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Wikel

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[54] **5-(2-AMINOPHENYL)PYRAZOLE-3-CARBOXYLIC ACIDS AND ESTERS THEREOF**

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[52] **U.S. Cl.** ..... **260/310 R;** 424/273

[51] **Int. Cl.** **C07d 47/02**

[58] **Field of Search** ..... 260/310 R

[56] **References Cited**

FOREIGN PATENTS OR APPLICATIONS

535,564 1/1957 Canada ..... 260/310 R

OTHER PUBLICATIONS

Chemical Abstracts Vol. 59: 15214b (1963).

Chemical Abstracts Vol. 52: 3784g (1956).

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[57] **ABSTRACT**

5-(2-Aminophenyl)pyrazole-3-carboxylic acids, useful as intermediates in the preparation of compounds useful as complement inhibitors, are prepared by reacting a 2-nitroacetophenone with a dialkyl oxalate in the presence of a strong base and in an inert solvent to give the corresponding alkyl 2-nitrobenzoylpyruvate, condensing the alkyl 2-nitrobenzoylpyruvate with hydrazine in an inert solvent to give an alkyl 5-(2-nitrophenyl)-pyrazole-3-carboxylate, reducing the nitro group catalytically to give the alkyl 5-(2-aminophenyl)pyrazole-3-carboxylate, and, if desired, hydrolyzing the ester to the free acid.

2 Claims, No Drawings

5-(2-AMINOPHENYL)PYRAZOLE-3-CARBOXYLIC ACIDS AND ESTERS THEREOF

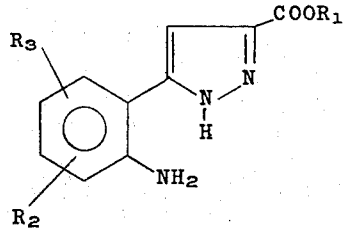
BACKGROUND OF THE INVENTION

This invention relates to 5-(2-aminophenyl)pyrazole-3-carboxylic acids and alkyl esters thereof. More particularly, this invention relates to 5-(2-aminophenyl)pyrazole-3-carboxylic acids and alkyl esters thereof which are useful as intermediates in the preparation of compounds useful as complement inhibitors, and to a process for preparing said 5-(2-aminophenyl)pyrazole-3-carboxylic acids and esters.

Malfunction of the serum complement system is known to be involved in glomerulonephritis and is believed to be involved in serum sickness and in certain inflammatory diseases such as rheumatoid arthritis. Consequently, an effective complement inhibitor would substantially block the malfunction of the serum complement system and hence would be useful in the treatment of such diseases.

SUMMARY OF THE INVENTION

In accordance with the present invention, novel 5-(2-aminophenyl)pyrazole-3-carboxylic acids and alkyl esters thereof are provided having the following general formula:



wherein R_1 is hydrogen or C_1–C_3 alkyl and R_2 *and* R_3 are monovalent groups independently selected from the group consisting of hydrogen, methyl, methoxy, fluoro, chloro, and bromo, with the limitation that R_2 and R_3 must be different unless each of R_2 and R_3 is hydrogen.

The compounds of the present invention are prepared by the process which comprises the steps of (1) reacting a 2-nitroacetophenone with a C_1–C_3 dialkyl oxalate in the presence of a strong base, in an inert solvent, and at a temperature of from about −40°C to about 100°C, and then acidifying the reaction mixture to give the corresponding alkyl 2-nitrobenzoylpyruvate; (2) condensing the alkyl 2-nitrobenzoylpyruvate with hydrazine in an inert solvent and at a temperature of from about 0°C to about 100°C to give an alkyl 5-(2-nitrophenyl)pyrazole-3-carboxylate; (3) reducing catalytically the nitro group of the alkyl 5-(2-nitrophenyl)pyrazole-3-carboxylate, in an inert solvent, at an initial hydrogen pressure of from about 15 to about 100 psig, and at a temperature of from about 0°C to about 50°C, to give the alkyl 5-(2-aminophenyl)pyrazole-3-carboxylate; and, if desired, (4) hydrolyzing the alkyl 5-(2-aminophenyl)-pyrazole-3-carboxylate to the free acid.

