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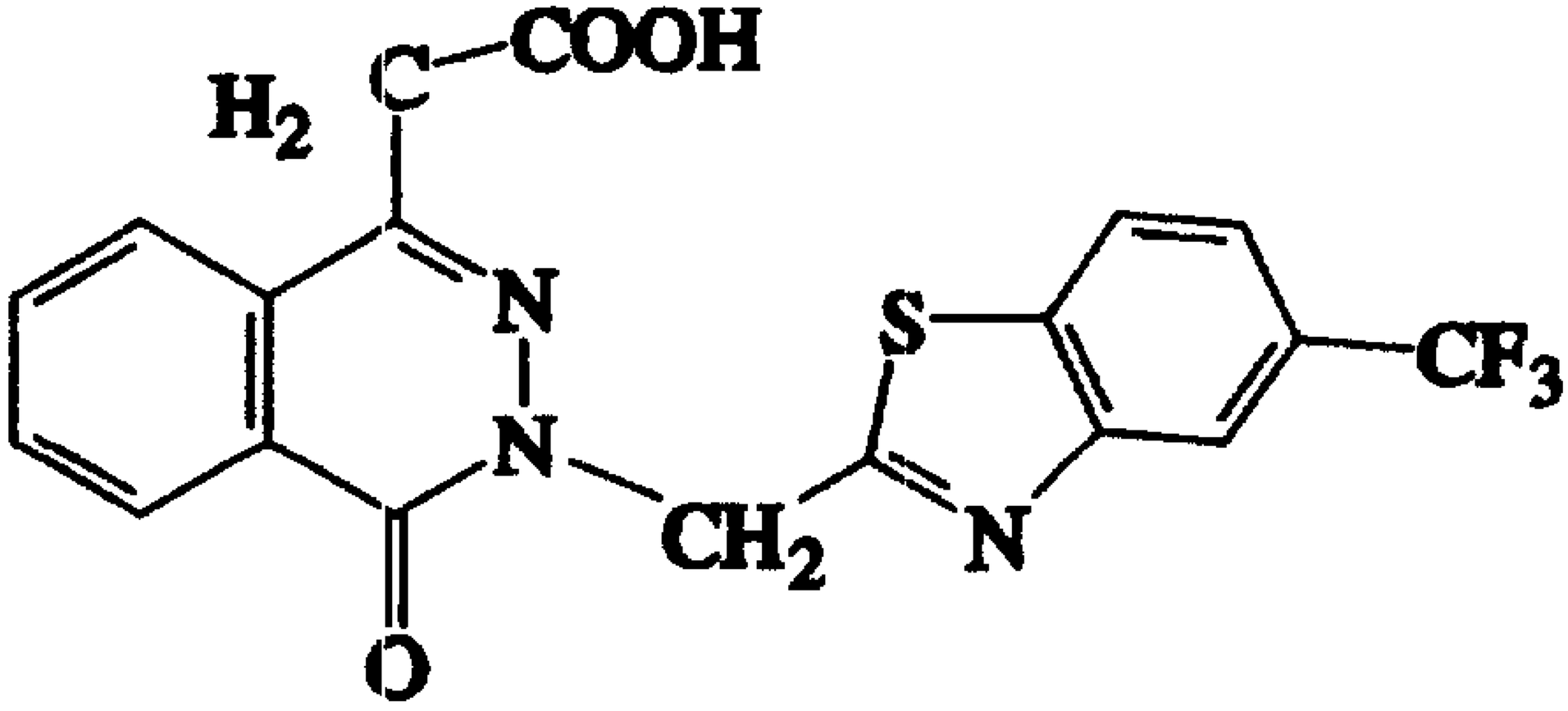
(72) Inventeur/Inventor:
JOHNSON, Brian Frank, US

(73) Propriétaire/Owner:
PFIZER INC., US

(74) Agent: SMART & BIGGAR

(54) Titre : INHIBITION DE L'ALDOSE REDUCTASE DANS LA PREVENTION OU LE TRAITEMENT OU LA RETROCESSION DE LA CARDIOMYOPATHIE DIABETIQUE

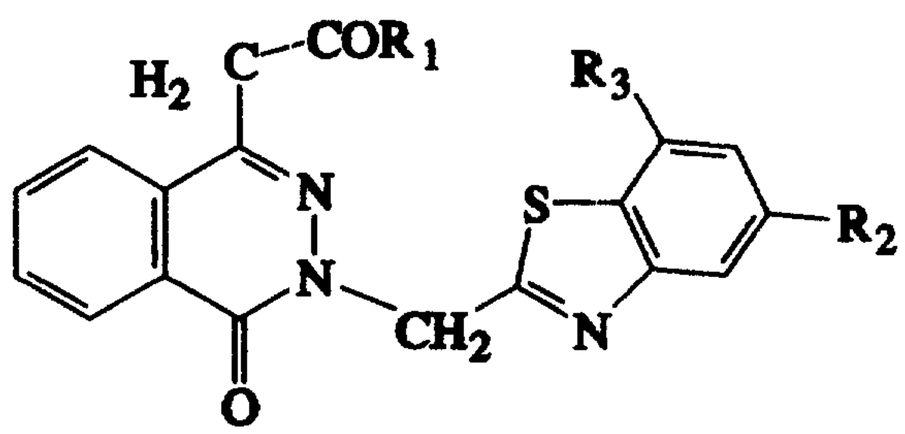
(54) Title: ALDOSE REDUCTASE INHIBITION IN PREVENTING OR REVERSING DIABETIC CARDIOMYOPATHY



