

603842
COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952

LODGED AT SUB-OFFICE
20 NOV 1987
Melbourne

APPLICATION FOR A STANDARD PATENT

X
We FUJISAWA PHARMACEUTICAL CO., LTD.
Of No. 3, 4-chome, Doshomachi, Higashi-ku,
Osaka-shi, Osaka 541,
Japan.

hereby apply for the grant of a Standard Patent for an invention entitled:

"NEW BENZOTHIADIAZINE COMPOUNDS, PROCESSES FOR THE PREPARATION
THEREOF AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME"

which is described in the accompanying ~~provisional~~
complete specification.

Details of basic application(s):—

<u>Number</u>	<u>Convention Country</u>	<u>Date</u>
8627857	UNITED KINGDOM	21st November 1986
8714598	UNITED KINGDOM	22nd June 1987
8720659	UNITED KINGDOM	2nd September 1987

APPLICATION ACCEPTED AND AMENDMENTS

4 - 9 - 87

The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little
Coliins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

Dated this 20th day of November 19 87

To: THE COMMISSIONER OF PATENTS

H. H. Rimington
(a member of the firm of DAVIES &
COLLISON for and on behalf of the Applicant).

Davies & Collison, Melbourne and Canberra.

COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952
DECLARATION IN SUPPORT OF CONVENTION OR
NON-CONVENTION APPLICATION FOR A PATENT

Insert title of invention.

In support of the Application made for a patent for an invention
entitled: "New benzothiadiazine compounds, processes for the
preparation thereof and pharmaceutical composition
comprising the same"

~~X~~
~~Wx~~ I, Tomokichiro Fujisawa
Of Fujisawa Pharmaceutical Co., Ltd.,
Of No. 3, 4-chome, Doshomachi, Higashi-ku,
Osaka-shi, Osaka 541,
Japan.

Insert full name(s) and address(es)
of Declarant(s) being the appli-
cant(s) or person(s) authorized to
sign on behalf of an applicant
company.

Cross out whichever of paragraphs
1(a) or 1(b) does not apply.

1(a) relates to application made
by individual(s).

1(b) relates to application made
by company; insert name of
applicant company.

do solemnly and sincerely declare as follows :-

1. (a) ~~XXXX~~ ~~the application is made for the patent~~
~~XXXX~~

or (b) I am authorized by

FUJISAWA PHARMACEUTICAL CO., LTD.

Cross out whichever of paragraphs
2(a) or 2(b) does not apply.

2(a) relates to application made
by inventor(s)

2(b) relates to application made
by company(s) or person(s) who
are not inventor(s); insert full
name(s) and address(es) of inven-
tors.

the applicant..... for the patent to make this declaration on ^{its} behalf.
~~XXXX~~

2. (a) ~~XXXX~~ ~~the actual inventor(s) of the invention~~
~~XXXX~~

or (b) (1) Teruo OKU (4) Katsuya NAKAMURA
(2) Eishiro TODO (5) Hiroshi KAYAKIRI
(3) Chiyoshi KASAHARA (6) Masashi HASHIMOTO
(See over for addresses)

~~IX~~ the actual inventor.....S..... of the invention and the facts upon which the applicant.....
~~are~~
~~is~~ entitled to make the application are as follows :-

The actual inventors assigned the invention
to the said applicant.

State manner in which appli-
cant(s) derive title from inven-
tor(s)

Cross out paragraphs 3 and 4
for non-convention applications.
For convention applications
insert basic country(s) followed
by date(s) and basic applicant(s).

3. The basic application....S..... as defined by Section 141 of the Act ~~XXXX~~ were made
in UNITED KINGDOM on the 21st November 1986.....
by FUJISAWA PHARMACEUTICAL CO., LTD.
in UNITED KINGDOM on the 22nd June 1987.....
by FUJISAWA PHARMACEUTICAL CO., LTD.
in UNITED KINGDOM on the 2nd September 1987.....
by FUJISAWA PHARMACEUTICAL CO., LTD.

4. The basic application....S.... referred to in paragraph 3 of this Declaration ~~XX~~ were
the first application....S.... made in a Convention country in respect of the invention the subject
of the application.

Insert place and date of signature.

Declared at Osaka this 28th day of October 1987

Signature of Declarant(s) (no
attestation required).

Tomokichiro Fujisawa
Tomokichiro Fujisawa, President

Note: Initial all alterations.

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- (4) No. 9-6-307, Inarimae, Yatabemachi, Tsukuba-gun, Ibaraki
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(12) PATENT ABRIDGMENT (11) Document No. AU-B-81465/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 603842

(54) Title
NEW BENZOTHIADIAZINE COMPOUNDS, PROCESSES FOR THE PREPARATION
THEREOF AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

International Patent Classification(s)
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C07D 417/12

(21) Application No. : 81465/87 (22) Application Date : 20.11.87

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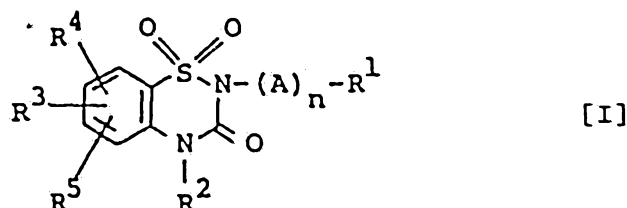
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(56) Prior Art Documents
AU 63589/86 C07D 285/24
DE 1067028
CH 460032

(57) Claim
1. A compound of the formula:



wherein R¹ is phenyl which may be substituted with
halogen, lower alkyl, lower alkoxy,
halo(lower)alkyl, lower alkylamino,
lower alkylthio, aryloxy, carboxy,
lower alkoxy-carbonyl, carboxy(lower)-
alkyl or lower alkoxy-carbonyl(lower)-
alkyl;
cyclo(lower)alkyl;
lower alkyl which may be substituted

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(10) 603842

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with carboxy or lower alkoxycarbonyl
pyrimidinyl; or pyridyl which may be
substituted with lower alkyl;

A is lower alkylene,

n is an integer of 0 or 1,

R² is lower alkyl,

R³ is hydrogen; hydroxy; halogen; halo-
(lower)alkyl; lower alkyl; lower
alkylamino; lower alkanoyl; lower
alkanoyl(lower)alkylamino; lower
alkoxy which may be substituted with
aryl, phthalimido, pyranyl, amino,
carboxy, lower alkoxycarbonyl or
cyclo(lower)alkyl which may be
substituted with amino(lower)alkyl or
lower alkoxycarbonylamino(lower)-
alkyl; or cyclo(lower)alkyloxy which
may be substituted with carboxy or
lower alkoxycarbonyl;

R⁴ is hydrogen or halogen, and

R⁵ is hydrogen or halogen,

provided that

R¹ is phenyl substituted with lower alkoxy,
lower alkylamino, lower alkylthio,
aryloxy, carboxy, lower
alkoxycarbonyl, carboxy(lower)alkyl
or lower alkoxycarbonyl(lower)alkyl;
lower alkyl substituted with carboxy
or lower alkoxycarbonyl; pyrimidinyl;
or pyridyl substituted with lower
alkyl,

when R³ is hydrogen or halogen,
and pharmaceutically acceptable salt thereof.

8. A method for the treatment of bone diseases in human being or animals by administering to a human being or animal in need of such treatment a therapeutically effective amount of a compound of claim 1.

603842

COMMONWEALTH OF AUSTRALIA

PATENT ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

CLASS

INT. CLASS

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority:

Related Art:

This document contains the
amendments made under
Section 49 and is correct for
printing

NAME OF APPLICANT: FUJISAWA PHARMACEUTICAL CO., LTD.

ADDRESS OF APPLICANT: No. 3, 4-chome, Doshomachi, Higashi-ku,
Osaka-shi, Osaka 541,
Japan.

NAME(S) OF INVENTOR(S) Teruo OKU Katsuya NAKAMURA
EISHIRO TODO Hiroshi KAYAKIRI
Chiyoshi KASAHARA Masashi HASHIMOTO

ADDRESS FOR SERVICE: DAVIES & COLLISON, Patent Attorneys
1 Little Collins Street, Melbourne, 3000.

COMPLETE SPECIFICATION FOR THE INVENTION ENTITLED:

"New benzothiadiazine compounds, processes for the preparation
thereof and pharmaceutical composition comprising the same"

The following statement is a full description of this invention,
including the best method of performing it known to us :-

NEW BENZOTHIADIAZINE COMPOUNDS, PROCESSES
FOR THE PREPARATION THEREOF AND PHARMA-
CEUTICAL COMPOSITION COMPRISING THE SAME

This invention relates to new benzothiadiazine compounds and pharmaceutically acceptable salts thereof.

More particularly, it relates to new benzothiadiazine compounds and pharmaceutically acceptable salts thereof which have, for example, inhibitory activities on bone resorption, to processes for the preparation thereof, to a pharmaceutical composition comprising the same and to a method for the treatment of bone diseases characterized by abnormal bone metabolism in human being or animals.

10 One object of this invention is to provide new and useful benzothiadiazine compounds and pharmaceutically acceptable salts thereof which possess, for example, inhibitory activities on bone resorption.

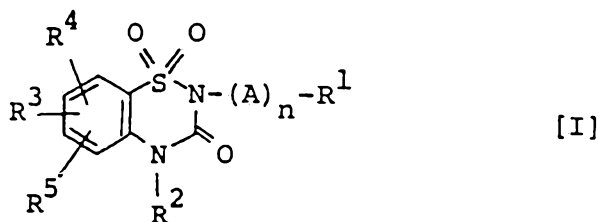
15 Another object of this invention is to provide processes for the preparation of said benzothiadiazine compounds or salts thereof.

A further object of this invention is to provide a

pharmaceutical composition comprising, as an active ingredient, said benzothiadiazine compounds and pharmaceutically acceptable salts thereof.

Still further object of this invention is to provide a therapeutical method for the treatment of bone diseases characterized by abnormal bone metabolism such as osteoporosis, Paget's bone disease, osteolysis, hypercalcemia of malignancy and rheumatoid arthritis.

The object benzothiadiazine compounds of this invention are new and can be represented by the following general formula [I] :



wherein R¹ is phenyl which may be substituted with halogen, lower alkyl, lower alkoxy, halo(lower)alkyl, lower alkylamino, lower alkylthio, aryloxy, carboxy, lower alkoxycarbonyl, carboxy(lower)-alkyl or lower alkoxycarbonyl(lower)-alkyl; cyclo(lower)alkyl; lower alkyl which may be substituted with carboxy or lower alkoxycarbonyl pyrimidinyl; or pyridyl which may be substituted with lower alkyl;

A is lower alkylene,

n is an integer of 0 or 1,

R² is lower alkyl,

R³ is hydrogen; hydroxy; halogen; halo-(lower)alkyl; lower alkyl; lower



alkylamino; lower alkanoyl; lower alkanoyl(lower)alkylamino; lower alkoxy which may be substituted with aryl, phthalimido, pyranyl, amino, carboxy, lower alkoxycarbonyl or cyclo(lower)alkyl which may be substituted with amino(lower)alkyl or lower alkoxycarbonylamino(lower)-alkyl; or cyclo(lower)alkyl oxy which may be substituted with carboxy or lower alkoxycarbonyl;

R^4 is hydrogen or halogen, and

R^5 is hydrogen or halogen,

provided that

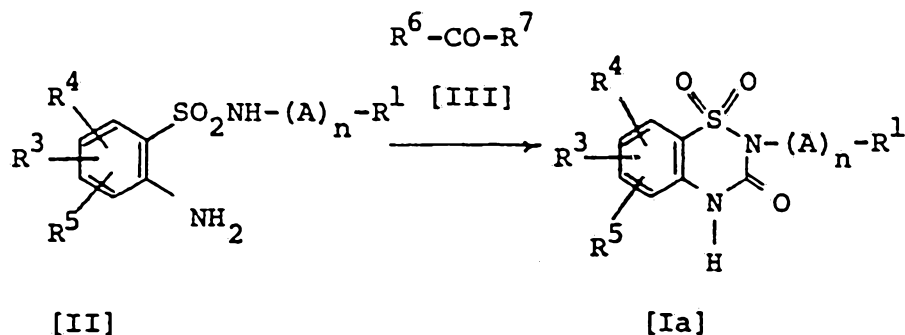
R^1 is phenyl substituted with lower alkoxy, lower alkylamino, lower alkylthio, aryloxy, carboxy, lower alkoxycarbonyl, carboxy(lower)alkyl or lower alkoxycarbonyl(lower)alkyl; lower alkyl substituted with carboxy or lower alkoxycarbonyl; pyrimidinyl; or pyridyl substituted with lower alkyl,

when R^3 is hydrogen or halogen,

and a pharmaceutically acceptable salt thereof.

The object compound [I] of the present invention can be prepared by the following processes.

Process 1

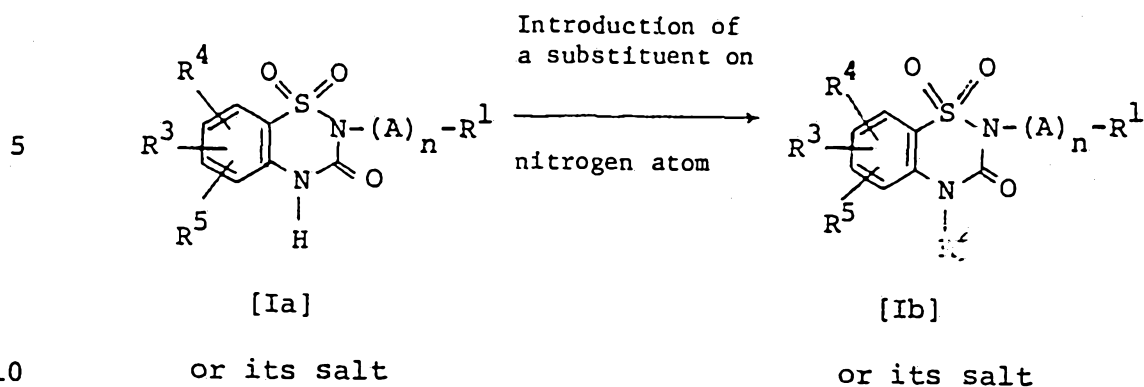


or its reactive derivative at the amino group or its salt

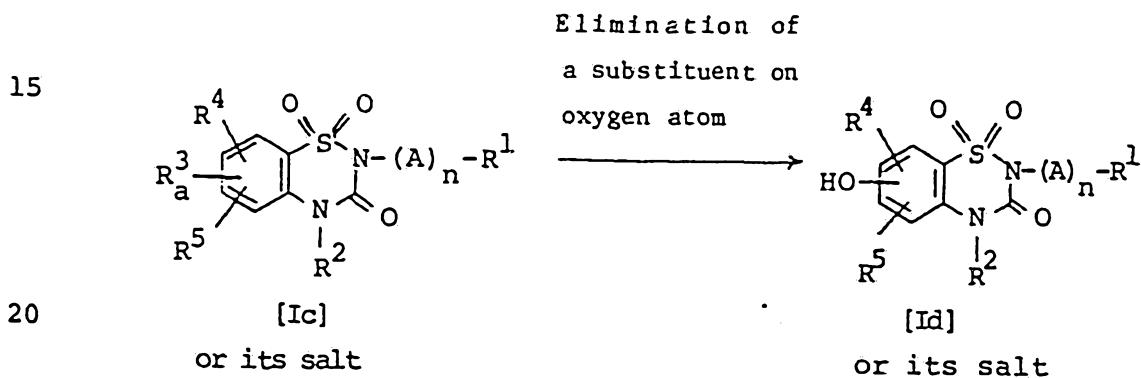
or its salt



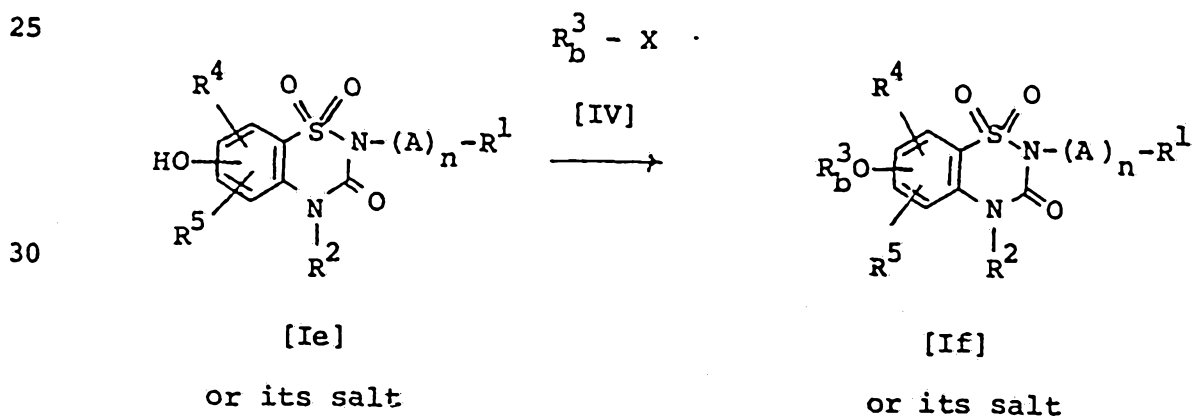
Process 2



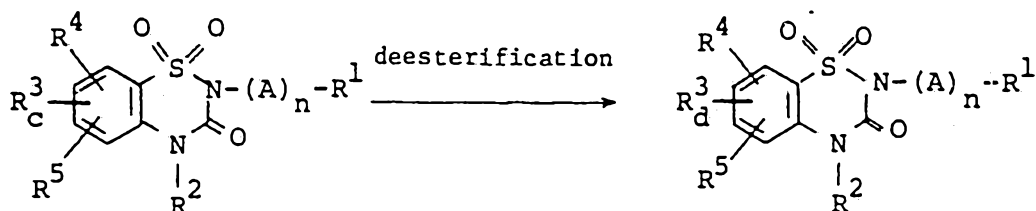
Process 3



Process 4



Process 5



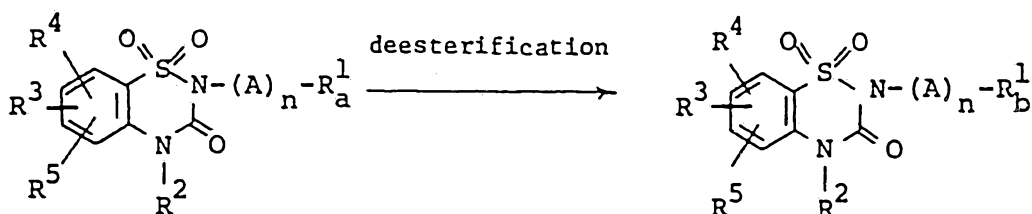
[Ig]

[Ih]

or its salt

or its salt

Process 6



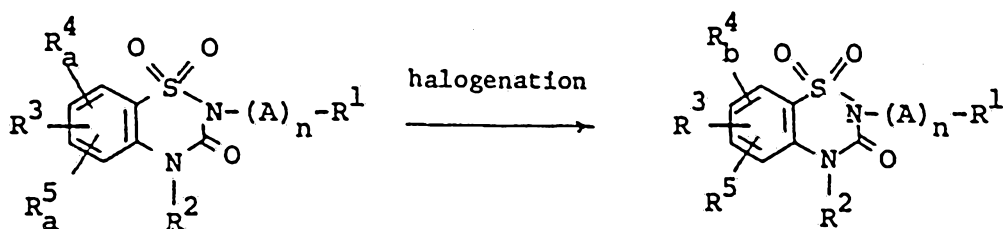
[Ii]

[Ij]

or its salt

or its salt

Process 7



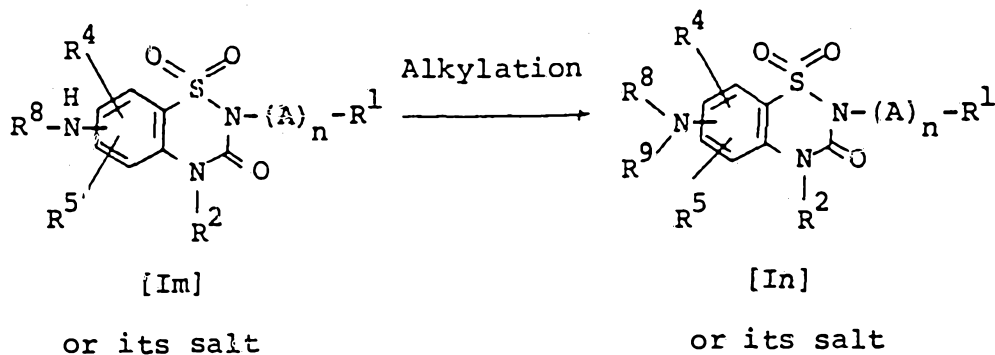
[Ik]

[Il]

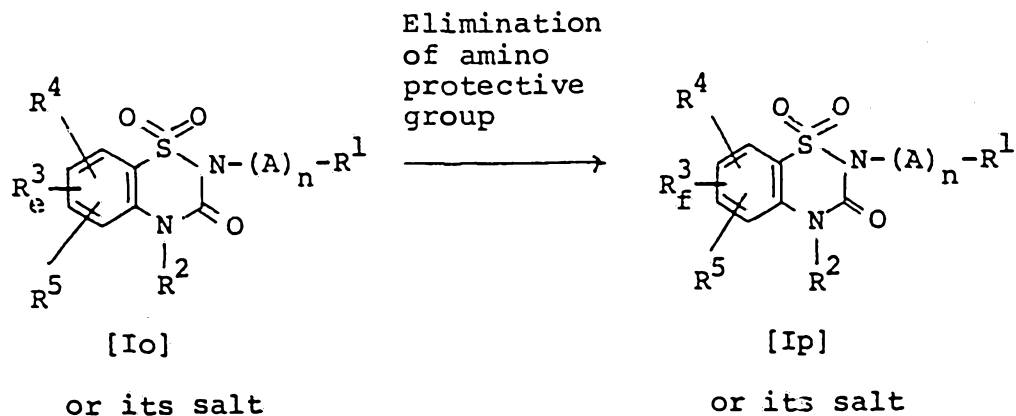
or its salt

or its salt

Process 8



Process 9



25

wherein R^1 , R^2 , R^3 , R^4 , R^5 , A and n are each as defined above,

30

R_a^1 is phenyl substituted with lower alkoxy-carbonyl(lower)alkyl or lower alkoxy-carbonyl; or lower alkoxy-carbonyl(lower)alkyl;

R_b^1 is phenyl substituted with carboxy-(lower)alkyl or carboxy; or carboxy(lower)alkyl;

35

R_a^3 is lower alkoxy which may be substituted with aryl, cyclo(lower)alkyl, carboxy or lower alkoxy carbonyl; or cyclo(lower)alkyloxy which may be substituted with carboxy or lower



alkoxycarbonyl;

5 R_b^3 is lower alkyl which may be substituted with aryl, phthalimido, pyranyl, carboxy, lower alkoxycarbonyl or cyclo(lower)alkyl which may be substituted with lower alkoxycarbonylamino(lower)alkyl; or cyclo(lower)alkyl which may be substituted with carboxy or lower alkoxycarbonyl;

10 R_c^3 is lower alkoxycarbonyl(lower)alkoxy which may be substituted with cyclo(lower)alkyl; or lower alkoxycarbonylcyclo(lower)alkyloxy;

15 R_d^3 is carboxy(lower)alkoxy which may be substituted with cyclo(lower)alkyl; or carboxycyclo(lower)alkyloxy;

20 R_e^3 is lower alkanoyl(lower)alkylamino or lower alkoxy substituted with phthalimido or cyclo(lower)alkyl substituted with lower alkoxycarbonyl amino(lower)alkyl,

R_f^3 is lower alkylamino or lower alkoxy substituted with amino or cyclo(lower)alkyl substituted with amino(lower)alkyl,

25 R_a^4 is hydrogen,

R_b^4 is halogen,

R_a^5 is hydrogen,

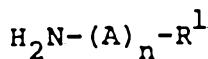
R^6 and R^7 are each halogen, lower alkoxy or imidazolyl,

R^8 and R^9 are each lower alkyl, and

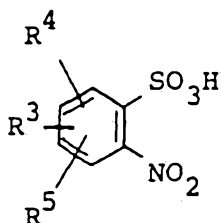
30 X is leaving group.

Among the starting compounds in the above processes, the compound [II] is novel and can be prepared by the processes as illustrated in the following.



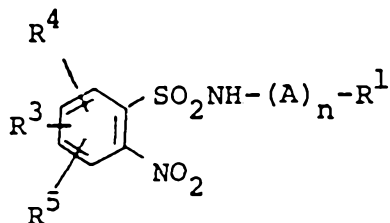


[VI]



or its reactive
derivative at the
amino group or
its salt

Process A



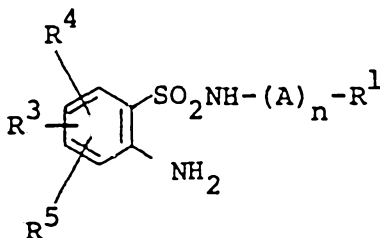
[VII]

[V]
or its reactive
derivative at the
sulfo group
or its salt

or its salt

15
reduction

Process B



[II]

or its salt

25 wherein R¹, R³, R⁴, R⁵, A and n are each as defined above.

30 In the above and subsequent description of the
present specification, suitable example and illustrations
for the various definitions to be included within the
scope of the invention are explained in detail as follows :

The term "lower" is intended to mean 1 to 6 carbon
atom(s) unless otherwise indicated.

35 The number of the substituent on phenyl for R¹
may be 1 to 3, preferably 1 or 2.



5 Suitable examples of the lower alkyl include a
straight or branched one such as methyl, ethyl, propyl,
isopropyl, butyl, isobutyl, tert-butyl, pentyl or hexyl.

10 Suitable examples of "lower alkyl" moiety in the
terms "halo(lower)alkyl", "lower alkylamino", "lower
alkylthio", "amino(lower)alkyl", "lower alkoxycarbonyl
amino(lower)alkyl", "lower alkanoyl(lower)alkylamino",
"carboxy(lower)alkyl" and "lower alkoxycarbonyl(lower)-
alkyl" can be referred to the ones as exemplified above.

15 Suitable examples of "halo(lower)alkyl" include
"monohalo(lower)alkyl" [e.g. chloromethyl, bromomethyl
fluoromethyl, etc.], "dihalo(lower)alkyl" [e.g.
dichloromethyl, dibromomethyl, difluoromethyl, etc.] and
20 "trihalo(lower)alkyl" [e.g. trichloromethyl,
tribromomethyl, trifluoromethyl, trifluoroethyl, etc.].

25 Suitable example of "lower alkylamino" include
"mono(lower)alkylamino" [e.g. methylamino, ethylamino,
isopropylamino, hexylamino, etc.] and
"di(lower)alkylamino" [e.g. dimethylamino, diethylamino,
dipropylamino, methylethylamino, etc.].

30 Suitable examples of the lower alkylene group
include a straight or branched one such as methylene,



ethylene, trimethylene, tetramethylene, pentamethylene,
5 hexamethylene, propylene, methylethylene, ethylethylene,
propylethylene, isopropylethylene or
methylpentamethylene.

Suitable examples of "halogen" include chlorine,
10 bromine, iodine and fluorine.

Suitable examples of "lower alkoxy" and "lower
alkoxy" moiety in the terms "carboxy(lower)alkoxy" and
"lower alkoxycarbonyl(lower)alkoxy" include methoxy,
15 ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy,
pentyloxy and hexyloxy.

Suitable examples of "aryl" include phenyl, tolyl,
xylyl, cumenyl and naphthyl.
20

Suitable examples of "aryloxy" include phenoxy
tolyloxy and naphthyloxy.

Suitable examples of "cyclo(lower)alkyl" include
25 cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Suitable example of "cyclo(lower)alkyl" moiety in
the terms "cyclo(lower)alkyloxy", "carboxycyclo(lower)-
alkyloxy" and "lower alkoxycarbonylcyclo(lower)alkyloxy"
30 can be referred to the ones as exemplified above.

Suitable examples of "lower alkanoyl" moiety in the
terms "lower alkanoylamino" and "lower alkanoyl(lower)-



alkylamino" include formyl, acetyl, propionyl, valeryl
5 and pivaloyl.

Suitable "leaving group" includes hydroxy and acid
residue, and suitable examples of "acid residue" may be
halogen (e.g. chlorine, bromine, iodine, or fluorine)
10 sulfonyloxy (e.g. methanesulfonyloxy, benzenesulfonyloxy,
toluenesulfonyloxy, etc.), in which the preferred example
is halogen.

Suitable "lower alkoxy carbonyl" moiety in the term
15 "lower alkoxy carbonyl amino(lower)alkyl" includes
methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl,
isopropoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl,
pentyloxycarbonyl, hexyloxycarbonyl, etc.

20 Suitable "lower alkoxy carbonyl" in the term "lower
alkoxy carbonyl(lower)alkyl", "lower alkoxy carbonyl-
(lower)alkoxy" and "lower alkoxy carbonylcyclo-
(lower)alkyloxy" includes methoxycarbonyl,
ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl,
25 butoxycarbonyl and tert-butoxycarbonyl, etc. in which
more preferred example is C₁-C₄ alkoxy carbonyl and the
most preferred one may be ethoxycarbonyl.

Suitable pharmaceutically acceptable salts of the
30 object compound [I] are conventional non-toxic salts and
include an organic acid salt [e.g. formate, acetate,
trifluoroacetate, maleate, tartrate, methanesulfonate,



benzenesulfonate, toluenesulfonate, etc.], an inorganic
5 acid salt [e.g. hydrochloride, hydrobromide, sulfate,
phosphate, etc.] a salt with an amino acid [e.g. arginine
salt, ornithine salt, etc.], a salt with base such as
alkali metal salt [e.g. sodium salt, potassium salt,
etc.] or an alkaline earth metal salt [e.g. calcium salt,
10 magnesium salt, etc.].

In this respect, it is to be noted that the
compounds [Ia] to [Ip] are included within the scope of
the compound [I], and accordingly the suitable salts of
15 these compounds [Ia] to [Ip] are to be referred to those
as exemplified for the object compounds [I] in the above.

It is also to be noted that the object compound [I]
and the starting compound [II] includes one or more
20 stereoisomers due to asymmetric carbon atom in the
molecule, and all of such isomers of the compound [I] are
included within the scope of this invention.

The processes for preparing the object compound [I]
25 or salts thereof are explained in detail in the
following.



Process 1

The object compound [Ia] or its salt can be prepared by reacting the compound [II] or its reactive derivative at the amino group or its salt with the compound [III].

Suitable reactive derivatives at the amino group of the compound [II] include conventional ones used in amidation, for example, Schiff's base type imino or its tautomeric enamine type isomer formed by reaction of the compound [II] with a carbonyl compound, a silyl derivative formed by reaction of the compound [II] with a silyl compound such as trimethylsilylacetamide, bis(trimethylsilyl)acetamide or the like, a derivative formed by reaction of the compound [II] with phosphorus trichloride or phosgene, and the like.

This reaction is usually carried out in a conventional



solvent such as tetrahydrofuran, dioxane, methylene chloride, chloroform, benzene, dimethylformamide, dimethyl sulfoxide or any other organic solvent which does not adversely influence the reaction.

5 The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

Process 2

10 The compound [Ib] or its salt can be prepared by subjecting the compound [Ia] or its salt to introduction reaction of a substituent on nitrogen atom.

15 The present introduction reaction can be carried out by reacting the compound [Ia] or its salt with a compound of the formula : $R_a^2 - X$ wherein R_a^2 and X are each as defined above.

20 The present introduction reaction can also be carried out by reacting the compound [Ia] or its salt with di(lower)alkyl sulfate [e.g. dimethyl sulfate, diethyl sulfate, etc.], diazo(lower)alkane [e.g. diazomethane, diazoethane, etc.], and the like.

25 The reaction using di(lower)alkyl sulfate or a compound of the formula : $R_a^2 - X$ is usually carried out in a solvent such as water, acetone, ethanol, ether, N,N-dimethylformamide or any other solvent which does not adversely influence the reaction. The present reaction is preferably carried out in the presence of a base such as an inorganic base or an organic base.

30 Suitable organic or inorganic base may be alkali metal hydride [e.g. sodium hydride, potassium hydride, etc.], alkaline earth metal hydride [e.g. calcium hydride, magnesium hydride, etc.], alkali metal hydroxide [e.g. sodium hydroxide, potassium hydroxide, etc.], alkali metal carbonate [e.g. sodium carbonate, potassium carbonate, etc.], alkali metal bicarbonate
35 [e.g. sodium bicarbonate, potassium bicarbonate, etc.],

alkali metal fluoride [e.g. potassium fluoride, cesium fluoride, etc.], alkali metal alkoxide [e.g. sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.], trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4,3,0]non-5-ene, 1,4-diazabicyclo[2,2,2]octane, 1,5-diazabicyclo[5,4,0]-undecene-5 or the like.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction using diazoalkane is usually carried out in a solvent such as ether, tetrahydrofuran or the like. The reaction temperature is not critical and the reaction is usually carried out under cooling or at ambient temperature.

Process 3

The object compound [Id] or its salt can be prepared by subjecting the compound [Ic] or its salt to elimination reaction of a substituent on oxygen atom.

The reaction is preferably carried out in the presence of a Lewis acid, for example, boron halide (e.g. boron trichloride, boron tribromide, etc.), hydrohalogenic acid (e.g. hydrobromic acid, hydroiodic acid etc.) and the like.

The reaction is usually carried out without a solvent or in a solvent which does not adversely influence the reaction such as chloroform, methylene chloride, carbon tetrachloride or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Process 4

The object compound [If] or its salt can be prepared by reacting the compound [Ie] or its salt with the compound [IV].

The present reaction is preferably carried out in the presence of a base such as an inorganic base or an organic base as explained in Process 2.

This reaction is usually carried out in a conventional solvent such as water, methanol, ethanol, propanol, tetralin, tetrahydrofuran, dioxane, chloroform, toluene, N,N-dimethylformamide, dimethylsulfoxide or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction is usually carried out under cooling, at ambient temperature or under heating.

Process 5

The object compound [Ih] or its salt can be prepared by subjecting the compound [Ig] or its salt to deesterification reaction.

The deesterification reaction can be carried out by conventional hydrolysis, reduction and the like.

The hydrolysis reaction can be carried out in the presence of a base or an acid, and suitable base may be the inorganic base as explained in Process 2.

Suitable acid may be an organic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, etc.).

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, acetone, dichloromethane, methanol, ethanol, propanol, pyridine, N,N-dimethylformamide, tetrahydrofuran, etc., or a mixture thereof, and further in case that the base or acid to be used in this reaction is in liquid, it can also be used as a solvent.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to heating. In the present reaction, in case that R^1 is phenyl substituted with esterified carboxy or esterified carboxy(lower)alkyl; or esterified carboxy(lower)alkyl, it may be converted during the reaction to phenyl substituted with carboxy or carboxy(lower)alkyl; or carboxy(lower)alkyl, respectively. This case is also included within the scope of the present reaction.

Process 6

The object compound [Ij] or its salt can be prepared by subjecting the compound [Ii] or its salt to deesterification reaction.

This reaction may be carried out in substantially the same manner as Process 5, and therefore the reaction mode [e.g. hydrolysis, reduction, etc.] and reaction conditions [e.g. reducing agent, base, acid, solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 5.

In the present reaction, in case that R^3 is lower alkoxy substituted with esterified carboxy or cyclo(lower)-alkyloxy substituted with esterified carboxy, it may be converted during the reaction to lower alkoxy substituted with carboxy or cyclo(lower)alkyloxy substituted with carboxy, respectively. This case is also included within the scope of the present reaction.

Process 7

The object compound [Il] or its salt can be prepared by halogenating the compound [Ik] or its salt.