The compounds of the present invention are useful as intermediates in the preparation of certain 5-[2-(N-substituted amino)phenyl]pyrazole-3-carboxylic acids which are useful as complement inhibitors.

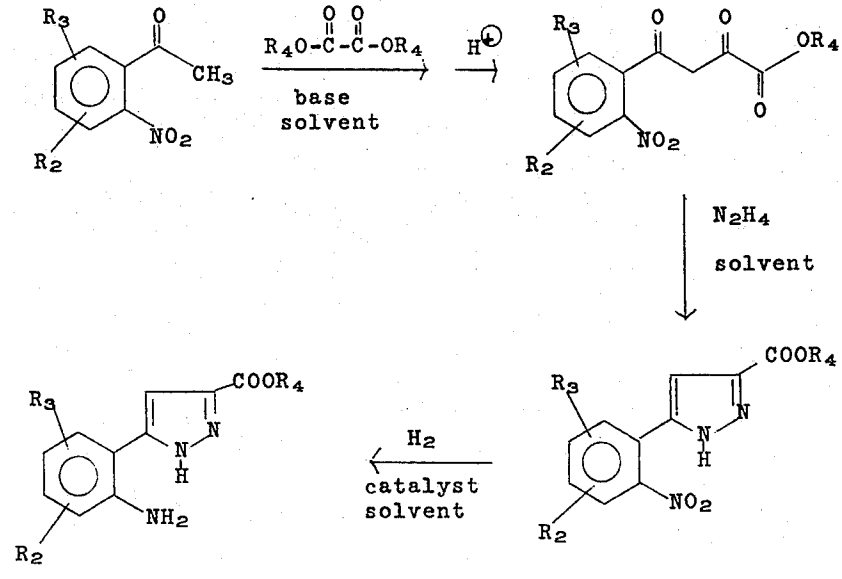
DETAILED DESCRIPTION OF THE INVENTION

Examples of compounds coming within the foregoing general formula include, among others,

5-(2-Aminophenyl)pyrazole-3-carboxylic acid,
Methyl 5-(2-aminophenyl)pyrazole-3-carboxylate,
Ethyl 5-(2-aminophenyl)pyrazole-3-carboxylate,
Propyl 5-(2-aminophenyl)pyrazole-3-carboxylate,
Isopropyl 5-(2-aminophenyl)pyrazole-3-carboxylate,
Methyl 5-(2-amino-3-methylphenyl)pyrazole-3-carboxylate,
Isopropyl 5-(2-amino-4-fluorophenyl)pyrazole-3-carboxylate,
Methyl 5-(2-amino-6-methoxyphenyl)pyrazole-3-carboxylate,
5-(2-Amino-3-methyl-6-methoxyphenyl)pyrazole-3-carboxylic acid,
Ethyl 5-(2-amino-3-methyl-5-bromophenyl)pyrazole-3-carboxylate, and
Methyl 5-(2-amino-4-chloro-5-methoxyphenyl)pyrazole-3-carboxylate.

The referred compounds are the esters; i.e., R_1 preferably is C_1–C_3 alkyl.

The process of the present invention can be represented by the following reaction scheme:



wherein R_4 is C_1–C_3 alkyl and R_2 and R_3 are as defined hereinbefore. Briefly, a 2-nitroacetophenone is reacted with a dialkyl oxalate in the presence of a strong base and in an inert solvent, then the reaction mixture is acidified to give the corresponding alkyl 2-nitrobenzoylpyruvate. The alkyl 2-nitrobenzoylpyruvate then is condensed with hydrazine in an inert solvent to give an alkyl 5-(2-nitrophenyl)pyrazole-3-carboxylate. The nitro group of the alkyl 5-(2-nitrophenyl)pyrazole-3-carboxylate is reduced catalytically in an inert solvent to give the alkyl 5-(2-aminophenyl)pyrazole-3-carboxylate. Optionally, but not preferably, the alkyl 5-(2-aminophenyl)pyrazole-3-carboxylate can be hydrolyzed by known methods to the 5-(2-aminophenyl)pyrazole-3-carboxylic acid.

