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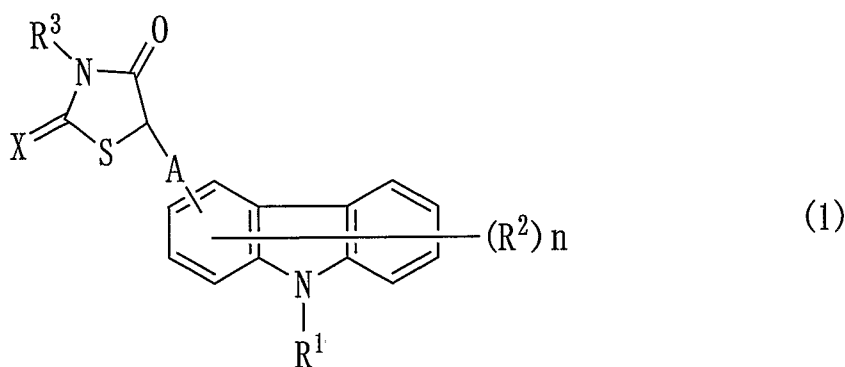
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(54) Title: CARBAZOLE COMPOUND



(57) Abstract: The present invention provides a carbazole compound represented by formula (1) or a salt thereof, wherein A is a direct bond, a lower alkylene group, or a lower alkylidene group; X is an oxygen atom or a sulfur atom; R¹ is a hydrogen atom, etc; R² is a lower alkoxy group, etc; and R³ is a hydrogen atom, etc. The carbazole compound or salt thereof of the present invention induces the production of TFF, and thus is usable for the treatment and/or prevention of disorders such as alimentary tract diseases, oral diseases, upper respiratory tract diseases, respiratory tract diseases, eye diseases, cancers, and wounds.



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DESCRIPTION
CARBAZOLE COMPOUND

TECHNICAL FIELD

5 The present invention relates to a carbazole compound.

BACKGROUND OF THE INVENTION

10 The trefoil factor family (TFF) is a group of highly stable peptides, having a three-leaved clover-like structure formed from six cysteine residues. Three TFF peptides (TFF1, TFF2 and TFF3) have been identified so far in humans. TFFs are present in mucus-related tissues such as the alimentary tract, and are secreted mainly by mucus-
15 secreting cells. The expression of TFF peptides is up-regulated in the vicinity of damaged mucosa and in regenerating glands. It is reported that the main functions of TFF peptides lie in the augmentation of cell migration processes (motogenic effects), protection of cells, and
20 suppression of apoptosis [Nature Reviews, Molecular Cell Biology, Vol. 4: 721-732(2003)].

 TFF2 is a peptide of 106 amino acid residues, initially isolated from porcine pancreas. The TFF2 peptide is abundant in the gastric mucous neck cells, the pyloric
25 region of the stomach, the mucosa surrounding ulcers, the regenerative mucosa, the overlying mucus layer, Brunner's glands, and so forth.

 It has been confirmed with experiments using rats that TFF2 prevents the development of colitis and gastric
30 ulceration and also accelerates the healing thereof [Gastroenterology 108: 108-116(1995); Gastroenterology 110: 489-497(1996); Alim. Pharmacol. Ther., 14: 1033-1040(2000); Gut, 45: 516-522(1999); Gut, 44: 636-642, 1999; and J. Leukoc. Biol., Vol. 75: 214-223(2004)].

35 Other experiments show that indomethacin-induced

gastric ulcers are exacerbated in TFF2 knockout mice [J. Clin. Invest., Vol. 109: 193-204(2002)].

Eur. J. Clin. Invest., 32: 519-527(2002) discloses the ability of TFF2 to stabilize mucus.

5 Am. J. Respir. Cell Mol. Biol., Vol. 29: 458-464(2003) teaches that TFF2 might be involved in regulating the proliferation of damaged airway epithelia.

It can be understood from the above that TFF2 plays key roles in protection against and repair of mucosal injury.
10 With regard to diseases which are likely to be cured with TFF2, improved therapeutic effects are expected by a promotion of endogenous TFF2 production.

Gastroenterology, 126: 796-808(2004) discloses that TFF3 is effective for curing alimentary tract mucositis such
15 as stomatitis induced by the administration of carcinostatics. Science, Vol. 274: 259-262(1996) and Gastroenterology, 119: 691-698(2000) conclude, from the fact that stomach cancer was developed in TFF1 knockout mice, that the TFF1 gene may function as a tumor suppressor gene. Nature Reviews,
20 Molecular Cell Biology, Vol. 4: 721-732(2003) and Int. J. Mol. Med., 12: 3-9(2003) suggest that TFF2 may act in a similar way as TFF1 and TFF3.

As compounds for up-regulating TFF2 expression, ligands for peroxisome proliferator-activated receptor- γ
25 (PPAR γ) (e.g., indomethacin, aspirin, prostaglandin J₂ and troglitazone) are known [FEBS Lett., 488: 206-210(2001); Alim. Pharmacol. Ther., 18 (suppl. 1): 119-125(2003); FEBS Lett., 558: 33-38(2004); and Can. Res., 61: 2424-2428(2001)].

Among various proteins, keratinocyte growth factor
30 (KGF) is reported to enhance TFF2 and TFF3 expressions in rat lower gastrointestinal tracts [Am. J. Physiol. Regul. Integr. Comp. Physiol., 284: R564-R573(2003)].

Some studies teach pharmacological actions of the TFF peptides themselves, and suggest the possibility of their
35 application in clinical medicine (WO92/14837, WO02/102403,

and WO02/46226).

WO01/002377 and WO02/051409 disclose various compounds having a substituent containing a 2,4-dioxo-thiazolidinyl or 4-oxo-2-thioxo-thiazolidinyl moiety on a heteroaryl skeleton such as a quinoline. These documents also disclose that such compounds exhibit telomerase inhibitory activity.

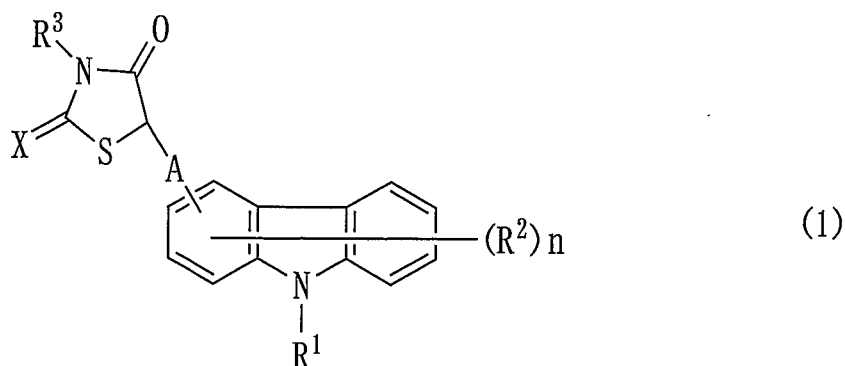
DISCLOSURE OF THE INVENTION

An object of the present invention is to provide a novel compound capable of up-regulating TFF.

The present inventors carried out extensive research to develop a novel compound capable of up-regulating endogenous TFF, and as a result, they found that compounds of the following formula (1) can up-regulate endogenous TFF, particularly TFF2. The present invention has been accomplished based on these findings.

The present invention provides compounds and uses as described in Items 1 to 16 below.

Item 1. A compound represented by formula (1)



or a salt thereof,

wherein A is a direct bond, a lower alkylene group, or a lower alkylidene group;

X is an oxygen atom or a sulfur atom;

R¹ is one of the following (1-1) to (1-21):

(1-1) a hydrogen atom,

- (1-2) a lower alkyl group,
- (1-3) a phenyl lower alkyl group optionally substituted on the phenyl ring with one or more members selected from the group consisting of a phenyl group (optionally substituted on the phenyl ring with one or more phenyl groups), lower alkyl groups, lower alkoxy groups, halogen atoms, $-(B)_1NR^6R^7$ groups, a nitro group, a carboxy group, lower alkoxycarbonyl groups, a cyano group, phenyl lower alkoxy groups, a phenoxy group, a piperidinyl lower alkoxycarbonyl groups, amino lower alkoxycarbonyl groups optionally substituted with one or two cycloalkyl groups, 2-imidazolinyllcarbonyl groups optionally substituted on the 2-imidazoline ring with one or more lower alkylthio groups, 3-pyrrolinyllcarbonyl groups optionally substituted on the 3-pyrroline ring with one or more lower alkyl groups, thiazolidinyllcarbonyl groups optionally substituted on the thiazolidine ring with a phenyl group, 3-azabicyclo[3.2.2]nonylcarbonyl groups, piperidinyl lower alkyl groups, anilino lower alkyl groups optionally substituted on the amino group with one or two lower alkyl groups, phenylthio lower alkyl groups, indolinyll lower alkyl groups, piperidinylcarbonyl groups optionally substituted on the piperidine ring with one or more lower alkyl groups, pyridyl groups, thienyl groups, lower alkylsulfinyl groups, lower alkylsulfonyl groups, and lower alkylthio groups,
- (1-4) a cycloalkyl lower alkyl group,
- (1-5) a phenoxy lower alkyl group,
- (1-6) a naphthyl lower alkyl group,
- (1-7) a lower alkoxy lower alkyl group,
- (1-8) a carboxy lower alkyl group,
- (1-9) a lower alkoxycarbonyl lower alkyl group,
- (1-10) a pyridyl lower alkyl group optionally substituted on the pyridine ring with one or more members selected from the group consisting of halogen atoms; piperidinyl groups; a morpholino group; piperazinyl groups optionally substituted on the piperazine ring with one or more members selected from

- the group consisting of a phenyl group and lower alkyl groups; thienyl groups optionally substituted with one or more halogen atoms; a phenyl group optionally substituted with one or more halogen atoms; pyridyl groups; piperidinyl
- 5 lower alkyl groups; phenylthio lower alkyl groups; biphenyl groups; lower alkyl groups optionally substituted with one or more halogen atoms; pyridylamino groups; pyridylcarbonylamino groups; lower alkoxy groups; anilino lower alkyl groups optionally substituted on the amino group with one or two
- 10 lower alkyl groups; anilino groups optionally substituted on the amino group with one or two lower alkyl groups; and furyl groups,
- (1-11) a cyano lower alkyl group,
- (1-12) a phenyl group,
- 15 (1-13) a quinolyl lower alkyl group,
- (1-14) a lower alkoxy lower alkoxy-substituted lower alkyl group,
- (1-15) a hydroxy-substituted lower alkyl group,
- (1-16) a lower alkyl group substituted with one or more
- 20 halogen atoms,
- (1-17) a lower alkanoyloxy group optionally substituted with one or more halogen atoms,
- (1-18) a lower alkoxy carbonyl group optionally substituted with one or more halogen atoms,
- 25 (1-19) a benzoyl group,
- (1-20) a phenylsulfonyl group optionally substituted on the phenyl ring with one or more members selected from the group consisting of halogen atoms, lower alkyl groups optionally substituted with one or more halogen atoms, a phenyl group, a
- 30 phenoxy group, lower alkoxy groups optionally substituted with one or more halogen atoms, a cyano group, and lower alkanoylamino groups,
- (1-21) a naphthylsulfonyl group;

R^2 is one of the following (2-2) to (2-6):

- 35 (2-2) a lower alkoxy group,

(2-3) a lower alkyl group optionally substituted with one or more phenyl groups,

(2-4) a carboxy lower alkoxy group,

(2-5) a lower alkoxycarbonyl lower alkoxy group,

5 (2-6) a hydroxy group;

n is an integer from 0 to 7, provided that when n is no less than 2, n R²s may be the same or different;

R³ is one of the following (3-1) to (3-6):

(3-1) a hydrogen atom,

10 (3-2) a lower alkyl group optionally substituted with one or more phenyl groups,

(3-3) a hydroxy-substituted lower alkyl group,

(3-4) a cycloalkyl lower alkyl group,

(3-5) a carboxy lower alkyl group,

15 (3-6) a lower alkoxycarbonyl lower alkyl group,

B is a carbonyl group or an -NHCO- group;

l is 0 or 1; and

R⁶ and R⁷ each independently represent one of the following (4-1) to (4-6):

20 (4-1) a hydrogen atom,

(4-2) a lower alkyl group,

(4-3) a lower alkanoyl group,

(4-4) a phenyl group optionally substituted on the phenyl ring with one or more members selected from the group

25 consisting of halogen atoms; lower alkyl groups optionally substituted with one or more halogen atoms; a phenoxy group; lower alkoxy groups optionally substituted with one or more halogen atoms; lower alkylthio groups; lower alkylsulfonyl groups; amino groups optionally substituted with one or two

30 members selected from the group consisting of lower alkyl groups and lower alkanoyl groups; pyrrolidinyl groups optionally substituted on the pyrrolidine ring with one or more oxo groups; piperidinyl groups optionally substituted on the piperidine ring with one or more lower alkyl groups;

35 lower alkenyl groups; an aminosulfonyl group; a hydroxy

group; carbamoyl groups optionally substituted with one or more lower alkyl groups; phenyl lower alkoxy groups; and a cyano group,

- (4-5) a cycloalkyl group optionally substituted on the
5 cycloalkyl ring with one or more lower alkyl groups,
(4-6) a thiazolyl group.

Item 2. The compound according to Item 1 or a salt thereof,
wherein A is a lower alkylene group, or a lower
10 alkylidene group;

X is an oxygen atom or a sulfur atom;

R¹ is the following (1-1), (1-2), (1-3), (1-4), (1-6), (1-10), (1-13), (1-16), (1-17), (1-18), (1-19), (1-20), or (1-21):

- 15 (1-1) a hydrogen atom,
(1-2) a lower alkyl group,
(1-3) a phenyl lower alkyl group optionally substituted on the phenyl ring with one or more members selected from the group consisting of a phenyl group (optionally substituted on
20 the phenyl ring with one or more phenyl groups), lower alkyl groups, lower alkoxy groups, halogen atoms, -(B)₁NR⁶R⁷ groups, a nitro group, a carboxy group, lower alkoxycarbonyl groups, a cyano group, phenyl lower alkoxy groups, a phenoxy group, a piperidinyl lower alkoxycarbonyl groups, amino lower
25 alkoxycarbonyl groups optionally substituted with one or two cycloalkyl groups, 2-imidazolinyllcarbonyl groups optionally substituted on the 2-imidazoline ring with one or more lower alkylthio groups, 3-pyrrolinyllcarbonyl groups optionally substituted on the 3-pyrroline ring with one or more lower
30 alkyl groups, thiazolidinyllcarbonyl groups optionally substituted on the thiazolidine ring with a phenyl group, 3-azabicyclo[3.2.2]nonylcarbonyl groups, piperidinyl lower alkyl groups, anilino lower alkyl groups optionally substituted on the amino group with one or two lower alkyl
35 groups, phenylthio lower alkyl groups, indolinyll lower alkyl

groups, piperidinylcarbonyl groups optionally substituted on the piperidine ring with one or more lower alkyl groups, pyridyl groups, thienyl groups, lower alkylsulfinyl groups, lower alkylsulfonyl groups, and lower alkylthio groups,

5 (1-4) a cycloalkyl lower alkyl group,
(1-6) a naphthyl lower alkyl group,
(1-10) a pyridyl lower alkyl group optionally substituted on the pyridine ring with one or more members selected from the group consisting of halogen atoms; piperidinyl groups; a

10 morpholino group; piperazinyl groups optionally substituted on the piperazine ring with one or more members selected from the group consisting of a phenyl group and lower alkyl groups; thienyl groups optionally substituted with one or more halogen atoms; a phenyl group optionally substituted

15 with one or more halogen atoms; pyridyl groups; piperidinyl lower alkyl groups; phenylthio lower alkyl groups; biphenyl groups; lower alkyl groups optionally substituted with one or more halogen atoms; pyridylamino groups; pyridylcarbonylamino groups; lower alkoxy groups; anilino lower alkyl groups

20 optionally substituted on the amino group with one or two lower alkyl groups; anilino groups optionally substituted on the amino group with one or two lower alkyl groups; and furyl groups,

(1-13) a quinolyl lower alkyl group,

25 (1-16) a lower alkyl group substituted with one or more halogen atoms,
(1-17) a lower alkanoyloxy group optionally substituted with one or more halogen atoms,
(1-18) a lower alkoxycarbonyl group optionally substituted

30 with one or more halogen atoms,
(1-19) a benzoyl group,
(1-20) a phenylsulfonyl group optionally substituted on the phenyl ring with one or more members selected from the group consisting of halogen atoms, lower alkyl groups optionally

35 substituted with one or more halogen atoms, a phenyl group, a

phenoxy group, lower alkoxy groups optionally substituted with one or more halogen atoms, a cyano group, and lower alkanoylamino groups,

(1-21) a naphthylsulfonyl group;

5 R^2 is the following (2-2) or (2-3):

(2-2) a lower alkoxy group,

(2-3) a lower alkyl group optionally substituted with one or more phenyl groups;

n is an integer from 0 to 2, provided that when n is 2, n R^2 s may be the same or different;

R^3 is the following (3-1) or (3-2):

(3-1) a hydrogen atom,

(3-2) a lower alkyl group optionally substituted with one or more phenyl groups;

15 B is a carbonyl group or an -NHCO- group;

l is 0 or 1; and

R^6 and R^7 each independently represent the following

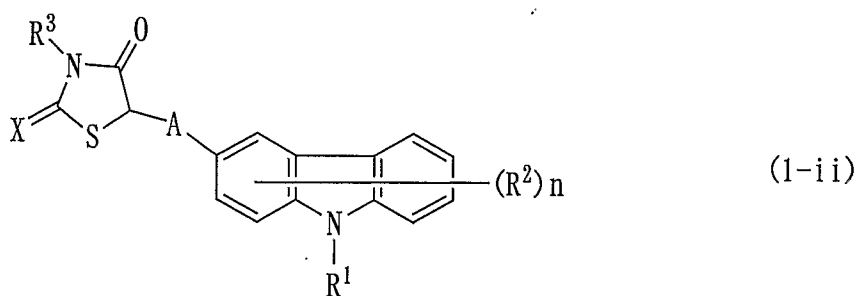
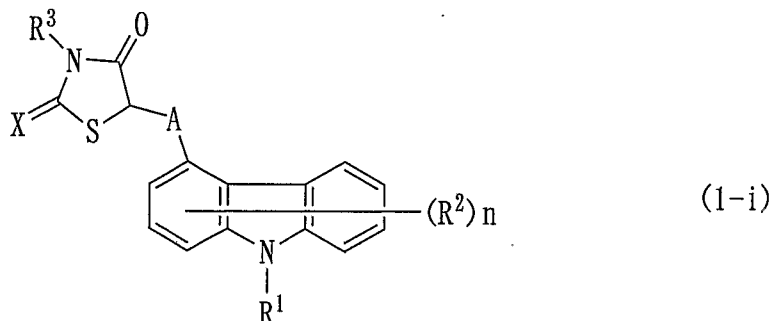
(4-1), (4-4), (4-5), or (4-6):

(4-1) a hydrogen atom,

20 (4-4) a phenyl group optionally substituted on the phenyl ring with one or more members selected from the group consisting of halogen atoms; lower alkyl groups optionally substituted with one or more halogen atoms; a phenoxy group; lower alkoxy groups optionally substituted with one or more
25 halogen atoms; lower alkylthio groups; lower alkylsulfonyl groups; amino groups optionally substituted with one or two members selected from the group consisting of lower alkyl groups and lower alkanoyl groups; pyrrolidinyl groups optionally substituted on the pyrrolidine ring with one or
30 more oxo groups; piperidinyl groups optionally substituted on the piperidine ring with one or more lower alkyl groups; lower alkenyl groups; an aminosulfonyl group; a hydroxy group; carbamoyl groups optionally substituted with one or more lower alkyl groups; phenyl lower alkoxy groups; and a
35 cyano group,

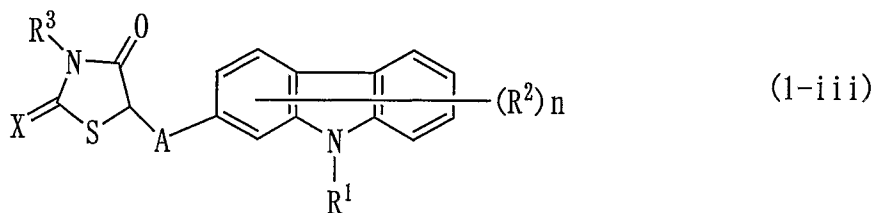
(4-5) a cycloalkyl group optionally substituted on the cycloalkyl ring with one or more lower alkyl groups,
 (4-6) a thiazolyl group.

- 5 Item 3. The compound or a salt thereof according to Item 1 having one of the following formula:



10

, or



wherein A, X, R¹, R², R³ and n are each the same as defined in Item 1.

- 15 Item 4. The compound or a salt thereof according to Item 3, wherein A is a lower alkylene group, or a lower alkylidene group.

- Item 5. The compound or a salt thereof according to Item 4,
 20 wherein X is an oxygen atom or an sulfur atom.

Item 6. The compound or a salt thereof according to Item 5, wherein R¹ is

- (1-3) a phenyl lower alkyl group optionally substituted on the phenyl ring with one or more members selected from the group consisting of a phenyl group (optionally substituted on the phenyl ring with one or more phenyl groups), lower alkyl groups, lower alkoxy groups, halogen atoms, -(B)₁NR⁶R⁷ groups (wherein B, l, R⁶, and R⁷ are each the same as defined in item 1), a nitro group, a carboxy group, lower alkoxycarbonyl groups, a cyano group, phenyl lower alkoxy groups, a phenoxy group, a piperidinyl lower alkoxycarbonyl groups, amino lower alkoxycarbonyl groups optionally substituted with one or two cycloalkyl groups, 2-imidazolinylcarbonyl groups optionally substituted on the 2-imidazoline ring with one or more lower alkylthio groups, 3-pyrrolinylcarbonyl groups optionally substituted on the 3-pyrroline ring with one or more lower alkyl groups, thiazolidinylcarbonyl groups optionally substituted on the thiazolidine ring with a phenyl group, 3-azabicyclo[3.2.2]nonylcarbonyl groups, piperidinyl lower alkyl groups, anilino lower alkyl groups optionally substituted on the amino group with one or two lower alkyl groups, phenylthio lower alkyl groups, indolinyl lower alkyl groups, piperidinylcarbonyl groups optionally substituted on the piperidine ring with one or more lower alkyl groups, pyridyl groups, thienyl groups, lower alkylsulfinyl groups, lower alkylsulfonyl groups, and lower alkylthio groups, or
- (1-20) a phenylsulfonyl group optionally substituted on the phenyl ring with one or more members selected from the group consisting of halogen atoms, lower alkyl groups optionally substituted with one or more halogen atoms, a phenyl group, a phenoxy group, lower alkoxy groups optionally substituted with one or more halogen atoms, a cyano group, and lower alkanoylamino groups.

Item 7. The compound according to Item 6, wherein n is 0.

Item 8. The compound according to Item 6, wherein R² is
5 lower alkoxy group and n is 1.

Item 9. A pharmaceutical composition comprising as an active
ingredient the compound (1) or a salt thereof according to
Item 1.
10

Item 10. A prophylactic and/or therapeutic agent for a
disorder on which an up-regulation of TFF has a prophylactic
and/or therapeutic effect, comprising as an active ingredient
the compound (1) or a salt thereof according to Item 1.
15

Item 11. The prophylactic and/or therapeutic agent according
to Item 10, wherein the disorder on which an up-regulation of
TFF has a prophylactic and/or therapeutic effect is an
alimentary tract disease, oral disease, upper respiratory
20 tract disease, respiratory tract disease, eye disease, cancer,
or wound.

Item 12. A use of the compound (1) or a salt thereof
according to Item 1 for manufacturing a prophylactic and/or
25 therapeutic agent for a disorder on which an up-regulation of
TFF has a prophylactic and/or therapeutic effect.

Item 13. A method for preventing and/or treating a disorder
on which TFF up-regulation has a prophylactic and/or
30 therapeutic effect, comprising administering to a patient an
effective amount of compound (1) or a salt thereof according
to Item 1.

Item 14. The disorder on which TFF up-regulation has a
35 prophylactic and/or therapeutic effect identified in either

one of Items 10 to 13 is drug-induced ulcers, peptic gastric ulcers, ulcerative colitis, Crohn's diseases, drug-induced enteritis, ischemic colitis, irritable bowel syndrome, ulcers developed after endoscopic demucosation, acute gastritis, chronic gastritis, reflux esophagitis, esophageal ulcer, Barrett esophagus, gastrointestinal mucositis, hemorrhoidal diseases, stomatitis, Sjogren syndrome, xerostomia, rhinitis, pharyngitis, bronchial asthma, chronic obstructive lung diseases, dry eye, or keratoconjunctivitis.

10

Item 15. A prophylactic and/or therapeutic agent for alimentary tract diseases, oral diseases, upper respiratory tract diseases, respiratory tract diseases, eye diseases, cancers, or wounds, the agent comprising a compound that induces the production of TFF.

15

Item 16. TFF identified in either one of Items 10 to 15 is TFF2.

20

Specific examples of groups in the above formula (1) are as follows.

"Lower" as used herein indicates C_{1-6} unless otherwise noted.

Examples of lower alkylene groups include straight or branched C_{1-6} alkylene groups, such as methylene, ethylene, trimethylene, 2-methyltrimethylene, 2,2-dimethylethylene, 2,2-dimethyltrimethylene, 1-methyltrimethylene, methylmethylene, ethylmethylene, tetramethylene, pentamethylene, hexamethylene, etc.

30

Examples of lower alkylidene groups include straight or branched C_{1-6} alkylidene groups, such as methylidene, ethylidene, propylidene, butylidene, pentylidene, hexylidene, etc.

Examples of lower alkyl groups include straight or branched C_{1-6} alkyl groups, such as methyl, ethyl, n-propyl,

35

isopropyl, *n*-butyl, isobutyl, *tert*-butyl, *sec*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, isohexyl, 3-methylpentyl, 2-ethylbutyl, etc.

5 Examples of phenyl groups (optionally substituted on the phenyl ring with one or more phenyl groups) include phenyl groups optionally substituted with one or two phenyl groups, such as phenyl, (2-, 3-, or 4-)phenylphenyl, 2,3-diphenylphenyl, etc.

10 Examples of lower alkoxy groups include straight or branched C₁₋₆ alkoxy groups, such as methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentyloxy, isopentyloxy, neopentyloxy, *n*-hexyloxy, isohexyloxy, 3-methylpentyloxy, etc.

15 Examples of halogen atoms include fluorine, chlorine, bromine, and iodine.

Examples of lower alkoxycarbonyl groups include alkoxycarbonyl groups wherein the alkoxy moiety is a straight or branched C₁₋₆ alkoxy group, such as methoxycarbonyl, ethoxycarbonyl, *n*-propoxycarbonyl, isopropoxycarbonyl, *n*-butoxycarbonyl, isobutoxycarbonyl, *tert*-butoxycarbonyl, *sec*-butoxycarbonyl, *n*-pentyloxycarbonyl, neopentyloxycarbonyl, *n*-hexyloxycarbonyl, isohexyloxycarbonyl, 3-methylpentyloxycarbonyl, etc.

20

Examples of phenyl lower alkoxy groups include phenylalkoxy groups wherein the alkoxy moiety is a straight or branched C₁₋₆ alkoxy group, such as benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 3-phenylpropoxy, 4-phenylbutoxy, 5-phenylpentyloxy, 6-phenylhexyloxy, 1,1-dimethyl-2-phenylethoxy, 2-methyl-3-phenylpropoxy, etc.

25

30 Examples of piperidinyl lower alkoxycarbonyl groups include piperidinylalkoxycarbonyl groups wherein the alkoxy moiety is a straight or branched C₁₋₆ alkoxy group, such as [(1-, 2-, 3-, or 4-)piperidinyl]methoxycarbonyl, 2-[(1-, 2-, 3-, or 4-)piperidinyl]ethoxycarbonyl, 1-[(1-, 2-, 3-, or 4-)piperidinyl]ethoxycarbonyl, 3-

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[(1-, 2-, 3-, or 4-)piperidinyl]propoxycarbonyl, 4-
[(1-, 2-, 3-, or 4-)piperidinyl]butoxycarbonyl, 5-
[(1-, 2-, 3-, or 4-)piperidinyl]pentyloxycarbonyl, 6-
[(1-, 2-, 3-, or 4-)piperidinyl]hexyloxycarbonyl, 1,1-
5 dimethyl-2-[(1-, 2-, 3-, or 4-)piperidinyl]ethoxycarbonyl, 2-
methyl-3-[(1-, 2-, 3-, or 4-)piperidinyl]propoxy carbonyl,
etc.

Examples of cycloalkyl groups include C₃₋₈
cycloalkyl groups, such as cyclopropyl, cyclobutyl,
10 cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, etc.

Examples of amino lower alkoxycarbonyl groups
optionally substituted with one or two cycloalkyl groups
include:

amino-substituted alkoxycarbonyl groups wherein the
15 alkoxy moiety is a straight or branched C₁₋₆ alkoxy group,
optionally substituted with one or two C₃₋₈ cycloalkyl groups;
such as aminomethoxycarbonyl, 2-aminoethoxycarbonyl,
cyclopropylaminomethoxycarbonyl, 2-
cyclohexylaminoethoxycarbonyl, 1-
20 cyclobutylaminoethoxycarbonyl, 3-
cyclopentylaminopropoxycarbonyl, 4-
cycloheptylaminobutoxycarbonyl, 5-
cyclooctylaminopentyloxycarbonyl, 6-
cyclohexylaminohexyloxycarbonyl, 1,1-dimethyl-2-
25 cyclohexylaminoethoxycarbonyl, 2-methyl-3-
cyclopropylaminopropoxycarbonyl, 2-(*N*-cyclopropyl-*N*-
cyclohexylamino)ethoxycarbonyl, etc.

Examples of lower alkylthio groups include straight
or branched C₁₋₆ alkylthio groups such as methylthio,
30 ethylthio, *n*-propylthio, isopropylthio, *n*-butylthio, *tert*-
butylthio, *n*-pentylthio, *n*-hexylthio, etc.

Examples of 2-imidazolinylcarbonyl groups
optionally substituted on the 2-imidazoline ring with one or
more lower alkylthio groups include 2-imidazolinylcarbonyl
35 groups optionally substituted on the 2-imidazoline ring with

one to three lower alkylthio groups, such as (1-, 2-, 4-, or 5-)2-imidazolinyllcarbonyl, 2-methylthio-(1-, 4-, or 5-)2-imidazolinyllcarbonyl, 2-ethylthio-(1-, 4-, or 5-)2-imidazolinyllcarbonyl, 4-propylthio-(1-, 2-, or 5-)2-imidazolinyllcarbonyl, 5-isopropylthio-(1-, 2-, or 4-)2-imidazolinyllcarbonyl, 2-n-butylthio-(1-, 4-, or 5-)2-imidazolinyllcarbonyl, 2-n-pentylthio-(1-, 4-, or 5-)2-imidazolinyllcarbonyl, 2-n-hexylthio-(1-, 4-, or 5-)2-imidazolinyllcarbonyl, 2,4-dimethylthio-(1- or 5-)2-imidazolinyllcarbonyl, 2,4,5-trimethylthio-(1-)2-imidazolinyllcarbonyl, etc.

Examples of 3-pyrrolinyllcarbonyl groups optionally substituted on the 3-pyrroline ring with one or more lower alkyl groups include 3-pyrrolinyllcarbonyl groups optionally substituted on the 3-pyrroline ring with one to three straight or branched C₁₋₆ alkyl groups, such as (1-, 2-, or 3-)3-pyrrolinyllcarbonyl, 2-methyl-(1-, 2-, 3-, 4-, or 5-)3-pyrrolinyllcarbonyl, 2-ethyl-(1-, 2-, 3-, 4-, or 5-)3-pyrrolinyllcarbonyl, 3-propyl-(1-, 2-, 4-, or 5-)3-pyrrolinyllcarbonyl, 4-isopropyl-(1-, 2-, 3-, or 5-)3-pyrrolinyllcarbonyl, 5-n-butyl-(1-, 2-, 3-, 4-, or 5-)3-pyrrolinyllcarbonyl, 2-n-pentyl-(1-, 2-, 3-, 4-, or 5-)3-pyrrolinyllcarbonyl, 2-n-hexyl-(1-, 2-, 3-, 4-, or 5-)3-pyrrolinyllcarbonyl, 2,5-dimethyl-(1-, 2-, 3-, 4-, or 5-)3-pyrrolinyllcarbonyl, 2,4-dimethyl-(1-, 2-, 3-, or 5-)3-pyrrolinyllcarbonyl, 2,3-dimethyl-(1-, 2-, 4-, or 5-)3-pyrrolinyllcarbonyl, 2,4,5-trimethylthio-(1-, 2-, 3-, or 5-)3-pyrrolinyllcarbonyl, etc.

Examples of thiazolidinyllcarbonyl groups optionally substituted on the thiazolidine ring with a phenyl group includes (2-, 3-, 4-, or 5-)thiazolidinyllcarbonyl, 2-phenyl-(3-, 4-, or 5-)thiazolidinyllcarbonyl, 3-phenyl-(2-, 4-, or 5-)thiazolidinyllcarbonyl, 4-phenyl-(2-, 3-, or 5-)thiazolidinyllcarbonyl, 5-phenyl-(2-, 3-, or 4-)thiazolidinyllcarbonyl, etc.

Examples of piperidinylloweralkyl groups include piperidinyllalkyl groups wherein the alkyl moiety is a straight or branched C₁₋₆ alkyl group, such as [(1-, 2-, 3-, or 4-) piperidinyllmethyl, 2-[(1-, 2-, 3-, or 4-) piperidinyll]ethyl, 1-[(1-, 2-, 3-, or 4-)piperidinyll]ethyl, 3-[(1-, 2-, 3-, or 4-) piperidinyll]propyl, 4-[(1-, 2-, 3-, or 4-)piperidinyll]butyl, 5-[(1-, 2-, 3-, or 4-) piperidinyll]pentyl, 6-[(1-, 2-, 3-, or 4-) piperidinyll]hexyl, 1,1-dimethyl-2-[(1-, 2-, 3-, or 4-) piperidinyll]ethyl, 2-methyl-3-[(1-, 2-, 3-, or 4-) piperidinyll]propyl, etc.

Examples of anilino lower alkyl groups optionally substituted on the amino group with one or two lower alkyl groups include anilinoalkyl groups optionally substituted on the amino group with one or two straight and/or branched C₁₋₆ alkyl groups, such as anilinomethyl, N-methylanilinomethyl, N-ethylanilinomethyl, N-n-propylanilinomethyl, N-isopropylanilinomethyl, N-n-butylianilinomethyl, N-sec-butylianilinomethyl, N-tert-butylianilinomethyl, N-n-pentylianilinomethyl, N-n-hexylanilinomethyl, 2-anilinoethyl, 2-(N-methylanilino)ethyl, 2-(N-ethylanilino)ethyl, 2-(N-n-propylanilino)ethyl, 2-(N-isopropylanilino)ethyl, 2-(N-n-butylianilino)ethyl, 2-(N-sec-butylianilino)ethyl, 2-(N-tert-butylianilino)ethyl, 2-(N-n-pentylianilino)ethyl, 2-(N-n-hexylanilino)ethyl, 3-anilinopropyl, 3-(N-methylanilino)propyl, 4-(N-ethylanilino)butyl, 4-(N-n-propylanilino)butyl, 5-(N-isopropylanilino)pentyl, 5-(N-n-butylianilino)pentyl, 6-(N-sec-butylianilino)hexyl, 6-(N-tert-butylianilino)hexyl, 6-(N-n-pentylianilino)hexyl, 6-(N-n-hexylanilino)hexyl, etc.

Examples of phenylthio lower alkyl groups include phenylthioalkyl groups wherein the alkyl moiety is a straight or branched C₁₋₆ alkyl group, such as phenylthiomethyl, 2-phenylthioethyl, 1-phenylthioethyl, 3-phenylthiopropyl, 4-phenylthiobutyl, 5-phenylthiopentyl, 6-phenylthiohexyl, 1,1-dimethyl-2-phenylthioethyl, 2-methyl-3-phenylthiopropyl, etc.

Examples of indolinyl lower alkyl groups include indolinylalkyl groups wherein the alkyl moiety is a straight or branched C₁₋₆ alkyl group, such as [(1-, 2-, 3-, 4-, 5-, 6-, or 7-)indolinyl]methyl, 2-[(1-, 2-, 3-, 4-, or 5-)indolinyl]ethyl, 1-[(1-, 2-, 3-, 4-, 5-, 6-, or 7-)indolinyl]ethyl, 3-[(1-, 2-, 3-, 4-, 5-, 6-, or 7-)indolinyl]propyl, 4-[(1-, 2-, 3-, 4-, 5-, 6-, or 7-)indolinyl]butyl, 5-[(1-, 2-, 3-, 4-, 5-, 6-, or 7-)indolinyl]pentyl, 6-[(1-, 2-, 3-, 4-, 5-, 6-, or 7-)indolinyl]hexyl, 1,1-dimethyl-2-[(1-, 2-, 3-, 4-, 5-, 6-, or 7-)indolinyl]ethyl, 2-methyl-3-[(1-, 2-, 3-, 4-, 5-, 6-, or 7-)indolinyl]propyl, etc.

Examples of piperidinylcarbonyl groups optionally substituted on the piperidine ring with one or more lower alkyl groups include piperidinylcarbonyl groups optionally substituted on the piperidine ring with one to three straight and/or branched C₁₋₆ alkyl groups, such as (1-, 2-, 3-, or 4-)piperidinylcarbonyl, 1-methyl-(2-, 3-, or 4-)piperidinylcarbonyl, 1-ethyl-(2-, 3-, or 4-)piperidinylcarbonyl, 1-n-propyl-(2-, 3-, or 4-)piperidinylcarbonyl, 1-n-butyl-(2-, 3-, or 4-)piperidinylcarbonyl, 1-n-pentyl-(2-, 3-, or 4-)piperidinylcarbonyl, 1-n-hexyl-(2-, 3-, or 4-)piperidinylcarbonyl, 1,2-dimethyl-(3-, 4-, 5-, or 6-)piperidinylcarbonyl, 1,2,3-trimethyl-(4-, 5-, or 6-)piperidinylcarbonyl, 2-n-propyl-(1-, 3-, 4-, 5-, or 6-)piperidinylcarbonyl, 3-ethyl-(1-, 2-, 4-, 5-, or 6-)piperidinylcarbonyl, 2-methyl-4-isopropyl-(1-, 3-, 5-, or 6-)piperidinylcarbonyl, etc.

Examples of lower alkylsulfinyl groups include straight and branched C₁₋₆ alkylsulfinyl groups, such as methylsulfinyl, ethylsulfinyl, n-propylsulfinyl, isopropylsulfinyl, n-butylsulfinyl, isobutylsulfinyl, tert-butylsulfinyl, sec-butylsulfinyl, n-pentylsulfinyl, isopentylsulfinyl, neopentylsulfinyl, n-hexylsulfinyl,

isohexylsulfinyl, 3-methylpentylsulfinyl, etc.

Examples of lower alkylsulfonyl groups include straight or branched C₁₋₆ alkyl sulfonyl groups, such as methylsulfonyl, ethylsulfonyl, *n*-propylsulfonyl,

5 isopropylsulfonyl, *n*-butylsulfonyl, isobutylsulfonyl, *tert*-butylsulfonyl, *sec*-butylsulfonyl, *n*-pentylsulfonyl, isopentylsulfonyl, neopentylsulfonyl, *n*-hexylsulfonyl, isohexylsulfonyl, 3-methylpentylsulfonyl, etc.

