SPRUSON & FERGUSON

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

In support of the convention application made for a patent for an invention entitled:

Hydantoin Derivatives

I, Ei Mochida, Representative, of Mochida Pharmaceutical Co., Ltd., 7, Yotsuya 1-chome, Shinjuku-ku, Tokyo, 160, Japan do solemnly and sincerely declare as follows:

1. I am authorised by Mochida Pharmaceutical Co., Ltd., the applicant for the patent to make this declaration on its behalf.

2. The basic applications as defined by Section 141 of the Act were made in United States of America on 24 August, 1988 by Ei Mochida, Kimihiro Murakami, Kazuo Kato, Katsuaki Kato, Jun Okuda and Ichitomo Miwa and in Japan on 25 February, 1989 by Mochida Pharmaceutical Co., Ltd.

3. Ei Mochida of 5-4, Komagome 2-chome, Toshima-ku, Tokyo 170; Kimihiro Murakami of 169-2, Subashiri Oyama-cho, Suntou-gun, Shizuoka 410-14; Kazuo Kato of 29-6, Fujimidai, Mishima-shi, Shizuoka 411; Katsuaki Kato of 5-15-25, Nukuiminami-cho, Koganei-shi, Tokyo 184; Jun Okuda of 3-1110, Tsuchihara, Tenpaku-cho, Tenpaku-ku, Nagoya-shi, Aichi 468 and Ichitomo Miwa of A-305 Miyukiyama-Park-Mansion, 1201, Miyukiyama, Tenpaku-ku, Nagoya-shi, Aichi 468, all in Japan, are the actual inventors of the invention and the facts upon which the applicant is entitled to make the application are as follows:-

   The said applicant is the assignee of the actual inventors.

4. The basic applications referred to in paragraph 2 of this Declaration were the first applications made in a Convention country in respect of the inventions the subject of the application.

DECLARED at Tokyo, Japan this 9th day of August 1990

E. Mochida
.....
Signature of Declarant(s)

TO: THE COMMISSIONER OF PATENTS
AUSTRALIA

Ref: S&F 121246

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HYDANTOIN DERIVATIVES

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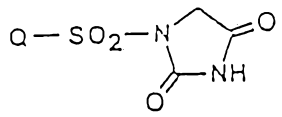
(57) Claim

1. Hydantoin derivatives represented by the formula (I):



(I)

and non-toxic salts, solvates and solvates of non-toxic salts thereof; wherein Q represents a mono- or a fused heterocyclic group which may be substituted by one or more substituents which are same or different and selected from a group consisting of a halogen atom, a lower alkyl group, a nitro group, a cyano group, an optionally protected carboxy group, an optionally protected carboxymethyl group, a halogenated lower alkyl group, a lower alkylthio

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group, a lower alkylcarbonyl group, a lower alkoxy group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, an optionally protected hydroxy group, an optionally protected amino group, a carbamoyl group and a phenyl group.

14. A method of treating and/or preventing various forms of diabetic complications based on the accumulation of polyol metabolites in an animal requiring such treatment and/or prevention, comprising administering to said animal an effective amount of a compound as defined in claim 11 or a composition as defined in claim 13.

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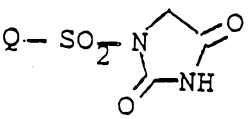
(54) Title: HYDANTOIN DERIVATIVES



(I)

(57) Abstract

The present invention relates to hydantoin derivatives, represented by formula (I), and non-toxic salts, solvates and solvates of non-toxic salts thereof; wherein Q represents a mono- or a fused heterocyclic group which may be substituted by one or more substituents which are same or different and selected from a group consisting of a halogen atom, an alkyl group, a nitro group, a cyano group, an optionally protected carboxy group, an optionally protected carboxymethyl group, a halogenated alkyl group, an alkylthio group, an alkylcarbonyl group, an alkoxy group, an alkylsulfinyl group, an alkylsulfonyl group, an optionally protected hydroxy group, an optionally protected amino group, a carbamoyl group and a phenyl group.

HYDANTOIN DERIVATIVES

BACKGROUND OF THE INVENTION

The present invention relates to novel hydantoin derivatives, processes for producing hydantoin derivatives, and pharmaceutical compositions containing at least one of said hydantoin derivatives as aldose reductase inhibitors.

Cataract, peripheral neuropathy, retinopathy and nephropathy associated with diabetes mellitus result from abnormal accumulation of polyol metabolites converted from sugars by aldose reductase. For example, sugar cataract results from damage of lens provoked by change in osmotic pressure induced by abnormal accumulation of polyol metabolites converted from glucose or galactose by aldose reductase in lens [see J.H. Kinoshita et al., Biochim. Biophys. Acta, 158, 472 (1968) and cited references in the report]. And some reports were submitted about undesirable effect of abnormal accumulation of polyol metabolites in lens, peripheral nerve cord and kidney of the diabetic animals [see A. Pirie et al. Exp. Eye Res., 3, 124 (1964); L.T. Chylack Jr. et al., Invest. Opthal., 8, 401 (1969); J.D. Ward et al., Diabetologia, 6, 531 (1970)]. Consequently, it is important to inhibit aldose reductase as strongly as

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possible for treating and/or preventing diabetic complications mentioned above. Although several compounds have been offered as aldose reductase inhibitors, none of them is fully sufficient in inhibitory activity against the enzyme. Therefore, it has been desired to develop new compounds having a stronger inhibitory activity against aldose reductase.

SUMMARY OF THE INVENTION

An object of the present invention is to provide novel hydantoin derivatives and salts, solvates and solvates of salts thereof.

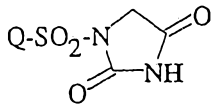
Another object of the present invention is to provide processes for producing said novel hydantoin derivatives.

A further object of the present invention is to provide pharmaceutical compositions comprising at least one of said novel hydantoin derivatives having an inhibitory activity against aldose reductase.

The present inventors previously found that sulfonylhydantoin derivatives had a strong inhibitory activity against aldose reductase and accomplished an invention on aldose reductase inhibitors (JP Kokai 58 109418, 62 67075, 62 201873 and 1 61465). And M.S. Malamas et al. U.S. Pat. No. 4,743,611 disclosed naphthalenesulfonyl hydantoin derivatives useful as aldose reductase inhibitors. And Ohishi et al. disclosed benzofuranylsulfonyl glycine derivatives useful as drugs of treatment of diabetic complications (JP Kokai 62 155269).

Furthermore, the present inventors have made extensive researches on a series of compounds having an inhibitory activity against aldose reductase and found novel hydantoin derivatives having an extremely strong inhibitory activity against aldose reductase. They are extremely useful for the treatment and/or prevention of various forms of diabetic complications based on the accumulation of polyol metabolites.

According to a first embodiment of this invention, there is provided hydantoin derivatives represented by the formula (I):



(I)

and non-toxic salts, solvates and solvates of non-toxic salts thereof; wherein Q represents a mono- or a fused heterocyclic group which may be substituted by one or more substituents which are same or different and selected from a group consisting of a halogen atom, a lower alkyl group, a nitro group, a cyano group, an optionally protected carboxy group, an optionally protected carboxymethyl group, a halogenated lower alkyl group, a lower alkylthio group, a lower alkylcarbonyl group, a lower alkoxy group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, an optionally protected hydroxy group, an optionally protected amino group, a carbamoyl group and a phenyl group.

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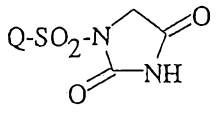
According to a second embodiment of this invention, there is provided a process for producing hydantoin derivatives represented by the formula (I):



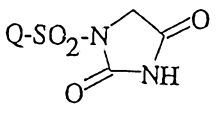
(I)

wherein Q represents a mono- or a fused heterocyclic group which may be substituted by one or more substituents which are same or different and selected from a group consisting of a halogen atom, a lower alkyl group, a nitro group, a cyano group, an optionally protected carboxy group, an optionally protected carboxymethyl group, a halogenated lower alkyl group, a lower alkylthio group, a lower alkylcarbonyl group, a lower alkoxy group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, an optionally protected hydroxy group, an optionally protected amino group, a carbamoyl group and a phenyl group, by cyclization of a sulfonylglycine derivative represented by the formula (V)

$$Q\text{-}SO_2NHCH_2CONH_2 \qquad (V)$$

wherein Q has the same significance as defined above, with a haloformic acid ester.

According to a third embodiment of this invention, there is provided a process for producing hydantoin derivatives represented by the formula (I):



(I)

wherein Q represents a mono- or a fused heterocyclic group which may be substituted by one or more substituents which are same or different and selected from a group consisting of a halogen atom, a lower alkyl group, a nitro group, a cyano group, an optionally protected carboxy group, an optionally protected carboxymethyl group, a halogenated lower alkyl group, a lower alkylthio group, a lower alkylcarbonyl group, a lower

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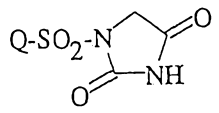
alkoxy group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, an optionally protected hydroxy group, an optionally protected amino group, a carbamoyl group and a phenyl group, by cyclizing a sulfonylglycine derivative represented by the formula (VI):

$$Q\text{-}SO_2NHCH_2CO\text{-}R^1 \qquad (VI)$$

wherein Q has the same significance as defined above, and R^1 represents a hydroxy group or an alkoxy group, with a thiocyanate derivative, then oxidizing the cyclized product.

According to a fourth embodiment of this invention, there is provided a pharmaceutical composition which comprises at least one of hydantoin derivatives represented by the formula (I):


(I)

and non-toxic salts, solvates and solvates of non-toxic salts thereof; wherein Q represents a mono- or a fused heterocyclic group which may be substituted by one or more substituents which are same or different and selected from a group consisting of a halogen atom, a lower alkyl group, a nitro group, a cyano group, an optionally protected carboxy group, an optionally protected carboxymethyl group, a halogenated lower alkyl group, a lower alkylthio group, a lower alkylcarbonyl group, a lower alkoxy group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, an optionally protected hydroxy group, an optionally protected amino group, a carbamoyl group and a phenyl group and a pharmaceutically acceptable diluent, excipient, carrier and/or adjuvant.

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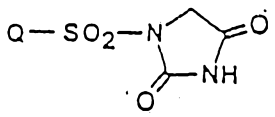
DETAILED DESCRIPTION OF THE INVENTION

As a result of extensive investigations concerning development of hydantoin derivatives having a satisfactory inhibitory activity against aldose reductase, the present inventors have found that novel hydantoin derivatives represented by the formula (I) satisfy this requirement and have accomplished the present invention.

The present invention is based on the selection of a hydantoin which is bonded through a sulfonyl group to various substituents at the 1-position of the hydantoin skeleton.

The present invention is directed to novel hydantoin derivatives represented by the formula (I):



(I)

and non-toxic salts, solvates and solvates of non-toxic salts thereof; wherein Q represents a mono- or a fused heterocyclic group which may be substituted by one or more substituents which are same or different and selected from a group consisting of a halogen atom, a lower alkyl group, a nitro group, a cyano group, an optionally protected carboxy group, an optionally protected carboxymethyl group, a halogenated lower alkyl group, a lower alkylthio

group, a lower alkylcarbonyl group, a lower alkoxy group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, an optionally protected hydroxy group, an optionally protected amino group, a carbamoyl group and a phenyl group.

The present invention is also directed to the process for preparing above-mentioned hydantoin derivatives.

The present invention is further directed to pharmaceutical compositions characterized by containing at least one of these hydantoin derivatives as active component(s).

Compounds of the present invention and non-toxic salts, solvates and solvates of non-toxic salts thereof represents a satisfactory inhibitory activity against aldose reductase and a preventing activity against cataracts, neuropathy in experimental animal models.

Compounds of the present invention and non-toxic salts, solvates and non-toxic salts thereof are free of central nervous system side effects such as anti-convulsant activity and low toxicity, so useful for the treatment and/or prevention of various forms of

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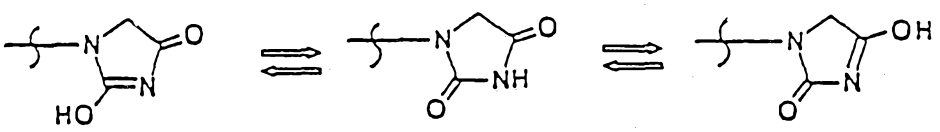
diabetic complications such as neuropathy, autonomic disease, cataract, retinopathy, neuropathy and microvascular disease.

In the hydantoin derivatives of the present invention represented by the general formula (I), it is known that the hydantoin moiety exhibits tautomerism as shown below:



Since these tautomeric isomers are generally deemed to be the same substance, the compounds of the present invention represented by the formula (I) also include all of these tautomeric isomers.

The compounds represented by the formula (I) may form salts with base. Typical examples of salts with base of the compounds represented by the formula (I) include pharmaceutically acceptable salts such as alkali metal salts (such as sodium salts, potassium salts, etc.), alkaline earth metal salts (such as magnesium salts, calcium salts, etc.), salts with organic bases (such as ammonium salts, benzylamine salts, diethylamine salts, etc.) or salts of amino acids (such as arginine salts, lysine salts, etc.). These salts of the compounds represented by the

formula (I) may be mono-salts or di-salts which may be salts of the hydantoin moiety and/or salts of the carboxy group contained in the Q group.

The compounds represented by the formula (I) may also form acid addition salts. Typical example of acid addition salts of the compounds represented by the formula (I) include pharmaceutically acceptable salts, such as salts of inorganic acids (such as hydrochlorides, hydrobromides, sulfates, phosphates, etc.), salts of organic acids (such as acetates, citrates, maleates, tartrates, benzoates, ascorbate, ethanesulfonates, toluenesulfonates, etc.) or salts of amino acids (such as aspartates, glutamates, etc.). These salts of the compounds represented by the formula (I) may be salts of the heterocyclic moiety in the Q group.

In the compounds of the present invention represented by the formula (I), term "lower" can be defined more specifically as a straight or branched chain having 1 to 4 carbon atoms.

In the compounds of the present invention represented by the formula (I), the heterocyclic group can be defined as a mono heterocyclic group such as pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiazolinyl,

thiadiazolyl, thiatriazolyl, thienyl, furyl, pyrrolidinyl, imidazolidinyl, thiazolidinyl, pyridyl or its N-oxide, pyrazinyl, pyrimidinyl, pyridazinyl, piperidyl, piperazinyl, morpholinyl, triazinyl, etc., or a fused heterocyclic group such as indolyl, isoindolyl, benzimidazolyl, quinolyl, isoquinolyl, quinazolinyl, cinnolinyl, phthalazinyl, quinoxalinyl, indazolyl, benzotriazolyl, benzoxazolyl, benzoxadiazolyl, benzothiazolyl, benzothiadiazolyl, benzisoxazolyl, benzisothiazolyl, benzothienyl (benzo[b]thienyl or benzo[c]thienyl), tetrahydrobenzothienyl, benzofuranyl (benzo[b]furanyl or isobenzofuranyl), chromenyl, chromanyl, coumarinyl, chromonyl, triazolopyridyl, tetrazolopyridyl, purinyl, thiazolopyrimidinyl, triazolopyrimidinyl, thiadiazolopyrimidinyl, thiazolopyridazinyl, naphthyridinyl, xanthenyl, phenoxathiinyl, phenoxazinyl, phenothiazinyl, carbazolyl, etc., preferably indolyl, benzimidazolyl, benzotriazolyl, benzothiazolyl, benzisoxazolyl, benzisothiazolyl, benzothienyl, tetrahydrobenzothienyl, benzofuranyl, coumarinyl, chromonyl, more preferably benzo[b]thienyl or benzo[b]furanyl. The above-mentioned heterocyclic groups may be substituted with a group such as a lower alkyl group (such as methyl, ethyl, isopropyl, tert-butyl, etc.), a lower alkylcarbonyl group (such as

acetyl, propanoyl, butanoyl, etc.), a lower alkoxy group (such as methoxy, ethoxy, isopropoxy, tert-butoxy, etc.), a phenyl group, a cyano group, a carbamoyl group, an optionally protected carboxy group, an optionally protected carboxymethyl group, a nitro group, a halogenated lower alkyl group (such as trifluoromethyl, pentafluoroethyl, etc.), an optionally protected hydroxy group, an optionally protected amino group, (such as acyl amino, etc.), a lower alkylthio group, a lower alkylsulfinyl group, a lower alkyl sulfonyl group or a halogen atom (such as fluoro, chloro, bromo, iodo etc.), or combination of any of these groups.

In a mono- heterocyclic group, a compound unsubstituted or substituted with 1 or 2 substituents which are the same or different and selected from a group consisting of a halogen atom or a phenyl group, is preferable.

In a fused heterocyclic group, a compound unsubstituted or substituted with 1 to 3 substituents which are the same or different and selected from a group consisting of a halogen atom, a lower alkyl group, a halogenated lower alkyl group, a lower alkylthio group or a cyano group, is preferable.

When a fused heterocyclic group is a benzo[b]-furan-2-yl group which may be substituted, the said substituents are preferably 1 to 3 halogen atoms.

The compounds of the present invention represented by the formula (I) can be produced by the processes described as follows.

Namely;

The starting material of sulfonyl halide represented by the formula (II):

$$Q\text{-}SO_2\text{-}Y \qquad (II)$$

wherein Q represents a mono- or a fused heterocyclic group which may be substituted by one or more substituents which are same or different and selected from a group consisting of a halogen atom, a lower alkyl group, a nitro group, a cyano group, an optionally protected carboxy group, an optionally protected carboxymethyl group, a halogenated lower alkyl group, a lower alkylthio group, a lower alkylcarbonyl group, a lower alkoxy group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, an optionally protected hydroxy group, an optionally protected amino group, a carbamoyl group and a phenyl group and Y represents a halogen atom, is prepared as follows.

A compound Q-H wherein Q has the same significance as defined above and H represents a hydrogen atom is reacted with a base (such as n-butyllithium or lithium

diisopropylamide, etc.) and sulfur dioxide and then reacted with a halogenating reagent (such as chlorine, bromine, phosphorus pentachloride, thionyl chloride, N-chlorosuccinimide or N-bromosuccinimide, etc.) to obtain an objective compound.

Further, Q-H wherein Q has the same significance as defined above is reacted with a halosulfonic acid (preferably chlorosulfonic acid, etc.) to obtain directly an objective compound.

Further, a sulfonic acid derivative of Q-H ($Q\text{-}SO_3H$) wherein Q has the same significance as defined above is reacted with sodium bicarbonate to give a corresponding salt, and then reacted with a halogenating reagent (such as phosphorus pentachloride, thionyl chloride or thionyl bromide, etc.) to obtain an objective compound.

Further, a S-benzyl derivative of Q-H ($Q\text{-}S\text{-}CH_2C_6H_5$) wherein Q has the same significance as defined above is reacted with a halogenating reagent (such as chlorine, etc.) to obtain an objective compound.

Further, an amine derivative of Q-H ($Q\text{-}NH_2$) wherein Q has the same significance as defined above is reacted with a nitrite salt (such as sodium nitrite, etc.), and then reacted with sulfur dioxide and a halogenating reagent (such as copper (I) chlo-

ride or copper (II) chloride, etc.) to obtain an objective compound.

The sulfonyl halide derivative, obtained above mentioned procedure is reacted with a glycine derivative represented by the formula (III):

$$NH_2CH_2CO\text{-}R \qquad (III)$$

wherein R represents a hydroxy group, an alkoxy group or an amino group which may be substituted by an alkoxycarbonyl group, to give the corresponding sulfonylglycine derivative represented by the formula (IV):

$$Q\text{-}SO_2NHCH_2CO\text{-}R \qquad (IV)$$

wherein Q and R have the same significance as defined above. Such a condensation reaction is carried out generally in an aqueous solution, in an organic solvent (such as dichloromethane, chloroform, dioxane, tetrahydrofuran, acetonitrile, ethyl acetate, acetone, N,N-dimethylformamide, etc.) or in a mixed solvent of an aqueous solution and an organic solvent, preferably in the presence of deacidifying agent. As the deacidifying agent, triethylamine, diethylaniline, pyridine, etc. is employed in the organic solvent system, and in the aqueous system, aqueous alkali

(such as sodium carbonate, sodium bicarbonate, potassium carbonate, sodium hydroxide, etc.) is employed. The condensation reaction is carried out at temperatures ranging from about -20 to 80°C, preferably 0°C to room temperature.

When R represents an amino group in the formula (IV), the sulfonylglycine derivative is represented by the formula (V):

$$Q\text{-}SO_2NHCH_2CONH_2 \qquad (V)$$

wherein Q has the same significance as defined above.

The sulfonylglycine derivative represented by the formula (V) is cyclized using a haloformic acid ester (such as methyl chloroformate, ethyl chloroformate, etc.) in the presence of a base (such as sodium hydride, potassium hydride, butyllithium, etc.) to give the corresponding hydantoin derivative of the present invention represented by the formula (I). The cyclization reaction is carried out generally in an inert solvent (such as N,N-dimethylformamide, dimethylsulfoxide, ethyl ether, tetrahydrofuran, dioxane, dichloromethane, etc.) and at temperatures ranging from about -20 to 120°C, preferably 0 to 80°C.

