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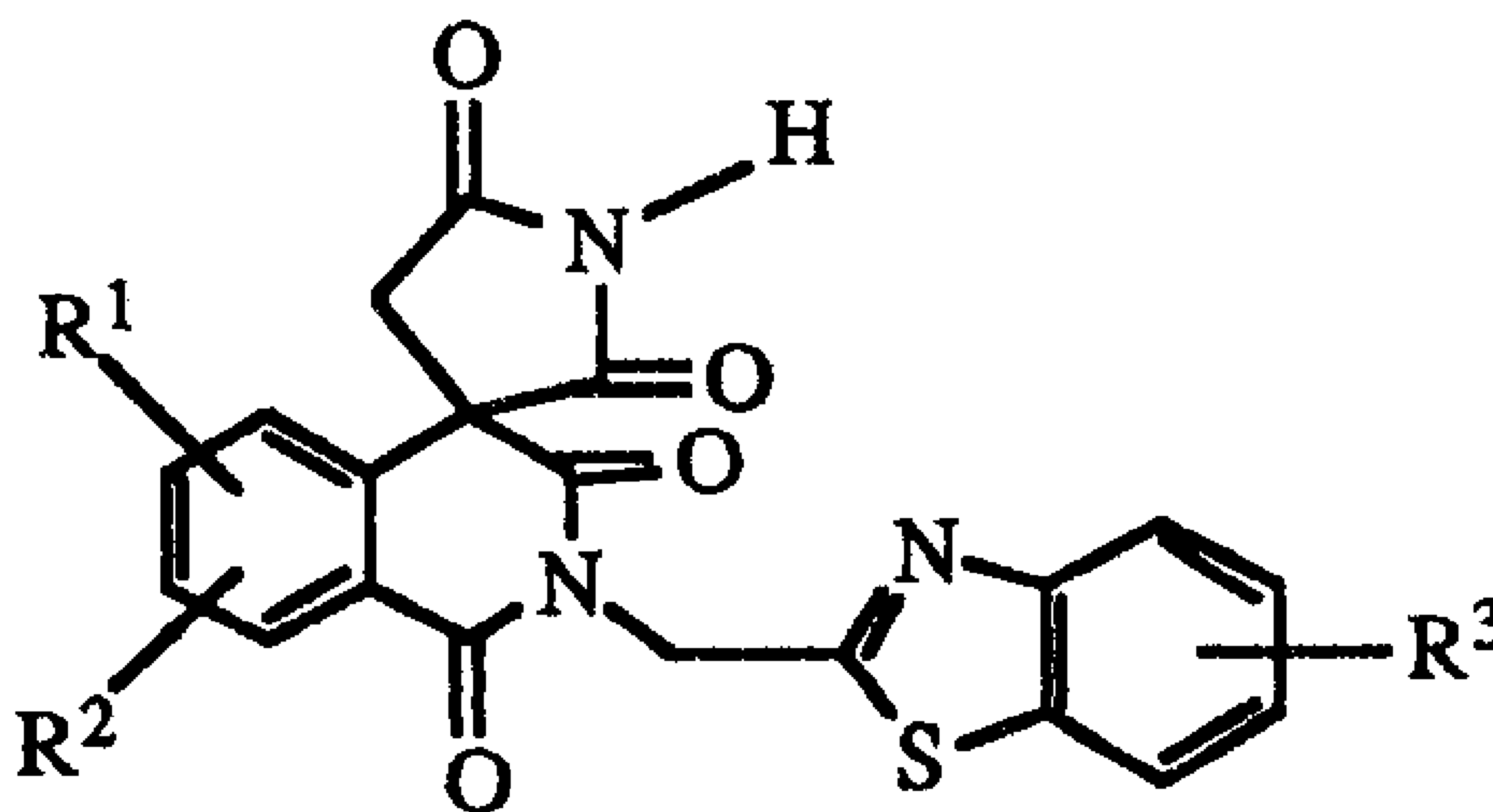
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(54) Titre : SPIRO-ISOQUINOLEINEPYRROLIDINE ET LEURS ANALOGUES, UTILES COMME AGENTS INHIBITEURS DE L'ALDOSE-REDUCTASE

(54) Title: SPIRO-ISOQUINOLINE-PYRROLIDINES AND ANALOGS THEREOF USEFUL AS ALDOSE REDUCTASE INHIBITORS



(I)

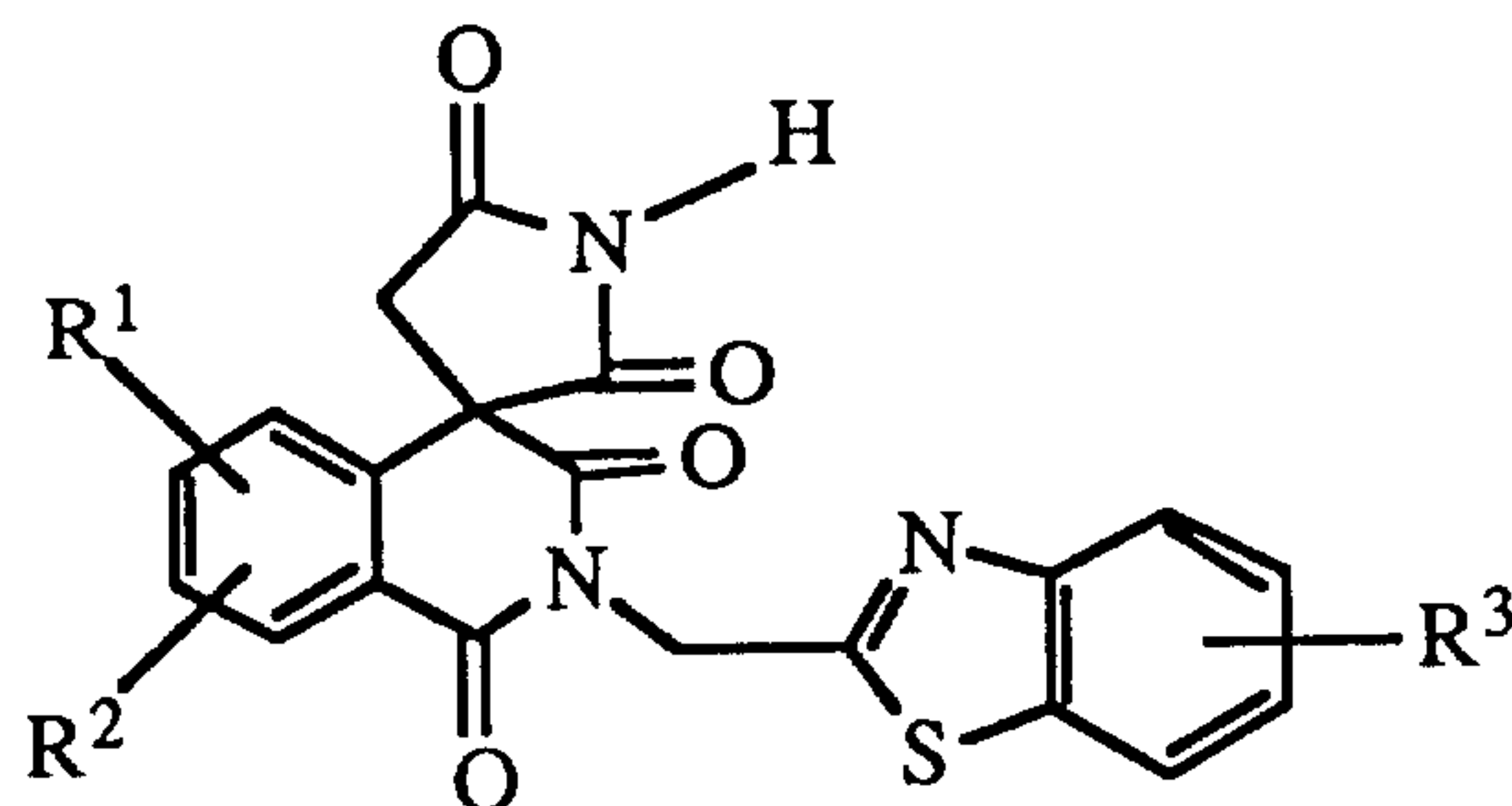
(57) Abrégé/Abstract:

This invention relates to spiro-isoquinoline-pyrrolidines having the structural formula (I) and their pharmaceutically acceptable salts thereof (see formula I). wherein R¹ and R² 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; and R³ is hydrogen, 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. The invention also relates 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 diabetes mellitus associated complications.



ABSTRACT

This invention relates to spiro-isoquinoline-pyrrolidines having the structural formula (I) and their pharmaceutically acceptable salts thereof.



(I)

wherein R¹ and R² are independently hydrogen, alkyl containing 1 to 6 carbon
 5 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; and R³ is hydrogen, 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
 10 carbon atoms and lower alkyl contains 1 to 5 carbon atoms. The invention also
 relates 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 diabetes mellitus associated complications.

SPIRO-ISOOQUINOLINE-PYRROLIDINES AND ANALOGS THEREOF
USEFUL AS ALDOSE REDUCTASE INHIBITORS

Background of the Invention

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This invention relates to spiro-isoquinoline-pyrrolidines and their pharmaceutically acceptable salts thereof, 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
10 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
15 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
20 achieved with the currently available therapies.

