9603837-
IPOS copy

THIS SHEET HAS BEEN REPLACED

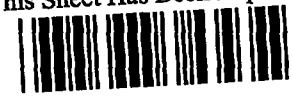
N'-ALKYL-SPIRO-ISOQUINOLINE-PYRROLIDINE TETRONES AND ANALOGS THEREOF USEFUL AS ALDOSE REDUCTASE INHIBITORS

This invention relates to N'-alkyl-spiro-isoquinoline-pyrrolidine tetrones to processes for their preparation, to methods for using the compounds, and to pharmaceutical preparations thereof. The compounds have pharmaceutical properties which render them beneficial for the prevention or treatment of complications associated with diabetes mellitus.

The use of insulin and/or oral hypoglycemic agents in the treatment of diabetes mellitus has prolonged the life of many of these patients. However, their use has not had a demonstrable impact on the development of diabetic complications such as neuropathy, nephropathy, retinopathy, cataracts and vascular disease which accompany the underlying metabolic disorder. There is little question that chronic hyperglycemia plays a major role in the genesis of these complications, and that complete normalization of blood glucose would likely prevent most if not all complications. For a number of reasons, though, chronic normalization of blood glucose has not been achieved with the currently available therapies.

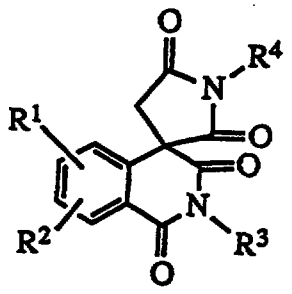
The long-term complications of diabetes develop in tissues where glucose uptake is independent of insulin. In these tissues, which include the lens, retina, kidney and peripheral nerves, the systemic hyperglycemia of diabetes is rapidly transposed into high tissular concentrations of glucose. In all of these tissues this excess glucose is rapidly metabolized by the sorbitol pathway. The intense diabetes-induced flux of glucose through this pathway appears to initiate a cascade of biochemical alterations which slowly progress to cell dysfunction and structural damage. Aldose reductase, the key enzyme in the sorbitol pathway, reduces glucose to sorbitol at the expense of the cofactor NADPH. In animal models of diabetes, compounds which inhibit aldose reductase have been shown to prevent the biochemical, functional and morphological changes induced by hyperglycemia. Early studies by J. H. Kinoshita and collaborators implicated aldose reductase in the etiology of diabetic cataracts. More recent studies have provided compelling evidence that aldose reductase also plays a significant role in the initiation of diabetic nephropathy,

This Sheet Has Been Replaced



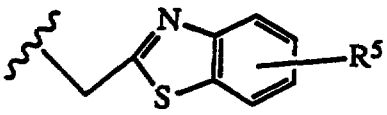
retinopathy and neuropathy (cf McCaleb et al, J Diab. Comp., 2 16,1989; Robinson et al, Invest. Ophthalmol. Vis. Sci., 30, 2285, 1989; Notvest and Inserra, Diabetes, 36, 500,1987.

The N'-alkyl-spiro-isoquinoline-pyrrolidine tetrones of the present invention are represented by formula (I):



(I)

wherein R^1 and R^2 are independently hydrogen, alkyl containing 1 to 6 carbon atoms, halogen, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms; R^3 is hydrogen, lower alkyl containing 1 to 6 carbon atoms, aryl, aryl(lower alkyl) or halogen substituted aryl(lower alkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms, or benzothiazole of structural formula



(Ia)

wherein R^5 is hydrogen, halogen, alkyl containing 1 to 6 carbon atoms, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 5 carbon atoms; and R^4 is alkyl containing 1 to 12 carbon atoms, aryl, aryl(lower alkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms,

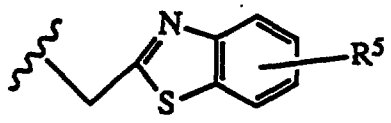
This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

acyl, carboalkoxy, or $-(CH_2)_nCO_2H$, $-(CH_2)_nOH$, wherein n is 1 to 6.

Examples of 'aryl' are phenyl and naphthyl, Examples of acyl are lower alkyl-C(O)- or aryl-C(O)-. Examples of carboalkoxy are loweralkoxy-C(O)-. Examples of halogen are fluorine, chlorine and bromine. Examples of R^1 and/or R^2 are hydrogen or halogen e.g fluorine such as 6-F. Examples of R^3 are (mono- or di-halo substituted phenyl)lower alkyl wherein lower alkyl contains 1 - 3 carbon atoms, or benzothiazolylmethyl of formula Ia wherein R^5 is hydrogen, halogen or trifluoromethyl. For example R^3 may be 4-bromo-2-fluorophenylmethyl or (5-trifluoromethylbenzothiazol-2-yl)methyl. Examples of R^4 are C_1 - C_3 alkyl such as methyl or ethyl.

A more preferred group of compounds of the present invention are the compounds of formula (I) wherein R^1 and R^2 are independently hydrogen or halogen; R^3 is a mono- or dihalogen substituted aryl(loweralkyl) wherein aryl contains 6 carbon atoms and lower alkyl contains 1 to 3 carbon atoms, or benzothiazole of structural formula



(Ia)

wherein R^5 is hydrogen, halogen or trifluoromethyl; and R^4 is alkyl containing 1 to 3 carbon atoms.

The most preferred compounds of the present invention are set forth below:

2-[(4-bromo-2-fluorophenyl)methyl]-1'-methyl-spiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2'3,5'(2H)-tetrone;

This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

2-[(4-bromo-2-fluorophenyl)methyl]-1'-ethylspiro[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone;

2-[(4-bromo-2-fluorophenyl)methyl]-1'-ethyl-6-fluorospiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone;

2-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-1'-methylspiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone;

1'-ethyl-6-fluoro-2-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]spiro-[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone.

The compounds of formula (I) all possess at least one asymmetric carbon atom, namely the spiro carbon atom at position 3' of the pyrrolidine ring. The compounds of formula (I) therefore exist, and may be isolated, in two or more stereoisomeric forms. This invention encompasses the compounds of formula (I) in racemic form or in any optically active form.

The N'-alkyl-spiro-isoquinoline-pyrrolidine tetrones can be prepared by the processes described hereinafter.

A method is provided for preventing or relieving diabetes mellitus associated complications in a diabetic mammal by administering to said mammal a prophylactic or alleviating amount of the compounds of formula (I). Such complications include neuropathy, nephropathy, retinopathy, keratopathy, diabetic uveitis, and cataracts.

The compounds of formula (I), when admixed with a pharmaceutically acceptable carrier, form a pharmaceutical composition which can be used according to the preceding method.

The N'-alkyl-spiro-isoquinoline-pyrrolidine tetrones of this invention may be administered to mammals, for example, man, cattle, or rabbits, either alone or in dosage forms, i.e., capsules or tablets, combined with pharmacologically acceptable excipients.

This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

The compounds of this invention may be given orally. However, the method of administering the present active ingredients of this invention is not to be construed as limited to a particular mode of administration. For example, the compounds may be administered topically directly to the eye in the form of drops of sterile, buffered ophthalmic solutions, preferably of pH 7.2-7.6. Also, they may be administered orally in solid form containing such excipients as starch, milk sugar, certain types of clay and so forth. They may also be administered orally in the form of solutions or they may be injected parenterally. For parenteral administration, they may be used in the form of a sterile solution, preferaby of pH 7.2-7.6, containing a pharmaceutically acceptable buffer.

The dosage of the N'-alkyl-spiro-isoquinoline-pyrrolidine tetrones will vary with the form of administration and the particular compound chosen. Furthermore, it will vary with the particular host under treatment. Generally, treatment is initiated with small dosages substantially less than the optimal dose of the compound. Thereafter, the dosage is increased by small increments until efficacy is obtained. In general, the compounds of this invention are most desirably administered at a concentration level that will generally afford effective results without causing any harmful or deleterious side effects. For topical administration, a 0.05-1.0% solution may be administered dropwise in the eye. The frequency of instillation varies with the subject under treatment from a drop every two or three days to once daily. For oral or parenteral administration a preferred level of dosage ranges from about 0.1 mg to about 1.0 mg per kilo of body weight per day, although aforementioned variations will occur. However, a dosage level that is in the range of from about 0.1 mg to about 1.0 mg per kilo of body weight per day is most satisfactory.

Unit dosage forms such as capsules, tablets, pills and the like may contain from about 5.0 mg to about 25.0 mg of the active ingredients of this invention with a pharmaceutical carrier. Thus, for oral administration, capsules can contain from between about 5.0 mg to about 25.0 mg of the active ingredients of this invention with or without a pharmaceutical diluent. Tablets, either effervescent or noneffervescent, can contain between about 5.0 to 25.0 mg of the active ingredients of this invention together with conventional pharmaceutical carriers. Thus tablets, which may be coated and either effervescent or noneffervescent, may be prepared according to the known art. Inert diluents or carriers, for example, magnesium carbonate or lactose, can be used together with conventional disintegrating agents for example, magnesium stearate.

This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

The N'-alkyl-spiro-isoquinoline-pyrrolidine tetrones also can be used in combination with insulin or oral hypoglycemic agents to produce a beneficial effect in the treatment of diabetes mellitus. In this instance, commercially available insulin preparations or oral hypoglycemic agents, exemplified by acetohexamide, chlorpropamide, tolazamide, tolbutamide and phenformin, are suitable. The compounds hereof can be administered sequentially or simultaneously with insulin or the oral hypoglycemic agent. Suitable methods of administration, compositions and doses of the insulin preparation or oral hypoglycemic agent are described in medical textbooks; for instance, Physicians' Desk Reference, 42 ed., Medical Economics Co., Oradell, N.J., U.S.A., 1988.

The aldose reductase inhibiting property of the compounds of this invention and the utilization of the compounds in preventing, diminishing and alleviating diabetic complications are demonstrable in experiments using galactosemic rats, see Dvornik et al., Science, 182, 1146 (1973). Such experiments are exemplified hereinbelow after the listing of the following general comments pertaining to these experiments:

(a) Four or more groups of six male rats, 50-70 g, Sprague-Dawley strain, were used. The first group, the control group, was fed a mixture of laboratory chow (rodent Laboratory Chow, Purina) and glucose at 20% (w/w %) concentration. An untreated galactosemic group was fed a similar diet in which galactose was substituted for glucose. The third group was fed a diet prepared by mixing a given amount of the test compound with the galactose containing diet. The concentration of galactose in the diet of the treated groups was the same as that for the untreated galactosemic group.

(b) After four days, the animals were killed by euthanization. Both the lens and sciatic nerve were removed, weighed and stored frozen for polyol determination.

(c) The polyol determination was performed by a modification of the procedure of M. Kraml and L. Cosyns, Clin. Biochem., 2, 373 (1969). Only two minor reagent changes were made: (a) the rinsing mixture was an aqueous 5% (w/v) trichloroacetic acid solution and (b) the stock solution was prepared by dissolving 25 mg of dulcitol in 100 mL of an aqueous trichloroacetic acid solution. [N.B.: For each experiment the average value found in the tissue from rats fed the glucose diet was

This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

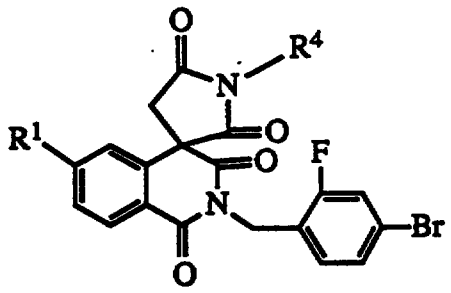
subtracted from the individual values found in the corresponding tissue in galactose-fed rats to obtain the amount of polyol accumulated.] The aldose reductase inhibiting effects of the compounds of formula (I) were also tested by employing an in vitro testing procedure similar to that described by S. Hayman and J.H. Kinoshita, J. Biol. Chem., 240, 877 (1965). In the present case the procedure of Hayman and Kinoshita was modified in that the final chromatography step was omitted in the preparation of the enzyme from bovine lens.

The following tabulated results show that the N'-alkyl-spiro-isoquinoline-pyrrolidine tetrones of this invention show the property that they are active both in vitro and in vivo and diminish the accumulation of dulcitol in the lenses, sciatic nerves and diaphragm of rats fed galactose. The figures under L, N, and D represent the percentage decrease of dulcitol accumulation in the tissues of the lens, sciatic nerve, and diaphragm, respectively, for treated rats as compared to untreated rats.

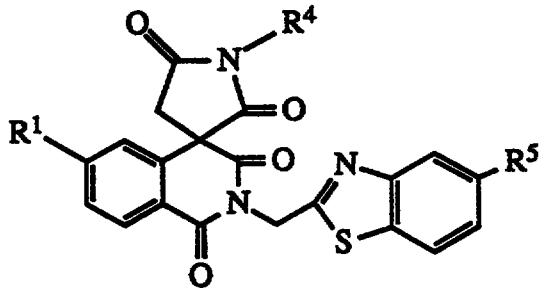
This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

ALDOSE REDUCTASE INHIBITORS



		% inhibition in vitro	% lowering dulcitol accumulation dose	in vivo		
R^1	R^4	10^{-5}M	mg/kg	%L	%N	%D
H	$-CH_3$	0	0.5	NS	50	61
			1.1	NS	76	75
			10.2	31	95	94
H	$-CH_2CH_3$	0	0.5	NS	37	56
			0.9	NS	65	73
F	$-CH_2CH_3$	0	0.5	NS	19	65
			1.0	NS	74	84



			% Inhibition In Vitro	% Lowering Galactitol Accumulation In Vivo Dose			
R^1	R^4	R^5	10^{-6}M	mg/kg/day	(%)L	(%)N	(%)D
H	CH_3	CF_3	0	9.5	NS	82	100
F	C_2H_5	CF_3	0	10	NS	NS	59

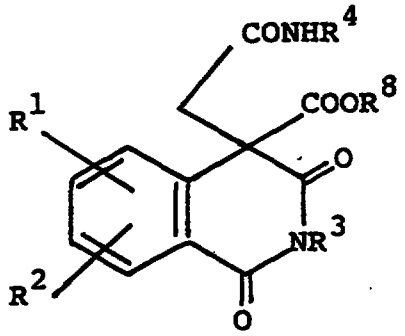
This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

This invention provides processes for preparing compounds of formula I. These processes include:

a) cyclising an amide of formula (A)

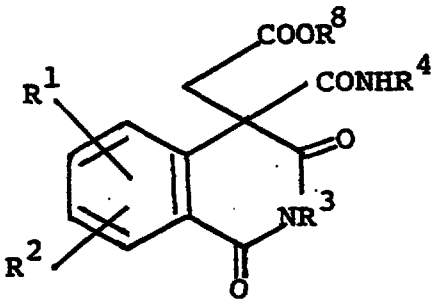


(A)

wherein R^1, R^2, R^3 and R^4 are as defined above and $COOR^8$ is ester group, using a suitable base such as sodium hydride to give a compound of formula I;

or

b) cyclising a compound of formula (B)



(B)

wherein R^1, R^2, R^3, R^4 and $COOR^8$ are as defined above using a suitable base such as sodium hydride or lithium bis-(trimethylsilyl)amide to give a compound of formula I;

or

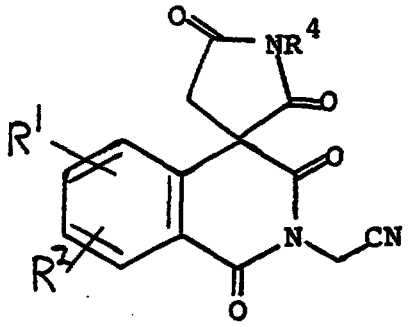
c) acylating a compound of formula I as shown above wherein R^4 is hydrogen and R^{1-3} are as defined above to give a corresponding compound of formula I wherein R^4 is acyl or carboalkoxy;

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

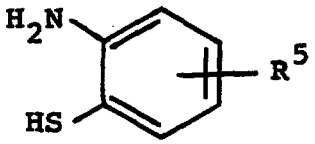
or

d) reacting a compound of formula



(D)

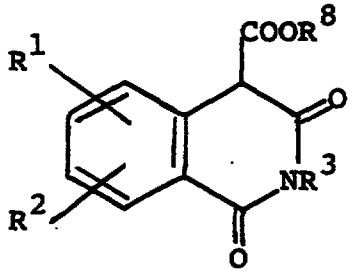
with a 2-aminothiophenol of formula



(E)

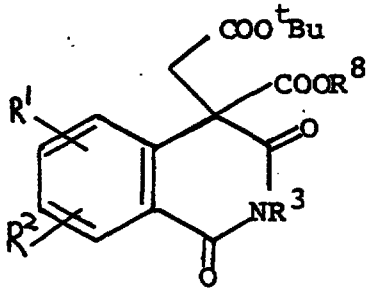
to give a compound of formula I wherein R^3 is a benzothiazolylmethyl group of formula Ia.

Starting materials of formulae (A) and (B) can be prepared via intermediates of formula (G) shown below:



(G)

wherein R^1, R^2, R^3, and $COOR^8$ are as defined above. Examples of R^8 are alkyl groups such as C_1-C_4 alkyl especially methyl. R^8 may also be ^tBu. For example compounds of formula (A) are prepared by reacting a compound of formula (G) with $Br(CH_2)_n$- CO_2-^tBu in the presence of a suitable base e.g Li-$N(SiMe_3)_2$ to give a compound of formula



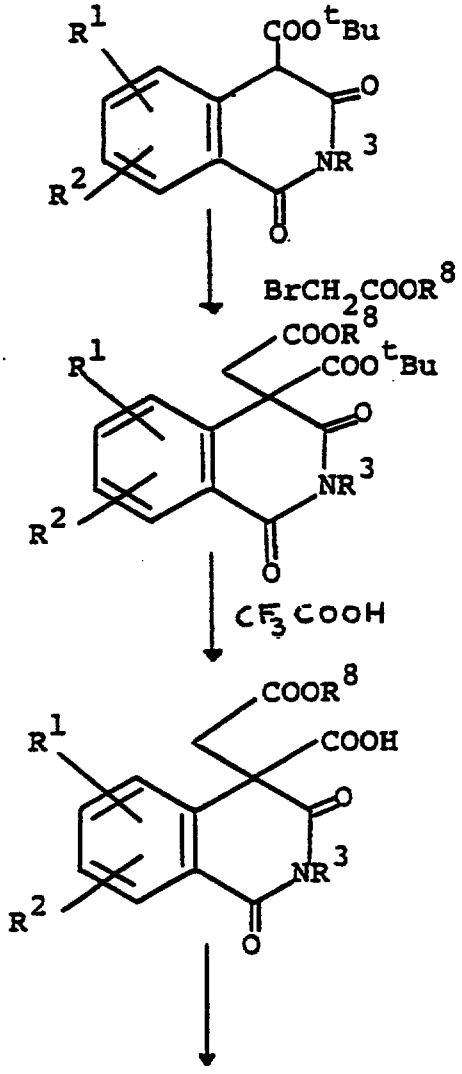
(H)

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

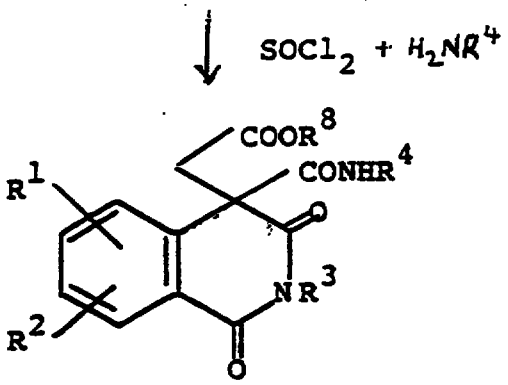
wherein R^1, R^2 and R^3 are as defined above and $COOR^8$ is an ester group (other than ^tBu ester); treating the compound of formula (H) with trifluoracetic acid to remove the ^tBu group, reacting the resulting acid with a coupling agent, e.g 1-(2-dimethyl-aminopropyl)-2-ethylcarbodiimide in the presence of 1-hydroxy benzotriazole, followed by an amine of formula H_2NR^4 to give the amide of formula (A).

Intermediates of formula (B) may be prepared via the route



This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED



where $COOR^8$ is an ester group providing R^8 is not ^tBu. Other routes to the various intermediates will be apparent to the skilled chemist.

Starting materials for the processes herein described are known compounds or may be prepared by analogous methods.

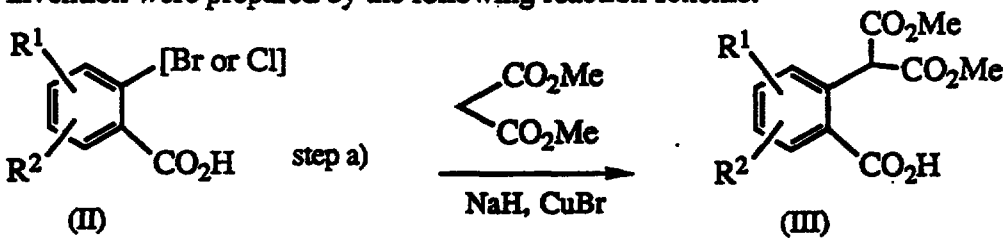
The following processes exemplify the abovementioned routes to compounds of formula I.

