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(54) Title: THIAZOLIDINE DERIVATIVE

(57) Abstract: The present invention provides thiazolidine derivatives for use in the treatment of diseases related to telomerase activity, e.g., malignant tumors. In one aspect of the present invention, the thiazolidine derivative is of the formula (I): where A, X, Y^1 and Y^2 are those defined herein.

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Thiazolidine Derivative

CROSS-REFERENCES TO RELATED APPLICATIONS

[01] This application claims the benefit of U.S. Provisional Application No. 60/259,123, filed December 30, 2001, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[02] The present invention relates to thiazolidine derivatives for use in the treatment of diseases related to telomerase activity, e.g., malignant tumors.

BACKGROUND OF THE INVENTION

[03] Telomeres are present at the termini of eukaryotic chromosomes and are believed to be essential to the stabilization of chromosomes. In humans, the telomere sequence consists of repetitions of TTAGGG from the 5' end. Although there are few exceptions, telomeres in normal cells usually undergo a gradual reduction in length as the cell divides. The cell becomes an aged cell (M1 phase) and ceases to divide when the telomeres are shortened to a certain length. However, when there is mutation in a cancer suppressor gene, e.g., p53 gene, the cell keeps dividing until the telomeres are reduced to extremely short lengths resulting in instability of the chromosomes and the cell death (M2 phase). See, for example, *Proc. Natl. Acad. Sci. USA*, vol. 89, pp. 10114-10118 (1992) and *Trends in Cell Biology*, vol. 5, pp. 293-297 (1995).

[04] In addition, it is believed that 80% or more cancer cells express an enzyme called telomerase, which extends telomeres. *Journal of the NCI*, vol. 87, pp. 884-894 (1995). Telomerase is a reverse transcription enzyme that extends telomeres using RNA as a template. Telomerase is composed of a template RNA (hTR) and a catalytic subunit protein (hTERT). It is believed that the telomerase in cancer cells suppresses or prevents shortening of the telomeres, thereby rendering the cancer cells immortal, i.e., indefinitely growing by maintaining the length of the telomeres. This theory, often referred to as the "telomere hypothesis", was proposed in 1992 by Cal Harley et al. *Proc. Natl. Acad. Sci. USA*, vol. 89, pp. 10114-10118 (1992). The telomere hypothesis has been supported experimentally. For example, administration of an antisense agent against hTR results in telemere reduction and cancer cell death. *Science*, vol. 269, pp. 1236-1240 (1995). In addition, expression of a dominant-negative mutant hTERT which inhibits wild type telomerase also results in telomere reduction and cancer cell death. *Genes & Development*, vol. 13, pp. 2388-2399 (1999) and *Nature Medicine*, vol. 5, pp. 1164-1170 (1999). Therefore, it is believed that compounds that specifically inhibit telomerase may be used as a new type of antitumor agents by inducing a telomere reduction and limiting the life span of cancer cells. Such compounds are expected to be low-toxicity antitumor agents with minimal affect on normal tissues, because the telomerase is expressed only in cancer cells with few exceptions, such as reproductive cells, etc.

[05] Examples of known low molecular weight compounds that inhibit telomerase in vitro include: nucleic acid analogs, e.g., AZTTP, ddGTP [*Mol. Cell. Biol.*, vol. 16, pp. 53-65 (1996)], and 7-deaza-dGTP [*Biochemistry*, vol. 35, pp. 15611-15617 (1996)]; hetero 5-membered ring fused pyridine derivatives [U.S. Patent Nos. 5,656,638 and 5,760,062]; benzothiophene derivatives [U.S. Patent No. 5,703,116]; pyridine derivatives [U.S. Patent Nos. 5,767,278 and 5,770,613]; anthraquinones [*J. Med. Chem.*, vol. 40, pp. 2113-2116 (1997) and Japanese Laid-Open Patent Publication No. 11-35457]; triazine derivatives [Japanese Laid-Open Patent Publication No. 11-60573]; and phenylisothiazole derivatives [WO99/08679]. In addition, telomerase inhibitory activity and reduction of telomere in cancer cells have been associated with catechins, which are present in green teas. *Biochem. Biophys. Res. Commun.*, vol. 249, pp. 391-396 (1998). Other reported telomerase inhibitors include TMPyP4, a porphyrin having positive charge. *J. Am. Chem. Soc.*, vol. 120, pp. 3261-3262 (1998) and WO98/33503.

[06] Thiazolidine derivatives are known to have a wide variety of pharmaceutical activities, such as reducing blood sugar level and blood fat level [Japanese Laid-Open Patent Publication No. 55-22636, Japanese Laid-Open Patent Publication No. 61-85372, Japanese Laid-Open Patent Publication No. 1-272573, Japanese Laid-Open Patent Publication No. 1-272574, EP Patent Publication No. 454501A, U.S. Patent No. 5,925,656, *J. Med. Chem.*, vol. 35, p. 1853 (1992), etc.]. Some thiazolidine derivatives are anti-allergic [Japanese Laid-Open Patent Publication No. 2-62864], inhibit dopamine β-hydroxylase [Japanese Laid-Open Patent Publication No. 7-173143]; inhibit cathepsin D [Japanese Laid-Open Patent Publication No. 7-258235]; inhibit monoamine oxidase B (MAO-B) [U.S. Patent No. 5,326,770]; anti-inflammatory [U.S. Patent No. 5,143,929]; enhance retinoid action [*Biol. Pharm. Bull.*), vol. 21 (no. 5), pp. 547-549 (1998); inhibit aldose reductase [EP Patent

Publication No. 398179A]; and the like. Still other thiazolidine derivatives are useful as a photosensitive material [U.S. Patent No. 3,719,480].

[07] In addition, certain kinds of thiazolidine derivatives are reported to exhibit differentiation induction and growth inhibitory activity against colon carcinoma cells [*Nature Med.*, vol. 4 (no. 9), pp. 1046-1052 (1998)].

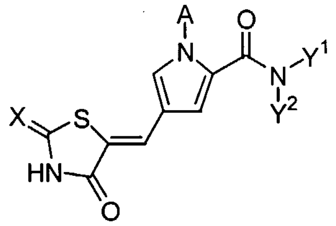
[08] WO97/40017 describes thiazolidine derivatives which have a protein tyrosine phosphatase inhibitory action, and therefore are useful for the treatment of certain types of cancer, but fails to provide any specific data.

[09] However, no telomerase inhibiting activity of thiazolidine derivatives has been reported to date.

BRIEF SUMMARY OF THE INVENTION

[10] One aspect of the present invention provides novel thiazolidine derivatives. Such thiazolidine derivatives have an excellent telomerase inhibitory activity or antitumor activity.

[11] One particular aspect of the present invention provides a compound of the Formula:



(I)

or a pharmaceutically acceptable salt thereof,

wherein A is hydrogen, or substituted or unsubstituted aralkyl, each of Y^1 and Y^2 is independently hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted lower aralkyl, or Y^1 and Y^2 together with the nitrogen atom to which they are attached to form a substituted or unsubstituted heterocyclic group, and X is oxygen or sulfur.

[12] In one embodiment, each of Y^1 and Y^2 is independently substituted or unsubstituted lower alkyl, or substituted or unsubstituted aralkyl.

[13] Another aspect of the present invention provides a telomerase inhibitor comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[14] Yet another aspect of the present invention provides a pharmaceutical composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[15] Still another aspect of the present invention provides an antitumor agent comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[16] Hereinafter, a compound of Formula (I) may be denoted as Compound (I). Similar notations apply to compounds of formulae with any other numerals.

[17] Respective groups in the formulae described herein are subject to the following definitions.

[18] "Lower alkyl" refers to a linear or branched saturated monovalent hydrocarbon moiety of 1 to 6 carbon atoms, e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and hexyl.

[19] "Alkylene" refers to a linear or branched saturated divalent hydrocarbon moiety of one to six carbon atoms.

[20] "Lower alkenyl" refers to a linear or branched hydrocarbon moiety of 2 to 10 carbon atoms and having one or more double bonds, e.g., vinyl, allyl, 1-propenyl, methacryl, crotyl, 1-butenyl, 3-butenyl, 2-pentenyl, 4-pentenyl, 2-hexenyl, 5-hexenyl, 1-decenyl, isoprenyl, and 3,7-dimethyl-2,6-octadienyl.

[21] "Aryl" refers to an aromatic moiety having 6 to 14 carbon atoms, e.g., phenyl, naphthyl, and anthryl.

[22] "Aralkyl" refers to a moiety –R'–R" where R' is an alkylene group and R" is an aryl group as defined above. Specific examples of the aralkyl include benzyl, phenethyl, phenylpropyl, naphthylmethyl, naphthylethyl, diphenylmethyl, and the like.

[23] "Heterocyclic group" refers to a cyclic ring moiety having at least one nitrogen atom in the ring structure. Heterocyclic groups include 5-membered or 6-membered monocyclic heterocyclic groups and fused heterocyclic groups, such as bicyclic or tricyclic moieties in which 3 to 8-membered ring(s) are fused. The heterocyclic group may additionally include other nitrogen atom(s), oxygen atom(s), and/or sulfur atom(s). Exemplary heterocyclic groups include pyrrolidinyl, piperidino, piperazinyl, morpholino, thiomorpholino, homopiperidino, homopiperazinyl, tetrahydropyridyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, imidazolyl, pyrrolyl, benzimidazolyl, and the like.

[24] "Cycloalkyl" refers to a monovalent cyclic hydrocarbon moiety of three to eight ring carbons, e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

[25] "Halogen" when referring to a substituent refers to iodine, bromine, chlorine, or fluorine. The number of halogen substituents in a particular moiety can be one to the largest substitutable number, preferably 1 to 3.

[26] "Alicyclic heterocyclic group" refers to an alicyclic cyclic ring moiety in which at least one ring atom is selected from the group consisting of nitrogen, oxygen, and sulfur. Alicyclic heterocyclic groups include 5-membered or 6-membered monocyclic alicyclic heterocyclic groups and fused alicyclic heterocyclic groups, such as bicyclic or tricyclic moieties in which 3 to 8-membered ring(s) are fused. Exemplary alicyclic heterocyclic groups include pyrrolidinyl, piperidino, piperazinyl, morpholino, thiomorpholino, homopiperidino, homopiperazinyl, tetrahydropyridyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridyl, and the like.

[27] "Heteroaryl" refers to an aromatic ring moiety in which at least one ring atom is selected from the group consisting of nitrogen, oxygen, and sulfur. Heteroaryl groups include 5-membered or 6-membered monocyclic aromatic heterocyclic groups and fused aromatic heterocyclic groups, such as bicyclic or tricyclic moieties in which 3 to 8-membered ring(s) are fused. Exemplary heteroaryls include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinolyl, isoquinolyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, cinnolinyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, thienyl, furyl, thiazolyl, isothiazolyl, oxazolyl, isooxazolyl, indolyl, indazolyl, benzimidazolyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, benzothienyl, benzofuryl, purinyl, benzodioxolyl, and the like.

[28] Hereinafter, the substituents for the respective groups will be described.

(1) Substituted aralkyl

[29] "Substituted aralkyl" includes from one to the largest substitutable number of substitutions, preferably 1 to 3 substitutions. Exemplary substituents include lower alkyl which is optionally substituted with halogen or arylsulfonyl; cyano; aryl; halogen; lower alkoxy which is optionally substituted with halogen; cycloalkyl; lower alkoxy carbonyl; carboxy; alicyclic heterocyclic groups; heteroaryl; methylenedioxy; ethylenedioxy; and the like. Preferred substituents for substituted aralkyl include cyano, aryl, halogen atoms, lower alkoxy, carboxy, heteroaryl, and lower alkyl which is optionally substituted with halogen or arylsulfonyl.

(2) Substituted lower alkyl and Substituted lower alkenyl

[30] "Substituted lower alkyl" and "substituted lower alkenyl" include from one to the largest substitutable number of substitutions, preferably 1 to 3 substitutions. Exemplary substituents include lower alkoxy; cyano; halogen; cycloalkyl; hydroxy; alicyclic heterocyclic groups which is optionally substituted with oxo; heteroaryl; and the like. Preferred substituents include cycloalkyl.