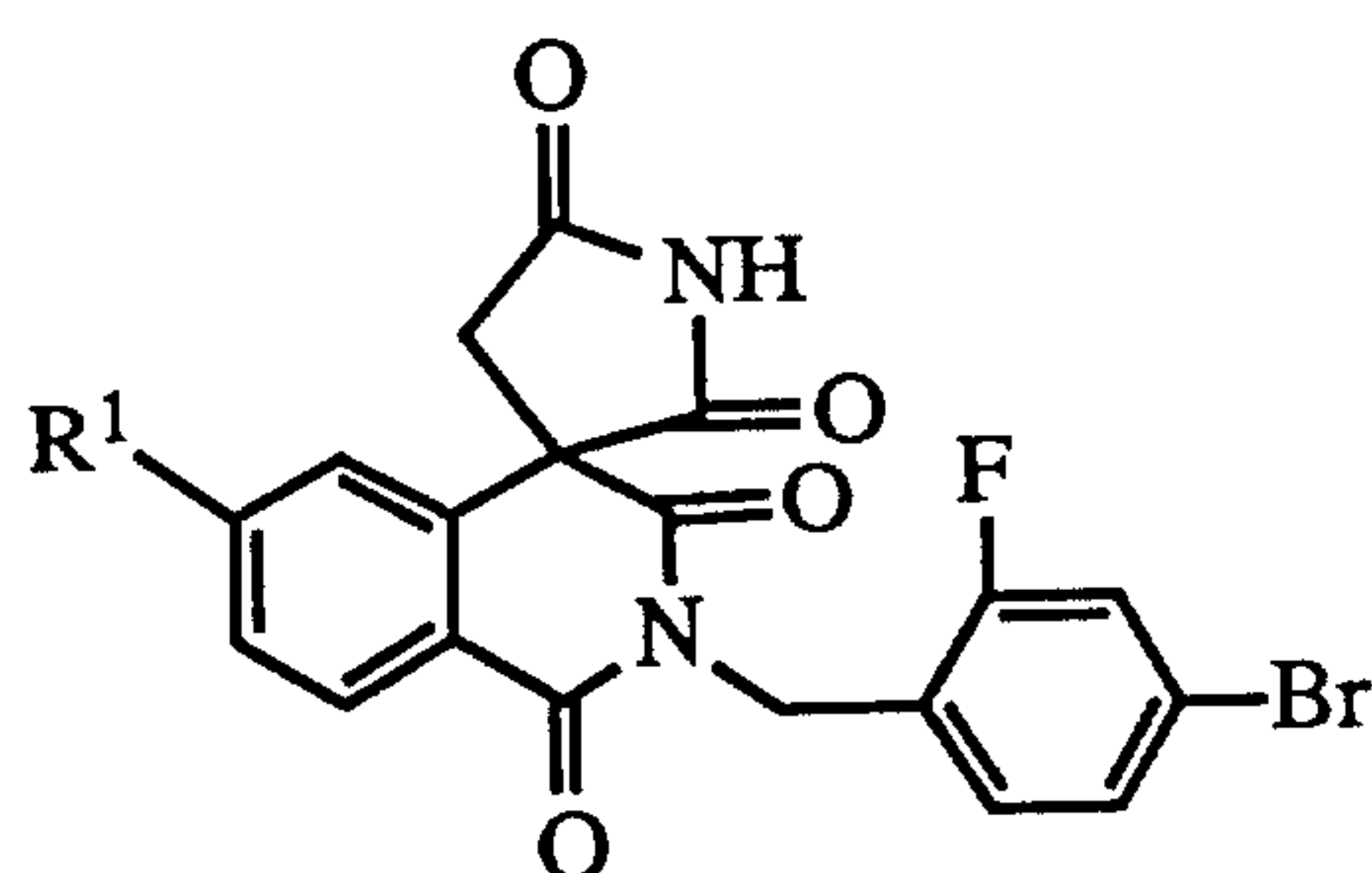
The long-term complications of diabetes develop in tissues where glucose uptake is independent of insulin. In these tissues, which include the lens, retina, kidney and peripheral nerves, the systemic hyperglycemia of diabetes is rapidly
25 transposed into high tissular concentrations of glucose. In all 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
30 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
35 aldose reductase also plays a significant role in the initiation of diabetic nephropathy,

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

Prior Art

5 The closest prior art is U.S. Patent No. 4,927,831, which discloses the spiro-isoquinoline-pyrrolidine tetrones of formula



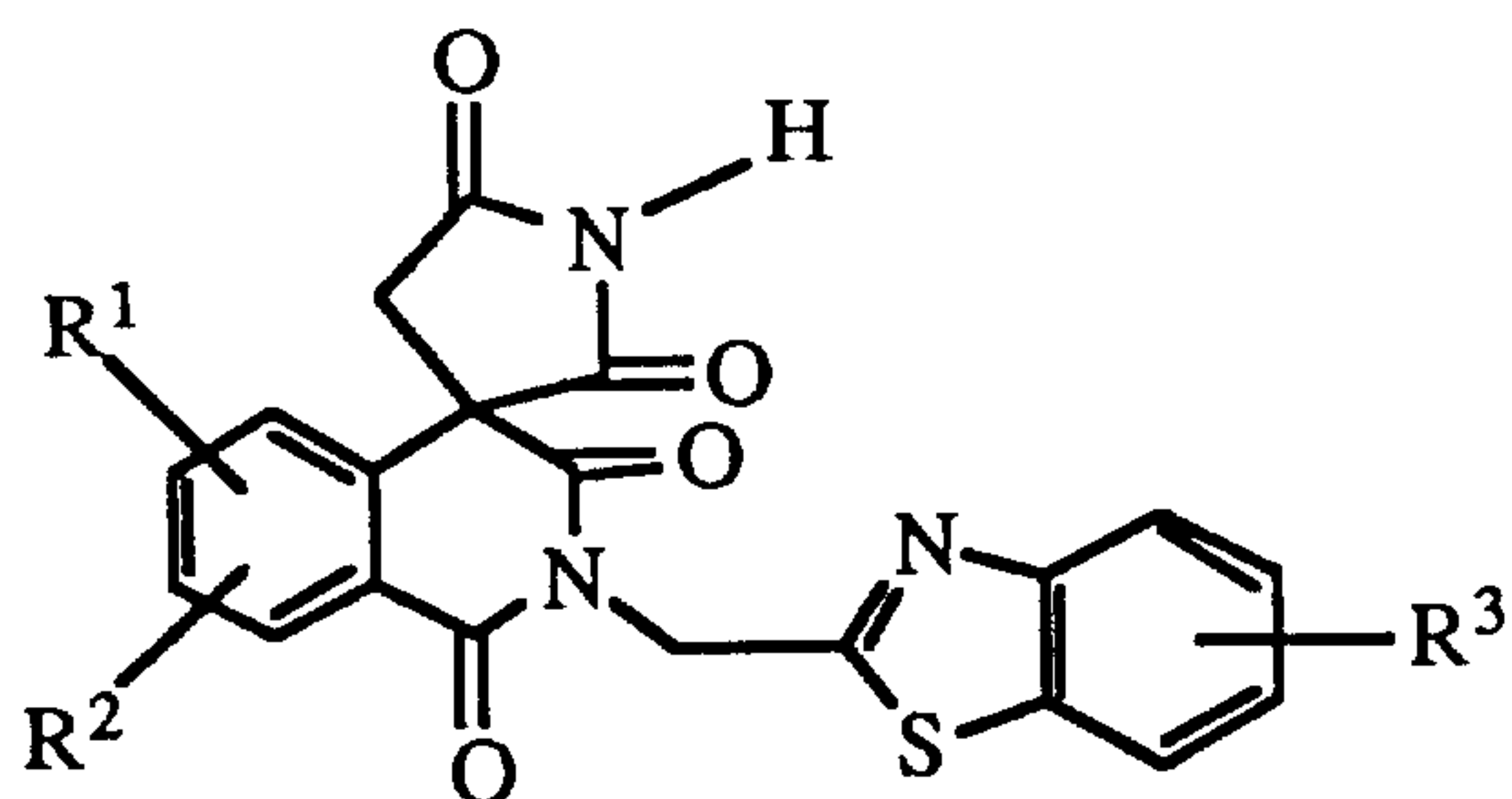
(R¹ is hydrogen or fluorine)

useful as aldose reductase inhibitors for treating complications of diabetes and galactosemia.

10

Summary of Invention

The spiro-isoquinoline-pyrrolidines of the present invention are represented by formula (I):



(I)

wherein R¹ and R² 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
5 contains 1 to 6 carbon atoms; and R³ is hydrogen, 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.

10 A more preferred group of compounds of the present invention are the compounds of formula (I) wherein R¹ and R² are independently hydrogen or halogen; and R³ is hydrogen, halogen or trifluoromethyl.

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

15

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

20

2-(2-benzothiazolylmethyl)-6-fluorospiro[isoquinoline-4(1H),3'-
pyrrolidine]-1,2',3,5'(2H)-tetrone;

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

25

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
30 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 spiro-isoquinoline-pyrrolidines can be prepared by the processes described
35 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.

5

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.

10

The spiro-isoquinoline-pyrrolidines 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.

15

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, preferably of pH 7.2-7.6, containing a pharmaceutically acceptable buffer.

20

25

The dosage of the spiro-isoquinoline-pyrrolidines 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

30

35

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
5 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
10 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.

15 The spiro-isoquinoline-pyrrolidines 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
20 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.

25 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
30 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
35 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

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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.

5 (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.

10 (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 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.