When R represents an amino group protected with an alkoxycarbonyl group, the sulfonylglycine derivative

is cyclized in the presence of a base (such as sodium hydride etc.) to give the corresponding hydantoin derivative of the present invention represented by the formula (I).

When R represents a hydroxy group or an alkoxy group in the formula (IV), the sulfonylglycine derivative is represented by the formula (VI):

$$Q\text{-}SO_2NHCH_2CO\text{-}R^1 \qquad (VI)$$

wherein Q has the same significance as defined above and R^1 represents a hydroxy group or an alkoxy group. The sulfonylglycine derivative represented by the formula (VI) is cyclized with a thiocyanate derivative (such as ammonium thiocyanate, potassium thiocyanate, etc.) in the presence of an acid anhydride (such as acetic anhydride, propionic anhydride, etc.) and, if necessary and desired, a base (such as pyridine, triethylamine, etc.) to give the corresponding 2-thiohydantoin derivative. If necessary and desired, the cyclization reaction is carried out after hydrolysis of ester when R^1 represents an alkoxy group. The cyclization reaction is carried out generally in an inert solvent (such as pyridine, triethylamine, N,N-dimethylformamide, dimethylsulfoxide, etc.) and at temperatures ranging

from 0 to 120 °C, preferably room temperature to 100°C. Further, the 2-thiohydantoin derivative obtained by said cyclization is oxidized using oxidizing agent (such as nitric acid, chlorine, iodine chloride, potassium permanganate, hydrogen peroxide, dimethylsulfoxide-sulfuric acid, etc.) to give the corresponding hydantoin derivatives of the present invention represented by the formula (I).

To demonstrate the utility of the compounds of the present invention, experimental examples of representative compounds are shown below.

Compounds in the present invention

Compound 1: 1-(benzo[b]thien-2-ylsulfonyl)-hydantoin

Compound 2: 1-(3-chlorobenzo[b]thien-2-yl-sulfonyl)hydantoin

Compound 3: 1-(5-chlorobenzo[b]thien-2-yl-sulfonyl)hydantoin

Compound 4: 1-(benzo[b]furan-2-ylsulfonyl)hydantoin

Compound 5: 1-(5-chlorobenzo[b]furan-2-ylsulfonyl)-hydantoin

Compound 6: 1-(5-bromobenzo[b]furan-2-ylsulfonyl)-hydantoin

Compound 7: 1-(benzothiazol-2-ylsulfonyl)hydantoin

Compound 8: 1-(coumarin-6-ylsulfonyl)hydantoin

Compound 9: 1-(2,5-dichlorothien-3-ylsulfonyl)-hydantoin

Compound 10: 1-(4,5-dibromothien-2-ylsulfonyl)-hydantoin

Compound 11: 1-(6-chlorobenzo[b]thien-2-yl-sulfonyl)hydantoin

Compound 12: 1-(7-chlorobenzo[b]thien-2-yl-sulfonyl)hydantoin

Compound 13: 1-(3-isopropylbenzo[b]thien-2-yl-sulfonyl)hydantoin

Compound 14: 1-(3-trifluoromethylbenzo[b]thien-2-ylsulfonyl)hydantoin

Compound 15: 1-(3-bromobenzo[b]thien-2-yl-sulfonyl)hydantoin

Compound 16: 1-(3-methoxybenzo[b]thien-2-yl-sulfonyl)hydantoin

Compound 17: 1-(3-methylsulfonylbenzo[b]thien-2-ylsulfonyl)hydantoin

Compound 18: 1-(3-cyanobenzo[b]thien-2-yl-sulfonyl)hydantoin

Compound 19: 1-(3-bromo-7-fluorobenzo[b]thien-2-ylsulfonyl)hydantoin

Compound 20: 1-(2-chlorobenzo[b]thien-3-yl-sulfonyl)hydantoin

Compound 21: 1-(4-iodobenzo[b]furan-2-ylsulfonyl)-

hydantoin

Compound 22: 1-(4,6-dichlorobenzo[b]furan-2-yl-sulfonyl)hydantoin

Compound 23: 1-(3-bromobenzo[b]furan-2-ylsulfonyl)-hydantoin

Compound 24: 1-(5-fluorobenzo[b]thien-2-yl-sulfonyl)hydantoin

Compound 25: 1-(4-chlorobenzo[b]thien-2-yl-sulfonyl)hydantoin

Compound 26: 1-(benzo[b]isothiazol-3-ylsulfonyl)-hydantoin

Compound 27: 1-(5-nitrobenzo[b]thien-2-yl-sulfonyl)hydantoin

Compound 28: 1-(5-carboxybenzo[b]thien-2-yl-sulfonyl)hydantoin

Compound 29: 1-(4,5-dichlorobenzo[b]furan-2-yl-sulfonyl)hydantoin

Compound 30: 1-(5,6-dichlorobenzo[b]furan-2-yl-sulfonyl)hydantoin

Compound 31: 1-(3-bromo-4,6-dichlorobenzo[b]furan-2-ylsulfonyl)hydantoin

Compound 32: 1-(3-chlorobenzo[b]furan-2-ylsulfonyl)-hydantoin

Compound 33: 1-(7-fluorobenzo[b]furan-2-ylsulfonyl)-hydantoin

Compound 34: 1-(3-bromo-7-fluorobenzo[b]furan-2-yl-

sulfonyl)hydantoin

Reference compounds

Compound A: sorbinil : [(S)-6-Fluoro-2,3-dihydro-spiro(4H-1-benzopyran-4,4'-imidazolidine)-2', 5'-dione] (synthesized by the method of R. S. sarges et al. : see J. Med. Chem., 28, 1716 (1985))

Experimental Example 1

The inhibitory activities of hydantoin derivatives on bovine lens aldose reductase were measured according to the procedure of Inagaki et al. (K. Inagaki et al., Arch. Biochem. Biophys., 216, 337 (1982)) with slight modifications. Assays were performed in 0.1 M phosphate buffer (pH 6.2) containing 0.4 M ammonium sulfate, 10 mM DL-glyceraldehyde, 0.16 mM nicotinamide adenine dinucleotide phosphate, reduced form (NADPH) and aldose reductase (0.010-0.016 units) in a total volume of 1.0 ml. To this mixture was added 10 µl of the solution of each hydantoin derivative to be tested, and the decrease in absorbance at 340 nm was measured with a spectrophotometer.

The concentrations of typical hydantoin derivatives of the present invention required to produce 50% inhibition are shown in table 1.

Table 1

Compounds	IC_{50} (μmol/l)
1	0.39
2	0.12
3	0.24
5	0.36
6	0.30
7	0.34
8	0.22
9	0.29
10	0.26
11	0.27
12	0.19
13	0.14
14	0.13
15	0.12
16	0.27
17	0.38

Compounds 1 to 31 of the present invention showed stronger inhibitory activities against aldose reductase than reference compound A did. Above all, several compounds were ten times or more potent than reference compound A.

Experimental Example 2

Hydantoin derivatives of the present invention were examined for acute toxicity. Groups of 5 ICR strain mice were orally administered with compound 1, 2, 4, 5, 6, 9, 23, 25, 29, 30, 32, 33 or 34 of the present invention in a dose of 1 g/kg, and no change was observed in any of the groups over the one-week period after the administration.

Since the compounds of the present invention have strong inhibitory activities against aldose reductase, show lower toxicity and show stronger preventing activities against cataracts, neuropathy in animal ~~and show stronger reducing activities of hypoglycemia in animal~~ models than known compounds, pharmaceutical compositions containing at least one of these compounds as active component(s) are useful for the treatment and/or prevention of diabetic complications based on the accumlation of polyol metabolites.

The hydantoin derivatives provided by the present

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Table 1(continued)

Compounds	IC_{50}(μmol/l)
18	0.19
19	0.085
20	0.30
21	0.24
22	0.17
23	0.16
24	0.32
25	0.17
26	0.47
27	0.27
28	0.40
29	0.061
30	0.083
31	0.054
A	0.65

invention can be employed as pharmaceutical compositions, for example, in the form of pharmaceutical compositions containing hydantoin derivatives together with appropriate pharmaceutically acceptable carrier or medium such as sterilized water, edible oils, non-toxic organic solvents or non-toxic solubilizer such as glycerin or propylene glycol. They may be mixed with excipients, binders, lubricants, coloring agents, corrigents, emulsifying agents or suspending agents such as Tween 80 or arabic gum to prepare tablets, capsules, powders, granules, subtilized granules, syrups, eye drops, suppositories, ointments, inhalants, aqueous or oily solutions or emulsion or suspensions for injections. These agents can be administered either orally or parenterally (such as intravenous administration, intramuscular administration, subcutaneous administration, intrarectal administration, percutaneous administration or permucosal administration etc.), and the amount of administration may be in the range of 1 to 3000 mg/day, preferably 10 to 500 mg/day when the preparation is tablets, capsules, powders, injections, suppositories, syrups, inharants or ointments, 1 μg to 10 mg/day, preferably 10 μg to 1 mg/day when the preparation is eye drops, and 1 to 10 % composition when the preparation is ointments, and may also be

adjusted according to the patient conditions and can administered once or divided 2 to 6 times or by instillation, etc.

Hereafter the present invention will be described with references to the examples below but is not deemed to be limited thereof.

Example 1

Preparation of 1-(benzo[b]thien-2-ylsulfonyl)-hydantoin (compound 1).

Step 1

Preparation of benzo[b]thien-2-ylsulfonyl chloride.

To a solution of benzo[b]thiophen (38.3 g) in anhydrous ether (180 ml) was added dropwise 1.6 M solution of n-butyllithium in hexane (220 ml) under ice-cooling and nitrogen atmosphere. After refluxing for 40 minutes, into the solution was bubbled sulfur dioxide for 2.75 hours with stirring at -30°C. Then the solution was stirred for 1 hour and the formed precipitate was separated by filtration to give lithium benzo[b]thien-2-ylsulfinate. Into the suspension of the product in concentrated hydrochloric acid (400 ml) and water (100 ml) was bubbled chlorine gas for 1.5 hours with stirring at -5°C. The resulting solution was poured into ice-water (500 ml) and extracted with dichloromethane (1.5 l x 2) and the organic layer was washed with saturated aqueous NaCl solution. After drying over anhydrous magnesium sulfate, dichloromethane was removed in vacuo, and the residue was purified by silica gel column chromatography to give 40.4 g of the objective compound.

IR (KBr, cm^{-1}): 1495, 1384, 1189, 1168, 1155

NMR ($CDCl_3$, ppm): 7.49 - 7.68 (2H, m),
7.86 - 8.03 (2H, m),
8.14 (1H, s)

Step 2

Preparation of N-(benzo[b]thien-2-ylsulfonyl)-glycine.

To a solution of potassium carbonate (28.9 g) and glycine (15.7 g) in water (450 ml) was added benzo[b]thien-2-ylsulfonyl chloride (40.4 g) at room temperature and the mixture was stirred under reflux for 30 minutes. After cooling to room temperature, the resulting solution was acidified with 2 M hydrochloric acid to a pH in the range of 1 to 2 and the formed precipitate was separated by filtration to give 36.3 g of the objective compound.

Melting point: 171.3 - 172.4°C

IR (KBr, cm^{-1}): 3267, 1735, 1352, 1258, 1115

NMR (DMSO-d_6, ppm): 3.73 (2H, d, J = 6.0 Hz),
7.39 - 7.61 (2H, m), 7.77 -
8.13 (3H, m), 8.51 (1H, d,
J = 6.0 Hz), 12.68 (1H, bs)

Step 3

Preparation of 1-(benzo[b]thien-2-ylsulfonyl)-2-thiohydantoin.

Anhydrous pyridine (12.6 ml), ammonium thiocyanate

(10.1 g) and acetic anhydride (40 ml) were added to the product obtained in Step 2 (16.3 g) and the mixture was heated with stirring for 15 minutes at 80°C. After cooling to room temperature, the resulting solution was poured into ice-water (300 ml) and the formed precipitate was separated by filtration to give 8.6 g of the objective compound.

Melting point: 218.6°C (decomposition)

IR (KBr, cm^{-1}): 1759, 1374, 1255, 1171, 1157

NMR (DMSO-d_6, ppm): 4.74 (2H, s), 7.35 - 7.69 (2H, m), 8.04 - 8.21 (2H, m), 8.45 (1H, s), 12.72 (1H, bs)

Step 4

Preparation of 1-(benzo[b]thien-2-ylsulfonyl)-hydantoin.

To a suspension of iodine monochloride (7.12 ml) in 1 M hydrochloric acid (200 ml) were added successively the product obtained in Step 3 (8.50 g) and dichloromethane (200 ml). The mixture was stirred for 20 minutes at room temperature. After adding sodium bicarbonate (6.85 g), the reaction mixture was stirred for 15 minutes and extracted twice with ethyl acetate (1 l + 300 ml). The organic layer was washed with successive saturated aqueous sodium bisulfite solution and saturated aqueous NaCl solution. After drying over anhydrous magnesium sulfate, ethyl acetate

was removed in vacuo and the residue was washed with dichloromethane to give 4.83 g of the objective compound.

Melting point: 251.8 - 254 2°C

IR (KBr, cm^{-1}): 3245, 1803, 1740, 1376, 1352, 1167

NMR (DMSO-d_6, ppm): 4.48 (2H, s), 7.51 - 7.63 (2H, m), 8.05 - 8.20 (2H, m), 8.33 (1H, s), 11.71 (1H, bs)

Example 2

Preparation of 1-(benzo[b]furan-2-ylsulfonyl)-hydantoin (compound 4).

Step 1

Preparation of benzo[b]furan-2-ylsulfonyl chloride.

Starting from benzo[b]furan, the objective compound was obtained in a manner similar to Step 1 of Example 1.

IR (KBr, cm^{-1}): 1533, 1389, 1244, 1193, 1166

NMR ($CDCl_3$, ppm): 7.32 - 7.82 (5H, m)

Step 2

Preparation of N-(benzo[b]furan-2-ylsulfonyl)-glycine.

Starting from benzo[b]furan-2-ylsulfonyl chloride, the objective compound was obtained in a manner

similar to Step 2 of Example 1.

Melting point: 177.0 - 178.2°C

IR (KBr, cm^{-1}): 3289, 1724, 1347, 1162

NMR (DMSO-d_6, ppm): 3.77 (2H, d, J = 6.3 Hz), 7.35 - 7.81 (5H, m), 8.72 (1H, t, J = 6.3 Hz), 12.69 (1H, bs)

Step 3

Preparation of 1-(benzo[b]furan-2-ylsulfonyl)-2-thiohydantoin.

To a suspension of the product obtained in Step 2 (37.0 g) and ammonium thiocyanate (24.3 g) in acetic anhydride (100 ml) was added dropwise anhydrous pyridine (30.5 ml) and the mixture was heated with stirring for 1.5 hours at 70 - 80°C. After cooling to room temperature, the resulting solution was poured into ice (800 g) and the formed precipitate was separated. The precipitate was washed with water and dried to give 18.5 g of the objective compound.

Melting point: 213.0°C (decomposition)

IR (KBr, cm^{-1}): 3080, 1759, 1386, 1255, 1167, 1086

NMR (DMSO-d_6, ppm): 4.76 (2H, s), 7.34 - 8.04 (5H, m), 12.81 (1H, bs)

Step 4

Preparation of 1-(benzo[b]furan-2-ylsulfonyl)

hydantoin.

Starting from the product obtained in Step 3, the objective compound was obtained in a manner similar to Step 4 of Example 1.

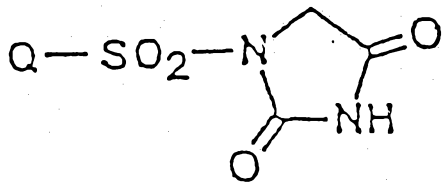
Melting point: 255.9 - 256.4°C

IR (KBr, cm^{-1}): 1803, 1735, 1398, 1360, 1166

NMR (DMSO-d_6, ppm): 4.49 (2H, s), 7.33 - 8.08 (5H, m), 11.79 (1H, bs)

Compounds of Example 3 to 39 prepared in a manner similar to Example 1 are summarized in the following table 2 together with corresponding IR and NMR data and melting points.

Table 2



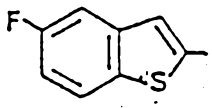
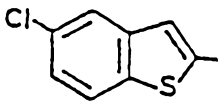
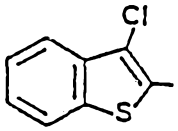
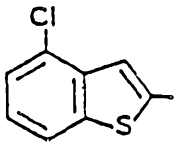
Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
3		1735,1508, 1382,1167	4.47(2H,s), 7.40~8.30(3H,m), 8.30(1H,s), 11.73(1H,bs)	275.2 (dec.)
4		1739,1380, 1192	4.45(2H,s), 7.57~7.69(1H,m), 8.15~8.25(2H,m), 8.29(1H,s), 11.70(1H,bs)	>300
5		1728,1381, 1183,1162	4.64(2H,s), 7.58~7.81(2H,m), 7.96~8.06(1H,m), 8.18~8.29(1H,m), 11.82(1H,bs)	278.3 (dec.)
6		3270,1741, 1379,1162	4.51(2H,s), 7.52~7.67(2H,m), 8.16~8.23(2H,m), 11.74(1H,bs)	271.1 ~ 272.2

Table 2 (continued)

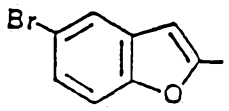
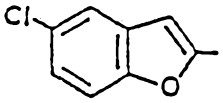
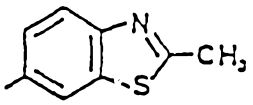
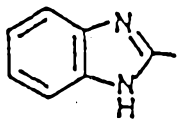
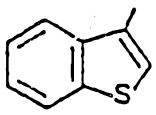
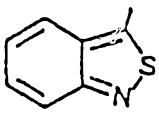
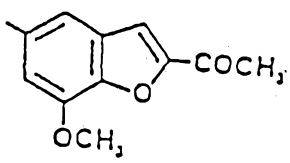
Ex. No.	Q	IR (KBr, cm^{-1})	NMR (DMSO-d_6, ppm)	M.P. (℃)
7		3400, 1730, 1663, 1614, 1380, 1169	3.96 (2H, s), 7.61~8.06 (4H, m)	270.2 (dec.)
8		3379, 1616, 1608, 1381, 1233, 1166	3.98 (2H, s), 7.47~7.90 (4H, m)	290.0 (dec.)
9		1740, 1376, 1166	2.88 (3H, s), 4.53 (2H, s), 8.10 (2H, s), 8.80 (1H, s), 11.59 (1H, bs)	258.0 (dec.)
10		3328, 1740, 1390, 1159	4.60 (2H, s), 7.33~7.78 (5H, m), 11.85 (1H, bs)	222.8 (dec.)
11		1741, 1380, 1162	4.54 (2H, s), 7.52~7.63 (2H, m), 8.10~8.29 (2H, m), 8.86 (1H, s), 11.58 (1H, bs)	218.3 ~ 226.7
12		1739, 1377, 1165	4.49 (2H, s), 7.50~8.28 (4H, m), 11.68 (1H, bs)	237.8 ~ 243.0
13		1746, 1682, 1363, 1158	2.59 (3H, s), 4.07 (3H, s), 4.51 (2H, s), 7.57~8.13 (3H, m), 11.55 (1H, bs)	263.0 (dec.)

Table 2 (continued)

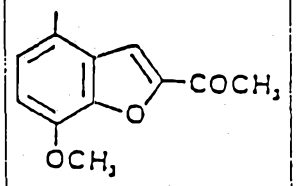
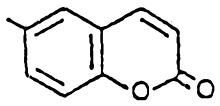
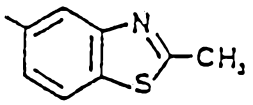
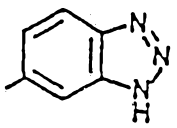
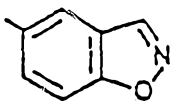
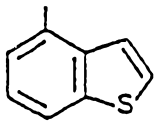
Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
14		1735, 1691, 1387, 1173	2.63(3H,s), 4.10(3H,s), 4.54(2H,s), 7.36(1H,d,J=8.6Hz), 8.02(2H,m), 11.56(1H,bs)	242.3 ~ 244.1
15		1303, 1746, 1716, 1377, 1164	4.51(2H,s), 6.64(1H,d,J=9.9Hz), 7.62(1H,d,J=8.9Hz), 8.11~8.46(3H,m), 11.60(1H,bs)	262.8 ~ 267.8
16		1741, 1371, 1169	2.87(3H,s), 4.55(2H,s), 7.95~8.51(3H,m), 11.59(1H,bs)	245.2 ~ 246.3
17		1741, 1362, 1168	4.55(2H,s), 8.12(2H,s), 8.82(1H,s), 12.67(1H,bs)	
18		3098, 1743, 1385, 1364, 1186, 1162, 1067	4.52(2H,s), 7.99~8.66(3H,m), 9.45(1H,d,J=1.0Hz), 11.59(1H,bs)	203 (dec.)
19		3095, 1741, 1373, 1360, 1177, 1150	4.56(2H,s), 7.51~8.51(5H,m), 11.59(1H,bs)	238.7 ~ 244.9

Table 2 (continued)

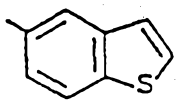
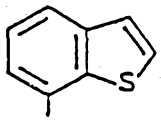
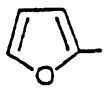
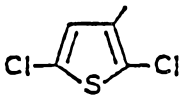
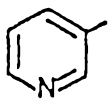
Ex. No.	Q	IR (KBr, cm^{-1})	NMR (DMSO-d_6, ppm)	M.P. (℃)
20		1729, 1362, 1166	4.54 (2H, s), 7.66~8.59 (5H, m), 11.56 (1H, bs)	268.4 ~ 271.4
21		3174, 1735, 1390, 1170	4.61 (2H, s), 7.57~7.74 (2H, m), 7.95~8.34 (3H, m), 11.55 (1H, bs)	242.9 ~ 244.3
22		1800, 1742, 1396, 1162	4.43 (2H, s), 6.78 (1H, m), 7.45 (1H, d, J=3.6Hz), 8.09 (1H, m), 11.72 (1H, bs)	243.0 ~ 244.2
23		3227, 1735, 1365, 1183, 1171	4.51 (2H, s), 7.55 (1H, s), 11.76 (1H, bs)	251.2 ~ 251.3
24		1742, 1375, 1174	4.53 (2H, s), 7.71 (1H, m), 8.40 (1H, m), 8.89~9.14 (2H, m), 11.65 (1H, bs)	175.5 (dec.)