(3) Substituted heterocyclic group

[31] "Substituted heterocyclic group" includes from one to the largest substitutable number of substitutions, preferably 1 to 3 substitutions. Exemplary substituents include lower alkyl; aralkyl; heteroarylcarbonyl; lower alkanoyl; and aryl which is optionally substituted with halogen; and the like.

[32] "Aryl substituted with halogen" include from one to the largest substitutable number of halogens, preferably 1 to 3 halogens.

[33] In one embodiment of Compound (I), preferably Y^1 and Y^2 are independently substituted or unsubstituted lower alkyl, or substituted or unsubstituted aralkyl.

[34] Exemplary pharmaceutically acceptable salts of Compound (I) include pharmaceutically acceptable acid addition salts, metal salts, ammonium salts, organic amine addition salts, amino acid addition salts, and the like.

[35] Exemplary pharmaceutically acceptable acid addition salts of Compound (I) include inorganic acid salts, e.g., hydrochlorides, sulfates, nitrates, and phosphates; and organic acid salts, e.g., acetates, maleates, fumarates, citrates, methanesulfonates, oxalates, malonates, succinates, and tartarates. Exemplary pharmaceutically acceptable metal salts of Compound (I) include alkali metal salts, e.g., sodium salts and potassium salts; alkaline-earth metal salts, e.g., magnesium salts and calcium salts; aluminum salts; zinc salts; and the like. Exemplary pharmaceutically acceptable ammonium salts of Compound (I) include ammonium, tetramethylammonium, and the like. Exemplary pharmaceutically acceptable organic amine addition salts of Compound (I) include addition salts of morpholine, piperidine, and the like. Exemplary pharmaceutically acceptable amino acid addition salts of Compound (I) include addition salts of glycine, phenylalanine, lysine, asparatic acid, glutamic acid, and the like.

[36] It is envisaged that some species of Compound (I) according to the present invention may have various stereoisomers, regioisomers, tautomers, and the like. It is intended that the present invention encompasses all such possible isomers and a mixture thereof, the mixture ratio being arbitrarily selected.

[37] Hereinafter, a method for producing Compound (I) will be described.

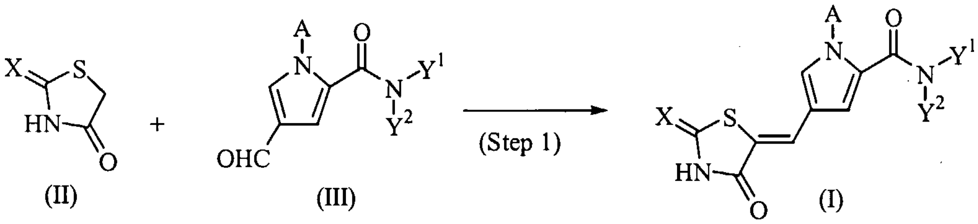
[38] If any of the defined groups are susceptible to modification under the described conditions or otherwise unsuitable for practicing the method described below, it is possible to adopt a method commonly used in synthetic organic chemistry, e.g., protection and deprotection of functional groups, to facilitate production. See, for example, Protective Groups in Organic Synthesis, T.W.Greene, John Wiley & Sons, Inc. (1981), etc.

[39] The order of reaction steps, such as introduction of substituents, may be altered, if necessary.

Production Method 1

[40] Compound (I) can be produced by the following reaction:

Step 1



where A, X, Y^1 and Y^2 are those defined herein.

[41] Compound (I) can be obtained by condensing Compound (II) (a thiazolidine derivative) and Compound (III). Compound (III) can be obtained by the methods described below.

[42] The condensation reaction can be carried out in the presence of a base, if necessary, and in a solvent, if necessary.

[43] Exemplary bases include piperidine, piperidinium acetate, diethylamine, pyridine, sodium acetate, potassium carbonate, sodium carbonate, butyl lithium, lithium diisopropylamide, and the like. The amount of base used can be 0.1 to 10 equivalents of Compound(III).

[44] Suitable solvents include alcohol, such as methanol, ethanol, propanol and the like; ether, such as diethyl ether, tetrahydrofuran (THF), 1,2-dimethoxyethane, dioxane, and the like; hydrocarbon, such as hexane, benzene, toluene, xylene, and the like; or a combination thereof.

[45] The amount of Compound (II) used can be 2 to 10 equivalents of Compound (III).

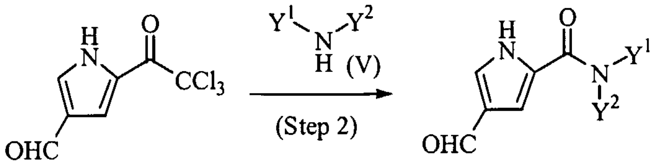
[46] The reaction is carried out at a temperature in the range from room temperature to 200 °C, preferably from 50 °C to 100 °C, for 0.1 to 50 hours.

[47] Hereinafter, a method for producing Compound (III) will be described.

Production Method 2

[48] Compound (IIIa), i.e., Compound (III) in which A is a hydrogen atom, can be produced according to the following reaction:

Step 2



(IV) (IIIa)

where Y^1 and Y^2 are those defined herein.

[49] Compound (IIIa) can be obtained by reacting Compound (IV) with Compound (V) in an inert solvent, in the presence of a base if necessary.

[50] The amount of Compound (V) used can be 1 to 4 equivalents, preferably 1 to 2 equivalents, of Compound (IV).

[51] Exemplary suitable inert solvents include N,N-dimethylformamide, tetrahydrofuran, chloroform, and the like.

[52] Exemplary bases for Step 2 include inorganic bases, e.g., potassium carbonate, sodium carbonate, cesium carbonate, sodium hydride, potassium tert-butoxide, and the like, which may be used in 1 to 4 equivalents, preferably 1 to 2 equivalents, of Compound (IV); and organic bases, e.g., butyl lithium, and the like, which may be used in 1 to 4 equivalents, preferably 1 to 1.5 equivalents, of Compound (IV).

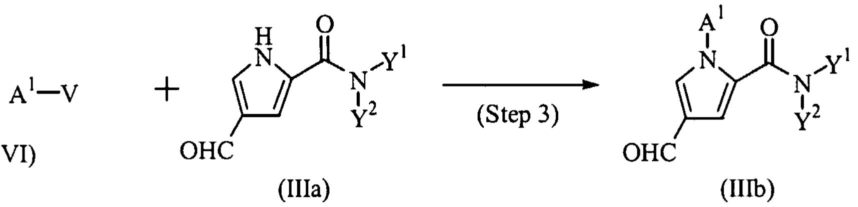
[53] The reaction is typically carried out at a temperature range of from -78 °C to the boiling point of the solvent used. Preferably, the reaction temperature range is from room temperature to the boiling point of the solvent used. The reaction time is typically 1 to 72 hours, preferably from 1 to 48 hours.

[54] Compound (IV) can be obtained by a method described in *J. Org. Chem.*, vol. 43, pp. 4849-4853 (1978) or variations thereof.

Production Method 3

[55] Compound (IIIb), i.e., Compound (III) in which A is a group other than a hydrogen atom, can be produced using the following reaction:

Step 3



where Y^1 and Y^2 are those defined herein. A^1 is same as A other than hydrogen. V is a leaving group, such as halogen, p-toluenesulfonyloxy, or methanesulfonyloxy.

[56] Compound (IIIb) can be obtained by reacting Compound (IIIa) with Compound (VI) in an inert solvent, in the presence of a base.

[57] The amount of Compound (VI) used can be 1 to 4 equivalents, preferably 1 to 2 equivalents, of Compound (IIIa).

[58] Exemplary inert solvents for Step 3 include N,N-dimethylformamide, tetrahydrofuran, dimethoxyethane, 1,4-dioxane, and the like.

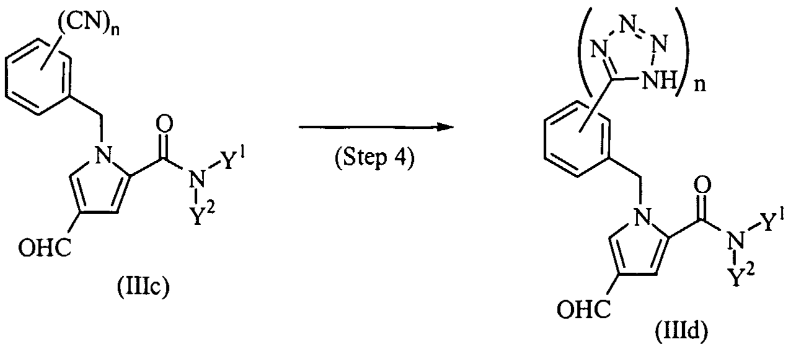
[59] Exemplary bases for Step 3 include inorganic bases, e.g., sodium carbonate, cesium carbonate, sodium hydride, potassium tert-butoxide, and the like, which may be used in 1 to 4 equivalents, preferably 1 to 2 equivalents, of Compound (IIIa); and organic bases, e.g., 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine, 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene, 1,8-diazabicyclo[4.3.0]undec-7-ene, and the like, which may be used in 1 to 4 equivalents, preferably 1 to 1.5 equivalents, of Compound (IIIa).

[60] Typically, the reaction is carried out at a temperature range of from 0 °C to the boiling point of the solvent used. Preferably, the reaction temperature is from room temperature to the boiling point of the particular solvent used. The reaction time is typically from 1 to 72 hours, preferably from 1 to 48 hours.

Production Method 4

[61] Compound (IIId), i.e., Compound (III) in which A is benzyl substituted with tetrazolyl, can be produced using the following reaction:

Step 4



where Y^1 and Y^2 are those defined herein, and n is an integer from 1 to 5.

[62] Compound (IIId) can be obtained by reacting Compound (IIIc) with sodium azide in an inert solvent in the presence of ammonium chloride, trimethylammomium chloride, or the like.

[63] Suitable inert solvents for Step 4 include N,N-dimethylformamide, N-methyl-2-pyrrolidinone, and the like.

[64] Sodium azide may be used in 1 to 10 equivalents, preferably 1 to 5 equivalents, of Compound (IIIc).

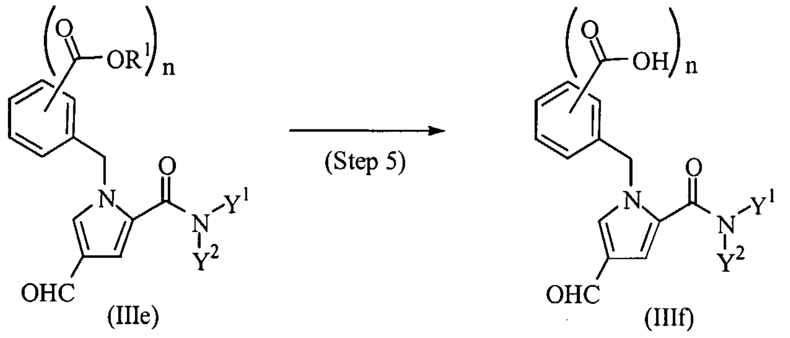
[65] Ammonium chloride or trimethylammomium chloride may be used in 1 to 10 equivalents, preferably 1 to 5 equivalents, of Compound (IIIc).

[66] Typically, the reaction is carried out at a temperature range of from room temperature to the boiling point of the solvent used. Preferably, the reaction temperature is in the range of from 50 °C to the boiling point of the solvent used. Typically, the reaction time is from 1 to 72 hours, preferably from 1 to 48 hours.

Production Method 5

[67] Compound (IIIf), i.e., Compound (III) in which A is benzyl substituted with carboxy, can be produced using the following reaction:

Step 5



where, Y^1, Y^2, and n are those defined herein and R^1 is lower alkyl.

[68] Compound (IIIf) can be obtained by hydrolyzing the ester group of Compound (IIIe). Such hydrolysis is typically conducted in an organic solvent in the presence of an aqueous solution of an inorganic base.