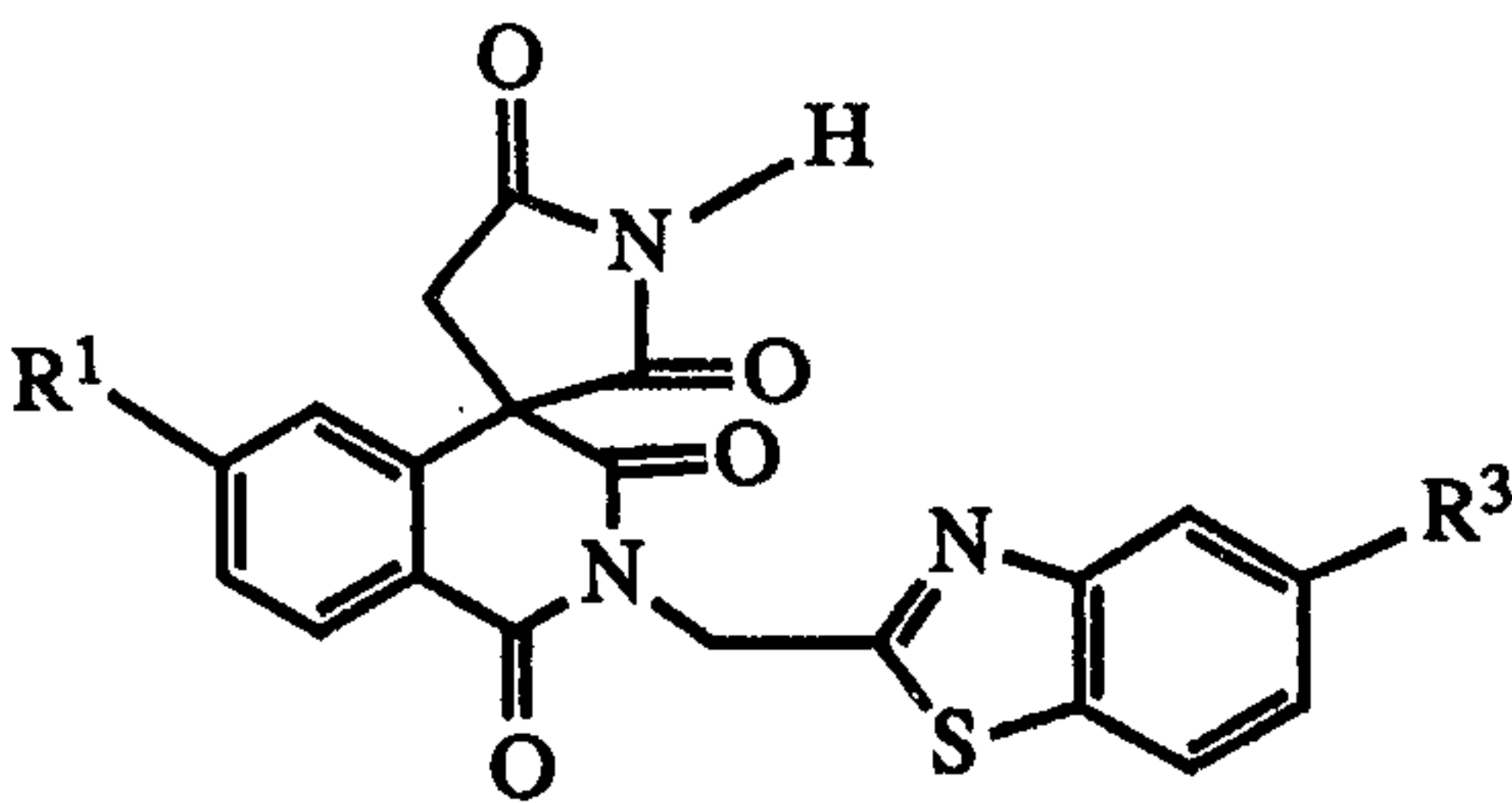
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The following tabulated results show that the spiro-isoquinoline-pyrrolidines of this invention show the property that they are active both in vitro and in vivo and diminish the accumulation of dulcitol in the lenses, sciatic nerves and diaphragm of 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.

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ALDOSE REDUCTASE INHIBITORS



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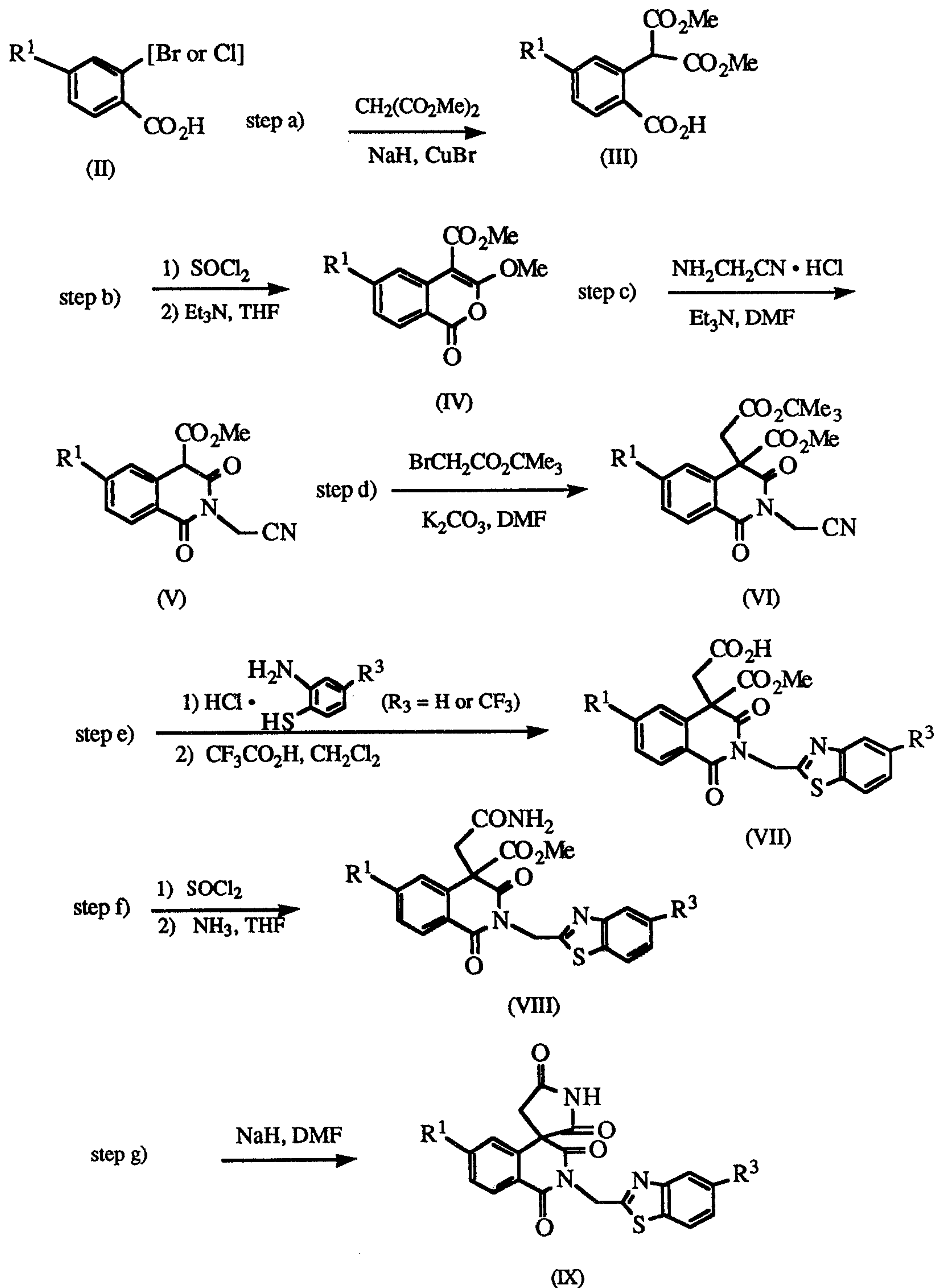
		% inhibition <u>In Vitro</u>				% Lowering Galactitol Accumulation <u>In Vivo</u>			
	<u>R¹</u>	<u>R³</u>	<u>10⁻⁶M</u>	<u>10⁻⁷ M</u>	<u>4 x 10⁻⁸M</u>	<u>Dose</u> <u>mg/kg/day</u>	<u>(%)L</u>	<u>(%)N</u>	<u>(%)D</u>
	H	H	97	92	81	1.1	NS	48	NS
15	H	CF ₃	95	93	90	1.1	22	100	89
						0.5	NS	49	94
	F	H	96	94	91	4.6	NS	63	93
20	F	CF ₃	95	94	92	1.0	NS	53	85

25

30

The Process:

The spiro-isoquinoline-pyrrolidines of the present invention were prepared by the following reaction scheme:



Step a) Reacting either 2-bromobenzoic acid or 2-chlorobenzoic acid of formula (II) wherein R^1 is 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 is as defined above.

5

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

10 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 Et_3N in a conventional solvent which does not adversely influence the reaction, for example, tetrahydrofuran, can produce the compound of formula (IV), wherein R^1 is as defined above.

15

Step c) The compound of formula (IV), wherein R^1 is 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 (V), wherein R^1 is as defined above.

20

Step d) The compound of formula (V), wherein R^1 is 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 (VI), wherein R^1 is as defined above.

25

Step e) The compound of formula (VI), wherein R^1 is as defined above, can be reacted with 2-aminothiophenols (R^3 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 (VII), wherein R^1 and R^3 are as defined above.

30

35

Step f) The compound of formula (VII), wherein R¹ and R³ are as defined above, can be reacted with thionyl chloride under refluxing conditions to produce the corresponding acid chloride which upon treatment with a saturated tetrahydrofuran-ammonium solution produces the compound of formula (VIII), wherein R¹ and R³ are as defined above.

Step g) The compound of formula (VIII), wherein R¹ and R³ 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 (IX), wherein R¹ and R³ are as defined above.

The following examples further illustrate this invention:

EXAMPLE 1

15

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

Step a)

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(2-Carboxyphenyl)propanedioic Acid Dimethyl Ester

25

To a rapidly stirred cold suspension (0°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 N₂ 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 H₂O (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 MgSO₄. Evaporation gave an off-white solid which was recrystallized from Et₂O/hexane (-20°C) to give a white solid (34.2 g, 90.9%).

35

^1H NMR (DMSO- d_6 , 400 MHz): δ 3.67 [s, 6H, $-\text{CH}(\text{CO}_2\text{CH}_3)_2$], 5.72 [s, 1H, $-\text{CH}(\text{CO}_2\text{CH}_3)_2$], 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, $-\text{CO}_2\text{H}$)

5

IR (KBr, cm^{-1}): 3300-2700 (CO_2H), 1750 ($\text{C}=\text{O}$), 1730 ($\text{C}=\text{O}$),
1680 ($\text{C}=\text{O}$)
MS (m/e): 252 (M^+), 220 ($\text{M}^+-\text{CH}_3\text{OH}$), 188 ($\text{M}^+-2\times\text{CH}_3\text{OH}$)

10

Anal. Calcd.: C, 57.14; H, 4.80
Found: C, 57.05; H, 4.78
M.P. 119-120°C.

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

15

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

^1H NMR (DMSO- d_6 , 400 MHz): δ 3.68 [s, 6H, $(-\text{CO}_2\text{Me})_2$], 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)

20

IR (KBr, cm^{-1}): 3400-2700 (CO_2H), 1730 ($\text{C}=\text{O}$), 1680 ($\text{C}=\text{O}$)
MS (m/e): 270 (M^+), 238 ($\text{M}^+-\text{CH}_3\text{OH}$), 210 ($\text{M}^+-\text{CH}_3\text{OH}$, $-\text{CO}$), 151 ($\text{M}^+-\text{CH}_3\text{OH}$, $-\text{CO}$, $-\text{CO}_2\text{CH}_3$)

25

Anal. Calcd.: C, 53.34; H, 4.10
Found: C, 53.36; H, 3.93

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M.P. 121.5-123.0°C.