Examples of "phenyl lower alkyl groups optionally
10 substituted on the phenyl ring with one or more members selected from the group consisting of a phenyl group (optionally substituted on the phenyl ring with one or more phenyl groups); lower alkyl groups; lower alkoxy groups; halogen atoms; -(B)₁NR⁶R⁷ groups; a nitro group; a carboxy
15 group; lower alkoxycarbonyl groups; a cyano group; phenyl lower alkoxy groups; a phenoxy group; piperidinyl lower alkoxycarbonyl groups; amino lower alkoxycarbonyl groups optionally substituted with one or two cycloalkyl groups; 2-imidazolinylcarbonyl groups optionally substituted on the 2-
20 imidazoline ring with one or more lower alkylthio groups; 3-pyrrolinylcarbonyl groups optionally substituted on the pyrroline ring with one or more lower alkyl groups; a thiazolidinylcarbonyl groups optionally substituted on the thiazolidine ring with a phenyl group; 3-azabicyclo[3.2.2]
25 nonylcarbonyl groups; piperidinyl lower alkyl groups; anilino lower alkyl groups optionally substituted on the amino group with one or two lower alkyl groups; phenylthio lower alkyl groups; indolinyl lower alkyl groups; piperidinylcarbonyl groups optionally substituted on the piperidine ring with one
30 or more lower alkyl groups; pyridyl groups; thienyl groups; lower alkylsulfinyl groups; lower alkylsulfonyl groups; and lower alkylthio groups" include:

mono- or di-phenylalkyl groups, wherein the alkyl moiety is a straight or branched C₁₋₆ alkyl group, optionally
35 substituted on the phenyl ring with one to three members

selected from the group consisting of a phenyl group (optionally substituted on the phenyl ring with one to three phenyl groups); the above-described straight and branched C₁₋₆ alkyl groups; the above-described straight and branched C₁₋₆ alkoxy groups; halogen atoms; the below-described -(B)₁NR⁶R⁷ groups; a nitro group; a carboxyl group; the above-described straight or branched C₁₋₆ alkoxycarbonyl groups; a cyano group; the above-described phenylalkoxy groups wherein the alkoxy moiety is a straight or branched C₁₋₆ alkoxy group; a phenoxy group; the above-described piperidinylalkoxycarbonyl groups wherein the alkoxy moiety is a straight or branched C₁₋₆ alkoxy group; the above-described aminoalkoxycarbonyl groups wherein the alkoxy moiety is a straight or branched C₁₋₆ alkoxy group, optionally substituted with one or two C₃₋₈ cycloalkyl groups; the above-described 2-imidazolinyllcarbonyl groups optionally substituted on the 2-imidazoline ring with one to three straight and/or branched C₁₋₆ alkylthio groups; the above-described 3-pyrrolinyllcarbonyl groups optionally substituted on the 3-pyrroline ring with one to three straight and/or branched C₁₋₆ alkyl groups; thiazolidinyllcarbonyl groups optionally substituted on the thiazolidine ring with a phenyl group; 3-azabicyclo[3.2.2]nonylcarbonyl groups; piperidinylalkyl groups wherein the alkyl moiety is a straight or branched C₁₋₆ alkyl group; anilinoalkyl groups wherein the alkyl moiety is a straight or branched C₁₋₆ alkyl group, optionally substituted on the amino group with one or two straight and/or branched C₁₋₆ alkyl groups; phenylthioalkyl groups wherein the alkyl moiety is a straight or branched C₁₋₆ alkyl group; indolinyllalkyl groups wherein the alkyl moiety is a straight or branched C₁₋₆ alkyl group; the above-described piperidinylcarbonyl groups optionally substituted on the piperidine ring with one to three straight and/or branched C₁₋₆ alkyl groups; pyridyl groups; thienyl groups; alkylsulfinyl groups wherein the alkyl moiety is a straight

or branched C₁₋₆ alkyl group; alkylsulfonyl groups wherein the alkyl moiety is a straight or branched C₁₋₆ alkyl group; and alkylthio groups wherein the alkyl moiety is a straight or branched C₁₋₆ alkyl group;

- 5 such as benzyl, 1-phenethyl, 2-phenethyl, 3-phenylpropyl, 2-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, 4-phenylpentyl, 6-phenylhexyl, 2-methyl-3-phenylpropyl, 1,1-dimethyl-2-phenylethyl, 1,1-diphenylmethyl, 2,2-diphenylethyl, 3,3-diphenylpropyl, 1,2-diphenylethyl, (2-, 3-, or 4-phenylbenzyl, 4-[(2-, 3-, or 4-)phenylphenyl]benzyl, 4-[N-(3-pyridyl)aminocarbonyl]benzyl, 4-[N-(2-methoxyphenyl)aminocarbonyl]benzyl, 4-[2-(2-piperidinyl)ethoxycarbonyl]benzyl, 4-[2-(cyclohexylamino)ethoxycarbonyl]benzyl, 4-(N-cyclohexyl-N-
- 10 methylaminocarbonyl)benzyl, 4-(N,N-di-n-butylaminocarbonyl)benzyl, 4-[2-methylthio-1-(2-imidazolyl)carbonyl]benzyl, 4-(N,N-diisobutylaminocarbonyl)benzyl, 4-[2,5-dimethyl-1-(3-pyrrolinyl)carbonyl]benzyl, 4-(3-thiazolidinylcarbonyl)benzyl,
- 15 4-[1-(3-azabicyclo[3.2.2]nonylcarbonyl)benzyl, 4-(N-n-butylaminocarbonyl)benzyl, 4-(N-cyclopropylaminocarbonyl)benzyl, 4-[3,5-dimethyl-1-piperidinylcarbonyl]benzyl, 4-(N-ethyl-N-cyclohexylaminocarbonyl)benzyl, 4-(N-n-propylaminocarbonyl)benzyl, 4-[N-(1-methyl-1-cyclopentyl)aminocarbonyl]benzyl, 4-[N-(1-methyl-1-cyclohexyl)aminocarbonyl]benzyl, 4-phenylbenzyl, 2-phenylbenzyl, 3-phenylbenzyl, 4-tert-butylbenzyl, 4-aminobenzyl, 4-nitrobenzyl, 4-methoxycarbonylbenzyl, 4-
- 20 carboxybenzyl, 3-methoxy-4-chlorobenzyl, 4-methoxybenzyl, 2,4,6-trimethoxybenzyl, 3,4-dichlorobenzyl, 2-chlorobenzyl, 4-chlorobenzyl, 4-bromobenzyl, 2,4,6-trifluorobenzyl, 4-fluorobenzyl, 4-cyanobenzyl, 4-piperidinylcarbonylbenzyl, 4-anilinocarbonylbenzyl, 4-(N-cyclohexylaminocarbonyl)benzyl,
- 25 4-(N-cyclohexylamino)benzyl, 4-methylbenzyl, 3,4-

dimethylbenzyl, 3,4,5-trimethylbenzyl, 4-benzyloxybenzyl, 4-ethylaminocarbonylbenzyl, 4-isopropylaminocarbonylbenzyl, 4-[N-(4-chlorophenyl)aminocarbonyl]benzyl, 4-[N-(4-isopropylphenyl)aminocarbonyl]benzyl, 4-[N-(4-phenoxyphenyl)aminocarbonyl]benzyl, 4-[N-(3-phenoxyphenyl)aminocarbonyl]benzyl, 4-[N-(4-methoxyphenyl)aminocarbonyl]benzyl, 4-phenoxybenzyl, 4-ethanolylaminobenzyl, 4-(N-acetylamino)benzyl, 4-[N-(4-isopropylphenyl)aminocarbonyl]benzyl, 4-[2-methyl-(1-, 3-, 4-, 5-, or 6-)piperidinylcarbonyl]benzyl, 4-(N-methyl-N-n-pentylaminocarbonyl)benzyl, 4-[N-(2-methylcyclohexyl)aminocarbonyl]benzyl, 4-[2-phenyl-(3-, 4-, or 5-)thiazolidinylcarbonyl]benzyl, 4-[N-methyl-(2-methoxyanilino)carbonyl]benzyl, 4-(3-methylthioanilinocarbonyl)benzyl, 4-(2-methylthioanilinocarbonyl)benzyl, 4-(3,4-dichloroanilinocarbonyl)benzyl, 4-(4-trifluoromethoxy-4-anilinocarbonyl)benzyl, 4-anilinocarbonylbenzyl, 4-(4-chloroanilinocarbonyl)benzyl, 4-(4-methoxyanilinocarbonyl)benzyl, 4-(3-methoxyanilinocarbonyl)benzyl, 4-(2-chloroanilinocarbonyl)benzyl, 4-(4-methylanilinocarbonyl)benzyl, 4-(2,4-dimethoxyanilinocarbonyl)benzyl, 4-(4-methoxy-5-chloroanilinocarbonyl)benzyl, 4-(2-methoxy-5-acetylaminoanilinocarbonyl)benzyl, 4-(3,4-dimethoxyanilinocarbonyl)benzyl, 4-[2-(1-methylallyl)anilinocarbonyl]benzyl, 4-(3-trifluoromethoxyanilinocarbonyl)benzyl, 4-(2-methylanilinocarbonyl)benzyl, 4-(2-fluoroanilinocarbonyl)benzyl, 4-(3-fluoroanilinocarbonyl)benzyl, 4-(4-fluoroanilinocarbonyl)benzyl, 4-(3-dimethylaminoanilinocarbonyl)benzyl, 4-(4-ethoxyanilinocarbonyl)benzyl, 4-(3-trifluoromethylanilinocarbonyl)benzyl, 4-(4-

- trifluoromethylanilinocarbonyl)benzyl, 4-(3-acetylaminoanilinocarbonyl)benzyl, 4-(4-acetylaminoanilinocarbonyl)benzyl, 4-[N-methyl-(3-methylanilino)carbonyl]benzyl, 4-(2-phenoxyanilinocarbonyl)benzyl, 4-(3-phenoxyanilinocarbonyl)benzyl, 4-(4-phenoxyanilinocarbonyl)benzyl, 4-(3,5-dichloroanilinocarbonyl)benzyl, 4-(2,3-dimethylanilinocarbonyl)benzyl, 4-(2,4-dimethylanilinocarbonyl)benzyl, 4-(3,5-dimethylanilinocarbonyl)benzyl, 4-(3,5-difluoroanilinocarbonyl)benzyl, 4-(3-fluoro-4-methoxyanilinocarbonyl)benzyl, 4-(4-aminosulfonylanilinocarbonyl)benzyl, 4-(4-methyl-3-methoxyanilinocarbonyl)benzyl, 4-(3-chloro-4-methoxyanilinocarbonyl)benzyl, 4-(3-chloro-4-methylanilinocarbonyl)benzyl, 4-(3-methoxy-5-trifluoromethylanilinocarbonyl)benzyl, 4-(3-chloro-4-fluoroanilinocarbonyl)benzyl, 4-[(2-, 4- or 5-thiazolylaminocarbonyl)benzyl, 4-(3-chloro-4-hydroxyanilinocarbonyl)benzyl, 4-(2-chloro-5-acetylaminoanilinocarbonyl)benzyl, 4-(4-methylthioanilinocarbonyl)benzyl, 4-(4-isopropylanilinocarbonyl)benzyl, 4-(4-tert-butylanilinocarbonyl)benzyl, 4-{4-[2-oxo-(1-, 3-, 4-, or 5-pyrrolidinyl)anilinocarbonyl]benzyl, 4-(4-methylcarbamoylanilinocarbonyl)benzyl, anilinocarbonylbenzyl, 4-(2-benzyloxyanilinocarbonyl)benzyl, 4-(4-vinylanilinocarbonyl)benzyl, 4-(4-acetylaminoanilinocarbonyl)benzyl, 4-(3-acetylaminoanilinocarbonyl)benzyl, 4-(4-trifluoromethylanilinocarbonyl)benzyl, 4-[N-methyl-(4-chloroanilino)carbonyl]benzyl, 4-[(2-chloroanilino)carbonyl]benzyl, 4-[(3-cyanoanilino)carbonyl]benzyl, 4-[(4-cyanoanilino)carbonyl]benzyl, 4-[(2-cyanoanilino)carbonyl]benzyl, 4-[(2-chloro-4-

fluoroanilino)carbonyl]benzyl, (2-, 3-, or 4-)(1-
 piperidinylmethyl)benzyl, (2-, 3-, or 4-)(N-
 methylanilinomethyl)benzyl, (2-, 3-, or 4-)
 (phenylthiomethyl)benzyl, (2-, 3-, or 4-)(1-
 5 indolylmethyl)benzyl, (2-, 3-, or 4-)pyridin-(2-, 3-, or 4-)
 ylbenzyl, (2-, 3-, or 4-)thiophen-(2- or 3-)ylbenzyl, (2-, 3-,
 or 4-)methylsulfinylbenzyl, (2-, 3-, or 4-)
 ethylsulfinylbenzyl, (2-, 3-, or 4-)propylsulfinylbenzyl, (2-,
 3-, or 4-)methylsulfonylbenzyl, (2-, 3-, or 4-)
 10 ethylsulfonylbenzyl, (2-, 3-, or 4-)propylsulfonylbenzyl, (2-,
 3-, or 4-)methylthiobenzyl, (2-, 3-, or 4-)ethylthiobenzyl,
 (2-, 3-, or 4-)propylthiobenzyl, etc.

Examples of cycloalkyl lower alkyl groups include
 C₃₋₈ cycloalkylalkyl groups wherein the alkyl moiety is a
 15 straight or branched C₁₋₆ alkyl group, such as
 cyclopropylmethyl, cyclohexylmethyl, 2-cyclopropylethyl, 1-
 cyclobutylethyl, cyclopentylmethyl, 3-cyclopentylpropyl, 4-
 cyclohexylbutyl, 5-cycloheptylpentyl, 6-cyclooctylhexyl, 1,1-
 dimethyl-2-cyclohexylethyl, 2-methyl-3-cyclopropylpropyl, etc.

20 Examples of phenoxy lower alkyl groups include
 phenoxy alkyl groups wherein the alkyl moiety is a straight
 or branched C₁₋₆ alkyl group, such as phenoxymethyl, 2-
 phenoxyethyl, 1-phenoxyethyl, 3-phenoxypropyl, 4-phenoxybutyl,
 1,1-dimethyl-2-phenoxyethyl, 5-phenoxypropyl, 6-phenoxyhexyl,
 25 1-phenoxyisopropyl, 2-methyl-3-phenoxypropyl, etc.

Examples of naphthyl lower alkyl groups include
 naphthylalkyl groups wherein the alkyl moiety is a straight
 or branched C₁₋₆ alkyl group, such as (1- or 2-)naphthylmethyl,
 2-[(1- or 2-)naphthyl]ethyl, 1-[(1- or 2-)naphthyl]ethyl,
 30 3-[(1- or 2-)naphthyl]propyl, 4-[(1- or 2-)naphthyl]butyl,
 5-[(1- or 2-)naphthyl]pentyl, 6-[(1- or 2-)naphthyl]hexyl,
 1,1-dimethyl-2-[(1- or 2-)naphthyl]ethyl, 2-methyl-3-[(1- or
 2-)naphthyl]propyl, etc.

Examples of lower alkoxy lower alkyl groups include
 35 alkoxyalkyl groups wherein the alkoxy moiety is a straight or

branched C₁₋₆ alkoxy group and the alkyl moiety is a straight or branched C₁₋₆ alkyl group, such as methoxymethyl, 2-methoxyethyl, 1-ethoxyethyl, 2-ethoxyethyl, 3-n-butoxypropyl, 4-n-propoxybutyl, 1-methyl-3-isobutoxypropyl, 1,1-dimethyl-2-n-pentyloxyethyl, 5-n-hexyloxypentyl, 6-methoxyhexyl, 1-ethoxyisopropyl, 2-methyl-3-methoxypropyl, etc.

Examples of carboxy lower alkyl groups include carboxyalkyl groups wherein the alkyl moiety is a straight or branched C₁₋₆ alkyl group, such as carboxymethyl, 2-carboxyethyl, 1-carboxyethyl, 3-carboxypropyl, 4-carboxybutyl, 5-carboxypentyl, 6-carboxyhexyl, 1,1-dimethyl-2-carboxyethyl, 2-methyl-3-carboxypropyl, etc.

Examples of lower alkoxy carbonyl lower alkyl groups include alkoxy carbonyl alkyl groups wherein the alkoxy moiety is a straight or branched C₁₋₆ alkoxy group and the alkyl moiety is a straight or branched C₁₋₆ alkyl group, such as methoxycarbonylmethyl, ethoxycarbonylmethyl, 2-methoxycarbonylethyl, 2-ethoxycarbonylethyl, 1-ethoxycarbonylethyl, 3-methoxycarbonylpropyl, 3-ethoxycarbonylpropyl, 4-ethoxycarbonylbutyl, 5-isopropoxycarbonylpentyl, 6-n-propoxycarbonylhexyl, 1,1-dimethyl-2-n-butoxycarbonylethyl, 2-methyl-3-tert-butoxycarbonylpropyl, 2-n-pentyloxycarbonylethyl, n-hexyloxycarbonylmethyl, etc.

Examples of "piperazinyl groups optionally substituted on the piperazine ring with one or more members selected from the group consisting of a phenyl group and lower alkyl groups" include:

piperazinyl groups optionally substituted on the piperazine ring with one to three members selected from the group consisting of a phenyl group and straight and branched C₁₋₆ alkyl groups;

such as (1- or 2-)piperazinyl, 4-methyl-(1-, 2-, or 3-)piperazinyl, 4-ethyl-(1-, 2-, or 3-)piperazinyl, 4-n-propyl-(1-, 2-, or 3-)piperazinyl, 4-tert-butyl-(1-, 2-, or

3-)piperazinyl, 4-sec-butyl-(1-, 2-, or 3-)piperazinyl, 4-n-butyl-(1-, 2-, or 3-)piperazinyl, 4-n-pentyl-(1-, 2-, or 3-)piperazinyl, 4-n-hexyl-(1-, 2-, or 3-)piperazinyl, 3,4-dimethyl-(1-, 2-, 5-, or 6-)piperazinyl, 3,4,5-trimethyl-(1-
5 or 2-)piperazinyl, 4-phenyl-(1-, 2-, or 3-)piperazinyl, 2,4-diphenyl-(1-, 3-, 5-, or 6-)piperazinyl, 2,3,4-triphenyl-(1-, 5-, or 6-)piperazinyl, 4-phenyl-2-methyl-(1-, 3-, 5-, or 6-)piperazinyl, etc.

Examples of thienyl group optionally substituted
10 with one or more halogen atoms include thienyl groups optionally substituted with one to three halogen atoms, such as (2- or 3-)thienyl, 2-chloro-(3-, 4-, or 5-)thienyl, 4-bromo-(2-, 3-, or 5-)thienyl, 5-fluoro-(2-, 3-, or 4-)thienyl, 3-iodo-(2-, 4-, or 5-)thienyl, 2,3-dichloro-(4- or 5-)thienyl,
15 2,4,5-trichloro-3-thienyl, 2-fluoro-(3-, 4-, or 5-) thienyl, etc.

Examples of phenyl groups optionally substituted with one or more halogen atoms include phenyl groups optionally substituted with one to three halogen atoms, such
20 as phenyl, (2-, 3-, or 4-)chlorophenyl, (2-, 3-, or 4-)fluorophenyl, (2-, 3-, or 4-)bromophenyl, (2-, 3-, or 4-)iodophenyl, (2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-)dichlorophenyl, (2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-)difluorophenyl, (2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-)dibromophenyl, (2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-)diiodophenyl, (2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-)trichlorophenyl, (2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-)trifluorophenyl, (2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-)tribromophenyl, (2,3,4-, 2,3,5-,
25 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-)triiodophenyl, 2-chloro-3-fluorophenyl, etc.

Examples of lower alkyl groups substituted with one or more halogen atoms include straight or branched C₁₋₆ alkyl groups substituted with one to three halogen atoms, such as,
35 trifluoromethyl, trichloromethyl, chloromethyl, bromomethyl,

fluoromethyl, iodomethyl, difluoromethyl, dibromomethyl, 2-chloroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 3-chloropropyl, 2,3-dichloropropyl, 4,4,4-trichlorobutyl, 4-fluorobutyl, 5-chloropentyl, 3-chloro-2-methylpropyl, 5-bromohexyl, 5,6-dibromohexyl, etc.

Examples of pyridylamino groups include (2-, 3-, or 4-)pyridylamino groups.

Examples of pyridylcarbonylamino groups include (2-, 3-, or 4-)pyridylcarbonylamino groups.

Examples of anilino groups optionally substituted on the amino group with one or two lower alkyl groups include anilino groups optionally substituted on the amino group with one or two straight and/or branched C₁₋₆ alkyl groups, such as anilino, *N*-methylanilino, *N*-ethylanilino, *N*-*n*-propylanilino, *N*-isopropylanilino, *N*-*n*-butylanilino, *N*-*sec*-butylanilino, *N*-*tert*-butylanilino, *N*-*n*-pentylanilino, *N*-*n*-hexylanilino, etc.

Examples of pyridyl lower alkyl groups include pyridylalkyl groups wherein the alkyl moiety is a straight or branched C₁₋₆ alkyl group, such as [(2-, 3-, or 4-)pyridyl]methyl, 2-[(2-, 3-, or 4-)pyridyl]ethyl, 1-[(2-, 3-, or 4-)pyridyl]ethyl, 3-[(2-, 3-, or 4-)pyridyl]propyl, 4-[(2-, 3-, or 4-)pyridyl]butyl, 1,1-dimethyl-2-[(2-, 3-, or 4-)pyridyl]ethyl, 5-[(2-, 3-, or 4-)pyridyl]pentyl, 6-[(2-, 3-, or 4-)pyridyl]hexyl, 1-[(2-, 3-, or 4-)pyridyl]isopropyl, 2-methyl-3-[(2-, 3-, or 4-)pyridyl]propyl, etc.

Examples of "pyridyl lower alkyl groups optionally substituted on the pyridine ring with one or more members selected from the group consisting of halogen atoms; piperidinyl groups; a morpholino group; piperazinyl groups optionally substituted on the piperazine ring with one or more members selected from the group consisting of a phenyl group and lower alkyl groups; thienyl groups optionally substituted with one or more halogen atoms; a phenyl group optionally substituted with one or more halogen atoms; pyridyl groups; piperidinyl lower alkyl groups; phenylthio

lower alkyl groups; biphenyl groups; lower alkyl groups optionally substituted with one or more halogen atoms; pyridylamino groups; pyridylcarbonylamino groups; lower alkoxy groups; anilino lower alkyl groups optionally substituted on the amino group with one or two lower alkyl groups; anilino groups optionally substituted on the amino group with one or two lower alkyl groups; and furyl groups" include:

pyridyl alkyl groups wherein the alkyl moiety is a C₁₋₆ straight or branched alkyl group, optionally substituted on the pyridine ring with one to three members selected from the group consisting of the above-described halogen atoms; piperidinyl groups; a morpholino group; the above-described piperazinyl groups optionally substituted on the piperazine ring with one to three members selected from the group consisting of a phenyl group and straight and branched C₁₋₆ alkyl groups; thienyl groups optionally substituted with one to three halogen atoms; a phenyl group optionally substituted with one to three halogen atoms; pyridyl groups; piperidinylalkyl groups wherein the alkyl moiety is a straight or branched C₁₋₆ alkyl group; phenylthioalkyl groups wherein the alkyl moiety is a straight or branched C₁₋₆ alkyl group; biphenyl groups; lower alkyl groups wherein the alkyl moiety is a straight or branched C₁₋₆ alkyl group, optionally substituted with one to three halogen atoms; pyridylamino groups; pyridylcarbonylamino groups; straight and branched C₁₋₆ alkoxy groups; anilinoalkyl groups wherein the alkyl moiety is a straight or branched C₁₋₆ alkyl group, optionally substituted on the amino group with one or two straight and/or branched C₁₋₆ alkyl groups; the above-described anilino groups optionally substituted on the amino group with one or two straight and/or branched C₁₋₆ alkyl groups, and furyl groups;

such as (2-, 3-, or 4-)pyridylmethyl, 2-[(2-, 3-, or 4-)pyridyl]ethyl, 1-[(2-, 3-, or 4-)pyridyl]ethyl, 3-[(2-,

3-, or 4-)pyridyl]propyl, 4-[(2-, 3-, or 4-)pyridyl]butyl,
1,1-dimethyl-2-[(2-, 3-, or 4-)pyridyl]ethyl, 5-[(2-, 3-, or
4-)pyridyl]pentyl, 6-[(2-, 3-, or 4-)pyridyl]hexyl, 1-[(2-,
3-, or 4-)pyridyl]isopropyl, 2-methyl-3-[(2-, 3-, or 4-)
5 pyridyl]propyl, (2-chloro-3-pyridyl)methyl, [2-chloro-(3-, 4-,
5-, or 6-)pyridyl]methyl, [2,3-dichloro-(4-, 5-, or 6-)
pyridyl]methyl, [2-bromo-(3-, 4-, 5-, or 6-)pyridyl]methyl,
[2,4,6-trifluoro-(3-, 5-, or 6-)pyridyl]methyl, [2-(1-
piperidinyl)-(3-, 4-, 5-, or 6-)pyridyl]methyl, [2-(4-
10 morpholino)-(3-, 4-, 5-, or 6-)pyridyl]methyl, [2-(4-methyl-
1-piperazinyl)-(3-, 4-, 5-, or 6-)pyridyl]methyl, 2-[2-(4-
ethyl-1-piperazinyl)-(3-, 4-, 5-, or 6-)pyridyl]ethyl, 3-[2-
(4-isopropyl-1-piperazinyl)-(3-, 4-, 5-, or 6-)pyridyl]propyl,
4-[2-(4-sec-butyl-1-piperazinyl)-(3-, 4-, 5-, or 6-)
15 pyridyl]butyl, 5-[2-(4-n-pentyl-1-piperazinyl)-(3-, 4-, 5-,
or 6-)pyridyl]pentyl, 6-[2-(4-n-hexyl-1-piperazinyl)-(3-, 4-,
5-, or 6-)pyridyl]hexyl, [2-(4-phenyl-2-methyl-1-
piperazinyl)-(3-, 4-, 5-, or 6-)pyridyl]methyl, [2-(4-phenyl-
1-piperazinyl)-(3-, 4-, 5-, or 6-)pyridyl]methyl, [2-(3-
20 thienyl)-(3-, 4-, 5-, or 6-)pyridyl]methyl, [2-(2-
chlorothiophen-5-yl)-(3-, 4-, 5-, or 6-)pyridyl]methyl, [2-
phenyl-(3-, 4-, 5-, or 6-)pyridyl]methyl, [2-(2-
chlorophenyl)-(3-, 4-, 5-, or 6-)pyridyl]methyl, 2-[2,4-
diphenyl-(3-, 5-, or 6-)pyridyl]ethyl, 3-[2-(2-pyridyl)-6-(3-
25 thienyl)-(3-, 4-, or 5-)pyridyl]propyl, 4-(3-anilino-(2-, 4-,
5-, or 6-)pyridyl]butyl, 5-[2-(4-morpholino)-(3-, 4-, 5-, or
6-)pyridyl]pentyl, 6-[2-(1-piperidinyl)-(3-, 4-, 5-, or 6-)
pyridyl]hexyl, [2-(2-pyridyl)-(3-, 4-, 5-, or 6-)
pyridyl]methyl, [2-(3-pyridyl)-(3-, 4-, 5-, or 6-)
30 pyridyl]methyl, (3-, 4-, 5-, or 6-)(1-piperidinylmethyl)-2-
pyridylmethyl, (3-, 4-, 5-, or 6-)phenylthiomethyl-2-
pyridylmethyl, (4-, 5-, or 6-)biphenyl-3-pyridylmethyl, (4-,
5-, or 6-)trifluoromethyl-3-pyridylmethyl, (4-, 5-, or 6-)(2-
pyridylamino)-3-pyridylmethyl, (4-, 5-, or 6-)[(2- or 3-)
35 pyridylcarbonylamino]-3-pyridylmethyl, 3,5-dimethyl-4-

methoxy-2-pyridylmethyl, (3-, 4-, 5-, or 6-)(N-methylanilinomethyl)-2-pyridylmethyl, [2-(N-methylanilino)-(3-, 4-, 5-, or 6-)pyridyl]methyl, [2-(3-furyl)-(3-, 4-, 5-, or 6-)pyridyl]methyl, 2-[2-(N-ethylanilino)-(3-, 4-, 5-, or 6-)pyridyl]ethyl, 3-[2-(N-n-propylanilino)-(3-, 4-, 5-, or 6-)pyridyl]propyl, 4-[2-(N-n-butylnilino)-(3-, 4-, 5-, or 6-)pyridyl]ethyl, 5-[2-(N-n-pentylnilino)-(3-, 4-, 5-, or 6-)pyridyl]pentyl, 6-[2-(N-n-hexylnilino)-(3-, 4-, 5-, or 6-)pyridyl]hexyl, etc.

Examples of cyano lower alkyl groups include cyanoalkyl groups wherein the alkyl moiety is a straight or branched C₁₋₆ alkyl group, such as cyanomethyl, 2-cyanoethyl, 1-cyanoethyl, 3-cyanopropyl, 4-cyanobutyl, 1,1-dimethyl-2-cyanoethyl, 5-cyanopentyl, 6-cyanoethyl, 1-cyanoisopropyl, 2-methyl-3-cyanopropyl, etc.

Examples of quinolyl lower alkyl groups include quinolylalkyl groups wherein the alkyl moiety is a straight or branched C₁₋₆ alkyl group, such as [(2-, 3-, 4-, 5-, 6-, 7-, or 8-)quinolyl]methyl, 2-[(2-, 3-, 4-, 5-, 6-, 7-, or 8-)quinolyl]ethyl, 1-[(2-, 3-, 4-, 5-, 6-, 7-, or 8-)quinolyl]ethyl, 3-[(2-, 3-, 4-, 5-, 6-, 7-, or 8-)quinolyl]propyl, 4-[(2-, 3-, 4-, 5-, 6-, 7-, or 8-)quinolyl]butyl, 1,1-dimethyl-2-[(2-, 3-, 4-, 5-, 6-, 7-, or 8-)quinolyl]ethyl, 5-[(2-, 3-, 4-, 5-, 6-, 7-, or 8-)quinolyl]pentyl, 6-[(2-, 3-, 4-, 5-, 6-, 7-, or 8-)quinolyl]hexyl, 1-[(2-, 3-, 4-, 5-, 6-, 7-, or 8-)quinolyl]isopropyl, 2-methyl-3-[(2-, 3-, 4-, 5-, 6-, 7-, or 8-)quinolyl]propyl, etc.

Examples of lower alkoxy lower alkoxy-substituted lower alkyl groups include alkoxyalkoxy-substituted alkyl groups wherein each of the two alkoxy moieties is a straight or branched C₁₋₆ alkoxy group and the alkyl moiety is a straight or branched C₁₋₆ alkyl group, such as methoxymethoxymethyl, 2-(methoxymethoxy)ethyl, 1-(ethoxymethoxy)ethyl, 3-(2-n-butoxyethoxy)propyl, 4-(3-n-

propoxypropoxy)butyl, 1,1-dimethyl-2-(4-*n*-
pentyloxybutoxy)ethyl, 5-(5-*n*-hexyloxypropyloxy)pentyl, 6-(6-
methoxyhexyloxy)hexyl, 1-ethoxymethoxyisopropyl, 2-methyl-3-
(2-methoxyethoxy)propyl, 3,3-dimethyl-3-(methoxymethoxy)
5 propyl, etc.

Examples of hydroxy-substituted lower alkyl groups
include straight or branched C₁₋₆ alkyl groups substituted
with one to three hydroxy groups, such as hydroxymethyl, 2-
hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 2,3-
10 dihydroxypropyl, 4-hydroxybutyl, 3,4-dihydroxybutyl, 1,1-
dimethyl-2-hydroxyethyl, 5-hydroxypentyl, 6-hydroxyhexyl,
3,3-dimethyl-3-hydroxypropyl, 2-methyl-3-hydroxypropyl,
2,3,4-trihydroxybutyl, etc.

Examples of lower alkanoyl groups optionally
15 substituted with one or more halogen atoms include straight
and branched C₁₋₆ alkanoyl groups optionally substituted with
one to three halogen atoms, such as formyl, acetyl, propionyl,
butyryl, isobutyryl, pentanoyl, tert-butylcarbonyl, hexanoyl,
chloroacetyl, dibromoacetyl, trifluoroacetyl, 3-
20 chloropropionyl, 4-fluorobutyryl, 5-bromopentanoyl, 6-
chlorohexanoyl, etc.

Examples of lower alkoxy carbonyl groups optionally
substituted with one or more halogen atoms include
alkoxy carbonyl groups wherein the alkoxy moiety is a straight
25 or branched C₁₋₆ alkoxy group optionally substituted with one
to three halogen atoms, such as, in addition to the above-
described lower alkoxy carbonyl groups,
trifluoromethoxycarbonyl, trichloromethoxycarbonyl,
chloromethoxycarbonyl, bromomethoxycarbonyl,
30 fluoromethoxycarbonyl, iodomethoxycarbonyl,
difluoromethoxycarbonyl, dibromomethoxycarbonyl, 2-
chloroethoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, 2,2,2-
trichloroethoxycarbonyl, 3-chloropropoxycarbonyl, 2,3-
dichloropropoxycarbonyl, 4,4,4-trichlorobutoxycarbonyl, 4-
35 fluorobutoxycarbonyl, 4,4,4-trifluorobutoxycarbonyl, 5-

chloropentyloxycarbonyl, 3-chloro-2-methylpropoxycarbonyl, 5-bromohexyloxycarbonyl, 5,6-dibromohexyloxycarbonyl; etc.

Examples of lower alkoxy groups optionally substituted with one or more halogen atoms include straight or branched C₁₋₆ alkoxy groups optionally substituted with one to three halogen atoms, such as, in addition to the above-described lower alkoxy groups, trifluoromethoxy, trichloromethoxy, chloromethoxy, bromomethoxy, fluoromethoxy, iodomethoxy, difluoromethoxy, dibromomethoxy, 2-chloroethoxy, 2,2,2-trifluoroethoxy, 2,2,2-trichloroethoxy, 3-chloropropoxy, 2,3-dichloropropoxy, 4,4,4-trichlorobutoxy, 4-fluorobutoxy, 5-chloropentyloxy, 3-chloro-2-methylpropoxy, 5-bromohexyloxy, 5,6-dibromohexyloxy, etc.

Examples of lower alkanoyl groups include straight or branched C₁₋₆ alkanoyl groups, such as formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, tert-butylcarbonyl, hexanoyl, etc.

Examples of lower alkanoyl amino groups include amino groups substituted with one or two straight and/or branched C₁₋₆ alkanoyl groups, such as formylamino, acetylamino, propionylamino, butyrylamino, isobutyrylamino, pentanoylamino, tert-butylcarbonylamino, hexanoylamino, N,N-diacetylamino, N-acetyl-N-propionylamino, etc.

Examples of "phenylsulfonyl groups optionally substituted on the phenyl ring with one or more members selected from the group consisting of halogen atoms, lower alkyl groups optionally substituted with one or more halogen atoms, a phenyl group, a phenoxy group, lower alkoxy groups optionally substituted with one or more halogen atoms, a cyano group, and lower alkanoyl amino groups" include:

phenylsulfonyl groups optionally substituted on the phenyl ring with one or two members selected from the group consisting of halogen atoms, the above-described lower alkyl groups optionally substituted with one to three halogen atoms, a phenyl group, a phenoxy group, the above-described lower

alkoxy groups optionally substituted with one to three halogen atoms, a cyano group, and the above-described lower alkanoylamino groups;

such as phenylsulfonyl, (2-, 3-, or 4-)

- 5 chlorophenylsulfonyl, (2-, 3-, or 4-)fluorophenylsulfonyl, (2-, 3-, or 4-)bromophenylsulfonyl, (2-, 3-, or 4-)iodophenylsulfonyl, (2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-)dichlorophenylsulfonyl, (2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-)difluorophenylsulfonyl, (2,3-, 2,4-, 2,5-, 2,6-, 3,4-,
10 or 3,5-)dibromophenylsulfonyl, (2-, 3-, or 4-)methylphenylsulfonyl, (2-, 3-, or 4-)ethylphenylsulfonyl, (2-, 3-, or 4-)propylphenylsulfonyl, (2-, 3-, or 4-)isopropylphenylsulfonyl, (2-, 3-, or 4-)pentylphenylsulfonyl, (2,3-, 2,4-, 2,5-, 2,6-, 3,4-, or 3,5-)dimethylphenylsulfonyl,
15 (2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, or 3,4,5-)trimethylphenylsulfonyl, (2-, 3-, or 4-)chloromethylphenylsulfonyl, (2-, 3-, or 4-)dichloromethylphenylsulfonyl, (2-, 3-, or 4-)trifluoromethylphenylsulfonyl, (2-, 3-, or 4-)[(1- or 2-)
20 chloroethyl]phenylsulfonyl, (2-, 3-, or 4-)phenylphenylsulfonyl, (2-, 3-, or 4-)phenoxyphenylsulfonyl, (2-, 3-, or 4-)methoxyphenylsulfonyl, (2-, 3-, or 4-)ethoxyphenylsulfonyl, (2-, 3-, or 4-)propoxyphenylsulfonyl, (2-, 3-, or 4-)chloromethoxyphenylsulfonyl, (2-, 3-, or
25 4-)dichloromethoxyphenylsulfonyl, (2-, 3-, or 4-)trifluoromethoxyphenylsulfonyl, (2-, 3-, or 4-)[(1- or 2-)chloroethoxy]phenylsulfonyl, (2-, 3-, or 4-)cyanophenylsulfonyl, (2-, 3-, or 4-)formylaminophenylsulfonyl, (2-, 3-, or 4-)acetylaminophenyl sulfonyl, (2-, 3-, or 4-)
30 propionylaminophenylsulfonyl, 2-methyl-3-chlorophenylsulfonyl, etc.

Examples of naphthylsulfonyl groups include (1- or 2-)naphthylsulfonyl groups.

- Examples of lower alkyl groups optionally
5 substituted with one or more phenyl groups include straight

or branched C₁₋₆ alkyl groups optionally substituted with one to three phenyl groups, such as, in addition to the above-described lower alkyl groups, phenylmethyl, diphenylmethyl, triphenylmethyl, 2-phenylethyl, 2,2,2-triphenylethyl, 3-phenylpropyl, 2,3-diphenylpropyl, 4,4,4-triphenylbutyl, 4-phenylbutyl, 5-phenylpentyl, 6-phenylhexyl, 5,6-diphenylhexyl, etc.

Examples of carboxy lower alkoxy groups include carboxyalkoxy groups wherein the alkoxy moiety is a straight or branched C₁₋₆ alkoxy group, such as carboxymethoxy, 2-carboxyethoxy, 1-carboxyethoxy, 3-carboxypropoxy, 4-carboxybutoxy, 5-carboxypentyloxy, 6-carboxyhexyloxy, 1,1-dimethyl-2-carboxyethoxy, 2-methyl-3-carboxypropoxy, etc.

Examples of lower alkoxy carbonyl lower alkoxy groups include alkoxy carbonyl alkoxy groups wherein each of the two alkoxy moieties is a straight or branched C₁₋₆ alkoxy group, such as methoxycarbonylmethoxy, ethoxycarbonylmethoxy, 2-methoxycarbonylethoxy, 2-ethoxycarbonylethoxy, 1-ethoxycarbonylethoxy, 3-methoxycarbonylpropoxy, 3-ethoxycarbonylpropoxy, 4-ethoxycarbonylbutoxy, 5-isopropoxycarbonylpentyloxy, 6-n-propoxycarbonylhexyloxy, 1,1-dimethyl-2-n-butoxycarbonylethoxy, 2-methyl-3-tert-butoxycarbonylpropoxy, 2-n-pentyloxycarbonylethoxy, n-hexyloxycarbonylmethoxy, etc.