[69] Suitable organic solvents for Step 5 include methanol, ethanol, acetone, tetrahydrofuran, 1,4-dioxane, and the like.

[70] Examples of the aqueous solution of an inorganic base include aqueous solutions of sodium hydroxide, potassium hydroxide, lithium hydroxide, or the like. The aqueous solution of an inorganic base may be used in 1 to 10 equivalents, preferably 1 to 5 equivalents, of Compound (IIIe).

[71] The reaction is generally carried out at a temperature range of from room temperature to the boiling point of the solvent used, preferably from room temperature to 50 °C, for 1 to 72 hours, preferably for 1 to 48 hours.

[72] A desired compound according to the above-described production methods may be isolated and purified by a purification method which is commonly used in synthetic organic chemistry, e.g., filtration, extraction, washing, drying, concentration, recrystallization, and/or various chromatography techniques. Furthermore, the desired compound may be purified by a purification method which is commonly used in general parallel synthesis methods, e.g., methods using scavenger resin and/or ion exchange resin techniques.

[73] A salt of Compound (I) can be obtained from a free form of Compound (I) by forming a salt by usual methods. For example, Compound (I) can be dissolved or suspended in an appropriate solvent and a predetermined acid or base can be added. The resulting salt can then be isolated and/or purified. Alternatively, a salt of Compound (I) can be obtained directly from the reaction and optionally be purified.

[74] Compound (I) or a pharmaceutically acceptable salt thereof may be in the form of an adduct with water or various solvents. Such adducts are also encompassed within the present invention.

[75] Compound (I) or a pharmaceutically acceptable salt thereof may be used as such or in various forms of pharmaceutical formulations depending on the pharmacological effects and purpose of administration thereof. When used as a drug, an effective amount of Compound (I) or a pharmaceutically acceptable salt thereof may be uniformly mixed with a pharmaceutically acceptable carrier. Such a carrier may be in a wide range of forms depending on the particular formulation desired for administration. Such a drug composition is preferably in a unit dosage form appropriate for oral or parenteral administration (e.g., via injection).

[76] Tablets can be formulated using any of the conventional methods known to one skill in the art and can include an excipient, a disintegrator, a lubricant, a binder and/or a surfactant. Exemplary excipients include lactose, glucose, sucrose, mannitol, methyl cellulose, and the like. Exemplary disintegrators include starch, sodium alginate, carboxymethyl cellulose calcium, crystalline cellulose, and the like. Exemplary lubricants include magnesium stearate, talc, and the like. Exemplary binders include gelatin,

polyvinylalcohol, polyvinylpyrrolidone, hydroxypropyl cellulose, methyl cellulose, and the like. Exemplary surfactants include sucrose fatty acid esters, sorbitan fatty acid esters, and the like. Such tablets preferably contain 1 to 300 mg of an active ingredient per tablet.

[77] Granules can be prepared using any of the conventional methods known to one skilled in the art by adding suitable components, e.g., excipients such as lactose or sucrose; disintegrators such as starch; and/or binders such as gelatin. Similarly, powder forms can be prepared using any of the conventional methods known to one skilled in the art by adding suitable components, for example, an excipient, such as lactose or mannitol.

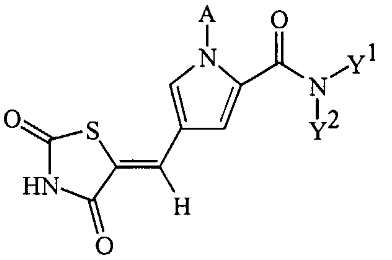
[78] Capsule formulation can include gelatin, water, sucrose, gum Arabic, sorbitol, glycerin, crystalline cellulose, magnesium stearate talc, and/or the like. Such capsules preferably contain 1 to 300 mg of an active ingredient per capsule.

[79] Injectable form can include a solvent, such as water, saline, vegetable oils (e.g., olive oil or peanut oil), ethyl oleate or propylene glycol; a solubilizer, such as sodium benzoate, sodium salicylate, and urethane; an isotonizing agent, such as sodium chloride or glucose; a preservative, such as phenol, cresol, p-hydroxy benzoate, or chlorobutanol; an antioxidant, such as ascorbic acid or sodium pyrosulfite; and the like.

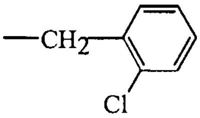
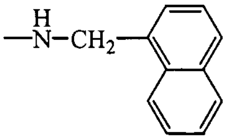
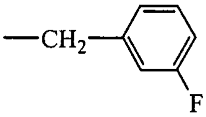
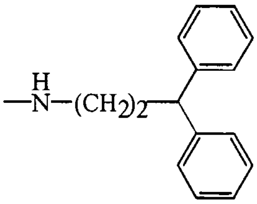
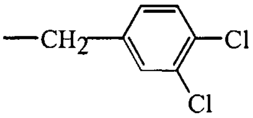
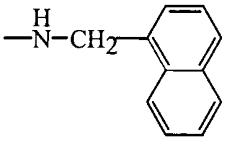
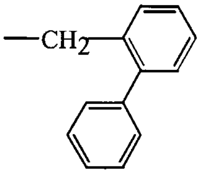
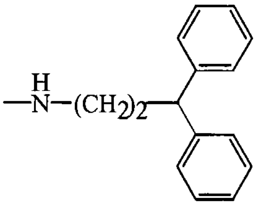
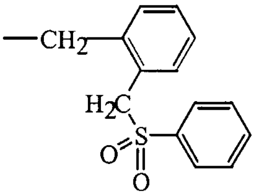
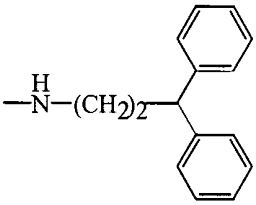
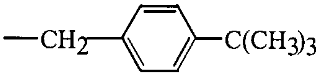
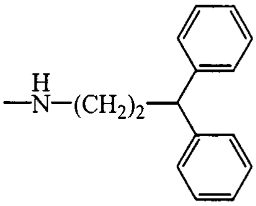
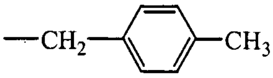
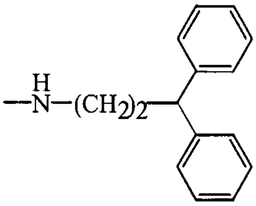
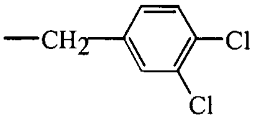
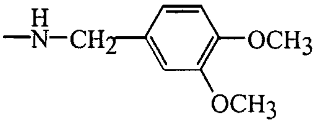
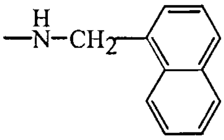
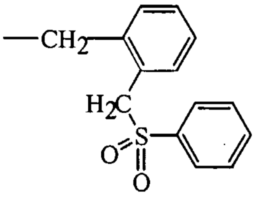
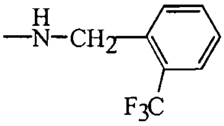
[80] Compound (I) or a pharmaceutically acceptable salt thereof can be orally or parenterally (e.g., via injection) administered. Although the effective dose and administration frequency may vary depending on the mode of administration, the age, weight, and/or symptoms of each patient and/or the like, it is generally preferable to administer 0.01 to 20 mg/kg of Compound (I) or a pharmaceutically acceptable salt thereof, over one to four times per day.

[81] Specific examples compounds of Formula (I) are shown in Tables 1 and 2 below. However, it should be appreciated that the scope of the present invention is not limited to such specific examples.

Table 1



Example No.	Compound No.	A	NY^1Y^2

1	1		
2	2		
3	3		
4	4		
5	5		
6	6		
7	7		
8	8		
9	9		
10	10		

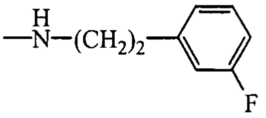
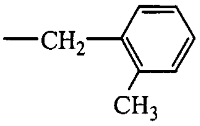
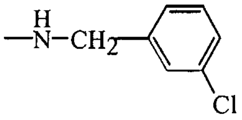
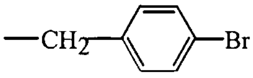
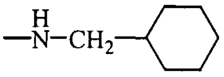
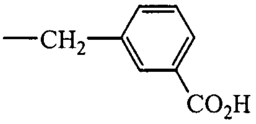
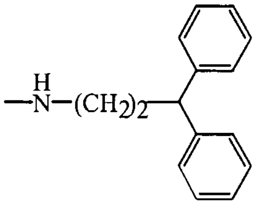
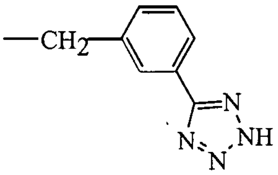
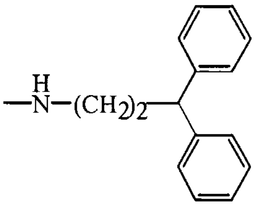
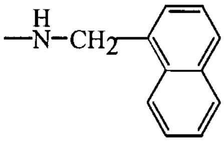
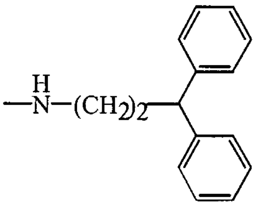
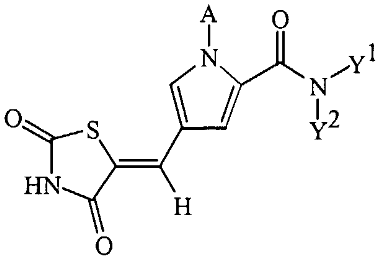
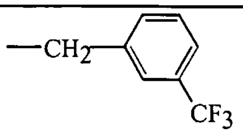
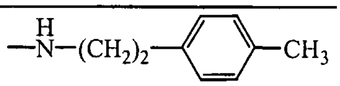
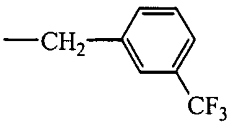
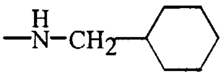
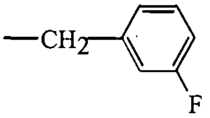
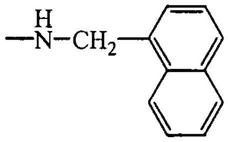
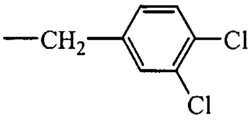
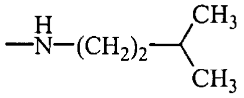
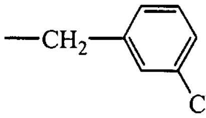
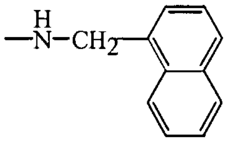
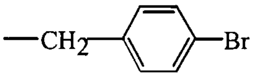
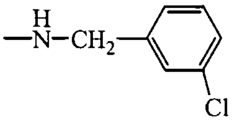
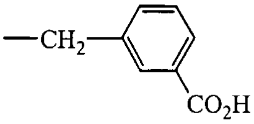
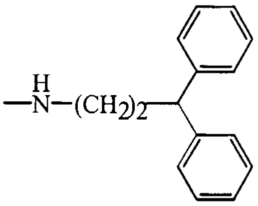
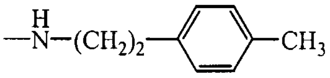
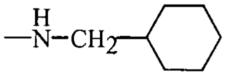
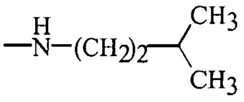
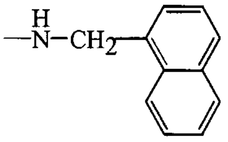
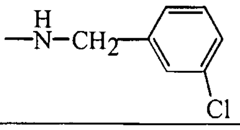
11	11		
12	12		
13	13		
14	14		
15	15		
16	16	H	
17	17	H	

Table 2



Example No.	Compound No.	A	NY^1Y^2
18	18		
19	19		

20	20		
21	21		
22	22		
23	23		
24	24		
25	25	H	
26	26	H	
27	27	H	
28	28	H	
29	29	H	

[82] The pharmacological activity of representative compounds of Formula (I) are illustrated below.