The first step, which involves reacting a 2-nitroacetophenone with a dialkyl oxalate, preferably with dimethyl oxalate, essentially is a known procedure. See, for example, L. Musajo, et al., Gazz. chim. ital., 80, 161 (1950) [C.A., 45, 624 (1951)], and K. Makino, et al., Kumamoto Med. J., 6, 122 (1954) [C.A., 49, 6179 (1954)]. In general, both starting materials are either commercially-available or readily prepared by known procedures. Normally and preferably, the molar ratio of the 2-nitroacetophenone to the dialkyl oxalate will be about 1:1, although an excess of either reactant can be employed, if desired. Thus, said molar ratio can vary from about 2:1 to about 1:2. The molar ratio of strong base to the dialkyl oxalate can vary from about 1:1 to about 1.2:1, and preferably from about 1:1 to about 1.1:1. Most preferably, the molar ratio of base to oxalate will be about 1:1. Examples of suitable strong bases include, among others, alkali metal hydroxides, such as lithium hydroxide, sodium hydroxide, potassium hydroxide, rubidium hydroxide, and cesium hydroxide; alkali metal C_1–C_4 alkoxides, such as sodium methoxide, potassium ethoxide, lithium isopropoxide, cesium propoxide, rubidium butoxide, sodium sec-butoxide, lithium t-butoxide, and the like; C_1–C_4 alkyl lithium compounds, such as methyl lithium, ethyl lithium, propyl lithium, isopropyl lithium, butyl lithium, sec-butyl lithium, isobutyl lithium, and t-butyl lithium; alkali metal hydrides, such as lithium hydride, sodium hydride, potassium hydride, rubidium hydride, and cesium hydride; and the like. The preferred bases are the alkali metal alkoxides. Of course, the base must be significantly soluble in the reaction solvent, and preferably will be substantially, i.e., at least about 50 percent, soluble. Most preferably, the base will be completely soluble in the reaction solvent. Generally, the solvent must be inert. Examples of such solvents include, among others, alkanols, such as methanol, ethanol, propanol, and isopropanol; aromatic hydrocarbons, such as benzene, toluene, the xylenes, and the like; aliphatic hydrocarbons, such as pentane, hexane, octane, and the like; ethers, such as diether ether, diisopropyl ether, methyl butyl ether, tetrahydrofuran, 1,4-dioxane, and the like; and such miscellaneous solvents as N,N-dimethylformamide, N,N-dimethylacetamide, and dimethyl sulfoxide. The preferred solvents are the alkanols. The choice of a particular preferred solvent is important only when it is desired to isolate the alkyl 2-nitrobenzoylpyruvate in pure form. That is, when the alkyl moiety of the alkanol solvent is different from the alkyl moiety of the dialkyl oxalate, transesterification can result in the formation of two alkyl 2-nitrobenzoylpyruvates having different alkyl moieties. Consequently, when using an alkanol solvent, it is preferred that the alkyl moieties of the alkanol and the dialkyl oxalate be the same. The amount of solvent employed is not critical, provided adequate agitation can be maintained during the reaction. Typically, the amount of solvent employed will constitute about 50 percent by weight of the total reaction mixture. The reaction temperature, which can vary from about −40°C to about 100°C, is to some extent dependent upon the base-solvent combination employed. When both a preferred base and a preferred solvent are used, the reaction temperature can vary from about −20°C to about 20°C. The reaction time is not critical and can vary from about 15 minutes to about 24 hours. Typically, the reaction time will vary from about 1 to about 18 hours. When the reaction is complete, the alkyl 2-nitrobenzoyl-pyruvate normally has precipitated as the enolate. The precipitate is isolated and dissolved in water. Acidification of the resulting aqueous solution results in the precipitation of the alkyl 2-nitrobenzoylpyruvate which can be purified, if desired, by standard techniques. The acid used in said acidificatioon is not critical and can be either organic or inorganic. Examples of suitable acids include, among others, organic carboxylic acids, such as acetic acid, propionic acid, chloroacetic acid, trichloroacetic acid, benzoic acid, m-nitrobenzoic acid, p-bromobenzoic acid, and the like; organic sulfonic acids, such as methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, and the like; and inorganic acids, such as hydrochloric acid, sulfuric acid, phosphoric acid, and the like. The organic acids are preferred, with the organic carboxylic acids being most preferred.

