also be induced indirectly through the recruitment of inflammatory cells (particularly macrophages) and their subsequent release of angiogenic cytokines (*e.g.*, TNF-α, b-FGF).

[5] A variety of other diseases and disorders are also associated with, or characterized by, undesired angiogenesis. For example, enhanced or unregulated angiogenesis has been implicated in a number of diseases and medical conditions including, but not limited to, ocular neovascular diseases, choroidal neovascular diseases, retina neovascular diseases, rubeosis (neovascularization of the angle), viral diseases, genetic diseases, inflammatory diseases, allergic diseases, and autoimmune diseases. Examples of such diseases and conditions include, but are not limited to: diabetic retinopathy; retinopathy of prematurity; corneal graft rejection; neovascular glaucoma; retrolental fibroplasia; arthritis; and proliferative vitreoretinopathy.

[6] Accordingly, compounds that can control angiogenesis or inhibit the production of certain cytokines, including TNF-α, may be useful in the treatment and prevention of various diseases and conditions.

[6a] WO 2008/11516 A2 discloses 4'-O-substituted isoindoline derivatives and compositions comprising them which may be useful in managing cancer and other diseases and conditions.

[6b] Nakamura et al. (Chem Pharm Bull, 54(12), 1709-1714, 2006) discloses mono- and dihydroxylated metabolites of thalidomide which may be useful for their TNF-α production inhibitory activity.

[6c] However, the above references do not disclose or suggest the presently disclosed compounds.

2.2 METHODS OF TREATING CANCER

[7] Current cancer therapy may involve surgery, chemotherapy, hormonal therapy and/or radiation treatment to eradicate neoplastic cells in a patient (*see*, *e.g.*, Stockdale, 1998, *Medicine*, vol. 3, Rubenstein and Federman, eds., Chapter 12, Section IV). Recently, cancer therapy could also involve biological therapy or immunotherapy. All of these approaches pose significant drawbacks for the patient. Surgery, for example, may be contraindicated due to the health or age of a patient or may be unacceptable to the patient.

[8] Additionally, surgery may not completely remove neoplastic tissue. Radiation therapy is only effective when the neoplastic tissue exhibits a higher sensitivity to radiation than normal tissue. Radiation therapy can also often elicit serious side effects. Hormonal therapy is rarely given as a single agent. Although hormonal therapy can be effective, it is often used to prevent or delay recurrence of cancer after other treatments have

removed the majority of cancer cells. Biological therapies and immunotherapies are limited in number and may produce side effects such as rashes or swellings, flu-like symptoms, including fever, chills and fatigue, digestive tract problems or allergic reactions.

[9] With respect to chemotherapy, there are a variety of chemotherapeutic agents available for treatment of cancer. A majority of cancer chemotherapeutics act by inhibiting DNA synthesis, either directly, or indirectly by inhibiting the biosynthesis of deoxyribonucleotide triphosphate precursors, to prevent DNA replication and concomitant

[102] Examples of cancer and precancerous conditions include, but are not limited to, those described in U.S. patent nos. 6,281,230 and 5,635,517 to Muller *et al.*, in various U.S. patent publications to Zeldis, including publication nos. 2004/0220144A1, published November 4, 2004 (Treatment of Myelodysplastic Syndrome); 2004/0029832A1, published February 12, 2004 (Treatment of Various Types of Cancer); and 2004/0087546, published May 6, 2004 (Treatment of Myeloproliferative Diseases). Examples also include those described in WO 2004/103274, published December 2, 2004. ~~All of these references are incorporated herein in their entireties by reference.~~

[103] Specific examples of cancer include, but are not limited to, cancers of the skin, such as melanoma; lymph node; breast; cervix; uterus; gastrointestinal tract; lung; ovary; prostate; colon; rectum; mouth; brain; head and neck; throat; testes; kidney; pancreas; bone; spleen; liver; bladder; larynx; nasal passages; and AIDS-related cancers. The compounds are also useful for treating cancers of the blood and bone marrow, such as multiple myeloma and acute and chronic leukemias, for example, lymphoblastic, myelogenous, lymphocytic, and myelocytic leukemias. The compounds provided herein can be used for treating, preventing or managing either primary or metastatic tumors.

[104] Other specific cancers include, but are not limited to, advanced malignancy, amyloidosis, neuroblastoma, meningioma, hemangiopericytoma, multiple brain metastase, glioblastoma multiforms, glioblastoma, brain stem glioma, poor prognosis malignant brain tumor, malignant glioma, recurrent malignant glioma, anaplastic astrocytoma, anaplastic oligodendroglioma, neuroendocrine tumor, rectal adenocarcinoma, Dukes C & D colorectal cancer, unresectable colorectal carcinoma, metastatic hepatocellular carcinoma, Kaposi's sarcoma, karotype acute myeloblastic leukemia, chronic lymphocytic leukemia (CLL), Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma, low grade follicular lymphoma, metastatic melanoma (localized melanoma, including, but not limited to, ocular melanoma), malignant mesothelioma, malignant pleural effusion mesothelioma syndrome, peritoneal carcinoma, papillary serous carcinoma, gynecologic sarcoma, soft tissue sarcoma, scleroderma, cutaneous vasculitis, Langerhans cell histiocytosis, leiomyosarcoma, fibrodysplasia ossificans progressive, hormone refractory prostate cancer, resected high-risk soft tissue sarcoma, unresectable hepatocellular carcinoma, Waldenstrom's macroglobulinemia, smoldering myeloma, indolent myeloma, fallopian tube cancer, androgen independent prostate cancer, androgen dependent stage IV non-metastatic prostate cancer, hormone-insensitive prostate cancer, chemotherapy-insensitive prostate cancer,

papillary thyroid carcinoma, follicular thyroid carcinoma, medullary thyroid carcinoma, and leiomyoma. In a specific embodiment, the cancer is metastatic. In another embodiment, the cancer is refractory or resistant to chemotherapy or radiation.

[105] In one embodiment, provided herein are methods of treating, preventing or managing various forms of leukemias such as chronic lymphocytic leukemia, chronic myelocytic leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia and acute myeloblastic leukemia, including leukemias that are relapsed, refractory or resistant, as disclosed in U.S. publication no. 2006/0030594, published February 9, 2006~~, which is incorporated in its entirety by reference~~.

[106] The term "leukemia" refers malignant neoplasms of the blood-forming tissues. The leukemia includes, but is not limited to, chronic lymphocytic leukemia, chronic myelocytic leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia and acute myeloblastic leukemia. The leukemia can be relapsed, refractory or resistant to conventional therapy. The term "relapsed" refers to a situation where patients who have had a remission of leukemia after therapy have a return of leukemia cells in the marrow and a decrease in normal blood cells. The term "refractory or resistant" refers to a circumstance where patients, even after intensive treatment, have residual leukemia cells in their marrow.

[107] In another embodiment, provided herein are methods of treating, preventing or managing various types of lymphomas, including Non-Hodgkin's lymphoma (NHL). The term "lymphoma" refers a heterogenous group of neoplasms arising in the reticuloendothelial and lymphatic systems. "NHL" refers to malignant monoclonal proliferation of lymphoid cells in sites of the immune system, including lymph nodes, bone marrow, spleen, liver and gastrointestinal tract. Examples of NHL include, but are not limited to, mantle cell lymphoma (MCL), lymphocytic lymphoma of intermediate differentiation, intermediate lymphocytic lymphoma (ILL), diffuse poorly differentiated lymphocytic lymphoma (PDL), centrocytic lymphoma, diffuse small-cleaved cell lymphoma (DSCCL), follicular lymphoma, and any type of the mantle cell lymphomas that can be seen under the microscope (nodular, diffuse, blastic and mantle zone lymphoma).

[108] Examples of diseases and disorders associated with, or characterized by, undesired angiogenesis include, but are not limited to, inflammatory diseases, autoimmune diseases, viral diseases, genetic diseases, allergic diseases, bacterial diseases, ocular neovascular diseases, choroidal neovascular diseases, retina neovascular diseases, and rubeosis (neovascularization of the angle). Specific examples of the diseases and disorders associated with, or characterized by, undesired angiogenesis include, but are not limited to,

arthritis, endometriosis, Crohn's disease, heart failure, advanced heart failure, renal impairment, endotoxemia, toxic shock syndrome, osteoarthritis, retrovirus replication, wasting, meningitis, silica-induced fibrosis, asbestos-induced fibrosis, veterinary disorder, malignancy-associated hypercalcemia, stroke, circulatory shock, periodontitis, gingivitis, macrocytic anemia, refractory anemia, and 5q-deletion syndrome.

[109] Examples of pain include, but are not limited to those described in U.S. patent publication no. 2005/0203142, published September 15, 2005~~, which is incorporated herein by reference~~. Specific types of pain include, but are not limited to, nociceptive pain, neuropathic pain, mixed pain of nociceptive and neuropathic pain, visceral pain, migraine, headache and post-operative pain.

[110] Examples of nociceptive pain include, but are not limited to, pain associated with chemical or thermal burns, cuts of the skin, contusions of the skin, osteoarthritis, rheumatoid arthritis, tendonitis, and myofascial pain.

[111] Examples of neuropathic pain include, but are not limited to, CRPS type I, CRPS type II, reflex sympathetic dystrophy (RSD), reflex neurovascular dystrophy, reflex dystrophy, sympathetically maintained pain syndrome, causalgia, Sudeck atrophy of bone, algoneurodystrophy, shoulder hand syndrome, post-traumatic dystrophy, trigeminal neuralgia, post herpetic neuralgia, cancer related pain, phantom limb pain, fibromyalgia, chronic fatigue syndrome, spinal cord injury pain, central post-stroke pain, radiculopathy, diabetic neuropathy, post-stroke pain, luetic neuropathy, and other painful neuropathic conditions such as those induced by drugs such as vincristine and velcade.

[112] As used herein, the terms "complex regional pain syndrome," "CRPS" and "CRPS and related syndromes" mean a chronic pain disorder characterized by one or more of the following: pain, whether spontaneous or evoked, including allodynia (painful response to a stimulus that is not usually painful) and hyperalgesia (exaggerated response to a stimulus that is usually only mildly painful); pain that is disproportionate to the inciting event (*e.g.*, years of severe pain after an ankle sprain); regional pain that is not limited to a single peripheral nerve distribution; and autonomic dysregulation (*e.g.*, edema, alteration in blood flow and hyperhidrosis) associated with trophic skin changes (hair and nail growth abnormalities and cutaneous ulceration).

[113] Examples of MD and related syndromes include, but are not limited to, those described in U.S. patent publication no. 2004/0091455, published May 13, 2004~~, which is incorporated herein by reference~~. Specific examples include, but are not limited to, atrophic (dry) MD, exudative (wet) MD, age-related maculopathy (ARM), choroidal

neovascularisation (CNVM), retinal pigment epithelium detachment (PED), and atrophy of retinal pigment epithelium (RPE).

[114] Examples of skin diseases include, but are not limited to, those described in U.S. publication no. 2005/0214328A1, published September 29, 2005~~, which is incorporated herein by reference~~. Specific examples include, but are not limited to, keratoses and related symptoms, skin diseases or disorders characterized with overgrowths of the epidermis, acne, and wrinkles.

[115] As used herein, the term "keratosis" refers to any lesion on the epidermis marked by the presence of circumscribed overgrowths of the horny layer, including but not limited to actinic keratosis, seborrheic keratosis, keratoacanthoma, keratosis follicularis (Darier disease), inverted follicular keratosis, palmoplantar keratoderma (PPK, keratosis palmaris et plantaris), keratosis pilaris, and stucco keratosis. The term "actinic keratosis" also refers to senile keratosis, keratosis senilis, verruca senilis, plana senilis, solar keratosis, keratoderma or keratoma. The term "seborrheic keratosis" also refers to seborrheic wart, senile wart, or basal cell papilloma. Keratosis is characterized by one or more of the following symptoms: rough appearing, scaly, erythematous papules, plaques, spicules or nodules on exposed surfaces (*e.g.*, face, hands, ears, neck , legs and thorax), excrescences of keratin referred to as cutaneous horns, hyperkeratosis, telangiectasias, elastosis, pigmented lentigines, acanthosis, parakeratosis, dyskeratoses, papillomatosis, hyperpigmentation of the basal cells, cellular atypia, mitotic figures, abnormal cell-cell adhesion, dense inflammatory infiltrates and small prevalence of squamous cell carcinomas.

[116] Examples of skin diseases or disorders characterized with overgrowths of the epidermis include, but are not limited to, any conditions, diseases or disorders marked by the presence of overgrowths of the epidermis, including but not limited to, infections associated with papilloma virus, arsenical keratoses, sign of Leser-Trélat, warty dyskeratoma (WD), trichostasis spinulosa (TS), erythrokeratodermia variabilis (EKV), ichthyosis fetalis (harlequin ichthyosis), knuckle pads, cutaneous melanoacanthoma, porokeratosis, psoriasis, squamous cell carcinoma, confluent and reticulated papillomatosis (CRP), acrochordons, cutaneous horn, cowden disease (multiple hamartoma syndrome), dermatosis papulosa nigra (DPN), epidermal nevus syndrome (ENS), ichthyosis vulgaris, molluscum contagiosum, prurigo nodularis, and acanthosis nigricans (AN).

[117] Examples of pulmonary disorders include, but are not limited to, those described in U.S. publication no. 2005/0239842A1, published October 27, 2005~~, which is incorporated herein by reference~~. Specific examples include pulmonary hypertension and

related disorders. Examples of pulmonary hypertension and related disorders include, but are not limited to: primary pulmonary hypertension (PPH); secondary pulmonary hypertension (SPH); familial PPH; sporadic PPH; precapillary pulmonary hypertension; pulmonary arterial hypertension (PAH); pulmonary artery hypertension; idiopathic pulmonary hypertension; thrombotic pulmonary arteriopathy (TPA); plexogenic pulmonary arteriopathy; functional classes I to IV pulmonary hypertension; and pulmonary hypertension associated with, related to, or secondary to, left ventricular dysfunction, mitral valvular disease, constrictive pericarditis, aortic stenosis, cardiomyopathy, mediastinal fibrosis, anomalous pulmonary venous drainage, pulmonary venoocclusive disease, collagen vasular disease, congenital heart disease, HIV virus infection, drugs and toxins such as fenfluramines, congenital heart disease, pulmonary venous hypertension, chronic obstructive pulmonary disease, interstitial lung disease, sleep-disordered breathing, alveolar hypoventilation disorder, chronic exposure to high altitude, neonatal lung disease, alveolar-capillary dysplasia, sickle cell disease, other coagulation disorder, chronic thromboemboli, connective tissue disease, lupus including systemic and cutaneous lupus, schistosomiasis, sarcoidosis or pulmonary capillary hemangiomatosis.

[118] Examples of asbestos-related disorders include, but not limited to, those described in U.S. publication no. 2005/0100529, published May 12, 2005~~, which is incorporated herein by reference~~. Specific examples include, but are not limited to, mesothelioma, asbestosis, malignant pleural effusion, benign exudative effusion, pleural plaques, pleural calcification, diffuse pleural thickening, rounded atelectasis, fibrotic masses, and lung cancer.

[119] Examples of parasitic diseases include, but are not limited to, those described in U.S. publication no. 2006/0154880, published July 13, 2006~~, which is incorporated herein by reference~~. Parasitic diseases include diseases and disorders caused by human intracellular parasites such as, but not limited to, *P. falcifarium*, *P. ovale*, *P. vivax*, *P. malariae*, *L. donovari*, *L. infantum*, *L. aethiopica*, *L. major*, *L. tropica*, *L. mexicana*, *L. braziliensis*, *T. Gondii*, *B. microti*, *B. divergens*, *B. coli*, *C. parvum*, *C. cayetanensis*, *E. histolytica*, *I. belli*, *S. mansonii*, *S. haematobium*, *Trypanosoma ssp.*, *Toxoplasma ssp.*, and *O. volvulus*. Other diseases and disorders caused by non-human intracellular parasites such as, but not limited to, *Babesia bovis*, *Babesia canis*, *Banesia Gibsoni*, *Besnoitia darlingi*, *Cytauxzoon felis*, *Eimeria ssp.*, *Hammondia ssp.*, and *Theileria ssp.*, are also encompassed. Specific examples include, but are not limited to, malaria, babesiosis, trypanosomiasis, leishmaniasis, toxoplasmosis, meningoencephalitis, keratitis, amebiasis, giardiasis,

cryptosporidiosis, isosporiasis, cyclosporiasis, microsporidiosis, ascariasis, trichuriasis, ancylostomiasis, strongyloidiasis, toxocariasis, trichinosis, lymphatic filariasis, onchocerciasis, filariasis, schistosomiasis, and dermatitis caused by animal schistosomes.

[120] Examples of immunodeficiency disorders include, but are not limited to, those described in U.S. application no. 11/289,723, filed November 30, 2005. Specific examples include, but not limited to, adenosine deaminase deficiency, antibody deficiency with normal or elevated Igs, ataxia-telangiectasia, bare lymphocyte syndrome, common variable immunodeficiency, Ig deficiency with hyper-IgM, Ig heavy chain deletions, IgA deficiency, immunodeficiency with thymoma, reticular dysgenesis, Nezelof syndrome, selective IgG subclass deficiency, transient hypogammaglobulinemia of infancy, Wistcott-Aldrich syndrome, X-linked agammaglobulinemia, X-linked severe combined immunodeficiency.