Test Example 1: In vitro telomerase inhibitory activity

[83] The telomerase inhibitory activity of Compound (I) was measured by a known method (U.S. Patent No. 5,760,062). Briefly, a DMSO solution of each test compound was mixed with telomerase (obtained by partial purification of a nucleus extract from HEK293 cells) in the presence of substrates (i.e., oligodeoxynucleotide and deoxynucleotide triphosphate). The mixture was incubated. The resulting reaction product (i.e., DNA including the telomere sequence) was adsorbed on a membrane, and hybridized with a

labeled oligonucleotide probe having a complementary sequence to the telomere sequence. For each test compound, an inhibition rate was calculated based on the ratio of the signal intensity of the label between the membrane obtained in the presence of the test compound and the membrane obtained in the absence of any test compounds (control). A compound concentration at which each compound achieves a 50% inhibition of enzyme activity relative to the control was defined as IC_{50}. The results are shown in Table 3.

Table 3: In vitro telomerase inhibitory activity

Compound No.	IC_{50}(μmol/L)	Compound No.	IC_{50}(μmol/L)
1	4.9	11	3.5
2	3.9	14	4.7
3	3.7	15	4.7
4	2.1	18	3.4
5	1.7	19	2.3
6	2.7	20	2.8
7	2.7	21	5.0
8	8.4	22	4.1
9	4.3	24	4.3
10	3.8	26	6.2

Test Example 2: In vivo telomerase inhibitory activity

[84] After each test compound was allowed to contact a human kidney cancer cell line Caki-1 for 24 hours, a cell extract was prepared using a known method (U.S. Patent No. 5,629,154) and enzyme activity was measured. Briefly, a cell extract was prepared using a buffer solution containing 0.5% CHAPS (i.e., 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate). Using this extraction, a TRAP (Telomeric Repeat Amplification Protocol) assay was performed in vitro ($TRAP_{EZE}{}^{TM}$ ELISA Telomerase Detection Kit; Intergen). For each test compound, the ratio (%) of enzyme activity between the extract from cells which were treated with the test compound and the extract from cells which were not treated with any test compound was calculated. The results are shown in Table 4.

Table 4: In vivo telomerase inhibitory activity

Cpd. No.	concentration (μmol/L)	enzyme activity (%)	Cpd. No.	concentration (μmol/L)	enzyme activity (%)
4	30	65	15	30	75
5	30	46	18	30	66
7	30	76	19	10	81
9	30	68	20	10	41
10	30	22	21	30	13
12	30	75	22	30	14
13	30	46	23	30	32

[85] As the above results show, compounds of Formula (I) have an excellent telomerase inhibitory activity, and therefore are useful as therapeutic agents for diseases related to telomerase activity, e.g., malignant tumors.

EXAMPLES

[86] Hereinafter, Examples of the present invention will be described. The physicochemical data concerning the respective compounds in the Examples were measured by using the following equipment:

^{1}H NMR:	JEOL JNM-EX270 (270 MHz) /JEOL JNM-GX270 (270 MHz)
FABMS:	JEOL JMS-HX110
ESIMS:	Micromass Quattro

Example 1 (Compound 1)

[87] To a solution of 4-formyl-2-(trichloroacetyl)pyrrole (400 mg, 1.66 mmol), obtained by a method described in *J. Org. Chem.*, vol. 43, pp. 4849-4853 (1978), in N,N-dimethylformamide (4 mL) was added 1-naphthalenemethylamine (318 μL, 2.16 mmol). The resulting mixture was stirred at room temperature for 13 hours, diluted with ethyl acetate, and washed successively with water, an aqueous solution of hydrochloric acid (1 M), and a saturated aqueous solution of sodium bicarbonate. After the organic layer was dried over anhydrous magnesium sulfate, the solvent was removed under a reduced pressure. The resulting residue was dissolved in N,N-dimethylformamide (10 mL), and 2-chlorobenzyl bromide (324 μL, 2.49 mmol), 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene (1.5 g, 3.3 mmol), and potassium iodide (276 mg, 1.66 mmol) were added. The resulting mixture was stirred at 30 °C for 15 hours. After the reaction mixture was filtered, the filtrate was diluted with ethyl acetate, and washed successively with water and brine. After the organic layer was dried over anhydrous magnesium sulfate, the solvent was removed under a reduced pressure. The resulting residue was dissolved in ethanol (15 mL), and 2,4-thiazolidinedione (234 mg, 1.99 mmol) and piperidine (197 μL, 1.99 mmol) were added. The resulting mixture was stirred at 70 °C for 17 hours. After the reaction mixture was cooled to room temperature, an aqueous solution of hydrochloric acid (1 M) was added to adjust pH of the reaction mixture to pH 4. The precipitated solid was collected and recrystallized from-propanol to obtain Compound 1 (417 mg, 0.83 mmol, 50%).

[88] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 4.83 (d, J = 5.5 Hz, 2H), 5.79 (s, 2H), 6.53 (dd, J = 7.4, 1.5 Hz, 1H), 7.16-7.58 (m, 8H), 7.64 (d, J = 1.8 Hz, 1H), 7.66 (s, 1H), 7.82 (d, J = 7.9 Hz, 1H), 7.92 (dd, J = 7.4, 1.8 Hz, 1H), 8.05 (d, J = 7.9 Hz, 1H), 8.98 (br t, J = 5.5 Hz, 1H), 12.27 (br s, 1H). ESIMS (m/z) $(M-H)^-$ Calcd for $C_{27}H_{20}N_3ClO_3S$, 501; Found, 500. Elemental Analysis. Calcd for $C_{27}H_{20}N_3ClO_3S$: C, 64.60; H, 4.02; N, 8.37. Found: C, 64.66; H, 4.20; N, 8.33. IR (KBr tab.): 1724, 1718, 1677, 1652, 1646, 1637, 1600, 1577, 1558, 1550, 1519, 1508, 1396, 1330, 1274 cm^{-1}.

Example 2 (Compound 2)

[89] To a solution of 4-formyl-2-(trichloroacetyl)pyrrole (539 mg, 2.24 mmol) in N,N-dimethylformamide (9 mL) and chloroform (3 mL) was added 3,3-diphenylpropylamine (676 mg, 3.20 mmol). The resulting mixture was stirred at 55 °C for 15 hours. The solvent was removed under a reduced pressure. The resulting residue was dissolved in chloroform (18 mL), and N-methylisatoic anhydride polystyrene (1.28 g, 2.56 mmol) was added. The mixture was stirred at room temperature for 15 hours, filtered, and concentrated. The resulting residue was dissolved in N,N-dimethylformamide (9 mL), and 3-fluorobenzyl bromide (392 μL, 3.20 mmol) and tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphospholine on polystyrene (2.0 g, 6.33 mmol) were added. The mixture was stirred at 30 °C for 15 hours, filtered, and concentrated under a reduced pressure. The residue was dissolved in chloroform (17 mL) and methanol (2 mL), and N-(2-mercaptoethyl)aminomethylpolystyrene (800 mg, 1.20 mmol) and BioRad® AG1-X8OH$^-$ form (2.88 g, 5.76 mmol) were added. The mixture was stirred at room temperature for 15 hours, filtered, and concentrated under a reduced pressure. The residue was dissolved in ethanol (13 mL), and 2,4-thiazolidinedione (328 mg, 2.80 mmol) and piperidine (253 μL, 2.56 mmol) were added. The mixture was stirred at 70 °C for 16 hours. After the reaction mixture was cooled to room temperature, an aqueous solution of hydrochloric acid (1 mol/L) was added to adjust pH of the mixture to pH 4. The precipitated solid was collected by filtration and recrystallized from ethanol to obtain Compound 2 (385 mg, 0.71 mmol, 32%).

[90] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.22 (dt, J = 6.9, 7.6 Hz, 2H), 3.07-3.14 (m, 2H), 3.94 (t, J = 7.6 Hz, 1H), 5.64 (s, 2H), 6.90-7.44 (m, 15H), 7.64 (s, 1H), 7.67 (d, J = 1.6 Hz, 1H), 8.37 (br t, J = 5.6 Hz, 1H), 12.31 (br s, 1H). ESIMS (m/z) $(M-H)^-$ Calcd for $C_{31}H_{26}N_3FO_3S$, 539; Found, 538. Elemental Analysis. Calcd for $C_{31}H_{26}N_3FO_3S$: C, 69.00; H, 4.86; N, 7.79. Found: C, 69.12; H, 5.01; N, 7.78. IR (KBr tab.): 1733, 1716, 1677, 1652, 1637, 1612, 1577, 1558 cm^{-1}.

[91] Using an appropriate amine and aralkyl halide instead of 1-naphthalenemethylamine and 2-chlorobenzyl, where applicable, compounds of Examples 3 to 8 below were obtained by a method similar to Example 1 above.

Example 3 (Compound 3)

[92] From 4-formyl-2-(trichloroacetyl)pyrrole (400 mg, 1.66 mmol), Compound 3 (516 mg, 0.96 mmol, 58%) was obtained by using 1-naphthalenemethylamine (318 μL, 2.16 mmol) and 3,4-dichlorobenzyl bromide (518 mg, 2.16 mmol).

[93] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 4.89 (d, J = 5.6 Hz, 2H), 5.68 (s, 2H), 7.09 (dd, J = 6.1, 2.1 Hz, 1H), 7.17 (d, J = 1.7 Hz, 1H), 7.33-7.53 (m, 6H), 7.61 (d, J = 1.7 Hz, 1H), 7.63 (s, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.99 (dd, J = 7.3, 1.9 Hz, 1H), 8.05 (dd, J = 7.6, 1.9 Hz, 1H), 8.90 (br t, J = 5.6 Hz, 1H), 12.16 (br s, 1H). ESIMS (m/z) $(M-H)^-$ Calcd for $C_{27}H_{19}Cl_2N_3O_3S$, 535; Found, 534. Elemental Analysis. Calcd for $C_{27}H_{19}Cl_2N_3O_3S$: C, 60.45; H, 3.57; N, 7.83. Found: C, 60.26; H, 3.49; N, 7.73. IR(KBr tab.): 1733, 1718, 1675, 1654, 1647, 1637, 1624, 1610, 1558, 1554, 1522, 1508, 1491, 1473, 1396, 1387 cm^{-1}.

Example 4 (Compound 4)

[94] From 4-formyl-2-(trichloroacetyl)pyrrole (400 mg, 1.66 mmol), Compound 4 (320 mg, 0.53 mmol, 32%) was obtained by using 3,3-diphenylpropylamine (423 mg, 2.00 mmol) and 2-(bromomethyl)biphenyl (365 μL, 2.00 mmol).

[95] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.16 (dt, J = 7.4, 6.8 Hz, 2H), 3.02 (br, 2H), 3.88 (t, J = 7.4 Hz, 1H), 5.58 (s, 2H), 6.54 (d, J = 7.1 Hz, 1H), 7.03 (s, 1H), 7.12-7.48 (m, 19H), 7.62 (s, 1H), 8.30 (br, 1H), 12.28 (br s, 1H). ESIMS (m/z) $(M+H)^+$ Calcd for $C_{37}H_{31}N_3O_3S$, 597; Found, 598. Elemental Analysis. Calcd for $C_{37}H_{31}N_3O_3S \cdot 0.1H_2O$: C, 73.90; H, 5.26; N, 6.99. Found: C, 73.92; H, 5.27; N, 6.98. IR(KBr tab.): 1720, 1701, 1697, 1678, 1664, 1655, 1649, 1637, 1605, 1578, 1558, 1543, 1535, 1518, 1497, 1493 cm^{-1}.

Example 5 (Compound 5)

[96] From 4-formyl-2-(trichloroacetyl)pyrrole (400 mg, 1.66 mmol), Compound 5 (537 mg, 0.80 mmol, 48%) was obtained by using 3,3-diphenylpropylamine (423 mg, 2.00 mmol) and 1-bromomethyl-2-[(phenylsulfonyl)methyl]benzene (650 mg, 2.00 mmol).

