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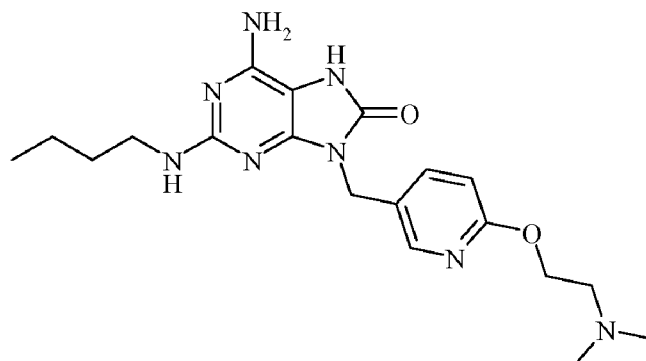
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(54) Title: USE OF A TLR7 AGONIST FOR THE TREATMENT OF CANCER



(I).

(57) Abstract: The invention relates to a novel method of treatment or prophylaxis of cancer, which comprises administering to a patient in need thereof a therapeutically effective amount of a TLR7 agonist of Formula (I), or a pharmaceutically acceptable salt thereof.



Use of 6-amino-2-butylamino-9-((6-(2-(dimethylamino)ethoxy)pyridin-3-yl)methyl-7,9-dihydro-8H-purin-8-one for the treatment of cancer.

Field of the Invention

The present invention relates to the use of a TLR7 agonist, or a pharmaceutically acceptable salt thereof, in the treatment or prophylaxis of cancer.

Background of the Invention

Toll-like receptors (TLRs) are expressed on a variety of immune cells, including macrophages and dendritic cells (DCs). TLRs recognise molecular motifs on pathogens called pathogen-associated molecular patterns (PAMPs) (1). To date, 13 TLRs have been identified in man, these include TLRs 1, 2, 4, 5 and 6, which are confined to the cell surface and TLRs 3, 7, 8 and 9 which are expressed in endosomes. Different TLRs recognise different pathogen-derived ligands, for example TLRs 2 (bacterial lipoproteins), 3 (double-stranded RNA/poly (I:C)), 4 (lipopolysaccharides), 5 (flagellin), 7 (single-stranded RNA) and 9 (CpG-containing DNA) (2). Ligation of TLRs on antigen-presenting cells, such as DCs, leads to production of proinflammatory cytokines, DC maturation and priming of the adaptive immune system (3). TLR7 and TLR9 are expressed by plasmacytoid dendritic cells (pDCs) and ligand recognition leads to the secretion of interferon- α (INF- α) (4). Preclinical studies investigating the effects of activation of TLRs, using bacterial or viral components, dosed as monotherapy and/or combined with anti-tumor agents, have shown tumour growth inhibition in a variety of murine tumour models (5). Moreover, intravesical instillation of attenuated *Bacillus Calmette-Guérin* (BCG), is an immunotherapy used in bladder cancer, which functions in part, through the activation of the TLR4 system (9).

Several small molecule TLR7 agonists have been described, including the imidazoquinoline, imiquimod, which has been used to treat a number of dermatological conditions e.g. genital warts, molluscum contagiosum and melanoma. In the case of melanoma, topically applied imiquimod (Aldara, Graceway Pharmaceuticals, Bristol, TN) demonstrated therapeutic responses in cutaneous metastatic melanoma and lentigo maligna (6) and has been approved for the treatment of superficial basal cell carcinoma (BCC) (7). Preclinical and clinical studies indicate that imiquimod is likely to function through the induction of type 1 IFN and IFN-inducible genes, which in turn can have direct effects on tumour cell growth and/or harness components of the adaptive immune system (6, 7).

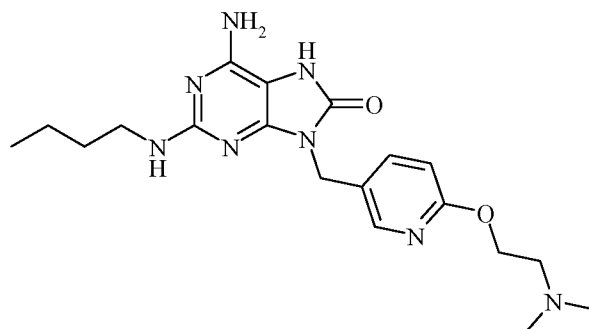
852A is another imidazoquinoline, which unlike imiquimod, is suitable for systemic administration. Currently 852A is in phase II clinical trials in a number of cancer indications, including melanoma (8).

Nevertheless, there remains a need for further TLR7 agonists which are more effective in the treatment of cancer by reason of their superior potency and/or advantageous physical properties (for example, higher permeability, and/or lower plasma protein binding) and/or favourable toxicity profiles and/or favourable metabolic profiles in comparison with other known TLR7 agonists, for example 852A.

As now demonstrated herein, the TLR7 agonist 6-amino-2-(butylamino)-9-({6-[2-(dimethylamino)ethoxy]pyridin-3-yl}methyl)-7,9-dihydro-8*H*-purin-8-one (referred to herein as Compound 1 or the compound of Formula (I)) is capable of producing a pronounced inhibition of tumour growth in a mouse model. In addition, this agonist is shown to activate immune cells and to elevate plasma cytokine levels in mice. As a consequence of these observed effects, 6-amino-2-(butylamino)-9-({6-[2-(dimethylamino)ethoxy]pyridin-3-yl}methyl)-7,9-dihydro-8*H*-purin-8-one is expected to be a more effective compound in the treatment or prophylaxis of cancer.

Summary of the Invention

There is therefore provided a method of treatment or prophylaxis of cancer, which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I), namely 6-amino-2-(butylamino)-9-({6-[2-(dimethylamino)ethoxy]pyridin-3-yl}methyl)-7,9-dihydro-8*H*-purin-8-one, or a pharmaceutically acceptable salt thereof:



(I).

According to another aspect of the invention, there is provided the compound of Formula (I) as defined hereinbefore, or a pharmaceutically-acceptable salt thereof, for use in the treatment or prophylaxis of cancer.

According to a further aspect of the invention, there is provided the use of the
5 compound of Formula (I) as defined hereinbefore, or a pharmaceutically-acceptable salt thereof, for the preparation of a medicament for the treatment or prophylaxis of cancer.

According to a further aspect of the invention, there is provided a medicament for the treatment or prophylaxis of cancer, comprising a compound of Formula (I) as defined hereinbefore, or a pharmaceutically acceptable salt thereof, as an active ingredient.

10 Description of the Invention

As used herein, the term "treatment" is intended to have its normal everyday meaning of dealing with a disease in order to entirely or partially relieve one, some or all of its symptoms, or to correct or compensate for the underlying pathology.

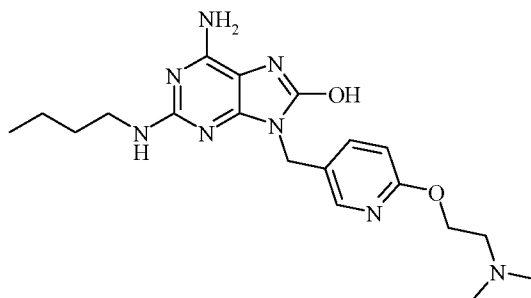
As used herein, the term "prophylaxis" is intended to have its normal everyday
15 meaning and includes primary prophylaxis to prevent the development of the disease and secondary prophylaxis whereby the disease has already developed and the patient is temporarily or permanently protected against exacerbation or worsening of the disease or the development of new symptoms associated with the disease.