Table 2 (continued)

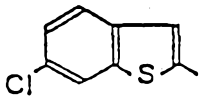
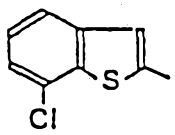
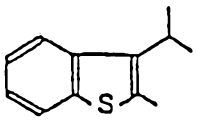
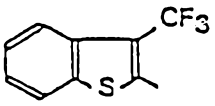
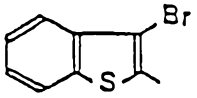
Ex. No.	Q	IR (KBr, cm^{-1})	NMR (DMSO-d_6, ppm)	M.P. (℃)
25		1800, 1750, 1739, 1381, 1160	4.46 (2H, s), 7.57 (1H, dd, J=8.6, 1.7Hz), 8.11 (1H, d, J=8.6Hz), 8.33 (2H, s)	249.1 ~ 251.3
26		3096, 1786, 1734, 1376, 1166	4.48 (2H, s), 7.50~7.81 (1H, m), 8.11 (1H, dd, J=6.6, 1.3Hz), 8.44 (1H, s), 11.74 (1H, bs)	235.0 (dec.)
27		3210, 1809, 1728, 1392, 1160	1.46 (6H, d, J=7.3Hz), 3.96~4.28 (1H, m), 4.52 (2H, s), 7.48~7.67 (2H, m), 8.07~8.32 (2H, m), 11.76 (1H, bs)	174.1 ~ 176.6
28		1733, 1379, 1180	4.53 (2H, s), 7.66~8.38 (4H, m), 11.95 (1H, bs)	243.2 (dec.)
29		3160, 1805, 1725, 1379, 1183	4.70 (2H, s), 7.57~8.28 (4H, m), 11.86 (1H, bs)	288.0 ~ 289.5

Table 2 (continued)

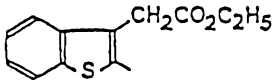
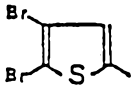
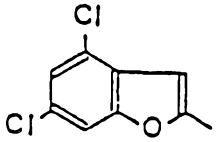
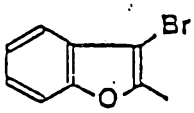
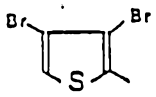
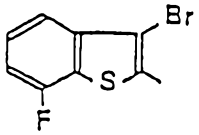
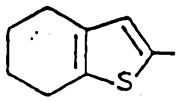
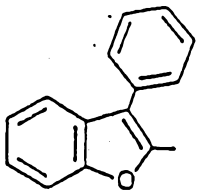
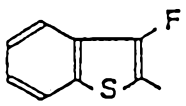
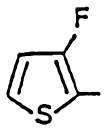
Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
30		1804,1744, 1378,1178	1.16(3H,t,J=7.0Hz), 4.07(2H,q,J=7.0Hz), 4.42(2H,s), 4.47(2H,s), 7.53~7.66(2H,m), 7.99~8.20(2H,m), 11.73(1H,bs)	196.0 ~ 197.5
31		3300,1779, 1729,1382, 1173,1167	4.44(2H,s), 7.95(1H,s), 11.75(1H,bs)	283.2 (dec.)
32		3270,1807, 1742,1389, 1169	4.45(2H,s), 7.72(1H,d,J=1.6Hz), 7.96(1H,d,J=1.0Hz), 8.07(1H,dd, J=1.6,1.0Hz), 11.78(1H,bs)	290.8 (dec.)
33		3220,1800, 1783,1397, 1176,1154	4.52(2H,s), 7.43~7.91(4H,m)	265.7 ~ 267.9
34		3080,1805, 1725,1378, 1187,1177	4.62(2H,s), 8.40(1H,s), 11.84(1H,bs)	278.0 (dec.)
35		3209,3177, 1812,1726, 1490,1379, 1305,1176, 1162	4.69(2H,s), 7.51~7.90(3H,m), 11.90(1H,bs)	286.0 (dec.)

Table 2 (continued)

Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
36		3210, 1806, 1735, 1364, 1158,	1.62~1.92(4H, m), 2.46~2.91(4H, m), 4.40(2H, s), 7.60(1H, s), 11.61(1H, bs)	248.3 ~ 249.5
37		1810, 1793, 1396, 1177	4.34(2H, s), 7.43~7.88(9H, m), 11.76(1H, bs)	220.4 (dec.)
38		3230, 1742, 1389, 1183	4.47(2H, s), 7.53~8.13(4H, m), 11.72(1H, bs)	256.0 ~ 258.0
39		3103, 1805, 1787, 1729, 1534, 1426, 1383, 1366, 1169	4.41(2H, s), 7.21(1H, d, J=5.6Hz), 8.12(1H, dd, J=5.6, 4.3Hz), 11.73(1H, bs)	238.2 ~ 240.9

Example 40

Preparation of 1-(4,5-diphenylthien-2-yl-sulfonyl)hydantoin.

Step 1

Preparation of 4,5-diphenylthien-2-ylsulfonyl chloride.

Starting from 2,3-diphenylthiophen, the objective compound was obtained in a manner similar to Step 1 of Example 1.

IR (KBr, cm^{-1}): 1382, 1172, 1038, 698, 583

NMR ($CDCl_3$, ppm): 7.27 - 7.33 (10H, m),
7.89 (1H, s)

Step 2

Preparation of N-(4,5-diphenylthien-2-yl-sulfonyl)glycine ethyl ester.

To a suspension of 4,5-diphenylthien-2-yl-sulfonyl chloride (36.5 g) and glycine ethyl ester hydrochloride (30.4 g) in dichloromethane (320 ml) was added slowly triethylamine (30.3 ml) under ice-cooling and the mixture was stirred for 160 minutes at room temperature. Water (200 ml) was added to the resulting solution and the mixture was extracted with dichloromethane. The organic layer was washed with successive 1 M hydrochloric acid, water and saturated aqueous NaCl solution. After drying over anhydrous magnesium sulfate, dichloromethane was removed in

vacuo and the residue was reprecipitated from ethyl acetate and hexane to give 41.1 g of the objective compound.

Melting point: 151.2 - 152.7°C

IR (KBr, cm^{-1}): 3266, 1734, 1354, 1231, 1215, 1164, 1127

NMR (DMSO-d_6, ppm): 1.12 (3H, t, J = 7.1 Hz), 3.88 (2H, d, J = 6.3 Hz), 4.04 (2H, q, J = 7.1 Hz), 6.84 - 7.44 (10H, m), 7.67 (1H, s), 8.57 (1H, t, J = 6.3 Hz)

Step 3

Preparation of N-(4,5-diphenylthien-2-yl-sulfonyl)glycine.

A solution of sodium hydroxide (12.4 g) in water (73 ml) was added to a solution of the product obtained in Step 2 (41.4 g) in tetrahydrofuran (730 ml) and the mixture was stirred for 25 minutes at 60°C. After removing the solvent, water (300 ml) was added to the residue and the resulting solution was acidified with concentrated hydrochloric acid to a pH 1 under ice-cooling. The acidified solution was extracted with ethyl acetate (800 ml) and the organic layer was washed with successive water and saturated aqueous NaCl solution. After drying over anhydrous

sodium sulfate, ethyl acetate was removed in vacuo and the residue was reprecipitated from ethyl acetate and hexane to give 37.6 g of the objective compound.

Melting point: 172.2 - 174.4°C

IR (KBr, cm^{-1}): 3200, 1736, 1353, 1159

NMR (DMSO-d_6, ppm): 3.78 (2H, d, J = 5.9 Hz), 7.12 - 7.42 (10H, m), 7.67 (1H, s), 8.39 (1H, t, J = 5.9 Hz), 12.78 (1H, bs)

Step 4

Preparation of 1-(4,5-diphenylthien-2-yl-sulfonyl)-2-thiohydantoin.

Starting from the product obtained in Step 3, the objective compound was obtained in a manner similar to Step 3 of Example 1.

Melting point: 213.2 - 215.4°C

IR (KBr, cm^{-1}): 1752, 1446, 1376, 1168, 1083

NMR (DMSO-d_6, ppm): 4.77 (2H, s), 7.32 - 7.46 (10H, m), 8.12 (1H, s), 12.73 (1H, bs)

Step 5

Preparation of 1-(4,5-diphenylthien-2-yl-sulfonyl)hydantoin.

Starting from the product obtained in Step 4, the objective compound was obtained in a manner similar to Step 4 of Example 1.

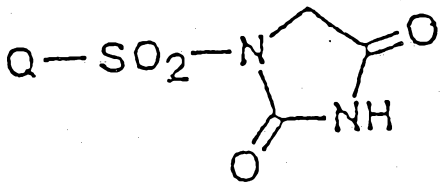
Melting point: 242.5 - 243.9°C

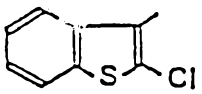
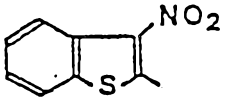
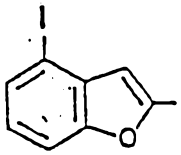
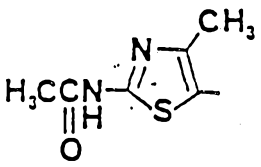
IR (KBr, cm^{-1}): 1737, 1386, 1165

NMR (DMSO-d_6, ppm): 4.53 (2H, s), 7.32 - 7.45 (10H, m), 8.00 (1H, s), 11.72 (1H, bs)

Compounds of Example 41 and 44 prepared in a manner similar to Example 40 are summarized in the following table 3 together with corresponding IR and NMR data and melting points.

Table 3



Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
41		3170, 1787, 1732, 1365, 1171	4.61(2H,s), 7.50~7.61(2H,m), 8.04~8.26(2H,m), 11.72(1H,bs)	215.0 ~ 219.0
42		3214, 1778, 1725, 1528, 1439, 1346	4.53(2H,s), 7.49~7.68(2H,m), 8.03~8.17(2H,m), 11.87(1H,bs)	221.1 ~ 223.2
43		1810, 1742, 1391, 1165, 1139	4.48(2H,s), 7.28~7.89(4H,m), 11.61(1H,bs)	277.0 (dec.)
44		3190, 3040, 1795, 1750, 1372, 1170	2.19(3H,s), 2.54(3H,s), 4.41(2H,s), 11.61(1H,bs), 12.73(1H,bs)	>300

Example 45

Preparation of 1-(5-nitrobenzo[b]thien-2-yl-sulfonyl)hydantoin. (compound 27).

Step 1

Preparation of 5-nitrobenzo[b]thien-2-yl-sulfonyl chloride.

To a solution of 5-nitrobenzo[b]thiophen (60 g) in anhydrous tetrahydrofuran (2 l) was added dropwise a solution of lithium diisopropylamide comprising 1.6 M n-butyllithium in hexane (240 ml) and diisopropylamine (57.8 ml) and anhydrous ether (170 ml) with stirring at -70°C under nitrogen atmosphere. After stirring for 30 minutes, into the solution was bubbled sulfur dioxide for 90 minutes with stirring at -70°C. Then the solution was stirred for 1 hour at room temperature and the formed precipitate was separated by filtration to give lithium 5-nitrobenzo[b]-thien-2-ylsulfinate. Into the suspension of the product in concentrated hydrochloric acid (500 ml) and water (125 ml) was bubbled chlorine gas for 3 hours with sufficiently stirring at below 0°C. After stirring for 1 hour at room temperature, the resulting suspension was extracted with dichloromethane (400 ml x 2) and the organic layer was washed with successive water and saturated aqueous NaCl solution. After drying over anhydrous sodium sulfate, dichloromethane

was removed in vacuo, and the residue was purified by silica gel column chromatography to give 21 g of the objective compound.

IR (KBr, cm^{-1}): 1602, 1519, 1378, 1340, 1172

NMR ($CDCl_3$, ppm): 8.10 (1H, d, J= 8.9 Hz),
8.31 (1H, s),
8.46 (1H, dd, J = 8.9, 2.0 Hz),
8.90 (1H, d, J = 2.0 Hz)

Step 2

Preparation of N-(5-nitrobenzo[b]thien-2-ylsulfonyl)glycine.

Starting from 5-nitrobenzo[b]thien-2-ylsulfonyl chloride, the objective compound was obtained in a manner similar to Step 2 of Example 1.

Melting point: 187.2 - 194.8°C

IR (KBr, cm^{-1}): 3325, 1734, 1530, 1377, 1351, 1159

NMR (DMSO-d_6, ppm): 3.76 (2H, d, J = 5.9 Hz), 8.22 (1H, s), 8.32 - 8.91 (4H, m), 12.72 (1H, bs)

Step 3

Preparation of 1-(5-nitrobenzo[b]thien-2-ylsulfonyl)-2-thiohydantoin.

Starting from the product obtained in Step 2, the objective compound was obtained in a manner similar to Step 3 of Example 1.

Melting point: 217.4°C (decomposition)

IR (KBr, cm^{-1}): 1762, 1521, 1470, 1389, 1347, 1248, 1173, 1087

NMR (DMSO-d_6, ppm): 4.73 (2H, s), 8.25 - 9.09 (4H, m), 12.78 (1H, bs)

Step 4

Preparation of 1-(5-nitrobenzo[b]thien-2-yl-sulfonyl)hydantoin.

A mixture of the product obtained in Step 3 (1.66 g) and 50% (w/v) nitric acid (35 ml) was heated with stirring for 6 hours at 60°C and the resulting solution was poured into ice-water (150 ml). The formed precipitate was separated by filtration and washed with acetone to give 0.47 g of the objective compound.

Melting point: 282.4°C (decomposition)

IR (KBr, cm^{-1}): 3100, 1737, 1522, 1385, 1349, 1176

NMR (DMSO-d_6, ppm): 4.47 (2H, s), 8.22 - 9.05 (4H, m), 11.70 (1H, bs)

Example 46

Preparation of 1-(5-cyanobenzo[b]thien-2-yl-sulfonyl)hydantoin.

Step 1

Preparation of 5-cyanobenzo[b]thien-2-yl-

sulfonyl chloride.

Starting from benzo[b]thien-5-ylcarbonitrile, the objective compound was obtained in a manner similar to Step 1 of Example 45.

IR (KBr, cm^{-1}): 2236, 1500, 1376, 1171, 577

NMR (DMSO-d_6, ppm): 7.56 (1H, s), 7.70 (1H, dd, J = 8.9, 2.0 Hz), 8.15 (1H, d, J = 8.9 Hz), 8.37 (1H, d, J = 2.0 Hz)

Step 2

Preparation of N-(5-cyanobenzo[b]thien-2-yl-sulfonyl)glycine.

Starting from 5-cyanobenzo[b]thien-2-ylsulfonyl chloride, the objective compound was obtained in a manner similar to Step 2 of Example 1.

IR (KBr, cm^{-1}): 3289, 2235, 1714, 1350, 1153

NMR (DMSO-d_6, ppm): 3.75 (2H, d, J = 5.6 Hz), 7.87 (1H, dd, J = 8.6, 1.3 Hz), 8.06 (1H, s), 8.34 (1H, d, J = 8.6 Hz), 8.56 (1H, d, J = 1.3 Hz), 8.70 (1H, t, J = 5.6 Hz), 12.69 (1H, bs)

Step 3

Preparation of 1-(5-cyanobenzo[b]thien-2-yl-sulfonyl)-2-thiohydantoin.

Starting from the product obtained in Step 2, the

objective compound was obtained in a manner similar to Step 3 of Example 1.

IR (KBr, cm^{-1}): 2231, 1762, 1451, 1243, 1173, 1077

NMR (DMSO-d_6, ppm): 4.73 (2H, s), 7.95 (1H, dd, J = 8.6, 1.7 Hz), 8.41 (1H, d, J = 8.6 Hz), 8.53 (1H, s), 8.63 (1H, d, J = 1.7 Hz), 12.72 (1H, bs)

Step 4

Preparation of 1-(5-cyanobenzo[b]thien-2-yl-sulfonyl)hydantoin.

A mixture of the product obtained in Step 3 (0.39 g) and 50% (w/v) nitric acid (8.2 ml) was heated with stirring for 5 minutes at 80°C, then for 30 minutes at room temperature and the resulting solution was poured into ice-water (35 ml). The formed precipitate was separated by filtration and washed with acetone (100 ml) to give 0.11 g of the objective compound.

Melting point: 276.3°C (decomposition)

IR (KBr, cm^{-1}): 3100, 2231, 1740, 1386, 1172

NMR (DMSO-d_6, ppm): 4.47 (2H, s), 7.95 (1H, dd, J = 8.6, 1.7 Hz), 8.41 (1H, s), 8.42 (1H, d, J = 8.6 Hz), 8.65 (1H, d, J = 1.7 Hz), 11.75(1H, bs)

Example 47

Preparation of 1-(5-carboxybenzo[b]thien-2-yl-sulfonyl)hydantoin (compound 28).

To the suspension of the product obtained in Step 4 of Example 46 (0.1 g) in water (1.5 ml) was added slowly concentrated sulfuric acid (1.5 ml) and acetic acid (1.5 ml) under ice-cooling and the mixture was stirred under reflux for 2 hours. After cooling to room temperature, the formed precipitate was separated by filtration and washed with acetone (20 ml). The washings were concentrated in vacuo and the residue was triturated with ether (2 ml) to give 0.02 g of the objective compound.

Melting point: >300°C

IR (KBr, cm^{-1}): 1743, 1690, 1380, 1163

NMR (DMSO-d_6, ppm): 4.46 (2H, s), 8.07 (1H, dd, J = 8.6, 1.7 Hz), 8.28 (1H, d, J = 8.6 Hz), 8.48 (1H, s), 8.69(1H, d, J = 1.7 Hz)

Example 48

Preparation of 1-(indol-2-ylsulfonyl)hydantoin.

Step 1

Preparation of 1-benzenesulfonylindol-2-yl-sulfonyl chloride.

To a solution of lithium diisopropylamide comprising 1.6 M n-butyllithium in hexane (422 ml), diisopropylamine (101 ml) and anhydrous ether (260 ml) was added dropwise a solution of 1-benzenesulfonylindole (150 g) in anhydorous ether (2060 ml) with stirring at 0°C. After stirring for 15 minutes at 0°C, the solution was poured into sulfuryl chloride (125 ml) at -50°C and stirred for 2 hours. The resulting solution was poured into ice-water (2.5 l) and stirred sufficiently and then the organic layer was extracted. The aqueous layer was extracted with ethyl acetate (2 l) and the combined organic layer was washed with successive water and saturated aqueous NaCl solution. After drying over anhydrous sodium sulfate, ether and ethyl acetate were removed in vacuo and the residue was triturated with ether to give 146 g of the objective compound.

IR (KBr, cm^{-1}): 1513, 1387, 1378, 1245, 1188

NMR ($CDCl_3$, ppm): 7.29 - 8.36 (10H, m)

Step 2

Preparation of N-(1-benzenesulfonylindol-2-yl-sulfonyl)glycine ethyl ester.

Starting from 1-benzenesulfonylindol-2-ylsulfonyl chloride, the objective compound was obtained in a manner similar to Step 2 of Example 40.

IR (KBr, cm^{-1}): 3335, 1746, 1346, 1338, 1171

NMR (DMSO-d_6, ppm): 1.11 (3H, t, J = 7.3 Hz),
3.94 (2H, d, J = 5.6 Hz),
4.06 (2H, q, J = 7.3 Hz),
6.38 (1H, t, J = 5.6 Hz),
7.14 - 8.32 (10H, m)

Step 3

Preparation of N-(indol-2-ylsulfonyl)glycine.