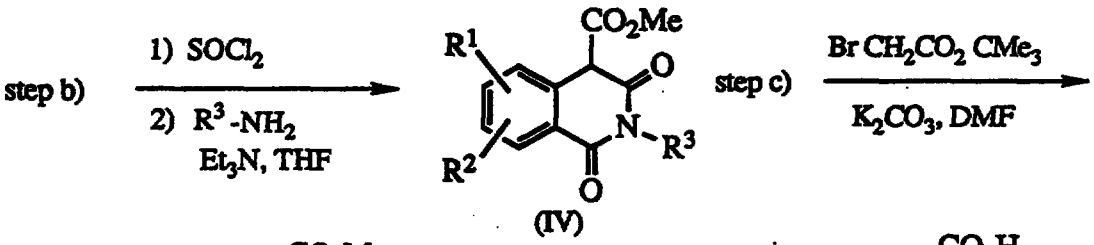
This Sheet Has Been Replaced

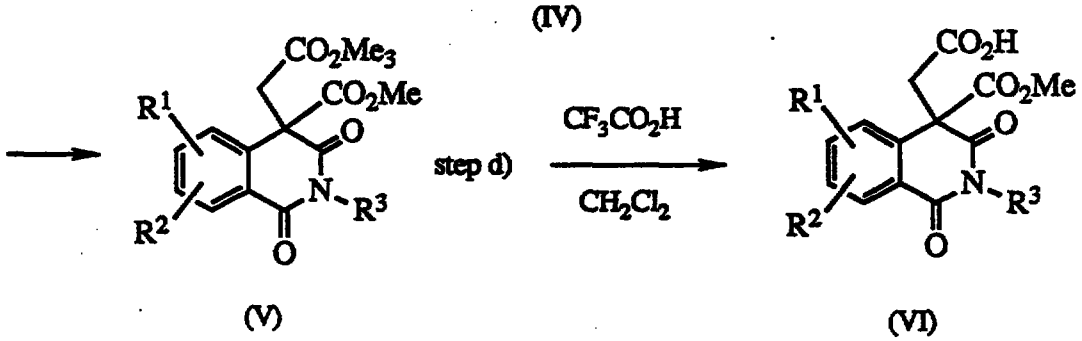
THIS SHEET HAS BEEN REPLACED

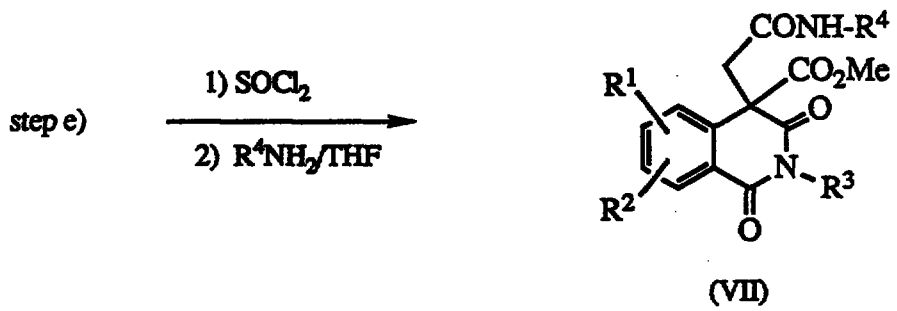
Process A

The N'-alkyl-spiro-isoquinoline-pyrrolidine tetrones of the present invention were prepared by the following reaction scheme:





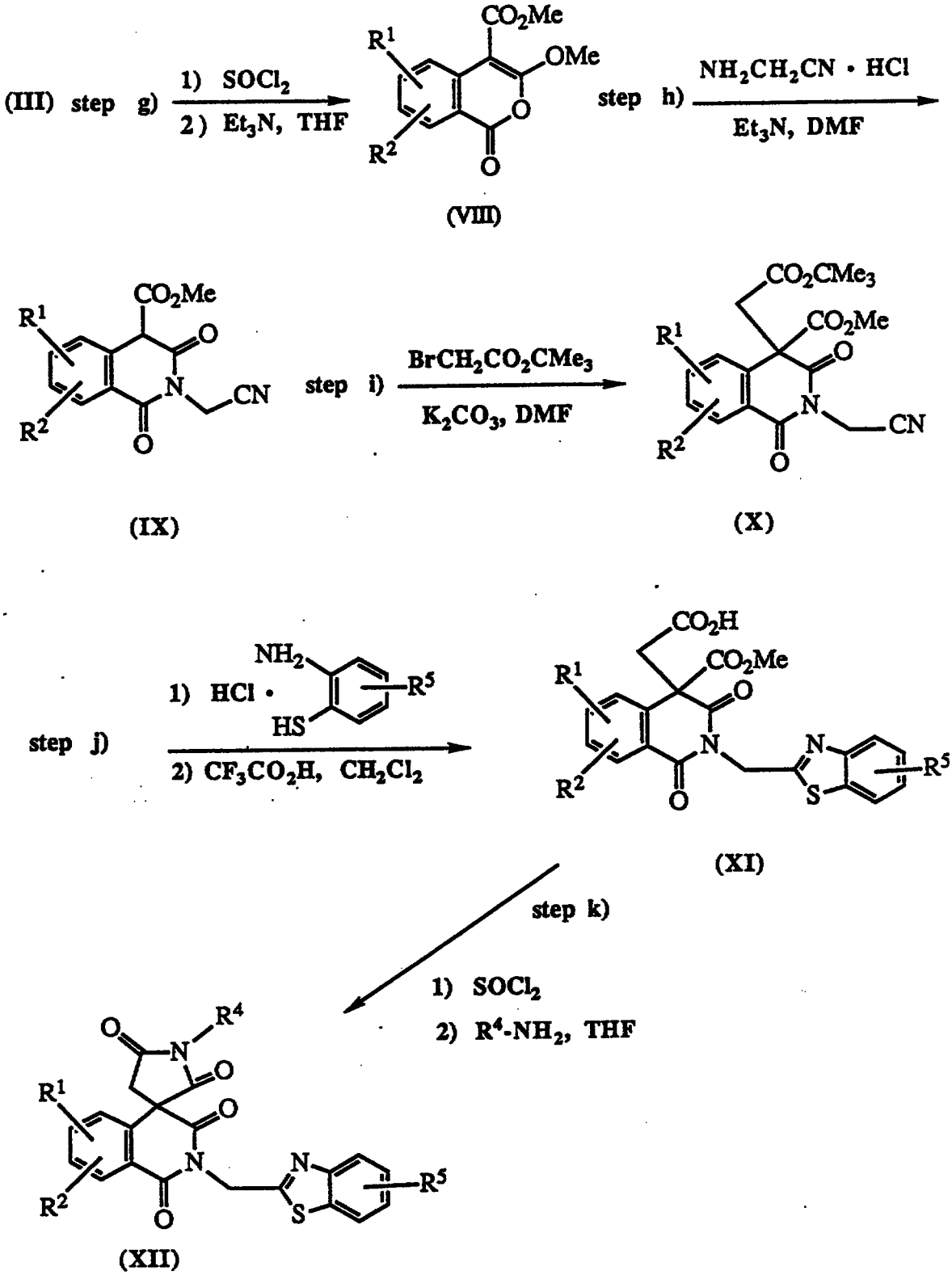






This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED



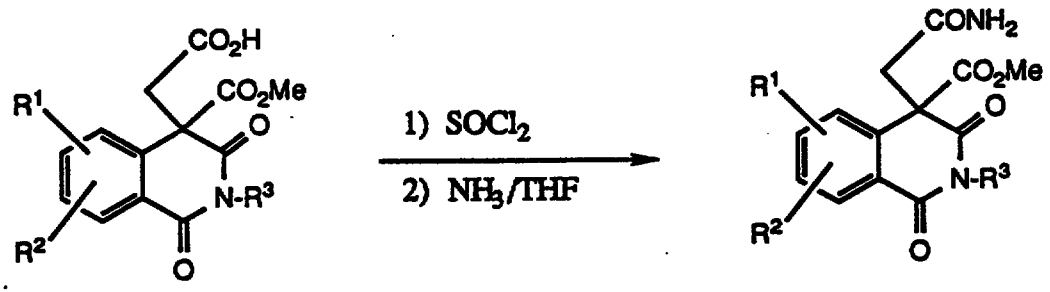
wherein R^1, R^2, R^3, R^4, and R^5 are as defined above.

This Sheet Has Been Replaced

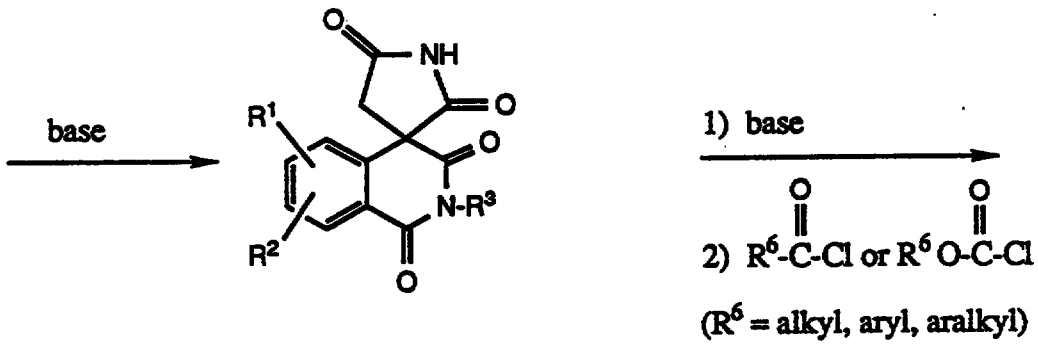
THIS SHEET HAS BEEN REPLACED

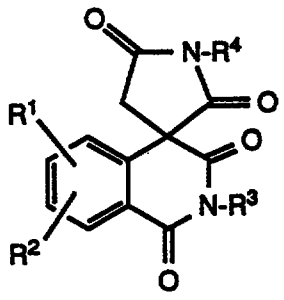
Process B

Some compounds of formula (I), wherein R^1, R^2, and R^3 are as defined above and R^4 is acyl or carboalkoxy, can be made by the process B.



(VI)





(I)

wherein R^1, R^2, and R^3 are as defined above and R^4 is acyl or carboalkoxy.

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

Step a) Reacting either 2-bromobenzoic acid or 2-chlorobenzoic acid of formula (II) wherein R^1 and R^2 are as defined above with dimethyl malonate and NaH in the presence of a catalytic amount of CuBr to produce the propanedioic acid dimethyl ester of formula (III) wherein R^1 and R^2 are as defined above.

The 2-bromobenzoic acids or 2-chlorobenzoic acids of formula (II) required for the present invention are commerically available compounds or can be prepared by known methods.

Step b) The propanedioic acid dimethyl ester of formula (III) can be reacted with thionyl chloride under refluxing conditions to produce the corresponding acid chloride which upon treatment with an amine R^3 -NH_2 in the presence of triethylamine in a conventional solvent which does not adversely influence the reaction, for example, tetrahydrofuran, can produce the compound of formula (IV) wherein R^1, R^2 and R^3 are as defined above.

Step c) The compound of formula (IV), wherein R^1, R^2 and R^3 are as defined above, is reacted with an inorganic base such as potassium carbonate in a conventional solvent which does not adversely influence the reaction, for example, N,N-dimethylformamide, and subsequent addition of the tert-butyl bromoacetate produces the compound of the formula (V), wherein R^1, R^2 and R^3 are as defined above.

Step d) The compound of formula (V), wherein R^1, R^2 and R^3 are as defined above, is hydrolyzed with an organic acid such as trifluoroacetic acid in a conventional solvent which does not adversely influence the reaction, for example, methylene chloride, to produce the compound of formula (VI), wherein R^1, R^2 and R^3 are as defined above.

Step e) The compound of formula (VI), wherein R^1, R^2 and R^3 are as defined above, can be reacted with thionyl chloride under refluxing conditions to produce the corresponding acid chloride, which upon treatment with R^4-NH_2 wherein R^4 is as defined above produces the amide of formula (VII), wherein R^1, R^2, R^3 and R^4 are as defined above. However, in the case when R^4=Me the initially formed amide (VII, when R^4=Me) cyclizes under these conditions to the final product (I, when R^4=Me).

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

Step f) The amide of formula (VII), wherein R^1, R^2, R^3 and R^4 are as defined above, is reacted with a base such as sodium hydride in a conventional solvent which does not adversely influence the reaction, for example, N,N-dimethylformamide, to produce the compound of the formula (I), wherein R^1, R^2, R^3 and R^4 are as defined above.

Step g) The propanedioic acid dimethyl ester of formula (III) can be reacted with thionyl chloride under refluxing conditions to produce the corresponding acid chloride which upon treatment with Et_3N in a conventional solvent which does not adversely influence the reaction, for example, tetrahydrofuran, can produce the compound of formula (VIII), wherein R^1 and R^2 are as defined above.

Step h) The compound of formula (VIII), wherein R^1 and R^2 are as defined above, is reacted with aminoacetonitrile hydrochloride in the presence of Et_3N in a conventional solvent which does not adversely influence the reaction, for example, N,N-dimethylformamide, produces the compound of the formula (IX), wherein R^1 and R^2 are as defined above.

Step i) The compound of formula (IX), wherein R^1 and R^2 are as defined above, is reacted with an inorganic base such as potassium carbonate in a conventional solvent which does not adversely influence the reaction, for example, N,N-dimethylformamide and subsequent addition of the tert-butyl bromoacetate produces the compound of formula (X), wherein R^1 and R^2 are as defined above.

Step j) The compound of formula (X), wherein R^1 and R^2 are as defined above, can be reacted with 2-aminothiophenols (R^5 is as defined above) under refluxing conditions in a conventional solvent which does not adversely influence the reaction, for example, ethyl alcohol, and subsequent treatment of the crude product with an organic acid such as trifluoroacetic acid in a conventional solvent which does not adversely influence the reaction, for example, methylene chloride, to produce the compound of formula (XI), wherein R^1, R^2 and R^5 are as defined above.

Step k) The compound of formula (XI), wherein R^1, R^2 and R^5 are as defined above, can be reacted with thionyl chloride under refluxing conditions to produce the corresponding acid chloride which upon treatment with R^4-NH_2 (wherein R^4 is as defined above) in a conventional solvent which does not adversely influence the

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

reaction, for example, tetrahydrofuran, produces the compound of formula (XII), wherein R^1, R^2, R^4, and R^5 are as defined above. However, in the case that the initially formed amide does not cyclize under the reaction conditions, cyclization can be achieved in a similar manner as that of Step f.

The following examples further illustrate this invention:

EXAMPLE 1

2-[(4-Bromo-2-fluorophenyl)methyl]-1'-methylspiro[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

Step a)

(2-Carboxyphenyl)propanedioic Acid Dimethyl Ester

To a rapidly stirred cold suspension (O°C) of 2-bromobenzoic acid (30.0 g, 149.32 mmol), cuprous bromide (2.14 g, 14.93 mmol) and dimethyl malonate (300 mL) was added NaH (80% in mineral oil, 10.75 g, 358.37 mmol) over a 30 minute period, while a stream of dry N_2 was passed over the mixture. After the addition of the NaH had been completed, the mixture was stirred for 10 minutes at room temperature and 30 minutes at 70°C (external oil bath temperature). At this point, the suspension had turned to a solid mass, which was dissolved in H_2O (1000 mL). The aqueous layer was extracted with diethyl ether (3x500 mL) and was acidified with HCl (2N). The mixture was extracted with EtOAc and dried over $MgSO_4$. Evaporation gave an off-white solid which was recrystallized from Et_2O/hexane (-20°C) to give a white solid (34.2 g, 90.9%).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.67 [s, 6H, -CH(CO_2CH_3)$_2$], 5.72 [s, 1H, -CH(CO_2CH_3)$_2$], 7.3 (d, J=7.76 Hz, 1H, Ar-H), 7.45 (dt, J=7.66 Hz, 1.12 Hz, 1H, Ar-H), 7.6 (dt, J=7.66 Hz, 1.45 Hz, 1H, Ar-H), 7.94 (dd, J=7.8 Hz, 1.33 Hz, 1H, Ar-H), 13.2 (s, 1H, -CO_2H)

IR (KBr, cm^{-1}):	3300-2700 (br), 1750 (s), 1730 (s), 1680 (s), 1430 (m), 730 (m)
MS (m/e):	252 (M^+), 220 (M^+-CH_3OH), 188 (M^+-2xCH_3OH)
Anal. Calcd.:	C, 57.14; H, 4.80
Found:	C, 57.05; H, 4.78.
M.P. 119-120°C.	

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

The following compound was prepared in substantially the same manner as that of Example 1, Step a):

(2-Carboxy-6-fluorophenyl)propanedioic Acid Dimethyl Ester

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.68 [s, 6H, (–CO_2Me)$_2$], 5.79 (s, 1H, Ar-H), 7.12 (dd, J=10.06 Hz, 2.61 Hz, 1H, Ar-H), 7.33 (dt, J=8.48 Hz, 2.64 Hz, 1H, Ar-H), 8.03 (dd, 8.77 Hz, 6.17 Hz, 1H, Ar-H)

IR (KBr, cm^{-1}): 3400-2700 (br), 1730 (s), 1680 (s), 750 (m)
MS (m/e): 270 (M^+), 238 (M^+-CH_3OH), 210 (M^+-CH_3OH, -CO), 151 (M^+ -CH_3OH, -CO, -CO_2CH_3)
M.P. 121.5-123.0°C.

Step b)

2-[(4-Bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic Acid Methyl Ester

A mixture of (2-carboxyphenyl)propanedioic acid dimethyl ester (5.0 g, 19.84 mmol) and $SOCl_2$ (20 g) was refluxed for 1 and 1/2 hours. The volatiles were removed in vacuo and the acid chloride was dissolved in THF (20 mL). In a second flask were placed 4-bromo-2-fluorobenzylamine (4.67 g, 22.91 mmol), triethylamine (15.96 mL, 114.55 mmol) and THF (150 mL). The contents of the first flask were added to the second flask and the mixture was stirred for 30 minutes. The formed suspension was poured into H_2O (1000 mL), stirred for 10 minutes and acidified with HCl (2N). The mixture was extracted with EtOAc and the organic layer was dried over $MgSO_4$. Evaporation gave a yellowish solid which was recrystallized from acetone/ether/hexane (at -20°C) to yield a white solid (6.01 g, 74.6%).

^{1}H NMR (DMSO-d_6, 400 MHz): δ [3.67, 3.99 (s, 3H, -$CO_2$$\underline{CH_3}$, tautomeric)], [5.06 (q, J=15.4 Hz), 5.29 (s), 2H, N-$\underline{CH_2}$-, tautomeric], 5.03 (s, 1H, -$\underline{CH}CO_2CH_3$, tautomeric), 7.07-8.44 (m, 7H, Ar-H, tautomeric)

IR (KBr, cm^{-1}): 1675 (s), 1610 (s), 1490 (s), 7.95 (m)
MS (m/e): 405 (M^+), 373 (M^+-MeOH)

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

Anal. Calcd.: C, 53.22; H, 3.23; N, 3.45
Found: C, 52.91; H, 3.20; N, 3.27

M.P. 149-150°C.

The following compound was prepared in substantially the same manner as that of Example 1, Step b):

2-[(4-Bromo-2-fluorophenyl)methyl]-6-fluoro-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic Acid Methyl Ester

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.98 (s, 3H, -$CO_2\underline{CH_3}$), 5.27 (s, 2H, -$N\underline{CH_2}$-), 7.08 (t, J=7.95 Hz, 2H, Ar-$\underline{H}$), 7.2 (m, 1H, Ar-$\underline{H}$), 7.34 (m, 2H, Ar-$\underline{H}$, -$\underline{OH}$), 7.54 (m, 1H, Ar-$\underline{H}$), 8.1-8.26 (m, 2H, Ar-$\underline{H}$)

IR (KBr, cm^{-1}): 1680 (s), 1660 (s), 1610 (s), 785 (m)
MS (m/e): 423 (M^+), 391 (M^+-CH_3OH)

Anal. Calcd.: C, 50.97; H, 2.85; N, 3.30
Found: C, 50.86; H, 2.86; N, 3.33

M.P. 157-158°C.

Step c)

2-[(4-Bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic Acid 1,1-Dimethylethyl Ester

To a suspension of 2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic acid methyl ester (4.79 g, 11.58 mmol), K_2CO_3 (3.19 g, 23.16 mmol) in DMF (100 mL) was added tert-butyl bromoacetate (2.81 mL, 17.37 mmol). After stirring at 75°C for 1 hour, the mixture was poured into H_2O, extracted with EtOAc and dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc, 4/1) gave a clear oil (5.69 g, 94.5%).

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.04 [s, 9H, -C(CH$_3$)$_3$], 3.53 (s, 3H, -CO$_2$CH$_3$), 3.60 [dd, J=17.7 Hz, 2H, -CH$_2$CO$_2$C(CH$_3$)$_3$], 5.14 (s, 2H, NCH$_2$-), 7.17 (t, J=8.25 Hz, 1H, Ar-H), 7.36 (dd, J=8.36 Hz, 1.75 Hz, 1H, Ar-H), 7.6 (m, 3H, Ar-H), 7.77 (dt, J=7.2 Hz, 1.27 Hz, 1H, Ar-H), 8.19 (dd, J=8.25 Hz, 1.54 Hz, 1H, Ar-H)

IR ($CHCl_3$, cm^{-1}):	1720 (s), 1675 (s), 1360 (s), 765 (m)
MS (m/e):	520 $(M+H)^+$, 464 [M^+-C(CH$_3$)$_3$].

The following compound was prepared in substantially the same manner as that of Example 1, Step c):

2-[(4-Bromo-2-fluorophenyl)methyl]-6-fluoro-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic Acid 1,1-Dimethylethyl Ester

^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.1 (s, 9H, -CMe$_3$), 3.55 (s, 3H, -CO$_2$CH$_3$), 3.62 (d, J=1.75 Hz, 1H, -CH$_2$CO$_2$CMe$_3$), 3.75 (d, J=17.5 Hz, 1H, -CH$_2$CO$_2$CMe$_3$), 5.15 (s, 2H, -NCH$_2$-), 7.15 (t, J=8.2 Hz, 1H, Ar-H), 7.35 (d, J=8.2 Hz, 1H, Ar-H), 7.45-7.7 (m, 3H, Ar-H), 8.38 (dd, J=8.16 Hz, 5.70 Hz, 1H, Ar-H)

IR (KBr, cm^{-1}):	1750 (s), 1720 (s), 1675 (s)
M/S (m/e):	538 $(M+H)^+$, 481 (M^++H, -tert-butyl)
Anal. Calcd.:	C, 53.55; H, 4.12; N, 2.60
Found:	C, 53.49; H, 4.00; N. 2.63.

Step d)

2-[(4-Bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic Acid

A mixture of 2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic acid 1,1-dimethylethyl ester (5.19, 9.81 mmol), CH_2Cl_2 (100 mL) and CF_3CO_2H (20 mL) was stirred at room temperature for 5 hours. The volatiles were removed in vacuo and the residue was

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

purified by flash chromatography on acid washed silica gel (5% H_3PO_4 in MeOH), to give a white solid (4.12 g, 90.5%).

^1H NMR (DMSO-d_6, 400 MHz): δ 3.54 (s, 3H, -$CO_2\underline{CH_3}$), 3.64 (dd, J=17.67 Hz, 2H, -$\underline{CH_2}CO_2H$), 5.12 (dd, J=15.34 Hz, 2H, -$N\underline{CH_2}$-), 7.14 (t, J=8.22 Hz, 1H, Ar-$\underline{H}$), 7.3 (d, J=8.3 Hz, 1H, Ar-$\underline{H}$), 7.5-7.6 (m, 3H, Ar-$\underline{H}$), 7.76 (d, 7.4 Hz, 1H, Ar-$\underline{H}$), 8.16 (d, J=7.8 Hz, 1H, Ar-H), 12.35 (s, 1H, -$CO_2\underline{H}$)

IR (KBr, cm^{-1}): 3280 (m), 3500-2500 (br), 1750 (s), 1720 (s), 1675 (s), 1350 (s), 875 (m)

MS (m/e): 463 (M^+), 445 (M^+-H-OH)

Anal. Calcd. for $C_{20}H_{15}BrFNO_6 \cdot 0.2\ H_2O$: C, 51.28; H, 3.30; N, 2.99
Found: C, 51.26; H, 3.48; N, 2.95
M.P. 139-140°C.

The following compound was obtained in substantially the same manner as that of Example 1, Step d):

2-[(4-Bromo-2-fluorophenyl)methyl]-6-fluoro-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic Acid

^1H NMR (DMSO-d_6, 400 MHz): δ 3.56 (s, 3H, -$CO_2\underline{CH_3}$), 3.6 (d, J=17.9 Hz, 1H, -$\underline{CH_2}CO_2H$), 3.8 (d, J=17.9 Hz, 1H, -$\underline{CH_2}CO_2H$), 5.1 (dd, J=15.5 Hz, 2H, -$N\underline{CH_2}$-), 7.12 (d, J=8.23 Hz, 1H, Ar-$\underline{H}$), 7.31 (dd, J=8.28 Hz, 1.68 Hz, 1H, Ar-$\underline{H}$), 7.45 (dt, J=8.56 Hz, 2.5 Hz, 1H, Ar-$\underline{H}$), 7.54 (dd, J=9.77 Hz, 1.89 Hz, 1H, Ar-$\underline{H}$), 7.64 (dd, J=9.61 Hz, 2.46 Hz, 1H, Ar-$\underline{H}$), 8.23 (dd, J=8.79 Hz, 5.81 Hz, 1H, Ar-$\underline{H}$), 12.67 (brs, 1H, -$CO_2\underline{H}$)

IR (KBr, cm^{-1}): 3400-2700 (br), 1745 (s), 1710 (s), 1670 (s), 770 (m)
MS (m/e): 481 (M^+), 405 (M^+-CO_2, -CH_3OH)

Anal. Cald.: C, 49.81; H, 2.93; N, 2.90
Found: C, 49.94; H, 3.03; N, 2.84

M.P. 132-133.5°C.