It is envisaged that for the methods of treatment or prophylaxis of cancer
20 mentioned herein, the compound of Formula (I), or a pharmaceutical composition comprising a therapeutically effective amount of the compound of Formula (I), will be administered to a mammal, more particularly a human being. Similarly, for the uses of the compound of Formula (I), or a pharmaceutical composition comprising a therapeutically effective amount of the compound of Formula (I), for the treatment or prophylaxis of
25 cancer mentioned herein, it is envisaged that the compound of Formula (I) will be administered to a mammal, more particularly a human being.

The compound of Formula (I), or a pharmaceutically acceptable salt thereof, is expected to be of use in the treatment or prophylaxis of cancer, including prostate cancer, bladder cancer, breast cancer, lung cancer, uterus cancer, pancreatic cancer, liver cancer,
30 renal cancer, ovarian cancer, esophageal cancer, colon cancer, rectal cancer, colorectal cancer, stomach cancer, skin cancer, head and neck cancer or cerebral tumor, and malignant myeloma (e.g., leukemia) and lymphoproliferative tumor such as Hodgkin's

lymphoma or non-Hodgkin's lymphoma. The compound of Formula (I), or a pharmaceutically acceptable salt thereof, is also expected to be of use in the treatment or prophylaxis of metastasis, tumour recurrence and paraneoplastic syndrome. The compound of Formula (I), or a pharmaceutically acceptable salt thereof, is expected to be of particular use in the treatment or prophylaxis of colorectal cancer, renal cancer, melanoma and ovarian cancer.

The compound of Formula (I) and tautomers thereof are chemically equivalent. As such, the compound of Formula (I) of the present invention also includes tautomers thereof, in particular the hydroxy tautomer of Formula (1A):



(IA)

With respect to the pharmaceutically acceptable salts mentioned herein, such salts include acid addition salts and base addition salts. For example, acid addition salts include inorganic acid salts such as hydrochloride, hydrobromide, sulfate, hydroiodide, nitrate, phosphate, etc., and organic acid salts such as citrate, oxalate, acetate, formate, propionate, benzoate, trifluoroacetate, fumarate, maleate, succinate, tartrate, lactate, pyruvate, methanesulfonate, benzenesulfonate, para-toluenesulfonate, etc. Base addition salts include inorganic base salts such as sodium salt, potassium salt, calcium salt, magnesium salt, ammonium salt, etc., and organic base salts such as triethyl ammonium salt, triethanol ammonium salt, pyridinium salt, diisopropyl ammonium salt, etc., and additionally amino acid salts derived from basic or acidic amino acids including arginine, aspartic acid and glutamic acid.

It will be understood that a compound of the present invention may exist in solvated, for example as a hydrate or ethanolate, as well as unsolvated forms. The present invention encompasses all such solvated forms of the compound of Formula (I).

A compound of Formula (I) could also be administered in the form of a prodrug which is broken down in the human or animal body to give a compound of Formula (I).

Examples of prodrugs include in vivo hydrolysable esters of a compound of Formula (I). Various forms of prodrugs are known in the art. For examples of such prodrug derivatives, see:

- a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985);
- b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);
- c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- d) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); and N. Kakeya, et al., Chem Pharm Bull, 32, 692 (1984).

The compound of Formula (I) would normally be administered to a mammal at a unit dose within the range of approximately 0.0001-100 mg/kg, more suitably 0.0001-10, 0.0001-1, 0.0001-0.1, 0.0001-0.01, or more suitably still 0.0001-0.001 mg/kg and this would normally provide a therapeutically-effective dose. In one embodiment of the invention, the compound of Formula (I) is administered to a mammal at a unit dose of about 0.15 µg/kg. A unit dose form such as an injection would usually contain, for example 0.001-100, 0.001-10, 0.001-1, 0.001-0.1 or 0.001-0.01 mg of active ingredient. Preferably a daily dose in the range of 0.0001-20, 0.0001-10, 0.0001-1, 0.0001-0.1, 0.0001-0.01 or 0.0001-0.001 mg/kg would be employed. However, the daily dose will necessarily be varied depending upon the patient, the particular route of administration, and the severity of the illness being treated. Accordingly, the practitioner who is treating any particular patient may determine the optimum dosage.

An example of an appropriate preclinical dosing schedule for the compound of Formula (I) would be 0.1 mg/kg once a week, wherein the compound is administered by injection.

Liquid preparations suitable for injection may be prepared as sterile isotonic liquid preparations. The injection may be prepared by using aqueous media comprising saline solution, glucose solution, or a mixture of saline solution and glucose solution.

Examples of parenteral preparations of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, suitable for injection are as follows:

- A. 0.1 mg/ml to 1.5 mg/ml of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in normal saline adjusted to pH5.
- B. 0.1 mg/ml to 9 mg/ml of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in 40% $\pm$ 5% dimethylacetamide (DMA): 40% $\pm$ 5% polyethylene glycol (PEG400): and 20% $\pm$ 5% water.
- C. 0.1 mg/ml to 2.4 mg/ml of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, in 10% $\pm$ 5% DMSO: and 90% $\pm$ 5% normal saline.

DMSO = Dimethyl sulfoxide

Normal Saline = 0.9 % weight/volume sodium chloride in water

The compound of Formula (I), or a pharmaceutically acceptable salt thereof, could also be administered as an air spray for inhalation. The air spray (e.g., spray, aerosol, dry powder preparation, etc.) could be optionally formulated as an aqueous solution or suspension, or as an aerosol delivered from a pressurized pack such as a pressurised metered dose inhaler by using, for example, a liquefied propellant. A dry powder preparation may also be used. An aerosol appropriate for inhalation may be either a suspension or solution, and would typically contain the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and any appropriate propellants such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or a mixture thereof. Specifically, it may contain hydrofluoroalkane, particularly 1, 1, 1, 2-tetrafluoroethane, heptafluoroalkane (HFA) such as 1, 1, 1, 2, 3, 3, 3-heptafluoro-n-propane, or a mixture thereof. An aerosol may optionally contain an additional preparation excipient well-known to those skilled in the art such as surfactant (e.g., oleic acid or lecithin) and cosolvent (e.g., ethanol), etc. Specifically, an aerosol preparation could be delivered using the inhaler known as "Turbuhaler™".