A solution of sodium hydroxide (1.6 g) in water (7 ml) was added to a solution of the product obtained in Step 2 (4.22 g) in tetrahydrofuran (70 ml) at room temperature and the mixture was stirred for 5 minutes at 65 - 75°C. After removing tetrahydofuran in vacuo, a solution of sodium hydroxide (0.4 g) in water (23 ml) was added to the residue and the mixture was stirred for 5 hours at 65 - 75°C. After cooling to room temperature, the resulting solution was washed with ether, acidified with 6 M hydrochloric acid to a pH 1 under ice-cooling and extracted with ethyl acetate (15 ml × 3). The organic layer was washed with successive water and saturated aqueous NaCl solution. After drying over anhydrous sodium sulfate, ethyl acetate was removed in vacuo and the residue was triturated with ethyl acetate and hexane to give 1.66 g of the objective compound.

Melting point: 170.2 - 171.9°C

IR (KBr, cm^{-1}): 3328, 1707, 1340, 1155, 1145

NMR (DMSO-d_6, ppm): 3.73 (2H, d, J = 6.3 Hz), 6.94 - 7.70 (5H, m), 8.05 (1H, t, J = 6.3 Hz), 11.90 (1H, bs), 12.67 (1H, bs)

Step 4

Preparation of 1-(indol-2-ylsulfonyl)-2-thiohydantoin.

Starting from the product obtained in Step 3, the objective compound was obtained in a manner similar to Step 3 of Example 1.

Melting point: 209.2 - 210.4°C

IR (KBr, cm^{-1}): 3131, 3103, 1755, 1473, 1367, 1249, 1197, 1165, 1147, 1079

NMR (DMSO-d_6, ppm): 4.81 (2H, s), 7.08 - 7.78 (5H, m), 12.33 (1H, bs), 12.66 (1H, bs)

Step 5

Preparation of 1-(indol-2-ylsulfonyl)hydantoin.

Starting from the product obtained in Step 4, the objective compound was obtained in a manner similar to Step 4 of Example 1.

Melting point: 287.1°C (decomposition)

IR (KBr, cm^{-1}): 3290, 1787, 1725, 1389, 1365, 1156

NMR (DMSO-d_6, ppm): 4.67 (2H, s), 7.29 - 7.58 (5H, m), 11.67 (1H, bs),

12.63 (1H, bs)

Example 49

Preparation of 1-(2-carboxychromon-6-ylsulfonyl)-hydantoin.

Step 1

Preparation of 2-methoxycarbonylchromon-6-yl-sulfonyl chloride.

To a solution of methyl 6-aminochromon-2-carboxylate (20 g) in water (132 ml) was added concentrated sulfuric acid (26.4 ml) and then sodium nitrite (9.0 g) at 0°C. After stirring for 30 minutes, to the solution was added sulfur dioxide (19.7 ml), acetic acid (112 ml), concentrated hydrochloric acid (26 ml) and copper (II) chloride dihydrate (11.2 g) and then the mixture was stirred for 15 minutes. The formed precipitate was separated by filtration and dissolved in dichloromethane (600 ml) and the resulting solution was washed with saturated aqueous NaCl solution. After drying over anhydrous sodium sulfate, dichloromethane was removed in vacuo to give 22 g of the objective compound.

IR (KBr, cm^{-1}): 1744, 1661, 1381, 1287, 1174, 600

NMR (DMSO-d_6, ppm): 6.96 (1H, s), 7.70 (1H, d, J = 8.6 Hz),

8.04 (1H, dd, J = 8.6, 2.0 Hz), 8.25 (1H, d, J = 2.0 Hz)

Step 2

Preparation of N-(2-methoxycarbonylchromon-6-yl-sulfonyl)glycine.

To a suspension of 2-methoxycarbonylchromon-6-yl-sulfonyl chloride (20.0 g) in acetone (600 ml) was added slowly a solution of glycine (6.15 g), sodium hydroxide (3.28 g) and sodium bicarbonate (6.11 g) in water (300 ml) and the mixture was stirred for 85 minutes at room temperature. After adjusting a pH of the resulting solution to ca. 6 with 6 M hydrochloric acid, acetone was removed in vacuo and insoluble matters were filtered off. The filtrate was acidified with 2 M hydrochloric acid to a pH 1 under ice-cooling. The acidified solution was extracted with ethyl acetate (350 ml × 3) and the organic layer was washed with successive water and saturated aqueous NaCl solution. After drying over anhydrous sodium sulfate, ethyl acetate was removed in vacuo and the residue was purified by silica gel column chromatography to give 5.45 g of the objective compound.

Melting point: 210.6 - 212.8°C

IR (KBr, cm^{-1}): 3327, 1746, 1716, 1659, 1288, 1266, 1165

NMR (DMSO-d_6, ppm): 3.67 (2H, d, J = 5.9 Hz),
3.96 (3H, s), 7.04 (1H, s),
7.89 - 8.42 (4H, m)

Step 3

Preparation of 1-(2-methoxycarbonylchromon-6-yl-sulfonyl)-2-thiohydantoin.

Starting from the product obtained in Step 2, the objective compound was obtained in a manner similar to Step 3 of Example 1.

Melting point: 217.4°C (decomposition)

IR (KBr, cm^{-1}): 1746, 1660, 1443, 1374, 1282,
1260, 1174

NMR (DMSO-d_6, ppm): 3.96 (3H, s), 4.84 (2H, s),
7.07 (1H, s), 7.97 - 8.71
(3H, m), 12.68 (1H, bs)

Step 4

Preparation of 1-(2-methoxycarbonylchromon-6-yl-sulfonyl)hydantoin.

Starting from the product obtained in Step 3, the objective compound was obtained in a manner similar to Step 4 of Example 1.

Melting point: >300°C

IR (KBr, cm^{-1}): 1751, 1741, 1664, 1617, 1375,
1177,

NMR (DMSO-d_6, ppm): 3.96 (3H, s), 4.52 (2H, s)
7.07 (1H, s), 7.98 - 8.64

(3H, m)

Step 5

Preparation of 1-(2-carboxychromon-6-ylsulfonyl)-hydantoin.

A solution of the product obtained in Step 4 (2.27 g) in a saturated aqueous sodium bicarbonate solution (22.7 ml) was stirred for 2 hours at 40°C. The resulting solution was washed with ethyl acetate and acidified with 2 M hydrochloric acid to a pH 1 under ice-cooling and the formed precipitate was separated by filtration to give 0.82 g of the objective compound.

Melting point: 279.3°C (decomposition)

IR (KBr, cm^{-1}): 3220, 1751, 1663, 1376, 1172

NMR (DMSO-d_6, ppm): 4.54 (2H, s), 7.02 (1H, s), 7.95 - 8.61 (3H, m), 11.63 (1H, bs)

Example 50

Preparation of 1-(benzothiazol-2-ylsulfonyl)-hydantoin (compound 7).

Step 1

Preparation of 2-benzylthiobenzothiazole.

To a solution of 2-benzothiazolthiol (250 g) in N,N-dimethylformamide (1 l) was added triethylamine (208 ml) under ice-cooling and dropwise a solution of

benzyl bromide (178 ml) in N,N-dimethylformamide (300 ml) and the mixture was stirred for 40 minutes. The resulting solution was poured into water (10 l) and the formed precipitate was separated by filtration and dissolved in dichloromethane (3 l). After drying over anhydorpus magnesium sulfate, dichloromethane was removed in vacuo to give 378 g of the objective compound.

Step 2

Preparation of benzothiazol-2-ylsulfonyl chloride.

Into a mixture of 2-benzylthiobenzothiazole (100 g) and acetic acid (500 ml) in water (500 ml) was bubbled chlorine gas for 1.5 hours with stirring at -15°C. The resulting solution was poured into ice-water (1.5 l), the formed precipitate was separated by filtration to give 90.9 g of the objective compound.

Step 3

Preparation of N-(benzothiazol-2-ylsulfonyl)-glycinamide.

To a suspension of glycinamide hydrochloride (43 g) in dioxane (1 l) was added benzothiazol-2-yl-sulfonyl chloride (90.9 g) under ice-cooling and a pH of the mixture was adjusted to 8 with saturated aqueous sodium bicarbonate solution. After stirring for 1.5 hours, the resulting solution was concentrated in vacuo. Water (1.5 l) was added to the residue and

the solution was acidified with concentrated hydrochloric acid to a pH 2. The formed precipitate was separated by filtration to give 59.8 g of the objective compound.

Melting point: 179.7 - 181.8°C

IR (KBr, cm^{-1}): 3426, 1682, 1346, 1165

NMR (DMSO-d_6, ppm): 3.73 (2H, s), 7.08 (1H, bs), 7.36 (1H, bs), 7.52 - 8.29 (4H, m), 8.80 (1H, bs)

Step 4

Preparation of N^2-(benzothiazol-2-yl-sulfonyl)-N^2-methoxycarbonylglycinamide.

To a solution of the product obtained in Step 3 (102.3 g) in N,N-dimethylformamide (1.2 l) was added slowly 60% sodium hydride (16.7 g) under ice-cooling and the mixture was stirred for 1 hour at room temperature. Methyl chlorocarbonate (35.8 g) was added to the above mentioned mixture followed by stirring for 1 hour at room temperature. After removing the solvent, water (3.5 l) was added to the residue and the formed precipitate was separated by filtration to give 60.5 g of the objective compound.

Melting point: 153.1°C (decomposition)

IR (KBr, cm^{-1}): 3459, 3346, 1737, 1689, 1386, 1343, 1250, 1171

NMR (DMSO-d_6, ppm): 3.70 (3H, s), 4.51 (2H, s),

7.30 (1H, bs), 7.60 - 7.76 (3H, m), 8.20 - 8.39 (2H, m)

Step 5

Preparation of 1-(benzothiazol-2-ylsulfonyl)-hydantoin.

To a solution of the product obtained in Step 4 (20.0 g) in N,N-dimethylformamide (200 ml) was added slowly 60% sodium hydride (2.67 g) and the mixture was stirred for 13.5 hours at 70°C. After removing the solvent, water (1 l) was added to the residue and the solution was extracted with ethyl acetate (1.5 l) and the organic layer was washed with saturated aqueous NaCl solution. After drying over anhydrous sodium sulfate, ethyl acetate was removed in vacuo and the residue was washed with acetone-chloroform (100 ml + 200 ml) to give 2.12 g of the objective compound.

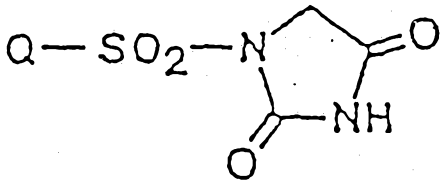
Melting point: 260.4 - 261.9°C

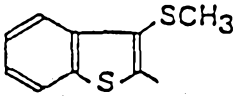
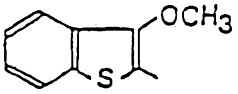
IR (KBr, cm^{-1}): 3200, 3105, 1739, 1393, 1355, 1173

NMR (DMSO-d_6, ppm): 4.55 (2H, s), 7.61 - 7.81 (2H, m), 8.18 - 8.40 (2H, m), 11.88 (1H, bs)

Compounds of Example 51 and 52 prepared in a manner similar to Example 50 are summarized in the following table 4 together with corresponding IR and NMR data and melting points.

Table 4



Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
51		3200, 1801, 1724, 1374, 1180	2.47(3H,s), 4.77(2H,s), 7.60~7.76(2H,m), 8.09~8.25(2H,m), 11.83(1H,bs)	213.2 ~ 222.0
52		3240, 1990, 1728, 1371, 1163	4.18(3H,s), 4.55(2H,s), 7.55~7.66(2H,m), 8.06~8.14(2H,m), 11.70(1H,bs)	239.7 ~ 241.3

Example 53

Preparation of 1-(benzo[c]thien-1-ylsulfonyl)-hydantoin.

Step 1

Preparation of N^2-(benzo[c]thien-1-yl-sulfonyl)glycinamide.

To a solution of benzo[c]thiophen (5.5 g) in anhydrous ether (50 ml) was added 1.6 M solution of n-butyllithium in hexane (52.2 ml) at -20°C under nitrogen atmosphere. After stirring for 1 hour, into the solution was bubbled sulfur dioxide for 1 hour with stirring at -20°C. Ether was removed in vacuo and the residue was suspended in isopropanol (200 ml) and water (200 ml). To the suspension was added N-chlorosuccinimide (6.5 g) at 0°C. After stirring for 30 minutes at 0°C, N-chlorosuccinimide (1.63 g) was added and the mixture was stirred for additional 1 hour. The resulting solution was extracted with dichloromethane (1 l × 2) and the organic layer was washed with successive water and saturated aqueous NaCl solution. After drying over anhydrous sodium sulfate, dichloromethane was removed in vacuo under cooling. Using this residue and glycinamide hydrochloride, the objective compound was obtained in a manner similar to Step 3 of Example 50.

NMR (DMSO-d_6, ppm): 3.40 (2H, d, J = 6.9 Hz),

7.06 - 8.22 (5H, m), 8.49 (1H, s)

Step 2

Preparation of N^2-(benzo[c]thien-1-ylsulfonyl)-N^1-methoxycarbonylglycinamide.

To a solution of the product obtained in Step 1 (0.45 g) in N,N-dimethylformamide (5 ml) was added slowly 60% sodium hydride (75 mg) under ice-cooling and the mixture was stirred for 30 minutes at room temperature. Methyl chlorocarbonate (0.14 ml) was added to the above mentioned mixture followed by stirring for 20 minutes at room temperature. 60% sodium hydride (75 mg) was added to the solution and the mixture was stirred for 1.5 hours at room temperature, then 15 minutes at 70°C. After cooling to room temperature, water (20 ml) was added to the resulting mixture and this aqueous solution was extracted with ethyl acetate (20 ml × 3). The organic layer was washed with successive water and saturated aqueous NaCl solution. After drying over anhydrous magnesium sulfate, ethyl acetate was removed in vacuo and the residue was purified by silica gel columun chromatography to give 0.18 g of the objective compound.

NMR ($CDCl_3$, ppm): 3.74 (3H, s), 4.24 (2H, d, J = 5.3 Hz), 5.92 (1H, t, J = 5.3

Hz), 7.17 - 8.31 (6H, m)

Step 3

Preparation of 1-(benzo[c]thien-1-ylsulfonyl)-hydantoin.

To a solution of the product obtained in Step 2 (0.18 g) in N,N-dimethylformamide (3 ml) was added slowly 60% sodium hydride (48 mg) and the mixture was stirred for 2.5 hours at 70°C. After removing the solvent, ice water (20 ml) was added to the residue and a pH of the solution was adjusted to 4 with 1 M hydrochloric acid. The resulting solution was extracted with ethyl acetate (20 ml × 3) and the organic layer was washed with saturated aqueous NaCl solution. After drying over anhydrous magnesium sulfate, ethyl acetate was removed in vacuo and the residue was triturated with dichloromethane to give 0.03 g of the objective compound.

Melting point: 223.6 - 226.9°C

IR (KBr, cm^{-1}): 1736, 1378, 1185, 1162, 1152

NMR (DMSO-d_6, ppm): 4.51 (2H, s), 7.20 - 8.16 (4H, m), 8.82 (1H, s), 11.54 (1H, bs)

Example 54

Preparation of 1-(3-carboxymethylbenzo[b]-thien-2-ylsulfonyl)hydantoin.

A mixture of the product obtained in Step 4 of Example 30 (0.85 g) and 60% (w/v) nitric acid (9 ml) was heated with stirring for 140 minutes at 70°C. After cooling to room temperature, the formed precipitate was separated by filtration and washed with ether to give 0.21 g of the objective compound.

Melting point: 224.4°C (decomposition)

IR (KBr, cm^{-1}): 3220, 1800, 1736, 1718, 1374, 1170

NMR (DMSO-d_6, ppm): 4.32 (2H, s), 4.47 (2H, s),
7.55 - 7.65 (2H, m),
7.99 - 8.19 (2H, m),
11.71(1H, bs)

Example 55

Preparation of 1-(3-methylsulfinylbenzo[b]thien-2-ylsulfonyl)hydantoin.

To a suspension of the product obtained in Example 51 (0.65 g) in dichloromethane (26 ml) was added m-chloroperbenzoic acid (0.41 g) and the mixture was stirred for 1.5 hours at room temperature. The resulting solution was concentrated in vacuo and the residue was washed with ether (30 ml). The residue was purified by silica gel column chromatography to give 0.48 g of the objective compound.

Melting point: 215.0 - 221.0°C

IR (KBr, cm^{-1}): 1792, 1743, 1379, 1180

NMR (DMSO-d_6, ppm): 3.10 (3H, s), 4.57 (2H, s),
7.51 - 8.89 (4H,m),
11.81 (1H, bs)

Example 56

Preparation of 1-(3-methylsulfonylbenzo[b]thien-2-ylsulfonyl)hydantoin (compound 17).

To a suspension of the product obtained in Example 51 (0.65 g) in ethyl acetate (26 ml) was added m-chloroperbenzoic acid (0.82 g) and the mixture was stirred under reflux for 1.5 hours. Additional m-chloroperbenzoic acid (0.16 g) was added and the mixture was stirred under reflux for more 1.5 hours. The resulting solution was concentrated in vacuo and the residue was washed with successive methanol and ether to give 0.40 g of the objective compound.

Melting point: 224.0 - 245.0°C

IR (KBr, cm^{-1}): 1771, 1372, 1324, 1179

NMR (DMSO-d_6, ppm): 3.47 (3H, s), 4.63 (2H, s),
7.66 - 8.59 (4H,m),
11.90(1H, bs)

Example 57

Preparation of 1-(3-cyanobenzo[b]thien-2-yl-sulfonyl)hydantoin (compound 18).

To a mixture of the product obtained in Example 29

(11.3 g) and copper (I) cyanide (4.1 g) was added pyridine (42 ml). After stirring at 70 °C for 17 hours, a solution of Iron (III) chloride hexahydrate (15.7 g) in concentrated hydrochloric acid (3.9 ml) and water (23.6 ml) was added slowly to the solution and the resultant mixture was heated with stirring for 5 minutes at 50 °C. The formed precipitate was separated by filtration and the filtrate was extracted with ethyl acetate (300 ml) and the organic layer was washed with successive water and saturated aqueous NaCl solution and dried over anhydrous sodium sulfate. Above mentioned precipitate was extracted by ethanol and this ethanol solution was combined with above mentioned organic layer. The resulting solution was concentrated in vacuo and purified by silica gel column chromatography to give 1.21 g of the objective compound.

Melting point: 238.9 - 242.5°C

IR (KBr, cm^{-1}): 2233, 1807, 1746, 1736, 1388, 1167

NMR (DMSO-d_6, ppm): 4.51 (2H, s), 7.70 - 8.47 (4H, m), 11.83 (1H, bs)

Example 58

Preparation of 1-(3-hydroxybenzo[b]thien-2-yl-

sulfonyl)hydantoin.

A mixture of the product obtained in Example 52 (2.5 g), acetic acid (7 ml) and 47% hydrobromic acid (8.9 ml) was stirred for 1 hour at room temperature and heated for 1 hour at 40 °C, for more 1 hour at 50°C. To the mixture was added additional acetic acid (7 ml) and 47% hydrobromic acid (8.9 ml) and heated with stirring for 1 hour at 60°C, for 2 hours at 80°C. The resulting solution was poured into water (300 ml) and extracted with ethyl acetate (1.2 l). After drying over anhydrous magnesium sulfate, ethyl acetate was removed in vacuo and the residue was dissolved in acetone (800 ml). After decoloring with activated charcoal, acetone was removed in vacuo and the residue was washed with successive ethyl acetate and ether to give 1.13 g of the objective compound.

Melting point: 171.8 °C (decomposition)

IR (KBr, cm^{-1}): 3260, 1800, 1735, 1358, 1185, 1164

NMR (DMSO-d_6, ppm): 4.60 (2H, s), 7.46 - 8.19 (4H, m), 11.70 (1H, bs)

Example 59

Preparation of 1-(3-carbamoylbenzo[b]thien-2-ylsulfonyl)hydantoin.

A mixture of the product obtained in Example 57 (0.84 g) and 80%(v/v) sulfuric acid (16.3 ml) was heated with stirring for 8 hours at 70°C and the resulting solution was poured into ice-water (200 ml). The formed precipitate was separated by filtration and washed with successive water, ethanol and acetone to give 0.16 g of the objective compound.

Melting point: 241.9 - 244.6°C

IR (KBr, cm^{-1}): 3412, 3197, 1795, 1741, 1376, 1162

NMR (DMSO-d_6, ppm): 4.51 (2H, s),
7.56 - 8.44 (6H, m),
11.73 (1H, bs)

Example 60

Preparation of 1-(3-carboxybenzo[b]thien-2-yl-sulfonyl,hydantoin.