(57) Abrégé/Abstract:
Disclosed is use of aldose reductase inhibitors in the treatment, prevention or reversal of diabetic cardiomyopathy in a human subject. The aldose reductase inhibitor, for example may be a compound of the formula: (see above formula) (wherein R_1 is OH or a prodrug group capable of being removed in vivo to produce a compound of formula I wherein R_1 is OH; and R_2 and R_3 are the same or different and are selected from the group consisting of hydrogen, trifluormethyl, fluoro, chloro and bromo) or a pharmaceutically acceptable salt thereof, e.g., zopolrestat.

ABSTRACT

Disclosed is use of aldose reductase inhibitors in the treatment, prevention or reversal of diabetic cardiomyopathy in a human subject. The aldose reductase inhibitor, for example may be a compound of the formula:



(I)

(wherein R_1 is OH or a prodrug group capable of being removed *in vivo* to produce a compound of formula I wherein R_1 is OH; and R_2 and R_3 are the same or different and are selected from the group consisting of hydrogen, trifluormethyl, fluoro, chloro and bromo) or a pharmaceutically acceptable salt thereof, e.g., zopolrestat.

ALDOSE REDUCTASE INHIBITION IN PREVENTING OR REVERSING DIABETIC CARDIOMYOPATHY

FIELD OF THE INVENTION

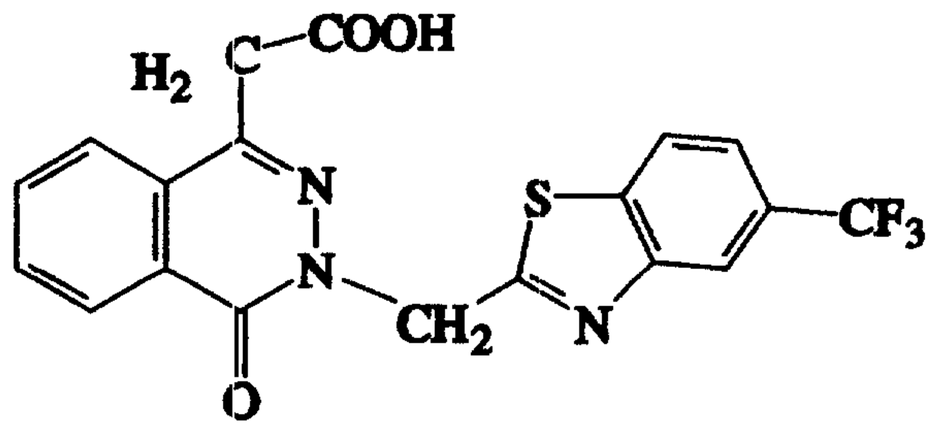
This invention relates to the use of aldose reductase inhibitors in the treatment or reversal of diabetic cardiomyopathy in a human subject.

BACKGROUND OF THE INVENTION

Of all identified diabetic sequelae, perhaps the most physiologically deleterious are those complications involving the cardiovascular system. These may, for exarnple, involve the blood or nervous supply to the heart or the heart muscle (myocardium) directly. An associated disease state related to myocardial abnormalities is diabetic cardiomyopathy, an affliction in which subjects afflicted therewith manifest such symptomes as, inter alia, an overall reduction in cardiac performance, reduced ventricular compliance as characterized by slowed, incomplete cardiac filling (diastolic dysfunction), an increased incidence of congestive heart failure and a markedly enhanced potential for death during episodes of myocardial infarction. Moreover, secondary indicators such as the development of interstitial and myocellular tissue abnormalities (including interstitial, perivascular and focal scar-like connective tissue accumulations) may be present in addition to microangiopathy (including thickening of the capillary basement membrane, pericapillary edema and capillary microaneurysms). These characteristic abnormalities define the syndrome of diabetic cardiomyopathy. Detailed discussions of this condition may be found, for example, in F. S. Fein, et. al., "Diabetic Cardiomyopathy", Cardiovascular Drugs and Therapy, Vol. 8, pp. 65-73, 1994, and D. S. H. Bell, "Diabetic Cardiomyopathy", Diabetes Care, Vol. 18, pp. 708-714, 1995 and pertinent references cited therein.