Examples of amino groups optionally substituted with one or two members selected from the group consisting of lower alkyl groups and lower alkanoyl groups include amino groups optionally substituted with one or two members selected from the group consisting of straight and branched C₁₋₆ alkyl groups and straight and branched C₁₋₆ alkanoyl groups, such as amino, methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, tert-butylamino, n-pentylamino, n-hexylamino, dimethylamino, diethylamino, di-n-propylamino, di-n-butylamino, di-n-pentylamino, di-n-hexylamino, N-methyl N-ethylamino, N-ethyl-N-n-propylamino, N-methyl-N-n-

butylamino, *N*-methyl-*N*-*n*-hexylamino, formylamino, acetylamino, propionylamino, butyrylamino, isobutyrylamino, pentanoylamino, tert-butylcarbonylamino, hexanoylamino, *N,N*-diacetylamino, *N*-acetyl-*N*-propionylamino, *N*-methyl-*N*-acetylamino, *N*-ethyl-*N*-propionylamino, etc.

Examples of pyrrolidinyl groups optionally substituted on the pyrrolidine ring with one or more oxo groups include pyrrolidinyl groups optionally substituted on the pyrrolidine ring with one or two oxo groups, such as (1-, 2-, or 3-)pyrrolidinyl, 2-oxo-(1-, 3-, 4-, or 5-)pyrrolidinyl, 2,5-dioxo(1- or 3-)pyrrolidinyl, etc.

Examples of piperidinyl groups optionally substituted on the piperidine ring with one or more lower alkyl groups include piperidinyl groups optionally substituted on the piperidine ring with one to three straight and/or branched C₁₋₆ alkyl groups, such as (1-, 2-, 3-, or 4-)piperidinyl, 1-methyl-(2-, 3-, or 4-)piperidinyl, 1-ethyl-(2-, 3-, or 4-)piperidinyl, 1-*n*-propyl-(2-, 3-, or 4-)piperidinyl, 1-isopropyl-(2-, 3- or 4-)piperidinyl, 1-*n*-butyl-(2-, 3-, or 4-)piperidinyl, 1-*n*-pentyl-(2-, 3-, or 4-)piperidinyl, 1-*n*-hexyl-(2-, 3-, or 4-)piperidinyl, 1,2-dimethyl-(3-, 4-, 5-, or 6-)piperidinyl, 1,2,3-trimethyl-(4-, 5-, or 6-)piperidinyl, 2-*n*-propyl-(1-, 3-, 4-, 5-, or 6-)piperidinyl, 3-ethyl-(1-, 2-, 4-, 5-, or 6-)piperidinyl, 2-methyl-4-isopropyl-(1-, 3-, 5-, or 6-)piperidinyl, etc.

Examples of lower alkenyl groups include straight or branched C₂₋₆ alkenyl groups containing one to three double bonds, such as vinyl, 1-propenyl, 1-methyl-1-propenyl, 2-methyl-1-propenyl, 2-propenyl, 2-butenyl, 1-butenyl, 3-butenyl, 2-pentenyl, 1-pentenyl, 3-pentenyl, 4-pentenyl, 1,3-butadienyl, 1,3-pentadienyl, 2-pentene-4-yl, 2-hexenyl, 1-hexenyl, 5-hexenyl, 3-hexenyl, 4-hexenyl, 3,3-dimethyl-1-propenyl, 2-ethyl-1-propenyl, 1,3,5-hexatrienyl, 1,3-hexadienyl, 1,4-hexadienyl, etc.

Examples of carbamoyl groups optionally substituted

with one or more lower alkyl groups include carbamoyl groups optionally substituted with one or two straight and/or branched C₁₋₆ alkyl groups, such as carbamoyl, methylcarbamoyl, ethylcarbamoyl, n-propylcarbamoyl, isopropylcarbamoyl, n-butylcarbamoyl, tert-butylcarbamoyl, n-pentylcarbamoyl, n-hexylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, di-n-propylcarbamoyl, di-n-butylcarbamoyl, di-n-pentylcarbamoyl, di-n-hexylcarbamoyl, N-methyl-N-ethylcarbamoyl, N-ethyl-N-n-propylcarbamoyl, N-methyl-N-n-butylcarbamoyl, N-methyl-N-n-hexylcarbamoyl, etc.

Examples of "phenyl groups optionally substituted on the phenyl ring with one or more members selected from the group consisting of halogen atoms; lower alkyl groups optionally substituted with one or more halogen atoms; a phenoxy group; lower alkoxy groups optionally substituted with one or more halogen atoms; lower alkylthio groups; lower alkylsulfonyl groups; amino groups optionally substituted with one or two members selected from the group consisting of lower alkyl groups and lower alkanoyl groups; pyrrolidinyl groups optionally substituted on the pyrrolidine ring with one or more oxo groups; piperidinyl groups optionally substituted on the piperidine ring with one or more lower alkyl groups; lower alkenyl groups; an aminosulfonyl group; a hydroxy group; carbamoyl groups optionally substituted with one or more lower alkyl groups; phenyl lower alkoxy groups; and a cyano group" include:

phenyl groups optionally substituted on the phenyl ring with one to three members selected from the group consisting of the above-described halogen atoms; the above-described straight and branched C₁₋₆ alkyl groups optionally substituted with one to three halogen atoms; a phenoxy group; the above-described straight and branched C₁₋₆ alkoxy groups optionally substituted with one to three halogen atoms; the above-described straight and branched C₁₋₆ alkylthio groups; the above-described straight and branched C₁₋₆ alkylsulfonyl

groups; the above-described amino groups optionally substituted with one or two members selected from the group consisting of straight and branched C₁₋₆ alkyl groups and straight and branched C₁₋₆ alkanoyl groups; the above-described pyrrolidinyl groups optionally substituted on the pyrrolidine ring with one or two oxo groups; the above-described piperidinyl groups optionally substituted on the piperidine ring with one to three straight and/or branched C₁₋₆ alkyl groups; the above-described straight or branched C₂₋₆ alkenyl groups containing one to three double bonds; an aminosulfonyl group; a hydroxy group; the above-described carbamoyl groups optionally substituted with one or two straight and/or branched C₁₋₆ alkyl groups; the above-described phenylalkoxy groups wherein the alkoxy moiety is a straight or branched C₁₋₆ alkoxy group; and a cyano group;

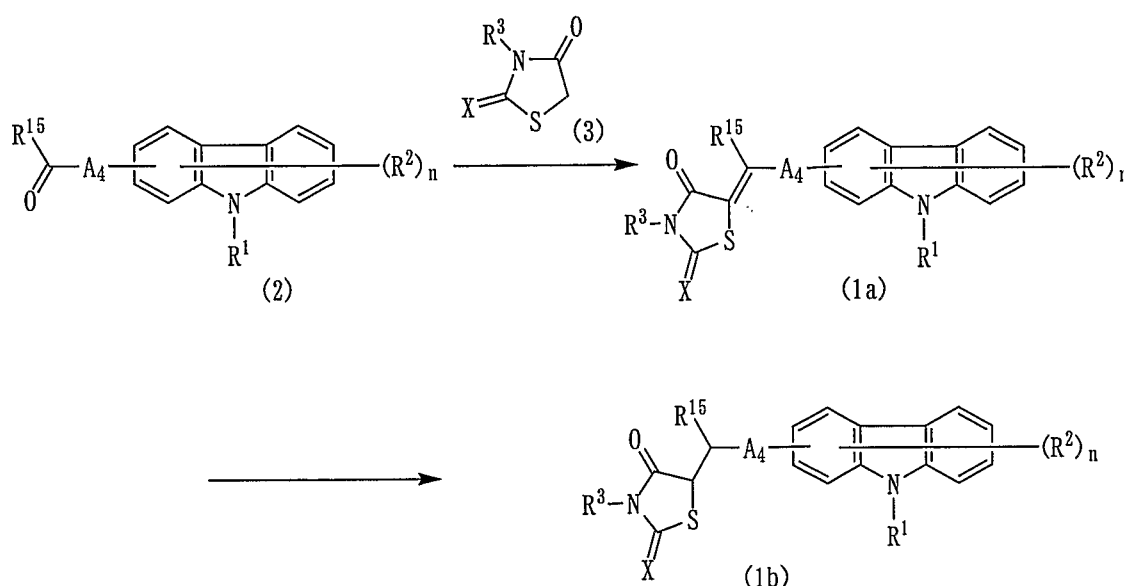
such as phenyl, 4-phenoxyphenyl, 3-phenoxyphenyl, 2-phenoxyphenyl, 4-isopropylphenyl, 3-isopropylphenyl, 2-isopropylphenyl, 4-*tert*-butylphenyl, 4-methylphenyl, 3-methylphenyl, 2-methylphenyl, 2,3-dimethylphenyl, 2,4-dimethylphenyl, 3,5-dimethylphenyl, 2,4,6-trimethylphenyl, 4-methyl-3-methoxyphenyl, 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, 2-trifluoromethylphenyl, 4-methyl-3-chlorophenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-bromophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3,4,5-trichlorophenyl, 2,4,6-trifluorophenyl, 3,5-difluorophenyl, 3-chloro-4-fluorophenyl, 2-chloro-5-fluorophenyl, 3-fluoro-4-methoxyphenyl, 3-chloro-4-methoxyphenyl, 3-chloro-4-hydroxyphenyl, 4-methoxyphenyl, 3-methoxyphenyl, 2-methoxyphenyl, 2,4-dimethoxyphenyl, 3,4-dimethoxyphenyl, 2,4,6-trimethoxyphenyl, 2-methoxy-5-chlorophenyl, 2-methoxy-5-acetylamino-phenyl, 2-chloro-5-acetylamino-phenyl, 4-ethoxyphenyl, 4-trifluoromethoxyphenyl, 3-trifluoromethoxyphenyl, 2-trifluoromethoxyphenyl, 3-methoxy-5-trifluoromethylphenyl, 4-methylthiophenyl, 3-

methylthiophenyl, 2-methylthiophenyl, 2-(1-methyl-1-vinyl)phenyl, 4-vinylphenyl, 3-dimethylaminophenyl, 4-methylaminophenyl, 2-(N-methyl-N-acetyl amino)phenyl, 3-acetylaminophenyl, 4-propionylaminophenyl, 4-acetylaminophenyl, 2-acetylaminophenyl, 4-aminosulfonylphenyl, 3-aminosulfonylphenyl, 2-aminosulfonylphenyl, 4-methylthiophenyl, 3-methylthiophenyl, 2-methylthiophenyl, 4-methylsulfonylphenyl, 3-methylsulfonylphenyl, 2-methylsulfonylphenyl, 4-methylcarbamoylphenyl, 3-carbamoylphenyl, 2-ethylcarbamoylphenyl, 2-benzyloxyphenyl, 3-benzyloxyphenyl, 4-benzyloxyphenyl, 2-phenylphenyl, 3-phenylphenyl, 4-phenylphenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-[2-oxo-(1-, 3-, 4-, or 5-)pyrrolidinyl]phenyl, 3-[2,5-dioxo-(1- or 3-)pyrrolidinyl]phenyl, 4-[4-methyl-(1-, 2-, or 3-)piperazinyl]phenyl, 3-[4-ethyl-(1-, 2-, or 3-)piperazinyl]phenyl, 2-[4-isopropyl-(1-, 2-, or 3-)piperazinyl]phenyl, etc.

Examples of cycloalkyl groups optionally substituted on the cycloalkyl ring with one or more lower alkyl groups include C₃₋₈ cycloalkyl groups optionally substituted on the cycloalkyl ring with one to three straight and/or branched C₁₋₆ alkyl groups, such as, in addition to the above-described cycloalkyl groups, 1-methylcyclopropyl, 1-methylcyclopentyl, 1-methylcyclohexyl, 2-methylcyclohexyl, 1-methylcyclobutyl, 1-ethylcyclooctyl, 1-n-propylcycloheptyl, 1,2-dimethylcyclohexyl, 1,4,5-trimethylcyclooctyl, 1-n-butylcyclopropyl, 1-n-pentylcyclopentyl, 1-n-hexylcyclohexyl, etc.

The compounds of the present invention can be produced according to, for example, Reaction Schemes 1 to 9. All the starting materials and target compounds shown in Reaction Schemes 1 to 9 may be in the form of suitable salts. Examples of such salts are as described for the compound of Formula (1) below.

Reaction Scheme 1



wherein R^1 , R^2 , R^3 , X , and n are as defined above, R^{15} is a hydrogen atom or lower alkyl group, and A_4 represents a direct bond or lower alkylene group, provided that the total number of carbon atoms of the group substituting the carbazole skeleton, i.e., $-\text{CH}(R^{15})-\text{A}_4-$, is no greater than 6.

The reaction of Compound (2) with Compound (3) is carried out in a suitable solvent in the presence of a basic compound or acid.

Examples of solvents usable herein are aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as diethyl ether, tetrahydrofuran, dioxane, monoglyme and diglyme; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform and carbon tetrachloride; lower alcohols such as methanol, ethanol, isopropanol, butanol, *tert*-butanol and ethylene glycol; aliphatic acids such as acetic acid; acid anhydrides such as acetic anhydride; esters such as ethyl acetate and methyl acetate; ketones such as acetone and methyl ethyl ketone; acetonitrile; pyridine; dimethyl sulfoxide; *N,N*-dimethylformamide; hexamethylphosphoric triamide; mixed solvents of such solvents, etc.

Examples of basic compounds are carbonates such as sodium carbonate, potassium carbonate, sodium

hydrogencarbonate, potassium hydrogencarbonate and cesium carbonate; metal hydroxides such as sodium hydroxide, potassium hydroxide and calcium hydroxide; sodium hydride; potassium hydride; potassium; sodium; sodium amide; metal
5 alcoholates such as sodium methyllate, sodium ethyllate and sodium *n*-butoxide; piperidine, pyridine, imidazole, *N*-ethyl-diisopropylamine, dimethylaminopyridine, triethylamine, trimethylamine, dimethylaniline, *N*-methyldmorpholine, 1,5-diazabicyclo[4.3.0]nonene-5 (DBN), 1,8-
10 diazabicyclo[5.4.0]undecene-7 (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), and other organic bases and mixtures thereof.

Examples of acids are organic acids such as *p*-toluenesulfonic acid and other sulfonic acids, and acetic
15 acid, trifluoroacetic acid, trichloroacetic acid and other aliphatic acids; inorganic acids such as hydrochloric acid, sulfuric acid, hydrobromic acid, and phosphoric acid; and mixtures thereof.

In the present invention, a basic compound and an
20 acid may be used in combination.

Basic compound or acid is usually used in a catalytic amount, and preferably about 0.01 to about 1 mol, per mol of Compound (2).

Compound (3) is usually used in an amount of at
25 least 1 mol, and preferably about 1 to about 2 mol, per mol of Compound (2).

The reaction is usually carried out at about room temperature to about 200°C, and preferably about room temperature to about 150°C. The reaction is usually finished
30 in about 0.5 to about 20 hours.

The reaction for producing Compound (1b) from Compound (1a) is carried out, for example, either without a solvent or in a suitable solvent, in the presence of a reducing agent.

35 Examples of solvents usable herein are water, lower

alcohols such as methanol, ethanol, isopropanol, butanol, tert-butanol and ethylene glycol, acetonitrile, aliphatic acids such as formic acid and acetic acid, ethers such as diethyl ether, tetrahydrofuran, dioxane, monoglyme and diglyme, aromatic hydrocarbons such as benzene, toluene and xylene, halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform and carbon tetrachloride, *N,N*-dimethylformamide, mixtures of such solvents, etc.

Examples of reducing agents are mixtures of silicon dioxide and pyridine compounds such as diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate; sodium borohydride, lithium borohydride, sodium cyanoborohydride, sodium triacetoxo borohydride, aluminium lithium hydride, and other hydride reducing agents; mixtures of such hydride reducing agents; palladium black, palladium carbon, platinum oxide, platinum black, Raney nickel, and other catalytic hydrogenation reducing agents; etc.

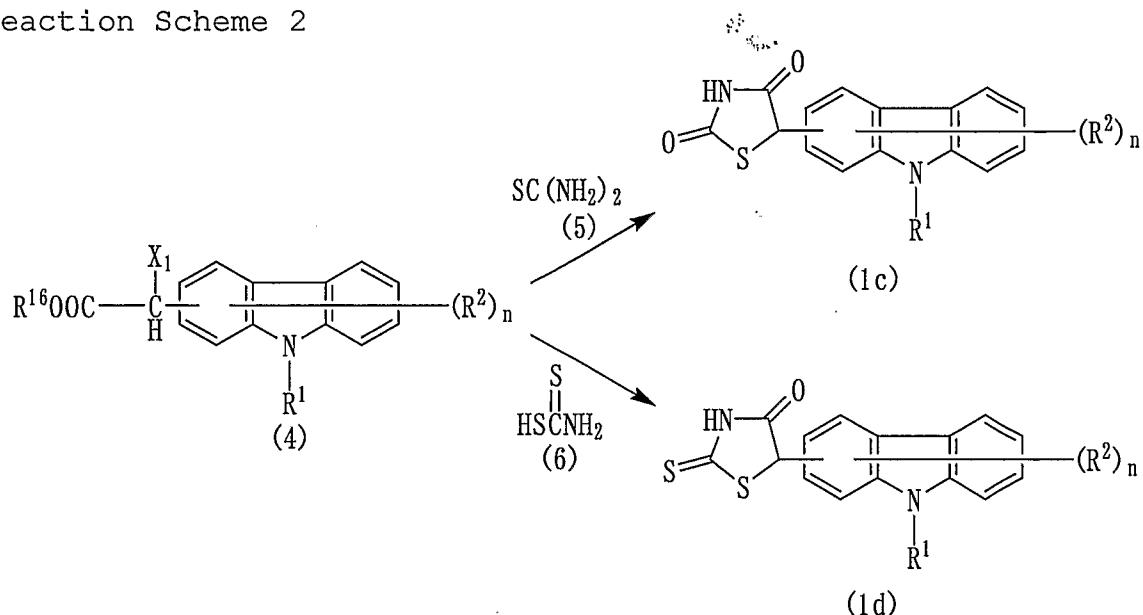
When a mixture of a pyridine compound and silicon dioxide is used as a reducing agent, a suitable reaction temperature is usually about room temperature to about 200°C, and preferably about room temperature to about 150°C. The reaction is usually finished in about 0.5 to about 50 hours. The pyridine compound is usually used in an amount of at least 1 mol, and preferably 1 to 3 mol, per mol of Compound (1a). Silicon dioxide is usually used in an amount of at least 1 mol, and preferably 1 to 10 mol, per mol of Compound (1a).

When a hydride reducing agent is used, a suitable reaction temperature is usually about -80 to about 100°C and preferably about -80 to about 70°C. The reaction is usually finished in about 30 minutes to about 60 hours. The hydride reducing agent is usually used in an amount of about 0.1 to about 20 mol, and preferably about 0.1 to about 6 mol, per mol of Compound (1b). In particular, when lithium borohydride is used as a hydride reducing agent, it is

preferable to use diethyl ether, tetrahydrofuran, dioxane, monoglyme, diglyme, and other ethers, and benzene, toluene, xylene, and other aromatic hydrocarbons as solvents. Amine such as pyridine, trimethylamine, triethylamine and *N*-ethyl-diisopropylamine; inorganic base such as sodium hydroxide; and/or ligand such as dimethylglyoxime, 2,2'-bipyridyl and 1,10-phenanthroline may be added to the reaction system of the reaction. When sodium borohydride is used as a hydride reducing agent, one or more cobalt compounds such as cobalt(II) chloride, cobalt(III) chloride and cobalt(II) acetate may be added to the reaction system of the reaction in the presence of amine such as pyridine, trimethylamine, triethylamine and *N*-ethyl-diisopropylamine; inorganic base such as sodium hydroxide; and/or ligand such as dimethylglyoxime, 2,2'-bipyridyl and 1,10-phenanthroline.

When a catalytic hydrogenation reducing agent is used, the reaction is usually carried out at about -30 to about 100°C, and preferably about 0 to about 100°C, in a hydrogen atmosphere of about atmospheric pressure to about 20 atm, and preferably about atmospheric pressure to about 10 atm, or in the presence of formic acid, ammonium formate, cyclohexene, hydrazine hydrate, or like hydrogen donor. The reaction is usually finished in about 1 to about 12 hours. The catalytic hydrogenation reducing agent is usually used in an amount of about 0.01 to about 5 times, and preferably about 1 to about 3 times, the weight of Compound (1a).

Reaction Scheme 2



wherein R^1 , R^2 , and n are as defined above; X_1 is a halogen atom; and R^{16} is a lower alkyl group.

- 5 Compound (1c) is produced by reacting Compound (4) and Compound (5) in a suitable solvent in the presence of a basic compound followed by acid treatment. This acid treatment is hereinafter referred to as "Acid Treatment A".

- Examples of solvents usable herein are water,
- 10 aromatic hydrocarbons such as benzene, toluene and xylene, ethers such as diethyl ether, tetrahydrofuran, dioxane, 2-methoxyethanol, monoglyme and diglyme, halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform and carbon tetrachloride, lower alcohols such as
- 15 methanol, ethanol, isopropanol, butanol, *tert*-butanol and ethylene glycol, aliphatic acids such as acetic acid, esters such as ethyl acetate and methyl acetate, ketones such as acetone and methyl ethyl ketone, acetonitrile, pyridine, dimethyl sulfoxide, *N,N*-dimethylformamide,
- 20 hexamethylphosphoric triamide, mixed solvents of such solvents, etc.

- Examples of basic compounds are carbonates such as sodium carbonate, potassium carbonate, sodium
- hydrogencarbonate, potassium hydrogencarbonate and cesium
- 25 carbonate, metal hydroxides such as sodium hydroxide,

potassium hydroxide and calcium hydroxide, sodium hydride, potassium hydride, potassium, sodium, sodium amide, metal alcoholates such as sodium methylate, sodium ethylate and sodium *n*-butoxide, sodium acetate, piperidine, pyridine, 5 imidazole, *N*-ethyldiisopropylamine, dimethylaminopyridine, triethylamine, trimethylamine, dimethylaniline, *N*-methylemorpholine, DBN, DBU, DABCO, other organic bases, and mixtures thereof.

Basic compound is usually used in an amount of at least about 1 mol, and preferably about 1 to about 3 mol, per 10 mol of Compound (4).

Compound (5) is usually used in an amount of at least about 1 mol, and preferably about 1 to about 2 mol, per mol of Compound (4).

15 The reaction is usually carried out at about room temperature to about 200°C, and preferably about room temperature to about 150°C. The reaction is usually finished in about 0.5 to about 10 hours.

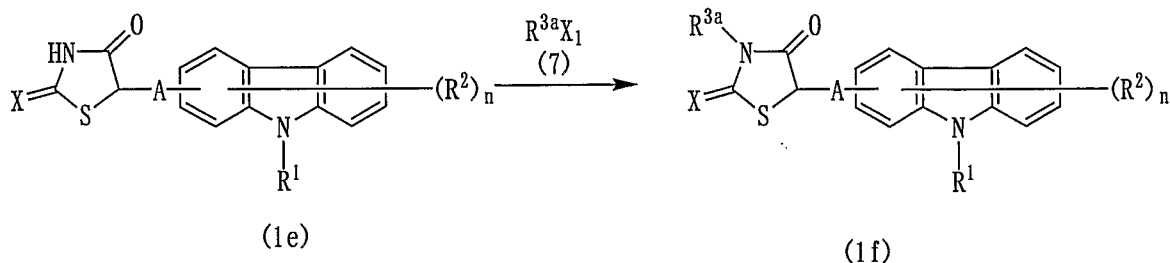
Examples of acids usable in acid-treating the 20 reaction product are inorganic acids such as hydrochloric acid, sulfuric acid, hydrobromic acid, and the like. Such acids are usually used in a large excess relative to the reaction product to be treated.

Examples of solvents usable in the acid treatment 25 include those that are usable in the reaction of Compound (4) with Compound (5) above.

The acid treatment is usually carried out at about room temperature to about 200°C, and preferably about room temperature to about 150°C. The acid treatment is usually 30 finished in about 0.5 to about 30 hours.

The reaction of Compound (4) with Compound (6) is carried out under the same conditions selected for the reaction of Compound (4) with Compound (5).

Reaction Scheme 3



wherein R^1 , R^2 , X , A , X_1 , and n are as defined above; and R^{3a} is a group other than a hydrogen atom as defined in connection with R^3 above.

The reaction of Compound (1e) and Compound (7) is carried out in a suitable inert solvent in the presence of a basic compound.

Examples of inert solvents usable herein are aromatic hydrocarbons such as benzene, toluene and xylene, ethers such as diethyl ether, tetrahydrofuran, dioxane, 2-methoxyethanol, monoglyme and diglyme, halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform and carbon tetrachloride, lower alcohols such as methanol, ethanol, isopropanol, butanol, *tert*-butanol and ethylene glycol, aliphatic acids such as acetic acid, esters such as ethyl acetate and methyl acetate, ketones such as acetone and methyl ethyl ketone, acetonitrile, pyridine, dimethyl sulfoxide, *N,N*-dimethylformamide, hexamethylphosphoric triamide, mixed solvents of such solvents, etc.

Examples of basic compounds are carbonates such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate and cesium carbonate, metal hydroxides such as sodium hydroxide, potassium hydroxide and calcium hydroxide, sodium hydride, potassium hydride, potassium, sodium, sodium amide, metal alcoholates such as sodium methylate, sodium ethylate, sodium *n*-butoxide, sodium *tert*-butoxide and potassium *tert*-butoxide, pyridine, imidazole, *N*-ethyldiisopropylamine,

dimethylaminopyridine, triethylamine, trimethylamine, dimethylaniline, *N*-methylmorpholine, DBN, DBU, DABCO, other organic bases, and mixtures thereof.

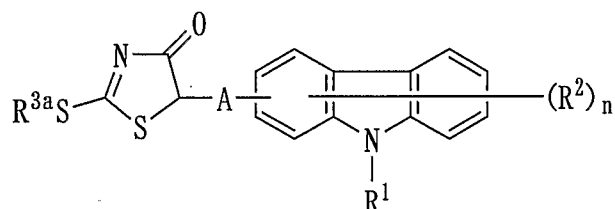
Basic compound is usually used in an amount of at least 1 mol, and preferably 1 to 10 mol, per mol of Compound (1e).

Compound (7) is usually used in an amount of at least 1 mol, and preferably 1 to 10 mol, per mol of Compound (1e).

The reaction is usually carried out at about 0 to about 200°C, and preferably 0 to about 150°C. The reaction is usually finished in about 5 minutes to about 80 hours.

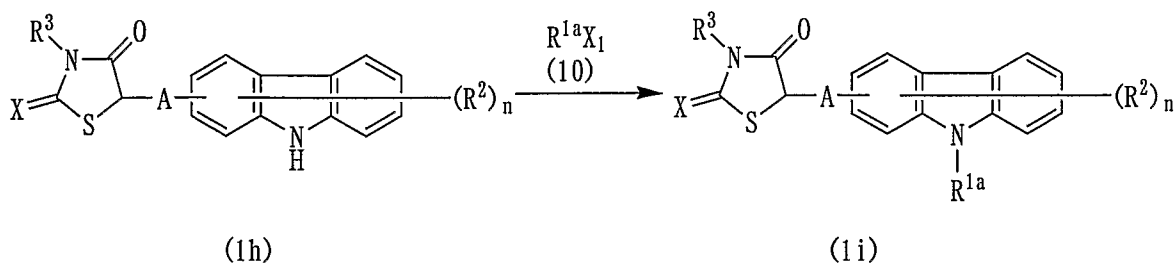
Sodium iodide, potassium iodide, or like alkali metal halide compound may be introduced into the reaction system of the reaction.

When a Compound (1e) in which X is sulfur is used in the reaction of Compound (1e) with Compound (7), a compound represented by the formula:



wherein R^1 , R^2 , R^{3a} , A, and n are as defined above, is sometimes generated. This compound can be easily separated from the reaction mixture.

Reaction Scheme 4

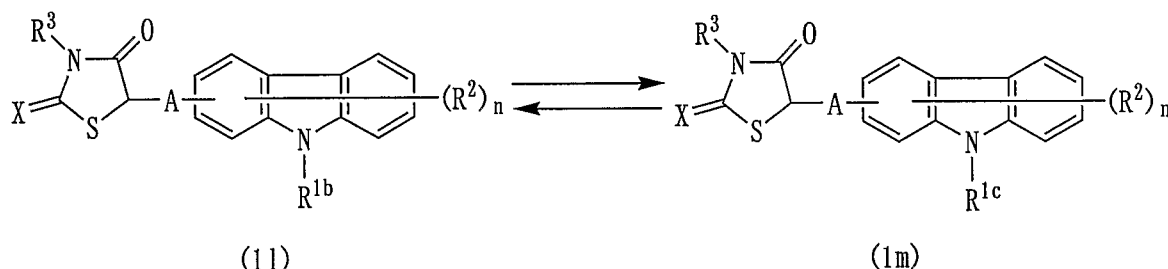


wherein R^2 , R^3 , X, A, X_1 , and n are as defined above, and R^{1a} is a group other than a hydrogen atom as defined in

connection with R¹.

The reaction of Compound (1h) with Compound (10) is carried out under the same conditions as described in connection with the reaction of Compound (1e) with Compound (7) shown in Reaction Scheme 3 above.

Reaction Scheme 5



wherein R², R³, X, A, and n are as defined above; R^{1b} is a group as defined in (1-9) in connection with R¹ above; and R^{1c} is a group as defined in (1-8) in connection with R¹ above.

The reaction to produce Compound (1m) from Compound (1l) is carried out by hydrolyzing Compound (1l).

This hydrolysis reaction is performed, for example, either in a suitable solvent or without a solvent, in the presence of an acid or basic compound.

Examples of usable solvents are water, lower alcohols such as methanol, ethanol, isopropanol and *tert*-butanol, ketones such as acetone and methyl ethyl ketone, ethers such as diethyl ether, dioxane, tetrahydrofuran, monoglyme and diglyme, aliphatic acids such as acetic acid and formic acid, esters such as methyl acetate and ethyl acetate, halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane, carbon tetrachloride, dimethyl sulfoxide, *N,N*-dimethylformamide, hexamethylphosphoric triamide, mixed solvents of such solvents, etc.

Examples of acids are mineral acids such as hydrochloric acid, sulfuric acid and hydrobromic acid; and organic acids such as formic acid, acetic acid, trifluoroacetic acid, *p*-toluenesulfonic acid and other

sulfonic acids. Such acids may be used singly or as a combination of two or more such acids.

Examples of basic compounds are carbonates such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate and potassium hydrogencarbonate; metal hydroxides such as sodium hydroxide, potassium hydroxide, calcium hydroxide and lithium hydroxide; etc. Such basic compounds may be used singly or as a combination of two or more such compounds.

10 The hydrolysis reaction advantageously proceeds usually at about 0 to about 200°C, and preferably about 0 to about 150°C. The reaction is usually finished in about 10 minutes to about 30 hours.

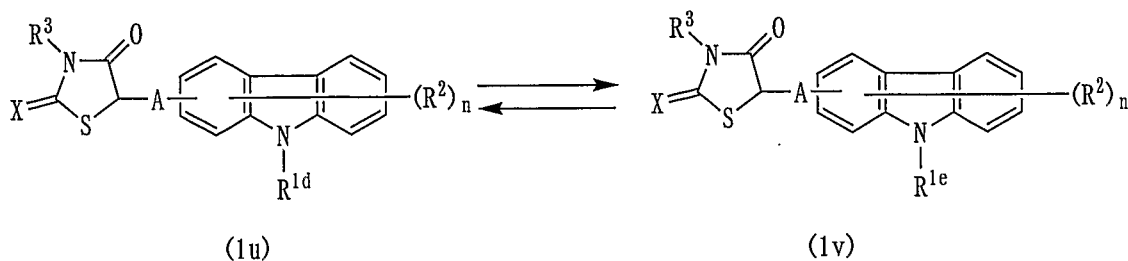
The reaction for producing Compound (11) from Compound (1m) can be carried out by reacting Compound (1m) with a compound represented by the formula



wherein R^{23} is a lower alkyl group.

20 Conditions usually selected for esterification reactions are applicable to the reaction. For example, it may be carried out in the presence of one or more mineral acids such as hydrochloric acid, sulfuric acid, etc, and/or one or more halogenating agents such as thionyl chloride, phosphorus oxychloride, phosphorus pentachloride, phosphorus trichloride, etc. Compound (50) is used in a large excess relative to Compound (1m). The reaction advantageously progresses usually at about 0 to about 150°C, and preferably about 50 to about 100°C. The reaction is usually finished in about 1 to about 10 hours.

Reaction Scheme 6

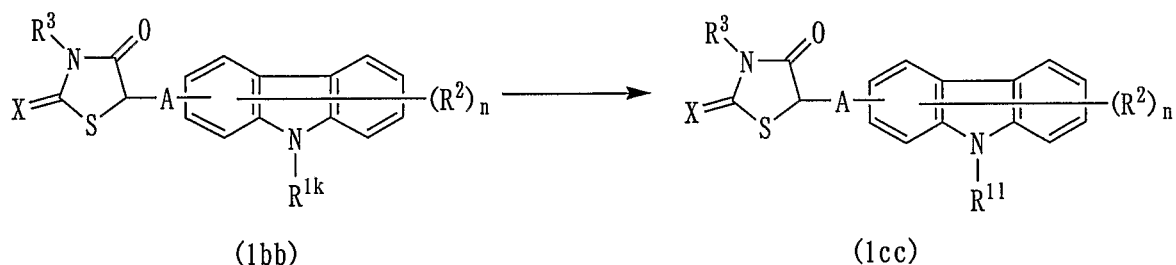


wherein R^2 , R^3 , X , A , and n are as defined above; R^{1d} is a group as defined in (1-3) in connection with R^1 above except for having at least one lower alkoxy carbonyl group on the phenyl ring; and R^{1e} is a group as defined in (1-3) in connection with R^1 above except for having at least one carboxy group on the phenyl ring.

The reaction for producing Compound (1v) from Compound (1u) is carried out under the same conditions as described in connection with the reaction for producing Compound (1m) from Compound (1l) shown in Reaction Scheme 5 above.

The reaction for producing Compound (1u) from Compound (1v) is carried out under the same conditions as described in connection with the reaction for producing Compound (1l) from Compound (1m) shown in Reaction Scheme 5 above.

Reaction Scheme 7



wherein R^2 , R^3 , X , A , and n are as defined above; R^{1k} is a group as defined in (1-3) in connection with R^1 above except for having at least one nitro group on the phenyl ring; and R^{11} is a group as defined in (1-3) in connection with R^1 above except for having at least one amino group on the phenyl ring.

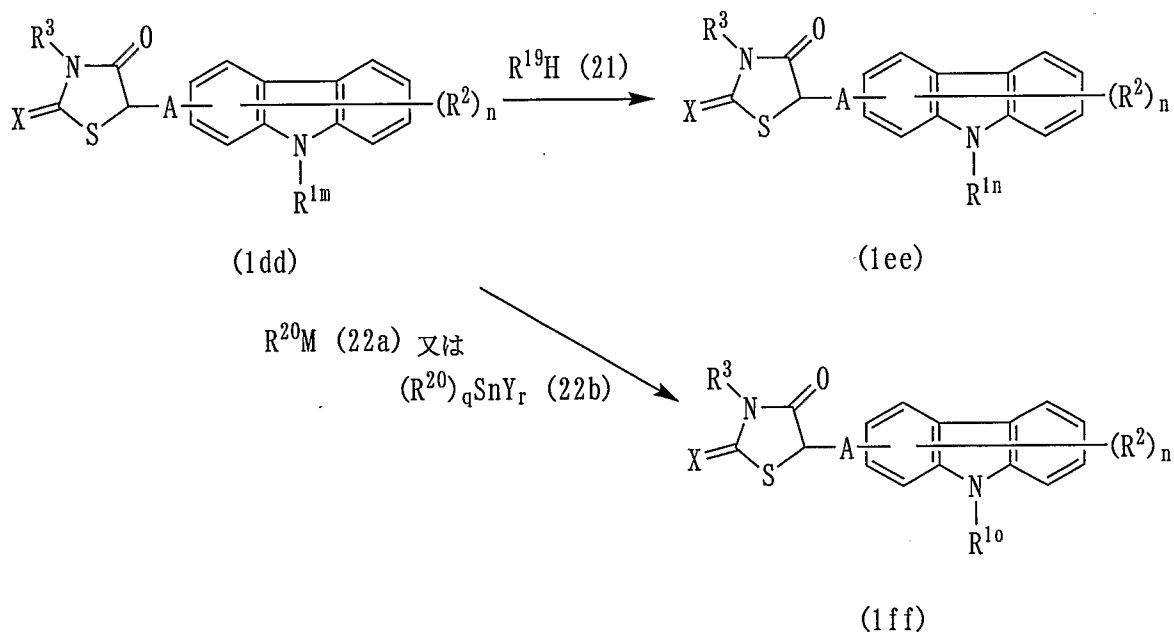
The reaction for producing Compound (1cc) from Compound (1bb) can be carried out by, for example, (1) reducing Compound (1bb) in a suitable solvent using a catalytic hydrogenation reducing agent, or (2) reducing
5 Compound (1bb) in a suitable inert solvent using as a reducing agent a mixture of an acid with a metal or metal salt, a mixture of a metal or metal salt with an alkali metal hydroxide, sulfide, or ammonium salt, or the like.

When using Method (1) above, examples of usable
10 solvents are water, acetic acid, alcohols such as methanol, ethanol and isopropanol, hydrocarbons such as *n*-hexane and cyclohexane, ethers such as dioxane, tetrahydrofuran, diethyl ether and diethylene glycol dimethyl ether, esters such as ethyl acetate and methyl acetate, aprotic polar solvents such
15 as *N,N*-dimethylformamide, mixtures of such solvents, etc. Examples of usable catalytic hydrogenation reducing agents include palladium, palladium black, palladium carbon, platinum carbon, platinum, platinum oxide, copper chromite, Raney nickel, etc. Such reducing agents may be used singly
20 or as a combination of two or more such agents. Reducing agent is usually used in an amount of about 0.02 times to equal to the weight of Compound (1bb). The reaction temperature is usually about -20 to about 150°C, and preferably about 0 to about 100°C. The hydrogen pressure is
25 usually about 1 to 10 atm. The reaction is usually finished in about 0.5 to about 100 hours. An acid such as hydrochloric acid may be introduced into the reaction system of the reaction.

When using Method (2) above, a mixture of iron,
30 zinc, tin, or tin(II) chloride, with a mineral acid such as hydrochloric acid, or sulfuric acid; or a mixture of iron, iron(II) sulfate, zinc, or tin, with an alkali metal hydroxide such as sodium hydroxide, a sulfide such as ammonium sulfide, aqueous ammonia, or an ammonium salt such
35 as ammonium chloride, or the like can be used as a reducing

agent. Examples of inert solvents are water, acetic acid, alcohols such as methanol and ethanol, ethers such as dioxane, mixtures of such solvents, etc. Conditions for the reduction reaction can be suitably selected according to the reducing agent to be used. For example, when a mixture of tin(II) chloride and hydrochloric acid is used as a reducing agent, it is advantageous to carry out the reaction at about 0 to about 150°C for about 0.5 to about 10 hours. Reducing agent is used in an amount of at least 1 mol, and usually about 1 to 5 mol, per mol of Compound (1bb).

