1-12, 20 |
| X | U.S., A, 3,931,176, Published 6 January 1976 | 1-5 |
| X | U.S., A, 4,280,998, Published 28 July 1981 | 1-12, 20 |
| X | U.S., A, 4,238,490, Published 9 December 1980 | 1-5 |
| X,P | U.S., A, 4,298,609, Published 3 November 1981 | 1-5 |
| X | JP, A, 51-43776, Published 14 April 1976 | 1-5 |
| X | JP, A, 54-19987, Published 15 February 1979 | 1-5 |
| X | GB, A, 840,522, Published 6 July 1960 | 1-5, 13-19 |
| X,A | N, European J. Med. Chem. Issued February 1979, Nannini et al, Synthesis and Pharmacological Activity of some 5,6-diphenyl-pyridazines, pp. 53-60 | 1-20 |

* Special categories of cited documents: [15]

"A" document defining the general state of the art

"E" earlier document but published on or after the international filing date

"L" document cited for special reason other than those referred to in the other categories

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but on or after the priority date claimed

"T" later document published on or after the international filing date or priority date and not in conflict with the application, but cited to understand the principle or theory underlying the invention

"X" document of particular relevance

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search [2] | Date of Mailing of this International Search Report [2] |
|---|---|
| November 5, 1982 | 16 NOV 1982 |
| International Searching Authority [1] | Signature of Authorized Officer [20] |
| ISA/US | Theresa Hendricks |

Form PCT/ISA/210 (second sheet) (October 1977)