PI(3,4)P2. The PIKKs are protein kinases that control cell growth (mTORC1) or monitor genomic integrity (ATM, ATR, DNA-PK, and hSmg-1).

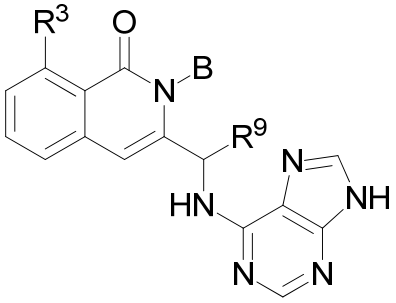
[0007] The delta (δ) isoform of class I PI3K has been implicated, in particular, in a number of diseases and biological processes. PI3K δ is expressed primarily in hematopoietic cells including leukocytes such as T-cells, dendritic cells, neutrophils, mast cells, B-cells, and macrophages. PI3K δ is integrally involved in mammalian immune system functions such as T-cell function, B-cell activation, mast cell activation, dendritic cell function, and neutrophil activity. Due to its integral role in immune system function, PI3K δ is also involved in a number of diseases related to undesirable immune response such as allergic reactions, inflammatory diseases, inflammation mediated angiogenesis, rheumatoid arthritis, auto-immune diseases such as lupus, asthma, emphysema and other respiratory diseases. Other class I PI3K involved in immune system function includes PI3K γ, which plays a role in leukocyte signaling and has been implicated in inflammation, rheumatoid arthritis, and autoimmune diseases such as lupus.

[0008] Downstream mediators of the PI3K signal transduction pathway include Akt and mammalian target of rapamycin (mTOR). Akt possesses a plckstrin homology (PH) domain that binds PIP3, leading to Akt kinase activation. Akt phosphorylates many substrates and is a central downstream effector of PI3K for diverse cellular responses. One important function of Akt is to augment the activity of mTOR, through phosphorylation of TSC2 and other mechanisms. mTOR is a serine-threonine kinase related to the lipid kinases of the PI3K family. mTOR has been implicated in a wide range of biological processes including cell growth, cell proliferation, cell motility and survival. Disregulation of the mTOR pathway has been reported in various types of cancer. mTOR is a multifunctional kinase that integrates growth factor and nutrient signals to regulate protein translation, nutrient uptake, autophagy, and mitochondrial function.

[0009] As such, kinases, particularly PI3Ks are prime targets for drug development. There remains a need for PI3K inhibitors suitable for drug development. The present invention addresses this need and provides related advantages as well by providing new classes of kinase inhibitors.

SUMMARY

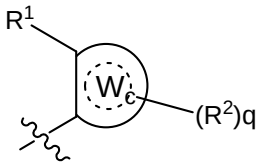
[0009a] In one aspect of the present disclosure, there is provided a compound of Formula V-A:



Formula V-A

or a pharmaceutically acceptable salt thereof, wherein

B is a moiety of Formula II:



Formula II

wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl;

q is an integer of 0 or 1;

R^1 is hydrogen, alkyl, or halo;

R^2 is alkyl or halo;

R^3 is halo;

R^9 is hydrogen, alkyl, or heterocycloalkyl;

wherein alkyl is optionally substituted with one or more halo.

[0009b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

[0009c] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of a disorder in a subject, wherein said disorder is one or more of cancer, bone disorder, inflammatory disease, immune disease, respiratory disease, thrombosis, or cardiac disease.

[0009d] In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of one or more of asthma, emphysema, allergy, dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, chronic obstructive pulmonary disorder (COPD), psoriasis, multiple sclerosis, disorders related to diabetic complications, lupus erythematosus, scleroderma, graft versus host disease, restenosis, or atherosclerosis in a subject.

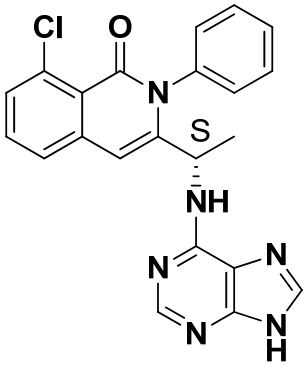
[0009e] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein or a pharmaceutical composition as disclosed herein, in the manufacture of medicament for the treatment of cancer in a subject.

[0009f] In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disorder in a subject, wherein the disorder is selected from one or more of cancer, bone disorder, inflammatory disease, immune disease, respiratory disease, thrombosis, and cardiac disease.

[0009g] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer in a subject.

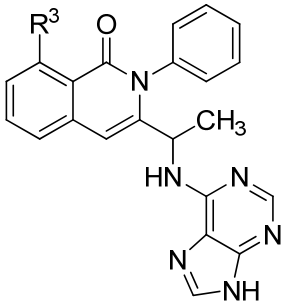
[0009h] In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for inhibiting a phosphatidyl inositol-3 kinase (PI3 kinase) in a cell.

[0009i] In a further aspect of the present disclosure, there is provided a compound of the formula:



(Compound 292).

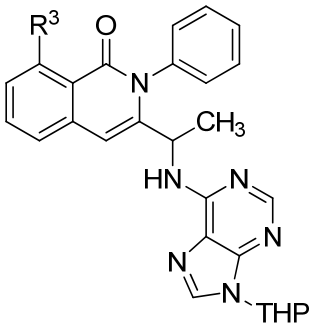
[0009j] In another aspect of the present disclosure, there is provided a process for preparing a compound of formula:



or a pharmaceutically acceptable salt thereof, wherein

R^3 is halo;

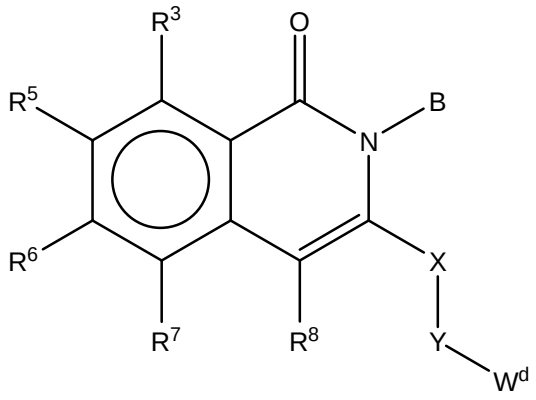
comprising deprotecting a compound of formula:



wherein the deprotection occurs in the presence of an acid.

[0009k] In a further aspect of the present disclosure, there is provided a compound disclosed herein or a pharmaceutical composition disclosed herein, for use in the treatment of a disorder in a subject, wherein said disorder is one or more of cancer, bone disorder, inflammatory disease, immune disease, respiratory disease, thrombosis, or cardiac disease; or for use in the treatment of asthma, emphysema, allergy, dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, chronic obstructive pulmonary disorder (COPD), psoriasis, multiple sclerosis, disorders related to diabetic complications, lupus erythematosus, scleroderma, graft versus host disease, restenosis, or atherosclerosis in a subject; or for use in inhibiting a phosphatidyl inositol-3 kinase (PI3 kinase) in a cell.