This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

Steps e, f)

2-[4-Bromo-2-fluorophenyl)methyl]-1'-ethylspiro[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

A mixture of 2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic acid (2.0 g, 4.31 mmol) and $SOCl_2$ (10 g) was refluxed for 1 hour. The volatiles were removed in vacuo and the acid chloride was dissolved in THF (10 mL). In a second flask was placed a freshly prepared saturated NH_2Et/THF solution (20 mL) and the contents of the first flask were added slowly. After 10 minutes the mixture was poured into H_2O, acidified with HCl (2N), extracted with EtOAc and the organic extracts were dried over $MgSO_4$. Evaporation gave a crude product which was dissolved in DMF (10 mL) and NaH (80% dispersion in oil, 129.3 mg, 4.31 mmol) was added portionwise. After 20 minutes the mixture was quenched with HCl (2N), extracted with EtOAc and dried over $MgSO_4$. Purification by flash chromatography (hexane/EtOAc, 4/1) and crystallization from ether/hexane (at -20°C) gave a white solid (1.4 g, 70.7%).

^1H NMR (DMSO-d_6, 400 MHz): δ 1.01 (t, J=7.2 Hz, 3H, -$NCH_2\underline{CH_3}$), 3.4 (d, J=18.2 Hz, 1H, -$\underline{CH_2}$CONEt-), 3.48 (q, J=7.2 Hz, 2H, -$N\underline{CH_2}CH_3$), 3.52 (d, J=18.2 Hz, 1H, -$\underline{CH_2}$CONEt-), 5.07 (s, 2H, -$N\underline{CH_2}$-), 7.15 (t, J=8.23 Hz, 1H, Ar-H), 7.33 (dd, J=8.3 Hz, 1.76 Hz, 1H, Ar-H), 7.53 (dd, J=9.84 Hz, 1.9 Hz, 1H, Ar-H), 7.61-7.65 (m, 2H, Ar-H), 7.78 (dt, J=7.65 Hz, 1.43 Hz, 1H, Ar-H), 8.17 (dd, J=8.19 Hz, 1.49 Hz, 1H, Ar-H)

IR (KBr, cm^{-1}):	1720 (s), 1690 (s)
MS (m/e):	458 (M^+), 387 (M^+-CONEt-), 359 (M^+-CONEtCO-)
Anal. Calcd.:	C, 54.92; H, 3.51; N, 6.10
Found:	C, 54.92; H, 3.40; N, 6.13

M.P. 153-154°C.

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

The following compound was obtained in substantially the same manner as that of Example 1, Steps e, f):

2-[(4-Bromo-2-fluorophenyl)methyl]-1'-ethyl-6-fluorospiro[isoquinoline-4(H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.0 (t, J=7.17 Hz, 3H, -NCH$_2$CH$_3$), 3.41-3.48 (m, 4H, -CH$_2$CONEt-, -NCH$_2$CH$_3$), 5.05 (s, 2H, -NCH$_2$-), 7.14 (t, J=8.2 Hz, 1H, Ar-H), 7.33 (dd, J=8.2 Hz, 1.66 Hz, 1H, Ar-H), 7.47 (dt, J=8.6 Hz, 2.47 Hz, 1H, Ar-H), 7.52 (dd, J=9.8 Hz, 1.9 Hz, 1H, Ar-H), 7.72 (dd, J=9.8 Hz, 1H, 2.42 Hz, 1H, Ar-H), 8.23 (dd, J=8.8 Hz, 5.86 Hz, 1H, Ar-H)

IR (KBr, cm^{-1}):	1720 (s), 1695 (s)
M/S (m/e):	476 (M$^+$), 405 (M$^+$-CONEt-), 377 (M$^+$-CONEtCO-)
Anal. Calcd.:	C, 52.85; H, 3.17; N, 5.87
Found:	C, 52.71; H, 2.97; N, 5.84

M.P. 185-186°C.

EXAMPLE 1A

2-[(4-Bromo-2-fluorophenyl)methyl]-1'-methylspiro[isoquinoline-4(H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

A mixture of 2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic acid (2.0 g, 4.31 mmol) and $SOCl_2$ (10 g) was refluxed for 1 hour. The volatiles were removed in vacuo and the acid chloride was dissolved in THF (10 mL). In a second flask was placed a freshly prepared saturated NH_2Me/THF solution (20 mL) and the contents of the first flask were added slowly. After 10 minutes the mixture was poured into H_2O, acidified with HCl (2N), extracted with EtOAc and the organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc, 4/1) gave an off-white solid which was recrystallized from ether/hexane (at -20°C) to give a white solid (1.2 g, 62.5%).

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

^{1}NMR (DMSO-d_6, 400 MHz): δ 2.93 (s, 3H, $\underline{CH_3}$), 3.32 (s, 3H, -$CO_2\underline{CH_3}$), 3.41 (d, J=18.2 Hz, 1H, -$\underline{CH_2}$CONMe-), 3.54 (d, J=18.2 Hz, 1H, -$\underline{CH_2}$CONMe-), 5.07 (s, 2H, -N$\underline{CH_2}$-), 7.16 (t, J=8.3 Hz, 1H, Ar-$\underline{H}$), 7.33 (dd, J=8.3 Hz, 2.5 Hz, 1H, Ar-$\underline{H}$), 7.54 (dd, J=9.96 Hz, 2.07 Hz, 1H, Ar-$\underline{H}$), 7.61-7.67 (m, 2H, Ar-$\underline{H}$), 7.77 (dt, J=7.26 Hz, 1.45 Hz, 1H, Ar-$\underline{H}$), 8.16 (dd, J=8.3 Hz, 1.87 Hz, 1H, Ar-$\underline{H}$)

IR (KBr, cm^{-1}):	1710 (s), 1680 (s)
MS (m/e):	444 (M^+), 387 (M^+-CONMe-), 359 (M^+-CONMeCO-)
Anal. Calcd.:	C, 53.95; H, 3.17; N, 6.29
Found:	C, 53.69; H, 2.87; N, 6.21

M.P. 78-79°C.

EXAMPLE 2

2-[[5-(Trifluoromethyl)-2-benzothiazolyl]methyl]-1'-methylspiro[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

Step g)

3-Methoxy-1-oxo-1H-2-benzopyran-4-carboxylic Acid Methyl Ester

A mixture of (2-carboxyphenyl)propanedioic acid dimethyl ester (10.09 g, 39.68 mmol) and $SOCl_2$ (100 g) was refluxed for 2 hours. The volatiles were removed $\underline{in\ vacuo}$ and the crude product (acid chloride) was dissolved in THF (200 mL). Triethylamine (27.64 mL, 198.4 mmol) was added and the mixture was stirred for 30 minutes. The yellowish suspension was poured into HCl (1N, 1000 mL), extracted with EtOAc and the organic extracts were dried over $MgSO_4$. Evaporation and crystallization from acetone/ether/hexane (at -20°C) gave a white solid (87.6 g, 94.4%).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.82 (s, 3H, -$CO_2\underline{Me}$), 4.03 (s, 3H, -O$\underline{Me}$), 7.42 (t, J=7.26 Hz, 1H, Ar-$\underline{H}$), 7.8 (t, J=8.2 Hz, 1H, Ar-$\underline{H}$), 7.9 (d, J=8.3 Hz, 1H, Ar-$\underline{H}$), 8.1 (d, J=7.26 Hz, 1H, Ar-$\underline{H}$).

IR (KBr, cm^{-1}):	1740 (C=O), 1685 (C=O)
MS (m/e):	234 (16, M^+), 206 (38.5, M^+-CO), 203 (12, M^+-OMe)

This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

Anal. Calcd.: C, 61.59; H, 4.30
Found: C, 61.82; H, 4.29

M.P. 129-130°C.

The following compound was prepared in substantially the same manner as that of Example 1, Step g):

6-Fluoro-3-methoxy-1-oxo-1H-2-benzopyran-4-carboxylic Acid Methyl Ester

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.81 (s, 3H, -$CO_2\underline{CH_3}$), 4.06 (s, 3H, -$O\underline{CH_3}$), 7.27 (dt, J=8.3 Hz, 1H, Ar-H), 7.8 (dd, J=11.83 Hz, 2.49 Hz, 1H, Ar-H), 8.16 (dd, J=8.92 Hz, 6.2 Hz, 1H, Ar-H)

IR (KBr, cm^{-1}): 1750 (C=O), 1685 (C=O)

MS (m/e): 252 (24, M^+), 224 (54, M^+-CO)

Anal. Calcd.: C, 57.15; H, 3.60
Found: C, 57.19; H, 3.57

M.P. 142-143°C.

Step h)

2-(Cyanomethyl)-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinoline carboxylic Acid Methyl Ester

To a solution of 3-methoxy-1-oxo-1H-2-benzopyran-4-carboxylic acid methyl ester (8.0 g, 34.19 mmol) in DMF (100 mL) was added aminoacetonitrile hydrochloride (6.32 g, 68.37 mmol) and the suspension was stirred until all the materials have dissolved. Triethylamine (14.3 mL, 102.57 mmol) was added and the mixture was stirred at 100°C for 30 minutes, and then poured into H_2O, acidified with HCl (2N) and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and crystallization from acetone/ether/hexane (at -20°C) gave a yellowish solid (6.5 g, 73.7%).

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

^{1}H NMR (DMSO-d_6, 400 MHz): δ [3.7 (s), 3.98 (s), 3H, -$CO_2\underline{CH_3}$, rotameric], [4.92 (s), 5.44 (s), 2H, -$N\underline{CH_2}CN$, rotameric], 7.2-8.4 (m, 4H, Ar-$\underline{H}$, rotameric)

IR (KBr, cm^{-1}): 3400 (OH), 1670 (C=O)

MS (m/e): 258 (20, M^+), 226 (43, M^+-MeOH), 199 (13, M^+-CO_2Me)

Anal. Calcd.: C, 60.47; H, 3.90; N, 10.85
Found: C, 60.27; H, 3.77; N, 10.69

M.P. 169-171°C.

The following compound was prepared in substantially the same manner as that of Example 1, Step h):

2-(Cyanomethyl)-6-fluoro-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinoline carboxylic Acid Methyl Ester

Anal. Calcd.: C, 56.53; H, 3.28; N, 10.14
Found: C, 56.45; H, 3.22; N, 10.13

M.P. 178-179°C.

Step i)

2-(Cyanomethyl)-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic Acid 1,1-Dimethylethyl Ester

To a suspension of 2-(cyanomethyl)-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinoline carboxylic acid methyl ester (6.5 g, 25.19 mmol), K_2CO_3 (6.95 g, 50.38 mmol) and anhydrous DMF (100 mL) was added tert-butyl bromoacetate (6.1 mL, 37.79 mmol). After stirring at 85°C for 3 hours, the mixture was poured into H_2O, acidified with HCl (2N) and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography on silica gel (hexane/EtOAc 4/1) gave a white solid (8.5 g, 90.7%).

This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.03 (s, 9H, -CO_2 $\underline{CMe_3}$), 3.58 (s, 3H, -$CO_2\underline{CH_3}$), 3.64 (s, 2H, -$\underline{CH_2}CO_2$-), 5.05 (s, 2H, -N$\underline{CH_2}$CN), 7.64 (m, 2H, Ar-$\underline{H}$), 7.78 (dd, J=7.4 Hz, 2.0 Hz, 1H, Ar-$\underline{H}$), 8.24 (dd, J=8.2 Hz, 1.6 Hz, 1H, Ar-$\underline{H}$)

IR (KBr, cm^{-1}): 1745 (C=O), 1730 (C=O), 1670 (C=O)

MS (m/e): 373 (38, M^+ + H), 317 (100, M^+ + H, -CME_3)

Anal. Calcd.:	C, 61.28; H, 5.41; N, 7.52
Found:	C, 61.61; H, 5.49; N, 7.13

M.P. 48-50°C.

The following compound was obtained in substantially the same manner as that of Example 1, Step i):

2-(Cyanomethyl)-6-fluoro-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic Acid 1,1-Dimethylethyl Ester

Anal. Calcd.:	C, 58.46; H, 4.91; N, 7.18
Found:	C, 58.65; H, 4.98; N, 7.08

M.P. 133-135°C.

Step j)

1,2,3,4-Tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-2-[[(5-trifluoromethyl)-2-benzothiazolyl]methyl]-4-isoquinolineacetic Acid

To a mixture of 3-amino-4-mercaptobenzotrifluoride hydrochloride (6.1 g, 26.2 mmol) and EtOH (150 mL) was added Et_3N (3.65 mL). After stirring for 10 minutes, 2-(cyanomethyl)-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinoline-acetic acid 1,1-dimethylethyl ester (6.5 g, 17.47 mmol) was added and the mixture was refluxed for 15 hours, poured into H_2O, acidified with HCl (2N) and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation gave an oil (9.6 g) which was dissolved in CH_2Cl_2 (80 mL). Trifluoroacetic acid (20 mL) was added and the mixture was stirred at room temperature for 8 hours. The volatiles were removed in

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

vacuo and the residue was purified by flash chromatography on acid washed (5%, H_3PO_4 in MeOH) silica gel to give a white solid (6.3 g, 73.3%).

^1H NMR (DMSO-d_6, 400 MHz): δ 3.57 (s, 3H, -$CO_2\underline{CH_3}$), 3.68 (dd, J=17.85 Hz, 2H, -$\underline{CH_2}CO_2H$), 5.61 (s, 2H, -$N\underline{CH_2}$-), 7.62 (m, 2H, Ar-$\underline{H}$), 7.81 (m, 2H, Ar-$\underline{H}$), 8.2 (dd, J=7.9 Hz, 1.04 Hz, 1H, Ar-$\underline{H}$), 8.33 (dd, J=8.5 Hz, 0.92 Hz, 1H, Ar-$\underline{H}$), 8.34 (d, J=0.83 Hz, 1H, Ar-$\underline{H}$)

IR (KBr, cm^{-1}): 3200-2500 (CO_2H), 1750 (C=O), 1710 (C=O), 1670 (C=O)

MS (m/e): 492 (6, M^+), 448 (6, M^+-CO_2), 416 (62, M^+-CO_2, -MeOH)

Anal. Calcd.:	C, 53.66; H, 3.07; N, 5.69
Found:	C, 53.40; H, 3.01; N, 5.54

M.P. 199-201°C.

The following compounds were prepared in substantially the same manner as that of Example 1, Step j):

1,2,3,4-Tetrahydro-4-(methoxycarbonyl-1,3-dioxo-2-[(2-benzothiazolyl)methyl]-4-isoquinolineacetic Acid

Anal. Calcd.:	C, 59.43; H, 3.80; N, 6.60
Found:	C, 59.37; H, 3.74; N, 6.43

M.P. 189-190°C.

6-Fluoro-1,2,3,4-tetrahydro-4-(methoxycarbonyl-1,3-dioxo-2-[[(5-trifluoromethyl)-2-benzothiazolyl]methyl]-4-isoquinolineacetic Acid

Anal. Calcd.:	C, 51.77; H, 2.76; N, 5.49
Found:	C, 51.62; H, 2.97; N, 5.18

M.P. 103-105°C.

This Sheet Has Been Replaced



THIS SHEET HAS BEEN REPLACED

Step k)

2-[(5-Trifluoromethyl)-2-benzothiazolyl]methyl]-1'-methylspiro [isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

A mixture of 1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-2-[[(5-trifluoromethyl)-2-benzothiazolyl)methyl]-4-isoquinolineacetic acid (2.0 g, 4.06 mmol) and $SOCl_2$ (20 g) was refluxed for 1 hour. The volatiles were removed in vacuo and the product (acid chloride) was dissolved in THF (10 mL). To a second flask was placed a freshly prepared, saturated NH_2Me/THF solution (20 mL) and the contents of the first flask were added slowly. After stirring for 10 minutes, the mixture was poured into H_2O (500 mL) acidified with HCl (2N) extracted with EtOAc and dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc 2/1) gave a white solid (1.35 g, 80.3%).

^1H NMR (DMSO-d_6, 400 MHz): δ 2.96 (s, 3H, N-CH_3), 3.43 (d, J=18.26 Hz, 1H, -HCHCO-), 3.56 (d, J=18.26 Hz, 1H, -HCHCO-), 5.56 (s, 2H, -NCH_2-), 7.66 (m, 2H, Ar-H), 7.82 (m, 2H, Ar-H), 8.20 (d, J=7.88 Hz, 1H, Ar-H), 8.33 (m, 2H, Ar-H)

IR (KBr, cm^{-1}): 1720 (C=O), 1700 (C=O), 1670 (C=O)
MS (m/e): 473 (100, M^+)

Anal. Calcd.: C, 55.81; H, 2.98; N, 8.88
Found: C, 56.22; H, 2.97; N, 8.80
M.P. 179-180°C.

The following compound was prepared in substantially the same manner as that of Example 1, Step k):

1'-Ethyl-6-fluoro-2-[[5-(trifluoromethyl)-2-benzothiazolyl]-methyl]spiro[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

Anal. Calcd.: C, 54.66; H, 2.99; N, 8.31
Found: C, 54.97; H, 2.88; N, 8.35
M.P. 154-156°C.

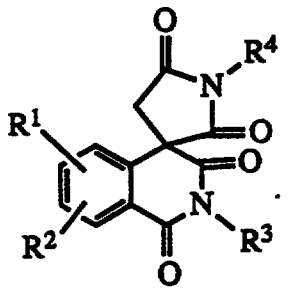
This Sheet Has Been Replaced

* C L M S *

THIS SHEET HAS BEEN REPLACED

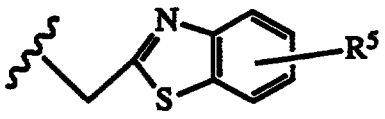
CLAIMS

1. A compound of formula (I)



(I)

wherein R^1 and R^2 are independently hydrogen, alkyl containing 1 to 6 carbon atoms, halogen, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms; R^3 is hydrogen, lower alkyl containing 1 to 6 carbon atoms, aryl, aryl(lower alkyl) or halogen substituted aryl(lower alkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms, or benzothiazole of structural formula



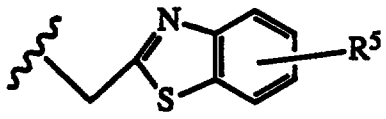
(Ia)

wherein R^5 is hydrogen, halogen, alkyl containing 1 to 6 carbon atoms, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 5 carbon atoms; and R^4 is alkyl containing 1 to 12 carbon atoms, aryl, aryl(loweralkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms, acyl, carboalkoxy, $-(CH_2)_nCO_2H$ or $-(CH_2)_nOH$, wherein n is 1 to 6.

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

2. A compound according to claim 1 wherein R^1 and R^2 are independently hydrogen or halogen; R^3 is a mono- or dihalogen substituted aryl(lower alkyl) wherein aryl contains 6 carbon atoms and lower alkyl contains 1 to 3 carbon atoms, or benzothiazole of structural formula



wherein R^5 is hydrogen, halogen or trifluoromethyl; and R^4 is alkyl containing 1 to 3 carbon atoms.

3. A compound according to claim 2 which is

2-[(4-bromo-2-fluorophenyl)methyl]-1'-methylspiro[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone.

4. A compound according to claim 2 which is

2-[(4-bromo-2-fluorophenyl)methyl]-1'-ethylspiro[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone.

5. A compound according to claim 2 which is

2-[(4-bromo-2-fluorophenyl)methyl]-1'-ethyl-6-fluorospiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone.

6. A compound according to claim 2 which is

2-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-1'-methylspiro[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone.

7. A compound according to claim 2 which is

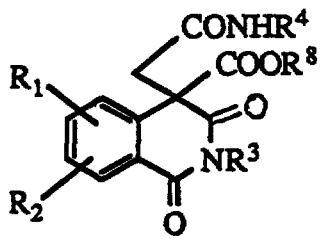
1'-ethyl-6-fluoro-2-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]spiro-[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone.

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

8. A process for preparing a compound of formula I as claimed in Claim 1 which comprises one of the following:

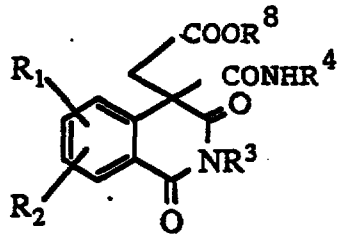
a) cyclising an amide of formula (A)



(A)

wherein R^1, R^2, R^3 and R^4 are as defined in Claim 1 and $COOR^8$ is an ester group, using a suitable base to give a compound of formula I;

b) cyclising a compound of formula (B)



(B)

wherein R^1, R^2, R^3 and $COOR^8$ are as defined above using a suitable base to give a compound of formula I;

or

c) acylating a compound of formula I as shown in Claim 1 wherein R^4 is hydrogen and R^{1-3} are as defined in Claim 1 to give a corresponding compound of formula I wherein R^4 is acyl or carboalkoxy.

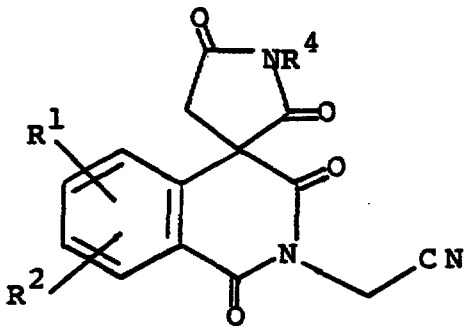
This Sheet Has Been Replaced

* C L M S *

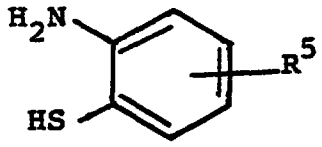
THIS SHEET HAS BEEN REPLACED

or

d) reacting a compound of formula



with a 2-aminothiophenol of formula



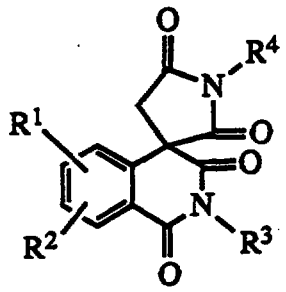
in which formulae R^1, R^2, R^4 and R^5 are as defined in Claim 1 to give a compound of formula I wherein R^3 is a benzothiazolylmethyl group of formula Ia.

