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(54) Thiadiazoline derivatives for treating cancer

Thiadiazolin-Derivate zur Behandlung von Krebs

Dérivés de thiadiazoline pour le traitement du cancer

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(56) References cited:
WO-A-00/42029 **JP-A- 2000 229 959**

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(Cont. next page)

- **DING Y ET AL: "Syntheses and anticancer activity of ribonucleoside analogues containing thio-substituted five-membered heterocyclic base" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 7, no. 13, 8 July 1997 (1997-07-08), pages 1607-1610, XP004136265 ISSN: 0960-894X**

Description

Technical Field

[0001] The present invention relates to an antitumor agent comprising a thiadiazoline derivative or a pharmacologically acceptable salt thereof as an active ingredient, and a thiadiazoline derivative or a pharmacologically acceptable salt thereof which is useful for therapeutic treatment of a tumor.

Background Art

[0002] In chemotherapies of cancers, a variety of anticancer agents including antimitotic agents such as taxane and vinca alkaloid, topoisomerase inhibitors, alkylating agents and the like have been used. These agents have side effects such as bone marrow toxicity and neuropathy, a problem of drug resistance and the like. Therefore, novel anticancer agents which have improvement in the above problems have so far been desired.

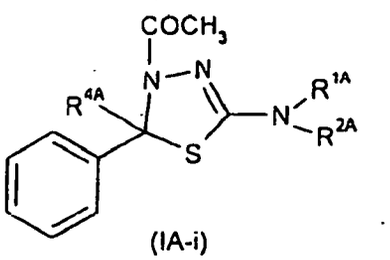
[0003] It is known that thiadiazoline derivatives have inhibitory activity against transcription factor STAT6 activation, antagonistic action of integrin, and the control of insect or acarid pests (Japanese Published Unexamined Patent Application No. 2000-229959, WO01/56994, US6235762). In addition, it is known that the derivatives have antibacterial activity, ACE inhibitory activity and the like [J. Bangladesh Chem. Soc., Vol. 5, p. 127 (1992), WO93/22311, Japanese Published Unexamined Patent Application No. 62-53976 (1987)].

Disclosure of the Invention

[0004] An object of the present invention is to provide a thiadiazoline derivative or a pharmacologically acceptable salt thereof which is useful for therapeutic treatment of a human malignant tumor, for example, breast cancer, gastric cancer, ovarian cancer, colon cancer, lung cancer, brain tumor, laryngeal cancer, hematological cancer, urinary or genital tumor including bladder cancer and prostatic cancer, renal cancer, skin carcinoma, hepatic carcinoma, pancreatic, cancer or auterine cancer. Another object of the present invention is to provide an antitumor agent comprising a thiadiazoline derivative or a pharmacologically acceptable salt thereof as an active ingredient.

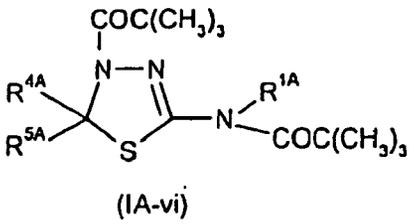
[0005] The present invention relates to the following (1) to (9).

(1) A compound of formula



(IA-i)

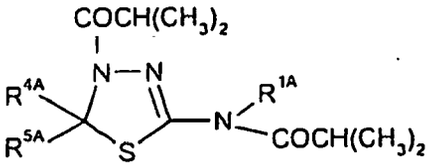
wherein
R^{1A} is -H, R^{2A} is $-CO(CH_2)_4CH_3$ and R^{4A} is $-CH_2NHSO_2CH_3$;
or a compound of formula



(IA-vi)

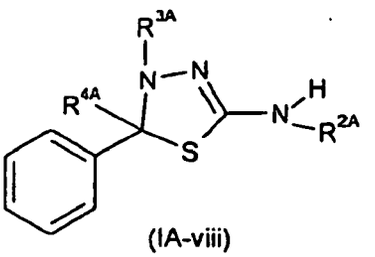
wherein

R^{1A} is -H, R^{4A} is $-CH_2NHSO_2CH_3$ and R^{5A} is -Phenyl;
R^{1A} is -H, R^{4A} is $-CH_2NHSO_2CH_2CH_3$ and R^{5A} is -Phenyl;
R^{1A} is -H, R^{4A} is $-(CH_2)_2NHSO_2CH_3$ and R^{5A} is -Phenyl;
or a compound of formula



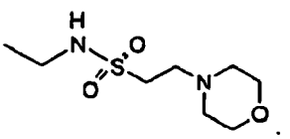
(IA-vii)

wherein
R^{1A} is -H, R^{4A} is $-(CH_2)_2NHSO_2CH_2$ and R^{5A} is -Phenyl; or
R^{1A} is -H, R^{4A} is $-CH_2NHSO_2CH_3$ and R^{5A} is -Phenyl;
or a compound of formula



(IA-viii)

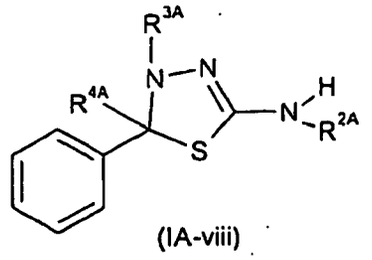
wherein
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2CH_3$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2CH_2Cl$;
R^{2A} is $-COCH_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2CH_2Cl$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2CH=CH_2$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COC(CH_3)_3$ and R^{4A} is $-CH_2NHSO_2CH=CH_2$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is



;

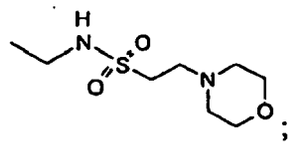
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is-$CH_2NHSO_2(CH_2)_2NHCH_2CH_3$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2N(CH_3)_2$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2NH(CH_2)_2OH$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COC(CH_3)_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COC(CH_3)_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2N(CH_3)_2$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH(CH_3)_2$ and R^{4A} is $<CH_2)_2NHSO_2CH_3$;
R^{2A} is $-COCH_2CH_3$, R^{3A} is $-COCH_2CH_3$ and R^{4A} is $-(CH_2)_2NHSO_2CH_3$; or
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_2CH_3$ and R^{4A} is $-(CH_2)_2NHSO_2CH_3$;
or a pharmacologically acceptable salt thereof.

(2) A compound according to (1) of formula



(IA-viii)

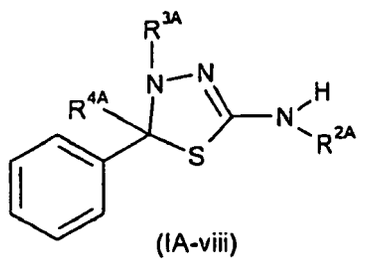
wherein
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2CH_3$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2CH_2Cl$;
R^{2A} is $-COCH_3$, R^{3A} is $COCH_3$ and R^{4A} is $-CH_2NHSO_2CH_2Cl$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2CH=CH_2$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COC(CH_3)_3$ and R^{4A} is $-CH_2NHSO_2CH=CH_2$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is



;

R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2N(CH_3)_2$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2NH(CH_2)_2OH$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COC(CH_3)_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COC(CH_3)_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2N(CH_3)_2$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH(CH_3)_2$ and R^{4A} is $-(CH_2)_2$ $NHSO_2CH_3$;
R^{2A} is $-COCH_2CH_3$, R^{3A} is $-COCH_2CH_3$ and R^{4A} is $-CH_2)_2$ $NHSO_2CH_3$; or
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_2CH_3$ and R^{4A} is $-(CH_2)_2$ $NHSO_2CH_3$;
or a pharmacologically acceptable salt thereof.

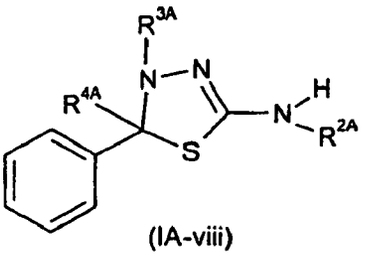
(3) A compound according to (1) or (2) of formula



(IA-viii)

wherein
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2CH=CH_2$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COC(CH_3)_3$ and R^{4A} is $-CH_2NHSO_2CH=CH_2$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COC(CH_3)_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$; or
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH(CH_3)_2$ and R^{4A} is $-(CH_2)_2NHSO_2CH_3$;
or a pharmacologically acceptable salt thereof.

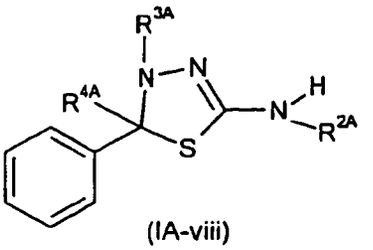
(4) A compound according to anyone of (1) to (3) of formula



(IA-viii)

wherein
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COC(CH_3)_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$;
or a pharmacologically acceptable salt thereof.

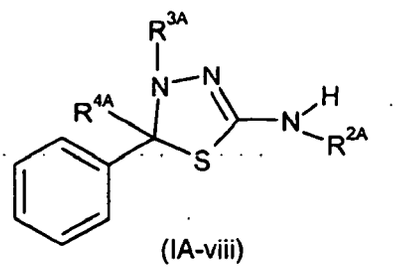
(5) A compound according to anyone of (1) to (3) of formula



(IA-viii)

wherein
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH(CH_3)_2$ and R^{4A} is $-(CH_2)_2NHSO_2CH_3$
or a pharmacologically acceptable salt thereof.

(6) A pharmaceutical composition comprising a compound of formula



(IA-viii)

wherein
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COC(CH_3)_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$;
or a pharmacologically acceptable salt thereof.

(7) A compound according to any one of (1) to (5) for use as a medicament.

(8) A compound according to any one of (1) to (5) for use as an anti-tumor medicament.

(9) A compound for use according to any one of (1) to (5) for use in the treatment of a human malignant tumor.

(10) A compound for use according to (8) wherein the human malignant tumor is breast cancer, gastric cancer,

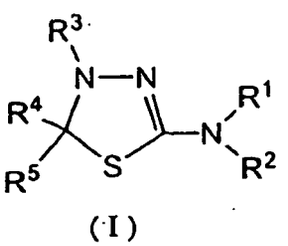
ovarian cancer, colon cancer, lung cancer, brain tumor, laryngeal cancer, hematological cancer, urinary or genital tumor including bladder cancer and prostatic cancer, renal cancer, skin carcinoma, hepatic carcinoma, pancreatic cancer, or uterine cancer.

(11) Use of the compound according to anyone of (1) to (5) for the manufacture of a medicament for the treatment of human malignant tumor.

(12) The use according to (10) wherein the human malignant tumor is breast cancer, gastric cancer, ovarian cancer, colon cancer, lung cancer, brain tumor, laryngeal cancer, hematological cancer, urinary or genital tumor including bladder cancer and prostatic cancer, renal cancer, skin carcinoma, hepatic carcinoma, pancreatic cancer, or uterine cancer.

[0006] Examples of the pharmacologically acceptable salt of compounds (IA-i), (IA-vi), (IA-vii), and (IA-viii) include pharmacologically acceptable acid addition salts, metal salts, ammonium salts, organic amine addition salts, and amino acid addition salts. Examples of the acid addition salt include an inorganic salt such as a hydrochloride, a sulfate and a phosphate, an organic acid salt such as an acetate, a maleate, a fumarate, a tartrate, a citrate, a lactate, an aspartate, a glutamate, and succinate. Examples of the metal salt include an alkali metal salt such as a sodium salt and a potassium salt, an alkaline-earth metal salt such as a magnesium salt and a calcium salt, an aluminium salt, and a zinc salt. Examples of the ammonium salt include a salt of ammonium, and tetramethylammonium. Examples of the organic amine addition salt include an addition salt with morpholine, or piperidine. Examples of the amino acid addition salt include an addition salt with lysine, glycine, and phenylalanine.

[0007] Next, the methods of preparing the compound (I), represented by the general formula (I)



(I)

<wherein

R^1 and R^4 are the same or different and each represents

a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocyclic group, or substituted or unsubstituted aryl;

R^2 represents

a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkyl,
$-C(=W)R^6$ [wherein

W represents

an oxygen atom or a sulfur atom

R^6 represents

a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted heterocyclic group,
$-NR^7R^8$ (wherein

R^7 and R^8 are the same or different and each represents

a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or a substituted or unsubstituted heterocyclic group, or

R^7 and R^8 are combined together with the adjacent nitrogen atom to form a substituted or unsubstituted heterocyclic group),

$-OR^9$ (wherein

R^9 represents

substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted aryl) or

$-SR^{10}$ (wherein

R^{10} represents

substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted aryl)]

$-NR^{11}R^{12}$ (wherein

R^{11} and R^{12} are the same or different and each represents

a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkyl, or
$-C(=O)R^{13}$ [wherein

R^{13} represents

substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted heterocyclic group,
$-NR^7AR^{8A}$ (wherein R^{7A} and R^{8A} have the same meanings as those of the aforementioned R^7 and R^8, respectively), or
$-OR^{9A}$ (wherein R^{9A} has the same meaning as that of the aforementioned R^9)]} or

$-SO_2R^{14}$ (wherein

R^{14} represents

substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted aryl, or a substituted or unsubstituted heterocyclic group), or

R^1 and R^2 are combined together with the adjacent nitrogen atom to form a substituted or unsubstituted heterocyclic group,
R^5 represents

substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocyclic group, or substituted or unsubstituted aryl, or

R^4 and R^5 are combined together to represent

$-(CR^{28}R^{29})_{m1}-Q-(CR^{28A}R^{29A})_{m2}-$ (wherein

Q represents

a single bond, substituted or unsubstituted phenylene, or cycloalkylene,

m1 and m2 are the same or different and each represents

an integer of from 0 to 4, with the proviso that m1 and m2 are not 0 at the same time,

R^{28}, R^{29}, R^{28A} and R^{29A} are the same or different and each represents a hydrogen atom, substituted or unsubstituted lower alkyl,

$-OR^{30}$ [wherein

R^{30} represents

a hydrogen atom,
substituted or unsubstituted lower alkyl,
substituted or unsubstituted lower alkenyl,
$-CONR^{31}R^{32}$ (wherein

R^{31} and R^{32} are the same or different and each represents

a hydrogen atom, substituted or unsubstituted lower alkyl, a substituted or unsubstituted heterocyclic group, or substituted or unsubstituted aryl),

$-SO_2NR^{33}R^{34}$ (wherein

R^{33} and R^{34} are the same or different and each represents

a hydrogen atom, substituted or unsubstituted lower alkyl, a substituted or unsubstituted heterocyclic group, or substituted or unsubstituted aryl), or

$-COR^{35}$ (wherein

R^{35} represents

a hydrogen atom, substituted or unsubstituted lower alkyl, a substituted or unsubstituted heterocyclic group, or substituted or unsubstituted aryl)],

$-NR^{36}R^{37}$ [wherein

R^{36} and R^{37} are the same or different and each represents

a hydrogen atom,
substituted or unsubstituted lower alkyl,
$-COR^{38}$ (wherein

R^{38} represents

a hydrogen atom, substituted or unsubstituted lower alkyl, a substituted or unsubstituted heterocyclic group, substituted or unsubstituted aryl, substituted or unsubstituted lower alkoxy, substituted or unsubstituted aryloxy, amino, substituted or unsubstituted lower alkylamino, substituted or unsubstituted di(lower alkyl)amino, or substituted or unsubstituted arylamino), or