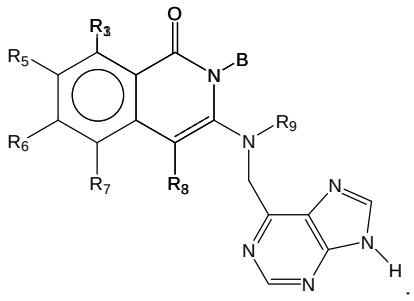
[0010] The present disclosure also provides compounds of Formula I below or pharmaceutically acceptable salts thereof, wherein



Formula I

[0011] W_d is heterocycloalkyl, aryl or heteroaryl;

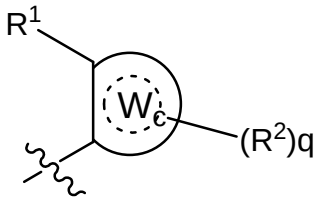
[0012] B is alkyl or a moiety of Formula II;



Formula VI

[0036] In some of the embodiments of the compound of Formula VI, R^3 is-H, -CH_3, -Cl, or –F, and R^5, R^6, R^7, and R^8 are independently hydrogen.

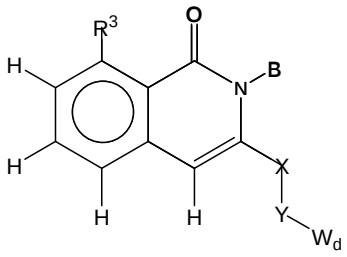
[0037] In some of the embodiments of Formula VI, B is a moiety of Formula II;



Formula II

wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and q is an integer of 0, 1, 2, 3, or 4.

[0038] In the present disclosure a compound and its pharmaceutically acceptable salts having the structure of Formula I-1 is also provided, wherein:



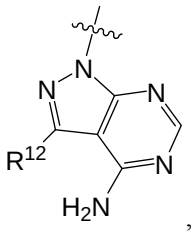
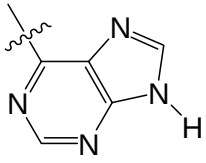
Formula I-1

[0039] B is a moiety of Formula II;

[0040] wherein W_c in B is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and q is an integer of 0, 1, 2, 3, or 4;

[0041] X is absent or $–(CH(R^9))_z$-, and z is an integer of 1;

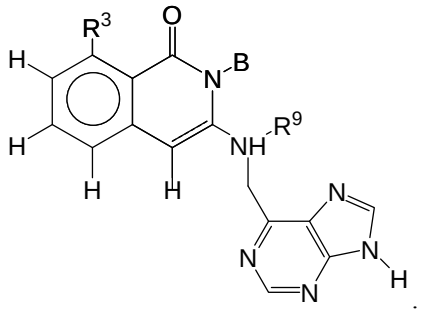
[0042] Y is absent, or -$N(R^9)$-;

[0043] when Y is absent, Wd is:  , or when Y is present, Wd is: 

[0044] R^1 is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, amido, alkoxycarbonyl, sulfonamido, halo, cyano, or nitro;

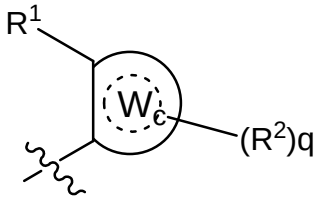
[0045] R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, heteroarylalkyl, alkoxy, amino, halo, cyano, hydroxy or nitro;

[0046] R^3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, aryl or heteroaryl;



Formula VI-A

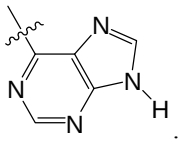
[0053] In some embodiments, a compound of Formula I or Formula I-1 is the compound wherein B is a moiety of Formula II;



Formula II

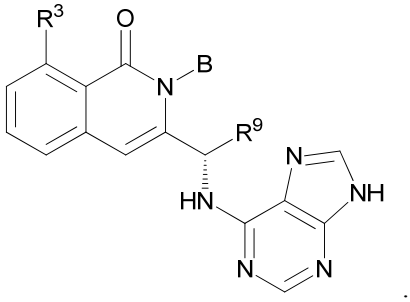
wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl; q is an integer of 0 or 1; R^1 is hydrogen, alkyl, or halo; R^2 is alkyl or halo; andR^3 is hydrogen, alkyl, or halo. In some embodiments, when both X and Y are present then Y is –NH-. In other embodiments, R^3 is -H, -CH_3, -CH_2CH_3, -CF_3, -Cl or –F. In further embodiments, R^3 is methyl or chloro. In other embodiments, R^3 is haloalkyl. For example, R^3 is -CF_3, -CH_2F or –CHF_2.

[0054] In some embodiments of the compound of Formula I or Formula I-1 , X is –$(CH(R^9))_z$-, wherein R^9 is methyl and z = 1; and

Wd is .

[0055] In other embodiments of the compound of Formula I or Formula I-1, the compound is predominately in an (S)-stereochemical configuration.

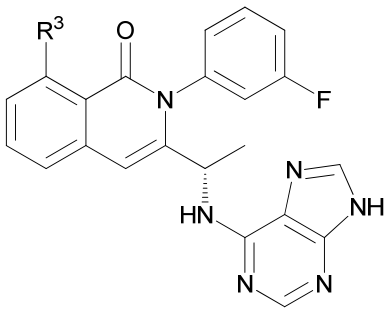
[0056] In further embodiments of the compound of the present disclosure, the compound has a structure of Formula V-A2:



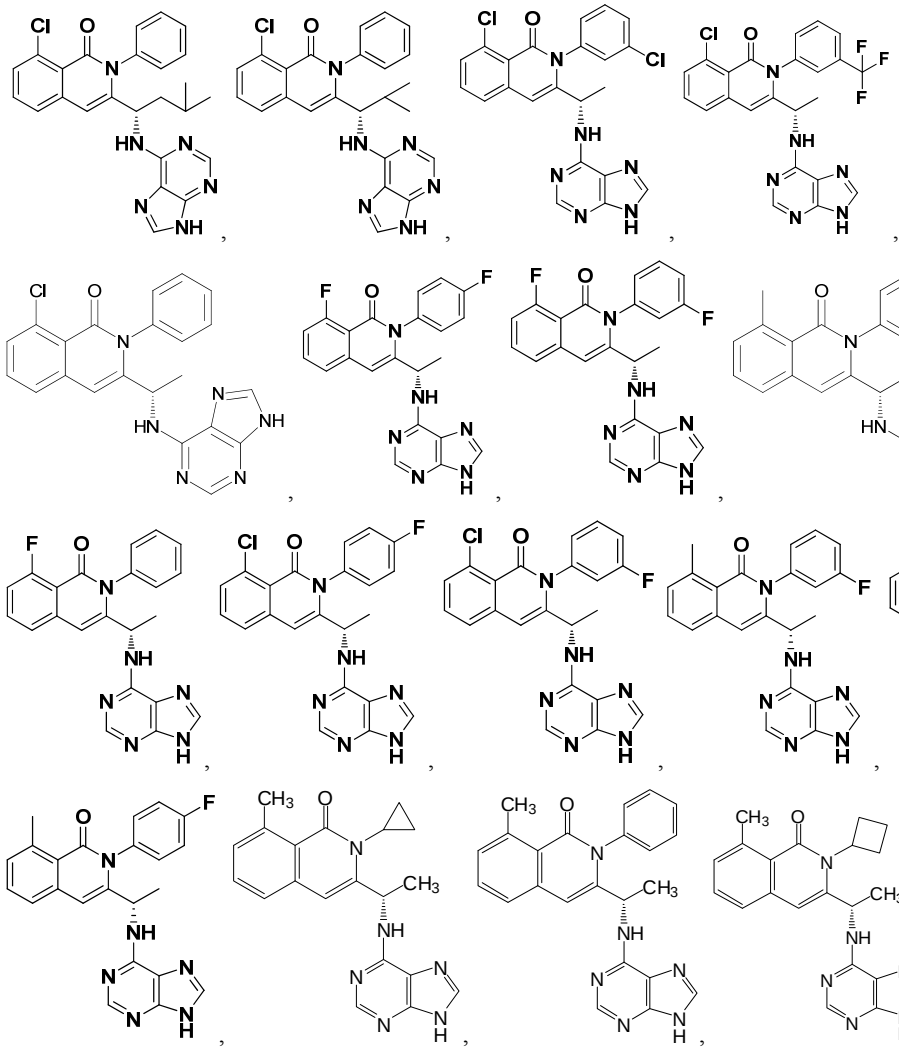
Formula V-A2

or its pharmaceutically acceptable salt thereof, wherein

B is a moiety of Formula II:



[0072] In some embodiments, the compound has the Formula:



acceptable salts thereof.

[0073] In the present disclosure, a pharmaceutical composition is also provided which comprises a pharmaceutically acceptable excipient and one or more compounds of any formulae provided herein, including but not limited to Formula I, I-1, IV, IV-A, V, V-A, V-A2, V-B, VI, and VI-A. In some embodiments, the composition is a liquid, solid, semi-solid, gel, or an aerosol form.

[0074] In the present disclosure, a method of inhibiting a phosphatidyl inositol-3 kinase (PI3 kinase), is also provided comprising: contacting the PI3 kinase with an effective amount of one or more compounds disclosed herein. For instance, the step of contacting involves the use of one or more compounds of any formulae provided herien including but not limited to Formula I, I-1, IV, IV-A, V, V-A, V-A2, V-B, VI, and VI-A. In some embodiments, the step of contacting

comprises contacting a cell that contains said PI3 kinase. In some embodiments of the method, the inhibition takes place in a subject suffering from a disorder associated with malfunctioning of one or more types of PI3 kinase. Some exemplary diseases involving malfunctioning of one or more types of PI3 kinases are selected from the group consisting of autoimmune diseases, rheumatoid arthritis, respiratory disease, allergic reactions, and various types of cancers. Where desired, the compound used in the method has the structure of Formula IV, wherein R^{11} is amino and R^{12} is substituted phenyl.

[0075] In some embodiments of the method, the inhibition takes place in a subject suffering from rheumatoid arthritis or a respiratory disease, and wherein the compound has the structure of Formula IV, and wherein R^{11} is amino and R^{12} is bicyclic heteroaryl.

[0076] In some embodiments, the method comprises administering a second therapeutic agent to the subject.

[0077] The present disclosure also provides a method of treating a disease manifesting an undesired immune response. The method comprises the step of administering to a subject in need thereof, one or more compounds disclosed herein including compounds of Formula I, I-1, IV, IV-A, V, V-A, V-A2, V-B, VI, and/or VI-A, in an amount that is effective in ameliorating said undesired immune response. In some embodiments, the one or more compounds inhibit T-cell independent B-cell activation as evidenced by a reduction in production of anti-TNP IgG3 by at least about five folds when administered in an amount less than about 30mg/kg BID dose to a test animal.

[0078] In some embodiments, the disease treated is associated with swelling or pain of a joint of a subject. The method can be effective in ameliorating one or more rheumatoid arthritis symptoms as evidenced by reduction in mean joint diameter by at least about 10% after 17 days and/or reduction in ankle diameter by at least 5-10% or more after several days to weeks of treatment, including for example reduction in ankle diameter by at least 5% after 7 days of treatment. In another embodiment, the undesired immune response is evidenced by enhanced production of anti-type II collagen antibodies, and the use of one or more subject compounds reduces the serum anti-type II collagen level at an ED50 of less than about 10 mg/kg.

INCORPORATION BY REFERENCE

[0079] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0080] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0081] FIG. 1 depicts an exemplary protocol for measuring T-cell independent production of TNP specific antibodies *in vivo*.

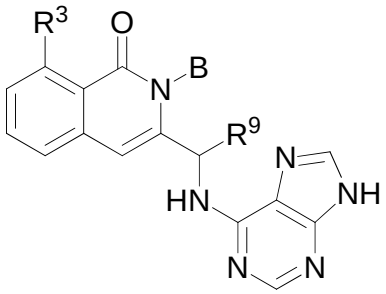
[0082] FIG. 2 depicts the fold reduction in TNP specific IgG3 response to antigens provided by compounds 7 and 53 of formula IV as compared to a vehicle control, when administered orally.

[0083] FIG. 3 depicts the dose-dependent effect of twice daily oral administration of compound 53 of formula IV in reducing the increase in ankle diameter over time in a collagen-induced developing arthritis model in rats. Also depicted

CLAIMS

WHAT IS CLAIMED IS:

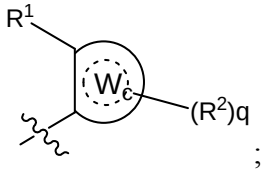
1. A compound of Formula V-A:



Formula V-A

or a pharmaceutically acceptable salt thereof, wherein

B is a moiety of Formula II:



;

Formula II

wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl;

q is an integer of 0 or 1;

R^1 is hydrogen, alkyl, or halo;

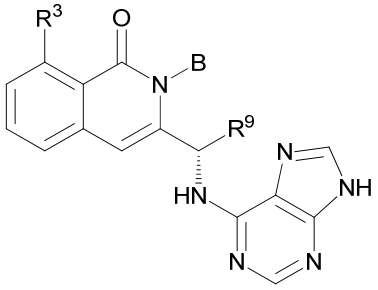
R^2 is alkyl or halo;

R^3 is halo;

R^9 is hydrogen, alkyl, or heterocycloalkyl;

wherein alkyl is optionally substituted with one or more halo.

2. The compound of claim 1 of the Formula V-A2:



Formula V-A2

or a pharmaceutically acceptable salt thereof.

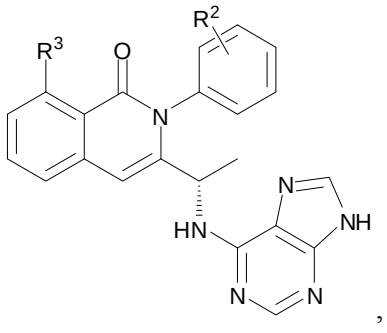
3. The compound of claim 1 or 2, wherein R^3 is -F.