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Step b)

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 SOCl₂ (100 g) was refluxed for 2 hours. The volatiles were removed 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 MgSO₄. Evaporation and crystallization from acetone/ether/hexane (at -20°C) gave a white solid (87.6 g, 94.4%).

¹H NMR (DMSO-d₆, 400 MHz): δ 3.82 (s, 3H, -CO₂Me), 4.03 (s, 3H, -OMe), 7.42 (t, J=7.26 Hz, 1H, Ar-H), 7.8 (t, J=8.2 Hz, 1H, Ar-H), 7.9 (d, J=8.3 Hz, 1H, Ar-H), 8.1 (d, J=7.26 Hz, 1H, Ar-H)

15

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)

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

20

M.P. 129-130°C.

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

25

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

¹H NMR (DMSO-d₆, 400 MHz): δ 3.81 (s, 3H, -CO₂CH₃), 4.06 (s, 3H, -OCH₃), 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)

30

IR (KBr, cm⁻¹): 1750 (C=O), 1685 (C=O)

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

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- 13 -

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

M.P. 142-143°C.

5

Step c)

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

10 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 H₂O, acidified with
15 HCl (2N) and extracted with EtOAc. The organic extracts were dried over MgSO₄.
Evaporation and crystallization from acetone/ether/hexane (at -20°C) gave a yellowish
solid (6.5 g, 73.7%).

20 ¹H NMR (DMSO-d₆, 400 MHz): δ [3.7 (s), 3.98 (s), 3H, -CO₂CH₃,
tautomeric], [4.92 (s), 5.44 (s), 2H, -NCH₂CN, tautomeric], 7.2-8.4 (m, 4H, Ar-H,
tautomeric)

IR (KBr, cm⁻¹): 3400 (OH), 1670 (C=O)

25 MS (m/e): 258 (20, M⁺), 226 (43, M⁺-MeOH), 199 (13,
M⁺-CO₂Me)

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

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M.P. 169-171°C.

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Step d)

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M.P. 48-50°C.

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

5 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.

10

Step e)

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

15

To a mixture of 3-amino-4-mercaptobenzotrifluoride hydrochloride (6.1 g, 26.2 mmol) and EtOH (150 mL) was added Et₃N (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 H₂O, acidified with HCl (2N) and extracted with
20 EtOAc. The organic extracts were dried over MgSO₄. Evaporation gave an oil (9.6 g) which was dissolved in CH₂Cl₂ (80 mL). Trifluoroacetic acid (20 mL) was added and the mixture was stirred at room temperature for 8 hours. The volatiles were removed in vacuo and the residue was purified by flash chromatography on acid washed (5%, H₃PO₄ in MeOH) silica gel to give a white solid (6.3 g, 73.3%).

25

¹H NMR (DMSO-d₆, 400 MHz): δ 3.57 (s, 3H, -CO₂CH₃), 3.68 (dd, J=17.85 Hz, 2H, -CH₂CO₂H), 5.61 (s, 2H, -NCH₂-), 7.62 (m, 2H, Ar-H), 7.81 (m, 2H, Ar-H), 8.2 (dd, J=7.9 Hz, 1.04 Hz, 1H, Ar-H), 8.33 (dd, J=8.5 Hz, 0.92 Hz, 1H, Ar-H), 8.34 (d, J=0.83 Hz, 1H, Ar-H)

30

IR (KBr, cm⁻¹): 3200-2500 (CO₂H), 1750 (C=O), 1710 (C=O), 1670 (C=O)

MS (m/e): 492 (6, M⁺), 448 (6, M⁺-CO₂), 416 (62, M⁺-CO₂, -MeOH)

Anal. Calcd.: C, 53.66; H, 3.07; N, 5.69

35

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 e):

5 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

10

M.P. 189-190°C.

6-Fluoro-1,2,3,4-tetrahydro-4-(methoxycarbonyl-1,3-dioxo-2-
15 [[(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.

20

Step f)

4-[(Aminocarboxyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-
2-[[[(5-trifluoromethyl)-2-benzothiazolyl)methyl]-4-isoquinoline-
25 carboxylic Acid Methyl Ester

25

A mixture of 1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-2-[[[(5-trifluoromethyl)-2-benzothiazolyl)methyl]-4-isoquinolineacetic acid (2.5 g, 5.08 mmol) and SOCl₂ (25 g) was refluxed for 1 hour. The volatiles were removed in vacuo and the product (acid chloride) was taken in THF (20 mL) and added to a freshly prepared, 30 saturated NH₃, THF solution (20 mL). After stirring for 10 minutes, the mixture was poured into HCl (1N, 500 mL), extracted with EtOAc and dried over MgSO₄. Evaporation and purification by flash chromatography on silica gel (hexane/EtOAc, 1/1) gave a light yellow solid (2.1 g, 84%).

35

¹ H NMR (DMSO-d₆, 400 MHz) δ 3.53 (dd, J=16.6 Hz, 2H, -CH₂CONH₂), 3.56 (s, 3H, CO₂CH₃), 5.53 (d, J=15.77 Hz, 1H, -NHCH-), 5.6 (d, J=15.77 Hz, 1H, -NHCH-), 6.84 (br s, 1H, -CONH-), 7.49 (m, 2H, Ar-H, -CONH-), 7.6 (t, J=7.47 Hz, 1H, Ar-H), 7.68 (m, 2H, Ar-H), 8.17 (dd, J=7.9z, 1.45 Hz, 1H, Ar-H), 8.34 (m, 2H, Ar-H)

IR (KBr, cm⁻¹): 3420 (NH), 3180 (NH), 1745 (C=O), 1710 (C=O), 1660 (C=O)

MS(m/e): 491 (10, M⁺)

Anal. Calcd.: C, 53.77; H, 3.28; N, 8.55

Found: C, 54.23; H, 3.26; N, 8.39

M.P. 198-200°C.

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

4-[(Aminocarbonyl)methyl]-6-fluoro-1,2,3,4-tetrahydro-1,3-dioxo-2-[[[(5-trifluoromethyl)-2-benzothiazolyl]methyl]-4-isoquinoline-carboxylic Acid Methyl Ester

Anal. Calcd.: C, 51.87; H, 2.97; N, 8.25

Found: C, 51.87; H, 2.93; N, 8.01

M.P. 144-146°C.

Step g)

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

To a mixture of 4-[(aminocarbonyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-2-[[[(5-trifluoromethyl)-2-benzothiazolyl]methyl]-4-isoquinolineacetic acid methyl ester (1.6 g, 3.34 mmol) and anhydrous DMF (20 mL) was added NaH (80% dispersion in oil, 106.2 mg, 3.34 mmol) portionwise over a 5 minute period. After stirring for 30

minutes, the mixture was poured into H₂O (1000 mL), acidified with HCl (2N), extracted with EtOAc and dried over MgSO₄. Evaporation and purification by flash chromatography on silica gel (hexane/EtOAc 1/2) gave a white solid (1.2 g, 80.3%).

5 ¹H NMR (DMSO-d₆, 400 MHz) δ 3.44 (dd, J=18.26 Hz, 2H, -CH₂CO-), 5.56 (s, 2H, NCH₂), 7.66 (dt, J=7.26 Hz, 1.04 Hz, 1H, Ar-H), 7.75 (m, 2H, Ar-H), 7.82 (dt, J=7.88 Hz, 1.66 Hz, 1H, Ar-H), 8.22 (dd, J=7.88 Hz, 1.45 Hz, 1H, Ar-H), 8.33 (m, 2H, Ar-H), 12.05 (s, 1H, -CONHCO-)

10 IR (KBr, cm⁻¹): 3400 (NH), 3240 (NH), 1725 (C=O), 1680 (C=O)

MS(m/e): 459 (82, M⁺)

15 Anal. Calcd.: C, 54.90; H, 2.63; N, 9.15
Found: C, 55.17; H, 2.71; N, 9.06
M.P. 122-124°C.

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

20 2-(2-Benzothiazolylmethyl)spiro[isoquinoline-4(1H),3'-pyrrolidine)-1,2',3,5'(2H)-tetrone

25 Anal. Calcd.: C, 61.37; H, 3.35; N, 10.74
Found: C, 61.09; H, 3.47; N, 10.59

M.P. 225-227°C.

30 6-Fluoro-2-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]spiro-[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

Anal. Calcd.: C, 52.84; H, 2.32; N, 8.80
Found: C, 52.76; H, 2.43; N, 8.53

35 M.P. 123-125°C.

2-(2-Benzothiazolylmethyl)-6-fluorospiro[isoquinoline-4(1H),3'-
pyrrolidine]-1,2',3,5'(2H)-tetrone