$-SO_2R^{39}$ (wherein

R^{39} represents

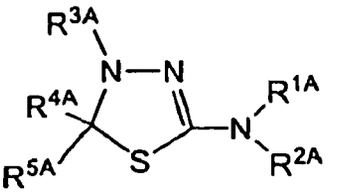
substituted or unsubstituted lower alkyl, a substituted or unsubstituted heterocyclic group, or substituted or unsubstituted aryl)], or

$-CO_2R^{40}$ (wherein

R^{40} represents

a hydrogen atom, substituted or unsubstituted lower alkyl, or substituted or unsubstituted aryl), and

when m1 or m2 is an integer of 2 or more, each R^{28}, R^{29}, R^{28A} and R^{29A} may be the same or different, respectively, and any two of R^{28}, R^{29}, R^{28A} and R^{29A} which are bound to the adjacent two carbon atoms may be combined to form a bond), and R^3 represents
a hydrogen atom or
$-C(=W^A)R^{6A}$ (wherein W^A and R^{6A} have the same meanings as those of the aforementioned W and R^6, respectively)
>, and the compound (IA),



(IA)

{wherein R^{1A}, R^{2A}, R^{3A}, R^{4A} and R^{5A} have the same meanings as those of the aforementioned R^1, R^2, R^3, R^4 and R^5, respectively, with the proviso that when R^{2A} and R^{3A} are the same to be $-CONHR^{8B}$ (wherein R^{8B} represents a substituted or unsubstituted lower alkyl, or substituted or unsubstituted aryl), and

(i) R^{4A} is a hydrogen atom, or
(ii) one of R^{4A} and R^{5A} is substituted or unsubstituted lower alkyl,
then the other of R^{4A} and R^{5A} only represents substituted or unsubstituted cycloalkyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted lower alkynyl
[provided that

(a) when R^{1A}, R^{2A} and R^{3A} are hydrogen atoms, and
one of R^{4A} and R^{5A} is methyl,

the other of R^{4A} and R^{5A} is not any of phenyl, 4-nitrophenyl, 4-aminophenyl, 4-bromophenyl, 3-nitrophenyl and 4-methoxy-3-nitrophenyl,

(b) when R^{1A} and R^{2A} are hydrogen atoms, R^{3A} is acetyl,

(i) and one of R^{4A} and R^{5A} is methyl,

the other of R^{4A} and R^{5A} is not any of methyl, ethyl, phenyl, 4-methoxyphenyl, 2-naphthylsulfonylmethyl, 4-bromophenylsulfonylmethyl and 4-chlorophenylsulfonylmethyl, and

(ii) and R^{4A} is a hydrogen atom,

R^{5A} is not any of phenyl, 4-nitrophenyl, 4-chlorophenyl, 4-methoxyphenyl, 4-dimethylaminophenyl and pyridyl,

(c) when R^{1A} is a hydrogen atom, R^{2A} and R^{3A} are acetyl,

(i) and one of R^{4A} and R^{5A} is methyl,

the other of R^{4A} and R^{5A} is not any of methyl, ethyl, propyl, butyl, hexyl, heptyl, phenyl, benzyl, acetylmethyl, tert-butoxycarbonylmethyl, ethoxycarbonylmethyl, 4-bromophenylsulfonylmethyl, 4-

bromophenylsulfonylethyl, 4-chlorophenylsulfonylmethyl, 3,4-dichlorophenylsulfonylmethyl, 3,4-dichlorophenylsulfonylethyl, 3,4-dimethylphenylsulfonylmethyl, phenylsulfonylmethyl, 4-methylphenylsulfonylmethyl, 4-methylphenylsulfonylethyl, 4-(acetylamino)phenylsulfonylethyl, 4-bromophenylsulfonylethyl, 2-(4-methylphenylsulfonyl)-2-phenylethyl, 2-(4-methylphenylthio)-2-phenylethyl, 2-naphthylsulfonylethyl, 2-naphthylsulfonylmethyl, phenethyl, 3-benzoyloxyphenyl, 2-oxo-2H-1-benzopyran-3-yl, 2-furyl, 5-nitro-2-furyl, 5-methyl-2-furyl, 2-thienyl, 5-chloro-2-thienyl, 3-acetoxyphenyl, 3-nitrophenyl, 4-nitrophenyl, 4-fluorophenyl, 3-acetylaminophenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-ethylphenyl, 4-methylphenyl, 4-bromophenyl, 4-nonyloxyphenyl, 4-phenylphenyl, 3,4-dimethoxyphenyl, 1,3-benzodioxol-5-yl, 4-(benzimidazol-2-ylamino)phenyl, 4-(l-methylbenzimidazol-2-ylamino)phenyl, 3-pyridyl, 2-naphthyl, 2-acetylamino-4-acetyl-1,3,4-thiadiazolin-5-yl and 4-acetylaminophenylsulfonylmethyl,

(ii) and one of R^{4A} and R^{5A} is phenyl,

the other of R^{4A} and R^{5A} is not any of phenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-nitrophenyl, ethoxycarbonylmethyl, isobutyl, sec-butyl, n-butyl and acetylaminomethyl,

(iii) and one of R^{4A} and R^{5A} is 2-acetoxyphenyl,

the other of R^{4A} and R^{5A} is not 2-phenylethenyl,

(iv) and R^{4A} is a hydrogen atom or 4-methoxyphenyl,

R^{5A} is not 4-methoxyphenyl,

(v) and R^{4A} is a hydrogen atom,

R^{5A} is not any of phenyl, 4-nitrophenyl, 4-chlorophenyl,
4-dimethylaminophenyl and pyridyl,

(vi) and R^{4A} and R^{5A} are combined to represent

$-(CH_2)_{m1}-Q-(CH_2)_{m2}-$ (wherein m1, m2 and Q have the same meanings as those of the aforementioned, respectively),
$-(CH_2)_{m1}-Q-(CH_2)_{m2}-$ wherein Q is a single bond and the sum of m1 and m2 is 5, is excluded

(vii) and one of R^{4A} and R^{5A} is 1,2,3-triacetoxypropyl,

the other of R^{4A} and R^{5A} is not 3,4-dihydro-3-oxo-2-quinoxalinyl, and

(viii) and one of R^{4A} and R^{5A} is ethyl,

the other of R^{4A} and R^{5A} is not ethyl,

(d) when R^{1A} and R^{4A} are hydrogen atoms, and

(i) R^{2A} and R^{3A} are the same to be propionyl or benzoyl or
(ii) R^{2A} is propionyl and R^{3A} is acetyl,

R^{5A} is not phenyl,

(e) when R^{1A} and R^{3A} are hydrogen atoms,
R^{2A} is acetyl, and
one of R^{4A} and R^{5A} is methyl,

the other of R^{4A} and R^{5A} is not either of phenyl and 3,4-dichlorophenylsulfonylethyl,

(f) when R^{1A} is phenyl, R^{2A} and R^{3A} are acetyl,

(i) and one of R^{4A} and R^{5A} is methyl,

the other of R^{4A} and R^{5A} is not either of 4-acetoxy-6-methyl-2-oxo-2H-pyran-3-yl and 2-oxo-2 H-1-benzopyran-3-yl,and

(ii) and R^{4A} is phenyl,

R^{5A} is not phenyl,

(g) when R^{1A} is methyl, R^{2A} and R^{3A} are acetyl,

(i) and R^{4A} is a hydrogen atom,

R^{5A} is not phenyl,

(ii) and one of R^{4A} and R^{5A} is methyl,

the other of R^{4A} and R^{5A} is not either of ethoxycarbonylethyl and ethoxycarbonylpropyl,

(h) when R^{1A}, R^{2A} and R^{4A} are methyl, and
R^{5A} is pyridyl,

R^{3A} is not $-COR^{C}$ (wherein R^{C} represents methyl, chloromethyl, methoxy, ethoxycarbonylmethyl or ethoxycarbonylethenyl),

(j) when one of R^{1A} and R^{2A} is a hydrogen atom,
the other of R^{1A} and R^{2A} is ethyl, and
R^{3A} is a hydrogen atom or acetyl,

R^{4A} and R^{5A} are not methyl at the same time,

(k) when R^{1A} is 4-chlorophenyl,
R^{2A} is a hydrogen atom, and
one of R^{4A} and R^{5A} is methyl,

the other of R^{4A} and R^{5A} is not (1-methylbenzimidazol-2-ylamino)phenyl, and R^{3A} is not acetyl,

(m) when R^{1A} is phenyl, 4-chlorophenyl, 4-methylphenyl or 4-methoxyphenyl,
R^{2A} is a hydrogen atom, and
R^{4A} and R^{5A} are methyl,

R^{3A} is not any of acetyl, 4-chlorophenoxyacetyl, 2-chlorophenoxyacetyl, 3-methylphenoxyacetyl and phenylaminocarbonyl,

(n) when R^{2A} and R^{3A} are acetyl,
one of R^{4A} and R^{5A} is methyl,

(i) and the other of R^{4A} and R^{5A} is 1H-benzotriazol-1-ylmethyl,

R^{1A} is not any of cyclohexyl, benzyl, phenyl, 2-methylphenyl and 4-methoxyphenyl,

(ii) and the other of R^{4A} and R^{5A} is 2-methylbenzimidazol-1-ylmethyl or 2-ethylbenzimidazol-1-ylmethyl,

R^{1A} is not any of cyclohexyl, phenyl and 4-bromophenyl,

(o) when R^{1A} is a hydrogen atom,
R^{2A} is acetyl, and
R^{4A} and R^{5A} are methyl,

R^{3A} is not benzoyl,

(p) when one of R^{1A} and R^{2A} is hydrogen atom,
the other of R^{1A} and R^{2A} is methyl, and
R^{4A} and R^{5A} are both methyl or both ethyl,

R^{3A} is not any of acetyl, benzoyl, pivaloyl, 3-nitrobenzoyl, 2-fluorobenzoyl, 4-fluorobenzoyl, 2-trifluoromethylbenzoyl and 3-trifluoromethylbenzoyl, and

(q) when R^{1A} is methyl,
R^{2A} is methylaminocarbonyl, and
R^{4A} and R^{5A} are both methyl or both ethyl,

R^{3A} is not any of acetyl, benzoyl, pivaloyl, 2-fluorobenzoyl, 4-fluorobenzoyl, 2-trifluoromethylbenzoyl, 3-trifluoromethylbenzoyl and 4-trifluoromethylbenzoyl]},

are described as follows.

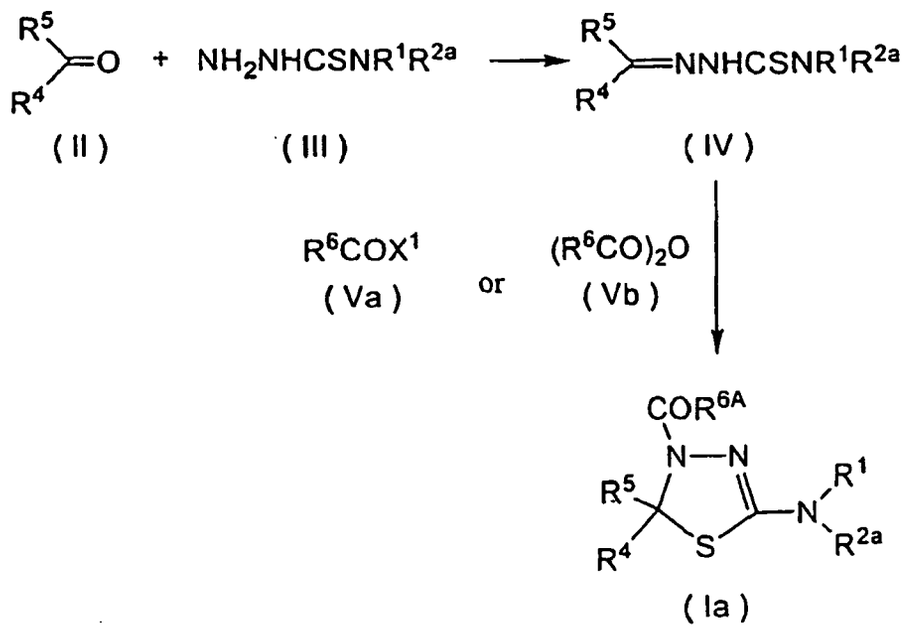
[0008] In the preparing methods as shown below, when the defined group changes under the conditions of the method carried out, or the method is inappropriate for carrying out, the desired compound can be obtained by using the protection and deprotection of the groups which are ordinarily used in the synthetic organic chemistry [e.g., Protective Groups in Organic Synthesis, T. W. Greene, John Wiley & Sons Inc. (1981)] and the like. In addition, the order of the steps for introducing a substituent and the like may be changed, if necessary.

[0009] Compound (I) can be prepared according to the following reaction steps.

[0010] Compound (IA) can also be prepared in the similar manner as in the preparing methods of Compound (I) as shown below.

Preparing method 1

[0011] Among Compound (I), Compound (Ia) wherein R^2 is a hydrogen atom, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted cycloalkyl, or R^1 and R^2 are combined to form a substituted or unsubstituted heterocyclic group together with the adjacent nitrogen atom, and R^3 is $-C(=O)R^{6A}$ can be obtained from Compound (II) and Compound (III),via Compound (IV), in accordance with known methods [e.g., J. Heterocyclic Chem., Vol. 21, p. 599 (1984) and the like]:

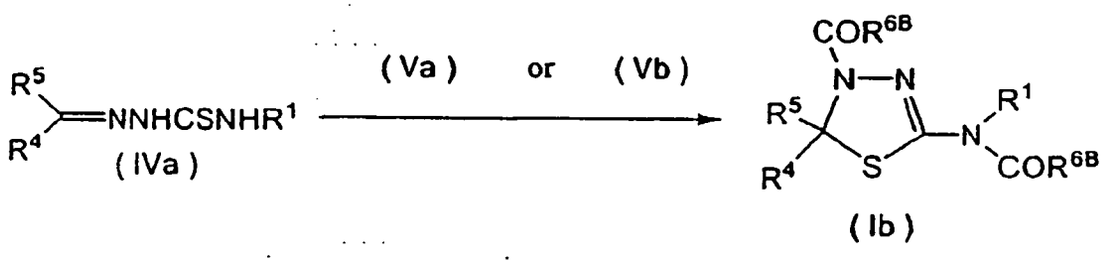


(wherein R^1, R^4, R^5, R^6 and R^{6A} have the same meanings as those mentioned above, respectively, X^1 is a chlorine atom, a bromine atom or an iodine atom, and R^{2a} represents a hydrogen atom, substituted or unsubstituted lower alkyl,

substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted cycloalkyl among the definition of the aforementioned R^2, or R^1 and R^{2a} are combined to form a substituted or unsubstituted heterocyclic group together with the adjacent nitrogen atom.)

Preparing method 2

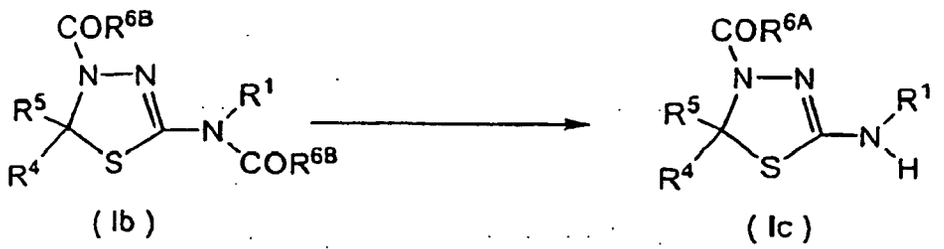
[0012] Among Compound (I), Compound (Ib) wherein R^2 and R^3 are the same to be $-C(=O)R^{6B}$ (wherein R^{6B} has the same meaning as that of the aforementioned R^6) can be obtained from Compound (IVa) among Compound (IV) prepared by the preparing method 1 wherein R^{2a} is a hydrogen atom, and Compound (Va) or Compound (Vb) in accordance with known methods [e.g., J. Bangladesh Chem. Soc., Vol. 5, p. 127 (1992), J. Org. Chem., Vol. 45, p. 1473 (1980), Patent of East Germany No. 243930, and the like]:



(wherein R^1, R^4, R^5 and R^{6B} have the same meanings as those mentioned above, respectively.)