The anti-cancer treatment described hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy or immunotherapy. Such chemotherapy could be administered concurrently, simultaneously, sequentially or separately to treatment with the compound of the invention and may include one or more of the following categories of anti-tumour agents:-

- (i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, oxaliplatin, carboplatin,

cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea); antitumour antibiotics (for example anthracyclines like

5 adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere and polokinese inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

10 (ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and idoxifene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole

15 and exemestane) and inhibitors of 5 α -reductase such as finasteride;

(iii) anti-invasion agents [for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341), *N*-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-

20 ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; J. Med. Chem., 2004, 47, 6658-6661) and bosutinib (SKI-606), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase];

(iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti-erbB2

25 antibody trastuzumab [HerceptinTM], the anti-EGFR antibody panitumumab, the anti-erbB1 antibody cetuximab [Erbix, C225] and any growth factor or growth factor receptor antibodies disclosed by Stern *et al.* Critical reviews in oncology/haematology, 2005, Vol. 54, pp11-29); such inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors

30 such as

N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine

(erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib); inhibitors of the hepatocyte growth factor family; inhibitors of the insulin growth factor family; inhibitors of the platelet-derived growth factor family such as imatinib and/or nilotinib (AMN107); inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006), tipifarnib (R115777) and lonafarnib (SCH66336)), inhibitors of cell signalling through MEK and/or AKT kinases, c-kit inhibitors, abl kinase inhibitors, PI3 kinase inhibitors, Plt3 kinase inhibitors, CSF-1R kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti-vascular endothelial cell growth factor antibody bevacizumab (Avastin™) and for example, a VEGF receptor tyrosine kinase inhibitor such as vandetanib (ZD6474), vatalanib (PTK787), sunitinib (SU11248), axitinib (AG-013736), pazopanib (GW 786034) and 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v \beta 3$ function and angiostatin)];

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

(vii) an endothelin receptor antagonist, for example zibotentan (ZD4054) or atrasentan;

(viii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(ix) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(x) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines, approaches using anti-idiotypic antibodies, approaches to decrease the function of immune suppressive cells such as regulatory T cells, myeloid-derived suppressor cells or IDO (indoleamine 2,3,-deoxygenase)-expressing dendritic cells, and approaches using cancer vaccines consisting of proteins or peptides derived from tumour-associated antigens such as NY-ESO-1, MAGE-3, WT1 or Her2/neu.

For example, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, may be combined with cyclophosphamide for the treatment of cancer, particularly colorectal cancer. Preclinically, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, may be used at a dose of 0.1-1 mg/kg once or twice weekly and the cyclophosphamide may be used at a dose of 50 mg/kg, once as a single priming dose, or once weekly. In a clinical setting the compound of Formula (I), or a pharmaceutically acceptable salt thereof, could be used at a unit dose in the range of 0.0001- 0.1 mg/kg, for example at a unit dose of about 0.15 µg/kg, and the cyclophosphamide could be given to a patient at a dose of 50 mg orally, twice weekly 1 week on and 1 week off for 1 month or more, Ghiringhelli *et al.*, Cancer Immunol Immunother (2007) 56:641-648. However, the daily dosages would necessarily be varied depending upon the patient, the particular route of administration, and the severity of the illness being treated. Accordingly, the practitioner who is treating any particular patient would determine the optimum dosage.

In one embodiment of the invention, there is therefore provided a therapeutic combination which comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and cyclophosphamide.

In one embodiment of the invention, there is provided a combination product which comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and cyclophosphamide.

The term "therapeutic combination" as referred to in this description is intended to mean any combination of the specified pharmaceutical agents that produces a therapeutic effect upon administration.

The term “combination product” as referred to in this description is intended to mean any product that comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and another specified pharmaceutical agent or agents and includes, but is not limited to, an individual pharmaceutical preparation comprising both a compound of Formula (I) and another specified pharmaceutical agent or agents (i.e. a combined preparation), a kit of parts comprising pharmaceutical preparations of a compound of Formula (I) and another specified pharmaceutical agent or agents as individual or separate preparations, storage means for pharmaceutical preparations of a compound of Formula (I) and another specified pharmaceutical agent or agents as either individual or separate preparations and/or means for dispensing pharmaceutical preparations of a compound of Formula (I) and another specified pharmaceutical agent or agents as either individual or separate preparations, wherein the term “individual pharmaceutical preparation” or “individual preparations” is intended to mean a single pharmaceutical preparation which comprises both a compound of Formula (I) and another specified pharmaceutical agent or agents and wherein the term “separate preparations” is intended to mean two or more different pharmaceutical preparations one of which comprises a compound of Formula (I) and the others of which each comprise another specified pharmaceutical agent.

In a further aspect of the invention, there is provided a method of treatment or prophylaxis of cancer, for example colorectal cancer, which comprises administering to a patient in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and cyclophosphamide.

In another aspect of the invention, there is provided a therapeutic combination or a combination product comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and cyclophosphamide, for use in the treatment or prophylaxis of cancer, for example colorectal cancer.

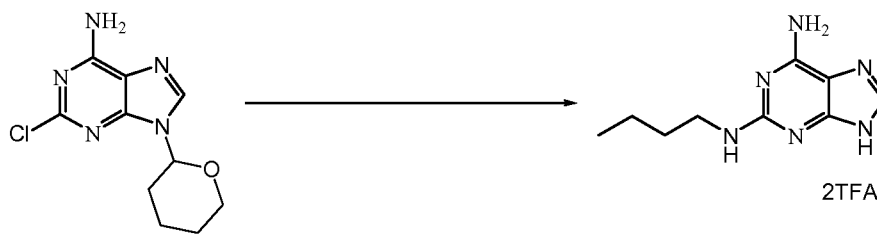
In another aspect, the present invention provides the use of a therapeutic combination or a combination product comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and cyclophosphamide, in the manufacture of a medicament for the treatment or prophylaxis of cancer, for example colorectal cancer.

In another aspect, the present invention provides a medicament for the treatment or prophylaxis of cancer, comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and cyclophosphamide as active ingredients.

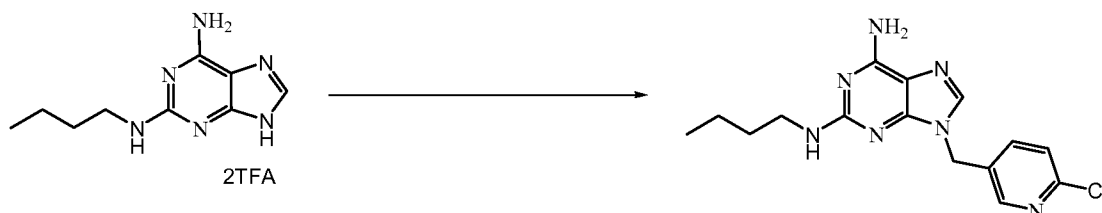
The following examples are for illustration purposes and are not intended to limit the scope of the invention.