5

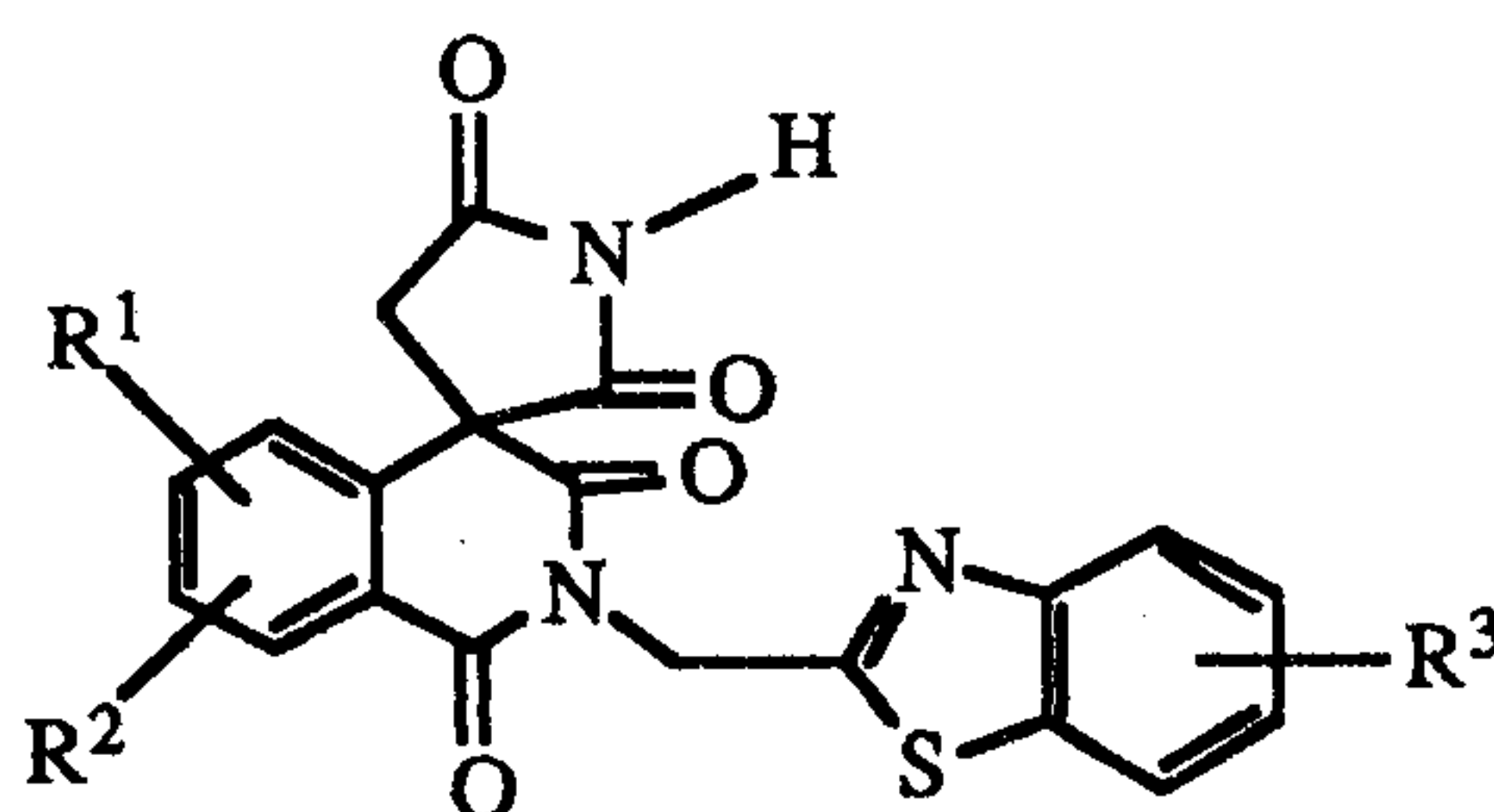
Anal. Calcd.: C, 58.68; H, 2.95; N, 10.26
Found: C, 58.77; H, 3.12; N, 10.11

M.P. 198-199°C.

10

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE
PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

- 5 1. The compounds of structural formula (I)



(I)

wherein R¹ and R² are independently hydrogen, alkyl containing 1 to 6 carbon atoms,
10 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; and R³ is hydrogen, alkyl containing 1 to 6 carbon
atoms, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or
15 aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl
contains 1 to 5 carbon atoms.

2. The compounds according to claim 1 wherein R¹ and R² are independently
hydrogen or halogen; and R³ is hydrogen, halogen or trifluoromethyl.

- 20 3. The compound according to claim 2

2-(2-benzothiazolylmethyl)spiro[isoquinoline-4(1H),3'-pyrrolidine]-
1,2',3,5'(2H)-tetrone.

- 25 4. The compound according to claim 2

2-(2-benzothiazolylmethyl)-6-fluorospiro[isoquinoline-4(1H),3'-
pyrrolidine]-1,2',3,5'(2H)-tetrone.

5. The compound according to claim 2

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

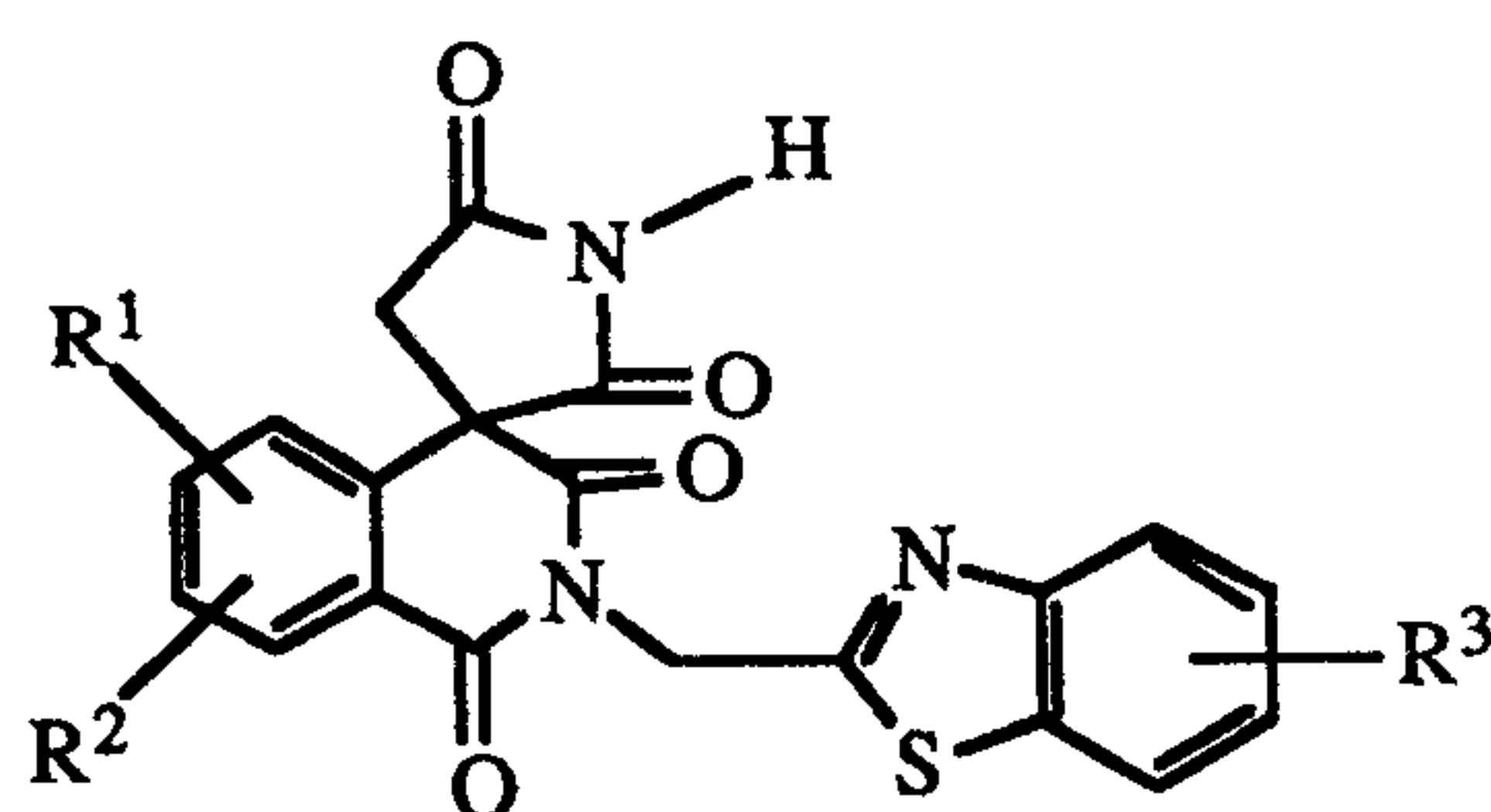
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6. The compound according to claim 2

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

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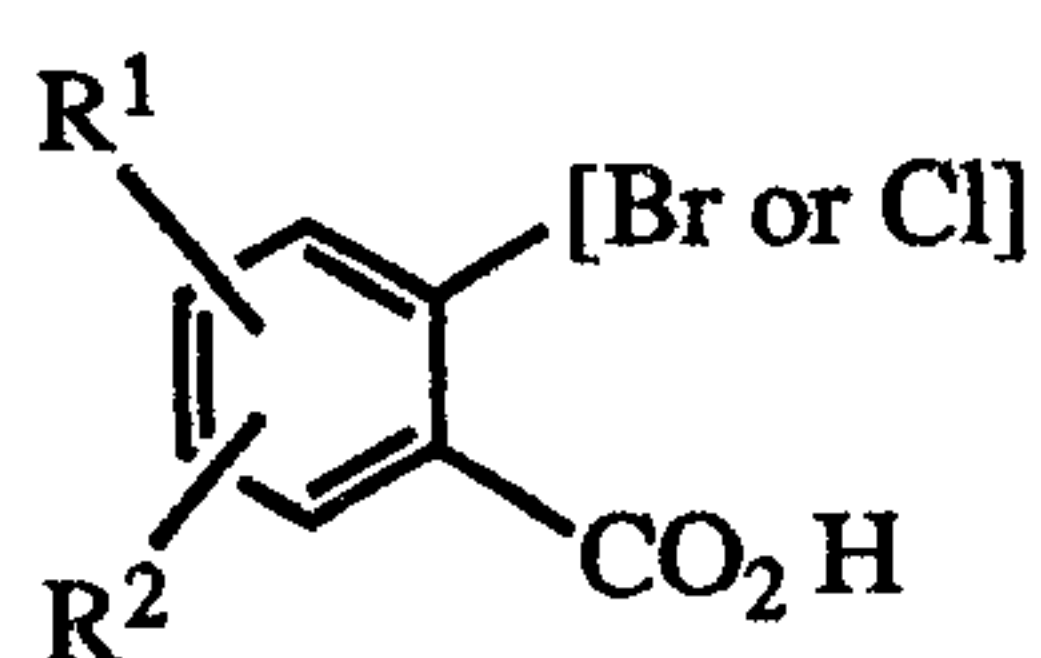
7. The process for the production of compounds of formula (I)



(I)

15 wherein R¹ and R² 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; and R³ is hydrogen, alkyl containing 1 to 6 carbon atoms, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or
20 aryl(lower alkyl)oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 5 carbon atoms which comprises:

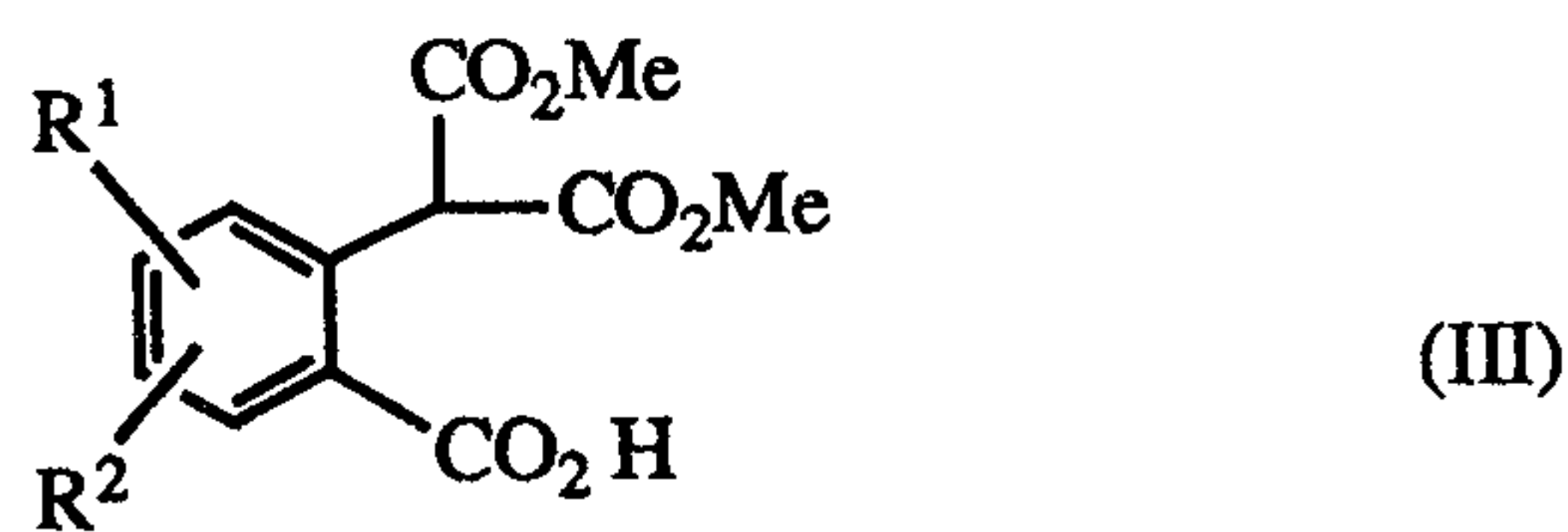
a) reacting the compound of formula (II)



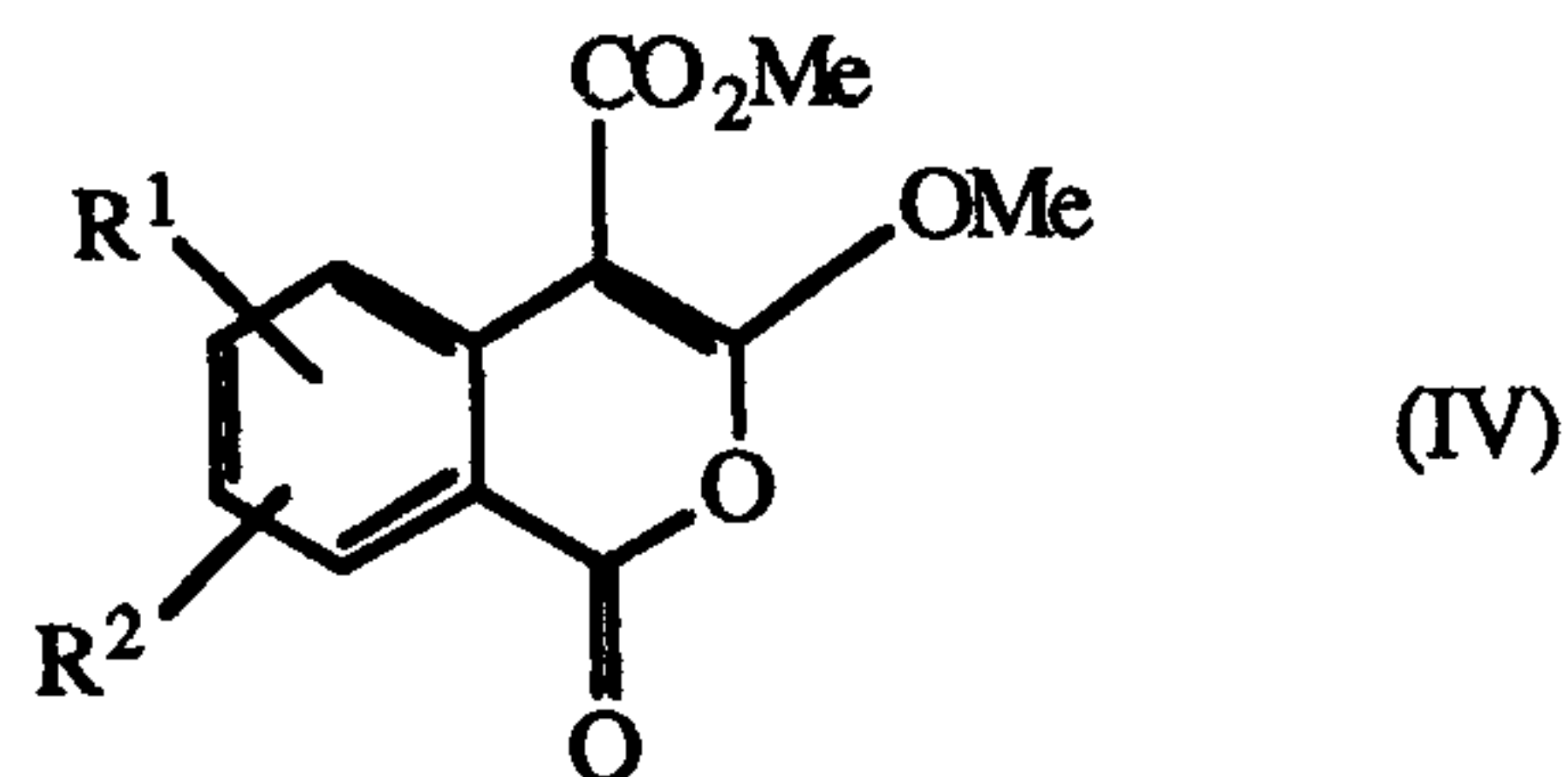
(II)

25

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 compound of formula (III)

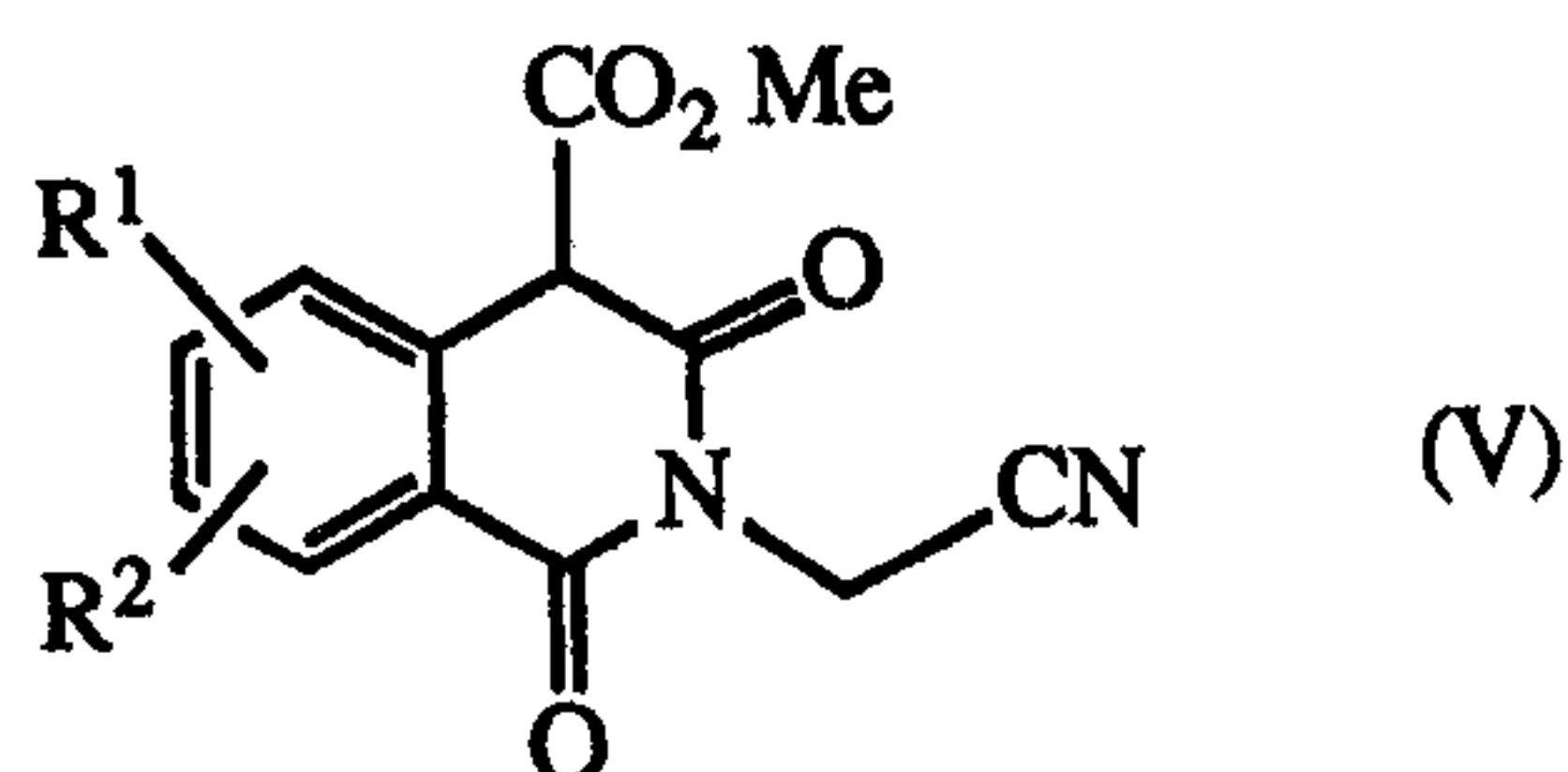


10 b) reacting the compound of formula (III) wherein R^1 and R^2 are as defined above with $SOCl_2$ and subsequently treating with Et_3N in a conventional solvent to produce the compound of formula (IV)