Suitable halogenating agent of this reaction may include conventional ones for example, halogen [e.g. chlorine, bromine, iodine, etc.], sulfuryl halide [e.g. sulfuryl chloride, sulfuryl bromide, etc.],

N-halosuccinimide [e.g. N-chlorosuccinimide, N-bromosuccinimide, etc.], pyridinium hydrohalide perhalide [e.g. pyridinium hydrobromide perbromide, pyridinium hydrochloride perchloride, etc.], quarternary ammonium perhalide [e.g. phenyltrimethylammonium perbromide, etc.], ω -trihaloacetophenone [e.g. ω -tribromoacetophenone, etc.], cupric or potassium bromide, selenium oxychloride, or the like. These halogenating agents may be selected according to the kind of the starting compound [Ik] to be used.

This reaction is usually carried out in a conventional solvent such as chloroform, methylene chloride, carbon tetrachloride, acetic acid, a mixture of hydrogen halide [e.g. hydrogen bromide, hydrogen chloride, etc.] and acetic acid, water, dimethylformamide or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling, at ambient temperature or under warming or heating.

Process 8

The compound [In] or its salt can be prepared by subjecting the compound [Im] or its salt to alkylation reaction.

The alkylating agent to be used in the present alkylation reaction may include di(lower)alkyl sulfate [e.g. dimethyl sulfate, diethyl sulfate, etc.], diazo(lower)alkane [e.g. diazomethane, diazoethane, etc.], lower alkyl halide [e.g. methyl iodide, ethyl iodide, etc.], lower alkyl sulfonate [e.g. methyl p-toluenesulfonate, etc.], and the like.

The reaction using di(lower)alkyl sulfate, lower alkyl halide or lower alkyl sulfonate is usually carried out in a solvent such as water, acetone, ethanol, ether, tetrahydrofuran, dimethylformamide or any other solvent which does not adversely influence the reaction.

The present reaction is preferably carried out in the presence of a base such as an inorganic base or an organic base as mentioned for Process 2. The reaction temperature is not critical and the reaction is usually carried out under cooling to heating around boiling point of the solvent.

The reaction using diazoalkane is usually carried out in a solvent such as ether, tetrahydrofuran or the like. The reaction temperature is not critical and the reaction is usually carried out under cooling or at ambient temperature. The compound [In] or its salt can also be prepared by reacting the compound [Im] or its salt with alkane aldehyde in the presence of reducing agent. Suitable alkane aldehyde may include formaldehyde, acetaldehyde, propionaldehyde and the like. Suitable reducing agent can be referred to the ones as mentioned for Process B. This reaction is usually carried out in a conventional solvent such as water, methanol, ethanol, propanol, tetralin, tetrahydrofuran, acetonitrile, dioxane, chloroform, toluene, dimethylformamide, dimethylsulfoxide or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature or under cooling or warming.

Process 9 :

The object compound [Ip] or its salt thereof can be prepared by subjecting the compound [Io] or its salt to elimination reaction of amino protective group.

The present elimination reaction is carried out in accordance with a conventional method such as hydrolysis; reduction; a method by reacting the compound [Io] wherein the protective group is acyl group with iminohalogenating agent and then with iminoetherifying agent, and,

if necessary, subjecting the resulting compound to hydrolysis; or the like. The hydrolysis may include a method using an acid or base or hydrazine and the like. These methods may be selected depending on the kind of the protective groups to be eliminated.

Among these methods, hydrolysis using an acid is one of the common and preferable method for eliminating the protective group such as substituted or unsubstituted alkoxy-carbonyl (e.g. t-pentyloxy-carbonyl, t-butoxy-carbonyl, etc.), alkanoyl (e.g. formyl, acetyl, etc.), cycloalkoxy-carbonyl, substituted or unsubstituted aralkoxy-carbonyl (e.g. benzyloxy-carbonyl, substituted benzyloxy-carbonyl, etc.), ar(lower)alkyl (e.g. benzyl, trityl, etc.) or the like.

Suitable acid may include an organic or an inorganic acid, for example, formic acid, trifluoroacetic acid, benzenesulfonic acid, p-toluenesulfonic acid, hydrochloric acid and the like, and preferable acid is, for example, formic acid, trifluoroacetic acid, hydrochloric acid, etc. The acid suitable for the reaction can be selected according to the kind of protective group to be eliminated. When the elimination reaction is conducted with the acid, it can be carried out in the presence or absence of a solvent. Suitable solvent may include a conventional organic solvent (e.g., methanol, ethanol, tetrahydrofuran, etc.), water or a mixture thereof. When trifluoroacetic acid is used, the elimination reaction may preferably be carried out in the presence of anisole.

The hydrolysis using hydrazine is commonly applied for eliminating the protective group, for example, succinyl or phthaloyl.

The hydrolysis with a base is preferably applied for eliminating acyl group, for example, haloalkanoyl (e.g. dichloroacetyl, trifluoroacetyl, etc.) etc.

Suitable base may include, for example, an inorganic base and an organic base as exemplified above for Process 2. The hydrolysis using a base is often carried out in water, a conventional organic solvent or a mixture thereof.

Among the protective group, the acyl group can be generally eliminated by hydrolysis as mentioned above or by the other conventional hydrolysis. In case that the acyl group is halogen substituted-alkoxycarbonyl or 8-quinolyloxycarbonyl, they are eliminated by treating with a heavy metal such as copper, zinc or the like.

The reductive elimination is generally applied for eliminating the protective group, for example, haloalkoxycarbonyl (e.g. trichloroethoxycarbonyl, etc.), substituted or unsubstituted aralkoxycarbonyl (e.g. benzyloxycarbonyl, substituted benzyloxycarbonyl etc.), 2-pyridylmethoxycarbonyl, etc. Suitable reduction may include, for example, reduction with an alkali metal borohydride (e.g. sodium borohydride, etc.) and the like.

The reaction temperature is not critical and may be suitably selected in accordance with the kind of the protective group of the amino group and the elimination method as mentioned above, and the present reaction is preferably carried out under a mild condition such as under cooling, at ambient temperature or slightly elevated temperature.

The processes for preparing the starting compound [II] or its salt are explained in detail in the following.

Process A

The compound [VII] or its salt can be prepared by reacting the compound [V] or its reactive derivative at the sulfo group or its salt with the compound [VI]

or its reactive derivative at the amino group or its salt.

Suitable example of the reactive derivative at the sulfo group may include conventional ones such as acid halide (e.g. acid chloride, acid bromide, etc.) acid anhydride, activated ester or amide, and the like.

Suitable example of the reactive derivative at the amino group can be referred to the ones as mentioned above for Process 1.

The reaction can preferably be conducted in the presence of an organic or inorganic base as explained in Process 2.

The reaction is usually carried out in a solvent. A suitable solvent to be used may be water, alcohol [e.g. methanol, ethanol, propanol, etc.], acetonitrile or any other conventional organic solvent such as diethyl ether, dioxane, tetrahydrofuran, etc. or a mixture thereof. Additionally, the aforementioned liquid bases can also be used as a solvent.

The reaction is preferably carried out under cooling to heating.

Process B

The compound [II] or its salt can be prepared by reducing the compound [VII] or its salt.

The reaction may include chemical reduction and catalytic reduction, which are carried out in a conventional manner.

Suitable reducing agents to be used in chemical reduction are a metal [e.g. tin, zinc, iron, etc.], a combination of such metal and/or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid,

propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.], a combination of such metal and/or metallic compound and base [e.g. ammonia, ammonium chloride, sodium hydroxide, etc.], a metal hydride compound such as aluminum hydride compound [e.g. lithium aluminum hydride, sodium aluminum hydride, aluminum hydride, lithium trimethoxyaluminum hydride, lithium tri-t-butoxyaluminum hydride, etc.], borohydride compound [e.g. sodium borohydride, lithium borohydride, sodium cyanoborohydride, tetramethylammonium borohydride, borane, diborane, etc.], a phosphorus compound [e.g. phosphorus trichloride, phosphorus tribromide, triphenylphosphine, triethylphosphine, etc.] and the like.

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalyst [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalyst [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalyst [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalyst [e.g. reduced cobalt, Raney cobalt, etc.], iron catalyst [e.g. reduced iron, Raney iron, etc.], copper catalyst [e.g. reduced copper, Raney copper, Ullman copper, etc.], or the like.

The reduction is usually carried out in a solvent. A suitable solvent to be used may be water, alcohol [e.g. methanol, ethanol, propanol, etc.], acetonitrile or any other conventional organic solvent such as diethyl ether, dioxane, tetrahydrofuran, etc. or a mixture thereof.

The reaction is preferably carried out under warming to heating.

The compounds thus obtained by Processes 1 to 9 and Processes A and B may be converted into aforesaid pharmaceutically acceptable salts thereof according to a conventional manner.

5 The object compound [I] and pharmaceutically acceptable salts thereof possess, for example, strong inhibitory activities on bone resorption, and useful for therapeutical treatment of bone diseases characterized by abnormal bone metabolism such as osteoporosis,
10 Paget's bone disease, osteolysis, hypercalcemia of malignancy and rheumatoid arthritis.

 For therapeutic purpose, the compounds [I] and pharmaceutically acceptable salts thereof of the present invention can be used in a form of pharmaceutical
15 preparation containing one of said compounds, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral
20 or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, solution, suspension, emulsion, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

 While the dosage of the compounds [I] will vary depending upon the age and condition of the patient,
25 an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound [I] may be effective for treating said bone diseases.
30 In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

 In order to illustrate the usefulness of the object compound [I], the pharmacological test data of same representative compounds of the compound [I] are
35 shown in the following.

Test method :

Neonatal calvaria were dissected aseptically from 1-2 day old rat (Wistar), washed in Dulbecco's modified eagle's medium and divided along the sagittal suture. The calvaria halves were pooled and randomized in the different groups. The calvaria halves were cultured separately as free-floating bones in multi-well dishes containing a 2 ml of Dubecco's modified eagle's medium, with 10% heat-inactivated (56°C for 1 hr) fetal calf serum. Treatment of hPTH(1-34) ($1 \times 10^{-8} \text{M}$) and the Test Compound ($1 \times 10^{-5} \text{M}$) was begun at zero time. All incubations were performed at 37°C, under an atmosphere of 95% air and 5% CO₂ for 6 days. Bone resorption was determined by measuring the accumulation of calcium in the medium at 6 days. The concentration of total calcium in culture medium was measured by OCPC method with a spectrophotometer (Hitachi model U-3200, Tokyo, Japan).

As comparative data, similar tests were conducted using culture medium with hPTH ($1 \times 10^{-8} \text{M}$) only, and culture medium without both hPTH and Test Compound.

Test results were represented in terms of percentage of inhibition calculated by the following formula :

$$\text{Inhibition (\%)} = \frac{C_P - C_D}{C_P - C_0} \times 100$$

C_D: the concentration of total calcium in culture medium treated with both hPTH and Test Compound

C₀: the concentration of total calcium in control culture medium without both hPTH and Test Compound

C_P: the concentration of total calcium in culture medium treated with hPTH only

Test Compounds :

- (a) 2-(4-Chlorophenyl)-6-isopropoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (Example 4 and Example 6-(22))
- 5 (b) 2-(4-Chlorophenyl)-4-methyl-6-(2-methylpropoxy)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (Example 6-(24) and Example 10)
- (c) 2-(4-Chlorophenyl)-4-methyl-6-cyclohexylmethoxy-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
- 10 (Example 6-(25) and Example 11)
- (d) 2-(4-Trifluoromethylphenyl)-4-methyl-6-isopropoxy-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (Example 6-(23) and Example 9)
- (e) 2-(4-Chlorophenyl)-6-(1-carboxyethoxy)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
- 15 (R,S mixture) (Example 6-(29), Example 14, Example 15-(5))
- (f) (1R)-(+)-2-(4-Chlorophenyl)-6-(1-carboxyethoxy)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one
- 20 1,1-dioxide (Example 6-(44), Example 15-(12), Example 16-(5))

Test Results :

Test Compound	Inhibition (%)
(a)	79.7
(b)	56.1
(c)	62.5
(d)	52.9
(e)	67.9
(f)	50.2

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

5 Preparation 1

10 To a mixture of 4-chloroaniline (14.51 g) and 4-methoxy-2-nitrobenzenesulfonyl chloride (28.54 g) was added dropwise aqueous sodium hydroxide solution (0.7 N, 162 ml) over a period of 30 minutes at 70°C. After addition, the mixture was stirred for 30 minutes at the same temperature. The cooled mixture was diluted with aqueous 1N-hydrochloric acid. The separated oil was extracted with ethyl acetate. The extract was dried over magnesium sulfate and concentrated under reduced pressure. The yellow solid was triturated with n-hexane and collected by filtration to yield 4-methoxy-2-nitro-N-(4-chlorophenyl)benzenesulfonamide (37.23 g).

15 mp : 56-60°C

20 IR (CHCl₃) : 1600, 1540, 1490, 1170 cm⁻¹

25 NMR (CDCl₃, δ) : 3.92 (3H, s), 6.90-7.80 (7H, m),
7.70 (1H, d, J=9Hz)

30 Preparation 2

35 To a mixture of 4-methoxy-2-nitro-N-(4-chlorophenyl)-benzenesulfonamide (37.2 g) and ammonium chloride (75.4 g) in a mixture of methanol (400 ml) and water

(continued to the next page)

(400 ml) was added iron (76.4 g) in small portions over a period of one and half hours at 100°C. The reaction mixture was refluxed for 8 hours and the hot mixture was filtrated. The filtrated cake was washed with hot methanol. The combined filtrates were evaporated under reduced pressure and the residue was extracted three times with ethyl acetate. The extracts were washed with water, dried, and concentrated to give crude product, which was purified by silica gel column-chromatography (elution by methylene chloride) to yield 2-amino-4-methoxy-N-(4-chlorophenyl)benzenesulfonamide (25.77 g).

mp : 94-96°C

IR (Nujol) : 3400, 3300, 1600, 1580, 1500 cm^{-1}

NMR (CDCl_3 , δ) : 3.76 (3H, s), 4.90 (2H, br s), 6.20-6.30 (2H, m), 6.90-7.50 (6H, m)

Preparation 3

In a similar manner to that of Preparation 1, there were obtained the following compounds.

(1) 4-Methoxy-2-nitro-N-(p-tolyl)benzenesulfonamide

mp : 100-101°C

IR (Nujol) : 3320, 1600, 1540, 1390, 1240, 1150 cm^{-1}

NMR (CDCl_3 , δ) : 2.28 (3H, s), 3.90 (3H, s), 6.90-7.40 (6H, m), 7.70 (1H, d, J=9Hz)

(2) 4-Methoxy-2-nitro-N-(phenyl)benzenesulfonamide

mp : 126-128°C

IR (Nujol) : 3400, 3300, 1600, 1540, 1460, 1170 cm^{-1}

NMR (CDCl_3 , δ) : 3.90 (3H, s), 6.96 (1H, dd, J=2Hz and 9Hz), 7.10-7.40 (5H, m), 7.72 (1H, d, J=9Hz)

- (3) 4-Methoxy-2-nitro-N-(4-trifluoromethylphenyl)-benzenesulfonamide

mp : 108-110°C

IR (Nujol) : 1600, 1540, 1460, 1330, 1170, 1120 cm^{-1}

NMR (CDCl_3 , δ) : 3.90 (3H, s), 7.02 (1H, dd, $J=2\text{Hz}$ and 9Hz), 7.20-7.70 (5H, m), 7.83 (1H, d, $J=9\text{Hz}$)

- (4) 4-Methoxy-2-nitro-N-(3,4-dichlorophenyl)benzenesulfonamide

mp : 146-150°C

IR (Nujol) : 3300, 1610, 1550, 1470, 1380 cm^{-1}

NMR (CDCl_3 , δ) : 3.90 (3H, s), 6.90-7.40 (5H, m), 7.30 (1H, d, $J=9\text{Hz}$)

- (5) 4-Methoxy-2-nitro-N-(4-fluorophenyl)benzenesulfonamide

mp : 98-100°C

IR (Nujol) : 3350, 1600, 1530, 1380, 1240, 1170 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 3.85 (3H, s), 7.00-7.20 (4H, m), 7.30 (1H, dd, $J=2\text{Hz}$ and 9Hz), 7.55 (1H, d, $J=2\text{Hz}$), 7.82 (1H, d, $J=9\text{Hz}$), 10.5 (1H, br s)

- (6) 4-Isopropoxy-2-nitro-N-(4-methoxyphenyl)benzenesulfonamide

IR (CHCl_3) : 1600, 1540, 1510, 1390, 1240, 1160 cm^{-1}

NMR (CDCl_3 , δ) : 1.37 (6H, d, $J=6\text{Hz}$), 3.77 (3H, s), 4.62 (1H, m), 6.78 (1H, d, $J=9\text{Hz}$), 6.90 (1H, dd, $J=2\text{Hz}$ and 9Hz), 7.00-7.30 (4H, m), 7.62 (1H, d, $J=9\text{Hz}$)

(7) 2-Nitro-N-(4-chlorophenyl)benzenesulfonamide

mp : 120-123°C

IR (Nujol) : 3300, 1600, 1550, 1490, 1460, 1340,
1170, 1160 cm^{-1}

NMR (CDCl_3 , δ) : 7.00-7.40 (4H, m), 7.50-7.95
(4H, m)

(8) 4-Chloro-2-nitro-N-(4-chlorophenyl)benzenesulfonamide

mp : 116-118°C

IR (Nujol) : 1540, 1490, 1460, 1360, 1240, 1180,
1170 cm^{-1}

NMR (CDCl_3 , δ) : 7.10-7.33 (4H, m), 7.55 (1H, dd,
J=2Hz and 9Hz), 7.75 (1H, d, J=9Hz),
7.83 (1H, d, J=2Hz)

(9) 4-Methoxy-2-nitro-N-(2-chlorophenyl)benzenesulfonamide

mp : 94-95°C

IR (Nujol) : 3350, 3300, 1600, 1540, 1480, 1460,
1180 cm^{-1}

NMR (CDCl_3 , δ) : 3.90 (3H, s), 6.90-7.40 (5H, m),
7.60-7.90 (2H, m)

(10) 4-Methoxy-2-nitro-N-(3-chlorophenyl)benzenesulfonamide

mp : 137-138°C

IR (Nujol) : 3300, 1610, 1590, 1550, 1330, 1170
 cm^{-1}

NMR (CDCl_3 , δ) : 3.82 (3H, s), 7.00 (1H, dd,
J=2Hz and 9Hz), 7.10-7.40 (5H, m), 7.89
(1H, d, J=9Hz)

(11) 4-Isopropoxy-2-nitro-N-(4-chlorophenyl)benzenesulfonamide

IR (CHCl_3) : 1600, 1540, 1490, 1390, 1170 cm^{-1}
NMR (CDCl_3 , δ) : 1.36 (6H, d, $J=6\text{Hz}$), 4.62 (1H, m), 6.92 (1H, dd, $J=2\text{Hz}$ and 9Hz), 7.0-7.5 (6H, m), 7.69 (1H, d, $J=9\text{Hz}$)

5

- (12) 4-Methoxy-2-nitro-N-(4-chlorobenzyl)benzenesulfonamide
mp: 110.5-111.5°C

IR (Nujol) : 3320, 1610, 1530, 1165 cm^{-1}

NMR (CDCl_3 , δ) : 3.93 (3H, s), 4.25 (2H, s),
5.65 (1H, br.s), 7.05 (1H, d d, $J=2.5$ and 8.8Hz),
7.18 and 7.20 (4H, ABq, $J=8.8\text{Hz}$),
7.30 (1H, d, $J=2.5\text{Hz}$), 7.88 (1H, d, $J=8.8\text{Hz}$)

10

- (13) 4-Methoxy-2-nitro-N-cyclohexylbenzenesulfonamide
mp: 91-93°C

IR (Nujol) : 3320, 1605, 1540, 1330, 1155, 1050 cm^{-1}

NMR (CDCl_3 , δ) : 1.05-1.4 (5H, m), 1.45-1.9 (5H, m),
3.27 (1H, br), 3.94 (3H, s), 5.13 (1H, d, $J=7.3\text{Hz}$),
7.16 (1H, d d, $J=2.5$ and 8.8Hz), 7.43 (1H, d, $J=2.5\text{Hz}$), 8.03 (1H, d, $J=8.8\text{Hz}$)

15

20

- (14) 4-Isopropoxy-2-nitro-N-(2-pyridyl)benzenesulfonamide
mp: 123-125°C

IR (Nujol) : 1635, 1620, 1605, 1240, 1150 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 1.25 (6H, d, $J=5.5\text{Hz}$),
4.65-4.85 (1H, m), 6.8-6.9 (1H, m),
7.10-7.17 (1H, m), 7.26 (1H, dd, $J=2\text{Hz}$ and 9Hz),
7.40 (1H, d, $J=2\text{Hz}$), 7.75-7.87 (1H, m),
7.9-7.98 (2H, m).

25

30

- (15) 4-Methoxy-2-nitro-N-(pentyl)benzenesulfonamide
mp: 48-50°C

IR (Nujol) : 3300, 1600, 1560, 1350, 1340, 1160 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 0.85 (3H, t, $J=7\text{Hz}$), 1.10-1.60 (6H, m), 3.05 (2H, q, $J=7\text{Hz}$), 3.94 (3H, s),

35

5.13 (1H, bs), 7.15 (1H, dd, J=3Hz and 9Hz),
7.35 (1H, d, J=3Hz), 8.04 (1H, d, J=9Hz)

(16) 4-Acetylamino-2-nitro-N-(4-chlorophenyl)-
benzenesulfonamide

5

mp: 207-209°C

IR (Nujol) : 3370, 3230, 1695, 1590, 1250, 1170,
1155 cm⁻¹

NMR (DMSO-d₆, δ) : 2.15 (3H, s), 7.15 and 7.35 (4H,
ABq, J=9.0Hz), 7.72-7.85 (1H, m),
7.85-8.0 (1H, m), 8.17 (1H, s), 10.7 (1H, s),
10.75 (1H, s)

10

(17) 4-Methoxy-2-nitro-N-(4-methoxycarbonylphenyl)-
benzenesulfonamide

15

mp: 170°C (dec.)

IR (Nujol) : 3250, 1690, 1605, 1545, 1295 cm⁻¹

NMR (DMSO-d₆, δ) : 3.79 (3H, s), 3.87 (3H, s),
7.25 and 7.90 (4H, ABq, J=8.5Hz), 7.33 (1H,
dd, J=2Hz and 9Hz), 7.60 (1H, d, J=2.0Hz),
7.96 (1H, d, J=9Hz), 11.11 (1H, s)

20

(18) 4-Cyclohexylmethoxy-2-nitro-N-(2-pyridyl)-
benzenesulfonamide

25

mp: 164°C (dec.)

IR (Nujol) : 3140, 1640, 1610, 1560, 1155 cm⁻¹

NMR (DMSO-d₆, δ) : 0.9-1.4 (5H, m), 1.5-1.9 (6H, m),
3.89 (2H, d, J=6Hz), 6.8-6.9 (1H, m),
7.1-7.2 (1H, m), 7.26 (1H, dd, J=2.4Hz and
8.8Hz), 7.43 (1H, d, J=2.4Hz), 7.75-7.90 (1H, m),
7.9-8.0 (1H, m), 7.95 (1H, d, J=8.8Hz).

30

(19) 4-Methoxy-2-nitro-N-(4-methoxycarbonylmethylphenyl)-
benzenesulfonamide

35

mp: 93-94°C

IR (Nujol) : 3330, 1715, 1545, 1160 cm^{-1}
NMR ($\text{DMSO}-d_6$, δ) : 3.33 (2H, s), 3.58 (3H, s),
3.86 (3H, s), 7.05 and 7.15 (4H, ABq,
J=8.3Hz), 7.32 (1H, d d, J=2.0 and 8.8Hz),
7.56 (1H, d, J=2.0Hz), 7.56 (1H, d, J=8.8Hz),
10.52 (1H, s)

(20) 4-Methoxy-2-nitro-N-(3-ethoxycarbonylpropyl)-
benzenesulfonamide

mp: 55-56°C

IR (Nujol) : 3350, 1720, 1610, 1550, 1470,
1380, 1280, 1170 cm^{-1}

NMR (CDCl_3 , δ) : 1.25 (3H, t, J=7Hz), 1.86 (2H, m),
2.39 (2H, t, J=7Hz), 3.12 (2H, q, J=7Hz),
4.12 (2H, q, J=7Hz), 3.94 (3H, s), 5.33 (1H, bs),
7.15 (1H, dd, J=2Hz and 9Hz), 7.33 (1H, d,
J=2Hz), 8.03 (1H, d, J=9Hz)

(21) 4-Methyl-2-nitro-N-(4-chlorophenyl)benzenesulfonamide

mp: 112-114°C

IR (Nujol) : 3350, 1600, 1550, 1490, 1430,
1380, 1360, 1340, 1170 cm^{-1}

NMR (CDCl_3 , δ) : 2.48 (3H, s), 7.14 (2H, d,
J=8Hz), 7.24 (2H, d, J=8Hz), 7.38 (1H, d,
J=8Hz), 7.67 (1H, s), 7.70 (1H, d, J=8Hz)

(22) 4-Isopropoxy-2-nitro-N-[2-(4,6-dimethylpyridyl)]-
benzenesulfonamide

mp: 175-180°C

IR (Nujol) : 1620, 1540, 1390, 1300, 1230, 1150 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 1.30 (6H, d, J=6Hz), 2.20
(3H, s), 2.30 (3H, s), 4.80 (1H, m),
6.50 (1H, s), 6.82 (1H, s), 7.22 (1H, dd,
J=2Hz and 9Hz), 7.42 (1H, d, J=2Hz),
7.92 (1H, d, J=9Hz)

(23) 4-Trifluoromethyl-2-nitro-N-(4-chlorophenyl)-
benzenesulfonamide

mp: 88-90°C

IR (Nujol) : 3300, 1550, 1490, 1400, 1320,
1160, 1140, 1080 cm^{-1}

NMR (CDCl_3 , δ) : 7.14 (2H, d, $J=9\text{Hz}$), 7.26 (2H,
d, $J=9\text{Hz}$), 7.86 (1H, d, $J=9\text{Hz}$),
7.98 (1H, d, $J=9\text{Hz}$), 8.11 (1H, s).

(24) 4-Isopropoxy-2-nitro-N-(2-pyrimidinyl)-
benzenesulfonamide

mp: 218-220°C

IR (Nujol) : 1610, 1580, 1440, 1380, 1350,
1240, 1110 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 1.30 (6H, d, $J=6\text{Hz}$), 4.80 (1H, m),
7.05 (1H, t, $J=4\text{Hz}$), 7.30 (1H, dd, $J=2\text{Hz}$ and
9Hz), 7.48 (1H, d, $J=2\text{Hz}$), 8.10 (1H, d, $J=9\text{Hz}$),
8.50 (2H, d, $J=4\text{Hz}$)

(25) 4-Methoxy-2-nitro-N-(4-phenoxyphenyl)-
benzenesulfonamide

mp: 130-132°C

IR (Nujol) : 3330, 1600, 1540, 1240, 1170 cm^{-1}

NMR (CDCl_3 , δ) : 3.90 (3H, s), 6.85-7.40 (11H, m),
7.70 (1H, d, $J=9\text{Hz}$)

(26) 4-Methoxy-2-nitro-N-(4-isopropylphenyl)-
benzenesulfonamide

mp: 108-109°C

IR (Nujol) : 3300, 1605, 1545, 1165 cm^{-1}

NMR (CDCl_3 , δ) : 1.20 (6H, d, $J=7\text{Hz}$), 2.85 (1H, m),
3.90 (3H, s), 6.97 (1H, dd, $J=2\text{Hz}$ and 9Hz),
7.05-7.15 (4H, m), 7.32 (1H, d, $J=2\text{Hz}$),
7.72 (1H, d, $J=9\text{Hz}$).

(27) 4-Methoxy-2-nitro-N-[(3-chloro-4-methyl)phenyl]-benzenesulfonamide

mp: 138-139°C

IR (Nujol) : 3300, 1600, 1545, 1170 cm^{-1}

NMR (CDCl_3 , δ) : 2.38 (3H, s), 3.90 (3H, s),
7.00 (1H, dd, J=2Hz and 9Hz), 7.05-7.15
(2H, m), 7.22 (1H, d, J=2Hz), 7.33 (1H, d,
J=2Hz), 7.75 (1H, d, J=9Hz).

(28) 4-Methoxy-2-nitro-N-(4-methylthiophenyl)-benzenesulfonamide

mp: 120-121°C

IR (Nujol) : 3250, 3100, 1600, 1550, 1490,
1245, 1170 cm^{-1}

NMR (CDCl_3 , δ) : 2.44 (3H, s), 3.90 (3H, s),
6.97 (1H, dd, J=2Hz and 9Hz), 7.12 (4H, s),
7.31 (1H, d, J=2Hz), 7.70 (1H, d, J=9Hz)

(29) 4-Methoxy-2-nitro-N-(4-dimethylaminophenyl)-benzenesulfonamide

mp: 127-128°C

IR (Nujol) : 3350, 3340, 1600, 1540, 1520,
1350, 1280, 1230, 1160 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 2.82 (6H, s), 3.86 (3H, s),
6.60 (2H, d, J=9Hz), 6.91 (2H, d, J=9Hz),
7.28 (1H, dd, J=2Hz and 9Hz),
7.53 (1H, d, J=2Hz), 7.73 (1H, d, J=9Hz).

Preparation 4

In a similar manner to that of Preparation 2, there were obtained the following compounds.

- 5 (1) 2-Amino-4-methoxy-N-(P-tolyl)benzenesulfonamide
 IR (CHCl₃) : 3500, 3400, 1610, 1570, 1450,
 1150 cm⁻¹
 NMR (CDCl₃, δ) : 2.23 (3H, s), 3.75 (3H, s),
 4.90 (2H, br s), 6.18-6.25 (2H, m),
 10 6.85-7.10 (4H, m), 7.40 (1H, d, J=9Hz)

- (2) 2-Amino-4-methoxy-N-(phenyl)benzenesulfonamide
 mp : 112-114°C
 IR (Nujol) : 3500, 3400, 3200, 1630, 1610,
 1500, 1470 cm⁻¹
 NMR (CDCl₃, δ) : 3.75 (3H, s), 4.90 (2H, br s),
 6.10-6.30 (2H, m), 7.00-7.30 (5H, m),
 7.40 (1H, d, J=9Hz)

- 15 (3) 2-Amino-4-methoxy-N-(4-trifluoromethylphenyl)-
 benzenesulfonamide
 mp : 92-94°C
 IR (Nujol) : 3400, 3300, 1620, 1600, 1460, 1330,
 1130 cm⁻¹
 20 NMR (CDCl₃, δ) : 3.60 (3H, s), 6.00 (2H, br s),
 6.18 (1H, dd, J=2Hz and 9Hz), 6.22 (1H, d,
 J=2Hz), 7.22 (2H, d, J=7Hz), 7.52 (1H, d,
 J=9Hz), 7.60 (2H, d, J=7Hz), 10.7 (1H, br s)

- (4) 2-Amino-4-methoxy-N-(3,4-dichlorophenyl)benzenesulfonamide

mp : 135-138°C

IR (Nujol) : 3400, 3300, 1600, 1470, 1380 cm^{-1}

NMR (CDCl_3 , δ) : 3.77 (3H, s), 4.85 (2H, br s),
6.19 (1H, d, J=2Hz), 6.27 (1H, dd, J=2Hz, and
9Hz), 6.80 (1H, br s)

- (5) 2-Amino-4-methoxy-N-(4-fluorophenyl)benzenesulfonamide

mp : 94-97°C

IR (CHCl_3) : 3500, 3400, 3200, 1630, 1600, 1460,
1310, 1220 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 3.65 (3H, s), 5.95 (2H, br s),
6.13 (1H, dd, J=2Hz and 9Hz), 6.22 (1H, d,
J=2Hz), 7.35 (1H, d, J=9Hz)

- (6) 2-Amino-4-isopropoxy-N-(4-methoxyphenyl)benzenesulfonamide

IR (CHCl_3) : 3500, 3350, 1720, 1600, 1510,
1240 cm^{-1}

NMR (CDCl_3 , δ) : 1.30 (6H, d, J=6Hz), 3.75 (3H, s),
4.50 (1H, m), 4.80 (2H, br s), 6.12-6.20
(2H, m), 6.72 (2H, d, J=7Hz), 6.95 (2H, d,
J=7Hz), 7.80 (1H, d, J=9Hz)

- (7) 2-Amino-N-(4-chlorophenyl)benzenesulfonamide

mp : 100-105°C

IR (Nujol) : 1620, 1490, 1460, 1450, 1320, 1150,
1140 cm^{-1}

NMR (CDCl_3 , δ) : 4.85 (2H, br s), 6.60-6.80 (2H, m),
6.90-7.40 (5H, m), 7.50 (1H, d,
J=9Hz)

- (8) 2-Amino-4-chloro-N-(4-chlorophenyl)benzenesulfonamide

mp : 114-115°C

IR (Nujol) : 1610, 1590, 1480, 1440, 1310, 1160,
1140 cm⁻¹

NMR (CDCl₃, δ) : 4.95 (2H, br s), 6.63 (1H, dd,
J=2Hz and 9Hz), 6.72 (1H, d, J=2Hz),
6.90-7.30 (4H, m), 7.38 (1H, d, J=9Hz)

(9) 2-Amino-4-methoxy-N-(2-chlorophenyl)benzene-
sulfonamide

mp : 137-138°C

IR (Nujol) : 3700, 3500, 3300, 1640, 1600, 1570,
1380, 1320, 1220, 1140 cm⁻¹

NMR (CDCl₃, δ) : 3.75 (3H, s), 4.99 (2H, br s),
6.12 (1H, d, J=2Hz), 6.22 (1H, dd, J=2Hz and
9Hz), 6.90-7.70 (5H, m)

(10) 2-Amino-4-methoxy-N-(3-chlorophenyl)benzene-
sulfonamide

mp : 138-140°C

IR (Nujol) : 3450, 3350, 3250, 1640, 1600, 1460,
1380, 1160, 1140 cm⁻¹

NMR (CDCl₃, δ) : 3.75 (3H, s), 4.90 (2H, br s),
6.20 (1H, d, J=2Hz), 6.25 (1H, dd, J=2Hz and
9Hz), 6.75 (1H, br s), 6.90-7.30 (3H, m),
7.45 (1H, d, J=9Hz)

(11) 2-Amino-4-isopropoxy-N-(4-chlorophenyl)benzene-
sulfonamide

IR (CHCl₃) : 3400, 3300, 3100, 1650, 1600, 1490,
1320 cm⁻¹

NMR (CDCl₃, δ) : 1.30 (6H, d, J=6Hz), 1.50 (1H, m),
4.85 (2H, br s), 6.10-6.25 (2H, m), 6.90-7.25
(4H, m), 7.90 (1H, d, J=9Hz)

(12) 2-Amino-4-methoxy-N-(4-chlorobenzyl)benzenesulfonamide

mp : 121-122°C

IR (Nujol) : 3470, 3370, 3250, 1620, 1600, 1565,
1265 cm⁻¹

NMR (CDCl₃, δ) : 3.81 (3H, s), 4.00 (2H, d, J=6.0Hz),
4.85 (2H, s), 4.96 (1H, t, J=6.0Hz), 6.21 (1H,
d, J=2.4Hz), 6.34 (1H, dd, J=2.4 and 8.8Hz),
7.13 and 7.23 (4H, ABq, J=8.5Hz), 7.61 (1H, d,
J=8.8Hz)

(13) 2-Amino-4-methoxy-N-cyclohexylbenzenesulfonamide

mp : 95-98°C

IR (Nujol) : 3450, 3360, 3280, 1650, 1600, 1575,
1300, 1130, 1065 cm⁻¹

NMR (CDCl₃, δ) : 1.0-1.4 (5H, m), 1.4-1.8 (5H, m),
2.95-3.15 (1H, m), 3.81 (3H, s), 4.58 (1H, d,
J=7.5Hz), 4.84 (2H, s), 6.22 (1H, d, J=2.3Hz),
6.35 (1H, dd, J=2.3 and 8.8Hz), 7.64 (1H, d,
J=8.8Hz)

(14) 2-Amino-4-isopropoxy-N-(2-pyridyl)benzenesulfonamide

mp : 176-177°C

IR (Nujol) : 3460, 3370, 1630, 1610, 1260 cm⁻¹

NMR (DMSO-d₆, δ) : 1.23 (6H, d, J=6Hz), 4.4-4.6
(1H, m), 6.0 (2H, br s), 6.15 (1H, dd,
J=2Hz and 9Hz), 6.22 (1H, d, J=2Hz),
6.85-6.95 (1H, m), 7.0-7.10 (1H, m), 7.52
(1H, d, J=9Hz), 7.6-7.75 (1H, m), 8.03-8.1
(1H, m)

(15) 2-Amino-4-methoxy-N-(pentyl)benzenesulfonamide

IR (Nujol) : 3500, 3350, 1620, 1320, 1300, 1160,
1140 cm⁻¹

NMR (DMSO-d₆, δ) : 0.85 (3H, t, J=7Hz),

1.05-1.60 (6H, m), 2.85 (2H, q, J=7Hz),
3.80 (3H, s), 4.60 (1H, t, J=7Hz), 4.90
(2H, br s), 6.25 (1H, d, J=3Hz), 6.85
(1H, dd, J=3Hz and 9Hz), 7.62 (1H, d, J=9Hz)

5

(16) 2-Amino-4-methoxy-N-(4-methoxycarbonylphenyl)-
benzenesulfonamide

mp : 195°C (dec.)