[121] Examples of CNS disorders include, but are not limited to, those described in U.S. publication no. 2005/0143344, published June 30, 2005~~, which is incorporated herein by reference~~. Specific examples include, but are not limited to, include, but are not limited to, Amyotrophic Lateral Sclerosis, Alzheimer Disease, Parkinson Disease, Huntington's Disease, Multiple Sclerosis other neuroimmunological disorders such as Tourette Syndrome, delerium, or disturbances in consciousness that occur over a short period of time, and amnestic disorder, or discreet memory impairments that occur in the absence of other central nervous system impairments.

[122] Examples of CNS injuries and related syndromes include, but are not limited to, those described in U.S. publication no. 2006/0122228, published June 8, 2006~~, which is incorporated herein by reference~~. Specific examples include, but are not limited to, CNS injury/damage and related syndromes, include, but are not limited to, primary brain injury, secondary brain injury, traumatic brain injury, focal brain injury, diffuse axonal injury, head injury, concussion, post-concussion syndrome, cerebral contusion and laceration, subdural hematoma, epidermal hematoma, post-traumatic epilepsy, chronic vegetative state, complete SCI, incomplete SCI, acute SCI, subacute SCI, chronic SCI, central cord syndrome, Brown-Sequard syndrome, anterior cord syndrome, conus medullaris syndrome, cauda equina syndrome, neurogenic shock, spinal shock, altered level of consciousness, headache, nausea, emesis, memory loss, dizziness, diplopia, blurred vision, emotional lability, sleep disturbances, irritability, inability to concentrate, nervousness, behavioral impairment, cognitive deficit, and seizure.

[123] Other disease or disorders include, but not limited to, viral, genetic, allergic, and autoimmune diseases. Specific examples include, but not limited to, HIV, hepatitis, adult respiratory distress syndrome, bone resorption diseases, chronic pulmonary inflammatory diseases, dermatitis, cystic fibrosis, septic shock, sepsis, endotoxic shock, hemodynamic shock, sepsis syndrome, post ischemic reperfusion injury, meningitis, psoriasis, fibrotic disease, cachexia, graft versus host disease, graft rejection, auto-immune disease, rheumatoid spondylitis, Crohn's disease, ulcerative colitis, inflammatory-bowel disease, multiple sclerosis, systemic lupus erythematosus, ENL in leprosy, radiation damage, cancer, asthma, or hyperoxic alveolar injury.

[124] Examples of atherosclerosis and related conditions include, but are not limited to, those disclosed in U.S. publication no. 2002/0054899, published May 9, 2002, ~~which is incorporated herein by reference~~. Specific examples include, but are not limited to, all forms of conditions involving atherosclerosis, including restenosis after vascular intervention such as angioplasty, stenting, atherectomy and grafting. All forms of vascular intervention are contemplated herein, including diseases of the cardiovascular and renal system, such as, but not limited to, renal angioplasty, percutaneous coronary intervention (PCI), percutaneous transluminal coronary angioplasty (PTCA), carotid percutaneous transluminal angioplasty (PTA), coronary by-pass grafting, angioplasty with stent implantation, peripheral percutaneous transluminal intervention of the iliac, femoral or popliteal arteries, and surgical intervention using impregnated artificial grafts. The following chart provides a listing of the major systemic arteries that may be in need of treatment, all of which are contemplated herein:

[125] Examples of dysfunctional sleep and related syndromes include, but are not limited to, those disclosed in U.S. publication no. 2005/0222209A1, published October 6, 2005, ~~which is incorporated herein by reference~~. Specific examples include, but are not limited to, snoring, sleep apnea, insomnia, narcolepsy, restless leg syndrome, sleep terrors, sleep walking sleep eating, and dysfunctional sleep associated with chronic neurological or inflammatory conditions. Chronic neurological or inflammatory conditions, include, but are not limited to, Complex Regional Pain Syndrome, chronic low back pain, musculoskeletal pain, arthritis, radiculopathy, pain associated with cancer, fibromyalgia, chronic fatigue syndrome, visceral pain, bladder pain, chronic pancreatitis, neuropathies (diabetic, post-herpetic, traumatic or inflammatory), and neurodegenerative disorders such as Parkinson's Disease, Alzheimer's Disease, amyotrophic lateral sclerosis, multiple sclerosis, Huntington's Disease, bradykinesia; muscle rigidity; parkinsonian tremor; parkinsonian gait; motion freezing; depression; defective long-term memory, Rubinstein-Taybi syndrome (RTS); dementia; postural instability; hypokinetic disorders; synuclein disorders; multiple system atrophies; striatonigral degeneration; olivopontocerebellar atrophy; Shy-Drager syndrome; motor neuron disease with parkinsonian features; Lewy body dementia; Tau pathology disorders; progressive supranuclear palsy; corticobasal degeneration; frontotemporal dementia; amyloid pathology disorders; mild cognitive impairment; Alzheimer disease with parkinsonism; Wilson disease; Hallervorden-Spatz disease; Chediak-Hagashi disease; SCA-3 spinocerebellar ataxia; X-linked dystonia parkinsonism; prion disease; hyperkinetic disorders; chorea; ballismus; dystonia tremors; Amyotrophic Lateral Sclerosis (ALS); CNS trauma and myoclonus.

[126] Examples of hemoglobinopathy and related disorders include, but are not limited to, those described in U.S. publication no. 2005/0143420A1, published June 30, 2005, ~~which is incorporated herein by reference~~. Specific examples include, but are not limited to, hemoglobinopathy, sickle cell anemia, and any other disorders related to the differentiation of CD34+ cells.

[127] Examples of TNFα related disorders include, but are not limited to, those described in WO 98/03502 and WO 98/54170, ~~both of which are incorporated herein in their entireties by reference~~. Specific examples include, but are not limited to: endotoxemia or toxic shock syndrome; cachexia; adult respiratory distress syndrome; bone resorption diseases such as arthritis; hypercalcemia; Graft versus Host Reaction; cerebral malaria; inflammation; tumor growth; chronic pulmonary inflammatory diseases; reperfusion injury; myocardial infarction; stroke; circulatory shock; rheumatoid arthritis;

Crohn's disease; HIV infection and AIDS; other disorders such as rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, psoriatic arthritis and other arthritic conditions, septic shock, sepsis, endotoxic shock, graft versus host disease, wasting, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythromatosis, ENL in leprosy, HIV, AIDS, and opportunistic infections in AIDS; disorders such as septic shock, sepsis, endotoxic shock, hemodynamic shock and sepsis syndrome, post ischemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic disease, cachexia, graft rejection, oncogenic or cancerous conditions, asthma, autoimmune disease, radiation damages, and hyperoxic alveolar injury; viral infections, such as those caused by the herpes viruses; viral conjunctivitis; or atopic dermatitis.

[128] In other embodiments, the use of compounds provided herein in various immunological applications, *i.e.*, use of compounds provided herein in combination with a vaccination, for example, as vaccine adjuvant. Although any methods and manners of use of compounds provided herein in combination with a vaccine are contemplated herein, a non-limiting example of such uses is the use of compounds provided herein as vaccine adjuvants, according to the administration regimens disclosed in U.S. Provisional Application No. 60/712,823, filed September 1, 2005~~, which is incorporated herein in its entirety by reference~~. These embodiments also relate to the uses of compounds provided herein in combination with vaccines to treat or prevent cancer or infectious diseases, and other various uses of compounds provided herein, such as, but not limited to, reduction or desensitization of allergic reactions.

[129] Doses of a compound provided herein, or a pharmaceutically acceptable salt, solvate, clathrate, stereoisomer or prodrug thereof, vary depending on factors such as: specific indication to be treated, prevented, or managed; age and condition of a patient; and amount of second active agent used, if any. Generally, a compound provided herein, or a pharmaceutically acceptable salt, solvate, clathrate, stereoisomer or prodrug thereof, may be used in an amount of from about 0.1 mg to about 500 mg per day, and can be adjusted in a conventional fashion (*e.g.*, the same amount administered each day of the treatment, prevention or management period), in cycles (*e.g.*, one week on, one week off), or in an amount that increases or decreases over the course of treatment, prevention, or management. In other embodiments, the dose can be from about 1 mg to about 300 mg, from about 0.1 mg to about 150 mg, from about 1 mg to about 200 mg, from about 10 mg to about 100 mg, from about 0.1 mg to about 50 mg, from about 1 mg to about 50 mg, from about 10 mg to about 50 mg, from about 20 mg to about 30 mg, or from about 1 mg to about 20 mg.

raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer.

[136] Specific second active agents include, but are not limited to, 2-methoxyestradiol, telomestatin, inducers of apoptosis in mutiple myeloma cells (such as, for example, TRAIL), statins, semaxanib, cyclosporin, etanercept, doxycycline, bortezomib, oblimersen (Genasense®), remicade, docetaxel, celecoxib, melphalan, dexamethasone (Decadron®), steroids, gemcitabine, cisplatinum, temozolomide, etoposide, cyclophosphamide, temodar, carboplatin, procarbazine, gliadel, tamoxifen, topotecan, methotrexate, Arisa®, taxol, taxotere, fluorouracil, leucovorin, irinotecan, xeloda, CPT-11, interferon alpha, pegylated interferon alpha (*e.g.*, PEG INTRON-A), capecitabine, cisplatin, thiotepa, fludarabine, carboplatin, liposomal daunorubicin, cytarabine, doxetaxol, pacilitaxel, vinblastine, IL-2, GM-CSF, dacarbazine, vinorelbine, zoledronic acid, palmitronate, biaxin, busulphan, prednisone, bisphosphonate, arsenic trioxide, vincristine, doxorubicin (Doxil®), paclitaxel, ganciclovir, adriamycin, estramustine sodium phosphate (Emcyt®), sulindac, and etoposide.

[137] In another embodiment, examples of specific second agents according to the indications to be treated, prevented, or managed can be found in the following references,

all of which are incorporated herein in their entireties: U.S. patent nos. 6,281,230 and 5,635,517; U.S. publication nos. 2004/0220144, 2004/0190609, 2004/0087546, 2005/0203142, 2004/0091455, 2005/0100529, 2005/0214328, 2005/0239842, 2006/0154880, 2006/0122228,and 2005/0143344; and U.S. provisional application no. 60/631,870.

[138] Examples of second active agents that may be used for the treatment, prevention and/or management of pain include, but are not limited to, conventional therapeutics used to treat or prevent pain such as antidepressants, anticonvulsants, antihypertensives, anxiolytics, calcium channel blockers, muscle relaxants, non-narcotic analgesics, opioid analgesics, anti-inflammatories, cox-2 inhibitors, immunomodulatory agents, alpha-adrenergic receptor agonists or antagonists, immunosuppressive agents, corticosteroids, hyperbaric oxygen, ketamine, other anesthetic agents, NMDA antagonists, and other therapeutics found, for example, in the *Physician's Desk Reference* 2003. Specific examples include, but are not limited to, salicylic acid acetate (Aspirin®), celecoxib (Celebrex®), Enbrel®, ketamine, gabapentin (Neurontin®), phenytoin (Dilantin®), carbamazepine (Tegretol®), oxcarbazepine (Trileptal®), valproic acid (Depakene®), morphine sulfate, hydromorphone, prednisone, griseofulvin, penthonium, alendronate, dyphenhydramide, guanethidine, ketorolac (Acular®), thyrocalcitonin, dimethylsulfoxide (DMSO), clonidine (Catapress®), bretylium, ketanserin, reserpine, droperidol, atropine, phentolamine, bupivacaine, lidocaine, acetaminophen, nortriptyline (Pamelor®), amitriptyline (Elavil®), imipramine (Tofranil®), doxepin (Sinequan®), clomipramine (Anafranil®), fluoxetine (Prozac®), sertraline (Zoloft®), naproxen, nefazodone (Serzone®), venlafaxine (Effexor®), trazodone (Desyrel®), bupropion (Wellbutrin®), mexiletine, nifedipine, propranolol, tramadol, lamotrigine, vioxx, ziconotide, ketamine, dextromethorphan, benzodiazepines, baclofen, tizanidine and phenoxybenzamine.

[139] Examples of second active agents that may be used for the treatment, prevention and/or management of macular degeneration and related syndromes include, but are not limited to, a steroid, a light sensitizer, an integrin, an antioxidant, an interferon, a xanthine derivative, a growth hormone, a neutrotrophic factor, a regulator of neovascularization, an anti-VEGF antibody, a prostaglandin, an antibiotic, a phytoestrogen, an anti-inflammatory compound or an antiangiogenesis compound, or a combination thereof. Specific examples include, but are not limited to, verteporfin, purlytin, an angiostatic steroid, rhuFab, interferon-2α, pentoxifylline, tin etiopurpurin, motexafin, lucentis, lutetium, 9-fluoro-11,21-dihydroxy-16,

17-1-methylethylidinebis(oxy)pregna-1,4-diene-3,20-dione, latanoprost (see U.S. Patent No. 6,225,348), tetracycline and its derivatives, rifamycin and its derivatives, macrolides, metronidazole (U.S. Patent Nos. 6,218,369 and 6,015,803), genistein, genistin, 6'-O-Mal genistin, 6'-O-Ac genistin, daidzein, daidzin, 6'-O-Mal daidzin, 6'-O-Ac daidzin, glycitein, glycitin, 6'-O-Mal glycitin, biochanin A, formononetin (U.S. Patent No. 6,001,368), triamcinolone acetomide, dexamethasone (U.S. Patent No. 5,770,589), thalidomide, glutathione (U.S. Patent No. 5,632,984), basic fibroblast growth factor (bFGF), transforming growth factor b (TGF-b), brain-derived neurotrophic factor (BDNF), plasminogen activator factor type 2 (PAI-2), EYE101 (Eyetech Pharmaceuticals), LY333531 (Eli Lilly), Miravant, and RETISERT implant (Bausch & Lomb). ~~All of the references cited herein are incorporated in their entireties by reference.~~

[140] Examples of second active agents that may be used for the treatment, prevention and/or management of skin diseases include, but are not limited to, keratolytics, retinoids, α-hydroxy acids, antibiotics, collagen, botulinum toxin, interferon, steroids, and immunomodulatory agents. Specific examples include, but are not limited to, 5-fluorouracil, masoprocol, trichloroacetic acid, salicylic acid, lactic acid, ammonium lactate, urea, tretinoin, isotretinoin, antibiotics, collagen, botulinum toxin, interferon, corticosteroid, transretinoic acid and collagens such as human placental collagen, animal placental collagen, Dermalogen, AlloDerm, Fascia, Cymetra, Autologen, Zyderm, Zyplast, Resoplast, and Isolagen.

[141] Examples of second active agents that may be used for the treatment, prevention and/or management of pulmonary hypertension and related disorders include, but are not limited to, anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, vasodilators, prostacyclin analogues, endothelin antagonists, phosphodiesterase inhibitors (e.g., PDE V inhibitors), endopeptidase inhibitors, lipid lowering agents, thromboxane inhibitors, and other therapeutics known to reduce pulmonary artery pressure. Specific examples include, but are not limited to, warfarin (Coumadin®), a diuretic, a cardiac glycoside, digoxin-oxygen, diltiazem, nifedipine, a vasodilator such as prostacyclin (*e.g.*, prostaglandin I2 (PGI2), epoprostenol (EPO, Floran®), treprostinil (Remodulin®), nitric oxide (NO), bosentan (Tracleer®), amlodipine, epoprostenol (Floran®), treprostinil (Remodulin®), prostacyclin, tadalafil (Cialis®), simvastatin (Zocor®), omapatrilat (Vanlev®), irbesartan (Avapro®), pravastatin (Pravachol®), digoxin, L-arginine, iloprost, betaprost, and sildenafil (Viagra®).

[178] Lubricants that can be used in pharmaceutical compositions and dosage forms include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures thereof. If used at all, lubricants may be used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

[179] In one embodiment, a solid oral dosage form comprises a compound provided herein, anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

4.5.2 Controlled Release Dosage Forms

[180] Active ingredients such as the compounds provided herein can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,376,461; 6,419,961; 6,589,548; 6,613,358; 6,699,500 ~~each of which is incorporated herein by reference~~. Such dosage forms can be used to provide slow or controlled release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients provided herein. Thus, the compositions provided encompass single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled release.

polyvinyl acetate, that is surrounded by an outer polymeric membrane, e.g., polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The active ingredient then diffuses through the outer polymeric membrane in a release rate controlling step. The percentage of active ingredient in such parenteral compositions is highly dependent on the specific nature thereof, as well as the needs of the subject.

1.1.3 PARENTERAL DOSAGE FORMS

[184] Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. In some embodiments, administration of a parenteral dosage form bypasses patients' natural defenses against contaminants, and thus, in these embodiments, parenteral dosage forms are sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

[185] Suitable vehicles that can be used to provide parenteral dosage forms are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

[186] Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms. For example, cyclodextrin and its derivatives can be used to increase the solubility of a compound provided herein. *See, e.g.*, U.S. Patent No. 5,134,127~~, which is incorporated herein by reference~~.

compound provided herein. Luciferase activity is assayed using luciferase lysis buffer and substrate (Promega) and measured using a luminometer (Turner Designs).