Preparing method 3

[0013] Among Compound (Ia), Compound (Ic) wherein R^2 is a hydrogen atom and R^3 is $C(=O)R^{6A}$ can be obtained by the following step from Compound (Ib) prepared by the Preparing method 2:



(wherein R^1, R^4, R^5, R^{6A} and R^{6B} have the same meanings as those mentioned above, respectively.)

[0014] Compound (Ic) can be obtained by treatment of Compound (Ib) in an inert solvent, for example, N,N-dimethylformamide and the like, in the presence of an appropriate base such as sodium hydride and the like, at a temperature between 0˚C and 80˚C for 10 minutes to 10 hours. The base is preferably used in an amount of 1 to 5 equivalents to Compound (Ib).

[0015] Alternatively, Compound (Ic) can also be obtained by the following method.

[0016] Compound (Ic) can be obtained by treatment of Compound (Ib) in an inert solvent, for example, aqueous or anhydrous ethanol, acetonitrile, chloroform and the like, in the presence of an appropriate base such as hydrazine monohydrate, aqueous sodium hydroxide and the like, at a temperature between 0˚C and 50˚C for 1 to 10 hours. The base is preferably used in an amount of 2 to 10 equivalents to Compound (Ib).

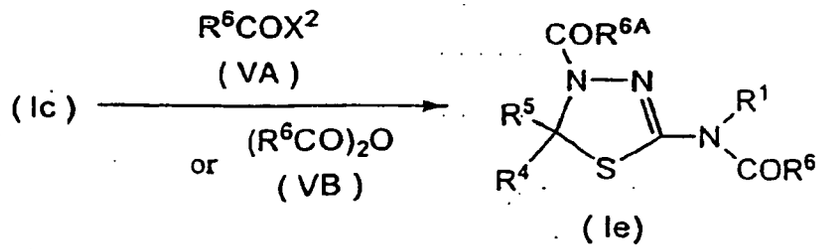
[0017] Compound (Ic) can also be obtained by the following method.

[0018] Compound (Ic) can be obtained by treatment of Compound (Ib) in a solvent such as methanol, tert-butanol and the like, in the presence of a reducing agent such as sodium borohydride and the like, and if necessary, in the presence of cerium chloride heptahydrate and the like, at a temperature between -10˚C and 100˚Cfor 0.1 to 15 hours. The reducing agent is preferably used in an amount of 1 to 200 equivalents to Compound (Ib).

Preparing method 4

[0019] Among Compound (I), Compound (Ie) wherein R^2 is $-C(=O)R^6$ and R^3 is $-C(=O)R^{6A}$ can be obtained by the

following step from Compound (Ic) obtained by the Preparing method 1 or 3.

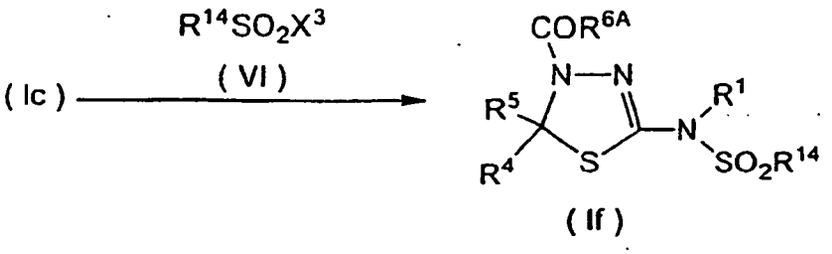


(wherein R^1, R^4, R^5, R^6 and R^{6A} have the same meanings as those mentioned above, respectively, and X^2 has the same meaning as that of the aforementioned X^1.)

[0020] Compound (Ie) can be obtained by allowing Compound (Ic) to react with Compound (VA) or Compound (VB) in an inert solvent, for example, acetone, ethyl acetate, acetonitrile, N,N-dimethylformamide, dichloromethane and the like, in the presence of an appropriate base such as pyridine, 4-(dimethylamino)pyridine (DMAP), sodium hydride and the like, at a temperature between 0˚C and 120˚C for 2 to 12 hours. The base and Compound (VA) or Compound (VB) are preferably used, respectively, in an amount of 1 to 3 equivalents to Compound (Ic).

Preparing method 5

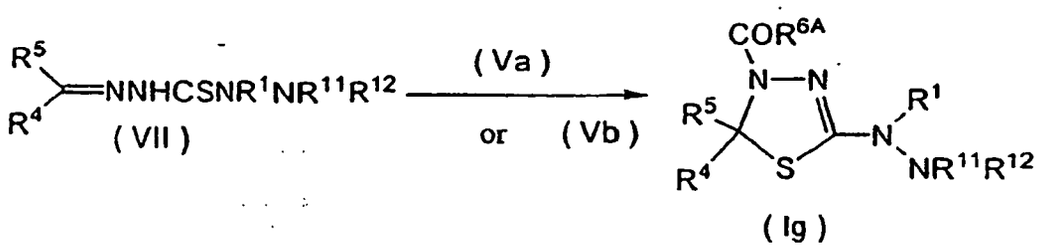
[0021] Among Compound (I), Compound (If) wherein R^2 is $-SO_2R^{14}$ and R^3 is $-C(=O)R^{6A}$ can be obtained from Compound (Ic) prepared by the Preparing method 1 or 3 in accordance with the method described in for example, Shin-Jikken-Kagaku-Koza (New Experiment Chemistry Lecture) Vol. 14, p. 1803 (Maruzen, 1978):



(wherein R^1, R^4, R^5, R^{6A} and R^{14} have the same meanings as those mentioned above, respectively, and X^3 has the same meaning as that of the aforementioned X^1.)

Preparing method 6

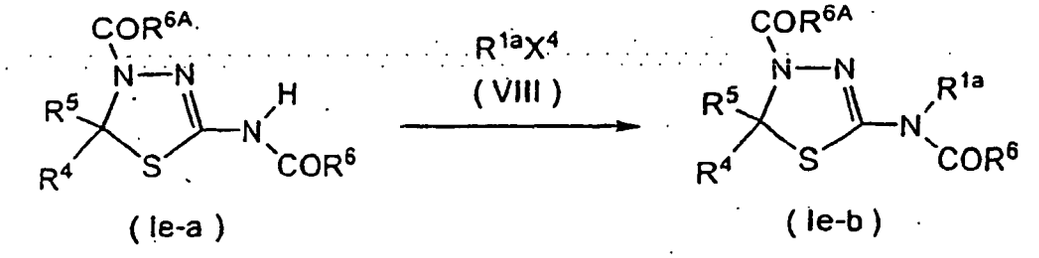
[0022] Among Compound (I), Compound (Ig) wherein R^2 is $-NR^{11}R^{12}$ and R^3 is $-C(=O)R^{6A}$ can be obtained from Compound (VII) prepared in accordance with the method described in Indian J. Chem., Section B, Vol. 31(B), p. 547 (1992) in accordance with the methods described in for example, Indian J. Chem., Section B, Vol. 31B(8), p. 547 (1992), Phosphorus Sulfur & Silicon & the Related Elements, Vol. 122, p. 307 (1997) and the like,:



(wherein R^1, R^4, R^5, R^{6A}, R^{11} and R^{12} have the same meanings as those mentioned above, respectively.)

Preparing method 7

[0023] Among Compound (Ie), Compound (Ie-b) wherein R^1 is substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted cycloalkyl can be obtained by the following step from Compound (Ie-a) among Compound (Ie) wherein R^1 is a hydrogen atom prepared by the Preparing method 4:



(Ie-a) (Ie-b)

(wherein R^4, R^5, R^6 and R^{6A} have the same meanings as those mentioned above, respectively, X^4 has the same meaning as that of the aforementioned X^1, and R^{1a} represents substituted or unsubstituted lower alkyl,a substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted cycloalkyl among the definition of the aforementioned R^1.)

[0024] Compound (Ie-b) can be obtained by allowing Compound (Ie-a) to react with Compound (VIII) in an inert solvent, for example, N,N-dimethylformamide and the like, in the presence of an appropriate base such as sodium hydroxide, at a temperature between 0˚C and room temperature for 1 to 24 hours. The base and Compound (VIII) are preferably used in amounts of 2 to 5 equivalents and 2 to 3 equivalents, respectively, to Compound (Ie-a).

Preparing method 8

[0025] Among Compound (I), Compound (Ih) wherein R^3 is a hydrogen atom can be obtained by the methods described in for example, Phosphorus, Sulfur and Silicone and the Related Elements, Vol. 122, p. 307 (1997) and Chem. Ber., Vol. 123, p. 691 (1990) and the like, or the methods similar to the aforementioned methods.

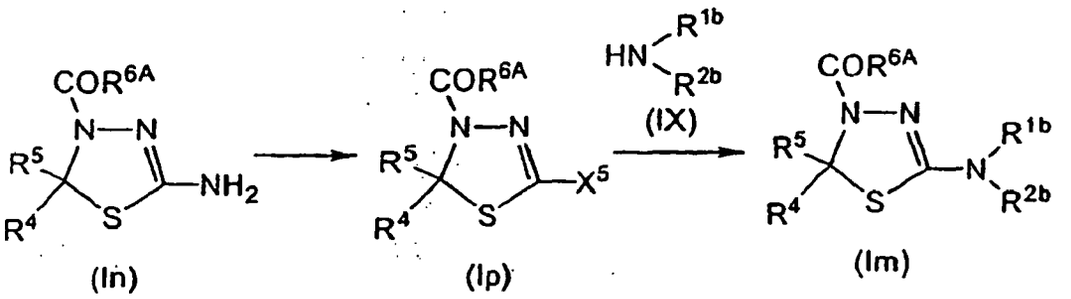
Preparing method 9

[0026] Among Compound (I), Compound (Ij) wherein R^2 and/or R^3 is -C(=S)R^6 and/or -C(=S)R^{6A}, respectively, can be obtained by thiocarbonylation of Compound (Ik) wherein the corresponding R^2 and/or R^3 is -C(=O)R^6 and/or -C(=O)R^{6A}, respectively, among Compound (Ia) to Compound (Ih) obtained by the aforementioned the Preparing methods 1 to 7.

[0027] For example, Compound (Ij) can be obtained by treatment of Compound (Ik) in a solvent such as toluene and tetrahydrofuran, with an appropriate thiocarbonylating agent such as 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphethane-2,4-disulfide (Lawesson's reagent), phosphorus pentasulfide and the like, at a temperature between room temperature and the boiling point of the solvent for 1 to 24 hours. The thiocarbonylating agent is preferably used in an amount of 2 to 10 equivalents to Compound (Ik).

Preparing method 10

[0028] Among Compound (I), Compound (Im) wherein R^3 is -C(=O)R^{6A} and R^1 and R^{2f} are combined to form a substituted or unsubstituted heterocyclic group together with the adjacent nitrogen atom can be obtained by the following step from Compound (In) wherein R^1 and R^{2a} are hydrogen atoms among Compound (Ia) prepared by the Preparing method 1, or from Compound (In) wherein R^1 is a hydrogen atom among Compound (Ic) prepared by the Preparing method 3:



(wherein R^4, R^5 and R^{6A} have the same meanings as those mentioned above, respectively, X^5 has the same meaning as that of the aforementioned X^1, R^{1b} and R^{2b} represent a substituted or unsubstituted heterocyclic group formed together with the adjacent nitrogen atom, said heterocyclic group formed together with the adjacent nitrogen atom has the same meaning as that of the aforementioned heterocyclic group (vii) formed together with the adjacent nitrogen atom, and the substituent in said substituted heterocyclic group formed together with the adjacent nitrogen atom has the same meaning as that of the aforementioned substituent (xiii) in the heterocyclic group.)

[0029] Compound (Ip) can be obtained from Compound (In) by the methods described in for example, Chem. Commun., Vol. 8, p. 873 (1998) and the like, or the methods similar to the aforementioned methods.

[0030] Compound (Im) can be obtained by allowing Compound (Ip) to react with Compound (IX) in an inert solvent, for example, dichloromethane and the like, at a temperature between 0˚C and 60˚C for 10 minutes to 24 hours. Compound (IX) is preferably used in an amount of 2 to 50 equivalents to Compound (Ip).

[0031] Alternatively, Compound (Im) can also be obtained from Compound (Ie-c) wherein R^1 is a hydrogen atom and R^6 is an alkyl group substituted with carboxyl group among Compound (Ie) prepared by the Preparing method 4 by the method described in for example, Synthesis-Stuttgart, Vol. 5, p. 420 (1991) or the methods similar to the aforementioned method.

[0032] Moreover, Compound (Im) can also be obtained from Compound (Ie-d) wherein R^1 is a hydrogen atom and R^6 is an alkyl group substituted with halogen among Compound (Ie) by the method described in for example, Shin-Jikken-Kagaku-Koza (New Experiment Chemistry Lecture) Vol. 14, p. 1174 (Maruzen, 1978) and the like, or the methods similar to the aforementioned methods.

[0033] Furthermore, among Compound (I), Compound (Ij-a) wherein R^3 is $-C(=S)R^{6A}$ and R^1 and R^2 are combined to form a substituted or unsubstituted heterocyclic group together with the adjacent nitrogen atom can be obtained from Compound (Im) in the similar manner as the aforementioned the Preparing method 9.

[0034] In Compound (I), conversion of the functional group contained in R^1, R^2, R^3, R^4 or R^5 can also be carried out by the aforementioned steps, or also by the other known methods [e.g.. Comprehensive Organic Transformations, R. C. Larock (1989) and the like].

[0035] Compound (I) having the desired functional group at the desired position can be obtained by carrying out the aforementioned methods in appropriate combination.

[0036] The intermediates and the objective compounds in the aforementioned preparation methods can be purified and isolated by conducting a purification method ordinarily used in the synthetic organic chemistry such as filtration, extraction, washing, drying, concentration, recrystallization, various chromatography such as high performance liquid chromatography, thin layer chromatography, silica gel chromatography and the like. The intermediates can also be subjected to the next reaction without paticular purification.

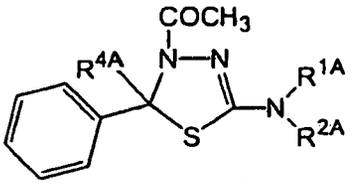
[0037] Some compounds of the present invention may exist as position isomers, geometrical isomers, optical isomers, tautomers. Geometrical isomers, optical isomers, tautomers and mixtures thereof can be used for the antitumor agent of the present invention.

[0038] To obtain a salt of Compound (IAi), (IA-vi), (IA-vii), or (IA-viiii), when said compound is obtained as a salt form, it may be purified as it is. When said compound is obtained as a free form, it may be dissolved or suspended in an appropriate solvent, and added with an appropriate acid or base to form a salt and then be isolated.

[0039] In addition, Compound (IAi), (IA-vi), (IA-vii), or (IA-viiii) or a pharmacologically acceptable salt thereof may exist in the form of adducts with water or variety of solvents, which also can be used for the antitumor agent of the present invention.