IR (Nujol) : 3460, 3370, 3230, 1690, 1610,
1300 cm^{-1}

10

NMR (DMSO- d_6 , δ) : 3.65 (3H, s), 3.75 (3H, s),
6.03 (2H, br s), 6.15-6.30 (2H, m), 7.14 and
7.80 (4H, ABq, J=9.5Hz), 7.50 (1H, d, J=9.5Hz),
10.68 (1H, br s)

15

(17) 2-Amino-4-cyclohexylmethoxy-N-(2-pyridyl)benzene-
sulfonamide

mp : 213-214°C

IR (Nujol) : 3460, 3360, 1630, 1620, 1130 cm^{-1}

20

NMR (DMSO- d_6 , δ) : 0.85-1.4 (5H, m), 1.55-1.85
(6H, m), 3.70 (2H, d, J=6Hz), 6.0 (2H, br s),
6.16 (1H, dd, J=2.3Hz and 8.8Hz), 6.23 (1H, d,
J=2.3Hz), 6.83-6.95 (1H, m), 7.0-7.08 (2H, m),
7.53 (1H, d, J=8.8Hz), 7.6-7.72 (1H, m),
8.0-8.1 (1H, m)

25

(18) 2-Amino-4-methoxy-N-(4-methoxycarbonylmethylphenyl)-
benzenesulfonamide

mp : 111-113°C

IR (Nujol) : 3450, 3360, 3270, 1720, 1595,
1135 cm^{-1}

30

NMR (DMSO- d_6 , δ) : 3.54 (2H, s), 3.57 (3H, s),
3.67 (3H, s), 5.99 (2H, s, NH_2), 6.1-6.2
(1H, m), 6.22-6.27 (1H, m), 6.96 and 7.10
(4H, ABq, J=8.2Hz), 7.42 (1H, d, J=8.8Hz),
10.1 (1H, br s)

35

(19) 2-Amino-4-methoxy-N-(3-ethoxycarbonylpropyl)-
benzenesulfonamide

mp : 53-54°C

IR (Nujol) : 3500, 3400, 3300, 1710, 1630, 1610,
1570, 1470, 1380, 1310, 1270, 1220,
1160 cm^{-1}

NMR (CDCl_3 , δ) : 1.24 (3H, t, $J=7\text{Hz}$), 1.76 (2H, m),
2.33 (2H, t, $J=7\text{Hz}$), 2.91 (2H, q, $J=7\text{Hz}$),
3.80 (3H, s), 4.10 (2H, q, $J=7\text{Hz}$), 4.85 (1H,
br s), 6.23 (1H, d, $J=2\text{Hz}$), 6.35 (1H, dd,
 $J=2\text{Hz}$ and 9Hz), 7.61 (1H, d, $J=9\text{Hz}$)

(20) 2-Amino-4-methyl-N-(4-chlorophenyl)benzenesulfon-
amide

mp : 96-98°C

IR (Nujol) : 3400, 3300, 3100, 1610, 1500, 1330,
1230, 1140 cm^{-1}

NMR (CDCl_3 , δ) : 2.25 (3H, s), 4.77 (2H, br s),
6.50 (1H, d, $J=8\text{Hz}$), 6.54 (1H, s), 7.00 (2H,
d, $J=8\text{Hz}$)

(21) 2-Amino-4-isopropoxy-N-[2-(4,6-dimethylpyridyl)]-
benzenesulfonamide

mp : 180-182°C

IR (Nujol) : 3450, 3350, 3250, 1620, 1600, 1400,
1250, 1130 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 1.22 (6H, d, $J=6\text{Hz}$), 2.15 (3H,
s), 2.22 (3H, s), 4.50 (1H, m), 5.85 (2H, br s),
6.12 (1H, d, $J=9\text{Hz}$), 6.22 (1H, s), 6.50 (1H, s),
6.70 (1H, s), 7.50 (1H, d, $J=9\text{Hz}$)

(22) 2-Amino-4-trifluoromethyl-N-(4-chlorophenyl)-
benzenesulfonamide

mp : 100-102°C

IR (Nujol) : 3420, 3350, 1630, 1500, 1340, 1190,
1140, 1090 cm^{-1}

NMR (CDCl_3 , δ) : 5.00 (2H, br s), 6.70-7.40 (6H, m),
7.70 (1H, d, $J=9\text{Hz}$)

5 (23) 2-Amino-4-isopropoxy-N-(2-pyrimidinyl)benzenesulfon-
amide

mp : 204-206°C

IR (Nujol) : 3400, 3300, 1610, 1580, 1500, 1450,
1380, 1320, 1130 cm^{-1}

10 NMR ($\text{DMSO}-d_6$, δ) : 1.25 (6H, d, $J=6\text{Hz}$), 1.45 (1H,
m), 6.00 (2H, br s), 6.15 (1H, d, $J=9\text{Hz}$),
7.00 (1H, t, $J=4\text{Hz}$), 7.60 (1H, d, $J=9\text{Hz}$),
8.50 (2H, d, $J=4\text{Hz}$), 11.4 (1H, br s)

15 (24) 2-Amino-4-methoxy-N-(4-phenoxyphenyl)benzenesulfon-
amide

mp : 100-101°C

IR (Nujol) : 3460, 3360, 3270, 1600, 1310, 1245,
1135 cm^{-1}

20 NMR (CDCl_3 , δ) : 3.50 (2H, br), 3.77 (3H, s),
6.25 (1H, d, $J=2\text{Hz}$), 6.26 (1H, dd, $J=2\text{Hz}$ and
9Hz), 6.73 (1H, br s), 6.80-7.45 (10H, m)

25 (25) 2-Amino-4-methoxy-N-(4-isopropylphenyl)benzene-
sulfonamide

mp : 98-99°C

IR (Nujol) : 3460, 3360, 3260, 1605, 1575, 1305,
1215 cm^{-1}

30 NMR (CDCl_3 , δ) : 1.18 (6H, d, $J=7\text{Hz}$), 2.82 (1H, m),
3.45 (2H, br), 3.76 (3H, s), 6.23 (1H, dd,
 $J=2\text{Hz}$ and 9Hz), 6.25 (1H, d, $J=2\text{Hz}$), 6.72
(1H, br s), 6.95 and 7.05 (4H, ABq, $J=9\text{Hz}$),
7.40 (1H, d, $J=9\text{Hz}$)

35 (26) 2-Amino-4-methoxy-N-[(3-chloro-4-methyl)phenyl]-
benzenesulfonamide

mp : 138-139°C

IR (Nujol) : 3420, 3350, 3250, 1600, 1315, 1140 cm^{-1}

NMR (CDCl_3 , δ) : 2.27 (3H, s), 3.45 (2H, br),
6.24 (1H, d, J=2Hz), 6.27 (1H, dd, J=2Hz and
9Hz), 6.80 (1H, br s), 6.85 (1H, dd, J=2Hz
and 9Hz), 7.05 (1H, d, J=9Hz), 7.08 (1H, d,
J=2Hz), 7.43 (1H, d, J=9Hz)

(27) 2-Amino-4-methoxy-N-(4-methylthiophenyl)benzene-
sulfonamide

mp : 91-92°C

IR (Nujol) : 3450, 3375, 3250, 1625, 1600, 1570,
1490, 1215, 1160, 1140 cm^{-1}

NMR (CDCl_3 , δ) : 2.51 (3H, s), 3.86 (3H, s),
6.50 (1H, d, J=2Hz), 6.82 (1H, dd, J=2Hz and
9Hz), 7.36 (4H, s), 7.79 (1H, d, J=9Hz),
8.51 (1H, s)

(28) 2-Amino-4-methoxy-N-(4-dimethylaminophenyl)-
benzenesulfonamide

mp : 119-121°C

IR (Nujol) : 3450, 3440, 3350, 3250, 1600, 1520,
1210, 1160, 1140 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 2.79 (6H, s), 3.68 (3H, s),
6.10 (1H, dd, J=2Hz and 9Hz), 6.24 (1H, d,
J=2Hz), 6.55 (2H, d, J=9Hz), 6.85 (2H, d,
J=9Hz), 7.26 (1H, d, J=9Hz), 9.42 (1H, s)

Preparation 5

To a solution of 4-acetylamino-2-nitro-N-(4-chlorophenyl)benzenesulfonamide (4.85 g) in ethyl acetate (485 ml) was added 10% palladium on carbon, and the mixture was hydrogenated at room temperature under atmospheric pressure for seven hours. The catalyst was removed by filtration and the solvent was

evaporated under reduced pressure. The residue was
trituated with diisopropyl ether and collected by
filtration to give 4-acetylamino-2-amino-N-(4-
chlorophenyl)benzenesulfonamide as colorless powder
(4.76 g).

mp : 127°C (dec.)

IR (Nujol) : 3340, 1665, 1600, 1310, 1135 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.01 (3H, s), 5.87 (2H, br),

6.67-6.75 (1H, m), 7.0-7.56 (6H, m),

9.95 (1H, br), 10.4 (1H, br)

(continued to the next page)

Example 1

A mixture of 2-amino-4-methoxy-N-(4-chlorophenyl)-benzenesulfonamide (24.37 g) and 1,1'-carbonyldiimidazole (18.93 g) in dried dioxane (500 ml) was refluxed overnight and then concentrated to dryness. The residue was washed with methanol and collected by filtration to yield 2-(4-chlorophenyl)-6-methoxy-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (23.9 g).

mp : 229-230°C

IR (Nujol) : 1700, 1610, 1600, 1480, 1360, 1300 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.38 (1H, br s), 3.85 (3H, s), 6.30-7.00 (2H, m), 7.40-7.70 (4H, m), 7.85 (1H, d, $J=9\text{Hz}$)

Example 2

To a solution of 2-(4-chlorophenyl)-6-methoxy-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (23.50 g) in dried N,N-dimethylformamide (150 ml) was added sodium hydride (60% oil dispersion) in one portion at 0°C. The suspension was stirred for one hour at ambient temperature and then methyl iodide (5.18 ml) was added therein at the same temperature. The reaction mixture was stirred for one and half hours at ambient temperature and then poured into ice water. The separated solid was filtered, dried and recrystallized from ethanol to yield 2-(4-chlorophenyl)-6-methoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (21.07 g) as a white needle crystal.

mp : 167-168°C

IR (Nujol) : 1710, 1600, 1330, 1180, 1130 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.42 (3H, s), 3.95 (3H, s), 6.95-7.10 (2H, m), 7.38-7.65 (2H, m), 8.90 (1H, d, $J=9\text{Hz}$)

Example 3

To a solution of 2-(4-chlorophenyl)-6-methoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (21.0 g) in methylene chloride (200 ml) was added boron tribromide (1N solution in methylene chloride, 89.2 ml) at ambient temperature. The mixture was stirred for 8 hours at the same temperature and then poured into ice water. The separated solid was collected by filtration, dried, and recrystallized from ethanol to yield 2-(4-chlorophenyl)-6-hydroxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (18.86 g).

mp : $>250^{\circ}\text{C}$

IR (Nujol) : 3300, 1660, 1650, 1610 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 3.45 (3H, s), 6.80 (1H, d, $J=9\text{Hz}$), 7.90 (1H, s), 7.35-7.65 (4H, m), 7.70 (1H, d, $J=9\text{Hz}$)

Example 4

A suspension of 2-(4-chlorophenyl)-6-hydroxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (15.33 g), potassium carbonate (7.50 g) and 2-iodopropane (5.43 ml) in N,N-dimethylformamide (150 ml) was stirred for 2 hours at 60°C . The mixture was poured into ice water. The separated solid was collected by filtration, dried, and recrystallized from ethanol to yield 2-(4-chlorophenyl)-6-isopropoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (13.54 g) as a white crystal.

mp : $157-159^{\circ}\text{C}$

IR (Nujol) : 1700, 1605, 1460, 1330, 1320, 1300 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 1.32 (3H, s), 1.35 (3H, s), 3.50 (3H, s), 4.89 (1H, m), 7.00 (1H, d, $J=9\text{Hz}$), 7.02 (1H, s), 7.35-7.60 (4H, m), 7.85 (1H, d, $J=9\text{Hz}$)

Example 5

In a similar manner to that of Example 1, there were obtained the following compounds.

- 5 (1) 6-Methoxy-2-(p-tolyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 228-230°C
IR (Nujol) : 1710, 1700, 1630, 1610, 1480, 1400,
1340, 1200, 1120 cm^{-1}
10 NMR (DMSO- d_6 , δ) : 2.38 (3H, s), 3.88 (3H, s),
6.70-7.10 (2H, m), 7.20-7.50 (4H, m), 7.85
(1H, d, J=9Hz), 11.45 (1H, br s)
- 15 (2) 6-Methoxy-2-phenyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 203-235°C
IR (Nujol) : 3500, 1700, 1690, 1610, 1590, 1460,
1370 cm^{-1}
20 NMR (DMSO- d_6 , δ) : 3.85 (3H, s), 6.80 (1H, s),
6.95 (1H, d, J=9Hz), 7.30-7.70 (5H, m),
7.82 (1H, d, J=9Hz), 11.5 (1H, br s)
- 25 (3) 6-Methoxy-2-(4-trifluoromethylphenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 202-204°C
IR (Nujol) : 1700, 1610, 1590, 1460, 1380, 1320,
1180 cm^{-1}
30 NMR (DMSO- d_6 , δ) : 3.85 (3H, s), 6.50 (1H, d, J=2Hz), 6.85 (1H, dd, J=2Hz and 9Hz),
7.62 (2H, d, J=7Hz), 7.72 (2H, d, J=7Hz),
7.80 (1H, d, J=9Hz)
- 35 (4) 2-(3,4-Dichlorophenyl)-6-methoxy-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 239-240°C

IR (Nujol) : 1720, 1600, 1470, 1360, 1190 cm^{-1}

NMR (DMSO-d_6 , δ) : 3.45 (3H, s), 6.70-7.00

(2H, m), 7.45 (1H, d, $J=8\text{Hz}$), 7.70-7.95

(3H, m), 11.50 (1H, br s)

5

- (5) 2-(4-Fluorophenyl)-6-methoxy-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 224-225°C

IR (Nujol) : 3250, 3150, 1690, 1600, 1360, 1290,
1180, 1170, 1150 cm^{-1}

NMR (DMSO-d_6 , δ) : 3.85 (3H, s), 6.80 (1H, s),

6.92 (1H, d, $J=10\text{Hz}$), 7.30-7.60 (4H, m),

7.85 (1H, d, $J=10\text{Hz}$)

- (6) 6-Isopropoxy-2-(4-methoxyphenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 208-210°C

IR (Nujol) : 3200, 1700, 1620, 1590, 1460 cm^{-1}

NMR (DMSO-d_6 , δ) : 1.32 (6H, d, $J=6\text{Hz}$), 3.82

(3H, s), 4.69 (1H, m), 6.76 (1H, d, $J=2\text{Hz}$),

6.90 (1H, dd, $J=2\text{Hz}$ and 9Hz), 7.05 (2H, d,

$J=7\text{Hz}$), 7.30 (2H, d, $J=7\text{Hz}$), 7.80 (1H, d,

$J=9\text{Hz}$), 11.4 (1H, br s)

- (7) 6-Chloro-2-(4-chlorophenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 235-237°C

(Continued to the next page)

IR (Nujol) : 1720, 1710, 1600, 1580, 1460, 1310,
1170, 1160, 1100 cm^{-1}

NMR (DMSO-d_6 , δ): 7.20-7.75 (6H, m), 7.98 (1H, d, $J=9\text{Hz}$), 11.8 (1H, br s)

- (8) 2-(2-Chlorophenyl)-6-methoxy-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 234-235°C

IR (Nujol) : 3400, 1720, 1620, 1600, 1590, 1460,
1320, 1290, 1140 cm^{-1}

NMR (DMSO-d_6 , δ) : 3.87 (3H, s), 6.87 (1H, s),
9.24 (1H, dd, $J=2\text{Hz}$ and 9Hz), 7.50-7.72 (4H,
m), 7.84 (1H, d, $J=9\text{Hz}$), 11.6 (1H, br s)

- (9) 2-(3-Chlorophenyl)-6-methoxy-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 204-205°C

IR (Nujol) : 1700, 1590, 1470, 1370, 1350, 1200,
1170, 1140 cm^{-1}

NMR (DMSO-d_6 , δ) : 3.90 (3H, s), 6.80 (1H, d,
 $J=2\text{Hz}$), 6.92 (1H, dd, $J=2\text{Hz}$ and 9Hz), 7.30-7.75
(3H, m), 7.85 (1H, d, $J=9\text{Hz}$)

- (10) 2-(4-Chlorophenyl)-6-isopropoxy-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 132-133°C

IR (Nujol) : 1700, 1460, 1370, 1340 cm^{-1}

NMR (DMSO-d_6 , δ) : 1.32 (6H, d, $J=6\text{Hz}$), 4.70 (1H, m),
6.78 (1H, d, $J=2\text{Hz}$), 6.90 (1H, dd, $J=2\text{Hz}$ and
 9Hz), 7.42 (2H, d, $J=7\text{Hz}$), 7.60 (2H, d, $J=7\text{Hz}$),
7.90 (1H, d, $J=9\text{Hz}$)

- (11) 2-(4-Chlorobenzyl)-6-methoxy-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 199-200°C

IR (Nujol) : 3200, 3060, 1695, 1610, 1590, 1335,
1320 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.84 (3H, s), 4.95 (2H, s),
6.77 (1H, d, $J=2.0\text{Hz}$), 6.90 (1H, dd, $J=2.0$ and
9.0Hz), 7.35 and 7.40 (4H, ABq, $J=8.7\text{Hz}$),
7.80 (1H, d, $J=9.0\text{Hz}$), 11.37 (1H, br)

5

(12) 2-Cyclohexyl-6-methoxy-2H-1,2,4-benzothiadiazine-
3(4H)-one 1,1-dioxide

mp : 190-191°C

IR (Nujol) : 3200, 3070, 1690, 1600, 1185, 1170 cm^{-1}

10

NMR (DMSO- d_6 , δ) : 1.0-1.5 (3H, m), 1.5-1.95
(5H, m), 2.1-2.4 (2H, m), 3.82 (3H, s),
4.2-4.45 (1H, m), 6.73 (1H, s), 6.85 (1H,
dd, $J=2.2$ and 8.8Hz), 7.72 (1H, d, $J=8.8\text{Hz}$),
11.17 (1H, br)

15

(13) 6-Isopropoxy-2-(2-pyridyl)-2H-1,2,4-benzothiadiazine-
3(4H)-one 1,1-dioxide

mp : 183-184°C

IR (Nujol) : 3450, 1745, 1615, 1340 cm^{-1}

20

NMR (DMSO- d_6 , δ) : 1.32 (6H, d, $J=6\text{Hz}$), 4.6-4.8
(1H, m), 6.81 (1H, d, $J=2.2\text{Hz}$), 6.90 (1H,
 $J=2.2\text{Hz}$ and 8.8Hz), 7.45-7.6 (2H, m),
7.76 (1H, d, $J=8.8\text{Hz}$), 7.95-8.06 (1H, m),
8.55-8.65 (1H, m), 11.48 (1H, br s)

25

(14) 6-Methoxy-2-pentyl-2H-1,2,4-benzothiadiazine-3(4H)-
one 1,1-dioxide

mp : 100-104°C

IR (Nujol) : 1690, 1610, 1600, 1470, 1350,
1330 cm^{-1}

30

NMR (DMSO- d_6 , δ) : 0.85 (3H, t, $J=6\text{Hz}$), 1.15-1.40
(4H, m), 1.50-1.70 (2H, m), 3.73 (3H, t, $J=7\text{Hz}$),
3.83 (3H, s), 6.73 (1H, d, $J=2\text{Hz}$), 6.87 (1H,
dd, $J=2\text{Hz}$ and 9Hz), 7.76 (1H, d, $J=9\text{Hz}$)

35

(15) 6-Acetylamino-2-(4-chlorophenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : >250°C

IR (Nujol) : 3360, 1725, 1600, 1325 cm^{-1}

5 NMR (DMF- d_6 , δ) : 2.11 (3H, s), 7.4-7.5 (3H, m),
7.55-7.67 (2H, m), 7.80-7.90 (2H, m),
10.51 (1H, s), 11.60 (1H, s)

(16) 6-Methoxy-2-(4-methoxycarbonylphenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

10

mp : 231-233°C

IR (Nujol) : 3260, 1720, 1695, 1600, 1335,
1320 cm^{-1}

15 NMR (DMSO- d_6 , δ) : 3.88 (3H, s), 3.91 (3H, s),
6.84 (1H, d, J=2Hz), 6.95 (1H, dd, J=2Hz and
9Hz), 7.60 and 8.10 (4H, ABq, J=8.5Hz),
7.85 (1H, d, J=9Hz), 11.58 (1H, br s)

(17) 6-Cyclohexylmethoxy-2-(2-pyridyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

20

mp : 206-208°C

IR (Nujol) : 3150, 1745, 1610, 1595, 1340, 1325,
1310, 1180 cm^{-1}

25 NMR (DMSO- d_6 , δ) : 0.9-1.4 (5H, m), 1.55-1.9
(6H, m), 3.99 (2H, d, J=6Hz), 6.82 (1H, d,
J=2.1Hz), 6.92 (1H, dd, J=2.1Hz and 8.8Hz)
7.45-7.6 (2H, m), 7.77 (1H, d, J=8.8Hz),
7.95-8.08 (1H, m), 8.55-8.65 (1H, m),
11.49 (1H, br s)

(18) 2-(4-Methoxycarbonylmethylphenyl)-6-methoxy-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

30

mp : 214-215°C

IR (Nujol) : 3200, 1720, 1700, 1340 cm^{-1}

35 NMR (DMSO- d_6 , δ) : 3.65 (3H, s), 3.79 (2H, s),
3.86 (3H, s), 6.80-6.85 (1H, m), 6.43

(1H, dd, J=2.0 and 9.0Hz), 7.35 and 7.45
(4H, ABq, J=8.3Hz), 7.85 (1H, d, J=9.0Hz),
11.5 (1H, br)

- 5 (19) 2-(3-Ethoxycarbonylpropyl)-6-methoxy-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 118-120°C

IR (Nujol) : 3250, 1730, 1700, 1450, 1380,
1320 cm^{-1}

10 NMR (DMSO- d_6 , δ) : 1.15 (3H, t, J=7Hz), 1.88
(2H, m), 2.34 (2H, t, J=7Hz), 3.35 (1H, br s),
3.60-3.80 (2H, m), 6.88 (1H, dd, J=2Hz and
9Hz), 7.77 (1H, d, J=9Hz)

- 15 (20) 2-(4-Chlorophenyl)-6-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 245-248°C

IR (Nujol) : 1690, 1610, 1590, 1490, 1350, 1190,
1150, 1090 cm^{-1}

20 NMR (DMSO- d_6 , δ) : 2.41 (3H, s), 3.35 (1H, br s),
7.13 (1H, s), 7.18 (1H, d, J=8Hz), 7.46
(2H, d, J=8Hz), 7.60 (2H, d, J=8Hz), 7.79
(1H, d, J=8Hz)

- 25 (21) 2-[2-(4,6-Dimethylpyridyl)]-6-isopropoxy-2H-
1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 188-190°C

IR (Nujol) : 3600, 1740, 1600, 1330, 1180 cm^{-1}

30 NMR (DMSO- d_6 , δ) : 1.33 (6H, d, J=8Hz), 2.35 (3H, s),
2.45 (3H, s), 4.72 (1H, m), 6.80 (1H, d,
J=2Hz), 6.90 (1H, dd, J=2Hz and 9Hz),
7.10 (1H, s), 7.25 (1H, s), 7.75 (1H, d,
J=9Hz)

- 35 (22) 2-(4-Chlorophenyl)-6-trifluoromethyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 234-235°C

IR (Nujol) : 1720, 1600, 1490, 1360, 1340,
1190, 1140, 1090 cm⁻¹

NMR (DMSO-d₆, δ) : 7.40-7.80 (6H, m), 8.17 (1H,
d, J=9Hz)

5

(23) 6-Isopropoxy-2-(2-pyrimidinyl)-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 168-170°C

IR (Nujol) : 3600, 1740, 1600, 1570, 1350, 1320,
1180 cm⁻¹

NMR (DMSO-d₆, δ) : 1.30 (6H, d, J=6Hz), 4.72
(1H, m), 6.80 (1H, d, J=2Hz), 6.92 (1H, dd,
J=2Hz and 9Hz), 7.70 (1H, t, J=4Hz),
7.80 (1H, d, J=9Hz), 9.00 (2H, d, J=4Hz),
11.65 (1H, br s)

10

15

(24) 6-Methoxy-2-(4-phenoxyphenyl)-2H-1,2,4-benzo-
thiadiazine-3(4H)-one 1,1-dioxide

mp : 247-248°C

IR (Nujol) : 3210, 3110, 3060, 1700, 1595, 1340,
1245 cm⁻¹

NMR (DMSO-d₆, δ) : 3.86 (3H, s), 6.81 (1H, d,
J=2Hz), 6.92 (1H, dd, J=2Hz and 9Hz),
7.00-7.55 (9H, m), 7.82 (1H, d, J=9Hz),
11.47 (1H, br)

25

(25) 2-(4-Isopropylphenyl)-6-methoxy-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 213-214°C

IR (Nujol) : 3200, 2960, 1695, 1610, 1590, 1195 cm⁻¹

NMR (DMSO-d₆, δ) : 1.25 (6H, d, J=7Hz), 3.00
(1H, m), 3.86 (3H, s), 6.81 (1H, d, J=2Hz),
6.92 (1H, dd, J=2Hz and 9Hz), 7.30 and 7.40
(4H, ABq, J=8.5Hz), 7.81 (1H, d, J=9Hz),
11.45 (1H, br)

30

35

(26) 2-[(3-Chloro-4-methyl)phenyl]-6-methoxy-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 222-223°C

IR (Nujol) : 3220, 1710, 1600, 1180 cm^{-1}

NMR (DMSO-d_6 , δ) : 2.40 (3H, s), 3.87 (3H, s),
6.80 (1H, d, $J=2\text{Hz}$), 7.32 (1H, dd, $J=2\text{Hz}$ and
8.5Hz), 7.5 (1H, d, $J=2\text{Hz}$), 7.52 (1H, d,
 $J=8.5\text{Hz}$), 7.83 (1H, d, $J=9\text{Hz}$), 9.93 (1H, dd,
 $J=2\text{Hz}$ and 9Hz), 11.5 (1H, br s)

(27) 6-Methoxy-2-(4-methylthiophenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 218-219°C

IR (Nujol) : 1685, 1590, 1210, 1190, 1180 cm^{-1}

NMR (DMSO-d_6 , δ) : 2.51 (3H, s), 3.86 (3H, s),
6.81 (1H, d, $J=2\text{Hz}$), 6.92 (1H, dd, $J=2\text{Hz}$ and
9Hz), 7.31 (2H, d, $J=8\text{Hz}$), 7.39 (2H, d,
 $J=8\text{Hz}$), 7.82 (1H, d, $J=9\text{Hz}$)

(28) 2-(4-Dimethylaminophenyl)-6-methoxy-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : $>250^\circ\text{C}$

IR (Nujol) : 1680, 1600, 1520, 1350, 1210, 1170 cm^{-1}

NMR (DMSO-d_6 , δ) : 2.96 (6H, s), 3.85 (3H, s),
6.76 (2H, d, $J=9\text{Hz}$), 7.13 (2H, d, $J=9\text{Hz}$),
6.79 (1H, d, $J=2\text{Hz}$), 6.90 (1H, dd, $J=2\text{Hz}$
and 9Hz), 7.79 (1H, d, $J=9\text{Hz}$)

Example 6

In a similar manner to that of Example 2, there were obtained the following compounds.

(1) 6-Methoxy-4-methyl-2-(p-tolyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 170-173°C

IR (Nujol) : 1690, 1460, 1440, 1330, 1310, 1180,
1130 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.50 (3H, s), 3.95 (3H, s),
6.95-7.10 (2H, m), 7.20-7.40 (4H, m),
7.95 (1H, d, J=9Hz)

- (2) 6-Methoxy-4-methyl-2-phenyl-2H-1,2,4-benzothiadiazine-
3(4H)-one 1,1-dioxide

mp : 203-206°C

IR (Nujol) : 1710, 1700, 1600, 1450, 1330, 1300,
1220, 1180 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.50 (3H, s), 3.95 (3H, s),
7.00 (1H, d, J=9Hz), 7.05 (1H, s),
7.35-7.65 (5H, m), 7.88 (1H, d, J=9Hz)

- (3) 6-Methoxy-4-methyl-2-(4-trifluoromethylphenyl)-2H-
1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 165-168°C

IR (Nujol) : 1700, 1610, 1580, 1460, 1340, 1170,
1140 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.52 (3H, s), 3.95 (3H, s),
7.02 (1H, dd, J=2Hz and 9Hz), 7.10 (1H, d,
J=2Hz), 7.65 (2H, d, J=7Hz), 7.92 (1H, d,
J=9Hz), 7.98 (2H, d, J=7Hz)

- (4) 2-(3,4-Dichlorophenyl)-6-methoxy-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 150-151°C

IR (Nujol) : 1710, 1600, 1470, 1340, 1320 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.50 (3H, s), 3.95 (3H, s),
7.02 (1H, d, J=9Hz), 7.06 (1H, s), 7.45
(1H, d, J=8Hz), 7.70-8.00 (3H, m)

- (5) 2-(4-Fluorophenyl)-6-methoxy-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 203-204°C

IR (Nujol) : 1700, 1590, 1440 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.52 (3H, s), 3.95 (3H, s),
7.02 (1H, d, $J=9\text{Hz}$), 7.10 (1H, s),
7.30-7.60 (4H, m), 7.90 (1H, d, $J=9\text{Hz}$)

- (6) 6-Isopropoxy-2-(4-methoxyphenyl)-4-methyl-2H-
1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 182-183°C

IR (Nujol) : 1690, 1600, 1460, 1370, 1340 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.34 (6H, d, $J=6\text{Hz}$), 3.50
(3H, s), 3.82 (3H, s), 4.89 (1H, m), 7.00-7.08
(4H, m), 7.25-7.32 (2H, m), 7.84 (1H, d,
 $J=9\text{Hz}$)

- (7) 2-(4-Chlorophenyl)-4-methyl-2H-1,2,4-benzothiadiazine-
3(4H)-one 1,1-dioxide

mp : 178-180°C

IR (Nujol) : 1690, 1600, 1500, 1470, 1450, 1350,
1270, 1180, 1140 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.53 (3H, s), 7.40-8.00 (8H, m)

- (8) 6-Chloro-2-(4-chlorophenyl)-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 154-157°C

IR (Nujol) : 1700, 1590, 1560, 1460, 1340, 1310,
1180 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.51 (3H, s), 7.43 (2H, d,
 $J=8\text{Hz}$), 7.52 (1H, dd, $J=1\text{Hz}$ and 8Hz), 7.57 (2H,
d, $J=8\text{Hz}$), 7.78 (1H, d, $J=1\text{Hz}$), 8.00 (1H, d,
 $J=8\text{Hz}$)

- (9) 2-(2-Chlorophenyl)-6-methoxy-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 155-156°C

IR (Nujol) : 1710, 1600, 1460, 1330, 1300, 1180,
1140 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 3.54 (3H, s), 3.95 (3H, s),
7.03 (1H, dd, $J=2\text{Hz}$ and 9Hz), 7.11 (1H, d,
 $J=2\text{Hz}$), 7.50-7.70 (4H, m), 7.90 (1H, d, $J=9\text{Hz}$)

(10) 2-(3-Chlorophenyl)-6-methoxy-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 153-154°C

IR (Nujol) : 1710, 1600, 1590, 1460, 1340, 1320,
1180, 1130, 1060, 1030 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 3.51 (3H, s), 3.94 (3H, s),
7.02 (1H, dd, $J=2\text{Hz}$ and 9Hz), 7.07 (1H, d,
 $J=2\text{Hz}$), 7.34-7.65 (4H, m), 7.90 (1H, d,
 $J=9\text{Hz}$)

(11) 6-Isopropoxy-4-methyl-2-(p-tolyl)-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 163-165°C

IR (Nujol) : 1690, 1600, 1580, 1340, 1320, 1130,
1110 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 1.33 (3H, s), 1.36 (3H, s),
2.38 (3H, s), 3.49 (3H, s), 4.90 (1H, m),
6.90-7.10 (2H, m), 7.20-7.34 (4H, m),
7.84 (1H, d, $J=8\text{Hz}$)

(12) 6-Isopropoxy-4-methyl-2-phenyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 134-135°C

IR (Nujol) : 1690, 1600, 1580, 1450, 1340, 1190 cm^{-1}

NMR (CDCl_3 , δ) : 1.42 (6H, d, $J=6\text{Hz}$), 3.55 (3H, s),
4.70 (1H, m), 6.70-7.90 (2H, m), 7.35-7.60
(5H, m), 7.82 (1H, d, $J=9\text{Hz}$)

(13) 2-(3,4-Dichlorophenyl)-6-isopropoxy-4-methyl-

2E-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 109-110°C

IR (Nujol) : 1710, 1570, 1460, 1350, 1320 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.34 (6H, d, J=5Hz), 3.49
(3H, s), 4.90 (1H, m), 7.01 (1H, d, J=8Hz),
7.03 (1H, s), 7.45 (1H, d, J=9Hz), 7.74-7.89
(3H, m)

(14) 2-(4-Fluorophenyl)-6-isopropoxy-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 139-140°C

IR (Nujol) : 1700, 1600, 1570, 1460, 1380, 1330,
1210 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.33 (6H, d, J=6Hz), 3.50
(3H, s), 4.90 (1H, m), 6.98-7.02 (2H, m),
7.30-7.48 (4H, m), 7.85 (1H, d, J=9Hz)

(15) 2-(4-Chlorophenyl)-6-ethoxy-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 150-151°C

IR (Nujol) : 1680, 1600, 1580, 1460, 1350, 1320,
1220, 1190, 1130 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.39 (3H, t, J=7Hz), 3.50 (3H,
s), 4.23 (2H, q, J=7Hz), 7.00 (1H, dd, J=2Hz
and 9Hz), 7.05 (1H, d, J=2Hz), 7.40-7.63
(4H, m), 7.87 (1H, d, J=9Hz)

(16) 6-Benzoyloxy-2-(4-chlorophenyl)-4-methyl-2H-
1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 174-175°C

IR (Nujol) : 1690, 1600, 1590, 1460, 1320, 1310,
1180 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.34 (3H, s), 5.32 (2H, s),
7.07 (1H, dd, J=(Hz, 2Hz), 7.20 (1H, d, J=2Hz),
7.30-7.63 (9H, m), 7.90 (1H, d, J=9Hz)

(17) 2-(4-Chlorophenyl)-6-cyclopropylmethoxy-4-methyl-
2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 145-146°C

