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(54) Benzamide derivatives useful as cell differentiation inducers

Benzamid-Derivate, verwendbar als Zelldifferenzierungsinduktoren

Dérivés de benzamide, utiles comme inducteurs de différentiation cellulaire

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WO-A-96/21648 **WO-A-97/24328**

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Description

[0001] This invention relates to a differentiation-inducing agent. In particular, this invention relates to the use of a novel benzamide derivative for an anticancer drug or other drugs based on its differentiation-inducing activity.

[0002] Cancers have now become a top cause of death, exceeding heart and cerebrovascular diseases, and so many studies have been conducted with enormous expense and time to overcome cancers. They have not been, however, overcome in spite of a variety of investigations for therapy such as a surgical operation, a radiation therapy and thermotherapy. Among those therapies, chemotherapy is one of the main area for cancer treatment. To date, however, no satisfactory drugs have been discovered, and thus an anticancer drug with reduced toxicity and high therapeutic effect has been desired. Many of the conventional anticancer drugs show their effect by affecting mainly DNA to express their cytotoxicity and then injuring carcinoma cells. However, since they do not have sufficient selectivity between carcinoma cells and normal cells, adverse reactions expressed in normal cells have limited their use in therapy.

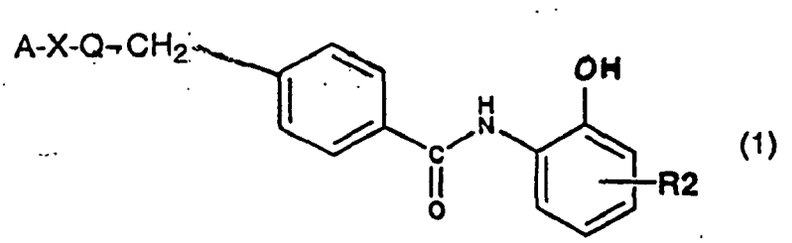
[0003] Meanwhile, differentiation-inducing agents among anticancer drugs are intended to induce differentiation of carcinoma cells for controlling their infinite proliferation, rather than directly kill the cells.

[0004] The agents may, therefore, be inferior to the anticancer drugs directly killing carcinoma cells, with regard to lessening of a carcinoma, but may be expected to have reduced toxicity and different selectivity. In fact, it is well known that retinoic acid, a differentiation-inducing agent, may be used for treatment of acute promyelogenous leukemia to exhibit a higher effect [Huang et al. , Blood, 72, 567-572 (1988) ; Castaign et al., Blood, 76, 1704-1709 (1990); Warrell et al., New Engl. J. Med. 324, 1385-1393(1991) etc.]. In addition, vitamin D derivatives exhibit differentiation-inducing effect, and thus their application for anticancer drugs have been investigated [e.g., Olsson et al, Cancer Res. 43, 5862-5867(1983) etc.].

[0005] As the results of these investigations, there have been reported applications for anticancer drugs, of a variety of differentiation-inducing agents such as vitamin D derivatives (JP-A 6-179622), isoprene derivatives (JP-A6-192073), tocopherol (JP-A6-256181), quinone derivatives (JP-A 6-305955), noncyclic polyisoprenoids (JP-A 6-316520), benzoic acid derivatives (JP-A 7-206765) and glycolipids (JP-A 7-258100). There have been no agents having sufficient level of effect for cancer treatment in spite of the investigations, and thus there has been greatly desired a highly safe agent effective to a variety of cancers

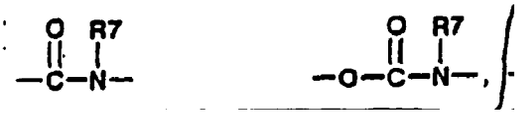
[0006] Preferred embodiments of this invention may provide compounds which exhibit differentiation-inducing effects and are useful as pharmaceutical agents such as therapeutic or improving agents for malignant tumors, autoimmune diseases, dermatologic diseases and parasitism.

[0007] We have intensely researched
and have found that novel benzamide derivatives having differentiation-inducing effect show antitumor effect. This invention provides a compound represented by formula (1) or a pharmaceutically acceptable salt thereof :



(1)

wherein A is a heterocyclic group, optionally substituted with 1 to 4 substituents selected from the group consisting of a halogen atom, a hydroxyl group, an amino group, a nitro group, a cyano group, an alkyl group having 1 to 4 carbons, an alkoxy group having to 4 carbons, an aminoalkyl group having 1 to 4 carbons, an alkylamino group having 1 to 4 carbons , an acyl group having 1 to 4 carbons, an acylamino group having 1 to 4 carbons, an alkylthio group having 1 to 4 carbons, a perfluoroalkyl group having 1 to 4 carbons, a perfluoroalkyloxy group having 1 to 4 carbons, a carboxyl group, an alkoxycarbonyl group having 1 to 4 carbons, a phenyl group and a heterocyclic group;
X is a moiety having a structure selected from : —(CH_2)e— and —$(CH_2)_g$—O—(CH_2)e— ,
wherein e is an integer of 1 to 4; and g is an integer of 0 to 4;
Q is a moiety having the structure



wherein R^7 is hydrogen or an alkyl having 1 to 4 carbons and optionally having 1 to 4 substituents selected from halogen, hydroxyl, amino, nitro, cyano, phenyl and heterocyclyl : and R^2 is a hydrogen atom,
a hydroxyl group, an alkyl group having 1 to 4 carbons, or an alkoxy group having 1 to 4 carbons, Preferred benzamide derivatives of this invention have differentiation-inducing effect and are useful as a drug such as a therapeutic or improving agent for malignant tumors, autoimmune diseases, dermatologic diseases and parasitism. In particular, they are highly effective as a carcinostatic agent, specifically to a hematologic malignancy and a solid carcinoma.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

[0008] In the above formula (1), n may be zero or an integer of 1 to 4.

[0009] Q in the above formula (1) is a moiety selected from:

wherein R^7 is as defined above.

[0010] X in the above formula (1) may be a moiety having the structure represented by formula (6);

$$-(CH_2)_e- \qquad (6)$$

wherein e is as defined above.

[0011] X in the above formula (1) may be also a moiety having the structure illustrated in formula (7):

$$-(CH_2)g\text{-}O\text{-}(CH_2)e- \qquad (7)$$

wherein e and g are as defined above.

[0012] As used herein, "1 to 4 carbons" means a carbon number per a single substituent; for example, for dialkyl substitution it means 2 to 8 carbons.

[0013] A heterocycle in the compound represented by formula (1) may be a monocyclic heterocycle having 5 or 6 members containing 1 to 4 nitrogen, oxygen or sulfur atoms or a bicyclic-fused heterocycle. The monocyclic heterocycle includes pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, pyrrole, pyrazole, isoxazole, isothiazole, imidazole, oxazole, thiazole, piperidine, piperazine, pyrrolidine, quinuclidine, tetrahydrofuran, morpholine and thiomorpholine.

[0014] The bicyclic fused heterocycle includes quinoline; isoquinoline; naphthyridine; fused pyridines such as furopyridine, thienopyridine, pyrrolopyridine, oxazolopyridine, imidazolopyridine and thiazolopyridine; benzofuran; benzothiophene; and benzimidazole.

[0015] A halogen may be fluorine, chlorine, bromine or iodine.

[0016] An alkyl having 1 to 4 carbons includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

[0017] An alkoxy having 1 to 4 carbons includes methoxy, ethoxy, n-propoxy, isopropoxy, allyloxy, n-butoxy, isobutoxy, sec-butoxy, and tert-butoxy.

[0018] An aminoalkyl having 1 to 4 carbons includes aminomethyl, 1-aminoethyl and 2-aminopropyl.

[0019] An alkylamino having 1 to 4 carbons includes N-methylamino, N,N-dimethylamino, N,N-diethylamino, N-methyl-N-ethylamino and N,N-diisopropylamino.