4. The compound of claim 1 or 2, wherein R^3 is -Cl.

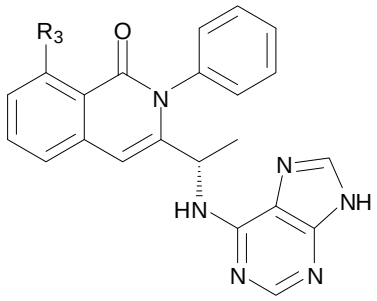
5. The compound of any one of claims 1-4, wherein R^9 is $-CH_3$ or $-CH_2CH_3$.

6. The compound of any one of claims 1-5, wherein W_c is phenyl or cyclopropyl, which is optionally substituted with at least one of $-CH_3$, $-CH_2CH_3$, $-CF_3$, -Cl, or -F.

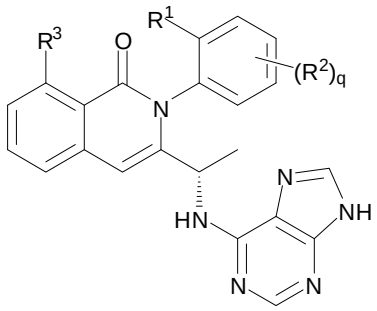
7. The compound of any one of claims 1-6, wherein the compound is a compound of formula:



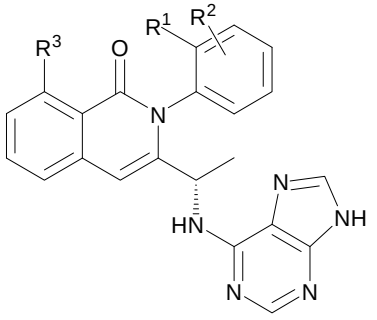
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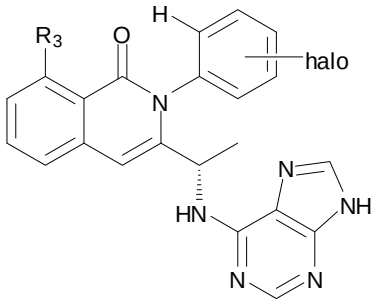
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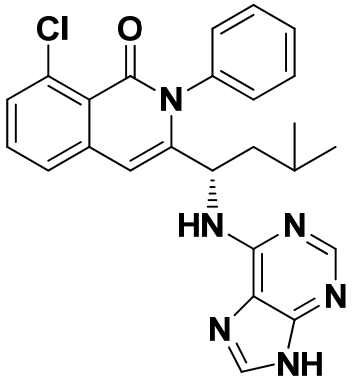
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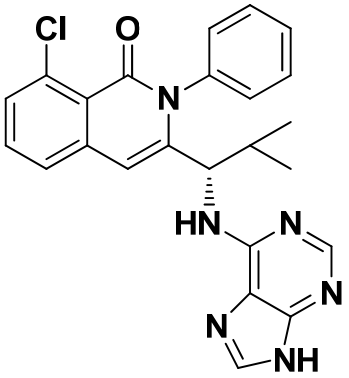
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or a pharmaceutically acceptable salt thereof.

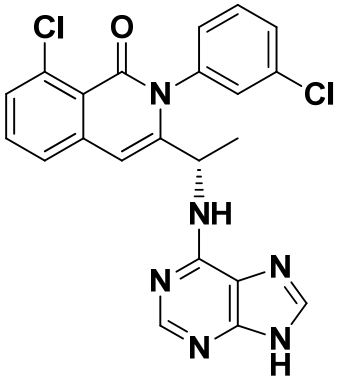
8. The compound of claim 1, wherein the compound is selected from:



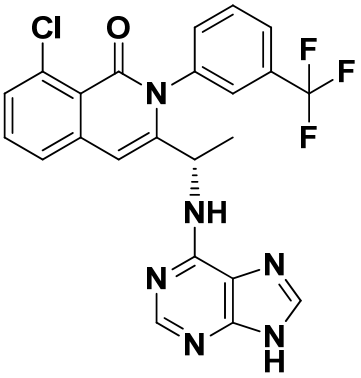
Compound 363,



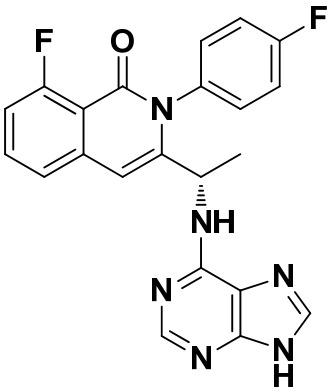
Compound 364,



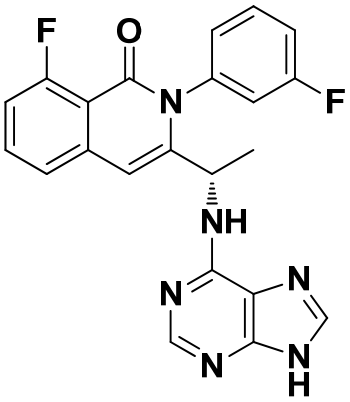
Compound 365



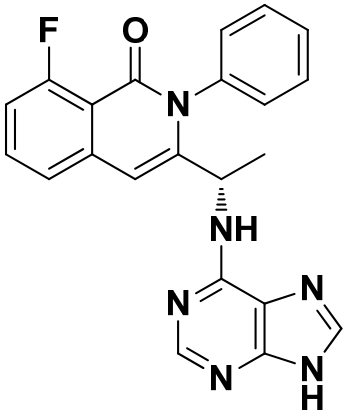
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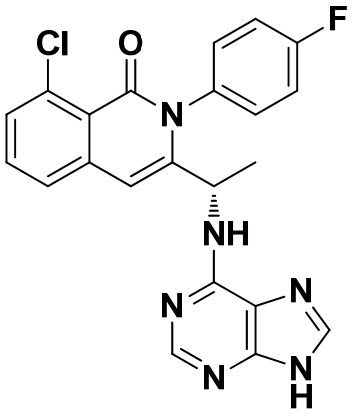
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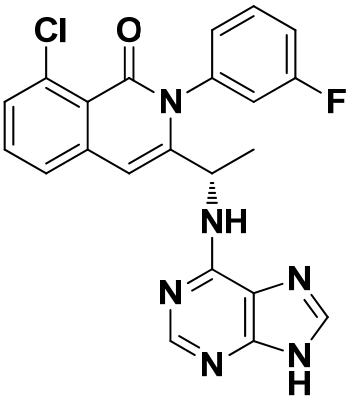
Compound 331