This Sheet Has Been Replaced

* C L M S *

THIS SHEET HAS BEEN REPLACED

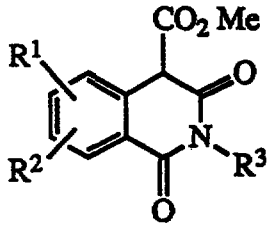
9. A process for preparing a compound of formula (I)



(I)

wherein R^1 and R^2 are independently hydrogen, alkyl containing 1 to 6 carbon atoms, halogen, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms; R^3 is hydrogen, lower alkyl containing 1 to 6 carbon atoms, aryl, aryl(lower alkyl) or halogen substituted aryl(lower alkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms; R^4 is alkyl containing 1 to 12 carbon atoms, aryl, aryl(lower alkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms, acyl, carboalkoxy, or $-(CH_2)_nCO_2H$, $-(CH_2)_n OH$, wherein n is 1 to 6 which comprises:

a) reacting the compound of formula (IV)

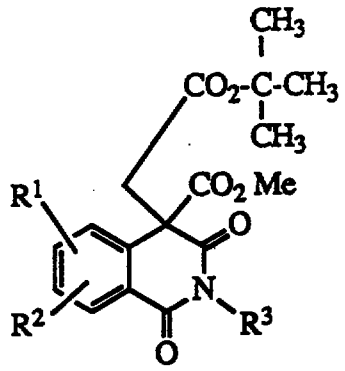


(IV)

wherein R^1, R^2, and R^3 are as defined above with an inorganic base in a conventional solvent and subsequently adding tert-butyl bromoacetate to produce the compound of the formula (V)

This Sheet Has Been Replaced

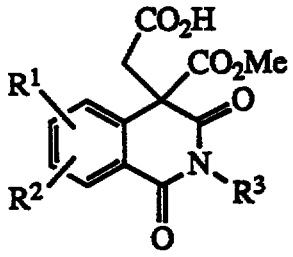
THIS SHEET HAS BEEN REPLACED



(V)

wherein R^1, R^2, and R^3 are as defined above;

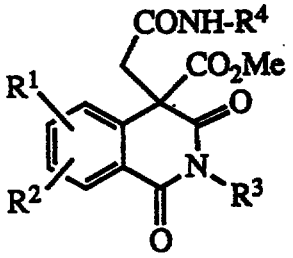
b) hydrolyzing said compound of formula (V) with an organic acid in a conventional solvent to produce the compound of formula (VI)



(VI)

wherein R^1, R^2, and R^3 are as defined above;

c) reacting said compound of formula (VI) with a coupling agent in a conventional solvent and subsequently adding R^4-NH_2 to produce the compound of formula (VII)



(VII)

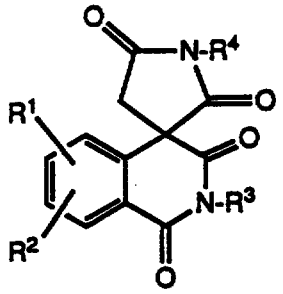
wherein R^1, R^2, R^3, and R^4 are as defined above;

d) reacting said compound of formula (VII) with a base in a conventional solvent to product the compound of formula (I).

This Sheet Has Been Replaced

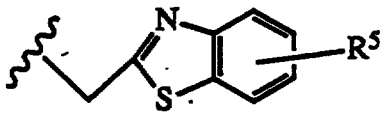
THIS SHEET HAS BEEN REPLACED

10. A process for the preparation of a compound of formula (I).



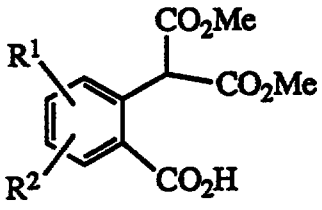
(I)

wherein R^1 and R^2 are independently hydrogen, alkyl containing 1 to 6 carbon atoms, halogen, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms; R^3 is benzothiazole of structural formula



wherein R^5 is hydrogen, halogen alkyl containing 1 to 6 carbon atoms, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 5 carbon atoms, and R^4 is alkyl containing 1 to 12 carbon atoms, aryl, aryl(lower alkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms, acyl, carboalkoxy, or $-(CH_2)_nCO_2H$, $-(CH_2)_nOH$, wherein n is 1 to 6 which comprises:

a) reacting the compound of formula (III)

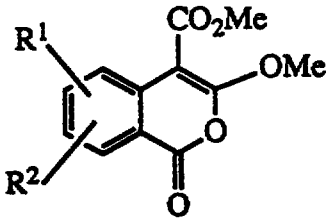


(III)

wherein R^1 and R^2 are as defined above with $SOCl_2$ and subsequent treatment with Et_3N in a conventional solvent to produce the compound of formula (VIII)

This Sheet Has Been Replaced

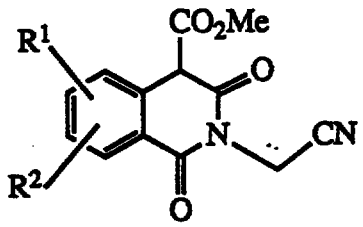
THIS SHEET HAS BEEN REPLACED



(VIII)

wherein R^1 and R^2 are as defined above

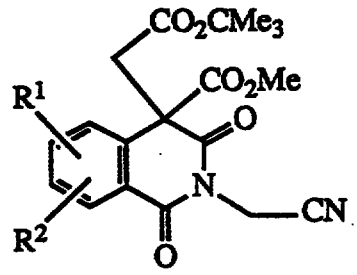
b) reacting said compound of formula (VIII) with aminoacetonitrile hydrochloride in the presence of Et_3N in a conventional solvent to produce the compound of formula (IX)



(IX)

wherein R^1 and R^2 are as defined above

c) reacting said compound of formula (IX) with an inorganic base in a conventional solvent and subsequently adding tert-butyl bromoacetate to produce the compound of formula (X)



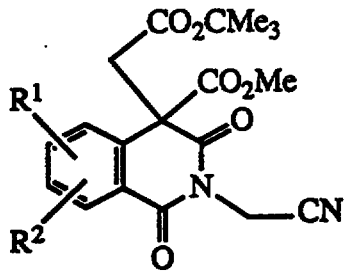
(X)

wherein R^1 and R^2 are as defined above

This Sheet Has Been Replaced

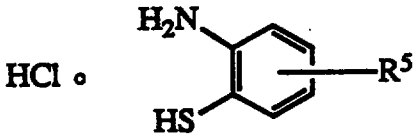
THIS SHEET HAS BEEN REPLACED

d) reacting said compound of formula (X)

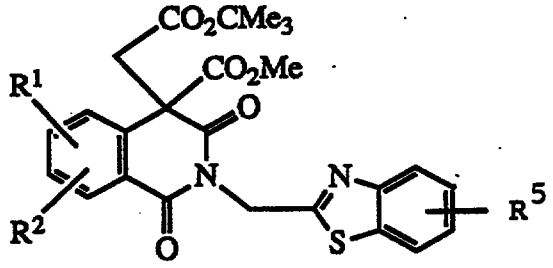


(X)

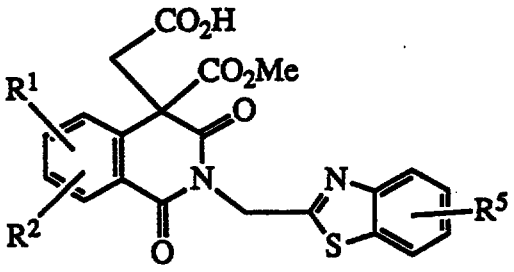
with a 2-aminothiophenol of structural formula



wherein R^5 is as defined above to produce the tert-butyl ester compound of structural formula



e) hydrolyzing the tert-butyl ester with an organic acid in a conventional solvent to produce compound of formula (XI)



(XI)

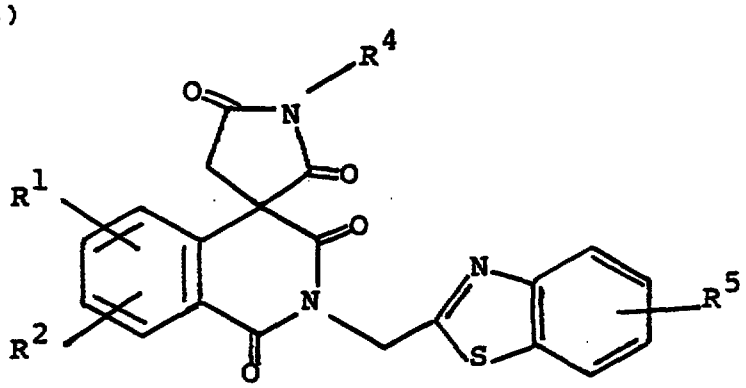
wherein R^1, R^2 and R^5 are as defined above.

This Sheet Has Been Replaced

* C L M S *

THIS SHEET HAS BEEN REPLACED

f) reacting said compound of formula (XI) with thionyl chloride and subsequently adding R^4-NH_2 in a conventional solvent to produce the compound of formula (Ib)



(Ib)

wherein R^1, R^2, R^4 and R^5 are as defined above.

11. A pharmaceutical composition which comprises a compound according to any one of Claims 1 to 7 and a pharmaceutically acceptable carrier.

12. A compound of formula I according to any one of Claims 1 to 7 for use as a pharmaceutical.

13. Use of a compound of formula I as defined in anyone of Claims 1 to 7 in the preparation of a medicament for the treatment or prevention of neuropathy, retinopathy, nephropathy or cataracts in a diabetic mammal.

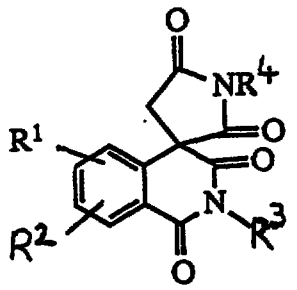
This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

ABSTRACT

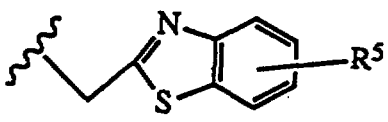
N'ALKYL-SPIRO-ISOQUINOLINE-PYRROLIDINE TETRONES AND ANALOGS THEREOF USEFUL AS ALDOSE REDUCTASE INHIBITORS

This invention relates to N'-alkyl-spiro-isoquinoline-pyrrolidine tetrones of formula



(I)

wherein R^1 and R^2 are independently hydrogen, alkyl containing to 1 to 6 carbon atoms, halogen, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 - 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms; R^3 is hydrogen, lower alkyl containing 1 to 6 carbon atoms, aryl, aryl(lower alkyl) or halogen substituted aryl(lower alkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms, or benzothiazole of structural formula



(Ia)

This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

wherein R^5 is hydrogen, halogen, alkyl containing 1 to 6 carbon atoms, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 5 carbon atoms; and R^4 is alkyl containing 1 to 12 carbon atoms, aryl, aryl(loweralkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms, acyl, carboalkoxy, $-(CH_2)_nCO_2H$ or $-(CH_2)_nOH$, wherein n is 1 to 6. The compounds have pharmaceutical properties which render them beneficial for the prevention of treatment of diabetes mellitus associated complications.

This Sheet Has Been Replaced



REPLACEMENT SHEET
22 NOV 1996

9603831

N'-ALKYL-SPIRO-ISOQUINOLINE-PYRROLIDINE TETRONES AND ANALOGS THEREOF USEFUL AS ALDOSE REDUCTASE INHIBITORS

This invention relates to N'-alkyl-spiro-isoquinoline-pyrrolidine tetrones to processes for their preparation, to methods for using the compounds, and to pharmaceutical preparations thereof. The compounds have pharmaceutical properties which render them beneficial for the prevention or treatment of complications associated with diabetes mellitus.

The use of insulin and/or oral hypoglycemic agents in the treatment of diabetes mellitus has prolonged the life of many of these patients. However, their use has not had a demonstrable impact on the development of diabetic complications such as neuropathy, nephropathy, retinopathy, cataracts and vascular disease which accompany the underlying metabolic disorder. There is little question that chronic hyperglycemia plays a major role in the genesis of these complications, and that complete normalization of blood glucose would likely prevent most if not all complications. For a number of reasons, though, chronic normalization of blood glucose has not been achieved with the currently available therapies.

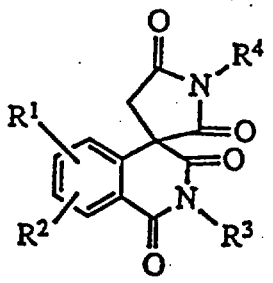
The long-term complications of diabetes develop in tissues where glucose uptake is independent of insulin. In these tissues, which include the lens, retina, kidney and peripheral nerves, the systemic hyperglycemia of diabetes is rapidly transposed into high tissular concentrations of glucose. In all of these tissues this excess glucose is rapidly metabolized by the sorbitol pathway. The intense diabetes-induced flux of glucose through this pathway appears to initiate a cascade of biochemical alterations which slowly progress to cell dysfunction and structural damage. Aldose reductase, the key enzyme in the sorbitol pathway, reduces glucose to sorbitol at the expense of the cofactor NADPH. In animal models of diabetes, compounds which inhibit aldose reductase have been shown to prevent the biochemical, functional and morphological changes induced by hyperglycemia. Early studies by J. H. Kinoshita and collaborators implicated aldose reductase in the etiology of diabetic cataracts. More recent studies have provided compelling evidence that aldose reductase also plays a significant role in the initiation of diabetic nephropathy,

96 03837 -7

REPLACEMENT SHEET
22 NOV 1996
THIS SHEET HAS BEEN REPLACED

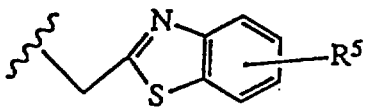
retinopathy and neuropathy (cf McCaleb et al, J Diab. Comp., 2 16,1989; Robinson et al, Invest. Ophthalmol. Vis. Sci., 30, 2285, 1989; Notvest and Inserra, Diabetes, 36, 500,1987.

The N'-alkyl-spiro-isoquinoline-pyrrolidine tetrones of the present invention are represented by formula (I):



(I)

wherein R^1 and R^2 are independently hydrogen, alkyl containing 1 to 6 carbon atoms, halogen, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms; R^3 is hydrogen, lower alkyl containing 1 to 6 carbon atoms, aryl, aryl(lower alkyl) or halogen substituted aryl(lower alkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms, or benzothiazole of structural formula



(Ia)

wherein R^5 is hydrogen, halogen, alkyl containing 1 to 6 carbon atoms, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 5 carbon atoms; and R^4 is alkyl containing 1 to 12 carbon atoms, aryl, aryl(lower alkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms,

This Sheet Has Been Replaced

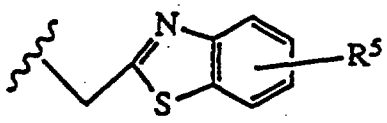
THIS SHEET HAS BEEN REPLACED

REPLACEMENT SHEET
22 NOV 1996

acyl, carboalkoxy, or $-(CH_2)_nCO_2H$, $-(CH_2)_nOH$, wherein n is 1 to 6.

Examples of 'aryl' are phenyl and naphthyl, Examples of acyl are lower alkyl-C(O)- or aryl-C(O)-. Examples of carboalkoxy are loweralkoxy-C(O)-. Examples of halogen are fluorine, chlorine and bromine. Examples of R^1 and/or R^2 are hydrogen or halogen e.g fluorine such as 6-F. Examples of R^3 are (mono- or di-halo substituted phenyl)lower alkyl wherein lower alkyl contains 1 - 3 carbon atoms, or benzothiazolylmethyl of formula Ia wherein R^5 is hydrogen, halogen or trifluoromethyl. For example R^3 may be 4-bromo-2-fluorophenylmethyl or (5-trifluoromethylbenzothiazol-2-yl)methyl. Examples of R^4 are C_1 - C_3 alkyl such as methyl or ethyl.

A more preferred group of compounds of the present invention are the compounds of formula (I) wherein R^1 and R^2 are independently hydrogen or halogen; R^3 is a mono- or dihalogen substituted aryl(loweralkyl) wherein aryl contains 6 carbon atoms and lower alkyl contains 1 to 3 carbon atoms, or benzothiazole of structural formula



(Ia)

wherein R^5 is hydrogen, halogen or trifluoromethyl; and R^4 is alkyl containing 1 to 3 carbon atoms.

The most preferred compounds of the present invention are set forth below:

2-[(4-bromo-2-fluorophenyl)methyl]-1'-methyl-spiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2'3,5'(2H)-tetrone;

This Sheet Has Been Replaced



REPLACEMENT SHEET
22 NOV 1996

2-[(4-bromo-2-fluorophenyl)methyl]-1'-ethylspiro[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone;

2-[(4-bromo-2-fluorophenyl)methyl]-1'-ethyl-6-fluorospiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone;

2-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-1'-methylspiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone;

1'-ethyl-6-fluoro-2-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]spiro-[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone.

The compounds of formula (I) all possess at least one asymmetric carbon atom, namely the spiro carbon atom at position 3' of the pyrrolidine ring. The compounds of formula (I) therefore exist, and may be isolated, in two or more stereoisomeric forms. This invention encompasses the compounds of formula (I) in racemic form or in any optically active form.

The N'-alkyl-spiro-isoquinoline-pyrrolidine tetrones can be prepared by the processes described hereinafter.

A method is provided for preventing or relieving diabetes mellitus associated complications in a diabetic mammal by administering to said mammal a prophylactic or alleviating amount of the compounds of formula (I). Such complications include neuropathy, nephropathy, retinopathy, keratopathy, diabetic uveitis, and cataracts.

The compounds of formula (I), when admixed with a pharmaceutically acceptable carrier, form a pharmaceutical composition which can be used according to the preceding method.

The N'-alkyl-spiro-isoquinoline-pyrrolidine tetrones of this invention may be administered to mammals, for example, man, cattle, or rabbits, either alone or in dosage forms, i.e., capsules or tablets, combined with pharmacologically acceptable excipients.

THIS SHEET HAS BEEN REPLACED

REPLACEMENT SHEET
22 NOV 1996

The compounds of this invention may be given orally. However, the method of administering the present active ingredients of this invention is not to be construed as limited to a particular mode of administration. For example, the compounds may be administered topically directly to the eye in the form of drops of sterile, buffered ophthalmic solutions, preferably of pH 7.2-7.6. Also, they may be administered orally in solid form containing such excipients as starch, milk sugar, certain types of clay and so forth. They may also be administered orally in the form of solutions or they may be injected parenterally. For parenteral administration, they may be used in the form of a sterile solution, preferaby of pH 7.2-7.6, containing a pharmaceutically acceptable buffer.

The dosage of the N'-alkyl-spiro-isoquinoline-pyrrolidine tetrones will vary with the form of administration and the particular compound chosen. Furthermore, it will vary with the particular host under treatment. Generally, treatment is initiated with small dosages substantially less than the optimal dose of the compound. Thereafter, the dosage is increased by small increments until efficacy is obtained. In general, the compounds of this invention are most desirably administered at a concentration level that will generally afford effective results without causing any harmful or deleterious side effects. For topical administration, a 0.05-1.0% solution may be administered dropwise in the eye. The frequency of instillation varies with the subject under treatment from a drop every two or three days to once daily. For oral or parenteral administration a preferred level of dosage ranges from about 0.1 mg to about 1.0 mg per kilo of body weight per day, although aforementioned variations will occur. However, a dosage level that is in the range of from about 0.1 mg to about 1.0 mg per kilo of body weight per day is most satisfactory.

Unit dosage forms such as capsules, tablets, pills and the like may contain from about 5.0 mg to about 25.0 mg of the active ingredients of this invention with a pharmaceutical carrier. Thus, for oral administration, capsules can contain from between about 5.0 mg to about 25.0 mg of the active ingredients of this invention with or without a pharmaceutical diluent. Tablets, either effervescent or noneffervescent, can contain between about 5.0 to 25.0 mg of the active ingredients of this invention together with conventional pharmaceutical carriers. Thus tablets, which may be coated and either effervescent or noneffervescent, may be prepared according to the known art. Inert diluents or carriers, for example, magnesium carbonate or lactose, can be used together with conventional disintegrating agents for example, magnesium stearate.

This Sheet Has Been Replaced

REPLACEMENT SHEET
22 NOV 1996

The N'-alkyl-spiro-isoquinoline-pyrrolidine tetrones also can be used in combination with insulin or oral hypoglycemic agents to produce a beneficial effect in the treatment of diabetes mellitus. In this instance, commercially available insulin preparations or oral hypoglycemic agents, exemplified by acetohexamide, chlorpropamide, tolazamide, tolbutamide and phenformin, are suitable. The compounds hereof can be administered sequentially or simultaneously with insulin or the oral hypoglycemic agent. Suitable methods of administration, compositions and doses of the insulin preparation or oral hypoglycemic agent are described in medical textbooks; for instance, Physicians' Desk Reference, 42 ed., Medical Economics Co., Oradell, N.J., U.S.A., 1988.

The aldose reductase inhibiting property of the compounds of this invention and the utilization of the compounds in preventing, diminishing and alleviating diabetic complications are demonstrable in experiments using galactosemic rats, see Dvornik et al., Science, 182, 1146 (1973). Such experiments are exemplified hereinbelow after the listing of the following general comments pertaining to these experiments:

(a) Four or more groups of six male rats, 50-70 g, Sprague-Dawley strain, were used. The first group, the control group, was fed a mixture of laboratory chow (rodent Laboratory Chow, Purina) and glucose at 20% (w/w %) concentration. An untreated galactosemic group was fed a similar diet in which galactose was substituted for glucose. The third group was fed a diet prepared by mixing a given amount of the test compound with the galactose containing diet. The concentration of galactose in the diet of the treated groups was the same as that for the untreated galactosemic group.

(b) After four days, the animals were killed by euthanization. Both the lens and sciatic nerve were removed, weighed and stored frozen for polyol determination.

(c) The polyol determination was performed by a modification of the procedure of M. Kraml and L. Cosyns, Clin. Biochem., 2, 373 (1969). Only two minor reagent changes were made: (a) the rinsing mixture was an aqueous 5% (w/v) trichloroacetic acid solution and (b) the stock solution was prepared by dissolving 25 mg of dulcitol in 100 mL of an aqueous trichloroacetic acid solution. [N.B.: For each experiment the average value found in the tissue from rats fed the glucose diet was

THIS SHEET HAS BEEN REPLACED

REPLACEMENT SHEET
22 NOV 1996

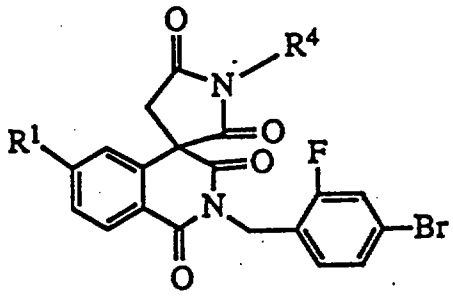
subtracted from the individual values found in the corresponding tissue in galactose-fed rats to obtain the amount of polyol accumulated.] The aldose reductase inhibiting effects of the compounds of formula (I) were also tested by employing an in vitro testing procedure similar to that described by S. Hayman and J.H. Kinoshita, J. Biol. Chem., 240, 877 (1965). In the present case the procedure of Hayman and Kinoshita was modified in that the final chromatography step was omitted in the preparation of the enzyme from bovine lens.

The following tabulated results show that the N'-alkyl-spiro-isoquinoline-pyrrolidine tetrones of this invention show the property that they are active both in vitro and in vivo and diminish the accumulation of dulcitol in the lenses, sciatic nerves and diaphragm of rats fed galactose. The figures under L, N, and D represent the percentage decrease of dulcitol accumulation in the tissues of the lens, sciatic nerve, and diaphragm, respectively, for treated rats as compared to untreated rats.