[0020] An acyl having 1 to 4 carbons includes acetyl, propanoyl and butanoyl.

[0021] An acylamino having 1 to 4 carbons includes acetylamino, propanoylaminol and butanoylamino. .

[0022] An alkylthio having 1 to 4 carbons includes methylthio, ethylthio and propylthio.

[0023] A perfluoroalkyl having 1 to 4 carbons includes trifluoromethyl and pentafluoroethyl.

[0024] A perfluoroalkyloxy having 1 to 4 carbons includes trifluoromethoxy and pentafluoroethoxy.

[0025] An alkoxycarbonyl having 1 to 4 carbons includes methoxycarbonyl and ethoxycarbonyl.

[0026] An optionally substituted alkyl having 1 to 4 carbons includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl,

sec-butyl and tert-butyl and these having 1 to 4 substituents selected from the group consisting of a halogen, hydroxyl, amino, nitro, cyano, phenyl and a heterocycle.

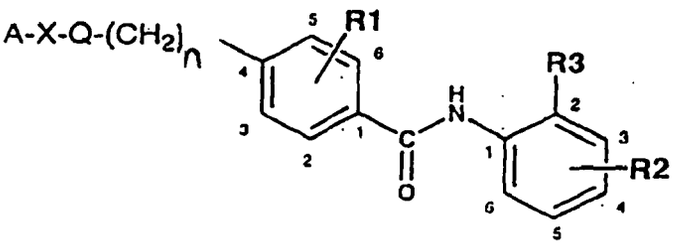
[0027] A pharmaceutically acceptable salt of the compound of this invention includes salts with an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid and phosphoric acid; and with an organic acid such as acetic acid, lactic acid, tartaric acid, malic acid, succinic acid, fumaric acid, maleic acid, citric acid, benzoic acid, trifluroacetic acid, p-toluenesulfonic acid and methanesulfonic acid.

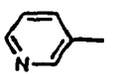
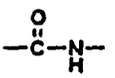
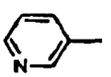
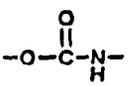
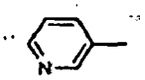
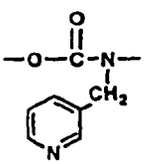
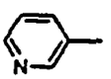
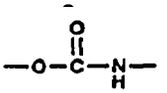
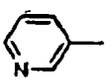
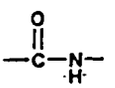
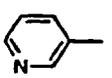
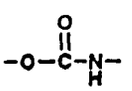
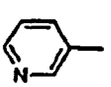
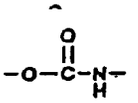
[0028] As used herein, a "drug" includes a therapeutic and/or improving agent for, for example, an autoimmune disease, dermatologic disease or parasitism, in addition to a anticancer drug.

[0029] When having asymmetric carbon or carbons, the compound represented by formula (1) may be obtained as an individual stereoisomer or a mixture of stereoisomers including a racemic modification. This invention encompasses the above-specified different forms, which may be also used as an active ingredient.

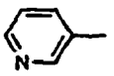
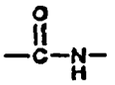
[0030] Representative compounds of this invention represented by formula (1) are specifically shown in Table 1, but this invention is not intended to be limited to these.

Table 1



Compound No.	A	X	Q	n	R1	R2	R3
1		-O- CH_2-		1	H	H	OH
2		-CH_2-		1	H	H	OH
3		-CH_2-		1	H	H	OH
4		-CH_2-		1	H	4- OH	OH
5		-CH_2-		1	H	H	OH
6		-CH_2-		1	H	5- CH_3	OH
7		-CH_2-		1	H	5- OCH_3	OH

(continued)

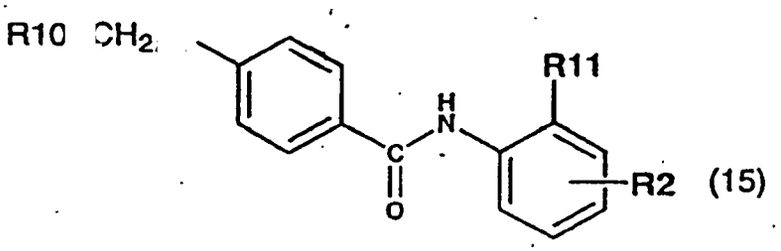
Compound No.	A	X	Q	n	R1	R2	R3
8		$-(CH_2)_2-$		1	H	H	OH

[0031] The compound of this invention may be prepared as described below.

(a) A compound represented by formula (14);

$$A\text{-}X\text{-}R^9 \qquad (14)$$

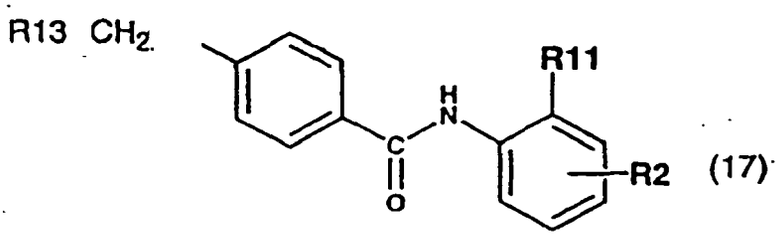
wherein A and X are as defined above; R^9 is -C(=O)OH is condensed with a compound represented by formula (15);



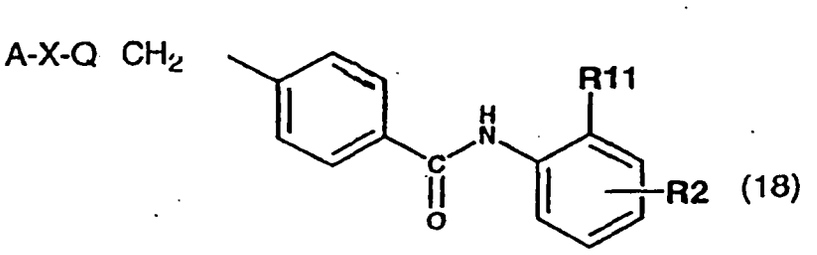
wherein R^2 is as defined above; R^{10} is NH_2; R^{11} is a hydroxyl group protected with a protecting group commonly used in a peptide-forming reaction, including benzyl; or
(b) A compound represented by formula (16)

$$A\text{-}X\text{-}OH \qquad (16),$$

wherein A and x are as defined above,
is condensed with a compound represented by formula (17):

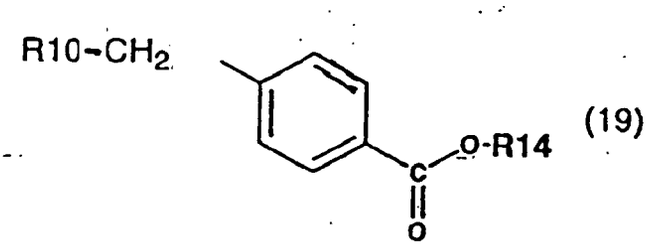


wherein R^2 and R^{11} are as defined above; R^{13} is $-NH_2$;
using an agent such as N,N'-carbonyldiimidazole, N,N'-thiocarbonyldiimidazole, phosgene or thiophosgene, to give a compound represented by formula (18):



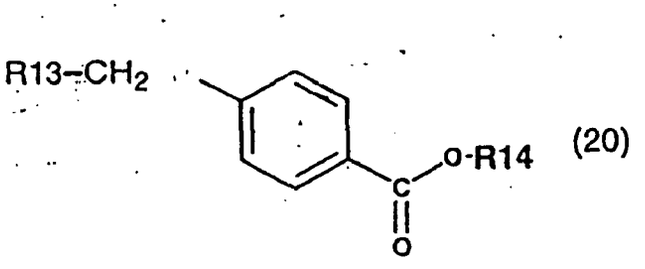
wherein A, X, Q, R^2 and R^{11} are as defined above, whose protecting group is then removed to give the compound of this invention; or