Reaction Scheme 8



wherein R^2 , R^3 , X , A , and n are as defined above;

R^{1m} is a group as defined in (1-10) in connection with R^1 above except for having at least one halogen atom on the pyridine ring;

R^{1n} is a group as defined in (1-10) in connection with R^1 above except for having on the pyridine ring at least one member selected from piperidinyl groups; morpholino group; piperazinyl groups optionally substituted on the piperazine ring with one or more members selected from the group consisting of a phenyl group and lower alkyl groups; and

anilino groups optionally substituted on the amino group with one or more lower alkyl groups;

R^{10} is a group as defined in (1-10) in connection with R^1 above except for having at least one member selected from

5 thienyl groups optionally having one or more halogen atoms, phenyl groups optionally having one or more halogen atoms, pyridyl groups and biphenyl groups;

R^{19} is a piperidinyl group; morpholino group; piperazinyl group optionally substituted on the piperazine ring with one or more members selected from the group consisting of a phenyl group and lower alkyl groups; anilino group optionally substituted on the amino group with one or two lower alkyl groups; pyridylamino group; or pyridylcarbonylamino group;

10 R^{20} is a thienyl group optionally having one or more halogen atoms, phenyl group optionally having one or more halogen atoms, pyridyl group, or biphenyl group;

M is an alkali metal such as lithium, potassium, sodium or the like, $-MgX_1$ (X_1 is as defined above), $-ZnX_1$ (X_1 is as defined above), or $-B(OH)_2$;

20 Y is a lower alkyl group;

q is 1 to 4; and

r is 1 to 3, provided that $q + r$ equals 4.

The reaction of Compound (1dd) with Compound (21) is carried out in a suitable solvent in the presence of a basic compound and a catalyst.

25 Examples of solvents and basic compounds usable herein include those that are usable in the reaction of Compound (1e) with Compound (7) shown in Reaction Scheme 3 above.

30 Examples of catalysts are bis(tributyltin)/bis(dibenzylideneacetone)palladium, R-tris(dibenzylideneacetone)dipalladium, S-tris(dibenzylideneacetone)dipalladium, palladium(II) acetate, and other palladium compounds; R-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (R-BINAP), S-2,2'-bis(diphenylphosphino)-

35

1,1'-binaphthyl (*S*-BINAP), *RAC*-2,2'-bis(diphenylphosphino)-
1,1'-binaphthyl (*RAC*-BINAP), 2,2-

bis(diphenylimidazolidinylidene), and other compounds; 4,5-
bis(diphenylphosphino)-9,9-dimethylxanthene, and other

5 xanthene compounds; *tert*-butylphosphine, *tert*-butylphosphine
tetrafluoroborate, and other alkylphosphines; salts thereof;
mixtures thereof; etc.

Basic compound is usually used in an amount of at
least 1 mol, and preferably 1 to 2 mol, per mol of Compound
10 (1dd).

Catalyst is used in a typical catalytic amount
relative to Compound (1dd).

Compound (21) is usually used in an amount of at
least 1 mol, and preferably 1 to 2 mol, per mol of Compound
15 (1dd).

The reaction is usually carried out at about room
temperature to about 200°C, and preferably about room
temperature to about 150°C. The reaction is usually finished
in about 0.5 to about 20 hours.

20 The reaction of Compound (1dd) with Compound (22a)
or (22b) is carried out in a suitable solvent in the presence
of a basic compound and a catalyst.

Solvents usable herein include, in addition to
water, those that are usable in the reaction of Compound (1e)
25 with Compound (7) shown in Reaction Scheme 3 above.

Basic compounds usable herein include those that
are usable in the reaction of Compound (1e) with Compound (7)
shown in Reaction Scheme 3 above.

Examples of catalysts are
30 tetrakis(triphenylphosphine)palladium(0),
dichlorobis(triphenylphosphine)palladium(II), and other
palladium compounds.

Basic compound is usually used in an amount of at
least 1 mol, and preferably 1 to 5 mol, per mol of Compound
35 (1dd)

Catalyst is usually used in an amount of 0.001 to 1 mol, and preferably 0.01 to 0.5 mol, per mol of Compound (1dd).

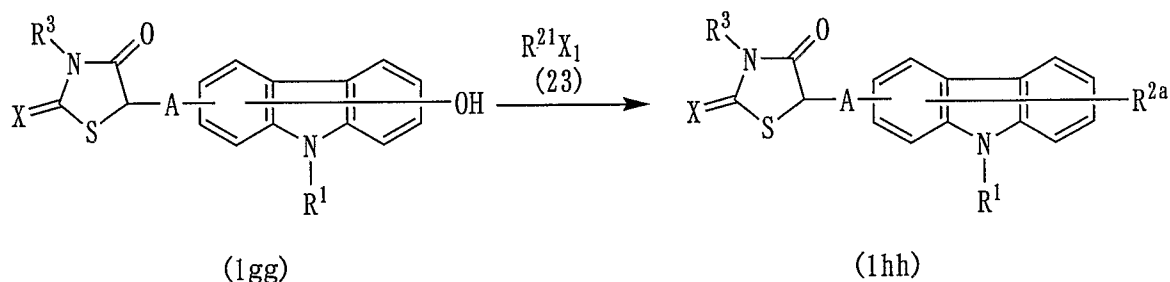
Compound (21) is usually used in an amount of at least 1 mol, and preferably 1 to 5 mol, per mol of Compound (1dd).

The reaction is usually carried out at about -30 to about 200°C, and preferably about 0 to about 150°C. The reaction is usually finished in about 0.5 to about 20 hours.

10 [0160]

With respect to the reaction, when M is an alkali metal salt or MgX_1 , the reaction proceeds in the absence of basic compound and catalyst.

Reaction Scheme 9



15

wherein R^1 , R^3 , X , A , and X_1 are as defined above;

R^{2a} is a group as defined in (2-2), (2-4), and (2-5) in connection with R^2 above; and

R^{21} is a lower alkyl group; carboxy lower alkyl group; or lower alkoxy carbonyl lower alkyl group.

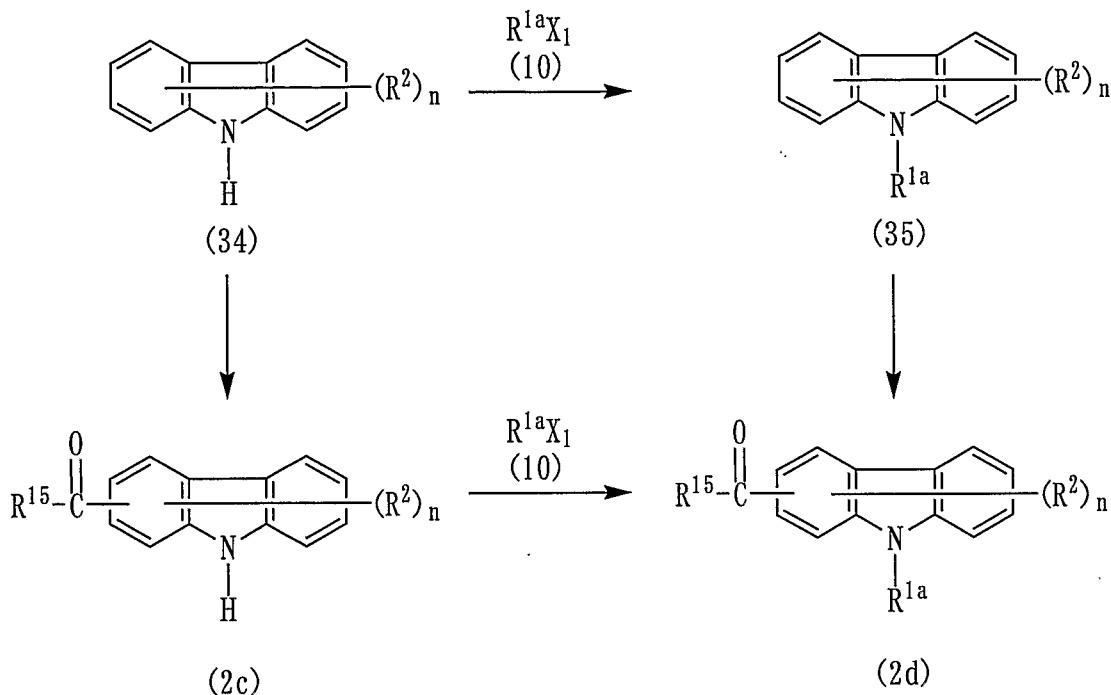
20

The reaction of Compound (1gg) with Compound (23) is carried out under the same conditions as described in connection with the reaction of Compound (1e) with Compound (7) shown in Reaction Scheme 3 above.

25

Compound (2) used as a starting material as shown in the reaction scheme given above can be produced according to, for example, Reaction Scheme 10 below. Other starting materials are either known or easily obtainable by a known method.

Reaction Scheme 10



wherein R^{1a} , R^2 , R^{15} , X_1 , and n are as defined above.

The reaction for producing, from Compound (34),
 5 Compound (2c) wherein R^{15} is a hydrogen atom, and the
 reaction for producing, from Compound (35), Compound (2d)
 wherein R^{15} is a hydrogen atom, are carried out, in a
 suitable solvent in the presence of a catalyst, by separately
 reacting Compound (34) and Compound (35) with a compound
 10 represented by



wherein X_1 is as defined above, X_2 is a halogen atom, and R^{24}
 is a lower alkyl group.

Solvents usable herein include those that are
 15 usable in the reaction of Compound (1dd) with Compound (22)
 shown in Reaction Scheme 8 above.

Examples of catalysts are titanium tetrachloride
 and other titanium compounds; tin(IV) chloride and other tin
 compounds; aluminium chloride and other aluminium compounds;
 20 etc. Catalyst is usually used in an amount of at least 1 mol,
 and preferably 1 to 5 mol, per mol of Compound (34) or (35).

Compound (52) is usually used in an amount of at

least 1 mol, and preferably 1 to 5 mol, per mol of Compound (34) or (35).

The reaction is usually carried out at about 0 to about 70°C, and preferably about 0 to about 50°C. The
5 reaction is usually finished in about 1 minute to about 24 hours.

The reaction for producing, from Compound (34), Compound (2c) wherein R¹⁵ is a hydrogen atom, and the reaction for producing, from Compound (35), Compound (2d)
10 wherein R¹⁵ is a hydrogen atom, can be carried out, in the presence of a halogenating agent and an acid, by separately reacting Compound (34) and Compound (35) with *p*-formaldehyde and then hexamethylenetetramine.

Examples of halogenating agents usable herein are
15 hydrochloric acid, hydrobromic acid, etc. Examples of acids are sulfuric acid, phosphoric acid, and other inorganic acids; *p*-toluenesulfonic acid, formic acid, acetic acid, and other organic acids; and mixtures of such acids. Halogenating agent and acid are usually used in large excess.

20 *p*-Formaldehyde is usually used in an amount at least 0.1 times, and preferably 0.1 times to equal to, Compound (34) or (35).

Hexamethylenetetramine is usually used in an amount of at least 1 mol, and preferably 1 to 5 mol, per mol of
25 compound (34) or (35).

The reaction is usually carried out at about room temperature to about 150°C, and preferably about room temperature to about 100°C. The reaction is usually finished in about 0.5 to about 10 hours.

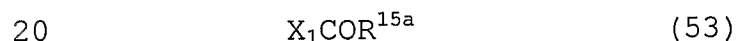
30 The reaction for producing, from Compound (34), Compound (2c) wherein R¹⁵ is a hydrogen atom and the reaction for producing, from Compound (35), Compound (2d) wherein R¹⁵ is a hydrogen atom can be carried out, in a suitable solvent in the presence of an acid, by separately reacting Compound
35 (34) and Compound (35) with hexamethylenetetramine.

These reactions are generally called Duff reactions. Acids usable herein are those that are preferably used in Duff reactions, for example, acetic acid, boric acid/anhydrous glycerol, trifluoroacetic acid, methanesulfonic acid, etc. Acid is usually used in an amount at least equimolar, and preferably equimolar to a large excess, per mol of Compound (34) or (35).

Solvents usable herein include those that are usable in the reaction of Compound (1dd) with Compound (22) shown in Reaction Scheme 8 above.

The reactions are usually carried out at about room temperature to about 200°C, and preferably about room temperature to about 150°C. The reactions are usually finished in about 0.5 to about 10 hours.

Compound (2c) wherein R¹⁵ is a lower alkyl group and Compound (2d) wherein R¹⁵ is a lower alkyl group are produced by separately reacting, in a suitable solvent in the presence of an acid, reacting Compound (34) and Compound (35) with a compound represented by



wherein X₁ is as described above and R^{15a} is a lower alkyl group.

These reactions are generally called Friedel-Crafts reactions and performed in a suitable solvent in the presence of a Lewis acid.

Lewis acids usable herein include any Lewis acids typically used in such Friedel-Crafts reactions, and examples are aluminium chloride, zinc chloride, iron chloride, tin(IV) chloride, boron tribromide, boron trifluoride, concentrated sulfuric acid, etc.

Examples of usable solvents are carbon disulfide, nitrobenzene, chlorobenzene, and other aromatic hydrocarbons; dichloromethane, dichloroethane, carbon tetrachloride, tetrachloroethane, and other halogenated hydrocarbons; nitroethane, nitromethane, and other aliphatic nitro

compounds; mixed solvents of such solvents; etc.

Lewis acid is usually used in an amount of 1 to 6 mol per mol of compounds (34) or (35).

Compound (53) is usually used in an amount of at least 1 mol, and preferably 1 to 5 mol, per mol of Compound (34) or (35).

The reactions are usually carried out at about 0 to about 150°C, and preferably about 0 to about 100°C. The reactions are usually finished in about 0.5 to about 25 hours.

The reaction of Compound (34) with Compound (10) and the reaction of Compound (2c) with Compound (10) are carried out under the same conditions as described in connection with the reaction of Compound (1e) with Compound (7) shown in Reaction Scheme 3 above.

Each of the objective compounds obtained according to the above reaction schemes can be isolated and purified from the reaction mixture by, for example, after cooling the reaction mixture, performing an isolation procedure such as filtration, concentration, extraction, etc., to separate a crude reaction product, and then subjecting the crude reaction product to a usual purification procedure such as column chromatography, recrystallization, etc.

The compound of Formula (1) according to the present invention includes stereoisomers and optical isomers, and solvents such as hydrate, etc.

Among the compounds of the present invention, those having a basic group or groups can easily form salts with common pharmaceutically acceptable acids. Examples of such acids include hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and other inorganic acid, methanesulfonic acid, *p*-toluenesulfonic acid, acetic acid, citric acid, tartric acid, maleic acid, fumaric acid, malic acid, lactic acid and other organic acid, etc.

Among the compounds of the present invention, those having an acidic group or groups can easily form salts by

reacting with pharmaceutically acceptable basic compounds. Examples of such basic compounds include sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, etc.

The following is an explanation of pharmaceutical preparations comprising the compound of the present invention as an active ingredient.

Such pharmaceutical preparations are obtained by formulating the compound of the present invention into usual pharmaceutical preparations, using usually employed diluents or excipients such as fillers, extenders, binders, wetting agents, disintegrants, surfactants, lubricants, etc.

The form of such pharmaceutical preparations can be selected from various forms according to the purpose of therapy. Typical examples include tablets, pills, powders, solutions, suspensions, emulsions, granules, capsules, suppositories, injections (solutions, suspensions, etc.) and the like.

To form tablets, any of various known carriers can be used, including, for example, lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose and other excipients; water, ethanol, propanol, simple syrup, glucose solutions, starch solutions, gelatin solutions, carboxymethylcellulose, shellac, methylcellulose, potassium phosphate, polyvinylpyrrolidone and other binders; dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogencarbonate, calcium carbonate, fatty acid esters of polyoxyethylenesorbitan, sodium laurylsulfate, stearic acid monoglyceride, starch, lactose and other disintegrants; white sugar, stearin, cacao butter, hydrogenated oils and other disintegration inhibitors; quaternary ammonium base, sodium lauryl sulfate and other absorption promoters; glycerin, starch and other wetting agents; starch, lactose, kaolin, bentonite, colloidal silicic

acid and other adsorbents; purified talc, stearates, boric acid powder, polyethylene glycol and other lubricants; etc.

Such tablets may be coated with usual coating materials as required, to prepare, for example, sugar-coated
5 tablets, gelatin-coated tablets, enteric-coated tablets, film-coated tablets, double- or multi-layered tablets, etc.

To form pills, any of various known carriers can be used, including, for example, glucose, lactose, starch, cacao butter, hydrogenated vegetable oils, kaolin, talc and other
10 excipients; gum arabic powder, tragacanth powder, gelatin, ethanol and other binders; laminaran, agar and other disintegrants; etc.

To form suppositories, any of various known carriers can be used, including, for example, polyethylene
15 glycol, cacao butter, higher alcohols, esters of higher alcohols, gelatin, semisynthetic glycerides, etc.

To form an injection, a solution, emulsion or suspension is sterilized and preferably made isotonic with blood. Any of various known widely used diluents can be
20 employed to prepare the solution, emulsion or suspension. Examples of such diluents include water, ethanol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, fatty acid esters of polyoxyethylene sorbitan, etc. In this case, the pharmaceutical preparation
25 may contain sodium chloride, glucose or glycerin in an amount sufficient to prepare an isotonic solution, and may contain usual solubilizers, buffers, analgesic agents, etc., and further, if necessary, coloring agents, preservatives, flavors, sweetening agents, etc., and/or other medicines.

30 The proportion of the compound of the present invention in the pharmaceutical preparation is not limited and can be suitably selected from a wide range. It is usually preferable that the pharmaceutical preparation contain the compound of the present invention in a proportion
35 of 1 to 70 wt.%.

The route of administration of the pharmaceutical preparation according to the present invention is not limited, and the preparation is administered by a route suitable for the form of the preparation, patient's age and sex, conditions of the disease, and other conditions. For example, tablets, pills, solutions, suspensions, emulsions, granules and capsules are administered orally. Injections are intravenously administered singly or as mixed with usual injection transfusions such as glucose solutions, amino acid solutions or the like, or singly administered intramuscularly, intracutaneously, subcutaneously or intraperitoneally, as required. Suppositories are administered intrarectally.

The dosage of the pharmaceutical preparation is suitably selected according to the method of use, patient's age and sex, severity of the disease, and other conditions, and is usually about 0.001 to about 100 mg/kg body weight/day, and preferably 0.001 to 50 mg/kg body weight/day, in single or divided doses.

Since the dosage varies depending on various conditions, a dosage smaller than the above range may be sufficient or a dosage larger than the above range may be required.

The compound of the present invention induces TFF production, such as TFF2 production, and thus is useful as an active ingredient of a TFF inducer (up-regulator), particularly TFF2 inducer.

The compound of the present invention can be used, based on its TFF production inducing activity, as an agent for preventing or treating various diseases, for example, mucosal injury, in human and veterinary medicines. Specific examples of diseases for which preventive or therapeutic effects can be obtained based on TFF production inducing activity, particularly TFF2 production inducing activity, include acute and chronic alimentary tract diseases of various origins (e.g., drug-induced ulcers, peptic gastric

ulcers, ulcerative colitis, Crohn's disease, drug-induced enteritis, ischemic colitis, irritable bowel syndrome, ulcers developed after endoscopic demucosation, acute gastritis, chronic gastritis, reflux esophagitis, esophageal ulcer, Barrett esophagus, gastrointestinal mucositis (such as gastrointestinal mucositis caused by chemotherapy, radiotherapy, etc.), hemorrhoidal diseases, etc.); oral diseases (e.g., stomatitis (such as stomatitis caused by chemotherapy or radiotherapy, aphthous stomatitis, etc.), Sjögren syndrome, xerostomia, etc.); upper respiratory tract diseases (e.g., rhinitis, pharyngitis, etc.); respiratory tract diseases (e.g., bronchial asthma, chronic obstructive lung diseases, etc.); eye diseases (e.g., dry eye, keratoconjunctivitis, etc.); cancers; wounds; etc.

The compound of the present invention has few side effects and is highly safe.

The compounds of formula (1) and salts thereof encompassed by the present invention can be administered in combination with TFF peptides (TFF1, TFF2, TFF3, etc.), other type of compounds having an inducing activity of TFF production, and/or other drugs (such as, anti-inflammatory agents, anti-ulcer drugs, etc).

The patents, patent applications and publications cited herein are incorporated by reference.

25

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 shows a comparison between the nucleotide sequence of the PCR product cloned to the plasmid pCR-Blunt-TFF2pro (Sequence Number 1 in Sequence Listing) and the counterpart of the hTFF2 promoter region reported in a gene bank (GenBank accession AB038162).

Best Mode for Carrying Out the Invention

The following Examples are intended to illustrate

the present invention in further detail.

Reference Example 1

Synthesis of 9-(2,2,2-trifluoroacetyl)-9H-carbazole-3-carbaldehyde

5 To 500 ml of dichloromethane was dissolved 17.1 g
(64 mmol) of 9-(2,2,2-trifluoroacetyl)-9H-carbazole.
Subsequently, 8.7 ml (97 mmol) of dichloromethyl methyl ether
was added to the resultant solution at room temperature, and
the resultant mixture was cooled in an ice-water bath. To
10 the resultant solution was added 22.3 ml (161 mmol) of
titanium tetrachloride dropwise while keeping the temperature
below 10°C (for about one hour). The reaction mixture was
stirred at room temperature overnight and poured into 1.5 l
of iced water, and the insoluble matter was then filtered out
15 to separate the filtrate. An aqueous layer was extracted
with dichloromethane, the combined organic layer was washed
with water twice and with saturated brine once. The washed
organic layer was dried over anhydrous magnesium sulfate
followed by filtration, and then concentrated under reduced
20 pressure. The residue was purified by silica gel column
chromatography (n-hexane : ethyl acetate = 9 : 1), and the
resultant purified material was concentrated to dryness under
reduced pressure, obtaining 10.7 g of white powder 9-(2,2,2-
trifluoroacetyl)-9H-carbazole-3-carbaldehyde (yield: 51%).

25 ¹H-NMR (CDCl₃) δ (ppm): 7.53 (1H, d, J = 7.5 Hz),
7.60-7.64 (1H, m), 8.04 (1H, dd, J = 7.9 Hz, J = 1.2 Hz),
8.08 (1H, dd, J = 7.7 Hz, J = 0.7 Hz), 8.14 (1H, d, J = 8.0
Hz), 8.23 (1H, d, J = 8.7 Hz), 8.80 (1H, s), 10.14 (1H, s).

30 Reference Example 2

Synthesis of tert-butyl 3-formylcarbazole-9-carboxylate

A tetrahydrofuran (THF) solution containing 0.20 g
(1.0 mmol) of 9H-carbazole-3-carbaldehyde and 25 mg (0.2
mmol) of 4-dimethylaminopyridine was cooled with ice. After
35 adding 0.47 ml (3.3 mmol) of triethylamine and 0.52 ml (2.2

mmol) of di-tert-butylidicarbonate, the resultant mixture was stirred at room temperature overnight. The resultant reaction mixture was concentrated under reduced pressure and the residue thereof was dissolved in ethyl acetate. The resultant solution was then washed with water and saturated brine. The thus-obtained solution was dried over anhydrous magnesium sulfate followed by filtration, and then concentrated to dryness under reduced pressure, giving 0.33 g (quantitative yield) of pale yellow powder tert-butyl 3-formylcarbazole-9-carboxylate.

$^1\text{H-NMR}$ (CDCl_3) δ (ppm): 1.78 (9H, s), 7.41 (1H, t, $J = 7.5$ Hz), 7.53 (1H, t, $J = 7.8$ Hz), 7.98-8.00 (1H, m), 8.05 (1H, dd, $J = 7.6$ Hz, $J = 0.4$ Hz), 8.29 (1H, d, $J = 8.4$ Hz), 8.46 (1H, d, $J = 8.6$ Hz), 8.49 (1H, t, $J = 0.7$ Hz), 10.12 (1H, s).

Reference Example 3

Synthesis of 9-cyclohexylmethyl-9H-carbazole-3-carbaldehyde

Sodium hydride (60% in oil, 0.44 g, 11 mmol) was washed with n-hexane, and then suspended in 5 ml of dimethylformamide (DMF). A DMF solution (5 ml) containing 1.95 g (10 mmol) of 9H-carbazole-3-carbaldehyde was added to the suspension while cooling with ice, and the resultant mixture was stirred at room temperature for one hour. The thus-obtained suspension was cooled with ice again, after adding 1.54 ml (11 mmol) of cyclohexylmethylbromide thereto, the mixture was stirred at room temperature overnight. Water was added to the reaction mixture and extraction was conducted with ethyl acetate. The thus-obtained organic layer was washed with water and saturated brine. The washed organic layer was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 4 : 1). Subsequently, the purified material was then concentrated to dryness under reduced pressure, giving 2.21 g (yield: 76%) of pale yellow

powder 9-cyclohexylmethyl-9H-carbazole-3-carbaldehyde.
Melting point: 128.8°C

Reference Example 4

5 Synthesis of ethyl 9-(4-bromobenzyl)-1-methyl-9H-carbazole-3-carboxylate

To a DMF solution containing 0.55 g (2.2 mmol) of ethyl 1-methyl-9H-carbazole-3-carboxylate was added 96 mg (2.4 mmol) of sodium hydride (60% in oil) while cooling with ice, followed by stirring at room temperature for 30 minutes. The thus-obtained reactant was cooled with ice again, 0.60 g (2.4 mmol) of 4-bromobenzylbromide was added thereto and stirred at room temperature for 30 minutes. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The thus-obtained organic layer was washed with water and dried over anhydrous magnesium sulfate. The resultant dry substance was subjected to filtration and concentrated under reduced pressure. Subsequently, the residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 10 : 1 to 6 : 1) and the resultant purified material was concentrated to dryness under reduced pressure, giving 0.93 g (quantitative yield) of white powder ethyl 9-(4-bromobenzyl)-1-methyl-9H-carbazole-3-carboxylate.

¹H-NMR (CDCl₃) δppm : 1.45 (3H, t, J = 7.1 Hz), 4.43 (2H, q, J = 7.1 Hz), 5.74 (2H, s), 6.86 (2H, d, J = 8.5 Hz), 7.21-7.50 (5H, m), 7.88 (1H, d, J = 1.4 Hz), 8.16 (1H, d, J = 7.7 Hz), 8.72 (1H, d, J = 1.4 Hz).

Reference Example 5

30 Synthesis of [9-(4-bromobenzyl)-1-methyl-9H-carbazol-3-yl]methanol

A THF solution containing 0.60 g (1.42 mmol) of ethyl 9-(4-bromobenzyl)-1-methyl-9H-carbazole-3-carboxylate was cooled with ice, 108 mg (2.84 mmol) of lithium aluminum hydride was added thereto, and the resultant mixture was then

stirred at room temperature for one hour. A sodium sulfate decahydrate was added to the thus-obtained reactant, followed by stirring for one hour. After filtering out insoluble matter, the filtrate was concentrated to dryness under reduced pressure, giving white powder [9-(4-bromobenzyl)-1-methyl-9H-carbazol-3-yl]methanol (quantitative yield).

$^1\text{H-NMR}$ (CDCl_3) δppm : 2.62 (3H, s), 4.82 (2H, s), 5.71 (2H, s), 6.86 (2H, d, $J = 8.5$ Hz), 7.20-7.50 (5H, m), 8.04 (1H, s), 8.10 (1H, $J = 8.3$ Hz).

10

Reference Example 6

Synthesis of 9-(4-bromobenzyl)-1-methyl-9H-carbazole-3-carbaldehyde

To a dimethyl sulfoxide (DMSO) solution (3 ml) containing 0.50 g (1.31 mmol) of [9-(4-bromobenzyl)-1-methyl-9H-carbazol-3-yl]methanol was added 0.37 g (2.05 mmol) of o-iodoxybenzoic acid, followed by stirring at room temperature for two hours. After adding water and ethyl acetate, the insoluble matter was filtered out from the reaction solution and the filtrate was separated therefrom. The resultant organic layer was washed with water and dried over anhydrous magnesium sulfate followed by concentration to dryness under reduced pressure, giving 0.38 g (yield: 76%) of white powder 9-(4-bromobenzyl)-1-methyl-9H-carbazole-3-carbaldehyde.

$^1\text{H-NMR}$ (CDCl_3) δppm : 2.69 (3H, s), 5.76 (2H, s), 6.88 (2H, d, $J = 8.4$ Hz), 7.25-7.52 (5H, m), 7.72 (1H, s), 8.17 (1H, d, $J = 7.7$ Hz), 8.51 (1H, s), 10.07 (1H, s).

Reference Example 7

Synthesis of methyl 4-o-tolylamino benzoate

To 150 ml of toluene were added 12.5 g (82.7 mmol) of methyl 4-aminobenzoate, 15.6 g (91.0 mmol) of 2-bromotoluene, 1.03 g (1.65 mmol) of RAC-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (RAC-BINAP), 0.37 g (1.65 mmol) of palladium (II) acetate, and 53.9 g (165 mmol)

of cesium carbonate. After stirring the mixture at 100°C for 4 hours and cooling it to room temperature, insoluble matter was filtered out therefrom. The filtrate was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Subsequently, the residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 10 : 1 to 5 : 1). The thus-obtained purified material was concentrated under reduced pressure, giving 0.93 g (yield: 99%) of methyl 4-o-tolylamino benzoate in a form of pale yellow oily matter.

¹H-NMR (CDCl₃) δppm : 2.25 (3H, s), 3.88 (3H, s), 5.69 (1H, bs), 6.79 (2H, d, J = 8.5 Hz), 7.09 (1H, dd, J = 7.4 Hz, J = 1.3 Hz), 7.15-7.30 (3H, m), 7.89 (2H, d, J = 8.5 Hz).

15

Reference Example 8

Synthesis of methyl 8-methyl-9H-carbazole-3-carboxylate

To an acetic acid solution (40 ml) containing 4.0 g (16.6 mmol) of methyl 4-o-tolylamino benzoate was added 4.84 g (21.6 mmol) of palladium (II) acetate, followed by stirring at 100°C for two hours. The thus-obtained reactant was cooled to room temperature and concentrated under reduced pressure. Subsequently, the residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 8 : 1 to 5 : 1). The resultant purified material was concentrated to dryness under reduced pressure, giving 0.92 g (yield: 23%) of white powder methyl 8-methyl-9H-carbazole-3-carboxylate.

¹H-NMR (DMSO-d₆) δppm : 2.57 (3H, s), 3.89 (3H, s), 7.14 (1H, dd, J = 7.4 Hz, J = 7.2 Hz), 7.26 (1H, d, J = 7.2 Hz), 7.57 (1H, d, J = 8.5 Hz), 8.02 (1H, dd, J = 8.5 Hz, J = 1.7 Hz), 8.07 (1H, d, J = 7.4 Hz), 8.77 (1H, d, J = 1.7 Hz), 11.6 (1H, bs).

Reference Example 9

Synthesis of methyl 9-(4-bromobenzyl)-8-methyl-9H-carbazole-

35

3-carboxylate

Using methyl 8-methyl-9H-carbazole-3-carboxylate and 4-bromobenzylbromide as starting compounds, methyl 9-(4-bromobenzyl)-8-methyl-9H-carbazole-3-carboxylate was

5 synthesized in the same manner as in Reference Example 3.

$^1\text{H-NMR}$ (CDCl_3) δppm : 2.62 (3H, s), 3.97 (3H, s), 5.73 (2H, s), 6.86 (2H, d, $J = 8.4$ Hz), 7.19-7.25 (2H, m), 7.39 (2H, d, $J = 8.4$ Hz), 8.03-8.12 (2H, m), 8.83 (1H, d, $J = 1.4$ Hz).

10

Reference Example 10

Synthesis of [9-(4-bromobenzyl)-8-methyl-9H-carbazol-3-yl]methanol

Using methyl 9-(4-bromobenzyl)-8-methyl-9H-carbazole-3-carboxylate as a starting compound, [9-(4-bromobenzyl)-8-methyl-9H-carbazol-3-yl]methanol was

15 synthesized in the same manner as in Reference Example 5.

$^1\text{H-NMR}$ (CDCl_3) δppm : 2.64 (3H, s), 4.85 (2H, s), 5.72 (2H, s), 6.87 (2H, d, $J = 8.5$ Hz), 7.19-7.30 (3H, m), 7.35-7.43 (3H, m), 7.95 (1H, dd, $J = 1.5$ Hz, $J = 8.6$ Hz), 7.96-8.00 (1H, m), 8.06 (1H, d, $J = 1.2$ Hz).

20

Reference Example 11

Synthesis of 9-(4-bromobenzyl)-8-methyl-9H-carbazole-3-carbaldehyde

25

Using [9-(4-bromobenzyl)-8-methyl-9H-carbazol-3-yl]methanol as a starting compound, 9-(4-bromobenzyl)-8-methyl-9H-carbazole-3-carbaldehyde was synthesized in the same manner as in Reference Example 6.

$^1\text{H-NMR}$ (CDCl_3) δppm : 2.64 (3H, s), 5.76 (2H, s), 6.88 (2H, d, $J = 8.5$ Hz), 7.19-7.30 (3H, m), 7.33 (1H, d, $J = 8.6$ Hz), 7.35-7.43 (2H, m), 7.95 (1H, dd, $J = 1.5$ Hz, $J = 8.6$ Hz), 8.03-8.11 (1H, m), 8.63 (1H, d, $J = 1.2$ Hz), 10.10 (1H, s).

30

35

Reference Example 12

Synthesis of 9-(6-chloropyridin-3-ylmethyl)-9H-carbazole-3-carbaldehyde

Using 9H-carbazole-3-carbaldehyde and 6-chloropyridin-3-ylmethylchloride as starting compounds, 9-(6-chloropyridin-3-ylmethyl)-9H-carbazole-3-carbaldehyde was synthesized in the same manner as in Reference Example 3.

$^1\text{H-NMR}$ (CDCl_3) δppm : 5.56 (2H, s), 7.20 (1H, d, $J = 8.2$ Hz), 7.26-7.29 (1H, m), 7.35-7.39 (2H, m), 7.43 (1H, d, $J = 8.5$ Hz), 7.51-7.54 (1H, m), 8.01 (1H, dd, $J_1 = 1.5$ Hz, $J_2 = 8.5$ Hz), 8.20 (1H, d, $J = 8.5$ Hz), 8.38 (1H, d, $J = 2.2$ Hz), 8.66 (1H, d, $J = 1.5$ Hz), 10.12 (1H, s).

Reference Example 13

Synthesis of [9-(6-chloropyridin-3-ylmethyl)-8-methyl-9H-carbazol-3-yl]methanol

1.0 g (3.12 mmol) of 9-(6-chloropyridin-3-ylmethyl)-9H-carbazole-3-carbaldehyde was dissolved in 20 ml of THF and 2 ml of water, and 59 mg (1.56 mmol) of sodium borohydride and 4 ml of water were added to the thus-obtained solution while cooling with ice, followed by stirring at room temperature for one hour. Acetic acid (0.36 ml) was added to the thus-obtained reactant while cooling with ice and then stirred for 15 minutes. A saturated aqueous solution of sodium hydrogencarbonate and ethyl acetate were added to the thus-obtained reactant, and then separated. The obtained organic layer was washed with saturated brine and then dried over anhydrous sodium sulfate. The dried organic layer was subjected to filtration and concentrated under reduced pressure, giving 1.08 g of pale yellow amorphous solid [9-(6-chloropyridin-3-ylmethyl)-8-methyl-9H-carbazol-3-yl]methanol.

$^1\text{H-NMR}$ (CDCl_3) δppm : 4.87 (2H, s), 5.51 (2H, s), 7.15 (1H, d, $J = 8.3$ Hz), 7.20-7.40 (4H, m), 7.45-7.55 (2H, m), 8.10 - 8.20 (2H, m), 8.30-8.40 (1H, m).

Reference Example 14

Synthesis of 9-(6-chloropyridin-3-ylmethyl)-3-(tetrahydropyran-2-yloxymethyl)-9H-carbazole

To 20 ml of dichloromethane were added 1.08 g (3.12 mmol) of [9-(6-chloropyridin-3-ylmethyl)-8-methyl-9H-carbazol-3-yl]methanol, 0.157 g (0.62 mmol) of pyridinium p-toluenesulfonate and 0.34 ml (3.7 mmol) of 3,4-dihydro-2H-pyran. After stirring at room temperature overnight, the reaction mixture was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated brine, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 5 : 1). The purified material was concentrated under reduced pressure, giving 1.18 g (yield: 93%) of 9-(6-chloropyridin-3-ylmethyl)-3-(tetrahydropyran-2-yloxymethyl)-9H-carbazole as yellow oily matter.

$^1\text{H-NMR}$ (CDCl_3) δppm : 1.50-2.00 (6H, m), 3.55-3.65 (1H, m), 3.95-4.10 (1H, m), 4.47 (1H, d, $J = 11.5$ Hz), 4.75-4.85 (1H, m), 4.96 (1H, d, $J = 11.5$ Hz), 5.50 (2H, s), 7.05-7.55 (7H, m), 8.05-8.20 (2H, m), 8.37 (1H, d, $J = 7.4$ Hz).

Reference Example 15

Synthesis of 9-(3,4,5,6-tetrahydro-2H-[1,2']bipyridin-5'-ylmethyl)-3-(tetrahydropyran-2-yloxymethyl)-9H-carbazole

To 11 ml of toluene were added 0.55 g (1.35 mmol) of 9-(6-chloropyridin-3-ylmethyl)-3-(tetrahydropyran-2-yloxymethyl)-9H-carbazole, 0.20 ml (2.03 mmol) of piperidine, 15.2 mg (0.068 mmol) of palladium (II) acetate, 23.6 mg (0.081 mmol) of tri-tert-butylphosphonium tetrafluoroborate and 0.20 g (2.1 mmol) of sodium t-butoxide. After stirring at 100°C for three hours, the resultant reactant was cooled to room temperature, and then insoluble matter was filtered out therefrom. The filtered solid material was washed with ethyl acetate. The resultant liquid was combined with the filtrate and concentrated under reduced pressure. The residue

was purified by silica gel column chromatography (n-hexane : ethyl acetate = 2.5 : 1). The purified material was concentrated under reduced pressure, giving 0.32 g (yield: 52%) of 9-(3,4,5,6-tetrahydro-2H-[1,2']bipyridin-5'-ylmethyl)-3-(tetrahydropyran-2-yloxymethyl)-9H-carbazole in the form of yellow oily matter.

¹H-NMR (CDCl₃) δppm : 1.40-1.95 (12H, m), 3.30-3.65 (5H, m), 3.95-4.10 (1H, m), 4.67 (1H, d, J = 11.4 Hz), 4.75-4.85 (1H, m), 4.95 (1H, d, J = 11.4 Hz), 5.36 (2H, s), 6.47 (1H, d, J = 9.9 Hz), 7.10-7.60 (6H, m), 8.05-8.20 (3H, m).

Reference Example 16

Synthesis of 9-(3,4,5,6-tetrahydro-2H-[1,2']bipyridin-5'-ylmethyl)-9H-carbazole-3-carbaldehyde

To an ethanol solution (6 ml) containing 0.32 g (0.72 mmol) of 9-(3,4,5,6-tetrahydro-2H-[1,2']bipyridin-5'-ylmethyl)-3-(tetrahydropyran-2-yloxymethyl)-9H-carbazole were added 134 mg (0.70 mmol) of p-toluenesulfonic acid monohydrate and 5 ml of water. The mixture was stirred at 60°C for 2.5 hours, and refluxed under heating for one hour. The thus-obtained reactant was cooled to room temperature and then neutralized by adding sodium hydrogencarbonate. Subsequently, the resultant neutralized substance was concentrated under reduced pressure. The residue was extracted with ethyl acetate and washed with water and saturated brine, followed by concentration under reduced pressure. The residue was then purified by silica gel column chromatography (n-hexane : ethyl acetate = 4 : 1 to 2 : 1). The purified material was concentrated under reduced pressure, and the resultant residue was dissolved in 4 ml of DMSO. To the thus-obtained solution was added 122 mg (0.44 mmol) of o-iodoxybenzoic acid, followed by stirring at room temperature for 13 hours. Water and ethyl acetate were added to the thus-obtained reaction mixture and then separated. Subsequently, the resultant organic layer was washed with

water (twice) and saturated brine (once), dried over anhydrous sodium sulfate, and then concentrated under reduced pressure, giving 125 mg (yield: 48%) of 9-(3,4,5,6-tetrahydro-2H-[1,2']bipyridin-5'-ylmethyl)-9H-carbazole-3-carbaldehyde in the form of yellow oily matter.