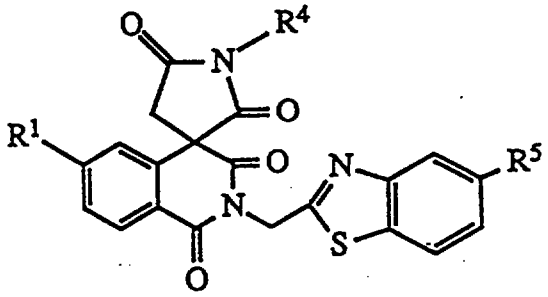
This Sheet Has Been Replaced

REPLACEMENT SHEET
22 NOV 1996

ALDOSE REDUCTASE INHIBITORS



		% inhibition in vitro	% lowering dulcitol accumulation dose	in vivo		
R^1	R^4	10^{-5}M	mg/kg	%L	%N	%D
H	$-CH_3$	0	0.5	NS	50	61
			1.1	NS	76	75
			10.2	31	95	94
H	$-CH_2CH_3$	0	0.5	NS	37	56
			0.9	NS	65	73
F	$-CH_2CH_3$	0	0.5	NS	19	65
			1.0	NS	74	84



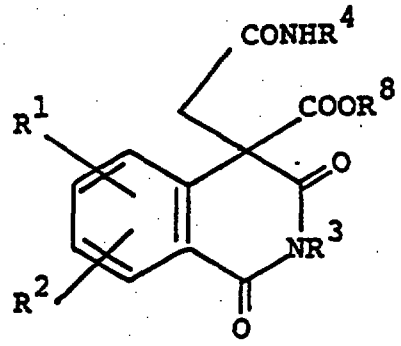
			% Inhibition In Vitro	% Lowering Galactitol Accumulation In Vivo		
				Dose			
R^1	R^4	R^5	10^{-6}M	mg/kg/day	(%)L	(%)N	(%)D
H	CH_3	CF_3	0	9.5	NS	82	100
F	C_2H_5	CF_3	0	10	NS	NS	59

THIS SHEET HAS BEEN REPLACED

REPLACEMENT SHEET
22 NOV 1996

This invention provides processes for preparing compounds of formula I. These processes include:

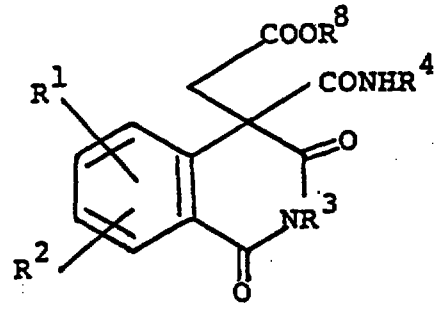
a) cyclising an amide of formula (A)



(A)

wherein R^1, R^2, R^3 and R^4 are as defined above and $COOR^8$ is ester group, using a suitable base such as sodium hydride to give a compound of formula I;
or

b) cyclising a compound of formula (B)



(B)

wherein R^1, R^2, R^3, R^4 and $COOR^8$ are as defined above using a suitable base such as sodium hydride or lithium bis-(trimethylsilyl)amide to give a compound of formula I;
or

c) acylating a compound of formula I as shown above wherein R^4 is hydrogen and R^{1-3} are as defined above to give a corresponding compound of formula I wherein R^4 is acyl or carboalkoxy;

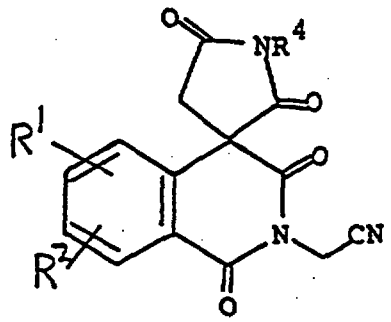
This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

REPLACEMENT SHEET
22 NOV 1996

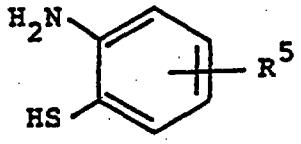
or

d) reacting a compound of formula



(D)

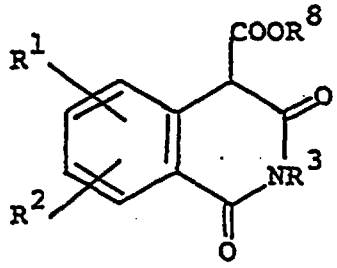
with a 2-aminothiophenol of formula



(E)

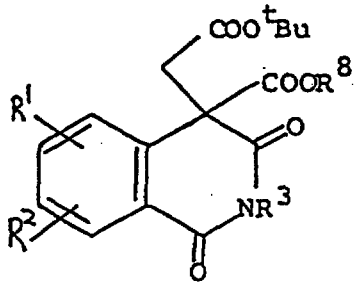
to give a compound of formula I wherein R^3 is a benzothiazolylmethyl group of formula Ia.

Starting materials of formulae (A) and (B) can be prepared via intermediates of formula (G) shown below:



(G)

wherein R^1, R^2, R^3, and $COOR^8$ are as defined above. Examples of R^8 are alkyl groups such as C_1-C_4 alkyl especially methyl. R^8 may also be ^tBu. For example compounds of formula (A) are prepared by reacting a compound of formula (G) with $Br(CH_2)_n$- CO_2-^tBu in the presence of a suitable base e.g Li-$N(SiMe_3)_2$ to give a compound of formula



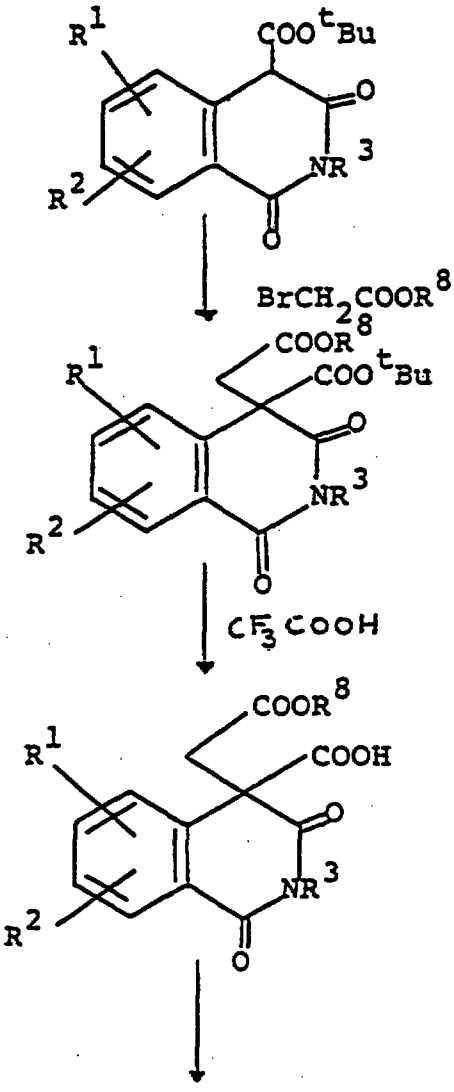
(H)

This Sheet Has Been Replaced

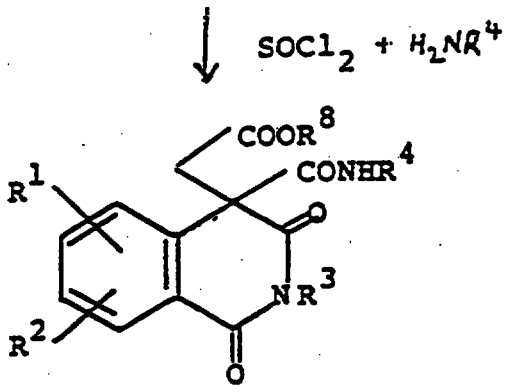
REPLACEMENT SHEET
22 NOV 1996

wherein R^1, R^2 and R^3 are as defined above and $COOR^8$ is an ester group (other than ^tBu ester); treating the compound of formula (H) with trifluoracetic acid to remove the ^tBu group, reacting the resulting acid with a coupling agent, e.g 1-(2-dimethyl-aminopropyl)-2-ethylcarbodiimide in the presence of 1-hydroxy benzotriazole, followed by an amine of formula H_2NR^4 to give the amide of formula (A).

Intermediates of formula (B) may be prepared via the route



REPLACEMENT SHEET
22 NOV 1996



where $COOR^8$ is an ester group providing R^8 is not ^tBu. Other routes to the various intermediates will be apparent to the skilled chemist.

Starting materials for the processes herein described are known compounds or may be prepared by analogous methods.

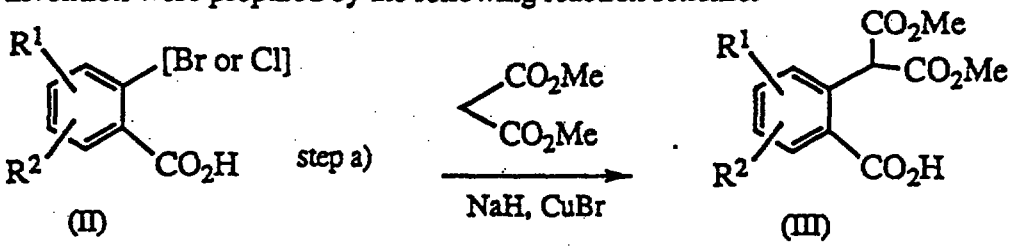
The following processes exemplify the abovementioned routes to compounds of formula I.

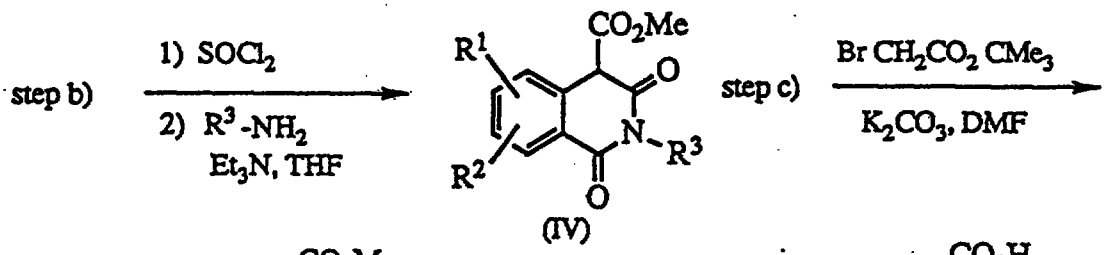
THIS SHEET HAS BEEN REPLACED

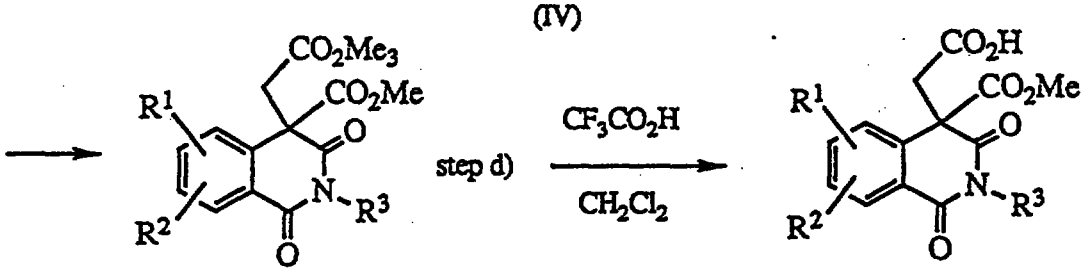
REPLACEMENT SHEET
22 NOV 1996

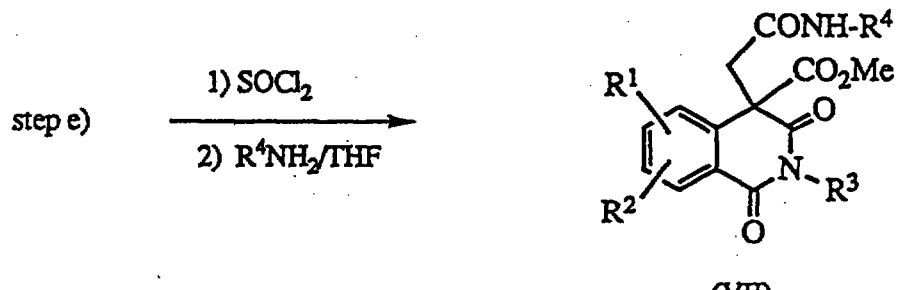
Process A

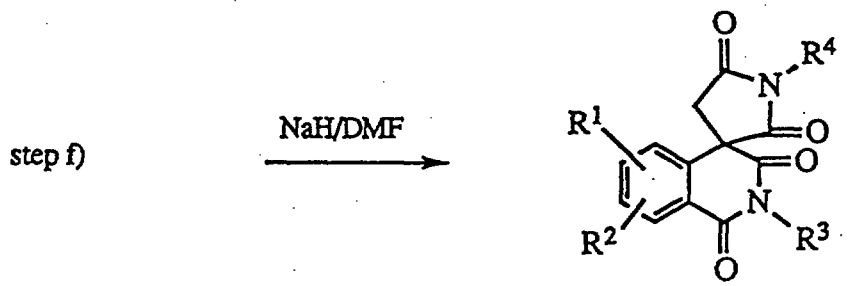
The N'-alkyl-spiro-isoquinoline-pyrrolidine tetrones of the present invention were prepared by the following reaction scheme:





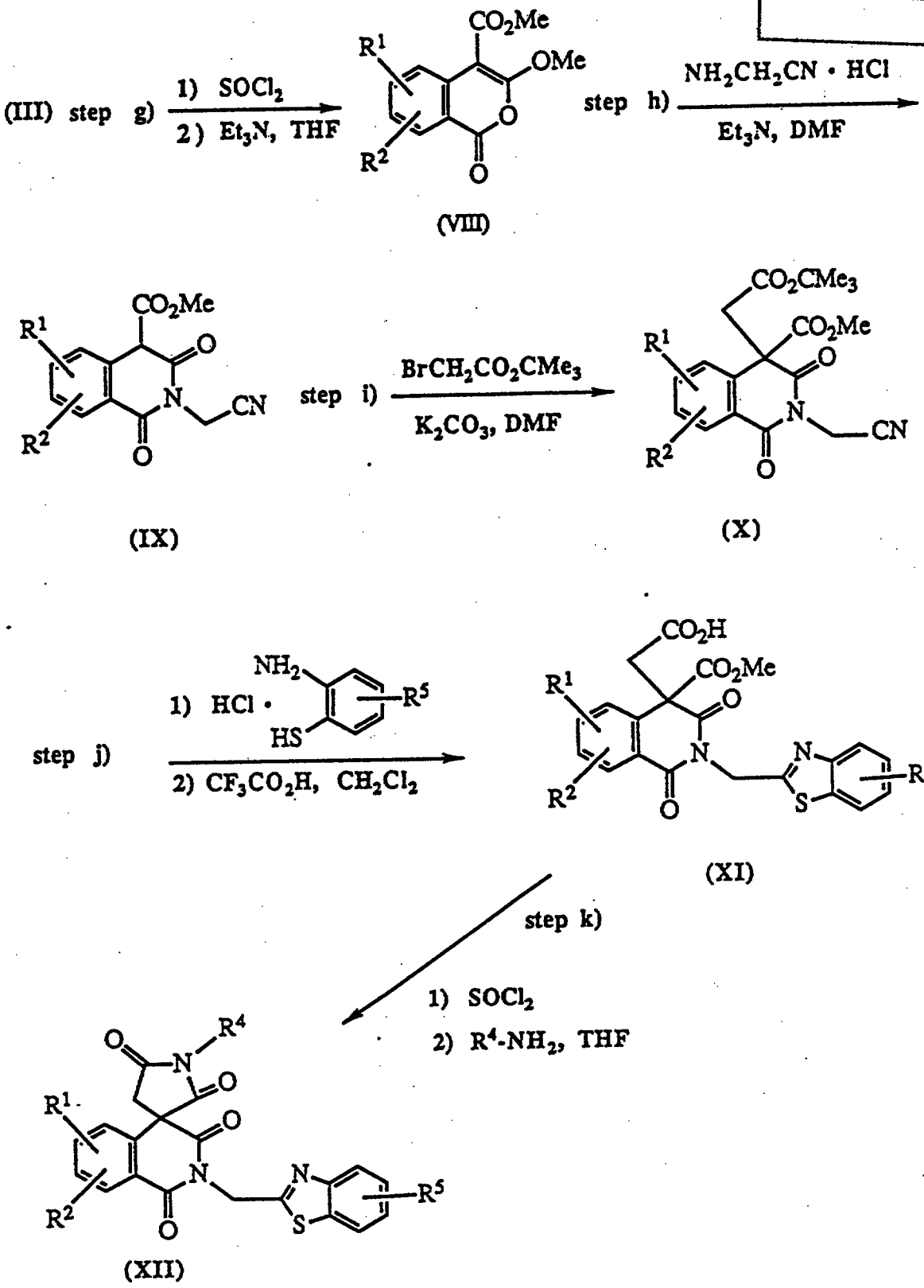






This Sheet Has Been Replaced

REPLACEMENT SHEET
22 NOV 1996



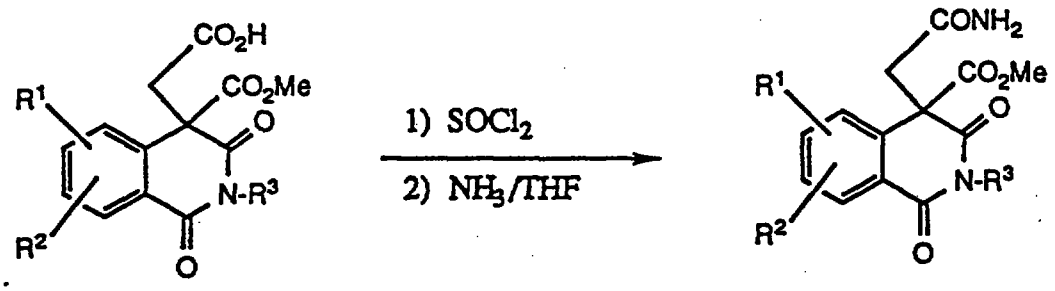
wherein R^1, R^2, R^3, R^4, and R^5 are as defined above.

THIS SHEET HAS BEEN REPLACED

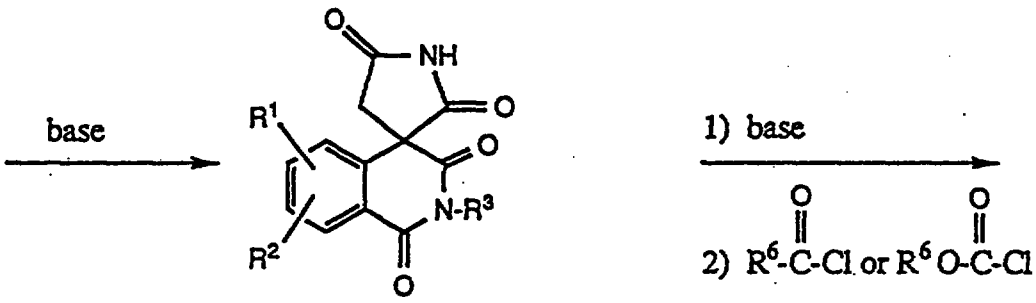
REPLACEMENT SHEET
22 NOV 1996

Process B

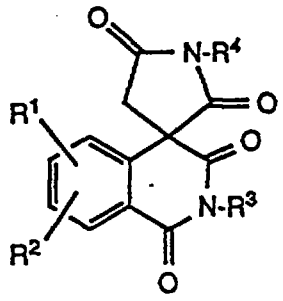
Some compounds of formula (I), wherein R^1, R^2, and R^3 are as defined above and R^4 is acyl or carboalkoxy, can be made by the process B.



(VI)



(R^6 = alkyl, aryl, aralkyl)



(I)

wherein R^1, R^2, and R^3 are as defined above and R^4 is acyl or carboalkoxy.

This Sheet Has Been Replaced

REPLACEMENT SHEET
22 NOV 1996

Step a) Reacting either 2-bromobenzoic acid or 2-chlorobenzoic acid of formula (II) wherein R^1 and R^2 are as defined above with dimethyl malonate and NaH in the presence of a catalytic amount of CuBr to produce the propanedioic acid dimethyl ester of formula (III) wherein R^1 and R^2 are as defined above.

The 2-bromobenzoic acids or 2-chlorobenzoic acids of formula (II) required for the present invention are commerically available compounds or can be prepared by known methods.

Step b) The propanedioic acid dimethyl ester of formula (III) can be reacted with thionyl chloride under refluxing conditions to produce the corresponding acid chloride which upon treatment with an amine R^3 -NH_2 in the presence of triethylamine in a conventional solvent which does not adversely influence the reaction, for example, tetrahydrofuran, can produce the compound of formula (IV) wherein R^1, R^2 and R^3 are as defined above.

Step c) The compound of formula (IV), wherein R^1, R^2 and R^3 are as defined above, is reacted with an inorganic base such as potassium carbonate in a conventional solvent which does not adversely influence the reaction, for example, N,N-dimethylformamide, and subsequent addition of the tert-butyl bromoacetate produces the compound of the formula (V), wherein R^1, R^2 and R^3 are as defined above.

Step d) The compound of formula (V), wherein R^1, R^2 and R^3 are as defined above, is hydrolyzed with an organic acid such as trifluoroacetic acid in a conventional solvent which does not adversely influence the reaction, for example, methylene chloride, to produce the compound of formula (VI), wherein R^1, R^2 and R^3 are as defined above.

Step e) The compound of formula (VI), wherein R^1, R^2 and R^3 are as defined above, can be reacted with thionyl chloride under refluxing conditions to produce the corresponding acid chloride, which upon treatment with R^4-NH_2 wherein R^4 is as defined above produces the amide of formula (VII), wherein R^1, R^2, R^3 and R^4 are as defined above. However, in the case when R^4=Me the initially formed amide (VII, when R^4=Me) cyclizes under these conditions to the final product (I, when R^4=Me).

REPLACEMENT SHEET
22 NOV 1996

Step f) The amide of formula (VII), wherein R^1, R^2, R^3 and R^4 are as defined above, is reacted with a base such as sodium hydride in a conventional solvent which does not adversely influence the reaction, for example, N,N-dimethylformamide, to produce the compound of the formula (I), wherein R^1, R^2, R^3 and R^4 are as defined above.

Step g) The propanedioic acid dimethyl ester of formula (III) can be reacted with thionyl chloride under refluxing conditions to produce the corresponding acid chloride which upon treatment with Et_3N in a conventional solvent which does not adversely influence the reaction, for example, tetrahydrofuran, can produce the compound of formula (VIII), wherein R^1 and R^2 are as defined above.

Step h) The compound of formula (VIII), wherein R^1 and R^2 are as defined above, is reacted with aminoacetonitrile hydrochloride in the presence of Et_3N in a conventional solvent which does not adversely influence the reaction, for example, N,N-dimethylformamide, produces the compound of the formula (IX), wherein R^1 and R^2 are as defined above.

Step i) The compound of formula (IX), wherein R^1 and R^2 are as defined above, is reacted with an inorganic base such as potassium carbonate in a conventional solvent which does not adversely influence the reaction, for example, N,N-dimethylformamide and subsequent addition of the tert-butyl bromoacetate produces the compound of formula (X), wherein R^1 and R^2 are as defined above.

Step j) The compound of formula (X), wherein R^1 and R^2 are as defined above, can be reacted with 2-aminothiophenols (R^5 is as defined above) under refluxing conditions in a conventional solvent which does not adversely influence the reaction, for example, ethyl alcohol, and subsequent treatment of the crude product with an organic acid such as trifluoroacetic acid in a conventional solvent which does not adversely influence the reaction, for example, methylene chloride, to produce the compound of formula (XI), wherein R^1, R^2 and R^5 are as defined above.