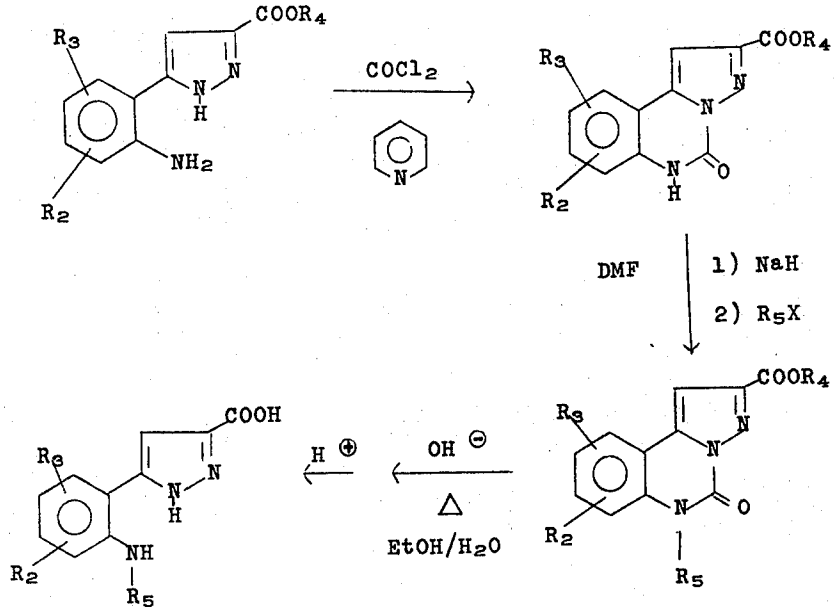
The second step of the process of the present invention requires condensing hydrazine with the alkyl 2-nitrobenzoyl-pyruvate obtained above. In general, the molar ratio of hydrazine to the alkyl 2-nitrobenzoylpyruvate can vary from about 1:1 to about 3:1 or even higher. Preferably, this molar ratio will vary from about 1:1 to about 1.1:1. In general, any inert solvent can be used. Examples of such solvents include those listed as suitable in the first step, and additionally, aliphatic carboxylic acid esters, such as methyl acetate, ethyl acetate, butyl acetate, and the like; and halogen-containing hydrocarbons, such as methylene chloride, ethylene dichloride, chloroform, carbon tetrachloride, chlorobenzene, bromobenzene, and the like. The preferred solvents are the alkanols. The amount of solvent employed is not critical, although the solvent normally will constitute at least about 50 percent by weight of the total reaction mixture. However, the solvent often will constitute up to about 95 percent by weight of the total reaction mixture when the alkyl 2-nitrobenzoylpyruvate has but limited solubility in the solvent. The reaction temperature can vary from about 0°C to about 100°C, preferably from about 10°C to about 40°C, and most preferably will be ambient temperature. The parameters discussed hereinabove with respect to the reaction time in the first step apply here, also. The alkyl 5-(2-nitrophenyl)pyrazole-3-carboxylate which is obtained is isolated and, if desired, purified in accordance with standard procedures. It should be noted that the alkyl 5-(2-nitrophenyl)pyrazole-3-carboxylate is light-sensitive; i.e., the compound turns to a lavender to purple color

upon exposure to light. Consequently, it is desirable to the appropriate precautions while carrying out the second step, which precautions are well known to those skilled in the art. However, the color change which occurs upon exposure of the compound to light apparently has no significant effect upon the chemical structure of the compound.

In the third step of the process of the present invention, the nitro group of the alkyl 5-(2-nitrophenyl)pyrazole-3-carboxylate is catalytically reduced to an amino group in accordance with known procedures. Briefly, the compound is dissolved in an inert solvent, examples of such solvents being those listed with respect to step two above. Again, the preferred solvents are the alkanols. The amount of solvent is not critical and typically will constitute from about 50 to about 95 percent by weight of the total reaction mixture. Suitable catalysts include, among others, 5 percent rhodium on alumina, 5 percent rhodium on activated charcoal, ruthenium oxide, platinum oxide, 5 percent palladium on activated charcoal, and other like catalysts known to catalyze the reduction of aromatic nitro groups. The amount of catalyst employed can vary from about 0.1 percent to about 20 percent by weight, based on the amount of alkyl 5-(2-nitrophenyl)pyrazole-3-carboxylate; about ten percent by weight of catalyst has been found to give satisfactory results. The initial hydrogen pressure can vary from about 15 to about 100 psig, with from about 45 to about 60 psig being preferred. The reduction temperature normally will vary from about 0°C to about 50°C. The reduction is exothermic; hence, some care must be exercised to keep the reduction under control. The reaction mixture is worked up according to standard procedures in order to isolate the alkyl 5-(2-aminophenyl)pyrazole-3-carboxylate which can be purified, if desired.