[97] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.18 (dt, J = 7.1, 7.8 Hz, 2H), 3.02 (br, 2H), 3.91 (t, J = 7.8 Hz, 1H), 4.83 (s, 2H), 5.63 (s, 2H), 6.72 (d, J = 7.3 Hz, 1H), 6.88-7.38 (m, 14H), 7.49-7.90 (m, 7H), 8.36 (br, 1H), 12.29 (br s, 1H). ESIMS (m/z) $(M-H)^-$ Calcd for $C_{38}H_{33}N_3O_5S_2$, 675; Found, 674. Elemental Analysis. Calcd for $C_{38}H_{33}N_3O_5S_2$: C,

67.54; H, 4.92; N, 6.22. Found: C, 67.46; H, 5.01; N, 5.97. IR (KBr tab.): 1734, 1716, 1707, 1701, 1686, 1676, 1670, 1662, 1652, 1647, 1637, 1624, 1616, 1608, 1583, 1578 cm^{-1}.

Example 6 (Compound 6)

[98] From 4-formyl-2-(trichloroacetyl)pyrrole (400 mg, 1.66 mmol), Compound 6 (434 mg, 0.73 mmol, 44%) was obtained by using 3,3-diphenylpropylamine (423 mg, 2.00 mmol) and 4-(tert-butyl)benzyl ??? bromide (368 µL, 2.00 mmol).

[99] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.21 (s, 9H), 2.25 (dt, J = 6.6, 7.8 Hz, 2H), 3.10 (dt, J = 6.6, 5.4 Hz, 2H), 3.96 (t, J = 7.8 Hz, 1H), 5.58 (s, 2H), 6.95 (d, J = 1.5 Hz, 1H), 7.06 (s, 1H), 7.09 (s, 1H), 7.12-7.14 (m, 2H), 7.27-7.38 (m, 10H), 7.64 (s, 2H), 8.36 (br t, J = 5.4 Hz, 1H), 12.29 (br s, 1H). ESIMS (m/z) $(M-H)^-$ Calcd for $C_{35}H_{35}N_3O_3S$, 577; Found, 576. Elemental Analysis. Calcd for $C_{35}H_{35}N_3O_3S \cdot 0.2CH_3CH_2OH \cdot 0.1H_2O$: C, 72.21; H, 6.23; N, 7.14. Found: C, 72.23; H, 6.18; N, 7.19. IR (KBr tab.): 1714, 1707, 1701, 1691, 1686, 1672, 1655, 1647, 1637 cm^{-1}.

Example 7 (Compound 7)

[100] From 4-formyl-2-(trichloroacetyl)pyrrole (400 mg, 1.66 mmol), Compound 7 (523 mg, 0.98 mmol, 59%) was obtained by using 3,3-diphenylpropylamine (423 mg, 2.00 mmol) and 4-methylbenzyl bromide (370 mg, 2.00 mmol).

[101] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.16-2.35 (br, 2H) , 2.23 (s, 3H), 3.04-3.18 (br, 2H), 3.95 (t, J = 7.6 Hz, 1H), 5.56 (s, 2H), 6.98 (d, J = 1.7 Hz, 1H), 7.02-7.13 (m, 4H), 7.14-7.29 (m, 10H), 7.61 (d, J = 1.7 Hz, 1H), 7.63 (s, 1H), 8.32 (br t, J = 5.4 Hz, 1H), 12.27 (br s, 1H). ESIMS (m/z) $(M-H)^-$ Calcd for $C_{32}H_{29}N_3O_3S$, 535; Found, 534. Elemental Analysis. Calcd for $C_{32}H_{29}N_3O_3S$: C, 71.75; H, 5.46; N, 7.84. Found: C, 71.89; H, 5.50; N, 7.58. IR (KBr tab.): 1736, 1718, 1697, 1684, 1678, 1664, 1655, 1647, 1635, 1630, 1624, 1608, 1578, 1570, 1558, 1554 cm^{-1}.

Example 8 (Compound 8)

[102] From 4-formyl-2-(trichloroacetyl)pyrrole (539 mg, 2.24 mmol), Compound 8 (307 mg, 0.56 mmol, 25%) was obtained by using 3,4-dimethoxybenzylamine (482 µL, 3.20 mmol) and 3,4-dichlorobenzyl bromide (768 mg, 3.20 mmol).

[103] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 3.68(s, 3H), 3.72 (s, 3H), 4.30 (s, 2H), 5.64 (s, 2H), 6.67 (d, J = 8.2 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.84 (s, 1H), 7.06 (dd, J = 6.3, 2.0 Hz, 1H), 7.13 (d, J = 1.7 Hz, 1H), 7.37 (d, J = 2.0 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.64 (s, 1H), 7.72 (d, J = 1.7 Hz, 1H), 8.88 (br s, 1H), 12.31 (br s, 1H). ESIMS (m/z) $(M-H)^-$ Calcd for $C_{25}H_{21}Cl_2N_3O_5S$, 545; Found, 544. Elemental Analysis. Calcd for

$C_{25}H_{21}Cl_2N_3O_5S{\cdot}0.5H_2O$: C, 54.06; H, 3.99; N, 7.57. Found: C, 54.15; H, 3.96; N, 7.27. IR (KBr tab.): 1736, 1699, 1695, 1674, 1651, 1630, 1606, 1556, 1531, 1518, 1489, 1471, 1394, 1385, 1321 cm^{-1}.

Example 9 (Compound 9)

[104] To a solution of 4-formyl-2-(trichloroacetyl)pyrrole (3.0 g, 12.5 mmol) in N,N-dimethylformamide (30 mL) was added 1-naphthalenemethylamine (2.38 mL, 16.2 mmol). The mixture was stirred at room temperature for 16 hours, diluted with ethyl acetate, and washed successively with water, an aqueous solution of hydrochloric acid (1 mol/L), a saturated aqueous solution of sodium bicarbonate, and brine. After the organic layer was dried over anhydrous magnesium sulfate, the solvent was removed under a reduced pressure. The residue was purified through silica gel column chromatography (hexane/ethyl acetate = 1:1). The resulting compound was dissolved in N,N-dimethylformamide (8 mL) and cooled in an ice bath. To this cooled solution was added potassium tert-butoxide (407 mg, 3.63 mmol), potassium iodide (501 mg, 3.02 mmol), and 4-(tert-butyl)benzyl bromide (830 μL, 4.53 mmol). The reaction mixture was stirred at room temperature for 1.5 hours, diluted with water, and extracted with ethyl acetate. After the organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified through silica gel column chromatography (hexane/ethyl acetate = 2:1). The resulting compound was dissolved in ethanol (17 mL). To this solution was added 2,4-thiazolidinedione (229 mg, 1.96 mmol) and piperidine (193 μL, 1.95 mmol). The resulting mixture was stirred at 70 °C for 2.5 hours. After the reaction mixture was cooled to room temperature, an aqueous solution of hydrochloric acid (1 M) was added to adjust pH of the reaction mixture to pH 4. The precipitated solid was collected by filtration and recrystallized from ethanol to obtain Compound 9 (286 mg, 0.55 mmol, 4%).

[105] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.24 (s, 9H), 4.87 (d, J = 5.8 Hz, 2H), 5.63 (s, 2H), 7.07 (d, J = 8.2 Hz, 2H), 7.11 (d, J = 1.8 Hz, 1H), 7.26 (d, J = 8.2 Hz, 2H), 7.37-7.59 (m, 4H), 7.63 (s, 1H), 7.68 (d, J = 1.8 Hz, 1H), 7.85 (dd, J = 6.9, 2.6 Hz, 1H), 7.89-7.97 (m, 1H), 8.08-8.18 (m, 1H), 8.93 (t, J = 5.8 Hz, 1H), 12.27 (br s, 1H). ESIMS (m/z) $(M+H)^+$ Calcd for $C_{31}H_{29}N_3O_3S$, 523; Found, 524. Elemental Analysis. Calcd for $C_{31}H_{29}N_3O_3S$: C, 71.10; H, 5.58; N, 8.02. Found: C, 71.15; H, 5.79; N, 8.12. IR (KBr tab.): 1731, 1682, 1655, 1643, 1601, 1551, 1524, 1394, 1333, 1296, 1275, 1142 cm^{-1}.

[106] Using an appropriate amine and aralkyl halide instead of 1-naphthalenemethylamine and 2-chlorobenzyl, where applicable, compounds of Examples 10 to 13 below were obtained by a method similar to Example 1 above.

Example 10 (Compound 10)

[107] From 4-formyl-2-(trichloroacetyl)pyrrole (3.0 g, 12.5 mmol), Compound 10 (1.18 g, 1.84 mmol, 15%) was obtained by using 2-(trifluoromethyl)benzylamine (2.27 mL, 16.3 mmol) and 1-bromomethyl-2-[(phenylsulfonyl)methyl]benzene (2.0 g, 6.15 mmol).

[108] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 4.52 (d, J = 5.3 Hz, 2H), 4.82 (s, 2H), 5.67 (s, 2H), 6.70 (d, J = 6.9 Hz, 1H), 7.07 (d, J = 6.3 Hz, 1H), 7.14-7.33 (m, 5H), 7.38-7.88 (m, 9H), 8.99 (t, J = 5.3 Hz, 1H), 12.33 (br s, 1H). FABMS (m/z) $(M+H)^+$ Calcd for $C_{31}H_{24}F_3N_3O_5S_2$, 639; Found, 640. Elemental Analysis. Calcd for $C_{31}H_{24}F_3N_3O_5S_2$: C, 58.21; H, 3.78; N, 6.57. Found: C, 58.37; H, 3.83; N, 6.54. IR (KBr tab.): 1738, 1697, 1657, 1633, 1614, 1552, 1516, 1387, 1317, 1292, 1255, 1161, 1136 cm^{-1}.

Example 11 (Compound 11)

[109] From 4-formyl-2-(trichloroacetyl)pyrrole (3.0 g, 12.5 mmol), Compound 11 (1.55 g, 3.07 mmol, 25%) was obtained by using 3-fluorophenethylamine (2.12 mL, 16.2 mmol) and 4-(tert-butyl)benzyl bromide (2.08 mg, 11.32 mmol).

[110] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 1.24 (s, 9H), 2.81 (t, J = 6.9 Hz, 2H), 3.42 (dt, J = 5.9, 6.9 Hz, 2H), 5.58 (s, 2H), 6.95 (d, J = 1.7 Hz, 1H), 6.98-7.12 (m, 5H), 7.24-7.37 (m, 3H), 7.62 (s, 1H), 7.63 (d, J = 1.7 Hz, 1H), 8.42 (t, J = 5.9 Hz, 1H), 12.27 (br s, 1H). ESIMS (m/z) $(M+H)^+$ Calcd for $C_{28}H_{28}FN_3O_3S$, 505; Found, 506. Elemental Analysis. Calcd for $C_{28}H_{28}FN_3O_3S$: C, 66.51; H, 5.58; N, 8.31. Found: C, 66.74; H, 5.78; N, 8.29. IR (KBr tab.): 1724, 1709, 1703, 1678, 1651, 1599, 1551, 1520, 1485, 1396, 1327, 1296, 1284 cm^{-1}.

Example 12 (Compound 12)

[111] From 4-formyl-2-(trichloroacetyl)pyrrole (3.0 g, 12.5 mmol), Compound 12 (920 mg, 1.97 mmol, 16%) was obtained by using 3-chlorobenzylamine (1.98 mL, 16.3 mmol) and α-bromo-o-xylene (2.06 mL, 15.3 mmol).