(c) In order to produce a compound of formula (21), either: (i) a compound represented by formula (14) is condensed with a compound represented by formula (19);



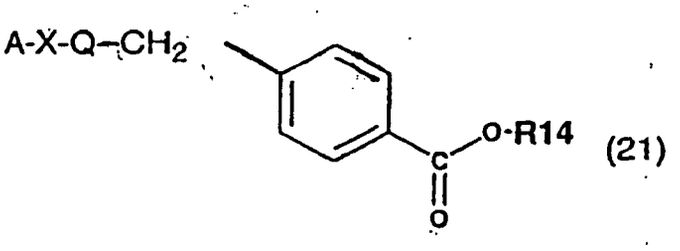
wherein R^{10} is as defined above; R^{14} is a methyl, ethyl or tert-butyl group; or (ii) A compound represented by formula (16) is

condensed with a compound represented by formula (20);

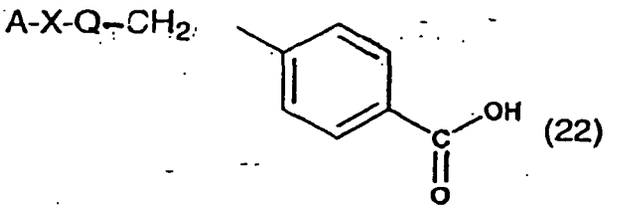


wherein R^{13} and R^{14} are as defined above;

using an agent such as N,N'-carbonyldiimidazole, N,N'-thiocarbonyldiimidazole, phosgene or thiophosgene, to give said compound represented by formula (21) :

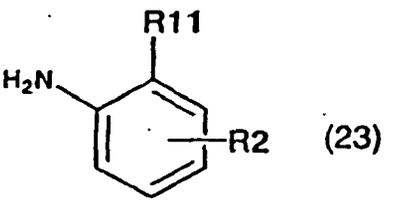


wherein A, X, Q, and R^{14} are as defined above. The compound formula (21) is then hydrolyzed to give a compound represented by formula (22);



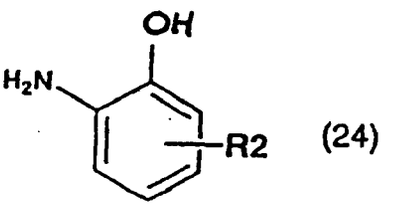
(22)

wherein A, X and Q are as defined above. The product is condensed with a compound represented by formula (23);



(23)

wherein R^2 and R^{11} are as defined above;
to give a compound represented by formula (18) whose protecting group is then removed to give the compounds of this invention; or
(d) A compound represented with formula (22) is
condensed with a compound represented by formula (24);

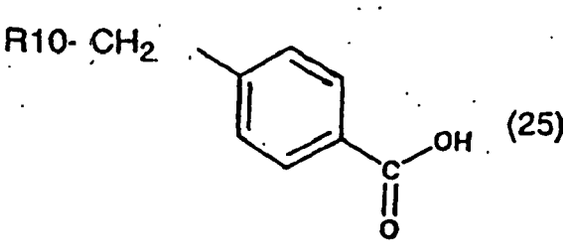


(24)

wherein R^2 is as defined above; to give the compound of this invention.

[0032] Preparation procedures for typical intermediates are shown below.

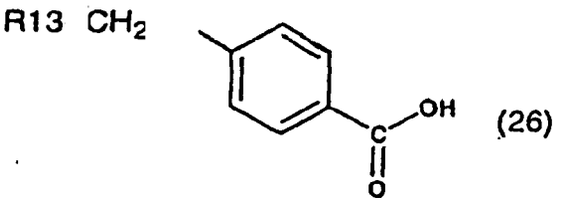
[0033] A compound represented by formula (15) may be prepared by introducing an appropriate protecting group to a benzoic acid derivative represented by formula (25) ;



(25)

wherein R^{10} is as defined above; condensing the product with a compound represented by formula (23), and removing the protecting group of the condensation product.

[0034] A compound represented by formula (17) may be prepared by introducing an appropriate protecting group to a benzoic acid derivative represented by formula (26) ;



(26)

wherein R^{13} is as defined above; condensing the product with a compound represented by formula (23), and removing the protecting group of the condensation product.

[0035] A compound represented by formula (23) may be prepared by introducing a protecting group to a compound represented by formula (24).

[0036] Next, reactions used for preparation of the compound of this invention will be described.

[0037] The condensation reaction in (a) may be an amide-bond forming reaction for a usual peptide using, for example, an activated ester, a mixed acid anhydride or an acid halide. For example, a carboxylic acid, i.e., a compound represented by formula (14) may be condensed with a phenol derivative such as 2,4,5-trichlorophenol, pentachlorophenol and 4-nitrophenol, or an N-hydroxy compound such as N-hydoxysuccinimide and N-hydroxybenzotriazole, in the presence of dicyclohexylcarbodiimide, to be converted into an activated ester, which is then condensed with an amine represented by formula (15) to give the desired product.

[0038] Alternatively, a carboxylic acid represented by formula (14)
may be reacted with, for example, oxalyl chloride, thionyl chloride or phosphorus oxychloride to be converted into an acid chloride, which is then condensed with an amine represented by formula (15)
to give the desired product.

[0039] Furthermore, a carboxylic acid represented by formula (14) may be reacted with, for example, isobutyl chlorocarbonate or methanesulfonyl chloride to be converted into a mixed acid anhydride, which is then condensed with an amine represented by formula (15) to give the desired product.

[0040] The above condensation reaction may be conducted solely using a peptide condensing agent such as dicyclohexylcarbodiimide, N,N'-carbonyldiimidazole, diphenyl phosphoric azide, diethylphosphorylcyanide, 2-chloro-1,3-dimethylimidazolonium chloride, etc.

[0041] The reaction may be usually conducted at -20 to +50 ˚C for 0.5 to 48 hours. Solvents which may be used include aromatic hydrocarbons such as benzene and toluene; ; ethers such as tetrahydrofuran, dioxane and diethyl ether; halogenated hydrocarbons such as dichloromethane and chloroform; N,N-dimethylformamide; alcohols such as methanol and ethanol; and mixtures thereof. If necessary, an organic, base such as triethylamine and pyridine may be added.

[0042] The condensation reaction in (b) may be conducted by activating a compound represented by either formula (16) or (17) with, for example, phosgene, thiophosgene, N,N'-carbonyldiimidazolel or N,N'-thiocarbonyldiimidazole and then reacting the activated product with the other compound. The reaction may be usually conducted at -20 to +50 ˚C for 0.5 to 48 hours. Solvents which may be used include aromatic hydrocarbons such as benzene and toluene; ; ethers such as tetrahydrofuran, dioxane and diethyl ether; halogenated hydrocarbons such as dichloromethane and chloroform; N,N-dimethylformamide; and mixtures. If necessary, an organic base such as triethylamine or pyridine may be added.

[0043] The condensation reaction in (c) may be conducted as the condensation in (b).

[0044] The protecting group of the compound represented by formula (17) may be removed under the conditions used in a common peptide-forming reaction.

[0045] A salt of a compound represented by formula (1) may be formed during preparation of the compound, but is usually formed by treating the compound with a pharmaceutically acceptable acid. Such an acid includes inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid and phosphoric acid; ; and organic acids such as acetic acid, tartaric acid, fumaric acid, maleic acid, citric acid, benzoic acid, trifluroacetic acid and p-toluenesulfonic acid.

[0046] A compound represented by formula (1) may be purified or isolated by a usual separation method such as extraction, recrystallization or column chromatography.

[0047] The novel benzamide derivative of this invention has differentiation-inducing effect and thus is useful as a therapeutic and/or improving agent to a variety of diseases such as malignant tumors, autoimmune diseases, dermatologic diseases and parasitism.

