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PYRIDAZINONE ACETIC ACIDS AS ALDOSE REDUCTASE INHIBITORS

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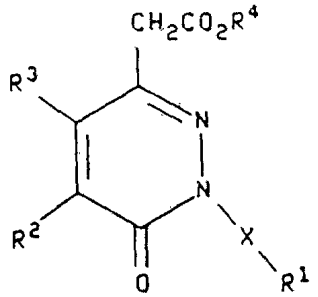
(57)

These compounds can also be used as hypouricemic agents, useful for lowering blood uric acid levels. The invention further relates to novel pharmaceutical compositions containing such compounds and to a method of using these compounds.

CLAIMS

1. A compound of the formula



I

wherein

X is CH_2, CH_2CH_2, $-CH(CH_3)$, or $-CH_2-\overset{Y}{\overset{\|}{C}}-NH$;

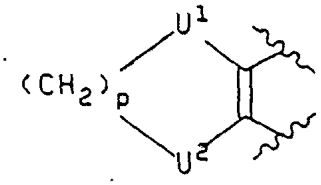
Y=O or S;

R^1 is benzothiazol-2-yl optionally substituted with one or two substitutents that are independently selected from

.../2

fluorine, chlorine, bromine, methyl, and trifluoromethyl;

R^2 and R^3 are independently selected from hydrogen, (C_1-C_4) alkyl, fluorine, chlorine, bromine, and trifluoromethyl or R^2 and R^3 taken together with the carbons to which they are attached form a group W, wherein W is



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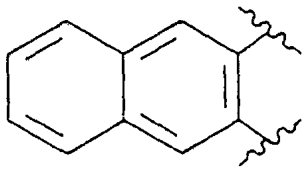
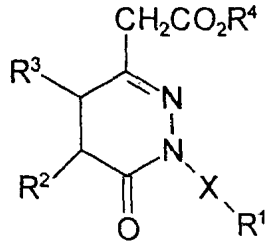


wherein p is 1 or 2 and U^1 and U^2 are independently CH_2, O or S with the proviso that both U^1 and U^2 are not O or S;

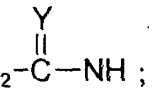
R^4 is hydrogen or a prodrug group;

or a pharmaceutically acceptable salt thereof.

9. A compound of the formula



wherein

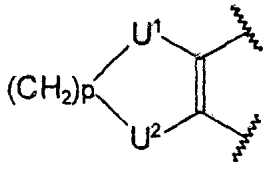
X is CH_2, CH_2CH_2, -CH(CH_3), or 

;

Y=O or S;

R^1 is an optionally substituted group selected from phenyl, benzoxazol-2-yl, benzofuran-2-yl, benzothiophen-2-yl, thiazolopyridin-2-yl, oxazolopyridin-2-yl, 3-phenyl 1,2,4-oxadiazol-5-yl, and 5-phenyl-1,2,4-oxadiazol-3-yl wherein said substituted groups are substituted with one or two substituents that are independently selected from fluorine, chlorine, bromine, methyl, and trifluoromethyl;

R^2 and R^3 are independently selected from hydrogen, (C_1-C_4) alkyl, fluorine, chlorine, bromine, and trifluoromethyl or R^2 and R^3 taken together with the carbons to which they are attached form a group W, wherein W is



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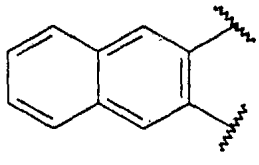

wherein p is 1 or 2 and U^1 and U^2 are independently CH_2, O or S with the proviso that both U^1 and U^2 are not O or S; R^4 is hydrogen or a prodrug group;

or a pharmaceutically acceptable salt thereof.

CORRECTED VERSION *

PCT

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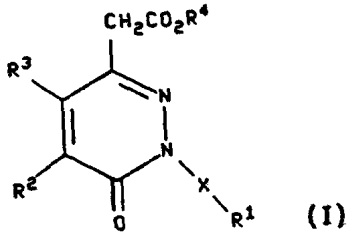
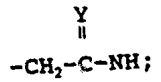
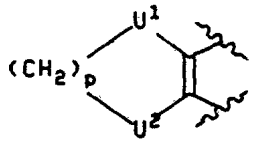


(I)



(a)



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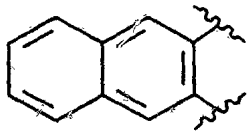


(c)

(57) Abstract

Compounds having aldose reductase inhibitory activity of formula (I) wherein X CH_2, CH_2CH_2, -$CHCH_3$, (a); Y = O or S; R^1 is an optionally substituted phenyl, benzothiazol-2-yl, benzoxazol-2-yl, benzofuran-2-yl, benzothiophen-2-yl, thiazolopyridin-2-yl, oxazolopyridin-2-yl, 3-phenyl 1,2,4-oxadiazol-5-yl, and 5-phenyl-1,2,4-oxadiazol-3-yl wherein said substituted groups are substituted with one or more and preferably two substituents that are independently selected from fluorine, chlorine, bromine, methyl, and trifluoromethyl; R^2 and R^3 are independently selected from hydrogen, fluorine, chlorine, bromine, (C_1-C_4) alkyl, methyl (C_1-C_4) alkylthio, (C_1-C_4) alkoxy and trifluoromethyl or R^2 and R^3 taken together with the carbons to which they are attached form a group W, wherein W is (b) or (c) wherein p is 1 or 2 and U^1 and U^2 are independently CH_2, O or S with the proviso that both U^1 and U^2 are not O or S; R^4 is hydrogen or a prodrug group; or a pharmaceutically acceptable salt thereof.

PYRIDAZINONE ACETIC ACIDS

Background of the Invention

This invention relates to novel pyridazinone acetic acids and derivatives thereof which are aldose reductase inhibitors and which are useful in the treatment of certain chronic complications arising from diabetes mellitus, such as diabetic cataracts, retinopathy, nephropathy and neuropathy. These compounds can also be used as hypouricemic agents, useful for lowering blood uric acid levels. The invention further relates to novel pharmaceutical compositions containing such compounds and to a method of using these compounds.

In the past, various attempts have been made to obtain more effective oral anti-diabetic agents. U.S. Patent No. 3,821,383 discloses aldose reductase inhibitors like 1,3-dioxo-1H-benz-[d,e]-isoquinoline-2-(3H)-acetic acid and derivatives thereof to be useful for the treatment of chronic complications of diabetes. U.S. Patent 4,226,875 teaches the use of spiro-oxazolidinediones for treating complications of diabetes as aldose reductase inhibitors. Such aldose reductase inhibitors function by inhibiting the activity of the enzyme aldose reductase, which is primarily responsible for regulating the reduction of aldoses, such as glucose and galactose, to the corresponding polyols, such as sorbitol and galactitol, in humans and other animals. In this way, unwanted accumulations of galactitol in the lens of galactosemic subjects and of sorbitol in the lens, peripheral nerves and kidneys of various diabetic subjects are prevented or reduced. Accordingly, such compounds are of therapeutic value as aldose reductase inhibitors for controlling certain chronic diabetic complications, including those of an ocular nature, since it is known in the art that the presence of polyols in the lens of the eye leads to cataract formation, with a concomitant loss of lens clarity.

French Patent Publication No. 2647676 relates to pyridazinone derivatives having substituted benzyl side

chains and benzothiazole side chains which are described as being inhibitors of aldose reductase.

U.S. Patent 4,251,528 discloses aromatic carbocyclic oxophthalazinyl acetic acids having aldose reductase inhibiting properties. The patent mentions that 2-(2-pyrid-2-ylethyl)-3,4-dihydro-4-oxophthalazin-1-ylacetic acid does not inhibit aldose reductase. Heterocyclic oxophthalazinyl acetic acids and their ethyl esters having an effect on the blood clotting system are disclosed in Chemical Abstracts 1970, 73, 77173y.

U.S. Patent No. 4,939,140 is directed to heterocyclic oxophthalazinyl acetic acids.

U. S. Patent No. 4,868,301 is directed to processes and intermediates for the preparation of oxophthalazinyl acetic acids having benzothiazole or other heterocyclic side chains.

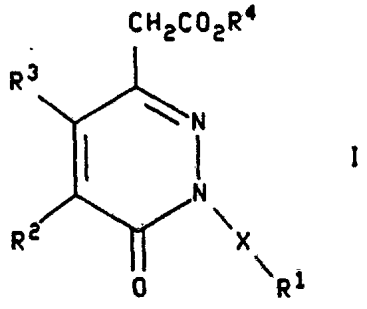
U. S. Patent No. 4,996,204 is directed to Pyridopyridazinone acetic acids.

European Patent Publication No. 0,397,350 is directed to a process and intermediates for the preparation of oxophthalazinyl acids and analogs thereof.

International Application No. PCT/US89/05637 relates to substituted oxophthalazinyl acetic acids and analogs thereof.

Summary of the Invention

The present invention relates to a compound of the formula



I

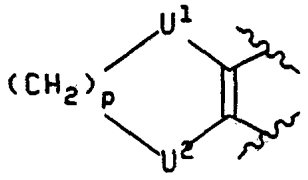
wherein

X is CH_2, CH_2CH_2, $-CH(CH_3)$ or $-CH_2-\overset{Y}{\overset{\|}{C}}-NH$;

Y = O or S;

R^1 is an optionally substituted group selected from phenyl, benzothiazol-2-yl, benzoxazol-2-yl, benzofuran-2-yl, benzothiophen-2-yl, thiazolopyridin-2-yl, oxazolopyridin-2-yl, 3-phenyl 1,2,4-oxadiazol-5-yl, and 5-phenyl-1,2,4-oxadiazol-3-yl wherein said substituted groups are substituted with one or two substituents that are independently selected from fluorine, chlorine, bromine, methyl, methylthio, methoxy, hydroxy and trifluoromethyl;

R^2 and R^3 are independently selected from hydrogen, fluorine, chlorine, bromine, (C_1-C_4)alkyl, (C_1-C_4)alkylthio, (C_1-C_4)alkoxy and trifluoromethyl or R^2 and R^3 taken together with the carbons to which they are attached form a group W, wherein W is



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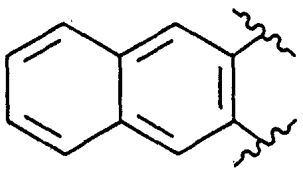


wherein p is 1 or 2 and U^1 and U^2 are independently CH_2, O or S with the proviso that both U^1 and U^2 are not O or S;

R^4 is hydrogen, or a prodrug group;

or a pharmaceutically acceptable salt thereof.