[112] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.27 (s, 3H), 4.36 (d, J = 5.9 Hz, 2H), 5.65 (s, 2H), 6.45 (d, J = 7.3 Hz, 1H), 7.02-7.23 (m, 5H), 7.24-7.36 (m, 3H), 7.55 (d, J = 1.7 Hz, 1H), 7.55 (s, 1H), 8.97 (t, J = 5.9 Hz, 1H), 12.33 (br s, 1H). FABMS (m/z) $(M+H)^+$ Calcd for $C_{24}H_{20}ClN_3O_3S$, 465; Found, 466. Elemental Analysis. Calcd for $C_{24}H_{20}ClN_3O_3S$:

C, 61.86; H, 4.33; N, 9.02. Found: C, 61.81; H, 4.51; N, 9.04. IR (KBr tab.): 1730, 1684, 1659, 1639, 1603, 1551, 1527, 1400, 1333, 1309, 1292, 1269, 1136 cm^{-1}.

Example 13 (Compound 13)

[113] From 4-formyl-2-(trichloroacetyl)pyrrole (3.0 g, 12.5 mmol), Compound 13 (1.03 g, 2.05 mmol, 16%) was obtained by using aminomethylcyclohexane (2.11 mL, 16.3 mmol) and 4-bromobenzyl bromide (3.07 g, 12.3 mmol).

[114] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 0.78-0.89 (m, 2H), 1.09-1.61 (m, 3H), 1.34-1.49 (m, 1H), 1.50-1.72 (m, 5H), 2.98 (t, J = 6.3 Hz, 2H), 5.58 (s, 2H), 7.01 (d, J = 1.7 Hz, 1H), 7.06 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.64 (s, 1H), 7.67 (d, J = 1.7 Hz, 1H), 8.31 (t, J = 6.3 Hz, 1H), 12.30 (br s, 1H). FABMS (m/z) $(M+H)^+$ Calcd for $C_{23}H_{24}BrN_3O_3S$, 501; Found, 502. Elemental Analysis. Calcd for $C_{23}H_{24}BrN_3O_3S$: C, 54.98; H, 4.81; N, 8.36. Found: C, 54.95; H, 4.89; N, 8.32. IR (KBr tab.): 1734, 1684, 1635, 1610, 1558, 1531, 1489, 1444, 1392 cm^{-1}.

Example 14 (Compound 14)

[115] To a solution of 4-formyl-2-(trichloroacetyl)pyrrole (202 mg, 0.84 mmol) was dissolved in N,N-dimethylformamide (4 mL) and chloroform (1 mL) was added 3,3-diphenylpropylamine (234 mg, 1.20 mmol). The mixture was stirred at 55 °C for 15 hours and concentrated. The residue was dissolved in chloroform (9 mL). To this solution was added N-methylisatoic anhydride polystyrene (640 mg, 1.28 mmol), and the resulting mixture was stirred at room temperature for 15 hours. The reaction mixture was filtered and concentrated. The resulting residue was dissolved in N,N-dimethylformamide (5 mL). To this solution was added methyl 3-(bromomethyl)benzoate (275 mg, 1.20 mmol) and 2-(tert-butylimino)-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene (750 mg, 2.36 mmol). The reaction mixture was stirred at 30 °C for 15 hours, filtrated, and concentrated by distillation under a reduced pressure. The residue was dissolved in chloroform (6 mL) and methanol (1 mL), and N-(2-mercaptoethyl)aminomethylpolystyrene (300 mg, 0.45 mmol) and BioRad® AG1-X80H$^-$ form (855 mg, 2.16 mmol) were added. The mixture was stirred at room temperature for 15 hours, filtered, and concentrated. The residue was dissolved in methanol (5 mL) and an aqueous solution of sodium hydroxide (1 M, 5 mL, 5.0 mmol) was added. The mixture was stirred at 80 °C for 0.5 hours. An aqueous solution of hydrochloric acid (1 M) was added to adjust pH of the reaction mixture to pH 4, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under a reduced pressure. The residue was dissolved in ethanol (10 mL), and 2,4-thiazolidinedione (124 mg, 1.06 mmol) and piperidine (217 µL, 2.19 mmol) were added. The mixture was refluxed with stirring for 12 hours. Thereafter, an aqueous solution of hydrochloric acid (1 M) was added to adjust pH of the reaction mixture to pH 4, and extracted with chloroform. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated. The crude solid was recrystallized from ethanol to yield Compound 14 (120 mg, 0.21 mmol, 25%).

[116] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.20 (dt, J = 6.8, 7.6 Hz, 2H), 3.06 (dt, J = 6.8, 5.3 Hz, 2H), 3.91 (t, J = 7.6 Hz, 1H), 5.68 (s, 2H), 7.03 (d, J = 1.5 Hz, 1H), 7.10-7.30 (m, 10H), 7.31-7.45 (m, 2H), 7.64 (s, 1H), 7.68 (s, 2H), 7.82 (d, J = 7.4 Hz, 1H), 8.36 (t, J = 5.3 Hz, 1H). ESIMS (m/z) (M-H)$^-$ Calcd for $C_{32}H_{27}N_3O_5S$, 565; Found, 564. Elemental Analysis. Calcd for $C_{32}H_{27}N_3O_5S \cdot 0.4(CH_3)_2CHOH \cdot 0.2H_2O$: C, 66.41; H, 5.27; N, 6.99. Found: C, 66.44; H, 5.38; N, 7.19. IR (KBr tab.): 1734, 1716, 1697, 1686, 1670, 1664, 1653, 1647, 1635, 1630, 1624, 1608, 1577, 1570, 1568 cm^{-1}.

Example 15 (Compound 15)

[117] To a solution of 4-formyl-2-(trichloroacetyl)pyrrole (404 mg, 1.68 mmol) in N,N-dimethylformamide (7 mL) and chloroform (2 mL) was added 3,3-diphenylpropylamine (507 mg, 2.40 mmol). The mixture was stirred at 55 °C for 15 hours and concentrated under a reduced pressure. The residue was dissolved in chloroform (18 mL) and N-methylisatoic anhydride polystyrene (1.28 g, 2.56 mmol) was added. The mixture was stirred at room temperature for 15 hours, filtered, and concentrated. The residue was dissolved in N,N-dimethylformamide (9 mL) and 3-cyanobenzyl bromide (471 mg, 2.40 mmol) and 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene (1.5 g, 4.75 mmol) were added. The mixture was stirred at 30 °C for 15 hours, filtered, and concentrated under a reduced pressure. The residue was dissolved in chloroform (13 mL) and methanol (1.5 mL). To this solution was added N-(2-mercaptoethyl)aminomethylpolystyrene (600 mg, 0.90 mmol) and BioRad® AG1-X8OH$^-$ form (1.71 g, 4.32 mmol). The mixture was stirred at room temperature for 15 hours, filtered, and concentrated under a reduced pressure. The residue was dissolved in N-methyl-2-pyrrolidinone (15 mL), and trimethylammomium chloride (504 mg, 5.27 mmol) and sodium azide (343 mg, 5.28 mmol) were added. The mixture was stirred at 110 °C for 4 hours. An aqueous solution of hydrochloric acid (1 M) was added to adjust pH of the reaction mixture to pH 4. The resulting mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and the solvent was

removed under a reduced pressure. The residue was dissolved in ethanol (10 mL), and 2,4-thiazolidinedione (209 mg, 1.78 mmol) and piperidine (368 μL, 3.72 mmol) were added. The mixture was refluxed with stirring for 12 hours. Thereafter, an aqueous solution of hydrochloric acid (1 M) was added, and the mixture was extracted with chloroform. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was triturated with ethyl acetate to yield Compound 15 (85 mg, 0.14 mmol, 9%).

[118] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.13 (dt, J = 7.1, 7.6 Hz, 2H), 2.94-3.03 (m, 2H), 3.82 (t, J = 7.6 Hz, 1H), 5.66 (s, 2H), 6.99 (s, 1H), 7.03-7.23 (m, 11H), 7.45 (t, J = 7.8 Hz, 1H), 7.60 (s, 1H), 7.65 (d, J = 1.7 Hz, 1H), 7.76 (s, 1H), 7.82 (d, J = 7.9 Hz, 1H), 8.31 (t, J = 5.3 Hz, 1H). ESIMS (m/z) $(M+H)^+$ Calcd for $C_{32}H_{27}N_7O_3S$, 589; Found, 590. IR (KBr tab.): 1689, 1686, 1664, 1655, 1647, 1635, 1630, 1624, 1608, 1578, 1558, 1545, 1541, 1533, 1527, 1522 cm^{-1}.

Example 16 (Compound 16)

[119] 4-Formyl-2-(trichloroacetyl)pyrrole (539 mg, 2.24 mmol) was dissolved in N,N-dimethylformamide (5 mL), and 1-naphthalenemethylamine (470 μL, 3.20 mmol) was added thereto. The resultant mixture was stirred at room temperature for 13 hours. The reaction mixture was diluted with ethyl acetate, and the mixture was washed with water, a 1 mol/L aqueous solution of hydrochloric acid, and a saturated sodium bicarbonate, sequentially. After the organic layer was dried over anhydrous magnesium sulfate, the solvent was removed under a reduced pressure. The obtained residue was dissolved in ethanol (10 mL), and 2,4-thiazolidinedione (315 mg, 2.69 mmol) and piperidine (266 μL, 2.69 mmol) were added thereto, and the mixture was refluxed with stirring for 1.5 hours. Thereafter, 2,4-thiazolidinedione (79 mg, 0.67 mmol) and piperidine (67 μL, 0.67 mmol) were further added thereto, and the mixture was further refluxed with stirring for 4.5 hours. The reaction mixture was cooled to room temperature, a 1 mol/L aqueous solution of hydrochloric acid was added thereto so as to adjust the reaction mixture to pH4; and precipitated crystals were collected through filtration. The crude crystals thus obtained were allowed to recrystalize from 2-propanol, whereby Compound 16 (543 mg, 1.44 mmol, 64%) was obtained.

[120] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 4.95 (d, J = 5.6 Hz, 2H), 7.14 (s, 1H), 7.45-7.68 (m, 5H), 7.75(s, 1H), 7.85 (dd, J = 6.9, 2.6 Hz, 1H), 7.86 (dd, J = 6.9 H, 6.4 Hz, 1H), 8.18 (dd, J = 6.9, 2.6 Hz, 1H), 8.90 (t, J = 5.6 Hz, 1H), 12.23 (s, 1H), 12.29 (s, 1H).

ESIMS (m/z) $(M-H)^-$ Calcd for $C_{20}H_{15}N_3O_3S$, 377; Found, 376. Elemental Analysis. Calcd for $C_{20}H_{15}N_3O_3S$: C, 63.65; H, 4.01; N, 11.13. Found: C, 63.77; H, 3.84; N, 11.10. IR (KBr tab.): 1736, 1730, 1687, 1682, 1651 cm^{-1}.

Example 17 (Compound 17)

[121] 4-Formyl-2-(trichloroacetyl)pyrrole (539 mg, 2.24 mmol) was dissolved in N,N-dimethylformamide (5 mL), and 3,3-diphenylpropylamine (676 mg, 3.20 mmol) was added thereto. The resultant mixture was stirred at room temperature for 13 hours. The reaction mixture was diluted with ethyl acetate, and the mixture was washed with water, a 1 mol/L aqueous solution of hydrochloric acid, and a saturated aqueous solution of sodium bicarbonate, sequentially. After the organic layer was dried over anhydrous magnesium sulfate, the solvent was removed under a reduced pressure. The obtained residue was dissolved in ethanol (10 mL), and 2,4-thiazolidinedione (315 mg, 2.69 mmol) and piperidine (266 μL, 2.69 mmol) were added thereto, and the mixture was refluxed with stirring for 1.5 hours. Thereafter, 2,4-thiazolidinedione (79 mg, 0.67 mmol) and piperidine (67 μL, 0.67 mmol) were further added thereto, and the mixture was further refluxed with stirring for 4.5 hours. The reaction mixture was cooled to room temperature, a 1 mol/L aqueous solution of hydrochloric acid was added thereto so as to adjust the reaction mixture to pH4, and precipitated crystals were collected through filtration. The crude crystals thus obtained were allowed to recrystalize from 2-propanol, whereby Compound 17 (721 mg, 1.67 mmol, 75%) was obtained.