[0048] As used herein, a "malignant tumor" includes hematologic malignancy such as acute leukemia, malignant lymphoma, multiple myeloma and macroglobulinemia as well as solid tumors such as colon cancer, cerebral tumor, head and neck tumor, breast carcinoma, pulmonary cancer, esophageal cancer, gastric cancer, hepatic cancer, gallbladder cancer, bile duct cancer, pancreatic cancer, nesidioblastoma, renal cell carcinoma, adrenocortical cancer, urinary

bladder carcinoma, prostatic cancer, testicular tumor, ovarian carcinoma, uterine cancer, chorionic carcinoma, thyroid cancer, malignant carcinoid tumor, skin cancer, malignant melanoma, osteogenic sarcoma, soft tissue sarcoma, neuroblastoma, Wilms tumor and retinoblastoma.

[0049] An autoimmune disease includes rheumatism, diabetes, systemic lupus erythematodes, human autoimmune lymphocytotic lymphadenopathy, immunoblastic lymphadenopathy, Crohn disease and ulcerative colitis.

[0050] A dermatologic disease includes psoriasis, acne, eczema and atopic dermatitis.

[0051] Parasitism includes diseases such as malaria.

[0052] Indications for the compound of this invention are not limited to these specific examples.

[0053] The active ingredient of this invention useful as a drug may be used in the form of a general pharmaceutical composition. The pharmaceutical composition may be prepared with generally used diluents or excipients such as filler, extender, binder, moisturizing agent, disintegrator, surfactant and lubricant. The pharmaceutical composition may have a variety of dosage forms depending on its therapeutic purpose; typically tablet, pill, powder, solution, suspension, emulsion, granule, capsule, injection (e.g., solution, suspension) and suppository.

[0054] For preparing tablets, a variety of carriers well-known in the art may be used. Such a carrier includes excipients such as lactose, glucose, starch, calcium carbonate, kaoline, crystalline cellulose and silicic acid; binders such as water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose and polyvinyl pyrrolidone; disintegrators such as dried starch, sodium alginate, powdered agar, calcium carmelose, starch and lactose; disintegration retarders such as sucrose, cocoa butter and hydrogenated oil; absorption promoters such as quaternary ammonium base and sodium lauryl sulfate; moisturizing agents such as glycerin and starch; adsorbents such as starch, lactose, kaoline, bentonite, colloidal silicic acid; and glidants such as talc, stearates and polyethylene glycol. The tablet may be, if necessary, one coated with a common coating; for example, sugar-coated tablet, gelatin-coated tablet, enteric coated tablet, film-coated tablet, double-layer tablet and multilayer tablet.

[0055] In forming pills, a variety of carriers well-known in the art may be used. Such a carrier includes excipients such as crystalline cellulose, lactose, starch, hydrogenated vegetable oil, kaoline and talc; binders such as powdered acacia, powdered tragacanth gum and gelatin; disintegrators such as calcium carmelose and agar.

[0056] Capsule may be prepared by blending an active ingredient with a variety of the above carriers as usual and filling the resulting blend into, for example, a hard or soft gelatin capsule or the like.

[0057] For preparing injection, solution, emulsion and suspension are sterilized and preferably isotonic with blood. It may be prepared using diluents commonly used in the art; for example, water, ethanol, macrogol, propylene glycol, ethoxylated isostearyl alcohol, polyoxyisostearyl alcohol and polyoxyethylene sorbitan fatty acid esters. The pharmaceutical preparation may contain sodium chloride necessary to prepare an isotonic solution, glucose or glycerin, as well as usual solubilizers, buffers and soothing agents.

[0058] Suppository may be formed using a variety of well-known carriers; for example, semi-synthetic glyceride, cocoa butter, higher alcohols, higher alcohol esters and polyethylene glycol.

[0059] Furthermore, the pharmaceutical composition may contain coloring agents, preservatives, perfumes, flavors, sweeteners and/or other drugs.

[0060] The amount of the active ingredient in the pharmaceutical composition of this invention may be, as appropriate, selected from a wide range with no limitations, and is generally about 1 to 70 % by weight in the composition, preferably about 5 to 50 % by weight.

[0061] An administration route of the pharmaceutical composition is not limited, and selected depending on patient's age, sex, severity of disease and other conditions. For example, tablet, pill, solution, suspension, emulsion, granule and capsule may be orally administered; injection may be intravenously administered solely or in combination with a common infusion fluid ingredient such as glucose or amino acids. or if necessary, intramuscularly, subcutaneously or intraperitoneally as a sole preparation. Suppository may be intrarectally administered.

[0062] Dose of the pharmaceutical preparation of this invention may be selected, depending on their dosage form, patient's age, sex and severity of disease, and other conditions, as appropriate, but the amount of the active ingredient may be generally about 0.0001 to 100 mg/kg a day. It is recommended that a unit dosage form may contain about 0.001 to 1000 mg of the active ingredient.

[0063] The compound represented by formula (1) of this invention or a salt thereof exhibits no or low toxicity which is acceptable as the anticancer agent at the dose showing pharmacological effects.

Examples

[0064] This invention will be specifically illustrated with, but is not limited to, the following examples, where the numbers in parentheses indicate those of the compounds shown in the above detailed description.

Method Example M1

Preparation of N-(2-aminophenyl)-4-(N-benzoylaminomethyl)benzamide hydrochloride

[0065] NOTE: this is not a compound of the present invention but its method of preparation is of use.

(M1-1) To a suspension of 21.16 g of 4-aminomethylbenzoic acid(140 mmol) in 450 mL of dichloromethane was added 42 mL of triethylamine (300 mmol). Under ice-cooling, 60.4 g of trifluoroacetic anhydride (287 mmol) in 50 mL of dichloromethane were added dropwise, maintaining the inner temperature at 3 to 8 ˚C, and then the mixture was stirred four 3 hours. The reaction mixture was poured into a saturated aqueous sodium bicarbonate solution, and was acidified with 10 % hydrochloric acid. The gel precipitate was collected by filtration and dried to give 30.4g of 4-(N-trifluoroacetylaminomethyl)benzoic acid (Yield: 87.8 %) as an opalescent solid.

^{1}H NMR (270 MHz, DMSO-d_6) δ ppm: 4.47 (2H, d, J=5.8 Hz), 7.39(2H, d, J=8.1 Hz), 7.93(2H, d, J=8.1 Hz), 10.08 (1H, t, J=5.8 Hz), 12.95 (1H, br.s.)

(M1-2) To a solution of 108 g of o-phenylenediamine (1.0 mol) in 1000 mL of dioxane was added 500 mL of 1N sodium hydroxide aq., and then 218 g of tert-butyldicarbonate (1.1 mol) in 500 mL of dioxane under ice-cooling. After stirring for 6 hours at room temperature, the mixture was left overnight. The mixture was concentrated to 1/2 volume by evaporation, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was purified by column chromatography (eluent: chloroform) to give a solid, which was then washed with diethyl ether to give 68.4 g of N-tert-butoxycarbonyl-o-phenylenediamine (Yield: 32.8 %) as a white solid.

^{1}HNMR (270 MHz, CDCl3) δ ppm: 1.51 (9H, s), 3.75 (2H, s), 6.26 (1H, s), 6.77(1H, d, J=8.1 Hz), 6.79 (1H, dd, J=7.3, 8.1 Hz), 7.00 (1H, dd, J=7.3, 8.1 Hz), 7.27 (1H, d, J=8.1 Hz)

(M1-3) To a suspension of 30 g of the compound from the process (1-1) (121 mmol) in 200 mL of dichloromethane were slowly added dropwise 21 g of oxalyl chloride (165 mmol) with intermittently adding DMF (0.1 mL per 2 mL addition), maintaining the inner temperature within 10 to 15 ˚C by ice-cooling. After completion of the addition, the mixture was stirred until bubble generation ceased, and then at 40 ˚C for an additional hour. After evaporation, excess oxalyl chloride was azeotropically removed with toluene, and then the residue was redissolved in 100 mL of dichloroethane. The prepared acid chloride solution was added dropwise to a solution of 22.88 g of the compound from the process (1-2) (110 mmol) in 100 mL of dichloromethane and 200 mL of pyridine, maintaining the inner temperature within 7 to 9 ˚C by ice-cooling.