Step k) The compound of formula (XI), wherein R^1, R^2 and R^5 are as defined above, can be reacted with thionyl chloride under refluxing conditions to produce the corresponding acid chloride which upon treatment with R^4-NH_2 (wherein R^4 is as defined above) in a conventional solvent which does not adversely influence the

REPLACEMENT SHEE
22 NOV 1996

reaction, for example, tetrahydrofuran, produces the compound of formula (XII), wherein R^1, R^2, R^4, and R^5 are as defined above. However, in the case that the initially formed amide does not cyclize under the reaction conditions, cyclization can be achieved in a similar manner as that of Step f.

The following examples further illustrate this invention:

EXAMPLE 1

2-[(4-Bromo-2-fluorophenyl)methyl]-1'-methylspiro[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

Step a)

(2-Carboxyphenyl)propanedioic Acid Dimethyl Ester

To a rapidly stirred cold suspension (O°C) of 2-bromobenzoic acid (30.0 g, 149.32 mmol), cuprous bromide (2.14 g, 14.93 mmol) and dimethyl malonate (300 mL) was added NaH (80% in mineral oil, 10.75 g, 358.37 mmol) over a 30 minute period, while a stream of dry N_2 was passed over the mixture. After the addition of the NaH had been completed, the mixture was stirred for 10 minutes at room temperature and 30 minutes at 70°C (external oil bath temperature). At this point, the suspension had turned to a solid mass, which was dissolved in H_2O (1000 mL). The aqueous layer was extracted with diethyl ether (3x500 mL) and was acidified with HCl (2N). The mixture was extracted with EtOAc and dried over $MgSO_4$. Evaporation gave an off-white solid which was recrystallized from Et_2O/hexane (-20°C) to give a white solid (34.2 g, 90.9%).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.67 [s, 6H, -CH(CO_2CH_3)$_2$], 5.72 [s, 1H, -CH(CO_2CH_3)$_2$], 7.3 (d, J=7.76 Hz, 1H, Ar-H), 7.45 (dt, J=7.66 Hz, 1.12 Hz, 1H, Ar-H), 7.6 (dt, J=7.66 Hz, 1.45 Hz, 1H, Ar-H), 7.94 (dd, J=7.8 Hz, 1.33 Hz, 1H, Ar-H), 13.2 (s, 1H, -CO_2H)

IR (KBr, cm^{-1}):	3300-2700 (br), 1750 (s), 1730 (s), 1680 (s), 1430 (m), 730 (m)
MS (m/e):	252 (M^+), 220 (M^+-CH_3OH), 188 (M^+-2xCH_3OH)
Anal. Calcd.:	C, 57.14; H, 4.80
Found:	C, 57.05; H, 4.78.
M.P. 119-120°C.	

REPLACEMENT SHEET
22 NOV 1996

The following compound was prepared in substantially the same manner as that of Example 1, Step a):

(2-Carboxy-6-fluorophenyl)propanedioic Acid Dimethyl Ester

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.68 [s, 6H, (–CO_2Me)$_2$], 5.79 (s, 1H, Ar-H), 7.12 (dd, J=10.06 Hz, 2.61 Hz, 1H, Ar-H), 7.33 (dt, J=8.48 Hz, 2.64 Hz, 1H, Ar-H), 8.03 (dd, 8.77 Hz, 6.17 Hz, 1H, Ar-H)

IR (KBr, cm^{-1}): 3400-2700 (br), 1730 (s), 1680 (s), 750 (m)
MS (m/e): 270 (M^+), 238 (M^+-CH_3OH), 210 (M^+-CH_3OH, -CO), 151 (M^+ -CH_3OH, -CO, -CO_2CH_3)
M.P. 121.5-123.0°C.

Step b)

2-[(4-Bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic Acid Methyl Ester

A mixture of (2-carboxyphenyl)propanedioic acid dimethyl ester (5.0 g, 19.84 mmol) and $SOCl_2$ (20 g) was refluxed for 1 and 1/2 hours. The volatiles were removed in vacuo and the acid chloride was dissolved in THF (20 mL). In a second flask were placed 4-bromo-2-fluorobenzylamine (4.67 g, 22.91 mmol), triethylamine (15.96 mL, 114.55 mmol) and THF (150 mL). The contents of the first flask were added to the second flask and the mixture was stirred for 30 minutes. The formed suspension was poured into H_2O (1000 mL), stirred for 10 minutes and acidified with HCl (2N). The mixture was extracted with EtOAc and the organic layer was dried over $MgSO_4$. Evaporation gave a yellowish solid which was recrystallized from acetone/ether/hexane (at -20°C) to yield a white solid (6.01 g, 74.6%).

^{1}H NMR (DMSO-d_6, 400 MHz): δ [3.67, 3.99 (s, 3H, -$CO_2$$CH_3$, tautomeric)], [5.06 (q, J=15.4 Hz), 5.29 (s), 2H, N-CH_2-, tautomeric], 5.03 (s, 1H, -$CHCO_2CH_3$, tautomeric), 7.07-8.44 (m, 7H, Ar-H, tautomeric)

IR (KBr, cm^{-1}): 1675 (s), 1610 (s), 1490 (s), 7.95 (m)
MS (m/e): 405 (M^+), 373 (M^+-MeOH)

REPLACEMENT SHEET
22 NOV 1996

Anal. Calcd.:	C, 53.22; H, 3.23; N, 3.45
Found:	C, 52.91; H, 3.20; N, 3.27

M.P. 149-150°C.

The following compound was prepared in substantially the same manner as that of Example 1, Step b):

2-[(4-Bromo-2-fluorophenyl)methyl]-6-fluoro-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic Acid Methyl Ester

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.98 (s, 3H, -$CO_2\underline{CH_3}$), 5.27 (s, 2H, -$N\underline{CH_2}$-), 7.08 (t, J=7.95 Hz, 2H, Ar-$\underline{H}$), 7.2 (m, 1H, Ar-$\underline{H}$), 7.34 (m, 2H, Ar-$\underline{H}$, -$\underline{OH}$), 7.54 (m, 1H, Ar-$\underline{H}$), 8.1-8.26 (m, 2H, Ar-$\underline{H}$)

IR (KBr, cm^{-1}):	1680 (s), 1660 (s), 1610 (s), 785 (m)
MS (m/e):	423 (M^+), 391 (M^+-CH_3OH)

Anal. Calcd.:	C, 50.97; H, 2.85; N, 3.30
Found:	C, 50.86; H, 2.86; N, 3.33

M.P. 157-158°C.

Step c)

2-[(4-Bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic Acid 1,1-Dimethylethyl Ester

To a suspension of 2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic acid methyl ester (4.79 g, 11.58 mmol), K_2CO_3 (3.19 g, 23.16 mmol) in DMF (100 mL) was added tert-butyl bromoacetate (2.81 mL, 17.37 mmol). After stirring at 75°C for 1 hour, the mixture was poured into H_2O, extracted with EtOAc and dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc, 4/1) gave a clear oil (5.69 g, 94.5%).

REPLACEMENT SHEET
22 NOV 1996

^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.04 [s, 9H, -C($\underline{CH_3}$)$_3$], 3.53 (s, 3H, -CO$_2\underline{CH_3}$), 3.60 [dd, J=17.7 Hz, 2H, -$\underline{CH_2}$CO$_2$C(CH$_3$)$_3$], 5.14 (s, 2H, N$\underline{CH_2}$-), 7.17 (t, J=8.25 Hz, 1H, Ar-$\underline{H}$), 7.36 (dd, J=8.36 Hz, 1.75 Hz, 1H, Ar-$\underline{H}$), 7.6 (m, 3H, Ar-$\underline{H}$), 7.77 (dt, J=7.2 Hz, 1.27 Hz, 1H, Ar-H), 8.19 (dd, J=8.25 Hz, 1.54 Hz, 1H, Ar-$\underline{H}$)

IR ($CHCl_3$, cm^{-1}):	1720 (s), 1675 (s), 1360 (s), 765 (m)
MS (m/e):	520 $(M+H)^+$, 464 [M^+-C(CH$_3$)$_3$].

The following compound was prepared in substantially the same manner as that of Example 1, Step c):

2-[(4-Bromo-2-fluorophenyl)methyl]-6-fluoro-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic Acid 1,1-Dimethylethyl Ester

^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.1 (s, 9H, -C$\underline{Me_3}$), 3.55 (s, 3H, -CO$_2\underline{CH_3}$), 3.62 (d, J=1.75 Hz, 1H, -$\underline{CH_2}$CO$_2$CMe$_3$), 3.75 (d, J=17.5 Hz, 1H, -$\underline{CH_2}$CO$_2$CMe$_3$), 5.15 (s, 2H, -N$\underline{CH_2}$-), 7.15 (t, J=8.2 Hz, 1H, Ar-H), 7.35 (d, J=8.2 Hz, 1H, Ar-$\underline{H}$), 7.45-7.7 (m, 3H, Ar-H), 8.38 (dd, J=8.16 Hz, 5.70 Hz, 1H, Ar-$\underline{H}$)

IR (KBr, cm^{-1}):	1750 (s), 1720 (s), 1675 (s)
M/S (m/e):	538 $(M+H)^+$, 481 (M^++H, -tert-butyl)
Anal. Calcd.:	C, 53.55; H, 4.12; N, 2.60
Found:	C, 53.49; H, 4.00; N. 2.63.

Step d)

2-[(4-Bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic Acid

A mixture of 2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic acid 1,1-dimethylethyl ester (5.19, 9.81 mmol), CH_2Cl_2 (100 mL) and CF_3CO_2H (20 mL) was stirred at room temperature for 5 hours. The volatiles were removed $\underline{in\ vacuo}$ and the residue was

REPLACEMENT SHEET
22 NOV 1996

purified by flash chromatography on acid washed silica gel (5% H_3PO_4 in MeOH), to give a white solid (4.12 g, 90.5%).

^1H NMR (DMSO-d_6, 400 MHz): δ 3.54 (s, 3H, -$CO_2\underline{CH_3}$), 3.64 (dd, J=17.67 Hz, 2H, -$\underline{CH_2}CO_2H$), 5.12 (dd, J=15.34 Hz, 2H, -$N\underline{CH_2}$-), 7.14 (t, J=8.22 Hz, 1H, Ar-$\underline{H}$), 7.3 (d, J=8.3 Hz, 1H, Ar-$\underline{H}$), 7.5-7.6 (m, 3H, Ar-$\underline{H}$), 7.76 (d, 7.4 Hz, 1H, Ar-$\underline{H}$), 8.16 (d, J=7.8 Hz, 1H, Ar-H), 12.35 (s, 1H, -$CO_2\underline{H}$)

IR (KBr, cm^{-1}): 3280 (m), 3500-2500 (br), 1750 (s), 1720 (s), 1675 (s), 1350 (s), 875 (m)

MS (m/e): 463 (M^+), 445 (M^+-H-OH)

Anal. Calcd. for $C_{20}H_{15}BrFNO_6 \cdot 0.2\ H_2O$: C, 51.28; H, 3.30; N, 2.99
Found: C, 51.26; H, 3.48; N, 2.95
M.P. 139-140°C.

The following compound was obtained in substantially the same manner as that of Example 1, Step d):

2-[(4-Bromo-2-fluorophenyl)methyl]-6-fluoro-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic Acid

^1H NMR (DMSO-d_6, 400 MHz): δ 3.56 (s, 3H, -$CO_2\underline{CH_3}$), 3.6 (d, J=17.9 Hz, 1H, -$\underline{CH_2}CO_2H$), 3.8 (d, J=17.9 Hz, 1H, -$\underline{CH_2}CO_2H$), 5.1 (dd, J=15.5 Hz, 2H, -$N\underline{CH_2}$-), 7.12 (d, J=8.23 Hz, 1H, Ar-$\underline{H}$), 7.31 (dd, J=8.28 Hz, 1.68 Hz, 1H, Ar-$\underline{H}$), 7.45 (dt, J=8.56 Hz, 2.5 Hz, 1H, Ar-$\underline{H}$), 7.54 (dd, J=9.77 Hz, 1.89 Hz, 1H, Ar-$\underline{H}$), 7.64 (dd, J=9.61 Hz, 2.46 Hz, 1H, Ar-$\underline{H}$), 8.23 (dd, J=8.79 Hz, 5.81 Hz, 1H, Ar-$\underline{H}$), 12.67 (brs, 1H, -$CO_2\underline{H}$)

IR (KBr, cm^{-1}): 3400-2700 (br), 1745 (s), 1710 (s), 1670 (s), 770 (m)
MS (m/e): 481 (M^+), 405 (M^+-CO_2, -CH_3OH)

Anal. Cald.: C, 49.81; H, 2.93; N, 2.90
Found: C, 49.94; H, 3.03; N, 2.84

M.P. 132-133.5°C.

REPLACEMENT SHEET
22 NOV 1996

Steps e, f)

2-[4-Bromo-2-fluorophenyl)methyl]-1'-ethylspiro[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

A mixture of 2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic acid (2.0 g, 4.31 mmol) and $SOCl_2$ (10 g) was refluxed for 1 hour. The volatiles were removed in vacuo and the acid chloride was dissolved in THF (10 mL). In a second flask was placed a freshly prepared saturated NH_2Et/THF solution (20 mL) and the contents of the first flask were added slowly. After 10 minutes the mixture was poured into H_2O, acidified with HCl (2N), extracted with EtOAc and the organic extracts were dried over $MgSO_4$. Evaporation gave a crude product which was dissolved in DMF (10 mL) and NaH (80% dispersion in oil, 129.3 mg, 4.31 mmol) was added portionwise. After 20 minutes the mixture was quenched with HCl (2N), extracted with EtOAc and dried over $MgSO_4$. Purification by flash chromatography (hexane/EtOAc, 4/1) and crystallization from ether/hexane (at -20°C) gave a white solid (1.4 g, 70.7%).

^1H NMR (DMSO-d_6, 400 MHz): δ 1.01 (t, J=7.2 Hz, 3H, -$NCH_2\underline{CH_3}$), 3.4 (d, J=18.2 Hz, 1H, -$\underline{CH_2}$CONEt-), 3.48 (q, J=7.2 Hz, 2H, -$N\underline{CH_2}CH_3$), 3.52 (d, J=18.2 Hz, 1H, -$\underline{CH_2}$CONEt-), 5.07 (s, 2H, -$N\underline{CH_2}$-), 7.15 (t, J=8.23 Hz, 1H, Ar-H), 7.33 (dd, J=8.3 Hz, 1.76 Hz, 1H, Ar-H), 7.53 (dd, J=9.84 Hz, 1.9 Hz, 1H, Ar-H), 7.61-7.65 (m, 2H, Ar-H), 7.78 (dt, J=7.65 Hz, 1.43 Hz, 1H, Ar-H), 8.17 (dd, J=8.19 Hz, 1.49 Hz, 1H, Ar-H)

IR (KBr, cm^{-1}):	1720 (s), 1690 (s)
MS (m/e):	458 (M^+), 387 (M^+-CONEt-), 359 (M^+-CONEtCO-)
Anal. Calcd.:	C, 54.92; H, 3.51; N, 6.10
Found:	C, 54.92; H, 3.40; N, 6.13

M.P. 153-154°C.

REPLACEMENT SHEET
22 NOV 1996

The following compound was obtained in substantially the same manner as that of Example 1, Steps e, f):

2-[(4-Bromo-2-fluorophenyl)methyl]-1'-ethyl-6-fluorospiro[isoquinoline-4(H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.0 (t, J=7.17 Hz, 3H, -NCH$_2$CH$_3$), 3.41-3.48 (m, 4H, -CH$_2$CONEt-, -NCH$_2$CH$_3$), 5.05 (s, 2H, -NCH$_2$-), 7.14 (t, J=8.2 Hz, 1H, Ar-H), 7.33 (dd, J=8.2 Hz, 1.66 Hz, 1H, Ar-H), 7.47 (dt, J=8.6 Hz, 2.47 Hz, 1H, Ar-H), 7.52 (dd, J=9.8 Hz, 1.9 Hz, 1H, Ar-H), 7.72 (dd, J=9.8 Hz, 1H, 2.42 Hz, 1H, Ar-H), 8.23 (dd, J=8.8 Hz, 5.86 Hz, 1H, Ar-H)

IR (KBr, cm^{-1}):	1720 (s), 1695 (s)
M/S (m/e):	476 (M$^+$), 405 (M$^+$-CONEt-), 377 (M$^+$-CONEtCO-)
Anal. Calcd.:	C, 52.85; H, 3.17; N, 5.87
Found:	C, 52.71; H, 2.97; N, 5.84

M.P. 185-186°C.

EXAMPLE 1A

2-[(4-Bromo-2-fluorophenyl)methyl]-1'-methylspiro[isoquinoline-4(H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

A mixture of 2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic acid (2.0 g, 4.31 mmol) and $SOCl_2$ (10 g) was refluxed for 1 hour. The volatiles were removed in vacuo and the acid chloride was dissolved in THF (10 mL). In a second flask was placed a freshly prepared saturated NH_2Me/THF solution (20 mL) and the contents of the first flask were added slowly. After 10 minutes the mixture was poured into H_2O, acidified with HCl (2N), extracted with EtOAc and the organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc, 4/1) gave an off-white solid which was recrystallized from ether/hexane (at -20°C) to give a white solid (1.2 g, 62.5%).

REPLACEMENT SHEET
22 NOV 1996

^{1}NMR (DMSO-d_6, 400 MHz): δ 2.93 (s, 3H, $\underline{CH_3}$), 3.32 (s, 3H, -$CO_2\underline{CH_3}$), 3.41 (d, J=18.2 Hz, 1H, -$\underline{CH_2}$CONMe-), 3.54 (d, J=18.2 Hz, 1H, -$\underline{CH_2}$CONMe-), 5.07 (s, 2H, -N$\underline{CH_2}$-), 7.16 (t, J=8.3 Hz, 1H, Ar-$\underline{H}$), 7.33 (dd, J=8.3 Hz, 2.5 Hz, 1H, Ar-$\underline{H}$), 7.54 (dd, J=9.96 Hz, 2.07 Hz, 1H, Ar-$\underline{H}$), 7.61-7.67 (m, 2H, Ar-$\underline{H}$), 7.77 (dt, J=7.26 Hz, 1.45 Hz, 1H, Ar-$\underline{H}$), 8.16 (dd, J=8.3 Hz, 1.87 Hz, 1H, Ar-$\underline{H}$)

IR (KBr, cm^{-1}):	1710 (s), 1680 (s)
MS (m/e):	444 (M^+), 387 (M^+-CONMe-), 359 (M^+-CONMeCO-)
Anal. Calcd.:	C, 53.95; H, 3.17; N, 6.29
Found:	C, 53.69; H, 2.87; N, 6.21

M.P. 78-79°C.

EXAMPLE 2

2-[[5-(Trifluoromethyl)-2-benzothiazolyl]methyl]-1'-methylspiro[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

Step g)

3-Methoxy-1-oxo-1H-2-benzopyran-4-carboxylic Acid Methyl Ester

A mixture of (2-carboxyphenyl)propanedioic acid dimethyl ester (10.09 g, 39.68 mmol) and $SOCl_2$ (100 g) was refluxed for 2 hours. The volatiles were removed $\underline{in\ vacuo}$ and the crude product (acid chloride) was dissolved in THF (200 mL). Triethylamine (27.64 mL, 198.4 mmol) was added and the mixture was stirred for 30 minutes. The yellowish suspension was poured into HCl (1N, 1000 mL), extracted with EtOAc and the organic extracts were dried over $MgSO_4$. Evaporation and crystallization from acetone/ether/hexane (at -20°C) gave a white solid (87.6 g, 94.4%).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.82 (s, 3H, -$CO_2\underline{Me}$), 4.03 (s, 3H, -$\underline{OMe}$), 7.42 (t, J=7.26 Hz, 1H, Ar-$\underline{H}$), 7.8 (t, J=8.2 Hz, 1H, Ar-$\underline{H}$), 7.9 (d, J=8.3 Hz, 1H, Ar-$\underline{H}$), 8.1 (d, J=7.26 Hz, 1H, Ar-$\underline{H}$).

IR (KBr, cm^{-1}):	1740 (C=O), 1685 (C=O)
MS (m/e):	234 (16, M^+), 206 (38.5, M^+-CO), 203 (12, M^+-OMe)

REPLACEMENT SHEET
22 NOV 1996

Anal. Calcd.: C, 61.59; H, 4.30
Found: C, 61.82; H, 4.29

M.P. 129-130°C.

The following compound was prepared in substantially the same manner as that of Example 1, Step g):

6-Fluoro-3-methoxy-1-oxo-1H-2-benzopyran-4-carboxylic Acid Methyl Ester

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.81 (s, 3H, -$CO_2\underline{CH_3}$), 4.06 (s, 3H, -$O\underline{CH_3}$), 7.27 (dt, J=8.3 Hz, 1H, Ar-H), 7.8 (dd, J=11.83 Hz, 2.49 Hz, 1H, Ar-H), 8.16 (dd, J=8.92 Hz, 6.2 Hz, 1H, Ar-H)

IR (KBr, cm^{-1}): 1750 (C=O), 1685 (C=O)

MS (m/e): 252 (24, M^+), 224 (54, M^+-CO)

Anal. Calcd.: C, 57.15; H, 3.60
Found: C, 57.19; H, 3.57

M.P. 142-143°C.

Step h)

2-(Cyanomethyl)-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinoline carboxylic Acid Methyl Ester

To a solution of 3-methoxy-1-oxo-1H-2-benzopyran-4-carboxylic acid methyl ester (8.0 g, 34.19 mmol) in DMF (100 mL) was added aminoacetonitrile hydrochloride (6.32 g, 68.37 mmol) and the suspension was stirred until all the materials have dissolved. Triethylamine (14.3 mL, 102.57 mmol) was added and the mixture was stirred at 100°C for 30 minutes, and then poured into H_2O, acidified with HCl (2N) and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and crystallization from acetone/ether/hexane (at -20°C) gave a yellowish solid (6.5 g, 73.7%).

REPLACEMENT SHEET
22 NOV 1996

^{1}H NMR (DMSO-d_6, 400 MHz): δ [3.7 (s), 3.98 (s), 3H, -$CO_2\underline{CH_3}$, rotameric], [4.92 (s), 5.44 (s), 2H, -$N\underline{CH_2}CN$, rotameric], 7.2-8.4 (m, 4H, Ar-$\underline{H}$, rotameric)

IR (KBr, cm^{-1}): 3400 (OH), 1670 (C=O)

MS (m/e): 258 (20, M^+), 226 (43, M^+-MeOH), 199 (13, M^+-CO_2Me)

Anal. Calcd.: C, 60.47; H, 3.90; N, 10.85
Found: C, 60.27; H, 3.77; N, 10.69

M.P. 169-171°C.

The following compound was prepared in substantially the same manner as that of Example 1, Step h):

2-(Cyanomethyl)-6-fluoro-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinoline carboxylic Acid Methyl Ester

Anal. Calcd.: C, 56.53; H, 3.28; N, 10.14
Found: C, 56.45; H, 3.22; N, 10.13

M.P. 178-179°C.

Step i)

2-(Cyanomethyl)-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic Acid 1,1-Dimethylethyl Ester

To a suspension of 2-(cyanomethyl)-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinoline carboxylic acid methyl ester (6.5 g, 25.19 mmol), K_2CO_3 (6.95 g, 50.38 mmol) and anhydrous DMF (100 mL) was added tert-butyl bromoacetate (6.1 mL, 37.79 mmol). After stirring at 85°C for 3 hours, the mixture was poured into H_2O, acidified with HCl (2N) and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography on silica gel (hexane/EtOAc 4/1) gave a white solid (8.5 g, 90.7%).