IR (Nujol) : 1690, 1600, 1580, 1540, 1330 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.30-0.45 (4H, m), 1.30
(1H, m), 3.45 (3H, s), 4.01 (2H, d, $J=7\text{Hz}$),
6.90-7.10 (2H, m), 7.35-7.70 (4H, m),
7.85 (1H, d, $J=9\text{Hz}$)

(18) 2-(2-Chlorophenyl)-6-isopropoxy-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 150-152°C

IR (Nujol) : 1700, 1600, 1580, 1450, 1360, 1320,
1200 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.34 (6H, d, $J=6\text{Hz}$), 3.52 (3H, s),
4.90 (1H, m), 6.95-7.10 (2H, m), 7.50-7.70
(4H, m), 7.86 (1H, d, $J=9\text{Hz}$)

(19) 2-(3-Chlorophenyl)-6-isopropoxy-4-methyl-2H-
1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 126-127°C

IR (Nujol) : 1700, 1600, 1590, 1380, 1330, 1310,
1180 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.34 (6H, d, $J=6\text{Hz}$), 3.49 (3H, s),
4.90 (1H, m), 6.98-7.03 (2H, m), 7.37-7.65
(4H, m), 7.86 (1H, d, $J=9\text{Hz}$)

(20) 2-(4-Chlorophenyl)-4-methyl-6-propoxy-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 142-143°C

IR (Nujol) : 1700, 1690, 1610, 1580, 1340, 1320 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.02 (3H, t, $J=7\text{Hz}$), 1.30 (2H,
q, $J=7\text{Hz}$), 3.50 (3H, s), 4.10 (2H, t, $J=7\text{Hz}$),
6.95-7.10 (2H, m), 7.40-7.70 (4H, m),
7.90 (1H, d, $J=9\text{Hz}$)

(21) 6-Butoxy-2-(4-chlorophenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 102-103°C

IR (Nujol) : 1700, 1600, 1340, 1320, 1180, 1130 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.96 (3H, t, J=7Hz), 1.35-1.90 (4H, m), 3.50 (3H, s), 4.18 (2H, t, J=7Hz), 6.95-7.10 (2H, m), 7.35-7.70 (4H, m), 8.90 (1H, d, J=9Hz)

(22) 2-(4-Chlorophenyl)-6-isopropoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 157-159°C

IR (Nujol) : 1700, 1605, 1460, 1330, 1320, 1300 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.32 (3H, s), 1.35 (3H, s), 3.50 (3H, s), 4.89 (1H, m), 7.00 (1H, d, J=9Hz), 7.02 (1H, s), 7.35-7.60 (4H, m), 7.85 (1H, d, J=9Hz)

(23) 2-(4-Trifluoromethylphenyl)-4-methyl-6-isopropoxy-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 158-160°C

IR (Nujol) : 1690, 1600, 1460, 1370, 1320, 1130 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.34 (6H, d, J=6Hz), 3.50 (3H, s), 4.90 (1H, m), 7.00-7.10 (2H, m), 7.64 (2H, d, J=7Hz), 7.80-8.00 (3H, m)

(24) 2-(4-Chlorophenyl)-4-methyl-6-(2-methylpropoxy)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 108-110°C

IR (Nujol) : 1690, 1600, 1580, 1460, 1340, 1320, 1190 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.02 (6H, d, J=7Hz), 2.08 (1H, m), 3.51 (3H, s), 3.95 (2H, d, J=8Hz), 6.99-7.06 (2H, m), 7.39-7.63 (4H, m), 7.87 (1H, d, J=9Hz)

(25) 2-(4-Chlorophenyl)-4-methyl-6-cyclohexylmethoxy-
2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 127-129°C

IR (Nujol) : 1690, 1600, 1590, 1460, 1320, 1310,
1180, 1130 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.04-1.40 (5H, m), 1.50-1.90
(6H, m), 3.50 (3H, s), 3.98 (2H, d, $J=6\text{Hz}$),
6.98-7.05 (2H, m), 7.38-7.63 (4H, m), 7.86
(1H, d, $J=9\text{Hz}$)

(26) 2-(4-Chlorobenzyl)-6-methoxy-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 132-133°C

IR (Nujol) : 1675, 1600, 1350, 1330, 1195 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.47 (3H, s), 3.92 (3H, s),
4.96 (2H, s), 6.98 (1H, d, $J=9.0\text{Hz}$), 7.00 (1H,
s), 7.35 and 7.40 (4H, ABq, $J=8.7\text{Hz}$), 7.87 (1H, d,
 $J=9.0\text{Hz}$)

(continued to the next page)

- (27) 2-(4-Chlorophenyl)-6-carboxymethoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 228-230°C

IR (Nujol) : 1730, 1690, 1600, 1460, 1340, 1320 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.34 (1H, brs), 3.50 (3H, s),

4.95 (2H, s), 6.99 (1H, dd, $J=9\text{Hz}$ and 2Hz),

7.11 (1H, d, $J=2\text{Hz}$), 7.35-7.65 (4H, m),

7.89 (1H, d, $J=9\text{Hz}$)

- (28) 2-(4-Chlorophenyl)-6-[1-(ethoxycarbonyl)ethoxy]-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (R,S mixture)

mp : 111-112°C

IR (Nujol) : 1750, 1690, 1605, 1340, 1210, 1140 cm^{-1}

NMR (CDCl_3 , δ) : 1.29 (3H, t, $J=7.1\text{Hz}$), 1.69 (3H,

d, $J=6.7\text{Hz}$), 3.52 (3H, s), 4.26 (2H, q, $J=7.1\text{Hz}$),

4.88 (1H, q, $J=6.7\text{Hz}$),

6.73 (1H, dd, $J=8.7\text{Hz}$ and 2.0Hz), 6.84 (1H, d,

$J=2.0\text{Hz}$), 7.35 and 7.46 (4H, ABq, $J=8.6\text{Hz}$),

7.83 (1H, d, $J=8.7\text{Hz}$)

- (29) 2-(4-Chlorophenyl)-6-(1-carboxyethoxy)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 179.5-180.5°C (R,S mixture)

IR (Nujol) : 3250, 1760, 1665, 1600, 1350 cm^{-1}

NMR (CDCl_3 , δ) : 1.74 (3H, d, $J=6.7\text{Hz}$),

3.52 (3H, s), 4.94 (1H, q, $J=6.7\text{Hz}$),

5.54 (1H, brs), 6.76 (1H, dd, $J=1.9\text{Hz}$ and

8.7Hz), 7.40 (4H, ABq, $J=8.6\text{Hz}$),

7.85 (1H, d, $J=8.7\text{Hz}$)

- (30) 2-(4-Chlorophenyl)-6-(1-ethoxycarbonyl-1-methylethoxy)-4-methyl-2H-1,2,4-benzothiadiazine-3(4E)-one 1,1-dioxide

mp : 184-185°C

IR (Nujol) : 1720, 1700, 1580, 1370, 1340 cm^{-1}

NMR (CDCl_3 , δ) : 1.30 (3H, t, $J=7\text{Hz}$), 1.73 (6H, s), 3.53 (3H, s), 4.28 (2H, q, $J=7\text{Hz}$), 6.68 (1H, dd, $J=9\text{Hz}$ and 2Hz), 6.80 (1H, d, $J=2\text{Hz}$), 7.37 (2H, d, $J=9\text{Hz}$), 7.50 (2H, d, $J=9\text{Hz}$), 7.81 (1H, d, $J=9\text{Hz}$)

(31) 2-(4-Chlorophenyl)-6-(3-ethoxycarbonylpropoxy)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 90-92°C

IR (Nujol) : 1730, 1700, 1600, 1580, 1470, 1330, 1320 cm^{-1}

NMR (CDCl_3 , δ) : 1.28 (3H, t, $J=7\text{Hz}$), 2.17 (2H, m), 2.54 (2H, t, $J=7\text{Hz}$), 3.54 (3H, s), 4.15 (2H, t, $J=7\text{Hz}$), 4.17 (2H, q, $J=7\text{Hz}$), 6.70-6.90 (2H, m), 7.30-7.55 (4H, m), 7.84 (1H, d, $J=9\text{Hz}$)

(32) 2-(4-Chlorophenyl)-6-(1-ethoxycarbonylpropoxy)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 105-108°C

IR (Nujol) : 1750, 1690, 1600, 1580, 1210 cm^{-1}

NMR (CDCl_3 , δ) : 1.11 (3H, t, $J=7\text{Hz}$), 1.29 (3H, t, $J=7\text{Hz}$), 2.06 (2H, m), 3.50 (3H, s), 4.26 (2H, q, $J=7\text{Hz}$), 4.69 (1H, t, $J=6\text{Hz}$), 6.74 (1H, dd, $J=9\text{Hz}$ and 6Hz), 6.84 (1H, d, $J=2\text{Hz}$), 7.30-7.50 (4H, m), 7.83 (1H, d, $J=9\text{Hz}$)

(33) 2-(4-Chlorophenyl)-6-(1-ethoxycarbonylcyclobutyloxy)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 140-142°C

IR (Nujol) : 1730, 1690, 1610, 1590, 1360 cm^{-1}
NMR (CDCl_3 , δ) : 1.69 (3H, t, $J=7\text{Hz}$), 1.85-2.90
(6H, m), 3.46 (3H, s), 4.20 (2H, q, $J=7\text{Hz}$),
5 6.57 (1H, dd, $J=9\text{Hz}$ and 2Hz),
6.92 (1H, d, $J=2\text{Hz}$), 7.41 (2H, d, $J=8\text{Hz}$),
7.60 (2H, d, $J=8\text{Hz}$), 7.87 (1H, d, $J=9\text{Hz}$)

(34) 2-(4-Chlorophenyl)-6-(1-carboxy-1-methylethoxy)-
4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one
1,1-dioxide

mp : 208-210°C

IR (Nujol) : 3250, 1750, 1670, 1600, 1350, 1330 cm^{-1}
NMR (CDCl_3 , δ) : 1.75 (6H, s), 3.51 (3H, s),
10 6.74 (1H, dd, $J=9\text{Hz}$ and 2Hz), 6.83 (1H, d,
15 $J=2\text{Hz}$), 7.34 (2H, d, $J=9\text{Hz}$), 7.46 (2H, d,
 $J=9\text{Hz}$), 7.82 (1H, d, $J=9\text{Hz}$)

(35) 2-(4-Chlorophenyl)-6-(3-carboxypropoxy)-4-methyl-
2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 170-171°C

IR (Nujol) : 1700, 1600, 1580, 1330, 1310 cm^{-1}
NMR (CDCl_3 , δ) : 2.19 (2H, m), 2.62 (2H, t, $J=7\text{Hz}$),
20 3.54 (3H, s), 4.17 (2H, t, $J=6\text{Hz}$),
25 6.70-6.90 (2H, m), 7.35 (2H, d, $J=9\text{Hz}$),
7.47 (2H, d, $J=9\text{Hz}$), 7.84 (1H, d, $J=9\text{Hz}$)

(36) 2-(4-Chlorophenyl)-6-(1-carboxypropoxy)-4-methyl-
2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 179-181°C

IR (Nujol) : 3250, 1760, 1680, 1600, 1590,
30 1380, 1200 cm^{-1}
NMR (CDCl_3 , δ) : 1.15 (3H, t, $J=7\text{Hz}$), 2.11 (2H, m),
3.53 (3H, s), 4.78 (1H, t, $J=6\text{Hz}$),
35 6.76 (1H, dd, $J=9\text{Hz}$ and 2Hz), 6.86 (1H, d,
 $J=2\text{Hz}$), 7.30-7.50 (4H, m), 7.85 (1H, d, $J=9\text{Hz}$)

(37) 2-(4-Chlorophenyl)-6-(1-carboxycyclobutyloxy)-
4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one
1,1-dioxide

mp : 148-151°C

IR (Nujol) : 1700, 1600, 1380, 1320, 1180 cm^{-1}

NMR (CCl_3 , δ) : 2.00-2.30 (2H, m), 2.50-2.75
(2H, m), 2.78-2.95 (2H, m), 3.51 (3H, s),
6.53 (1H, dd, J=9Hz and 2Hz), 6.73 (1H, d,
J=2Hz), 7.34 (2H, d, J=9Hz), 7.46 (2H, d,
J=9Hz), 7.80 (1H, d, J=9Hz)

(38) 4-Isopropyl-2-(4-Chlorophenyl)-6-methoxy-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 166-168°C

IR (Nujol) : 1690, 1600, 1570, 1460, 1340, 1300

cm^{-1}
NMR ($\text{DMSO}-d_6$, δ) : 1.54 (6H, d, J=6Hz), 3.94 (3H,
s), 4.61 (1H, m), 6.90-7.10 (2H, m),
7.30-7.70 (4H, m), 7.85 (1H, d, J=9Hz)

(39) 2-(4-Chlorophenyl)-6-isopropoxy-4-isopropyl-2H-1,
2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 158-160°C

IR (Nujol) : 1690, 1590, 1490, 1460, 1340, 1300
 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 1.34 (6H, d, J=6Hz), 1.52 (6H,
d, J=6Hz), 4.58 (1H, m), 4.88 (1H, m),
6.90-7.05 (2H, m), 7.30-7.65 (4H, m), 7.82
(1H, d, J=9Hz)

(40) 2-(4-Chlorophenyl)-4-ethyl-6-methoxy-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 106-107°C

IR (Nujol) : 1690, 1600, 1570, 1490, 1460, 1350,
1310 cm^{-1}

NMR (DMSO- D_6 , δ) : 1.28 (3H, t, J=7Hz), 3.95 (3H, s), 4.14 (2H, q, J=7Hz), 7.03 (1H, d, J=9Hz), 7.09 (1H, s), 7.42 (2H, d, J=9Hz), 7.60 (2H, d, J=9Hz), 7.90 (1H, d, J=9Hz)

5

(41) 2-(4-Chlorophenyl)-4-ethyl-6-isopropoxy-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 167-168°C

IR (Nujol) : 1700, 1600, 1580, 1460, 1340, 1310 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.26 (3H, t, J=7Hz), 1.34 (6H, d, J=6Hz), 4.13 (2H, q, J=7Hz), 7.05-7.09 (2H, m), 7.42 (2H, d, J=9Hz), 7.60 (2H, d, J=9Hz), 7.87 (2H, d, J=9Hz)

(42) (1R)-(+)-2-(4-Chlorophenyl)-6-[1-(ethoxycarbonyl)ethoxy]-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 86-88°C

$[\alpha]_D +24.0^\circ$ (C=1.0, EtOH)

IR (Nujol) : 1740, 1690, 1680, 1600, 1590, 1500, 1210, 1185 cm^{-1}

NMR (CDCl $_3$, δ) : 1.30 (3H, t, J=7Hz), 1.69 (3H, d, J=7Hz), 3.53 (3H, s), 4.26 (2H, q, J=7Hz), 4.87 (1H, q, J=7Hz), 6.74 (1H, dd, J=2Hz and 9Hz), 6.83 (1H, d, J=9Hz), 7.35 (2H, d, J=9Hz), 7.46 (2H, d, J=9Hz), 7.83 (1H, d, J=9Hz)

30

(43) (1S)-(-)-2-(4-Chlorophenyl)-6-[1-(ethoxycarbonyl)ethoxy]-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 96-98°C

$[\alpha]_D -24.7^\circ$ (C=1.0, EtOH)

IR (Nujol) : 1730, 1690, 1680, 1600, 1590, 1340, 1190 cm^{-1}

35

NMR (CDCl₃, δ) : 1.29 (3H, t, J=7Hz), 1.69 (3H, d, J=7Hz), 3.52 (3H, s), 4.26 (2H, q, J=7Hz), 4.88 (1H, q, J=7Hz), 6.74 (1H, d, J=9Hz), 6.83 (1H, s), 7.35 (2H, d, J=9Hz), 7.46 (2H, d, J=9Hz), 7.83 (1H, d, J=9Hz)

(44) (1R)-(+)-2-(4-Chlorophenyl)-6-(1-carboxyethoxy)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 75-85 °C

$[\alpha]_D^{25} +16.4^\circ$ (C=1.0, EtOH)

IR (Nujol) : 3200, 1740, 1700, 1690, 1660, 1600, 1580, 1380, 1130 cm⁻¹

NMR (CDCl₃, δ) : 1.77 (3H, d, J=7Hz), 3.55 (3H, s), 4.98 (1H, q, J=7Hz), 6.79 (1H, dd, J=2Hz and 9Hz), 6.88 (1H, d, J=2Hz), 7.37 (2H, d, J=9Hz), 7.49 (2H, d, J=9Hz), 7.88 (1H, d, J=9Hz)

(45) (1S)-(-)-2-(4-Chlorophenyl)-6-(1-carboxyethoxy)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 85-95 °C

$[\alpha]_D^{25} -17.0^\circ$ (C=1.0, EtOH)

IR (Nujol) : 3200, 1740, 1700, 1665, 1600, 1580, 1200, 1130 cm⁻¹

NMR (CDCl₃, δ) : 1.75 (3H, d, J=7Hz), 3.52 (3H, s), 4.95 (1H, q, J=7Hz), 6.50 (1H, bs), 6.75 (1H, dd, J=2Hz and 9Hz), 6.88 (1H, d, J=2Hz), 7.32 (2H, d, J=9Hz), 7.45 (2H, d, J=9Hz), 7.85 (1H, d, J=9Hz)

(46) 2-Cyclohexyl-6-methoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 124.5-126°C

IR (Nujol) : 1690, 1595, 1325, 1310, 1300,
1175 cm⁻¹

NMR (DMSO-d₆, δ) : 1.0-1.5 (3H, m), 1.55-1.9 (5H, m), 2.05-2.35 (2H, m), 3.45 (3H, s), 3.90 (3H, s), 4.15-4.4 (1H, m), 6.95 (1H, d, J=8.3Hz), 6.97 (1H, s), 7.78 (1H, d, J=8.3Hz)

(47) 6-Isopropoxy-4-methyl-2-(2-pyridyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 173-174°C

IR (Nujol) : 1700, 1600, 1590, 1340, 1215 cm⁻¹

NMR (CDCl₃, δ) : 1.40 (6H, d, J=6Hz), 3.53 (3H, s), 4.6-4.8 (1H, m), 6.73-6.85 (2H, m), 7.35-7.55 (2H, m), 7.82 (1H, d, J=8.7Hz), 7.8-7.95 (1H, m), 8.6-8.68 (1H, m)

(48) 6-Methoxy-4-methyl-2-pentyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 85-88°C

IR (Nujol) : 1690, 1600, 1450, 1330, 1310,
1180 cm⁻¹

NMR (DMSO-d₆, δ) : 0.84 (3H, t, J=6Hz), 1.10-1.40 (4H, m), 1.50-1.75 (2H, m), 3.47 (3H, s), 3.75 (2H, t, J=7Hz), 3.91 (3H, s), 6.90-7.05 (2H, m), 7.82 (1H, d, J=9Hz)

(49) 2-(4-Chlorophenyl)-4-methyl-6-(N-methylacetyl-amino)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 168-172°C

IR (Nujol) : 1690, 1655, 1590, 1340 cm⁻¹

NMR (CDCl₃, δ) : 2.09 (3H, s), 3.38 (3H, s), 3.57 (3H, s), 7.10-7.55 (6H, m), 7.95-8.05 (1H, m)

(50) 6-Methoxy-2-(4-methoxycarbonylphenyl)-4-methyl-
2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 153-156°C

IR (Nujol) : 1725, 1690, 1590, 1320, 1280 cm^{-1}

NMR (DMSO-d_6 , δ) : 3.52 (3H, s), 3.89 (3H, s),
3.95 (3H, s), 6.97-7.13 (2H, m), 7.55 and
8.10 (4H, ABq, $J=8.3\text{Hz}$), 7.90 (1H, d, $J=8.8\text{Hz}$)

(51) 6-Cyclohexylmethoxy-4-methyl-2-(2-pyridyl)-2H-
1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 161.5-162.5°C

IR (Nujol) : 1700, 1600, 1310 cm^{-1}

NMR (CDCl_3 , δ) : 0.95-1.45 (5H, m), 1.65-2.0 (6H, m),
3.54 (3H, s), 3.86 (2H, d, $J=6\text{Hz}$), 6.73-6.85
(2H, m), 7.35-7.55 (2H, m), 7.82 (1H, d,
 $J=8.5\text{Hz}$), 7.81-7.95 (1H, m), 8.6-8.67 (1H, m)

(52) 2-(4-Methoxycarbonylmethylphenyl)-6-methoxy-4-methyl-
2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 173-176°C

IR (Nujol) : 1735, 1690, 1600, 1335, 1320 cm^{-1}

NMR (DMSO-d_6 , δ) : 3.52 (3H, s), 3.65 (3H, s),
3.79 (2H, s), 3.95 (3H, s), 6.96-7.10 (2H, m),
7.33 and 7.43 (4H, ABq, $J=8.3\text{Hz}$), 7.88 (1H,
d, $J=8.7\text{Hz}$)

(53) 2-(3-Ethoxycarbonylpropyl)-6-methoxy-4-methyl-2H-
1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 63-65°C

IR (Nujol) : 1740, 1690, 1600, 1480, 1380, 1360,
1340, 1320, 1180 cm^{-1}

NMR (CDCl_3 , δ) : 1.23 (3H, t, $J=7\text{Hz}$), 2.06 (2H, m),
2.37 (2H, t, $J=7\text{Hz}$), 3.49 (3H, s), 3.90 (3H, s),
3.96 (2H, t, $J=7\text{Hz}$), 4.09 (2H, q, $J=7\text{Hz}$),
6.69 (1H, d, $J=2\text{Hz}$), 6.80 (1H, dd, $J=2\text{Hz}$ and
9Hz), 7.79 (1H, d, $J=9\text{Hz}$)

(54) 2-(4-Chlorophenyl)-4,6-dimethyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 164-166°C

IR (Nujol) : 1700, 1600, 1490, 1350, 1330, 1280,
1180, 1090 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.50 (3H, s), 3.51 (3H, s),
7.28 (1H, d, J=8Hz), 7.41 (2H, d, J=9Hz),
7.50 (1H, s), 7.60 (2H, d, J=9Hz), 7.84
(1H, d, J=8Hz)

(55) 2-[2-(4,6-Dimethylpyridyl)]-6-isopropoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 202-203°C

IR (Nujol) : 1700, 1600, 1580, 1350, 1320,
1180 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.37 (6H, d, J=6Hz), 2.34 (3H, s), 2.48 (3H, s), 3.49 (3H, s), 4.89 (1H, m),
7.01 (1H, d, J=9Hz), 7.04 (1H, s), 7.13 (1H, s), 7.24 (1H, s), 7.80 (1H, d, J=9Hz)

(56) 2-(4-Chlorophenyl)-4-methyl-6-trifluoromethyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 148-150°C

IR (Nujol) : 1700, 1380, 1360, 1270, 1190, 1140,
1080 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.60 (3H, s), 7.45 (2H, d, J=9Hz), 7.62 (2H, d, J=9Hz), 7.81 (1H, d, J=8Hz), 7.96 (1H, s), 8.21 (1H, d, J=8Hz)

(57) 6-Isopropoxy-4-methyl-2-(2-pyrimidinyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 176-178°C

IR (Nujol) : 1700, 1600, 1400, 1380, 1350, 1330,
1280, 1230 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.33 (6H, d, J=6Hz),

3.53 (3H, s), 4.90 (1H, m), 7.00 (1H, dd, J=2Hz and 9Hz), 7.10 (1H, d, J=7Hz), 7.67 (1H, t, J=4Hz), 7.84 (1H, t, J=9Hz), 8.97 (2H, d, J=4Hz)

5

(58) 6-Methoxy-4-methyl-2-(4-phenoxyphenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 184-186°C

IR (Nujol) : 1690, 1590, 1330, 1180 cm⁻¹

10

NMR (DMSO-d₆, δ) : 3.52 (3H, s), 3.94 (3H, s), 6.95-7.55 (11H, m), 7.89 (1H, d, J=9Hz)

(59) 2-(4-Isopropylphenyl)-6-methoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

15

mp : 158-159°C

IR (Nujol) : 1700, 1595, 1330, 1310, 1125 cm⁻¹

NMR (DMSO-d₆, δ) : 1.24 (6H, d, J=7Hz), 2.98 (1H, m), 3.51 (3H, s), 3.94 (3H, s), 7.01 (1H, dd, J=2Hz and 9Hz), 7.06 (1H, d, J=2Hz), 7.27 and 7.39 (4H, ABq, J=8Hz), 7.87 (1H, d, J=9Hz)

20

(60) 2-[(3-Chloro-4-methyl)phenyl]-6-methoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

25

mp : 208-211°C

IR (Nujol) : 1695, 1595, 1315, 1180 cm⁻¹

NMR (DMSO-d₆, δ) : 2.40 (3H, s), 3.51 (3H, s), 3.94 (3H, s), 7.02 (1H, dd, J=2Hz and 9Hz), 7.07 (1H, d, J=2Hz), 7.39 (1H, dd, J=2Hz and 8Hz), 7.46 (1H, d, J=2Hz), 7.52 (1H, d, J=8Hz), 7.89 (1H, d, J=9Hz)

30

(61) 6-Methoxy-4-methyl-2-(4-methylthiophenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

35

mp : 154-155°C

IR (Nujol) : 1690, 1610, 1580, 1490, 1310, 1185,
1135 cm^{-1}

NMR (CDCl_3 , δ) : 2.51 (3H, s), 3.54 (3H, s),
3.93 (3H, s), 6.76 (1H, d, $J=2\text{Hz}$), 6.83 (1H,
5 dd, $J=2\text{Hz}$ and 9Hz), 7.32 (4H, s), 7.85 (1H,
d, $J=9\text{Hz}$)

(62) 2-(4-Dimethylaminophenyl)-6-methoxy-4-methyl-2H-
1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 244-245°C

IR (Nujol) : 1690, 1600, 1520, 1330, 1310, 1180,
1130 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 2.96 (6H, s), 3.50 (3H, s),
3.94 (3H, s), 6.75 (2H, d, $J=9\text{Hz}$), 7.10
15 (2H, d, $J=9\text{Hz}$), 7.02 (1H, dd, $J=2\text{Hz}$ and 9Hz),
7.02 (1H, d, $J=2\text{Hz}$), 7.85 (1H, d, $J=9\text{Hz}$)

(63) 2-(4-Chlorobenzyl)-6-isopropoxy-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

IR (Neat) : 2980, 1680, 1600, 1580, 1330, 1180,
1110 cm^{-1}

NMR (CDCl_3 , δ) : 1.38 (6H, d, $J=6.0\text{Hz}$), 3.45
(3H, s), 4.55-4.75 (1H, m), 5.00 (2H, s),
6.65 (1H, d, $J=1.9\text{Hz}$), 6.77 (1H, dd,
25 $J=1.9$ and 8.8Hz), 7.27 and 7.40 (4H, ABq,
 $J=8.4\text{Hz}$), 7.80 (1H, d, $J=8.8\text{Hz}$)

(64) 2-Cyclohexyl-6-isopropoxy-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 111-112°C

IR (Nujol) : 1685, 1605, 1330, 1180, 1110 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 1.0-1.45 (3H, m), 1.31 (6H, d,
 $J=6.0\text{Hz}$), 1.5-1.9 (5H, m), 2.05-2.35 (2H, m),
3.43 (3H, s), 4.25-4.4 (1H, m), 4.84 (1H, m),
35 6.91 (1H, s), 6.78 (1H, d, $J=9.0\text{Hz}$),
7.75 (1H, d, $J=9.0\text{Hz}$)

(65) 6-Isopropoxy-4-methyl-2-pentyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 44-46°C

IR (Nujol) : 1690, 1600, 1580, 1460, 1340, 1320,
1190 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 0.84 (3H, t, $J=6\text{Hz}$), 1.05-1.40
(4H, m), 1.31 (6H, d, $J=6\text{Hz}$), 1.50-1.75
(2H, m), 3.44 (3H, s), 3.74 (2H, t, $J=7\text{Hz}$),
4.85 (1H, m), 6.90-7.05 (2H, m), 7.78 (1H,
d, $J=9\text{Hz}$)

(66) 6-Isopropoxy-2-(4-isopropoxycarbonylphenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 128-129°C

IR (Nujol) : 1720, 1710, 1610, 1340, 1280 cm^{-1}

NMR (CDCl_3 , δ) : 1.38 (6H, d, $J=6.8\text{Hz}$), 1.43 (6H,
d, $J=6.5\text{Hz}$), 3.54 (3H, s), 4.63-4.8 (1H, m),
5.2-5.35 (1H, m), 6.76 (1H, d, $J=2\text{Hz}$),
6.82 (1H, dd, $J=2\text{Hz}$ and 8.7Hz) 7.50 and
8.15 (4H, ABq, $J=8.4\text{Hz}$), 7.8 (1H, d, $J=8.7\text{Hz}$)

(67) 2-(4-Isopropoxycarbonylmethylphenyl)-6-isopropoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 117-120°C

IR (Nujol) : 1730, 1690, 1595, 1335, 1325 cm^{-1}

NMR (CDCl_3 , δ) : 1.24 (6H, d, $J=6.0\text{Hz}$), 1.41 (6H,
d, $J=6.0\text{Hz}$), 3.52 (3H, s), 3.63 (2H, s),
4.6-4.8 (1H, m), 4.9-5.1 (1H, m), 6.7-6.85
(2H, m), 7.3-7.5 (4H, m), 7.75-7.80 (1H, m)

(68) 4-Isopropoxy-2-(3-isopropoxycarbonylpropyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

IR (CHCl_3) : 1720, 1700, 1600, 1580, 1340, 1270,
1120 cm^{-1}

NMR (CDCl_3 , δ) : 1.12 (6H, d, $J=6\text{Hz}$), 1.30 (6H, d, $J=6\text{Hz}$), 1.99 (2H, m), 2.28 (2H, t, $J=7\text{Hz}$), 3.41 (3H, s), 3.90 (2H, t, $J=7\text{Hz}$), 4.60 (1H, m), 4.92 (1H, m), 6.60 (1H, d, $J=2\text{Hz}$), 6.70 (1H, dd, $J=2\text{Hz}$ and 9Hz), 7.70 (1H, d, $J=9\text{Hz}$)

(69) 2-(4-Chlorophenyl)-5,7-dichloro-6-isopropoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 185-188°C

IR (Nujol) : 1710, 1470, 1380, 1360, 1190 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 1.38 (6H, d, $J=6\text{Hz}$), 3.33 (3H, s), 4.75 (1H, m), 7.44 (2H, d, $J=9\text{Hz}$), 7.61 (2H, d, $J=9\text{Hz}$), 8.14 (1H, s)

(70) (1R)-(+)-6-[1-(Ethoxycarbonyl)ethoxy]-4-methyl-2-phenyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 137.5-139°C

IR (Nujol) : 1740, 1700, 1605, 1340, 1210, 1140 cm^{-1}

NMR (CDCl_3 , δ) : 1.30 (3H, t, $J=7\text{Hz}$), 1.69 (3H, d, $J=7\text{Hz}$), 3.53 (3H, s), 4.26 (2H, q, $J=7\text{Hz}$), 4.88 (1H, q, $J=7\text{Hz}$), 6.73 (1H, dd, $J=2\text{Hz}$ and 9Hz), 6.84 (1H, d, $J=2\text{Hz}$), 7.35-7.55 (5H, m), 7.84 (1H, d, $J=9\text{Hz}$)

(71) (1R)-(+)-6-[1-(Ethoxycarbonyl)ethoxy]-4-methyl-2-(4-phenoxyphenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 128-130°C

IR (Nujol) : 1740, 1685, 1610, 1330, 1195, 1130 cm^{-1}

NMR (CDCl_3 , δ) : 1.29 (3H, t, $J=7\text{Hz}$), 1.69 (3H, d, $J=7\text{Hz}$), 3.53 (3H, s), 4.26 (2H, q, $J=7\text{Hz}$),

4.88 (1H, q, J=7Hz), 6.75 (1H, dd, J=2Hz
and 9Hz), 6.83 (1H, d, J=2Hz), 7.0-7.45
(9H, m), 7.85 (1H, d, J=9Hz)

5 (72) (1R)-(+) -6-[1-(ethoxycarbonyl)ethoxy]-2-(4-isopropyl-
phenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-
one 1,1-dioxide

mp : 154-155°C

10 IR (Nujol) : 1740, 1695, 1600, 1340, 1310, 1200,
1130 cm⁻¹

15 NMR (CDCl₃, δ) : 1.27 (6H, d, J=7Hz), 1.29 (3H,
t, J=7Hz), 1.69 (3H, d, J=7Hz), 2.95 (1H, m),
3.52 (3H, s), 4.26 (2H, q, J=7Hz), 4.88 (1H,
q, J=7Hz), 6.73 (1H, dd, J=2Hz and 9Hz),
6.83 (1H, d, J=2Hz), 7.32 (4H, s), 7.83 (1H,
d, J=9Hz)

20 (73) (1R)-(+) -2-[(3-Chloro-4-methyl)phenyl]-6-[1-(
ethoxycarbonyl)ethoxy]-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 149-150°C

IR (Nujol) : 1740, 1685, 1600, 1335 cm⁻¹

25 NMR (DMSO-d₆, δ) : 1.21 (3H, t, J=7Hz), 1.58
(3H, d, J=7Hz), 2.40 (3H, s), 3.48 (3H, s),
4.18 (2H, q, J=7Hz), 5.33 (1H, q, J=7Hz),
6.95 (1H, dd, J=2Hz and 9Hz), 7.08 (1H, d,
J=2Hz), 7.30 (1H, dd, J=2Hz and 8Hz), 7.47
(1H, d, J=2Hz), 7.51 (1H, d, J=8Hz),
30 7.87 (1H, d, J=9Hz)

(74) (1R)-(+) -2-Cyclohexyl-6-[1-(ethoxycarbonyl)ethoxy]-
4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one
1,1-dioxide

mp : 139-141°C

35 IR (Nujol) : 1740, 1690, 1600, 1580, 1340, 1300,
1200, 1170 cm⁻¹

NMR (CDCl₃, δ) : 1.28 (3H, t, J=6Hz), 1.16-1.45
(3H, m), 1.66 (3H, d, J=6Hz), 1.80-1.92 (5H,
m), 2.22-2.42 (2H, m), 3.44 (3H, s), 4.23
(2H, q, J=6Hz), 4.29-4.49 (1H, m), 4.83 (1H,
q, J=6Hz), 6.65 (1H, dd, J=2Hz and 8Hz), 6.71
(1H, d, J=2Hz), 7.74 (1H, d, J=6Hz)

(75) (1R)-(+) -6-[1-(Ethoxycarbonyl)ethoxy]-4-methyl-2-
(4-methylphenyl)-2H-1,2,4-benzothiadiazine-3(4H)-
one 1,1-dioxide

mp : 134-135°C

IR (Nujol) : 1740, 1680, 1600, 1580, 1340, 1320,
1200, 1130 cm⁻¹

NMR (CDCl₃, δ) : 1.30 (3H, t, J=6Hz), 1.69 (3H, d,
J=6Hz), 2.40 (3H, s), 3.52 (3H, s), 4.25
(2H, q, J=6Hz), 4.88 (1H, q, J=6Hz), 6.70
(1H, dd, J=2Hz and 8Hz), 6.82 (1H, d, J=2Hz),
7.28 (4H, s), 7.83 (1H, d, J=8Hz)

(76) (1R)-(+) -6-[1-(Ethoxycarbonyl)ethoxy]-4-methyl-2-
(2-pyridyl)-2H-1,2,4-benzothiadiazine-3(4H)-one
1,1-dioxide

mp : 153-154°C

IR (Nujol) : 1740, 1690, 1605, 1580, 1460, 1330,
1205, 1115 cm⁻¹

NMR (CDCl₃, δ) : 1.29 (3H, t, J=7Hz), 1.69 (3H,
d, J=7Hz), 3.52 (3H, s), 4.25 (2H, q, J=7Hz),
4.86 (1H, q, J=7Hz), 6.72 (1H, dd, J=2Hz and
8Hz), 6.84 (1H, d, J=2Hz), 7.38-7.51 (2H, m),
7.82 (1H, d, J=8Hz), 7.90 (1H, dd, J=2Hz and
8Hz), 8.62-8.66 (1H, m)

(77) (1R)-(+) -2-(3,4-Dichlorophenyl)-6-[1-(ethoxy-
carbonyl)ethoxy]-4-methyl-2H-1,2,4-benzothiadiazine-
3(4H)-one 1,1-dioxide

mp : 108-110°C

IR (Nujol) : 1720, 1685, 1600, 1190, 1135 cm^{-1}

NMR (CDCl_3 , δ) : 1.30 (3H, t, $J=8\text{Hz}$), 1.69 (3H, d, $J=7\text{Hz}$), 3.53 (3H, s), 4.29 (2H, q, $J=8\text{Hz}$), 4.87 (1H, q, $J=7\text{Hz}$), 6.74 (1H, dd, $J=2\text{Hz}$ and 9Hz), 6.83 (1H, d, $J=2\text{Hz}$), 7.28 (1H, dd, $J=2\text{Hz}$ and 9Hz), 7.53 (1H, d, $J=2\text{Hz}$), 7.55 (1H, d, $J=9\text{Hz}$), 7.83 (1H, d, $J=9\text{Hz}$)

(78) (1R)-(+)-2-(3-Chlorophenyl)-6-[1-(ethoxycarbonyl)-ethoxy]-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 135-137°C

IR (Nujol) : 1740, 1700, 1600, 1580, 1340, 1210 cm^{-1}

NMR (CDCl_3 , δ) : 1.30 (3H, t, $J=7\text{Hz}$), 1.70 (3H, d, $J=7\text{Hz}$), 3.46 (3H, s), 4.27 (2H, q, $J=7\text{Hz}$), 4.86 (1H, q, $J=7\text{Hz}$), 6.81-7.37 (6H, m), 7.85 (1H, d, $J=9\text{Hz}$)

(79) (1R)-(+)-2-(2-Chlorophenyl)-6-[1-(ethoxycarbonyl)-ethoxy]-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

IR (CHCl_3) : 1745, 1700, 1605, 1580, 1350, 1320, 1140 cm^{-1}

NMR (CDCl_3 , δ) : 1.30 (3H, t, $J=7\text{Hz}$), 1.69 (3H, d, $J=7\text{Hz}$), 3.54 (3H, s), 4.27 (2H, q, $J=7\text{Hz}$), 4.88 (1H, q, $J=7\text{Hz}$), 6.70-7.72 (6H, m), 7.82 (1H, d, $J=9\text{Hz}$)

(80) (1R)-(+)-6-[1-(Ethoxycarbonyl)ethoxy]-2-(4-fluorophenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 100-102°C

IR (Nujol) : 1740, 1680, 1605, 1370, 1340 cm^{-1}

NMR (CDCl₃, δ) : 1.30 (3H, t, J=7Hz), 1.69 (3H, d, J=7Hz), 3.52 (3H, s), 4.26 (2H, q, J=7Hz), 4.88 (1H, q, J=7Hz), 6.71-7.43 (6H, m), 7.83 (1H, d, J=9Hz)

5

(81) (1R)-(+)-6-[1-(Ethoxycarbonyl)ethoxy]-4-methyl-2-(4-methylthiophenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 156-157°C

10

IR (Nujol) : 1720, 1605, 1600, 1580, 1205, 1180, 1130 cm⁻¹

15

NMR (CDCl₃, δ) : 1.29 (3H, t, J=7Hz), 1.69 (3H, d, J=7Hz), 2.50 (3H, s), 3.52 (3H, s), 4.25 (2H, q, J=7Hz), 4.87 (1H, q, J=7Hz), 6.72 (1H, dd, J=2Hz and 9Hz), 6.82 (1H, d, J=2Hz), 7.32 (4H, s), 7.83 (1H, d, J=9Hz)

20

(82) (1R)-(+)-2-(4-Dimethylaminophenyl)-6-[1-(ethoxycarbonyl)ethoxy]-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 190-192°C

IR (Nujol) : 1715, 1680, 1600, 1195, 1130 cm⁻¹

25

NMR (CDCl₃, δ) : 1.29 (3H, t, J=7Hz), 1.67 (3H, d, J=7Hz), 3.00 (6H, s), 3.51 (3H, s), 4.25 (2H, q, J=7Hz), 4.87 (1H, q, J=7Hz), 6.69-6.81 (4H, m), 7.24 (2H, d, J=8Hz), 7.84 (1H, d, J=8Hz)

30

(83) (1R)-(+)-6-(1-Carboxyethoxy)-4-methyl-2-phenyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 184-185.5°C

IR (Nujol) : 3200, 1750, 1660, 1610, 1320, 1180 cm⁻¹

35

NMR (CDCl₃, δ) : 1.74 (3H, d, J=7Hz), 3.53 (3H, s), 3.55-4.1 (1H, br), 4.95 (1H, q, J=7Hz), 6.76 (1H, dd, J=2Hz and 9Hz), 6.85 (1H, d, J=2Hz), 7.35-7.55 (5H, m), 7.86 (1H, d, J=9Hz)

(84) (1R)-(+)-6-(1-Carboxyethoxy)-4-methyl-2-(4-phenoxyphenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 106°C (dec.)