[0040] Specific examples of Compound (IAi), (IA-vi), (IA-vii), or (IA-viiii) obtained by the present invention are shown in the following Tables.

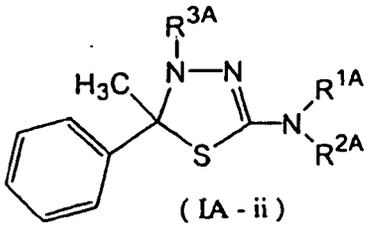
Table 1



(IA - i)

Example No.	Compound No.	R^{1A}	R^{2A}	R^{4A}
7	7	$-CH_3$	$-COCH_3$	$-CH_3$ (Reference example)
133	140	-H	$-CO(CH_2)_4CH_3$	$-CH_2NHSO_2CH_3$

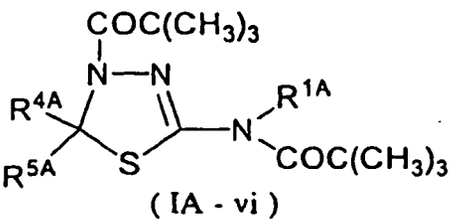
Table 2



(IA - ii)

Example No.	Compound No.	R^{1A}	R^{2A}	R^{3A}
12	15	$-CH_3$	-H	$-COCH_3$ (Reference Example)
14	17	$-CH_3$	-H	$-COCH_2CH_3$ (Reference Example)
15	18	$-CH_3$	$-COCH_3$	$-COCH_2CH_3$ (Reference Example)
16	19	$-CH_3$	$COCH_2CH_3$	$-COCH_2CH_3$ (Reference Example)
76	79	$-CH_2CH=CH_2$	$-COCH_3$	$-COCH_3$ (Reference Example)
* Ph: phenyl				

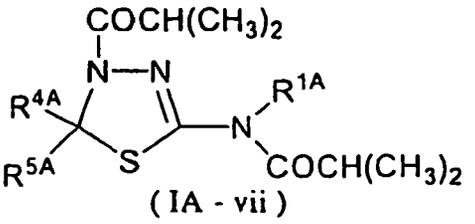
Table 6



(IA - vi)

Example No.	Compound No.	R^{1A}	R^{4A}	R^{5A}
88	95	-H	$-CH_2NHSO_2CH_3$	-Ph
90	97	-H	$-CH_2NHSO_2CH_2CH_3$	-Ph
92	99	-H	$-(CH_2)_2NHSO_2CH_3$	-Ph
* Ph: phenyl				

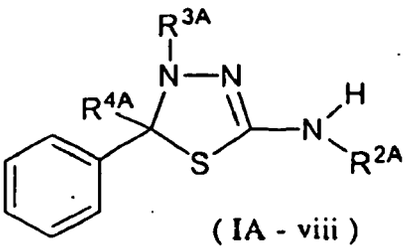
Table 7



(IA - vii)

Example No.	Compound No.	R^{1A}	R^{4A}	R^{5A}
93	100	-H	$-(CH_2)_2NHSO_2CH_3$	-Ph
95	102	$-COCH(CH_3)_2$	$-CH_2NHSO_2CH_3$	-Ph (Reference Example)
96	103	-H	$-CH_2NHSO_2CH_3$	-Ph
* Ph: phenyl				

Table 8



(IA - viii)

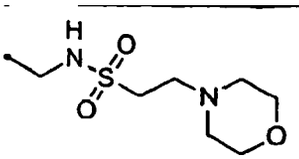
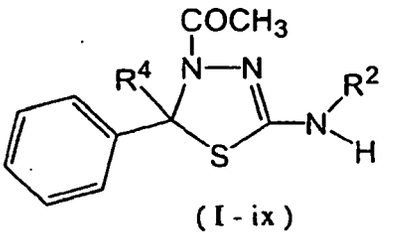
Example No.	Compound No.	R^{2A}	R^{3A}	R^{4A}
111	118	-H	$-COCH_3$	$-CH_2NHSO_2CH_3$ (Reference Example)
112	119	$-COC(CH_3)_3$	$-COCH_3$	$-CH_2NHSO_2CH_3$
160	168	$-COC(CH_3)_2$	$-COCH_3$	$-CH_2NHSO_2CH_2Cl$
160	169	$-COCH_3$	$-COCH_3$	$-CH_2NHSO_2CH_2Cl$
161	170	$-COC(CH_3)_3$	$-COCH_3$	$-CH_2NHSO_2CH=CH_2$
161	171	$-COC(CH_3)_3$	$-COC(CH_3)_3$	$-CH_2NHSO_2CH=CH_2$
162	172	$-COC(CH_3)_3$	$-COCH_3$	
163	173	$-COC(CH_3)_3$	$-COCH_3$	$-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$
164	174	$-COC(CH_3)_3$	$-COCH_3$	$-CH_2NHSO_2(CH_2)_2N(CH_3)_2$
165	175	$-COC(CH_3)_3$	$-COCH_3$	$-CH_2NHSO_2(CH_2)_2NH(CH_2)_2$ OH
166	176	$-COC(CH_3)_3$	$-COC(CH_3)_3$	$-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$
167	177	$-COC(CH_3)_3$	$-COC(CH_3)_3$	$-CH_2NHSO_2(CH_2)_2N(CH_3)_2$
170	180	-H	$-COCH(CH_3)_2$	$-(CH_2)_2NHSO_2CH_3$ (Reference Example)
171	181	$-COC(CH_3)_3$	$-COCH(CH_3)_2$	$-(CH_2)_2NHSO_2CH_3$
175	185	$-COCH_2CH_3$	$-COCH_2CH_3$	$-(CH_2)_2NHSO_2CH_3$
176	186	-H	$-COCH_2CH_3$	$(CH_2)_2NHSO_2CH_3$ (Reference Example)
177	187	$-COC(CH_3)_3$	$-COCH_2CH_3$	$-(CH_2)_2NHSO_2CH_3$

Table 11



(I - ix)

Example No.	Compound No.	R^2	R^4
1	1	$-COCH_3$	$-CH_3$ (Reference Example)
* Ph: phenyl			

[0041] Next, the pharmacological activity of typical Compounds (I) will be explained by the following test example.

Test example 1: Antiproliferative activity in HCT 116 human colon cancer cells

[0042] HCT 116 cells (ATCC No.: CCL-247) were placed on a 96-well microtiter plate (Nunc, 167008) at a density of $1x10^3$ cells/well. The plate was incubated in a 5% CO_2 incubator at 37˚C for 24 hours, and then to the plate was added test compounds diluted stepwise to 100 mL/well in total, and the plate was further incubated in a 5% CO_2 incubator at 37˚C for 72 hours. To the culture medium, the XTT (sodium 3'-[1-(phenylaminocarbonyl)-3,4-tetrazolium]-bis(4-methoxy-6-nitro)benzenesulfonic acid hydrate) labeling mixture (Roche Diagnostics, 1465015) was dispensed in 50 mL/well portions, then the plate was incubated in a 5% CO_2 incubator at 37˚C for 1 hour, and the absorbance was measured at 490 nm and 655 nm with a microplate spectrophotometer (Bio-Rad, Model 550). The inhibitory activity against cell proliferation was shown as a concentration of 50% proliferation inhibition, GI_{50}.
GI_{50} calculation method: The value (difference in absorbance) was calculated by subtracting the absorbance at 655nm from the absorbance at 490nm of each well. The difference in absorbance obtained from the cells untreated with a test compound was defined as 100%, and compared with the difference in absorbance obtained from the cells treated with the solution of the compound in the known concentration, and thereby the concentration of the compound of 50% inhibition against cell proliferation was calculated to obtain GI_{50}.

[0043] The results of the typical compounds obtained in Test example 1 are shown in Table 14. Compounds 170, and 173 showed the GI_{50} value less than 10 μ mol/L.

Table 14

Compound No.	GI_{50} (μ mol/L)
1*	1.0
7*	0.48
18*	0.62
99	0.063
* (reference compounds)	

[0044] Compounds (IA-i), (IA-vi), (IA-vii), and (IA-viii), or a pharmacologically acceptable salt thereof, per se, can be administered, however, are generally desired to be provided as a form of various pharmaceutical preparations. Also, the pharmaceutical preparations are used for animals or human.

[0045] The pharmaceutical preparations according to the present invention can comprise as an active ingredient a compound of the invention, or a pharmacologically acceptable salt thereof, solely or as a mixture with any other effective ingredient for the treatment. The pharmaceutical preparations are manufactured by mixing the active ingredient with one or more of pharmacologically acceptable carriers using any method well known in the technical field of pharmaceutical science.

[0046] As for administration routes, it is preferred to chose the most effective route for the treatment such as oral administration or parenteral administration, for example, intravenous administration and the like.

[0047] Examples of,formulations for administration include tablets, injections and the like.

[0048] Examples of the pharmaceutical carrier used include lactose, mannitol, glucose, hydroxypropyl cellulose, starch, magnesium stearate, sorbitan fatty acid ester, glyceric acid ester, polyvinyl alcohol, distilled water for injection, physiological saline, propylene glycol, polyethylene glycol, ethanol and the like. The pharmaceutical preparation according to the present invention may comprise other various additives such as excipients, lubricants, binders, disintegrator, isotonicities and emulsifiers.

[0049] Compounds (IA-i), (IA-vi), (IA-vii), and (IA-viii), or a pharmacologically acceptable salt thereof are generally administered systemically or locally in the form of an oral or parenteral preparation when used for the aforementioned purpose. The dose and the frequency of administration may vary depending on the administration form, the age and body weight of a patient, nature and severity of the condition to be treated, and the like. Generally, 0.1 to 1,000 mg/kg, preferably 0.5 to 500 mg/kg per single administration for an adult may be administered orally or parenterally, once a day or a few times a day, or may be continuously administered intravenously for 1 to 24 hours a day. However, the dose and the frequency of administration may vary depending on the aforementioned various conditions and the like.

Best Mode for Carrying out the Invention

[0050] The present invention will be explained in detail with reference to the following examples.

[0051] The spectra of proton nuclear magnetic resonance (^{1}H NMR) used in Examples were measured at 270 or 300 MHz, and exchangeable hydrogen may not always be clearly observed depending on the compound and the measurement conditions. For the descriptions of the multiplicity of signals, those generally applied are used, and the symbol "br" represents an apparent broad signal.

Example 1 (Compound 1) (Reference Example)

[0052] Step 1: Acetophenone (4.00 g, 33.3 mmol) and thiosemicarbazide (3.15 g, 34.6 mmol) were dissolved in methanol (30 mL). To the solution was added hydrochloric acid (0.1 mL) and the mixture was vigorously stirred at room temperature for 15 hours. To the reaction mixture was added water (30 mL), and the deposited crystals were collected by filtration. The collected crystals were washed with water and diisopropyl ether, and then dried to obtain acetophenone=thiosemicarbazone (5.64 g, 88%).

^{1}H NMR (270 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H), 7.37-7.40 (m, 3H), 7.91-7.94 (m, 3H), 8.27 (br s, 1H), 10.21 (br s, 1H)

Step 2: Acetophenone=thiosemicarbazone (300 mg, 0.889 mmol) obtained above was dissolved in acetic anhydride (1.0 mL, 11 mmol). After being refluxing under heating, the solution was cooled to room temperature with vigorous stirring. To the reaction mixture was added diisopropyl ether (3 mL), and the deposited crystals were collected by filtration. After the collected crystals were suspended in diisopropyl ether and stirred for 3 hours, the crystals were collected by filtration and dried to obtain Compound 1 (195 mg, 72%).

^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 2.01 (s, 3H), 2.19 (s, 3H), 2.28 (s, 3H), 7.24-7.36 (br s, 5H), 11.63 (br s, 1H)

Example 7 (Compound 7) (Reference Example)

[0053] Step 1: In a manner similar to that in Step 1 of Example 1, acetophenone=4-methylthiosemicarbazone (1.51 g, 77%) was obtained from 4-methylthiosemicarbazide (1.00 g, 9.51 mmol) and acetophenone (1.33 mL, 11.4 mmol).

Step 2: In a manner similar to that in Step 2 of Example 1, Compound 7 (1.03 g, 47%) was obtained from acetophenone=4-methylthiosemicarbazone (1.00 g, 9.51 mmol) obtained above.

^{1}H NMR (270 MHz, DMSO-d_6) δ (ppm): 2.21 (s, 3H), 2.23 (s, 3H), 2.26 (s, 3H), 3.41(s, 3H), 7.28-7.36 (m, 5H)

Example 12 (Compound 15) (Reference Example)

[0054] Compound 7 (550 mg, 1.89 mmol) prepared in Example 7 was dissolved in N,N-dimethylformamide (10.0 mL). To the solution was added 60% sodium hydride (0.23 g, 5.75 mmol) and the mixture was stirred at room temperature for 30 minutes. To the reaction mixture was added water and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/1) to obtain Compound 15 (0.31 g, 66%).

^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 2.17 (s, 3H), 2.41 (s, 3H), 2.91 (br d, J = 5.0 Hz, 3H), 3.92 (br s, 1H). 7.25-7.47 (m, 5H)

Example 14 (Compound 17) (Reference Example)

[0055] In a manner similar to that in Example 12, Compound 17 (580 mg, 71%) was obtained from Compound 19 (1.00 g, 3.13 mmol) obtained in the after-mentioned Example 16.