[122] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.30 (dt, J = 6.9, 7.9 Hz, 2H), 3.12-3.19 (m, 2H), 4.02 (t, J = 7.9 Hz, 1H), 7.03 (s, 1H), 7.13-7.34 (m, 10H), 7.42 (s, 1H), 7.71 (s, 1H), 8.34 (t, J = 5.6 Hz, 1H), 12.18 (s, 1H), 12.23 (s, 1H). ESIMS (m/z) $(M-H)^-$ Calcd for $C_{24}H_{21}N_3O_3S$, 431; Found, 430. Elemental Analysis. Calcd for $C_{24}H_{21}N_3O_3S$: C, 66.80; H, 4.91; N, 9.74. Found: C, 66.81; H, 4.79; N, 9.90. IR (KBr tab.): 1672, 1641, 1608, 1568, 1531, 1527, 1323, 1230, 1132 cm^{-1}.

Example 18 (Compound 18)

[123] 4-Formyl-2-(trichloroacetyl)pyrrole (539 mg, 2.24 mmol) was dissolved in N,N-dimethylformamide (9 mL) and chloroform (3 mL), and 2-(p-tolyl)ethylamine (465 μL, 3.20 mmol) was added thereto. The resultant mixture was stirred at 55 °C for 15 hours. The solvent was removed under a reduced pressure. The obtained residue was dissolved in chloroform (18 mL). Then, N-methylisatoic acid anhydride polystyrene (1.28 g, 2.56 mmol) was added thereto, and the mixture was stirred at room temperature for 15 hours. After the

reaction mixture was filtered, the solvent was removed. The obtained residue was dissolved in N,N-dimethylformamide (9 mL). Then, 3-(trifluoromethyl)benzyl bromide (489 μL, 3.20 mmol) anc 3-2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene (2.0 g, 6.33 mmol) were added thereto, and the mixture was stirred at 30°C for 15 hours. After the reaction mixture was filtered, the solvent was removed under a reduced pressure. The obtained residue was dissolved in chloroform (17 mL) and methanol (2 mL). N-(2-mercaptoethyl)aminomethylpolystyrene (800 mg, 1.20 mmol) and BioRad® AG1-X80H$^-$ form (2.88 g, 5.76 mmol) were added thereto, and the mixture was stirred at room temperature for 15 hours. After the reaction mixture was filtered, the solvent was removed under a reduced pressure. The obtained residue was dissolved in ethanol (13 mL), and 2,4-thiazolidinedione (373 mg, 2.80 mmol) and piperidine (253 μL, 2.56 mmol) were added thereto, and the mixture was stirred at room temperature for 16 hours. Thereafter, a 1 mol/L aqueous solution of hydrochloric acid was added to the reaction mixture so as to adjust the reaction mixture to pH4, and precipitated crystals were collected through filtration. The crude crystals thus obtained were allowed to recrystalize from ethanol, whereby Compound 18 (574 mg, 1.08 mmol, 48%) was obtained.

[124] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.25 (s, 3H), 2.70 (t, J = 7.3 Hz, 2H), 3.27-3.44 (m, 2H), 5.73 (s, 2H), 7.02 (d, J = 8.2 Hz, 2H), 7.04 (s, 1H), 7.07 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 7.3 Hz, 1H), 7.52-7.65 (m, 4H), 7.80 (s, 1H), 8.50 (t, J = 5.3 Hz, 1H), 13.54 (s, 1H). ESIMS (m/z) (M-H)$^-$ Calcd for $C_{26}H_{22}F_3N_3O_2S_2$, 529; Found, 528. Elemental Analysis. Calcd for $C_{26}H_{22}F_3N_3O_2S_2$: C, 58.97; H, 4.19; N, 7.93. Found: C, 59.26; H, 4.30; N, 7.84. IR (KBr tab.): 1686, 1633, 1599, 1564, 1556, 1454, 1369, 1330, 1282, 1238, 1220, 1200, 1182, 1167 cm^{-1}.

[125] Using a method similar to that described in Example 18 above, the respective compounds of interest in Examples 19 to 23 below were obtained by using a corresponding amine instead of 2-(p-tolyl)ethylamine, and by using a corresponding aralkyl halide instead of 3-(trifluoromethyl)benzyl bromide.

Example 19 (Compound 19)

[126] From 4-formyl-2-(trichloroacetyl)pyrrole (539 mg, 2.24 mmol), Compound 19 (528 mg, 1.04 mmol, 46%) was obtained by using aminomethylcyclohexane (416 μL, 3.20 mmol) and 3-(trifluoromethyl)benzyl bromide (489 μL, 3.20 mmol).

[127] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 0.71-0.92 (m, 2H), 0.99-1.19 (m, 3H), 1.28-1.45 (m, 1H), 1.51-1.71 (m, 5H), 2.98 (t, J = 5.9 Hz, 2H), 5.71 (s, 2H), 7.05 (d, J =

1.7 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.46-7.61 (m, 4H), 7.79 (d, J = 1.7 Hz, 1H), 8.37 (t, J = 5.9 Hz, 1H), 13.54 (s, 1H). ESIMS (m/z) (M-H)$^-$ Calcd for $C_{24}H_{24}F_3N_3O_2S_2$, 507; Found, 506. Elemental Analysis. Calcd for $C_{24}H_{24}F_3N_3O_2S_2$: C, 56.79; H, 4.77; N, 8.28. Found: C, 57.09; H, 4.83; N, 8.23. IR (KBr tab.): 1686, 1635, 1599, 1560, 1452, 1369, 1331, 1284, 1236, 1219, 1200, 1184 cm^{-1}.

Example 20 (Compound 20)

[128] From 4-formyl-2-(trichloroacetyl)pyrrole (539 mg, 2.24 mmol), Compound 20 (293 mg, 0.58 mmol, 26%) was obtained by using 1-naphthalenemethylamine (470 μL, 3.20 mmol) and 3-fluorobenzyl bromide (393 μL, 3.20 mmol).

[129] ^{1}H-NMR (270 MHz, DMSO-d$_6$) δ (ppm): 4.48 (d, J = 5.3 Hz, 2H), 5.72 (s, 2H), 6.90-7.00 (m, 2H), 7.11 (td, J = 8.9, 2.6 Hz, 1H), 7.19 (d, J = 1.7 Hz, 1H), 7.21-7.58 (m, 6H), 7.81 (d, J = 1.7 Hz, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.94 (dd, J = 6.9, 2.3 Hz, 1H), 8.09 (dd, J = 7.3, 2.3 Hz, 1H), 9.00 (t, J = 5.3 Hz, 1H), 13.53 (s, 1H). ESIMS (m/z) (M-H)$^-$ Calcd for $C_{27}H_{20}FN_3O_2S_2$, 501; Found, 500. Elemental Analysis. Calcd for $C_{27}H_{20}FN_3O_2S_2 \cdot 0.1H_2O$: C, 64.54; H, 4.10; N, 8.30. Found: C, 64.58; H, 4.05; N, 8.13. IR (KBr tab.): 1687, 1626, 1622, 1603, 1552, 1454, 1284, 1273, 1254, 1240, 1217, 1182, 1151, 1138 cm^{-1}.

Example 21 (Compound 21)

[130] From 4-formyl-2-(trichloroacetyl)pyrrole (539 mg, 2.24 mmol), Compound 21 (215 mg, 0.45 mmol, 20%) was obtained by using isoamylamine (372 μL, 3.20 mmol) and 3,4-dichlorobenzyl bromide (768 mg, 3.20 mmol).

[131] ^{1}H-NMR (270 MHz, DMSO-d$_6$) δ (ppm): 0.86 (d, J = 6.3 Hz, 6H), 1.33 (dt, J = 6.9, 7.3 Hz, 2H), 1.42-1.56 (m, 1H), 3.14-3.21 (m, 2H), 5.62 (s, 2H), 7.05 (d, J = 1.7 Hz, 1H), 7.10 (dd, J = 8.3, 2.0 Hz, 1H), 7.38 (d, J = 2.0 Hz, 1H), 7.52 (s, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.77 (d, J = 1.7 Hz, 1H), 8.36 (t, J = 5.3 Hz, 1H), 13.55 (s, 1H). ESIMS (m/z) (M-H)$^-$ Calcd for $C_{21}H_{21}Cl_2N_3O_2S_2$, 481; Found, 480. Elemental Analysis. Calcd for $C_{21}H_{21}Cl_2N_3O_2S_2$: C, 52.28; H, 4.39; N, 8.71. Found: C, 52.61; H, 4.59; N, 8.72. IR (KBr tab.): 1718, 1706, 1701, 1697, 1686 cm^{-1}.

Example 22 (Compound 22)

[132] From 4-formyl-2-(trichloroacetyl)pyrrole (539 mg, 2.24 mmol), Compound 22 (87 mg, 0.17 mmol, 8%) was obtained by using 1-naphthalenemethylamine (470 μL, 3.20 mmol) and α-bromo-m-tolunitrile (627 mg, 3.20 mmol).

[133] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 4.86 (d, J = 5.0 Hz, 2H), 5.74 (s, 2H), 7.21 (s, 1H), 7.28-7.61 (m, 7H), 7.64-7.85 (m, 4H), 7.92 (s, 1H), 8.05 (d, J = 8.6 Hz, 1H), 9.00 (t, J = 5.0 Hz, 1H), 13.52 (s, 1H). ESIMS (m/z) $(M-H)^-$ Calcd for $C_{28}H_{20}N_4O_2S_2$, 508; Found, 507. Elemental Analysis. Calcd for $C_{28}H_{20}N_4O_2S_2 \cdot 0.6H_2O$: C, 64.75; H, 4.11; N, 10.79. Found: C, 64.76; H, 3.83; N, 11.03. IR (KBr tab.): 1709, 1701, 1686, 1655, 1649, 1637, 1603, 1551 cm^{-1}.

Example 23 (Compound 23)

[134] From 4-formyl-2-(trichloroacetyl)pyrrole (539 mg, 2.24 mmol), Compound 23 (446 mg, 0.82 mmol, 36%) was obtained by using 3-chlorobenzylamine (391 μL, 3.20 mmol) and 4-bromobenzyl bromide (800 mg, 3.20 mmol).

[135] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 4.38 (d, J = 5.8 Hz, 2H), 5.62 (s, 2H), 7.07 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 1.7 Hz, 1H), 7.15 (d, J = 5.8 Hz, 1H), 7.26-7.35 (m, 3H), 7.47 (d, J = 8.2 Hz, 2H), 7.53 (s, 1H), 7.78 (d, J = 1.7 Hz, 1H), 8.97 (t, J = 5.8 Hz, 1H), 13.53 (s, 1H). ESIMS (m/z) $(M-H)^-$ Calcd for $C_{23}H_{17}BrClN_3O_2S_2$, 545; Found, 544. Elemental Analysis. Calcd for $C_{23}H_{17}BrClN_3O_2S_2$: C, 50.51; H, 3.13; N, 7.68. Found: C, 50.71; H, 3.10; N, 7.63. IR (KBr tab.): 1676, 1670, 1662, 1653, 1637, 1624, 1603, 1578, 1570, 1558, 1551, 1533, 1527, 1524, 1518, 1508 cm^{-1}.