1.1.8 TNFA INHIBITION

[906] Using procedures substantially similar to those provided in Section 5.309.1 above, IC_{50} values for certain of the compounds provided herein for TNFα inhibition were determined. Tested compounds include the compounds of Examples 5.2, 5.6-5.24, 5.29-5.46, 5.48-5.69, 5.71-5.133, 5.136-5.143, 5.151-5.155, 5.158-5.188, 5.193-5.201, 5.207, 5.224-5.289, 5.293-5.296 and 5.299-5.308.

[907] The determined IC_{50} values ranged from about 0.02 nM to about 2 μM. These results show that compounds provided herein are useful as inhibitors of TNFα.

5.309.9 IL-2 Production

[908] Using procedures substantially similar to those described in Section 5.309.2. above, EC_{50} values of certain compounds provided herein for the production of IL-2 were also determined. Tested compounds include the compounds of Examples 5.2, 5.6-5.24, 5.30-5.46, 5.48-5.57, 5.59-5.69, 5.71-5.133, 5.136-5.137, 5.139-5.143, 5.151-5.188, 5.194-5.201, 5.207, 5.216-5.289, 5.293-5.296, 5.300 and 5.303-5.308.

[909] The determined EC_{50} values ranged from about 0.01 nM to about 1.4 μM. These results show that compounds provided herein are useful as stimulators of IL-2 production.

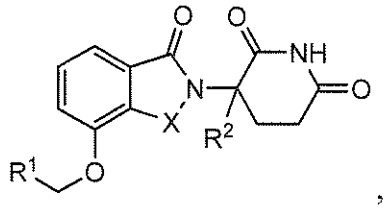
~~[910] The embodiments described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the claimed subject matter and are encompassed by the appended claims.~~

[910~~11~~] ~~All of the patents, patent applications and publications referred to herein are incorporated herein in their entireties.~~ Citation or identification of any reference in this application is not an admission that such reference is available as prior art to the claimed subject matter. The full scope of the invention is better understood with reference to the appended claims.

CLAIMS

What is claimed is:

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, wherein:

X is C=O ~~or CH_2~~;

R^1 is -Y-R^3;

R^2 is H or (C_1-C_6)alkyl;

Y is: 6 to 10 membered aryl, heteroaryl or heterocycle, each of which may be optionally substituted with one or more halogen; ~~or a bond;~~

R^3 is: -$(CH_2)_n$-aryl, -O-$(CH_2)_n$-aryl or -$(CH_2)_n$-O-aryl, wherein the aryl is optionally substituted with one or more: (C_1-C_6)alkyl, itself optionally substituted with one or more halogen; (C_1-C_6)alkoxy, itself substituted with one or more halogen; oxo; amino; carboxyl; cyano; hydroxyl; halogen; deuterium; 6 to 10 membered aryl or heteroaryl, optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)alkoxy or halogen; -$CONH_2$; or -COO-(C_1-C_6)alkyl, wherein the alkyl may be optionally substituted with one or more halogen;

-$(CH_2)_n$-heterocycle, -O-$(CH_2)_n$-heterocycle or -$(CH_2)_n$-O-heterocycle, wherein the heterocycle is optionally substituted with one or more: (C_1-C_6)alkyl, itself optionally substituted with one or more halogen; (C_1-C_6)alkoxy, itself substituted with one or more halogen; oxo; amino; carboxyl; cyano; hydroxyl; halogen; deuterium; 6 to 10 membered aryl or heteroaryl, optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)alkoxy or halogen; -$CONH_2$; or -COO-(C_1-C_6)alkyl, wherein the alkyl may be optionally substituted with one or more halogen; or

-$(CH_2)_n$-heteroaryl, -O-$(CH_2)_n$-heteroaryl or -$(CH_2)_n$-O-heteroaryl, wherein the heteroaryl is optionally substituted with one or more: (C_1-C_6)alkyl, itself optionally substituted with one or more halogen; (C_1-C_6)alkoxy, itself substituted with one or more halogen; oxo; amino; carboxyl; cyano;

hydroxyl; halogen; deuterium; 6 to 10 membered aryl or heteroaryl, optionally substituted with one or more (C_1-C_6)alkyl, (C_1-C_6)alkoxy or halogen; -$CONH_2$; or -COO-(C_1-C_6)alkyl, wherein the alkyl may be optionally substituted with one or more halogen; and

n is 0, 1, 2 or 3.

~~2. The compound of claim 1, wherein X is CH_2.~~

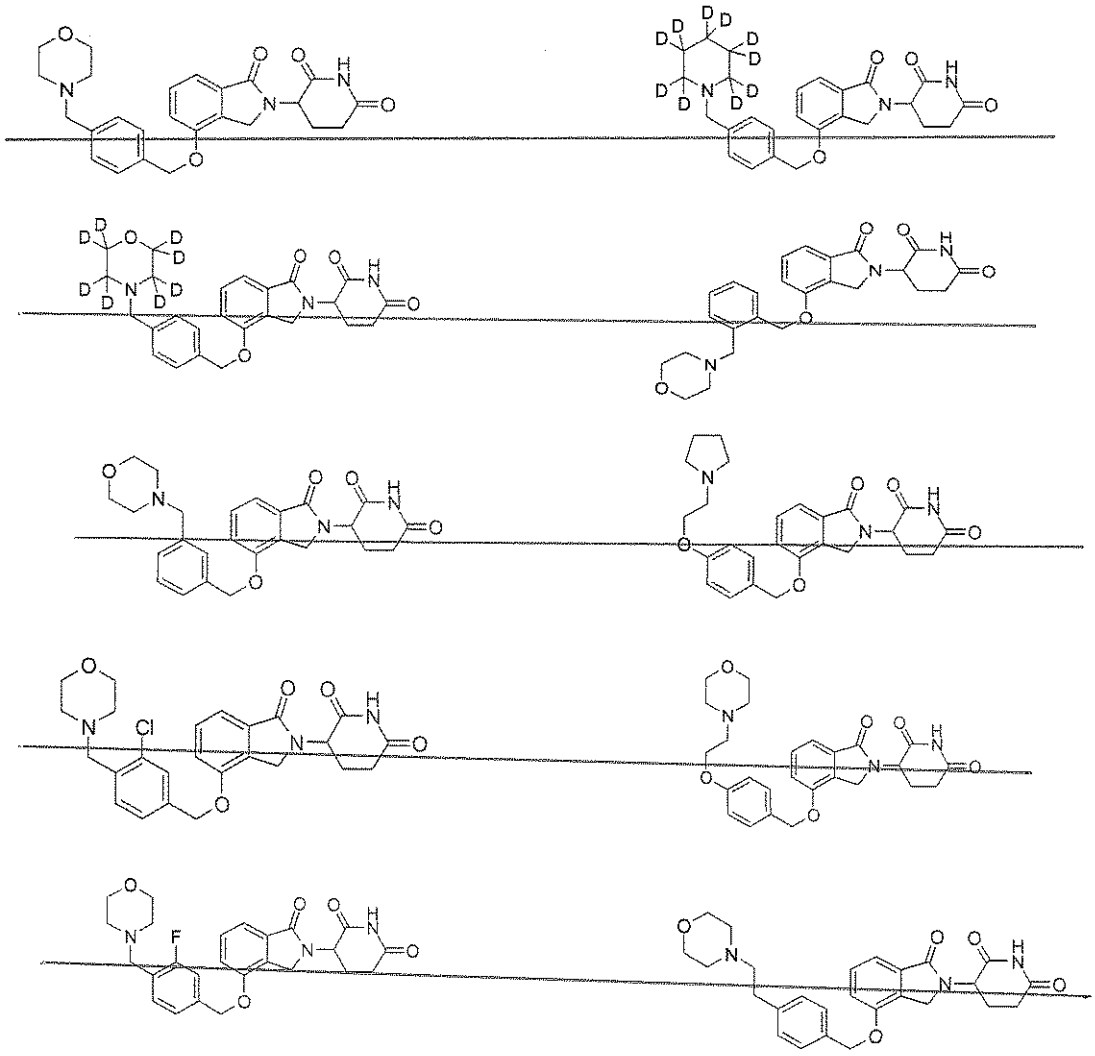
~~3~~2. The compound of claim 1, wherein Y is phenyl, and R^3 is -$(CH_2)_n$-heterocycle.

~~4~~3. The compound of claim 1, wherein Y is heteroaryl, and R^3 is -$(CH_2)_n$-heterocycle.

~~5. The compound of claim 1, wherein Y is a bond.~~

~~6. The compound of claim 1, wherein Y is a bond, and R^3 is -$(CH_2)_n$-heterocycle or -$(CH_2)_n$-heteroaryl.~~

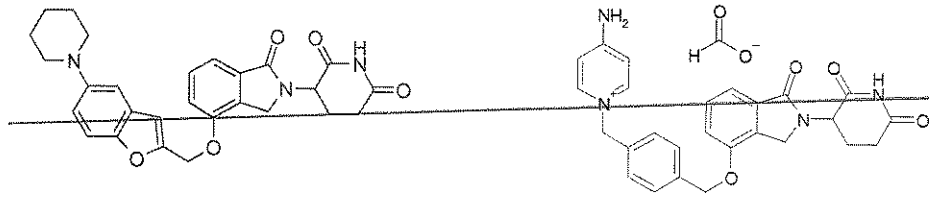
~~7~~4. The compound of claim 1, which is:

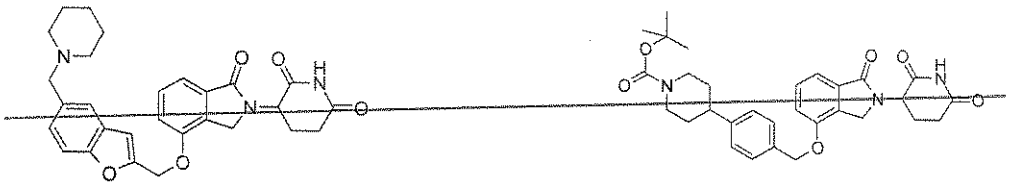


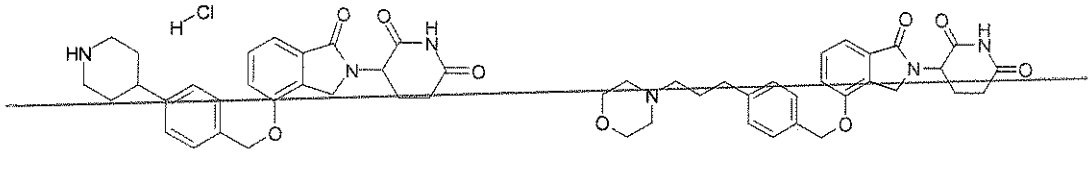


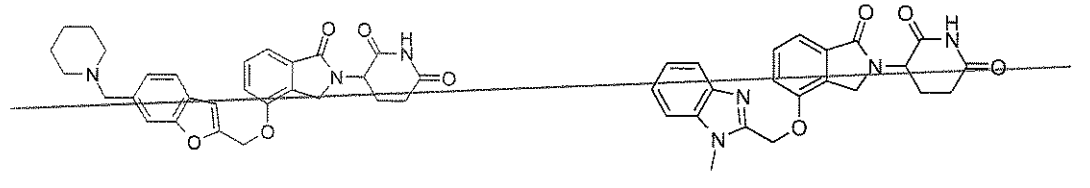






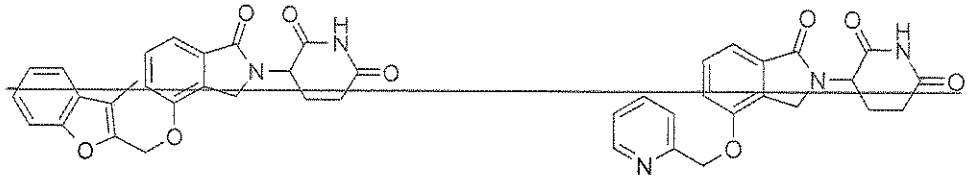


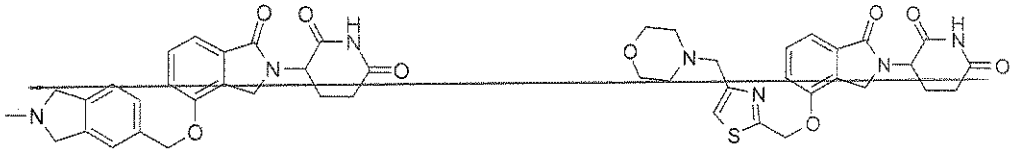


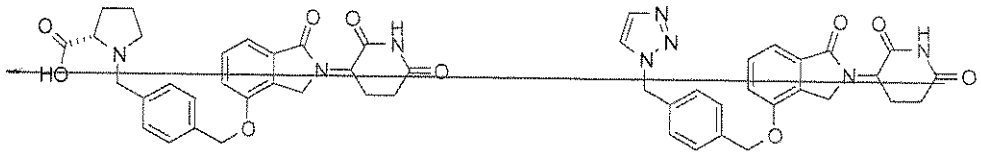


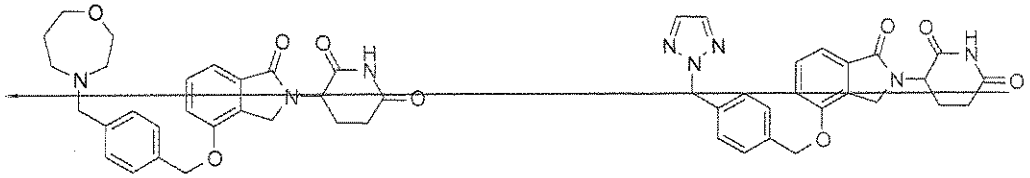


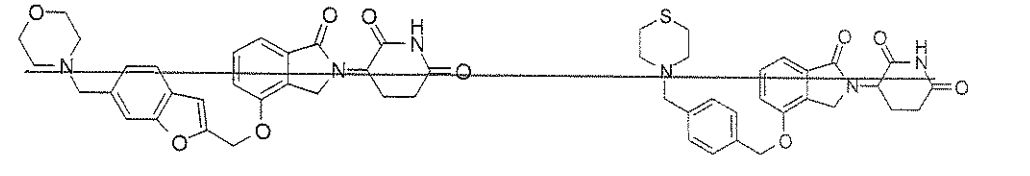


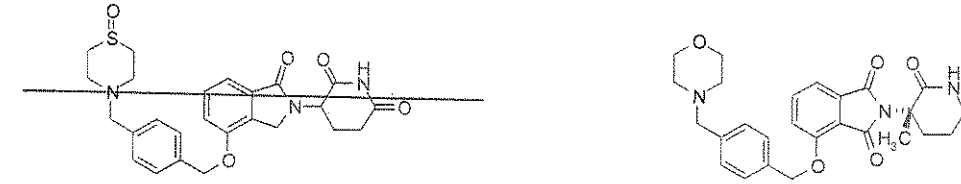


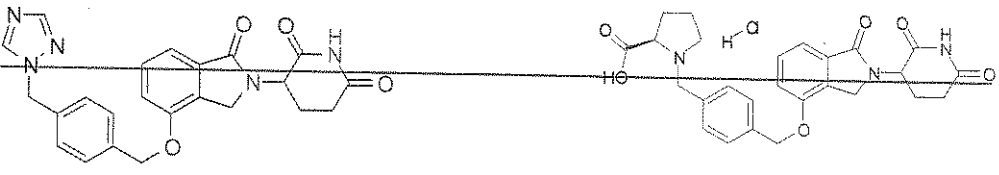


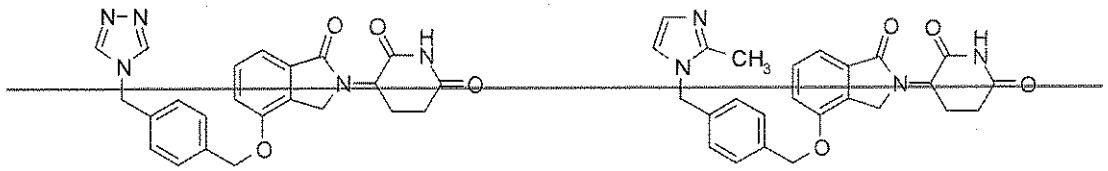


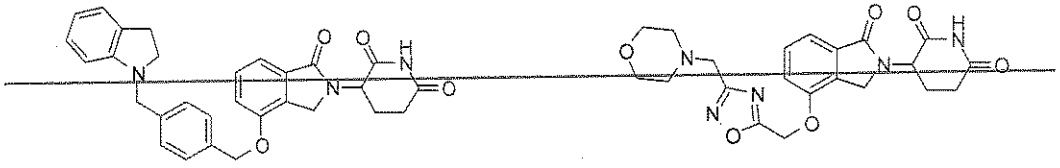




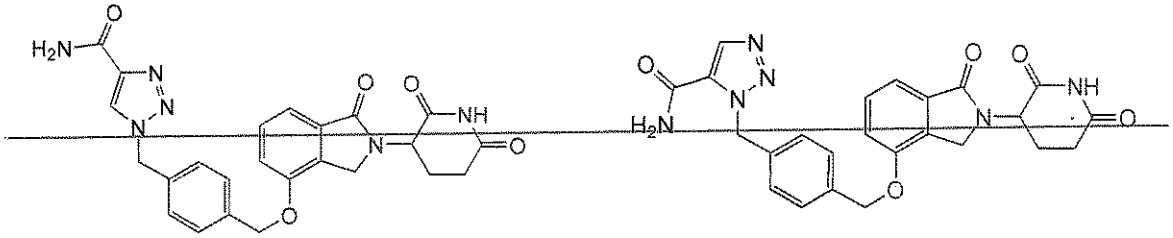


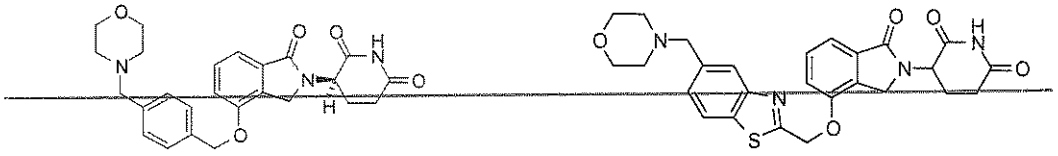


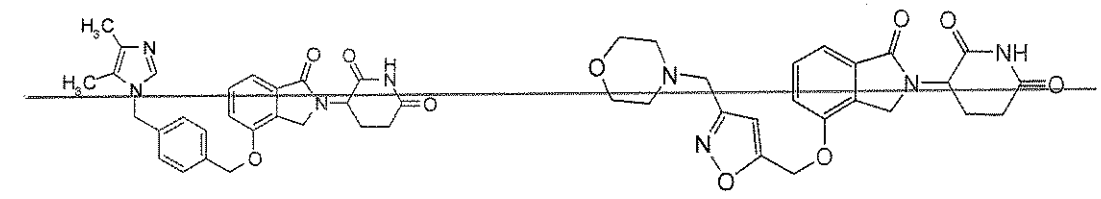


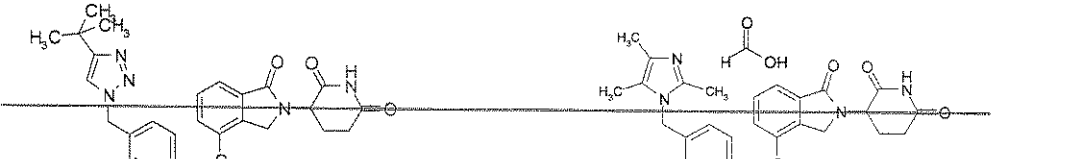


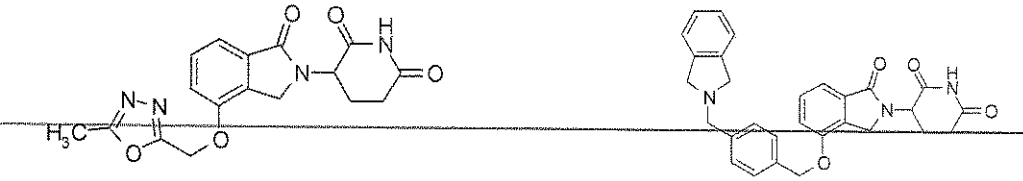




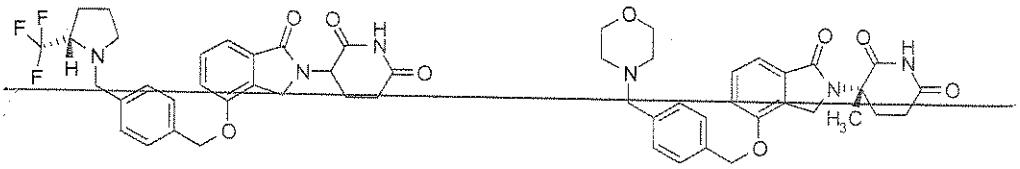


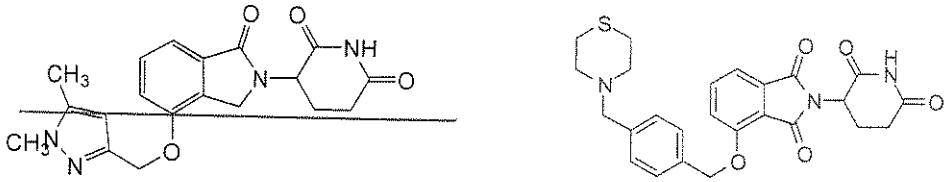


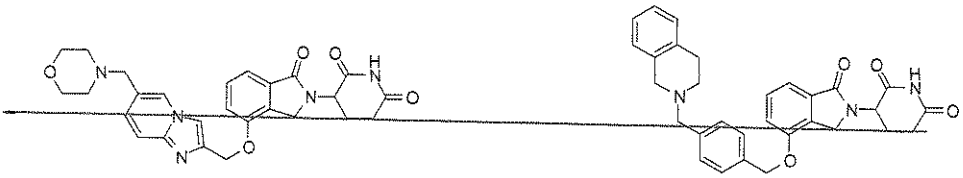


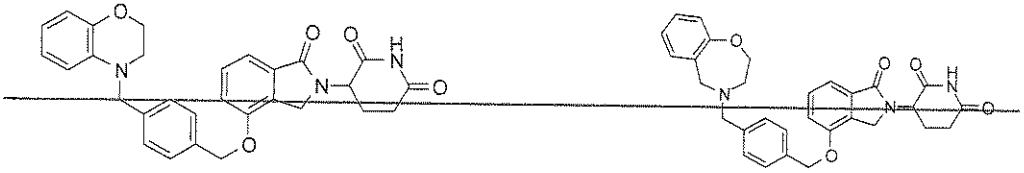


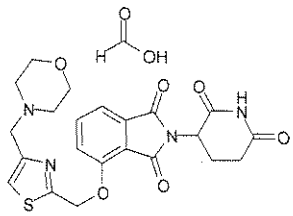


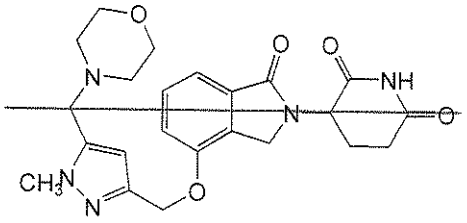


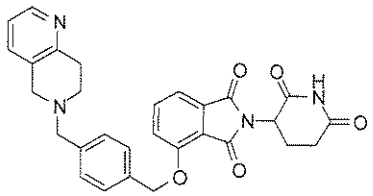


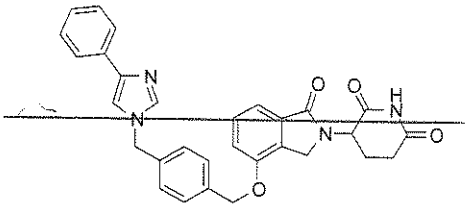




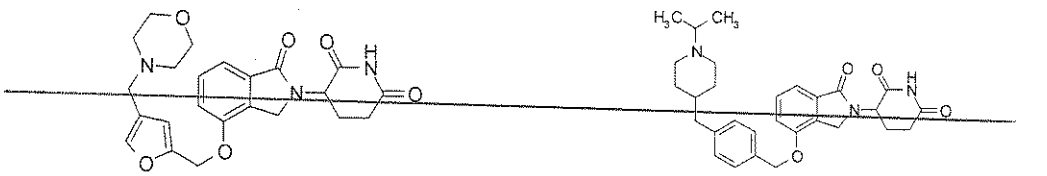


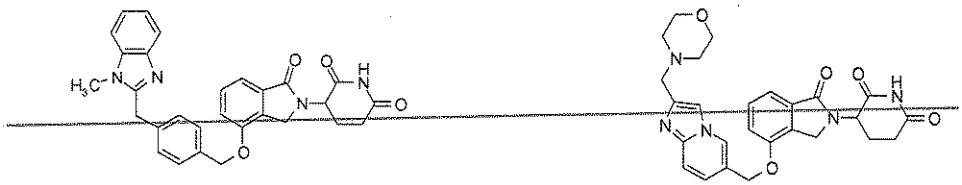




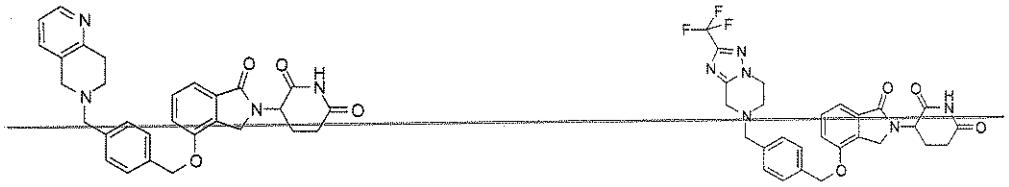




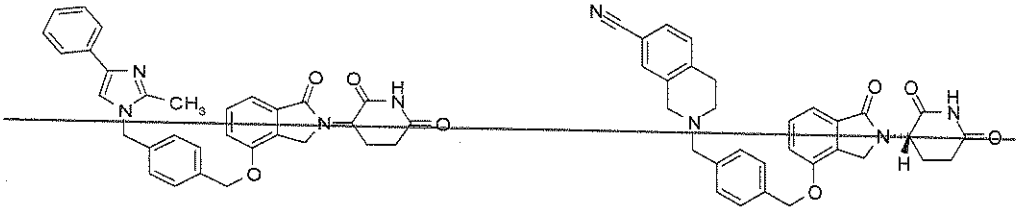


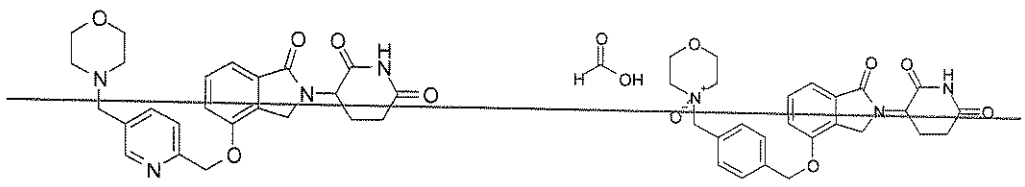




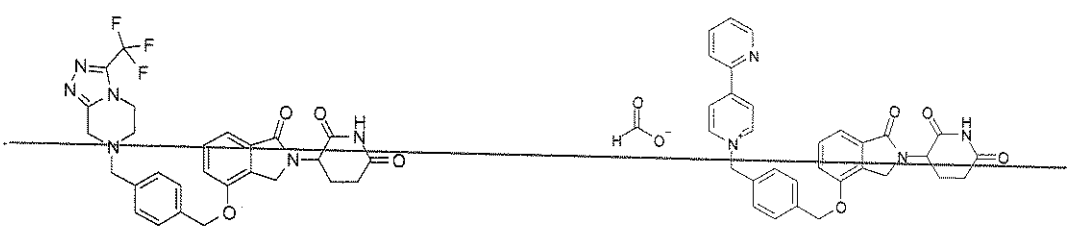


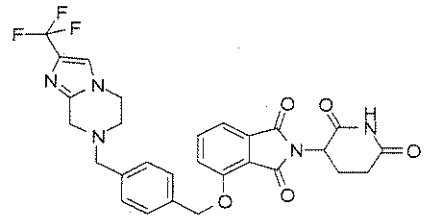
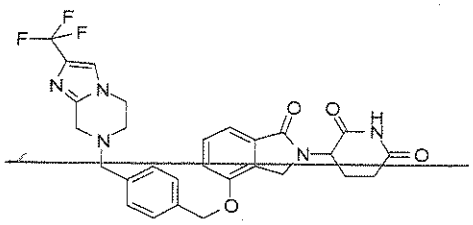
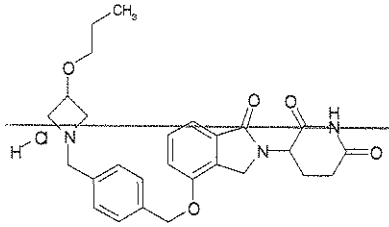
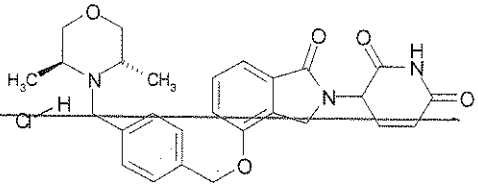
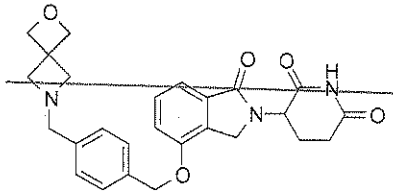
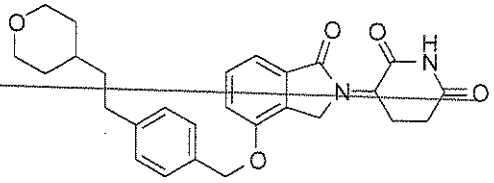
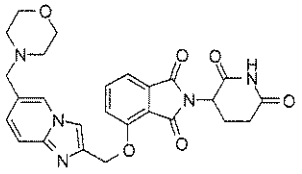
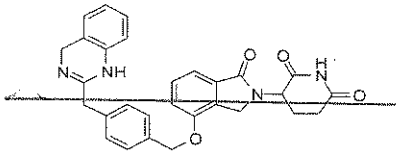
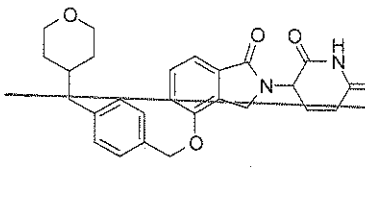


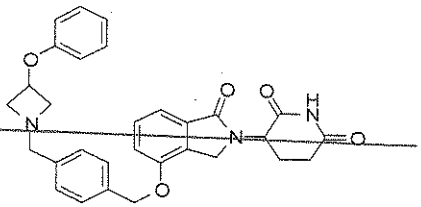


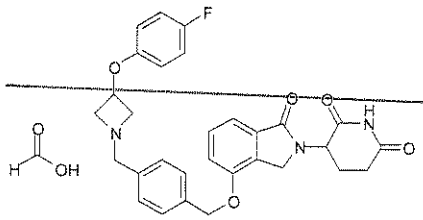
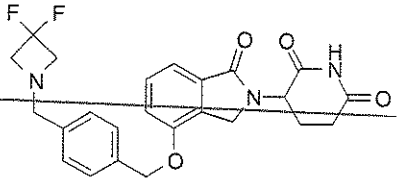
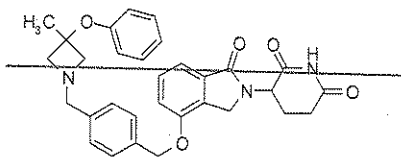
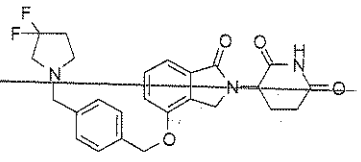
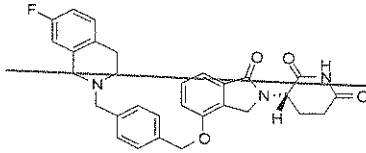
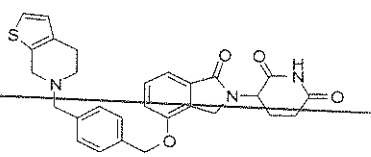