$^1\text{H-NMR}$ (CDCl_3) δppm : 1.50-1.70 (5H, m), 3.40-3.55 (4H, m), 5.43 (2H, s), 6.49 (1H, d, $J = 9.0$ Hz), 7.15-7.25 (1H, m), 7.30-7.40 (1H, m), 7.45-7.55 (3H, m), 7.95-8.05 (1H, m), 8.15-8.25 (2H, m), 9.07 (1H, s), 10.10 (1H, s).

10

Reference Example 17

Synthesis of 9-(6-thiophen-3-ylpyridin-3-ylmethyl)-9H-carbazole-3-carbaldehyde

To 24 ml of dimethoxyethane were added 1.2 g (3.7 mmol) of 9-(6-chloropyridin-3-ylmethyl)-9H-carbazole-3-carbaldehyde and 0.43 g (0.37 mmol) of tetrakis(triphenylphosphine)palladium. The mixture was stirred under an argon atmosphere at room temperature for 5 minutes. After adding 0.62 g (4.9 mmol) of 3-thiophene boron acid and 7.5 ml of 2M-aqueous sodium carbonate solution, the mixture was refluxed under heating in an argon atmosphere for 4 hours, and then cooled to room temperature. After adding ethyl acetate to the reaction mixture, the resultant mixture was washed with water twice and saturated brine once, and dried over anhydrous sodium sulfate. The thus-obtained dry substance was subjected to filtration and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 2 : 1) and then concentrated to dryness under reduced pressure, giving 1.26 g (yield: 91%) of yellow powder 9-(6-thiophen-3-ylpyridin-3-ylmethyl)-9H-carbazole-3-carbaldehyde.

$^1\text{H-NMR}$ (CDCl_3) δppm : 5.82 (2H, s), 7.35 (1H, t, $J = 7.6$ Hz), 7.54-7.57 (2H, m), 7.60 (1H, dd, $J_1 = 2.9$ Hz, $J_2 = 5.1$ Hz), 7.66 (1H, dd, $J_1 = 1.1$ Hz, $J_2 = 5.1$ Hz), 7.75 (1H, d, $J = 8.2$ Hz), 7.83 (1H, d, $J = 8.2$ Hz), 7.95 (1H, d, $J = 8.6$

35

Hz), 8.02 (1H, dd, $J_1 = 1.5$ Hz, $J_2 = 8.6$ Hz), 8.09 (1H, dd, $J_1 = 1.1$ Hz, $J_2 = 2.9$ Hz), 8.34 (1H, d, $J = 7.6$ Hz), 8.56 (1H, d, $J = 1.5$ Hz), 8.81 (1H, s), 10.08 (1H, s).

5 Reference Example 18

Synthesis of methyl 9-(4-bromobenzyl)-8-methoxy-9H-carbazole-3-carboxylate

Using methyl 8-methoxy-9H-carbazole-3-carboxylate and 4-bromobenzylbromide as starting compounds, methyl 9-(4-bromobenzyl)-8-methoxy-9H-carbazole-3-carboxylate was synthesized in the same manner as in Reference Example 3.

$^1\text{H-NMR}$ (CDCl_3) δppm : 3.88 (3H, s), 3.96 (3H, s), 5.83 (2H, s), 6.94-7.00 (3H, m), 7.18-7.38 (4H, m), 7.77 (1H, dd, $J = 7.8$ Hz, $J = 0.6$ Hz), 8.10 (1H, dd, $J = 8.7$ Hz, $J = 1.6$ Hz), 8.81 (1H, d, $J = 1.5$ Hz).

 Reference Example 19

Synthesis of [9-(4-bromobenzyl)-8-methoxy-9H-carbazol-3-yl]methanol

20 Using methyl 9-(4-bromobenzyl)-8-methoxy-9H-carbazole-3-carboxylate as a starting compound, [9-(4-bromobenzyl)-8-methoxy-9H-carbazol-3-yl]methanol was synthesized in the same manner as in Reference Example 5.

$^1\text{H-NMR}$ (CDCl_3) δppm : 3.88 (3H, s), 4.84 (2H, s), 5.81 (2H, s), 6.91-6.99 (3H, m), 7.13-7.41 (5H, m), 7.72 (1H, dd, $J = 7.8$ Hz, $J = 0.7$ Hz), 8.08 (1H, d, $J = 0.8$ Hz).

 Reference Example 20

Synthesis of 9-(4-bromobenzyl)-8-methoxy-9H-carbazole-3-carbaldehyde

30 Using [9-(4-bromobenzyl)-8-methoxy-9H-carbazol-3-yl]methanol as a starting compound, 9-(4-bromobenzyl)-8-methoxy-9H-carbazol-3-carbaldehyde was synthesized in the same manner as in Reference Example 6.

35 $^1\text{H NMR}$ (CDCl_3) δppm : 3.90 (3H, s), 5.85 (2H, s),

6.94-7.02 (3H, m), 7.20-7.30 (1H, m), 7.35-7.40 (3H, m), 7.78 (1H, dd, $J = 0.9$ Hz, $J = 7.9$ Hz), 7.95 (1H, dd, $J = 1.6$ Hz, $J = 8.6$ Hz), 8.56-8.62 (1H, m), 10.08 (1H, s).

5 Reference Example 21

Synthesis of ethyl 3-methyl-4-o-tolylamino benzoate

Using ethyl 4-amino-3-methyl-benzoate and 2-bromotoluene as starting compounds, ethyl 3-methyl-4-o-tolylamino benzoate was synthesized in the same manner as in
10 Reference Example 7.

$^1\text{H-NMR}$ (CDCl_3) δppm : 1.36 (3H, t, $J = 7.1$ Hz), 2.23 (3H, s), 2.31 (3H, s), 4.32 (2H, q, $J = 7.1$ Hz), 5.47 (1H, bs), 6.73 (1H, d, $J = 8.5$ Hz), 7.05-7.11 (1H, m), 7.19-7.28 (3H, m), 7.74 (1H, dd, $J = 8.5$ Hz, $J = 2.0$ Hz), 7.85 (1H, d,
15 $J = 1.4$ Hz).

Reference Example 22

Synthesis of ethyl 1,8-dimethyl-9H-carbazol-3-carboxylate

Using ethyl 3-methyl-4-o-tolylamino benzoate as a
20 starting compound, ethyl 1,8-dimethyl-9H-carbazole-3-carboxylate was synthesized in the same manner as in Reference Example 8.

$^1\text{H-NMR}$ (CDCl_3) δppm : 1.45 (3H, t, $J = 7.1$ Hz), 2.60 (3H, s), 2.61 (3H, s), 4.43 (2H, q, $J = 7.1$ Hz), 7.17-7.28
25 (2H, m), 7.94-8.01 (2H, m), 8.66 (1H, t, $J = 0.7$ Hz).

Reference Example 23

Synthesis of ethyl 9-(4-bromobenzyl)-1,8-dimethyl-9H-carbazole-3-carboxylate

30 Using ethyl 1,8-dimethyl-9H-carbazole-3-carboxylate and 4-bromobenzylbromide as starting compounds, ethyl 9-(4-bromobenzyl)-1,8-dimethyl-9H-carbazole-3-carboxylate was synthesized in the same manner as in Reference Example 3.

$^1\text{H-NMR}$ (CDCl_3) δppm : 1.44 (3H, t, $J = 7.1$ Hz), 2.57
35 (3H, s), 2.60 (3H, s), 4.42 (2H, q, $J = 7.1$ Hz), 5.94 (1H,

bs), 6.83 (2H, d, $J = 8.5$ Hz), 7.17-7.22 (2H, m), 7.40 (2H, d, $J = 8.5$ Hz), 7.84 (1H, d, $J = 0.7$ Hz), 8.04 (1H, dd, $J = 7.1$ Hz, $J = 1.8$ Hz), 8.68 (1H, d, $J = 1.4$ Hz).

5 Reference Example 24

Synthesis of [9-(4-bromobenzyl)-1,8-dimethyl-9H-carbazol-3-yl]methanol

Using ethyl 9-(4-bromobenzyl)-1,8-dimethyl-9H-carbazole-3-carboxylate as a starting compound, [9-(4-bromobenzyl)-1,8-dimethyl-9H-carbazol-3-yl]methanol was synthesized in the same manner as in Reference Example 5.

^1H -NMR (CDCl_3) δppm : 1.63 (1H, t, $J = 5.8$ Hz), 2.57 (6H, s), 4.81 (2H, d, $J = 5.8$ Hz), 5.93 (2H, s), 6.85 (2H, d, $J = 8.4$ Hz), 7.13-7.15 (3H, m), 7.39 (2H, d, $J = 8.4$ Hz), 7.97 (1H, s).

Reference Example 25

Synthesis of 9-(4-bromobenzyl)-1,8-dimethyl-9H-carbazole-3-carbaldehyde

Using [9-(4-bromobenzyl)-1,8-dimethyl-9H-carbazol-3-yl]methanol as a starting compound, 9-(4-bromobenzyl)-1,8-dimethyl-9H-carbazole-3-carbaldehyde was synthesized in the same manner as in Reference Example 6.

^1H NMR (CDCl_3) δppm : 2.58 (3H, s), 2.63 (3H, s), 5.97 (2H, s), 6.80-6.90 (2H, m), 7.15-7.30 (2H, m), 7.37-7.47 (2H, m), 7.68 (1H, s), 7.99-8.08 (1H, m), 8.48 (1H, d, $J = 1.4$ Hz), 10.06 (1H, s).

Reference Example 26

30 Synthesis of methyl 3-methoxy-4-o-tolylamino benzoate

Using methyl 4-amino-3-methoxy-benzoate and 2-bromotoluene as starting compounds, methyl 3-methoxy-4-o-tolylamino benzoate was synthesized in the same manner as in Reference Example 7.

35 ^1H -NMR (CDCl_3) δppm : 3.89 (6H, s), 3.95 (3H, s),

6.81-7.01 (3H, m), 7.28 (1H, d, $J = 8.4$ Hz), 7.44 (1H, d, $J = 7.7$ Hz), 7.53 (1H, d, $J = 1.7$ Hz), 7.60 (1H, dd, $J = 8.4$ Hz, $J = 1.7$ Hz).

5 Reference Example 27

Synthesis of methyl 1,8-dimethoxy-9H-carbazole-3-carboxylate

Using methyl 3-methoxy-4-o-tolylamino benzoate as a starting compound, methyl 1,8-dimethoxy-9H-carbazole-3-carboxylate was synthesized in the same manner as in
10 Reference Example 8.

$^1\text{H-NMR}$ (CDCl_3) δppm : 3.97 (3H, s), 4.01 (3H, s), 4.05 (3H, s), 6.92 (1H, d, $J = 7.4$ Hz), 7.20 (1H, t, $J = 7.9$ Hz), 7.57 (1H, d, $J = 1.2$ Hz), 7.68 (1H, d, $J = 7.9$ Hz), 8.45 (1H, d, $J = 1.2$ Hz), 8.67 (1H, bs).

15

Reference Example 28

Synthesis of methyl 9-(4-bromobenzyl)-1,8-dimethoxy-9H-carbazole-3-carboxylate

Using methyl 1,8-dimethoxy-9H-carbazole-3-carboxylate and 4-bromobenzylbromide as starting compounds,
20 methyl 9-(4-bromobenzyl)-1,8-dimethoxy-9H-carbazole-3-carboxylate was prepared in the same manner as in Reference Example 3.

$^1\text{H-NMR}$ (CDCl_3) δppm : 3.86 (3H, s), 3.92 (3H, s),
25 3.96 (3H, s), 6.16 (2H, s), 6.91 (2H, d, $J = 8.5$ Hz), 7.19 (1H, t, $J = 7.8$ Hz), 7.30 (2H, d, $J = 8.5$ Hz), 7.56 (1H, d, $J = 1.3$ Hz), 7.72 (1H, dd, $J = 7.8$ Hz, $J = 0.6$ Hz), 8.44 (1H, d, $J = 1.4$ Hz).

30 Reference Example 29

Synthesis of [9-(4-bromobenzyl)-1,8-dimethoxy-9H-carbazol-3-yl]methanol

Synthesis was conducted in the same manner as in Reference Example 5 using methyl 9-(4-bromobenzyl)-1,8-dimethoxy-9H-carbazole-3-carboxylate as a starting compound.
35

^1H -NMR (CDCl_3) δ ppm : 1.65 (1H, t, $J = 5.9$ Hz), 3.86 (3H, s), 3.88 (3H, s), 4.81 (2H, d, $J = 5.9$ Hz), 6.13 (2H, s), 6.86-6.93 (4H, m), 7.13 (1H, t, $J = 7.9$ Hz), 7.28 (2H, d, $J = 8.4$ Hz), 7.63-7.67 (2H, m).

5

Reference Example 30

Synthesis of 9-(4-bromobenzyl)-1,8-dimethoxy-9H-carbazole-3-carbaldehyde

Using [9-(4-bromobenzyl)-1,8-dimethoxy-9H-carbazol-
10 3-yl]methanol as a starting compound, 9-(4-bromobenzyl)-1,8-dimethoxy-9H-carbazole-3-carbaldehyde was synthesized in the same manner as in Reference Example 6.

^1H NMR (CDCl_3) δ ppm : 3.87 (3H, s), 3.94 (3H, s), 6.19 (2H, s), 6.87-6.96 (3H, m), 7.18-7.26 (1H, m), 7.43 (1H, d, $J = 1.2$ Hz), 7.72 (1H, dd, $J = 0.8$ Hz, $J = 7.8$ Hz), 8.18 (1H, d, $J = 1.3$ Hz), 10.03 (1H, s).

15

Reference Example 31

Synthesis of 9-(4-methanesulfonylbenzyl)-9H-carbazole-3-carbaldehyde and 9-(4-methanesulfinylbenzyl)-9H-carbazole-3-carbaldehyde
20

A dichloromethane solution (20 ml) containing 0.9 g (2.9 mmol) of 9-(4-methylsulfanylbenzyl)-9H-carbazole-3-carbaldehyde was cooled with ice, 1.25 g (7.2 mmol) of m-chloroperbenzoic acid was added thereto, and the resultant
25 mixture was stirred while cooling with ice for 30 minutes. After adding a saturated aqueous solution of sodium hydrogencarbonate, the thus-obtained reaction mixture was stirred, and then separated. The obtained dichloromethane
30 layer was washed with water and saturated brine, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 1 : 1). The purified material was concentrated to dryness, giving 1.13 g (yield: 62%) of white
35 powder 9-(4-methanesulfonyl benzyl)-9H-carbazole-3-

carbaldehyde.

Melting point: 204.2°C

The silica gel column was subjected to extraction with a solution containing dichloromethane and methanol in the ratio of dichloromethane : methanol = 5 : 1, and the obtained purified material was then concentrated to dryness, giving 0.53 g (yield: 31%) of white powder 9-(4-methanesulfinylbenzyl)-9H-carbazole-3-carbaldehyde.

Melting point: 177°C

10

Reference Example 32

Synthesis of 9-(4-ethylbenzenesulfonyl)-9H-carbazole-3-carbaldehyde

Sodium hydride (60% in oil, 49 mg, 1.2 mmol) was suspended in 5 ml of THF. After adding 0.20 g (1.0 mmol) of 9H-carbazole-3-carbaldehyde to the thus-obtained suspension, the mixture was stirred at room temperature for 20 minutes. Subsequently, 0.18 ml (1.1 mmol) of 4-ethylbenzenesulfonylchloride was added, and the thus-obtained mixture was stirred at room temperature for 3 hours. Water was added to the resultant reaction mixture, and then extraction with dichloromethane was conducted. The thus-obtained dichloromethane layer was washed with water and saturated brine, and then dried over anhydrous magnesium sulfate. The resultant dry substance was subjected to filtration and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 4 : 1). The resultant purified material was concentrated to dryness, giving 192 mg (yield: 52%) of white powder 9-(4-ethylbenzenesulfonyl)-9H-carbazole-3-carbaldehyde.

Melting point: 170.7°C

Reference Example 33

Synthesis of 9-(6-morpholin-4-ylpyridin-3-ylmethyl)-9H-

35

carbazole-3-carbaldehyde

To 15 ml of morpholine was added 1.5 g (4.7 mmol) of 9-(6-chloropyridin-3-ylmethyl)-9H-carbazole-3-carbaldehyde, followed by stirring under an argon atmosphere at 100°C for 6 hours and at 120°C for 16 hours. The thus-obtained reactant was cooled to room temperature and concentrated under reduced pressure. Ethyl acetate and water were added to the residue, and then separated. The resultant organic layer was washed with saturated brine three times. The washed organic layer was dried over anhydrous sodium sulfate and concentrated, and the resultant residue was then purified by silica gel column chromatography (n-hexane : ethyl acetate = 2 : 1 to 1 : 1). The purified material was concentrated to dryness under reduced pressure, giving 1.24 g (yield: 63%) of pale yellow powder 9-(6-morpholin-4-ylpyridin-3-ylmethyl)-9H-carbazole-3-carbaldehyde.

$^1\text{H-NMR}$ (CDCl_3) δppm : 3.44 (4H, t, $J = 4.9$ Hz), 3.77 (4H, t, $J = 4.9$ Hz), 5.30 (2H, s), 6.50 (1H, d, $J = 8.8$ Hz), 7.24 (1H, dd, $J_1 = 2.5$ Hz, $J_2 = 8.8$ Hz), 7.30-7.37 (1H, m), 7.45-7.55 (3H, m), 7.99 (1H, dd, $J_1 = 1.5$ Hz, $J_2 = 8.5$ Hz), 8.16-8.18 (2H, m), 8.63 (1H, d, $J = 1.5$ Hz), 10.10 (1H, s).

Reference Example 34

Synthesis of 9-(4-bromobenzyl)-1-methoxy-9H-carbazole-3-carbaldehyde

A toluene solution (10 ml) containing a reagent prepared by using 1.1 ml (3.5 mmol) of sodium bis(2-methoxyethoxy)aluminium hydride (65% toluene solution) and 0.34 ml (3.9 mmol) of morpholine was added dropwise to a toluene solution (10 ml) containing 0.50 g (1.2 mmol) of methyl 9-(4-bromobenzyl)-1-methoxy-9H-carbazole-3-carboxylate, and the resultant mixture was stirred at room temperature overnight. The reaction was stopped by adding water to the reaction mixture, and the thus-obtained reactant was subjected to extraction with ethyl acetate. The extract was

washed with water and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 10 : 1 to 5 : 1). The purified material was concentrated to dryness under reduced pressure, giving 0.5 g (quantitative yield) of white powder 9-(4-bromobenzyl)-1-methoxy-9H-carbazole-3-carbaldehyde.

^1H NMR (CDCl_3) δ ppm : 3.97 (3H, s), 5.86 (2H, s), 6.99 (2H, d, $J = 8.4$ Hz), 7.29-7.52 (6H, m), 8.14 (1H, d, $J = 7.8$ Hz), 8.24 (1H, d, $J = 1.2$ Hz), 10.06 (1H, s).

Reference Example 35

Synthesis of 9-(4-pyridin-2-ylbenzyl)-9H-carbazole-3-carbaldehyde

To 30 ml of toluene were added 1.5 g (4.1 mmol) of 9-(4-bromobenzyl)-9H-carbazole-3-carbaldehyde and 0.48 g (0.41 mmol) of tetrakis(triphenylphosphine)-palladium, and then added 1.82 g (4.9 mmol) of 2-tri-n-butylstannylpyridine dropwise. The thus-obtained mixture was refluxed under heating in a nitrogen atmosphere for 6 hours and then cooled to room temperature. After adding water and ethyl acetate, insoluble matter was filtered out from the reaction mixture. After conducting separation, the obtained organic layer was washed with water twice and saturated brine once, and then dried over anhydrous sodium sulfate. The resultant dry substance was subjected to filtration and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : methanol = 100 : 0 to 100 : 1). The thus-obtained purified material was concentrated to dryness under reduced pressure, giving 1.1 g (yield: 74%) of yellow powder 9-(4-pyridin-2-ylbenzyl)-9H-carbazole-3-carbaldehyde.

^1H -NMR ($\text{DMSO}-d_6$) δ ppm : 5.83 (2H, s), 7.23-7.37 (4H, m), 7.50-7.57 (1H, m), 7.76 (1H, d, $J = 8.2$ Hz), 7.83-8.03 (6H, m), 8.35 (1H, d, $J = 7.7$ Hz), 8.61-8.63 (1H, m), 8.82

(1H, d, J = 1.2 Hz), 10.08 (1H, s).

Using suitable starting compounds, compounds of Reference Examples 31, 45 and 75 were synthesized in the same manner as in Reference Example 1.

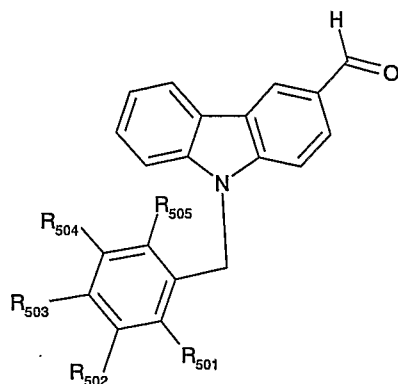
Using suitable starting compounds, compounds of Reference Examples 32, 34-41, 48-49, 71-74, and 77-85 were synthesized in the same manner as in Reference Example 3.

Using suitable starting compounds, compounds of Reference Examples 33, 42-43 and 86-90 were synthesized in the same manner as in Reference Example 17.

Using suitable starting compounds, compounds of Reference Examples 44, 46-47, 50-70 and 76 were obtained in the same manner as in Reference Example 32.

Using a suitable starting compound, a compound of Reference Example 91 was obtained in the same manner as in Reference Example 35.

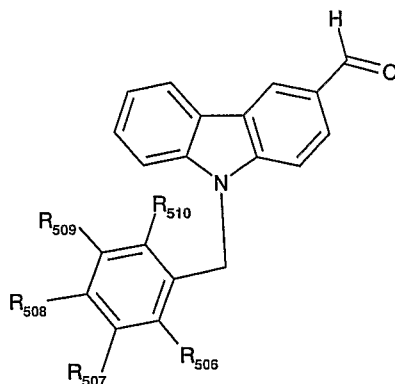
Table 1



5

Ref. Ex. No.	R ₅₀₁	R ₅₀₂	R ₅₀₃	R ₅₀₄	R ₅₀₅	M.p.(°C)
36	-H	-H	-H	-H	-H	136.2
37	-H	-H	-C ₆ H ₅	-H	-H	177.1
38	-H	-H	-C ₆ H ₄ C ₆ H ₅ (PARA)	-H	-H	251
39	-H	-H	-SCH ₃	-H	-H	136.5
40	-H	-H	-OCH ₃	-H	-H	130
41	-H	-H	-CN	-H	-H	173
42	-H	-H	-Cl	-H	-H	155.6
43	-Cl	-H	-H	-H	-H	127.6
44	-H	-H	-NO ₂	-H	-H	174.7
45	-H	-H	-CO ₂ CH ₃	-H	-H	168.1

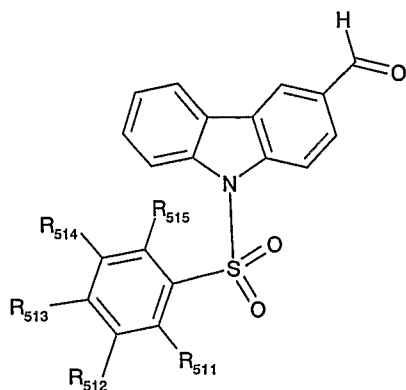
Table 2



5

Ref. Ex. No.	R ₅₀₆	R ₅₀₇	R ₅₀₈	R ₅₀₉	R ₅₁₀	NMR
46	-H	-H	-Br	-H	-H	¹ H-NMR (CDCl ₃) δppm: 5.49 (2H, s), 6.99 (2H, d, J = 8.4 Hz), 7.34 - 7.42 (5H, m), 7.50 (1H, td, J = 7.7, 1.0 Hz), 7.98 (1H, dd, J = 8.5, 1.5 Hz), 8.19 (1H, d, J = 7.8 Hz), 8.65 (1H, d, J = 1.3 Hz), 10.10 (1H, s)
47	-H	-H	-3-PYRIDYL	-H	-H	¹ H-NMR (DMSO-d ₆) δppm : 5.83 (2H, s), 7.30 (2H, d, J=7.6Hz), 7.34 (1H, t, J=7.6Hz), 7.43-7.45 (1H, m), 7.53-7.65 (3H, m), 7.77 (1H, d, J=8.4Hz), 7.89 (1H, d, J=8.4Hz), 7.98-8.02 (2H, m), 8.35 (1H, d, J=7.6Hz), 8.53 (1H, d, J=3.9Hz), 8.82 (2H, s), 10.08 (1H, s)
48	-H	-H	-3-THIENYL	-H	-H	¹ H-NMR (DMSO-d ₆) δppm : 5.78 (2H, s), 7.22 (2H, d, J=8.2Hz), 7.31-7.37 (1H, m), 7.47 (1H, dd, J1=1.3Hz, J2=5.0Hz), 7.50-7.57 (1H, m), 7.58-7.63 (3H, m), 7.74-7.79 (2H, m), 7.88 (1H, d, J=8.6Hz), 8.01 (1H, dd, J1=1.3Hz, J2=8.6Hz), 8.34 (1H, d, J=7.7Hz), 8.81 (1H, d, J=1.3Hz), 10.07 (1H, s)

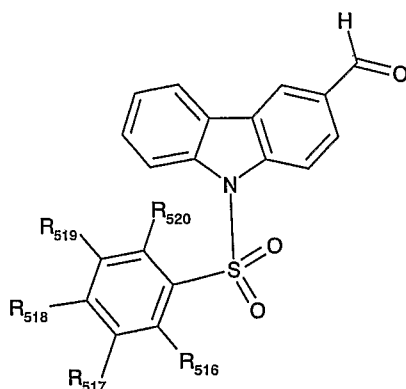
Table 3



5

Ref. Ex. No.	R ₅₁₁	R ₅₁₂	R ₅₁₃	R ₅₁₄	R ₅₁₅	M.p.(°C)
49	-H	-H	-Cl	-H	-H	168.3
50	-H	-H	-CH ₃	-H	-H	155.1
51	-H	-H	-C ₆ H ₅	-H	-H	206
52	-H	-H	-C ₅ H ₁₁	-H	-H	116.8
53	-H	-H	-I	-H	-H	194.5
54	-H	-H	-Br	-H	-H	182.8
55	-H	-H	-CN	-H	-H	201.5
56	-Cl	-H	-Cl	-H	-H	150.8
57	-H	-Cl	-Cl	-H	-H	156.3
58	-Cl	-H	-H	-H	-H	214.5
59	-H	-H	-NHCOCH ₃	-H	-H	221.6
60	-H	-H	-F	-H	-H	281.1
61	-H	-H	-CF ₃	-H	-H	196.1

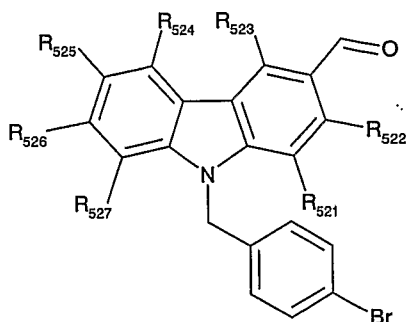
Table 4



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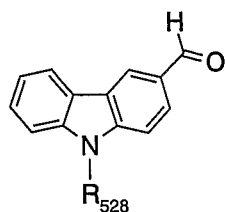
Ref. Ex. No.	R ₅₁₆	R ₅₁₇	R ₅₁₈	R ₅₁₉	R ₅₂₀	NMR
62	-H	-H	-OC ₆ H ₅	-H	-H	¹ H-NMR (CDCl ₃) dppm: 6.84 - 6.86 (2H, m), 6.94 - 6.96 (2H, m), 7.08 - 7.09 (1H, m), 7.33 - 7.46 (4H, m), 7.79 - 7.81 (2H, m), 7.97 - 8.03 (3H, m), 8.33 - 8.35 (1H, m), 8.46 - 8.48 (1H, m), 10.12 (1H, s)
63	-H	-H	-CH(CH ₃) ₂	-H	-H	¹ H-NMR (CDCl ₃) dppm: 1.14 (6H, d, J = 6.9 Hz), 2.84 (1H, quint, J = 6.9 Hz), 7.20 - 7.22 (2H, m), 7.26 - 7.45 (1H, m), 7.52 - 7.61 (1H, m), 7.78 - 7.80 (2H, m), 8.00 - 8.04 (2H, m), 8.37 (1H, d, J = 8.4 Hz), 8.46 - 8.50 (2H, m), 10.12 (1H, s)
64	-H	-H	-OCH ₃	-H	-H	¹ H-NMR (CDCl ₃) dppm: 3.74 (3H, s), 6.78 - 6.81 (2H, m), 7.43 (1H, t, J = 7.5 Hz), 7.56 (1H, td, J = 7.9, 1.1 Hz), 7.78 - 7.81 (2H, m), 7.99 - 8.03 (2H, m), 8.35 (1H, d, J = 8.4 Hz), 8.47 (2H, t, J = 8.8 Hz), 10.12 (1H, s)
65	-H	-CH ₃	-H	-H	-H	¹ H-NMR (CDCl ₃) dppm: 2.28 (3H, s), 7.22 - 7.28 (2H, m), 7.42 (1H, t, J = 6.2 Hz), 7.55 - 7.58 (1H, m), 7.65 - 7.67 (2H, m), 7.98 - 8.03 (2H, m), 8.34 (1H, d, J = 2.7 Hz), 8.46 (2H, t, J = 8.7 Hz), 10.11 (1H, s)
66	-CH ₃	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) dppm: 2.33 (3H, s), 7.28 - 7.31 (2H, m), 7.40 - 7.43 (2H, m), 7.90 - 8.10 (4H, m), 8.23 (1H, d, J = 8.7 Hz), 8.43 (2H, t, J = 8.5 Hz), 8.52 (1H, t, J = 1.5 Hz), 10.11 (1H, s)
67	-CH ₃	-H	-CH ₃	-H	-CH ₃	¹ H-NMR (CDCl ₃) dppm: 2.27 (3H, s), 2.43 (6H, s), 6.94 (2H, s), 7.39 (1H, td, J = 7.5, 0.8 Hz), 7.45 (1H, dt, J = 7.8, 1.2 Hz), 7.76 (1H, d, J = 8.3 Hz), 7.93 (1H, dd, J = 8.6, 1.6 Hz), 7.99 (1H, d, J = 8.6 Hz), 8.06 (1H, dd, J = 7.9, 0.6 Hz), 8.53 (1H, d, J = 1.3 Hz), 10.11 (1H, s)
68	-H	-H	-OCF ₃	-H	-H	¹ H-NMR (CDCl ₃) dppm: 7.18 (2H, d, J = 8.4 Hz), 7.46 (1H, d, J = 7.5 Hz), 7.59 (1H, td, J = 7.9, 1.1 Hz), 7.90 - 7.92 (2H, m), 8.01 - 8.05 (2H, m), 8.33 (1H, d, J = 8.4 Hz), 8.46 - 8.47 (2H, m), 10.13 (1H, s)

Table 5



Ref. Ex. No.	R ₅₂₁	R ₅₂₂	R ₅₂₃	R ₅₂₄	R ₅₂₅	R ₅₂₆	R ₅₂₇	NMR
69	-CH ₃	-H	-H	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) dppm:1.45 (3H, t, J = 7.1 Hz), 2.66 (3H, s), 4.43 (2H, q, J = 7.1 Hz), 5.74 (2H, s), 6.87 (2H, d, J = 8.52 Hz), 7.23-7.35 (2H, m), 7.35-7.49 (3H, m), 7.88 (1H, dd, J = 0.8, 1.4 Hz), 8.17 (1H, d, J = 7.7 Hz), 8.72 (1H, d, J = 1.4 Hz).
70	-H	-H	-H	-H	-H	-H	-CH ₃	¹ H-NMR (CDCl ₃) dppm:2.62 (3H, s), 3.97 (3H, s), 5.73 (2H, s), 6.82-6.90 (2H, m), 7.15-7.24 (3H, m), 7.34-7.42 (2H, m), 8.01-8.15 (2H, m), 8.83(1H, d, J = 1.4 Hz).
71	-H	-H	-H	-H	-H	-H	-OCH ₃	¹ H-NMR (CDCl ₃) dppm:3.88 (3H, s), 3.96 (3H, s), 5.83 (2H, s), 6.90-7.01 (3H, m), 7.16-7.40 (4H, m), 7.77 (1H, dd, J = 0.6, 7.8 Hz), 8.10 (1H, dd, J = 1.6, 8.7 Hz), 8.81 (1H, d, J = 1.5 Hz).
72	-H	-H	-H	-CH ₃	-H	-H	-CH ₃	¹ H-NMR (CDCl ₃) dppm:2.62 (3H, s), 2.94 (3H, s), 5.78 (2H, s), 6.87 (2H, d, J = 8.4 Hz), 7.03 (1H, d, J = 7.4 Hz), 7.14 (1H, d, J = 7.4 Hz), 7.29-7.45 (3H, m), 7.95 (1H, dd, J = 1.5, 8.6 Hz), 8.71 (1H, d, J = 1.3 Hz), 10.11 (1H, s).
73	-OCH ₃	-H	-H	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) dppm:3.95 (3H, s), 3.98 (3H, s), 5.84 (2H, s), 6.99 (2H, d, J = 8.3 Hz), 7.22-7.49 (4H, m), 7.61 (1H, s), 8.12 (1H, d, J = 7.7 Hz), 8.50 (1H, d, J = 0.9 Hz).
74	-CH ₃	-H	-H	-H	-H	-H	-CH ₃	¹ H-NMR (CDCl ₃) dppm:1.44 (3H, t, J = 7.1 Hz), 2.57 (3H, s), 2.60 (3H, s), 4.43 (2H, q, J = 7.1 Hz), 5.93 (2H, s), 6.84 (2H, d, J = 8.5 Hz), 7.13-7.22 (2H, m), 7.35-7.45 (2H, m), 7.84 (1H, d, J = 0.7 Hz), 8.03 (1H, dd, J = 2.0, 7.1 Hz), 8.68 (1H, d, J = 1.4 Hz).
75	-OCH ₃	-H	-H	-H	-H	-H	-OCH ₃	¹ H-NMR (CDCl ₃) dppm:3.86 (3H, s), 3.92 (3H, s), 3.96 (3H, s), 6.16 (2H, s), 6.86-6.95 (3H, m), 7.19 (1H, t, J = 7.9 Hz), 7.30 (2H, dd, J = 1.8, 6.6 Hz), 7.56 (1H, d, J = 1.3 Hz), 7.72 (1H, dd, J = 0.6, 7.8 Hz), 8.44 (1H, d, J = 1.4 Hz).

Table 6



5

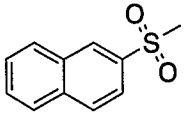
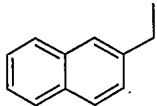
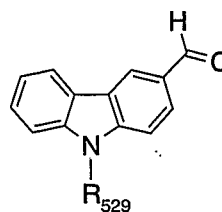
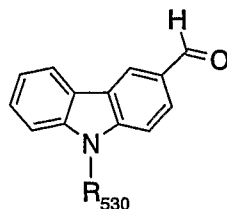
Ref. Ex. No.	R ₅₂₈	M.p.(°C)
76	-(CH ₂) ₃ Cl	86.8
77	-(CH ₂) ₃ CH ₃	63.4
78	-(CH ₂) ₄ CH ₃	60.5
79	-(CH ₂) ₅ CH ₃	72.3
80	-COC ₆ H ₅	149.6
81		179.2
82		178.5
83	-CH ₂ -cyclo-C ₆ H ₁₁	128.8
84	-(CH ₂) ₃ C ₆ H ₅	110.2
85	-CH ₂ -cyclo-C ₃ H ₅	80

Table 7



Ref. Ex. No.	R ₅₂₉	NMR
86	-(CH ₂) ₂ CH ₃	¹ H-NMR (CDCl ₃) dppm: 0.98 (3H, t, J = 7.4 Hz), 1.93 (2H, quint, J = 7.3 Hz), 4.30 (2H, d, J = 7.2 Hz), 7.32 (1H, td, J = 7.4, 0.8 Hz), 7.45 (1H, d, J = 7.5 Hz), 7.47 (1H, d, J = 8.2 Hz), 7.53 (1H, td, J = 7.7, 1.1 Hz), 8.00 (1H, dd, J = 8.5, 1.5 Hz), 8.15 (1H, d, J = 7.8 Hz), 8.60 (1H, d, J = 1.2 Hz), , 10.09 (1H, s)
87	-CH ₂ CH(CH ₃) ₂	¹ H-NMR (CDCl ₃) dppm: 0.99 (6H, d, J = 6.7 Hz), 2.38 (1H, quint, J = 6.9 Hz), 4.13 (2H, d, J = 7.5 Hz), 7.32 (1H, t, J = 7.5 Hz), 7.44 - 7.48 (2H, m), 7.52 (1H, t, J = 7.6 Hz), 8.00 (1H, dd, J = 8.5, 1.0 Hz), 8.16 (1H, d, J = 1.8 Hz), 8.61 (1H, s), 10.09 (1H, s)
88	-(CH ₂) ₂ CH(CH ₃) ₂	¹ H-NMR (CDCl ₃) dppm: 1.04 (6H, d, J = 6.4 Hz), 1.69 - 1.79 (3H, m), 4.35 (2H, d, J = 7.6 Hz), 7.33 (1H, td, J = 7.5, 0.6 Hz), 7.45 (1H, d, J = 7.9 Hz), 7.47 (1H, d, J = 8.3 Hz), 7.54 (1H, td, J = 7.5, 0.9 Hz), 8.01 (1H, dd, J = 8.5, 1.4 Hz), 8.16 (1H, d, J = 7.8 Hz), 8.61 (1H, d, J = 1.1 Hz), 10.09 (1H, s)
89	-CH ₂ CH(C ₂ H ₅) ₂	¹ H-NMR (CDCl ₃) dppm: 0.94 (6H, t, J = 7.4 Hz), 1.32 - 1.48 (4H, m), 1.99 - 2.04 (1H, m), 4.21 (2H, d, J = 7.5 Hz), 7.32 (1H, t, J = 7.4 Hz), 7.43 - 7.56 (3H, m), 8.00 (1H, dd, J = 8.6, 1.5 Hz), 8.16 (1H, d, J = 7.7 Hz), 8.61 (1H, d, J = 1.4 Hz), 10.09 (1H, s)
90		¹ H-NMR (DMSO-d ₆) dppm : 6.02 (2H, s), 7.10 (1H, d, J=8.5Hz), 7.33 (1H, t, J=7.7Hz), 7.48-7.60 (2H, m), 7.74 (2H, d, J=7.7Hz), 7.78-8.01 (4H, m), 8.25 (1H, d, J=8.5Hz), 8.35 (1H, d, J=7.7Hz), 8.82 (1H, d, J=0.9Hz), 10.08 (1H, s)
91		¹ H-NMR (DMSO-d ₆) dppm : 5.86 (2H, s), 7.35 (1H, t, J=7.6Hz), 7.39-7.46 (3H, m), 7.55-7.59 (2H, m), 7.85 (2H, t, J=7.6Hz), 7.95-8.00 (3H, m), 8.03 (1H, dd, J1=1.5Hz, J2=8.5Hz), 8.35 (1H, d, J=7.8Hz), 8.66 (1H, d, J=2.0Hz), 8.82(1H, d, J=1.2Hz), 10.08 (1H, s)
92		¹ H-NMR (CDCl ₃) dppm: 5.58 (2H, s), 7.07 (1H, dd, J1=3.8Hz, J2=5.0Hz), 7.34-7.38 (3H, m), 7.44 (1H, d, J=8.2Hz), 7.48-7.54 (4H, m), 8.00 (1H, dd, J1=1.5Hz, J2=8.5Hz), 8.20 (1H, d, J=7.8Hz), 8.51 (1H, d, J=1.5Hz), 8.66 (1H, d, J=1.5Hz), 10.11 (1H, s)
93		¹ H-NMR (DMSO-d ₆) dppm : 5.81 (2H, s), 6.95 (1H, d, J=0.7Hz), 7.34 (1H, t, J=7.5Hz), 7.54-7.57 (3H, m), 7.73 (1H, s), 7.82 (1H, d, J=8.5Hz), 7.94 (1H, d, J=8.5Hz), 8.01 (1H, d, J=8.5Hz), 8.25 (1H, s), 8.34(1H, d, J=7.5Hz), 8.54 (1H, s), 8.81 (1H, s), 10.08 (1H, s)
94		¹ H-NMR (CDCl ₃) dppm: 5.57 (2H, s), 6.87 (1H, d, J=4.0Hz), 7.26-7.29 (1H, m), 7.32-7.56 (6H, m), 8.00 (1H, dd, J1=1.5Hz, J2=8.5Hz), 8.20 (1H, d, J=7.7Hz), 8.46 (1H, d, J=1.5Hz), 8.66 (1H, d, J=1.5Hz), 10.11 (1H, s)

Table 8



5

Ref. Ex. No.	R ₅₃₀	NMR
90		¹ H-NMR (CDCl ₃) δppm: 5.65 (2H, s), 7.38 (2H, t, J=6.8Hz), 7.43-7.48 (5H, m), 8.01-8.03 (1H, m), 8.21 (1H, d, J=8.0Hz), 8.25 (1H, d, J=8.0Hz), 8.63 (1H, dd, J ₁ =1.1Hz, J ₂ =4.8Hz), 8.68 (2H, s), 9.13 (1H, d, J=2.1Hz), 10.12 (1H, s)
91		¹ H-NMR (CDCl ₃) δppm: 5.64 (2H, s), 7.28-7.55 (5H, m), 7.63-7.71 (1H, m), 7.76-7.82 (1H, m), 8.01 (1H, dd, J ₁ =1.5Hz, J ₂ =8.5Hz), 8.19-8.22 (1H, m), 8.29-8.34 (2H, m), 8.58-8.68 (3H, m), 10.12 (1H, s)

Example 1

Synthesis of 5-(9-benzenesulfonyl-9H-carbazol-2-ylmethyl)thiazolidine-2,4-dione

To a toluene solution (15 ml) containing 1.0 g (3.0 mmol) of 9-benzenesulfonyl-9H-carbazole-2-carbaldehyde and 0.38 g (3.3 mmol) of thiazolidine-2,4-dione were added catalytic amounts of piperidine and acetic acid. The thus-obtained solution was refluxed under heating for 1.5 hours. After allowing the reaction mixture to cool to room temperature, insoluble matter was separated out and washed with toluene. The filtered out material was suspended in 100 ml of toluene. Subsequently, 1.13 g (4.5 mmol) of diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylate and 1.5 g of silica gel were added to the thus-obtained suspension, followed by heat-reflux overnight. After distilling off the solvent, the residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 3 : 1). Following recrystallization from an ethyl acetate-n-hexane mixture

solvent, 0.91 g (yield: 70%) of white powder 5-(9-benzenesulfonyl-9H-carbazol-2-ylmethyl)thiazolidine-2,4-dione was obtained.