Example 24 (Compound 24)

[136] 4-Formyl-2-(trichloroacetyl)pyrrole (202 mg, 0.84 mmol) was dissolved in N,N-dimethylformamide (4 mL) and chloroform (1 mL), and 3,3-diphenylpropylamine (234 mg, 1.20 mmol) was added thereto. The resultant mixture was stirred at 55 °C for 15 hours. The solvent was removed under a reduced pressure. The obtained residue was dissolved in chloroform (9 mL). Then, N-methylisatoic anhydride polystyrene (640 mg, 1.28 mmol) was added thereto, and the mixture was stirred at room temperature for 15 hours. After the reaction mixture was filterted, the solvent was removed. The obtained residue was dissolved in N,N-dimethylformamide (5 mL). Then, methyl 3-(bromomethyl)benzoate (275 mg, 1.20 mmol) and 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene (750 mg, 2.36 mmol) were added thereto, and the mixture was stirred at 30°C for 15 hours. After the reaction mixture was filterted, the solvent was removed under a reduced pressure. The obtained residue was dissolved in chloroform (6 mL) and methanol (1 mL). N-(2-mercaptoethyl)aminomethylpolystyrene (300 mg, 0.45 mmol) and BioRad® AG1-X8OH^- form (855 mg, 2.16 mmol) were added thereto, and the mixture was stirred at room temperature for 15 hours. After the reaction mixture was filtered, the

solvent was removed under a reduced pressure. The obtained residue was dissolved in methanol (5 mL), and a 1 mol/L aqueous solution of sodium hydroxide (5 mL, 5.0 mmol) was added thereto, and the mixture was stirred at 80 °C for 0.5 hours. A 1 mol/L aqueous solution of hydrochloric acid was added thereto so as to adjust the reaction mixture to pH4, and the reaction mixture was subjected to extraction with ethyl acetate. After the organic layer was washed with water and brine, sequentially, and dried over anhydrous magnesium sulfate, the solvent was removed under a reduced pressure. The obtained residue was dissolved in ethanol (10 mL), and rhodanine (140 mg, 1.06 mmol) and piperidine (217 μL, 2.19 mmol) were added thereto, and the mixture was refluxed with stirring for 12 hours. Thereafter, a 1 mol/L aqueous solution of hydrochloric acid was added thereto so as to adjust the reaction liquid to pH 4, and the reaction mixture was subjected to extraction with chloroform. After the organic layer was washed with water and brine, sequentially, and dried over anhydrous magnesium sulfate, the solvent was removed under a reduced pressure. The crude crystals thus obtained were allowed to recrystalize from ethanol, whereby Compound 24 (205 mg, 0.35 mmol, 42%) was obtained.

[137] ^{1}H-NMR (270 MHz, DMSO-d_6) main peak δ (ppm): 2.22 (dt, J = 6.9, 7.6 Hz, 2H), 3.07 (dt, J = 6.9, 5.7 Hz, 2H), 3.91 (t, J = 7.6 Hz, 1H), 5.69 (s, 2H), 7.05 (d, J = 1.8 Hz, 1H), 7.11-7.31 (m, 10H), 7.32-7.46 (m, 2H), 7.51 (s, 1H), 7.68 (s, 1H), 7.76 (d, J = 1.8 Hz, 1H), 7.82 (d, J = 7.4 Hz, 1H), 8.40 (t, J = 5.6 Hz, 1H). ESIMS (m/z) $(M-H)^-$ Calcd for $C_{32}H_{27}N_3O_4S_2$, 581; Found, 580. Elemental Analysis. Calcd for $C_{32}H_{27}N_3O_4S_2 \cdot 0.1H_2O$: C, 62.56; H, 5.10; N, 6.78. Found: C, 62.53; H, 4.99; N, 6.70. IR (KBr tab.): 1707, 1701, 1697, 1691, 1686, 1655, 1647, 1637, 1630, 1624, 1603, 1578, 1570, 1560, 1551, 1545 cm^{-1}.

Example 25 (Compound 25)

[138] 4-Formyl-2-(trichloroacetyl)pyrrole (539 mg, 2.24 mmol) was dissolved in N,N-dimethylformamide (9 mL) and chloroform (3 mL), and 2-(p-tolyl)ethylamine (465 μL, 3.20 mmol) was added thereto. The resultant mixture was stirred at 55 °C for 15 hours. The solvent was removed under a reduced pressure. The obtained residue was dissolved in chloroform (18 mL). Then, N-methylisatoic acid anhydride polystyrene (1.28 g, 2.56 mmol) was added thereto, and the mixture was stirred at room temperature for 15 hours. After the reaction mixture was filtered, the solvent was removed. The obtained residue was dissolved in ethanol (13 mL), rhodanine (373 mg, 2.80 mmol) and piperidine (253 μL, 2.56 mmol) were added thereto, and the mixture was stirred at room temperature for 16 hours. Thereafter, a 1 mol/L aqueous solution of hydrochloric acid was added to the reaction

mixture so as to adjust the reaction mixture to pH 4, and precipitated crystals were collected through filtration. The crude crystals thus obtained were allowed to recrystalize from ethanol, whereby Compound 25 (184 mg, 0.50 mmol, 22%) was obtained.

[139] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 2.27 (s, 3H), 2.79 (t, J = 7.4 Hz, 2H), 3.44 (dt, J = 5.6, 7.4 Hz, 2H), 7.05 (s, 1H), 7.10 (d, J = 8.6 Hz, 2H), 7.12 (d, J = 8.6 Hz, 2H), 7.51 (s, 1H), 7.60 (s, 1H), 8.47 (t, J = 5.6 Hz, 1H), 12.28 (s, 1H), 13.49 (s, 1H). ESIMS (m/z) (M-H)$^-$ Calcd for $C_{18}H_{17}N_3O_2S_2$, 371; Found, 370. Elemental Analysis. Calcd for $C_{18}H_{17}N_3O_2S_2$: C, 58.20; H, 4.61; N, 11.31. Found: C, 58.33; H, 4.87; N, 11.28. IR (KBr tab.): 1635, 1628, 1599, 1576, 1570, 1560, 1551, 1541, 1533, 1527, 1524, 1518, 1508, 1498, 1491, 1473 cm^{-1}.

[140] Using a method similar to that described in Example 25 above, the respective compounds of interest in Examples 26 to 29 below were obtained by using a corresponding amine instead of 2-(p-tolyl)ethylamine.

Example 26 (Compound 26)

[141] From 4-formyl-2-(trichloroacetyl)pyrrole (539 mg, 2.24 mmol), Compound 26 (182 mg, 0.52 mmol, 23%) was obtained by using aminomethylcyclohexane (416 μL, 3.20 mmol).

[142] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 0.83-1.04 (m, 2H), 1.09-1.32 (m, 3H), 1.42-1.58 (m, 1H), 1.59-1.83 (m, 5H), 3.00 (t, J = 5.9 Hz, 2H), 7.09 (s, 1H), 7.48 (s, 1H), 7.58 (s, 1H), 8.35 (t, J = 5.9 Hz, 1H), 12.22 (s, 1H), 13.47 (s, 1H). ESIMS (m/z) (M-H)$^-$ Calcd for $C_{16}H_{19}N_3O_2S_2$, 349; Found, 348. Elemental Analysis. Calcd for $C_{16}H_{19}N_3O_2S_2$: C, 54.99; H, 5.48; N, 12.02. Found: C, 54.91; H, 5.65; N, 11.88. IR (KBr tab.): 1697, 1635, 1622, 1595, 1568, 1560, 1541, 1525, 1456, 1446, 1435, 1257, 1230, 1200, 1130 cm^{-1}.

Example 27 (Compound 27)

[143] From 4-formyl-2-(trichloroacetyl)pyrrole (539 mg, 2.24 mmol), Compound 27 (208 mg, 0.64 mmol, 29%) was obtained by using isoamylamine (372 μL, 3.20 mmol).

[144] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 0.91 (d, J = 6.6 Hz, 6H), 1.42 (dt, J = 7.6, 6.9 Hz, 2H), 1.49-1.73 (m, 1H), 3.26 (dt, J = 6.9, 6.6 Hz, 2H), 7.05 (d, J = 1.7 Hz, 1H), 7.51 (d, J = 1.7 Hz, 1H), 7.60 (s, 1H), 8.32 (t, J = 6.9 Hz, 1H), 12.27 (s, 1H), 13.49 (s, 1H). ESIMS (m/z) (M-H)$^-$ Calcd for $C_{14}H_{17}N_3O_2S_2$, 323; Found, 322. Elemental Analysis. Calcd for $C_{14}H_{17}N_3O_2S_2 \cdot 0.1H_2O \cdot 0.3CH_3CH_2OH$: C, 51.72; H, 5.65; N, 12.39. Found: C, 51.58; H, 5.66; N, 12.47. IR (KBr tab.): 1693, 1645, 1633, 1614, 1595, 1574, 1568, 1556, 1435, 1230, 1200, 1132 cm^{-1}.

Example 28 (Compound 28)

[145] From 4-formyl-2-(trichloroacetyl)pyrrole (539 mg, 2.24 mmol), Compound 28 (141 mg, 0.36 mmol, 16%) was obtained by using 1-naphthalenemethylamine (470 μL, 3.20 mmol).

[146] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 4.95 (d, J = 5.6 Hz, 2H), 7.17 (s, 1H), 7.41-7.73 (m, 6H), 7.86 (dd, J = 6.6, 2.6 Hz, 1H), 7.96 (dd, J = 6.6, 2.6 Hz, 1H), 8.17 (d, J = 9.2 Hz, 1H), 8.96 (t, J = 5.6 Hz, 1H), 12.40 (s, 1H), 13.49 (s, 1H). ESIMS (m/z) $(M-H)^-$ Calcd for $C_{20}H_{15}N_3O_2S_2$, 393; Found, 392. Elemental Analysis. Calcd for $C_{20}H_{15}N_3O_2S_2 \cdot 0.2H_2O$: C, 60.50; H, 3.91; N, 10.58. Found: C, 60.50; H, 4.11; N, 10.29. IR (KBr tab.): 1566, 1286, 1232, 1136 cm^{-1}.

Example 29 (Compound 29)

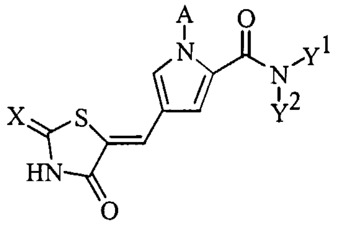
[147] From 4-formyl-2-(trichloroacetyl)pyrrole (539 mg, 2.24 mmol), Compound 29 (254 mg, 0.67 mmol, 30%) was obtained by using 3-chlorobenzylamine (391 μL, 3.20 mmol).

[148] ^{1}H-NMR (270 MHz, DMSO-d_6) δ (ppm): 4.46 (d, J = 5.6 Hz, 2H), 7.15 (s, 1H), 7.27-7.40 (m, 4H), 7.57 (s, 1H), 7.62 (s, 1H), 8.99 (t, J = 5.6 Hz, 1H), 12.38 (s, 1H), 13.51 (s, 1H). ESIMS (m/z) $(M-H)^-$ Calcd for $C_{16}H_{12}ClN_3O_2S_2$, 377; Found, 376. Elemental Analysis. Calcd for $C_{16}H_{12}ClN_3O_2S_2 \cdot 0.3H_2O$: C, 50.90; H, 3.55; N, 10.73. Found: C, 51.18; H, 3.44; N, 10.71. IR (KBr tab.): 1693, 1651, 1645, 1576, 1566, 1529, 1437, 1286, 1201, 1188 cm^{-1}.

[149] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

WHAT IS CLAIMED IS:

1. A Compound represented by Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

A is hydrogen, or substituted or unsubstituted aralkyl;

each Y^1 and Y^2 is independently hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, or substituted or unsubstituted lower aralkyl, or Y^1 and Y^2 together with the nitrogen atom to which they are attached to form a substituted or unsubstituted heterocyclic group; and

X is oxygen or sulfur.

2. The Compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein each of Y^1 and Y^2 is independently substituted or unsubstituted lower alkyl, or substituted or unsubstituted aralkyl.

3. A telomerase inhibitor comprising the Compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition comprising the Compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof.

5. An antitumor agent comprising the Compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/50041

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/425
US CL :514/369, 422, 423, 427; 546/280; 548/183
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/369, 422, 423, 427; 546/280; 548/183

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

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

STN;reg
structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,143,929 A (BELLIOTTI et al.) 01 September 1992, see entire document.	1-5
A	US 5,326,770 A (WILKERSON) 05 July 1994, see entire document.	1-5
A	US 5,925,656 A (KALLAM et al.) 20 July 1999, see entire document.	1-5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date		
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

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