To a suspension of the product obtained in Example 59 (0.60 g) in concentrated sulfuric acid (18 ml) was added sodium nitrite (2.4 g) under cooling at -15°C and the resulting suspension was stirred for 15 minutes at -15°C, for 30 minutes at 0°C and for 50 minutes at room temperature. To the mixture was added additional sodium nitrite (1.2 g) and stirred for 30 minutes at room temperature. After adjusting a pH of the resulting solution to ca. 9 with 0.1 M sodium bicarbonate, the resulting solution was washed with

ethyl acetate and acidified with concentrated hydrochloric acid to a pH about 2 and extracted with ethyl acetate (200 ml). The organic layer was washed with successive water and saturated aqueous NaCl solution. After drying over anhydrous sodium sulfate, ethyl acetate was removed in vacuo and the residue was purified by silica gel column chromatography to give 0.18 g of the objective compound.

Melting point: 228.8 - 235.1°C

IR (KBr, cm^{-1}): 3450, 1739, 1735, 1380, 1175

NMR (DMSO-d_6, ppm): 4.73 (2H, s),
7.45 - 8.17 (4H, m),
11.76 (1H, bs)

Example 61

Preparation of 1-(3-chlorobenzo[b]furan-2-yl-sulfonyl)hydantoin (compound 32).

Step 1

Preparation of 3-chlorobenzo[b]furan-2-yl-sulfonyl chloride.

To a solution of 3-chlorobenzo[b]furan (11.4 g) in anhydrous ether (62 ml) was added dropwise 1.5 M lithium diisopropylamide mono(tetrahydrofuran) in hexane (62 ml) under nitrogen atmosphere at -70°C. After stirring for 30 minutes, into the solution was bubbled sulfur dioxide for 1 hour with stirring at

-60°C. Then the solution was stirred for 1 hour at room temperature and the formed precipitate was separated by filtration to give lithium 3-chloro-benzo[b]furan-2-sulfinate. To the suspension of the product in dichloromethane (250 ml) was added N-chlorosuccinimide (11.0 g) at -50°C and stirred for 3 hours. After stirring for 2 hours under ice-cooling, insoluble matters were filtered off. Dichloromethane was removed in vacuo and the residue was purified by silica gel column chromatography to give 8.8 g of the objective compound.

Melting point: 60.6 - 68.2°C

IR (KBr, cm^{-1}): 1538, 1402, 1232, 1183, 1151, 1039

NMR ($CDCl_3$, ppm): 7.40 - 7.98 (4H, m)

Step 2

Preparation of N-(3-chlorobenzo[b]furan-2-yl-sulfonyl)glycine ethyl ester.

To a suspension of 3-chlorobenzo[b]furan-2-yl-sulfonyl chloride (8.6 g) and glycine ethyl ester hydrochloride (9.6 g) in dichloromethane (83 ml) was added slowly triethylamine (10.4 ml) under ice-cooling and then the resulting mixture was stirred for 30 minutes at room temperature. Water (150 ml) was added to the resultant solution and acidified with 1 M hydrochloric acid to a pH 2, and the acidified

solution was extracted with ethyl acetate (300 ml). After drying over anhydrous magnesium sulfate, ethyl acetate was removed in vacuo to give 10.2 g of the objective compound.

Melting point: 104.5 - 110.8°C

IR (KBr, cm^{-1}): 3203, 1736, 1365, 1230, 1149

NMR (DMSO-d_6, ppm): 1.01 (3H, t, J = 7.1 Hz), 3.89 (2H, q, J = 7.1 Hz), 3.94 (2H, s), 7.50 - 7.73 (4H, m), 9.12 (1H, bs)

Step 3

Preparation of N-(3-chlorobenzo[b]furan-2-yl-sulfonyl)glycine.

To a solution of N-(3-chlorobenzo[b]furan-2-yl-sulfonyl)glycine ethyl ester (10.2 g) in tetrahydrofuran (160 ml) was added drpowise a solution of sodium hydroxide (4.9 g) in water (16 ml) under ice-cooling and the resulting solution was stirred for 1 hour. After stirring for 30 minutes at room temperature, tetrahydrofuran was removed in vacuo. Water (200 ml) was added to the residue and then acidified with concentrated hydrochloric acid under ice-cooling to a pH 1 and the acidified solution was extracted with ethyl acetate (500 ml). The organic layer was washed with saturated aqueous NaCl solution. After drying over anhydrous magnesium sulfate, ethyl

acetate was removed in vacuo to give 9.2 g of the objective compound.

Melting point: 163.8 - 167.9°C

IR (KBr, cm^{-1}): 3236, 1709, 1369, 1232, 1153

NMR (DMSO-d_6, ppm): 3.84 (2H, d, J = 5.9 Hz),
7.38 - 7.81 (4H, m),
9.03 (1H, t, J = 5.9 Hz),
12.67 (1H, bs)

Step 4

Preparation of 1-(3-chlorobenzo[b]furan-2-yl-sulfonyl)-2-thiohydantoin.

To a mixture of N-(3-chlorobenzo[b]furan-2-yl-sulfonyl)glycine (9.2 g), ammonium thiocyanate (5.32 g) and acetic anhydride (18 ml) was added dropwise pyridine (6.68 ml) under ice-cooling and resulting mixture was stirred for 30 minutes at room temperature, for 30 minutes at 40°C and for 2 hours at 70 - 80°C. After cooling to room temperature, the resulting solution was poured into ice-water (300 ml) and the formed precipitate was separated by filtration and washed with water-ethanol to give 6.73 g of the objective compound.

Melting point: 195.4 - 204.7°C

IR (KBr, cm^{-1}): 3158, 1758, 1393, 1234, 1179

NMR (DMSO-d_6, ppm): 4.83 (2H, s), 7.56 - 7.90
(4H, m)

Step 5

Preparation of 1-(3-chlorobenzo[b]furan-2-yl-sulfonyl)hydantoin.

To a suspension of iodine monochloride (5.3 ml) in 1 M hydrochloric acid (160 ml) was added 1-(3-chlorobenzo[b]furan-2-ylsulfonyl)-2-thiohydantoin (6.7 g) and then dichloromethane (200 ml) dropwise. The mixture was stirred for 1.5 hours under ice-cooling and for 1.5 hours at room temperature. After adding saturated aqueous sodium sulfite solution, the reaction mixture was extracted with ethyl acetate (600 ml). The organic layer was washed with successive saturated aqueous sodium sulfite solution and saturated aqueous NaCl solution. After drying over anhydrous magnesium sulfate, ethyl acetate was removed in vacuo and the residue was washed with successive ether and ether-ethyl acetate to give 3.15 g of the objective compound.

Melting point: 246.6 - 256.8°C

IR (KBr, cm^{-1}): 3226, 1744, 1397, 1363, 1174, 1156

NMR (DMSO-d_6, ppm): 4.51 (2H, s), 7.54 - 7.89 (4H, m), 11.81 (1H, bs)

Example 62

Preparation of 1-(4-bromobenzo[b]furan-2-yl-

sulfonyl)hydantoin.

Step 1

Preparation of (3-bromophenyloxy)acetaldehyde dimethyl acetal.

To a suspension of 60% sodium hydride (60 g) in N,N-dimethylformamide (1.4 l) was added dropwise 3-bromophenol (260 g) under ice-cooling. After stirring for 10 minutes, to the solution was added dropwise bromoacetaldehyde dimethyl acetal (318 g) and the mixture was heated with stirring for 3 hours at 90°C. After cooling, water was added to the resulting solution and acidified with 1 M hydrochloric acid and then extracted with ether (3 l). The organic layer was washed with successive water, saturated aqueous sodium bicarbonate solution and saturated aqueous NaCl solution. After drying over anhydrous sodium sulfate, ether was removed in vacuo and the residue was purified by silica gel column chromatography to give 363.3 g of the objective compound.

IR (neat, cm^{-1}): 2941, 2835, 1615, 1506, 1458

NMR ($CDCl_3$, ppm): 3.44 (6H, s),
3.96 (2H, d, J = 5.0 Hz),
4.69 (1H, t, J = 5.0 Hz),
6.77 - 7.26 (4H, m)

Step 2

Preparation of mixture of 4-bromobenzo[b]furan

and 6-bromobenzo[b]furan.

Under ice-cooling, to phosphoric acid (413.5 ml) was added phosphorus pentoxide (344.2 g) and then chlorobenzene (870 ml). The resulting mixture was heated up to 125°C. To the mixture was added dropwise the solution of the product obtained in Step 1 (181.7 g) in chlorobenzene (150 ml) at 125°C and heated with stirring for 1 hour at 125°C. After cooling, the resulting mixture was poured into ice-water (2 l) and extracted with ether (2 l). The organic layer was washed with successive saturated aqueous sodium bicarbonate solution and saturated aqueous NaCl solution. After drying over anhydrous sodium sulfate, ether and chlorobenzene were removed in vacuo and the residue was purified by silica gel column chromatography to give 116 g of the objective compound.

Step 3

Preparation of 4-bromobenzo[b]furan-2-yl-sulfonyl chloride.

To a solution of the mixture obtained in Step 2 (100 g) in anhydrous ether (430 ml) was added dropwise 1.5 M lithium diisopropylamide mono(tetrahydrofuran) in cyclohexane (430 ml) under nitrogen atmosphere at -70°C. After stirring for 30 minutes, into the solution was bubbled sulfur dioxide for 1 hour with

stirring at -60°C. Then the solution was stirred for 3 hours at room temperature and the formed precipitate was separated by filtration to give a mixture of lithium 4-bromobenzo[b]furan-2-sulfinate and lithium 6-bromobenzo[b]furan-2-sulfinate. To the suspension of the products in dichloromethane (2 l) was added N-chlorosuccinimide (96 g) at -50°C and stirred for 3 hours under ice-cooling. Insoluble matters were filtered off and dichloromethane was removed in vacuo and the residue was purified by silica gel column chromatography to give 14.1 g of the objective compound.

Melting point: 87.2°C

IR (KBr, cm^{-1}): 1603, 1578, 1389, 1175, 1165

NMR ($CDCl_3$, ppm): 7.43 - 7.67 (4H, m)

Step 4

Preparation of N-(4-bromobenzo[b]furan-2-yl-sulfonyl)glycine ethyl ester.

Starting from the product obtained in Step 3 (14.1 g), the objective compound (16.8 g) was obtained in a manner similar to Step 2 of Example 61.

Melting point: 115.6 - 117.3°C

IR (KBr, cm^{-1}): 3199, 1361, 1221, 1158

NMR ($CDCl_3$, ppm): 1.18 (3H, t, J = 7.1 Hz),
3.97 (2H, d, J = 5.3 Hz),
4.09 (2H, q, J = 7.1 Hz),

5.45 (1H, t, J = 5.3 Hz),

7.26 - 7.58 (4H,m)

Step 5

Preparation of N-(4-bromobenzo[b]furan-2-yl-sulfonyl)glycine.

Starting from the product obtained in Step 4 (16.8 g), the objective compound (14.4 g) was obtained in a manner similar to Step 3 of Example 61.

Melting point: 180.0 - 182.1°C

IR (KBr, cm^{-1}): 3253, 1738, 1361, 1262, 1165

NMR (DMSO-d_6, ppm): 3.81 (2H, s), 7.38 -7.81 (4H, m), 8.85 (1H, bs)

Step 6

Preparation of 1-(4-bromobenzo[b]furan-2-yl-sulfonyl)-2-thiohydantoin.

To a suspension of the product obtained in Step 5 (14.4 g) and ammonium thiocyanate (7.2 g) in acetic anhydride (28 ml) was added dropwise pyridine (9.1 ml) and the mixture was heated with stirring for 2 hours at 60 - 70°C. After cooling to room temperature, the resulting solution was poured into ice-water (500 ml) and the formed precipitate was separated and washed with ethanol to give 10.7 g of the objective compound.

Melting point: 253.3°C

IR (KBr, cm^{-1}): 3140, 1756, 1391, 1248, 1166

NMR (DMSO-d_6, ppm): 4.77 (2H, s), 7.45 - 7.88

(3H, m), 7.95 (1H, s),
12.86 (1H, bs)

Step 7

Preparation of 1-(4-bromobenzo[b]furan-2-yl-sulfonyl)hydantoin.

Starting from the product obtained in Step 6 (10.7 g), the objective compound (4.3 g) was obtained in a manner similar to Step 5 of Example 61.

Melting point: 291.7 - 293.5°C

IR (KBr, cm^{-1}): 3240, 1741, 1390, 1355 1167

NMR (DMSO-d_6, ppm): 4.48 (2H, s), 7.45 - 7.90
(4H, m), 11.78 (1H, bs)

Example 63

Preparation of 1-(7-fluorobenzo[b]furan-2-yl-sulfonyl)hydantoin (compound 33).

Step 1

Preparation of 7-fluorobenzo[b]furan-2-yl-sulfonyl chloride.

Starting from 7-fluorobenzo[b]furan (10.4 g), the objective compound (5.7 g) was obtained in a manner similar to Step 1 of Example 61.

Melting point: 114°C

IR (KBr, cm^{-1}): 1596, 1546, 1372, 1267, 1178

NMR ($CDCl_3$, ppm): 7.24 - 7.69 (4H, m)

Step 2

Preparation of N-(7-fluorobenzo[b]furan-2-yl-sulfonyl)glycine ethyl ester.

Starting from the product obtained in Step 1 (5.7 g), the objective compound (6.45 g) was obtained in a manner similar to Step 2 of Example 61.

Melting point: 84.5°C

IR (KBr, cm^{-1}): 3238, 1734, 1376, 1232, 1165

NMR (DMSO-d_6, ppm): 1.03 (3H, t, J = 7.1 Hz),
3.89 (2H, d, J = 6.3 Hz),
3.92 (2H, q, J = 7.1 Hz),
7.32 - 7.66 (4H, m),
9.05 (1H, t, J = 6.3 Hz)

Step 3

Preparation of N-(7-fluorobenzo[b]furan-2-yl-sulfonyl)glycine.

Starting from the product obtained in Step 2 (6.4 g), the objective compound (5.42 g) was obtained in a manner similar to Step 3 of Example 61.

Melting point: 140.1°C (decomposition)

IR (KBr, cm^{-1}): 3303, 1734, 1349, 1262, 1160

NMR (DMSO-d_6, ppm): 3.80 (2H, d, J = 5.0 Hz),
7.28 - 7.66 (4H, m),
8.90 (1H, t, J = 5.0 Hz)

Step 4

Preparation of 1-(7-fluorobenzo[b]furan-2-yl-sulfonyl)-2-thiohydantoin.

To a suspension of the product obtained in Step 3 (5.4 g) and ammonium thiocyanate (3.32 g) in acetic anhydride (12.7 ml) was added dropwise pyridine (4.16 ml) under ice-cooling and nitrogen atmosphere. The mixture was heated with stirring for 2 hours at 70°C. After cooling to room temperature, the resulting solution was poured into ice-water (200 ml) and added small amount of ethanol and the formed precipitate was separated and dissolved in ethyl acetate (200 ml) and the solution was washed with successive water and saturated aqueous NaCl solution. After drying over anhydrous sodium sulfate, ethyl acetate was removed in vacuo and the residue was washed with ethanol to give 2.83 g of the objective compound.

Melting point: 229.9 - 232.0°C

IR (KBr, cm^{-1}): 3258, 1765, 1744, 1448, 1177

NMR (DMSO-d_6, ppm): 4.73 (2H, s), 7.39 - 7.77 (3H, m), 8.13 (1H, d, J = 2.6 Hz), 12.83 (1H, bs)

Step 5

Preparation of 1-(7-fluorobenzo[b]furan-2-yl-sulfonyl)hydantoin.

Starting from the product obtained in Step 4 (2.8 g), the objective compound (1.1 g) was obtained in a manner similar to Step 5 of Example 61.

Melting point: >300°C

IR (KBr, cm^{-1}): 3381, 1735, 1610, 1383, 1166

NMR (DMSO-d_6, ppm): 3.98 (2H, s), 7.34 - 7.71 (3H, m), 7.78 (1H, d, J = 3.0 Hz)

Example 64

Preparation of 1-(4,5-dichlorobenzo[b]furan-2-yl-sulfonyl)hydantoin (compound 29).

Step 1

Preparation of (3,4-dichlorophenyloxy)-acetaldehyde dimethyl acetal.

Starting from 3,4-dichlorophenol (200 g), the objective compound (218.8 g) was obtained in a manner similar to Step 1 of Example 62.

IR (neat, cm^{-1}): 2940, 2830, 1595, 1475, 1297, 1235

NMR ($CDCl_3$, ppm): 3.45 (6H, s),
3.96 (2H, d, J = 5.3 Hz),
4.69 (1H, t, J = 5.3 Hz),
6.78 (1H, dd, J = 8.9, 3.0 Hz),
7.02 (1H, d, J = 3.0 Hz),
7.31 (1H, d, J = 8.9 Hz)

Step 2

Preparation of mixture of 4,5-dichlorobenzo[b]-furan and 5,6-dichlorobenzo[b]furan.

Starting from the product obtained in Step 1

(218.8 g), the mixture of the objective compounds (102.1 g) was obtained in a manner similar to Step 2 of Example 62.

Step 3

Preparation of 4,5-dichlorobenzo[b]furan-2-yl-sulfonyl chloride and 5,6-dichlorobenzo[b]furan-2-ylsulfonyl chloride.

To a solution of the mixture obtained in Step 2 (100 g) in anhydrous ether (440 ml) was added dropwise 1.5 M lithium diisopropylamide mono(tetrahydrofuran) in cyclohexane (440 ml) under nitrogen atmosphere at -70°C over 1 hour, then into the solution was bubbled sulfur dioxide for 1.5 hours at -70°C. After stirring for 1 hour at room temperature, the solvent was removed in vacuo and ether was added to the residue. The formed precipitate was separated by filtration to give a mixture of lithium 4,5-dichlorobenzo[b]furan-2-sulfinate and lithium 5,6-dichlorobenzo[b]furan-2-sulfinate. To the suspension of the products in dichloromethane (1.8 l) was added N-chlorosuccinimide (92.1 g) at -50°C and stirred for 1.5 hours. At room temperature, insoluble matters were filtered off and dichloromethane was removed in vacuo and the residue was purified by silica gel column chromatography to give 17.4 g of 4,5-dichlorobenzo[b]furan-2-ylsulfonyl chloride and 7.4 g of 5,6-dichlorobenzo[b]furan-2-yl-

sulfonyl chloride, respectively.

4,5-dichlorobenzo[b]furan-2-ylsulfonyl chloride

Melting point: 114.6°C

IR (KBr, cm^{-1}): 1529, 1444, 1401, 1191

NMR (DMSO-d_6, ppm): 6.87 (1H, d, J = 1.0 Hz),
7.55 (1H, d, J = 8.9 Hz),
7.69 (1H, dd, J = 8.9, 1.0 Hz)

5,6-dichlorobenzo[b]furan-2-ylsulfonyl chloride

Melting point: 159.8°C

IR (KBr, cm^{-1}): 1537, 1390, 1163, 1081

NMR (DMSO-d_6, ppm): 6.87 (1H, d, J = 1.0 Hz),
7.92 (1H, s),
8.02 (1H, d, J = 1.0 Hz)

Step 4

Preparation of N-(4,5-dichlorobenzo[b]furan-2-ylsulfonyl)glycine ethyl ester.

Starting from 4,5-dichlorobenzo[b]furan-2-ylsulfonyl chloride obtained in Step 3 (17 g), the objective compound (18.2 g) was obtained in a manner similar to Step 2 of Example 61.

Melting point: 155.2 - 155.5°C

IR (KBr, cm^{-1}): 3199, 1737, 1225, 1160

NMR ($CDCl_3$, ppm): 1.05 (3H, t, J = 7.1 Hz),
3.92 (2H, s), 3.95 (2H, q,
J = 7.1 Hz), 7.56 (1H, s),

7.78 (2H, s), 9.09 (1H, bs)

Step 5

Preparation of N-(4,5-dichlorobenzo[b]furan-2-yl-sulfonyl)glycine.

Starting from the product obtained in Step 4 (18 g), the objective compound (16.2 g) was obtained in a manner similar to Step 3 of Example 61.

Melting point: 189.8 - 194.7°C

IR (KBr, cm^{-1}): 3320, 1719, 1366, 1256, 1162

NMR (DMSO-d_6, ppm): 3.83 (2H, d, J = 6.3 Hz),
7.56 (1H, s),
7.76 (2H, s),
8.97 (1H, t, J = 6.3 Hz)

Step 6

Preparation of 1-(4,5-dichlorobenzo[b]furan-2-yl-sulfonyl)-2-thiohydantoin.

Starting from the product obtained in Step 5 (16 g), the objective compound (7.4 g) was obtained in a manner similar to Step 4 of Example 61.

Melting point: 214.6 - 217.5°C

IR (KBr, cm^{-1}): 1793, 1762, 1445, 1167

NMR (DMSO-d_6, ppm): 4.77 (2H, s), 7.85 (2H, s),
8.11 (1H, s), 12.95 (1H, bs)

Step 7

Preparation of 1-(4,5-dichlorobenzo[b]furan-2-yl-sulfonyl)hydantoin.

To a suspension of iodine monochloride (6.3 ml) in 1 M hydrochloric acid (150 ml) were added successively the product obtained in Step 6 (7.3 g) and dropwise dichloromethane (150 ml) over 10 minutes. The mixture was stirred for 2.5 hours at room temperature. Under ice-cooling, to the solution was added saturated aqueous sodium sulfite solution and stirred for a while. The formed precipitate was separated by filtration and washed with successive water, ethanol and ether to give 4.8 g of the objective compound.