^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.13 (t, J = 7.2 Hz, 3H), 2.39 (s, 3H), 2.61 (q, J = 7.2 Hz, 2H), 2.88 (d, J = 6.3 Hz, 3H), 4.02 (br d, J = 6.3 Hz, 1H), 7.22-7.38 (m, 5H) Example 15 (Compound 18) (Reference Example)

[0056] Compound 17 (100 mg, 0.38 mmol) prepared in Example 14 was dissolved in acetone (2.0 mL). To the solution was added acetyl chloride (0.15 mL, 2.11 mmol) and pyridine (0.15 mL, 1.85 mmol), and the mixture was stirred at room temperature for 2 hours. To the reaction mixture was added ethyl acetate and 2 mol/L aqueous sodium hydroxide, and the solution was subjected to separation. The organic layer was washed with saturated aqueous ammonium chloride and saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate, and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane= 1/2) to obtain Compound 18 (0.07 g, 59%). ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.12 (t, J = 7.6 Hz, 3H), 2.27 (s, 3H), 2.35 (s, 3H), 2.65 (q, J = 7.6 Hz, 2H), 3.45 (s, 3H), 7.23-7.42 (m, 5H)

Example 16 (Compound 19) (Reference Example)

[0057] To acetophenone=4-methylthiosemicarbazone (2.00 g, 9.66 mmol) prepared in Step 1 of Example 7 was added propionic anhydride (8.67 mL, 67.6 mmol), and the mixture was heated and stirred at 100˚C for 3 hours. To the reaction mixture was added ethyl acetate and 2 mol/L aqueous sodium hydroxide. After the mixture was stirred at room temperature for 30 minutes, the mixture was subjected to separation. The organic layer was washed with saturated aqueous ammonium chloride and saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate, and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/2) to obtain Compound 19 (1.39 g, 45%).
^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.12 (t, J = 7.3 Hz, 3H), 1.17 (t, J = 7.5 Hz, 3H), 2.36 (s, 3H), 2.54 (q, J = 7.3 Hz, 2H), 2.66 (q, J = 7.5 Hz, 2H), 3.45 (s, 3H), 7.21-7.42 (m, 5H)

Example 76 (Compound 79) (Reference Example)

[0058] Step 1: To a solution of hydrazine monohydrate (1.00 mL, 20.6 mmol) in acetonitrile (5.00 mL) was added allyl isothiocyanate (2.00 mL, 20.4 mmol), and the mixture was stirred at 60˚C for 30 minutes. To the reaction mixture was added diethyl ether (50 mL), and the deposited solid was collected by filtration. The collected solid was dried to obtain 4-allylthiosemicarbazide (1.22 g, 46%).
^{1}H NMR (270 MHz, DMSO-d_6) δ (ppm): 4.11 (t, J = 5.3 Hz, 2H), 4.47 (br s, 2H), 5.03 (d, J = 12.3 Hz, 1H), 5.08 (d, J = 19.1 Hz, 1H), 5.86 (m, 1H), 7.88 (br s, 1H), 8.70 (br s, 1H) Step 2: In a manner similar to that in Step 1 of Example 1, acetophenone=4-allylthiosemicarbazone (1.74 g , 80%) was obtained from acetophenone (1.09 mL, 9.34 mmol) and 4-allylthiosemicarbazide (1.22 g, 9.31 mmol) prepared above.
^{1}H NMR (270 MHz, DMSO-d_6) δ (ppm): 2.31 (s, 3H), 4.25 (t, J = 5.8 Hz, 2H), 5.10 (d, J = 10.5 Hz, 1H), 5.18 (d, J = 17.5 Hz, 1H), 5.91 (m, 1H), 7.37-7.42 (m, 3H), 7.91-7.94 (m, 2H), 8.61 (t, J = 6.0 Hz, 1H), 10.3 (br s, 1H)
Step 3: Acetophenone=4-allylthiosemicarbazone (30 mg, 0.11 mmol) prepared above was dissolved in chloroform (0.5 mL), and to the solution was added acetyl chloride (0.17 mL, 2.32 mmol) and pyridine (0.190 mL, 2.31 mmol), and the solution was stirred at room temperature for 5 hours. To the reaction mixture was added 2 mol/L aqueous sodium hydroxide, then the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous ammonium chloride and saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/2) to obtain Compound 79 (25 mg, 89%).
^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 2.26 (s, 3H), 2.27 (s, 3H), 2.36 (s, 3H), 4.47-4.53 (m, 2H), 5.24 (d, J = 17.3 Hz, 1H), 5.29 (d, J = 10.5 Hz, 1H), 5.91 (m, 1H), 7.20-7.45 (m, 5H)
FAB-MS (m/z): 318 (M^++1)

Example 88 (Compound 95)

[0059] Step 1: 2-Aminoacetophenone hydrochloride (6.10 g, 35.5 mmol) was dissolved in dichloromethane (60 mL), and to the solution was added triethylamine (7.56 g, 74.9 mmol). The solution was cooled to 0˚C, and to the solution was added methanesulfonyl chloride (2.84 mL, 36.5 mmol). The solution was stirred at the same temperature for 5 minutes, and then at room temperature for 2 hours. To the reaction mixture was added water and 1 mol/L hydrochloric acid, and the mixture was extracted with chloroform. After the organic layer was dried over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. The residue was suspended in chloroform (5 mL) and the suspension was stirred, and then, the resulted crystals were collected by filtration to obtain 2-(methylsulfonylamino)acetophenone (4.58 g, 57%). Step 2: In a manner similar to that in Step 1 of Example 1, 2-(methylsulfonylamino)acetophenone=thiosemicarbazone (3.08 g, 51%) was obtained from 2-(methylsulfonylamino) acetophenone (4.58 g, 20.2 mmol) prepared above and thiosemicarbazide (1.84 g, 20.2 mmol).

Step 3: In a manner similar to that in Step 3 of Example 76, Compound 95 (1.81 g, 91%) was obtained from 2-(methylsulfonylamino)acetophenone=thiosemicarbazone (1.31 g, 4.36 mmol) prepared above, pivaloyl chloride (2.10 g, 17.4 mmol) and pyridine (1.38 g, 17.4 mmol).
^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.30 (s, 9H), 1.36 (s, 9H), 2.97 (s, 3H), 3.98 (dd, J = 5.3, 13.8 Hz, 1H), 4.64 (dd, J = 8.5, 13.8 Hz, 1H), 5.10 (br dd, J = 5.3, 8.5 Hz, 1H), 7.25-7.39 (m, 5H), 7.93 (br s, 1H)
AP-MS (m/z): 453 (M^+-1)

Example 90 (Compound 97)

[0060] Step 1: In a manner similar to that in Step 1 of Example 88, 2-(ethylsulfonylamino)acetophenone (367 mg, 39%) was obtained from 2-aminoacetophenone hydrochloride (714 mg, 4.16 mmol), triethylamine (1.45 mL, 10.4 mmol) and ethanesulfonyl chloride (0.434 mL, 4.58 mmol).
Step 2: In a manner similar to that in Step 1 of Example 1, 2-(ethylsulfonylamino)acetophenone=thiosemicarbazone (327 mg, 43%) was obtained from 2-(ethylsulfonylamino)acetophenone (367 mg, 1.61 mmol) prepared above and thiosemicarbazide (147 mg, 1.61 mmol).
Step 3: In a manner similar to that in Step 2 of Example 1, Compound 97 (39 mg, 25%) was obtained from 2-(ethylsulfonylamino)acetophenone=thiosemicarbazone (99 mg, 0.330 mmol), pivaloyl chloride (162 μL, 1.32 mmol) and pyridine (130 μL, 1.58 mmol).
^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.26 (s, 9H), 1.28 (t, J = 7.8 Hz, 3H), 1.29 (s, 9H), 3.09 (m, 2H), 3.97 (dd, J = 5.1, 13.5 Hz, 1H), 4.60 (dd, J = 8.1, 13.5 Hz, 1H), 4.99 (br dd, J = 5.1, 8.1 Hz, 1H), 7.25-7.38 (br s, 5H), 7.93 (br s, 1H)

Example 92 (Compound 99)

[0061] Step 1: Methane sulfonamide (0.476 g, 5.00 mmol) was dissolved in N,N-dimethylformamide (10 mL), and to the solution was added 60% sodium hydride (0.275 g, 5.00 mmol) and the mixture was stirred in a water bath for 20 minutes. To the reaction mixture was added 3-chloropropiophenone (843 mg, 5.00 mol). The mixture was stirred in a water bath for one hour, and further stirred at room temperature for 15 hours. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride and dried over anhydrous sodium sulfate, and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 20/1) to obtain 3-(methylsulfonylamino)propiophenone (240 mg, 21%).
Step 2: In a manner similar to that in Step 1 of Example 1, 3-(methylsulfonylamino)propiophenone=thiosemicarbazone (219 mg, 45%) was obtained-from 3-(methylsulfonylamino)propiophenone (388 mg, 1.71 mmol) prepared above and thiosemicarbazide (156 mg, 1.71 mmol).
Step 3: In a manner similar to that in Step 2 of Example 1, Compound 99 (218 mg, 86%) was obtained from 3-(methylsulfonylamino)propiophenone=thiosemicarbazone (200 mg, 0.696 mmol) obtained above, pivaloyl chloride (342 μL, 2.78 mmol) and pyridine (219 μL, 2.78 mmol).
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.30 (s, 9H), 1.34 (s, 9H), 2.56-2.65 (m, 1H), 2.94 (s, 3H), 3.21-3.44 (m, 2H), 3.58-3.70 (m, 1H), 4.45 (br s, 1H), 7.28-7.37 (m, 5H), 7.97 (br s, 1H)
AP-MS (m/z): 467 (M^--1)

Example 93 (Compound 100)

[0062] In a manner similar to that in Step 3 of Example 76, an oily compound was obtained from 3-(methylsulfonylamino) propiophenone=thiosemicarbazone (173 mg, 0.604 mmol) prepared in Step 2 of Example 92, isobutyryl chloride (316 μL 3.02 mmol) and pyridine (292 μL, 3.62 mmol). The oily compound was dissolved in methanol (10 mL). To the solution was added potassium carbonate (1.00 g, 7.24 mmol), and the mixture was vigorously stirred for 1 hour. The reaction mixture was filtered, and the filtrate was concentrated. And then, to the concentrate was added chloroform, water and 1.0 mol/L hydrochloric acid, and the solution was extracted with chloroform. The organic layer was washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by preparative thin layer chromatography (chloroform/methanol = 20/1) to obtain Compound 100 (111 mg, 41%).
^{1}H NMR (270 MHz, DMSO-d_6) δ (ppm): 0.99-1.07 (m, 12H), 2.55-2.66 (m, 2H), 2.80-3.00 (m, 1H), 2.89 (s, 3H), 3.05-3.17 (m, 1H), 3.24-3.38 (m, 2H), 7.15 (br t, J = 5.9 Hz, 1H), 7.24-7.39 (m, 5H), 11.6 (br s, 1H)

Example 95 (Compound 102) (Reference Example)

[0063] In a manner similar to that in Step 3 of Example 76, Compound 102 (64.6 mg, 39%) was obtained from

2-(methylsulfonylamino)acetophenone=thiosemicarbazone (100 mg, 0.333 mmol) prepared in Step 2 of Example 88, isobutyryl chloride (140 μL, 1.33 mmol) and pyridine (108 μ L, 1.33 mmol).
^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.17 (d, J = 6.9 Hz, 3H), 1.19 (d, J = 6.9 Hz, 3H), 1.25 (d, J = 6.9 Hz, 6H), 1.29 (d, J = 6.9 Hz, 6H), 3.05 (s, 3H), 3.10-3.30 (m, 3H), 4.01 (dd, J = 4.8, 14.2 Hz, 1H), 4.74 (dd, J = 7.8, 14.2 Hz, 1H), 5.37 (br s, 1H), 7.26-7.40 (m, 5H)

Example 96 (Compound 103)

[0064] Compound 102 (40.0 mg, 0.0805 mg) prepared in Example 95 was dissolved in methanol (10 mL). To the solution was added potassium carbonate (1.00 g, 7.24 mmol), and the mixture was vigorously stirred for 1 hour. The reaction mixture was filtered, and the filtrate was concentrated. Then, to the residue was added chloroform, 1mol/L hydrochloric acid and water, and the mixture was extracted with chloroform. The organic layer was washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by preparative thin layer chromatography (chloroform/methanol = 20/1) to obtain Compound 103 (24.2 mg, 84%).
^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.13 (d, J = 6.9 Hz, 3H), 1.18 (d, J = 6.9 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H), 1.23 (d, J = 6.9 Hz, 3H), 2.50 (m, 1H), 2.90 (s, 3H), 3.27 (m, 1H). 3.98 (dd, J = 5.0, 13.9 Hz, 1H), 4.60 (dd, J = 8.2, 13.9 Hz, 1H), 5.35 (br dd, J = 5.0, 8.2 Hz, 1H), 7.26-7.40 (m, 5H), 8.02 (br s, 1H)

Example 111 (Compound 118) (Reference Example)

[0065] In a manner similar to that in Step 3 of Example 76, Compound 118 (302 mg, 26%) was obtained from 2-(methylsulfonylamino)acetophenone=thiosemicarbazone (1.00 g, 3.49 mmol) prepared in Step 2 of Example 88, acetic anhydride (659 μL, 6.98 mmol) and pyridine (565 μ L, 6.98 mmol).
^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 2.29 (s, 3H), 2.99 (s, 3H), 4.04 (d, J = 14.0 Hz, 1H), 4.55 (d, J = 14.0 Hz, 1H), 7.30-7.41 (m, 5H)
AP-MS (m/z): 329 (M^++1)

Example 112 (Compound 119)

[0066] Compound 118 (10.6 mg, 0.0323 mmol) prepared in Example 111 was dissolved in tetrahydrofuran (80 mL). To the solution was added dimethylaminopyridine (7.9 mg, 0.0646 mmol) and pyridine (7.8 μ L, 0.0969 mmol), and the mixture was cooled to 0°C. To the solution was added pivaloyl chloride (20 μ L, 0.162 mmol), and the misture was stirred at 0°C for 5 minutes, and further stirred at room temperature for 4 hours. To the reaction mixture was added water and 1 mol/L hydrochloric acid, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography (chloroform/methanol = 12/1) to obtain Compound 119 (5.3 mg, 40%).
^{1}H-NMR (270 MHz, $CDCl_3$) δ (ppm): 1.27 (s, 9H), 2.32 (s, 3H), 2.95 (s, 3H), 3.98 (dd, J = 5.2, 14.0 Hz, 1H), 4.60 (dd, J = 8.1, 13.9 Hz, 1H), 5.40 (m, 1H), 7.29-7.40 (m, 5H), 8.11 (br s, 1H)

Example 133 (Compound 140)

[0067] Compound 118 (50 mg, 0.15 mmol) prepared in Example 111 was dissolved in dichloromethane (2 mL). To the solution was added pyridine (0.031 mL, 0.38 mmol) and hexanoyl chloride (0.053 mL, 0.38 mmol), and the mixture was stirred at room temperature for 2.5 hours. To the reaction mixture was further added pyridine (0.012 mL, 0.15 mmol) and hexanoyl chloride (0.021 mL, 0.15 mmol), and the mixture was stirred at the same temperature for 1 hour. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography (chloroform/methanol = 15/1) to obtain Compound 140 (52 mg, 80%).
^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 0.90 (t, J = 6.6 Hz, 3H), 1.22-1.41 (m, 4H), 1.64 (m, 2H), 2.31 (s, 3H), 2.32 (t, J = 7.5 Hz, 2H), 2.96 (s, 3H), 3.98 (dd, J = 5.4, 13.9 Hz, 1H), 4.60 (dd, J = 8.1, 13.9 Hz, 1H), 5.38 (dd, J = 5.4, 8.1 Hz, 1H), 7.20-7.44 (m, 5H), 8.02 (s, 1H)
AP-MS (m/z): 427 (M^++1)

Example 160 (Compounds 168 and 169)

[0068] Step 1: 2-Aminoacetophenone hydrochloride (4.56 g, 26.6 mmol) was dissolved in dichloromethane (250 mL).

To the solution was added triethylamine (9.30 mL, 66.7 mmol), and the mixture was stirred at room temperature for 10 minutes. After the reaction mixture was cooled to 0˚C, chloromethanesulfonyl chloride (purity 90%, 3.60 mL, 36.3 mmol) was added to the mixture, and the mixture was stirred at the same temperature for 1 hour. To the reaction mixture was added 2 mol/L hydrochloric acid, and the mixture was extracted with chloroform. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. To the residue was added diethyl ether, and the deposited crystals were collected by filtration and dried to obtain 2-(chloromethylsulfonylamino)acetophenone (5.00 g, 76%).
^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 4.67 (s, 2H), 4.94 (s, 2H), 7.54 (t, J = 8.1 Hz, 2H), 7.67 (t, J = 7.5 Hz, 1H), 7.97 (d, J = 8.1 Hz, 2H), 8.01 (br s, 1H)
AP-MS (m/z): 247 (M^+)
Step 2: 2-(Chloromethylsulfonylamino)acetophenone (1.00 g, 4.05 mmol) prepared above and thiosemicarbazide hydrochloride (1.03 g, 8.07 mmol) were dissolved in methanol (60 mL). To the solution was added concentrated hydrochloric acid (1.00 mL), and the mixture was stirred at 60˚C for 2 hours. The reaction mixture was concentrated, and to the residue was added ethyl acetate and saturated aqueous sodium hydrogencarbonate, and the mixture was subjected to separation. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/1 and 2/1) to obtain 2-(chloromethylsulfonylamino)acetophenone=thiosemicarbazone (0.51 g, 40%).
^{1}H NMR (300 MHz, DMSO-D_6) δ (ppm): 4.17 (s, 2H), 4.93 (s, 2H), 7.37-7.42 (m, 3H), 7.52-7.56 (m, 2H), 8.13 (br s, 1H), 8.48 (br, 2H), 8.85 (br s, 1H)
AP-MS (m/z): 319 (M^+)
Step 3: 2-(Chloromethylsulfonylamino)acetophenone=thiosemicarbazone (7.48 g, 23.4 mmol) prepared above was dissolved in chloroform (250 mL). To the solution was added pyridine (11.4 mL, 141 mmol) and pivaloyl chloride (8.70 mL, 70.6 mmol), and the mixture was stirred at room temperature for 30 minutes. To the reaction mixture was added acetic anhydride (4.40 mL, 46.6 mmol), and the mixture was further stirred at room temperature for 15 hours. To the reaction mixture was added 2 mol/L hydrochloric acid, and the mixture was extracted with chloroform. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/1 and 2/1) to obtain Compound 168 (3.56 g, 25%) and Compound 169 (1.77 g, 14%).