After addition, the mixture was warmed to room temperature, and was left overnight. After adding saturated sodium bicarbonate aq. to the reaction mixture, the resulting mixture was extracted with chloroform, and the organic layer was washed with saturated brine, dried and evaporated. To the residue was added methanol-diisopropyl ether, and the precipitated solid was collected by filtration and dried to give 28.1 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-(N-trifluoroacetylaminomethyl)benzamide (Yield: 58 %) as a light yellow solid.

^{1}H NMR (270 MHz, DMSO-d_6) δ ppm: 1.44 (9H, s), 4.48(2H, d, J=5.9 Hz), 7.12-7.23(2H, m), 7.44(2H, d, J=8.1 Hz), 7.54 (2H, d, J=8.1 Hz), 7.94 (2H, d, J=8.1 Hz), 8.68 (1H, br.s), 9.83 (1H, s), 10.10 (1H, br.t, J=5.9 Hz)

(M1-4) To a suspension of 13.12 g of the compound from the process (1-3) (30 mmol) in 120 mL of methanol and 180 mL of water were added 4.70 g of potassium carbonate (34.0 mmol), and the mixture was heated with stirring at 70 ˚C for 4 hours. It was extracted with chloroform, and the organic layer was washed with saturated brine, dried, evaporated and dried to give 10.3 g of 4-aminomethyl-N-[2-(N-tert-butoxycarbonyl)aminophenyl]benzamide (Yield: quantitative) as a light yellow amorphous solid.

^{1}H NMR (270 MHz, DMSO-d_6) δ ppm: 3.80(2H, s), 7.13-7.23(2H, m), 7.48-7.58(4H, m), 7.90(2H, d, J=8.1 Hz), 8.69 (1H, br.s), 9.77(1H, br.s)

(M1-5) To a solution of 0.11 g of the compound from the process (1-4) (0.44 mmol) in 5 mL of pyridine was added 0.08 g of benzoyl chloride (0.53 mmol), and the mixture was gradually warmed to room temperature and then stirred for 8 hours. Saturated sodium bicarbonate aq. was added, and then the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and evaporated. The residue was washed with diisopropyl ether, and the solid obtained was dried to give 0.14 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-(N-benzoylaminomethyl)benzamide (Yield: 71.4 %) as a white solid.

^{1}H NMR (270 MHz, DMSO-d_6) δ ppm: 1.44(9H, s), 4.56 (2H, d, J=5.9 Hz), 7.11-7.22 (2H, m), 7.46-7.56 (7H, m), 7.90-7.94 (4H,m), 8.67 (1H,s), 9.15 (1H, t, J=5.9Hz), 9.81 (1H, s)

(M 1-6) To a solution of 0.10 g of the compound from the process (1-5) (0.224 mmol) in 5 mL of dioxane and 1 mL of methanol was added 5 mL of 4N hydrochloric acid-dioxane, and the mixture was stirred at room temperature for 7 hours. To the residue after evaporation was added diisopropyl ether, and the formed solid was collected by filtration and dried to give 0.08 g of N-(2-aminophenyl)-4-(N-benzoylaminomethyl)benzamide hydrochloride (Yield: 93 %) as a light brown solid.

mp: 206-209 ˚C
^{1}HNMR (270 MHz, DMSO-d_6) δ ppm: 4.57 (2H, d, J=5.8 Hz), 7.27-7.38(4H, m), 7.47-7.59(5H, m), 7.92 (1H, d, J=8.1 1Hz), 8.05 (1H, d, J=8.1 Hz), 9.19 (1H, t, J=5.8 Hz), 10.38 (1H, br.s)
IR(KBr, cm^{-1}): 3286, 3003 (br.), 1630, 1551, 1492, 1306, 1250, 749, 695.
The compounds of Examples 1 to 3 were prepared, generally as described in Method Example M1. Their melting points (mp), ^{1}H NMR data and/or IR data are described below.

Example 1

N-(2-hydroxyphenyl)-4-[N-[3-(pyridin-3-yl)propionyl]aminomethyl]benzamide (Table 1: Compound 8)

[0066] mp: (amorphous)
^{1}H NMR(270 MHz. CD_3OD) δ ppm: 2.61(2H, t, J=7.3 Hz), 3.00 (2H, t, J=7.3 Hz), 4.39 (2H, s), 7.04 (1H, ddd, J=1.5, 8.1, 8.1 Hz), 7.25(2H, d, J=8.1 Hz), 7.33 (1H, dd, J=5.1, 8.11 H2), 7.69 (1H, d, J=8.1 Hz), 7.85 (2H, d, J=8.1 Hz), 7.86 (1H, d, J=8.1 Hz), 8.41(2H, br.s)
IR (neat) cm^{-1}: 3276, 1645, 1614, 1536, 1509, 1435, 1415, 1385, 1333, 1280, 1247, 1091, 737

Example 2

N-(2-hydroxyphenyl)-4-[N-(pyridin-3-yl)oxyacetylaminomethyl]benzamide table 1: Compound 1)

[0067] mp: (amorphous)
^{1}H NMR(270 MHz, DMSO-d_6) : 4.43 (2H, d, J=6.6 Hz), 4.69(2H, s), 6.83 (1H, t, J=6.6 Hz), 6.91 (1H, d, J=8.1 Hz), 7.68 (1H, d, J=6.6 Hz), 7.82(2H, d, J=8.1 Hz), 8.21 (1H, d, J=4.4 Hz), 8.35 (1H, d, J=2.2 Hz), 8.81 (1H, t, J=6.6 Hz), 9.48 (1H, s), 9.75 (1H, s)
IR (KBr) cm^{-1}: 3399, 1664, 1535, 1236, 1064

Example 3

N-(2-hydroxyphenyl)-4-(N-(pyridin-3-yl)acetylaminomethyl)benzamide (Table 1: Compound 5)

[0068] mp: 201-202 ˚C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 3.56(2H, s), 4.37 (2H, d, J=5.9 Hz), 6.83 (1H, ddd, J=1.5, 8.1, 8.1 Hz), 6.92 (1H, br.d, J=8.1 Hz), 7.03 (1H, ddd, J=1.5, 8.1, 8.1 Hz), 7.34 (1H, dd, J=3.7, 8.1 Hz), 7.37 (2H, d, J=8.1 Hz), 7.70(2H, d, J=8.1 Hz), 7.91(2H, d, J=8.1 Hz), 8.45 (1H, br.d, J=3.7 Hz), 8.49 (1H, s), 8.73 (1H, t, J=5.9 Hz), 9.47 (1H, s), 9.73 (1H, br.s)
IR(KBr)cm^{-1}: 3272, 3067, 1661, 1647, 1598, 1536, 1455, 1334, 1288, 1194, 1024, 742

Method Example M2

Preparation of N-(2-aminophenyl)-4-[N-Cpyridin-3-yl)methoxycarbonylaminomethyl]benzamide

[0069] [NOTE: This is not a compound of the present invention but its method of preparation is of use.]