Melting point: 152.4°C

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Example 2

Synthesis of 5-[9-(4-chlorobenzenesulfonyl)-3-methoxy-9H-carbazol-2-ylmethyl]thiazolidine-2,4-dione

Catalytic amounts of piperidine and acetic acid were added to a toluene solution (3 ml) containing 0.11 g (0.28 mmol) of 9-(4-chlorobenzenesulfonyl)-3-methoxy-9H-carbazole-2-carbaldehyde and 34 mg (0.29 mmol) of thiazolidine-2,4-dione. The thus-obtained solution was refluxed under heating for 2 hours and allowed to cool to room temperature. Toluene (15 ml), diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylate (0.14 g, 0.36 mmol) and silica gel (0.2 g) were added to the reaction mixture, followed by heat-reflux overnight. After distilling off the solvent, the residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 3 : 1). Following recrystallization from an ethyl acetate-n-hexane mixture solvent, 70 mg (yield: 70%) of white powder 5-[9-(4-chlorobenzenesulfonyl)-3-methoxy-9H-carbazol-2-ylmethyl]thiazolidine-2,4-dione was obtained. Melting point: 265.8°C

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Example 3

Synthesis of 5-{1-[9-(2,2,2-trifluoroacetyl)-9H-carbazol-3-yl]methylidene} thiazolidine-2,4-dione

Catalytic amounts of piperidine and acetic acid were added to a toluene solution (15 ml) containing 0.30 g (1.0 mmol) of 9-(2,2,2-trifluoroacetyl)-9H-carbazole-3-carbaldehyde and 0.13 g (0.29 mmol) of thiazolidine-2,4-dione, followed by heat-reflux overnight. The thus-obtained reaction mixture was allowed to cool to room temperature. Insoluble matter was separated out, washed with toluene and

35

dried, giving 0.37 g (yield: 92%) of yellow powder of 5- {1-[9-(2,2,2-trifluoroacetyl)-9H-carbazol-3-yl]methylidene} thiazolidine-2,4-dione.

Melting point: not lower than 300°C

5

Example 4

Synthesis of 5-(9H-carbazol-3-ylmethyl)thiazolidine-2,4-dione

0.30 g (0.77 mmol) of 5- { 1-[9-(2,2,2-trifluoroacetyl)-9H-carbazol-3-yl]methylidene } thiazolidine-2,4-dione was suspended in 5 ml of tetrahydrofuran (THF). 1.2 ml of pyridine and 1.15 ml of 2M lithium borohydride THF solution were added to the suspension, and the resultant mixture was then refluxed under heating for 4 hours. The thus-obtained reaction mixture was allowed to cool to room temperature and poured in ice-hydrochloric acid (concentrated hydrochloric acid, 1.5 ml), and the reactant was extracted with dichloromethane. The thus-obtained organic layer was washed with water and saturated brine, and then dried over magnesium sulfate. The resultant dry substance was subjected to filtration, and the solvent was distilled off under reduced pressure. Subsequently, the residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 2 : 1). The resultant purified material was concentrated to dryness, giving 0.16 g (yield: 77%) of pale yellow powder 5-(9H-carbazol-3-ylmethyl)thiazolidine-2,4-dione.

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Melting point 228.3°C

Example 5

Synthesis of 2-thioxo-5- {1-[9-(2,2,2-trifluoroacetyl)-9H-carbazol-3-yl]methylidene} thiazolidin-4-one

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Catalytic amounts of piperidine and acetic acid were added to a toluene solution (30 ml) containing 1.02 g (3.5 mmol) of 9-(2,2,2-trifluoroacetyl)-9H-carbazole-3-carbaldehyde and 0.51 g (3.85 mmol) of rhodanine, followed by heat-reflux overnight. The resultant reaction mixture was

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allowed to cool to room temperature. Insoluble matter was filtered out, washed with toluene, and then dried, giving 1.19 g (yield: 84%) of pale yellow powder 2-thioxo-5- {1-[9-(2,2,2-trifluoroacetyl)-9H-carbazol-3-yl]methylidene} thiazolidin-4-one.
Melting point: not lower than 300°C

Example 6

Synthesis of 2-thioxo-5-(9H-carbazol-3-ylmethyl)thiazolidin-4-one

1.0 g (2.5 mmol) of 2-thioxo-5- {1-[9-(2,2,2-trifluoroacetyl)-9H-carbazol-3-yl]methylidene} thiazolidin-4-one was suspended in 10 ml of THF, and 6.0 ml of pyridine and 6.0 ml of 2M lithium borohydride THF solution were added to the suspension, followed by heat-reflux for 3 hours. The reaction mixture was allowed to cool to room temperature, poured in ice-hydrochloric acid (concentrated hydrochloric acid, 6 ml), and subjected to extraction with dichloromethane. The resultant organic layer was washed with water and saturated brine, and then dried over magnesium sulfate. After filtering the resultant dry substance, the solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 2 : 1). Subsequently, the purified material was concentrated under reduced pressure, and the residue was washed with dichloromethane and hot ethanol, giving 0.30 g (yield: 39%) of pale yellow powder 2-thioxo-5-(9H-carbazol-3-ylmethyl)thiazolidin-4-one.
Melting point: 244.1°C

Example 7

Synthesis of 5-(6-trityl-9H-carbazol-3-ylmethyl)thiazolidine-2,4-dione

In 30 ml of toluene were suspended 0.30 g (1.0 mmol) of 5-(9H-carbazol-3-ylmethyl)thiazolidine-2,4-dione, 0.26 g

(1.0 mmol) of triphenylmethanol and 58 mg (0.30 mmol) of p-toluene sulfonic-acid monohydrate. The resultant suspension was refluxed under heating for 7 hours using a 100 ml reaction vessel equipped with Dean-Stark distillation apparatus. The reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate, and sequentially washed with a sodium hydrogencarbonate aqueous solution, water, and saturated brine. The washed reaction mixture was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 2 : 1). Subsequently, the purified material was concentrated to dryness under reduced pressure, giving 0.47 g (yield: 86%) of white powder 5-(6-trityl-9H-carbazol-3-ylmethyl)thiazolidine-2,4-dione.

Melting point: 166.4°C

Example 8

Synthesis of 3-trityl-5-(6-trityl-9H-carbazol-3-ylmethyl)thiazolidine-2,4-dione

To a N,N-dimethylformamide (DMF) solution (5 ml) containing 0.17 g (0.32 mmol) of 3-trityl-5-(6-trityl-9H-carbazol-3-ylmethyl)thiazolidine-2,4-dione were added 48 mg (0.35 mmol) of potassium carbonate and 98 mg (0.35 mmol) of trityl-chloride, and the resultant mixture was stirred at room temperature for 8 hours. After diluting with ethyl acetate, the reaction mixture was sequentially washed with water, and saturated brine. The washed reaction mixture was concentrated under reduced pressure, and the resultant residue was subjected to recrystallization from an ethyl acetate-n-hexane mixture solvent, giving 0.23 g (yield: 92%) of white powder 3-trityl-5-(6-trityl-9H-carbazol-3-ylmethyl)thiazolidine-2,4-dione.

Melting point: 185.5°C

Example 9

Synthesis of 5-(9H-carbazol-3-ylmethyl)-3-trityl-thiazolidine-2,4-dione

Using 5-(9H-carbazol-3-ylmethyl)thiazolidine-2,4-dione and trityl-chloride as starting compounds, 5-(9H-carbazol-3-ylmethyl)-3-trityl-thiazolidine-2,4-dione was synthesized in the same manner as in Example 8.
Melting point: 169.9°C

10 Example 10

Synthesis of 5-(9-benzoyl-9H-carbazol-3-ylmethyl)thiazolidine-2,4-dione

In toluene (10 ml) was suspended 0.4 g (1.0 mmol) of 5-[1-(9-benzoyl-9H-carbazol-3-yl)methylidene]thiazolidine-2,4-dione, and 0.38 g (1.5 mmol) of diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylate and 0.4 g of silica gel were added to the thus-obtained suspension, followed by heat-reflux overnight. The thus-obtained reaction mixture was cooled to room temperature, and the solvent contained therein was distilled off under reduced pressure. Subsequently, the residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 3:1). The purified material was concentrated to dryness, giving 0.40 g (yield: 99%) of white powder 5-(9-benzoyl-9H-carbazol-3-ylmethyl)thiazolidine-2,4-dione.
Melting point: 175.5°C

Example 11

Synthesis of 5-(9-benzoyl-9H-carbazol-3-ylmethyl)-2-thioxo-thiazolidin-4-one

In 40 ml of toluene was suspended 0.34 g (0.82 mmol) of 5-[1-(9-benzoyl-9H-carbazol-3-yl)methylidene]-2-thioxo-thiazolidin-4-one. Diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylate (0.31 g, 1.23 mmol) and silica gel (0.34 g) were added to the thus-obtained suspension, followed

by heat-reflux overnight. The thus-obtained reaction mixture was cooled to room temperature, and the solvent contained therein was then distilled off under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 3 : 1). The purified material was concentrated under reduced pressure, and the resultant residue was recrystallized from an ethyl acetate-n-hexane mixture solvent, giving 0.19 g (yield: 56%) of yellow powder 5-(9-benzoyl-9H-carbazol-3-ylmethyl)-2-thioxo-thiazolidin-4-one.

Melting point: 208.3°C

Example 12

Synthesis of 4-[3-(2,4-dioxothiazolidin-5-ylmethyl)carbazol-9-ylmethyl]benzoic acid

2.08 g (4.7 mmol) of methyl 4-[3-(2,4-dioxothiazolidin-5-ylmethyl)carbazol-9-ylmethyl]benzoate was dissolved in a mixed solvent of 30 ml of THF and 30 ml of ethanol, and 15 ml of 1N-lithium hydroxide aqueous solution was added dropwise to the thus-obtained solution. The thus-obtained reaction mixture was stirred at room temperature overnight and then neutralized with 1N-hydrochloric acid. The solvent was distilled off under reduced pressure, and reactant was extracted with an ethyl acetate. The resultant organic layer was sequentially washed with water, and saturated brine. The washed organic layer was concentrated under reduced pressure, and then the residue was purified by silica gel column chromatography (dichloromethane : methanol = 20 : 1). The purified material was concentrated under reduced pressure, and the residue was subjected to recrystallization from an ethyl acetate-n-hexane mixture solvent, giving 1.55 g (yield: 77%) of white powder 4-[3-(2,4-dioxothiazolidin-5-ylmethyl)carbazol-9-ylmethyl]benzoic acid.

Melting point: 232.8°C

Example 13

Synthesis of 4-[3-(2,4-dioxothiazolidin-5-ylmethyl)carbazol-9-ylmethyl]-N-thiazol-2-ylbenzamide

5 To 5 ml of DMF were added 0.43 g (1.0 mmol) of 4-[3-(2,4-dioxothiazolidin-5-ylmethyl)carbazol-9-ylmethyl]benzoic acid, 0.10 g (1.0 mmol) of 2-aminothiazole, 0.20 g (1.05 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC) and 0.16 g (1.05 mmol) of 1-hydroxybenzotriazole (HOBt). The mixture was stirred at room temperature overnight and at 40°C for 3 hours, and then cooled to room temperature. After adding water to the thus-obtained reaction mixture, the reactant was extracted with ethyl acetate. The thus-obtained organic layer was sequentially washed with 1N-hydrochloric acid, a saturated aqueous solution of sodium hydrogencarbonate, water, and saturated brine. The washed organic layer was concentrated under reduced pressure, and the residue was recrystallized from methanol, giving 0.28 g (yield: 55%) of white powder 4-[3-(2,4-dioxothiazolidin-5-ylmethyl)carbazol-9-ylmethyl]-N-thiazol-2-ylbenzamide.

Melting point: 290.7°C

Example 14

25 Synthesis of 5-[9-(4-chlorobenzenesulfonyl)-3-methoxy-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione

Using 9-(4-chlorobenzenesulfonyl)-3-methoxy-9H-carbazol-4-carbaldehyde and thiazolidine-2,4-dione as starting compounds, 5-[9-(4-chlorobenzenesulfonyl)-3-methoxy-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione was synthesized in the same manner as in Example 2.

Melting point: 181.3°C

Example 15

35 Synthesis of potassium salt of 5-[9-(4-

chlorobenzenesulfonyl)-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione

To a THF solution (30 ml) containing 1.0 g (2.12 mmol) of 5-[9-(4-chlorobenzenesulfonyl)-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione was added 0.24 g (2.12 mmol) of potassium t-butoxide, and the mixture was stirred at room temperature for one hour. The thus-obtained reaction mixture was concentrated under reduced pressure, followed by addition of diethyl ether to the resultant residue. Insoluble matter generated was filtered out and dried, giving 1.13 g of a white powder potassium salt of 5-[9-(4-chlorobenzenesulfonyl)-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione.

Melting point: 272.2°C

Example 16

Synthesis of potassium salt of 5-(9-ethyl-9H-carbazol-3-ylmethyl)thiazolidine-2,4-dione

Using 5-(9-ethyl-9H-carbazol-3-ylmethyl)thiazolidine-2,4-dione and potassium t-butoxide as starting compounds, the potassium salt of 5-(9-ethyl-9H-carbazol-3-ylmethyl)thiazolidine-2,4-dione was synthesized in the same manner as in Example 15.

Melting point: 212.2°C

Example 17

Synthesis of potassium salt of 5-[9-(4-bromobenzyl)-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione

Using 5-[9-(4-bromobenzyl)-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione and potassium t-butoxide as starting compounds, the potassium salt of 5-[9-(4-bromobenzyl)-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione was synthesized in the same manner as in Example 15.

Melting point: 269.7°C

Example 18

Synthesis of sodium salt of 5-[9-(4-chlorobenzenesulfonyl)-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione

5 Using 5-[9-(4-chlorobenzenesulfonyl)-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione and sodium t-butoxide as starting compounds, the sodium salt of 5-[9-(4-chlorobenzenesulfonyl)-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione was synthesized in the same manner as in Example 15.

10

Example 19

Synthesis of sodium salt of 5-(9-ethyl-9H-carbazol-3-ylmethyl)thiazolidine-2,4-dione

15 Using 5-(9-ethyl-9H-carbazol-3-ylmethyl)thiazolidine-2,4-dione and sodium t-butoxide as starting compounds, the sodium salt of 5-(9-ethyl-9H-carbazol-3-ylmethyl)thiazolidine-2,4-dione was synthesized in the same manner as in Example 15.

Melting point: 276.8°C

20

Example 20

Synthesis of sodium salt of 5-[9-(4-bromobenzyl)-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione

25 Using 5-[9-(4-bromobenzyl)-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione and sodium t-butoxide as starting compounds, the sodium salt of 5-[9-(4-bromobenzyl)-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione was synthesized in the same manner as in Example 15.

Melting point: 268.4°C

30

Example 21

Synthesis of 1/2 calcium salt of 5-[9-(4-bromobenzyl)-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione

35 Using 5-[9-(4-bromobenzyl)-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione and calcium methoxide as

starting compounds, 1/2 sodium salt of 5-[9-(4-bromobenzyl)-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione was synthesized in the same manner as in Example 15.

Melting point: 260.4°C

5

Example 22

Synthesis of 1/2 magnesium salt of 5-[9-(4-bromobenzyl)-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione

Using 5-[9-(4-bromobenzyl)-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione and magnesium ethoxide as starting compounds, 1/2 magnesium salt of 5-[9-(4-bromobenzyl)-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione was synthesized in the same manner as in Example 15.

Melting point: 190.6°C

15

Example 23

Synthesis of 5-[9-(4-aminobenzyl)-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione hydrochloride

5-[9-(4-nitrobenzyl)-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione (0.47 g, 1.09 mmol) was dissolved in a mixed solvent of ethyl acetate (10 ml) and ethanol (20 ml). Tin (II) chloride dihydrate (0.98 g, 4.36 mmol) was added to the thus-obtained solution, followed by heat-reflux for 7 hours. The thus-obtained reaction mixture was cooled to room temperature and concentrated under reduced pressure. Water and 1N-hydrochloric acid were added to the residue, and the insoluble matter deposited was filtered out. The filtered out material was suspended in a mixed solvent of ethyl acetate and THF, and the thus-obtained suspension was neutralized by adding triethylamine (1 mmol). After concentrating the neutralized suspension under reduced pressure, the resultant residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 2 : 1 to 2 : 3). The purified material was concentrated under reduced pressure, and 4N-hydrochloric acid/ethyl acetate was added to

35

the resultant residue. The deposited insoluble matter was filtered out and dried, giving 60 mg (yield: 14%) of white powder 5-[9-(4-aminobenzyl)-9H-carbazol-4-ylmethyl]thiazolidine-2,4-dione hydrochloride.

5 Melting point: 240.7°C

Example 24

Synthesis of 5-[9-(4-chlorobenzenesulfonyl)-9H-carbazol-3-ylmethyl]-2-thioxo-thiazolidin-4-one

10 Catalytic amounts of piperidine and acetic acid were added to a toluene solution (20 ml) containing 1.56 g (4.2 mmol) of 9-(4-chlorobenzenesulfonyl)-9H-carbazole-2-carbaldehyde and 0.62 g (4.6 mmol) of rhodanine, followed by heat-reflux for 2 hours. The thus-obtained reaction mixture
15 was allowed to cool to room temperature, and the resultant insoluble matter was filtered out and washed with toluene. Subsequently, the filtered out material was suspended in 150 ml of xylene. Diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylate (1.60 g, 6.3 mmol) and silica gel (2.0 g) were
20 added to the thus-obtained suspension, followed by heat-reflux overnight. After removing the solvent, the residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 3 : 1). Following recrystallization from dichloromethane, 0.54 g (yield: 26%) of pale yellow powder 5-
25 [9-(4-chlorobenzenesulfonyl)-9H-carbazol-3-ylmethyl]-2-thioxo-thiazolidin-4-one was obtained.
Melting point: 215.3°C

Example 25

30 Synthesis of 5-(9-benzenesulfonyl-9H-carbazol-3-ylmethyl)-2-thioxo-thiazolidin-4-one

Catalytic amounts of piperidine and acetic acid were added to a toluene solution (10 ml) containing 9-benzenesulfonyl-9H-carbazole-3-carbaldehyde (0.40 g, 1.2 mmol)
35 and rhodanine (0.17 g, 1.31 mmol), followed by heat-reflux

for 4 hours. The thus-obtained reaction mixture was allowed to cool to room temperature, and the resultant insoluble matter was filtered out and washed with toluene. After suspending the filtered out material in THF (3 ml), pyridine (1.7 ml) and 2M lithium borohydride THF solution (1.7 ml) were added to the suspension, followed by heat-reflux for 2 hours. The thus-obtained reaction mixture was allowed to cool to room temperature and poured in ice-hydrochloric acid. After extracting the reactant with dichloromethane, the resultant organic layer was sequentially washed with water and saturated brine, and then dried over anhydrous magnesium sulfate. The resultant dry substance was subjected to filtration, and the solvent contained therein was distilled out under reduced pressure. Subsequently, the residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 3 : 1). After concentrating the purified material under reduced pressure, the residue was recrystallized from a mixed solvent of ethyl acetate and n-hexane, giving 0.24 g (yield: 45%) of white powder 5-(9-benzenesulfonyl-9H-carbazol-3-ylmethyl)-2-thioxo-thiazolidin-4-one.

Melting point: 216.2°C

Example 26

Synthesis of 5-(9-benzenesulfonyl-9H-carbazol-3-ylmethyl)thiazolidine-2,4-dione

Catalytic amounts of piperidine and acetic acid were added to a toluene solution (10 ml) containing 9-benzenesulfonyl-9H-carbazole-3-carbaldehyde (0.37 g, 1.0 mmol) and thiazolidine-2,4-dione (0.13 g, 1.1 mmol), followed by heat-reflux for 6 hours. The thus-obtained reaction mixture was allowed to cool to room temperature. Subsequently, the insoluble matter was filtered out and washed with toluene. The filtered out material was suspended in THF (3 ml). To the thus-obtained suspension were added pyridine (1.2 ml) and

2M lithium borohydride THF solution (1.2 ml), followed by heat-reflux for 2.5 hours. The thus-obtained reaction mixture was allowed to cool to room temperature and poured in ice-hydrochloric acid, and the reactant was extracted with dichloromethane. The resultant organic layer was sequentially washed with water and saturated brine, followed by distillation of the solvent under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 3 : 1). The purified material was concentrated under reduced pressure, and the residue was recrystallized from a mixed solvent of ethyl acetate and n-hexane, giving 134 mg (yield: 30%) of white powder 5-(9-benzenesulfonyl-9H-carbazol-3-ylmethyl)thiazolidine-2,4-dione. Melting point: 227.2°C

15

Using suitable starting compounds, compounds of Examples 62-68, 72, 86-96, 99-110, 112 and 118 were synthesized in the same manner as in Example 1.

Using suitable starting compounds, compounds of Examples 27-57 were synthesized in the same manner as in Example 3.

Using suitable starting compounds, compounds of Examples 58, 76 and 97-98 were synthesized in the same manner as in Example 4.

Using suitable starting compounds, compounds of Examples 125-138 were synthesized in the same manner as in Example 5.

Using suitable starting compounds, compounds of Examples 146, 157 and 182 were synthesized in the same manner as in Example 6.

Using suitable starting compounds, compounds of Examples 61, 69-71, 73, 113-117, 119-124 and 139-145 were synthesized in the same manner as in Example 10.

Using suitable starting compounds, compounds of Examples 155-156, 177-181 and 183-185 were synthesized in the

same manner as in Example 11.

Using suitable starting compounds, compounds of Example 74-75 were synthesized in the same manner as in Example 13.

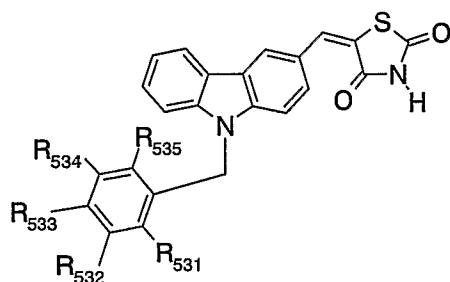
5 Using suitable starting compounds, compounds of Examples 148-154 and 159-176 were synthesized in the same manner as in Example 24.

10 Using suitable starting compounds, compounds of Examples 147 and 158 were synthesized in the same manner as in Example 25.

Using suitable starting compounds, compounds of Examples 59-60, 77-85 and 111 were synthesized in the same manner as in Example 26.

15

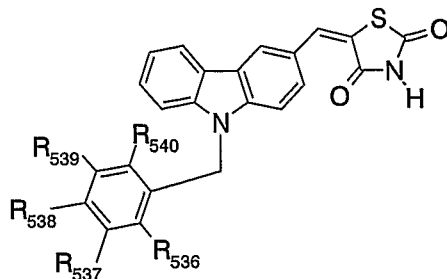
Table 9



Ex. No.	R ₅₃₁	R ₅₃₂	R ₅₃₃	R ₅₃₄	R ₅₃₅	M.p.(°C)
27	-H	-H	-H	-H	-H	>300

20

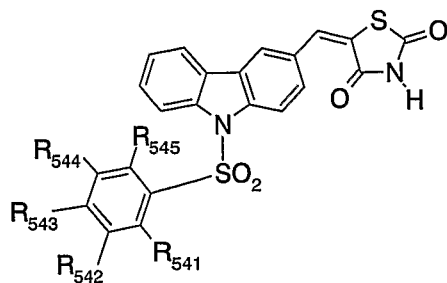
Table 10



5

Ex. No.	R ₅₃₆	R ₅₃₇	R ₅₃₈	R ₅₃₉	R ₅₄₀	NMR
28	-H	-H	-2-PYRIDYL	-H	-H	1H-NMR (DMSO-d ₆) dppm : 5.80 (2H, s), 7.29-7.33 (4H, m), 7.52 (1H, t, J=7.7Hz), 7.69 (1H, d, J=8.5Hz), 7.73 (1H, d, J=8.5Hz), 7.82-7.88 (3H, m), 7.98 (2H, s), 8.00 (1H, s), 8.29 (1H, d, J=7.7Hz), 8.46 (1H, s), 8.62 (1H, d, J=4.0Hz), 12.51 (1H, brs)
29	-H	-H	-3-PYRIDYL	-H	-H	1H-NMR (DMSO-d ₆) dppm : 5.80 (2H, s), 7.29-7.33 (3H, m), 7.44 (1H, dd, J ₁ =4.7Hz, J ₂ =8.1Hz), 7.53 (1H, t, J=7.7Hz), 7.64 (2H, d, J=8.1Hz), 7.69-7.71 (1H, m), 7.74 (1H, d, J=8.1Hz), 7.87 (1H, d, J=8.7Hz), 7.99-8.00 (2H, m), 8.28 (1H, d, J=7.7Hz), 8.46 (1H, s), 8.53 (1H, d, J=4.7Hz), 8.81 (1H, d, J=2.3Hz), 12.52 (1H, brs)
30	-H	-H	-3-THIENYL	-H	-H	1H-NMR (DMSO-d ₆) dppm : 5.74 (2H, s), 7.22 (2H, d, J=8.0Hz), 7.30 (1H, t, J=7.2Hz), 7.45-7.55 (2H, m), 7.58-7.63 (3H, m), 7.67-7.75 (2H, m), 7.77-7.78 (1H, m), 7.85 (1H, d, J=8.8Hz), 7.97 (1H, s), 8.27 (1H, d, J=8.0Hz), 8.44-8.45 (1H, m), 12.50 (1H, brs)
31	-H	-H	-NO ₂	-H	-H	1H-NMR (CDCl ₃) dppm: 5.91 (2H, s), 7.29 - 7.40 (3H, m), 7.51 (1H, t, J = 7.7 Hz), 7.66 - 7.70 (2H, m), 7.80 (1H, d, J = 8.7 Hz), 7.98 (1H, s), 8.16 (1H, d, J = 8.5 Hz), 8.30 (1H, d, J = 7.7 Hz), 8.47 (1H, s), 12.52 (1H, s)

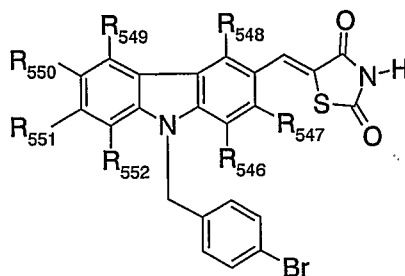
Table 11



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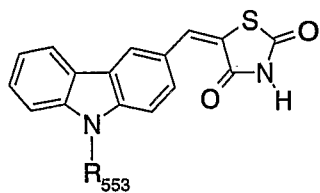
Ex. No.	R ₅₄₁	R ₅₄₂	R ₅₄₃	R ₅₄₄	R ₅₄₅	M.p.(°C)
32	-H	-H	-CH ₃	-H	-H	298.9
33	-H	-H	-C ₆ H ₅	-H	-H	>300
34	-H	-H	-Cl	-H	-H	>300

Table 12



Ex. No.	R ₅₄₆	R ₅₄₇	R ₅₄₈	R ₅₄₉	R ₅₅₀	R ₅₅₁	R ₅₅₂	NMR
35	-H	-H	-H	-H	-H	-H	-H	¹ H-NMR (DMSO-d ₆) δppm: 5.71 (2H, s), 7.13 (2H, d, J = 8.4 Hz), 7.31 (1H, t, J = 7.5 Hz), 7.31 (1H, t, J = 7.5 Hz), 7.47 - 7.52 (3H, m), 7.68 (2H, d, J = 8.4 Hz), 7.80 (1H, d, J = 8.7 Hz), 7.97 (1H, s), 8.27 (1H, d, J = 7.7 Hz), 8.44 (1H, d, J = 1.3 Hz), 12.51 (1H, br-s)
36	-OCH ₃	-H	-H	-H	-H	-H	-H	¹ H NMR (DMSO-d ₆) δppm: 3.97 (3H, s), 5.89 (2H, s), 7.08 (2H, d, J = 8.4 Hz), 7.22-7.34 (2H, m), 7.41-7.54 (3H, m), 7.60-7.70 (1H, m), 7.96 (1H, s), 8.06 (1H, s), 8.22 (1H, d, J = 7.7 Hz), 12.53 (1H, brs).
37	-H	-H	-H	-CH ₃	-H	-H	-CH ₃	¹ H NMR (DMSO-d ₆) δppm: 2.56 (3H, s), 2.86 (3H, s), 5.90 (2H, s), 6.87 (2H, d, J = 8.4 Hz), 7.00 (1H, d, J = 7.5 Hz), 7.08-7.20 (2H, m), 7.48 (2H, d, J = 8.3 Hz), 7.63-7.76 (2H, m), 8.04 (1H, s), 8.46 (1H, s), 12.51 (1H, s).
38	-CH ₃	-H	-H	-H	-H	-H	-H	¹ H NMR (DMSO-d ₆) δppm: 2.64 (3H, s), 5.89 (2H, s), 6.89 (2H, d, J = 8.5 Hz), 7.31 (1H, t, J = 7.4 Hz), 7.39 (1H, s), 7.42-7.52 (3H, m), 7.60 (1H, d, J = 8.3 Hz), 7.91 (1H, s), 8.26 (1H, d, J = 7.6 Hz), 8.33 (1H, d, J = 1.5 Hz), 12.51 (1H, s).
39	-H	-H	-H	-H	-H	-H	-CH ₃	¹ H NMR (DMSO-d ₆) δppm: 3.97 (3H, s), 5.89 (2H, s), 7.08 (2H, d, J = 8.4 Hz), 7.22-7.34 (2H, m), 7.41-7.54 (3H, m), 7.60-7.70 (1H, m), 7.96 (1H, s), 8.06 (1H, s), 8.22 (1H, d, J = 7.7 Hz), 12.53 (1H, brs).
40	-H	-H	-H	-H	-H	-H	-OCH ₃	¹ H NMR (DMSO-d ₆) δppm: 3.90 (3H, s), 5.89 (2H, s), 7.02-7.18 (3H, m), 7.18-7.30 (1H, m), 7.41-7.51 (2H, m), 7.60-7.70 (1H, m), 7.77 (1H, d, J = 8.7 Hz), 7.85 (1H, d, J = 7.6 Hz), 7.96 (1H, s), 8.40 (1H, d, J = 1.4 Hz), 12.51 (1H, s).
41	-CH ₃	-H	-H	-H	-H	-H	-CH ₃	¹ H NMR (DMSO-d ₆) δppm: 2.55 (3H, s), 2.59 (3H, s), 6.01 (2H, s), 6.85-6.96 (2H, m), 7.12-7.25 (2H, m), 7.37 (1H, s), 7.47-7.56 (2H, m), 7.90 (1H, s), 8.08-8.16 (1H, m), 8.30 (1H, s), 12.51 (1H, s).
42	-OCH ₃	-H	-H	-H	-H	-H	-OCH ₃	¹ H NMR (DMSO-d ₆) δppm: 3.88 (3H, s), (3H, s), 6.09 (2H, s), 6.90-6.99 (2H, m), 7.02-7.08 (1H, m), 7.15-7.25 (2H, m), 7.36-7.45 (2H, m), 7.70-7.80 (1H, m), 7.93 (1H, s), 7.98 (1H, s), 12.53 (1H, s).