REPLACEMENT SHE
22 NOV 1996

^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.03 (s, 9H, -CO_2 $\underline{CMe_3}$), 3.58 (s, 3H, -$CO_2\underline{CH_3}$), 3.64 (s, 2H, -$\underline{CH_2}CO_2$-), 5.05 (s, 2H, -N$\underline{CH_2}$CN), 7.64 (m, 2H, Ar-$\underline{H}$), 7.78 (dd, J=7.4 Hz, 2.0 Hz, 1H, Ar-$\underline{H}$), 8.24 (dd, J=8.2 Hz, 1.6 Hz, 1H, Ar-$\underline{H}$)

IR (KBr, cm^{-1}): 1745 (C=O), 1730 (C=O), 1670 (C=O)

MS (m/e): 373 (38, M^+ + H), 317 (100, M^+ + H, -CME_3)

Anal. Calcd.:	C, 61.28; H, 5.41; N, 7.52
Found:	C, 61.61; H, 5.49; N, 7.13

M.P. 48-50°C.

The following compound was obtained in substantially the same manner as that of Example 1, Step i):

2-(Cyanomethyl)-6-fluoro-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic Acid 1,1-Dimethylethyl Ester

Anal. Calcd.:	C, 58.46; H, 4.91; N, 7.18
Found:	C, 58.65; H, 4.98; N, 7.08

M.P. 133-135°C.

Step j)

1,2,3,4-Tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-2-[[(5-trifluoromethyl)-2-benzothiazolyl]methyl]-4-isoquinolineacetic Acid

To a mixture of 3-amino-4-mercaptobenzotrifluoride hydrochloride (6.1 g, 26.2 mmol) and EtOH (150 mL) was added Et_3N (3.65 mL). After stirring for 10 minutes, 2-(cyanomethyl)-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinoline-acetic acid 1,1-dimethylethyl ester (6.5 g, 17.47 mmol) was added and the mixture was refluxed for 15 hours, poured into H_2O, acidified with HCl (2N) and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation gave an oil (9.6 g) which was dissolved in CH_2Cl_2 (80 mL). Trifluoroacetic acid (20 mL) was added and the mixture was stirred at room temperature for 8 hours. The volatiles were removed in

REPLACEMENT SHEE
22 NOV 1996

vacuo and the residue was purified by flash chromatography on acid washed (5%, H_3PO_4 in MeOH) silica gel to give a white solid (6.3 g, 73.3%).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.57 (s, 3H, -$CO_2\underline{CH_3}$), 3.68 (dd, J=17.85 Hz, 2H, -$\underline{CH_2}CO_2H$), 5.61 (s, 2H, -N$\underline{CH_2}$-), 7.62 (m, 2H, Ar-$\underline{H}$), 7.81 (m, 2H, Ar-$\underline{H}$), 8.2 (dd, J=7.9 Hz, 1.04 Hz, 1H, Ar-$\underline{H}$), 8.33 (dd, J=8.5 Hz, 0.92 Hz, 1H, Ar-$\underline{H}$), 8.34 (d, J=0.83 Hz, 1H, Ar-$\underline{H}$)

IR (KBr, cm^{-1}): 3200-2500 (CO_2H), 1750 (C=O), 1710 (C=O), 1670 (C=O)

MS (m/e): 492 (6, M^+), 448 (6, M^+-CO_2), 416 (62, M^+-CO_2, -MeOH)

Anal. Calcd.:	C, 53.66; H, 3.07; N, 5.69
Found:	C, 53.40; H, 3.01; N, 5.54

M.P. 199-201°C.

The following compounds were prepared in substantially the same manner as that of Example 1, Step j):

1,2,3,4-Tetrahydro-4-(methoxycarbonyl-1,3-dioxo-2-[(2-benzothiazolyl)methyl]-4-isoquinolineacetic Acid

Anal. Calcd.:	C, 59.43; H, 3.80; N, 6.60
Found:	C, 59.37; H, 3.74; N, 6.43

M.P. 189-190°C.

6-Fluoro-1,2,3,4-tetrahydro-4-(methoxycarbonyl-1,3-dioxo-2-[[(5-trifluoromethyl)-2-benzothiazolyl]methyl]-4-isoquinolineacetic Acid

Anal. Calcd.:	C, 51.77; H, 2.76; N, 5.49
Found:	C, 51.62; H, 2.97; N, 5.18

M.P. 103-105°C.

REPLACEMENT SHEE
22 NOV 1996

Step k)

2-[(5-Trifluoromethyl)-2-benzothiazolyl]methyl]-1'-methylspiro [isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

A mixture of 1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-2-[[(5-trifluoromethyl)-2-benzothiazolyl)methyl]-4-isoquinolineacetic acid (2.0 g, 4.06 mmol) and $SOCl_2$ (20 g) was refluxed for 1 hour. The volatiles were removed in vacuo and the product (acid chloride) was dissolved in THF (10 mL). To a second flask was placed a freshly prepared, saturated NH_2Me/THF solution (20 mL) and the contents of the first flask were added slowly. After stirring for 10 minutes, the mixture was poured into H_2O (500 mL) acidified with HCl (2N) extracted with EtOAc and dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc 2/1) gave a white solid (1.35 g, 80.3%).

^1H NMR (DMSO-d_6, 400 MHz): δ 2.96 (s, 3H, N-CH_3), 3.43 (d, J=18.26 Hz, 1H, -HCHCO-), 3.56 (d, J=18.26 Hz, 1H, -HCHCO-), 5.56 (s, 2H, -NCH_2-), 7.66 (m, 2H, Ar-H), 7.82 (m, 2H, Ar-H), 8.20 (d, J=7.88 Hz, 1H, Ar-H), 8.33 (m, 2H, Ar-H)

IR (KBr, cm^{-1}): 1720 (C=O), 1700 (C=O), 1670 (C=O)
MS (m/e): 473 (100, M^+)

Anal. Calcd.: C, 55.81; H, 2.98; N, 8.88
Found: C, 56.22; H, 2.97; N, 8.80
M.P. 179-180°C.

The following compound was prepared in substantially the same manner as that of Example 1, Step k):

1'-Ethyl-6-fluoro-2-[[5-(trifluoromethyl)-2-benzothiazolyl]-methyl]spiro[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

Anal. Calcd.: C, 54.66; H, 2.99; N, 8.31
Found: C, 54.97; H, 2.88; N, 8.35
M.P. 154-156°C.

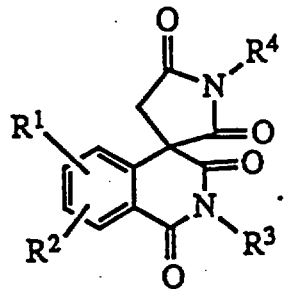
REPLACEMENT SHEET
22 NOV 1996

THIS SHEET HAS BEEN REPLACED

CLAIMS

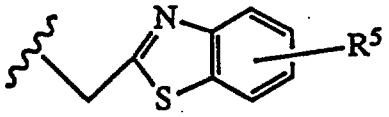
* C L M S *

1. A compound of formula (I)



(I)

wherein R^1 and R^2 are independently hydrogen, alkyl containing 1 to 6 carbon atoms, halogen, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms; R^3 is hydrogen, lower alkyl containing 1 to 6 carbon atoms, aryl, aryl(lower alkyl) or halogen substituted aryl(lower alkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms, or benzothiazole of structural formula



(Ia)

wherein R^5 is hydrogen, halogen, alkyl containing 1 to 6 carbon atoms, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 5 carbon atoms; and R^4 is alkyl containing 1 to 12 carbon atoms, aryl, aryl(loweralkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms, acyl, carboalkoxy, $-(CH_2)_nCO_2H$ or $-(CH_2)_nOH$, wherein n is 1 to 6.

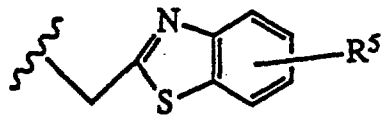
This Sheet Has Been Replaced

THIS SHEET HAS BEEN REPLACED

* C L M S *

REPLACEMENT SHEET
22 NOV 1996

2. A compound according to claim 1 wherein R^1 and R^2 are independently hydrogen or halogen; R^3 is a mono- or dihalogen substituted aryl(lower alkyl) wherein aryl contains 6 carbon atoms and lower alkyl contains 1 to 3 carbon atoms, or benzothiazole of structural formula



wherein R^5 is hydrogen, halogen or trifluoromethyl; and R^4 is alkyl containing 1 to 3 carbon atoms.

3. A compound according to claim 2 which is

2-[(4-bromo-2-fluorophenyl)methyl]-1'-methylspiro[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone.

4. A compound according to claim 2 which is

2-[(4-bromo-2-fluorophenyl)methyl]-1'-ethylspiro[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone.

5. A compound according to claim 2 which is

2-[(4-bromo-2-fluorophenyl)methyl]-1'-ethyl-6-fluorospiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone.

6. A compound according to claim 2 which is

2-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-1'-methylspiro[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone.

7. A compound according to claim 2 which is

1'-ethyl-6-fluoro-2-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]spiro-[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone.

This Sheet Has Been Replaced

* C L M S *

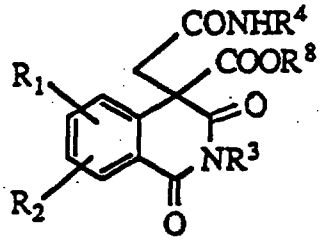
THIS SHEET HAS BEEN REPLACED

REPLACEMENT SHEET

22 NOV 1996

8. A process for preparing a compound of formula I as claimed in Claim 1 which comprises one of the following:

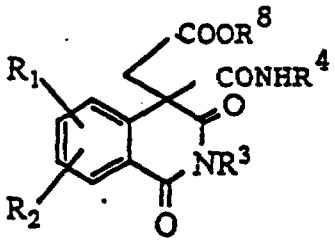
a) cyclising an amide of formula (A)



(A)

wherein R^1, R^2, R^3 and R^4 are as defined in Claim 1 and $COOR^8$ is an ester group, using a suitable base to give a compound of formula I;

b) cyclising a compound of formula (B)



(B)

wherein R^1, R^2, R^3 and $COOR^8$ are as defined above using a suitable base to give a compound of formula I;

or

c) acylating a compound of formula I as shown in Claim 1 wherein R^4 is hydrogen and R^{1-3} are as defined in Claim 1 to give a corresponding compound of formula I wherein R^4 is acyl or carboalkoxy.

This Sheet Has Been Replaced

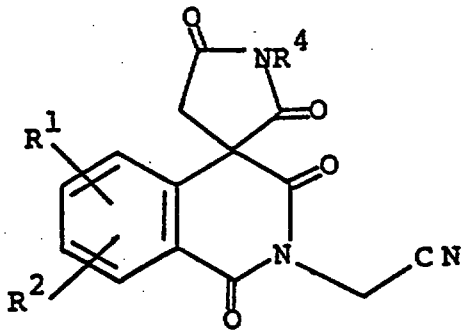
* C L M S *

THIS SHEET HAS BEEN REPLACED

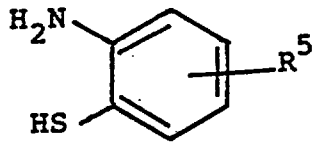
REPLACEMENT SHEET
22 NOV 1996

or

d) reacting a compound of formula



with a 2-aminothiophenol of formula



in which formulae R^1, R^2, R^4 and R^5 are as defined in Claim 1 to give a compound of formula I wherein R^3 is a benzothiazolylmethyl group of formula Ia.

This Sheet Has Been Replaced

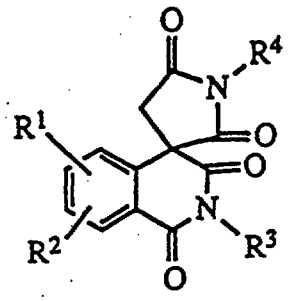
* C L M S *

THIS SHEET HAS BEEN REPLACED

REPLACEMENT SHEE

22 NOV 1996

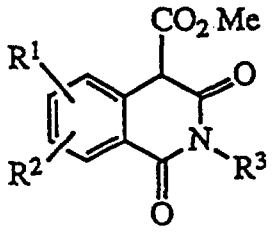
9. A process for preparing a compound of formula (I)



(I)

wherein R^1 and R^2 are independently hydrogen, alkyl containing 1 to 6 carbon atoms, halogen, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms; R^3 is hydrogen, lower alkyl containing 1 to 6 carbon atoms, aryl, aryl(lower alkyl) or halogen substituted aryl(lower alkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms; R^4 is alkyl containing 1 to 12 carbon atoms, aryl, aryl(lower alkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms, acyl, carboalkoxy, or $-(CH_2)_nCO_2H$, $-(CH_2)_n OH$, wherein n is 1 to 6 which comprises:

a) reacting the compound of formula (IV)

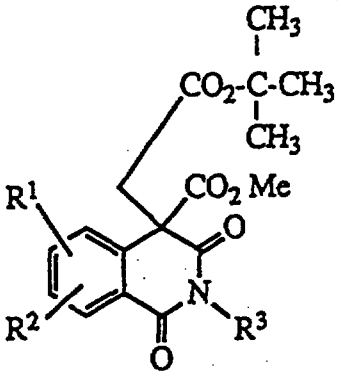


(IV)

wherein R^1, R^2, and R^3 are as defined above with an inorganic base in a conventional solvent and subsequently adding tert-butyl bromoacetate to produce the compound of the formula (V)

This Sheet Has Been Replaced

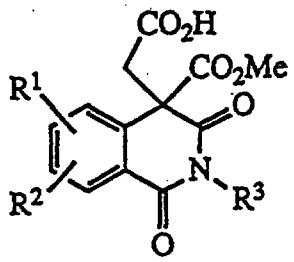
REPLACEMENT SHEET
22 NOV 1996



(V)

wherein R^1, R^2, and R^3 are as defined above;

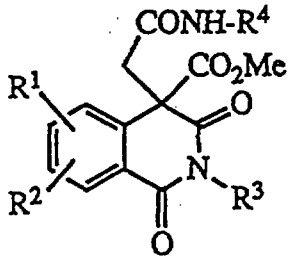
b) hydrolyzing said compound of formula (V) with an organic acid in a conventional solvent to produce the compound of formula (VI)



(VI)

wherein R^1, R^2, and R^3 are as defined above;

c) reacting said compound of formula (VI) with a coupling agent in a conventional solvent and subsequently adding R^4-NH_2 to produce the compound of formula (VII)



(VII)

wherein R^1, R^2, R^3, and R^4 are as defined above;

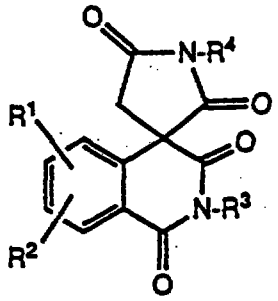
d) reacting said compound of formula (VII) with a base in a conventional solvent to product the compound of formula (I).

* C L M S *

THIS SHEET HAS BEEN REPLACED

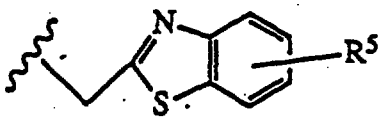
REPLACEMENT SHEET
22 NOV 1996

10. A process for the preparation of a compound of formula (I).



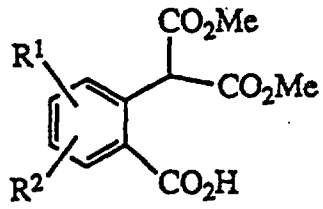
(I)

wherein R^1 and R^2 are independently hydrogen, alkyl containing 1 to 6 carbon atoms, halogen, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms; R^3 is benzothiazole of structural formula



wherein R^5 is hydrogen, halogen alkyl containing 1 to 6 carbon atoms, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 5 carbon atoms, and R^4 is alkyl containing 1 to 12 carbon atoms, aryl, aryl(lower alkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms, acyl, carboalkoxy, or $-(CH_2)_nCO_2H$, $-(CH_2)_nOH$, wherein n is 1 to 6 which comprises:

a) reacting the compound of formula (III)

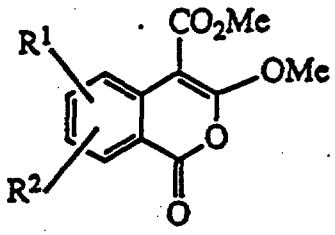


(III)

wherein R^1 and R^2 are as defined above with $SOCl_2$ and subsequent treatment with Et_3N in a conventional solvent to produce the compound of formula (VIII)

This Sheet Has Been Replaced

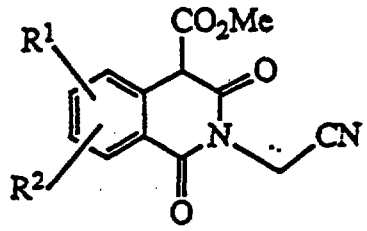
REPLACEMENT SHEET
22 NOV 1995



(VIII)

wherein R^1 and R^2 are as defined above

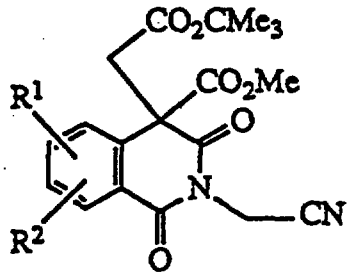
b) reacting said compound of formula (VIII) with aminoacetonitrile hydrochloride in the presence of Et_3N in a conventional solvent to produce the compound of formula (IX)



(IX)

wherein R^1 and R^2 are as defined above

c) reacting said compound of formula (IX) with an inorganic base in a conventional solvent and subsequently adding tert-butyl bromoacetate to produce the compound of formula (X)



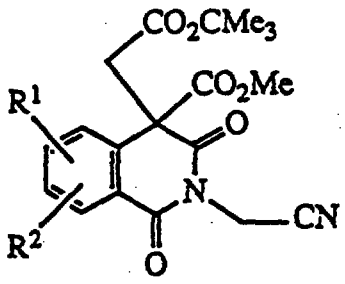
(X)

wherein R^1 and R^2 are as defined above

* C L M S *

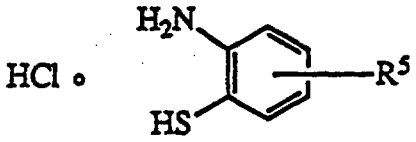
REPLACEMENT SHEE
22 NOV 1996

d) reacting said compound of formula (X)

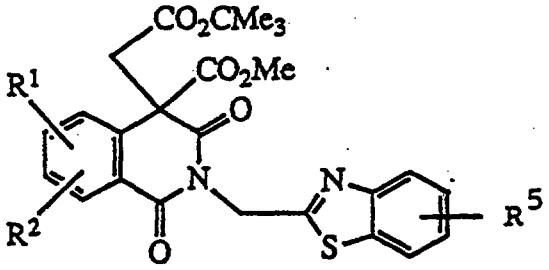


(X)

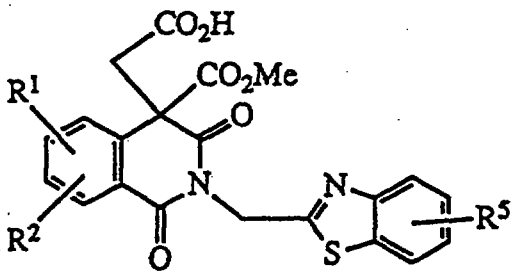
with a 2-aminothiophenol of structural formula



wherein R^5 is as defined above to produce the tert-butyl ester compound of structural formula



e) hydrolyzing the tert-butyl ester with an organic acid in a conventional solvent to produce compound of formula (XI)



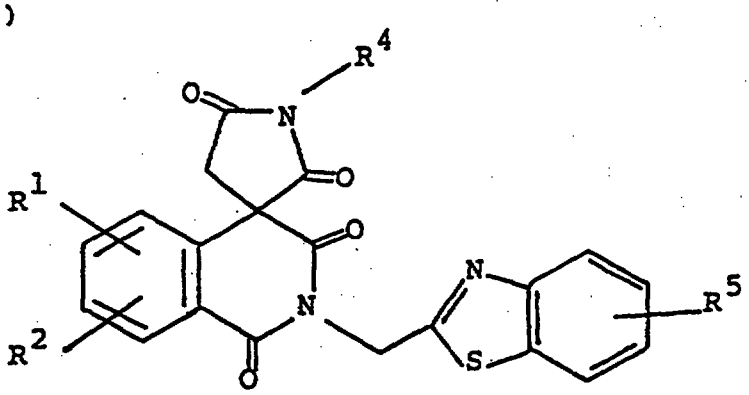
(XI)

wherein R^1, R^2 and R^5 are as defined above.

* C L M S *

REPLACEMENT SHEE
22 NOV 1996

f) reacting said compound of formula (XI) with thionyl chloride and subsequently adding R^4-NH_2 in a conventional solvent to produce the compound of formula (Ib)



(Ib)

wherein R^1, R^2, R^4 and R^5 are as defined above.

11. A pharmaceutical composition which comprises a compound according to any one of Claims 1 to 7 and a pharmaceutically acceptable carrier.

12. A compound of formula I according to any one of Claims 1 to 7 for use as a pharmaceutical.

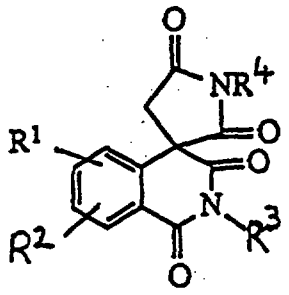
13. Use of a compound of formula I as defined in anyone of Claims 1 to 7 in the preparation of a medicament for the treatment or prevention of neuropathy, retinopathy, nephropathy or cataracts in a diabetic mammal.

REPLACEMENT SHEE
22 NOV 1996

ABSTRACT

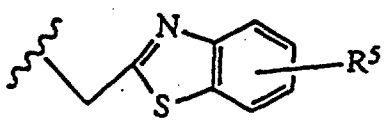
N'ALKYL-SPIRO-ISOQUINOLINE-PYRROLIDINE TETRONES AND ANALOGS THEREOF USEFUL AS ALDOSE REDUCTASE INHIBITORS

This invention relates to N'-alkyl-spiro-isoquinoline-pyrrolidine tetrones of formula



(I)

wherein R^1 and R^2 are independently hydrogen, alkyl containing to 1 to 6 carbon atoms, halogen, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 - 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms; R^3 is hydrogen, lower alkyl containing 1 to 6 carbon atoms, aryl, aryl(lower alkyl) or halogen substituted aryl(lower alkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms, or benzothiazole of structural formula



(Ia)

EP 0 393 737 A1

REPLACEMENT SHEET
22 NOV 1996

wherein R^5 is hydrogen, halogen, alkyl containing 1 to 6 carbon atoms, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 5 carbon atoms; and R^4 is alkyl containing 1 to 12 carbon atoms, aryl, aryl(loweralkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms, acyl, carboalkoxy, $-(CH_2)_nCO_2H$ or $-(CH_2)_nOH$, wherein n is 1 to 6. The compounds have pharmaceutical properties which render them beneficial for the prevention of treatment of diabetes mellitus associated complications.