(M2-1) To a solution of 384 mg of 3-pyridinemethanol (3.52 mmol) in 5 mL of dry THF were added. 523 mg of N, N'-carbonyldiimidazole (3.22 mmol) at room temperature. After stirring for an hour, to the mixture was added 1.0 g of the compound from Method Example 1, the process (M1-4) (2.93 mmol) in 6 mL of dry THF.
The mixture was left at room temperature overnight, 100 mL of chloroform was added, and the mixture was washed with water (3 × 20 mL) and then saturated brine, and dried over anhydrous magnesium sulfate. After evaporating the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (eluent: chloroform:methanol = 30:1) to give 1.27 g of N-[2-(N-tert-butoxycarbonyl)aminophenyl]-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Yield: quantitative) as an amorphous solid.
^{1}HNMR(270 MHz, $CDCl_3$) δ ppm: 1.51(9H, s), 4.45(2H, d, J=5.9 Hz), 5.16 (1H, s), 7.10-7.50(7H, m), 7.70 (1H, d, J=8.1 Hz), 7.80 (1H, d, J=7.3 Hz), 7.93 (1H, d, J=8.1 Hz), 8.57 (1H, d, J=4.4 Hz), 8.63 (1H, s), 9.17 (1H, s).
(M2-2) The compound from the process (M2-1) (1.2 g, 2.8 mmol) was dissolved in 10 mL of methanol. To the solution was added 20 mL of 4N-hydrochloric acid-dioxane. The mixture was stirred at room temperature for 1.5 hours, and then poured into diluted sodium-hydroxide aq. and extracted with chloroform (3 x 60 mL). The combined organic layer was washed twice with saturated brine, dried over anhydrous magnesium sulfate and concentrated to give 0.88 g of crystals, which were then recrystallized from 16 mL of ethanol, to give 668 mg of N-(2-aminophenyl)-

4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Yield: 73 %).

mp: 159-160 ˚C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.28(2H, d, J=5.9 Hz), 4.86(2H, s), 5.10(2H, s), 6.60(1H, t, J=7.3 Hz), 6.78(1H, d, J=7 Hz), 6.97(1H, t, J=7 Hz), 7.17(1H, d, J=8 Hz), 7.30-7.50(3H, m), 7.78(1H, d, J=8 Hz), 7.93(2H, d, J=8 Hz), 8.53 (1H, d, J=3.7 Hz), 8.59(1H, s), 9.61(1H, s).
IR(KBr)cm^{-1}: 3295, 1648, 1541, 1508, 1457, 1309, 1183, 742
The compounds of Examples 4 to 8 were prepared as described in method Example M2. Their melting points (mp), ^{1}H NMR data and/or IR data are shown below.

Example 4

N-(2-hydroxyphenyl)-4-[N-(pyridin-3-yl)methyl-N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide (Table 1: Compound 3)

[0070] mp: (amorphous)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.52(2H, s), 4.57(2H, s), 5.20(2H, s), 6.84(1H, t, J=6.6 Hz), 6.93(1H, d, J=6.6Hz), 7.03(1H, d, J=7.3Hz), 7.37(4H, m), 7.68(2H, dd, J=1.5, 8.1Hz), 7.92(2H, br.s), 8.53(4H, m), 9.49(1H, s), 9.77(1H, br.s)
IR(KBr)cm^{-1}: 3035, 1698, 1243, 1118, 754, 640

Example 5

N-(2-hydroxyphenyl)-4-[N-(pyridin-3-yl) methoxvcarbonylaminomethyl]benzamide (Table 1: Compound 2)

[0071] mp: 162-164 ˚c
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.29(1H, d, J=5.9 Hz), 5.10(2H, s), 6.83(1H, t, J=8.1 Hz), 6.92(1H, d, J=6.6 Hz), 7.07(1H, t, J=6.6 Hz), 7.39(2H, d, J=8.8 Hz), 7.43(1H, d, J=5.1 Hz), 7.68(2H, d, J=8.1 Hz), 7.80(1H, d, J=8.1 Hz), 7.92 (2H, d, J=8.1 Hz), 7.99(1H, t, J=5.9 Hz), 8.54(1H, d, J=4.4 Hz), 8.60(1H, s), 9.49(1H, s), 9.76(1H, br.s)
IR(KBr)cm^{-1}: 3333, 3259, 1694, 1645, 1529, 1267, 720

Example 6

N-(2,4-dihydroxyphenyl)-4-[N-(pyridin-3-yl) methoxycarbonylaminomethyl]benzamide (Table 1: Compound 4)

[0072] mp: (amorphous)
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.27(2H, d, J=6.6 Hz), 5.10(2H, s), 6.20(2H, dd, J=2.2, 8.1Hz), 6.39(2H, d, J=2.9 Hz), 6.88(2H, d, J=8.8 Hz), 7.33(1H, d, J=8.1 Hz), 7.41(1H, dd, J=5.1, 7.1 Hz), 7.89(1H, d, J=8.8 Hz), 7.98(1H,t, J=6.6Hz), 8.05(2H,s),8.52(1H,m), 8.59(1H, s), 9.30(2H, br.s)
IR(KBr)cm^{-1}: 3387, 1702, 1612, 1311, 1169, 845

Example 7

N-(2-hydroxy-5-methylphenyl)-4-[N-(pyridin-3-yl) methoxycarbonylaminomethyl]benzamide (Table 1: Compound 6)

[0073] mp: 155-155.5 ˚C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 2.22(3H, s), 4.29(2H, d, J=5,8 Hz), 5.11(2H, s), 6.82(2H, m), 7.39(2H, d, J=8.8Hz), 7.42(2H, m), 7.51(1H, s), 7.79(1H, d, J=8.1 Hz), 7.92(1H, d, J=8.1 Hz), 7.98(1H, t, J=5.9 Hz), 8.54(1H, d, J=4.4 Hz), 8.60(1H, s), 9.48(2H, d, J=8.1 Hz)
IR(KBr)cm^{-1}: 3306, 1723, 1655, 1525, 801, 639

Example 8

N-(2-hydroxy-5-methoxyphenyl)-4-[N-(pyridin-3-yl) methoxycarbonylaminomethyl]benzamide (Table 1: Compound 7)

[0074] mp: 175-176 ˚C
^{1}H NMR(270 MHz, DMSO-d_6) δ pom: 3.69(3H, s), 4.29(2H, d, J=5.9 Hz), 5.10(2H, s), 6.63(1H, dd, J=2.9, 8.7 Hz), 6.84 (1H, d, J=8.8 Hz), 7.41(4H, m), 7.79(1H, d, J=8.1 Hz), 7.91(1H, d, J=8.1 Hz), 7.99(1H, t, J=5.9 Hz), 8.54(1H, d, J=5.1 Hz), 8.60(1H, s), 9.31(1H, s), 9.45(1H, s)

IR(KBr)cm^{-1} :3305, 1687, 1573, 1262, 1039, 868

Comparative Example 1

N-(3-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide

[0075] The title compound was prepared by the method of Method Example M2.
mp: 156 ˚C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.27(2H, d, J=6.6 Hz), 5.06(2H, s), 5.10(2H, s), 6.20-6.40(1H, m), 6.80-7.10(3H, m), 7.30-7.50(3H, m), 7.70-8.00(4H, m), 8.53(1H, d, J=3.6 Hz), 8.59(1H, s), 9.88(1H, s)
IR(KBr)cm^{-1}: 3327, 3218, 1708, 1639, 1536, 1279, 1147, 1050, 859, 788

Comparative Example 2

N-(4-aminophenyl)-4-[N-(pyridin-3-yl)methoxycarbonylaminomethyl]benzamide

[0076] The title compound was prepared by the method of Method Example M2.
mp: 204-205˚C
^{1}H NMR(270 MHz, DMSO-d_6) δ ppm: 4.27(2H, d, J=6.6 Hz), 4.91(2H, s), 5.10(2H, s), 6.52(2H, d, J=8.8 Hz), 7.30-7.50 (5H, m), 7.70-8.00(4H, m), 8.50-8.60(2H, m), 9.80(1H, s)
IR(KBr)cm^{-1}: 3336, 3224, 1706, 1638, 1530, 1279, 1145, 1050, 1005, 827

Pharmacological test example 1

Test for induction of differentiation in A2780 cells

[0077] Increase of alkaline phosphatase (ALP) activity is known as an indicator for differentiation of human colon cancer cells. For example, it is known that sodium butylate may increase ALP activity (Young et al., Cancer Res., 45, 2976(1985); Morita et al., Cancer Res., 42, 4540(1982)). Thus, differentiation inducing action was evaluated using ALP activity as an indicator.