Example 1: Synthesis of 6-amino-2-(butylamino)-9-({6-[2-(dimethylamino)ethoxy]pyridin-3-yl}methyl)-7,9-dihydro-8H-purin-8-one (Compound 1)

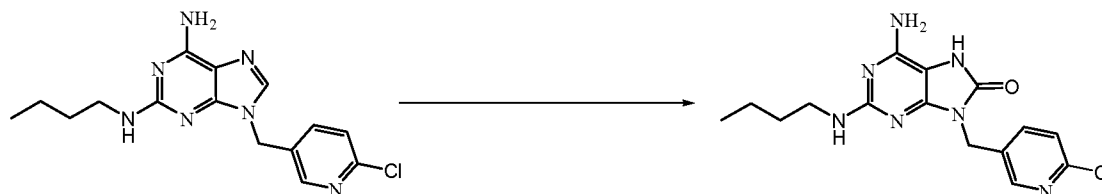
i) 2-Butylaminoadenine bis(trifluoroacetate)



2-Chloro-9-(tetrahydro-2H-pyran-2-yl)adenine (25 g, 100 mmol), butylamine (100 ml, 1 mol), and diisopropylmethylamine (34 ml, 200 mmol) were placed in an autoclave (500 ml), and the content of the autoclave was allowed to react at 150°C for 9 hours. To the reaction mixture, water (500 ml) was added at room temperature and then extracted with CHCl₃/MeOH=20/1 twice. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated in vacuo to give 2-butylamino-9-(tetrahydro-2H-pyran-2-yl)adenine. The compound was dissolved in methanol (150 ml), and trifluoroacetic acid (75 ml) was added thereto, and the mixture was stirred at room temperature for 48 hours and concentrated under reduced pressure. Ethyl acetate (50 ml) and hexane (150 ml) were sequentially added and the resulting solid was collected by filtration to afford titled compound as a pale yellow solid. Yield: 33.4 g (85%).

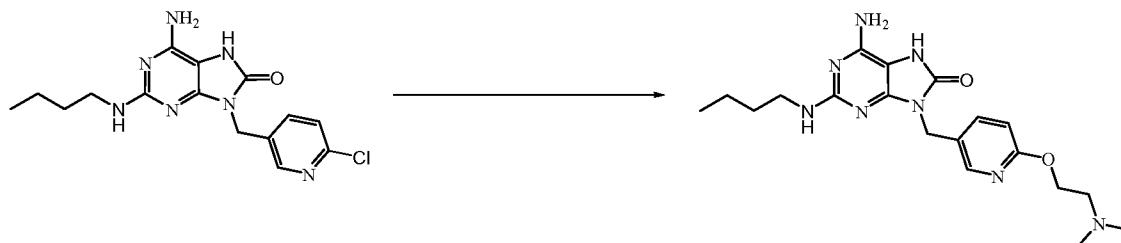
ii) 2-Butylamino-9-(6-chloropyridin-3-yl)methyladenine

Potassium carbonate (17.3 g, 125 mmol) and 2-chloro-5-chloromethylpyridine (4.86 g, 30.0 mmol) were added to the DMF solution (100 ml) of 2-butylaminoadenine bis(trifluoroacetate) (10.0 g, 25.0 mmol) obtained in i). The resultant was stirred while heating at 50°C for 4 hours. Water (200 ml) was added to the mixture at 0°C, and the precipitated solid was collected by filtration. The resulting solid was dissolved in $\text{CHCl}_3/\text{EtOH}=3/1$, and then washed with brine, dried over MgSO_4 , and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford titled compound as a pale yellow amorphous. Yield: 5.66 g (68%).

iii) 2-Butylamino-9-(6-chloropyridin-3-yl)methyl-8-oxoadenine

Chloroform solution (20 ml) of bromine (4.09 g, 25.6 mmol) was slowly added to the solution ($\text{CHCl}_3/\text{MeOH}=100/1$, 150 ml) of 2-butylamino-9-(6-chloropyridin-3-yl)methyladenine (5.66 g, 17.1 mmol) at 0°C. After stirred for 1.5 hours at 0°C, the mixture was concentrated in vacuo to give 8-bromo-2-butylamino-9-(6-chloropyridin-3-yl)methyladenine hydrobromide. Concentrated hydrochloric acid (70 ml) was added to the compound obtained above, and the resultant was allowed to react under reflux for 3 hours. The reaction solution was concentrated under reduced pressure, methanol (20 ml) and water (50 ml) was added to the residue under ice cooling, and the solution was neutralized with an aqueous solution of 28% ammonia. The precipitated solid was collected by filtration. The crude crystal was suspended in MeOH (20 ml) and water (100 ml), and stirred for 30 min. The precipitated solid was collected by filtration to afford titled compound as a white solid. Yield: 4.49 g (76%).

iv) 6-Amino-2-butylamino-9-[6-(2-dimethylaminoethoxy)pyridin-3-ylmethyl]- 7,9-dihydropurin-8-one



Dimethylaminoethanol (25 ml, 248 mmol) was slowly added to the suspension of sodium hydride (55% dispersion in mineral oil, 3.14 g, 71.9 mmol) in dioxane (25 mL) at 4 °C, and then stirred for 30 min at room temperature. 2-Butylamino-9-(6-chloropyridin-3-yl)methyl-8-oxoadenine (5.0 g, 14.4 mmol) obtained in iii) was added to the mixture then stirred for 4 hours under reflux. The reaction was quenched with water (100 ml) and conc. HCl aq. (20 ml) at 0 °C then extracted with CHCl₃/EtOH=3/1 three times. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford titled compound as white solid. 4.90 g, 12.2 mmol, 85% yield.

In vivo Biological Effects of Compound 1

The following datasets indicate *in vivo* responses of mice treated with Compound 1. Activation of the immune system following TLR7 ligation via Compound 1 is demonstrated herein, as determined by elevated cytokine levels in the plasma (including type I Interferons) (Example 2) and splenocyte activation (as determined by flow cytometric analysis of CD69 expression) (Example 3). The Compound 1 treated animals also demonstrated tumour growth inhibition, as indicated in the colorectal (CT26) (Example 4), renal (RENCA) (Example 5), and melanoma (B16-BL6) (Example 6) syngeneic murine tumour models detailed below. Compound 1 also showed enhanced CT26 tumour growth inhibition when combined with cyclophosphamide (CY) (Example 4), as detailed below.

Example 2: *Ex vivo* analysis of representative cytokine levels in plasma from pharmacodynamic experiment

Balb/C (female) mice were dosed i.v. with vehicle (saline) or Compound 1 (0.1, 1, 3 mg/kg). Timepoints samples taken ranged from 1 to 48 hours following single dose.

5 Plasma and spleen samples were taken at selected time points for *ex vivo* analysis as described.

Cytokines were detected in mouse plasma using a mouse cytokine multiplex immunoassay as set out in the kit instructions (Mouse Cytokine/Chemokine Lincoplex Kit, Linco Research Inc., 14 Research Park Dr., St. Charles, MO 63304, U.S.A.). The mouse
10 plasma was diluted 1:5 with assay buffer and a standard line was made up in matrix buffer diluted 1:5 in assay buffer to match. The representative cytokines quantified were IL-6 and TNF α (activation markers of plasmacytoid dendritic cells or natural type I interferon–producing cells), IL-12p70 and IFN γ (Th1 – type response), IL-10 (Th2 – type response), IP-10 and KC (downstream signaling of IFN's). The results of cytokine quantification are
15 shown in Figure 1. The results show that mice treated with Compound 1 had elevated cytokine levels.

Example 3: *Ex vivo* analysis of samples from pharmacodynamic study in Balb/c mice looking at splenocyte CD69 expression

20 CD69 is a very Early Activation Antigen expressed on the surface of activated T cells, B cells, natural killer cells, neutrophils and platelets. This experiment looked at mouse splenocyte CD69 expression levels by flow cytometry.