The present invention also relates to the pharmaceutically acceptable salts of the compounds of formula I. Such pharmaceutically acceptable salts include sodium, potassium, calcium and ammonium and those derived from lower alkylamines (e.g. ethylamine), lower alkanolamines (e.g. triethanolamine) and meglumine.

Specific preferred compounds of the invention are:

3,4-Dihydro-4-oxo-5,6-dimethyl-3-[(5,7 difluoro-2-benzothiazolyl)methyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-5,6-dimethyl-3-[(5-trifluoromethyl)-2-benzothiazoly)methyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-5,6-dimethyl-3-[[(2-fluoro-4-bromo)benzyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-5,6-cyclohexano-3[(5,7-difluoro-2-benzothiazolyl)methyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-5,6-cyclohexano-3-[[5(trifluoromethyl)-2-benzothiazolyl]methyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-5,6-cyclohexano-3-[(2-fluoro-4-bromo)benzyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-3-[(5,7-difluoro-2-benzothiazolyl)methyl]-1-pyridazineaceticacid;

3,4-Dihydro-4-oxo-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-6-methyl-3-[[5-trifluoromethyl]-2-benzothiazolyl]methyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-5,6-cyclopentano-3-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-1-pyridazineacetic acid;

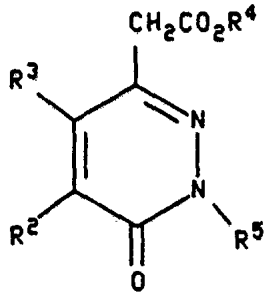
3,4-Dihydro-4-oxo-5,6-dimethyl-3-[(5-bromo-2-benzoxazolyl)methyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-5,6-dimethyl-3-[[3-(2,3-difluorophenyl)-1,2,4-oxadiazol-5-yl]-methyl]-1-pyridazineacetic acid; and

3,4-Dihydro-4-oxo-5,6-cyclohexano-3-[(5,7-dichloro-2-benzothiazolyl)methyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-5,6-dimethyl-3-[(5,7-dichloro-2-benzothiazolyl)methyl]-1-pyridazineacetic acid.

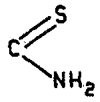
The present invention also relates to compounds which are useful as intermediates for preparing the compounds of formula I having the general formula:



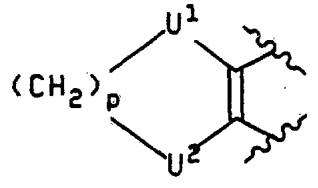
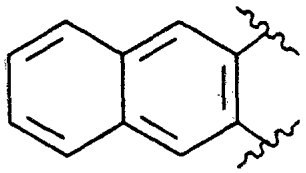
wherein

R^5 is hydrogen or XR^1 wherein

X is CH_2, CH_2CH_2, $-CH(CH_3)$, $-CH_2-\overset{O}{\overset{\|}{C}}-NH$ or $-CH_2-\overset{S}{\overset{\|}{C}}-NH$; and

R^1 is CN,  or an optionally substituted group selected from phenyl, benzothiazol-2-yl, benzoxazol-2-yl, benzofuran-2-yl, benzothiophen-2-yl, thiazolopyridin-2-yl, oxazolopyridin-2-yl, 3-phenyl 1,2,4-oxadiazol-5-yl, and 5-phenyl-1,2,4-oxadiazol-3-yl wherein said substituted groups are substituted with one or two substitutents that are independently selected from fluorine, chlorine, bromine, methyl, and trifluoromethyl;

R^2 and R^3 are independently selected from hydrogen, (C_1-C_4) alkyl, fluorine, chlorine, bromine, and trifluoromethyl or R^2 and R^3 taken together with the carbons to which they are attached form a group W, wherein W is

 or 

wherein p is 1 or 2 and U^1 and U^2 are independently CH_2, O or S with the proviso that both U^1 and U^2 are not O or S; and R^4 is (C_1-C_4)alkyl.

The present invention also relates to a pharmaceutical composition for inhibition of aldose reductase activity comprising a compound of formula I or a pharmaceutically

acceptable salt thereof in an amount effective in the inhibition of aldose reductase activity, in admixture with a pharmaceutically acceptable carrier. Specific and preferred compositions contain the specific and preferred compounds of formula I as described above.

The present invention further relates to a method of treating a diabetic host such as an animal or a human for diabetes-associated complications which comprises administering to the host an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof. Specific and preferred methods comprise administering specific and preferred compounds of formula I as described above.

The present invention further relates to a pharmaceutical composition which can be used for lowering blood uric acid levels in mammals, e.g., humans comprising a compound of formula I or a pharmaceutically acceptable salt thereof in an amount effective for lowering blood uric acid levels in a admixture with a pharmaceutically acceptable carrier.

The present invention also relates to a method of lowering blood uric acid levels in a mammalian subject which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof. Specific and preferred methods comprise administering specific and preferred compounds of formula I as described above.

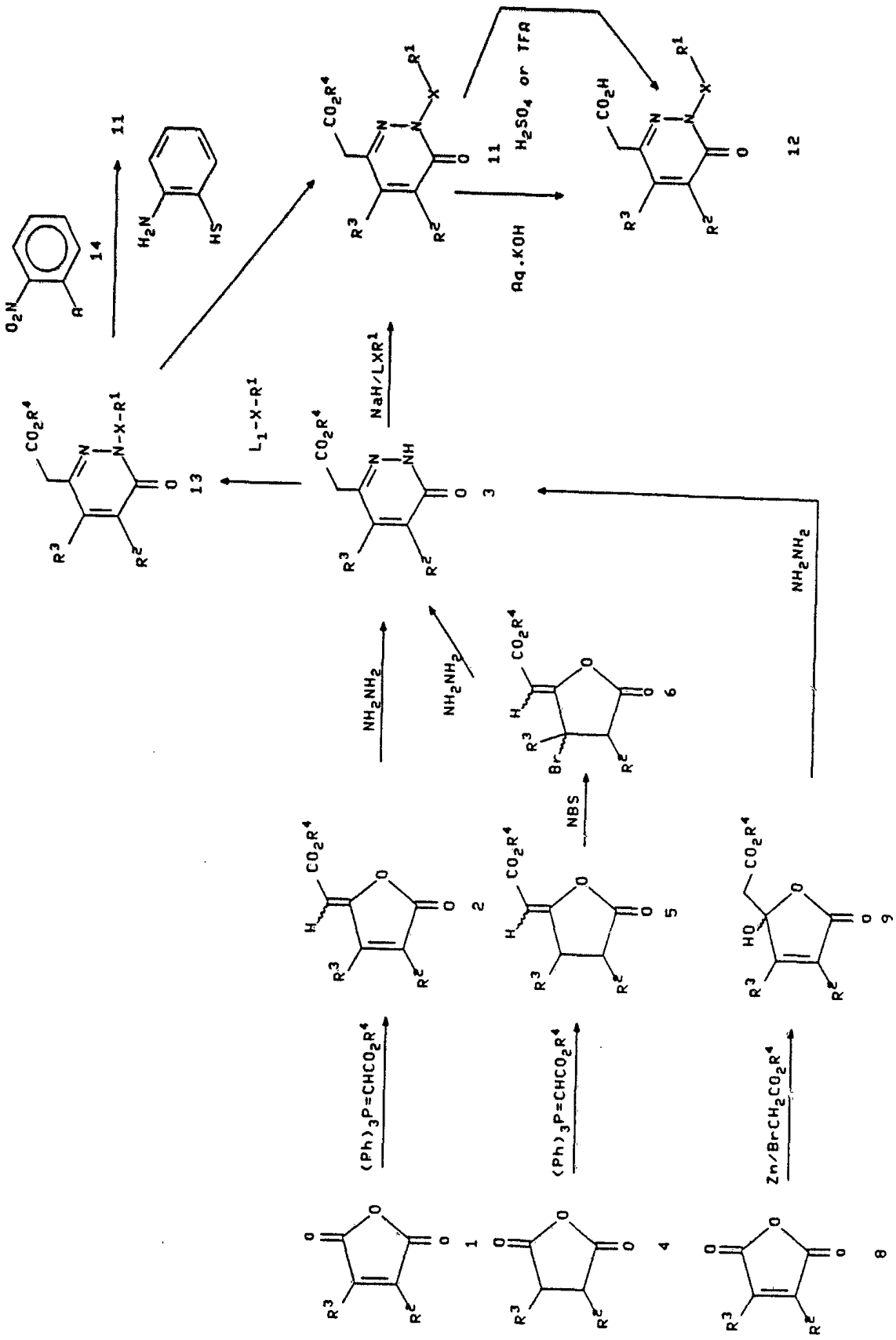
Detailed Description of the Invention

Unless otherwise indicated, the term "alkyl," as used herein, includes linear branched and cyclic groups as well as groups having both linear and cyclic or branched and cyclic portions.

The term "prodrug" as used in the definition of R^4 denotes a group that is converted in vivo resulting in replacement by hydrogen. Such groups are generally known in the art and include ester forming groups, to form an ester prodrug, such as benzyloxy, di(C_1-C_4)alkyl amino ethyloxy,

acetoxymethyl, pivaloyloxymethyl, phthalidoyl, ethoxy carbonyloxyethyl, 5-methyl-2-oxo-1,3-dioxol-4-yl methyl, and (C_1-C_4) alkoxy optionally substituted by N-morpholino and amide-forming groups such as di(C_1-C_4) alkylamino.