Melting point: 290.7 - 292.0°C (decomposition)

IR (KBr, cm^{-1}): 3256, 1742, 1391, 1356, 1168

NMR (DMSO-d_6, ppm): 4.47 (2H, s), 7.85 (2H, s), 7.98 (1H, s), 11.80 (1H, bs)

Example 65

Preparation of 1-(5,6-dichlorobenzo[b]furan-2-yl-sulfonyl)hydantoin (compound 30).

Step 1

Preparation of N-(5,6-dichlorobenzo[b]furan-2-yl-sulfonyl)glycine ethyl ester.

To a solution of 5,6-dichlorobenzo[b]furan-2-yl-sulfonyl chloride obtained in Step 3 of Example 64 (7.4 g) in dichloromethane (60 ml) was added glycine ethyl ester hydrochloride (7.95 g) and added slowly triethylamine (7.89 ml) under ice-cooling and nitrogen

atmosphere. The resulting solution was poured into water (100 ml) and acidified with 1 M hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with saturated aqueous NaCl solution and dried over anhydrous sodium sulfate. Ethyl acetate was removed in vacuo and the residue was washed with hexane to give 8.7 g of the objective compound.

Melting point: 132.7 - 133.5°C

IR (KBr, cm^{-1}): 3227, 1735, 1360, 1225, 1158

NMR (DMSO-d_6, ppm): 1.06 (3H, t, J = 6.9 Hz), 3.90 (2H, s), 3.95 (2H, q, J = 6.9 Hz), 7.52 (1H, s), 8.08 (1H, s), 8.20 (1H, s), 9.05 (1H, bs)

Step 2

Preparation of N-(5,6-dichlorobenzo[b]furan-2-yl-sulfonyl)glycine.

Starting from the product obtained in Step 1 (8.6 g), the objective compound (7.8 g) was obtained in a manner similar to Step 3 of Example 61.

Melting point: 192.6 - 201.8°C

IR (KBr, cm^{-1}): 3367, 1719, 1359, 1248, 1159

NMR (DMSO-d_6, ppm): 3.80 (2H, d, J = 5.9 Hz), 7.51 (1H, d, J = 1.0 Hz), 8.08 (1H, s),

8.19 (1H, d, J = 1.0 Hz),
8.92 (1H, t, J = 5.9 Hz)

Step 3

Preparation of 1-(5,6-dichlorobenzo[b]furan-2-yl-sulfonyl)-2-thiohydantoin.

Starting from the product obtained in Step 2 (7.7 g), the objective compound (3.7 g) was obtained in a manner similar to Step 4 of Example 61.

Melting point: >246.0°C (decomposition)

IR (KBr, cm^{-1}): 3100, 1743, 1449, 1246, 1166

NMR (DMSO-d_6, ppm): 4.73 (2H, s), 8.02 (1H, d, J = 1.0 Hz), 8.20 (1H, s), 8.26 (1H, d, J = 1.0 Hz), 12.82 (1H, bs)

Step 4

Preparation of 1-(5,6-dichlorobenzo[b]furan-2-yl-sulfonyl)hydantoin.

Starting from the product obtained in Step 3 (3.7 g), the objective compound (2.7 g) was obtained in a manner similar to Step 5 of Example 61.

Melting point: >300°C (decomposition)

IR (KBr, cm^{-1}): 1732, 1389, 1186, 1167

NMR (DMSO-d_6, ppm): 4.31 (2H, s), 7.82 (1H, d, J = 0.7 Hz), 8.16 (1H, s), 8.27 (1H, d, J = 0.7 Hz)

Example 66

Preparation of 1-(3-bromo-7-fluorobenzo[b]furan-2-ylsulfonyl)hydantoin (compound 34).

Step 1

Preparation of 2,3-dibromo-2,3-dihydro-7-fluorobenzo[b]furan.

To a solution of 7-fluorobenzo[b]furan (16 g) in carbon tetrachloride (40 ml) was added dropwise a solution of bromine (22 g) in carbon disulfide (40 ml) at -30°C and the solution was stirred for 1 hour. At room temperature, the formed precipitate was separated by filtration to give 34.4 g of the objective compound.

IR (KBr, cm^{-1}): 1634, 1601, 1489, 1459, 1279, 1179

NMR ($CDCl_3$, ppm): 5.74 (1H, d, J = 1.3 Hz), 6.93 (1H, s), 7.11 - 7.35 (3H, m)

Step 2

Preparation of 3-bromo-7-fluorobenzo[b]furan.

To a solution of potassium hydroxide (12.7 g) in ethanol (180 ml) was slowly added the product obtained in Step 1 (34 g) and stirred for 3 hours. The resulting solution was neutralized by acetic acid, then extracted with ether. The organic layer was washed with successive water and saturated aqueous

NaCl solution. After drying over anhydrous sodium sulfate, ether was removed in vacuo to give 24.1 g of the objective compound.

IR (neat, cm^{-1}): 3150, 1636, 1595, 1494, 1434, 1322

NMR ($CDCl_3$, ppm): 6.98 - 7.36 (3H, m), 7.68 (1H, s)

Step 3

Preparation of 3-bromo-7-fluorobenzo[b]furan-2-ylsulfonyl chloride.

Starting from the product obtained in Step 2 (24.1 g), the objective compound (12.2 g) was obtained in a manner similar to Step 1 of Example 61.

IR (KBr, cm^{-1}): 1602, 1533, 1385, 1168

NMR (DMSO-d_6, ppm): 7.33 - 7.39 (3H, m)

Step 4

Preparation of N-(3-bromo-7-fluorobenzo[b]furan-2-ylsulfonyl)glycine ethyl ester.

Starting from the product obtained in Step 3 (12.2 g), the objective compound (10.2 g) was obtained in a manner similar to Step 2 of Example 61.

Melting point: 126.2 - 126.4°C

IR (KBr, cm^{-1}): 3200, 1731, 1366, 1237, 1142

NMR (DMSO-d_6, ppm): 1.01 (3H, t, J = 7.1 Hz), 3.89 (2H, q, J = 7.1 Hz), 3.96 (2H, d, J = 5.6 Hz),

7.47 - 7.66 (3H, m),

9.32 (1H, t, J = 5.6 Hz)

Step 5

Preparation of N-(3-bromo-7-fluorobenzo[b]furan-2-ylsulfonyl)glycine.

Starting from the product obtained in Step 4 (10.2 g), the objective compound (7.25 g) was obtained in a manner similar to Step 3 of Example 61.

Melting point: 148.5 - 159.6°C

IR (KBr, cm^{-1}): 3223, 1716, 1373, 1246, 1163

NMR (DMSO-d_6, ppm): 3.86 (2H, s),

7.46 - 7.58 (3H, m),

9.18 (1H, bs)

Step 6

Preparation of 1-(3-bromo-7-fluorobenzo[b]furan-2-ylsulfonyl)-2-thiohydantoin.

Starting from the product obtained in Step 5 (7.2 g), the objective compound (5.07 g) was obtained in a manner similar to Step 4 of Example 61.

Melting point: 224.3 - 224.7°C (decomposition)

IR (KBr, cm^{-1}): 3290, 1793, 1765, 1235, 1141

NMR (DMSO-d_6, ppm): 4.83 (2H, s),

7.57 - 7.72 (3H, m),

12.93 (1H, bs)

Step 7

Preparation of 1-(3-bromo-7-fluorobenzo[b]furan-

2-ylsulfonyl)hydantoin.

To a suspension of iodine monochloride (3.3 ml) in 1 M hydrochloric acid (110 ml) was added the product obtained in Step 6 (5 g) and dropwise dichloromethane (140 ml). The mixture was stirred for 6 hours at room temperature and then additive iodine monochloride (1.7 ml) was added to the mixture and the resulting mixture was stirred for 1 hour. To the resulting solution was added saturated aqueous sodium sulfite solution and formed precipitate was separated by filtration. The organic layer was washed with saturated aqueous NaCl solution and dried over anhydrous magnesium sulfate. Formed precipitate was suspended in 1 M hydrochloric acid (100 ml) and the suspension was extracted with ethyl acetate. The organic layer was washed with saturated aqueous NaCl solution and dried over anhydrous magnesium sulfate. Both extracts were combined and the solvent was removed in vacuo. The resulting residue was washed with successive ethanol and ether to give 1.66 g of the objective compound.

Melting point: 266.6 - 270.6°C

IR (KBr, cm^{-1}): 3160, 1725, 1393, 1184, 1149

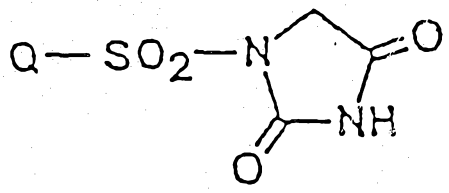
NMR (DMSO-d_6, ppm): 4.50 (2H, s), 7.53 - 7.77 (3H, m), 11.85 (1H, bs)

Compounds of Example 67 to 72 prepared in a manner

similar to Example 61 are summarized in the following table 5 together with corresponding IR and NMR data and melting points.

Intermediate compounds of Example 3 to 39, 41 to 44, 51, 52 and 67 to 72 are summarized in the following table 6 to 10 together with corresponding IR and NMR data and melting points.

Table 5



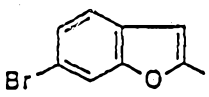
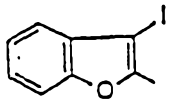
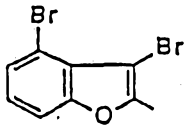
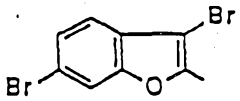
Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
67		1732, 1389, 1181, 1166	4.32(2H,s), 7.59(1H,dd, J=8.6, 1.7Hz), 7.82(1H,d,J=8.6Hz), 7.87(1H,d,J=1.7Hz), 8.12(1H,s)	>297 (dec.)
68		3216, 1734, 1397, 1363, 1175, 1151	4.54(2H,s), 7.51~7.75(4H,m), 11.82(1H,bs)	292 (dec.)
69		1742, 1394, 1183, 1174, 1153	4.55(2H,s), 7.55(1H,t,J=7.9Hz), 7.74(1H,dd, J=7.9, 1.3Hz), 7.91(1H,dd, J=7.9, 1.3Hz), 11.87(1H,bs)	256.3 ~ 258.6 (dec.)
70		3262, 1734, 1397, 1352, 1178, 1170	4.44(2H,s), 7.70(1H,d,J=1.0Hz), 7.71(1H,s), 8.22(1H,d,J=1.0Hz)	>249.2 (dec.)

Table 5 (continued)

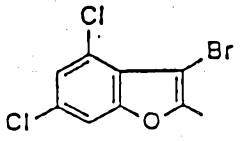
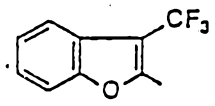
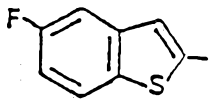
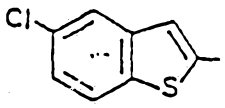
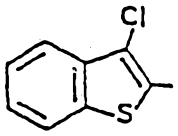
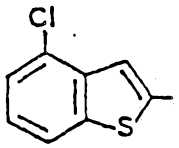
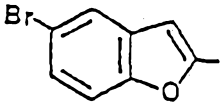
Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
71		3279, 1744, 1404, 1176, 1148	4.51(2H, s), 7.74(1H, d, J=1.7Hz), 8.16(1H, d, J=1.7Hz), 11.82(1H, bs)	249.5 ~ 251.7
72		3220, 1745, 1407, 1357, 1181, 1152,	4.48(2H, s), 7.58~7.97(4H, m)	238.8 ~ 240.8

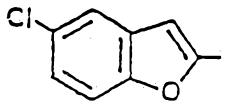
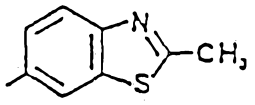
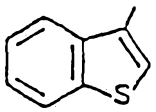
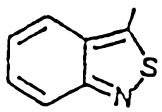
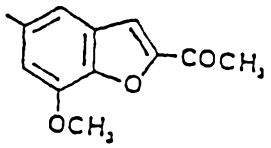
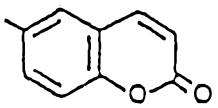
Table 6

Q-SO_2-Cl

Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
3		1500, 1392, 1216, 1174, 1001	7.12~8.00(3H, m), 7.43(1H, s)	
4		1588, 1493, 1169, 1078	7.55(1H, dd, J=8.9, 1.3Hz), 7.85(1H, d, J=8.9Hz), 7.95(1H, d, J=1.3Hz), 8.07(1H, s) *	
5		1592, 1480, 1391, 1248, 1180	7.37~8.01(4H, m)	
6		1584, 1544, 1493, 1388, 1170, 1007	7.35~7.95(3H, m), 7.42(1H, s)	
7		1530, 1372, 1275, 1240, 1160	7.46~7.92(3H, m), 7.58(1H, s) *	

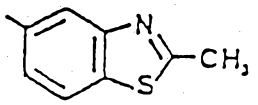
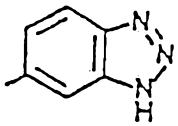
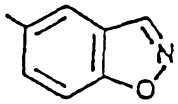
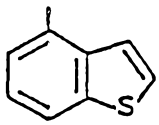
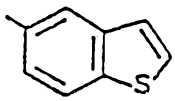
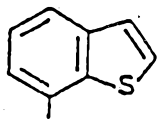
NMR data marked with asterisks (*) were measured in $CDCl_3$.

Table 6 (continued)

Ex. No.	Q	IR (KBr, cm^{-1})	NMR (DMSO-d_6, ppm)	M.P. (℃)
8		1531, 1394, 1164, 1080, 809	7.50~7.76 (3H, m), 7.59 (1H, s)	
9		1508, 1406, 1375, 1320, 1180	2.81 (3H, s), 7.74~8.24 (3H, m)	
11		1423, 1375, 1172	7.38~7.72 (2H, m), 7.84~8.01 (1H, m), 8.26~8.46 (1H, m), 8.51 (1H, s)	
12		1383, 1170, 750, 590	7.53~7.72 (2H, m), 7.87~8.03 (1H, m), 8.07~8.23 (1H, m)	
13			2.67 (3H, s), 4.13 (3H, s), 7.51~8.08 (3H, m)	
15		1734, 1375, 1169, 1102	6.51 (1H, d, J=9.6Hz), 7.36 (1H, d, J=8.6Hz), 7.85 (1H, dd, J=8.6, 2.0Hz), 8.02 (1H, d, J=2.0Hz), 8.16 (1H, d, J=9.6Hz)	

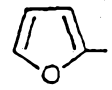
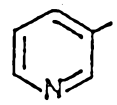
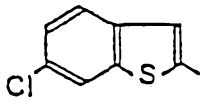
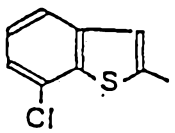
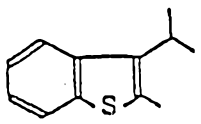
NMR data marked with asterisks (*) were measured in $CDCl_3$.

Table 6 (continued)

Ex. No.	Q	IR (KBr, cm^{-1})	NMR (DMSO-d_6, ppm)	M.P. (℃)
16		1415, 1381, 1371, 1237, 1172, 1151	2.81 (3H, s), 7.60~8.06 (3H, m),	
17		1617, 1383, 1371, 1216, 1173	7.70 (1H, dd, J=8.6, 1.0Hz), 7.87 (1H, d, J=8.6Hz), 8.08 (1H, d, J=1.0Hz)	
18		1604, 1380, 1192, 1161, 534	7.86 (1H, d, J=8.9Hz), 8.27 (1H, dd, J=8.9, 2.0Hz), 8.55 (1H, d, J=2.0Hz), 8.93 (1H, s) *	
19		1379, 1368, 1314, 1171, 1158	7.50 (1H, t, J=7.9Hz), 7.82 (1H, d, J=5.6Hz), 8.00~8.28 (3H, m) *	
20		1375, 1311, 1202, 1169, 1043	7.47~8.15 (5H, m)	
21			7.35~7.90 (5H, m)	

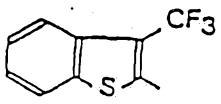
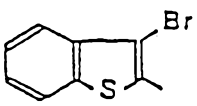
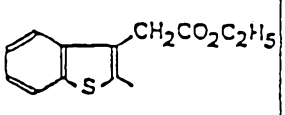
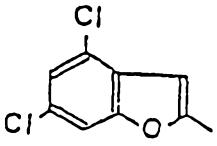
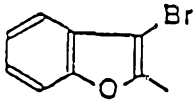
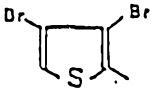
NMR data marked with asterisks (*) were measured in $CDCl_3$.

Table 6 (continued)

Ex. No.	Q	IR (KBr, cm^{-1})	NMR (DMSO-d_6, ppm)	M.P. (℃)
22		1457, 1395, 1214, 1166	7.05~7.14 (2H, m), 8.21~8.24 (1H, m)	
24		1625, 1590, 1522, 1377, 1175	8.00~8.98 (4H, m)	
25		1479, 1380, 1166, 1000, 548	7.37 (1H, dd, J=8.6, 1.3Hz), 7.44 (1H, s), 7.84 (1H, d, J=8.6Hz), 8.04 (1H, d, J=1.3Hz)	
26		1493, 1454, 1390, 1167	7.32~7.53 (2H, m), 7.62 (1H, s), 7.82~7.97 (1H, m)	
27		2968, 2935, 1503, 1465, 1375, 1167	1.59 (3H, d, J=7.3Hz), 4.11~4.44 (1H, m), 7.44~7.64 (2H, m), 7.83~7.94 (1H, m), 8.15~8.26 (1H, m) *	

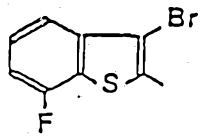
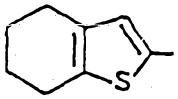
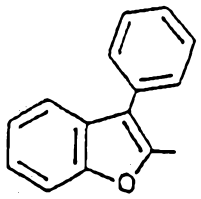
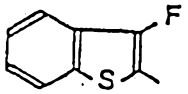
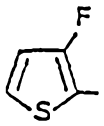
NMR data marked with asterisks (*) were measured in $CDCl_3$.

Table 6 (continued)

Ex No.	Q	IR (KBr, cm^{-1})	NMR (DMSO-d_6, ppm)	M.P. (℃)
28			7.42~8.06 (4H, m)	
29		1473, 1389, 1177, 533	7.51~8.11 (4H, m)	
30		1737, 1371, 1329, 1201, 1174	1.17 (3H, t, J=7.3Hz), 4.05 (2H, q, J=7.3Hz), 4.20 (2H, s), 7.29~7.39 (2H, m), 7.58~7.64 (1H, m), 7.82~7.88 (1H, m)	90.4 ~ 93.2 (dec.)
32		1575, 1530, 1394, 1384, 1174	7.47~7.69 (3H, m)	116.0 ~ 116.9
33		1520, 1395, 1231, 1148	7.31~7.67 (4H, m)	
34		1396, 1178, 1049	7.73 (1H, s)	101.3 ~ 103.0

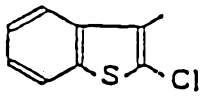
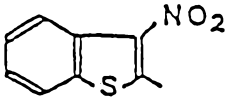
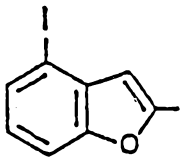
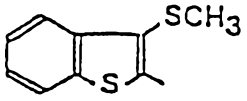
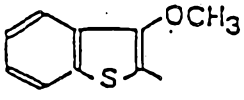
NMR data marked with asterisks (*) were measured in $CDCl_3$.

Table 6 (continued)

Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
35		1488, 1384, 1174, 570	7.26~7.92(3H, m)	90.0 ~ 92.0
36		2948, 1436, 1417, 1166	1.79~1.94(4H, m), 2.62~2.85(4H, m), 7.55(1H, s) *	
37		1398, 1242, 1182, 1147, 534	7.31~7.70(9H, m) *	76.2 ~ 77.4
38		1526, 1389, 1370, 1179, 570, 538	7.42~8.27(4H, m) *	
39			6.96(1H, d, J=5.6Hz), 7.66~7.77(1H, m) *	

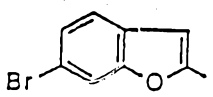
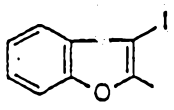
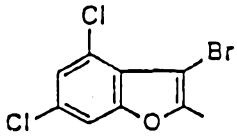
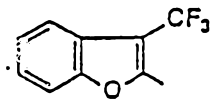
NMR data marked with asterisks (*) were measured in $CDCl_3$.

Table 6 (continued)

Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
41		1478, 1419, 1383, 1178	7.42~8.41(4H, m)	
42			7.45~7.85(3H, m), 8.40~8.50(1H, m)	
43		1381, 1161, 1086, 775	7.24~7.85(4H, m)	
51		1377, 1172, 1164, 762, 567	2.58(3H, s), 7.46~8.25(4H, m)	
52		1510, 1377, 1348, 1175, 578	4.09(3H, s), 7.36~7.74(4H, m)	

NMR data marked with asterisks (*) were measured in $CDCl_3$.