Spleen samples were taken from mice about 7 hours after dosing with Compound 1 and placed into cold media and packed in ice for transport back to lab using plastic bijoux
25 containing 2 mls media (media = 0.5% BSA (SIGMA A2153 albumin from bovine serum) / 2mM EDTA (Fluka 03690 Ethylenediaminetetraacetic acid solution pH 8 (0.5M)) in PBS (SIGMA D8537 Dulbeccos Phosphate Buffered saline)).

In a Class II cabinet, each spleen sample was gently pushed through a 70 μ m Falcon Cell Strainer into a petri dish containing about 5 mls media using the flat end of a
30 syringe plunger in order to obtain a single cell suspension. The suspension was transferred into a 15 mL Falcon tube and spun at 1300 rpm for 5 minutes and the supernatant poured off. The pellet was resuspended in 2.5 mls media per half spleen. 100uL was transferred

into labelled 5ml Falcon tubes (about 10^6 cells per tube) and 100uL of suspension from one of the control tubes was transferred into each of three tubes labelled A,B and C. 1uL of blocking antibody (552142, 2.4G2) was added to each tube and incubated for 5 minutes.

20uL of antibody cocktail (Antibody Cocktail example: 20 uL 553857 CD49 pan
5 NK-FITC; 20 uL 553237 CD69 PE; 20 ul 553065 CD3ε PECy5; 333 uL media) was then added to all tubes except A, B and C. To tube A was added 1uL 553857, to tube B 1uL 553237 and to tube C 1 uL 553065. All Antibodies were obtained from BD Pharmingen. The tubes were incubated for 20 minutes at 4°C and wrapped in foil to protect from light. The suspension was washed with 500 uL media and spun at 1300 rpm for 5 minutes and
10 the liquid poured off. 200uL Versalyse (lysing solution A0977 Beckman Coulter) was added to each tube and incubated for 10 minutes at room temp wrapped in foil. Tubes were centrifuged for 5 minutes at 1300 rpm, the supernatant poured off and resuspended in 600uL media. Samples were then ready to run on the flow cytometer [BD FACSCanto™ flow cytometer]. The collected data was analysed and the results are shown in Figure 1
15 demonstrating that there was an increase in CD69 +ve cells in mice treated with Compound 1.

Example 4: Tumour growth studies in CT-26, a murine syngeneic colorectal tumour model

20 Experiments were conducted on female mice (Balb/C genotype, at least 6 weeks old). CT-26 (ATCC number CRL-2638) mouse tumour allografts were established in mice from tumour cells (1×10^5) implanted subcutaneously in the flank of experimental animals. Tumour volumes were assessed at least twice weekly by bilateral Vernier calliper measurements. Mice were randomised into treatment groups when the tumour volume
25 reached approx 0.2cm^3 . Following randomisation, mice were treated with either drug vehicle (0.85% w/v physiological saline at pH 5) or Compound 1 (0.1 or 1mg/kg twice a week) administered intravenously (i. v.) on days 14, 17 and 21.

Tumour growth inhibition from the start of treatment was assessed by comparison of the differences in tumour growth rate between control and Compound 1 treated groups,
30 Figure 2.

The effects of combining Compound 1 with cyclophosphamide was also assessed in the CT-26 mouse tumour allograft model, as described above. Following CT-26 cell

implantation (Day 0): mice were treated with either drug vehicle (0.85% w/v physiological saline at pH 5); or Compound 1 (1mg/kg per dose) administered intravenously (i. v.) on days 3, 10 & 17; or cyclophosphamide (50mg/kg) administered once intraperitoneally (i.p.) on day 1; or cyclophosphamide plus Compound 1 (cyclophosphamide, 50mg/kg, i.p. day 1; Compound 1, 1mg/kg per dose, i.v. on days 3, 10 & 17).

Tumour growth inhibition from the start of treatment was assessed by comparison of the differences in tumour growth rate between control and the treatment groups described above, Figure 4.

Example 5: Tumour growth studies in Renca, a murine syngeneic renal carcinoma tumour model

Experiments were conducted on female mice (Balb/C genotype, at least 5 weeks old). Renca mouse tumour cells (Cancer Chemother Pharmacol . 1995; 36 (1): 7-12) were kindly provided by Dr. T. Fujioka at Department of Urology, Iwate Medical University School of Medicine. Renca mouse tumour cells (5×10^4) were implanted subcutaneously in the flank of mice on day 0. Mice were treated with either drug vehicle (0.85%w/v physiological saline at pH 5) or Compound 1 (0.1 or 1mg/kg twice a week) administered intravenously (i. v.) on days 1, 5, 8, 12, 15, and 19. Tumour volumes were assessed at least twice weekly by bilateral Vernier calliper measurements.

Tumour growth inhibition from the start of treatment was assessed by comparison of the differences in tumour growth rate between control and Compound 1 treated groups, Figure 3.

Example 6: Tumour metastasis studies in B16-BL6, a murine syngeneic melanoma lung metastasis tumour model

Experiments were conducted on female mice (C57BL/6J Jcl, at least 6 weeks old). B16-BL6 mouse melanoma cells (Am J Pathol. 1979;97(3):587-600, Cancer Res. 1980;40(5):1636-44) were kindly provided by Dr. I. Saiki at Hokkaido University. B16-BL6 mouse melanoma tumour cells (1×10^5) were injected intravenously into the tail vein of mice on day 0. Mice were treated with either drug vehicle (0.85%w/v physiological saline at pH 5) or Compound 1 (0.1 or 1mg/kg 4 times every 3 days) administered

intravenously (i. v.) on days 1, 4, 7, and 10. Mice were sacrificed on day 14, and the number of lung metastases was counted.

Tumour metastasis inhibition was assessed by comparison of the differences in the number of lung metastases between control and Compound 1 treated groups, Table 1.

5

Table 1 Tumour metastasis inhibition of Compound 1 in B16-BL6 lung metastasis model

Group	Regimen		Number of lung metastases
Vehicle	10 mL/kg	4q3d	29.7 $\pm$ 13.9
Compound 1	0.1 mg/kg	4q3d	9.2 $\pm$ 5.4 *
	1 mg/kg	4q3d	7.2 $\pm$ 3.1 *

The data are expressed as the mean $\pm$ SD of 6 mice.

* $p < 0.005$ vs vehicle (Wilcoxon test)

10

List of Figures

Figure 1: Plasma cytokine levels and percentage activated splenocytes taken from mice dosed i.v. with vehicle (saline) or Compound 1 (0.1, 1, 3mg/kg).

15 Figure 2: Compound 1 (1 & 0.1mg/kg i.v. twice weekly) vs. Vehicle Control (i.v. twice weekly) showed a maximum CT-26 tumour growth inhibition of 38.6 & 47.3% respectively ($p < 0.05$, 1 tailed t test) after 3 doses of treatment.