Aldose reductase inhibitors constitute a class of compounds which have become well known for their utility in the treatment of certain diabetic complications such as ocular cataract formation and diabetic neuropathy and nephropathy. Such compounds are well known to those skilled in the art and may be identified by standard biological methodology.

The compound zopolrestat, 3,4-dihydro-4-oxo-3-(5-trifluoromethylbenzothiazol-2-ylmethyl)phthalazin-1-ylacetic acid, is known, for example, from commonly assigned U.S. Patent 4,939,140, together with a number of related compounds, as having utility as aldose reductase inhibitors. Zopolrestat has the structure:



and, as in aldose reductase inhibitor, has utility in the treatment of certain complications arising from diabetes mellitus.

Other aldose reductase inhibitors are known to have use in the lowering of lipid levels in mammals, including humans. See, for example, U.S. Patent 4,492,706 and EP 0 310 931 A2, as well as commonly assigned U.S. Patent 5,391,551.

Commonly assigned U.S. Patent 5,064,830 discloses the use of certain oxophthalazinyl acetic acids, including zepolrestat, for the lowering of blood uric acid levels.

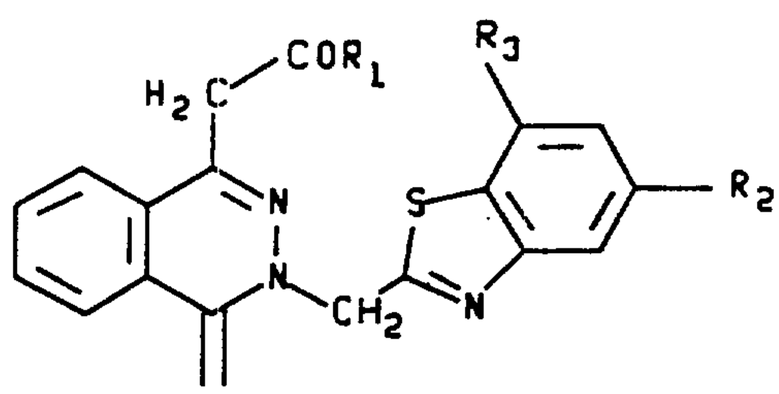
SUMMARY OF THE INVENTION

This invention is directed to medicine (i.e., pharmaceutical composition) for treating, or reversing diabetic cardiomyopathy in a human subject. The medicine comprises a therapeutically effective amount of an aldose

reductase inhibitor and a pharmaceutically acceptable carrier.

An aspect of the invention is directed to a commercial package which comprises a container, the medicine contained therein and a written matter which states that the medicine should or can be made for treating or reversing diabetic cardiomyopathy in a human subject.

Of particular interest in the medicine of the instant invention are certain compounds of structure (I), including zopolrestat, and their pharmaceutically acceptable salts as described hereinbelow:



(I)

DETAILED DESCRIPTION OF THE INVENTION

Any aldose reductase inhibitor may be employed as the active agent in treating or reversing diabetic cardiomyopathy according to the method of this invention.

As employed herein, the term "treatment" is specifically intended to incorporate partial prevention or prevention which, although greater than that which would result from taking no drug or from taking placebo, is less than 100% in addition to complete or substantially complete prevention. Therefore, the active compound may be employed prophylactically to prevent, blunt or stem the onset of diabetic cardiomyopathy in those patients who are deemed to be at particular risk. Additionally, the term "reversal" is also intended to include partial reversal or reversal which, although greater than that resulting from taking no drug or placebo, is less than 100% in addition to complete or substantially complete reversal.

The term "aldose reductase inhibitor" refers to compounds which function by inhibiting the activity of the enzyme aldose reductase, which is primarily responsible for regulating the metabolic reduction of aldoses, like glucose or galactose, to their corresponding polyols, such as sorbitol and galactitol, in the body. Progressive, abnormal accumulation of these polyol metabolites in the tissues of diabetic patients is invariably associated with major complications such as neuropathy, ocular cataract formation, nephritis, nephropathy, etc.

A variety of aldose reductase inhibitors are disclosed and referenced below. However, additional aldose reductase inhibitors will also be known to those skilled in the art. Where applicable, the common USAN names or other designations are shown in parentheses, together with reference to the appropriate patent literature disclosing the compound.