The compounds of the present invention are prepared as outlined in the following reaction scheme.


11
14
11
H_2SO_4 or TFA
Aq.KOH
12
L_1-X-R^1
NaH/LXR^1
13
3
NH_2NH_2
NH_2NH_2
NH_2NH_2
6
NBS
2
5
9
$(Ph)_3P=CHCO_2R^4$
$(Ph)_3P=CHCO_2R^4$
$Zn/BrCH_2CO_2R^4$
1
4
8

Anhydrides of formula 1,4 and 8 are either commercially available or may be prepared according to standard procedures. The compounds of formula 2 wherein R_3 is ethyl or t-butyl are prepared by reacting the compounds 1 with (t-butoxycarbonylmethylene)triphenylphosphorane or (carbothoxymethylene)triphenylphosphorane, respectively, in the Wittig reaction described in Tetrahedron Letters, 1965, 2537.

The compounds of formula 5 may also be prepared by the same procedure.

The compounds of formula 9 are obtained using standard Reformatsky reaction conditions with zinc or zinc-copper couple or using a variety of well-known modifications of the Reformatsky reaction (see, for example, Tetrahedron Letters, 1984, 2569). Suitable solvents for the conversion of 8 to 9 include aromatic hydrocarbons (e.g., benzene) and dialkyl ethers and cyclic ethers (e.g., tetrahydrofuran). The temperature is preferably maintained at about 35°C to about 100°C, more preferably at reflux.

A compound of the formula 6 is prepared by standard allylic bromination using N-bromosuccinic in refluxing carbon tetrachloride.

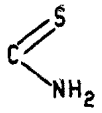
The compounds of formula 3 are prepared by reacting the compounds of formula 2, 6 or 9 with anhydrous or aqueous hydrazine in an alcoholic solvent (e.g., ethanol) at a temperature of about 20°C to about 80°C, preferably about 60°C. Thus the temperature may be room temperature or the reflux temperature of the solvent.

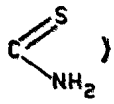
The compounds of formula 13 are obtained on reacting compounds of formula 3 with L-X-R^1 wherein L is chloro or bromo. The process is generally carried out in a polar solvent such as an alkanol having one to four carbon atoms (e.g. methanol or ethanol), dimethylformamide or dimethylsulfoxide, in the presence of a base. Suitable bases are alkali metal hydrides or alkoxides of one to four carbon atoms, such as sodium or potassium hydride, methoxide or ethoxide. When a hydride is used, a non-aqueous solvent

such as dimethylformamide is required. The reaction is run at room temperature, or at higher temperatures (about 100°C) to accelerate the process.

The compounds of formula 11 wherein R^1 is phenyl with hydroxy groups are prepared by demethylating the corresponding methoxy groups. Demethylation is effected by refluxing hydrobromic acid or borontribromide in methylene chloride at a temperature between about -70°C and about 0°C. The preferred temperature is between about -20°C and about 0°C.

The compounds of formula 11 wherein X is CH_2, CH_2CH_2 or $-CH(CH_3)$ and R^1 is optionally substituted benzothiazole are also prepared via the compounds of formula 13. The compounds of formula 13 wherein X is CH_2, CH_2CH_2, or $-CH(CH_3)$ and R^1 is CN are prepared by reacting compounds of formula 3 with L_1-X-R^1 (wherein L_1 is Cl or Br) in the presence of a base. Suitable bases are alkali metal hydrides or alkoxides of one to four carbon atoms. Suitable solvents for the reaction include non-aqueous solvents such as dimethylformamide and dimethylsulfoxide. The compounds of formula 13 wherein R^1 is CN are reacted with acid addition salts of 2-aminobenzenethiols or aminopyridinethiols (e.g., hydrochlorides) in C_1 to C_4 alkanols at a temperature from about 80°C to reflux temperature of the solvent to obtain compounds of the formula 11 wherein R^1 is optionally substituted benzothiazole. These procedures are also applicable to the preparation of compounds wherein R^1 is thiazolopyridine.

The compounds of formula 11 wherein R^1 is 5 or 7 monosubstituted or 5,7-disubstituted benzothiazole with substituents selected from fluorine, chlorine, bromine and trifluoromethyl are also prepared via compounds of the formula 13 wherein R^1 is CN or  . The compounds of formula 13 (wherein X is CH_2, CH_2CH_2, $CH(CH_3)$, R^1 is CN or

) are reacted with a compound of formula 14 where A is F, Cl, Br or I in the presence of hydrogen sulfide. Generally, the reaction is conducted in a polar solvent. Suitable solvents include sulfolane, pyridine and N-methyl pyrrolidone. The preferred solvent is dimethylformamide. The reaction temperature is generally between about 110°C and about 180°C, preferably the reflux temperature of the solvent. The compound of formula 13 wherein R^1 is CN is reacted with the compound of formula 14 in the presence of a tertiary amine. Suitable tertiary amines are tri-(C_2-C_6)alkylamines, e.g. triethylamine. These procedures are also applicable to the preparation of compounds wherein R^1 is thiazolopyridine. The compound of the formula 13 wherein X is CH_2, CH_2CH_2, or $CH(CH_3)$ and R^1 is  may be prepared by reacting a compound of the formula 13 wherein X is CH_2, CH_2CH_2 or $CH(CH_3)$ and R^1 is CN with hydrogen sulfide in the presence of tertiary amines such as tri (C_2-C_6)alkyl amines, e.g. triethylamine, in the presence of a solvent such as pyridine or dimethylformamide. Preferably, the reaction is conducted in dimethylformamide. Generally, the reaction is conducted at temperatures between about ambient temperature (generally, about 25°C) and about 100°C. Preferably, the reaction temperature is between about 40 and about 60°C.

Compounds of formula 11 wherein X is are prepared by reacting compounds of formula 11 wherein X is  with phosphorous pentasulfide in aromatic hydrocarbon solvents such as benzene, toluene or xylenes. The reaction is run at between room temperature and 100°C, preferably at between 40-60°C.

The compounds of formula 11 may be hydrolyzed to obtain compounds of formula 12. The hydrolysis is carried out in the presence of concentrated sulfuric acid or trifluoroacetic acid when R^4 is t-butyl at about 0°C to room temperature. When R^4 is methyl or ethyl, the hydrolysis proceeds at conventional temperatures and in the presence of acid or base such as mineral acid, for example hydrochloric acid, or an alkali metal hydroxide such as sodium or potassium hydroxide.

Unless otherwise indicated, the pressures of the foregoing reactions are not critical. Generally, the reaction pressures will be in the range of about 0.5 to 2 atmospheres, preferably ambient pressure (about one atmosphere).

The pharmaceutically acceptable salts of compounds of the formula I may be formed with pharmaceutically acceptable cations by conventional methods. Thus, these salts may be readily prepared by treating the compound of formula I with an aqueous solution of the desired pharmaceutically acceptable cation and evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, a lower alkyl alcohol solution of the compound of formula I may be mixed with an alkoxide of the desired metal and the solution subsequently evaporated to dryness. Suitable pharmaceutically acceptable cations for this purpose include, but are not limited to, alkali metal cations such as potassium and sodium, ammonium or water-soluble amine addition salts such as N-methylglucamine(meglumine), the lower alkanolammonium and other base salts with organic amines which are pharmaceutically acceptable, and alkaline earth metal cations such as calcium and magnesium.

The compounds of formula I and the pharmaceutically acceptable salts thereof (hereinafter, also referred to as the active compounds) are useful as inhibitors of the enzyme aldose reductase in the treatment of chronic complications of diabetes, such as diabetic cataracts, retinopathy nephropathy and neuropathy. The active compounds can also

be used for lowering blood uric acid levels in mammals, e.g. humans. Uric acid containing deposits (also known as trophi) resulting from unphysiologically elevated plasma uric acid levels tend to occur in various tissues throughout the body, leading to the disease condition known as gout and gouty arthritis. Uric acid containing deposits in such conditions may occur in cartilage, bone, bursae, tendons, connective tissue overlying bony prominences, as well as, subcutaneously and in the area of kidney. Elevated blood uric acid levels also occur in number of other disease conditions including myeloid leukemia, myeloid dysplasia, pernicious anemia, psoriasis, diabetes mellitus and renal disease. As used in the claims and specification hereof, treatment is meant to include both the prevention and alleviation of such conditions. The active compounds may be administered to a subject in need of treatment by a variety of conventional routes of administration, including orally, parenterally and topically. In general, these compounds will be administered orally or parenterally at dosages between about 2 and 100 mg/kg body weight of the subject to be treated per day, preferably from 5 to 50 mg/kg per day. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate does for the individual subject.

The active compounds may be administered alone or in combination with pharmaceutically acceptable carriers, in either single or multiple doses. Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. The pharmaceutical compositions formed by combining the active compounds and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms such as tablets, powders, lozenges, syrups, injectable solutions and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings,

binders, excipients and the like. Thus, for purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof.