Compound 168

[0069] ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.16 (s, 9H), 2.23 (s, 3H), 4.00 (dd, J = 11.3, 8.0 Hz, 1H), 4.47 (dd, J = 11.3, 2.5 Hz, 1H), 4.91 (d, J = 12.0 Hz, 1H), 4.97 (d, J = 12.0 Hz, 1H), 7.28-7.39 (m, 5H), 8.10 (br s, 1H), 11.2 (br s, 1H)
AP-MS (m/z): 446 (M^+)

Compound 169

[0070] ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.01 (s, 3H), 2.18 (s, 3H), 3.95 (d, J = 14.3 Hz, 1H), 4.45 (d, J = 14.3 Hz, 1H), 4.91 (d, J = 12.0 Hz, 1H), 4.97 (d, J = 12.0 Hz, 1H), 7.25-7.39 (m, 5H), 8.08 (br s, 1H), 11.6 (br s, 1H)
AP-MS (m/z): 404 (M^+)

Example 161 (Compounds 170 and 171)

[0071] Step 1: 2-Aminoacetophenone hydrochloride (1.00 g, 5.85 mmol) was dissolved in dichloromethane (50 mL). To the solution was added triethylamine (2.50 mL, 17.9 mmol), and the mixture was stirred at room temperature for 10 minutes. After the reaction mixture was cooled to 0˚C, chloroethanesulfonyl chloride (0.92 mL, 8.80 mmol) was added to the mixture, and the mixture was stirred at the same temperature for 15 minutes. To the reaction mixture was added 2 mol/L hydrochloric acid and the mixture was extracted with chloroform. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. To the residue was added a mixed solvent of ethyl acetate and n-hexane for crystallization to obtain 2-(vinylsulfonylamino)acetophenone (0.42 g, 32%).
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.54 (d, J = 4.5 Hz, 2H), 5.42 (br s, 1H), 5.94 (d, J = 9.9 Hz, 1H), 6.28 (d, J = 16.5 Hz, 1H), 6.53 (br dd, J = 16.2, 9.9 Hz, 1H), 7.52 (t, J = 7.5 Hz, 3H), 7.65 (t, J = 7.8 Hz, 1H), 7.93 (t, J = 5.1 Hz, 1H)
AP-MS (m/z): 225 (M^+)
Step 2: 2-(Vinylsulfonylamino)acetophenone (0.32 g, 1.42 mmol) prepared above and thiosemicarbazide hydrochloride (0.27 g, 2.13 mmol) were dissolved in methanol (20 mL). To the solution was added concentrated hydrochloric acid (2 drops), and the mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated. To the

residue was added ethyl acetate and saturated aqueous sodium hydrogencarbonate, and the mixture was subjected to separation. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/1) to obtain 2-(vinylsulfonylamino)acetophenone=thiosemicarbazone (0.25 g, 58%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.10 (s, 2H), 5.97 (d, J = 9.9 Hz, 1H), 6.25 (d, J = 16.8 Hz, 1H), 6.54 (dd, J = 16.8, 9.9 Hz, 1H), 7.24-7.27 (m, 2H), 7.42 (br s, 1H), 7.52-7.53 (m, 3H), 7.81 (br s, 1H), 8.70 (m, 1H)

AP-MS (m/z) : 297 (M^+)

Step 3: 2-(Vinylsulfonylamino)acetophenone=thiosemicarbazone (0.25 g, 0.83 mmol) prepared above was dissolved in acetone (10 mL). To the solution was added pyridine (0.34 mL, 4.17 mmol) and pivaloyl chloride (0.31 mL, 2.50 mmol), and the mixture was stirred at room temperature for 30 minutes. To the reaction mixture was added acetic anhydride (0.16 mL, 1.66 mmol), and the mixture was further stirred for 3 days at room temperature. The reaction mixture was concentrated, and to the residue was added ethyl acetate and 2 mol/L hydrochloric acid, and the mixture was subjected to separation. The organic layer was washed with saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/1) to obtain Compound 170 (0.18 g, 52%) and Compound 171 (0.10 g, 26%).

Compound 170

[0072] ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.27 (s, 9H), 2.31 (s, 3H), 3.87 (dd, J = 13.4, 5.0 Hz, 1H), 4.45 (dd, J = 13.4, 7.9 Hz, 1H), 5.57 (br s, 1H), 5.92 (d, J = 9.9 Hz, 1H), 6.25 (d, J = 16.5 Hz, 1H), 6.49 (dd, J = 16.5, 9.9 Hz, 1H), 7.27-7.34 (m, 5H), 8.22 (br s, 1H) AP-MS (m/z): 424 (M^+)

Compound 171

[0073] ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.29 (s, 9H), 1.33 (s, 9H), 3.85 (dd, J = 13.5, 4.8 Hz, 1H), 4.49 (dd, J = 13.5, 8.1 Hz, 1H), 5.29 (br s, 1H), 5.93 (br d, J = 9.9 Hz, 1H), 6.27 (br d, J = 16.5 Hz, 1H), 6.53 (br dd, J = 16.4, 9.6 Hz, 1H), 7.27-7.34 (m, 5H), 8.06 (br s, 1H) AP-MS (m/z): 466 (M^+)

Example 162 (Compound 172)

[0074] Compound 170 (0.05 g, 0.11 mmol) prepared in Step 3 of Example 161 was dissolved in acetonitrile (3 mL). To the solution was added morpholine (0.10 mL), and the mixture was stirred at 80˚C for 2 hours. The reaction mixture was concentrated, and the residue was purified by silica gel column chromatography (chloroform/methanol = 10/1) to obtain Compound 172 (0.04 g, 77%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.27 (s, 9H), 2.33 (s, 3H), 2.42-2.45 (m, 4H), 2.78 (dquin, J = 16.5, 6.0 Hz, 2H), 3.19 (t, J = 6.6 Hz, 2H), 3.65-3.68 (m, 4H), 4.04 (dd, J = 14.1, 4.8 Hz, 1H), 4.55 (dd, J = 14.1, 7.5 Hz, 1H), 5.73 (br s, 1H), 7.30-7.38 (m, 5H), 8.05 (br s, 1H)

AP-MS (m/z): 511 (M^+)

Example 163 (Compound 173)

[0075] In a manner similar to that in Example 162, Compound 173 (0.03 g, 66%) was obtained from Compound 170 (0.05 g, 0.11 mmol) prepared in Step 3 of Example 161 and 70% aqueous ethylamine (0.10 mL).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.10 (t, J = 6.9 Hz, 3H), 1.27 (s, 9H), 2.32 (s, 3H), 2.65 (quin, J = 7.2 Hz, 2H), 3.05-3.09 (m, 2H), 3.18-3.20 (m, 2H), 4.00 (d, J = 13.5 Hz, 1H), 4.55 (d, J = 13.8 Hz, 1H), 7.30-7.37 (m, 5H), 8.07 (br s, 1H)

AP-MS (m/z): 470 (M^++1)

Example 164 (Compound 174)

[0076] In a manner similar to that in Example 162, Compound 174 (0.03 g, 67%) was obtained from Compound 170 (0.05 g, 0.11 mmol) prepared in Step 3 of Example 161 and 2 mol/L dimethylamine methanol solution (0.10 mL).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.26 (s, 9H), 2.24 (s, 6H), 2.31 (s, 3H), 2.71-2.81 (m, 2H), 3.12-3.19 (m, 2H), 4.00 (d, J = 13.5 Hz, 1H), 4.56 (d, J = 13.5 Hz, 1H), 6.00 (br s, 1H), 7.31-7.36 (m, 5H), 8.06 (br s, 1H)

AP-MS (m/z): 469 (M^+)

Example 165 (Compound 175)

[0077] In a manner similar to that in Example 162, Compound 175 (0.03 g, 52%) was obtained from Compound 170 (0.05 g, 0.11 mmol) prepared in Step 3 of Example 161 and 2-aminoethanol (0.10 mL).
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.26 (s, 9H), 2.35 (s, 3H), 2.65-2.78 (m, 2H), 3.08-3.30 (m, 4H), 3.64 (t, J = 5.1 Hz, 2H), 3.98 (d, J = 13.5 Hz, 1H), 4.54 (d, J = 13.5 Hz, 1H), 7.26-7.38 (m, 5H), 8.25 (br s, 1H)
AP-MS (m/z): 485 (M^+)

Example 166 (Compound 176)

[0078] In a manner similar to that in Example 162, Compound 176 (0.01 g, 26%) was obtained from Compound 171 (0.05 g, 0.11 mmol) prepared in Step 3 of Example 161 and 70% aqueous ethylamine (0.10 mL).
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.18 (m, 3H), 1.28 (s, 9H), 1.34 (s, 9H), 2.63 (quin, J = 7.0 Hz, 2H), 2.73 (br q, J = 6.3 Hz, 1H), 2.84 (br q, J = 6.2 Hz, 1H), 3.18 (br t, J = 6.6 Hz, 2H), 4.02 (d, J = 13.2 Hz, 1H), 4.58 (d, J = 13.2 Hz, 1H), 5.85 (br s, 1H), 7.27-7.35 (m, 5H), 8.02 (br s, 1H)
AP-MS (m/z): 512 (M^++1)

Example 167 (Compound 177)

[0079] In a manner similar to that in Example 162, Compound 177 (0.02 g, 39%) was obtained from Compound 171 (0.05 g, 0.11 mmol) prepared in Step 3 of Example 161 and 2 mol/L dimethylamine methanol solution (0.10 mL).
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.28 (s, 9H), 1.34 (s, 9H), 2.25 (s, 6H), 2.73 (br q, J = 6.3 Hz, 1H), 2.84 (br q, J = 6.2 Hz, 1H), 3.18 (br t, J = 6.6 Hz, 2H), 4.02 (d, J = 13.2 Hz, 1H), 4.58 (d, J = 13.2 Hz, 1H), 5.85 (br s, 1H), 7.27-7.35 (m, 5H), 8.02 (br s, 1H) AP-MS (m/z): 512 (M^++1)

Example 170 (Compound 180) (Reference Example)

[0080] Compound 100 (304 mg, 0.0690 mmol) prepared in Example 93 and cerium chloride heptahydrate (257 mg, 0.690 mmol) were dissolved in methanol (800 mL). To the solution was gradually added sodium borohydride (522 mg, 13.8 mmol), and the mixture was stirred at room temperature for 20 minutes. The reaction mixture was concentrated under reduced pressure. To the residue was added 1 mol/L hydrochloric acid (100 mL), and the mixture was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/acetone/ethyl acetate/n-hexane = 9/1/1/1) to obtain Compound 180 (217 mg, 85%).
^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.14 (t, J = 7.0 Hz, 6H), 2.68 (m, 1H), 2.98 (s, 3H), 3.27 (m, 2H), 3.44 (m, 1H), 3.63 (m, 1H), 4.18 (br s, 2H), 4.51 (br s, 1H), 7.30 (m, 5H) AP-MS (m/z): 371 (M^++1)

Example 171 (Compound 181)

[0081] In a manner similar to that in Example 15, Compound 181 (87.3 mg, 71%) was obtained from Compound 180 (100 mg, 0.270 mmol) prepared in Example 170, pyridine (65.4 μL, 0.810 mmol) and pivaloyl chloride (83.4 μL, 0.676 mmol).
AP-MS (m/z): 455 (M^++1)

Example 175 (Compound 185)

[0082] In a manner similar to that in Step 3 of Example 92, Compound 185 (16.7 g, 85%) was obtained from 3-(methylsulfonylamino)propiophenone=thiosemicarbazone (14.4 g, 47.9 mmol), propionyl chloride (16.7 mL, 192 mmol) and pyridine (18.6 mL, 230 mmol).
^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.12 (t, J = 7.5 Hz, 3H), 1.19 (t, J = 7.3 Hz, 3H), 2.37 (m, 2H), 2.63 (m, 3H), 2.96 (s, 3H), 3.35 (m, 2H), 3.58 (m, 1H), 4.55 (br s, 1H), 7.20-7.35 (m, 5H), 8.01 (br s, 1H)

Example 176 (Compound 186) (Reference Example)

[0083] In a manner similar to that in Example 170, Compound 186 (11.7 g, 81%) was obtained from Compound 185 (16.7 g, 40.5 mmol) prepared in Example 175, cerium chloride heptahydrate (15.1 g, 40.5 mol) and sodium borohydride (12.8 g, 338 mol). ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.13 (t, J = 8.7 Hz, 3H), 2.61-2.71 (m, 3H), 2.97 (s, 3H), 3.27-3.47 (m, 2H), 3.60-3.67 (m, 1H), 4.21 (br s, 2H), 4.65 (br s, 1H), 7.26-7.36 (m, 5H)

Example 177 (Compound 187)

[0084] In a manner similar to that in Example 15, Compound 187 (90.3 mg, 76%) was obtained from Compound 186 (96.0 mg, 0.269 mmol) prepared in Example 176, pyridine (65.4 μ L, 0.810 mmol) and pivaloyl chloride (83.4 μ L, 0.676 mmol).
^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm): 1.13 (t, J = 6.0 Hz, 3H), 1.28 (s, 9H), 2.66 (m, 3H), 2.97 (s, 3H), 3.35 (m, 2H), 3.61 (m, 1H), 4.58 (br s, 1H), 7.32 (m, 5H), 8.08 (br s, 1H) AP-MS (m/z): 441 (M^++1)

Example 190 (Tablets)

[0085] Tablets comprising the following composition are obtained according to the conventional method.

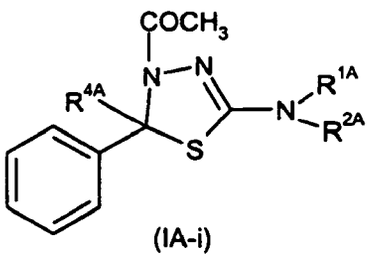
Compound 1	5 mg
Lactose	60 mg
Potato starch	30 mg
Polyvinyl alcohol	2 mg
Magnesium stearate	1 mg
Tar dye	trace

Industrial Applicability

[0086] The present invention provides a thiadiazoline derivative or a pharmacologically acceptable salt thereof which is useful for therapeutic treatment of a human malignant tumor, for example, breast cancer, gastric cancer, ovarian cancer, colon cancer, lung cancer, brain tumor, laryngeal cancer, hematological cancer, urinary or genital tumor including bladder cancer and prostatic cancer, renal cancer, skin carcinoma, hepatic carcinoma, pancreatic cancer, or uterine cancer. In addition, the present invention provides an antitumor agent comprising a thiadiazoline derivative or a pharmacologically acceptable salt thereof as an active ingredient.