1. 3-(4-bromo-2-fluorobenzyl)-3,4-dihydro-4-oxo-1-phthalazineacetic acid (ponalrestat, U.S. 4,251,528);

2. N-[6-methoxythio-5-(trifluoromethyl)-1-naphthoyl]sarcosine (tolrestat, U.S. 4,600,724);

3. 5-[Z,E)-β-methylcinnamylidene]-4-oxo-2-thioxo-3-thiazolideneacetic acid (epalrestat, U.S. 4,464,382, U.S. 4,791,126, and U.S. 4,831,045);

4. 3-(4-bromo-2-fluorobenzyl)-7-chloro-3,4-dihydro-2,4-dioxo-1(2H)-quinazolineacetic acid (zenarestat, U.S. 4,734,419, and U.S. 4,883,800);

5. 2R, 4R-6,7-dichloro-4-hydroxy-2-methylchroman-4-acetic acid (U.S. 4,883,410);

6. 2R, 4R-6,7-dichloro-6-fluoro-4-hydroxy-2-methylchroman-4-acetic acid (U.S. 4,883,410);

7. 3,4-dihydro-2,8-diisopropyl-3-oxo-2H-1,4-benzoxazine-4-acetic acid (U.S. 4, 771,050);

8. 3,4-dihydro-3-oxo-4-[(4,5,7-trifluoro-2-benzothiazolyl)methyl]-2H-1,4-benzothiazine-2-acetic acid (SPR-210, U.S. 5,252,571);

9. N-[3,5-dimethyl-4-[(nitromethyl)sulfonyl]phenyl]-2-methyl-benzeneacetamide (ZD 5522, U.S. 5,270,342 and U.S. 5,430,060);

10. (S)-6-fluorospiro[chroman-4,4'-imidazolidine]-2,5'-dione (sorbinil, U.S. 4,130,714);

11. d-2-methyl-6-fluoro-spiro(chroman-4', 4'imidazolidine)-2', 5'-dione (U.S. 4,540,704);

12. 2 -fluoro-spiro(9H-fluorene-9, 4'-imidazolidine)-2', 5'-dione (U.S. 4,438,272);

13. 2,7-di-fluoro-spiro(9H-fluorene-9, 4'-imidazolidine)-2', 5'-dione (U.S. 4, 436,745, and U.S. 4,438,272);

14. 2,7-di-fluoro-5-methoxy-spiro(9H-fluorene-9, 4'-imidazolidine)-2', 5'-dione (U.S. 4, 436,745, and U.S. 4,438,272);

15. 7-fluoro-spiro(5H-indenol[1,2b]pyridine-5, 3'-pyrrolidine)-2,5'-dione (U.S. 4,436,745, and U.S. 4,438,272);

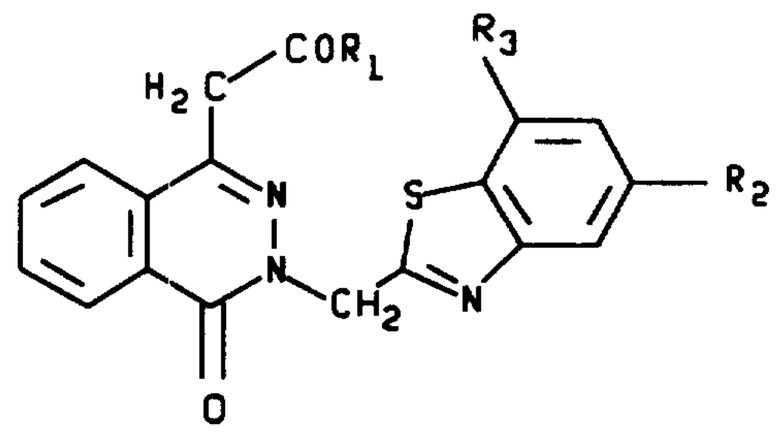
16. d-cis-6'-chloro-2', 3'-dihydro-2-'methyl-spiro-(imidazolidine-4,4'-4'-H-pyrano(2,3-b)pyridine)-2,5-dione (U.S. 4,980,357);

17. spiro[imidazolidine-4,5'-(6H)-quinoline]-2,5-dione-3'-chloro-7', 8'-dihydro-7'-methyl-(5'-cis) (U.S. 5,066,659);

18. (2S, 4S)-6-fluoro-2', 5'-dioxospiro(chroman-4,4'-imidazolidine)-2-carboxamide (US 5,447,964); and

19. 2-[(4-bromo-2-fluorophenyl)methyl]-6-fluoro-spiro[isoquinoline-4-(1H), 3'-pyrrolidine]-1, 2', 3, 5'-(2H)-tetrone (WAY-121509, U.S. 5,037,831).

Other compounds useful in the method of this invention are those compounds of formula (I) or the pharmaceutically acceptable salts thereof, wherein R_1 is hydroxy or a prodrug group capable of being removed in vivo to form a compound of formula (I) wherein R_1 is hydroxy; and R_2 and R_3 are the same or different and are selected from the group consisting of hydrogen, trifluoromethyl, fluoro, chloro, and bromo.