IR (Nujol) : 3600-2400, 1740, 1695, 1665, 1600, 1585, 1345, 1215 cm^{-1}

NMR (CDCl_3 , δ) : 1.74 (3H, d, $J=7\text{Hz}$), 3.53 (3H, s), 3.63 (1H, br), 4.95 (1H, q, $J=7\text{Hz}$), 6.76 (1H, dd, $J=2\text{Hz}$ and 9Hz), 6.85 (1H, d, $J=2\text{Hz}$), 7.0-7.45 (9H, m), 7.85 (1H, d, $J=9\text{Hz}$)

(85) (1R)-(+)-6-(1-Carboxyethoxy)-2-(4-isopropylphenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 74°C (dec.)

IR (Nujol) : 3600-2400, 1730, 1695, 1600, 1340, 1315 cm^{-1}

NMR (CDCl_3 , δ) : 1.27 (6H, d, $J=7\text{Hz}$), 1.74 (3H, d, $J=7\text{Hz}$), 2.76 (1H, m), 3.43 (1H, br), 3.52 (3H, s), 4.95 (1H, q, $J=7\text{Hz}$), 6.76 (1H, dd, $J=2\text{Hz}$ and 9Hz), 6.85 (1H, d, $J=2\text{Hz}$), 7.32 (4H, s), 7.85 (1H, d, $J=9\text{Hz}$)

(86) (1R)-(+)-6-(1-Carboxyethoxy)-2-[(3-chloro-4-methyl)phenyl]-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 184-186°C

IR (Nujol) : 3600-2500, 1720, 1700, 1595, 1330 cm^{-1}

NMR (CDCl_3 , δ) : 1.75 (3H, d, $J=7\text{Hz}$), 2.42 (3H, s), 3.25 (1H, br), 3.53 (3H, s), 4.94 (1H, q, $J=7\text{Hz}$), 6.77 (1H, dd, $J=2\text{Hz}$ and 9Hz), 6.85 (1H, d, $J=2\text{Hz}$), 7.23 (1H, dd, $J=2\text{Hz}$ and 8Hz), 7.34 (1H, d, $J=8\text{Hz}$), 7.41 (1H, d, $J=2\text{Hz}$), 7.85 (1H, d, $J=9\text{Hz}$)

(87) (1R)-(+)-6-(1-Carboxyethoxy)-4-methyl-2-(4-trifluoromethylphenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 162-163°C

IR (CHCl₃) : 3600-3300, 1720, 1690, 1600, 1340, 1320, 1130 cm⁻¹

NMR (CDCl₃, δ) : 1.75 (3H, d, J=6Hz), 3.54 (3H, s), 4.90-5.01 (1H, q, J=6Hz), 6.77 (1H, dd, J=2Hz and 8Hz), 6.87 (1H, d, J=2Hz), 7.54 (2H, d, J=8Hz), 7.74 (2H, d, J=8Hz), 7.86 (1H, d, J=8Hz)

(88) (1R)-(+)-6-(1-Carboxyethoxy)-2-cyclohexyl-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 76-77°C

IR (CHCl₃) : 3600-2400, 1720, 1680, 1600, 1330, 1310, 1170 cm⁻¹

NMR (CDCl₃, δ) : 1.20-1.45 (3H, m), 1.70 (3H, d, J=6Hz), 1.82-1.88 (5H, m), 2.20-2.38 (2H, m), 3.44 (3H, s), 4.35-4.47 (1H, m), 4.76 (1H, s), 4.89 (1H, q, J=6Hz), 6.67-6.74 (2H, m), 7.75 (1H, d, J=8Hz)

(89) (1R)-(+)-6-(1-Carboxyethoxy)-4-methyl-2-(4-methylphenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 182-183°C

IR (CHCl₃) : 1700, 1600, 1320, 1130 cm⁻¹

NMR (CDCl₃, δ) : 1.74 (3H, d, J=6Hz), 2.40 (3H, s), 3.17 (1H, br s), 3.52 (3H, s), 4.89-5.00 (1H, q, J=6Hz), 6.75 (1H, dd, J=2Hz and 8Hz), 6.84 (1H, d, J=2Hz), 7.29 (4H, s), 7.85 (1H, d, J=8Hz)

(90) (1R)-(+)-6-(1-Carboxyethoxy)-4-methyl-2-(2-pyridyl)-
2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 142-143°C

IR (Nujol) : 3700-2300, 1700, 1600, 1350, 1320,
1275, 1210, 1190 cm^{-1}

NMR (CDCl_3 , δ) : 1.56 (3H, d, $J=7\text{Hz}$), 3.47 (3H, s),
5.17 (1H, q, $J=7\text{Hz}$), 6.92 (1H, dd, $J=2\text{Hz}$ and
9Hz), 7.08 (1H, d, $J=2\text{Hz}$), 7.45-7.60 (2H, m),
7.84 (1H, d, $J=9\text{Hz}$), 8.00 (1H, m), 8.56-8.59
(1H, m)

(91) (1R)-(+)-6-(1-Carboxyethoxy)-2-(3,4-dichlorophenyl)-
4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-
dioxide

mp : 105-106°C

IR (Nujol) : 3250-2400, 1735, 1690, 1600, 1585,
1300, 1290, 1175 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 1.57 (3H, d, $J=7\text{Hz}$), 3.48 (3H,
s), 5.20 (1H, q, $J=7\text{Hz}$), 6.93 (1H, dd, $J=2\text{Hz}$
and 9Hz), 7.08 (1H, d, $J=2\text{Hz}$), 7.46 (1H, dd,
 $J=2\text{Hz}$ and 9Hz), 7.76-7.93 (3H, m),

(92) (1R)-(+)-6-(1-Carboxyethoxy)-2-(3-chlorophenyl)-4-
methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-
dioxide

mp : 174-176°C

IR (Nujol) : 1725, 1700, 1610, 1580, 1330, 1310,
1180 cm^{-1}

NMR (CDCl_3 , δ) : 1.74 (3H, d, $J=7\text{Hz}$), 2.72 (1H,
br s), 3.53 (3H, s), 4.95 (1H, q, $J=7\text{Hz}$),
6.74-7.51 (6H, m), 7.86 (1H, d, $J=9\text{Hz}$)

(93) (1R)-(+)-6-(1-Carboxyethoxy)-2-(2-chlorophenyl)-4-

methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 110-112°C

IR (Nujol) : 1740, 1700, 1600, 1580, 1375,
1190 cm^{-1}

NMR (CDCl_3 , δ) : 1.75 (3H, d, $J=7\text{Hz}$), 3.55 (3H, s),
4.95 (1H, q, $J=7\text{Hz}$), 6.74-7.67 (6H, m), 7.85
(1H, d, $J=9\text{Hz}$)

(94) (1R)-(+)-6-(1-Carboxyethoxy)-2-(4-fluorophenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 130-132°C

IR (Nujol) : 1740, 1700, 1600, 1500, 1380,
1210 cm^{-1}

NMR (CDCl_3 , δ) : 1.74 (3H, d, $J=7\text{Hz}$), 3.52 (3H, s),
4.94 (1H, q, $J=7\text{Hz}$), 5.80 (1H, br s), 6.74-7.43
(6H, m), 7.85 (1H, d, $J=9\text{Hz}$)

(95) (1R)-(+)-6-(1-Carboxyethoxy)-4-methyl-2-(4-methylthiophenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 143-144°C

IR (Nujol) : 3350-2300, 1730, 1660, 1600, 1580,
1190, 1090 cm^{-1}

NMR (CDCl_3 , δ) : 1.74 (3H, d, $J=7\text{Hz}$), 2.50 (3H, s),
3.53 (3H, s), 4.95 (1H, q, $J=7\text{Hz}$), 6.76 (1H,
dd, $J=2\text{Hz}$ and 9Hz), 6.85 (1H, d, $J=2\text{Hz}$), 7.32
(4H, s), 7.85 (1H, d, $J=9\text{Hz}$)

(96) (1R)-(+)-6-(1-Carboxyethoxy)-2-(4-dimethylamino-phenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 190°C (dec.)

IR (KBr) : 3400, 2750-2200, 1690, 1590, 1450,
1320, 1180, 1125 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.57 (3H, d, J=7Hz), 2.97 (6H, s),
3.47 (3H, s), 5.22 (1H, q, J=7Hz), 6.85 (2H,
d, J=9Hz), 7.15 (2H, d, J=9Hz), 6.92 (1H, dd,
J=2Hz and 9Hz), 7.05 (1H, d, J=2Hz), 7.85
(1H, d, J=9Hz)

(97) 6-[1-(Carboxy)cyclohexylmethoxy]-2-(4-chlorophenyl)-
4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-
dioxide

mp : 145-150°C

IR (Nujol) : 3300, 1700, 1600, 1580, 1370, 1310,
1190, 1130 cm^{-1}

NMR (CDCl_3 , δ) : 1.10-2.10 (11H, m), 3.40 (3H, s),
4.40 (1H, br s), 6.60 (1H, d, J=9Hz), 6.85
(1H, s), 7.25 (2H, d, J=9Hz), 7.42 (2H, d,
J=9Hz), 7.70 (1H, d, J=9Hz)

(98) (1R)-(+)-6-[1-(Ethoxycarbonyl)ethoxy]-4-methyl-2-(4-
trifluoromethylphenyl)-2H-1,2,4-benzothiadiazine-
3(4H)-one 1,1-dioxide

mp : 124-125°C

IR (Nujol) : 1720, 1685, 1595, 1330, 1130,
1060 cm^{-1}

NMR (CDCl_3 , δ) : 1.30 (3H, t, J=6Hz), 1.70 (3H, d,
J=6Hz), 3.54 (3H, s), 4.26 (2H, q, J=6Hz),
4.88 (1H, q, J=6Hz), 6.75 (1H, dd, J=2Hz and
8Hz), 6.85 (1H, d, J=2Hz), 7.55 (2H, d, J=8Hz),
7.75 (2H, d, J=8Hz), 7.84 (1H, d, J=8Hz)

(99) 6-Cyclohexylmethoxy-2-(4-cyclohexylmethoxycarbonyl-
phenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-
one 1,1-dioxide

mp : 119-121°C

IR (Nujol) : 1720, 1690, 1600, 1320 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.95-1.40 (10H, m),

1.55-1.95 (12H, m), 3.52 (3H, s), 4.00 (2H, d, J=5.8Hz), 4.15 (2H, d, J=5.8Hz), 6.97-7.10 (2H, m), 7.55 and 8.10 (4H, ABq, J=8.3Hz), 7.87 (1H, d, J=8.7Hz)

5

(100) 2-(4-Chlorophenyl)-4-methyl-6-(2-phthalimidoethoxy)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 175-180°C

IR (Nujol) : 1770, 1710, 1605, 1585 cm⁻¹

10

NMR (DMSO-d₆, δ) : 3.50 (3H, s), 4.0-4.1 (2H, m), 4.4-4.5 (2H, m), 6.95-7.05 (2H, m), 7.35-7.45 (2H, m), 7.55-7.56 (3H, m), 7.8-8.0 (4H, m)

(101) 6-[trans-4-(tert-Butoxycarbonylaminomethyl)-cyclohexylmethoxy]-2-(4-chlorophenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 133-136°C

15

IR (Nujol) : 3400, 1690, 1600, 1590, 1520, 1450, 1360, 1340, 1180 cm⁻¹

20

NMR (DMSO-d₆, δ) : 0.75-1.20 (4H, m), 1.40 (9H, s), 1.40-2.00 (6H, m), 2.73 (2H, t, J=6Hz), 3.50 (3H, s), 3.98 (2H, d, J=7Hz), 7.00 (1H, d, J=9Hz), 7.08 (1H, s), 7.40 (2H, d, J=9Hz), 7.60 (2H, d, J=9Hz), 7.88 (1H, d, J=9Hz)

25

(102) 2-(4-Chlorophenyl)-6-[1-(ethoxycarbonyl)cyclohexylmethoxy]-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

30

mp : 128-131°C

IR (Nujol) : 1730, 1690, 1600, 1590, 1380, 1180 cm⁻¹

NMR (CDCl₃, δ) : 1.30 (3H, t, J=8Hz), 1.10-2.10 (11H, m), 3.52 (3H, s), 4.25 (2H, q, J=8Hz), 4.50 (1H, d, J=5Hz), 6.75 (1H, dd, J=2Hz and 9Hz),

35

6.82 (1H, d, J=2Hz), 7.35 (2H, d, J=9Hz),
7.45 (2H, d, J=9Hz), 7.85 (1H, d, J=9Hz)

(103) 2-(4-Chlorophenyl)-4-methyl-6-[2-(tetrahydro-2H-
pyranyl)methoxy]-2H-1,2,4-benzothiadiazine-3(4H)-
one 1,1-dioxide

mp : >250°C

IR (Nujol) : 1700, 1600, 1580, 1490, 1340, 1320,
1190 cm⁻¹

NMR (DMSO-d₆, δ) : 1.20-1.90 (6H, m), 3.40-3.90
(3H, m), 3.50 (3H, s), 4.10 (2H, d, J=6Hz),
7.00 (1H, dd, J=2Hz and 9Hz), 7.10 (1H, d,
J=2Hz), 7.40 (2H, d, J=9Hz), 7.60 (2H, d,
J=9Hz), 7.86 (1H, d, J=9Hz)

(104) 2-(4-Carboxymethylphenyl)-6-isopropoxy-4-methyl-
2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 232-233°C

IR (Nujol) : 3600-2500, 1700, 1685, 1600 cm⁻¹

NMR (DMSO-d₆, δ) : 1.34 (6H, d, J=6.0Hz), 3.49
(3H, s), 3.66 (2H, s), 4.8-5.0 (1H, m),
6.95-7.01 (2H, m), 7.30 and 7.40 (4H, ABq,
J=8.0Hz), 7.84 (1H, d, J=9.0Hz)

(105) 2-(4-Carboxyphenyl)-6-isopropoxy-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 247.5-248.5°C

IR (Nujol) : 3200-2400, 1690, 1605 cm⁻¹

NMR (DMSO-d₆, δ) : 1.34 (6H, d, J=6.0Hz), 3.50
(3H, s), 4.80-5.0 (1H, m), 6.95-7.07 (2H, m),
7.51 and 8.09 (4H, ABq, J=8.3Hz), 7.86
(1H, d, J=8.4Hz), 13.3 (1H, br s)

(106) 2-(3-Carboxypropyl)-6-isopropoxy-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 150-152°C

IR (Nujol) : 1710, 1690, 1600, 1580, 1470, 1380,
1100 cm^{-1}

NMR (CDCl_3 , δ) : 1.38 (6H, d, $J=6\text{Hz}$), 2.05 (2H, m),
2.43 (2H, t, $J=7\text{Hz}$), 3.46 (3H, s), 3.98 (2H,
t, $J=7\text{Hz}$), 4.67 (1H, m), 6.67 (1H, d, $J=2\text{Hz}$),
6.76 (1H, dd, $J=2\text{Hz}$ and 9Hz), 7.76 (1H, d,
 $J=9\text{Hz}$)

10 (107) 2-(4-Carboxyphenyl)-6-cyclohexylmethoxy-4-methyl-
2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 240.5-241°C

IR (Nujol) : 3300-2400, 1690, 1600, 1330 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 1.40-1.95 (5H, m), 1.55-1.95
(6H, m), 3.52 (3H, s), 4.00 (1H, d, $J=5.8\text{Hz}$),
6.95-7.10 (2H, m), 7.50 and 8.05 (4H, ABq,
 $J=8.3\text{Hz}$), 7.86 (1H, d, $J=8.7\text{Hz}$), 13.3 (1H, br s)

20 (108) Hydrochloride salt of 6-[trans-4-(Aminomethyl)-
cyclohexylmethoxy]-2-(4-chlorophenyl)-4-methyl-2H-
1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : >250°C

IR (Nujol) : 3400, 1700, 1610, 1600, 1380, 1330,
1310, 1280, 1130 cm^{-1}

25 NMR ($\text{DMSO}-d_6$, δ) : 0.90-1.20 (4H, m), 1.40-2.10
(6H, m), 2.70 (2H, m), 3.50 (3H, s), 4.02
(2H, d, $J=7\text{Hz}$), 7.03 (1H, dd, $J=2\text{Hz}$ and 9Hz),
7.10 (1H, d, $J=2\text{Hz}$), 7.40 (2H, d, $J=9\text{Hz}$),
7.60 (2H, d, $J=9\text{Hz}$), 7.90 (1H, d, $J=9\text{Hz}$),
30 8.00 (1H, br s)

(109) 7-Chloro-6-isopropoxy-4-methyl-2-(2-pyridyl)-2H-
1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 193-194°C

35 IR (Nujol) : 1685, 1590, 1345 cm^{-1}

NMR (CDCl₃, δ) : 1.46 (6H, d, J=6Hz), 3.55 (3H, s),
4.6-4.85 (1H, m), 6.75 (1H, s), 7.35-7.55
(2H, m), 7.90 (1H, s), 7.85-7.95 (1H, m),
8.6-8.7 (1H, m)

5

(110) 7-Bromo-6-isopropoxy-4-methyl-2-(2-pyridyl)-2H-
1,2,4-benzothiadiazine-3(4H)-one 1,1 -dioxide

mp : 194.5-195.5°C

IR (Nujol) : 1690, 1590, 1345 cm⁻¹

10

NMR (CDCl₃, δ) : 1.47 (6H, d, J=6Hz), 3.55 (3H, s),
4.6-4.85 (1H, m), 6.71 (1H, s), 7.35-7.55
(2H, m), 7.85-7.95 (1H, m), 8.04 (1H, s),
8.60-8.70 (1H, m)

15

(111) 2-(4-Chlorophenyl)-5,7-dichloro-6-hydroxy-4-
methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-
dioxide

mp : 197-198°C

IR (Nujol) : 1720, 1700, 1500, 1360, 1180 cm⁻¹

20

NMR (DMSO-d₆, δ) : 3.55 (3H, s), 7.42 (2H, d,
J=9Hz), 7.60 (2H, d, J=9Hz), 8.00 (1H, s)

(continued to the next page)

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Example 7

In a similar manner to that of Example 3, there were obtained the following compounds.

- 5 (1) 6-Hydroxy-4-methyl-2-(p-tolyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 163-165°C
IR (Nujol) : 3400, 1670, 1610, 1590, 1480, 1340,
1320, 1220, 1190, 1140 cm^{-1}
10 NMR (DMSO- d_6 , δ) : 2.35 (3H, s), 3.40 (3H, s),
6.80 (1H, d, J=9Hz), 6.90 (1H, s), 7.10-7.40
(4H, m), 7.75 (1H, d, J=9Hz)
- 15 (2) 6-Hydroxy-4-methyl-2-phenyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 235-237°C
IR (Nujol) : 1680, 1610, 1590, 1470, 1330, 1210,
1190 cm^{-1}
20 NMR (DMSO- d_6 , δ) : 3.45 (3H, s), 6.80 (1H, d,
J=9Hz), 6.90 (1H, s), 7.30-7.60 (5H, m),
7.78 (1H, d, J=9Hz)
- 25 (3) 6-Hydroxy-4-methyl-2-(4-trifluoromethylphenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 230-233°C
IR (Nujol) : 3300, 1660, 1610, 1590, 1460, 1350,
1320, 1190, 1110 cm^{-1}
30 NMR (DMSO- d_6 , δ) : 3.42 (3H, s), 6.80 (2H, d,
J=9Hz), 6.90 (1H, s), 7.60 (2H, d, J=7Hz),
7.77 (1H, d, J=9Hz), 7.92 (2H, d, J=7Hz)
- 35 (4) 2-(3,4-Dichlorophenyl)-6-hydroxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : >250°C

IR (Nujol) : 3350, 1660, 1610, 1590, 1460, 1350,
1340 cm^{-1}

NMR (DMSO-d_6 , δ) : 3.45 (3H, s), 6.82 (1H, d,
J=8Hz), 6.86 (1H, s), 7.45 (1H, dd, J=2Hz and
9Hz), 7.65-7.90 (3H, m), 11.0 (1H, s)

(5) 2-(4-Fluorophenyl)-6-hydroxy-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 228-230°C

IR (Nujol) : 3400, 1650, 1610, 1580, 1460, 1350,
1210 cm^{-1}

NMR (DMSO-d_6 , δ) : 3.40 (3H, s), 6.80 (1H, d,
J=9Hz), 6.85 (1H, s), 7.30-7.60 (4H, m),
7.75 (1H, d, J=9Hz), 11.0 (1H, br s)

(6) 2-(2-Chlorophenyl)-6-hydroxy-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

(continued to the next page)

mp : 195-196°C

IR (Nujol) : 3400, 1670, 1620, 1590, 1470, 1460,
1330 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.48 (3H, s), 6.83 (1H, d,
J=9Hz), 6.93 (1H, s), 7.40-7.75 (4H, m),
7.77 (1H, d, J=9Hz), 11.0 (1H, br s)

(7) 2-(3-Chlorophenyl)-6-hydroxy-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 242-243°C

IR (Nujol) : 3500, 1680, 1660, 1610, 1590, 1460,
1370, 1320 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.45 (3H, s), 6.83 (1H, dd,
J=2Hz and 9Hz), 6.89 (1H, d, J=2Hz),
7.30-7.65 (4H, m), 7.77 (1H, d, J=9Hz)

(8) 2-(4-Chlorophenyl)-6-hydroxy-4-isopropyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 212-213 °C

IR (Nujol) : 3350, 1660, 1610, 1460, 1350, 1320
 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.52 (6H, d, J=6Hz), 4.52 (1H,
m), 6.81 (1H, d, J=9Hz), 6.96 (1H, s),
7.25-7.70 (4H, m), 7.72 (1H, d, J=9Hz)

(9) 2-(4-Chlorophenyl)-4-ethyl-6-hydroxy-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 253-255 °C

IR (Nujol) : 3300, 1640, 1610, 1580, 1460, 1350,
1330 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.28 (3H, t, J=7Hz), 4.05 (2H,
q, J=7Hz), 6.82 (1H, dd, J=2Hz and 9Hz), 6.90
(1H, d, J=2Hz), 7.42 (2H, d, J=9Hz), 7.60
(2H, d, J=9Hz), 7.78 (1H, d, J=9Hz)

- (10) 2-(4-Chlorobenzyl)-6-hydroxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 130-132°C

IR (Nujol) : 3250, 1645, 1610, 1580, 1335,
1180 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.41 (3H, s), 4.94 (2H, s),
6.80 (2H, d, $J=9.0\text{Hz}$), 6.82 (1H, s), 7.35
and 7.39 (4H, ABq, $J=8.6\text{Hz}$), 7.75 (1H, d,
 $J=9.0\text{Hz}$), 10.93 (1H, br s)

- (11) 2-Cyclohexyl-6-hydroxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 189-190°C

IR (Nujol) : 3300, 1665, 1610, 1585, 1320, 1200,
1180 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.0-1.5 (3H, m), 1.5-1.9
(5H, m), 2.05-2.35 (2H, m), 3.38 (3H, s),
4.2-4.4 (1H, m), 6.76 (1H, d, $J=8.2\text{Hz}$),
6.78 (1H, s), 7.66 (1H, d, $J=8.2\text{Hz}$),
10.84 (1H, br s)

- (12) 6-Hydroxy-4-methyl-2-pentyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 108-110°C

IR (Nujol) : 3300, 1640, 1600, 1580, 1460, 1340,
1180 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.84 (3H, t, $J=6\text{Hz}$), 1.10-1.40
(4H, m), 1.50-1.70 (2H, m), 3.40 (3H, s),
3.74 (2H, t, $J=7\text{Hz}$), 6.70-6.90 (2H, m),
7.70 (1H, d, $J=9\text{Hz}$), 10.9 (1H, br s)

- (13) 2-(4-Carboxyphenyl)-6-hydroxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : >250°C

IR (Nujol) : 3600-2500, 3350, 1705, 1610 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.46 (3H, s), 6.80-6.95 (2H, m),
7.50 and 8.05 (4H, ABq, $J=8.4\text{Hz}$), 7.80 (1H,
d, $J=8.7\text{Hz}$), 10.99 (1H, s)

5 (14) 2-(4-Carboxymethylphenyl)-6-hydroxy-4-methyl-2H-
1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : $>250^\circ\text{C}$

IR (Nujol) : 3210, 1715, 1665, 1620, 1585,
1340 cm^{-1}

10 NMR (DMSO- d_6 , δ) : 3.45 (3H, s), 3.66 (2H, s),
6.75-6.90 (2H, m), 7.30 and 7.40 (4H, ABq,
 $J=8.3\text{Hz}$), 7.75 (1H, d, $J=8.6\text{Hz}$), 10.96 (1H, s)

15 (15) 2-(3-Carboxypropyl)-6-hydroxy-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : $145-148^\circ\text{C}$

IR (Nujol) : 3300, 1690, 1600, 1590, 1470, 1380,
1340, 1120 cm^{-1}

20 NMR (DMSO- d_6 , δ) : 1.80 (2H, m), 2.24 (2H, t,
 $J=7\text{Hz}$), 3.40 (3H, s), 3.80 (2H, t, $J=7\text{Hz}$),
6.78 (1H, d, $J=9\text{Hz}$), 6.80 (1H, s), 7.71
(1H, d, $J=9\text{Hz}$), 10.8 (1H, br s)

25 (16) 6-Hydroxy-4-methyl-2-(4-phenoxyphenyl)-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : $239-240^\circ\text{C}$

IR (Nujol) : 3260, 1645, 1610, 1585, 1345,
1210 cm^{-1}

30 NMR (CDCl_3 , δ) : 3.51 (3H, s), 6.75-6.85 (2H, m),
7.0-7.45 (9H, m), 7.67-7.78 (1H, m)

(17) 6-Hydroxy-2-(4-isopropylphenyl)-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : $>250^\circ\text{C}$

35 IR (Nujol) : 3410, 3370, 1670, 1610, 1585, 1325 cm^{-1}

NMR (CDCl_3 , δ) : 1.23 (6H, d, $J=7\text{Hz}$), 2.93
(1H, m), 3.31 (1H, br s), 3.47 (3H, s),
6.70 (1H, d, $J=2\text{Hz}$), 6.72 (1H, dd, $J=2\text{Hz}$ and
9Hz), 7.28 (4H, s), 7.70 (1H, d, $J=9\text{Hz}$)

5

(18) 2-[(3-Chloro-4-methyl)phenyl]-6-hydroxy-4-methyl-
2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
mp : $>250^\circ\text{C}$

IR (Nujol) : 3400, 1670, 1610, 1590, 1325 cm^{-1}

10

NMR ($\text{DMSO}-d_6$, δ) : 2.39 (3H, s), 3.45 (3H, s),
6.82 (1H, dd, $J=2\text{Hz}$ and 9Hz), 6.88 (1H, d,
 $J=2\text{Hz}$), 7.28 (1H, dd, $J=2\text{Hz}$ and 8Hz),
7.44 (1H, d, $J=2\text{Hz}$), 7.51 (1H, d, $J=8\text{Hz}$),
7.76 (1H, d, $J=9\text{Hz}$)

15

(19) 6-Hydroxy-4-methyl-2-(4-methylthiophenyl)-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide
mp : $248-249^\circ\text{C}$

IR (Nujol) : 3250, 1670, 1610, 1580, 1330,
 1180 cm^{-1}

20

NMR ($\text{DMSO}-d_6$, δ) : 2.52 (3H, s), 3.45 (3H, s),
6.81 (1H, dd, $J=2\text{Hz}$ and 9Hz), 6.87 (1H, d,
 $J=2\text{Hz}$), 7.27 (2H, d, $J=9\text{Hz}$), 7.37 (2H, d,
 $J=9\text{Hz}$), 7.86 (1H, d, $J=9\text{Hz}$)

25

(20) 2-(4-Dimethylaminophenyl)-6-hydroxy-4-methyl-2H-
1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
mp : $190-191^\circ\text{C}$

IR (Nujol) : 3350, 1660, 1600, 1580, 1520, 1480,
 $1320, 1180, 1140\text{ cm}^{-1}$

30

NMR ($\text{DMSO}-d_6$, δ) : 2.95 (6H, s), 3.44 (3H, s),
6.73-6.85 (4H, m), 7.10 (2H, d, $J=9\text{Hz}$),
7.73 (1H, d, $J=8\text{Hz}$), 10.90 (1H, s)

35

Example 8

In a similar manner to that of Example 4, there were obtained the following compounds.