For parenteral administration, solutions of an active compound in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, the sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

The active compounds may not only be advantageously employed for the preparation of aqueous pharmaceutical compositions for parenteral administration, as described above, but also for the preparation of pharmaceutical compositions suitable for use as ophthalmic solutions. Such ophthalmic solutions are of principal interest for the treatment of diabetic cataracts by topical administration

and the treatment of such conditions in this manner is a preferred embodiment of the present invention. Thus, for the treatment of diabetic cataracts the active compounds of this invention are administered to the eye of an ophthalmic preparation prepared in accordance with conventional pharmaceutical practice, see for example "Remington's Pharmaceutical Sciences" 15th Edition, pages 1488 to 1501 (Mack Publishing Co., Easton, Pa). The ophthalmic preparation will contain an active compound in a concentration from about 0.01 to about 1% by weight, preferably from about 0.05 to about 0.5% in a pharmaceutically acceptable solution, suspension or ointment. Some variation in concentration will necessarily occur, depending on the particular compound employed, the condition of the subject to be treated and the like, and the person responsible for treatment will determine the most suitable concentration for the individual subject. The ophthalmic preparation will preferably be in the form of a sterile aqueous solution containing, if desired, additional ingredients, for example preservatives, buffers, tonicity agents, antioxidants and stabilizers, nonionic wetting or clarifying agents, viscosity-increasing agents and the like. Suitable preservatives include benzalkonium chloride, benzothonium chloride, chlorobutanol, thimerosal and the like. Suitable buffers include boric acid, sodium and potassium bicarbonate, sodium and potassium borate, sodium and potassium carbonate, sodium acetate, sodium biphosphate and the like, in amounts sufficient to maintain the pH at between about 6 to 8, preferably between about 7 and 7.5. Suitable tonicity agents are dextran 40, dextran 70, dextrose, glycerin, potassium chloride, propylene glycol, sodium chloride, and the like, such that the sodium chloride equivalent of the ophthalmic solution is in the range 0.9 plus or minus 0.2%. Suitable antioxidants and stabilizers include sodium bisulfite, sodium metabisulfite, sodium thiosulfite, thiourea and the like. Suitable wetting and clarifying agents include polysorbate 80, polysorbate 20,

poloxamer 282 and tyloxapol. Suitable viscosity-increasing agents include dextran 40, dextran 70, gelatin, glycerin, hydroxyethylcellulose, hydromethylpropylcellulose, lanolin, methylcellulose, petrolatum, polyethylene glycol, polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose and the like. The ophthalmic preparation will be administered topically to the eye of the subject in need of treatment by conventional methods, for example in the form of drops or by bathing the eye in the ophthalmic solution.

The activity of the compounds of the present invention as agents for the control of chronic diabetic complications may be determined by a number of standard biological or pharmacological tests. Suitable tests include (1) measuring their ability to inhibit the enzyme activity of isolated aldose reductase; (2) measuring their ability to reduce or inhibit sorbitol accumulation in the sciatic nerve and lens of acutely streptozotocinized, i.e. diabetic, rats; (3) measuring their ability to reverse already-elevated sorbitol levels in the sciatic nerve and lens of chronic streptozotocin-induced diabetic rats; (4) measuring their ability to prevent or inhibit galactitol formation in the lens of acutely galactosemic rats; (5) measuring their ability to delay cataract formation and reduce the severity of lens opacities in chronic galactosemic rats; (6) measuring their ability to prevent sorbitol accumulation and cataract formation in isolated rat lens incubated with glucose; and (7) measuring their ability to reduce already elevated sorbitol levels in isolated rat lens incubated with glucose.

The present invention is illustrated by the following examples. It will be understood, however, that the invention is not limited to the specific details of these examples. In the examples, melting points are uncorrected.

Example 1

t-butyl 3,4-dihydro-4-oxo-5,6-dimethyl-3-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-1-pyridazine-1-ylacetate

A. 3-oxo-4,5-dimethylfuran-1-ylidene acetic acid t-butyl ester

A solution of 2,3-dimethylmaleic anhydride (6.3 g, 50 mmol) and (t-butoxycarbonylmethylene) triphenylphosphorane (20.7 g, 55 mmol) in methylene chloride (200 mL) was refluxed for 16 hours. The solution was evaporated to dryness and the residue was purified by flash chromatography on silica gel using a 9:1 mixture of methylene chloride and ethyl acetate to obtain 3-oxo-4,4-dimethylfuran-1-ylidene acetic acid t-butyl ester (yield: 6.5 g; 60%).

B. t-butyl 5,6-dimethyl-4-oxo-pyridazine-1-ylacetate

A mixture of the tile compound of Example 1A (1.3 g, 4 mmol), ethanol (5 mL) and hydrazine hydrate (3.9 mL, 8 mmol) was stirred at room temperature for 1 hour. The reaction mixture was diluted with water (2 mL) and acidified with acetic acid (4 mL). The precipitated solid was collected, washed with water and then air-dried to obtain the title compound (yield: 1.3 g; 92%).

C. t-butyl 3,4-dihydro-4-oxo-5,6-dimethyl-3-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-1-pyridazine-1-ylacetate

To a solution of the title compound of Example 1B (476 mg, 2 mmol) in dimethylformamide (4 mL) was added potassium t-butoxide (236 mg, 2.1 mmol) and stirred for 30 minutes at room temperature. 2-Chloromethyl-5-trifluoromethylbenzothiazole (554 mg, 2.2 mmol) was added to the reaction mixture and stirring continued for another 3 hours. The reaction was quenched with water (20 mL), acidified to pH by addition of sufficient dilute hydrochloric acid and extracted with ethyl acetate. The ethyl acetate layer was collected, evaporated to dryness and the residue was chromatographed over silica gel. Elution with a 9:1 mixture of methylene chloride and ethyl acetate gave the title

compound (yield: 490 mg; 54%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.45(s, 9H), 2.1(s, 3H), 2.2(s, 3H), 3.6(s, 2H), 5.7(s, 2H), 7.5(d, J=8 Hz, 1H), 7.9(m, 1H), 8.25(d, J= 8Hz, 1H).

Example 2

t-butyl 3,4-dihydro-4-oxo-5,6-dimethyl-3-[(4-bromo-2-fluoro)benzyl-1 pyridazine-1-ylacetate.

The title compound was prepared according to the procedure set forth in Example 1C (yield: 87%). ^{1}H NMR ($CDCl_3$, 250 MHz)δ 1.45 (s, 9H), 2.08(s, 3H), 2.15 (s, 3H), 3.54 (s, 2H), 5.3 (s, 2H), 7.2 (m, 3H).

Example 3

3,4-dihydro-4-oxo-5,6-dimethyl-3-[[5-(trifluoromethyl-2-benzothiazolyl]methyl]-1-pyridazine acetic acid

The title compound of Example 1 (450 mg, 1 mmol) was added to concentrated sulfuric acid (2 mL) and stirred at room temperature for 30 minutes. The reaction was quenched with ice-water (20 mL) and the resulting solid was collected. The solid was crystallized from benzene to provide the title compound (yield: 270 mg; 68%), m.p. 174°C.

Example 4

3,4-dihydro-4-oxo-5,6-dimethyl-3-[(4-bromo-2-fluoro)benzyl)-1-pyridazine acetic acid

The title compound of Example 2 (740 mg, 1.74 mmol) was added to trifluoroacetic acid (2 mL) and stirred at room temperature for 30 min. The reaction was quenched with ice-water (15 mL) and the precipitated solid was collected, air-dried and crystallized from benzene to obtain the title compound (yield: 115 mg; 33%), m.p. 162°C.

Example 5

3-oxo-4,5-dihydrofuran-1-ylacetic acid, t-butyl ester

The title compound was prepared according to Example 1A starting from succinic anhydride in place of 2,3-dimethylmaleic anhydride (1.98 g, 20 mmol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.5 (s, 9H), 2.72 (m, 2H), 3.35 (m, 2H), 5.62 (m, 1H).

Example 6

5-bromo-3-oxo-4,5-dihydrofuran-1-ylacetic acid, t-butyl ester

A mixture of the title compound of Example 5 N-bromosuccinimide (1.96 g, 11 mmol) and carbon tetrachloride (25 mL) was refluxed under a UV lamp for 4 hours. The reaction was cooled, excess carbon tetrachloride was evaporated and the residue was chromatographed on silica gel. Elution with a 1:1 mixture of methylene chloride and n-hexane gave the title compound (yield, 2.1.g; 76%), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.5 (s,9H), 3.1 (m, 1H), 3.4 (m, 1H), 5.6 (s, 1H), 5.8 (m, 1H).

Example 7

4-oxo-3-H-pyridazine-1-ylidene acetic acid t-butyl ester

To a solution of the title compound of Example 6 (2.77 g, 10 mmol) in ethanol (10 mL) was added hydrazine hydrate (1 mL, 20 mmol) and then stirred at room temperature for 16 h. Excess ethanol was evaporated and the concentrate was extracted with ethyl acetate (15 mL). The organic extract was washed with water, collected and evaporated to dryness. The residue was chromatographed over silica gel. Elution with a 1:1 mixture of methylene chloride and ethyl acetate gave the title compound (yield, 1.03 g; 49%), m.p. 135°C.

Example 8

t-butyl-1,3-dihydro-1-hydroxy-3-oxo-5-methyl-1-isofuran acetate

To a solution of citraconic anhydride (11.2 g, 0.1 mol) in tetrahydrofuran (50 mL) was added zinc-copper couple (15.0 g, 0.15 mol). Then t-butyl bromoacetate (23.4 g, 0.12 mol) was added slowly and then refluxed for 3 hours. The reaction was cooled, filtered and the filtrate was concentrated under vacuum. The residue was partitioned between 6N hydrochloric acid (20 mL) and ethyl acetate (250 mL). The organic extract was collected and evaporated to dryness. The residue was chromatographed over silica gel. Elution with a 1:1 mixture of methylene chloride and ethyl

acetate gave the title compound (yield, 6.2; 27%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s,9H), 2.05 (s,3H), 5.85 (s,1H).

Example 9

t-butyl 5-methyl-4-oxo-pyridazine-1-ylacetate

The title compound of Example 8 was dissolved in ethanol (20 mL) and hydrazine hydrate (0.6 g, 12 mmol) was added to the solution. After stirring for 4 h at room temperature, the solution was concentrated by removing excess ethanol and the concentrate was triturated with 1N hydrochloric acid (10 mL). The resulting solid was collected, air-dried and crystallized from ethanol to obtain the title compound (yield, 0.58 g; 24%), m.p. 114-116°C.