(I)

Specific compounds of formula (I) which are particularly useful in the method provided by this invention include (with reference to values in formula (I) shown in brackets): 3,4-dihydro-4-oxo-3-(5-trifluoromethylbenzothiazol-2-ylmethyl)phthalazin-1-ylacetic acid (R_1 is OH; R_2 is CF_3 and R_3 is H); 3,4-dihydro-4-oxo-3-(5-fluorobenzothiazol-2-ylmethyl)phthalazin-1-ylacetic acid (R_1 is OH; R_2 is F and R_3 is H); 3,4-dihydro-4-oxo-3-(5-chlorobenzothiazol-2-ylmethyl)phthalazin-1-ylacetic acid (R_1 is OH; R_2 is Cl and R_3 is H); 3,4-dihydro-4-oxo-3-(5-bromobenzothiazol-2-ylmethyl)phthalazin-1-ylacetic acid (R_1 is OH; R_2 is Br and R_3 is H); 3-(5,7-difluorobenzothiazol-2-ylmethyl)-3,4-dihydro-4-oxophthalazin-1-ylacetic acid (R_1 is OH; R_2 and R_3 are both F); 3-(5,7-dichlorobenzothiazol-2-ylmethyl)-3,4-dihydro-4-oxophthalazin-1-ylacetic acid (R_1 is OH; R_2 and R_3 are both Cl); 3-(5,7-bistrifluoromethylbenzothiazol-2-ylmethyl)-3,4-dihydro-4-oxophthalazin-1-ylacetic acid (R_1 is OH; R_2 and R_3 are both CF_3). Zopolrestat (3,4-dihydro-4-oxo-3-(5-trifluoromethylbenzothiazol-2-ylmethyl)phthalazin-1-ylacetic acid (R_1 is OH; R_2 is CF_3; R_3 is H)) is particularly preferred.

Prodrug groups which are capable of being removed in vivo to produce a compound of formula (I), wherein R_1 is OH are generally known to those skilled in the art and may include, for example, ester-forming groups such as benzyloxy, di(C_1-C_4)alkylaminoethyloxy, acetoxymethoxy, pivaloyloxymethoxy, phthalidoyl, ethoxycarbonyloxyethoxy, 5-methyl-2-oxo-1,3-dioxol-4-ylmethoxy, (C_1-C_4)alkoxy optionally-substituted by morpholino and amide-forming groups such as di(C_1-C_4)alkylamino.

Preparative methods for synthesizing compounds of formula (I) which include such particulars as solvents, temperatures, catalysts and procedures for making and/or sources of precursor compounds may be obtained from the teachings of the aforementioned U.S. Patent 4,939,140 as well as the commonly assigned U.S. Patent 4,868,301.

Some of the compounds useful in this invention have asymmetric carbon atoms and therefore may exist in enantiomeric or diastereomeric configurations. Diastereomeric mixtures may be separated, if necessary, into their individual diastereomers on the basis of their physicochemical differences by methods known per se, for example, by chromatography and/or fractional crystallization.

Those skilled in the art will appreciate that many aldose reductase inhibitors, especially those compounds of formula (I) where R_1 is OH, may form basic addition salts, and such pharmaceutically acceptable basic addition salts are intended to be within the scope of this invention. Pharmaceutically acceptable basic addition salts of compounds of formula (I) may be formed with pharmaceutically acceptable cations by conventional methods. For instance, such salts may be prepared readily by treating a compound of formula (I) with an aqueous solution of the hydroxide of the desired pharmaceutically acceptable cation and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, a lower alkyl alcohol solution of a compound of formula (I) may be mixed with an alkoxide of a desired metal cation and the solution subsequently evaporated to dryness. Suitable pharmaceutically acceptable cations for this purpose may 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. In general, the sodium and N-methylglucamine salts are preferred.

It will also be appreciated that pharmaceutically acceptable acid addition salts may be formed with certain aldose reductase inhibitors of this invention and such acid addition salts are also intended to be included within the scope of the instant invention. These pharmaceutically acceptable acid addition salts may be formed by conventional techniques by treating a solution or suspension of the free base of a compound with about one chemical equivalent of a pharmaceutically acceptable acid. Isolation of the acid addition salts prepared in this manner is most conveniently accomplished by conventional concentration and recrystallization techniques. Representative of such pharmaceutically acceptable acid addition salts include acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic, cinnamic, fumaric, sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulfamic, sulfonic such as methanesulfonic, benzenesulfonic, and other related acids.

Some of the aforementioned compounds, including those of structure (I) may, under appropriate conditions, form solvates or hydrates and such compounds are also intended to be included within the scope of this invention.

The medicine of employing known aldose reductase inhibitors in accordance with the objectives of the instant invention, including aldose reductase inhibitors of formula

(I), comprises a therapeutically effective amount of such compound. They may be administered in any known method for therapeutically providing an active compound to a human subject including such conventional routes as oral, transdermal, intraduodenal, or parenteral administration. For purposes of the present invention, a dosage form adapted for oral administration is generally preferred. In carrying out the objectives of this invention, an amount of the aldose reductase inhibitor that is effective for treating or reversing diabetic cardiomyopathy is employed. Typically, an effective dose for the aldose reductase inhibitors of this invention is in the range of from about 0.1 mg per day to about 1,000 mg per day in either single (e.g., once-daily) or multiple doses. Preferred dosage ranges for compounds of formula (I), including zopolrestat, are from about 250 mg per day to about 1,000 mg per day in a single, oral dose. However, some variation in dosage will be necessary depending upon the condition of the patient being treated.