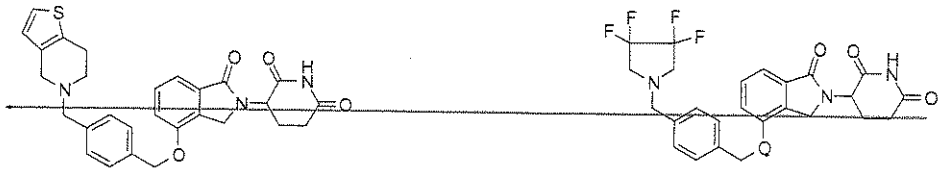


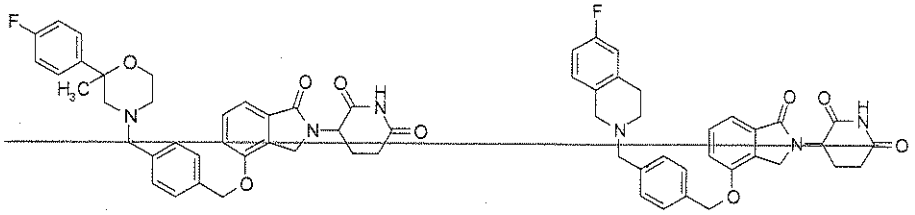


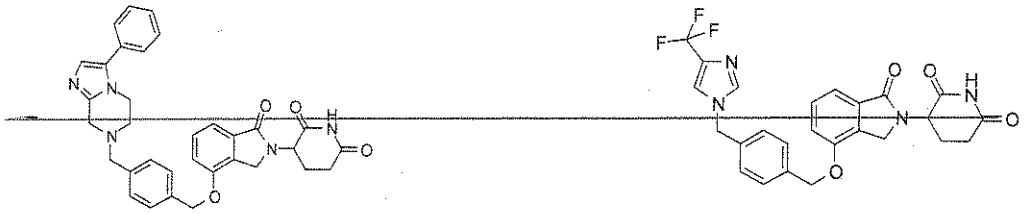










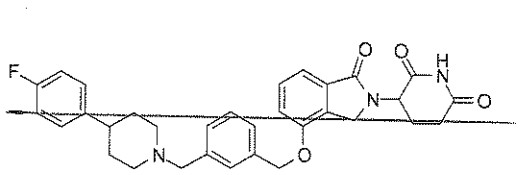


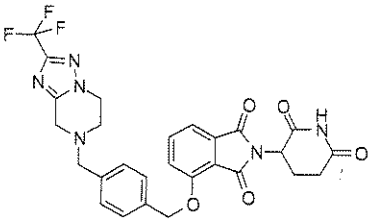







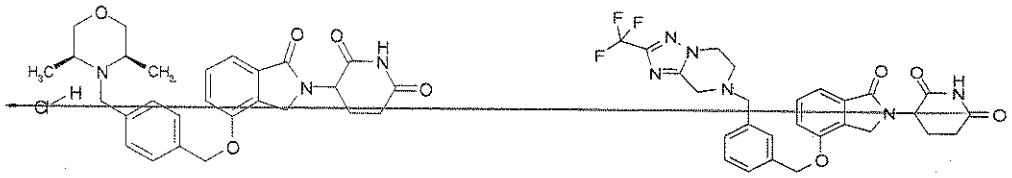


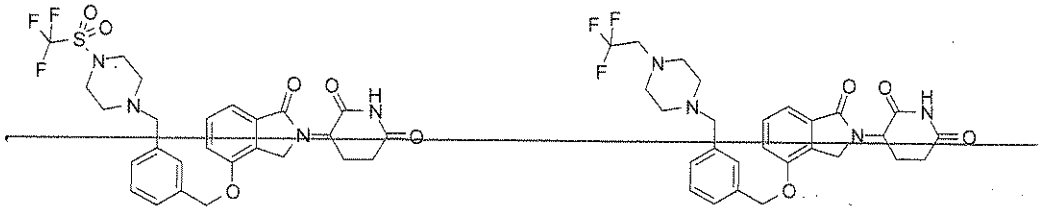


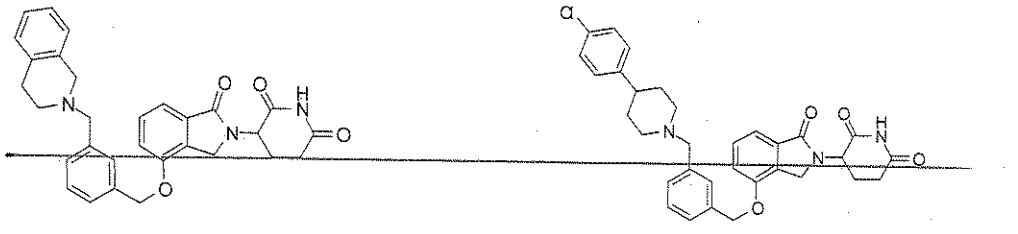


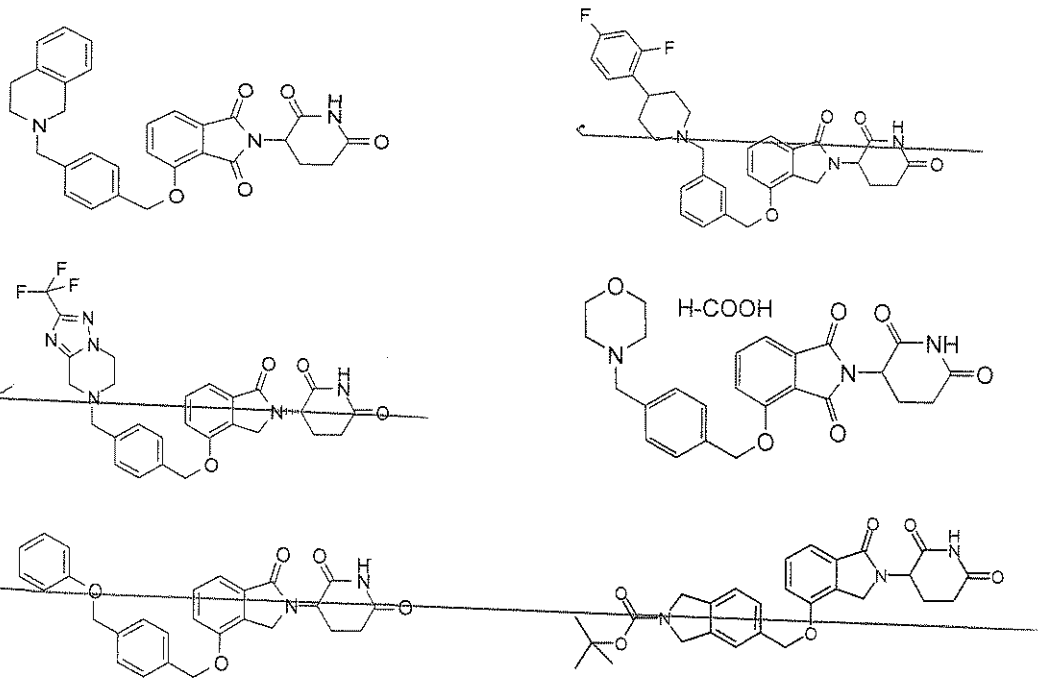






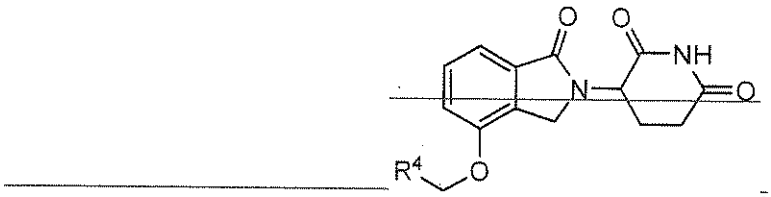






or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

~~8. A compound of formula (II):~~



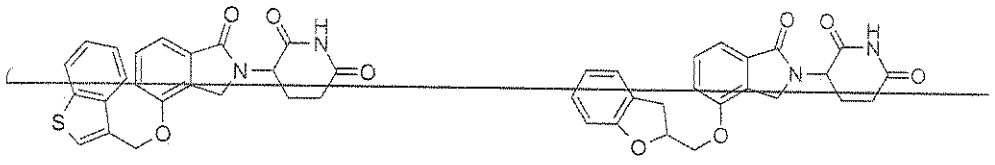
~~(II)~~

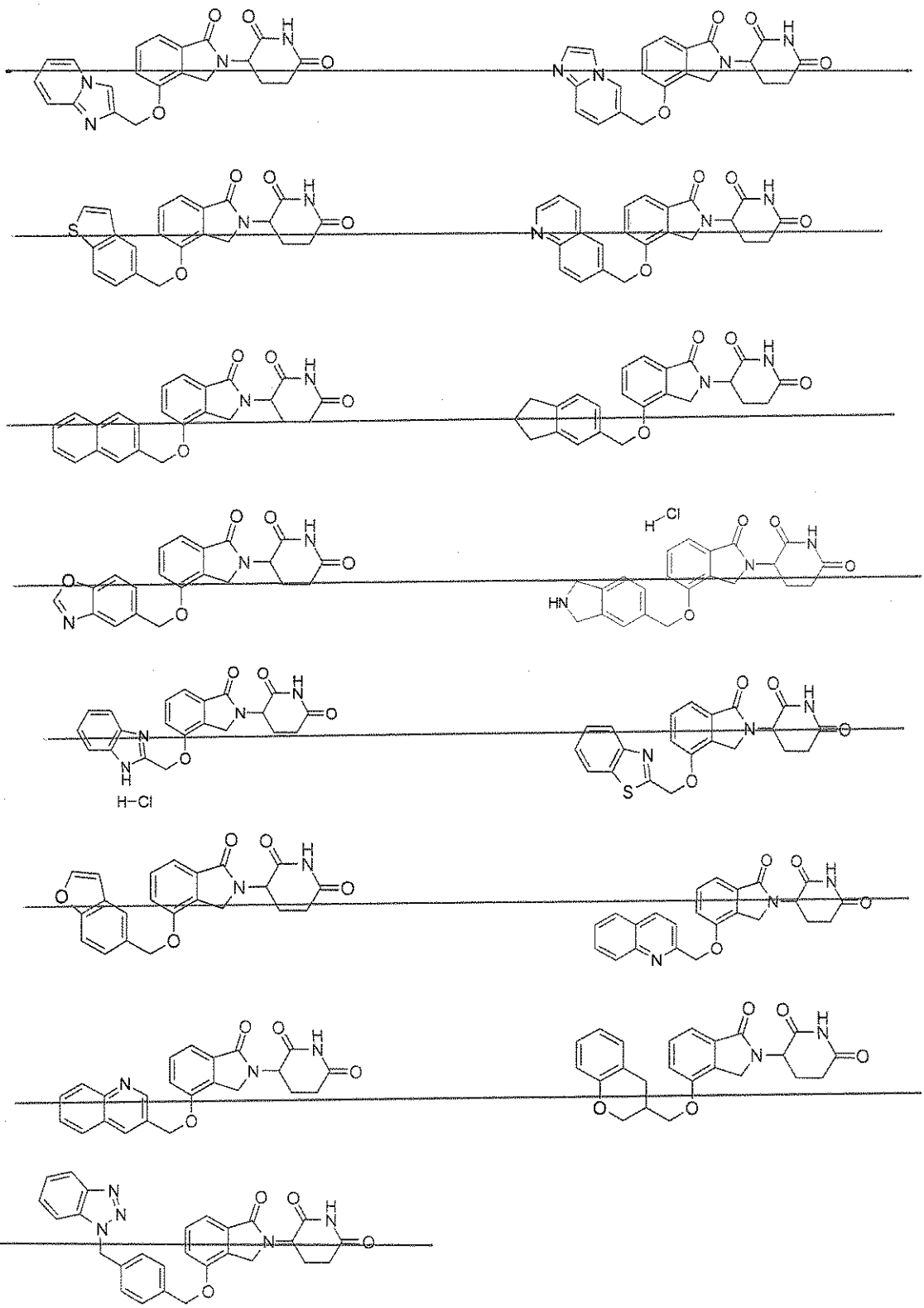
~~or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, wherein:~~

~~R^4 is unsubstituted 9 to 10 membered bicyclic ring is benzothiazole, quinoline, isoquinoline, naphthalene, 2,3-dihydro-1H-indene, benzo[d][1,2,3]triazole, imidazo[1,2-a]pyridine, benzofuran, 2,3-dihydrobenzofuran, benzothiophene, benzo[d]oxazole isoindoline or chroman;~~

~~with the proviso that if the bicyclic ring is benzofuran or benzothiophene, then the ring is not connected to the isoindole ring through the 2-position.~~

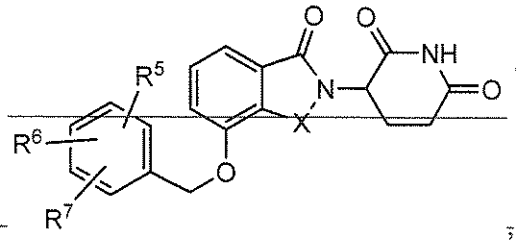
~~9. The compound of claim 8, which is:~~





~~or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.~~

10. A compound of formula (III):



(III)

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, wherein:

X is CH_2 or C=O;

R^5, R^6 and R^7 are each independently hydrogen, halogen, nitro, carbamoyl, amino, $-SO_2R^8$, $CONR^9R^{10}$, (C_1-C_6)alkyl or (C_1-C_6)alkoxy, said alkyl or alkoxy may be optionally substituted with one or more halogen, amino, hydroxyl, or NR^9R^{10};

R^8 is: (C_1-C_6)alkyl, optionally substituted with (C_1-C_6)alkyl or (C_6-C_{10})aryl; amino, optionally substituted with (C_1-C_6)alkyl or (C_6-C_{10})aryl; or 6 to 10 membered heterocycle, optionally substituted with (C_1-C_6)alkyl or (C_6-C_{10})aryl;

R^9 and R^{10} are each independently hydrogen, 6 to 10 membered aryl, -COO-(C_1-C_6)alkyl, (C_0-C_6)alkyl-CHO, (C_0-C_6)alkyl-COOH, (C_0-C_6)alkyl-$NR^{9'}R^{10'}$, (C_0-C_6)alkyl-(5 to 10 membered heterocycle), (C_1-C_6)alkyl-OH, (C_1-C_6)alkyl-O-(C_1-C_6)alkyl, (C_1-C_6)alkyl, or (C_3-C_6)cycloalkyl; or

R^9 and R^{10} together may form an optionally substituted 5 to 6 membered ring containing one or more heteroatoms; and

$R^{9'}$ and $R^{10'}$ are each independently hydrogen or (C_1-C_6)alkyl;

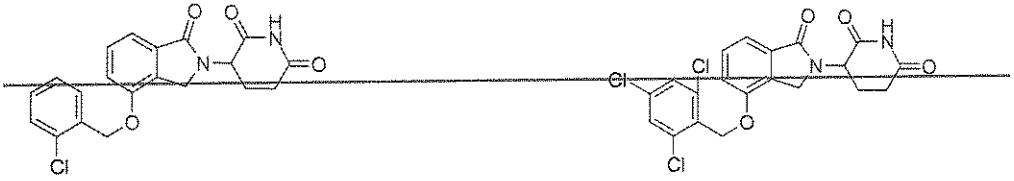
with the proviso that all of R^5-R^7 cannot be hydrogen; and

with the proviso that if one of R^5-R^7 is hydrogen and the remaining two of R^5-R^7 are both chloride, then the two chloride atoms cannot be on 3 and 4 position of the phenyl ring.

11. The compound of claim 10, wherein one of R^5-R^7 is hydrogen, and the remaining two of R^5-R^7 are each independently halogen, (C_1-C_6)alkoxy or (C_1-C_6)alkyl.

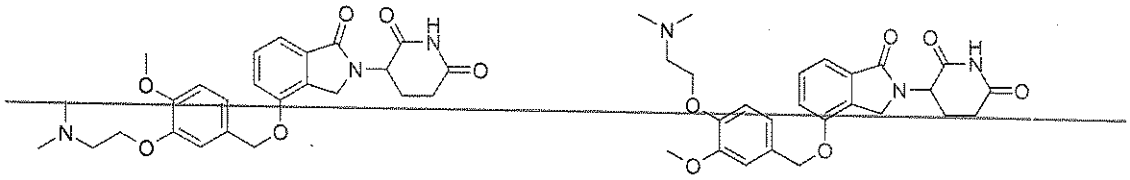
12. The compound of claim 10, wherein two of R^5-R^7 are hydrogen and the remaining one of R^5-R^7 is halogen, (C_1-C_6)alkoxy or (C_1-C_6)alkyl.