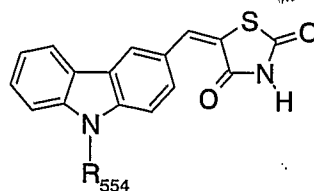
Table 13



5

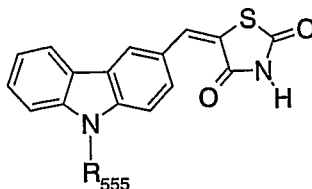
Ex. No.	R_{553}	M.p.(°C)
43	-H	>300
44	$-\text{CO}_2\text{C}(\text{CH}_3)_3$	>300
45	$-\text{COC}_6\text{H}_5$	>300

Table 1.4



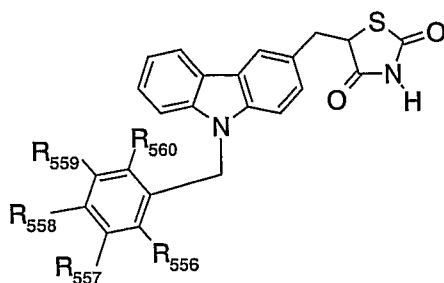
Ex. No.	R ₅₅₄	NMR
46	-C ₂ H ₅	NMR(DMSO-d ₆) dppm: 1.31(t; J=7.1Hz, 3H), 4.47(q; J=7.1Hz, 2H), 7.26(t, J=7.5Hz, 1H), 7.51(t, J=7.7Hz, 1H), 7.65-7.77 (m, 3H), 7.96(s, 1H), 8.22(d, J=7.8Hz, 1H), 8.40(s, 1H), 12.42(brs, 1H)
47		1H-NMR (DMSO-d ₆) dppm: 5.78 (2H, s), 7.25 - 7.60 (6H, m), 7.88 (1H, d, J = 8.6 Hz), 7.98 (1H, s), 8.27 (1H, d, J = 7.7 Hz), 8.40-8.50 (2H, m), 12.52 (1H, s)
48		1H-NMR (DMSO-d ₆) dppm : 5.83 (2H, s), 7.32 (1H, t, J=7.4Hz), 7.38-7.46 (3H, m), 7.52-7.56 (1H, m), 7.58 (1H, dd, J1=2.3Hz, J2=8.3Hz), 7.72 (1H, dd, J1=1.6Hz, J2=8.7Hz), 7.82 (1H, d, J=8.3Hz), 7.85 (1H, d, J=8.3Hz), 7.94 (1H, d, J=8.7Hz), 7.98-8.00 (3H, m), 8.29 (1H, d, J=7.8Hz), 8.46 (1H, d, J=1.6Hz), 8.66 (1H, d, J=2.1Hz), 12.52 (1H, brs)
49		1H-NMR (DMSO-d ₆) dppm : 5.79 (2H, s), 7.32 (1H, t, J=7.6Hz), 7.52-7.57 (2H, m), 7.60 (1H, dd, J1=3.0Hz, J2=5.0Hz), 7.66-7.67 (1H, m), 7.70-7.72 (1H, m), 7.75 (1H, d, J=8.3Hz), 7.80 (1H, d, J=8.3Hz), 7.92 (1H, d, J=8.7Hz), 7.96 (1H, s), 8.08-8.09 (1H, m), 8.28 (1H, d, J=7.6Hz), 8.45 (1H, s), 8.57 (1H, s), 13.00 (1H, brs)
50		1H-NMR (DMSO-d ₆) dppm : 5.86 (2H, s), 7.33 (1H, t, J=7.5Hz), 7.39-7.44 (2H, m), 7.49-7.59 (5H, m), 7.73 (1H, dd, J1=1.3Hz, J2=8.5Hz), 7.83 (1H, d, J=8.5Hz), 7.95 (2H, d, J=8.5Hz), 8.29 (1H, d, J=7.5Hz), 8.46 (1H, s), 8.69 (1H, s), 12.52 (1H, brs)
51		1H-NMR (DMSO-d ₆) dppm : 5.78 (2H, s), 7.11-7.12 (1H, m), 7.32 (1H, t, J=7.5Hz), 7.52-7.55 (2H, m), 7.59-7.60 (1H, m), 7.68 (1H, dd, J1=1.0Hz, J2=3.7Hz), 7.71 (1H, dd, J1=1.7Hz, J2=8.7Hz), 7.80 (2H, dd, J1=2.5Hz, J2=8.3Hz), 7.92 (1H, d, J=8.7Hz), 7.95 (1H, s), 8.27 (1H, d, J=7.7Hz), 8.45 (1H, s), 8.51 (1H, d, J=1.7Hz), 12.53 (1H, brs)
52		1H-NMR (DMSO-d ₆) dppm : 5.77 (2H, s), 6.94-6.95 (1H, m), 7.31 (1H, t, J=7.5Hz), 7.51-7.54 (2H, m), 7.59 (1H, d, J=8.2Hz), 7.70-7.72 (2H, m), 7.79 (1H, d, J=8.2Hz), 7.91 (1H, d, J=8.8Hz), 7.94 (1H, s), 8.24 (1H, s), 8.27 (1H, d, J=7.5Hz), 8.44 (1H, s), 8.54 (1H, s), 12.52 (1H, brs)
53		1H-NMR (DMSO-d ₆) dppm : 5.84 (2H, s), 7.33 (1H, t, J=7.7Hz), 7.48 (1H, dd, J1=4.8Hz, J2=8.2Hz), 7.54 (1H, t, J=7.7Hz), 7.62 (1H, dd, J1=2.0Hz, J2=8.2Hz), 7.72 (1H, dd, J1=1.4Hz, J2=8.2Hz), 7.82 (1H, d, J=8.2Hz), 7.93 (1H, d, J=4.1Hz), 7.95 (1H, d, J=4.1Hz), 7.97 (1H, s), 8.28 (1H, d, J=7.7Hz), 8.34 (1H, dt, J1=2.0Hz, J2=8.2Hz), 8.45 (1H, s), 8.60 (1H, dd, J1=1.4Hz, J2=4.8Hz), 8.69 (1H, d, J=1.4Hz), 9.17 (1H, d, J=1.4Hz), 12.48 (1H, brs)
54		1H-NMR (DMSO-d ₆) dppm : 5.86 (2H, s), 7.32 (1H, t, J=7.5Hz), 7.39-7.45 (1H, m), 7.51-7.57 (1H, m), 7.65 (1H, dd, J1=2.3Hz, J2=8.4Hz), 7.71 (1H, dd, J1=1.6Hz, J2=8.4Hz), 7.80 (1H, d, J=8.4Hz), 7.88-7.96 (3H, m), 8.26-8.33 (3H, m), 8.46 (1H, d, J=1.6Hz), 8.62-8.64 (1H, m), 8.67 (1H, d, J=1.6Hz), 13.02 (1H, brs)

Table 15



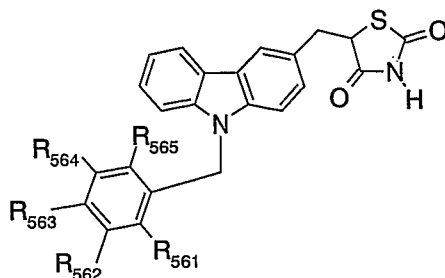
Ex. No.	R ₅₅₅	NMR
55		¹ H-NMR (DMSO-d ₆) δ ppm : 6.00 (2H, s), 7.07 (1H, d, J=8.6Hz), 7.31 (1H, t, J=7.2Hz), 7.47-7.52 (1H, m), 7.55-7.61 (1H, m), 7.66-7.79 (3H, m), 7.85 (1H, d, J=8.6Hz), 7.99 (3H, m), 8.25 (1H, d, J=8.6Hz), 8.29 (1H, d, J=7.6Hz), 8.47 (1H, d, J=1.4Hz), 12.52 (1H, brs)
56		¹ H-NMR (DMSO-d ₆) δ ppm : 2.29-2.31 (4H, m), 3.62 (4H, t, J=4.8Hz), 5.59 (2H, s), 6.70 (1H, d, J=8.7Hz), 7.28-7.32 (1H, m), 7.39 (1H, dd, J ₁ =2.3Hz, J ₂ =8.7Hz), 7.49-7.56 (1H, m), 7.69 (1H, dd, J ₁ =1.5Hz, J ₂ =8.7Hz), 7.81 (1H, d, J=8.2Hz), 7.93 (1H, d, J=8.7Hz), 7.96 (1H, s), 8.21 (1H, d, J=2.3Hz), 8.24 (1H, d, J=7.6Hz), 8.42 (1H, d, J=1.5Hz), 12.51 (1H, brs)
57		¹ H-NMR (DMSO-d ₆) δ ppm : 5.78 (2H, s), 7.14 (1H, d, J=4.3Hz), 7.32 (1H, t, J=7.6Hz), 7.50-7.59 (3H, m), 7.68-7.72 (1H, m), 7.78 (1H, d, J=4.3Hz), 7.82 (1H, d, J=4.3Hz), 7.92 (1H, d, J=8.7Hz), 7.97 (1H, s), 8.28 (1H, d, J=7.6Hz), 8.44-8.45 (1H, m), 8.49 (1H, d, J=1.7Hz), 12.53 (1H, brs)

Table 16



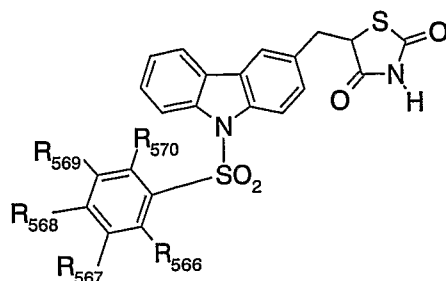
Ex.	R ₅₅₆	R ₅₅₇	R ₅₅₈	R ₅₅₉	R ₅₆₀	M.p.(°C)
58	-H	-H	-H	-H	-H	168.8
59	-H	-H	-C ₆ H ₅	-H	-H	207.1
60	-H	-H	-C ₆ H ₄ C ₆ H ₅ (PARA)	-H	-H	229.4
61	-H	-H	-Br	-H	-H	184.9
62	-H	-H	-Cl	-H	-H	176
63	-Cl	-H	-H	-H	-H	163.4
64	-H	-H	-CN	-H	-H	163.5
65	-H	-H	-OCH ₃	-H	-H	164.2
66	-H	-H	-SCH ₃	-H	-H	142.4
67	-H	-H	-SO ₂ CH ₃	-H	-H	229.2
68	-H	-H	-SOCH ₃	-H	-H	124
69	-H	-H	-3-THIENYL	-H	-H	199-200
70	-H	-H	-CO ₂ CH ₃	-H	-H	198.5
71	-H	-H	-NO ₂	-H	-H	109.2
72	-H	-H		-H	-H	173.2
73	-H	-H		-H	-H	221.7

Table 17



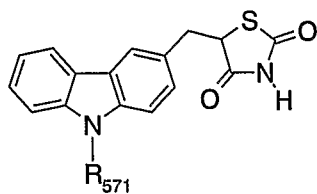
Ex. No.	R ₅₆₁	R ₅₆₂	R ₅₆₃	R ₅₆₄	R ₅₆₅	NMR
74	-H	-H	-2-PYRIDYL	-H	-H	1H-NMR (DMSO-d ₆) dppm: 3.26 (1H, dd, J ₁ =9.5Hz, J ₂ =14.1Hz), 3.59 (1H, dd, J ₁ =4.2Hz, J ₂ =14.1Hz), 5.00 (1H, dd, J ₁ =4.2Hz, J ₂ =9.5Hz), 5.74 (2H, s), 7.23 (1H, t, J=7.7Hz), 7.32 (2H, d, J=8.2Hz), 7.35 (1H, d, J=8.5Hz), 7.45 (1H, t, J=7.7Hz), 7.52 (1H, t, J=5.9Hz), 7.62 (1H, d, J=8.5Hz), 7.65 (1H, d, J=8.2Hz), 7.97 (2H, d, J=8.2Hz), 8.00 (1H, d, J=8.0Hz), 8.07-8.09 (2H, m), 8.15 (1H, d, J=7.7Hz), 8.69 (1H, d, J=4.8Hz), 12.04 (1H, s)
75	-H	-H	-3-PYRIDYL	-H	-H	1H-NMR (DMSO-d ₆) dppm: 3.26 (1H, dd, J ₁ =9.5Hz, J ₂ =14.1Hz), 3.59 (1H, dd, J ₁ =4.3Hz, J ₂ =14.1Hz), 5.00 (1H, dd, J ₁ =4.3Hz, J ₂ =9.5Hz), 5.74 (2H, s), 7.23 (1H, t, J=7.7Hz), 7.32-7.36 (3H, m), 7.45 (1H, t, J=7.7Hz), 7.63 (1H, d, J=8.3Hz), 7.67 (1H, d, J=8.3Hz), 7.73 (2H, d, J=8.3Hz), 7.86 (1H, dd, J ₁ =5.4Hz, J ₂ =7.7Hz), 8.07 (1H, s), 8.15 (1H, d, J=7.7Hz), 8.51 (1H, d, J=8.3Hz), 8.74 (1H, d, J=5.4Hz), 9.04 (1H, d, J=1.6Hz), 12.04 (1H, s)

Table 18



Ex. No.	R ₅₆₆	R ₅₆₇	R ₅₆₈	R ₅₆₉	R ₅₇₀	M.p.(°C)
76	-H	-H	-CH ₃	-H	-H	206.8
77	-H	-H	-C ₂ H ₅	-H	-H	178.4
78	-H	-H	-C ₆ H ₅	-H	-H	175.2
79	-H	-H	-OC ₆ H ₅	-H	-H	153
80	-H	-H	-CH(CH ₃) ₂	-H	-H	211.4
81	-H	-H	-OCH ₃	-H	-H	202.7
82	-H	-H	-H	-CH ₃	-H	180.8
83	-H	-H	-H	-H	-CH ₃	178.9
84	-CH ₃	-H	-CH ₃	-H	-CH ₃	217.3
85	-H	-H	-C ₆ H ₁₁	-H	-H	163.1
86	-H	-H	-Cl	-H	-H	227.7
87	-H	-H	-I	-H	-H	225.9
88	-H	-H	-Br	-H	-H	211.7
89	-H	-H	-F	-H	-H	242.7
90	-H	-H	-CF ₃	-H	-H	201.4
91	-H	-H	-Cl	-H	-Cl	201.9
92	-H	-H	-CN	-H	-H	257.7
93	-H	-H	-Cl	-Cl	-H	173.2
94	-H	-H	-H	-H	-Cl	167.2
95	-H	-H	-OCF ₃	-H	-H	201.3
96	-H	-H	-NHCOCH ₃	-H	-H	254.9

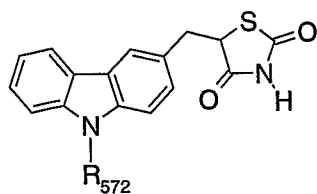
Table 19



5

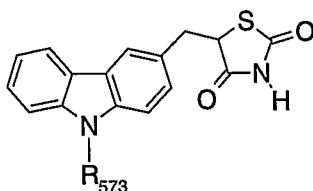
Ex. No.	R ₅₇₁	M.p.(°C)
97	-C ₂ H ₅	201-205
98	-CO ₂ C(CH ₃) ₃	175.5
99	-CH ₂ -cyclo-C ₆ H ₁₁	174.5
100	-(CH ₂) ₃ C ₆ H ₅	126.4
101	-CH ₃	217.4
102	-(CH ₂) ₃ Cl	144.1
103	-C ₃ H ₇	133.4
104	-C ₄ H ₉	162
105	-C ₅ H ₁₁	148.8
106	-C ₆ H ₁₃	134.2
107	-CH ₂ CH(CH ₃) ₂	153.6
108	-(CH ₂) ₂ CH(CH ₃) ₂	141.4
109	-CH ₂ CH(C ₂ H ₅) ₂	151
110	-CH ₂ -cyclo-C ₃ H ₅	156.2

Table 20



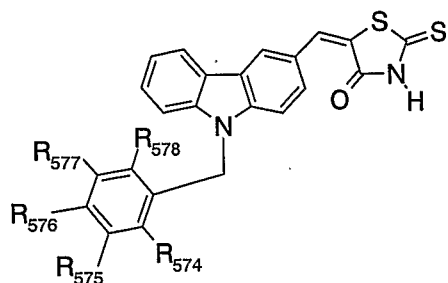
Ex. No.	R ₅₇₂	M.p.(°C)
111		184.5
112		210.9
113		164-168
114		275-276
115		125-129
116		219-223

115
Table 21



Ex. No.	R ₅₇₃	NMR
117		1H-NMR (DMSO-d ₆) dppm: 3.15-3.30 (1H, m), 3.50-3.65 (1H, m), 5.69 (2H, s), 7.15 - 7.70 (7H, m), 8.04 (1H, d, J = 0.9 Hz), 8.12 (1H, d, J = 7.7 Hz), 8.37 (1H, d, J = 2.2 Hz), 12.02 (1H, s)
118		1H-NMR (DMSO-d ₆) dppm: 1.40-1.60 (5H, m), 3.20-3.50 (5H, m), 3.55-3.60 (1H, m), 4.95-5.00 (1H, m), 5.47 (2H, s), 6.66 (1H, d, J = 8.9Hz), 7.20 (1H, t, J = 7.5Hz), 7.30-7.55 (3H, m), 7.70-7.80 (2H, m), 8.02 (1H, s), 8.10-8.20 (2H, m), 12.03 (1H, s)
119		1H-NMR (DMSO-d ₆) dppm : 3.26 (1H, dd, J ₁ =9.6Hz, J ₂ =14.1Hz), 3.38 (1H, dd, J ₁ =5.7Hz, J ₂ =14.1Hz), 5.10 (1H, dd, J ₁ =5.7Hz, J ₂ =9.6Hz), 5.76 (2H, s), 7.24 (1H, t, J=7.3Hz), 7.37 (1H, dd, J ₁ =1.5Hz, J ₂ =8.4Hz), 7.45-7.48 (1H, m), 7.65-7.74 (5H,m), 7.88 (1H, d, J=8.4Hz), 8.07 (1H, s), 8.15 (1H, d, J=7.7Hz), 8.22 (1H, d, J=1.9Hz), 8.56 (1H, d, J=1.9Hz), 12.05 (1H, s)
120		1H-NMR (DMSO-d ₆) dppm : 3.27 (1H, dd, J ₁ =9.6Hz, J ₂ =14.0Hz), 3.58 (1H, dd, J ₁ =4.4Hz, J ₂ =14.0Hz), 5.00 (1H, dd, J ₁ =4.4Hz, J ₂ =9.6Hz), 5.76 (2H, s), 7.24 (1H, t, J=7.5Hz), 7.37 (1H, dd, J ₁ =1.7Hz, J ₂ =8.3Hz), 7.40-7.48 (4H, m), 7.59 (1H, dd, J ₁ =2.1Hz, J ₂ =8.3Hz), 7.71 (1H, d, J=8.2Hz), 7.74 (1H, d, J=8.3Hz), 7.86 (1H, d, J=8.3Hz), 7.98 (2H, dd, J ₁ =1.7Hz, J ₂ =8.3Hz), 8.07 (1H, s), 8.15 (1H, d, J=7.5Hz), 8.63 (1H, d, J=1.7Hz), 12.04 (1H, s)
121		1H-NMR (DMSO-d ₆) dppm : 3.26 (1H, dd, J ₁ =9.6Hz, J ₂ =14.1Hz), 3.58 (1H, dd, J ₁ =4.2Hz, J ₂ =14.1Hz), 5.00 (1H, dd, J ₁ =4.2Hz, J ₂ =9.6Hz), 5.70 (2H, s), 7.11 (1H, dd, J ₁ =3.8Hz, J ₂ =4.9Hz), 7.23 (1H, t, J=7.6Hz), 7.36 (1H, dd, J ₁ =2.1Hz, J ₂ =9.4Hz), 7.46 (1H, t, J=7.6Hz), 7.52 (1H, dd, J ₁ =2.1Hz, J ₂ =8.3Hz), 7.59 (1H, dd, J ₁ =0.9Hz, J ₂ =4.9Hz), 7.68-7.69 (2H, m), 7.72 (1H, d, J=8.3Hz), 7.79 (1H, d, J=8.3Hz), 8.06 (1H, s), 8.14 (1H, d, J=7.8Hz), 8.48 (1H, d, J=1.7Hz), 12.04 (1H, s)
122		1H-NMR (DMSO-d ₆) dppm : 3.27 (1H, dd, J ₁ =9.5Hz, J ₂ =14.0Hz), 3.59 (1H, dd, J ₁ =4.2Hz, J ₂ =14.0Hz), 5.01 (1H, dd, J ₁ =4.2Hz, J ₂ =9.5Hz), 5.81 (2H, s), 7.24(1H, t, J=7.5Hz), 7.36-7.39 (1H, m), 7.47 (1H, t, J=7.5Hz), 7.68-7.77 (3H, m), 7.98 (1H, dd, J ₁ =5.5Hz, J ₂ =8.1Hz), 8.08-8.11 (2H, m), 8.16 (1H, d, J=7.5Hz), 8.70 (1H, d, J=1.7Hz), 8.84-8.86 (1H, m), 8.91-8.94 (1H, m), 9.37 (1H, d, J=1.7Hz), 12.06 (1H, s)
123		1H-NMR (DMSO-d ₆) dppm : 3.27 (1H, dd, J ₁ =9.5Hz, J ₂ =14.1Hz), 3.59 (1H, dd, J ₁ =4.3Hz, J ₂ =14.1Hz), 5.00 (1H, dd, J ₁ =4.3Hz, J ₂ =9.5Hz), 5.81 (2H, s), 7.24 (1H, t, J=7.6Hz), 7.37 (1H, dd, J ₁ =1.5Hz, J ₂ =8.3Hz), 7.45-7.48 (1H, m), 7.55 (1H, t, J=6.2Hz), 7.70 (1H, d, J=8.3Hz), 7.71 (1H, dd, J ₁ =2.2Hz, J ₂ =8.3Hz), 7.73 (1H, d, J=8.3Hz), 8.05-8.07 (2H, m), 8.15 (1H, d, J=7.6Hz), 8.31 (1H, d, J=8.3Hz), 8.38 (1H, d, J=8.3Hz), 8.68-8.69 (2H, m), 12.04 (1H, s)
124		1H-NMR (DMSO-d ₆) dppm : 3.26 (1H, dd, J ₁ =9.5Hz, J ₂ =14.1Hz), 3.58 (1H, dd, J ₁ =4.3Hz, J ₂ =14.1Hz), 5.00 (1H, dd, J ₁ =4.3Hz, J ₂ =9.5Hz), 5.70 (2H, s), 7.13 (1H, d J=4.0Hz), 7.23 (1H, t, J=7.6Hz), 7.36 (1H, dd, J ₁ =1.3Hz, J ₂ =8.3Hz), 7.46 (1H, t, J=7.6Hz), 7.54 (1H, dd, J ₁ =2.1Hz, J ₂ =8.3Hz), 7.57 (1H, d, J=4.0Hz), 7.68 (1H, d, J=8.3Hz), 7.71 (1H, d, J=8.3Hz), 7.79 (1H, d, J=8.3Hz), 8.06 (1H, s), 8.14 (1H, d, J=7.6Hz), 8.45 (1H, d, J=2.1Hz), 12.03 (1H, s)

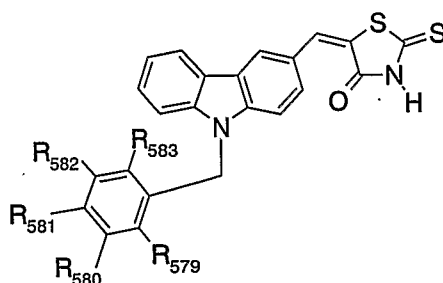
Table 22



Ex. No.	R ₅₇₄	R ₅₇₅	R ₅₇₆	R ₅₇₇	R ₅₇₈	M.p.(°C)
125	-H	-H	-H	-H	-H	282.1

5

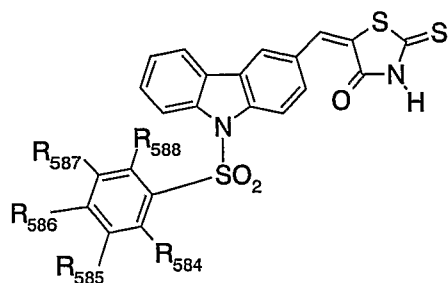
Table 23



Ex. No.	R ₅₇₉	R ₅₈₀	R ₅₈₁	R ₅₈₂	R ₅₈₃	NMR
126	-H	-H	-2-PYRIDYL	-H	-H	1H-NMR (DMSO-d ₆) dppm : 5.81 (2H, s), 7.29-7.34 (4H, m), 7.53 (1H, t, J=7.8Hz), 7.70 (1H, d, J=8.8Hz), 7.73 (1H, d, J=8.1Hz), 7.82-7.88 (4H, m), 7.99 (2H, d, J=8.1Hz), 8.32 (1H, d, J=7.8Hz), 8.47 (1H, s), 8.61-8.62 (1H, m), 13.76 (1H, brs)
127	-H	-H	-3-THIENYL	-H	-H	1H-NMR (DMSO-d ₆) dppm : 5.75 (2H, s), 7.22 (2H, d, J=8.0Hz), 7.31 (1H, t, J=7.5Hz), 7.45-7.55 (2H, m), 7.58-7.63 (3H, m), 7.66-7.82 (4H, m), 7.87 (1H, d, J=8.6Hz), 8.31 (1H, d, J=8.0Hz), 8.45-8.46 (1H, m), 13.76 (1H, brs)

10

Table 24

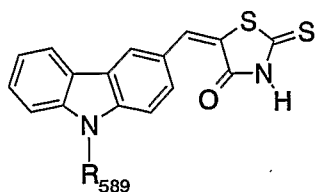


Ex. No.	R ₅₈₄	R ₅₈₅	R ₅₈₆	R ₅₈₇	R ₅₈₈	M.p.(°C)
128	-H	-H	-CH ₃	-H	-H	>300

5

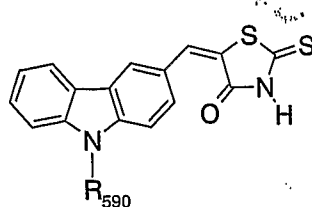
Table 25

10



Ex. No.	R ₅₈₉	M.p.(°C)
129	-COC ₆ H ₅	213.2

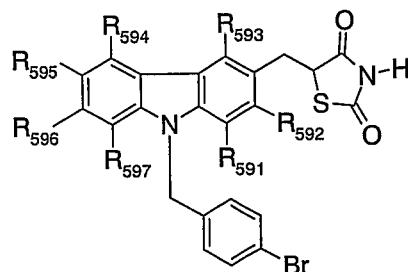
Table 26



Ex. No.	R ₅₉₀	NMR
130	-C ₂ H ₅	NMR(DMSO-d ₆) dppm : 1.32(t; J=7.1Hz, 3H), 4.49(q; J=7.1Hz, 2H), 7.28(t, J=7.5Hz, 1H), 7.52(t, J=7.8Hz, 1H), 7.66-7.82 (m, 4H), 8.25(d, J=7.8Hz, 1H), 8.40(s, 1H), 12.68(brs, 1H)
131		¹ H-NMR (DMSO-d ₆) dppm : 5.79 (2H, s), 7.32 (1H, t, J=7.4Hz), 7.52-7.56 (2H, m), 7.60 (1H, dd, J ₁ =3.0Hz, J ₂ =4.8Hz), 7.65-7.66 (1H, m), 7.70-7.71 (1H, m), 7.75 (1H, d, J=8.2Hz), 7.80 (2H, d, J=8.2Hz), 7.94 (1H, d, J=8.7Hz), 8.09 (1H, dd, J ₁ =1.2Hz, J ₂ =3.0Hz), 8.31 (1H, d, J=7.6Hz), 8.45 (1H, s), 8.56 (1H, s), 13.77 (1H, brs)
132		¹ H-NMR (DMSO-d ₆) dppm : 5.82 (2H, s), 7.33 (1H, t, J=7.5Hz), 7.41 (1H, d, J=7.3Hz), 7.45 (2H, t, J=7.5Hz), 7.55 (1H, t, J=8.4Hz), 7.58 (1H, dd, J ₁ =2.1Hz, J ₂ =8.4Hz), 7.72 (1H, dd, J ₁ =1.5Hz, J ₂ =8.7Hz), 7.80-7.83 (3H, m), 7.95 (1H, d, J=8.7Hz), 7.99 (2H, d, J=7.3Hz), 8.32 (1H, d, J=7.6Hz), 7.46 (1H, s), 8.66 (1H, d, J=2.1Hz), 13.77 (1H, brs)
133		¹ H-NMR (DMSO-d ₆) dppm : 5.86 (2H, s), 7.34 (1H, t, J=7.5Hz), 7.39-7.43 (2H, m), 7.50-7.59 (6H, m), 7.71-7.73 (1H, m), 7.83 (1H, d, J=8.5Hz), 7.96 (1H, d, J=8.5Hz), 8.32 (1H, d, J=7.5Hz), 8.46 (1H, s), 8.69 (1H, s), 13.78 (1H, brs)
134		¹ H-NMR (DMSO-d ₆) dppm : 5.78 (2H, s), 7.12 (1H, dd, J ₁ =3.8Hz, J ₂ =5.0Hz), 7.32 (1H, t, J=7.6Hz), 7.52-7.55 (2H, m), 7.59 (1H, dd, J ₁ =0.8Hz, J ₂ =5.0Hz), 7.68-7.71 (2H, m), 7.79-7.81 (3H, m), 7.93 (1H, d, J=8.6Hz), 8.31 (1H, d, J=7.6Hz), 8.45 (1H, s), 8.51 (1H, d, J=1.9Hz), 13.76 (1H, brs)
135		¹ H-NMR (DMSO-d ₆) dppm : 5.78 (2H, s), 6.95 (1H, d, J=1.0Hz), 7.32 (1H, t, J=7.7Hz), 7.52-7.54 (2H, m), 7.59 (1H, d, J=8.2Hz), 7.70-7.73 (2H, m), 7.79-7.81 (2H, m), 7.93 (1H, d, J=8.8Hz), 8.24 (1H, s), 8.31 (1H, d, J=7.7Hz), 8.45 (1H, s), 8.54 (1H, s), 13.76 (1H, brs)
136		¹ H-NMR (DMSO-d ₆) dppm : 5.87 (2H, s), 7.33 (1H, t, J=7.6Hz), 7.40-7.74 (1H, m), 7.55 (1H, t, J=7.6Hz), 7.63-7.67 (1H, m), 7.70-7.74 (1H, m), 7.81 (1H, d, J=8.3Hz), 7.85 (1H, s), 7.88-7.96 (2H, m), 8.26-8.34 (3H, m), 8.47 (1H, s), 8.63 (1H, d, J=4.7Hz), 8.67 (1H, s), 13.78 (1H, brs)
137		¹ H-NMR (DMSO-d ₆) dppm : 6.00 (2H, s), 7.08 (1H, d, J=8.6Hz), 7.32 (1H, t, J=7.4Hz), 7.47-7.53 (1H, m), 7.55-7.60 (1H, m), 7.66-7.79 (3H, m), 7.84-7.97 (4H, m), 8.25 (1H, d, J=8.6Hz), 8.33 (1H, d, J=7.4Hz), 8.47-8.48 (1H, m), 13.76 (1H, brs)
138		¹ H-NMR (DMSO-d ₆) dppm : 2.49-2.51 (4H, m), 3.62 (4H, t, J=4.8Hz), 5.60 (2H, s), 6.71 (1H, d, J=8.7Hz), 7.30 (1H, t, J=7.5Hz), 7.39 (1H, dd, J ₁ =2.4Hz, J ₂ =8.7Hz), 7.50-7.56 (1H, m), 7.68-7.72 (1H, m), 7.80-7.82 (2H, m), 7.95 (1H, d, J=8.7Hz), 8.21 (1H, d, J=2.4Hz), 8.28 (1H, d, J=8.0Hz), 8.43-8.44 (1H, m), 13.76 (1H, brs)

119

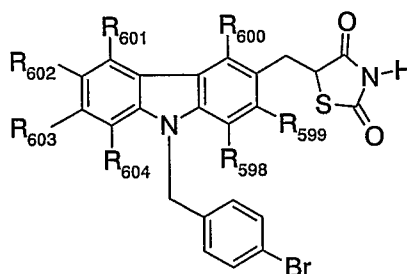
Table 27



Ex. No.	R ₅₉₁	R ₅₉₂	R ₅₉₃	R ₅₉₄	R ₅₉₅	R ₅₉₆	R ₅₉₇	M.p.(°C)
139	-OCH ₃	-H	-H	-H	-H	-H	-H	219.9-221.0
140	-H	-H	-H	-CH ₃	-H	-H	-CH ₃	252.0-252.6
141	-CH ₃	-H	-H	-H	-H	-H	-H	183.1-184.1
142	-H	-H	-H	-H	-H	-H	-CH ₃	211.6-213.8
143	-H	-H	-H	-H	-H	-H	-OCH ₃	210.7-212.5

5

Table 28

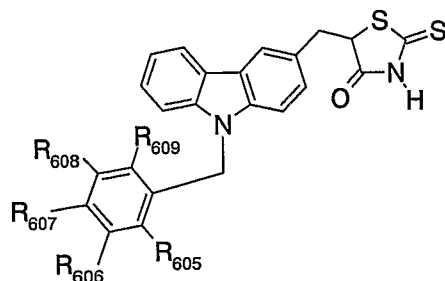


Ex. No.	R ₅₉₈	R ₅₉₉	R ₆₀₀	R ₆₀₁	R ₆₀₂	R ₆₀₃	R ₆₀₄	NMR
144	-CH ₃	-H	-H	-H	-H	-H	-CH ₃	¹ H NMR (DMSO-d ₆) δ ppm: 2.51 (3H, s), 2.52 (3H, s), 3.10-3.24 (1H, m), 3.45-3.60 (1H, m), 4.92-5.03 (1H, m), 5.94 (2H, s), 6.81-6.95 (2H, m), 7.01-7.18 (3H, m), 7.45-7.56 (2H, m) 7.90 (1H, s), 7.93-8.02 (1H, m), 12.06 (1H, s).
145	-OCH ₃	-H	-H	-H	-H	-H	-OCH ₃	¹ H NMR (DMSO-d ₆) δ ppm: 3.18 (1H, dd, J = 10.0, 14.0 Hz), 3.57 (1H, dd, J = 4.1, 14.0 Hz), 3.87 (6H, s), 5.02 (1H, dd, J = 4.1, 10.0 Hz), 6.05 (2H, s), 6.89-7.02 (4H, m), 7.13 (1H, t, J = 7.9 Hz), 7.35-7.42 (2H, m), 7.57 (1H, s), 7.65 (1H, d, J = 7.3 Hz), 12.06 (1H, s).

10

120

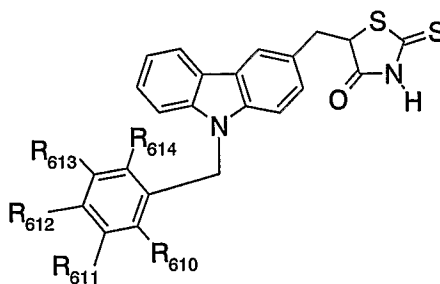
Table 29



Ex. No.	R ₆₀₅	R ₆₀₆	R ₆₀₇	R ₆₀₈	R ₆₀₉	M.p.(°C)
146	-H	-H	-H	-H	-H	199.4
147	-H	-H	-C ₆ H ₅	-H	-H	130.1
148	-H	-H	-Cl	-H	-H	123.9
149	-Cl	-H	-H	-H	-H	199.3
150	-H	-H	-Br	-H	-H	169.5
151	-H	-H	-CN	-H	-H	223.5
152	-H	-H	-OCH ₃	-H	-H	152
153	-H	-H	-SCH ₃	-H	-H	134.4
154	-H	-H	-SO ₂ CH ₃	-H	-H	219.9
155	-H	-H	-3-THIENYL	-H	-H	106-110

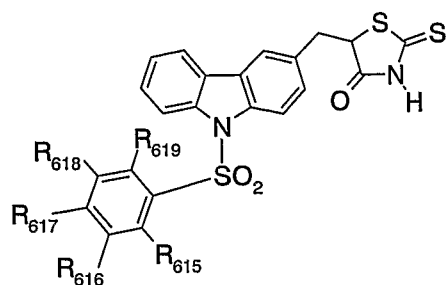
5

Table 30



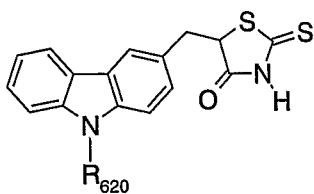
Ex. No.	R ₆₁₀	R ₆₁₁	R ₆₁₂	R ₆₁₃	R ₆₁₄	NMR
156	-H	-H	-2-PYRIDYL	-H	-H	1H-NMR (DMSO-d ₆) dppm : 3.32 (1H, dd, J ₁ =9.3Hz, J ₂ =14.1Hz), 3.57 (1H, dd, J ₁ =4.5Hz, J ₂ =14.1Hz), 5.12 (1H, dd, J ₁ =4.5Hz, J ₂ =9.3Hz), 5.75 (2H, s), 7.23 (1H, t, J=7.6Hz), 7.32 (2H, d, J=8.5Hz), 7.34 (1H, dd, J ₁ =1.5Hz, J ₂ =8.5Hz), 7.45 (1H, t, J=7.6Hz), 7.57 (1H, t, J=5.9Hz), 7.62 (1H, d, J=8.5Hz), 7.65 (1H, d, J=8.5Hz), 7.97 (2H, d, J=8.5Hz), 8.04-8.06 (2H, m), 8.12-8.16 (2H, m), 8.71 (1H, d, J=5.0Hz), 13.17 (1H, s)

Table 31



Ex. No.	R ₆₁₅	R ₆₁₆	R ₆₁₇	R ₆₁₈	R ₆₁₉	M.p.(°C)
157	-H	-H	-CH ₃	-H	-H	194.6
158	-H	-H	-C ₆ H ₅	-H	-H	231.5
159	-H	-H	-CF ₃	-H	-H	205
160	-H	-H	-F	-H	-H	233.5
161	-H	-H	-CN	-H	-H	241.4
162	-H	-H	-Cl	-H	-Cl	223.7
163	-H	-H	-Cl	-Cl	-H	185
164	-H	-H	-H	-H	-Cl	183.9
165	-H	-H	-OCF ₃	-H	-H	220.8

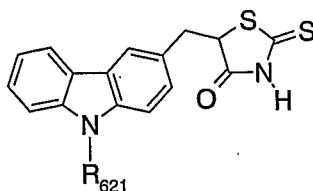
Table 32



5

Ex. No.	R ₆₂₀	M.p.(°C)
166	-CH ₃	168.5
167	-CH ₂ -cyclo-C ₆ H ₁₁	116.2
168	-(CH ₂) ₃ Cl	146.7
169	-C ₃ H ₇	149.7
170	-C ₄ H ₉	180.6
171	-C ₅ H ₁₁	153
172	-C ₆ H ₁₃	119.6
173	-CH ₂ CH(CH ₃) ₂	176.4
174	-(CH ₂) ₂ CH(CH ₃) ₂	165.9
175	-CH ₂ CH(C ₂ H ₅) ₂	163.8
176	-CH ₂ -cyclo-C ₃ H ₅	167.2
177		185-189
178		193-197
179		218-223
180		259-261
181		223-224

Table 33



Ex. No.	R ₆₂₁	NMR
182	-C ₂ H ₅	NMR(DMSO-d ₆) dppm : 1.31(t; J=7.1Hz, 3H), 3.33(dd; J=9.1, 14.2Hz, 1H), 2.56(dd; J=4.4, 14.2Hz, 1H), 4.43(q; J=7.1Hz, 2H), 5.11(dd; J=4.4, 9.1Hz, 1H), 7.19(t, J=7.5Hz, 1H), 7.35(d, J=8.3Hz, 1H), 7.45(t, J=8.3Hz, 1H), 7.56(d, J=8.3Hz, 1H), 7.60(d, J=8.3Hz, 1H), 8.01(s, 1H), 8.11(d, J=7.5Hz, 1H), 13.16(brs, 1H)
183		1H-NMR (DMSO-d ₆) dppm : 3.30-3.56 (2H, m), 5.12 (1H, dd, J1=4.5Hz, J2=9.3Hz), 5.74 (2H, s), 7.23 (1H, t, J=7.6Hz), 7.36 (1H, dd, J1=1.6Hz, J2=8.3Hz), 7.44-7.48 (1H, m), 7.62-7.65 (2H, m), 7.68-7.74 (3H, m), 7.83 (1H, d, J=8.3Hz), 8.06 (1H, s), 8.15 (1H, d, J=7.6Hz), 8.17 (1H, d, J=2.0Hz), 8.55 (1H, d, J=2.0Hz), 13.17 (1H, s)
184		1H-NMR (DMSO-d ₆) dppm : 3.32 (1H, dd, J1=9.3Hz, J2=14.1Hz), 3.57 (1H, dd, J1=4.5Hz, J2=14.1Hz), 5.12 (1H, dd, J1=4.5Hz, J2=9.3Hz), 5.74 (2H, s), 7.06 (1H, d, J=1.0Hz), 7.24(1H, t, J=7.2Hz), 7.36 (1H, dd, J1=1.6Hz, J2=8.4Hz), 7.45-7.48 (1H, m), 7.67-7.76 (4H, m), 7.79 (1H, t, J=1.6Hz), 8.06 (1H, d, J=1.0Hz), 8.15 (1H, d, J=7.7Hz), 8.39 (1H, s), 8.55 (1H, d, J=1.6Hz), 13.17 (1H, s)
185		1H-NMR (DMSO-d ₆) dppm : 3.33 (1H, dd, J1=9.2Hz, J2=14.1Hz), 3.57 (1H, dd, J1=4.5Hz, J2=14.1Hz), 5.13 (1H, dd, J1=4.5Hz, J2=9.2Hz), 5.79 (2H, s), 7.25 (1H, t, J=7.5Hz), 7.38 (1H, dd, J1=1.5Hz, J2=8.4Hz), 7.41-7.45 (2H, m), 7.48 (1H, t, J=8.1Hz), 7.50-7.55 (2H, m), 7.56-7.60 (2H, m), 7.73 (1H, d, J=8.4Hz), 7.75 (1H, d, J=8.4Hz), 8.07 (1H, s), 8.16 (1H, d, J=7.8Hz), 8.66 (1H, s), 13.17 (1H, s)

5

Test Example 1

Transcription promoting activity on human Trefoil Factor 2 (hTFF2) gene of test compounds was evaluated by means of an hTFF2 gene reporter assay.

10

(1) Preparation of hTFF2 gene reporter vector pGL3-hTFF2pro

DNA was extracted from HeLa cells (CCL-2, DAINIPPON PHARMACEUTICAL CO., LTD.) using a deoxyribonucleic acid (DNA)

extraction kit (DNeasy™ Tissue Kit, manufactured by QIAGEN). The hTFF2 promoter region was amplified using the extracted DNA as a template by means of the polymerase chain reaction (PCR). The oligomers 5'-CACGCGTCAGACTGGCAACCCCTGTC-3' and 5'-GAAGCTTCTAGCTCAGCTGCACCCAG-3' were selected as PCR primers to be amplified, based on the report by Beck et al. (Beck S., Sommer P., Blin N., Gott P., 5'-flanking motifs control cell-specific expression of trefoil factor genes (TFF), Int. J. Mol. Med. 2(3), 353-361 (1998)). Platinum® Pfx DNA polymerase was used as DNA polymerase. The PCR was performed under the conditions of denaturing for 30 seconds at 95°C, annealing for 30 seconds at 55°C and extending for 75 seconds at 68°C, and the procedures were repeated for 32 cycles.

15

The PCR products were separated and purified by 1 % agarose gel electrophoresis, and cloned to a pCR-BluntII-TOPO vector attached to a cloning kit (Zero Blunt® TOPO® PCR Cloning Kit, manufactured by Invitrogen Corporation). The produced plasmid pCR-Blunt-TFF2pro was introduced into *E.coli* for transformation (TOP 10 Ultracomp™ Cells, manufactured by Invitrogen Corporation), and transformant strain pCR-Blunt-TFF2pro/TOP10 was selectively cultured in LB agar medium containing 30µg/ml of Zeocin (Zeocin, manufactured by Invitrogen Corporation). The pCR-Blunt-TFF2pro/TOP10 was subjected to shaking culture in 50 ml of LB medium containing 30µg/ml of Zeocin at 37°C over night, and a plasmid was prepared using a plasmid preparation kit (Concert™ High Purity Midiprep System, manufactured by GIBCO BRL).

30

The nucleotide sequence of the PCR product cloned to

the plasmid pCR-Blunt-TFF2pro was determined. The determined nucleotide sequence was compared with the counterpart of hTFF2 promoter region reported in a gene bank (GenBank accession AB038162). The nucleotide sequence of the MluI-HindIII region cloned in pCR-Blunt-TFF2pro was identical to GenBank accession AB038162 (Fig. 1).