In any event, the person responsible for administration will determine the appropriate dosage amount for the individual subject requiring treatment.

According to this invention, at least one active compound is employed, either individually, together in combination with another aldose reductase inhibitor, in combination with a pharmaceutically acceptable carrier. Suitable carriers may include solid diluents or fillers, sterile aqueous solutions and various physiologically compatible organic solvents. The pharmaceutical compositions formed by combining the active compound and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms such as tablets, powders, lozenges, syrups, injectable solutions and so forth. These pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients, and the like. For purposes of the preferred route of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be used 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 used as fillers in soft and hard filled gelatin capsules. Preferred materials for this use 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, glycerine and various combinations thereof.

For parenteral administration, solutions of the compounds useful in this invention, including those of formula (I), in sesame or peanut oil, aqueous propylene glycol, or in 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 particular 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 in vivo utility of aldose reductase inhibitors in the treatment of human diabetic cardiomyopathy according to this invention can be demonstrated by a randomized, double-blind, placebo-controlled clinical trial utilizing zoplorestat as the active agent.

In this study, both male and female patients between 18 and 65 years of age having demonstrated diabetes mellitus as defined by World Health Organization criteria (W.H.O. 1980/85 Technical Report Series No. 646/727) were initially evaluated for evidence of impaired cardiac performance indicative of diabetic cardiomyopathy.

Accordingly, a placebo-controlled, single-blind baseline evaluation was performed on prospective patients over a four week period utilizing the determination of heart rate variability during controlled respiration, and during a Valsalva test, and radionuclide ventriculography using multi-gated acquistion (MUGA) methodology (B.L. Holman, "Heart Disease", 3rd Edition, Chapter 11).

Radioventriculogram (RVG) determinations were made at rest, and during selected stages of exertion using a bicycle system suitable for use during ventriculography. Indicators of greatest importance were those involving rate of filling into and ejection of blood from the left ventricle, systolic and end diastolic volume of the left ventricle, calculated stroke volume, ejection fraction and cardiac output. The assessment of left ventricular volumes adds important complimentary information to the measurement of systolic and diastolic function. Absolute ventricular volumes were calculated according to the method of Massardo, et. al., J. Nucl. Med., Vol. 31, pp. 450-456, 1990. To be admitted into the double-blind phase, each patient must have demonstrated either a peak filling rate below 3 EDV(End Diastolic Volume)/sec, resting systolic ejection fraction (EF) below 50% of EDV, or a subnormal increase in left ventricular ejection fraction between resting and maximal level of exertion.

The degree of impairment of cardiac autonomic activity may be shown by a reduction in the normal variability of EKG R-R interval, most obviously, during respiration. The standard deviation of the mean R-R interval for a five-minute period during quiet breathing is a commonly used method of determining R-R variation, which is primarily a measure of parasympathetic nervous system activity. See, for example, T. Roy, et. al., Am. J. Med., Vol. 87, pp. 382-388, 1989. The Valsalva test (Gorlin, et. al., Am. J. Med., Vol. 22, pp. 197-203, 1957) is a cardiovascular test that

relies upon evaluation of cardiac responses during and after a standardized increase in intrathoracic pressure (Valsalva maneuver). An abnormally low Valsalva ratio (the fastest heart rate during the Valsalva maneuver divided by the slowest heart rate after the Valsalva maneuver) may be due either to decreased cardiac parasympathetic or decreased cardiac or vascular sympathetic tone. Thus, it serves as a general autonomic test. Subjects with or without evidence of impaired cardiac autonomic activity were studied.

A stress thallium test was also performed with concurrent determination of EKG changes to preclude participation of any patient presenting unequivocal evidence of coronary artery disease. Prospective patients exhibiting such evidence were withdrawn from the study.

The single-blind placebo baseline evaluation was followed by a double-blind period of 52 weeks duration during which patients were randomly assigned to a treatment regimen consisting of either placebo, zopolrestat 500 mg once daily, or zopolrestat 1,000 mg once daily.

The evaluation of peak ejection fraction endpoints as determined by radionuclide ventriculography was conducted at weeks 4, 16 and 52 of the double-blind period.

As shown in Table 1 below, the treatment of patients with zopolrestat at 500 mg (zopolrestat B) and 1,000 mg (zopolrestat C) dosages resulted in a significant improvement in the ventricular peak ejection fraction during exercise as compared to placebo. Specifically, the baseline placebo group deteriorated over the 52 week period of study while the two zopolrestat groups exhibited higher ventricular peak ejection fraction than placebo. This indicates the utility of zopolrestat in both preventing the deterioration of cardiac function, and in reversing established abnormality.