20 Figure 3: Compound 1 (1 & 0.1mg/kg i.v. twice weekly) vs. Vehicle Control (i.v. twice weekly) showed a maximum Renca tumour growth inhibition of 81.2 & 77.3% respectively ($p < 0.05$, Student's t test) on day 19.

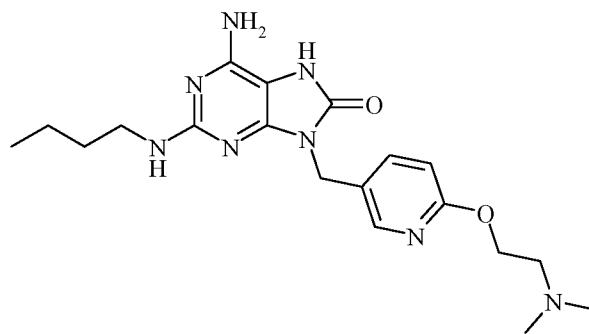
25 Figure 4: Compound 1 (1mg/kg i.v. once weekly), cyclophosphamide (50mg/kg i.p. once) or, Compound 1 (1mg/kg i.v. once weekly) + CY (50mg/kg i.p. once) vs. Vehicle Control (i.v. once weekly) showed a maximum CT-26 tumour growth inhibition of 65.8, 79.8 & 92.9% respectively ($p < 0.0005$, 1 tailed t test).

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Claims

1. A method of treatment or prophylaxis of cancer, which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I),
5 or a pharmaceutically acceptable salt thereof:



(I).

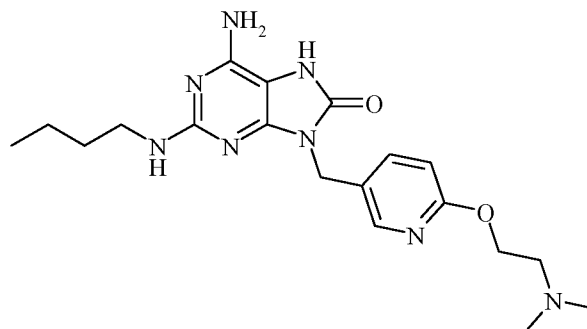
2. A method of treatment or prophylaxis of cancer according to Claim 1, wherein the
10 compound of Formula (I) is administered by injection.

3. A method of treatment or prophylaxis of cancer according to either of Claims 1 or 2, wherein the cancer is selected from prostate cancer, bladder cancer, breast cancer, lung cancer, uterus cancer, pancreatic cancer, liver cancer, renal cancer, colorectal cancer,
15 ovarian cancer, esophageal cancer, stomach cancer, skin cancer, cerebral tumor, head and neck cancer, malignant myeloma and lymphoproliferative tumor.

4. A method of treatment or prophylaxis of cancer according to Claim 3 wherein the cancer is selected from colorectal cancer, renal cancer and melanoma.

5. A method of treatment according to any one of Claims 1 to 4 wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a unit dose within the range of 0.0001-100, 0.0001-10, 0.0001-1, 0.0001-0.1, 0.0001-0.01 or 0.0001-0.001 mg/kg.

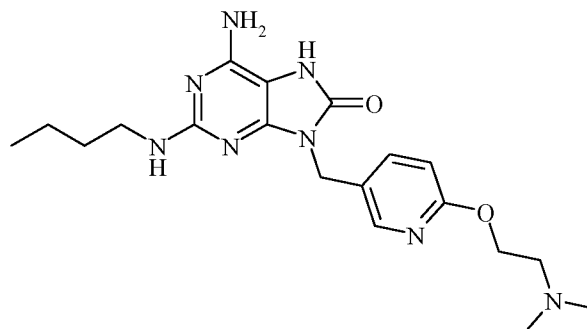
6. A compound of Formula (I), or a pharmaceutically acceptable salt thereof:



(I)

for use in the treatment or prophylaxis of cancer.

- 5 7. A compound according to Claim 6, wherein the compound is administered by injection.
8. A compound according to either one of Claims 6 or 7, wherein the cancer is selected from prostate cancer, bladder cancer, breast cancer, lung cancer, uterus cancer, pancreatic cancer, liver cancer, renal cancer, colorectal cancer, ovarian cancer, esophageal
10 cancer, stomach cancer, skin cancer, cerebral tumor, head and neck cancer, malignant myeloma and lymphoproliferative tumor.
9. A compound according to Claim 8, wherein the cancer is selected from colorectal
15 cancer, renal cancer and melanoma.
10. A compound according to any one of Claims 6 to 9, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a unit dose within the range of 0.0001-100, 0.0001-10, 0.0001-1, 0.0001-0.1, 0.0001-0.01 or 0.0001-
20 0.001 mg/kg.
11. Use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



(I)

for the preparation of a medicament for the treatment or prophylaxis of cancer.

5 12. A use according to Claim 11, wherein the compound is administered by injection.

13. A use according to either one of Claims 11 or 12, wherein the cancer is selected from prostate cancer, bladder cancer, breast cancer, lung cancer, uterus cancer, pancreatic cancer, liver cancer, renal cancer, colorectal cancer, ovarian cancer, esophageal cancer,
10 stomach cancer, skin cancer, cerebral tumor, head and neck cancer, malignant myeloma and lymphoproliferative tumor.

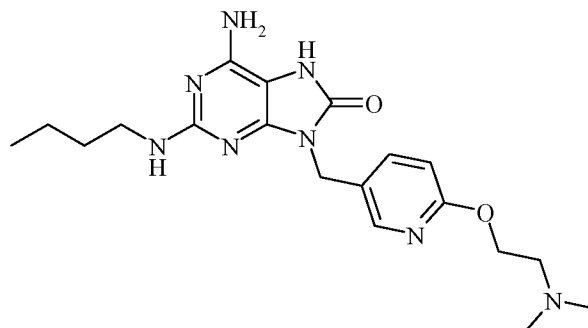
14. A use according to Claim 13, wherein the cancer is selected from colorectal cancer, renal cancer and melanoma.

15

15. A use according to any one of Claims 11 to 14, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a unit dose within the range of 0.0001-100, 0.0001-10, 0.0001-1, 0.0001-0.1, 0.0001-0.01 or 0.0001-0.001 mg/kg.

20

16. A medicament for the treatment or prophylaxis of cancer, comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



(I)

as an active ingredient.

- 5 17. A medicament according to Claim 16, wherein the compound is administered by injection.
18. A medicament according to either one of Claims 16 or 17, wherein the cancer is selected from prostate cancer, bladder cancer, breast cancer, lung cancer, uterus cancer,
10 pancreatic cancer, liver cancer, renal cancer, colorectal cancer, ovarian cancer, esophageal cancer, stomach cancer, skin cancer, cerebral tumor, head and neck cancer, malignant myeloma and lymphoproliferative tumor.
19. A medicament according to Claim 18, wherein the cancer is selected from
15 colorectal cancer, renal cancer and melanoma.
20. A medicament according to any one of Claims 16 to 19, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered at a unit dose within the range of 0.0001-100, 0.0001-10, 0.0001-1, 0.0001-0.1, 0.0001-0.01 or 0.0001-
20 0.001 mg/kg.