Example 10

(E) and (Z) 3-oxo-4,5-cyclohexanofuran-1-ylideneacetic acid t-butyl ester

The title compound was prepared in 46% yield (11.1 g) according to Example 1A, starting from 3,4,5,6-tetrahydrophthalic anhydride in place of 2,3-dimethylmaleic anhydride (15.2 g, 0.1 mol). This mixture of E and Z isomers was chromatographed over silica gel and eluted with a 9:1 mixture of methylene chloride and ethyl acetate. The less polar E isomer was eluted first. The more polar Z isomer was obtained from later fractions.

Example 11

t-butyl 3,4-dihydro-4-oxo-5,6-cyclohexanopyridazine-1-ylacetate

A mixture of (E) and (Z) 3-oxo-4,5-cyclohexanofuran-1-ylideneacetic acid t-butyl ester (5.0 g, 20 mmol) (The title compound of Example 10) was dissolved in ethanol (20 mL) and to the solution was added hydrazine hydrate (2.5 g, 50 mmol). This was refluxed for 4 h and then evaporated to a gummy residue. This was triturated with 1N hydrochloric acid (10 mL) to obtain the title compound as a white solid (yield, 2.18 g; 44%), m.p. 179-181°C.

Example 12

t-Butyl 3,4-dihydro-4-oxo-5,6-dimethyl-3-cyanomethyl-1-pyridazineacetate

To a solution of the title compound of Example 1B (7.05 g, 29.6 mmol) in DMF (65 ml) was added potassium tertbutoxide (3.65 g, 32.5 mmol) and stirred at ambient temperature for 30 min. Bromoacetonitrile (4.26 g, 35.5 mmol) was added to it and stirring was continued for another 1.5 h. The reaction was quenched with water (200 mL), acidified to pH 2 by addition of sufficient dilute hydrochloric acid and the resulting solid was collected. The solid was air-dried and then crystallised from a 3:1 mixture of cyclohexane and methylene chloride (6.26 g, 76%); mp, 120-123°C.

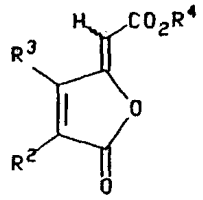
Example 13

Ethyl 3,4-dihydro-4-oxo-5,6-cyclohexano-3-cynanomethyl-1-pyridazineacetate

The title compound (liquid) was prepared according to Example 12, but starting from ethyl 5,6-cyclohexano-1-phthalazineacetate (yield, 58%); ^{1}HNMR ($CDCl_3$, 300 MHz) δ 1.25 (t, J=Hz, 3H), 1.8 (m,4H), 2.4 (m,2H), 2.6 (m, 2H), 4.1 (q, J=8 Hz, 2H), 5.0 (s, 2H).

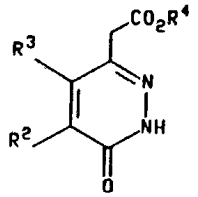
Additional compounds prepared in accordance with the present invention are shown in Tables 1-3. Tables 1-3 include melting point or NMR spectrum for the compounds described.

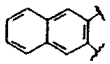
Table 1



R^2	R^3	R^4	Product
CH_3	CH_3	t-Bu	m.p.73-74C
$(CH_2)_3$		Et	m.p.64-65°C
$(CH_2)_4$		t-Bu	E-isomer, ^1H NMR($CDCl_3$, 250 MHz)δ 1.48(s, 9H), 1.73(m, 4H), 2.3(m, 2H), 2.75(m, 2H), 5.8(s,1H). Z-isomer, ^1H NMR ($CDCl_3$, 250 MHZ)δ 1.53 (s,9H), 1.75 (m, 4H), 2.35(m,4H), 5.25 (2, 1H)

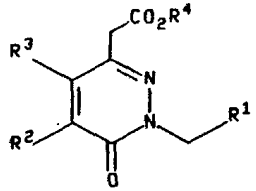
Table 2



R^2	R^3	R^4	Product
H	H	t-Bu	see Example 7
H	CH_3	t-Bu	see Example 9
CH_3	CH_3	t-Bu	see Example 1B
$(CH_2)_3$		Et	^1H NMR ($CDCl_3$, 250 MHz) δ 1.2 (t, J=8 MHz, 3H), 2.1 (m, 2H), 2.9 (m, 4H), 3.6 (s, 2H), 4.2 (q, J=8 MH2, 2H)
$(CH_2)_4$		t-Bu	see Example 11
		Et	m.p. 240-242°C

PCT/US92/01603

Table 3



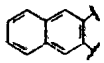
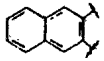
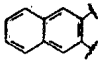
R^2	R^3	R^4	R^1	Product
H	H	t-Bu	5,7-difluorobenzothiazol-2-yl	m.p. 119°C
H	H	t-Bu	5-trifluoromethylbenzothiazol-2-yl	m.p. 134°C
H	CH_3	t-Bu	5-trifluoromethylbenzothiazol-2-yl	^{1}H NMR ($CDCl_3$, 250 MHZ)δ 1.45(s,9H), 2.17(s,3H), 3.55(s, 2H), 5.7(s. 2H), 6.72(m, 1H), 7.5(m, 1H), 7.92(m, 1H), 8.25(m. 1H)
CH_3	CH_3	t-Bu	5-trifluoromethylbenzothiazol-2-yl	Example 1C
CH_3	CH_3	t-Bu	5,7-difluorobenzothiazol-2-yl	^{1}H NMR ($CDCl_3$, 250 MHz)δ 1.45(s, 9H), 2.13(s,3H), 2.2(s, 3H), 3.6(s, 2H), 5.7(s, 2H), 6.9(m, 1H), 7.53(m, 1H)
CH_3	CH_3	t-Bu	4-bromo-2-fluorophenyl	Example 2
$(CH_2)_3$		Et	5,-trifluoromethylbenzothiazol-2yl	^{1}H NMR ($CDCl_3$, 200 MHz)δ 1.2(t, J=8Hz,3H),2.1(m,2H), 2.9(m, 4H), 3.6(s, 2H), 4.15 (q, J = 8Hz, 2H), 5.8(s,2H), 7.5(d, J = 9Hz, 1H), 7.6(d, J = 9Hz, 1H), 8.2 (s, 1H)

Table 3 (continued)

R^2	R^3	R^4	R^1	Product
$(CH_2)_4$		H	5-trifluoromethylbenzothiazol-2-yl	m.p. 201°C
$(CH_2)_4$		t-Bu	5-trifluoromethylbenzothiazol-2-yl	m.p. 136°C
$(CH_2)_4$		t-Bu	5,7-difluorobenzothiazol-2-yl	^{1}H NMR($CDCl_3$, 250 MHz) δ 1.45(2,9H), 1.73(m, 4H), 2.4(m, 2H), 2.63(m, 2H), 3.55(s, 2H), 5.3(s, 2H), 6.9(m, 1H), 7.6 (m, 1H)
$(CH_2)_4$		t-Bu	4-bromo-2-fluorophenyl	^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.45(s, 9H), 1.72(m, 4H), 2.4(m, 1H), 2.58(m,2H), 3.51(s,2H), 5.27(s, 2H), 7.2 (m, 3H)
H	H	H	5,7-difluorobenzothiazol-2-yl	m.p. 169°C
H	H	H	5-trifluoromethylbenzothiazol-2-yl	m.p.172-173°C
H	CH_3	H	5-trifluoromethylbenzothiazol-2-yl	m.p. 172°C
CH_3	CH_3	H	5-trifluoromethylbenzothiazol-2-yl	m.p 174°C
CH_3	CH_3	H	5,7-difluorobenzothiazol-2yl	m.p. 183°C
CH_3	CH_3	H	5-bromobenzoxazol-2-yl	m.p. 206-207°C
CH_3	CH_3	H	[3-(2,3-difluorophenyl)-1,2, 4-oxadiazol-5-yl]	m.p. 185-186°C
CH_3	CH_3	H	4-bromo-2-fluorophenyl	m.p. 162°C

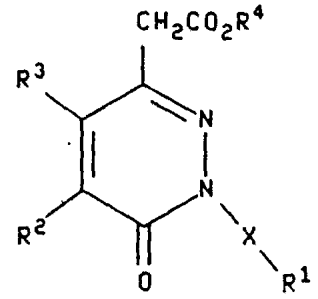
- 25 -

Table 3 (continued)

R^2	R^3	R^4	R^1	Product
$(CH_2)_3$		H	5-trifluoromethylbenzothiazol-2-yl	m.p. 184°C
$(CH_2)_4$		H	5-trifluoromethylbenzothiazol-2-yl	m.p. 201°C
$(CH_2)_4$		H	5,7-difluorobenzothiazol-2-yl	m.p. 157°C
$(CH_2)_4$		H	4-bromo-2-fluorophenyl	m.p. 164°C
		H	4-bromo-2-fluorophenyl	m.p. 202-204°C
		H	benzothiazol-2-yl	m.p. 207-208°C
		H	5-trifluoromethylbenzothiazol-2-yl	m.p. 224-225°C
CH_3	CH_3	t-Bu	5,7-dichlorobenzothiazol-2-yl	m.p. 113-116°C
$(CH_2)_4$		Et	5,7-dichlorobenzothiazol-2-yl	m.p. 136-139°C
CH_3	CH_3	H	5,7-dichlorobenzothiazol-2-yl	m.p 200-201.5°C
$(CH_2)_4$		H	5,7-dichlorobenzothiazol-2-yl	m.p. 193-195°C

CLAIMS

1. A compound of the formula



I

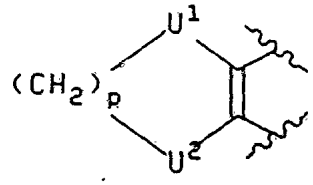
wherein

X is CH_2, CH_2CH_2, $-CH(CH_3)$, or $-CH_2-\overset{\overset{Y}{\|}}{C}-NH$;

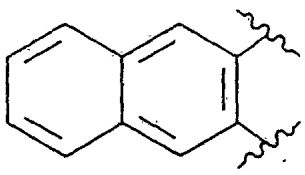
Y=O or S;

R^1 is benzothiazol-2-yl optionally substituted with one or two substitutents that are independently selected from fluorine, chlorine, bromine, methyl, and trifluoromethyl;

R^2 and R^3 are independently selected from hydrogen, (C_1-C_4) alkyl, fluorine, chlorine, bromine, and trifluoromethyl or R^2 and R^3 taken together with the carbons to which they are attached form a group W, wherein W is



or



wherein p is 1 or 2 and U^1 and U^2 are independently CH_2, O or S with the proviso that both U^1 and U^2 are not O or S;

R^4 is hydrogen or a prodrug group;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein X is CH_2, R^4 is hydrogen and R^2 and R^3 are each hydrogen or methyl or R^2 is hydrogen and R^3 is methyl or R^2 and R^3 taken together form a cyclohexyl ring or a cyclopentyl ring.