- 5 (1) 6-Isopropoxy-4-methyl-2-(p-tolyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 163-165°C
IR (Nujol) : 1690, 1600, 1580, 1340, 1320, 1130,
 1110 cm⁻¹
- 10 NMR (DMSO-d₆, δ) : 1.33 (3H, s), 1.36 (3H, s),
 2.38 (3H, s), 3.49 (3H, s), 4.90 (1H, m),
 6.90-7.10 (2H, m), 7.20-7.34 (4H, m),
 7.84 (1H, d, J=8Hz)
- 15 (2) 6-Isopropoxy-4-methyl-2-phenyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 134-135°C
IR (Nujol) : 1690, 1600, 1580, 1450, 1340, 1190
 cm⁻¹
- 20

(continued to the next page)

NMR (CDCl_3 , δ) : 1.42 (6H, d, $J=6\text{Hz}$), 3.55 (3H, s),
4.70 (1H, m), 6.70-7.90 (2H, m), 7.35-7.60
(5H, m), 7.82 (1H, d, $J=9\text{Hz}$)

- 5 (3) 2-(3,4-Dichlorophenyl)-6-isopropoxy-4-methyl-2H-
1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 109-110°C

IR (Nujol) : 1710, 1570, 1460, 1350, 1320 cm^{-1}

10 NMR ($\text{DMSO}-d_6$, δ) : 1.34 (6H, d, $J=5\text{Hz}$), 3.49
(3H, s), 4.90 (1H, m), 7.01 (1H, d, $J=8\text{Hz}$),
7.03 (1H, s), 7.45 (1H, d, $J=9\text{Hz}$),
7.74-7.89 (3H, m)

- 15 (4) 2-(4-Fluorophenyl)-6-isopropoxy-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 139-140°C

IR (Nujol) : 1700, 1600, 1570, 1460, 1380, 1330,
1210 cm^{-1}

20 NMR ($\text{DMSO}-d_6$, δ) : 1.33 (6H, d, $J=6\text{Hz}$), 3.50
(3H, s), 4.90 (1H, m), 6.98-7.02 (2H, m),
7.30-7.48 (4H, m), 7.85 (1H, d, $J=9\text{Hz}$)

- 25 (5) 2-(4-Chlorophenyl)-6-ethoxy-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 150-151°C

IR (Nujol) : 1680, 1600, 1580, 1460, 1350, 1320,
1220, 1190, 1130 cm^{-1}

30 NMR ($\text{DMSO}-d_6$, δ) : 1.39 (3H, t, $J=7\text{Hz}$), 3.50 (3H,
s), 4.23 (2H, q, $J=7\text{Hz}$), 7.00 (1H, dd, $J=2\text{Hz}$
and 9Hz), 7.05 (1H, d, $J=2\text{Hz}$), 7.40-7.63 (4H,
m), 7.87 (1H, d, $J=9\text{Hz}$)

- 35 (6) 6-Benzyloxy-2-(4-chlorophenyl)-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 174-175°C

IR (Nujol) : 1690, 1600, 1590, 1460, 1320,
1310, 1180 cm^{-1}

NMR (DMSO-d_6 , δ) : 3.34 (3H, s), 5.32 (2H, s),
7.07 (1H, dd, $J=9\text{Hz}$ and 2Hz), 7.20 (1H, d,
 $J=2\text{Hz}$), 7.30-7.63 (9H, m), 7.90 (1H, d,
 $J=9\text{Hz}$)

(7) 2-(4-Chlorophenyl)-6-cyclopropylmethoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 145-146°C

IR (Nujol) : 1690, 1600, 1580, 1540, 1330 cm^{-1}

NMR (DMSO-d_6 , δ) : 0.30-0.45 (4H, m), 1.30 (1H, m),
3.45 (3H, s), 4.01 (2H, d, $J=7\text{Hz}$), 6.90-7.10
(2H, m), 7.35-7.70 (4H, m), 7.85 (1H, d,
 $J=9\text{Hz}$)

(8) 2-(2-Chlorophenyl)-6-isopropoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 150-152°C

IR (Nujol) : 1700, 1600, 1580, 1450, 1360, 1320,
1200 cm^{-1}

NMR (DMSO-d_6 , δ) : 1.34 (6H, d, $J=6\text{Hz}$), 3.52
(3H, s), 4.90 (1H, m), 6.95-7.10 (2H, m),
7.50-7.70 (4H, m), 7.86 (1H, d, $J=9\text{Hz}$)

(9) 2-(3-Chlorophenyl)-6-isopropoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 126-127°C

IR (Nujol) : 1700, 1600, 1590, 1380, 1330, 1310,
1180 cm^{-1}

NMR (DMSO-d_6 , δ) : 1.34 (6H, d, $J=6\text{Hz}$), 3.49
(3H, s), 4.90 (1H, m), 6.98-7.03 (2H, m),
7.37-7.65 (4H, m), 7.86 (1H, d, $J=9\text{Hz}$)

- (10) 2-(4-Chlorophenyl)-4-methyl-6-propoxy-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 142-143°C

IR (Nujol) : 1700, 1690, 1610, 1580, 1340, 1320 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.02 (3H, t, J=7Hz), 1.80 (2H, q, J=7Hz), 3.50 (3H, s), 4.10 (2H, t, J=7Hz), 6.95-7.10 (2H, m), 7.40-7.70 (4H, m), 7.90 (1H, d, J=9Hz)

- (11) 6-Butoxy-2-(4-chlorophenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 102-103°C

IR (Nujol) : 1700, 1600, 1340, 1320, 1180, 1130 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.96 (3H, t, J=7Hz), 1.35-1.90 (4H, m), 3.50 (3H, s), 4.18 (2H, t, J=7Hz), 6.95-7.10 (2H, m), 7.35-7.70 (4H, m), 8.90 (1H, d, J=9Hz)

- (12) 6-Methoxy-4-methyl-2-(P-tolyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 170-173°C

IR (Nujol) : 1690, 1460, 1440, 1330, 1310, 1180, 1130 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.50 (3H, s), 3.95 (3H, s), 6.95-7.10 (2H, m), 7.20-7.40 (4H, m), 7.95 (1H, d, J=9Hz)

- (13) 6-Methoxy-4-methyl-2-phenyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 203-206°C

IR (Nujol) : 1710, 1700, 1600, 1450, 1330, 1300, 1220, 1180 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.50 (3H, s), 3.95 (3H, s),

7.00 (1H, d, J=9Hz), 7.05 (1H, s),
7.25-7.65 (5H, m), 7.88 (1H, d, J=9Hz)

(14) 6-Methoxy-4-methyl-2-(4-trifluoromethylphenyl)-2H-
1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 165-168°C

IR (Nujol) : 1700, 1610, 1580, 1460, 1340, 1170,
1140 cm^{-1}

NMR (DMSO-d_6 , δ) : 3.52 (3H, s), 3.95 (3H, s),
7.02 (1H, dd, J=2Hz and 9Hz), 7.10 (1H, d,
J=2Hz), 7.65 (2H, d, J=7Hz), 7.92 (1H, d,
J=9Hz), 7.98 (2H, d, J=7Hz)

(15) 2-(3,4-Dichlorophenyl)-6-methoxy-4-methyl-2H-
1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 150-151°C

IR (Nujol) : 1710, 1600, 1470, 1340, 1320 cm^{-1}

NMR (DMSO-d_6 , δ) : 3.50 (3H, s), 3.95 (3H, s),
7.02 (1H, d, J=9Hz), 7.06 (1H, s), 7.45 (1H,
d, J=8Hz), 7.70-8.00 (3H, m)

(16) 2-(4-Fluorophenyl)-6-methoxy-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 203-204°C

IR (Nujol) : 1700, 1590, 1440 cm^{-1}

NMR (DMSO-d_6 , δ) : 3.52 (3H, s), 3.95 (3H, s),
7.02 (1H, d, J=9Hz), 7.10 (1H, s),
7.30-7.60 (4H, m), 7.90 (1H, d, J=9Hz)

(17) 6-Isopropoxy-2-(4-methoxyphenyl)-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 182-183°C

IR (Nujol) : 1690, 1600, 1460, 1370, 1340 cm^{-1}

NMR (DMSO-d_6 , δ) : 1.34 (6H, d, J=6Hz), 3.50 (3H, s),
3.82 (3H, s), 4.89 (1H, m), 7.00-7.08 (4H, m),
7.25-7.32 (2H, m), 7.84 (1H, d, J=9Hz)

(18) 2-(2-Chlorophenyl)-6-methoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 155-156°C

IR (Nujol) : 1710, 1600, 1460, 1330, 1300, 1180, 1140 cm⁻¹

NMR (DMSO-d₆, δ) : 3.54 (3H, s), 3.95 (3H, s), 7.03 (1H, dd, J=2Hz and 9Hz), 7.11 (1H, d, J=2Hz), 7.50-7.70 (4H, m), 7.90 (1H, d, J=9Hz)

(19) 2-(3-Chlorophenyl)-6-methoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 153-154°C

IR (Nujol) : 1710, 1600, 1590, 1460, 1340, 1320, 1180, 1130, 1060, 1030 cm⁻¹

NMR (DMSO-d₆, δ) : 3.51 (3H, s), 3.94 (3H, s), 7.02 (1H, dd, J=2Hz and 9Hz), 7.07 (1H, d, J=2Hz), 7.34-7.65 (4H, m), 7.90 (1H, d, J=9Hz)

(20) 2-(4-Chlorophenyl)-6-methoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 167-168°C

IR (Nujol) : 1710, 1600, 1330, 1180, 1130 cm⁻¹

NMR (DMSO-d₆, δ) : 3.42 (3H, s), 3.95 (3H, s), 6.95-7.10 (2H, m), 7.38-7.65 (2H, m), 8.90 (1H, d, J=9Hz)

(21) 2-(4-Chlorobenzyl)-6-isopropoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

IR (Neat) : 2980, 1680, 1600, 1580, 1330, 1180, 1110 cm⁻¹

NMR (CDCl₃, δ) : 1.38 (6H, d, J=6.0Hz), 3.45 (3H, s), 4.55-4.75 (1H, m), 5.00 (2H, s), 6.65 (1H, d, J=1.9Hz), 6.77 (1H, dd, J=1.9 and 8.8Hz), 7.27 and 7.40 (4H, ABq, J=8.4Hz), 7.80 (1H, d, J=8.8Hz)

- (22) 4-Isopropyl-2-(4-Chlorophenyl)-6-methoxy-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 166-168°C

IR (Nujol) : 1690, 1600, 1570, 1460, 1340, 1300 cm⁻¹

NMR (DMSO-d₆, δ) : 1.54 (6H, d, J=6Hz), 3.94 (3H, s), 4.61 (1H, m), 6.90-7.10 (2H, m), 7.30-7.70 (4H, m), 7.85 (1H, d, J=9Hz)

- (23) 2-(4-Chlorophenyl)-6-isopropoxy-4-isopropyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 158-160°C

IR (Nujol) : 1690, 1590, 1490, 1460, 1340, 1300 cm⁻¹

NMR (DMSO-d₆, δ) : 1.34 (6H, d, J=6Hz), 1.52 (6H, d, J=6Hz), 4.58 (1H, m), 4.88 (1H, m), 6.90-7.05 (2H, m), 7.30-7.65 (4H, m), 7.82 (1H, d, J=9Hz)

- (24) 2-(4-Chlorophenyl)-4-ethyl-6-methoxy-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 106-107°C

IR (Nujol) : 1690, 1600, 1570, 1490, 1460, 1350, 1310 cm⁻¹

NMR (DMSO-d₆, δ) : 1.28 (3H, t, J=7Hz), 3.95 (3H, s), 4.14 (2H, q, J=7Hz), 7.03 (1H, d, J=9Hz), 7.09 (1H, s), 7.42 (2H, d, J=9Hz), 7.60 (2H, d, J=9Hz), 7.90 (1H, d, J=9Hz)

- (25) 2-(4-Chlorophenyl)-4-ethyl-6-isopropoxy-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 167-168°C

IR (Nujol) : 1700, 1600, 1580, 1460, 1340, 1310 cm⁻¹

NMR (DMSO-d₆, δ) : 1.26 (3H, t, J=7Hz), 1.34 (6H, d, J=6Hz), 4.13 (2H, q, J=7Hz), 7.05-7.09 (2H, m), 7.42 (2H, d, J=9Hz), 7.60 (2H, d, J=9Hz), 7.87 (2H, d, J=9Hz)

- (26) 2-Cyclohexyl-6-isopropoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 111-112°C

IR (Nujol) : 1685, 1605, 1330, 1180, 1110 cm^{-1}

NMR (DMSO-d_6 , δ) : 1.0-1.45 (3H, m), 1.31 (6H, d, $J=6.0\text{Hz}$), 1.5-1.9 (5H, m), 2.05-2.35 (2H, m), 3.43 (3H, s), 4.25-4.4 (1H, m), 4.84 (1H, m), 6.91 (1H, s), 6.78 (1H, d, $J=9.0\text{Hz}$), 7.75 (1H, d, $J=9.0\text{Hz}$)

- (27) 6-Isopropoxy-4-methyl-2-pentyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 44-46°C

IR (Nujol) : 1690, 1600, 1580, 1460, 1340, 1320, 1190 cm^{-1}

NMR (DMSO-d_6 , δ) : 0.84 (3H, t, $J=6\text{Hz}$), 1.05-1.40 (4H, m), 1.31 (6H, d, $J=6\text{Hz}$), 1.50-1.75 (2H, m), 3.44 (3H, s), 3.74 (2H, t, $J=7\text{Hz}$), 4.85 (1H, m), 6.90-7.05 (2H, m), 7.78 (1H, d, $J=9\text{Hz}$)

- (28) 6-Isopropoxy-2-(4-isopropoxycarbonylphenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 128-129°C

IR (Nujol) : 1720, 1710, 1610, 1340, 1280 cm^{-1}

NMR (CDCl_3 , δ) : 1.38 (6H, d, $J=6.8\text{Hz}$), 1.43 (6H, d, $J=6.5\text{Hz}$), 3.54 (3H, s), 4.63-4.8 (1H, m), 5.2-5.35 (1H, m), 6.76 (1H, d, $J=2\text{Hz}$), 6.82 (1H, dd, $J=2\text{Hz}$ and 8.7Hz), 7.50 and 8.15 (4H, ABq, $J=8.4\text{Hz}$), 7.83 (1H, d, $J=8.7\text{Hz}$)

- (29) 2-(4-Isopropoxycarbonylmethylphenyl)-6-isopropoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 117-120°C

IR (Nujol) : 1730, 1690, 1595, 1335, 1325 cm⁻¹

NMR (CDCl₃, δ) : 1.24 (6H, d, J=6.0Hz),
1.41 (6H, d, J=6.0Hz), 3.52 (3H, s), 3.63
(2H, s), 4.6-4.8 (1H, m), 4.9-5.1 (1H, m),
6.7-6.85 (2H, m), 7.3-7.5 (4H, m), 7.75-7.80
(1H, m)

(30) 6-Isopropoxy-2-(3-isopropoxycarbonylpropyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

IR (CHCl₃) : 1720, 1700, 1600, 1580, 1340, 1270,
1120 cm⁻¹

NMR (CDCl₃, δ) : 1.12 (6H, d, J=6Hz), 1.30 (6H, d, J=6Hz), 1.99 (2H, m), 2.28 (2H, t, J=7Hz),
3.41 (3H, s), 3.90 (2H, t, J=7Hz), 4.60 (1H, m), 4.92 (1H, m), 6.60 (1H, d, J=2Hz),
6.70 (1H, dd, J=2Hz and 9Hz), 7.70 (1H, d, J=9Hz)

(31) 2-(4-Chlorophenyl)-5,7-dichloro-6-isopropoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 185-188°C

IR (Nujol) : 1710, 1470, 1380, 1360, 1190 cm⁻¹

NMR (DMSO-d₆, δ) : 1.38 (6H, d, J=6Hz), 3.33
(3H, s), 4.75 (1H, m), 7.44 (2H, d, J=9Hz),
7.61 (2H, d, J=9Hz), 8.14 (1H, s)

(32) 2-(4-Chlorobenzyl)-6-methoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 132-133°C

IR (Nujol) : 1675, 1600, 1350, 1330, 1195 cm⁻¹

NMR (DMSO-d₆, δ) : 3.47 (3H, s), 3.92 (3H, s),
4.96 (2H, s), 6.98 (1H, d, J=9.0Hz), 7.00 (1H, s),

7.35 and 7.40 (4H, ABq, J=8.7Hz), 7.87 (1H, d, J=9.0Hz)

(33) 2-Cyclohexyl-6-methoxy-4-methyl-2H-1,2,4-benzothiadia-
zine-3(4H)-one 1,1-dioxide

mp : 124.5-126°C

IR (Nujol) : 1690, 1595, 1325, 1310, 1300,
1175 cm⁻¹

NMR (DMSO-d₆, δ) : 1.0-1.5 (3H, m), 1.55-1.9
(5H, m), 2.05-2.35 (2H, m), 3.45 (3H, s),
3.90 (3H, s), 4.15-4.4 (1H, m), 6.95 (1H, d,
J=8.3Hz), 6.97 (1H, s), 7.78 (1H, d, J=8.3Hz)

(34) 6-Isopropoxy-4-methyl-2-(2-pyridyl)-2H-1,2,4-benzothiadia-
zine-3(4H)-one 1,1-dioxide

mp : 173-174°C

IR (Nujol) : 1700, 1600 1590, 1340, 1215 cm⁻¹

NMR (CDCl₃, δ) : 1.40 (6H, d, J=6Hz), 3.53 (3H, s),
4.6-4.8 (1H, m), 6.73-6.85 (2H, m), 7.35-7.55
(2H, m), 7.82 (1H, d, J=8.7Hz), 7.8-7.95
(1H, m), 8.6-8.68 (1H, m)

(35) 6-Methoxy-4-methyl-2-pentyl-2H-1,2,4-benzothiadia-
zine-3(4H)-one 1,1-dioxide

mp : 85-88°C

IR (Nujol) : 1690, 1600, 1450, 1330, 1310, 1180 cm⁻¹

NMR (DMSO-d₆, δ) : 0.84 (3H, t, J=6Hz), 1.10-1.40
(4H, m), 1.50-1.75 (2H, m), 3.47 (3H, s),
3.75 (2H, t, J=7Hz), 3.91 (3H, s), 6.90-7.05
(2H, m), 7.82 (1H, d, J=9Hz)

(36) 6-Methoxy-2-(4-methoxycarbonylphenyl)-4-methyl-2H-
1,2,4-benzothiadia-
zine-3(4H)-one 1,1-dioxide

mp : 153-156°C

IR (Nujol) : 1725, 1690, 1590, 1320, 1280 cm⁻¹

NMR (DMSO- d_6 , δ) : 3.52 (3H, s), 3.89 (3H, s),
3.95 (3H, s), 6.97-7.13 (2H, m), 7.55 and 8.10
(4H, ABq, $J=8.3\text{Hz}$), 7.90 (1H, d, $J=8.8\text{Hz}$)

- 5 (37) 6-Cyclohexylmethoxy-4-methyl-2-(2-pyridyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 161.5-162.5°C

IR (Nujol) : 1700, 1600, 1310 cm^{-1}

10 NMR (CDCl_3 , δ) : 0.95-1.45 (5H, m), 1.65-2.0
(6H, m), 3.54 (3H, s), 3.86 (2H, d, $J=6\text{Hz}$),
6.73-6.85 (2H, m), 7.35-7.55 (2H, m), 7.82
(1H, d, $J=8.5\text{Hz}$), 7.81-7.95 (1H, m), 8.6-8.67
(1H, m)

- 15 (38) 2-(4-Methoxycarbonylmethylphenyl)-6-methoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 173-176°C

IR (Nujol) : 1735, 1690, 1600, 1335, 1320 cm^{-1}

20 NMR (DMSO- d_6 , δ) : 3.52 (3H, s), 3.65 (3H, s),
3.79 (2H, s), 3.95 (3H, s), 6.96-7.10 (2H, m),
7.33 and 7.43 (4H, ABq, $J=8.3\text{Hz}$), 7.88 (1H,
d, $J=8.7\text{Hz}$)

- 25 (39) 2-(3-Ethoxycarbonylpropyl)-6-methoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 63-65°C

IR (Nujol) : 1740, 1690, 1600, 1480, 1380, 1360,
1340, 1320, 1180 cm^{-1}

30 NMR (CDCl_3 , δ) : 1.23 (3H, t, $J=7\text{Hz}$), 2.06 (2H,
m), 2.37 (2H, t, $J=7\text{Hz}$), 3.49 (3H, s), 3.90
(3H, s), 3.96 (2H, t, $J=7\text{Hz}$), 4.09 (2H, q,
 $J=7\text{Hz}$), 6.69 (1H, d, $J=2\text{Hz}$), 6.80 (1H, dd,
 $J=2\text{Hz}$ and 9Hz), 7.79 (1H, d, $J=9\text{Hz}$)

(40) 2-[2-(4,6-Dimethylpyridyl)]-6-isopropoxy-4-methyl-
2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 202-203°C

IR (Nujol) : 1700, 1600, 1580, 1350, 1320,
1180 cm^{-1}

NMR (DMSO-d_6 , δ) : 1.37 (6H, d, $J=6\text{Hz}$), 2.34
(3H, s), 2.48 (3H, s), 3.49 (3H, s), 4.89
(1H, m), 7.01 (1H, d, $J=9\text{Hz}$), 7.04 (1H, s),
7.13 (1H, s), 7.25 (1H, s), 7.80 (1H, d,
 $J=9\text{Hz}$)

(41) 6-Isopropoxy-4-methyl-2-(2-pyrimidinyl)-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 176-178°C

IR (Nujol) : 1700, 1600, 1400, 1380, 1350, 1330,
1280, 1230 cm^{-1}

NMR (DMSO-d_6 , δ) : 1.33 (6H, d, $J=6\text{Hz}$), 3.53
(3H, s), 4.90 (1H, m), 7.00 (1H, dd, $J=2\text{Hz}$
and 9Hz), 7.10 (1H, d, $J=2\text{Hz}$), 7.67 (1H, t,
 $J=4\text{Hz}$), 7.84 (1H, t, $J=9\text{Hz}$), 8.97 (2H, d,
 $J=4\text{Hz}$)

(42) 6-Methoxy-4-methyl-2-(4-phenoxyphenyl)-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 184-186°C

IR (Nujol) : 1690, 1590, 1330, 1180 cm^{-1}

NMR (DMSO-d_6 , δ) : 3.52 (3H, s), 3.94 (3H, s),
6.95-7.55 (11H, m), 7.89 (1H, d, $J=9\text{Hz}$)

(43) 2-(4-Isopropylphenyl)-6-methoxy-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 158-159°C

IR (Nujol) : 1700, 1595, 1330, 1310, 1125 cm^{-1}

NMR (DMSO-d_6 , δ) : 1.24 (6H, d, $J=7\text{Hz}$), 2.98 (1H, m),
3.51 (3H, s), 3.94 (3H, s), 7.01 (1H, dd,

J=2Hz and 9Hz), 7.06 (1H, d, J=2Hz), 7.27
and 7.39 (4H, ABq, J=8Hz), 7.87 (1H, d,
J=9Hz)

- 5 (44) 2-[(3-Chloro-4-methyl)phenyl]-6-methoxy-4-methyl-
2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 208-211°C
IR (Nujol) : 1695, 1595, 1315, 1180 cm^{-1}
10 NMR (DMSO- d_6 , δ) : 2.40 (3H, s), 3.51 (3H, s),
3.94 (3H, s), 7.02 (1H, dd, J=2Hz and 9Hz),
7.07 (1H, d, J=2Hz), 7.39 (1H, dd, J=2Hz and
8Hz), 7.46 (1H, d, J=2Hz), 7.52 (1H, d, J=8Hz),
7.89 (1H, d, J=9Hz)
- 15 (45) 6-Methoxy-4-methyl-2-(4-methylthiophenyl)-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 154-155°C
IR (Nujol) : 1690, 1610, 1580, 1490, 1310, 1185,
1135 cm^{-1}
20 NMR (CDCl_3 , δ) : 2.51 (3H, s), 3.54 (3H, s), 3.93
(3H, s), 6.76 (1H, d, J=2Hz), 6.83 (1H, dd,
J=2Hz and 9Hz), 7.32 (4H, s), 7.85 (1H, d,
J=9Hz)
- 25 (46) 2-(4-Dimethylaminophenyl)-6-methoxy-4-methyl-2H-
1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 244-245°C
IR (Nujol) : 1690, 1600, 1520, 1330, 1310, 1180,
1130 cm^{-1}
30 NMR (DMSO- d_6 , δ) : 2.96 (6H, s), 3.50 (3H, s),
3.94 (3H, s), 6.75 (2H, d, J=9Hz), 7.10 (2H,
d, J=9Hz), 7.02 (1H, dd, J=2Hz and 9Hz),
7.02 (1H, d, J=2Hz), 7.85 (1H, d, J=9Hz)
- 35 (47) 2-(4-Carboxymethylphenyl)-6-isopropoxy-4-methyl-

2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 232-233°C

IR (Nujol) : 3600-2500, 1700, 1685, 1600 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.34 (6H, d, $J=6.0\text{Hz}$), 3.49
(3H, s), 3.66 (2H, s), 4.8-5.0 (1H, m),
6.95-7.01 (2H, m), 7.30 and 7.40 (4H, ABq,
 $J=8.0\text{Hz}$), 7.84 (1H, d, $J=9.0\text{Hz}$)

(48) 2-(4-Carboxyphenyl)-6-isopropoxy-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 247.5-248.5°C

IR (Nujol) : 3200-2400, 1690, 1605 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.34 (6H, d, $J=6.0\text{Hz}$), 3.50
(3H, s), 4.80-5.0 (1H, m), 6.95-7.07 (2H, m),
7.51 and 8.09 (4H, ABq, $J=8.3\text{Hz}$), 7.86
(1H, d, $J=8.4\text{Hz}$), 13.3 (1H, br s)

(49) 2-(3-Carboxypropyl)-6-isopropoxy-4-methyl-2H-1,2,4-
benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 150-152°C

IR (Nujol) : 1710, 1690, 1600, 1580, 1470, 1380,
1100 cm^{-1}

NMR (CDCl_3 , δ) : 1.38 (6H, d, $J=6\text{Hz}$), 2.05 (2H, m),
2.43 (2H, t, $J=7\text{Hz}$), 3.46 (3H, s), 3.98 (2H,
t, $J=7\text{Hz}$), 4.67 (1H, m), 6.67 (1H, d, $J=2\text{Hz}$),
6.76 (1H, dd, $J=2\text{Hz}$ and 9Hz), 7.76 (1H, d,
 $J=9\text{Hz}$)

(50) 2-(4-Carboxyphenyl)-6-cyclohexylmethoxy-4-methyl-
2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 240.5-241°C

IR (Nujol) : 3300-2400, 1690, 1600, 1330 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.40-1.95 (5H, m), 1.55-1.95
(6H, m), 3.52 (3H, s), 4.00 (1H, d, $J=5.8\text{Hz}$),
6.95-7.10 (2H, m), 7.50 and 8.05 (4H, ABq,
 $J=8.3\text{Hz}$), 7.86 (1H, d, $J=8.7\text{Hz}$), 13.3 (1H, br s)

(51) 7-Chloro-6-isopropoxy-4-methyl-2-(2-pyridyl)-2H-
1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (115
mg) as colorless needles

mp : 193-194°C

IR (Nujol) : 1685, 1590, 1345 cm^{-1}

NMR (CDCl_3 , δ) : 1.46 (6H, d, $J=6\text{Hz}$), 3.55 (3H, s),
4.6-4.85 (1H, m), 6.75 (1H, s), 7.35-7.55
(2H, m), 7.90 (1H, s), 7.85-7.95 (1H, m),
8.6-8.7 (1H, m)

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Example 9

A suspension of 6-hydroxy-4-methyl-2-(4-trifluoromethylphenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (124 mg), potassium carbonate (55 mg) and 2-iodopropane (68 mg) in N,N-dimethyl formamide (1 ml) was stirred for 2 hours at 60°C. The mixture was poured into ice water. The separated solid was collected by filtration, dried, and recrystallized from ethanol to yield 2-(4-trifluoromethylphenyl)-4-methyl-6-isopropoxy-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (78 mg).

mp : 158-160°C

IR (Nujol) : 1690, 1600, 1460, 1370, 1320, 1130 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.34 (6H, d, J=6Hz), 3.50

(3H, s), 4.90 (1H, m), 7.00-7.10 (2H, m),

7.64 (2H, d, J=7Hz), 7.80-8.00 (3H, m)

Example 10

A suspension of 2-(4-chlorophenyl)-6-hydroxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (250 mg), potassium carbonate (122 mg) and 1-iodoisobutane (163 mg) in N,N-dimethyl formamide (1 ml) was stirred for 2 hours at 60°C. The mixture was poured into ice water. The separated solid was collected by filtration, dried, and recrystallized from ethanol to yield 2-(4-chlorophenyl)-4-methyl-6-(2-methylpropoxy)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (169 mg).

mp : 108-110°C

IR (Nujol) : 1690, 1600, 1580, 1460, 1340, 1320, 1190 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.02 (6H, d, J=7Hz), 2.08 (1H, m), 3.51 (3H, s), 3.95 (2H, d, J=8Hz), 6.99-7.06 (2H, m), 7.39-7.63 (4H, m), 7.87 (1H, d, J=9Hz)

Example 11

A suspension of 2-(4-chlorophenyl)-6-hydroxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (250 mg), potassium carbonate (122 mg) and bromomethyl-cyclohexane (159 mg) in N,N-dimethyl formamide (1 ml) was stirred for 2 hours at 60°C. The mixture was poured into ice water. The separated solid was collected by filtration, dried, and recrystallized from ethanol to yield 2-(4-chlorophenyl)-4-methyl-6-cyclohexylmethoxy-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (230 mg).

mp : 127-129°C

IR (Nujol) : 1690, 1600, 1590, 1460, 1320, 1310, 1180, 1130 cm⁻¹

NMR (DMSO-d₆, δ) : 1.04-1.40 (5H, m), 1.50-1.90 (6H, m), 3.50 (3H, s), 3.98 (2H, d, J=6Hz), 6.98-7.05 (2H, m), 7.38-7.63 (4H, m), 7.86 (1H, d, J=9Hz)

(continued to the next page)

Example 12

A mixture of 2-(4-chlorophenyl)-6-hydroxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (500 mg), ethyl bromoacetate (0.2 ml), and potassium carbonate (245 mg) in N,N-dimethyl formamide (1 ml) was stirred at 80°C for 3 hours. The mixture was cooled and poured into ice-water. The separated solid was filtered and dissolved in a mixture of ethanol (15 ml) and tetrahydrofuran (15 ml). To the solution containing 2-(4-chlorophenyl)-6-ethoxycarbonylmethoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide was added aqueous 1N-sodium hydroxide solution (2.2 ml) in one portion at ambient temperature. The solution was stirred for one hour at ambient temperature and concentrated in vacuo. The residue was extracted with methylene chloride. The organic layer washed with brine, dried, and evaporated to give the crude product, which was recrystallized from methanol to yield 2-(4-chlorophenyl)-6-carboxymethoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (213 mg).

mp : 228-230°C

IR (Nujol) : 1730, 1690, 1600, 1460, 1340, 1320 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.34 (1H, brs), 3.50 (3H, s), 4.95 (2H, s), 6.99 (1H, dd, J=9Hz and 2Hz), 7.11 (1H, d, J=2Hz), 7.35-7.65 (4H, m), 7.89 (1H, d, J=9Hz)

Example 13

A mixture of 2-(4-chlorophenyl)-6-hydroxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (678 mg), ethyl 2-bromopropionate (362 mg), and potassium carbonate (207 mg) in dry N,N-dimethyl formamide (2 ml) was stirred overnight at ambient temperature. The mixture was poured into water and extracted twice with ethyl acetate. The organic layers

were washed with water, dried, and evaporated under reduced pressure. The residue was crystallized from n-hexane to yield 2-(4-chlorophenyl)-6-[1-(ethoxycarbonyl)ethoxy]-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (816 mg). (R,S mixture)

mp : 111-112°C

IR (Nujol) : 1750, 1690, 1605, 1340, 1210, 1140 cm^{-1}

NMR (CDCl_3 , δ) : 1.29 (3H, t, $J=7.1\text{Hz}$), 1.69 (3H, d, $J=6.7\text{Hz}$), 3.52 (3H, s), 4.26 (2H, q, $J=7.1\text{Hz}$), 4.88 (1H, q, $J=6.7\text{Hz}$), 6.73 (1H, dd, $J=8.7\text{Hz}$ and 2.0Hz), 6.84 (1H, d, $J=2.0\text{Hz}$), 7.35 and 7.46 (4H, ABq, $J=8.6\text{Hz}$), 7.83 (1H, d, $J=8.7\text{Hz}$)

Example 14

To a suspension of 2-(4-chlorophenyl)-6-[1-(ethoxycarbonyl)ethoxy]-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (400 mg) in a mixture of ethanol (5 ml) and water (5 ml) was added aqueous 1N-sodium hydroxide solution (1.1 ml) in one portion. The mixture was refluxed for half hour and concentrated in vacuo. The residue was dissolved in water and washed with ethyl ether. The aqueous layer was acidified with hydrochloric acid. The separated oil was extracted with ethyl acetate. The organic layer was washed with brine, dried, and evaporated to dryness. The residue was crystallized from a mixture of n-hexane and ethyl acetate to yield 2-(4-chlorophenyl)-6-(1-carboxyethoxy)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (240 mg).

mp : 179.5-180.5°C (R,S mixture)

IR (Nujol) : 3250, 1760, 1665, 1600, 1350 cm^{-1}

NMR (CDCl_3 , δ) : 1.74 (3H, d, $J=6.7\text{Hz}$), 3.52 (3H, s), 4.94 (1H, q, $J=6.7\text{Hz}$),

5.54 (1H, brs), 6.76 (1H, dd, J=1.9Hz and
8.7Hz), 7.40 (4H, ABq, J=8.6Hz),
7.85 (1H, d, J=8.7Hz)

5 Example 15

In a similar manner to that of Example 13, there
were obtained the following compounds.