	Dose mg/kg	fold increase in CD69 +ve cells				Maximal Cytokine (fold increase on control value)					
		NK	NK-T	T	B	IL-6	IL-10	IL-12(P70)	IFN-gamma	IP-10	KC TNF-alpha
Compound 1	vehicle	1	1	1	1	1	1	1	1	1	1
	0.1	12	4	10	66	131	2	4	2	6	17
	1	15	4	11	77	143	3	4	2	6	49
	3	16	4	11	83	166	6	8	2	6	33

Figure 1

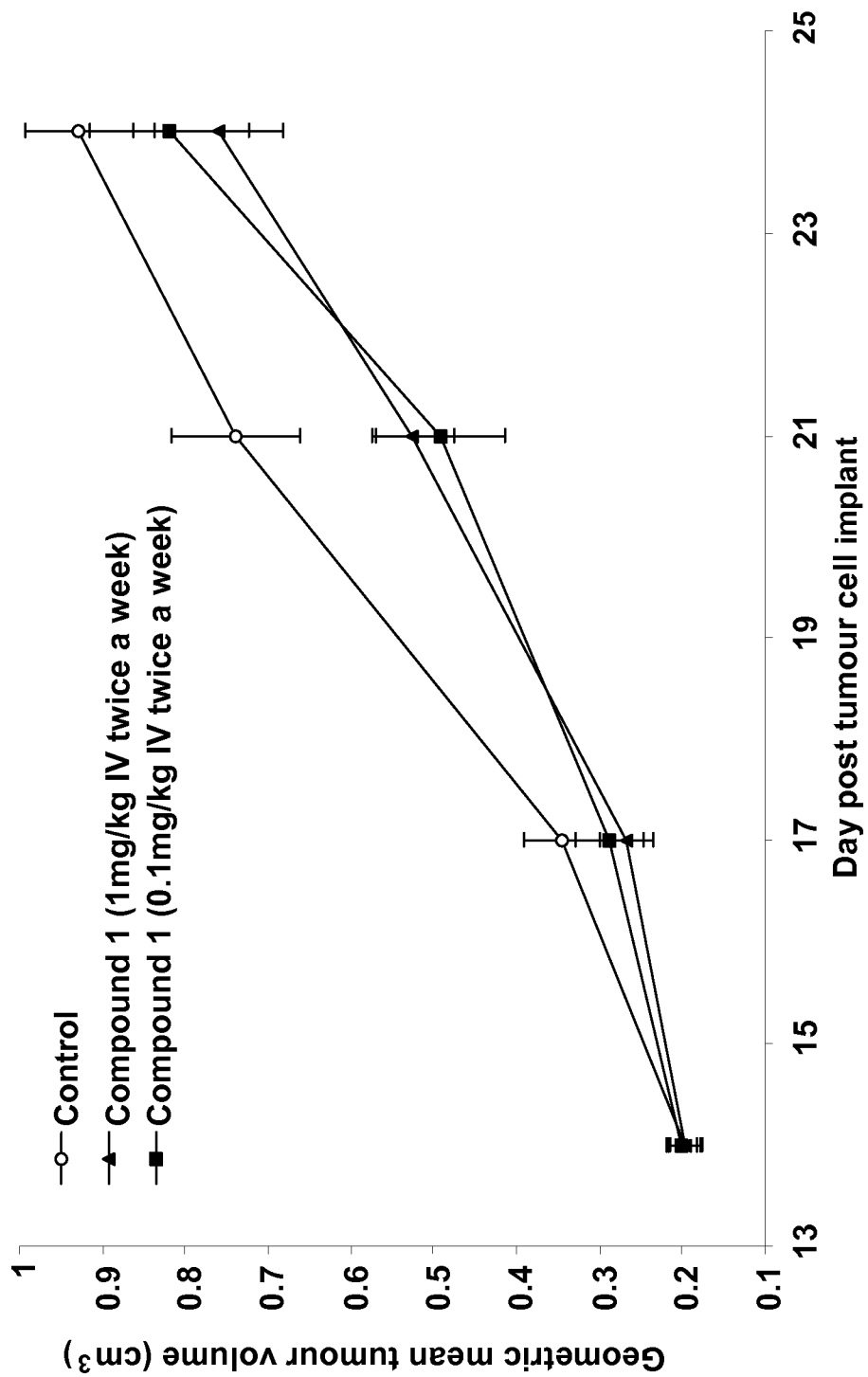


Figure 2

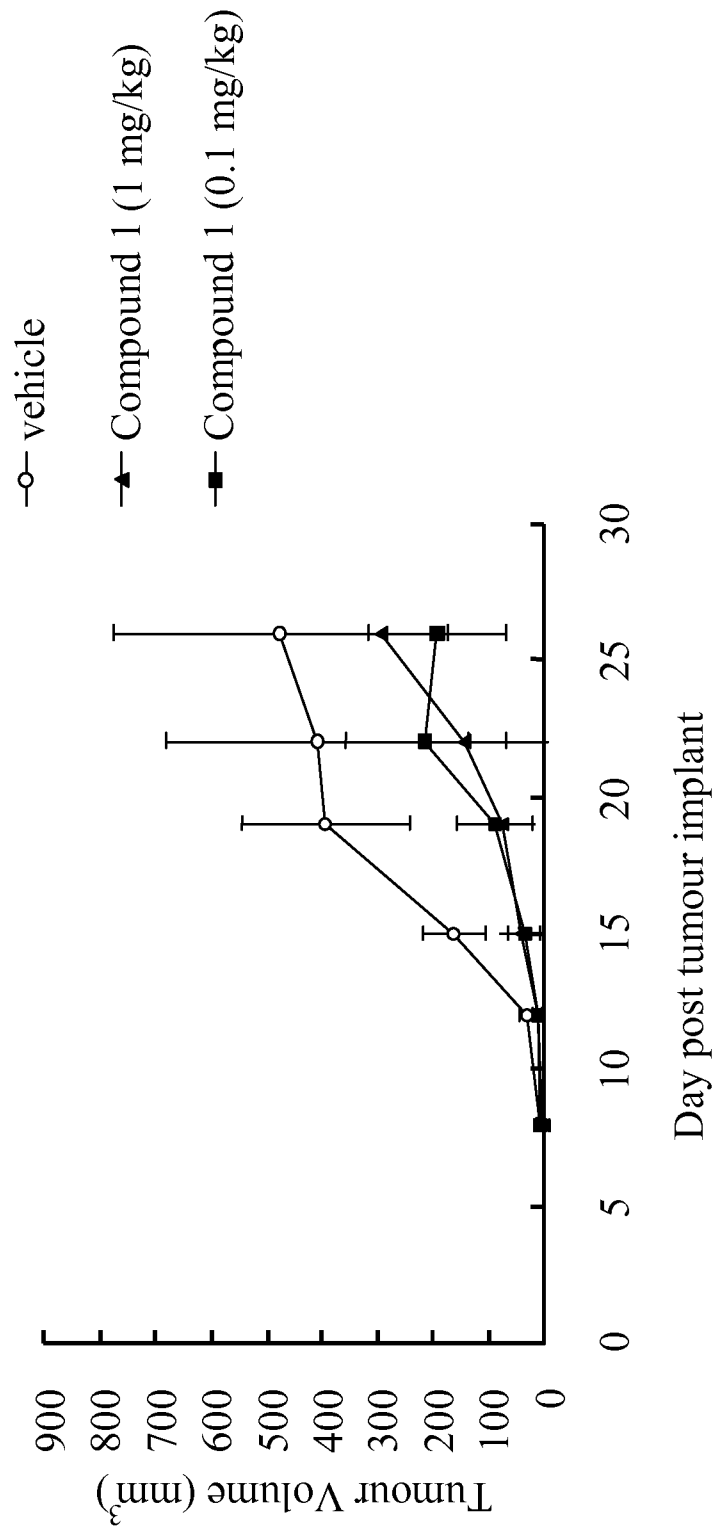


Figure 3

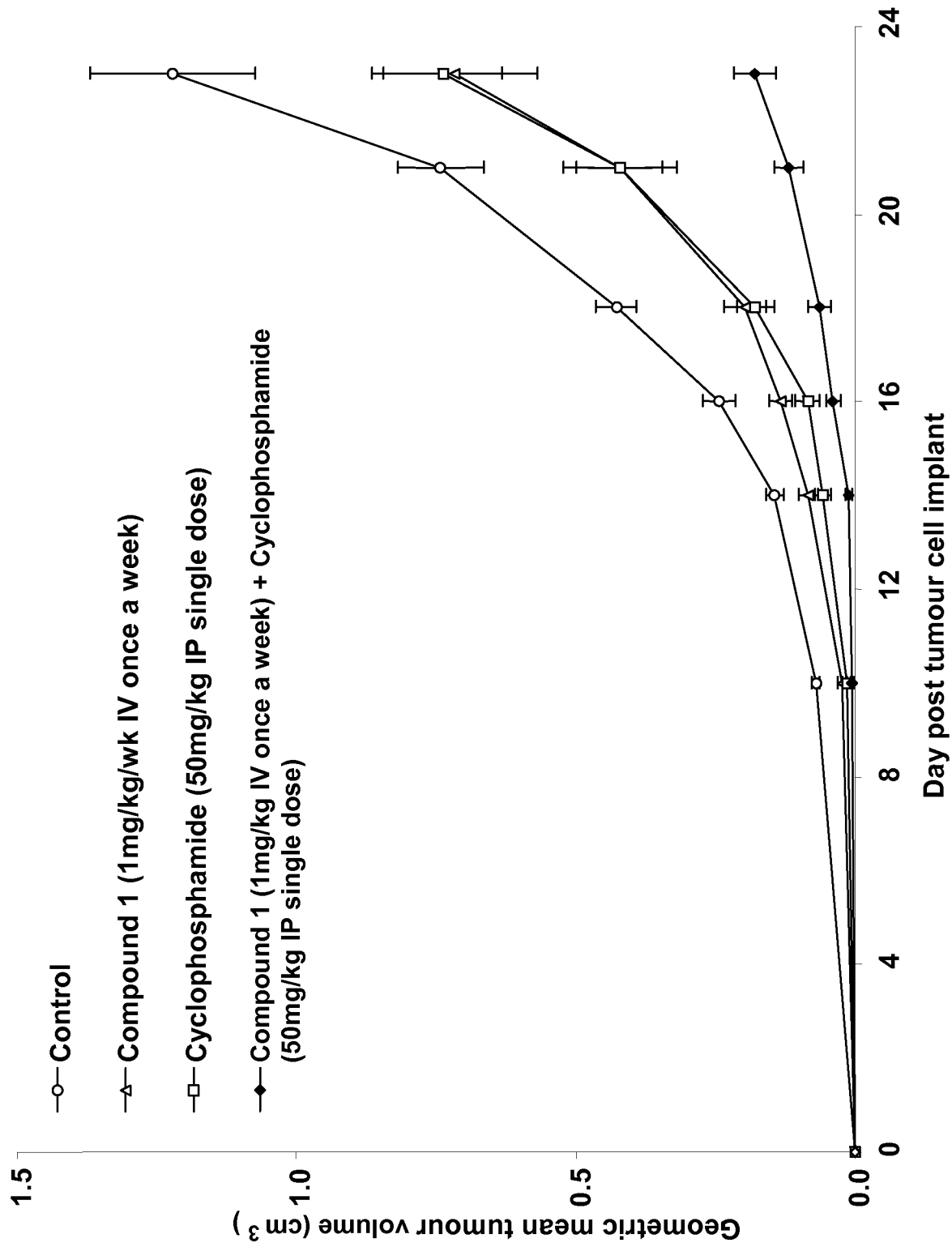


Figure 4

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2009/051036

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

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)

IPC: A61K, A61P, C07D

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

SE,DK,FI,NO classes as above

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

EPO-INTERNAL, WPI DATA, PAJ, CHEM. ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2008114817 A1 (DAINIPPON SUMITOMO PHARMA CO., LTD.), 25 Sept 2008 (25.09.2008), abstract, example 116 --	1-20
A	WO 02085905 A1, Japan Energy Corporation & Sumitomo Pharmaceuticals Co.Ltd, 31/10/2002: (abstract) Retrieved from: WPI database, WEEK 200302 , AN 2003-030131, examples --	1-20
A	JP2004137157 A1, Sumitomo Seiyaku KK, 13/05/2004: (abstract) Retrieved from: WPI database, WEEK 200435, AN: 2004-369091, examples --	1-20

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

* Special categories of cited documents:

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Date of the actual completion of the international search

23 October 2009

Date of mailing of the international search report

27-10-2009

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2009/051036