As indicated hereinbefore, an optional fourth step can be carried out, if desired, which step comprises hydrolyzing by known procedures the alkyl 5-(2-aminophenyl)pyrazole-3-carboxylate to the corresponding 5-(2-aminophenyl)pyrazole-3-carboxylic acid. This fourth step, however, is not preferred since the carboxylic acid moiety of the compounds of the present invention must be blocked in order to convert the compounds of the present invention to certain 5-[2-(N-substituted amino)phenyl]pyrazole-3-carboxylic acids which are useful as complement inhibitors.

The compounds of the present invention are converted to the complement inhibiting pyrazole-3-carboxylic acids in accordance with the following reaction scheme:



wherein R_2, R_3, and R_4 are as defined hereinbefore; R_5 is a monovalent group selected from the group consisting of methyl, benzyl, and monosubstituted benzyl in which the substituent is methyl, trifluoromethyl, methoxy, methylsulfonyl, fluoro, chloro, or bromo; and X is fluoro, chloro, or bromo. Thus, an alkyl 5-(2-aminophenyl)pyrazole-3-carboxylate is treated with phosgene in a large excess of pyridine to give the corresponding alkyl pyrazolo[1,5-c]quinazolin-5(6H)-one-2-carboxylate. The pyrazoloquinazolinone then is N-alkylated at the 6-position with an alkyl or aralkyl halide in the presence of a strong base, such as sodium hydride, and in the presence of a suitable solvent, such as N,N-dimethylformamide. The resulting 6-substituted pyrazoloquinazolinone is hydrolyzed to the corresponding 5-[2-(N-substituted amino)phenyl]pyrazole-3-carboxylic acid, typically by heating at reflux a mixture of the 6-substituted pyrazoloquinazolinone, potassium hydroxide, and aqueous ethanol. The reaction mixture then is cooled and made acidic with aqueous hydrochloric acid. The solid which forms is isolated by filtration and purified, if desired, according to known methods.

It will be apparent that in converting a compound of the present invention to a complement-inhibiting pyrazole-3-carboxylic acid, any carboxylic acid blocking group can be employed which is stable during the conversion and yet capable of being readily removed.

The activity of a complement-inhibiting pyrazole-3-carboxylic acid obtained as described above from a compound of the present invention is determined by the test procedure of W. T. Jackson, et al., reported at the 1971 Annual Meeting of the Federation of American Societies of Experimental Biology and abstracted in Federation Proceedings, Vol. 30, No. 2 (March–April), 1971.

The pyrazole-3-carboxylic acids obtained from compounds of the present invention are useful in inhibiting complement-induced hemolysis. Complement inhibitors find practical utility in the treatment of such diseases as glomerulo-nephritis, serum sickness, and certain inflammatory diseases such as rheumatoid arthritis.

Utilization of a complement inhibitor in general involves administering to a mammal parenterally, preferably intravenously or intraperitoneally, an effective amount of such a compound, typically at a dosage level sufficient to provide a concentration of the compound in the blood of from about 1 to about 400 μg/ml. Such a concentration on the average can be attained by the administration of a dose of from about 0.05 to about 32 mg/kg. The necessary concentration in the blood of complement inhibitor can be achieved by administering a single dose or up to about six smaller doses per day, depending upon the tolerance of the patient to the compound, persistence of the compound in the blood stream, and other factors. The complement inhibitor normally is formulated into a suitable pharmaceutical composition comprising the active ingredient in association with at least one pharmaceutically-acceptable carrier therefor by procedures well known in the art.

Suitable pharmaceutical carriers are described in E. W. Martin, et al., "Remington's Pharmaceutical Sciences," 14th Ed., Mack Publishing Company, Easton, Pa., 1965.