3. A compound according to claim 1 selected from the group consisting of:

3,4-Dihydro-4-oxo-5,6-dimethyl-3-[(5,7-difluoro-2-benzothiazolyl)methyl]-1-pyridazineacetic acid;

3,4,-Dihydro-4-oxo-5,6-dimethyl-3-[(5-trifluoromethyl)-2-benzothiazolyl)methyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-5,6-cyclohexano-3-[(5,7-difluoro-2-benzothiazolyl)methyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-5,6-cyclohexano-3-[[5(trifluoromethyl)-2-benzothiazolyl]methyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-3[(5,7-difluoro-2-benzothiazolyl)methyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-1-pyridazineacetic acid;

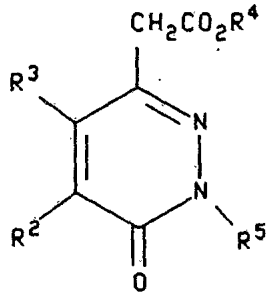
3,4-Dihydro-4-oxo-6-methyl-3-[[5-trifluoromethyl]-2-benzothiazolyl]methyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-5,6-cyclopentano-3-[[5(trifluoro-methyl)-2-benzothiazolyl]methyl]-1-pyridazineacetic acid.

3,4-Dihydro-4-oxo-5,6-cyclohexano-3-[(5,7-dichloro-2-benzothiazolyl)methyl]-1-pyridazineacetic acid; and

3,4-Dihydro-4-oxo-5,6-dimethyl-3-[(5,7-dichloro-2-benzothiazolyl)methyl]-1-pyridazineacetic acid.

4. A compound of the formula



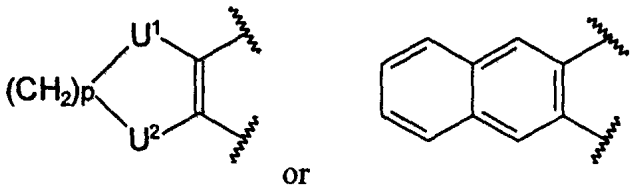
wherein

R^5 is hydrogen or XR^1 wherein

X is CH_2, CH_2CH_2, $-CH(CH_3)$, $-CH_2-\overset{O}{\overset{\|}{C}}-NH$ or $-CH_2-\overset{S}{\overset{\|}{C}}-NH$; and

R^1 is benzothiazol-2-yl optionally substituted with one or two substituents that are independently selected from fluorine, chlorine, bromine, methyl, and trifluoromethyl;

R^2 and R^3 are independently selected from hydrogen, $(C_1\text{-}C_4)$ alkyl, fluorine, chlorine, bromine, and trifluoromethyl or R^2 and R^3 taken together with the carbons to which they are attached form a group W, wherein W is



or

wherein p is 1 or 2 and U^1 and U^2 are independently CH_2, O or S with the proviso that both U^1 and U^2 are not O or S; and R^4 is $(C_1\text{-}C_4)$alkyl.

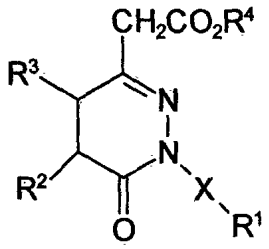
5. A compound according to claim 4 wherein R^2 and R^3 are each methyl, R^4 is $-C(CH_3)_3$ and R^5 is hydrogen.

6. A compound according to claim 4 wherein R^2 and R^3 taken together form a cyclohexyl ring, R^4 is ethyl and R^5 is hydrogen.

7. A compound according to claim 4 wherein R^2 and R^3 are each methyl, R^5 is XR^1 wherein X is CH_2, and R^4 is $-C(CH_3)_3$.

8. A compound according to claim 4 wherein R^2 and R^3 taken together form a cyclohexyl ring, R^5 is XR^1 wherein X is CH_2, and R^4 is ethyl.

9. A compound of the formula



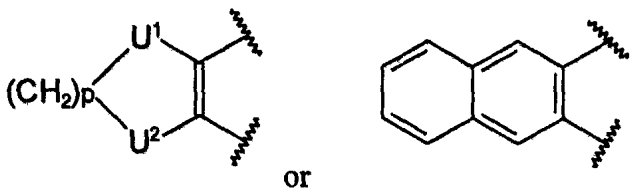
wherein

X is CH_2, CH_2CH_2, $-CH(CH_3)$, or  ;

Y=O or S;

R^1 is an optionally substituted group selected from phenyl, benzoxazol-2-yl, benzofuran-2-yl, benzothiophen-2-yl, thiazolopyridin-2-yl, oxazolopyridin-2-yl, 3-phenyl 1,2,4-oxadiazol-5-yl, and 5-phenyl-1,2,4-oxadiazol-3-yl wherein said substituted groups are substituted with one or two substituents that are independently selected from fluorine, chlorine, bromine, methyl, and trifluoromethyl;

R^2 and R^3 are independently selected from hydrogen, $(C_1\text{-}C_4)$ alkyl, fluorine, chlorine, bromine, and trifluoromethyl or R^2 and R^3 taken together with the carbons to which they are attached form a group W, wherein W is

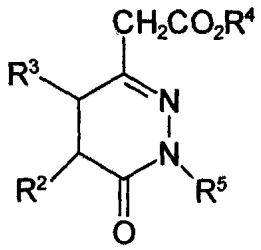


or

wherein p is 1 or 2 and U^1 and U^2 are independently CH_2, O or S with the proviso that both U^1 and U^2 are not O or S; R^4 is hydrogen or a prodrug group;

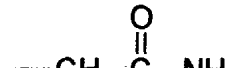
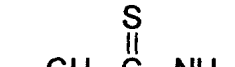
or a pharmaceutically acceptable salt thereof.

10. A compound of the formula

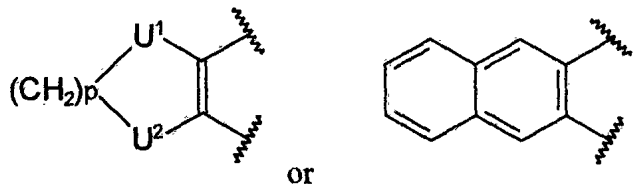


wherein

R^5 is hydrogen or XR^1 wherein

X is CH_2, CH_2-CH_2, -$CH(CH_3)$,  or  ; and R^1 is CN,  or an optionally substituted group selected from phenyl, benzoxazol-2-yl, benzofuran-2-yl, benzothiophen-2-yl, thiazolopyridin-2-yl, oxazolopyridin-2-yl, 3-phenyl 1,2,4-oxadiazol-5-yl, and 5-phenyl-1,2,4-oxadiazol-3-yl wherein said substituted groups are substituted with one or two substituents that are independently selected from fluorine, chlorine, bromine, methyl, and trifluoromethyl;

R^2 and R^3 are independently selected from hydrogen, $(C_1$-$C_4)$ alkyl, fluorine, chlorine, bromine, and trifluoromethyl or R^2 and R^3 taken together with the carbons to which they are attached form a group W, wherein W is



or

wherein p is 1 or 2 and U^1 and U^2 are independently CH_2, O or S with the proviso that both U^1 and U^2 are not O or S; and R^4 is $(C_1$-$C_4)$alkyl.

11. A compound according to claim 9 wherein R^1 is optionally substituted benzoxazol-2-yl or 3-phenyl-1,2,4-oxadiazol-5-yl.

12. A compound according to claim 9 wherein X is CH_2, R^1 is optionally substituted benzoxazol-2-yl, or 3-phenyl-1,2,4-oxadiazol-5-yl, R^2 and R^3 are each methyl, and R^4 is hydrogen.

13. A compound according to claim 9 selected from the group consisting of:

3,4-Dihydro-4-oxo-5,6-dimethyl-3-[(2-fluoro-4-bromo)benzyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-5,6-cyclohexano-3-[(2-fluoro-4-bromo)benzyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-5,6-dimethyl-3-[(5-bromo-2-benzoxazolyl)methyl]-1-pyridazineacetic acid; and

3,4-Dihydro-4-oxo-5,6-dimethyl-3-[[3-(2,3-difluorophenyl)-1,2,4-oxadiazol-5-yl]-methyl]-1-pyridazineacetic acid.

14. A pyridazinone acetic acid compound or derivative thereof, substantially as hereinbefore described with reference to the Examples.

15. A pharmaceutical composition for inhibition of aldose reductase activity comprising a compound of any one of claims 1 to 14 in an amount effective in the inhibition of aldose reductase activity in admixture with a pharmaceutically acceptable carrier.

16. A method of inhibiting aldose reductase activity in a diabetic host, comprising administering to the host an effective amount of a compound of any one of claims 1 to 14 or a composition of claim 15.

17. A pharmaceutical composition for lowering blood uric acid levels comprising a compound of any one of claims 1 to 14 in an amount effective for lowering blood uric acid levels in admixture with a pharmaceutically acceptable carrier.