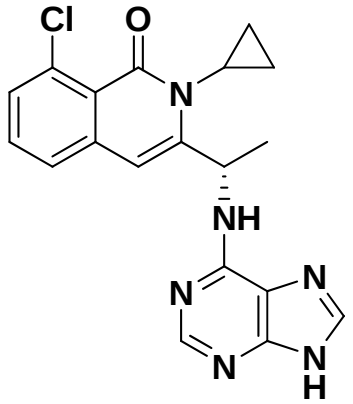
Compound 330,



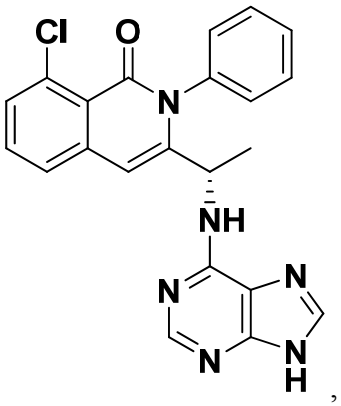
Compound 329,



Compound 328,



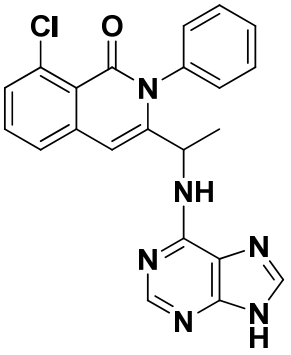
Compound 270, and



Compound 292,

or a pharmaceutically acceptable salt thereof.

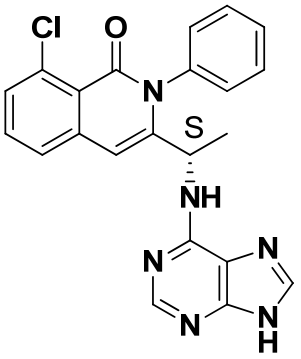
9. The compound of claim 1, wherein the compound is:



(Compound 237),

or a pharmaceutically acceptable salt thereof.

10. The compound of claim 1, wherein the compound is:



(Compound 292),

or a pharmaceutically acceptable salt thereof.

11. The compound of claim 1 or 9, wherein the compound is the S-enantiomer having an enantiomeric purity greater than 55%, greater than 80%, greater than 90%, or greater than 95%.

12. A pharmaceutical composition comprising the compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

13. A pharmaceutical composition comprising the compound of claim 10, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

14. Use of a compound of any one of claims 1-11 or a pharmaceutical composition of claim 12 or 13 in the manufacture of a medicament for the treatment of a disorder in a subject, wherein said disorder is one or more of cancer, bone disorder, inflammatory disease, immune disease, respiratory disease, thrombosis, or cardiac disease.

15. Use of a compound of any one of claims 1-11 or a pharmaceutical composition of claim 12 or 13 in the manufacture of a medicament for the treatment of one or more of asthma, emphysema, allergy, dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, chronic obstructive pulmonary disorder (COPD), psoriasis, multiple sclerosis, disorders related to diabetic complications, lupus erythematosus, scleroderma, graft versus host disease, restenosis, or atherosclerosis in a subject.

16. Use of a compound of any one of claims 1-11 or a pharmaceutical composition of claim 12 or 13 in the manufacture of a medicament for the treatment of cancer in a subject.

17. The use of claim 16, wherein the cancer is a leukemia or a lymphoma.

18. The use of claim 16, wherein the cancer is selected from thymus, brain, lung, squamous cell, skin, eye, retinoblastoma, intraocular melanoma, oral cavity and oropharyngeal, bladder, gastric, stomach, pancreatic, bladder, breast, cervical, head, neck, renal, kidney, liver, ovarian,

prostate, colorectal, esophageal, testicular, gynecological, thyroid, CNS, PNS, AIDS-related cancer, Kaposi's Sarcoma, mastocytosis, and viral-induced cancer.

19. The use of claim 16, wherein the cancer is selected from acute myelogenous leukemia (AML), acute lymphocytic leukemia, T-cell acute lymphocytic leukemia, chronic lymphocytic leukemia (CLL), hairy cell leukemia, myelodysplasia, myeloproliferative disorders, chronic myelogenous leukemia (CML), multiple myeloma (MM), myelodysplastic syndrome (MDS), human lymphotropic virus-type 1 (HTLV-1) leukemia, and B-cell acute lymphoblastic leukemia.

20. The use of claim 16, wherein the cancer is selected from diffuse large B-cell lymphoma, B-cell immunoblastic lymphoma, small non-cleaved cell lymphoma, human lymphotropic virus-type 1 (HTLV-1) leukemia/lymphoma, adult T-cell lymphoma, mantle cell lymphoma (MCL), Hodgkin disease, non-Hodgkin lymphomas, AIDS-related lymphoma, peripheral T-cell lymphoma, cutaneous T-cell lymphoma, multiple myeloma, and follicular lymphoma.

21. The use of claim 14, wherein the inflammatory or immune disease is one or more of:

(i) bursitis, lupus, acute disseminated encephalomyelitis (ADEM), Addison‘s disease, antiphospholipid antibody syndrome (APS), aplastic anemia, autoimmune hepatitis, coeliac disease, Crohn‘s disease, diabetes mellitus (type 1), Goodpasture's syndrome, Graves‘ disease, Guillain-Barré syndrome (GBS), Hashimoto's disease, inflammatory bowel disease, lupus erythematosus, myasthenia gravis, opsoclonus myoclonus syndrome (OMS), optic neuritis, Ord‘s thyroiditis, ostheoarthritis, uveoretinitis, pemphigus, polyarthritis, primary biliary cirrhosis, Reiter‘s syndrome, Takayasu‘s arteritis, temporal arteritis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, alopecia universalis, Chagas‘ disease, chronic fatigue syndrome, dysautonomia, endometriosis, hidradenitis suppurativa, interstitial cystitis, neuromyotonia, sarcoidosis, scleroderma, ulcerative colitis, vitiligo, vulvodynia, appendicitis, arteritis, arthritis, blepharitis, bronchiolitis, bronchitis, cervicitis, cholangitis, cholecystitis, chorioamnionitis, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatomyositis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis,

gingivitis, hepatitis, hidradenitis, ileitis, iritis, laryngitis, mastitis, meningitis, myelitis, myocarditis, myositis, nephritis, omphalitis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, uveitis, vaginitis, vasculitis, and vulvitis;

(ii) perennial allergic rhinitis, mesenteritis, acrodermatitis, angiodermatitis, atopic dermatitis, contact dermatitis, eczema, erythema multiforme, intertrigo, Stevens Johnson syndrome, toxic epidermal necrolysis, skin allergy, severe allergic reaction/anaphylaxis, allergic granulomatosis, allergic conjunctivitis, chorioretinitis, infectious keratoconjunctivitis, keratoconjunctivitis, ophthalmia neonatorum, trachoma, ocular inflammation, blepharoconjunctivitis, pericoronitis, rhinopharyngitis, sialadenitis, musculoskeletal system inflammation, adult onset Stills disease, Behcets disease, chondrocalcinosis, dactylitis, Felty syndrome, gout, infectious arthritis, Lyme disease, inflammatory osteoarthritis, periarthritis, Ross River virus infection, acute respiratory distress syndrome, acute bronchitis, acute sinusitis, allergic rhinitis, asthma, severe refractory asthma, pleurisy, seasonal allergic rhinitis, status asthmaticus, tracheobronchitis, serositis, neuromyelitis optica, poliovirus infection, Alport syndrome, balanitis, epididymo orchitis, focal segmental, glomerulosclerosis, glomerulonephritis, IgA nephropathy (Berger's Disease), orchitis, parametritis, pelvic inflammatory disease, pyelitis, pyelocystitis, hyperuricemia, aortitis, chylopericarditis, Dressler syndrome, endarteritis, extracranial temporal arteritis, HIV associated arteritis, intracranial temporal arteritis, Kawasaki disease, lymphangiophlebitis, Mondor disease, and periarteritis; and