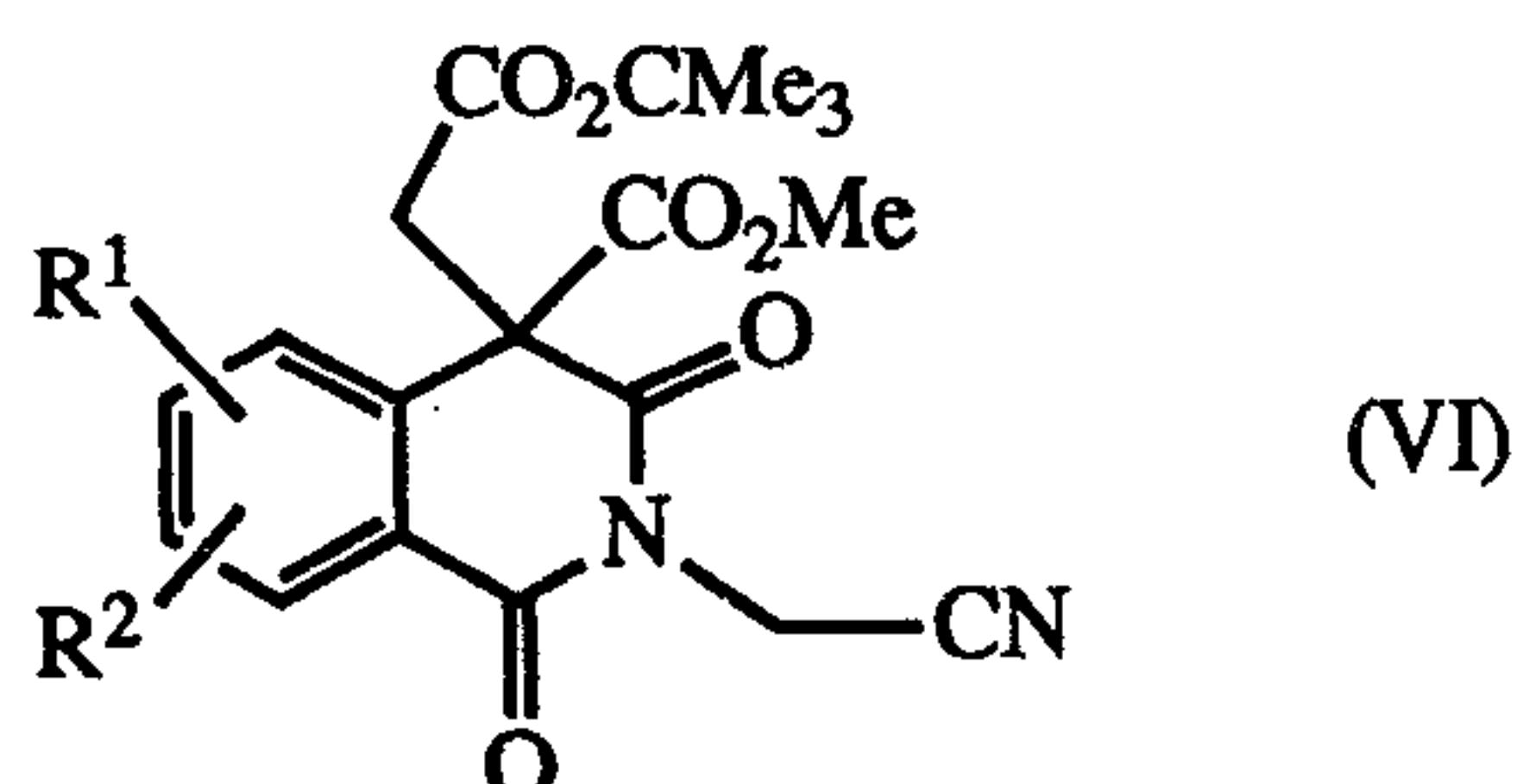
15 wherein R^1 and R^2 are as defined above

c) reacting said compound of formula (IV) with aminoacetonitrile hydrochloride in the presence of Et_3N in a conventional solvent to produce the compound of formula (V)



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

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

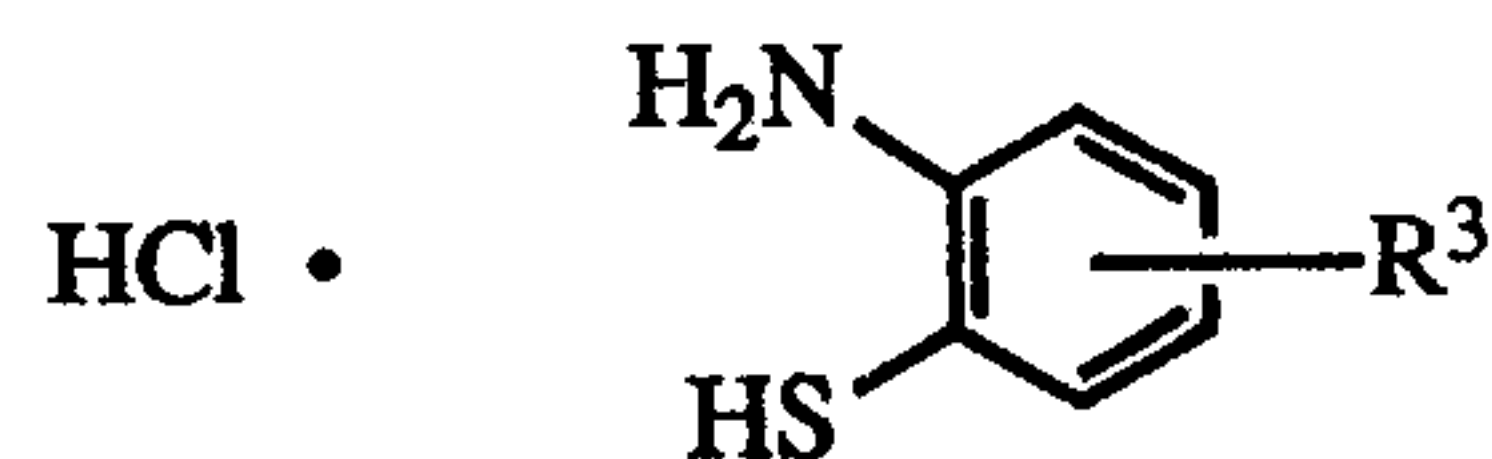


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wherein R¹ and R² are as defined above

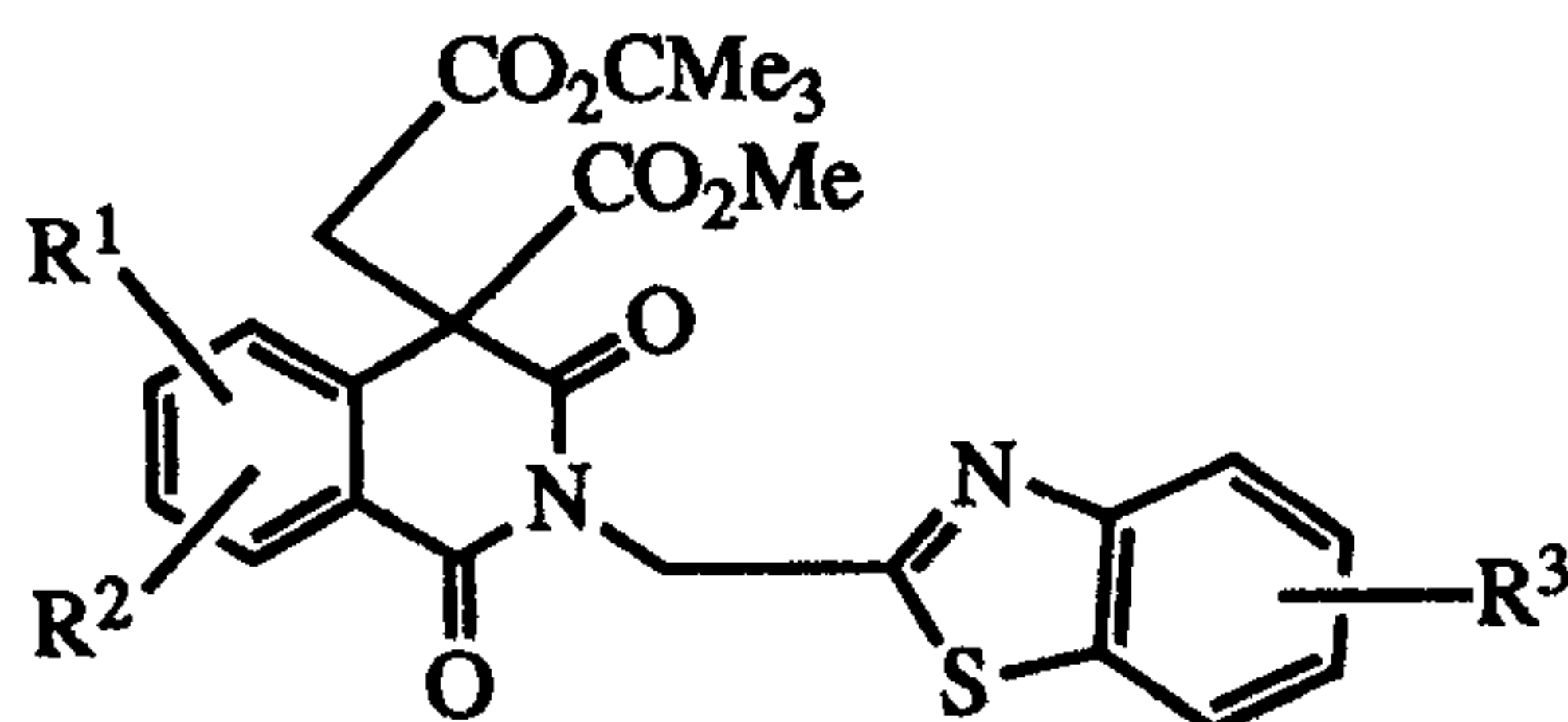
e) reacting said compound of formula (VI) with a 2-aminothiophenol of structural formula

10



wherein R³ is as defined above to produce the tert-butyl ester compound of structural formula