Experimental procedure

[0078] To each well of a 96-well plate was placed 0.1 mL of A2780 cells (15,000 cells/well) and the next day was added 0.1 mL of a sequential dilute of test solution with the medium. After incubation for 3 days, the cells on the plate were washed twice with a TBS buffer (20 mM Tris, 137 mMNaCl, pH 7.6). Then, to each well was added 0.05 mL of 0.6 mg/mL p-nitrophenylphosphate (9.6 % diethanolamine, 0.5 mM$MgCl_2$ (pH9.6)) solution, and the plate was incubated at room temperature for 30 min. The reaction was quenched with 0.05 mL/well of 3N sodium hydroxide aq. For each well, an absorbance at 405 nm was measured to determine the minimum concentration of the drug inducing increase of ALP activity (ALPmin).

Results

[0079] The results are shown in Table 2.

Table 2: Differentiation-inducing action to A2780 cells Test

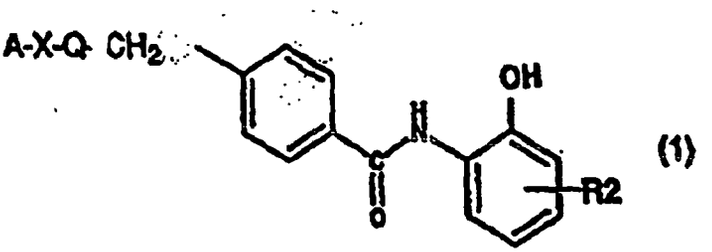
Test Compound	ALPmin (μM)
Example 1	10
Example 2	0.3
Example 3	10
Example 4	10
Example 5	1
Example 8	3
Como.Ex.1	>100

(continued)

Test Compound	ALPmin (μM)
Comp.Ex.2	>100

Claims

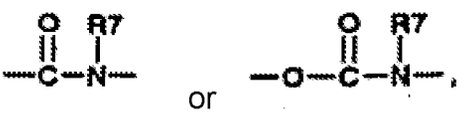
1. A compound represented by the formula (1):



wherein
A is a heterocyclic group, or a heterocyclic group, which has 1 to 4 substituents, wherein the substituent(s) for the heterocyclic group is (are) selected from the group consisting of a halogen atom, a hydroxyl group, an amino group, a nitro group, a cyano group, an alkyl group having 1 to 4 carbons, an alkoxy group having 1 to 4 carbons, an aminoalkyl group having 1 to 4 carbons, an alkylamino group having 1 to 4 carbons, an acyl group having 1 to 4 carbons, an acylamino group having 1 to 4 carbons, an alkylthio group having 1 to 4 carbons, a perfluoroalkyl group having 1 to 4 carbons, a perfluoroalkyloxy group having 1 to 4 carbons, a carboxyl group, an alkoxycarbonyl group having 1 to 4 carbons, a phenyl group and a heterocyclic group;
X is a moiety having a structure selected from:

$$-(CH_2)_e- \text{ and } -(CH_2)_g-O-(CH_2)_e-$$

wherein e is an integer of 1 to 4 and g is an integer of 0 to 4;
Q is a moiety having the structure



wherein R7 is a hydrogen atom, an alkyl group having 1 to 4 carbons or an alkyl group having 1 to 4 carbons which has 1 to 4 substituents selected from the group consisting of a halogen, hydroxyl, amino, nitro, cyano, phenyl, and a heterocycle;
R2 is a hydrogen atom, a hydroxyl group, an alkyl group having 1 to 4 carbons, or an alkoxy group having 1 to 4 carbons,
or a pharmaceutically acceptable salt thereof,

2. A compound or pharmaceutically acceptable salt thereof as claimed in claim 1, wherein A is a pyridyl group, or a pyridyl group which has 1 to 4 substituents selected from the group consisting of a halogen atom, a hydroxyl group, an amino group, a nitro group, a cyano group, an alkyl group having 1 to 4 carbons, an alkoxy group having 1 to 4 carbons, an aminoalkyl group having 1 to 4 carbons, an alkylamino group having 1 to 4 carbons, an acyl group having 1 to 4 carbons, an acylamino group having 1 to 4 carbons, an alkylthio group having 1 to 4 carbons, a perfluoroalkyl group having 1 to 4 carbons, a perfluoroalkyloxy group having 1 to 4 carbons, a carboxyl group, an alkoxycarbonyl group having 1 to 4 carbons, a phenyl group and a heterocyclic group.

3. A compound or pharmaceutically acceptable salt thereof as claimed in claim 1 or claim 2, wherein R2 is a hydrogen atom.

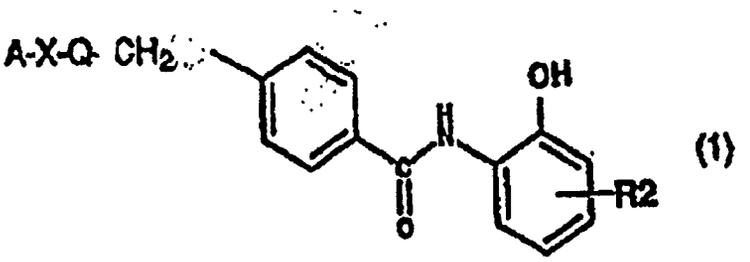
4. A pharmaceutical composition comprising, as active ingredient, one or more compounds or pharmaceutically acceptable salt(s) thereof as claimed in any one of claims 1 to 3.

5. An anti-cancer drug comprising, as active ingredient, one or more compounds or pharmaceutically acceptable salt (s) thereof as claimed in any one of claims 1 to 3.

6. Use of a compound or a pharmaceutically acceptable salt thereof represented by formula (1) as defined in claim 1 in the manufacture of a composition for use in treating cancer, autoimmune disease, dermatologic disease or parasitism.

Patentansprüche

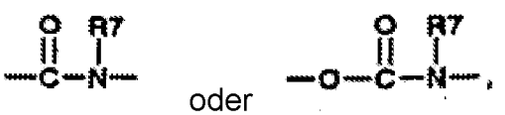
1. Eine Verbindung gemäß Formel (1):



worin
A eine heterozyklische Gruppe oder eine heterozyklische Gruppe mit 1 bis 4 Substituenten ist, worin die Substituenten der heterozyklischen Gruppe ausgewählt sind aus der Gruppe bestehend aus einem Halogenatom, einer Hydroxylgruppe, einer Aminogruppe, einer Nitrogruppe, einer Cyanogruppe, einer Alkylgruppe aufweisend 1 bis 4 Kohlenstoffe, einer Alkoxygruppe aufweisend 1 bis 4 Kohlenstoffe, einer Aminoalkylgruppe aufweisend 1 bis 4 Kohlenstoffe, einer Alkylaminogruppe aufweisend 1 bis 4 Kohlenstoffe, einer Acylgruppe aufweisend 1 bis 4 Kohlenstoffe, einer Acylaminogruppe aufweisend 1 bis 4 Kohlenstoffe, einer Alkylthiogruppe aufweisend 1 bis 4 Kohlenstoffe, einer Perfluoralkylgruppe aufweisend 1 bis 4 Kohlenstoffe, einer Perfluoralkyloxygruppe aufweisend 1 bis 4 Kohlenstoffe, einer Carboxylgruppe, einer Alkoxycarbonylgruppe aufweisend 1 bis 4 Kohlenstoffe, einer Phenylgruppe und einer heterozyklischen Gruppe;
X ist ein Rest, aufweisend eine Struktur, ausgewählt aus:

$$-(CH_2)_e- \text{ und } -(CH_2)_g-O-(CH_2)_e-$$

worin e eine ganze Zahl zwischen 1 und 4 ist und g eine ganze Zahl zwischen 0 und 4 ist;
Q ist ein Rest aufweisend die Struktur:



worin R7 ein Wasserstoffatom, eine Alkylgruppe aufweisend 1 bis 4 Kohlenstoffe oder eine Alkylgruppe aufweisend 1 bis 4 Kohlenstoffe, welche 1 bis 4 Substituenten aufweist, ausgewählt aus der Gruppe bestehend aus einem Halogen, Hydroxyl, Amino, Nitro, Cyano, Phenyl und einem Heterozyklus, ist;
R2 ist ein Wasserstoffatom, eine Hydroxylgruppe, eine Alkylgruppe aufweisend 1 bis 4 Kohlenstoffe oder eine

Alkoxygruppe aufweisend 1 bis 4 Kohlenstoffe;
oder ein pharmazeutisch akzeptables Salz davon.