(iii) jejunitis, mucositis, non alcoholic steatohepatitis, non viral hepatitis, autoimmune pancreatitis, perihepatitis, pouchitis, pseudomembranous colitis, rectosigmoiditis, salpingoperitonitis, sigmoiditis, steatohepatitis, Churg Strauss syndrome, ulcerative proctitis, irritable bowel syndrome, gastrointestinal inflammation, acute enterocolitis, anusitis, Balser necrosis, diverticulitis, enterohepatitis, eosinophilic esophagitis, esophagitis, hemorrhagic enteritis, hepatitis virus infection, hepatocholangitis, hypertrophic gastritis, ileocecitis, ankylosing spondylitis, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic

arthritis, cutaneous lupus, systemic lupus, lupus nephritis, AIDS, agammaglobulinemia, AIDS related complex, Brutons disease, Chediak Higashi syndrome, common variable immunodeficiency, DiGeorge syndrome, dysgammaglobulinemia, immunoglobulindeficiency, Job syndrome, Nezelof syndrome, phagocyte bactericidal disorder, Wiskott Aldrich syndrome, asplenia, elephantiasis, hypersplenism, lymphadenopathy, lymphedema, lymphocele, Nonne Milroy Meige syndrome, spleen disease, splenomegaly, thymoma, thymus disease, perivasculitis, pleuropericarditis, polyarteritis nodosa, thromboangiitis, thromboangiitis obliterans, thromboendocarditis, thrombophlebitis, and chronic obstructive pulmonary disease (COPD).

22. The use of claim 14, wherein the inflammatory or immune disease is asthma.

23. The use of claim 14, wherein the inflammatory or immune disease is rheumatoid arthritis.

24. The use of claim 23, wherein the compound is used in an amount effective to ameliorate one or more symptoms associated with rheumatoid arthritis selected from one or more of a reduction in the swelling of the joints, a reduction in serum anti-collagen levels, a reduction in bone resorption, a reduction in cartilage damage, a reduction in pannus, and a reduction in inflammation.

25. The use of any one of claims 14-24, further comprises use of one or more second therapeutic agents.

26. The use of claim 25, wherein the second therapeutic agent is a chemotherapeutic agent, optionally
wherein the chemotherapeutic agent is selected from mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, anti-androgens, alkyl sulfonates, aziridines, ethylenimines, methylamelamines, nitrogen mustards, nitrosureas, folic acid analogues, purine analogues, folic acid replenishers, taxanes, anti-estrogens, LHRH agonists, photodynamic therapies, triazenes, platinum containing

compounds, vinca alkaloids, taxoids, epipodophyllins, DHFR inhibitors, IMP dehydrogenase inhibitors, ribonucleotide reductase inhibitors, uracil analogues, cytocine analogues, Vitamin D analogues, isoprenylation inhibitors, dopaminergic neurotoxins, MDR inhibitors, Ca2+ ATPase inhibitors, tyrosine kinase inhibitors, proteasome inhibitors, and mTOR inhibitors; optionally wherein the chemotherapeutic agent is selected from the group consisting of imatinib, bortezomib, bicalutamide, adriamycin, thiotepa, busulfan, improsulfan, piposulfan, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide, trimethylolomelamine, chlorambucil, chlornaphazine, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, chlorozotocin, fotemustine, nimustine, ranimustine; aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, 5-fluorouracil (5-FU), denopterin, pteropterin, trimetrexate, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone, aminoglutethimide, mitotane, trilostane, frolinic acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, amsacrine, bestrabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, elfomithine, elliptinium acetate, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidamine, mitoguazone, mopidamol, nitracrine, pentostatin, phenamet; pirarubicin, podophyllinic acid, 2-ethylhydrazide, procarbazine, razoxane, sizofiran, spirogermanium; tenuazonic acid, triaziquone, 2,2',2"-trichlorotriethylamine, urethane, vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, arabinoside (“Ara-C”), paclitaxel, docetaxel, retinoic acid, esperamicins, capecitabine, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, toremifene, flutamide, nilutamide, leuprolide, goserelin, gemcitabine, 6-thioguanine, mercaptopurine, cisplatin,

carboplatin, vinblastine, platinum, mitomycin C, mitoxantrone, vincristine, vinorelbine, navelbine, novantrone, teniposide, daunomycin, aminopterin, xeloda, ibandronate, camptothecin-11 (CPT-11), topoisomerase inhibitor RFS 2000, difluoromethylornithine (DMFO), tamoxifen, raloxifene, megestrol, vertoporfin(BPD-MA), phthalocyanine, photosensitizer Pc4, demethoxy-hypocrellin A (2BA-2-DMHA), carmustine (BCNU), lomustine (CCNU), treosulfan, temozolomide, oxaliplatin, DHA-paclitaxel, Taxoprexin, PG-paclitaxel, paclitaxel poliglumex, CT-2103, XYOTAX, ANG1005, paclitaxel-EC-1, glucose-conjugated paclitaxel, etoposide, etoposide phosphate, topotecan, 9-aminocamptothecin, camptoirinotecan, irinotecan, crisnatol, mytomycin C, methotrexate, dichloromethotrexate, edatrexate, tiazofurin, ribavirin, EICAR, deferoxamine, ratitrexed, tegafur-uracil, cytosine arabinoside, fludarabine, EB 1089, CB 1093, KH 1060, lovastatin, 1-methyl-4-phenylpyridinium ion, staurosporine, actinomycin D, bleomycin A2, bleomycin B2, peplomycin, pegylated liposomal doxorubicin, pirarubicin, zorubicin, verapamil, thapsigargin, thalidomide, lenalidomide, axitinib (AG013736), bosutinib (SKI-606), cediranib (AZD2171), dasatinib (BMS-354825), erlotinib, gefitinib, lapatinib, lestaurtinib (CEP-701), neratinib (HKI-272), nilotinib, semaxanib (semaxinib, SU5416), sunitinib (SU11248), toceranib, vandetanib (ZD6474), vatalanib (PTK787, PTK/ZK), trastuzumab, bevacizumab, rituximab, cetuximab, panitumumab, ranibizumab, sorafenib, everolimus, alemtuzumab, gemtuzumab, ozogamicin, temsirolimus, ENMD-2076, PCI-32765, AC220, dovitinib lactate (TKI258, CHIR-258), BIBW 2992, SGX523, PF-04217903, PF-02341066, PF-299804, BMS-777607, ABT-869, MP470, BIBF 1120, AP24534, JNJ-26483327, MGCD265, DCC-2036, BMS-690154, CEP-11981, tivozanib (AV-951), OSI-930, MM-121, XL-184, XL-647, XL228, rapamycin, temsirolimus (CCI-779), ridaforolimus, AP23573 (Ariad), AZD8055 (AstraZeneca), BEZ235 (Novartis), BGT226 (Norvartis), XL765 (Sanofi Aventis), PF-4691502 (Pfizer), GDC0980 (Genetech), SF1126 (Semafoe), OSI-027 (OSI), oblimersen, leucovorin, pemetrexed, cyclophosphamide, prednisolone, dexamethasone, campathecin, plicamycin, asparaginase, methopterin, porfiromycin, melphalan, leurosidine, leurosine, trabectedin, discodermolide, and hexamethylmelamine, or a pharmaceutically acceptable salt thereof.