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-5
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 1-5 relate to a method for treatment of the human by therapy; see PCT rule 39.1(iv). Nevertheless, a search has been made for these claims. The search has been directed to the technical content of the claims.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2009/051036

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1939201 A1 (DAINIPPON SUMITOMO PHARMA CO. LTD.), 2 July 2008 (02.07.2008), abstract, examples 24-34 --	1-20
A	EP 1939202 A1 (DAINIPPON SUMITOMO PHARMA CO., LTD.), 2 July 2008 (02.07.2008), abstract, examples 12-18 --	1-20
A	WO 2007093901 A1 (PFIZER LIMITED), 23 August 2007 (23.08.2007), abstract, examples -- -----	1-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2009/051036

International patent classification (IPC)

A61K 31/522 (2006.01)

A61P 13/00 (2006.01)

A61P 17/00 (2006.01)

A61P 35/00 (2006.01)

C07D 473/28 (2006.01)

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SE2009/051036

WO	2008114817	A1	25/09/2008	AR	065784 A	01/07/2009
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EP	1939201	A1	02/07/2008	US	20090105212 A	23/04/2009
				WO	2007034917 A	29/03/2007
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				WO	2007034817 A	29/03/2007
WO	2007093901	A1	23/08/2007	AR	059481 A	09/04/2008
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				CA	2640672 A	23/08/2007
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				JP	2009528989 T	13/08/2009
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				MX	2008010611 A	12/11/2008
				NL	2000480 A	20/08/2007
				UY	30169 A	28/09/2007