Table 1

Mean Response from Radionuclide Ventriculography

Zopolrestat

Endpoint	Treatment	N	Week 52 Observed	Baseline
Max. Diff. on Ejection Fraction (%)	Placebo	18	6.36 (8.04)	10.44 (7.11)
	Zopolrestat B	18	9.27 (6.19)	6.14 (8.27)
	Zopolrestat C	20	7.97 (6.89)	4.05 (9.61)
Max. Ejection Fraction at Exercise (%)	Placebo	18	64.50 (10.19)	67.55 (8.02)
	Zopolrestat B	18	71.22 (5.59)	65.89 (7.60)
	Zopolrestat C	20	68.65 (8.30)	66.10 (8.68)

As shown in Table 2 below, this improvement in the maximum differential of ejection fraction at exercise is statistically significant.

Table 2

Treatment Comparison in Radionuclide Ventriculography

Zopolrestat

Endpoint	Week	N	Placebo vs. Zopolrestat	Placebo vs. Zopolrestat B	Placebo vs. Zopolrestat C	Zopolrestat B. vs Zopolrestat C
Max. Diff. on Ejection Fraction (%)	52	56	0.0078	0.0153	0.0223	NS
	16	63	NS	NS	NS	NS
	4	75	NS	NS	NS	NS
Max. Ejection Fraction at Exercise (%)	52	56	0.0011	0.0007	0.0194	0.2032
	16	63	0.0943	0.0698	NS	NS
	4	75	0.0924	0.0570	NS	NS

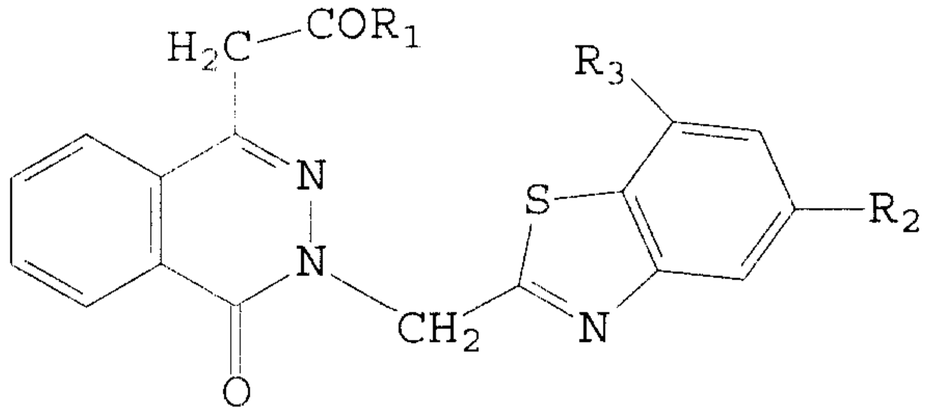
All determinations of statistical significance were derived from an analysis of covariance (ANCOVA) model with baseline response as covariate and treatment terms. Such statistical methodology is well known to those skilled in the art.

See, for example, A. A. Afifi, et. al, Statistical Analysis - A Computer Oriented Approach, 2nd Ed., pp. 262-274, (1979).

CLAIMS:

1. A medicine for treating diabetic cardiomyopathy in a human subject in need of such treatment, which comprises:

(a) a therapeutically effective amount of an aldose reductase inhibitor that is a compound of structural formula I:



(I)

(wherein R_1 is OH or a prodrug group capable of being removed in vivo to produce a compound of formula I wherein R_1 is OH; and R_2 and R_3 are the same or different and are selected from the group consisting of hydrogen, trifluoromethyl, fluoro, chloro and bromo) or a pharmaceutically acceptable salt thereof, and

(b) a pharmaceutically acceptable carrier.

2. The medicine as claimed in claim 1, wherein the compound I is selected from the group consisting of 3,4-dihydro-4-oxo-3-(5-trifluoromethylbenzothiazol-2-ylmethyl)phthalazin-1-ylacetic acid; 3,4-dihydro-4-oxo-3-(5-fluorobenzothiazol-2-ylmethyl)phthalazin-1-ylacetic acid, 3,4-dihydro-4-oxo-3-(5-chlorobenzothiazol-2-ylmethyl)phthalazin-1-ylacetic acid, 3,4-dihydro-4-oxo-3-(5-bromobenzothiazol-2-ylmethyl)phthalazin-1-ylacetic acid, 3-(5,7-difluorobenzothiazol-2-ylmethyl)-3,4-dihydro-4-oxophthalazin-1-ylacetic acid, 3-(5,7-dichlorobenzothiazol-2-ylmethyl)-3,4-dihydro-4-oxophthalazin-1-ylacetic acid, and

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3-(5,7-bistrifluoromethylbenzothiazol-2-ylmethyl)-3,4-dihydro-4-oxophthalazin-1-ylacetic acid.