2. Eine Verbindung oder ein pharmazeutisch akzeptables Salz davon gemäß Anspruch 1, worin A eine Pyridylgruppe, oder eine Pyridylgruppe aufweisend 1 bis 4 Substituenten, ausgewählt aus der Gruppe bestehend aus einem Halogenatom, einer Hydroxylgruppe, einer Aminogruppe, einer Nitrogruppe, einer Cyanogruppe, einer Alkylgruppe aufweisend 1 bis 4 Kohlenstoffe, einer Alkoxygruppe aufweisend 1 bis 4 Kohlenstoffe, einer Aminoalkylgruppe aufweisend 1 bis 4 Kohlenstoffe, einer Alkylaminogruppe aufweisend 1 bis 4 Kohlenstoffe, einer Acylgruppe aufweisend 1 bis 4 Kohlenstoffe, einer Acylaminogruppe aufweisend 1 bis 4 Kohlenstoffe, einer Alkylthiogruppe aufweisend 1 bis 4 Kohlenstoffe, einer Perfluoralkylgruppe aufweisend 1 bis 4 Kohlenstoffe, einer Perfluoralkyloxygruppe aufweisend 1 bis 4 Kohlenstoffe, einer Carboxylgruppe, einer Alkoxycarbonylgruppe aufweisend 1 bis 4 Kohlenstoffe, einer Phenylgruppe und einer heterozyklischen Gruppe ist.

3. Eine Verbindung oder ein pharmazeutisch akzeptables Salz davon gemäß Anspruch 1 oder 2, worin R2 ein Wasserstoffatom ist.

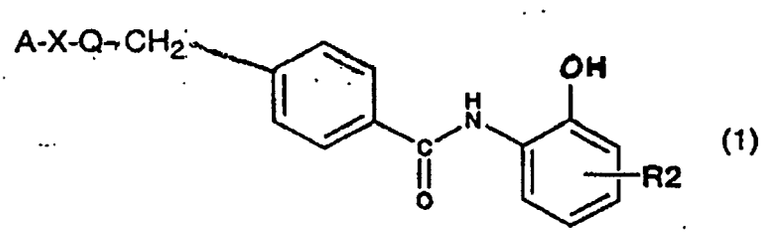
4. Eine pharmazeutische Zusammensetzung aufweisend, als aktiven Inhaltsstoff, eine oder mehrere Verbindungen gemäß einem der Absprüche 1-3, oder pharmazeutisch akzeptable Salze davon.

5. Ein Anti-Krebs Medikament aufweisend, als aktiven Inhaltsstoff, eine oder mehrere Verbindungen gemäß einem der Ansprüche 1-3, oder pharmazeutisch akzeptable Salze davon.

6. Verwendung einer Verbindung gemäß Formel (1), oder eines pharmazeutisch akzeptablen Salzes davon, wie in Anspruch 1 definiert, zur Herstellung einer Zusammensetzung zur Verwendung zur Behandlung von Krebs, Autoimmunerkrankungen, dermatologischen Erkrankungen oder Parasitismus.

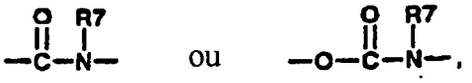
Revendications

1. Composé représenté par la formule (1) :



(1)

où
A est un groupe hétérocyclique, ou un groupe hétérocyclique qui a 1 à 4 substituants, où le ou les substituants pour le groupe hétérocyclique est (sont) choisis dans le groupe consistant en un atome d'halogène, un groupe hydroxyle, un groupe amino, un groupe nitro, un groupe cyano, un groupe alkyle ayant 1 à 4 carbones, un groupe alcoxy ayant 1 à 4 carbones, un groupe aminoalkyle ayant 1 à 4 carbones, un groupe alkylamino ayant 1 à 4 carbones, un groupe acyle ayant 1 à 4 carbones, un groupe acylamino ayant 1 à 4 carbones, un groupe alkylthio ayant 1 à 4 carbones, un groupe perfluoroalkyle ayant 1 à 4 carbones, un groupe perfluoroalkyloxy ayant 1 à 4 carbones, un groupe carboxyle, un groupe alcoxycarbonyle ayant 1 à 4 carbones, un groupe phényle et un groupe hétérocyclique ;
X est un groupement ayant une structure choisie parmi : $-(CH_2)_e-$ et $-(CH_2)_g-O-(CH_2)_e-$ où e est un entier de 1 à 4 et g est un entier de 0 à 4;
Q est un groupement ayant la structure :



où R7 est un atome d'hydrogène, un groupe alkyle ayant 1 à 4 carbones ou un groupe alkyle ayant 1 à 4 carbones qui a 1 à 4 substituants choisis dans le groupe consistant en un halogène, hydroxyle, amino, nitro, cyano, phényle et un hétérocycle ;
R2 est un atome d'hydrogène, un groupe hydroxyle, un groupe alkyle ayant 1 à 4 carbones ou un groupe alcoxy ayant 1 à 4 carbones,
ou sel pharmaceutiquement acceptable de celui-ci.

2. Composé ou sel pharmaceutiquement acceptable de celui-ci selon la revendication 1 où A est un groupe pyridyle, ou un groupe pyridyle qui a 1 à 4 substituants choisis dans le groupe consistant en un atome d'halogène, un groupe hydroxyle, un groupe amino, un groupe nitro, un groupe cyano, un groupe alkyle ayant 1 à 4 carbones, un groupe alcoxy ayant 1 à 4 carbones, un groupe aminoalkyle ayant 1 à 4 carbones, un groupe alkylamino ayant 1 à 4 carbones, un groupe acyle ayant 1 à 4 carbones, un groupe acylamino ayant 1 à 4 carbones, un groupe alkylthio ayant 1 à 4 carbones, un groupe perfluoroalkyle ayant 1 à 4 carbones, un groupe perfluoroalkyloxy ayant 1 à 4 carbones, un groupe carboxyle, un groupe alcoxycarbonyle ayant 1 à 4 carbones, un groupe phényle et un groupe hétérocyclique.

3. Composé ou sel pharmaceutiquement acceptable de celui-ci selon la revendication 1 ou la revendication 2 où R2 est un atome d'hydrogène.

4. Composition pharmaceutique comprenant, comme ingrédient actif, un ou plusieurs composés ou un ou plusieurs sels pharmaceutiquement acceptables de ceux-ci selon l'une quelconque des revendications 1 à 3.

5. Médicament anticancéreux comprenant, comme ingrédient actif, un ou plusieurs composés ou un ou plusieurs sels pharmaceutiquement acceptables de ceux-ci selon l'une quelconque des revendications 1 à 3.

6. Utilisation d'un composé ou d'un sel pharmaceutiquement acceptable de celui-ci représenté par la formule (1) selon la revendication 1 dans la fabrication d'une composition destinée à être utilisée dans le traitement d'un cancer, d'une maladie auto-immune, d'une maladie dermatologique ou d'un parasitisme.

REFERENCES CITED IN THE DESCRIPTION

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- **Morita et al.** *Cancer Res.,* 1982, vol. 42, 4540 **[0077]**