18. A method for lowering blood uric acid levels in a mammalian subject, which comprises administering to a mammal in need of lowering of blood uric acid levels an effective amount of a compound of any one of claims 1 to 14 or a composition of claim 17.

Dated 23 January, 1995

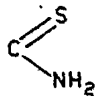
Pfizer Inc.

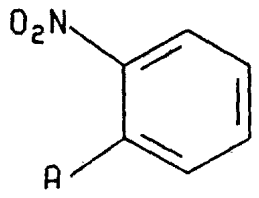
Patent Attorneys for the Applicant/Nominated Person

SPRUSON & FERGUSON

the compound of Formula I so formed to a pharamaceutically acceptable salt or prodrug thereof; or

(e) cyclocondensing a compound of the formula III above wherein

R^1 is CN,  , R^2 and R^3 are as defined above and R^4 is C_1-C_4 alkyl and X is CH_2, CH_2CH_2,$CH(CH_3)$ with a compound of the formula



wherein A is F, Cl, Br or I in a polar solvent in the presence of hydrogen sulfide; and

f. hydrolyzing the resulting compound in accordance with step (b) above to form a compound of Formula I wherein R^4 is hydrogen, and if desired, converting the compound of Formula I so formed to a pharmaceutically acceptable salt or prodrug thereof.

14. A process according to claim 13 wherein X is CH_2, R^4 is hydrogen and R^2 and R^3 are each hydrogen or methyl or R^2 is hydrogen and R^3 is methyl or R^2 and R^3 taken together form a cyclohexyl ring or a cyclopentyl ring.

15. A process according to claim 13 wherein said compound is selected from the group consisting of:

3,4-Dihydro-4-oxo-5,6-dimethyl-3-[(5,7-difluoro-2-benzothiazolyl)methyl]-1-pyridazineacetic acid;

3,4,-Dihydro-4-oxo-5,6-dimethyl-3-[(5-trifluoromethyl)-2-benzothiazolyl)methyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-5,6-cyclohexano-3-[(5,7-difluoro-2-benzothiazolyl)methyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-5,6-cyclohexano-3-[[5(trifluoromethyl)-2-benzothiazolyl]methyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-3[(5,7-difluoro-2-benzothiazolyl)methyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-1-pyridazineacetic acid;

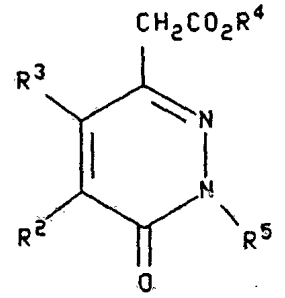
3,4-Dihydro-4-oxo-6-methyl-3-[[5-trifluoromethyl]-2-benzothiazolyl]methyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-5,6-cyclopentano-3-[[5(trifluoromethyl)-2-benzothiazolyl]methyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-5,6-cyclohexano-3-[(5,7-dichloro-2-benzothiazolyl)methyl]-1-pyridazineacetic acid; and

3,4-Dihydro-4-oxo-5,6-dimethyl-3-[(5,7-dichloro-2-benzothiazolyl)methyl]-1-pyridazineacetic acid.

16. A process for the preparation of a compound of the formula



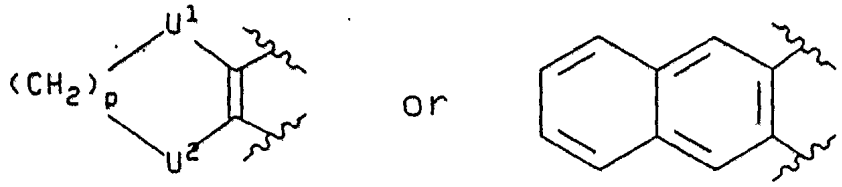
wherein

R^5 is hydrogen or XR^1 wherein

X is CH_2, CH_2CH_2, $-CH(CH_3)$, $-CH_2-\overset{O}{\overset{\|}{C}}-NH$ or $-CH_2-\overset{S}{\overset{\|}{C}}-NH$; and

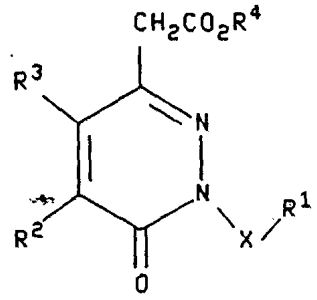
R^1 is benzothiazol-2-yl optionally substituted with one or two substitutents that are independently selected from fluorine, chlorine, bromine, methyl, and trifluoromethyl;

R^2 and R^3 are independently selected from hydrogen, (C_1-C_4) alkyl, fluorine, chlorine, bromine, and trifluoromethyl or R^2 and R^3 taken together with the carbons to which they are attached form a group W, wherein W is



wherein p is 1 or 2 and U^1 and U^2 are independently CH_2, O or S with the proviso that both U^1 and U^2 are not O or S; and R^4 is (C_1-C_4)alkyl comprising:

reacting a compound of the formula



III

wherein

X is $-\overset{O}{\overset{\|}{C}}-NH$ with phosphorous pentasulfide in the presence of an aromatic hydrocarbon solvent.

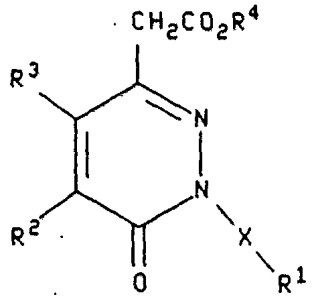
17. A process according to claim 16 wherein R^2 and R^3 are each methyl, R^4 is $-C(CH_3)_3$ and R^5 is hydrogen.

18. A process according to claim 16 wherein R^2 and R^3 taken together form a cyclohexyl ring, R^4 is ethyl and R^5 is hydrogen.

19. A process according to claim 16 wherein R^2 and R^3 are each methyl, R^5 is XR^1 wherein X is CH_2, and R^4 is $-C(CH_3)_3$.

20. A process according to claim 16 wherein R^2 and R^3 taken together form a cyclohexyl ring, R^5 is XR^1 wherein X is CH_2, and R^4 is ethyl.

21. A compound of the formula



I

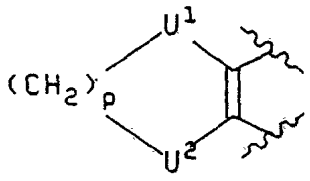
wherein

X is CH_2, CH_2CH_2, $-CH(CH_3)$, or $-CH_2-\overset{Y}{\overset{\|}{C}}-NH$;

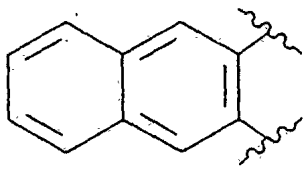
Y=O or S;

R^1 is an optionally substituted group selected from benzoxazol-2-yl, benzofuran-2-yl, benzothiophen-2-yl, thiazolopyridin-2-yl, oxazolopyridin-2-yl, 3-phenyl 1,2,4-oxadiazol-5-yl, and 5-phenyl-1,2,4-oxadiazol-3-yl wherein said substituted groups are substituted with one or two substitutents that are independently selected from fluorine, chlorine, bromine, methyl, and trifluoromethyl;

R^2 and R^3 are independently selected from hydrogen, (C_1-C_4) alkyl, fluorine, chlorine, bromine, and trifluoromethyl or R^2 and R^3 taken together with the carbons to which they are attached form a group W; wherein W is



or

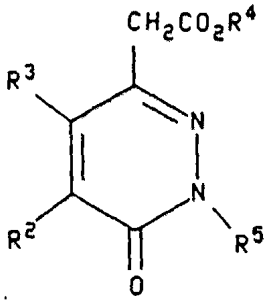


wherein p is 1 or 2 and U^1 and U^2 are independently CH_2, O or S with the proviso that both U^1 and U^2 are not O or S;

R^4 is hydrogen or a prodrug group;

or a pharmaceutically acceptable salt thereof.

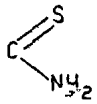
22. A compound of the formula



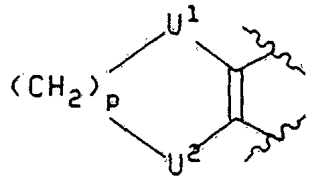
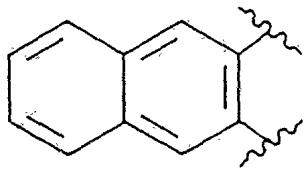
wherein

R^5 is hydrogen or XR^1 wherein

X is CH_2, CH_2CH_2, $-CH(CH_3)$, $-CH_2-\overset{O}{\overset{\|}{C}}-NH$ or $-CH_2-\overset{S}{\overset{\|}{C}}-NH$; and

R^1 is CN,  or an optionally substituted group selected from benzoxazol-2-yl, benzofuran-2-yl, benzothiophen-2-yl, thiazolopyridin-2-yl, oxazolopyridin-2-yl, 3-phenyl 1,2,4-oxadiazol-5-yl, and 5-phenyl-1,2,4-oxadiazol-3-yl wherein said substituted groups are substituted with one or two substitutents that are independently selected from fluorine, chlorine, bromine, methyl, and trifluoromethyl;

R^2 and R^3 are independently selected from hydrogen, (C_1-C_4) alkyl, fluorine, chlorine, bromine, and trifluoromethyl or R^2 and R^3 taken together with the carbons to which they are attached form a group W, wherein W is

 or 

wherein p is 1 or 2 and U^1 and U^2 are independently CH_2, O or S with the proviso that both U^1 and U^2 are not O or S; and R^4 is (C_1-C_4)alkyl.

23. A compound according to Claim 21 wherein R^1 is optionally substituted benzoxazol-2-yl or 3-phenyl-1,2,4-oxadiazol-5-yl.

24. A compound according to claim 21 wherein X is CH_2, R^1 is optionally substituted benzoxazol-2-yl, or 3-phenyl-1,2,4-oxadiazol-5-yl, R^2 and R^3 are each methyl, and R^4 is hydrogen.