Table 6 (continued)

Ex. No.	Q	IR (KBr, cm^{-1})	NMR (DMSO-d_6, ppm)	M.P. (℃)
67		1533, 1385, 1168, 1077	7.49~7.71 (3H, m), 7.86 (1H, s) *	82.1 ~ 82.9
68		1507, 1501, 1391, 1225, 1139	7.38~7.88 (4H, m) *	88.3 ~ 91.6
71			7.46 (1H, d, J=1.7Hz), 7.61 (1H, d, J=1.7Hz) *	
72			7.46~7.99 (4H, m) *	

NMR data marked with asterisks (*) were measured in $CDCl_3$.

Table 7

$Q-SO_2NHCH_2COOEt$

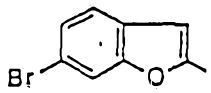
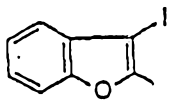
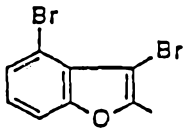
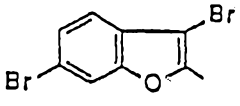
Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
67		3340,1742, 1357,1204, 1161	1.18(3H,t,J=7.3Hz), 3.96(2H,d,J=5.6Hz), 4.10(2H,q,J=7.3Hz), 5.51(1H,t,J=5.6Hz), 7.35~7.73(4H,m)	81.2 ~ 81.5
68		3184,1738, 1364,1225	1.00(3H,t,J=7.1Hz), 3.87(2H,q,J=7.1Hz), 3.92(2H,d,J=5.9Hz), 7.45~7.90(4H,m), 9.03(1H,t,J=5.9Hz)	130.4 ~ 134.1
69		3197,1737, 1366,1229, 1162	1.19(3H,t,J=7.1Hz), 4.02(2H,d,J=6.6Hz), 4.10(2H,d,J=7.1Hz), 5.64(1H,t,J=6.6Hz), 7.24~7.63(3H,m)	129.4 ~ 130.6
70		3295,1732, 1366,1232, 1147	1.18(3H,t,J=7.1Hz), 4.01(2H,d,J=6.6Hz), 4.08(2H,q,J=7.1Hz), 5.62(1H,t,J=6.6Hz), 7.52(2H,s), 7.74(1H,s)	132.9 ~ 133.4

Table 7 (continued)

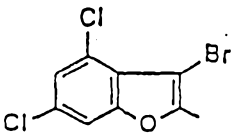
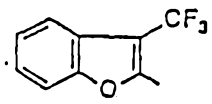
Ex. No.	Q	IR(KBr,cm^{-1})	NMR(DMSO-d_6,ppm)	M.P. (℃)
71		3236,1731, 1365,1233, 1148	1.20(3H,t,J=7.1Hz), 4.02(2H,d,J=4.9Hz), 4.11(2H,q,J=7.1Hz), 5.62(1H,t,J=4.9Hz), 7.38(1H,d,J=1.7Hz), 7.51(1H,d,J=1.7Hz)	167.3 ~ 169.2
72		3203,1739, 1371,1228, 1171	1.00(3H,t,J=6.9Hz), 3.90(2H,q,J=6.9Hz), 3.99(2H,d,J=6.6Hz), 7.44~7.89(4H,m), 9.39(1H,t,J=6.6Hz)	135.6 ~ 147.8

Table 8

$$Q-SO_2NHCH_2CO_2H$$

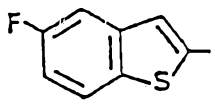
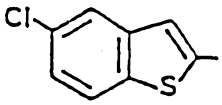
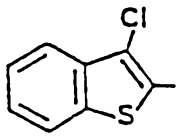
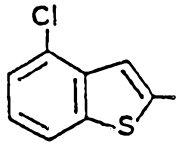
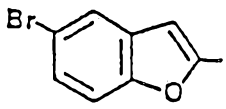
Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
3		3290, 1709, 1342, 1156	3.73(2H, d, J=5.9Hz), 7.31~8.22(4H, m), 8.59(1H, t, J=5.9Hz), 12.72(1H, bs)	162.7 ~ 164.2
4		3295, 1709, 1343, 1156	3.73(2H, d, J=5.9Hz), 7.49~8.17(4H, m), 8.59(1H, t, J=5.9Hz), 12.54(1H, bs)	186.9 ~ 189.1
5		3337, 1716, 1342, 1257, 1162	3.83(2H, d, J=6.3Hz), 7.52~8.24(4H, m), 8.87(1H, t, J=6.3Hz), 12.63(1H, bs)	156.6 ~ 161.0
6		3255, 1710, 1356, 1240, 1160	3.78(2H, d, J=5.9Hz), 7.44~8.13(4H, m), 8.66(1H, t, J=5.9Hz), 12.68(1H, bs)	197.0 ~ 199.2
7		3334, 1717, 1437, 1352, 1241, 1152	3.78(2H, s), 7.49(1H, s), 7.68(2H, s), 8.00(1H, s), 8.83(1H, bs)	192.4 ~ 194.1

Table 8 (Continued)

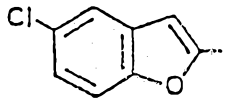
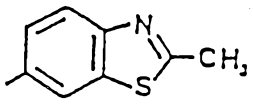
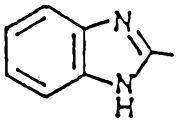
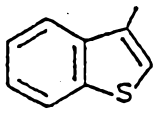
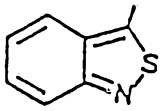
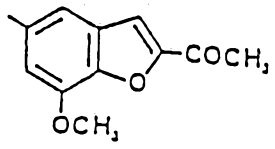
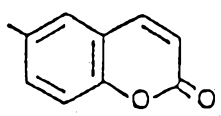
Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
8		3377, 1718, 1358, 1247, 1157	3.76(2H,s), 7.44~7.89(4H,m)	191.5 ~ 193.8
9		3290, 1720, 1340, 1170	2.86(3H,s), 3.63(2H,d,J=6.3Hz), 7.79~8.54(4H,m), 12.48(1H,bs)	237.7 (dec.)
10		3068, 1718, 1617, 1349, 1155	3.78(2H,s), 7.25~7.70(4H,m)	133.5 ~ 135.9
11		3318, 1724, 1339, 1241, 1152	3.64(2H,d,J=5.9Hz), 7.36~7.60(2H,m), 7.97~8.45(4H,m)	
12		3094, 1721, 1348, 1164	3.82(2H,s), 7.43~8.17(4H,m), 9.09(1H,bs), 12.51(1H,bs)	212.5 ~ 214.4
13		3290, 1733, 1655, 1331, 1158	2.58(3H,s), 3.61(2H,d,J=5.9Hz), 4.03(3H,s), 7.49~8.17(4H,m), 12.50(1H,bs)	215.0 ~ 217.6
15		3265, 1748, 1711, 1316, 1205, 1154	3.65(2H,d,J=5.9Hz), 6.62(1H,d,J=9.9Hz), 7.57(1H,d,J=8.6Hz), 7.92~8.25(4H,m), 12.69(1H,bs)	235.0 (dec.)

Table 8 (continued)

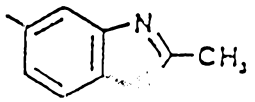
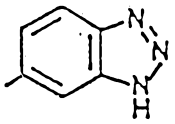
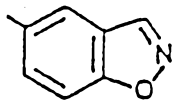
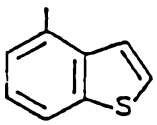
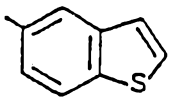
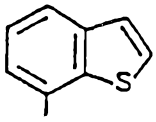
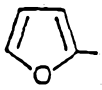
Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
16		3302, 1727, 1330, 1216, 1154	2.85(3H, s), 3.63(2H, d, J=5.9Hz), 7.73~8.29(4H, m)	257.2 (dec.)
17		3213, 1718, 1317, 1255, 1164, 1153	3.64(2H, d, J=5.6Hz), 7.73~8.38(4H, m)	243.5 ~ 245.3
18		3271, 1742, 1316, 1149,	3.64(2H, d, J=6.3Hz), 7.90~8.63(4H, m), 9.38(1H, s), 12.57(1H, bs)	165.3 ~ 168.5
19		3097, 1741, 1316, 1209, 1148	3.57(2H, d, J=5.9Hz), 7.39~8.33(6H, m)	
20		3186, 1765, 1751, 1732, 1335, 1145	3.60(2H, d, J=6.3Hz), 7.61~8.35(6H, m), 12.58(1H, bs)	
21		3282, 1727, 1309, 1161, 1137	3.65(2H, d, J=5.9Hz), 7.47~8.18(5H, m), 8.33(1H, t, J=5.9Hz), 12.64(1H, bs)	
22		3307, 1725, 1340, 1329, 1157	3.66(2H, d, J=6.3Hz), 6.58~7.90(3H, m), 8.38(1H, t, J=6.3Hz), 12.63(1H, bs)	

Table 8 (continued)

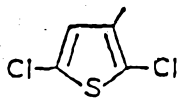
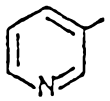
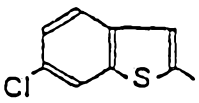
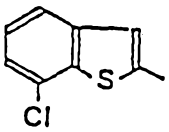
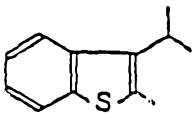
Ex. No.	Q	IR (KBr, cm^{-1})	NMR (DMSO-d_6, ppm)	M.P. (℃)
23		3358, 1728, 1348, 1236, 1166	3.76 (2H, d, J=5.9Hz), 7.28 (1H, s), 8.45 (1H, t, J=5.9Hz), 12.76 (1H, bs)	
24		3236, 1701, 1341, 1174,	3.70 (2H, d, J=5.9Hz), 7.54~8.24 (2H, m), 8.33 (1H, t, J=5.9Hz), 8.76~8.96 (2H, m), 12.70 (1H, bs)	220.4 ~ 223.8
25			3.74 (2H, s), 7.48~8.27 (4H, m), 8.55 (1H, bs)	210.1 ~ 213.3
26		3270, 1732, 1394, 1354, 1260, 1160	3.76 (2H, d, J=5.9Hz), 7.38~8.09 (4H, m), 8.65 (1H, t, J=5.9Hz), 12.74 (1H, bs)	193.0 ~ 205.0
27		3312, 2980, 2968, 1726, 1321, 1143	1.45 (6H, d, J=7.3Hz), 3.72 (2H, d, J=4.3Hz), 3.84~4.17 (1H, m), 7.42~8.30 (4H, m), 8.61 (1H, t, J=4.3Hz)	110.0 ~ 115.5

Table 8 (continued)

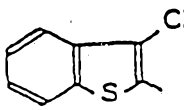
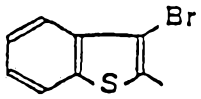
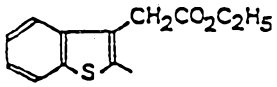
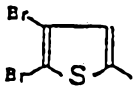
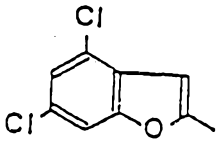
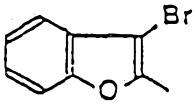
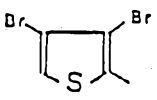
Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
28		3354,1730, 1421,1361, 1214,1164, 1122	3.73(2H,s), 7.57~8.25(4H,m)	141.3 ~ 144.5
29		3304,1725, 1709,1487, 1353,1249, 1160	3.86(2H,d,J=5.9Hz), 7.57~8.19(4H,m), 8.81(1H,t,J=5.9Hz)	149.1 ~ 153.3
30		3294,1735, 1158	1.17(3H,t,J=7.1Hz), 3.67(2H,d,J=6.3Hz), 4.08(2H,q,J=7.1Hz), 4.28(2H,s), 7.46~8.11(4H,m), 8.64(1H,t,J=6.3Hz)	125.0 ~ 126.9
31		3280,1734, 1372,1347, 1312,1255, 1167	3.72(2H,d,J=5.3Hz), 7.61(1H,s), 8.55(1H,t,J=5.3Hz), 12.85(1H,bs)	200.5 ~ 202.0
32		3275,1718, 1364,1161	3.82(2H,d,J=5.9Hz), 7.53(1H,s), 7.63(1H,d,J=1.6Hz), 7.99(1H,bs), 8.95(1H,t,J=5.9Hz)	194.2 ~ 196.4
33		1717,1709, 1437,1369, 1150	3.82(2H,d,J=5.9Hz), 7.36~7.80(4H,m), 8.95(1H,t,J=5.9Hz),	153.4 ~ 156.1
34		3340,1718, 1321,1252, 1153,1141, 1130	3.79(2H,d,J=5.9Hz), 8.17(1H,s), 8.72(1H,t,J=5.9Hz), 12.82(1H,bs)	203.5 ~ 205.2

Table 8 (continued)

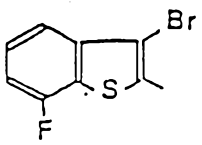
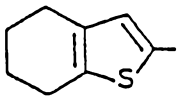
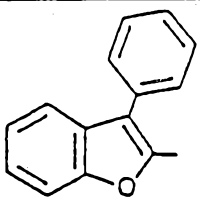
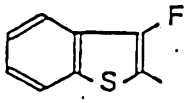
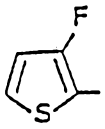
Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
35		3344, 1713, 1498, 1341, 1247, 1163	3.88(2H, d, J=6.3Hz), 7.43~7.82(3H, m), 8.98(1H, t, J=6.3Hz)	194.0 ~ 201.0
36		3315, 3201, 2433, 1752, 1443, 1326, 1187, 1158	1.50~1.98(4H, m), 2.40~2.88(4H, m), 3.59(2H, d, J=4.9Hz), 7.26(1H, s), 8.08(1H, t, J=4.9Hz)	141.2 ~ 143.2
37		3265, 1716, 1352, 1236, 1169, 1139	3.74(2H, s), 7.08~7.81(9H, m), 8.72(1H, bs)	151.4 ~ 153.7
38		3290, 1742, 1375, 1255, 1173, 1118	3.82(2H, d, J=5.9Hz), 7.45~8.16(4H, m), 8.84(1H, t, J=5.9Hz), 12.72(1H, bs)	129.7 ~ 134.2
39		3306, 3117, 1732, 1546, 1424, 1412, 1336, 1160	3.73(2H, d, J=5.9Hz), 7.11(1H, d, J=5.6Hz), 7.86(1H, dd, J=5.6, 4.3Hz), 8.54(1H, t, J=5.9Hz), 12.72(1H, bs)	167.4 ~ 169.4

Table 8 (continued)

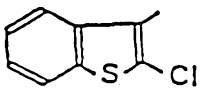
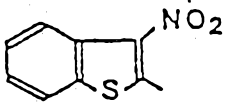
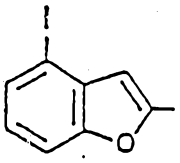
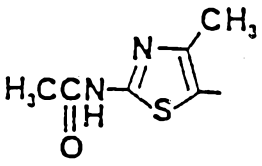
Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
41		3264, 1725, 1420, 1350, 1249, 1160	3.74(2H, d, J=5.6Hz), 7.45~8.31(4H, m), 8.60(1H, t, J=5.6Hz), 12.51(1H, bs)	126.0 ~ 129.5
42		1747, 1589, 1367, 1198	4.30(2H, d, J=5.9Hz), 7.21~8.34(4H, m), 9.94(1H, t, J=5.9Hz)	212.4 (dec.)
43		3265, 1717, 1362, 1248, 1159	3.83(2H, d, J=5.9Hz), 7.22~7.84(4H, m), 8.85(1H, t, J=5.9Hz), 12.66(1H, bs)	222.9 ~ 227.1
44		3290, 1707, 1560, 1338, 1167	2.16(3H, s), 2.43(3H, s), 3.65(2H, d, J=6.3Hz), 8.27(1H, t, J=6.3Hz), 12.45(1H, bs)	247.0 (dec.)

Table 8 (continued)

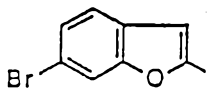
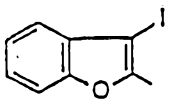
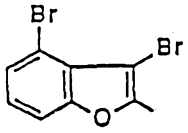
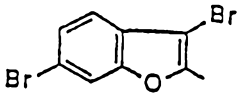
Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
67		3312, 1719, 1353, 1249, 1165	3.77(2H,s), 7.49~7.79(3H,m), 8.04(1H,s), 8.79(1H,bs)	186.5
68		3230, 1709, 1368, 1238, 1173	3.82(2H,d,J=5.9Hz), 7.44~7.73(4H,m), 8.88(1H,t,J=5.9Hz)	179.4 ~ 183.0
69		3280, 1716, 1369, 1238, 1168	3.85(2H,bs), 7.47(1H,dd, J=7.9,7.6Hz), 7.68(1H,dd, J=7.6,1.3Hz), 7.83(1H,dd, J=7.9,1.3Hz), 9.00(1H,bs)	222.9 ~ 227.1
70		3338, 1731, 1365, 1234, 1166	3.83(2H,bs), 7.63(2H,s), 8.14(1H,s), 9.00(1H,bs)	210.4 ~ 212.0

Table 8 (continued)

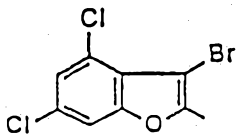
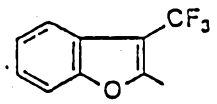
Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
71		3238, 1717, 1369, 1171, 1151	3.86(2H, d, J=6.3Hz), 7.66(1H, d, J=1.7Hz), 8.07(1H, d, J=1.7Hz), 9.15(1H, t, J=6.3Hz)	239.1 ~ 241.3
72		3247, 1716, 1373, 1239, 1173	3.89(2H, d, J=6.3Hz), 7.50~7.91(4H, m), 9.30(1H, t, J=6.3Hz)	162.0 ~ 178.1

Table 9

$Q-SO_2NHCH_2CONH_2$

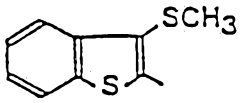
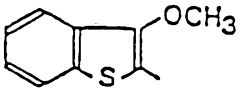
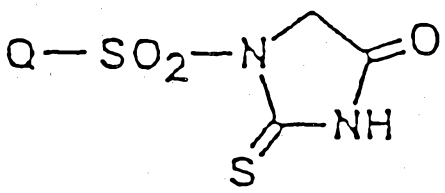
Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
51		3434, 3308, 3188, 1703, 1366, 1155	2.46(3H, s), 3.67(2H, d, J=4.6Hz), 7.10(1H, bs), 7.30(1H, bs), 7.53~8.16(5H, m)	180.4 ~ 181.1
52		3392, 1672, 1522, 1354, 1333, 1153, 1139	3.60(2H, s), 4.10(3H, s), 7.05(1H, bs), 7.20(1H, bs), 7.53~8.16(5H, m)	162.0 ~ 163.1

Table 10



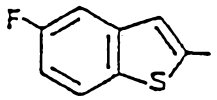
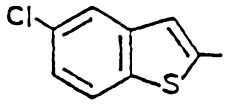
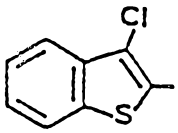
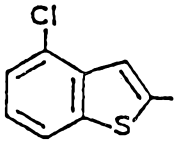
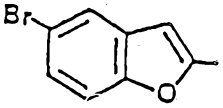
Ex. No.	Q	IR (KBr, cm^{-1})	NMR (DMSO-d_6, ppm)	M.P. (℃)
3		1757, 1391, 1253, 1176	4.74 (2H, s), 7.41~8.50 (4H, m), 12.76 (1H, bs)	240.4 ~ 242.5
4		1761, 1468, 1385, 1249, 1170	4.73 (2H, s), 7.50~8.46 (4H, m), 12.77 (1H, bs)	208.3 (dec.)
5		1784, 1756, 1462, 1374, 1245, 1173	4.92 (2H, s), 7.50~8.34 (4H, m), 12.95 (1H, bs)	275.3 (dec.)
6		1746, 1467, 1382, 1257, 1171	4.79 (2H, s), 7.53~8.40 (4H, m), 12.76 (1H, bs)	221.2 ~ 224.6
7		1751, 1436, 1392, 1237, 1165	4.74 (2H, s), 7.65~8.10 (4H, m), 12.72 (1H, bs)	186.7 ~ 187.7

Table 10 (continued)

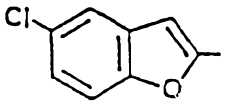
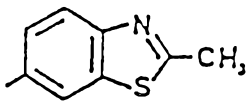
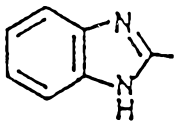
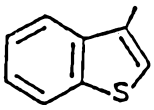
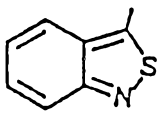
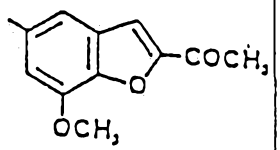
Ex. No.	Q	IR(KBr,cm^{-1})	NMR(DMSO-d_6,ppm)	M.P. (℃)
8		1750,1458, 1394,1164,	4.74(2H,s), 7.50~8.07(4H,m), 12.83(1H,bs)	213.9 (dec.)
9		1748,1378, 1245,1175	2.88(3H,s), 4.83(2H,s), 8.13(2H,s), 8.87(1H,s), 12.62(1H,bs)	240.4 (dec.)
10		1785,1758, 1449,1388, 1255,1185, 1160	4.84(2H,s), 7.26~7.86(4H,m), 12.94(1H,bs)	
11		3111,1793, 1762,1463, 1374,1174	4.87(2H,s), 7.47~7.68(2H,m), 8.04~8.28(2H,m), 9.01(1H,s), 12.64(1H,bs)	
12		1757,1386, 1167	4.83(2H,s), 7.50~8.34(4H,m), 12.77(1H,bs)	203.1 (dec.)
13		1764,1680, 1475,1361, 1319,1162	2.59(3H,s), 4.08(3H,s), 4.77(2H,s), 7.50~8.28(3H,m), 12.51(1H,bs)	244.0 (dec.)