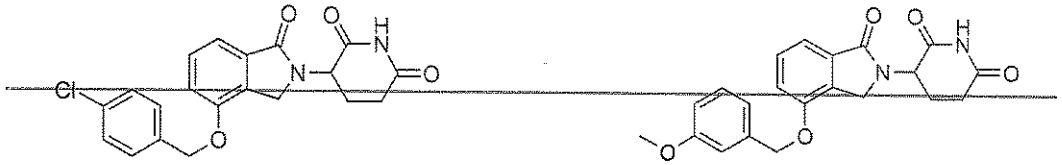
13. The compound of claim 10, which is:

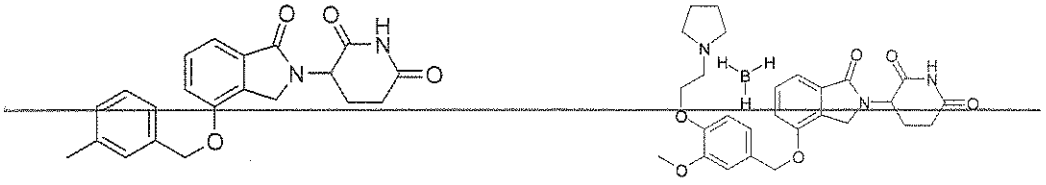


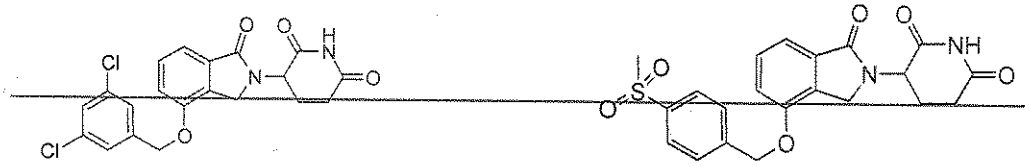


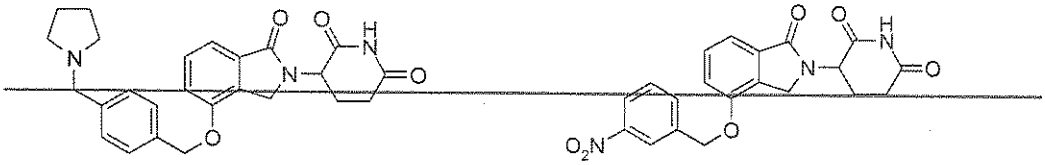


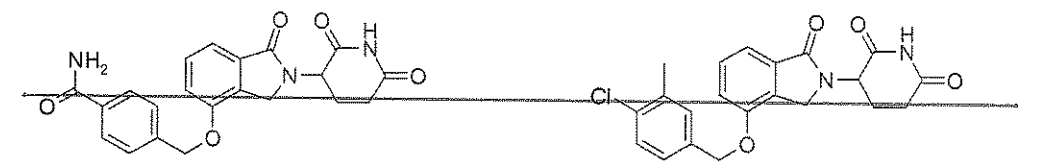


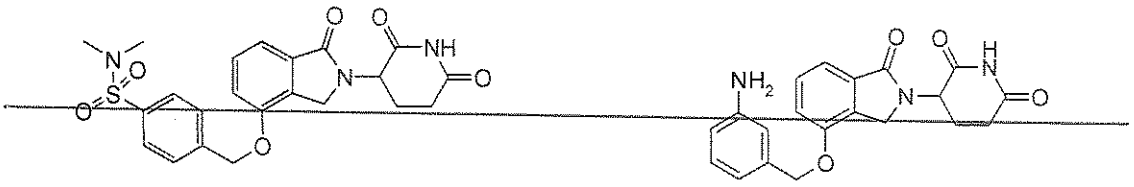
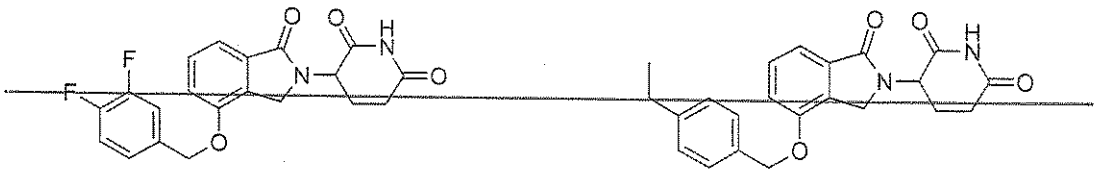
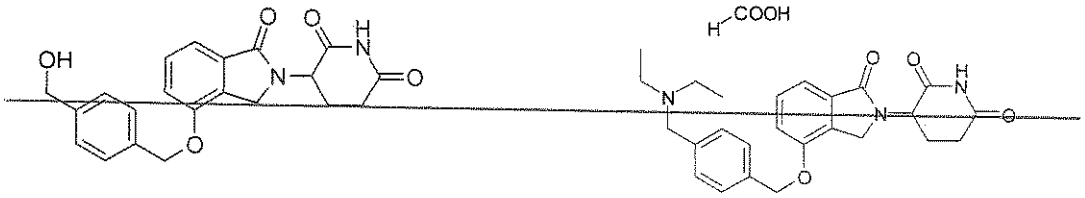
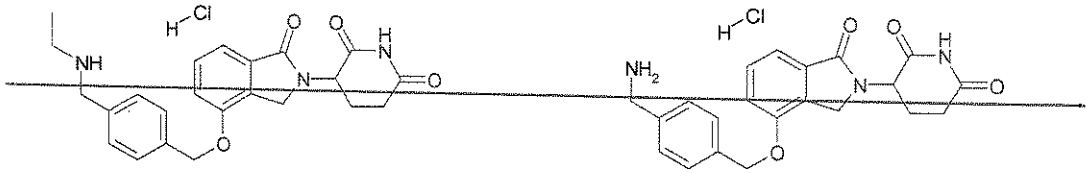
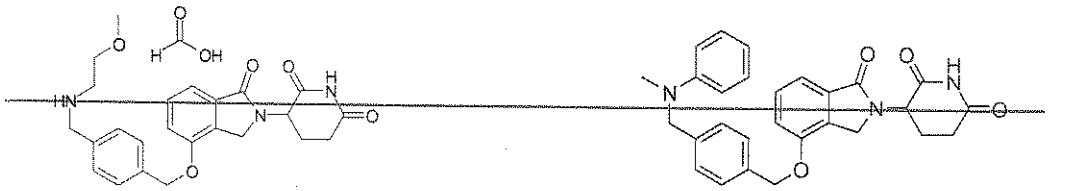


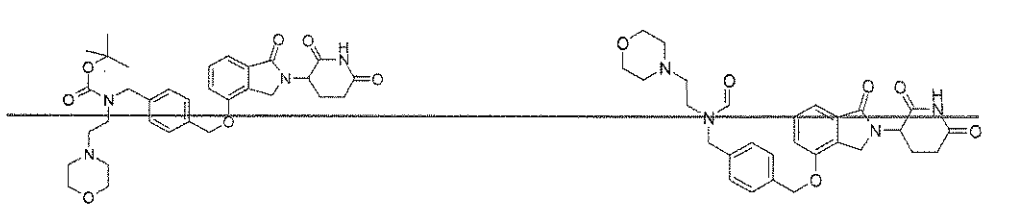


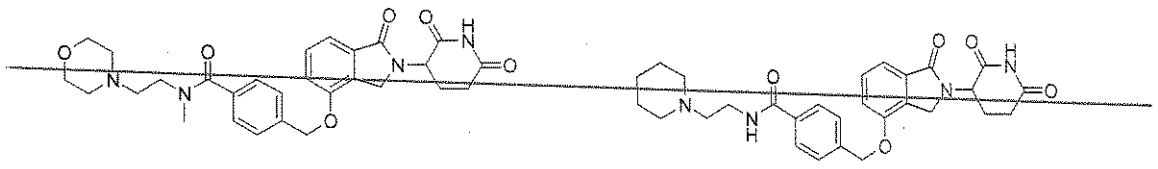


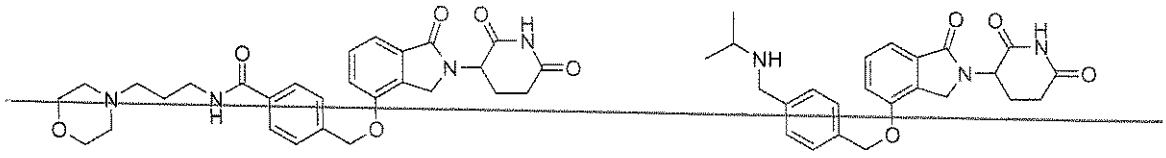


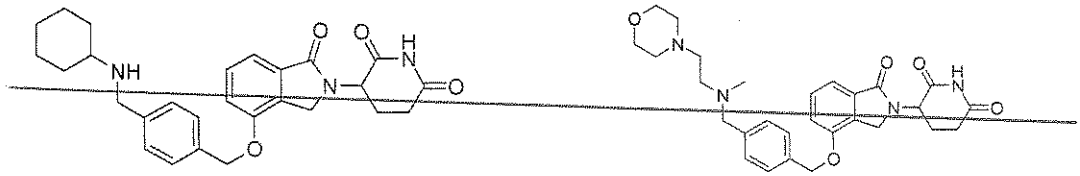


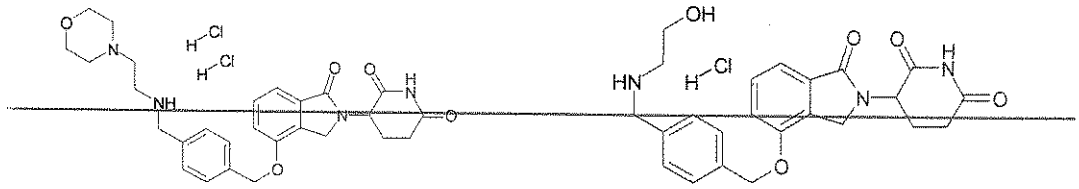







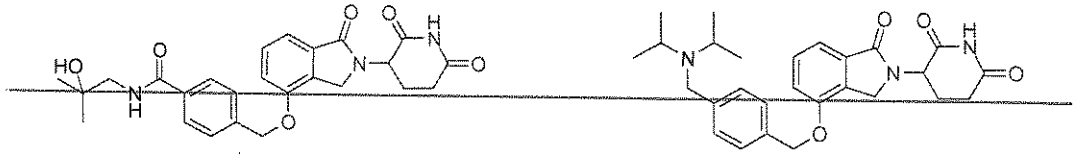


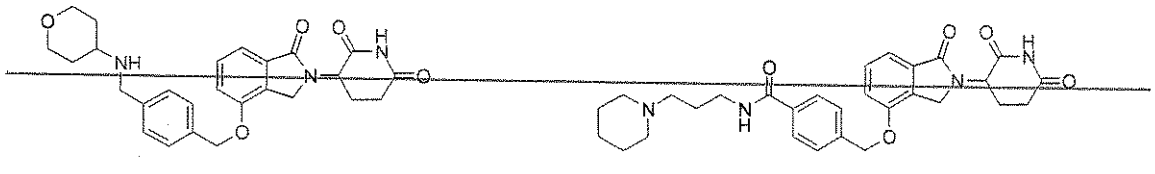



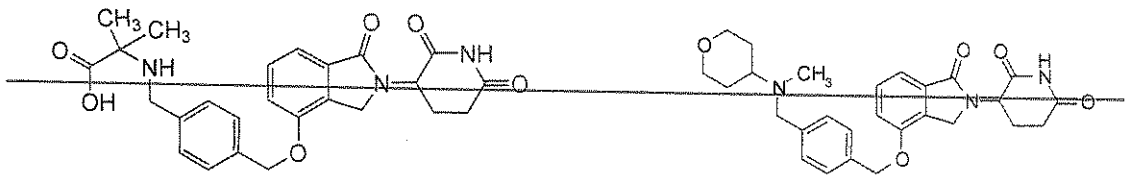


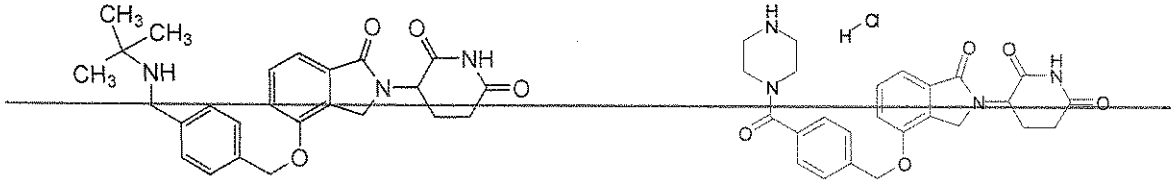


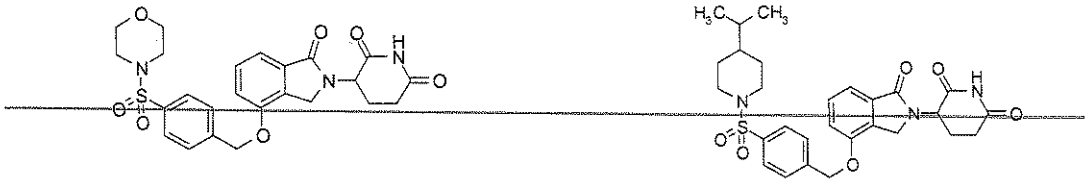


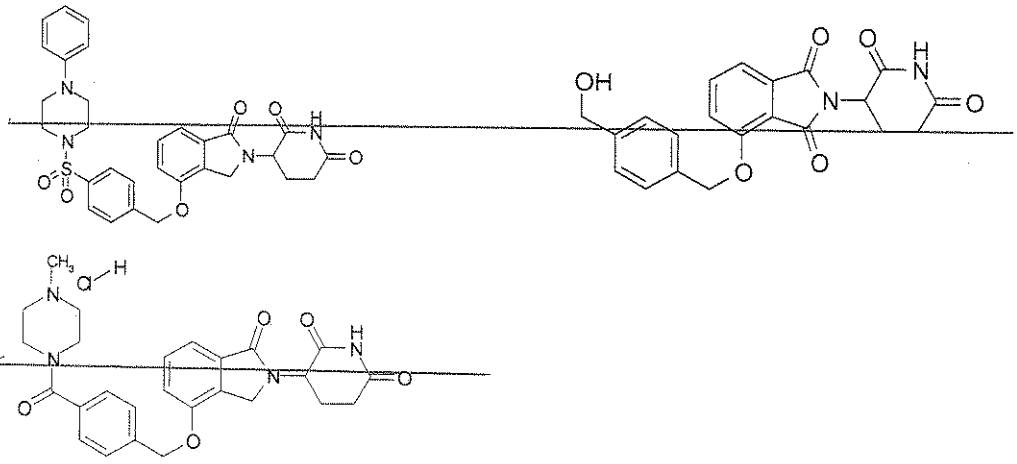






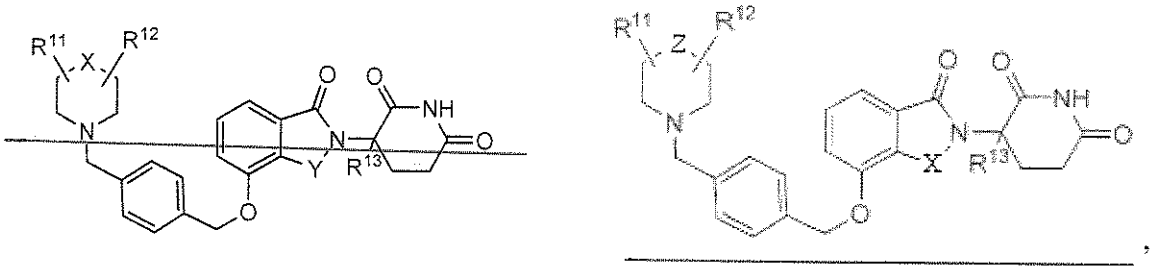






~~or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.~~

~~14~~5. A compound of formula (IV):



(IV)

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof, wherein:

~~XZ~~ is N or C;

~~YX~~ is ~~CH_2 or~~ C=O;

R^{11} and R^{12} are each independently hydrogen, -(C_1-C_6)alkyl, -(C_1-C_6)alkyl-(C_3-C_6)cycloalkyl, -(C_1-C_6)alkoxy, -(C_6-C_{10})aryl, -CO(C_1-C_6)alkyl, -CO(C_3-C_6)cycloalkyl, -CO(C_6-C_{10})aryl, -COO(C_1-C_6)alkyl, halogen, hydroxyl, oxo, 3 to 10 membered heterocycle, 6 to 10 membered heteroaryl, -NHCO(C_1-C_6)alkyl, -$(CH_2)_n$-phenyl, -SO_2(C_1-C_6)alkyl, -SO_2(C_3-C_6)cycloalkyl, -SO_2(C_6-C_{10})aryl or -$NR^{14}R^{15}$, wherein the alkyl, aryl or heteroaryl portion of each of the groups may be optionally substituted with one or more halogen, hydroxyl or -(C_1-C_6)alkoxy;

R^{13} is hydrogen or -(C_1-C_6)alkyl;

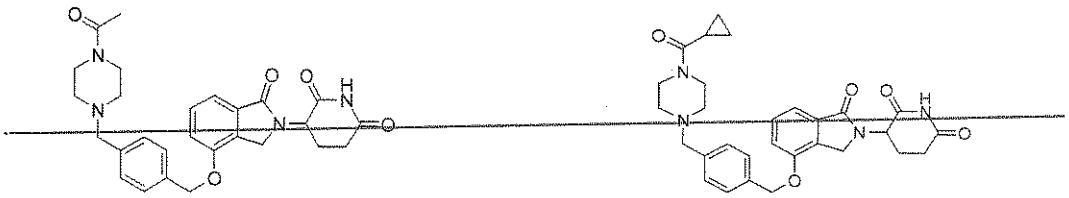
R^{14} and R^{15} are each independently hydrogen or -(C_1-C_6)alkyl; and

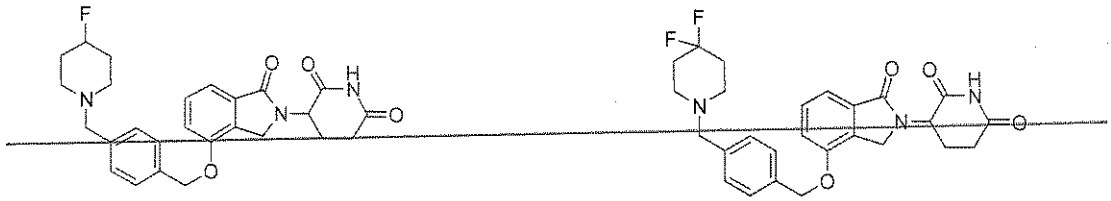
n is 0, 1, 2 or 3.

~~15~~6. The compound of claim ~~14~~5, wherein ~~XZ~~ is N.