25. A compound according to claim 21 selected from the group consisting of:

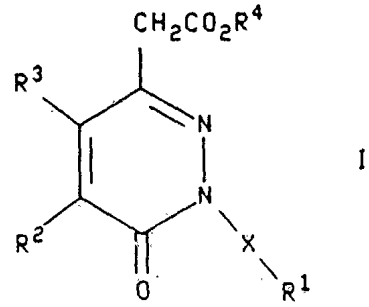
3',4-Dihydro-4-oxo-5,6-dimethyl-3-[[(2-fluoro-4-bromo)benzyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-5,6-cyclohexano-3-[(2-fluoro-4-bromo)benzyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-5,6-dimethyl-3-[(5-bromo-2-benzoxazolyl)methyl]-1-pyridazineacetic acid; and

3,4-Dihydro-4-oxo-5,6-dimethyl-3-[[3-(2,3-difluorophenyl)-1,2,4-oxadiazol-5-yl]-methyl]-1-pyridazineacetic acid.

26. A process for the preparation of a compound of the formula



I

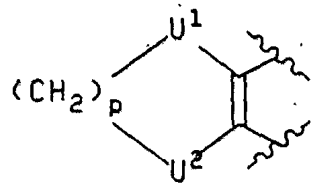
wherein

X is CH_2, CH_2CH_2, $-CH(CH_3)$, or $-CH_2-\overset{Y}{\overset{\|}{C}}-NH$;

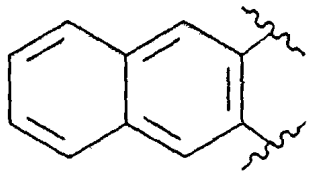
Y=O or S;

R^1 is an optionally substituted group selected from benzoxazol-2-yl, benzofuran-2-yl, benzothiophen-2-yl, thiazolopyridin-2-yl, oxazolopyridin-2-yl, 3-phenyl 1,2,4-oxadiazol-5-yl, and 5-phenyl-1,2,4-oxadiazol-3-yl wherein said substituted groups are substituted with one or two substitutents that are independently selected from fluorine, chlorine, bromine, methyl, and trifluoromethyl;

R^2 and R^3 are independently selected from hydrogen, (C_1-C_4) alkyl, fluorine, chlorine, bromine, and trifluoromethyl or R^2 and R^3 taken together with the carbons to which they are attached form a group W, wherein W is



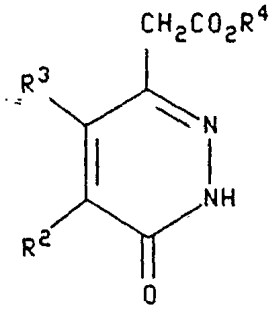
or



wherein p is 1 or 2 and U^1 and U^2 are independently CH_2, O or S with the proviso that both U^1 and U^2 are not O or S; R^4 is hydrogen or a prodrug group;

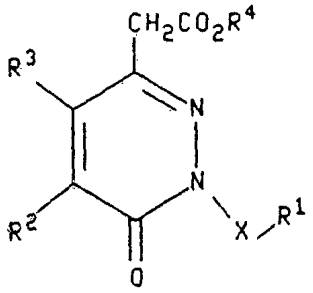
comprising:

(a) alkylating a compound of the formula



II

wherein R^2, and R^3 are as defined above and R^4 is C_1-C_4 alkyl with an alkylating agent of the formula L-X-R^1 wherein L is a leaving group such as chloro or bromo and X and R^1 are as defined above in the presence of a base to obtain a compound of the formula



III

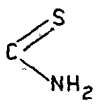
wherein R^1 is CN or optionally substituted benzothiazole; R^2 and R^3 are as defined above, R^4 is C_1-C_4 alkyl, X is CH_2, CH_2CH_2 or $-CH(CH_3)$; and

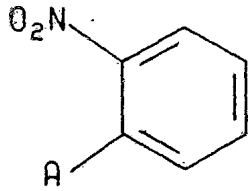
(b) hydrolyzing the compound of formula III with a strong acid or aqueous base, to form a compound of Formula I wherein R^4 is hydrogen, and if desired, converting a compound of Formula I so formed to a pharmaceutically acceptable salt or prodrug thereof; or

(c) cyclocondensing a compound of the formula III above wherein R^1 is CN; R^2 and R^3 are as defined above and R^4 is C_1-C_4 alkyl, X is CH_2, CH_2CH_2 or $-CH(CH_3)$ with substituted 2-aminobenzenethiol and acid addition salts in the presence of a polar solvent; and

(d) hydrolyzing the resulting compound of (c) in accordance with step (b) above, to form a compound of formula I wherein R^4 is hydrogen, and if desired, converting the compound of Formula I so formed to a pharamaceutically acceptable salt or prodrug thereof; or

(e) cyclocondensing a compound of the formula III above wherein

R^1 is CN,  , R^2 and R^3 are as defined above and R^4 is C_1-C_4 alkyl and X is CH_2, CH_2CH_2,$CH(CH_3)$ with a compound of the formula



wherein A is F, Cl, Br or I in a polar solvent in the presence of hydrogen sulfide; and

f. hydrolyzing the resulting compound in accordance with step (b) above to form a compound of Formula I wherein R^4 is hydrogen, and if desired, converting the compound of Formula I so formed to a pharmaceutically acceptable salt or prodrug thereof.

27. A process according to Claim 26 wherein R^1 is optionally substituted benzoxazol-2-yl or 3-phenyl-1,2,4-oxadiazol-5-yl.

28. A process according to claim 26 wherein X is CH_2, R^1 is optionally substituted benzoxazol-2-yl, or 3-phenyl-1,2,4-oxadiazol-5-yl, R^2 and R^3 are each methyl, and R^4 is hydrogen.

29. A process according to claim 26 wherein said compound is selected from the group consisting of:

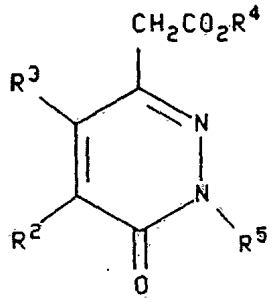
3,4-Dihydro-4-oxo-5,6-dimethyl-3-[[(2-fluoro-4-bromo)benzyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-5,6-cyclohexano-3-[(2-fluoro-4-bromo)benzyl]-1-pyridazineacetic acid;

3,4-Dihydro-4-oxo-5,6-dimethyl-3-[(5-bromo-2-benzoxazolyl)methyl]-1-pyridazineacetic acid; and

3,4-Dihydro-4-oxo-5,6-dimethyl-3-[[3-(2,3-difluorophenyl)-1,2,4-oxadiazol-5-yl]-methyl]-1-pyridazineacetic acid.

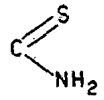
30. A process for the preparation of a compound of the formula



wherein

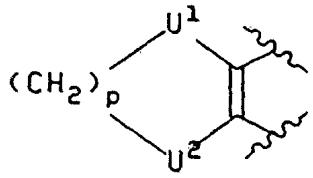
R^5 is hydrogen or XR^1 wherein

X is CH_2, CH_2CH_2, $-CH(CH_3)$, $-CH_2-\overset{O}{\overset{\|}{C}}-NH$ or $-CH_2-\overset{S}{\overset{\|}{C}}-NH$; and

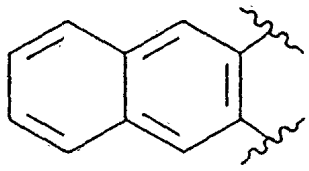
R^1 is CN,  or an optionally substituted group selected from benzoxazol-2-yl, benzofuran-2-yl, benzothiophen-2-yl, thiazolopyridin-2-yl, oxazolopyridin-2-yl, 3-phenyl 1,2,4-oxadiazol-5-yl, and 5-phenyl-1,2,4-oxadiazol-3-yl wherein said substituted groups are substituted with one or two substitutents that are

independently selected from fluorine, chlorine, bromine, methyl, and trifluoromethyl;

R^2 and R^3 are independently selected from hydrogen, (C_1-C_4) alkyl, fluorine, chlorine, bromine, and trifluoromethyl or R^2 and R^3 taken together with the carbons to which they are attached form a group W, wherein W is

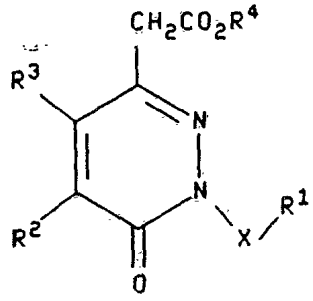


or



wherein p is 1 or 2 and U^1 and U^2 are independently CH_2, O or S with the proviso that both U^1 and U^2 are not O or S; and R^4 is (C_1-C_4)alkyl comprising:

reacting a compound of the formula



III

wherein

X is $-\overset{\overset{O}{\|}}{C}-NH$ with phosphorous pentasulfide in the presence of an aromatic hydrocarbon solvent.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/01603

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

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

Int.Cl. 5 C07D237/14; C07D417/06; C07D413/06; C07D405/06
C07D237/36; C07D237/26; A61K31/50

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	FR,A,2 647 676 (LABORATOIRES UPSA) 7 December 1990 cited in the application see page 26 - page 38	1,6,12, 16
A	EP,A,0 295 051 (PFIZER) 14 December 1988 cited in the application see claims	1,6,12, 16

* Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published 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; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
27 OCTOBER 1992	02. 11. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	FRANCOIS J.C.

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9201603 SA 59837

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 27/10/92

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
FR-A-2647676	07-12-90	None		
EP-A-0295051	14-12-88	AU-B-	593742	15-02-90
		AU-A-	1749188	15-12-88
		JP-A-	64003173	06-01-89
		SU-A-	1678208	15-09-91
		US-A-	4868301	19-09-89
		US-A-	4900844	13-02-90