3. The medicine as claimed in claim 1, wherein the compound I is 3,4-dihydro-4-oxo-3-(5-trifluoromethyl-benzothiazol-2-ylmethyl)phthalazin-1-ylacetic acid, zopolrestat.

4. The medicine as claimed in any one of claims 1 to 3, wherein the treatment is prevention or reversal of diabetic cardiomyopathy.

5. The medicine as claimed in any one of claims 1 to 4, which is in a form adapted for oral administration.

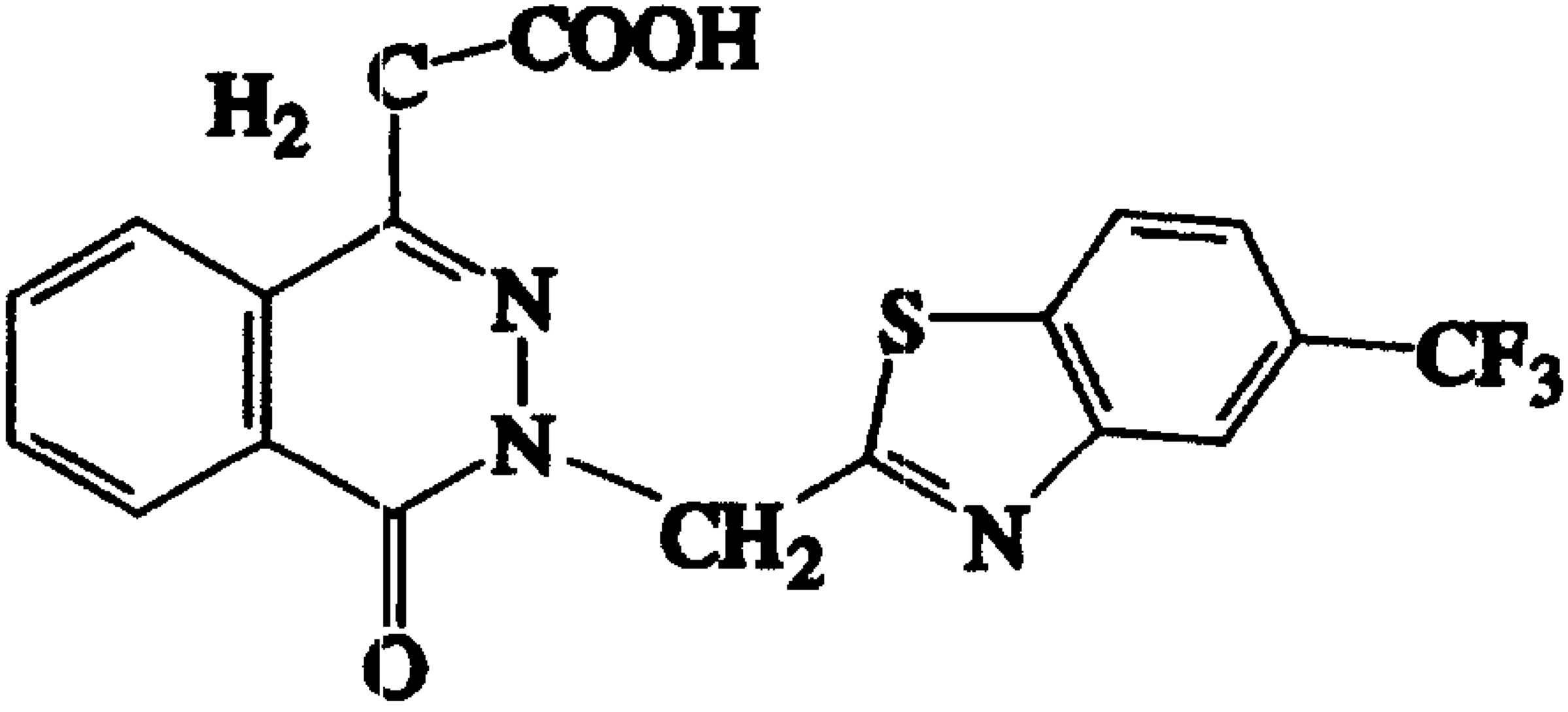
6. A medicine as claimed in any one of claims 1 to 5, of a daily dose of 0.1 mg to 1,000 mg of the aldose reductase inhibitor.

7. The medicine as claimed in any one of claims 1 to 5, of a single daily oral dose of from about 250 mg to about 1,000 mg of the aldose reductase inhibitor.

8. A commercial package comprising a container, the medicine as claimed in any one of claims 1 to 7 contained therein and a written matter which states that the medicine is to be used for treating or reversing diabetic cardiomyopathy in a human subject.

SMART & BIGGAR
OTTAWA, CANADA

PATENT AGENTS


COOH
H2
C
N
N
S
CF3
CH2
N
O