Fig. 1 shows in the upper register the nucleotide sequence and nucleotide numbering of the hTFF2 promoter region reported in GenBank (accession AB038162). The lower register shows the nucleotide sequence (see appended Sequence Number 1 shown in Sequence Listing) of the PCR product cloned in the plasmid pCR-Blunt-TFF2pro. The underlined portions indicate the recognition sequence (ACGCGT) of the restriction enzyme MluI and the recognition sequence (AAGCTT) of the restriction enzyme HindIII. The nucleotide sequences of the MluI-HindIII region are identical between the hTFF2 promoter region reported in GenBank (accession AB038162) and the PCR product cloned to the plasmid pCR-Blunt-TFF2pro. ATG enclosed in the box is the translation start codon and the arrow shows the transcription initiation site.

The plasmid pCR-Blunt-hTFF2pro was cleaved by the restriction enzymes MluI and HindIII, fractionated by 1% agarose gel electrophoresis, and the hTFF2 promoter region was purified using a nucleic acid purification kit (ConcertTM Matrix Gel Extraction System, manufactured by GIBCO BRL). The hTFF2 promoter region was inserted into the MluI-HindIII region of a commercial plasmid pGL-Basic (manufactured by Promega Corporation) using a ligation kit (Ligation high, manufactured by TOYOBO CO., LTD.) to produce pGL3-hTFF2pro.

The plasmid pGL3-hTFF2pro was introduced into *E. coli* for transformation (DH5 α Competent Cell, manufactured by TOYOBO CO., LTD.) and transformant strain pGL3-hTFF2pro/DH5 α was selectively cultured in LB agar medium containing 100 μ g/ml of
5 ampicillin.

The pGL3-hTFF2pro/DH5 α was inoculated into a 2-liter Erlenmeyer flask containing 400ml of LB medium containing 100 μ g/ml ampicillin, and subjected to 200 rpm shaking culture
10 at 37°C in a rotary shaker overnight. The plasmid pGL3-hTFF2pro was extracted and purified from the cultured cells using a plasmid preparation kit (EndoFree Plasmid Maxi Kit, manufactured by QIAGEN).

15 A commercial vector, pWLneo (manufactured by Stratagene), containing a drug-selection marker was introduced into *E. coli* for transformation (DH5 α Competent Cell, manufactured by TOYOBO CO., LTD.) and transformant strain pWLneo/DH5 α was selectively cultured in LB agar
20 medium containing 100 μ g/ml of ampicillin. The pWLneo/DH5 α was inoculated into a 1-liter Erlenmeyer flask containing 150ml of LB medium containing 100 μ g/ml of ampicillin, and subjected to 200 rpm shaking culture at 37°C in a rotary shaker overnight. The plasmid pWLneo was extracted and
25 purified from the cultured cells using a plasmid preparation kit (EndoFree Plasmid Maxi Kit, manufactured by QIAGEN).

(2) Preparation of cell line pGL3-hTFF2pro·pWL-neo/MKN-
45 #6-2 for hTFF2 gene reporter assay

30 Human gastric cancer cell line MKN-45 (JCRB0254, Health Science Research Resources Bank) was cultured in medium (IMDM

medium) composed of 500 ml of medium (Escove's Modified Dulbecco's Medium, manufactured by SIGMA), 50 ml of fetal bovine serum (manufactured by SIGMA) immobilized by heating at 56°C for 30 minutes, 5 ml of Penicillin-Streptomycin liquid (manufactured by SIGMA) and 20 ml of 200 mM L-glutamin (manufactured by SIGMA), using a culture dish having a diameter of 10 cm (CORNING Incorporated) placed in a 5% CO₂ incubator at 37°C. The cells were washed with buffer (Dulbecco's Phosphate Buffered Saline, manufactured by SIGMA) and subjected to trypsin (0.25% Trypsin-1mM EDTA·4Na, manufactured by SIGMA) treatment for suspension. The cells were suspended in the IMDM medium, stained using Trypan Blue Stain, 0.4% (tradename, Invitrogen Corporation) and the number of cells which did not stain was counted as live cells using a hemocytometer. The cells were washed once with buffer (Dulbecco's Phosphate Buffered Saline, manufactured by SIGMA) and 10⁶ live cells were suspended in a solution for gene transfer (0.25 M Mannitol/0.1 mM CaCl₂/0.1 mM MgCl₂/0.2 mM Tris-HCl, pH7.2 to 7.4) to which 10 µg of the prepared plasmid pGL3-hTFF2pro and 2 µg of the plasmid pWLneo were added. The plasmid-added cell suspension was transferred to a 1mm cuvette (manufactured by Bio-Rad Laboratories, Inc.) and gene introduction into cells was performed by means of electroporation using an SSH-1 cell fusion apparatus (Shimadzu Corporation). The cells were suspended in the IMDM medium, inoculated in a culture dish having a diameter of 10 cm (CORNING Incorporated) and cultured in a 5% CO₂ incubator at 37°C for 2 days. Selective culturing was then carried out using IMDM medium containing 400 µg/ml of Geneticin (manufactured by Invitrogen Corporation). 100 µl of the culture medium was then first inoculated into each well of a

96-well plate (manufactured by BD Falcon), and proliferated cells were sequentially subjected to passaged culturing in a 24-well plate (manufactured by BD Falcon) and further in a 6-well plate (manufactured by BD Falcon) to prepare pGL3-hTFF2pro·pWL-neo/MKN-45 #6 cells. The obtained pGL3-hTFF2pro·pWL-neo/MKN-45 #6 cells were suspended in IMDM medium containing 400 µg/ml of Geneticin, inoculated into a 96-well plate by means of limiting dilution for cloning to obtain single clone pGL3-hTFF2pro·pWL-neo/MKN-45 #6-2 cells. The pGL3-hTFF2pro·pWL-neo/MKN-45 #6-2 cells were proliferated in a 10 cm culture dish, harvested and cryopreserved.

(3) The hTFF2 genetic reporter assay using pGL3-hTFF2pro·pWL-neo/MKN-45 #6-2 cell line

pGL3-hTFF2pro·pWL-neo/MKN-45 #6-2 was thawed from the frozen state for use. The cells were inoculated into IMDM medium containing 400 µg/ml of Geneticin in a 10 cm culture dish and sequentially passaged every 3 to 5 days. During the passage culturing, the cells were washed with buffer (Dulbecco's Phosphate Buffered Saline, manufactured by SIGMA), and trypsin (0.25% Trypsin-1mM EDTA·4Na, manufactured by SIGMA) was added to separate the cells by treatment for 5 minutes at 37°C. The cell suspension was collected by adding IMDM medium, and the cells were stained using Trypan Blue Stain, 0.4% (tradename, Invitrogen Corporation) and the number of cells which did not stain was counted as live cells using a hemocytometer. A cell survival rate of 90 % or higher was confirmed prior to the live cells being used for the hTFF2 genetic reporter assay.

30

A day before test compounds were added, 100 µl of the

cell suspension containing about 7.5×10^4 cells was inoculated into each well of 96-well plates (manufactured by COSTAR) and cultured in a 5 % CO₂ incubator at 37 °C. The test compounds were prepared to have a concentration 200 times the final measurement concentration with dimethylsulfoxide (Wako Pure Chemical Industries, Ltd.). The test compounds having a predetermined concentration were respectively diluted 100 times with IMDM medium, and 100 µl of the diluted compounds was dispensed into wells of the 96-well plates. Dimethylsulfoxide was diluted 100 times with IMDM medium and added to those wells to which test compounds were not added. After the test compounds were added, the cells were cultured in a 5 % CO₂ incubator at 37 °C for 24 hours. When the culturing was completed, the culture supernatant was removed and the 96-well plates were frozen in a deep freezer (manufactured by SANYO Electric Co., Ltd.). The 96-well plates were thawed at room temperature when the luciferase activity was measured, and 100 µl of PicaGene LT2.0 (Wako Pure Chemical Industries, Ltd.) diluted two times with buffer (Dulbecco's Phosphate Buffered Saline, manufactured by SIGMA) was added to each well. The plates were allowed to stand at room temperature for at least 30 minutes and the luciferase activity was measured using a Labsystems Luminoskan (manufactured by ICN Biomedicals Inc.).

25

Taking the average measurement of the dimethylsulfoxide-added well groups in each plate as 100%, a percentage for each test compound to the dimethylsulfoxide-added well groups (control %) was calculated.

30

The results are shown in the table below.

Table 34

Test Compound	TFF2 Production Promoting Activity
Compound of Example 17	++
Compound of Example 24	++
Compound of Example 25	++
Compound of Example 26	++
Compound of Example 58	++
Compound of Example 59	++
Compound of Example 60	++
Compound of Example 61	++
Compound of Example 62	++
Compound of Example 63	+
Compound of Example 64	++
Compound of Example 65	++
Compound of Example 66	++
Compound of Example 67	++
Compound of Example 68	++
Compound of Example 69	++
Compound of Example 70	++
Compound of Example 71	++
Compound of Example 72	++
Compound of Example 73	++
Compound of Example 74	++
Compound of Example 75	++
Compound of Example 76	++
Compound of Example 77	++
Compound of Example 78	++
Compound of Example 79	++
Compound of Example 80	++
Compound of Example 81	++
Compound of Example 82	++
Compound of Example 83	++
Compound of Example 84	++
Compound of Example 85	++
Compound of Example 86	++
Compound of Example 87	++
Compound of Example 88	++
Compound of Example 89	++
Compound of Example 90	++

Table34 (continued)

Test Compound	TFF2 Production Promoting Activity
Compound of Example 91	++
Compound of Example 92	++
Compound of Example 93	++
Compound of Example 94	++
Compound of Example 95	++
Compound of Example 96	++
Compound of Example 97	+
Compound of Example 99	++
Compound of Example 100	++
Compound of Example 102	+
Compound of Example 103	++
Compound of Example 104	++
Compound of Example 105	++
Compound of Example 106	++
Compound of Example 107	+
Compound of Example 108	+
Compound of Example 109	++
Compound of Example 110	+
Compound of Example 111	++
Compound of Example 112	++
Compound of Example 113	++
Compound of Example 114	++
Compound of Example 115	++
Compound of Example 116	++
Compound of Example 117	++
Compound of Example 118	++
Compound of Example 119	++
Compound of Example 120	++
Compound of Example 121	++
Compound of Example 122	++
Compound of Example 123	++
Compound of Example 124	++
Compound of Example 139	++
Compound of Example 140	++
Compound of Example 141	++
Compound of Example 142	++
Compound of Example 143	++
Compound of Example 144	+
Compound of Example 146	++

Table34 (continued)

Test Compound	TFF2 Production Promoting Activity
Compound of Example 147	++
Compound of Example 148	++
Compound of Example 149	++
Compound of Example 150	++
Compound of Example 151	++
Compound of Example 152	++
Compound of Example 153	++
Compound of Example 154	++
Compound of Example 155	++
Compound of Example 156	++
Compound of Example 157	++
Compound of Example 158	++
Compound of Example 159	++
Compound of Example 160	++
Compound of Example 161	++
Compound of Example 162	++
Compound of Example 163	++
Compound of Example 164	++
Compound of Example 165	++
Compound of Example 166	+
Compound of Example 167	++
Compound of Example 168	++
Compound of Example 169	++
Compound of Example 170	++
Compound of Example 171	++
Compound of Example 172	++
Compound of Example 173	++
Compound of Example 174	++
Compound of Example 175	++
Compound of Example 176	++
Compound of Example 177	++
Compound of Example 178	++
Compound of Example 179	++
Compound of Example 180	++
Compound of Example 181	++
Compound of Example 182	++
Compound of Example 183	++
Compound of Example 184	++
Compound of Example 185	++

In the above table, a TFF2 production promoting activity of 1000% or higher at a test compound concentration of 10^{-6} M is indicated as "++" and a TFF2 production promoting activity of 300% or higher at a test compound concentration of 10^{-6} M as "+".

The above results show that the concentration of compound of the present invention for showing 300 % or higher TFF2 production promoting activity is less than 10^{-5} M, and more preferably less than 10^{-6} M.

Test Example 2

Healing effects on rat models with acetic acid-induced gastric ulcers

(1) Production of gastric ulcer by acetic acid

Rats were fasted from the previous day. A celiotomy was done in each rat under ether anesthesia, and the stomach was exteriorized. Subsequently, 20 μ L of a 30 % acetic acid solution was injected into the submucosa at the junction of the body of the glandular stomach and the pyloric antrum using a disposable syringe to produce a gastric ulcer.

(2) Test compound administration

Each test compound was suspended in a 0.5% carboxymethylcellulose (CMC) solution at concentrations of 0.75 or 2.5 mg/ml. The rats were orally administrated once a day for 8 days starting with the forth day from operation at doses of 3 or 10 mg/kg. A gastric tube and a syringe were used for the oral administration. The volumes of each test compound and vehicle (0.5% CMC) were 4 ml/kg.

(3) Dissection

On the next day the vehicle and the test compound were finally administrated to the rats, the rats were sacrificed
 5 by exsanguination under anesthesia with ether, and each stomach was removed. The removed stomachs were fixed in 1 % formalin for 15 minutes, dissected along the greater curvature of stomach to expose the ulcer, and the ulcerated area was measured.

10

(4) Measurement of the ulcerated area

The ulcerated area was measured under a stereo microscope (10 x) with an ocular micrometer (1 mm²/grid), and the percentage healing ratio was calculated. The test
 15 results were shown in the Table 35. The percentage healing ratio was calculated by the following formula.

$$20 \quad \text{Healing ratio (\%)} = \frac{\frac{\text{average ulcerated area of control group}}{\text{average ulcerated area of control group}} - \frac{\text{average ulcerated area of test compound group}}{\text{average ulcerated area of control group}}}{\text{average ulcerated area of control group}} \times 100$$

Table 35

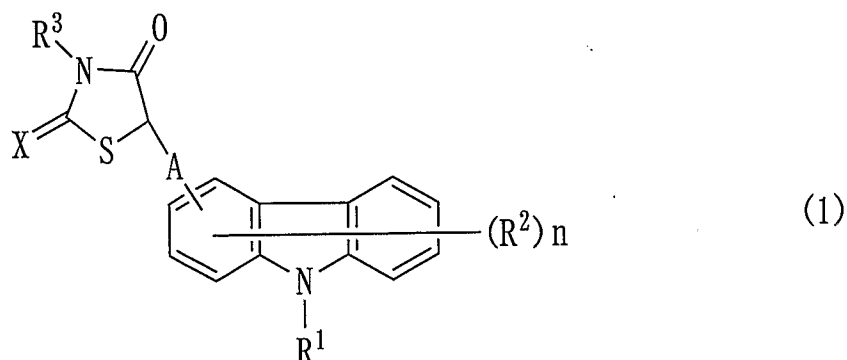
Test Compound	Dose (mg/kg)	Healing Ratio (%)
Example 26	3	>20
Example 61	1	>20
Example 76	10	>20
Example 77	3	>20
Example 78	3	>20
Example 86	3	>20
Example 97	10	>20
Example 117	3	>20
Example 158	3	>20

25

The Table 35 demonstrates that the compounds of the present invention are effective in preventing and/or treating mucosal injury.

CLAIMS

1. A compound represented by formula (1)



5

or a salt thereof,

wherein A is a direct bond, a lower alkylene group,
or a lower alkylidene group;

X is an oxygen atom or a sulfur atom;

10 R^1 is one of the following (1-1) to (1-21):

(1-1) a hydrogen atom, (1-2) a lower alkyl group,

(1-3) a phenyl lower alkyl group optionally substituted on
the phenyl ring with one or more members selected from the
group consisting of a phenyl group (optionally substituted on
the phenyl ring with one or more phenyl groups), lower alkyl
15 groups, lower alkoxy groups, halogen atoms, $-(B)_1NR^6R^7$ groups,
a nitro group, a carboxy group, lower alkoxy carbonyl groups,
a cyano group, phenyl lower alkoxy groups, a phenoxy group, a
piperidinyl lower alkoxy carbonyl groups, amino lower

20 alkoxy carbonyl groups optionally substituted with one or two
cycloalkyl groups, 2-imidazoliny carbonyl groups optionally
substituted on the 2-imidazoline ring with one or more lower
alkylthio groups, 3-pyrroliny carbonyl groups optionally
substituted on the 3-pyrroline ring with one or more lower
25 alkyl groups, thiazolidiny carbonyl groups optionally
substituted on the thiazolidine ring with a phenyl group, 3-
azabicyclo[3.2.2]nonyl carbonyl groups, piperidinyl lower
alkyl groups, anilino lower alkyl groups optionally

- substituted on the amino group with one or two lower alkyl groups, phenylthio lower alkyl groups, indolinyl lower alkyl groups, piperidinylcarbonyl groups optionally substituted on the piperidine ring with one or more lower alkyl groups,
- 5 pyridyl groups, thienyl groups, lower alkylsulfinyl groups, lower alkylsulfonyl groups, and lower alkylthio groups,
- (1-4) a cycloalkyl lower alkyl group,
- (1-5) a phenoxy lower alkyl group,
- (1-6) a naphthyl lower alkyl group,
- 10 (1-7) a lower alkoxy lower alkyl group,
- (1-8) a carboxy lower alkyl group,
- (1-9) a lower alkoxy carbonyl lower alkyl group,
- (1-10) a pyridyl lower alkyl group optionally substituted on the pyridine ring with one or more members selected from the
- 15 group consisting of halogen atoms; piperidinyl groups; a morpholino group; piperazinyl groups optionally substituted on the piperazine ring with one or more members selected from the group consisting of a phenyl group and lower alkyl groups; thienyl groups optionally substituted with one or
- 20 more halogen atoms; a phenyl group optionally substituted with one or more halogen atoms; pyridyl groups; piperidinyl lower alkyl groups; phenylthio lower alkyl groups; biphenyl groups; lower alkyl groups optionally substituted with one or more halogen atoms; pyridylamino groups; pyridylcarbonylamino
- 25 groups; lower alkoxy groups; anilino lower alkyl groups optionally substituted on the amino group with one or two lower alkyl groups; anilino groups optionally substituted on the amino group with one or two lower alkyl groups; and furyl groups,
- 30 (1-11) a cyano lower alkyl group,
- (1-12) a phenyl group,
- (1-13) a quinolyl lower alkyl group,
- (1-14) a lower alkoxy lower alkoxy-substituted lower alkyl group,
- 35 (1-15) a hydroxy-substituted lower alkyl group,

- (1-16) a lower alkyl group substituted with one or more halogen atoms,
- (1-17) a lower alkanoyloxy group optionally substituted with one or more halogen atoms,
- 5 (1-18) a lower alkoxycarbonyl group optionally substituted with one or more halogen atoms,
- (1-19) a benzoyl group,
- (1-20) a phenylsulfonyl group optionally substituted on the phenyl ring with one or more members selected from the group
- 10 consisting of halogen atoms, lower alkyl groups optionally substituted with one or more halogen atoms, a phenyl group, a phenoxy group, lower alkoxy groups optionally substituted with one or more halogen atoms, a cyano group, and lower alkanoylamino groups,
- 15 (1-21) a naphthylsulfonyl group;
- R^2 is one of the following (2-2) to (2-6):
- (2-2) a lower alkoxy group,
- (2-3) a lower alkyl group optionally substituted with one or more phenyl groups,
- 20 (2-4) a carboxy lower alkoxy group,
- (2-5) a lower alkoxycarbonyl lower alkoxy group,
- (2-6) a hydroxy group;
- n is an integer from 0 to 7, provided that when n is no less than 2, n R^2 s may be the same or different;
- 25 R^3 is one of the following (3-1) to (3-6):
- (3-1) a hydrogen atom,
- (3-2) a lower alkyl group optionally substituted with one or more phenyl groups,
- (3-3) a hydroxy-substituted lower alkyl group,
- 30 (3-4) a cycloalkyl lower alkyl group,
- (3-5) a carboxy lower alkyl group,
- (3-6) a lower alkoxycarbonyl lower alkyl group,
- B is a carbonyl group or an $-NHCO-$ group;
- l is 0 or 1; and
- 35 R^6 and R^7 each independently represent one of the

following (4-1) to (4-6):

(4-1) a hydrogen atom,

(4-2) a lower alkyl group,

(4-3) a lower alkanoyl group,

- 5 (4-4) a phenyl group optionally substituted on the phenyl ring with one or more members selected from the group consisting of halogen atoms; lower alkyl groups optionally substituted with one or more halogen atoms; a phenoxy group; lower alkoxy groups optionally substituted with one or more
10 halogen atoms; lower alkylthio groups; lower alkylsulfonyl groups; amino groups optionally substituted with one or two members selected from the group consisting of lower alkyl groups and lower alkanoyl groups; pyrrolidinyl groups optionally substituted on the pyrrolidine ring with one or
15 more oxo groups; piperidinyl groups optionally substituted on the piperidine ring with one or more lower alkyl groups; lower alkenyl groups; an aminosulfonyl group; a hydroxy group; carbamoyl groups optionally substituted with one or more lower alkyl groups; phenyl lower alkoxy groups; and a
20 cyano group,
(4-5) a cycloalkyl group optionally substituted on the cycloalkyl ring with one or more lower alkyl groups,
(4-6) a thiazolyl group.

- 25 2. The compound according to Claim 1 or a salt thereof, wherein A is a lower alkylene group, or a lower alkylidene group;

X is an oxygen atom or a sulfur atom;

- R¹ is the following (1-1), (1-2), (1-3), (1-4), (1-
30 6), (1-10), (1-13), (1-16), (1-17), (1-18), (1-19), (1-20), or (1-21):

(1-1) a hydrogen atom,

(1-2) a lower alkyl group,

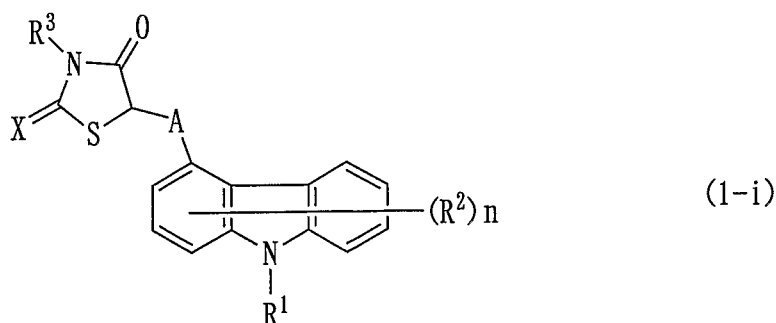
- (1-3) a phenyl lower alkyl group optionally substituted on
35 the phenyl ring with one or more members selected from the

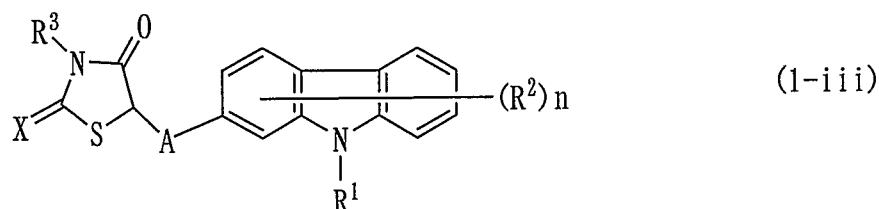
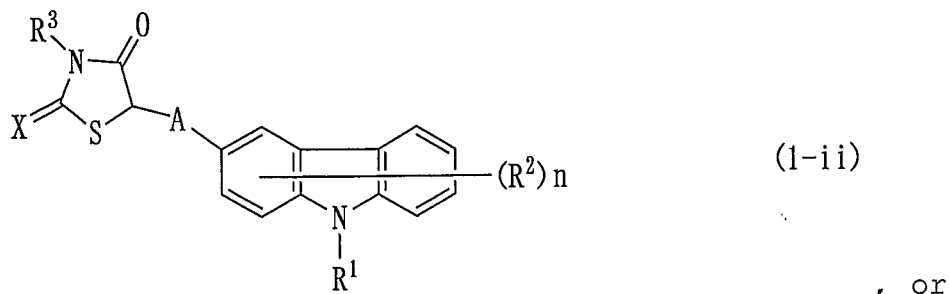
group consisting of a phenyl group (optionally substituted on the phenyl ring with one or more phenyl groups), lower alkyl groups, lower alkoxy groups, halogen atoms, $-(B)_1NR^6R^7$ groups, a nitro group, a carboxy group, lower alkoxycarbonyl groups, a cyano group, phenyl lower alkoxy groups, a phenoxy group, a piperidinyl lower alkoxycarbonyl groups, amino lower alkoxycarbonyl groups optionally substituted with one or two cycloalkyl groups, 2-imidazolinyllcarbonyl groups optionally substituted on the 2-imidazoline ring with one or more lower alkylthio groups, 3-pyrrolinyllcarbonyl groups optionally substituted on the 3-pyrroline ring with one or more lower alkyl groups, thiazolidinyllcarbonyl groups optionally substituted on the thiazolidine ring with a phenyl group, 3-azabicyclo[3.2.2]nonylcarbonyl groups, piperidinyl lower alkyl groups, anilino lower alkyl groups optionally substituted on the amino group with one or two lower alkyl groups, phenylthio lower alkyl groups, indolinyll lower alkyl groups, piperidinylcarbonyl groups optionally substituted on the piperidine ring with one or more lower alkyl groups, pyridyl groups, thienyl groups, lower alkylsulfinyl groups, lower alkylsulfonyl groups, and lower alkylthio groups, (1-4) a cycloalkyl lower alkyl group, (1-6) a naphthyl lower alkyl group, (1-10) a pyridyl lower alkyl group optionally substituted on the pyridine ring with one or more members selected from the group consisting of halogen atoms; piperidinyl groups; a morpholino group; piperazinyl groups optionally substituted on the piperazine ring with one or more members selected from the group consisting of a phenyl group and lower alkyl groups; thienyl groups optionally substituted with one or more halogen atoms; a phenyl group optionally substituted with one or more halogen atoms; pyridyl groups; piperidinyl lower alkyl groups; phenylthio lower alkyl groups; biphenyl groups; lower alkyl groups optionally substituted with one or more halogen atoms; pyridylamino groups; pyridylcarbonylamino

- groups; lower alkoxy groups; anilino lower alkyl groups optionally substituted on the amino group with one or two lower alkyl groups; anilino groups optionally substituted on the amino group with one or two lower alkyl groups; and furyl groups,
- (1-13) a quinolyl lower alkyl group,
- (1-16) a lower alkyl group substituted with one or more halogen atoms,
- (1-17) a lower alkanoyloxy group optionally substituted with one or more halogen atoms,
- (1-18) a lower alkoxy carbonyl group optionally substituted with one or more halogen atoms,
- (1-19) a benzoyl group,
- (1-20) a phenylsulfonyl group optionally substituted on the phenyl ring with one or more members selected from the group consisting of halogen atoms, lower alkyl groups optionally substituted with one or more halogen atoms, a phenyl group, a phenoxy group, lower alkoxy groups optionally substituted with one or more halogen atoms, a cyano group, and lower alkanoylamino groups,
- (1-21) a naphthylsulfonyl group;
- R^2 is the following (2-2) or (2-3):
- (2-2) a lower alkoxy group,
- (2-3) a lower alkyl group optionally substituted with one or more phenyl groups;
- n is an integer from 0 to 2, provided that when n is 2, n R^2 s may be the same or different;
- R^3 is the following (3-1) or (3-2):
- (3-1) a hydrogen atom,
- (3-2) a lower alkyl group optionally substituted with one or more phenyl groups;
- B is a carbonyl group or an $-NHCO-$ group;
- l is 0 or 1; and
- R^6 and R^7 each independently represent the following (4-1), (4-4), (4-5), or (4-6):

- (4-1) a hydrogen atom,
 (4-4) a phenyl group optionally substituted on the phenyl ring with one or more members selected from the group consisting of halogen atoms; lower alkyl groups optionally substituted with one or more halogen atoms; a phenoxy group; lower alkoxy groups optionally substituted with one or more halogen atoms; lower alkylthio groups; lower alkylsulfonyl groups; amino groups optionally substituted with one or two members selected from the group consisting of lower alkyl groups and lower alkanoyl groups; pyrrolidinyl groups optionally substituted on the pyrrolidine ring with one or more oxo groups; piperidinyl groups optionally substituted on the piperidine ring with one or more lower alkyl groups; lower alkenyl groups; an aminosulfonyl group; a hydroxy group; carbamoyl groups optionally substituted with one or more lower alkyl groups; phenyl lower alkoxy groups; and a cyano group,
 (4-5) a cycloalkyl group optionally substituted on the cycloalkyl ring with one or more lower alkyl groups,
 (4-6) a thiazolyl group.

3. The compound or a salt thereof according to Claim 1 having one of the following formula:





wherein A, X, R¹, R², R³, and n are each the same as defined in Claim 1.

5

4. The compound or a salt thereof according to Claim 3, wherein A is a lower alkylene group, or a lower alkylidene group.

10 5. The compound or a salt thereof according to Claim 4, wherein X is an oxygen atom or an sulfur atom.

6. The compound or a salt thereof according to Claim 5, wherein R¹ is

15 (1-3) a phenyl lower alkyl group optionally substituted on the phenyl ring with one or more members selected from the group consisting of a phenyl group (optionally substituted on the phenyl ring with one or more phenyl groups), lower alkyl groups, lower alkoxy groups, halogen atoms, -(B)₁NR⁶R⁷

20 groups (wherein B, l, R⁶, and R⁷ are each the same as defined in Claim 1), a nitro group, a carboxy group, lower alkoxycarbonyl groups, a cyano group, phenyl lower alkoxy groups, a phenoxy group, a piperidinyl lower alkoxycarbonyl groups, amino lower alkoxycarbonyl groups optionally

25 substituted with one or two cycloalkyl groups, 2-imidazolinyllcarbonyl groups optionally substituted on the 2-

imidazoline ring with one or more lower alkylthio groups, 3-pyrrolinylcarbonyl groups optionally substituted on the 3-pyrroline ring with one or more lower alkyl groups, thiazolidinylcarbonyl groups optionally substituted on the
5 thiazolidine ring with a phenyl group, 3-azabicyclo[3.2.2]nonylcarbonyl groups, piperidinyl lower alkyl groups, anilino lower alkyl groups optionally substituted on the amino group with one or two lower alkyl groups, phenylthio lower alkyl groups, indolinyl lower alkyl
10 groups, piperidinylcarbonyl groups optionally substituted on the piperidine ring with one or more lower alkyl groups, pyridyl groups, thienyl groups, lower alkylsulfinyl groups, lower alkylsulfonyl groups, and lower alkylthio groups, or (1-20) a phenylsulfonyl group optionally substituted on the
15 phenyl ring with one or more members selected from the group consisting of halogen atoms, lower alkyl groups optionally substituted with one or more halogen atoms, a phenyl group, a phenoxy group, lower alkoxy groups optionally substituted with one or more halogen atoms, a cyano group, and lower
20 alkanoylamino groups.

7. The compound according to Claim 6, wherein n is 0.

8. The compound according to Claim 6, wherein R² is
25 lower alkoxy group and n is 1.

9. A pharmaceutical composition comprising as an active ingredient the compound (1) or a salt thereof according to Claim 1.

30

10. A prophylactic and/or therapeutic agent for a disorder on which an up-regulation of TFF has a prophylactic and/or therapeutic effect, comprising as an active ingredient the compound (1) or a salt thereof according to Claim 1.

35

11. The prophylactic and/or therapeutic agent according to Claim 10, wherein the disorder on which an up-regulation of TFF has a prophylactic and/or therapeutic effect is an alimentary tract disease, oral disease, upper respiratory tract disease, respiratory tract disease, eye disease, cancer, or wound.

12. A use of the compound (1) or a salt thereof according to Claim 1 for manufacturing a prophylactic and/or therapeutic agent for a disorder on which an up-regulation of TFF has a prophylactic and/or therapeutic effect.

13. A method for preventing and/or treating a disorder on which TFF up-regulation has a prophylactic and/or therapeutic effect, comprising administering to a patient an effective amount of compound (1) or a salt thereof according to Claim 1.

14. The disorder on which TFF up-regulation has a prophylactic and/or therapeutic effect identified in either one of Claims 10 to 13 is drug-induced ulcers, peptic gastric ulcers, ulcerative colitis, Crohn's diseases, drug-induced enteritis, ischemic colitis, irritable bowel syndrome, ulcers developed after endoscopic demucosation, acute gastritis, chronic gastritis, reflux esophagitis, esophageal ulcer, Barrett esophagus, gastrointestinal mucositis, hemorrhoidal diseases, stomatitis, Sjogren syndrome, xerostomia, rhinitis, pharyngitis, bronchial asthma, chronic obstructive lung diseases, dry eye, or keratoconjunctivitis.

15. A prophylactic and/or therapeutic agent for alimentary tract diseases, oral diseases, upper respiratory tract diseases, respiratory tract diseases, eye diseases, cancers, or wounds, the agent comprising a compound that induces the production of TFF.

16. TFF identified in either one of Claims 10 to 15 is
TFF2.

1/1

Fig. 1

15631	GCTCAACCAT	CAGAAACAGA	CTGGCAACCC	CCTGTCATTT	CCCTGGCGTG
		<u>ACGCGTCAGA</u>	CTGGCAACCC	CCTGTCATTT	CCCTGGCGTG
15681	GGGAACTTCG	GGTCCCCTCT	GTCCTTCCCA	CCACACTTTT	CCCTCTTTCT
	GGGAACTTCG	GGTCCCCTCT	GTCCTTCCCA	CCACACTTTT	CCCTCTTTCT
15731	TTCCGGGTGT	CTACTCTCTG	GCTTCTGTCT	TCTCTGTCAG	GTCCACAGAA
	TTCCGGGTGT	CTACTCTCTG	GCTTCTGTCT	TCTCTGTCAG	GTCCACAGAA
15781	TCCTTCTCCA	GCACATCCTA	CCCCAGGAAG	GCCATGGGCT	GGGTCCCAGG
	TCCTTCTCCA	GCACATCCTA	CCCCAGGAAG	GCCATGGGCT	GGGTCCCAGG
15831	TGCCATCTTT	CAGAAGATGT	AGAGCATTCC	CATGGAACAA	AAATAACCCA
	TGCCATCTTT	CAGAAGATGT	AGAGCATTCC	CATGGAACAA	AAATAACCCA
15881	TTTCAGGGGT	TGGCTGAAAA	TGAACTTATT	AAAACCTGCC	TGTCACAGGC
	TTTCAGGGGT	TGGCTGAAAA	TGAACTTATT	AAAACCTGCC	TGTCACAGGC
15931	TACTCCGCTG	ACCCTGTCAG	CCTCATCTCC	ATGGAGAGCA	GCCCCCTCTG
	TACTCCGCTG	ACCCTGTCAG	CCTCATCTCC	ATGGAGAGCA	GCCCCCTCTG
15981	CTGAAGATGG	GACAAAGGGC	ATCGTGCTGC	GGTTGGGGAG	GCTCTAACCA
	CTGAAGATGG	GACAAAGGGC	ATCGTGCTGC	GGTTGGGGAG	GCTCTAACCA
16031	CAGCCCTGGG	AGCAGTCTCT	TACCTCCTCT	GAGATGCTTC	CCTTCCTCAG
	CAGCCCTGGG	AGCAGTCTCT	TACCTCCTCT	GAGATGCTTC	CCTTCCTCAG
16081	GGAGGGGACT	TTTCCATGCT	ATCTGCTGGC	CTGTACATTT	TCCCCAGTAA
	GGAGGGGACT	TTTCCATGCT	ATCTGCTGGC	CTGTACATTT	TCCCCAGTAA
16131	ACTTGGCCCT	AATATTTTCT	AAATTCCTGT	GGTCCCTGCC	CACTCTATCA
	ACTTGGCCCT	AATATTTTCT	AAATTCCTGT	GGTCCCTGCC	CACTCTATCA
16181	ATAGAAATGC	ATAGCTTATC	CCTTCCTGGG	TGTGACCCTG	TGTGTGCCCCA
	ATAGAAATGC	ATAGCTTATC	CCTTCCTGGG	TGTGACCCTG	TGTGTGCCCCA
16231	GCCCCAGACC	TGCACGTGGC	CGGTTTTCCA	CGCTGGCAGC	CTGGCATGAC
	GCCCCAGACC	TGCACGTGGC	CGGTTTTCCA	CGCTGGCAGC	CTGGCATGAC
16281	CCAACTCTCT	GTCCAGGGCA	GGAAGAGGTA	TCACCGAGCA	GGGAGAGAGT
	CCAACTCTCT	GTCCAGGGCA	GGAAGAGGTA	TCACCGAGCA	GGGAGAGAGT
16331	CACCCTGGCC	CGGAAGCCTC	GCCTGCACAG	GGCACAGCTG	CCTCTTGCCT
	CACCCTGGCC	CGGAAGCCTC	GCCTGCACAG	GGCACAGCTG	CCTCTTGCCT
16381	CCTCTTCGCC	TCCACGGTGG	AAGGGCTGGG	GCCACGGGGC	AGAGAAGAAA
	CCTCTTCGCC	TCCACGGTGG	AAGGGCTGGG	GCCACGGGGC	AGAGAAGAAA
16431	GTTATCTCT	GCTTGTTGGA	CAAACAGAGG	GGAGATTATA	AAACATACCC
	GTTATCTCT	GCTTGTTGGA	CAAACAGAGG	GGAGATTATA	AAACATACCC
16481	GGCAGTGGAC	ACCATGCAT [→] T	CTGCAAGCCA	CCCTGGGGTG	CAGCTGAGCT
	GGCAGTGGAC	ACCATGCATT	CTGCAAGCCA	CCCTGGGGTG	CAGCTGAGCT
16531	AGAC <u>ATG</u> GGA	CGGCGAGACG	CCCAGCTCCT		
	AGAAGCTT				

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2007/057016

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D417/06 A61K31/427 A61P1/00 A61P11/00 A61P27/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/40017 A (NOVONORDISK AS [DK]) 30 October 1997 (1997-10-30) claim 13; example 22	1-7,9
X	EP 1 526 159 A1 (MITSUBISHI PAPER MILLS LTD [JP]) 27 April 2005 (2005-04-27) claim 1; compounds B-6, D-6	1-5
X	JP 2003 264010 A (MITSUBISHI PAPER MILLS LTD) 19 September 2003 (2003-09-19) compounds A-5	1-5
X	JP 11 109547 A (FUJI PHOTO FILM CO LTD) 23 April 1999 (1999-04-23) compound 21	1-5
	----- -/--	

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

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- *O* document referring to an oral disclosure, use, exhibition or other means
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- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

29 June 2007

Date of mailing of the international search report

06/09/2007

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Beyss-Kahana, Ellen

INTERNATIONAL SEARCH REPORT

International application No

PCT/JP2007/057016

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/005683 A (NOVO NORDISK AS [DK]; OLSEN HELLE BIRK [DK]; KAARSHOLM NIELS CHRISTIAN) 19 January 2006 (2006-01-19) claim 56; examples 185,298,360 -----	1-9
X	WO 03/027081 A (NOVO NORDISK AS [DK]; OLSEN HELLE BIRK [DK]; KAARSHOLM NIELS C [DK]; M) 3 April 2003 (2003-04-03) page 4, lines 4-11; examples 163,164 -----	1-5
X	WO 2004/056347 A (NOVO NORDISK AS [DK]; KAARSHOLM NIELS CHRISTIAN [DK]; MADSEN PETER [DK]) 8 July 2004 (2004-07-08) claim 1; example 298 -----	1-5,9
X	BABYATSKY, M. W. ET AL.: "Oral trefoil peptides protect against ethanol- and indomethacin-induced gastric injury in rats" GASTROENTEROLOGY, vol. 110, no. 2, February 1996 (1996-02), pages 489-497, XP002439814 cited in the application abstract -----	16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2007/057016

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 13 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-14 and claim 16 partially

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-14 and claim 16 partially

Compounds according to formula (I) and their use

2. claim: 15 and claim 16 partially

A therapeutic agent that induces the production of TFF

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/JP2007/057016

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