15

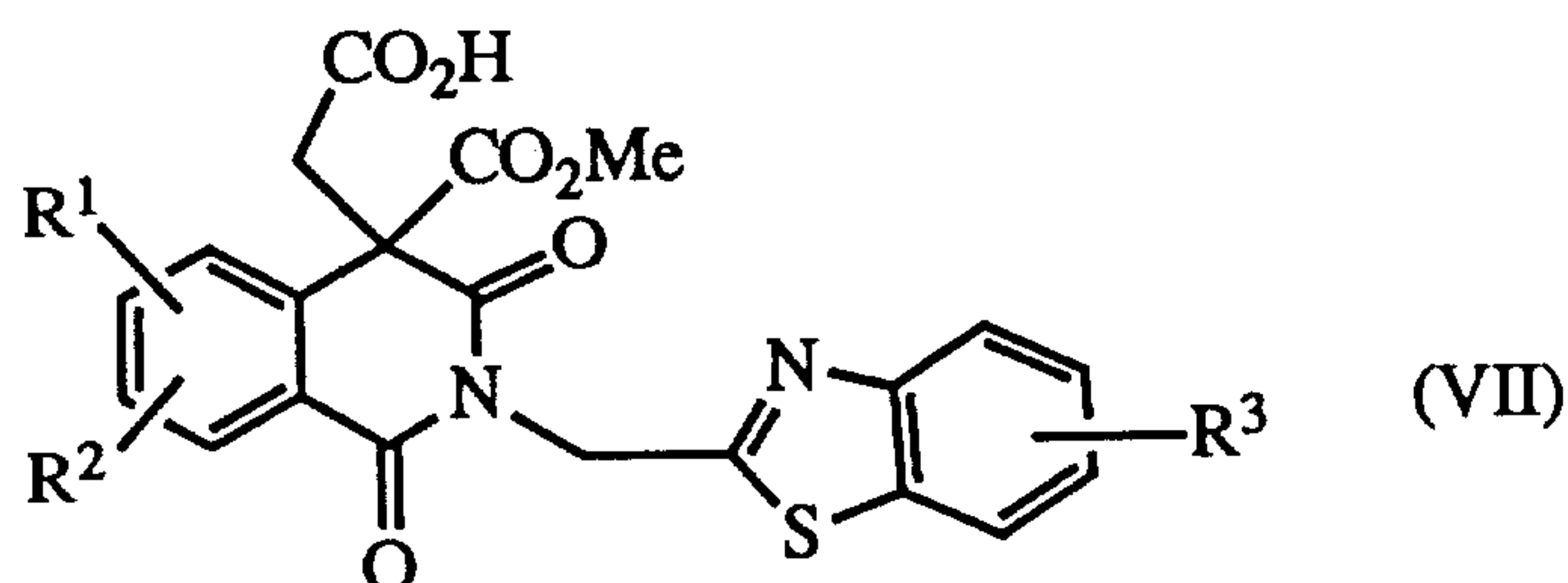


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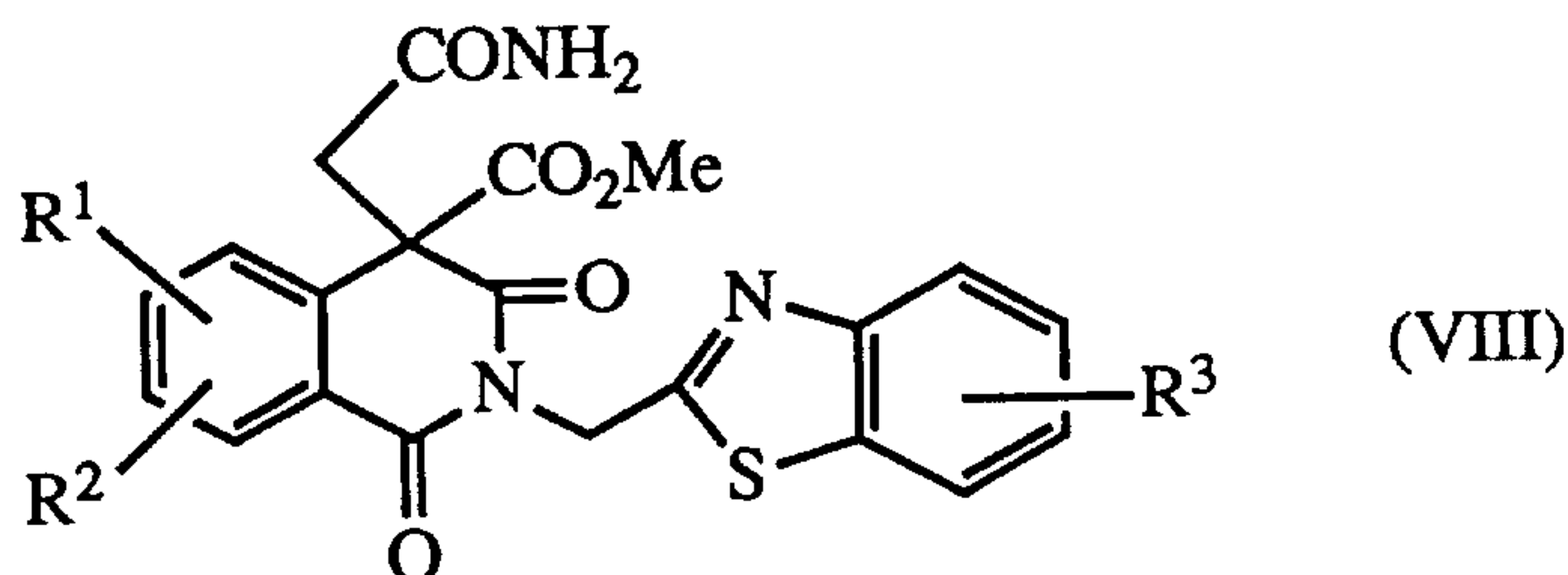
- 24 -

- f) hydrolyzing said tert-butyl ester with an organic acid in a conventional solvent to produce compound of formula (VII)



wherein R¹, R² and R³ are as defined above

- g) reacting said compound of formula (VII) with thionyl chloride and subsequently adding THF/NH₃ to produce the compound of formula (VIII)

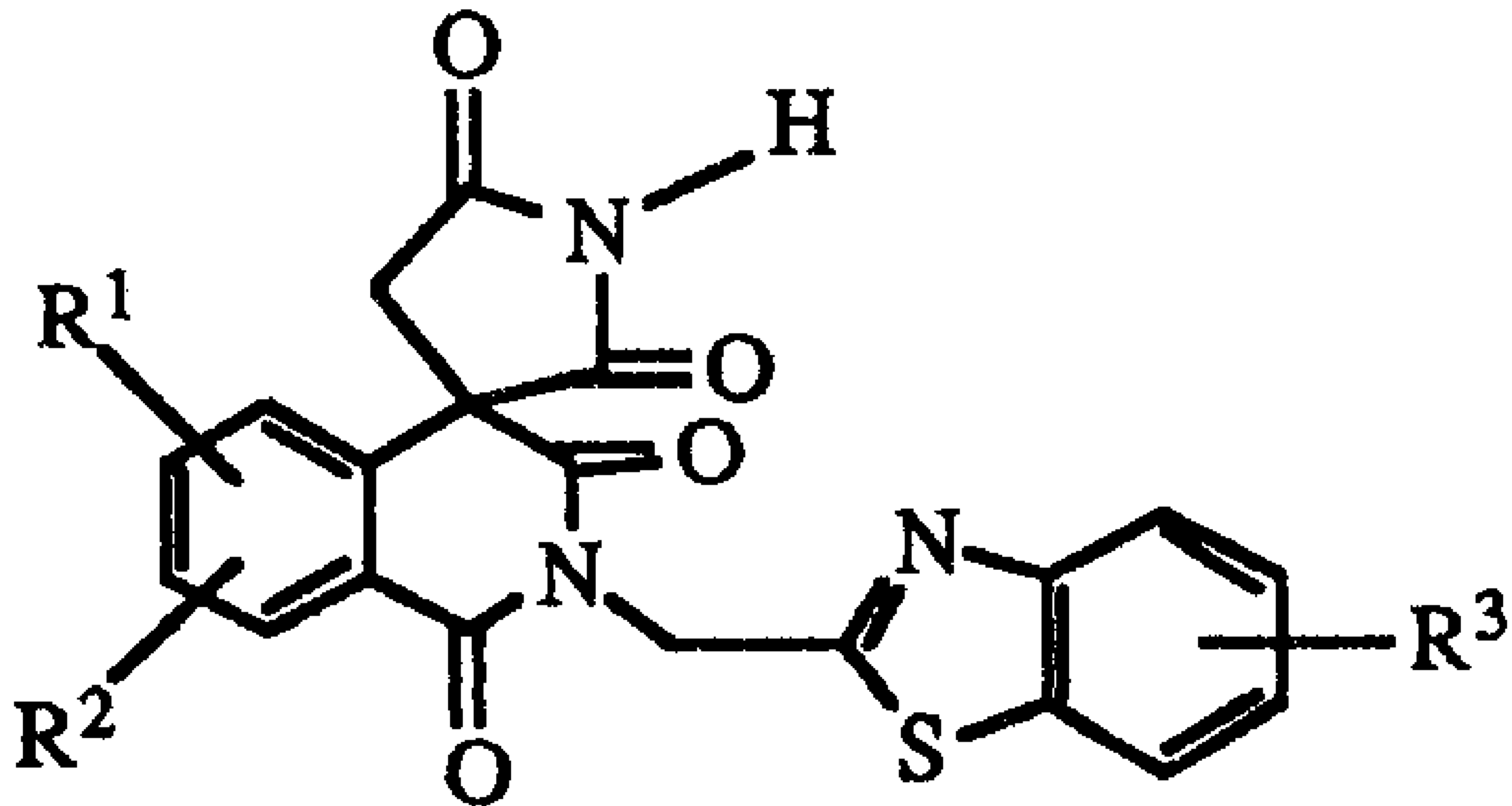


wherein R¹, R² and R³ are as defined above

- h) reacting said compound of formula (VIII) with a base in a conventional solvent to produce the compound of formula (I).

8. A pharmaceutical composition for preventing or relieving neuropathy, nephropathy, retinopathy, or cataracts in a diabetic mammal, which comprises an effective amount of claim 1 and a pharmaceutically acceptable carrier.

9. The use of an alleviating or prophylactic amount of a compound of claim 1 for preventing or relieving neuropathy, nephropathy, retinopathy, or cataracts in a diabetic mammal.



(I)