10 (1) 2-(4-Chlorophenyl)-6-(1-ethoxycarbonyl-1-methyl-
ethoxy)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-
one 1,1-dioxide
mp : 184-185°C
IR (Nujol) : 1720, 1700, 1580, 1370, 1340 cm^{-1}
15 NMR (CDCl_3 , δ) : 1.30 (3H, t, J=7Hz), 1.73 (6H, s),
3.53 (3H, s), 4.28 (2H, q, J=7Hz),
6.68 (1H, dd, J=9Hz and 2Hz), 6.80 (1H, d,
J=2Hz), 7.37 (2H, d, J=9Hz), 7.50 (2H, d,
J=9Hz), 7.81 (1H, d, J=9Hz)

20 (2) 2-(4-Chlorophenyl)-6-(3-ethoxycarbonylpropoxy)-
4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1
dioxide
mp : 90-92°C
IR (Nujol) : 1730, 1700, 1600, 1580, 1470,
25 1330, 1320 cm^{-1}
NMR (CDCl_3 , δ) : 1.28 (3H, t, J=7Hz), 2.17 (2H, m),
2.54 (2H, t, J=7Hz), 3.54 (3H, s), 4.15 (2H,
t, J=7Hz), 4.17 (2H, q, J=7Hz), 6.70-6.90
(2H, m), 7.30-7.55 (4H, m), 7.84 (1H, d, J=9Hz)

30 (3) 2-(4-Chlorophenyl)-6-(1-ethoxycarbonylpropoxy)-
4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one
1,1-dioxide
mp : 105-108°C
35 IR (Nujol) : 1750, 1690, 1600, 1580, 1210 cm^{-1}

NMR (CDCl_3 , δ) : 1.11 (3H, t, $J=7\text{Hz}$), 1.29 (3H, t, $J=7\text{Hz}$), 2.06 (2H, m), 3.50 (3H, s), 4.26 (2H, q, $J=7\text{Hz}$), 4.69 (1H, t, $J=6\text{Hz}$), 6.74 (1H, dd, $J=9\text{Hz}$ and 6Hz), 6.84 (1H, d, $J=2\text{Hz}$), 7.30-7.50 (4H, m), 7.83 (1H, d, $J=9\text{Hz}$)

(4) 2-(4-Chlorophenyl)-6-(1-ethoxycarbonylcyclobutyloxy)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 140-142°C

IR (Nujol) : 1730, 1690, 1610, 1590, 1360 cm^{-1}

NMR (CDCl_3 , δ) : 1.69 (3H, t, $J=7\text{Hz}$), 1.85-2.90 (6H, m), 3.46 (3H, s), 4.20 (2H, q, $J=7\text{Hz}$), 6.57 (1H, dd, $J=9\text{Hz}$ and 2Hz), 6.92 (1H, d, $J=2\text{Hz}$), 7.41 (2H, d, $J=8\text{Hz}$), 7.60 (2H, d, $J=8\text{Hz}$), 7.87 (1H, d, $J=9\text{Hz}$)

(5) 2-(4-Chlorophenyl)-6-(1-carboxyethoxy)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 179.5-180.5°C (R,S mixture)

IR (Nujol) : 3250, 1760, 1665, 1600, 1350 cm^{-1}

NMR (CDCl_3 , δ) : 1.74 (3H, d, $J=6.7\text{Hz}$), 3.52 (3H, s), 4.94 (1H, q, $J=6.7\text{Hz}$), 5.54 (1H, brs), 6.76 (1H, dd, $J=1.9\text{Hz}$ and 8.7Hz), 7.40 (4H, ABq, $J=8.6\text{Hz}$), 7.85 (1H, d, $J=8.7\text{Hz}$)

(6) 2-(4-Chlorophenyl)-6-(1-carboxy-1-methylethoxy)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 208-210°C

IR (Nujol) : 3250, 1750, 1670, 1600, 1350, 1330 cm^{-1}

NMR (CDCl_3 , δ) : 1.75 (6H, s), 3.51 (3H, s), 6.74 (1H, dd, $J=9\text{Hz}$ and 2Hz), 6.83 (1H, d, $J=2\text{Hz}$), 7.34 (2H, d, $J=9\text{Hz}$), 7.46 (2H, d, $J=9\text{Hz}$), 7.82 (1H, d, $J=9\text{Hz}$)

(7) 2-(4-Chlorophenyl)-6-(3-carboxypropoxy)-4-methyl-
2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 170-171°C
IR (Nujol) : 1700, 1600, 1580, 1330, 1310 cm^{-1}
NMR (CDCl_3 , δ) : 2.19 (2H, m), 2.62 (2H, t, J=7Hz),
3.54 (3H, s), 4.17 (2H, t, J=6Hz),
6.70-6.90 (2H, m), 7.35 (2H, d, J=9Hz),
7.47 (2H, d, J=9Hz), 7.84 (1H, d, J=9Hz)

(8) 2-(4-Chlorophenyl)-6-(1-carboxypropoxy)-4-methyl-
2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 179-181°C
IR (Nujol) : 3250, 1760, 1680, 1600, 1590,
1380, 1200 cm^{-1}
NMR (CDCl_3 , δ) : 1.15 (3H, t, J=7Hz), 2.11 (2H, m),
3.53 (3H, s), 4.78 (1H, t, J=6Hz),
6.76 (1H, dd, J=9Hz and 2Hz), 6.86 (1H, d,
J=2Hz), 7.30-7.50 (4H, m), 7.85 (1H, d, J=9Hz)

(9) 2-(4-Chlorophenyl)-6-(1-carboxycyclobutyloxy)-4-
methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-
dioxide
mp : 148-151°C
IR (Nujol) : 1700, 1600, 1380, 1320, 1180 cm^{-1}
NMR (CDCl_3 , δ) : 2.00-2.30 (2H, m), 2.50-2.75
(2H, m), 2.78-2.95 (2H, m), 3.51 (3H, s),
6.53 (1H, dd, J=9Hz and 2Hz), 6.73 (1H, d,
J=2Hz), 7.34 (2H, d, J=9Hz), 7.46 (2H, d,
J=9Hz), 7.80 (1H, d, J=9Hz)

(10) (1R)-(+)-2-(4-Chlorophenyl)-6-[1-(ethoxy-carbonyl)ethoxy]-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 86-88°C

$[\alpha]_D +24.0^\circ$ (C=1.0, EtOH)

IR (Nujol) : 1740, 1690, 1680, 1600, 1590, 1500, 1210, 1185 cm^{-1}

NMR (CDCl_3 , δ) : 1.30 (3H, t, J=7Hz), 1.69 (3H, d, J=7Hz), 3.53 (3H, s), 4.26 (2H, q, J=7Hz), 4.87 (1H, q, J=7Hz), 6.74 (1H, dd, J=2Hz and 9Hz), 6.83 (1H, d, J=9Hz), 7.35 (2H, d, J=9Hz), 7.46 (2H, d, J=9Hz), 7.83 (1H, d, J=9Hz)

(11) (1S)-(-)-2-(4-Chlorophenyl)-6-[1-(ethoxy-carbonyl)ethoxy]-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 96-98°C

$[\alpha]_D -24.7^\circ$ (C=1.0, EtOH)

IR (Nujol) : 1730, 1690, 1680, 1600, 1590, 1340, 1190 cm^{-1}

NMR (CDCl_3 , δ) : 1.29 (3H, t, J=7Hz), 1.69 (3H, d, J=7Hz), 3.52 (3H, s), 4.26 (2H, q, J=7Hz), 4.88 (1H, q, J=7Hz), 6.74 (1H, d, J=9Hz), 6.83 (1H, s), 7.35 (2H, d, J=9Hz), 7.46 (2H, d, J=9Hz), 7.83 (1H, d, J=9Hz)

(12) (1R)-(+)-2-(4-Chlorophenyl)-6-(1-carboxyethoxy)-4-methyl-2H-1,2,4-benzothiadiadiazine-3(4H)-one 1,1-dioxide

mp : 75-85°C

$[\alpha]_D +16.4^\circ$ (C=1.0, EtOH)

IR (Nujol) : 3200, 1740, 1700, 1690, 1660, 1600,
1580, 1380, 1130 cm^{-1}

NMR (CDCl_3 , δ) : 1.77 (3H, d, $J=7\text{Hz}$), 3.55 (3H,
s), 4.98 (1H, q, $J=7\text{Hz}$), 6.79 (1H, dd, $J=2\text{Hz}$
and 9Hz), 6.88 (1H, d, $J=2\text{Hz}$), 7.37 (2H, d,
 $J=9\text{Hz}$), 7.49 (2H, d, $J=9\text{Hz}$), 7.88 (1H, d,
 $J=9\text{Hz}$)

(13) (1S)-(-)-2-(4-Chlorophenyl)-6-(1-carboxyethoxy)-
4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-
dioxide

mp : 85-95 $^{\circ}\text{C}$

$[\alpha]_D -17.0^{\circ}$ ($C=1.0$, EtOH)

IR (Nujol) : 3200, 1740, 1700, 1665, 1600, 1580,
1200, 1130 cm^{-1}

NMR (CDCl_3 , δ) : 1.75 (3H, d, $J=7\text{Hz}$), 3.52 (3H,
s), 4.95 (1H, q, $J=7\text{Hz}$), 6.50 (1H, bs), 6.75
(1H, dd, $J=2\text{Hz}$ and 9Hz), 6.88 (1H, d, $J=2\text{Hz}$),
7.32 (2H, d, $J=9\text{Hz}$), 7.45 (2H, d, $J=9\text{Hz}$),
7.85 (1H, d, $J=9\text{Hz}$)

(continued to the next page)

(14) (1R)-(+)-6-[1-(Ethoxycarbonyl)ethoxy]-4-methyl-2-phenyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 137.5-139°C

IR (Nujol) : 1740, 1700, 1605, 1340, 1210, 1140 cm^{-1}

NMR (CDCl_3 , δ) : 1.30 (3H, t, $J=7\text{Hz}$), 1.69 (3H, d, $J=7\text{Hz}$), 3.53 (3H, s), 4.26 (2H, q, $J=7\text{Hz}$), 4.88 (1H, q, $J=7\text{Hz}$), 6.73 (1H, dd, $J=2\text{Hz}$ and 9Hz), 6.84 (1H, d, $J=2\text{Hz}$), 7.35-7.55 (5H, m), 7.84 (1H, d, $J=9\text{Hz}$)

(15) (1R)-(+)-6-[1-(Ethoxycarbonyl)ethoxy]-4-methyl-2-(4-phenoxyphenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 128-130°C

IR (Nujol) : 1740, 1685, 1610, 1330, 1195, 1130 cm^{-1}

NMR (CDCl_3 , δ) : 1.29 (3H, t, $J=7\text{Hz}$), 1.69 (3H, d, $J=7\text{Hz}$), 3.53 (3H, s), 4.26 (2H, q, $J=7\text{Hz}$), 4.88 (1H, q, $J=7\text{Hz}$), 6.75 (1H, dd, $J=2\text{Hz}$ and 9Hz), 6.83 (1H, d, $J=2\text{Hz}$), 7.0-7.45 (9H, m), 7.85 (1H, d, $J=9\text{Hz}$)

(16) (1R)-(+)-6-[1-(Ethoxycarbonyl)ethoxy]-2-(4-isopropylphenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 154-155°C

IR (Nujol) : 1740, 1695, 1600, 1340, 1310, 1200, 1130 cm^{-1}

NMR (CDCl_3 , δ) : 1.27 (6H, d, $J=7\text{Hz}$), 1.29 (3H, t, $J=7\text{Hz}$), 1.69 (3H, d, $J=7\text{Hz}$), 2.95 (1H, m), 3.52 (3H, s), 4.26 (2H, q, $J=7\text{Hz}$), 4.88 (1H, q, $J=7\text{Hz}$), 6.73 (1H, dd, $J=2\text{Hz}$ and 9Hz), 6.83 (1H, d, $J=2\text{Hz}$), 7.32 (4H, s), 7.83 (1H, d, $J=9\text{Hz}$)

(17) (1R)-(+)-2-[[3-Chloro-4-methyl]phenyl]-6-[1-(ethoxy-carbonyl)ethoxy]-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 149-150°C

5

IR (Nujol) : 1740, 1685, 1600, 1335 cm⁻¹

NMR (DMSO-d₆, δ) : 1.21 (3H, t, J=7Hz), 1.58 (3H, d, J=7Hz), 2.40 (3H, s), 3.48 (3H, s), 4.18 (2H, q, J=7Hz), 5.33 (1H, q, J=7Hz), 6.95 (1H, dd, J=2Hz and 9Hz), 7.08 (1H, d, J=2Hz), 7.30 (1H, dd, J=2Hz and 8Hz), 7.47 (1H, d, J=2Hz), 7.51 (1H, d, J=8Hz), 7.87 (1H, d, J=9Hz)

10

(18) (1R)-(+)-2-Cyclohexyl-6-[1-(ethoxycarbonyl)ethoxy]-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

15

mp : 139-141°C

IR (Nujol) : 1740, 1690, 1600, 1580, 1340, 1300, 1200, 1170 cm⁻¹

20

NMR (CDCl₃, δ) : 1.28 (3H, t, J=6Hz), 1.16-1.45 (3H, m), 1.66 (3H, d, J=6Hz), 1.80-1.92 (5H, m), 2.22-2.42 (2H, m), 3.44 (3H, s), 4.23 (2H, q, J=6Hz), 4.29-4.49 (1H, m), 4.83 (1H, q, J=6Hz), 6.65 (1H, dd, J=2Hz and 8Hz), 6.71 (1H, d, J=2Hz), 7.74 (1H, d, J=6Hz)

25

(19) (1R)-(+)-6-[1-(Ethoxycarbonyl)ethoxy]-4-methyl-2-(4-methylphenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

30

mp : 134-135°C

IR (Nujol) : 1740, 1680, 1600, 1580, 1340, 1320, 1200, 1130 cm⁻¹

NMR (CDCl₃, δ) : 1.30 (3H, t, J=6Hz), 1.69 (3H, d, J=6Hz), 2.40 (3H, s), 3.52 (3H, s), 4.25 (2H, q, J=6Hz), 4.88 (1H, q, J=6Hz), 6.70 (1H, dd,

35

J=2Hz and 8Hz), 6.82 (1H, d, J=2Hz),
7.28 (4H, s), 7.83 (1H, d, J=8Hz)

(20) (1R)-(+)-6-[1-(Ethoxycarbonyl)ethoxy]-4-methyl-2-(2-pyridyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 153-154°C

IR (Nujol) : 1740, 1690, 1605, 1580, 1460, 1330, 1205, 1115 cm⁻¹

NMR (CDCl₃, δ) : 1.29 (3H, t, J=7Hz), 1.69 (3H, d, J=7Hz), 3.53 (3H, s), 4.25 (2H, q, J=7Hz), 4.86 (1H, q, J=7Hz), 6.72 (1H, dd, J=2Hz and 8Hz), 6.84 (1H, d, J=2Hz), 7.38-7.51 (2H, m), 7.82 (1H, d, J=8Hz), 7.90 (1H, dd, J=2Hz and 8Hz), 8.62-8.66 (1H, m)

(21) (1R)-(+)-2-(3,4-Dichlorophenyl)-6-[1-(ethoxycarbonyl)ethoxy]-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 108-110°C

IR (Nujol) : 1720, 1685, 1600, 1190, 1135 cm⁻¹

NMR (CDCl₃, δ) : 1.30 (3H, t, J=8Hz), 1.69 (3H, d, J=7Hz), 3.53 (3H, s), 4.29 (2H, q, J=8Hz), 4.87 (1H, q, J=7Hz), 6.74 (1H, dd, J=2Hz and 9Hz), 6.83 (1H, d, J=2Hz), 7.28 (1H, dd, J=2Hz and 9Hz), 7.53 (1H, d, J=2Hz), 7.55 (1H, d, J=9Hz), 7.83 (1H, d, J=9Hz)

(22) (1R)-(+)-2-(3-Chlorophenyl)-6-[1-(ethoxycarbonyl)ethoxy]-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 135-137°C

IR (Nujol) : 1740, 1700, 1600, 1580, 1340, 1210 cm⁻¹

NMR (CDCl₃, δ) : 1.30 (3H, t, J=7Hz), 1.70 (3H, d, J=7Hz), 3.46 (3H, s), 4.27 (2H, q, J=7Hz),

4.86 (1H, q, J=7Hz), 6.81-7.37 (6H, m),
7.85 (1H, d, J=9Hz)

5 (23) (1R)-(+)-2-(2-Chlorophenyl)-6-[1-(ethoxycarbonyl)-ethoxy]-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

IR (CHCl₃) : 1745, 1700, 1605, 1580, 1350, 1320, 1140 cm⁻¹

10 NMR (CDCl₃, δ) : 1.30 (3H, t, J=7Hz), 1.69 (3H, d, J=7Hz), 3.54 (3H, s), 4.27 (2H, q, J=7Hz), 4.88 (1H, q, J=7Hz), 6.70-7.72 (6H, m), 7.82 (1H, d, J=9Hz)

15 (24) (1R)-(-)-6-[1-(Ethoxycarbonyl)ethoxy]-2-(4-fluorophenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 100-102°C

IR (Nujol) : 1740, 1680, 1605, 1370, 1340 cm⁻¹

20 NMR (CDCl₃, δ) : 1.30 (3H, t, J=7Hz), 1.69 (3H, d, J=7Hz), 3.52 (3H, s), 4.26 (2H, q, J=7Hz), 4.88 (1H, q, J=7Hz), 6.71-7.43 (6H, m), 7.83 (1H, d, J=9Hz)

25 (25) (1R)-(+)-6-[1-(Ethoxycarbonyl)ethoxy]-4-methyl-2-(4-methylthiophenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 156-157°C

IR (Nujol) : 1720, 1605, 1600, 1580, 1205, 1180 1130 cm⁻¹

30 NMR (CDCl₃, δ) : 1.29 (3H, t, J=7Hz), 1.69 (3H, d, J=7Hz), 2.50 (3H, s), 3.52 (3H, s), 4.25 (2H, q, J=7Hz), 4.87 (1H, q, J=7Hz), 6.72 (1H, dd, J=2Hz and 9Hz), 6.82 (1H, d, J=2Hz), 7.32 (4H, s), 7.83 (1H, d, J=9Hz)

35

(26) (1R)-(+)-2-(4-Dimethylaminophenyl)-6-[1-(ethoxy-carbonyl)ethoxy]-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 190-192°C

5 IR (Nujol) : 1715, 1680, 1600, 1195, 1130 cm^{-1}

NMR (CDCl_3 , δ) : 1.29 (3H, t, $J=7\text{Hz}$), 1.67 (3H, d, $J=7\text{Hz}$), 3.00 (6H, s), 3.51 (3H, s), 4.25 (2H, q, $J=7\text{Hz}$), 4.87 (1H, q, $J=7\text{Hz}$), 6.69-6.81 (4H, m), 7.24 (2H, d, $J=8\text{Hz}$), 7.84 (1H, d, $J=8\text{Hz}$)

(27) (1R)-(+)-6-(1-Carboxyethoxy)-4-methyl-2-phenyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 184-185.5°C

15 IR (Nujol) : 3200, 1750, 1660, 1610, 1320, 1180 cm^{-1}

NMR (CDCl_3 , δ) : 1.74 (3H, d, $J=7\text{Hz}$), 3.53 (3H, s), 3.55-4.1 (1H, br), 4.95 (1H, q, $J=7\text{Hz}$), 6.76 (1H, dd, $J=2\text{Hz}$ and 9Hz), 6.85 (1H, d, $J=2\text{Hz}$), 7.35-7.55 (5H, m), 7.86 (1H, d, $J=9\text{Hz}$)

(28) (1R)-(+)-6-(1-Carboxyethoxy)-4-methyl-2-(4-phenoxyphenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

25 mp : 106°C (dec.)

IR (Nujol) : 3600-2400, 1740, 1695, 1665, 1600, 1585, 1345, 1215 cm^{-1}

30 NMR (CDCl_3 , δ) : 1.74 (3H, d, $J=7\text{Hz}$), 3.53 (3H, s), 3.63 (1H, br), 4.95 (1H, q, $J=7\text{Hz}$), 6.76 (1H, dd, $J=2\text{Hz}$ and 9Hz), 6.85 (1H, d, $J=2\text{Hz}$), 7.0-7.45 (9H, m), 7.86 (1H, d, $J=9\text{Hz}$)

(29) (1R)-(+)-6-(1-Carboxyethoxy)-2-(4-isopropylphenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

35

mp : 74°C (dec.)

IR (Nujol) : 3600-2400, 1730, 1695, 1600, 1340,
1315 cm⁻¹

NMR (CDCl₃, δ) : 1.27 (6H, d, J=7Hz), 1.74 (3H, d,
J=7Hz), 2.76 (1H, m), 3.43 (1H, br), 3.52
(3H, s), 4.95 (1H, q, J=7Hz), 6.76 (1H, dd,
J=2Hz and 9Hz), 6.85 (1H, d, J=2Hz), 7.32
(4H, s), 7.85 (1H, d, J=9Hz)

10 (30) (1R)-(+)-6-(1-Carboxyethoxy)-2-[(3-chloro-4-methyl)-
phenyl]-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-
one 1,1-dioxide

mp : 184-186°C

15 IR (Nujol) : 3600-2500, 1720, 1700, 1595,
1330 cm⁻¹

20 NMR (CDCl₃, δ) : 1.75 (3H, d, J=7Hz), 2.42 (3H, s),
3.25 (1H, br), 3.53 (3H, s), 4.94 (1H, q,
J=7Hz), 6.77 (1H, dd, J=2Hz and 9Hz),
6.85 (1H, d, J=2Hz), 7.23 (1H, dd, J=2Hz and
8Hz), 7.34 (1H, d, J=8Hz), 7.41 (1H, d,
J=2Hz), 7.85 (1H, d, J=9Hz)

25 (31) (1R)-(+)-6-(1-Carboxyethoxy)-4-methyl-2-(4-
trifluoromethylphenyl)-2H-1,2,4-benzothiadiazine-
3(4H)-one 1,1-dioxide

mp : 162-163°C

IR (CHCl₃) : 3600-3300, 1720, 1690, 1600, 1340,
1320, 1130 cm⁻¹

30 NMR (CDCl₃, δ) : 1.75 (3H, d, J=6Hz), 3.54 (3H, s),
4.90-5.01 (1H, q, J=6Hz), 6.77 (1H, dd,
J=2Hz and 8Hz), 6.87 (1H, d, J=2Hz), 7.54
(2H, d, J=8Hz), 7.74 (2H, d, J=8Hz),
7.86 (1H, d, J=8Hz)

35 (32) (1R)-(+)-6-(1-Carboxyethoxy)-2-cyclohexyl-4-methyl-
2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 76-77°C

IR (CHCl₃) : 3600-2400, 1720, 1680, 1600, 1330,
1310, 1170 cm⁻¹

NMR (CDCl₃, δ) : 1.20-1.45 (3H, m), 1.70 (3H, d,
J=6Hz), 1.82-1.88 (5H, m), 2.20-2.38 (2H, m),
3.44 (3H, s), 4.35-4.47 (1H, m), 4.76 (1H, s),
4.89 (1H, q, J=6Hz), 6.67-6.74 (2H, m),
7.75 (1H, d, J=8Hz)

10 (33) (1R)-(+)-6-(1-Carboxyethoxy)-4-methyl-2-(4-methyl-
phenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-
dioxide

mp : 182-183°C

IR (CHCl₃) : 1700, 1600, 1320, 1130 cm⁻¹

15 NMR (CDCl₃, δ) : 1.74 (3H, d, J=5Hz), 2.40 (3H, s),
3.17 (1H, br s), 3.52 (3H, s), 4.89-5.00
(1H, q, J=6Hz), 6.75 (1H, dd, J=2Hz and 8Hz),
6.84 (1H, d, J=2Hz), 7.29 (4H, s), 7.85 (1H,
d, J=8Hz)

20 (34) (1R)-(+)-6-(1-Carboxyethoxy)-4-methyl-2-(2-pyridyl)-
2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 142-143°C

IR (Nujol) : 3700-2300, 1700, 1600, 1350, 1320,
1275, 1210, 1190 cm⁻¹

25 NMR (CDCl₃, δ) : 1.56 (3H, d, J=7Hz), 3.47 (3H, s),
5.17 (1H, q, J=7Hz), 6.92 (1H, dd, J=2Hz and
9Hz), 7.08 (1H, d, J=2Hz), 7.45-7.60 (2H, m),
7.34 (1H, d, J=9Hz), 8.00 (1H, m), 8.56-8.59
30 (1H, m)

(35) (1R)-(+)-6-(1-Carboxyethoxy)-2-(3,4-dichlorophenyl)-
4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-
dioxide

35 mp : 105-106°C

IR (Nujol) : 3250-2400, 1735, 1690, 1600, 1585,
1300, 1290, 1175 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 1.57 (3H, d, $J=7\text{Hz}$), 3.48 (3H, s), 5.20 (1H, q, $J=7\text{Hz}$), 6.93 (1H, dd, $J=2\text{Hz}$ and 9Hz), 7.08 (1H, d, $J=2\text{Hz}$), 7.46 (1H, dd, $J=2\text{Hz}$ and 9Hz), 7.76-7.93 (3H, m)

(36) (1R)-(+)-6-(1-Carboxyethoxy)-2-(3-chlorophenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 174-176°C

IR (Nujol) : 1725, 1700, 1610, 1580, 1330, 1310, 1180 cm^{-1}

NMR (CDCl_3 , δ) : 1.74 (3H, d, $J=7\text{Hz}$), 2.72 (1H, br s), 3.53 (3H, s), 4.95 (1H, q, $J=7\text{Hz}$), 6.74-7.51 (6H, m), 7.86 (1H, d, $J=9\text{Hz}$)

(37) (1R)-(+)-6-(1-Carboxyethoxy)-2-(2-chlorophenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 110-112°C

IR (Nujol) : 1740, 1700, 1600, 1580, 1375, 1190 cm^{-1}

NMR (CDCl_3 , δ) : 1.75 (3H, d, $J=7\text{Hz}$), 3.55 (3H, s), 4.95 (1H, q, $J=7\text{Hz}$), 6.74-7.67 (6H, m), 7.85 (1H, d, $J=9\text{Hz}$)

(38) (1R)-(+)-6-(1-Carboxyethoxy)-2-(4-fluorophenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 130-132°C

IR (Nujol) : 1740, 1700, 1600, 1500, 1380, 1210 cm^{-1}

NMR (CDCl_3 , δ) : 1.74 (3H, d, $J=7\text{Hz}$), 3.52 (3H, s), 4.94 (1H, q, $J=7\text{Hz}$), 5.80 (1H, br s), 6.74-7.43 (6H, m), 7.85 (1H, d, $J=9\text{Hz}$)

(39) (1R)-(+)-6-(1-Carboxyethoxy)-4-methyl-2-(4-methylthiophenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 143-144°C

IR (Nujol) : 3350-2300, 1730, 1660, 1600, 1580,
1190, 1090 cm^{-1}

NMR (CDCl_3 , δ) : 1.74 (3H, d, $J=7\text{Hz}$), 2.50 (3H, s),
3.53 (3H, s), 4.95 (1H, q, $J=7\text{Hz}$), 6.76 (1H,
dd, $J=2\text{Hz}$ and 9Hz), 6.85 (1H, d, $J=2\text{Hz}$),
7.32 (4H, s), 7.85 (1H, d, $J=9\text{Hz}$)

(40) (1R)-(+)-6-(1-Carboxyethoxy)-2-(4-dimethylamino-phenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 190°C (dec.)

IR (KBr) : 3400, 2750-2200, 1690, 1590, 1450,
1320, 1180, 1125 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 1.57 (3H, d, $J=7\text{Hz}$), 2.97 (6H,
s), 3.47 (3H, s), 5.22 (1H, q, $J=7\text{Hz}$), 6.85
(2H, d, $J=9\text{Hz}$), 7.15 (2H, d, $J=9\text{Hz}$), 6.92
(1H, dd, $J=2\text{Hz}$ and 9Hz), 7.05 (1H, d,
 $J=2\text{Hz}$), 7.85 (1H, d, $J=9\text{Hz}$)

(41) 6-[1-(Carboxy)cyclohexylmethoxy]-2-(4-chlorophenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 145-150°C

IR (Nujol) : 3300, 1700, 1600, 1580, 1370, 1310,
1190, 1130 cm^{-1}

NMR (CDCl_3 , δ) : 1.10-2.10 (11H, m), 3.40 (3H, s),
4.40 (1H, br s), 6.60 (1H, d, $J=9\text{Hz}$),
6.85 (1H, s), 7.25 (2H, d, $J=9\text{Hz}$),
7.43 (2H, d, $J=9\text{Hz}$), 7.70 (1H, d, $J=9\text{Hz}$)

Example 16

In a similar manner to that of Example 14, there were obtained the following compounds.

- 5 (1) 2-(4-Chlorophenyl)-6-(1-carboxy-1-methylethoxy)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 208-210°C

IR (Nujol) : 3250, 1750, 1670, 1600, 1350, 1330 cm^{-1}

10 NMR (CDCl_3 , δ) : 1.75 (6H, s), 3.51 (3H, s),
6.74 (1H, dd, $J=9\text{Hz}$ and 2Hz), 6.83 (1H, d, $J=2\text{Hz}$),
7.34 (2H, d, $J=9\text{Hz}$), 7.46 (2H, d, $J=9\text{Hz}$),
7.82 (1H, d, $J=9\text{Hz}$)

- 15 (2) 2-(4-Chlorophenyl)-6-(3-carboxypropoxy)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 170-171°C

IR (Nujol) : 1700, 1600, 1580, 1330, 1310 cm^{-1}

20 NMR (CDCl_3 , δ) : 2.19 (2H, m), 2.62 (2H, t, $J=7\text{Hz}$),
3.54 (3H, s), 4.17 (2H, t, $J=6\text{Hz}$),
6.70-6.90 (2H, m), 7.35 (2H, d, $J=9\text{Hz}$),
7.47 (2H, d, $J=9\text{Hz}$), 7.84 (1H, d, $J=9\text{Hz}$)

- 25 (3) 2-(4-Chlorophenyl)-6-(1-carboxypropoxy)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 179-181°C

IR (Nujol) : 3250, 1760, 1680, 1600, 1590,
1380, 1200 cm^{-1}

30 NMR (CDCl_3 , δ) : 1.15 (3H, t, $J=7\text{Hz}$), 2.11 (2H, m),
3.53 (3H, s), 4.78 (1H, t, $J=6\text{Hz}$),
6.76 (1H, dd, $J=9\text{Hz}$ and 2Hz),
6.86 (1H, d, $J=2\text{Hz}$), 7.30-7.50 (4H, m),
7.85 (1H, d, $J=9\text{Hz}$)

- (4) 2-(4-Chlorophenyl)-6-(1-carboxycyclobutyloxy)-
4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-
dioxide

mp : 148-151°C

IR (Nujol) : 1700, 1600, 1380, 1320, 1180 cm^{-1}

NMR (CDCl_3 , δ) : 2.00-2.30 (2H, m), 2.50-2.75 (2H, m),
2.78-2.95 (2H, m), 3.51 (3H, s), 6.53 (1H, dd, $J=9\text{Hz}$ and 2Hz), 6.73 (1H, d, $J=2\text{Hz}$),
7.34 (2H, d, $J=9\text{Hz}$), 7.46 (2H, d, $J=9\text{Hz}$),
7.80 (1H, d, $J=9\text{Hz}$)

- (5) (1R)-(+)-2-(4-Chlorophenyl)-6-(1-carboxyethoxy)-
4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one
1,1-dioxide

mp : 75-85 °C

$[\alpha]_D +16.4^\circ$ (C=1.0, EtOH)

IR (Nujol) : 3200, 1740, 1700, 1690, 1660, 1600,
1580, 1380, 1130 cm^{-1}

NMR (CDCl_3 , δ) : 1.77 (3H, d, $J=7\text{Hz}$), 3.55 (3H, s),
4.98 (1H, q, $J=7\text{Hz}$), 6.79 (1H, dd, $J=2\text{Hz}$ and 9Hz),
6.88 (1H, d, $J=2\text{Hz}$), 7.37 (2H, d, $J=9\text{Hz}$),
7.49 (2H, d, $J=9\text{Hz}$), 7.88 (1H, d, $J=9\text{Hz}$)

- (6) (1S)-(-)-2-(4-Chlorophenyl)-6-(1-carboxyethoxy)-
4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-
dioxide

mp : 85-95 °C

$[\alpha]_D -17.0^\circ$ (C=1.0, EtOH)

IR (Nujol) : 3200, 1740, 1700, 1665, 1600, 1580,
1200, 1130 cm^{-1}

NMR (CDCl_3 , δ) : 1.75 (3H, d, $J=7\text{Hz}$), 3.52 (3H, s),
4.95 (1H, q, $J=7\text{Hz}$), 6.50 (1H, bs), 6.75 (1H, dd, $J=2\text{Hz}$ and 9Hz),
6.88 (1H, d, $J=2\text{Hz}$), 7.32 (2H, d, $J=9\text{Hz}$), 7.45 (2H, d, $J=9\text{Hz}$),
7.85 (1H, d, $J=9\text{Hz}$)

- (7) (1R)-(+)-6-(1-Carboxyethoxy)-4-methyl-2-phenyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 184-185.5°C

IR (Nujol) : 3200, 1750, 1660, 1610, 1320,
1180 cm^{-1}

NMR (CDCl_3 , δ) : 1.74 (3H, d, $J=7\text{Hz}$), 3.53 (3H, s),
3.55-4.1 (1H, br), 4.95 (1H, q, $J=7\text{Hz}$),
6.76 (1H, dd, $J=2\text{Hz}$ and 9Hz), 6.85 (1H, d,
 $J=2\text{Hz}$), 7.35-7.55 (5H, m), 7.86 (1H, d,
 $J=9\text{Hz}$)

- (8) (1R)-(+)-6-(1-Carboxyethoxy)-4-methyl-2-(4-phenoxyphenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 106°C (dec.)

IR (Nujol) : 3600-2400, 1740, 1695, 1665, 1600,
1585, 1345, 1215 cm^{-1}

NMR (CDCl_3 , δ) : 1.74 (3H, d, $J=7\text{Hz}$), 3.53
(3H, s), 3.63 (1H, br), 4.95 (1H, q,
 $J=7\text{Hz}$), 6.76 (1H, dd, $J=2\text{Hz}$ and 9Hz),
6.85 (1H, d, $J=2\text{Hz}$), 7.0-7.45 (9H, m),
7.86 (1H, d, $J=9\text{Hz}$)

- (9) (1R)-(+)-6-(1-Carboxyethoxy)-2-(4-isopropylphenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 74°C (dec.)

IR (Nujol) : 3600-2400, 1730, 1695, 1600, 1340,
1315 cm^{-1}

NMR (CDCl_3 , δ) : 1.27 (6H, d, $J=7\text{Hz}$), 1.74 (3H, d,
 $J=7\text{Hz}$), 2.76 (1H, m), 3.43 (1H, br), 3.52
(3H, s), 4.95 (1H, q, $J=7\text{Hz}$), 6.76 (1H, dd,
 $J=2\text{Hz}$ and 9Hz), 6.85 (1H, d, $J=2\text{Hz}$), 7.32
(4H, s), 7.85 (1H, d, $J=9\text{Hz}$)

(10) (1R)-(+)-6-(1-Carboxyethoxy)-2-[(3-chloro-4-methyl)phenyl]-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 184-186°C

IR (Nujol) : 3600-2500, 1720, 1700, 1595, 1330 cm^{-1}

NMR (CDCl_3 , δ) : 1.75 (3H, d, $J=7\text{Hz}$), 2.42 (3H, s), 3.25 (1H, br), 3.53 (3H, s), 4.94 (1H, q, $J=7\text{Hz}$), 6.77 (1H, dd, $J=2\text{Hz}$ and 9Hz), 6.85 (1H, d, $J=2\text{Hz}$), 7.23 (1H, dd, $J=2\text{Hz}$ and 8Hz), 7.34 (1H, d, $J=8\text{Hz}$), 7.41 (1H, d, $J=2\text{Hz}$), 7.85 (1H, d, $J=9\text{Hz}$)

(11) (1R)-(+)-6-(1-Carboxyethoxy)-4-methyl-2-(4-trifluoromethylphenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 162-163°C

IR (CHCl_3) : 3600-3300, 1720, 1690, 1600, 1340, 1320, 1130 cm^{-1}

NMR (CDCl_3 , δ) : 1.75 (3H, d, $J=6\text{Hz}$), 3.54 (3H, s), 4.90-5.01 (1H, q, $J=6\text{Hz}$), 6.77 (1H, dd, $J=2\text{Hz}$ and 8Hz), 6.87 (1H, d, $J=2\text{Hz}$), 7.54 (2H, d, $J=8\text{Hz}$), 7.74 (2H, d, $J=8\text{Hz}$), 7.86 (1H, d, $J=8\text{Hz}$)

(12) (1R)-(+)-6-(1-Carboxyethoxy)-2-cyclohexyl-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 76-77°C

IR (CHCl_3) : 3600-2400, 1720, 1680, 1600, 1330, 1310, 1170 cm^{-1}

NMR (CDCl_3 , δ) : 1.20-1.45 (3H, m), 1.70 (3H, d, $J=6\text{Hz}$), 1.82-1.88 (5H, m), 2.20-2.38 (2H, m), 3.44 (3H, s), 4.35-4.47 (1H, m), 4.76 (1H, s), 4.89 (1H, q, $J=6\text{Hz}$), 6.67-6.74 (2H, m), 7.75 (1H, d, $J=8\text{Hz}$)

(13) (1R)-(+)-6-(1-Carboxyethoxy)-4-methyl-2-(4-methylphenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 182-183°C

IR (CHCl₃) : 1700, 1600, 1320, 1130 cm⁻¹

NMR (CDCl₃, δ) : 1.74 (3H, d, J=6Hz), 2.40 (3H, s), 3.17 (1H, br s), 3.52 (3H, s), 4.89-5.00 (1H, q, J=6Hz), 6.75 (1H, dd, J=2Hz and 8Hz), 6.84 (1H, d, J=2Hz), 7.29 (4H, s), 7.85 (1H, d, J=8Hz)

(14) (1R)-(+)-6-(1-Carboxyethoxy)-4-methyl-2-(2-pyridyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 142-143°C

IR (Nujol) : 3700-2300, 1700, 1600, 1350, 1320, 1275, 1210, 1190 cm⁻¹

NMR (CDCl₃, δ) : 1.56 (3H, d, J=7Hz), 3.47 (3H, s), 5.17 (1H, q, J=7Hz), 6.92 (1H, dd, J=2Hz and 9Hz), 7.08 (1H, d, J=2Hz), 7.45-7.60 (2H, m), 7.84 (1H, d, J=9Hz), 8.00 (1H, m), 8.56-8.59 (1H, m)

(15) (1R)-(+)-6-(1-Carboxyethoxy)-2-(3,4-dichlorophenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 105-106°C

IR (Nujol) : 3250-2400, 1735, 1690, 1600, 1585, 1300, 1290, 1175 cm⁻¹

NMR (DMSO-d₆, δ) : 1.57 (3H, d, J=7Hz), 3.48 (3H, s), 5.20 (1H, q, J=7Hz), 6.93 (1H, dd, J=2Hz and 9Hz), 7.08 (1H, d, J=2Hz), 7.46 (1H, dd, J=2Hz and 9Hz), 7.76-7.93 (3H, m)

(16) (1R)-(+)-6-(1-Carboxyethoxy)-2-(3-chlorophenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 174-176°C

IR (Nujol) : 1725, 1700, 1610, 1580, 1330, 1310,
1180 cm^{-1}

NMR (CDCl_3 , δ) : 1.74 (3H, d, $J=7\text{Hz}$), 2.72 (1H,
br s), 3.53 (3H, s), 4.95 (1H, q, $J=7\text{Hz}$),
6.74-7.51 (6H, m), 7.86 (1H, d, $J=9\text{Hz}$)

(17) (1R)-(+)-6-(1-Carboxyethoxy)-2-(2-chlorophenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 110-112°C

IR (Nujol) : 1740, 1700, 1600, 1580, 1375,
1190 cm^{-1}

NMR (CDCl_3 , δ) : 1.75 (3H, d, $J=7\text{Hz}$), 3.55 (3H, s),
4.95 (1H, q, $J=7\text{Hz}$), 6.74-7.67 (6H, m),
7.85 (1H, d, $J=9\text{Hz}$)

(18) (1R)-(+)-6-(1-Carboxyethoxy)-2-(4-fluorophenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 130-132°C

IR (Nujol) : 1740, 1700, 1600, 1500, 1380, 1210 cm^{-1}

NMR (CDCl_3 , δ) : 1.74 (3H, d, $J=7\text{Hz}$), 3.52 (3H, s),
4.94 (1H, q, $J=7\text{Hz}$), 5.80 (1H, br s),
6.74-7.43 (6H, m), 7.85 (1H, d, $J=9\text{Hz}$)

(19) (1R)-(+)-6-(1-Carboxyethoxy)-4-methyl-2-(4-methylthiophenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 143-144°C

IR (Nujol) : 3350-2300, 1730, 1660, 1600, 1580,
1190, 1090 cm^{-1}

NMR (CDCl_3 , δ) : 1.74 (3H, d, $J=7\text{Hz}$), 2.50 (3H, s),
3.53 (3H, s), 4.95 (1H, q, $J=7\text{Hz}$), 6.76
(1H, dd, $J=2\text{Hz}$ and 9Hz), 6.85 (1H, d, $J=2\text{Hz}$),
7.32 (4H, s), 7.85 (1H, d, $J=9\text{Hz}$)

(20) (1R)-(+)-6-(1-Carboxyethoxy)-2-(4-dimethylamino-phenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 190°C (dec.)