In addition to parenteral administration, the complement inhibitor can be administered to a mammal enterally, preferably orally. For enteral administration, the complement inhibitor normally is administered at a level of from about 1 to about 200 mg/kg of mammal body weight. Advantageously, the complement inhibitor is formulated in a dosage unit form containing from about 5 to about 500 mg, preferably from about 10 to about 150 mg, of active ingredient in association with suitable carriers, diluents, and the like.

The present invention is more fully described, without intending to limit it in any manner, by the following examples which illustrate the preparation of a compound of the present invention by means of the process of the present invention. In the examples, all temperatures are in degrees centigrade, unless otherwise specified.

EXAMPLE 1

Preparation of methyl 2-nitrobenzoylpyruvate

To a solution of 20 g of sodium methoxide and 43 g of dimethyl oxalate in 150 ml of methanol, under nitrogen and at a temperature of 0°, was added dropwise 60 g of 2-nitroacetophenone. The reaction mixture was allowed to warm slowly to ambient temperature and was stirred at ambient temperature overnight. To the solidified reaction mixture was added 125 ml of diethyl ether. The resulting slurry was filtered and the solid was washed thoroughly with additional diethyl ether. The dried solid was dissolved in about 1200 ml of water. The resulting solution was filtered to remove insoluble material. The filtrate was acidified with glacial acetic acid and cooled, and the precipitated solid was isolated by filtration to give, after drying, 77 g (84 percent) of methyl 2-nitrobenzoylpyruvate, mp 94°–95°. The following elemental analysis was obtained.

Calculated for $C_{11}H_9NO_6$:

C, 52.60; H, 3.61; N, 5.58; O, **38.22**

Found:

C, 52,38; H, 3.56; N, 5.44; O, **38.44**

EXAMPLE 2

Preparation of methyl 5-(2-nitrophenyl)pyrazole-3-carboxylate.

To a slurry of 77 g of methyl 2-nitrobenzoylpyruvate in 1600 ml of methanol at ambient temperature was added, in the dark, 11.5 ml of 85 percent hydrazine hydrate. The solution which resulted was allowed to stand in the dark overnight at ambient temperature. The reaction solution was distilled under reduced pressure, giving 56 g (75 percent) of methyl 5-(2-nitrophenyl)pyrazole-3-carboxylate. The following elemental analysis was obtained.

Calculated for $C_{11}H_9N_3O_4$:

C, 53.44; H, 3.67; N, 17.00; O, **25.89**

Found:

C, 53.42; H, 3.37; N, 17.26; O, **25.96**

EXAMPLE 3

Preparation of methyl 5-(2-aminophenyl)pyrazole-3-carboxylate.

Methyl 5-(2-nitrophenyl)pyrazole-3-carboxylate was reduced, using 25 g of the nitro compound, 570 ml of ethanol, 2.5 g of 5 percent palladium on activated charcoal, and an initial hydrogen pressure of 55 psig. The reduction required 1.5 hours, during which time the reaction temperature increased from ambient temperature to about 54°. Hydrogen uptake was 92 percent of theory. The reaction solution was treated with decolorizing carbon and filtered. The filtrate was distilled under reduced pressure to give 15 g (69 percent) of crude product which upon recrystallization from benzene/hexane gave 7.4 g of methyl 5-(2-aminophenyl)pyrazole-3-carboxylate, mp 131°–132°. The following elemental analysis was obtained.

Calculated for $C_{11}H_{11}N_3O_2$:

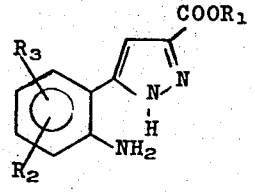
C, 60.82; H, 5.10; N, 19.34; O, **14.73**

Found:

C, 60.87; H, 5.0l; N, 19.52; O, **14.98**

What is claimed is:

1. A compound of the formula,



wherein R_1 is hydrogen or C_1–C_3 alkyl and R_2 and R_3 are monovalent groups independently selected from the group consisting of hydrogen, methyl, methoxy, fluoro, chloro, and bromo, with the limitation that R_2 and R_3 must be different unless each of R_2 and R_3 is hydrogen.

2. The compound of claim **1**, wherein R_1 is C_1–C_3 alkyl.

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