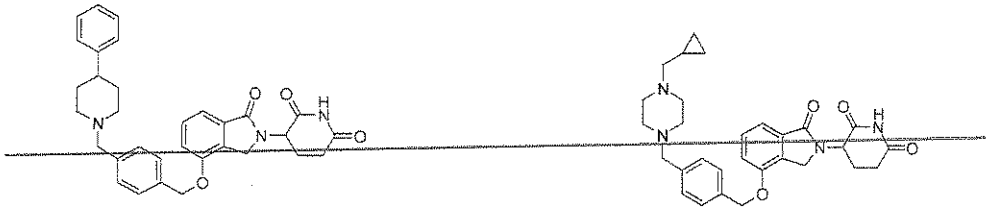
~~16. The compound of claim 14, wherein Y is CH_2.~~

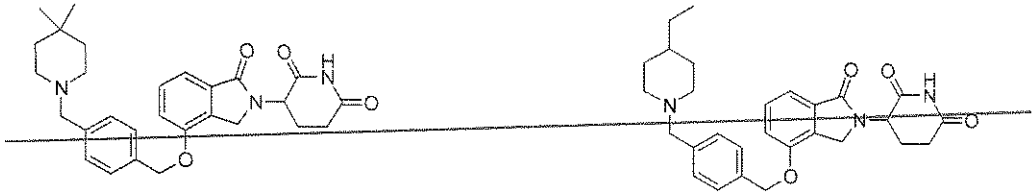
~~17~~7. The compound of claim ~~14~~5, which is:

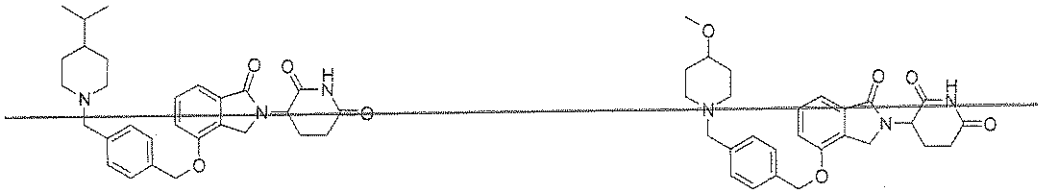


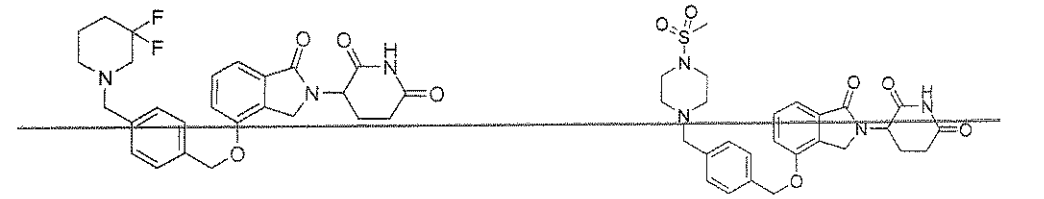


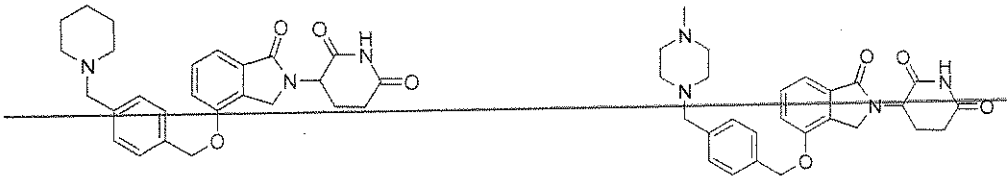


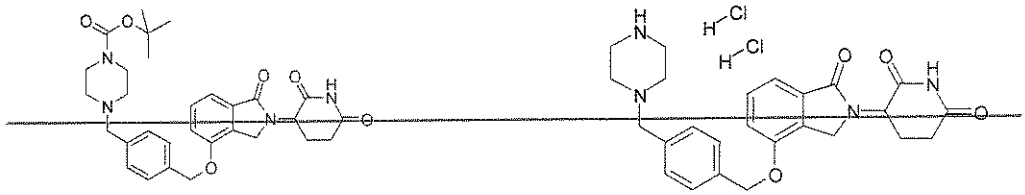




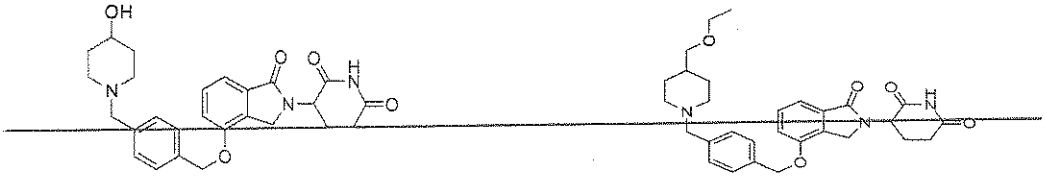




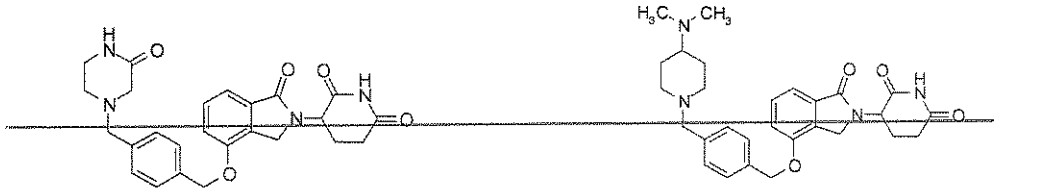




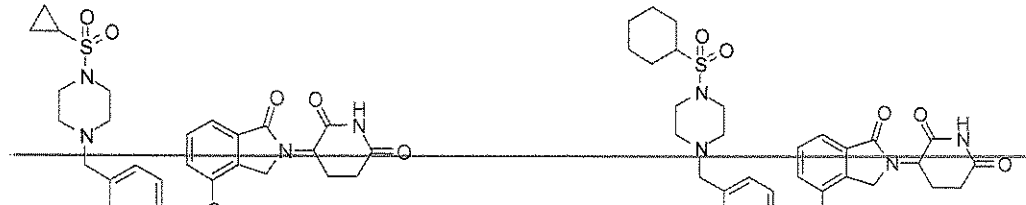






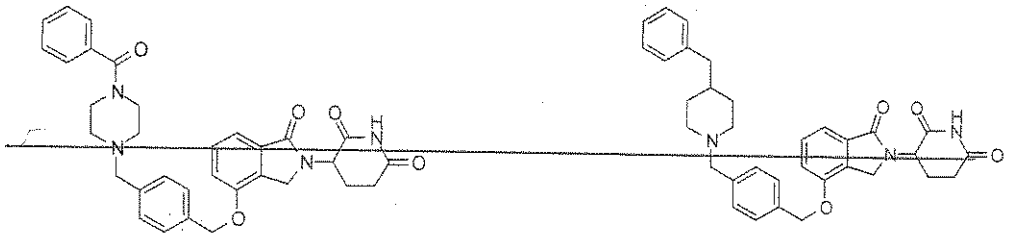


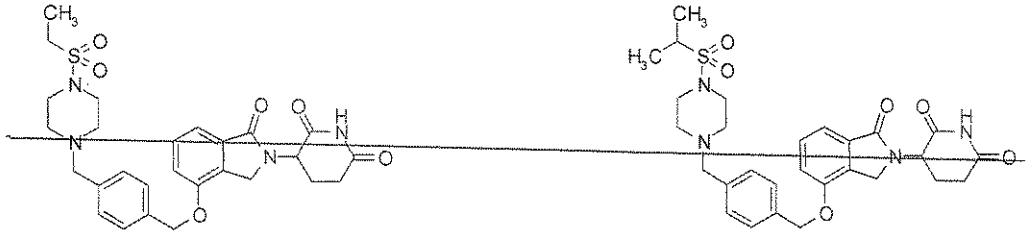


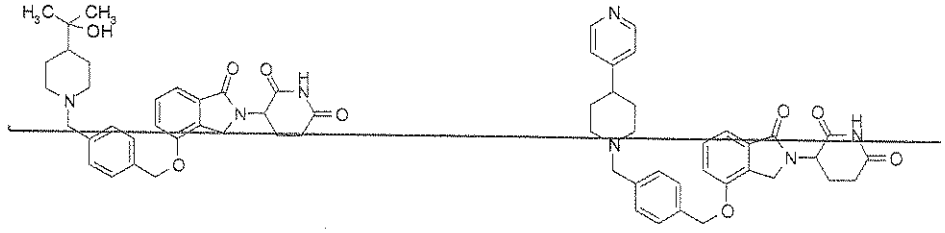


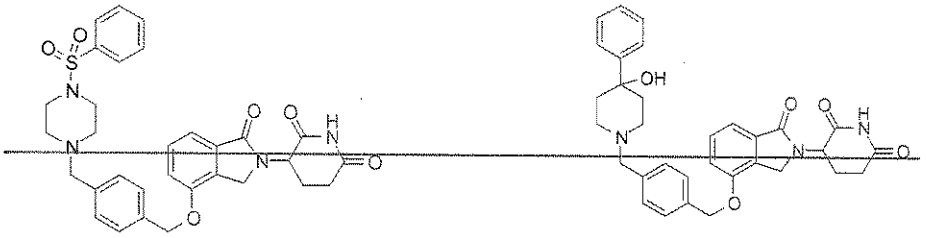


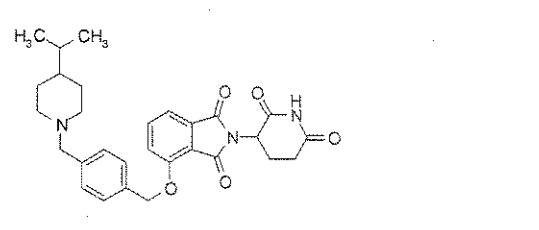


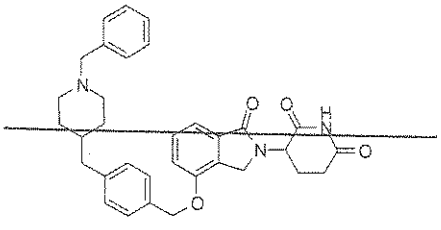


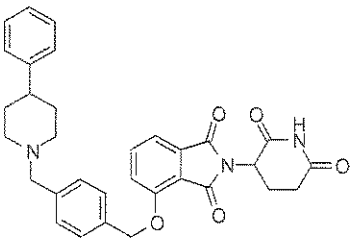


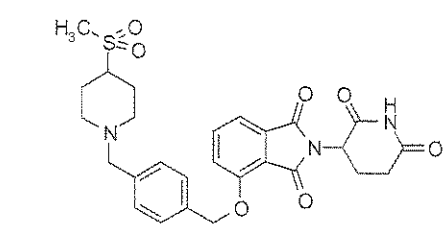


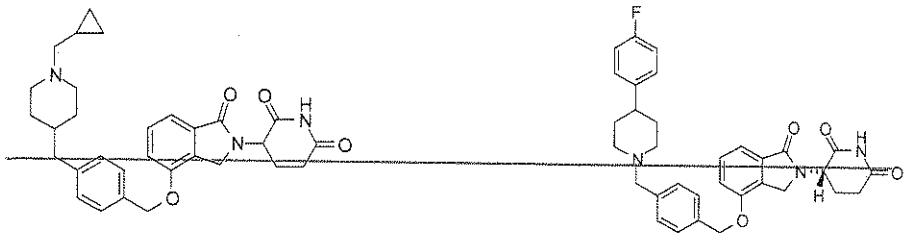


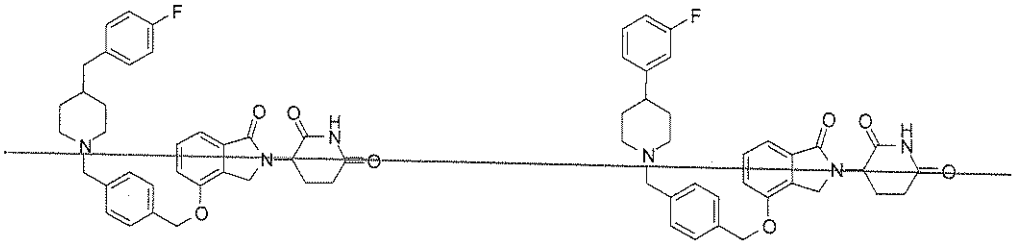




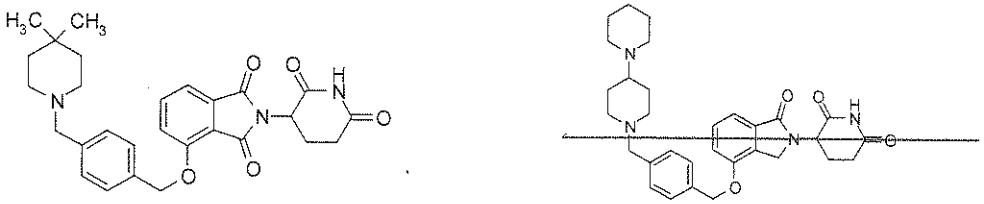


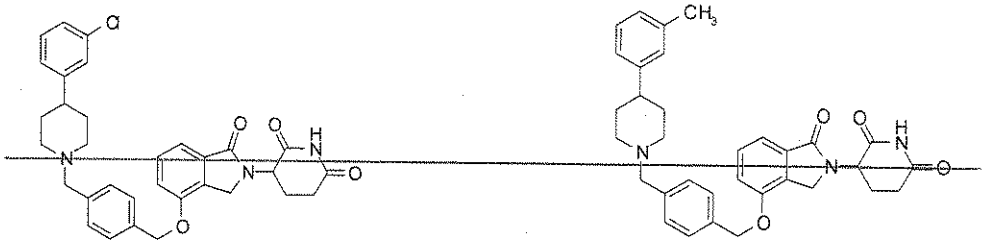


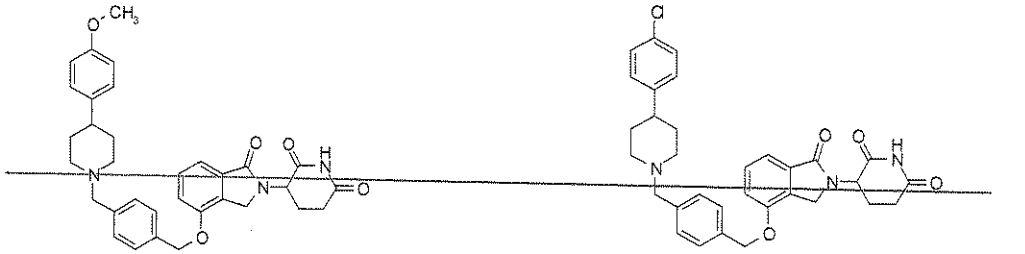


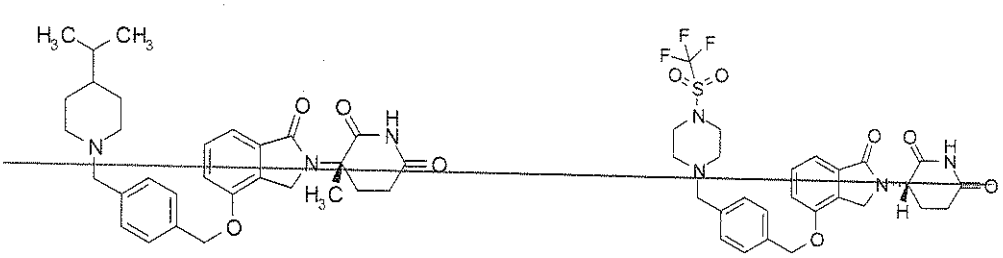


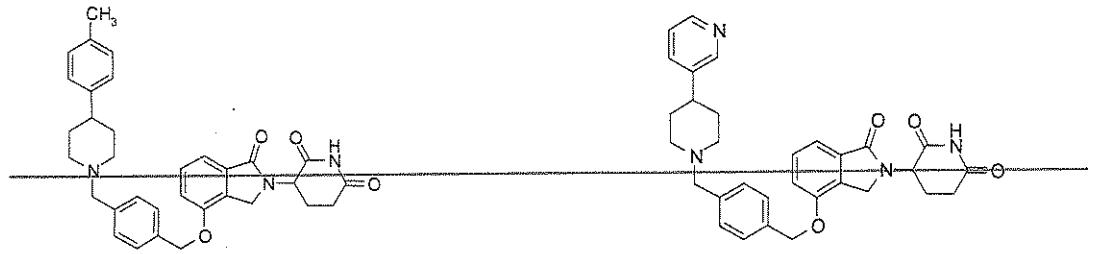


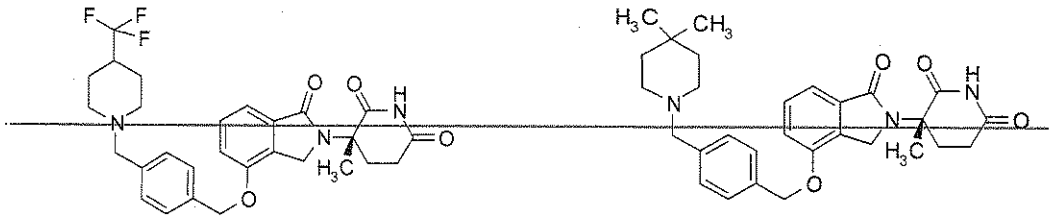


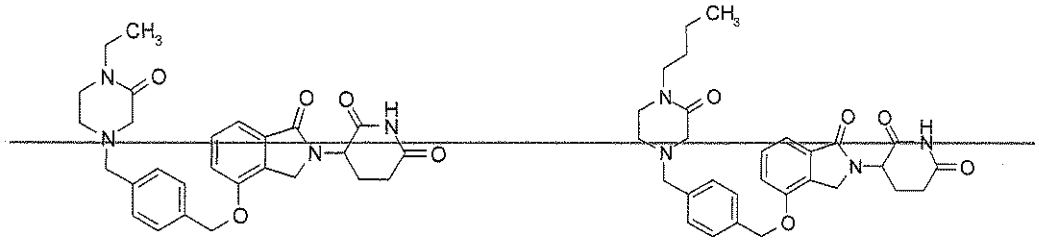


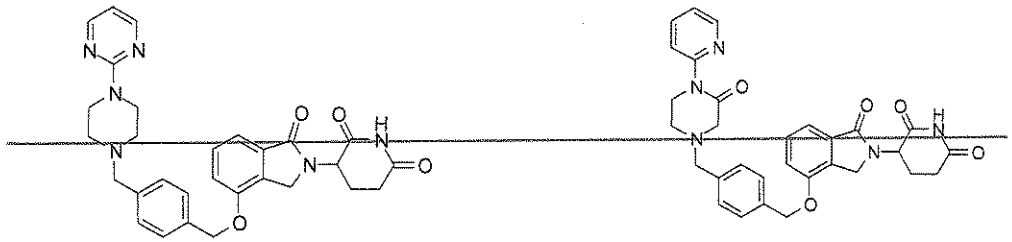


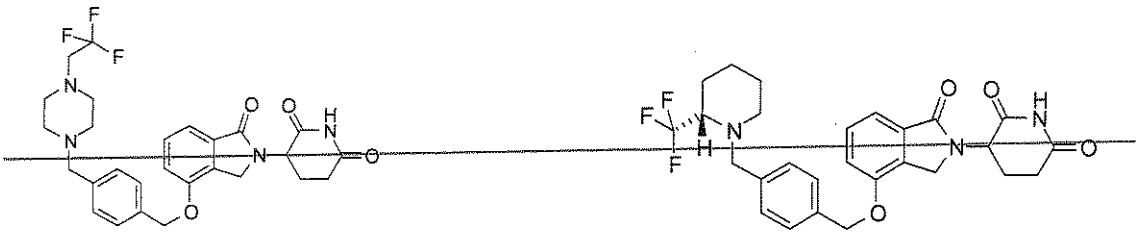


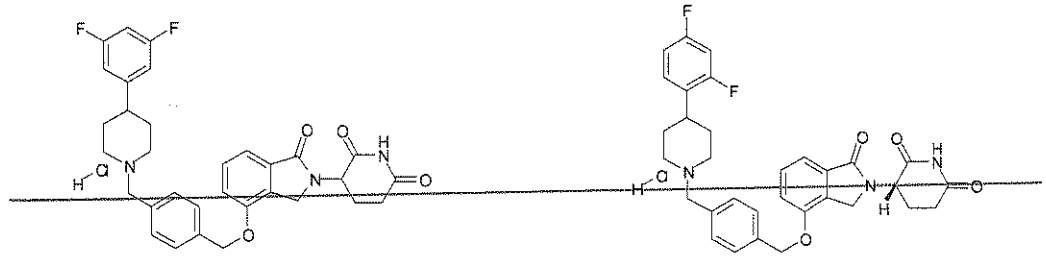


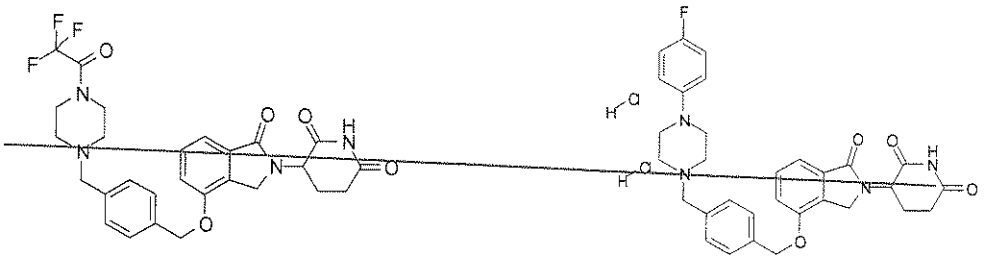


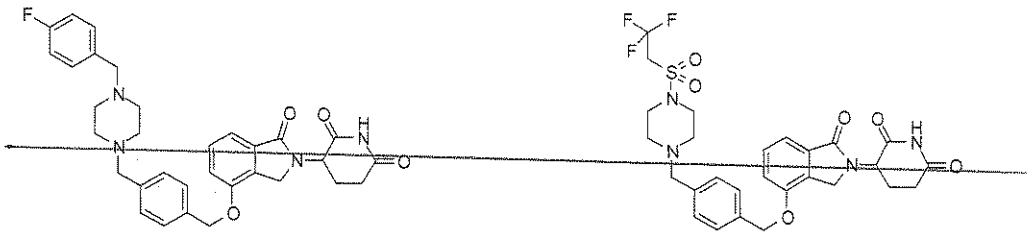


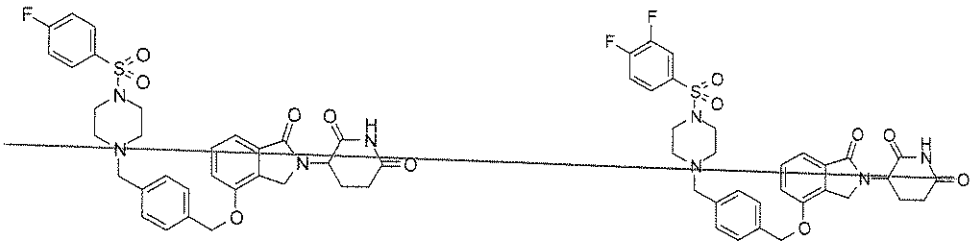


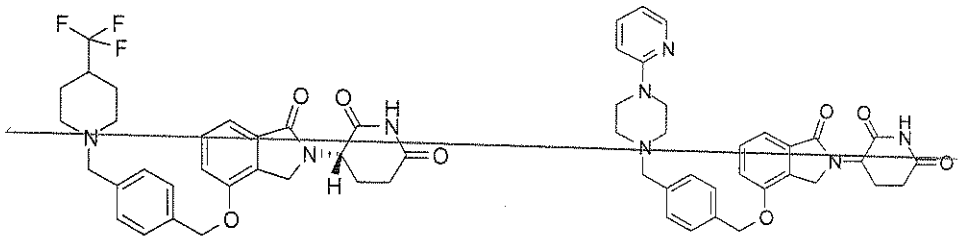


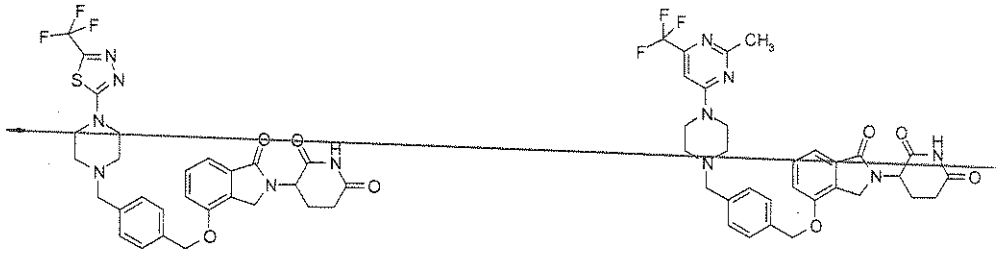


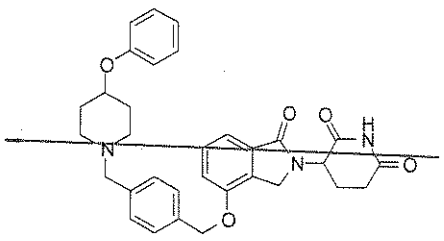


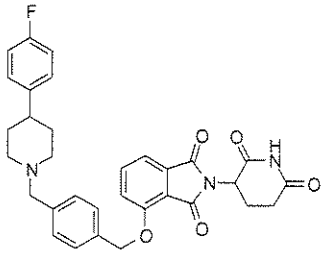


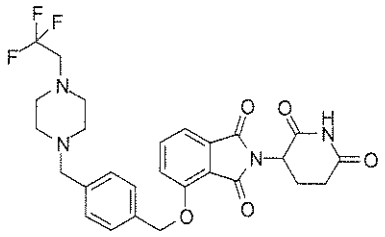
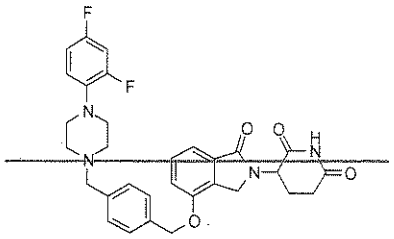
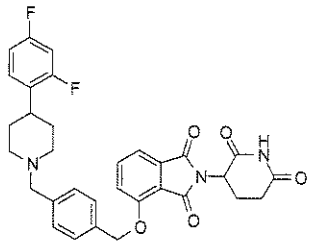
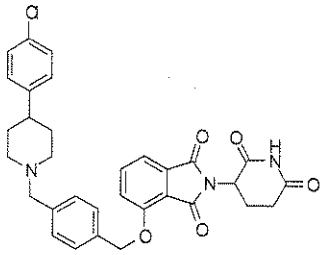
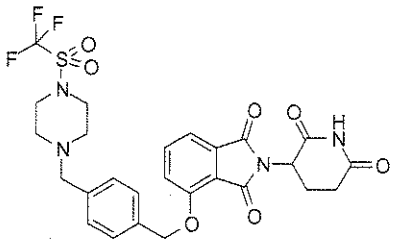
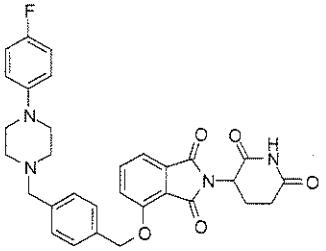






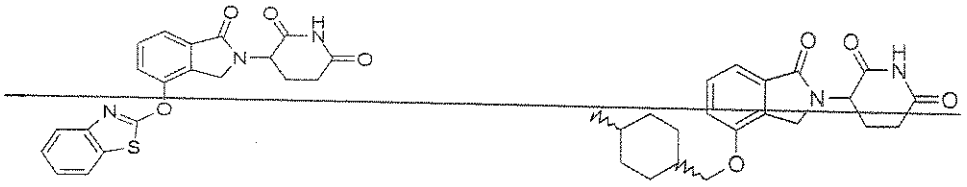
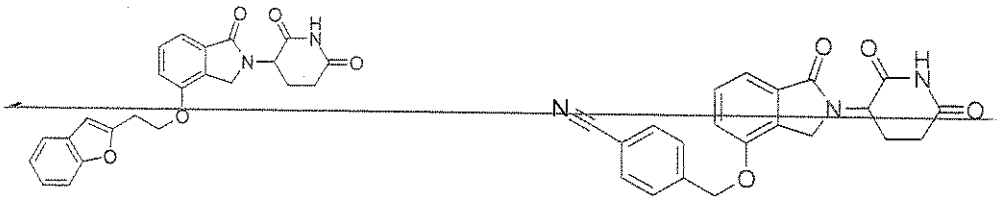
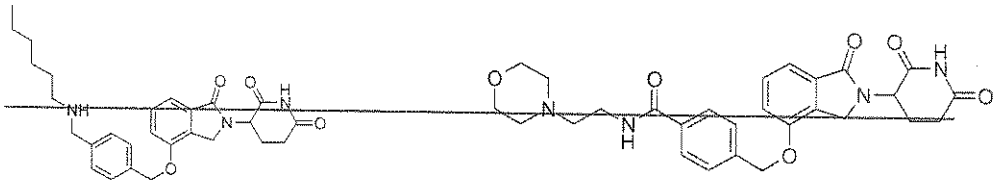
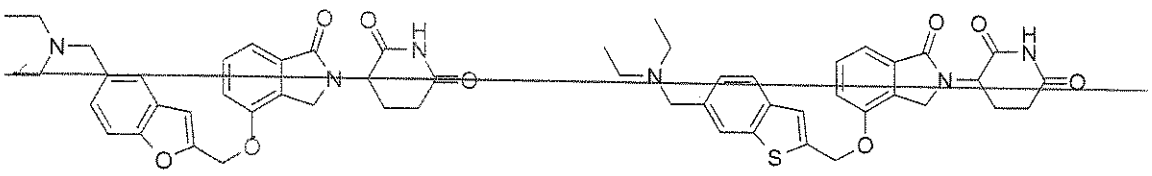


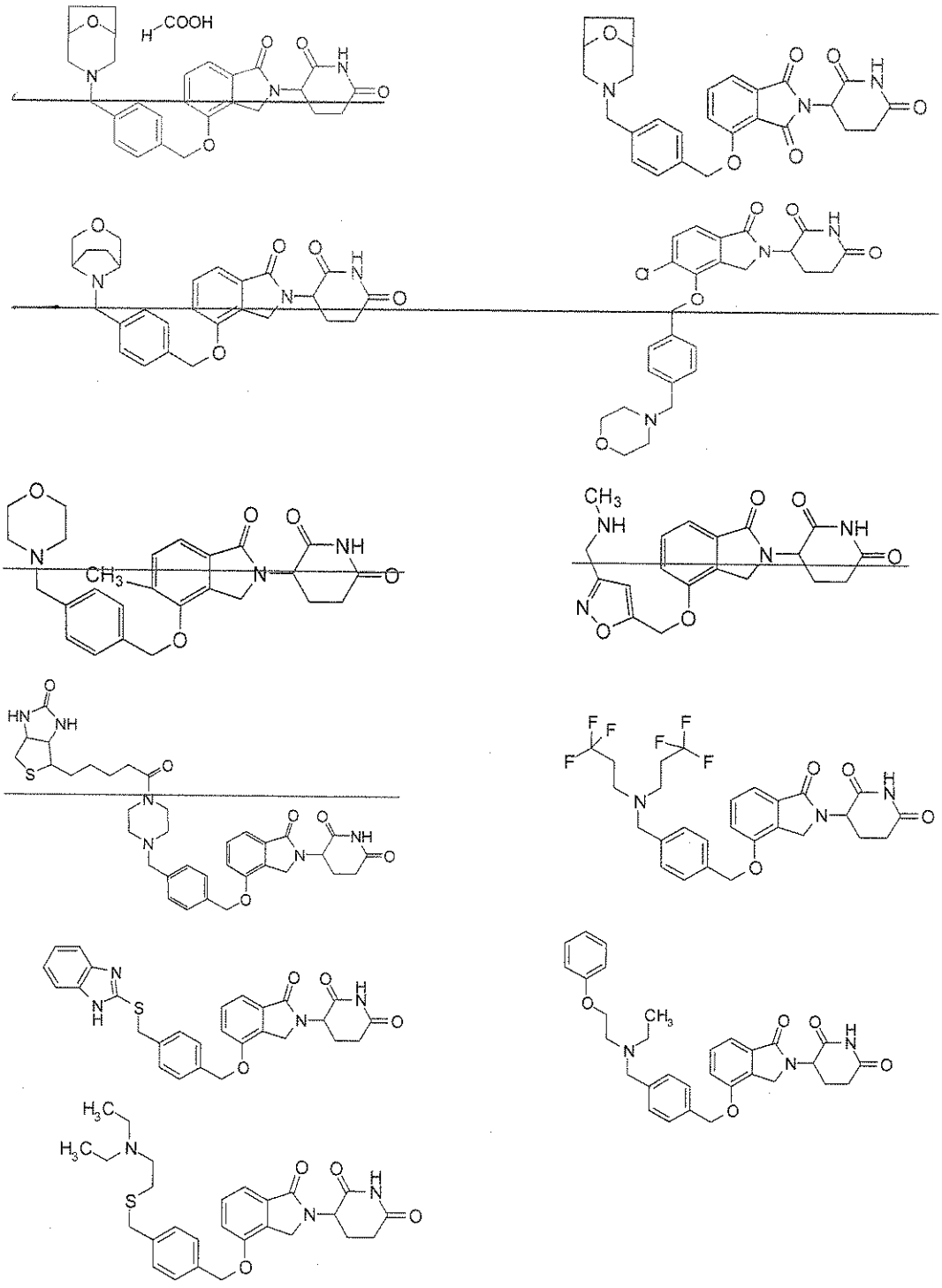


or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

~~188~~. A compound, which is:



or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

~~19~~9. A pharmaceutical composition comprising a compound of any one of claims 1-18, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

~~20~~10. A pharmaceutical composition comprising a compound of claims ~~1-18~~1-8, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof in the manufacture of a medicament for treating, managing or preventing a disease or disorder, wherein the disease

or disorder is cancer, ~~a disorder associated with angiogenesis, pain, macular degeneration or a~~

~~related syndrome, a skin disease, a pulmonary disorder, an asbestos-related disorder, a parasitic disease, an immunodeficiency disorder, a CNS disorder, CNS injury,~~

atherosclerosis or a related disorder, dysfunctional sleep or a related disorder, ~~an infectious disease,~~or hemoglobinopathy or a related disorder~~, or a TNFα related disorder~~.