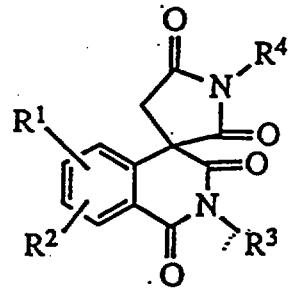
22 NOV 1996
3603831-1

REPLACEMENT SHEET
11 DEC 1997

retinopathy and neuropathy (cf McCaleb et al, J Diab. Comp., 2 16,1989; Robinson et al, Invest. Ophthalmol. Vis. Sci., 30, 2285, 1989; Notvest and Inserra, Diabetes, 36, 500,1987.

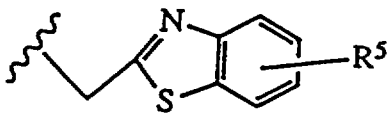
Spiro isoquinoline-pyrrolidine tetrones, unsubstituted in the pyrrolidine ring and possessing aldose reductase inhibitory activity are disclosed in EP-A-0365324. This invention provides further tetrones substituted in the pyrrolidine ring and possessing in vivo aldose reductase inhibitory activity.

The N'-alkyl-spiro-isoquinoline-pyrrolidine tetrones of the present invention are represented by formula (I):



I

wherein R^1 and R^2 are independently hydrogen, alkyl containing 1 to 6 carbon atoms, halogen, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms; R^3 is hydrogen, lower alkyl containing 1 to 6 carbon atoms, aryl, aryl(lower alkyl) or halogen substituted aryl(lower alkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms, or benzothiazole of structural formula



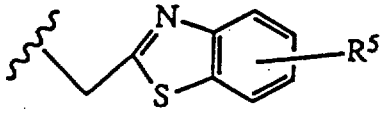
(Ia)

wherein R^5 is hydrogen, halogen, alkyl containing 1 to 6 carbon atoms, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 5 carbon atoms; and R^4 is

REPLACEMENT SHEET
11 DEC 1997

alkyl containing 1 to 12 carbon atoms,and aryl(lower alkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms,
Examples of 'aryl' are phenyl and naphthyl. Examples of halogen are fluorine, chlorine and bromine. Examples of R^1 and/or R^2 are hydrogen or halogen e.g fluorine such as 6-F. Examples of R^3 are (mono- or di-halo substituted phenyl)lower alkyl wherein lower alkyl contains 1 - 3 carbon atoms, or benzothiazolylmethyl of formula Ia wherein R^5 is hydrogen, halogen or trifluoromethyl. For example R^3 may be 4-bromo-2-fluorophenylmethyl or (5-trifluoromethylbenzothiazol-2-yl)methyl. Examples of R^4 are C_1 - C_3 alkyl such as methyl or ethyl.

A more preferred group of compounds of the present invention are the compounds of formula (I) wherein R^1 and R^2 are independently hydrogen or halogen; R^3 is a mono- or dihalogen substituted aryl(loweralkyl) wherein aryl contains 6 carbon atoms and lower alkyl contains 1 to 3 carbon atoms, or benzothiazole of structural formula



(Ia)

wherein R^5 is hydrogen, halogen or trifluoromethyl; and R^4 is alkyl containing 1 to 3 carbon atoms.

The most preferred compounds of the present invention are set forth below:

2-[(4-bromo-2-fluorophenyl)methyl]-1'-methyl-spiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2'3,5'(2H)-tetrone;

REPLACEMENT SHEET
11 DEC 1997

The compounds of this invention may be given orally. The compounds may also be administered topically directly to the eye in the form of drops of sterile, buffered ophthalmic solutions, preferably of pH 7.2-7.6. Also, they may be administered orally in solid form containing such excipients as starch, milk sugar, certain types of clay and so forth. They may also be administered orally in the form of solutions or they may be injected parenterally. For parenteral administration, they may be used in the form of a sterile solution, preferaby of pH 7.2-7.6, containing a pharmaceutically acceptable buffer.

The dosage of the N'-alkyl-spiro-isoquinoline-pyrrolidine tetrones will vary with the form of administration and the particular compound chosen. Furthermore, it will vary with the particular host under treatment. Generally, treatment is initiated with small dosages substantially less than the optimal dose of the compound. Thereafter, the dosage is increased by small increments until efficacy is obtained. In general, the compounds of this invention are most desirably administered at a concentration level that will generally afford effective results without causing any harmful or deleterious side effects. For topical administration, a 0.05-1.0% solution may be administered dropwise in the eye. The frequency of instillation varies with the subject under treatment from a drop every two or three days to once daily. For oral or parenteral administration a preferred level of dosage ranges from about 0.1 mg to about 1.0 mg per kilo of body weight per day, although aforementioned variations will occur. However, a dosage level that is in the range of from about 0.1 mg to about 1.0 mg per kilo of body weight per day is most satisfactory.

Unit dosage forms such as capsules, tablets, pills and the like may contain from about 5.0 mg to about 25.0 mg of the active ingredients of this invention with a pharmaceutical carrier. Thus, for oral administration, capsules can contain from between about 5.0 mg to about 25.0 mg of the active ingredients of this invention with or without a pharmaceutical diluent. Tablets, either effervescent or noneffervescent, can contain between about 5.0 to 25.0 mg of the active ingredients of this invention together with conventional pharmaceutical carriers. Thus tablets, which may be coated and either effervescent or noneffervescent, may be prepared according to the known art. Inert diluents or carriers, for example, magnesium carbonate or lactose, can be used together with conventional disintegrating agents for example, magnesium stearate.

REPLACEMENT SHEET
11 DEC 1997

subtracted from the individual values found in the corresponding tissue in galactose-fed rats to obtain the amount of polyol accumulated.] The aldose reductase inhibiting effects of the compounds of formula (I) were also tested by employing an in vitro testing procedure similar to that described by S. Hayman and J.H. Kinoshita, J. Biol. Chem., 240, 877 (1965). In the present case the procedure of Hayman and Kinoshita was modified in that the final chromatography step was omitted in the preparation of the enzyme from bovine lens.

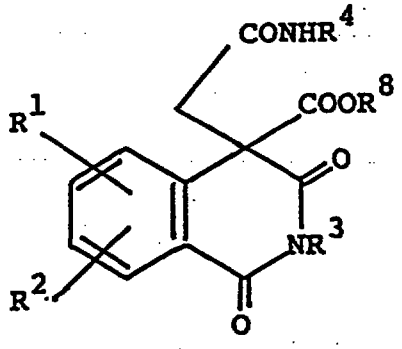
The following tabulated results show that the N'-alkyl-spiro-isoquinoline-pyrrolidine tetrones of this invention show the property that they are inactive in vitro and active in vivo and diminish the accumulation of dulcitol in the lenses, sciatic nerves and diaphragm of rats fed galactose. The figures under L, N, and D represent the percentage decrease of dulcitol accumulation in the tissues of the lens, sciatic nerve, and diaphragm, respectively, for treated rats as compared to untreated rats.

REPLACEMENT SHEET

11 DEC 2007

This invention provides processes for preparing compounds of formula I. These processes include:

a) cyclising an amide of formula (A)

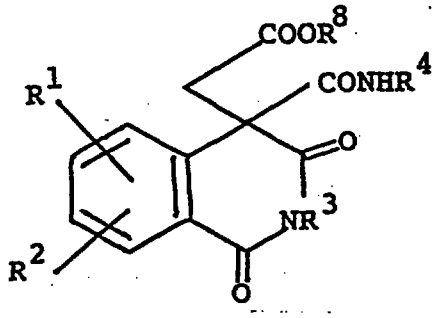


(A)

wherein R^1, R^2, R^3 and R^4 are as defined above and $COOR^8$ is ester group, using a suitable base such as sodium hydride to give a compound of formula I;

or

b) cyclising a compound of formula (B)



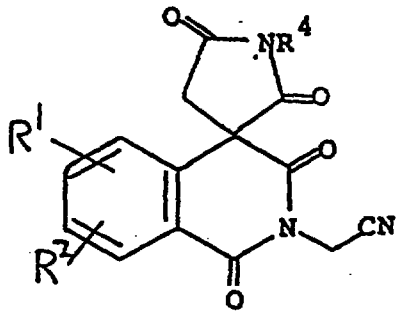
(B)

wherein R^1, R^2, R^3, R^4 and $COOR^8$ are as defined above using a suitable base such as sodium hydride or lithium bis-(trimethylsilyl)amide to give a compound of formula I;

or

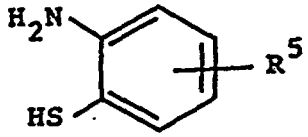
REPLACEMENT SHEET
11 DEC 1997

c) reacting a compound of formula



(D)

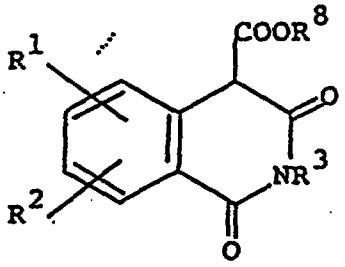
with a 2-aminothiophenol of formula



(E)

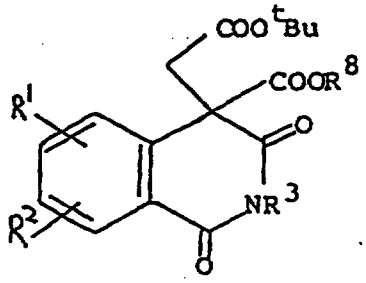
in which R^1, R^2, R^4 and R^5 are as defined above to give a compound of formula I wherein R~ is a benzothiazolylmethyl group of formula Ia.

Starting materials of formulae (A) and (B) can be prepared via intermediates of formula (G) shown below:



(G)

wherein R^1, R^2, R^3, and $COOR^8$ are as defined above. Examples of R^8 are alkyl groups such as C_1-C_4 alkyl especially methyl. R^8 may also be ^tBu. For example compounds of formula (A) are prepared by reacting a compound of formula (G) with $Br(CH_2)_n$- CO_2-^tBu in the presence of a suitable base e.g Li-$N(SiMe_3)_2$ to give a compound of formula

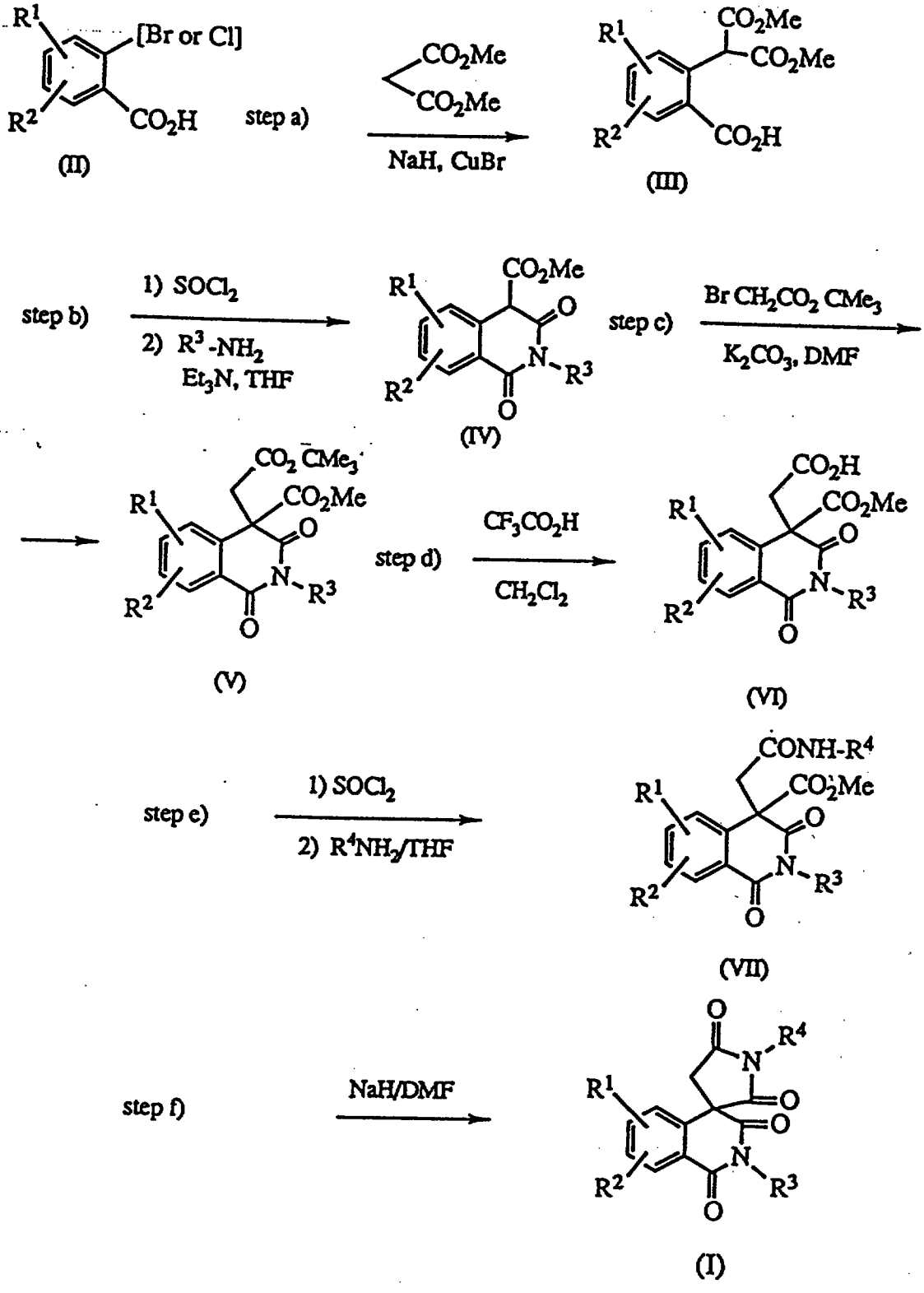


(H)

REPLACEMENT SHEET
11 DEC 1997

Process A

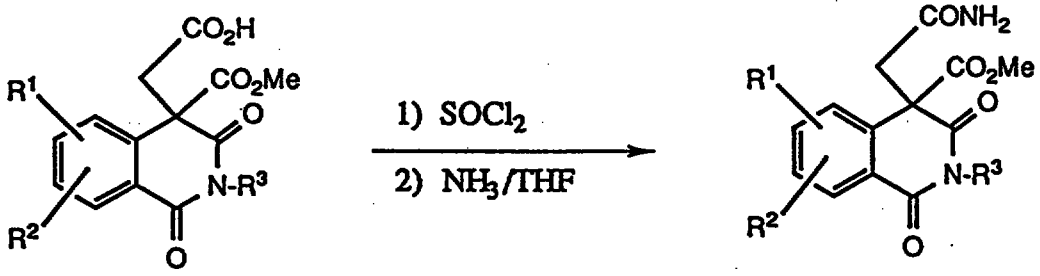
The N'-alkyl-spiro-isoquinoline-pyrrolidine tetrones of the present invention were prepared by the following reaction scheme:



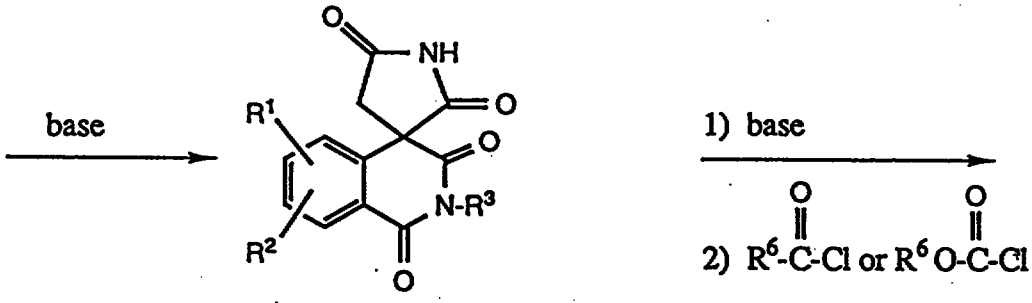
REPLACEMENT SHEET
11 DEC 1997

Process B

Some compounds of formula (I), wherein R^1, R^2, and R^3 are as defined above and R^4 is aryl-C(O)-, loweralkyl-C(O)- or lower alkoxy carbonyl, can be made by the process B.

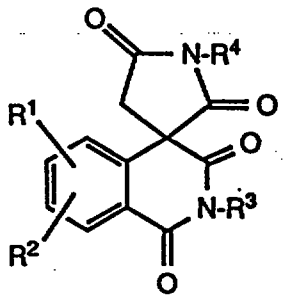


(VI)



(also known from EP 365324)

(R^6 = alkyl, aryl, aralkyl)



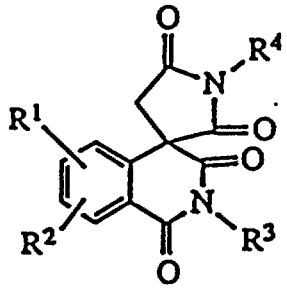
(I)

wherein R^1, R^2, and R^3 are as defined above and R^4 is aryl-C(O)-, loweralkyl-C(O)- or lower alkoxycarbonyl.

REPLACEMENT SHEET
11 DEC 1997

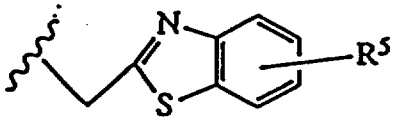
CLAIMS

1. A compound of formula (I)



(I)

wherein R^1 and R^2 are independently hydrogen, alkyl containing 1 to 6 carbon atoms, halogen, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms; R^3 is hydrogen, lower alkyl containing 1 to 6 carbon atoms, aryl, aryl(lower alkyl) or halogen substituted aryl(lower alkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms, or benzothiazolylmethyl of structural formula.

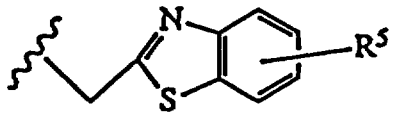


(Ia)

wherein R^5 is hydrogen, halogen, alkyl containing 1 to 6 carbon atoms, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 5 carbon atoms; and R^4 is alkyl containing 1 to 12 carbon atoms or aryl(lower alkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms.

REPLACEMENT SHEET
11 DEC 1987

2. A compound according to claim 1 wherein R^1 and R^2 are independently hydrogen or halogen; R^3 is a mono- or dihalogen substituted aryl(lower alkyl) wherein aryl contains 6 carbon atoms and lower alkyl contains 1 to 3 carbon atoms, or benzothiazolylmethyl of structural formula



wherein R^5 is hydrogen, halogen or trifluoromethyl; and R^4 is alkyl containing 1 to 3 carbon atoms.

3. A compound according to claim 2 which is

2-[(4-bromo-2-fluorophenyl)methyl]-1'-methylspiro[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone.

4. A compound according to claim 2 which is

2-[(4-bromo-2-fluorophenyl)methyl]-1'-ethylspiro[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone.

5. A compound according to claim 2 which is

2-[(4-bromo-2-fluorophenyl)methyl]-1'-ethyl-6-fluorospiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone.

6. A compound according to claim 2 which is

2-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-1'-methylspiro[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone.

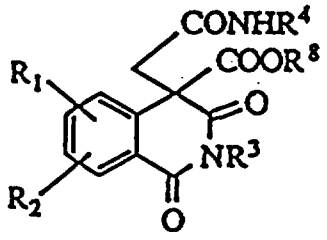
7. A compound according to claim 2 which is

1'-ethyl-6-fluoro-2-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]spiro-[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone.

REPLACEMENT SHEET
11 DEC 1997

8. A process for preparing a compound of formula I as claimed in Claim 1 which comprises one of the following:

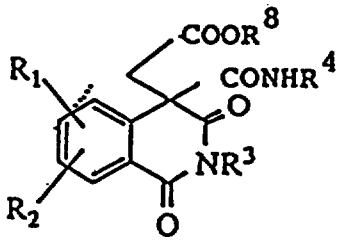
a) cyclising an amide of formula (A)



(A)

wherein R^1, R^2, R^3 and R^4 are as defined in Claim 1 and $COOR^8$ is an ester group, using a suitable base to give a compound of formula I;

b) cyclising a compound of formula (B)



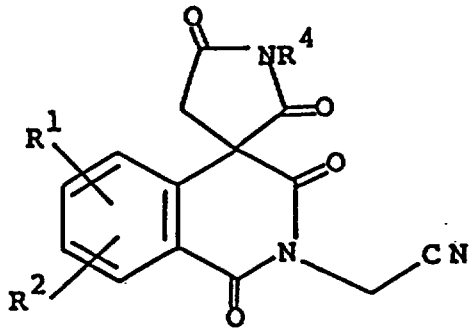
(B)

wherein R^1, R^2, R^3, R^4 and $COOR^8$ are as defined above using a suitable base to give a compound of formula I;

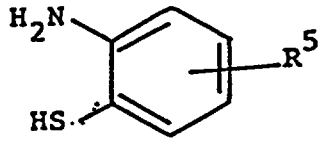
REPLACEMENT SHEET
11 DEC 1997

or

c) reacting a compound of formula



with a 2-aminothiophenol of formula

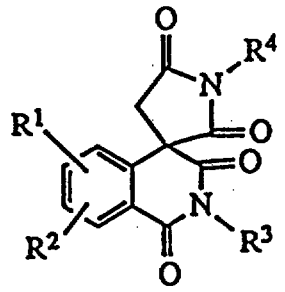


in which formulae R^1, R^2, R^4 and R^5 are as defined in Claim 1 to give a compound of formula I wherein R^3 is a benzothiazolylmethyl group of formula Ia.

* C L M S *

REPLACEMENT SHEET
11 DEC 1997

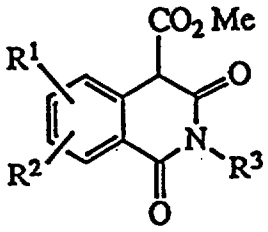
9. A process for preparing a compound of formula (I)



(I)

wherein R^1, R^2 and R^4 are as defined in Claim 1 and R^3 is hydrogen, lower alkyl containing 1 to 6 carbon atoms, aryl, aryl(lower alkyl) or halogen substituted aryl(lower alkyl) wherein aryl contains 6 to 10 carbon atoms and loweralkyl contains 1 to 6 carbon atoms; which comprises:

a) reacting the compound of formula (IV)

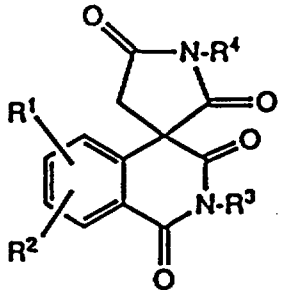


(IV)

wherein R^1, R^2, and R^3 are as defined above with an inorganic base in a conventional solvent and subsequently adding tert-butyl bromoacetate to produce the compound of the formula (V)

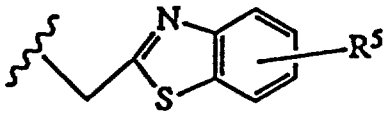
REPLACEMENT SHEET
11 DEC 1997

10. A process for the preparation of a compound of formula (I).



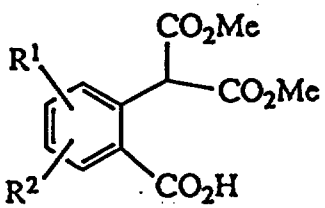
(I)

wherein R^1, R^2 and R^4 are as defined in Claim 1; R^3 is benzothiazolylmethyl of structural formula



wherein R^5 is hydrogen, halogen, alkyl containing 1 to 6 carbon atoms, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 5 carbon atoms, which comprises:

a) reacting the compound of formula (III)



(III)

wherein R^1 and R^2 are as defined above with $SOCl_2$ and subsequent treatment with Et_3N in a conventional solvent to produce the compound of formula (VIII)