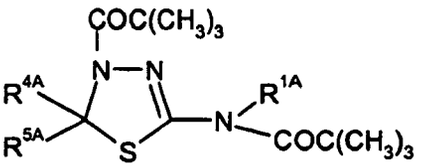
Claims

1. A compound of formula



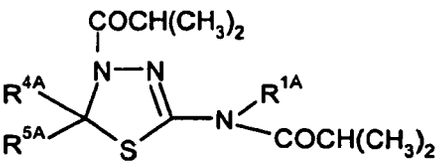
(IA-i)

wherein
R^{1A} is -H, R^{2A} is $-CO(CH_2)_4CH_3$ and R^{4A} is $-CH_2NHSO_2CH_3$;
or a compound of formula



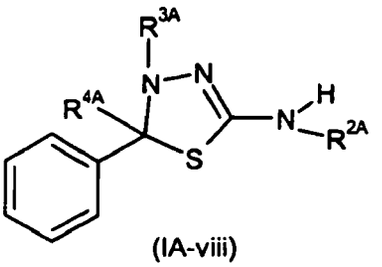
(IA-vi)

wherein
R^{1A} is -H, R^{4A} is $-CH_2NHSO_2CH_3$ and R^{5A} is -Phenyl;
R^{1A} is -H, R^{4A} is $-CH_2NHSO_2CH_2CH_3$ and R^{5A} is -Phenyl;
R^{1A} is -H, R^{4A} is $-(CH_2)_2NHSO_2CH_3$ and R^{5A} is -Phenyl;
or a compound of formula



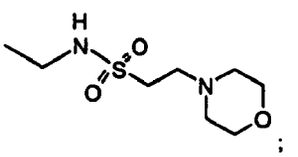
(IA-vii)

wherein
R^{1A} is -H, R^{4A} is $-(CH_2)_2NHSO_2CH_3$ and R^{5A} is -Phenyl; or
R^{1A} is -H, R^{4A} is $-CH_2NHSO_2CH_3$ and R^{5A} is -Phenyl;
or a compound of formula



(IA-viii)

wherein
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2CH_3$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2CH_2Cl$;
R^{2A} is $-COCH_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2CH_2Cl$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2CH=CH_2$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COC(CH_3)_3$ and R^{4A} is $-CH_2NHSO_2CH=CH_2$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is

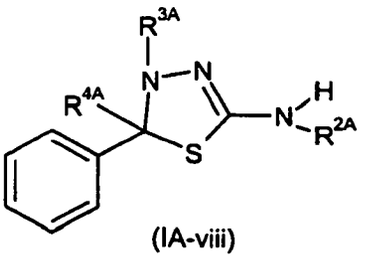


;

R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2N(CH_3)_2$;

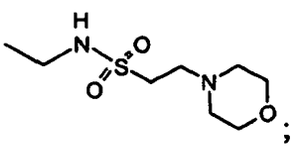
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHS0_2(CH_2)_2NH(CH_2)_2OH$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COC(CH_3)_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COC(CH_3)_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2N(CH_3)_2$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH(CH_3)_2$ and R^{4A} is $-(CH_2)_2NHSO_2CH_3$;
R^{2A} is $-COCH_2CH_3$, R^{3A} is $-COCH_2CH_3$ and R^{4A} is $-(CH_2)_2NHSO_2CH_3$; or
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_2CH_3$ and R^{4A} is $-(CH_2)_2NHSO_2CH_3$;
or a pharmacologically acceptable salt thereof.

2. A compound according to Claim 1 of formula



(IA-viii)

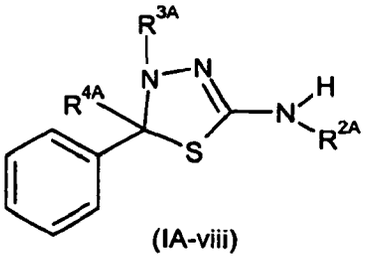
wherein
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2CH_3$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2CH_2Cl$;
R^{2A} is $-COCH_3$, R^{3A} is $COCH_3$ and R^{4A} is $-CH_2NHSO_2CH_2Cl$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2CH=CH_2$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COC(CH_3)_3$ and R^{4A} is $-CH_2NHSO_2CH=CH_2$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is



;

R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2N(CH_3)_2$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2NH(CH_2)_2OH$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COC(CH_3)_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COC(CH_3)_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2N(CH_3)_2$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH(CH_3)_2$ and R^{4A} is $-(CH_2)_2$ $NHSO_2CH_3$;
R^{2A} is $-COCH_2CH_3$, R^{3A} is $-COCH_2CH_3$ and R^{4A} is $-(CH_2)_2$ $NHSO_2CH_3$; or
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_2CH_3$ and R^{4A} is $-(CH_2)_2$ $NHSO_2CH_3$;
or a pharmacologically acceptable salt thereof.

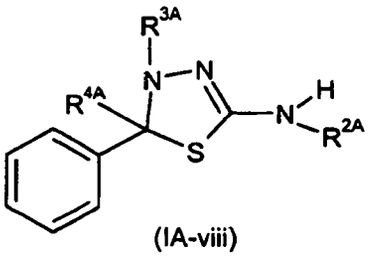
3. A compound according to Claim 1 or 2 of formula



(IA-viii)

wherein
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH_3$ and R^{4A} is $-CH_2NHSO_2CH=CH_2$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COC(CH_3)_3$ and R^{4A} is $-CH_2NHSO_2CH=CH_2$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-CONCH_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$;
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COC(CH_3)_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$; or
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH(CH_3)_2$ and R^{4A} is $-(CH_2)_2NHSO_2CH_3$;
or a pharmacologically acceptable salt thereof.

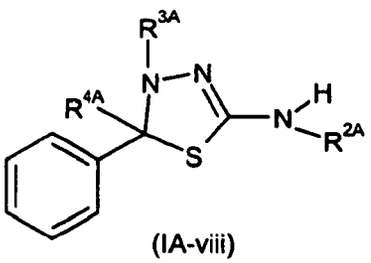
4. A compound according to anyone of Claims 1 to 3 of formula



(IA-viii)

wherein
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COC(CH_3)_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$;
or a pharmacologically acceptable salt thereof.

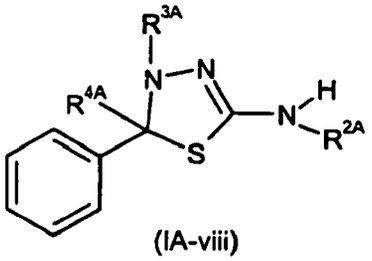
5. A compound according to anyone of Claims 1 to 3 of formula



(IA-viii)

wherein
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COCH(CH_3)_2$ and R^{4A} is $-(CH_2)_2NHSO_2CH_3$
or a pharmacologically acceptable salt thereof.

6. A pharmaceutical composition comprising a compound of formula



(IA-viii)

wherein
R^{2A} is $-COC(CH_3)_3$, R^{3A} is $-COC(CH_3)_3$ and R^{4A} is $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$;
or a pharmacologically acceptable salt thereof.

7. A compound according to any one of claims 1 to 5 for use as a medicament.

8. A compound according to any one of claims 1 to 5 for use as an anti-tumor medicament.

9. A compound according to any one of claims 1 to 5 for use in the treatment of a human malignant tumor.

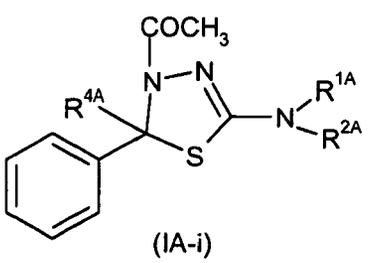
10. A compound for use according to claim 9 wherein the human malignant tumor is breast cancer, gastric cancer, ovarian cancer, colon cancer, lung cancer, brain tumor, laryngeal cancer, hematological cancer, urinary or genital tumor including bladder cancer and prostatic cancer, renal cancer, skin carcinoma, hepatic carcinoma, pancreatic cancer, or uterine cancer.

11. Use of the compound according to anyone of claims 1 to 5 for the manufacture of a medicament for the treatment of human malignant tumor.

12. The use according to claim 11, wherein the human malignant tumor is breast cancer, gastric cancer, ovarian cancer, colon cancer, lung cancer, brain tumor, laryngeal cancer, hematological cancer, urinary or genital tumor including bladder cancer and prostatic cancer, renal cancer, skin carcinoma, hepatic carcinoma, pancreatic cancer, or uterine cancer.

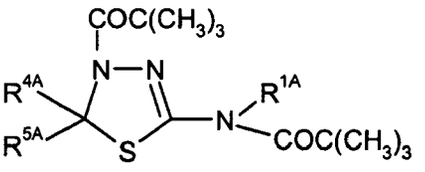
Patentansprüche

1. Verbindung der Formel



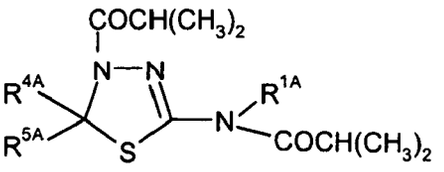
(IA-i)

worin
R^{1A} gleich -H ist, R^{2A} gleich $-CO(CH_2)_4CH_3$ ist und R^{4A} gleich $-CH_2NHSO_2CH_3$ ist;
oder eine Verbindung der Formel



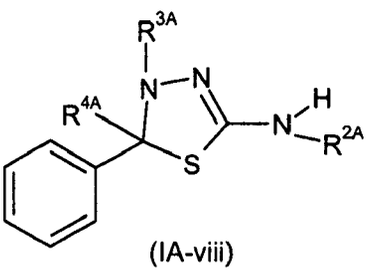
(IA-vi)

worin
R^{1A} gleich -H ist, R^{4A} gleich $-CH_2NHSO_2CH_3$ ist und R^{5A} gleich -Phenyl ist;
R^{1A} gleich -H ist, R^{4A} gleich $-CH_2NHSO_2CH_2CH_3$ ist und R^{5A} gleich -Phenyl ist;
R^{1A} gleich -H ist, R^{4A} gleich $-(CH_2)_2NHSO_2CH_3$ ist und R^{5A} gleich -Phenyl ist;
oder eine Verbindung der Formel



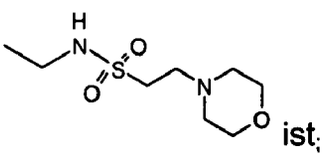
(IA-vii)

worin
R^{1A} gleich -H ist, R^{4A} gleich $-(CH_2)_2NHSO_2CH_3$ ist und R^{5A} gleich -Phenyl ist oder
R^{1A} gleich -H ist, R^{4A} gleich $-CH_2NHSO_2CH_3$ ist und R^{5A} gleich -Phenyl ist; oder eine Verbindung der Formel



(IA-viii)

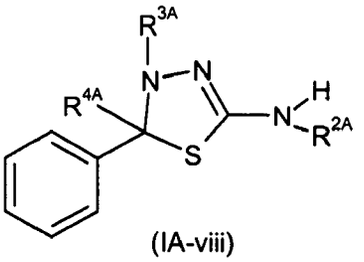
worin
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COCH_3$ ist und R^{4A} gleich $-CH_2NHSO_2CH_3$ ist;
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COCH_3$ ist und R^{4A} gleich $-CH_2NHSO_2CH_2Cl$ ist;
R^{2A} gleich $-COCH_3$ ist, R^{3A} gleich $-COCH_3$ ist und R^{4A} gleich $-CH_2NHSO_2CH_2Cl$ ist;
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COCH_3$ ist und R^{4A} gleich $-CH_2NHSO_2CH=CH_2$;
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COC(CH_3)_3$ ist und R^{4A} gleich $-CH_2NHSO_2CH=CH_2$ ist;
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COCH_3$ ist und R^{4A} gleich



ist;

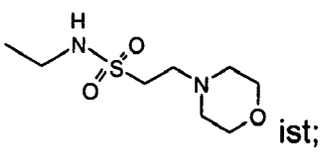
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COCH_3$ ist und R^{4A} gleich $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$ ist;
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COCH_3$ ist und R^{4A} gleich $-CH_2NHSO_2(CH_2)_2N(CH_3)_2$ ist;
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COCH_3$ ist und R^{4A} gleich $-CH_2NHSO_2(CH_2)_2NH(CH_2)_2OH$ ist;
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COC(CH_3)_3$ ist und R^{4A} gleich $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$ ist;
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COC(CH_3)_3$ ist und R^{4A} gleich $-CH_2NHSO_2(CH_2)_2N(CH_3)_2$ ist;
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COCH(CH_3)_2$ ist und R^{4A} gleich $-(CH_2)_2NHSO_2CH_3$ ist;
R^{2A} gleich $-COCH_2CH_3$ ist, R^{3A} gleich $-COCH_2CH_3$ ist und R^{4A} gleich $-(CH_2)_2NHSO_2CH_3$ ist oder
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COCH_2CH_3$ ist und R^{4A} gleich $-(CH_2)_2NHSO_2CH_3$ ist;
oder eines pharmakologisch akzeptablen Salzes davon.

2. Verbindung gemäß Anspruch 1 der Formel



(IA-viii)

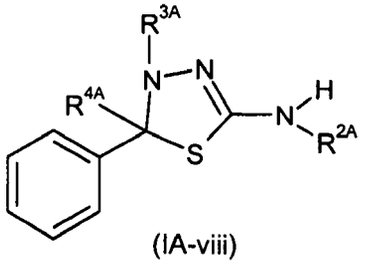
worin
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COCH_3$ ist und R^{4A} gleich $-CH_2NHSO_2CH_3$ ist;
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COCH_3$ ist und R^{4A} gleich $-CH_2NHSO_2CH_2Cl$ ist;
R^{2A} gleich $-COCH_3$ ist, R^{3A} gleich $COCH_3$ ist und R^{4A} gleich $-CH_2NHSO_2CH_2Cl$ ist;
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COCH_3$ ist und R^{4A} gleich $-CH_2NHSO_2CH=CH_2$ ist;
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COC(CH_3)_3$ ist und R^{4A} gleich $-CH_2NHSO_2CH=CH_2$ ist;
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COCH_3$ ist und R^{4A} gleich



ist;

R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COCH_3$ ist und R^{4A} gleich- $CH_2NHSO_2(CH_2)_2NHCH_2CH_3$ ist;
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COCH_3$ ist und R^{4A} gleich $-CH_2NHSO_2(CH_2)_2N(CH_3)_2$ ist;
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COCH_3$ ist und R^{4A} gleich $-CH_2NHSO_2(CH_2)_2NH(CH_2)_2OH$ ist;
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COC(CH_3)_3$ ist und R^{4A} gleich $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$ ist;
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COC(CH_3)_3$ ist und R^{4A} gleich $-CH_2NHSO_2(CH_2)_2N(CH_3)_2$ ist;
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COCH(CH_3)_2$ ist und R^{4A} gleich $-(CH_2)_2NHSO_2CH_3$ ist;
R^{2A} gleich $-COCH_2CH_3$ ist, R^{3A} gleich $-COCH_2CH_3$ ist und R^{4A} gleich $-(CH_2)_2NHSO_2CH_3$ ist oder
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COCH_2CH_3$ ist und R^{4A} gleich $-(CH_2)_2NHSO_2CH_3$ ist;
oder eines pharmakologisch akzeptablen Salzes davon.