Table 10 (continued)

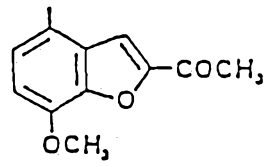
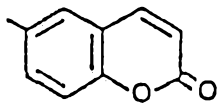
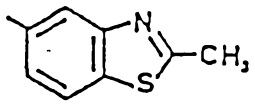
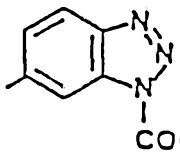
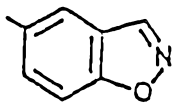
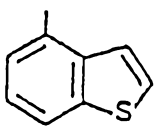
Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
14		1746, 1671, 1362, 1305, 1186, 1167	2.63(3H,s), 4.10(3H,s), 4.85(2H,s), 7.32(1H,d,J=8.9Hz), 7.95(1H,s), 8.14(1H,d,J=8.9Hz), 12.54(1H,bs)	
15		1745, 1467, 1385, 1360, 1170	4.81(2H,s), 6.65(1H,d,J=9.6Hz), 7.62(1H,d,J=8.9Hz), 8.04~8.58(3H,m), 12.66(1H,bs)	230.2 (dec.)
16		1762, 1613, 1370, 1241, 1174	2.87(3H,s), 4.85(2H,s), 7.92~8.64(3H,m), 12.61(1H,bs)	226.0 (dec.)
17		1755, 1459, 1380, 1169	2.96(3H,s), 4.89(2H,s), 8.41(2H,s), 9.06(1H,s), 12.60(1H,bs)	222.7 (dec.)
18		1759, 1459, 1370, 1243, 1189, 1162	4.83(2H,s), 7.99~8.75(3H,m), 9.46(1H,s), 12.64(1H,bs)	264.0 (dec.)
19		1745, 1476, 1362, 1267, 1199, 1170	4.90(2H,s), 7.46~8.55(5H,m), 12.63(1H,bs)	

Table 10 (continued)

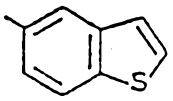
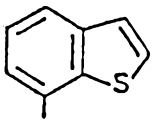
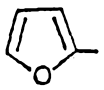
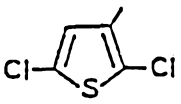
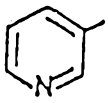
Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
20		1755, 1474, 1364, 1256, 1200, 1169	4.84(2H, s), 7.50~8.73(5H, m), 12.58(1H, bs)	
21		1743, 1459, 1390, 1346, 1172	4.91(2H, s), 7.55~8.31(5H, m), 12.71(1H, bs)	
22		1753, 1431, 1381, 1191, 1166	4.68(2H, s), 6.72~6.86(1H, m), 7.54(1H, d, J=3.6Hz), 8.10(1H, d, J=1.8Hz), 12.75(1H, bs)	
23		1795, 1758, 1452, 1432, 1374, 1177	4.77(2H, s), 7.65(1H, s), 12.85(1H, bs)	
24		1788, 1755, 1378, 1263, 1173	4.82(2H, s), 7.62~9.22(4H, m), 12.69(1H, bs)	221.0 (dec.)

Table 10 (continued)

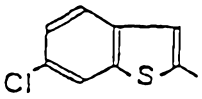
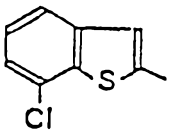
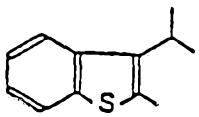
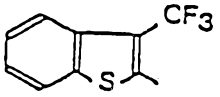
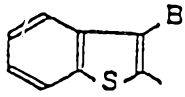
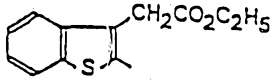
Ex. No.	Q	IR(KBr,cm^{-1})	NMR(DMSO-d_6,ppm)	M.P. (℃)
25		3320,1800, 1769,1458, 1370,1230	4.74(2H,s), 7.58(1H,dd, J=8.6,1.7Hz), 8.11(1H,d,J=8.6Hz), 8.36(1H,d,J=1.7Hz), 8.47(1H,s), 12.75(1H,bs)	249.6 (dec.)
26		3110,1791, 1751,1745, 1381,1180	4.76(2H,s), 7.50~7.82(1H,m), 8.11(1H,dd, J=7.6,1.3Hz), 8.57(1H,s), 12.79(1H,bs)	221.0 (dec.)
27		3140,1791, 1757,1459, 1346,1177	1.43(6H,d,J=6.9Hz), 3.63~3.96(1H,m), 7.47~7.61(1H,m), 8.07~8.31(1H,m), 12.84(1H,bs)	191.3 ~ 195.7
28		3120,1756, 1465,1366, 1175,1164	4.76(2H,s), 7.60~8.38(4H,m), 13.01(1H,bs)	232.1 ~ 233.5
29		3180,1782, 1755,1455, 1372,1170	4.95(2H,s), 7.56~8.32(4H,m), 12.92(1H,bs)	222.8 (dec.)
30		3220,1756, 1726,1376, 1173	1.14(3H,t,J=7.1Hz), 4.05(2H,q,J=7.1Hz), 4.41(2H,s), 4.77(2H,s), 7.55~7.72(2H,m), 8.02~8.20(2H,m), 12.81(1H,bs)	204.7 (dec.)

Table 10 (continued)

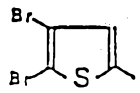
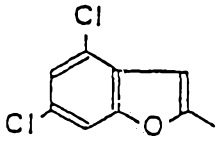
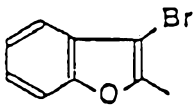
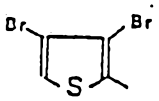
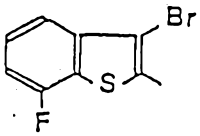
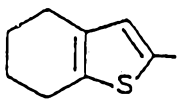
Ex. No.	Q	IR (KBr, cm^{-1})	NMR (DMSO-d_6, ppm)	M.P. (℃)
31		1793, 1473, 1392, 1191, 1174	4.69 (2H, s), 8.07 (1H, s), 12.78 (1H, bs)	203.0 (dec.)
32		3292, 1795, 1765, 1464, 1381, 1185, 1176	4.74 (2H, s), 7.73 (1H, d, J=1.7Hz), 8.06~8.09 (2H, m), 12.87 (1H, bs)	211.6 (dec.)
33		1795, 1759, 1460, 1384, 1149	4.83 (2H, s), 7.43~7.89 (4H, m), 12.96 (1H, bs)	212.8 ~ 219.9 (dec.)
34		3350, 1793, 1764, 1458, 1362, 1174	4.87 (2H, s), 8.44 (1H, s), 12.88 (1H, bs)	242.0 (dec.)
35		3289, 1795, 1770, 1492, 1458, 1359, 1180, 1156, 1085	4.97 (2H, s), 7.55~7.88 (3H, m), 13.01 (1H, bs)	254.0 (dec.)
36		3157, 1794, 1765, 1376, 1352, 1161	1.50~1.92 (4H, m), 2.46~2.94 (4H, m), 4.65 (2H, s), 7.72 (1H, s), 12.61 (1H, bs)	245.0 ~ 246.8

Table 10 (continued)

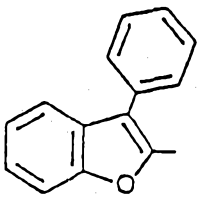
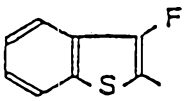
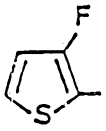
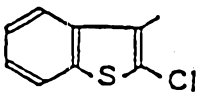
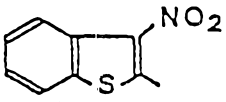
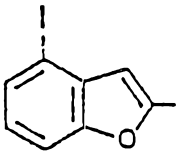
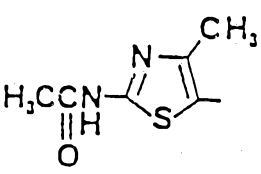
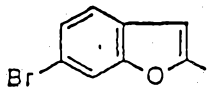
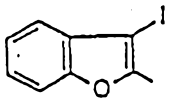
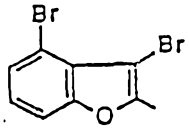
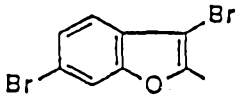
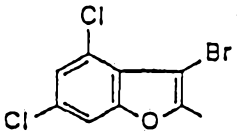
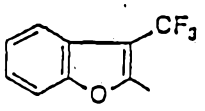
Ex. No.	Q	IR (KBr, cm^{-1})	NMR (DMSO-d_6, ppm)	M.P. (℃)
37		1786, 1750, 1446, 1370, 1348, 1178	4.37 (2H, s), 7.13~7.90 (9H, m), 12.82 (1H, bs)	183.8 (dec.)
38		3130, 1790, 1759, 1383, 1182	4.73 (2H, s), 7.57~8.15 (4H, m), 12.81 (1H, bs)	230.5 ~ 223.8
39		3107, 1755, 1537, 1469, 1423, 1376, 1248, 1173	4.66 (2H, s), 7.21 (1H, d, J=5.6Hz), 8.16 (1H, dd, J=5.6, 4.3Hz),	194.4 (dec.)
41		3268, 1790, 1765, 1459, 1348, 1178, 1160	4.93 (2H, s), 7.50~7.73 (2H, m), 8.04~8.29 (2H, m), 12.82 (1H, bs)	244.0 ~ 246.0
42		1790, 1763, 1460, 1348, 1182	4.68 (2H, s), 7.59~7.70 (2H, m), 8.14~8.40 (2H, m), 12.68 (1H, bs)	170.0 (dec.)
43		3125, 1744, 1456, 1332, 1162	4.77 (2H, s), 7.30~7.91 (4H, m), 12.85 (1H, bs)	210.9 (dec.)
44		3180, 1761, 1535, 1371, 1170	2.19 (3H, s), 2.54 (3H, s), 4.68 (2H, s), 12.64 (1H, bs), 12.75 (1H, bs)	250.0 (dec.)

Table 10 (continued)

Ex. No.	Q	IR(KBr, cm^{-1})	NMR(DMSO-d_6, ppm)	M.P. (℃)
67		3319, 1794, 1766, 1461, 1163	4.73(2H,s), 7.63(1H,d,J=8.6Hz), 7.85(1H,d,J=8.6Hz), 8.05(1H,s), 8.12(1H,s)	246.8 ~ 247.7
68		1735, 1397, 1228, 1173	4.88(2H,s), 7.56~7.90(4H,m), 13.04(1H,bs)	195 ~ 198
69		3330, 1792, 1764, 1456, 1174	4.86(2H,s), 7.57(1H,t,J=7.9Hz), 7.75(1H,dd, J=7.9,1.3Hz), 7.93(1H,dd, J=7.9,1.3Hz), 13.08(1H,bs)	219.5 ~ 222.3
70		3084, 1749, 1388, 1266, 1182	4.81(2H,s), 7.70(1H,s), 7.72(1H,s), 8.22(1H,s)	>240 (dec.)
71		3568, 1752, 1382, 1244, 1177	4.84(2H,s), 7.76(1H,d,J=1.6Hz), 8.17(1H,d,J=1.6Hz), 13.15(1H,bs)	220 (dec.)
72		3110, 1752, 1239, 1178, 1174	4.83(2H,s), 7.60~7.99(4H,m)	161.6 ~ 179.3

Now, typical but non-limiting examples of formulations of the compound of this invention will be shown below.

Formulation A (Capsules)

Compound 1, 300 g of weight, 685 g of lactose and 15 g of magnesium stearate were weighed and mixed until the mixture became homogeneous. The mixture was then filled in No. 1 hard gelatin capsule at 200 mg each to obtain capsule preparation.

Formulation B (Capsules)

Compound 23, 250 g of weight, 730 g of lactose and 20 g of magnesium stearate were weighed and mixed until the mixture became homogeneous. The mixture was then filled in No. 1 hard gelatin capsule at 200 mg each to obtain capsule preparation.

Formulation C (Tablets)

Compound 19, 300 g of weight, 550 g of lactose, 120 g of potato starch, 15 g of polyvinyl alcohol and 15 g of magnesium stearate were weighed. The weighed amount of compound 19, lactose and potato starch were mixed until accomplishing homogeneity. Then aqueous solution of polyvinylalcohol was added to the mixture and granulated by wet process. The granules were then

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dried, mixed with magnesium stearate and pressed into tablets, each weighing 200 mg.

Formulation D (Powder)

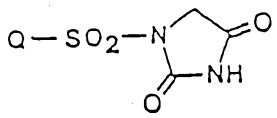
Compound 31, 200 g of weight, 790 g of lactose and 10 g of magnesium stearate were weighed and mixed until the mixture became homogeneous to obtain 20% powder preparation.

Formulation E (Suppositories)

Compound 29, 100 g of weight were weighed and ground by a mortar until the compound became fine powder. Then 180 g of polyethylene glycol 1500 and 720 g of polyethylene glycol 4000 were added to the compound and melted. The mixture was then pressed at 1 g each to obtain suppository preparation.

What is claimed is:

1. Hydantoin derivatives represented by the formula (I):



(I)

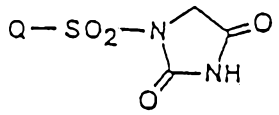
and non-toxic salts, solvates and solvates of non-toxic salts thereof; wherein Q represents a mono- or a fused heterocyclic group which may be substituted by one or more substituents which are same or different and selected from a group consisting of a halogen atom, a lower alkyl group, a nitro group, a cyano group, an optionally protected carboxy group, an optionally protected carboxymethyl group, a halogenated lower alkyl group, a lower alkylthio group, a lower alkylcarbonyl group, a lower alkoxy group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, an optionally protected hydroxy group, an optionally protected amino group, a carbamoyl group and a phenyl group.

2. Hydantoin derivatives as claimed in claim 1 wherein Q represents a benzo[b]thien-2-yl group which may be substituted, and non-toxic salts, solvates and solvates of non-toxic salts thereof.

3. Hydantoin derivatives as claimed in claim 1 wherein Q represents a benzo[b]furan-2-yl group which may be substituted, and non-toxic salts, solvates and solvates of non-toxic salts thereof.

4. Hydantoin derivatives as claimed in claim 3 wherein the said substituents are 1 to 3 halogen atoms.

5. A process for producing hydantoin derivatives represented by the formula (I):



(I)

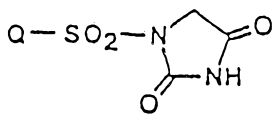
wherein Q represents a mono- or a fused heterocyclic group which may be substituted by one or more substituents which are same or different and selected from a group consisting of a halogen atom, a lower alkyl group, a nitro group, a cyano group, an optionally protected carboxy group, an optionally protected carboxymethyl group, a halogenated lower alkyl group, a lower alkylthio group, a lower alkylcarbonyl group, a lower alkoxy group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, an optionally protected hydroxy group, an optionally protected amino group, a carbamoyl group and a phenyl

group, by cyclization of a sulfonylglycine derivative represented by the formula (V)

$$Q\text{-}SO_2NHCH_2CONH_2 \qquad (V)$$

wherein Q has the same significance as defined above, with a haloformic acid ester.

6. A process for producing hydantoin derivatives represented by the formula (I):



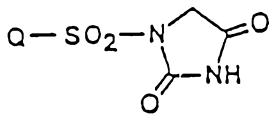
(I)

wherein Q represents a mono- or a fused heterocyclic group which may be substituted by one or more substituents which are same or different and selected from a group consisting of a halogen atom, a lower alkyl group, a nitro group, a cyano group, an optionally protected carboxy group, an optionally protected carboxymethyl group, a halogenated lower alkyl group, a lower alkylthio group, a lower alkylcarbonyl group, a lower alkoxy group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, an optionally protected hydroxy group, an optionally protected amino group, a carbamoyl group and a phenyl group, by cyclizing a sulfonylglycine derivative represented by the formula (VI):

$$Q\text{-}SO_2NHCH_2CO\text{-}R^1 \qquad (VI)$$

wherein Q has the same significance as defined above, and R^1 represents a hydroxy group or an alkoxy group, with a thiocyanate derivative, then oxidizing the cyclized product.

7. A pharmaceutical composition which comprises at least one of hydantoin derivatives represented by the formula (I):



(I)

and non-toxic salts, solvates and solvates of non-toxic salts thereof; wherein Q represents a mono- or a fused heterocyclic group which may be substituted by one or more substituents which are same or different and selected from a group consisting of a halogen atom, a lower alkyl group, a nitro group, a cyano group, an optionally protected carboxy group, an optionally protected carboxymethyl group, a halogenated lower alkyl group, a lower alkylthio group, a lower alkylcarbonyl group, a lower alkoxy group, a lower alkylsulfinyl group, a lower alkylsulfonyl group, an optionally protected hydroxy

group, an optionally protected amino group, a carbamoyl group and a phenyl group and a pharmaceutically acceptable diluent, excipient, carrier and/or adjuvant.

8. A pharmaceutical composition as claimed in claim 7 wherein Q represents a benzo[b]thien-2-yl group which may be substituted.

9. A pharmaceutical composition as claimed in claim 7 wherein Q represents a benzo[b]furan-2-yl group which may be substituted.

10. A pharmaceutical composition as claimed in claim 9 wherein the said substituents are 1 to 3 halogen atoms.

11. A hydantoin derivative substantially as herein described with reference to any one of Examples 1 to 72.

12. A process for producing a hydantoin derivative which process is substantially as herein described with reference to any one of Examples 1 to 72.

13. A pharmaceutical composition comprising a compound as defined in claim 11 together with a pharmaceutically acceptable carrier, diluent, excipient and/or adjuvant.

14. A method of treating and/or preventing various forms of diabetic complications based on the accumulation of polyol metabolites in an animal requiring such treatment and/or prevention, comprising administering to said animal an effective amount of a compound as defined in claim 11 or a composition as defined in claim 13.

DATED this EIGHTH day of JANUARY 1992
Mochida Pharmaceutical Co., Ltd.

Patent Attorneys for the Applicant
SPRUSON & FERGUSON

AUSTRALIAN PATENT OFFICE

KXW:1292v

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP 89/00851

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

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

IPC[5]: C 07 D 409/12, A 61 K 31/415, C 07 D 405/12, C 07 D 417/12

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	C 07 D 409/00, A 61 K 31/00, C 07 D 405/00, C 07 D 417/00

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

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	US, A, 4575507 (CHRISTOPHER A. LIPINSKI (PFIZER INC.)) 11 March 1986 --	
A	EP, A, 0173497 (PFIZER INC.) 5 March 1986 --	
A	EP, A, 0187387 (KAKEN PHARMACEUTICAL CO. LTD) 16 July 1986 --	
A	FR, M, 6097 (DAINIPPON PHARMACEUTICAL CO. LTD) 22 July 1968 --	
A	US, A, 3384643 (ADNAN A.R. SAYIGH and HENRI ULRICH (THE UPJOHN CO.) 21 May 1968 --	
A	Chemical Abstracts, vol. 97, no. 1, 5 July 1982, (Columbus, Ohio, US), A.M. El-Naggar et al.: "Synthesis of thiophene-2-sulfonyl -amino acid and dipeptide derivatives" see page 657, abstract 6774e & Egypt. J. Chem. 1981, 23(4), 273-9 --	

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* Special categories of cited documents: [10]

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

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

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

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

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

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

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
15th November 1989	06. 12. 89
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	T.K. WILLIS

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	Chemical Abstracts, vol. 95, no. 15, 12 October 1981, (Columbus, Ohio, US), see page 658, abstract 132725m A.M. El-Maghraby et al.: "Synthesis of new heterocyclic sulfonamides" & Indian J. Chem. Sect. B, 1981, 20B(3), 256-7 --	
A	US, A, 4743611 (M.S. MALAMAS & K. SESTANJ (AMERICAN HOME PRODUCTS) 10 May 1988, (cited in the application) --	
P,X	EP, A,0305947 (MOCHIDA PHARMACEUTICAL) 8 March 1989, see the whole document	1-14

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. JP 8900851 SA 30644

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 01/12/89
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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