IR (KBr) : 3400, 2750-2200, 1690, 1590, 1450,
1320, 1180, 1125 cm⁻¹

NMR (DMSO-d₆, δ) : 1.57 (3H, d, J=7Hz), 2.97 (6H, s), 3.47 (3H, s), 5.22 (1H, q, J=7Hz), 6.85 (2H, d, J=9Hz), 7.15 (2H, d, J=9Hz), 6.92 (1H, dd, J=2Hz and 9Hz), 7.05 (1H, d, J=2Hz), 7.85 (1H, d, J=9Hz)

(21) 6-[1-(Carboxy)cyclohexylmethoxy]-2-(4-chlorophenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 145-150°C

IR (Nujol) : 3300, 1700, 1600, 1580, 1370, 1310, 1190, 1130 cm⁻¹

NMR (CDCl₃, δ) : 1.10-2.10 (11H, m), 3.40 (3H, s), 4.40 (1H, br s), 6.60 (1H, d, J=9Hz), 6.85 (1H, s), 7.25 (2H, d, J=9Hz), 7.42 (2H, d, J=9Hz), 7.70 (1H, d, J=9Hz)

(continued to the next page)

Example 17

To a solution of (1R)-(+)-2-(4-chlorophenyl)-6-(1-carboxyethoxy)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (250 mg) in acetonitrile (5 ml) was added a solution of sodium bicarbonate (51 mg) in water (1 ml) in one portion at ambient temperature. The mixture was concentrated in vacuo. The residue was recrystallized from a mixture of ethanol and acetonitrile to yield sodium salt of (1R)-(+)-2-(4-chlorophenyl)-6-(1-carboxyethoxy)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (205 mg) as crystals.

mp : 225-230 °C

$[\alpha]_D^{25} +8.34^\circ$ (C=1.0, EtOH)

IR (Nujol) : 3300, 1710, 1600, 1580, 1380, 1210, 1190, 1130 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.43 (3H, d, J=7Hz), 3.45 (3H, s), 4.48 (1H, q, J=7Hz), 6.80 (1H, dd, J=2Hz and 9Hz), 6.95 (1H, d, J=2Hz), 7.42 (2H, d, J=9Hz), 7.59 (2H, d, J=9Hz), 7.77 (1H, d, J=9Hz)

Example 18

In a similar manner to that of Example 17, there was obtained the following compound.

Sodium salt of (1S)-(-)-2-(4-chlorophenyl)-6-(1-carboxyethoxy)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 210-215 °C

$[\alpha]_D^{25} -8.53^\circ$ (C=0.1, EtOH)

IR (Nujol) : 3550, 3400, 1710, 1600, 1380, 1220, 1180, 1120 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.44 (3H, d, J=7Hz), 3.45 (3H, s), 4.49 (1H, q, J=7Hz), 6.81 (1H, dd, J=2Hz and 9Hz), 7.39 (1H, d, J=2Hz), 7.42 (2H, d, J=9Hz), 7.59 (2H, d, J=9Hz), 7.77 (1H, d, J=9Hz)

Example 19

A mixture of 2-(4-carboxyphenyl)-6-hydroxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (0.13 g), potassium carbonate (0.103 g) and bromomethylcyclohexane (0.14 g) in dry N,N-dimethylformamide (1.3 ml) was stirred at 80°C for 16 hours. The cooled mixture was poured into diluted hydrochloric acid. The separated oil was extracted with diethyl ether. The organic layer was washed with water, aqueous sodium bicarbonate solution, and brine. The dried solvent was concentrated in vacuo to yield 6-cyclohexylmethoxy-2-(4-cyclohexylmethoxycarbonylphenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (0.13 g) as colorless crystals.

mp : 119-121°C

IR (Nujol) : 1720, 1690, 1600, 1320 cm⁻¹

NMR (DMSO-d₆, δ) : 0.95-1.40 (10H, m), 1.55-1.95 (12H, m), 3.52 (3H, s), 4.00 (2H, d, J=5.8Hz), 4.15 (2H, d, J=5.8Hz), 6.97-7.10 (2H, m), 7.55 and 8.10 (4H, ABq, J=8.3Hz), 7.87 (1H, d, J=8.7Hz)

Example 20

In a similar manner to that of Example 19, there were obtained the following compounds.

- (1) 2-(4-Chlorophenyl)-4-methyl-6-(2-phthalimidoethoxy)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 175-180°C

IR (Nujol) : 1770, 1710, 1605, 1585 cm⁻¹

NMR (DMSO-d₆, δ) : 3.50 (3H, s), 4.0-4.1 (2H, m), 4.4-4.5 (2H, m), 6.95-7.05 (2H, m), 7.35-7.45 (2H, m), 7.55-7.56 (3H, m), 7.8-8.0 (4H, m)

- (2) 6-[trans-4-(tert-Butoxycarbonylaminomethyl)-

cyclohexylmethoxy]-2-(4-chlorophenyl)-4-methyl-
2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
mp : 133-136°C

IR (Nujol) : 3400, 1690, 1600, 1590, 1520, 1450,
1360, 1340, 1180 cm⁻¹

NMR (DMSO-d₆, δ) : 0.75-1.20 (4H, m), 1.40
(9H, s), 1.40-2.00 (6H, m), 2.73 (2H, t,
J=6Hz), 3.50 (3H, s), 3.98 (2H, d, J=7Hz),
7.00 (1H, d, J=9Hz), 7.08 (1H, s), 7.40 (2H,
d, J=9Hz), 7.60 (2H, d, J=9Hz), 7.88 (1H, d,
J=9Hz)

(3) 2-(4-Chlorophenyl)-6-[1-(ethoxycarbonyl)cyclohexyl-
methoxy]-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-
one 1,1-dioxide

mp : 128-131°C

IR (Nujol) : 1730, 1690, 1600, 1590, 1380,
1180 cm⁻¹

NMR (CDCl₃, δ) : 1.30 (3H, t, J=8Hz), 1.10-2.10
(11H, m), 3.52 (3H, s), 4.25 (2H, q, J=8Hz),
4.50 (1H, d, J=5Hz), 6.75 (1H, dd, J=2Hz and
9Hz), 6.82 (1H, d, J=2Hz), 7.35 (2H, d, J=9Hz),
7.45 (2H, d, J=9Hz), 7.85 (1H, d, J=9Hz)

(4) 2-(4-Chlorophenyl)-4-methyl-6-[2-(tetrahydro-2H-
pyranyl)methoxy]-2H-1,2,4-benzothiadiazine-3(4H)-
one 1,1-dioxide

mp : >250°C

IR (Nujol) : 1700, 1600, 1580, 1490, 1340, 1320,
1190 cm⁻¹

NMR (DMSO-d₆, δ) : 1.20-1.90 (6H, m), 3.40-3.90
(3H, m), 3.50 (3H, s), 4.10 (2H, d, J=6Hz),
7.00 (1H, dd, J=2Hz and 9Hz), 7.10 (1H, d,
J=2Hz), 7.40 (2H, d, J=9Hz), 7.60 (2H, d,
J=9Hz), 7.86 (1H, d, J=9Hz)

Example 21

A solution of 2-(4-isopropoxycarbonylmethylphenyl)-6-isopropoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (95 mg) in a mixture of 1,4-dioxane (6 ml), water (2 ml) and conc. hydrochloric acid (1 ml) was refluxed for two hours. After the mixture was concentrated in vacuo, the residue was extracted two times with ethyl acetate. The combined organic layers were washed with water and brine, dried over MgSO_4 . After the solvent was evaporated under reduced pressure, the crystalline residue was recrystallized from ethanol to yield 2-(4-carboxymethylphenyl)-6-isopropoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (61 mg) as pale yellow crystals.

mp : 232-233°C

IR (Nujol) : 3600-2500, 1700, 1685, 1600 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 1.34 (6H, d, $J=6.0\text{Hz}$), 3.49 (3H, s), 3.66 (2H, s), 4.8-5.0 (1H, m), 6.95-7.01 (2H, m), 7.30 and 7.40 (4H, ABq, $J=8.0\text{Hz}$), 7.84 (1H, d, $J=9.0\text{Hz}$)

Example 22

In a similar manner to that of Example 21, there were obtained the following compounds.

(1) 2-(4-Carboxyphenyl)-6-isopropoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 247.5-248.5°C

IR (Nujol) : 3200-2400, 1690, 1605 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 1.34 (6H, d, $J=6.0\text{Hz}$), 3.50 (3H, s), 4.80-5.0 (1H, m), 6.95-7.07 (2H, m), 7.51 and 8.09 (4H, ABq, $J=8.3\text{Hz}$), 7.86 (1H, d, $J=8.4\text{Hz}$), 13.3 (1H, br s)

(2) 2-(3-Carboxypropyl)-6-isopropoxy-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 150-152°C

IR (Nujol) : 1710, 1690, 1600, 1580, 1470, 1380,
1100 cm^{-1}

NMR (CDCl_3 , δ) : 1.38 (6H, d, $J=6\text{Hz}$), 2.05 (2H, m),
2.43 (2H, t, $J=7\text{Hz}$), 3.46 (3H, s), 3.98
(2H, t, $J=7\text{Hz}$), 4.67 (1H, m), 6.67 (1H, d,
 $J=2\text{Hz}$), 6.76 (1H, dd, $J=2\text{Hz}$ and 9Hz), 7.76
(1H, d, $J=9\text{Hz}$)

Example 23

A solution of 6-cyclohexylmethoxy-2-(4-cyclohexyl-
methoxycarbonylphenyl)-4-methyl-2H-1,2,4-benzothiadiazine-
3(4H)-one 1,1-dioxide (0.12 g) in a mixture of conc.
hydrochloric acid (1 ml), water (2 ml) and 1,4-dioxane
(8 ml) was refluxed overnight. The mixture was
concentrated in vacuo. The residue was treated with
a mixture of ethyl acetate and aqueous 1N sodium
hydroxide solution. The precipitates were collected
by filtration, washed with ethyl acetate and then
dissolved in a mixture of ethyl acetate and aqueous 1N
hydrochloric acid. The organic layer was washed with
water, dried, and evaporated under reduced pressure.
The residue was recrystallized from ethanol to give
2-(4-carboxyphenyl)-6-cyclohexylmethoxy-4-methyl-2H-
1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide as
colorless crystals.

mp : 240.5-241°C

IR (Nujol) : 3300-2400, 1690, 1600, 1330 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 1.40-1.95 (5H, m), 1.55-1.95
(6H, m), 3.52 (3H, s), 4.00 (1H, d, $J=5.8\text{Hz}$),
6.95-7.10 (2H, m), 7.50 and 8.05 (4H, ABq,
 $J=8.3\text{Hz}$), 7.86 (1H, d, $J=8.7\text{Hz}$), 13.3 (1H,
br s)

Example 24

To a solution of 2-(4-chlorophenyl)-4-methyl-6-(N-methylacetyl-amino)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (0.14 g) in ethanol (2.8 ml) was added conc. hydrochloric acid (2.8 ml). The mixture was refluxed for one hour and neutralized with aqueous saturated NaHCO₃ solution. The resulting crystals were collected by filtration to give 2-(4-chlorophenyl)-4-methyl-6-(N-methylamino)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (0.105 g) as colorless powder.

mp : 207-209°C

IR (Nujol) : 3400, 1690, 1600, 1320 cm⁻¹

NMR (CDCl₃, δ) : 2.95 (3H, s), 3.51 (3H, s),

4.5 (1H, br), 6.28 (1H, br s), 6.4-6.5

(1H, m), 7.3-7.5 (4H, m), 7.62-7.7 (1H, m)

Example 25

In a similar manner to that of Example 24, there was obtained the following compound.

Hydrochloride salt of 6-[trans-4-(aminomethyl)-cyclohexylmethoxy]-2-(4-chlorophenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : >250°C

IR (Nujol) : 3400, 1700, 1610, 1600, 1380, 1330, 1310, 1280, 1130 cm⁻¹

NMR (DMSO-d₆, δ) : 0.90-1.20 (4H, m), 1.40-2.10

(6H, m), 2.70 (2H, m), 3.50 (3H, s), 4.02

(2H, d, J=7Hz), 7.03 (1H, dd, J=2Hz and 9Hz),

7.10 (1H, d, J=2Hz), 7.40 (2H, d, J=9Hz),

7.60 (2H, d, J=9Hz), 7.90 (1H, d, J=9Hz),

8.00 (1H, br s)

Example 26

To a solution of 2-(4-chlorophenyl)-4-methyl-6-(2-phthalimidoethoxy)-2H-1,2,4-benzothiadiazine-3(4H)-one

1,1-dioxide (0.153 g) in methanol (1.5 ml) was added hydrazine monohydrate (30 mg). After the mixture was refluxed for one hour, the reaction mixture was treated with conc. HCl and further refluxed for 30 minutes. The precipitate was removed by filtration and the filtrate was washed two times with ether. The aqueous layer was treated with aqueous 1N NaOH solution and extracted with ethyl acetate. The extract was washed with brine and dried over MgSO_4 . After the solvent was evaporated under reduced pressure, the residue was triturated with IPE. The colorless crystals were collected by filtration and recrystallized from ethanol to give 6-(2-aminoethoxy)-2-(4-chlorophenyl)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (30 mg) as colorless prisms.

mp : 175-176°C

IR (Nujol) : 3370, 3310, 1705, 1685, 1600, 1195 cm^{-1}

NMR (CDCl_3 , δ) : 1.66 (2H, br s), 3.19 (2H, br s), 3.54 (3H, s), 4.12 (2H, t, $J=5.0\text{Hz}$), 6.77-7.90 (2H, m), 7.35 and 7.46 (4H, ABq, $J=8.5\text{Hz}$), 7.85 (1H, d, $J=8.5\text{Hz}$)

Example 27

Into a solution of 6-isopropoxy-4-methyl-2-(2-pyridyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (0.174 g) in chloroform (5 ml) was bubbled chlorine gas for a few minutes at 5°C. The mixture was washed with aqueous sodium bicarbonate solution, dried and concentrated in vacuo. The residue was crystallized from ethanol to yield 7-chloro-6-isopropoxy-4-methyl-2-(2-pyridyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide (115 mg) as colorless needles.

mp : 193-194°C

IR (Nujol) : 1685, 1590, 1345 cm^{-1}

NMR (CDCl_3 , δ) : 1.46 (6H, d, $J=6\text{Hz}$), 3.55 (3H, s),

4.6-4.85 (1H, m), 6.75 (1H, s), 7.35-7.55
(2H, m), 7.90 (1H, s), 7.85-7.95 (1H, m),
8.6-8.7 (1H, m)

5 Example 28

In a similar manner to that of Example 27, there was obtained the following compound.

10 7-Bromo-6-isopropoxy-4-methyl-2-(2-pyridyl)-2H-
1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide

mp : 194.5-195.5°C

IR (Nujol) : 1690, 1590, 1345 cm⁻¹

NMR (CDCl₃, δ) : 1.47 (6H, d, J=6Hz), 3.55 (3H, s),

4.6-4.85 (1H, m), 6.71 (1H, s), 7.35-7.55

15 (2H, m), 7.85-7.95 (1H, m), 8.04 (1H, s),

8.60-8.70 (1H, m)

Example 29

20 Into a suspension of 2-(4-chlorophenyl)-6-hydroxy-
4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
(700 mg) in acetic acid (70 ml) was bubbled chlorine
gas to give the colorless solution at ambient temperature.
The mixture was poured into an ice water. The
precipitates was collected by filtration and recrystal-
25 lized from ethanol to yield 2-(4-chlorophenyl)-5,7-
dichloro-6-hydroxy-4-methyl-2H-1,2,4-benzothiadiazine-
3(4H)-one 1,1-dioxide (350 mg) as crystals.

mp : 197-198°C

IR (Nujol) : 1720, 1700, 1500, 1360, 1180 cm⁻¹

30 NMR (DMSO-d₆, δ) : 3.55 (3H, s), 7.42 (2H, d,

J=9Hz), 7.60 (2H, d, J=9Hz), 8.00 (1H, s)

Example 30

35 To a solution of 2-(4-chlorophenyl)-4-methyl-6-
(N-methylamino)-2H-1,2,4-benzothiadiazine-3(4H)-one

1,1-dioxide (55 mg) in dry THF (2 ml) was added a
1.5M solution of n-butyl lithium in n-Hexane (0.16 ml)
at -78°C. The mixture was stirred at 0°C for 30 minutes
and added methyl iodide (0.05 ml) at the same temperature.
5 After the mixture was stirred at 0°C for 30 minutes,
water was added. The mixture was extracted two times
with ethyl acetate and the combined organic layers
were washed with water and brine and dried over MgSO₄.
After the solvent was evaporated under reduced pressure,
10 the residue was purified by preparative thin layer
chromatography (eluted with a mixture of benzene and
acetone (9:1) to give 2-(4-chlorophenyl)-6-(N,N-
dimethylamino)-4-methyl-2H-1,2,4-benzothiadiazine-
3(4H)-one 1,1-dioxide (8 mg) as colorless powder.

15 mp : 205-206°C

IR (Nujol) : 1690, 1605 cm⁻¹

NMR (CDCl₃, δ) : 3.12 (6H, s), 3.54 (3H, s),
6.32 (1H, d, J=2.0Hz), 6.56 (1H, dd, J=2.0
and 9.0Hz), 7.35 and 7.45 (4H, ABq, J=8.8Hz),
20 7.70 (1H, d, J=9.0Hz)

Example 31

A mixture of 6-hydroxy-4-methyl-2-(4-trifluoromethyl-
phenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide
25 (1.56 g), (S)-(-)-ethyl-2-[[[4-methylphenyl)sulfonyl]-
oxy]propionate (1.37 g) and potassium carbonate (578 mg)
in N,N-dimethylformamide (15.6 ml) was stirred at
60-65°C for one hour. The cooled mixture was filtered
off and the filtrate was poured into a mixture of ice
30 and 1N-hydrochloric acid. The precipitates were
collected and dissolved in methylene chloride. The
solution was dried and concentrated in vacuo. The
residue was crystallized from diisopropyl ether to
yield (1R)-(+)-6-[1-(ethoxycarbonyl)ethoxy]-4-methyl-2-(4-
35 trifluoromethylphenyl)-2H-1,2,4-benzothiadiazine-3(4H)-one

1,1-dioxide (1.58 g).

mp : 124-125°C

IR (Nujol) : 1720, 1685, 1595, 1330, 1130,
1060 cm^{-1}

5 NMR (CDCl_3 , δ) : 1.30 (3H, t, $J=6\text{Hz}$), 1.70 (3H,
d, $J=6\text{Hz}$), 3.54 (3H, s), 4.26 (2H, q,
J=6Hz), 4.88 (1H, q, $J=6\text{Hz}$), 6.75 (1H, dd,
J=2Hz and 8Hz), 6.85 (1H, d, $J=2\text{Hz}$), 7.55
10 (2H, d, $J=8\text{Hz}$), 7.75 (2H, d, $J=8\text{Hz}$),
7.84 (1H, d, $J=8\text{Hz}$)

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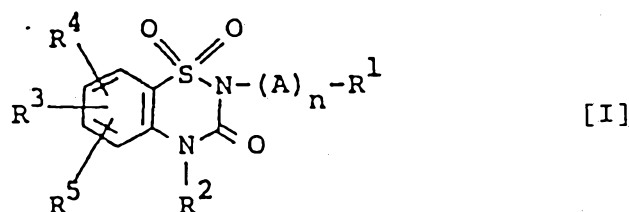
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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula:



10 wherein R¹ is phenyl which may be substituted with
halogen, lower alkyl, lower alkoxy,
halo(lower)alkyl, lower alkylamino,
lower alkylthio, aryloxy, carboxy,
15 lower alkoxy carbonyl, carboxy(lower)-
alkyl or lower alkoxy carbonyl(lower)-
alkyl;
cyclo(lower)alkyl;
lower alkyl which may be substituted
with carboxy or lower alkoxy carbonyl
20 pyrimidinyl; or pyridyl which may be
substituted with lower alkyl;

A is lower alkylene,

n is an integer of 0 or 1,

R² is lower alkyl,

25 R³ is hydrogen; hydroxy; halogen; halo-
(lower)alkyl; lower alkyl; lower
alkylamino; lower alkanoyl; lower
alkanoyl(lower)alkylamino; lower
alkoxy which may be substituted with
30 aryl, phthalimido, pyranlyl, amino,
carboxy, lower alkoxy carbonyl or
cyclo(lower)alkyl which may be
substituted with amino(lower)alkyl or
lower alkoxy carbonylamino(lower)-
35 alkyl; or cyclo(lower)alkyloxy which
may be substituted with carboxy or
lower alkoxy carbonyl;



R⁴ is hydrogen or halogen, and

R⁵ is hydrogen or halogen,

provided that

R¹ is phenyl substituted with lower alkoxy,
lower alkylamino, lower alkylthio,
aryloxy, carboxy, lower
alkoxycarbonyl, carboxy(lower)alkyl
or lower alkoxycarbonyl(lower)alkyl;
lower alkyl substituted with carboxy
or lower alkoxycarbonyl; pyrimidinyl;
or pyridyl substituted with lower
alkyl,

when R³ is hydrogen or halogen,
and pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein

R⁴ and R⁵ are both hydrogen, and
n is 0.

3. A compound according to claim 2, wherein

R¹ is phenyl which may be substituted with halogen,
lower alkyl, lower alkoxy, halo(lower)alkyl,
lower alkylamino, lower alkylthio, aryloxy,
carboxy, lower alkoxycarbonyl, carboxy(lower)-
alkyl or lower alkoxycarbonyl(lower)alkyl, and
R³ is lower alkoxy which may be substituted with
aryl, phthalimido, pyranyl, amino, carboxy,
lower alkoxycarbonyl or cyclo(lower)alkyl
which may be substituted with amino(lower)-
alkyl or lower alkoxycarbonylamino(lower)-
alkyl.

4. A compound according to claim 3, wherein

R¹ is phenyl substituted with halogen, and

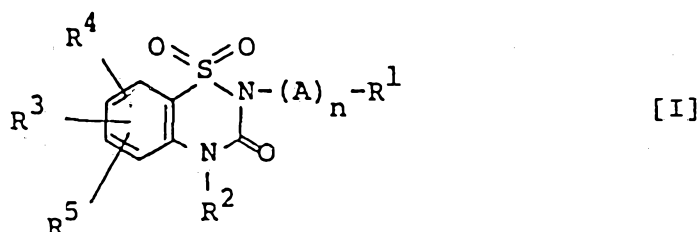
R³ is lower alkoxy substituted with carboxy.



5. A compound of claim 4, which is
(1R)-(+)-2-(4-Chlorophenyl)-6-(1-carboxyethoxy)-4-methyl-2H-1,2,4-benzothiadiazine-3(4H)-one 1,1-dioxide or its salt.

5

6. A process for preparing a compound of the formula:



10

wherein R¹ is phenyl which may be substituted with
halogen, lower alkyl, lower alkoxy,
halo(lower)alkyl, lower alkylamino,
lower alkylthio, aryloxy, carboxy,
lower alkoxycarbonyl, carboxy(lower)-
alkyl or lower alkoxycarbonyl(lower)-
alkyl;
cyclo(lower)alkyl;
lower alkyl which may be substituted
with carboxy or lower alkoxycarbonyl;
pyrimidinyl; or pyridyl which may be
substituted with lower alkyl;

15

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25

A is lower alkylene,
n is an integer of 0 or 1,
R² is lower alkyl,
R³ is hydrogen; hydroxy; halogen;
halo(lower)alkyl; lower alkyl; lower
alkylamino; lower alkanoylamine;
lower alkanoyl(lower)alkylamino;
lower alkoxy which may be substituted
with aryl, phthalimido, pyranlyl,
amino, carboxy, lower alkoxycarbonyl,
or cyclo(lower)alkyl which may be
substituted with amino(lower)alkyl or
lower alkoxycarbonylamino(lower)-

30

35



alkyl;

or cyclo(lower)alkyloxy which may be substituted with carboxy or lower alkoxycarbonyl;

5 R^4 is hydrogen or halogen, and

R^5 is hydrogen or halogen,

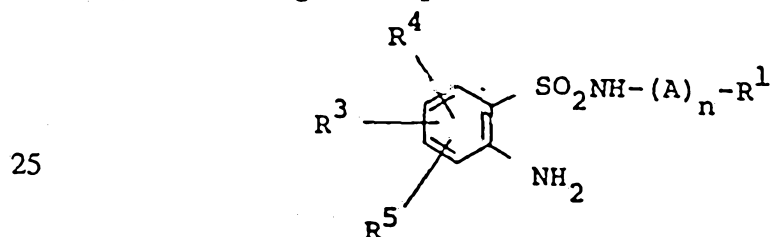
provided that

10 R^1 is phenyl substituted with lower alkoxy, lower alkylamino, lower alkylthio, aryloxy, carboxy, lower alkoxycarbonyl, carboxy(lower)alkyl or lower alkoxycarbonyl(lower)alkyl; lower alkyl substituted with carboxy or lower alkoxycarbonyl; pyrimidinyl; 15 or pyridyl substituted with lower alkyl,

when R^3 is hydrogen or halogen, or salt thereof, which comprises

20

(1) reacting a compound of the formula:



or its reactive derivative at the amino group or its salt

with a compound of the formula:

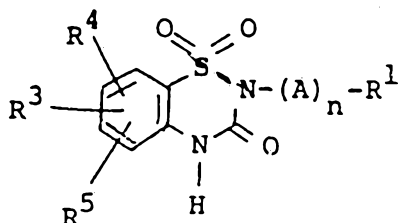
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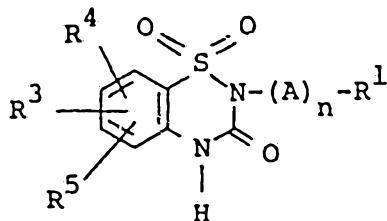


to give a compound of the formula:

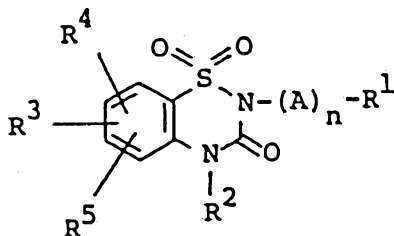


or its salt, in which R^1 , R^3 , R^4 , R^5 , A and n are each as defined above and R^6 and R^7 are each halogen, lower alkoxy or imidazolyl, or

(2) subjecting a compound of the formula:

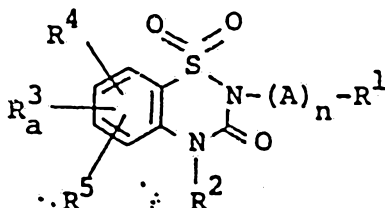


or its salt to introduction reaction of a substituent on nitrogen atom to give a compound of the formula:

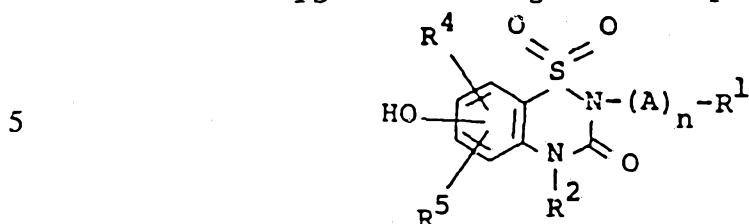


or its salt, in which R^1 , R^2 , R^3 , R^4 , R^5 , A and n are each as defined above, or

(3) subjecting a compound of the formula:



or its salt to elimination reaction of a substituent on an oxygen atom to give a compound of the formula:

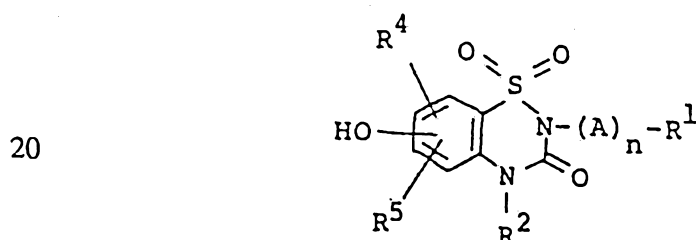


or its salt, in which R¹, R², R⁴, R⁵, A and n are each as defined above, and

10 R_a³ is lower alkoxy which may be substituted with aryl, cyclo(lower)alkyl, carboxy or lower alkoxy carbonyl; or cyclo(lower)alkyloxy which may be substituted with carboxy or lower alkoxy carbonyl, or

15

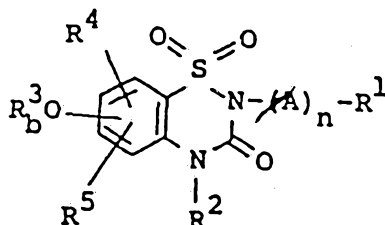
(4) reacting a compound of the formula:



or its salt with a compound of the formula:

R_b³-X to give a compound of the formula:

25



30

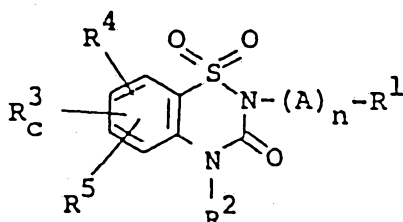
or its salt, in which R¹, R², R⁴, R⁵, A and n are each defined above,

35 R_b³ is lower alkyl which may be substituted with aryl, phthalimido, pyranlyl, carboxy, or cyclo(lower)alkyl which may be substituted with lower alkoxy carbonylamino(lower)alkyl; or cyclo(lower)alkyl which may be substituted

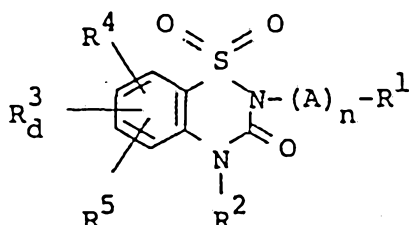


with carboxy or lower alkoxy carbonyl, and X is leaving group, or

(5) subjecting a compound of the formula:



or its salt to deesterification reaction to give a compound of the formula:



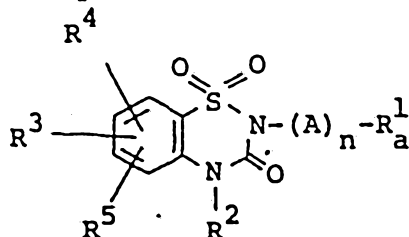
or its salt, in which R^1 , R^2 , R^4 , R^5 , A and n are each as defined above,

R_c^3 is lower alkoxy carbonyl(lower)alkoxy which may be substituted with cyclo(lower)alkyl; or

lower alkoxy carbonyl cyclo(lower)alkyloxy and

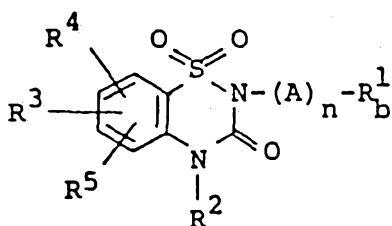
R_d^3 is carboxy(lower)alkoxy which may be substituted with cyclo(lower)alkyl; or carboxycyclo(lower)alkyloxy, or

(6) subjecting a compound of the formula:



or its salt to deesterification reaction to give a compound of the formula:

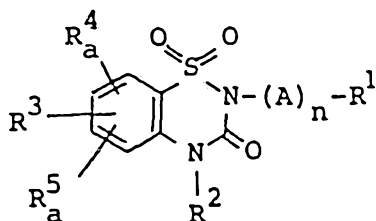




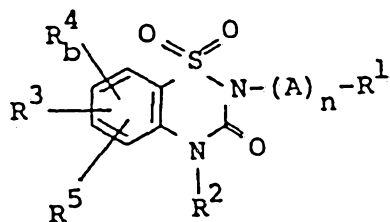
or its salt, in which R^2 , R^3 , R^4 , R^5 , A and n are each as defined above,

R_a^1 is phenyl substituted with lower alkoxy carbonyl- (lower)alkyl or lower alkoxy carbonyl; or lower alkoxy carbonyl(lower)alkyl, and R_b^1 is phenyl substituted with carboxy(lower)alkyl or carboxy; or carboxy(lower)alkyl, or

(7) halogenating a compound of the formula:



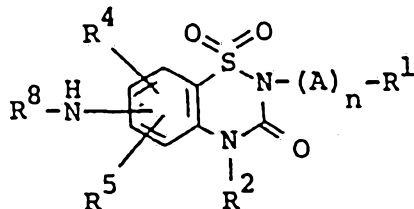
or its salt to give a compound of the formula:



or its salt, in which R^1 , R^2 , R^3 , R^5 , A and n are each as defined above,

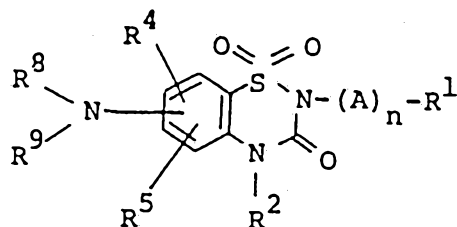
R_a^4 is hydrogen, R_b^4 is halogen and R_a^5 is hydrogen, or

(8) subjecting a compound of the formula:



or its salt to alkylation reaction to give a compound of the formula:

5

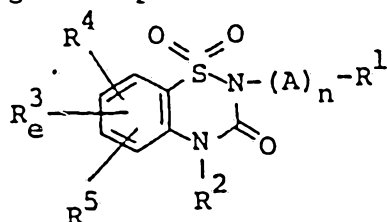


10

or its salt, in which R^1 , R^2 , R^4 , R^5 , A and n are each as defined above and R^8 and R^9 are each lower alkyl, or

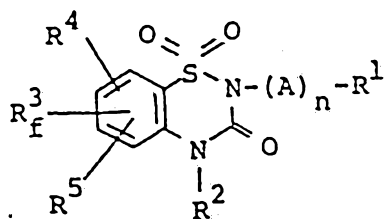
15 (9) subjecting a compound of the formula:

20



or its salt to elimination reaction of amino protective group to give a compound of the formula:

25



or its salt, in which R^1 , R^2 , R^4 , R^5 , A and n are each as defined above,

30

R^3_e is lower alkanoyl(lower)alkylamino or lower alkoxy substituted with phthalimido or cyclo(lower)alkyl substituted with lower alkoxy carbonylamino(lower)alkyl, and

35

R^3_f is lower alkylamino or lower alkoxy substituted with amino or cyclo(lower)alkyl substituted with amino(lower)alkyl.



7. A pharmaceutical composition comprising, as an
active ingredient, a compound of claim 1 or a
pharmaceutically acceptable salt thereof in
5 association with a pharmaceutically acceptable
carrier or excipient.
8. A method for the treatment of bone diseases in human
being or animals by administering to a human being
10 or animal in need of such treatment a
therapeutically effective amount of a compound of
claim 1.
9. Compounds of the general formula [I], methods for
15 their manufacture or pharmaceutical compositions or
methods of treatments involving them, substantially
as hereinbefore described with reference to the
Examples.
- 20

DATED this 27th day of August, 1990

25 Fujisawa Pharmaceutical Co., Ltd.
By Its Patent Attorneys
DAVIES & COLLISON