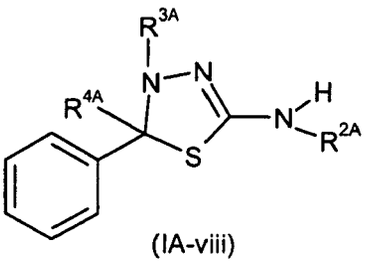
3. Verbindung gemäß Anspruch 1 oder 2 der Formel



(IA-viii)

worin
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COCH_3$ ist und R^{4A} gleich $-CH_2NHSO_2CH=CH_2$ ist;
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COC(CH_3)_3$ ist und R^{4A} gleich $-CH_2NHSO_2CH=CH_2$ ist;
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COCH_3$ ist und R^{4A} gleich $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$ ist;
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COC(CH_3)_3$ ist und R^{4A} gleich $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$ ist oder
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COCH(CH_3)_2$ ist und R^{4A} gleich $-(CH_2)_2NHSO_2CH_3$ ist;
oder eines pharmakologisch akzeptablen Salzes davon.

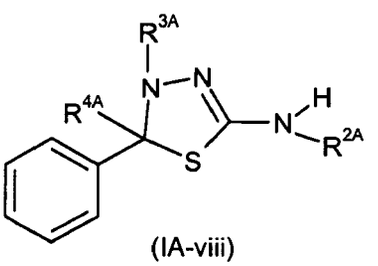
4. Verbindung gemäß einem der Ansprüche 1 bis 3 der Formel



(IA-viii)

worin
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COC(CH_3)_3$ ist und R^{4A} gleich $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$ ist;
oder eines pharmakologisch akzeptablen Salzes davon.

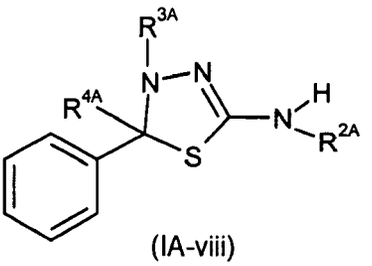
5. Verbindung gemäß einem der Ansprüche 1 bis 3 der Formel



(IA-viii)

worin
R^{2A} gleich $-COC(CH_3)_3$ ist, R^{3A} gleich $-COCH(CH_3)_2$ ist und R^{4A} gleich $-(CH_2)_2NHSO_2CH_3$ ist
oder eines pharmakologisch akzeptablen Salzes davon.

6. Pharmazeutische Zusammensetzung enthaltend eine Verbindung der Formel



(IA-viii)

worin
R^{2A} is -$COC(CH_3)_3$ ist, R^{3A} gleich -$COC(CH_3)_3$ ist und R^{4A} gleich -$CH_2NHSO_2(CH_2)_2NHCH_2CH_3$ ist;
oder eines pharmakologisch akzeptablen Salzes davon.

7. Verbindung gemäß einem der Ansprüche 1 bis 5 zur Verwendung als Arzneimittel.

8. Verbindung gemäß einem der Ansprüche 1 bis 5 zur Verwendung als ein Antitumor-Arzneimittel.

9. Verbindung gemäß einem der Ansprüche 1 bis 5 zur Verwendung bei der Behandlung eines bösartigen Tumors beim Menschen.

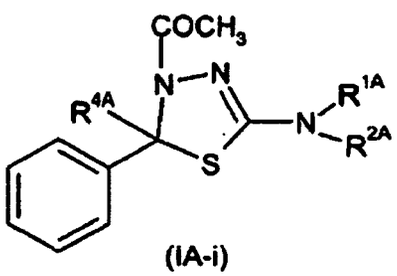
10. Verbindung zur Verwendung gemäß Anspruch 9, wobei der bösartige Tumor beim Menschen Brustkrebs, Magenkrebs, Eierstockkrebs, Dickdarmkrebs, Lungenkrebs, Gehirntumor, Kehlkopfkrebs, hämatologische Krebserkrankung, Urothelkarzinom oder Genitalkarzinom, einschließlich Blasen- und Prostatakrebs, Nierenkrebs, Hautkarzinom, Leberkarzinom, Bauchspeicheldrüsenkrebs oder Gebärmutterkrebs ist.

11. Verwendung der Verbindung gemäß einem der Ansprüche 1 bis 5 zur Herstellung eines Arzneimittels für die Behandlung eines bösartigen Tumors beim Menschen

12. Verwendung gemäß Anspruch 11, wobei der bösartige Tumor beim Menschen Brustkrebs, Magenkrebs, Eierstockkrebs, Dickdarmkrebs, Lungenkrebs, Gehirntumor, Kehlkopfkrebs, hämatologische Krebserkrankung, Urothelkarzinom oder Genitalkarzinom, einschließlich Blasen- und Prostatakrebs, Nierenkrebs, Hautkarzinom, Leberkarzinom, Bauchspeicheldrüsenkrebs oder Gebärmutterkrebs ist.

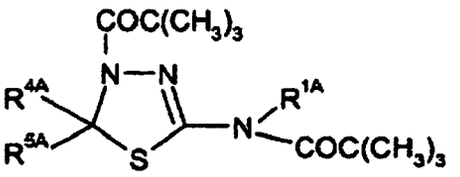
Revendications

1. Composé de formule



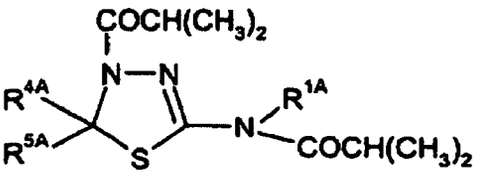
(IA-i)

dans laquelle
R^{1A} est -H, R^{2A} est -$CO(CH_2)_4CH_3$ et R^{4A} est -$CH_2NHSO_2CH_3$;
ou composé de formule



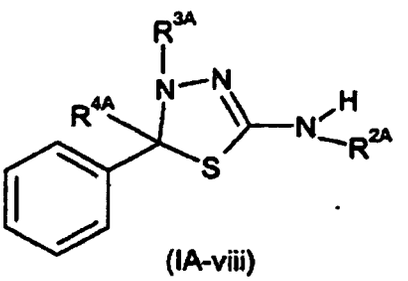
(IA-vi)

dans laquelle
R^{1A} est -H, R^{4A} est $-CH_2NHSO_2CH_3$ et R^{5A} est -phényle ;
R^{1A} est -H, R^{4A} est $-CH_2NHSO_2CH_2CH_3$ et R^{5A} est phényle ;
R^{1A} est -H, R^{4A} est $-(CH_2)_2NHSO_2CH_3$ et R^{5A} est -phényle ;
ou composé de formule



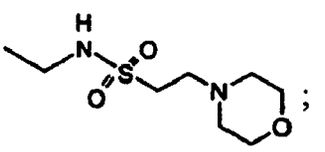
(IA-vii)

dans laquelle
R^{1A} est -H, R^{4A} est $-(CH_2)_2NHSO_2CH_3$ et R^{5A} est -phényle ; ou
R^{1A} est -H, R^{4A} est $-CH_2NHSO_2CH_3$ et R^{5A} est -phényle ;
ou composé de formule



(IA-viii)

dans laquelle
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COCH_3$ et R^{4A} est $-CH_2NHSO_2CH_3$;
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COCH_3$ et R^{4A} est $-CH_2NHSO_2CH_2Cl$;
R^{2A} est $-COCH_3$, R^{3A} est $-COCH_3$ et R^{4A} est $-CH_2NHSO_2CH_2Cl$;
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COCH_3$ et R^{4A} est $-CH_2NHSO_2CH=CH_2$;
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COC(CH_3)_3$ et R^{4A} est $-CH_2NHSO_2CH=CH_2$;
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COCH_3$ et R^{4A} est

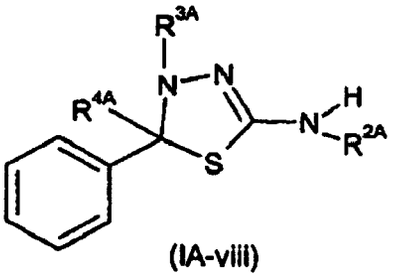


;

R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COCH_3$ et R^{4A} est $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$;

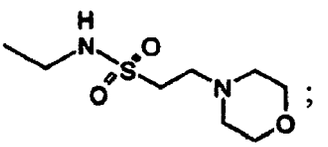
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COCH_3$ et R^{4A} est $-CH_2NHSO_2(CH_2)_2N(CH_3)_2$;
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COCH_3$ et R^{4A} est $-CH_2NHSO_2(CH_2)_2NH(CH_2)_2OH$;
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COC(CH_3)_3$ et R^{4A} est $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$;
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COC(CH_3)_3$ et R^{4A} est $-CH_2NHSO_2(CH_2)_2N(CH_3)_2$;
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COCH(CH_3)_2$ et R^{4A} est $-(CH_2)_2NHSO_2CH_3$;
R^{2A} est $-COCH_2CH_3$, R^{3A} est $-COCH_2CH_3$ et R^{4A} est $-(CH_2)_2NHSO_2CH_3$; ou
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COCH_2CH_3$ et R^{4A} est $-(CH_2)_2NHSO_2CH_3$;
ou un sel pharmacologiquement acceptable d'un tel composé.

2. Composé selon la revendication 1, de formule



(IA-viii)

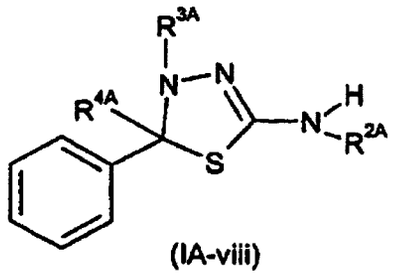
dans laquelle
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COCH_3$ et R^{4A} est $-CH_2NHSO_2CH_3$;
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COCH_3$ et R^{4A} est $-CH_2NHSO_2CH_2Cl$;
R^{2A} est $-COCH_3$, R^{3A} est $-COCH_3$ et R^{4A} est $-CH_2NHSO_2CH_2Cl$;
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COCH_3$ et R^{4A} est $-CH_2NHSO_2CH=CH_2$;
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COC(CH_3)_3$ et R^{4A} est $-CH_2NHSO_2CH=CH_2$;
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COCH_3$ et R^{4A} est



;

R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COCH_3$ et R^{4A} est $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$;
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COCH_3$ et R^{4A} est $-CH_2NHSO_2(CH_2)_2N(CH_3)_2$;
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COCH_3$ et R^{4A} est $-CH_2NHSO_2(CH_2)_2NH(CH_2)_2OH$;
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COC(CH_3)_3$ et R^{4A} est $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$;
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COC(CH_3)_3$ et R^{4A} est $-CH_2NHSO_2(CH_2)_2N(CH_3)_2$;
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COCH(CH_3)_2$ et R^{4A} est $-(CH_2)_2NHSO_2CH_3$;
R^{2A} est $-COCH_2CH_3$, R^{3A} est $-COCH_2CH_3$ et R^{4A} est $-(CH_2)_2NHSO_2CH_3$; ou
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COCH_2CH_3$ et R^{4A} est $-(CH_2)_2NHSO_2CH_3$;
ou un sel pharmacologiquement acceptable d'un tel composé.

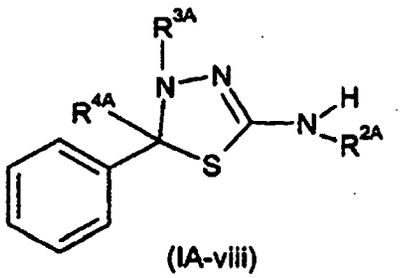
3. Composé selon la revendication 1 ou 2, de formule



(IA-viii)

dans laquelle
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COCH_3$ et R^{4A} est $-CH_2NHSO_2CH=CH_2$;
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COC(CH_3)_3$ et R^{4A} est $-CH_2NHSO_2CH=CH_2$;
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COCH_3$ et R^{4A} est $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$;
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COC(CH_3)_3$ et R^{4A} est $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$; ou
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COCH(CH_3)_2$ et R^{4A} est $-(CH_2)_2NHSO_2CH_3$;
ou un sel pharmacologiquement acceptable d'un tel composé.

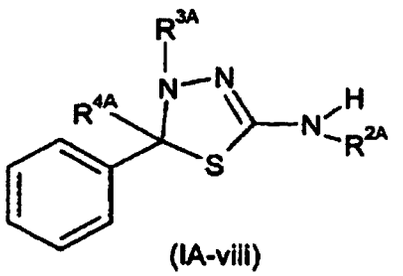
4. Composé selon l'une quelconque des revendications 1 à 3, de formule



(IA-viii)

dans laquelle
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COC(CH_3)_3$ et R^{4A} est $-CH_2NHSO_2(CH_2)_2NHCH_2CH_3$;
ou un sel pharmacologiquement acceptable d'un tel composé.

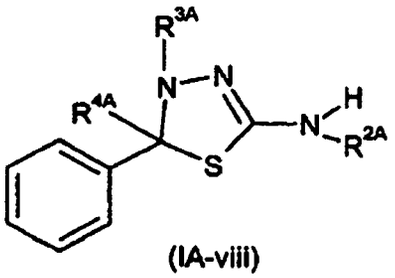
5. Composé selon l'une quelconque des revendications 1 à 3, de formule



(IA-viii)

dans laquelle
R^{2A} est $-COC(CH_3)_3$, R^{3A} est $-COCH(CH_3)_2$ et R^{4A} est $-(CH_2)_2NHSO_2CH_3$;
ou un sel pharmacologiquement acceptable d'un tel composé.

6. Composition pharmaceutique comprenant un composé de formule



(IA-viii)

dans laquelle
R^{2A} est -$COC(CH_3)_3$, R^{3A} est -$COC(CH_3)_3$ et R^{4A} est -CH2$NHSO_2(CH_2)_2NHCH_2CH_3$;
ou un sel pharmacologiquement acceptable d'un tel composé.

7. Composé selon l'une quelconque des revendications 1 à 5, pour une utilisation en tant que médicament.

8. Composé selon l'une quelconque des revendications 1 à 5, pour une utilisation en tant que médicament antitumoral.

9. Composé selon l'une quelconque des revendications 1 à 5, pour une utilisation dans le traitement d'une tumeur maligne humaine.

10. Composé pour une utilisation selon la revendication 9, dans lequel la tumeur maligne humaine est un cancer du sein, un cancer gastrique, un cancer de l'ovaire, un cancer du côlon, un cancer du poumon, une tumeur au cerveau, un cancer laryngé, un cancer du sang, une tumeur urinaire ou génitale, y compris un cancer de la vessie et un cancer de la prostate, un cancer du rein, un carcinome cutané, un carcinome hépatique, un cancer du pancréas, ou un cancer de l'utérus.

11. Utilisation du composé selon l'une quelconque des revendications 1 à 5 pour la fabrication d'un médicament destiné au traitement d'une tumeur maligne humaine.

12. Utilisation selon la revendication 11, dans laquelle la tumeur maligne humaine est un cancer du sein, un cancer gastrique, un cancer de l'ovaire, un cancer du côlon, un cancer du poumon, une tumeur au cerveau, un cancer laryngé, un cancer du sang, une tumeur urinaire ou génitale, y compris un cancer de la vessie et un cancer de la prostate, un cancer du rein, un carcinome cutané, un carcinome hépatique, un cancer du pancréas, ou un cancer de l'utérus.

REFERENCES CITED IN THE DESCRIPTION

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