27. The use of claim 25, wherein the second therapeutic agent is selected from

(i) an agent that inhibits IgE production or activity,

(ii) an anti-inflammatory drug,

(iii) anticoagulants,

(iv) a biotherapeutic agent,

(v) an anti-angiogenesis agents,

(vi) a diuretic agent,

(vii) a hormone or therapeutic peptide or protein, and

(viii) radiation therapy; optionally

wherein

(i) the agent that inhibits IgE production or activity is selected from TEI-9874, 2-(4-(6-cyclohexyloxy-2-naphtyloxy)phenylacetamide)benzoic acid, rapamycin, rapamycin analogs, TORC1 inhibitors, TORC2 inhibitors, anti-IgE antibodies, omalizumab, and TNX-901;

(ii) the anti-inflammatory drug is selected from acetylsalicylic acid, ibuprofen, naproxen, indomethacin, nabumetone, tolmetin, a corticosteroid, prednisone, chloroquine, and hydroxychloroquine;

(iii) the anticoagulant is selected from aspirin™, heparin, and coumadin;

(iv) the biotherapeutic agent is selected from tumor necrosis factor, interferon α, interferon γ, IL-1, IL-2, IL-4, IL-6, IL-12, GM-CSF, Herceptin™ (trastuzumab), T-DM1, bevacizumab, cetuximab, panitumumab, rituximab, and tositumomab;

(v) the anti-angiogenic agent is selected from metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, salbutamol, salmeterol, terbutalin, isoetharine, tulobuterol, orciprenaline or (-)-4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]-amino]methyl]benzenemethanol;

(vi) the diuretic agent is selected from amiloride, anticholinergics, ipratropium, atropine and oxitropium;

(vii) the hormone or therapeutic peptide or protein is selected from cortisone, hydrocortisone, prednisolone, xanthines, aminophylline, choline theophyllinate, lysine theophyllinate, theophylline, insulin and glucagon; or
(viii) the radiation therapy is selected from external-beam therapy, internal radiation therapy, implant radiation, stereotactic radiosurgery, systemic radiation therapy, radiotherapy and permanent or temporary interstitial brachytherapy.

28. The use of claim 25, wherein the second therapeutic agent is a therapeutic antibody.

29. The use of claim 28, wherein the therapeutic antibody is anti-CD20 antibody.

30. The use of claim 28, wherein the therapeutic antibody is selected from cetuximab, panitumumab, trastuzumab, rituximab, tositumomab, alemtuzumab, bevacizumab, and gemtuzumab.

31. Use of a compound of claim 9 or claim 10, or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of claim 9 or claim 10, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disorder in a subject, wherein the disorder is selected from one or more of cancer, bone disorder, inflammatory disease, immune disease, respiratory disease, thrombosis, and cardiac disease.

32. Use of a compound of claim 9 or 10, or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of claim 9 or 10, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer in a subject.

33. The use of claim 32, wherein the cancer is a leukemia or a lymphoma.

34. The use of claim 32, wherein the cancer is selected from thymus, brain, lung, squamous cell, skin, eye, retinoblastoma, intraocular melanoma, oral cavity and oropharyngeal, bladder, gastric, stomach, pancreatic, bladder, breast, cervical, head, neck, renal, kidney, liver, ovarian,

prostate, colorectal, esophageal, testicular, gynecological, thyroid, CNS, PNS, AIDS-related cancer, Kaposi's Sarcoma, mastocytosis, and viral-induced cancer.

35. The use of claim 32, wherein the cancer is selected from acute myelogenous leukemia (AML), acute lymphocytic leukemia, T-cell acute lymphocytic leukemia, chronic lymphocytic leukemia (CLL), hairy cell leukemia, myelodysplasia, myeloproliferative disorders, chronic myelogenous leukemia (CML), multiple myeloma (MM), myelodysplastic syndrome (MDS), human lymphotropic virus-type 1 (HTLV-1) leukemia, and B-cell acute lymphoblastic leukemia.

36. The use of claim 32, wherein the cancer is selected from diffuse large B-cell lymphoma, B-cell immunoblastic lymphoma, small non-cleaved cell lymphoma, human lymphotropic virus-type 1 (HTLV-1) leukemia/lymphoma, adult T-cell lymphoma, mantle cell lymphoma (MCL), Hodgkin disease, non-Hodgkin lymphomas, AIDS-related lymphoma, peripheral T-cell lymphoma, cutaneous T-cell lymphoma, multiple myeloma, and follicular lymphoma.

37. The use of claim 33, wherein the leukemia is chronic lymphocytic leukemia.

38. The use of claim 33, wherein the lymphoma is non-Hodgkin lymphoma.

39. The use of claim 33, wherein the lymphoma is diffuse large B-cell lymphoma.

40. The use of claim 33, wherein the lymphoma is mantle cell lymphoma.

41. The use of claim 33, wherein the lymphoma is adult T-cell lymphoma.

42. The use of any one of claims 31-41, further comprises use of one or more second therapeutic agents.

43. The use of claim 42, wherein the second therapeutic agent is a chemotherapeutic agent; optionally
wherein the chemotherapeutic agent is selected from mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes,

topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, anti-androgens, alkyl sulfonates, aziridines, ethylenimines, methylamelamines, nitrogen mustards, nitrosureas, folic acid analogues, purine analogues, folic acid replenishers, taxanes, anti-estrogens, LHRH agonists, photodynamic therapies, triazenes, platinum containing compounds, vinca alkaloids, taxoids, epipodophyllins, DHFR inhibitors, IMP dehydrogenase inhibitors, ribonucleotide reductase inhibitors, uracil analogues, cytocine analogues, Vitamin D analogues, isoprenylation inhibitors, dopaminergic neurotoxins, MDR inhibitors, Ca2+ ATPase inhibitors, tyrosine kinase inhibitors, proteasome inhibitors, and mTOR inhibitors; optionally wherein the chemotherapeutic agent is selected from the group consisting of imatinib, bortezomib, bicalutamide, adriamycin, thiotepa, busulfan, improsulfan, piposulfan, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide, trimethylolomelamine, chlorambucil, chlornaphazine, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, chlorozotocin, fotemustine, nimustine, ranimustine; aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, 5-fluorouracil (5-FU), denopterin, pteropterin, trimetrexate, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone, aminoglutethimide, mitotane, trilostane, frolinic acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, amsacrine, bestrabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, elfomithine, elliptinium acetate, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidamine, mitoguazone, mopidamol, nitracrine, pentostatin, phenamet; pirarubicin, podophyllinic acid, 2-ethylhydrazide, procarbazine, razoxane, sizofiran, spirogermanium; tenuazonic acid, triaziquone, 2,2',2''-trichlorotriethylamine, urethane,

vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, arabinoside ("Ara-C"), paclitaxel, docetaxel, retinoic acid, esperamicins, capecitabine, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, toremifene, flutamide, nilutamide, leuprolide, goserelin, gemcitabine, 6-thioguanine, mercaptopurine, cisplatin, carboplatin, vinblastine, platinum, mitomycin C, mitoxantrone, vincristine, vinorelbine, navelbine, novantrone, teniposide, daunomycin, aminopterin, xeloda, ibandronate, camptothecin-11 (CPT-11), topoisomerase inhibitor RFS 2000, difluoromethylornithine (DMFO), tamoxifen, raloxifene, megestrol, vertoporfin(BPD-MA), phthalocyanine, photosensitizer Pc4, demethoxy-hypocrellin A (2BA-2-DMHA), carmustine (BCNU), lomustine (CCNU), treosulfan, temozolomide, oxaliplatin, DHA-paclitaxel, Taxoprexin, PG-paclitaxel, paclitaxel poliglumex, CT-2103, XYOTAX, ANG1005, paclitaxel-EC-1, glucose-conjugated paclitaxel, etoposide, etoposide phosphate, topotecan, 9-aminocamptothecin, camptoirinotecan, irinotecan, crisnatol, mytomycin C, methotrexate, dichloromethotrexate, edatrexate, tiazofurin, ribavirin, EICAR, deferoxamine, ratitrexed, tegafur-uracil, cytosine arabinoside, fludarabine, EB 1089, CB 1093, KH 1060, lovastatin, 1-methyl-4-phenylpyridinium ion, staurosporine, actinomycin D, bleomycin A2, bleomycin B2, peplomycin, pegylated liposomal doxorubicin, pirarubicin, zorubicin, verapamil, thapsigargin, thalidomide, lenalidomide, axitinib (AG013736), bosutinib (SKI-606), cediranib (AZD2171), dasatinib (BMS-354825), erlotinib, gefitinib, lapatinib, lestaurtinib (CEP-701), neratinib (HKI-272), nilotinib, semaxanib (semaxinib, SU5416), sunitinib (SU11248), toceranib, vandetanib (ZD6474), vatalanib (PTK787, PTK/ZK), trastuzumab, bevacizumab, rituximab, cetuximab, panitumumab, ranibizumab, sorafenib, everolimus, alemtuzumab, gemtuzumab, ozogamicin, temsirolimus, ENMD-2076, PCI-32765, AC220, dovitinib lactate (TKI258, CHIR-258), BIBW 2992, SGX523, PF-04217903, PF-02341066, PF-299804, BMS-777607, ABT-869, MP470, BIBF 1120, AP24534, JNJ-26483327, MGCD265, DCC-2036, BMS-690154, CEP-11981, tivozanib (AV-951), OSI-930, MM-121, XL-184, XL-647, XL228, rapamycin, temsirolimus (CCI-779), ridaforolimus, AP23573 (Ariad), AZD8055 (AstraZeneca), BEZ235 (Novartis), BGT226 (Norvartis), XL765 (Sanofi Aventis), PF-4691502 (Pfizer), GDC0980 (Genetech), SF1126 (Semafoe), OSI-027 (OSI), oblimersen,

leucovorin, pemetrexed, cyclophosphamide, prednisolone, dexamethasone, campathecin, plicamycin, asparaginase, methopterin, porfiromycin, melphalan, leurosidine, leurosine, trabectedin, discodermolide, and hexamethylmelamine, or a pharmaceutically acceptable salt thereof.

44. The use of claim 42 wherein the second therapeutic agent is selected from
(i) an agent that inhibits IgE production or activity,
(ii) an anti-inflammatory drug,
(iii) anticoagulants,
(iv) a biotherapeutic agent,
(v) an anti-angiogenesis agents,
(vi) a diuretic agent,
(vii) a hormone or therapeutic peptide or protein, and
(viii) radiation therapy; optionally
wherein
(i) the agent that inhibits IgE production or activity is selected from TEI-9874, 2-(4-(6-cyclohexyloxy-2-naphtyloxy)phenylacetamide)benzoic acid, rapamycin, rapamycin analogs, TORC1 inhibitors, TORC2 inhibitors, anti-IgE antibodies, omalizumab, and TNX-901;
(ii) the anti-inflammatory drug is selected from acetylsalicylic acid, ibuprofen, naproxen, indomethacin, nabumetone, tolmetin, a corticosteroid, prednisone, chloroquine, and hydroxychloroquine;
(iii) the anticoagulant is selected from aspirin™, heparin, and coumadin;
(iv) the biotherapeutic agent is selected from tumor necrosis factor, interferon α, interferon γ, IL-1, IL-2, IL-4, IL-6, IL-12, GM-CSF, Herceptin™ (trastuzumab), T-DM1, bevacizumab, cetuximab, panitumumab, rituximab, and tositumomab;
(v) the anti-angiogenic agent is selected from metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, salbutamol, salmeterol, terbutalin,

isoetharine, tulobuterol, orciprenaline or (-)-4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]-amino]methyl]benzenemethanol;
(vi) the diuretic agent is selected from amiloride, anticholinergics, ipratropium, atropine and oxitropium;
(vii) the hormone or therapeutic peptide or protein is selected from cortisone, hydrocortisone, prednisolone, xanthines, aminophylline, choline theophyllinate, lysine theophyllinate, theophylline, insulin and glucagon; or
(viii) the radiation therapy is selected from external-beam therapy, internal radiation therapy, implant radiation, stereotactic radiosurgery, systemic radiation therapy, radiotherapy and permanent or temporary interstitial brachytherapy.

45. The use of claim 42, wherein the second therapeutic agent is a therapeutic antibody.

46. The use of claim 45, wherein the therapeutic antibody is anti-CD20 antibody.

47. The use of claim 45, wherein the therapeutic antibody is selected from cetuximab, panitumumab, trastuzumab, rituximab, tositumomab, alemtuzumab, bevacizumab, and gemtuzumab.

48. The use of claim 47, wherein the therapeutic antibody is rituximab.

49. The use of claim 43, wherein the chemotherapeutic agent is nitrogen mustard.

50. The use of claim 43, wherein the chemotherapeutic agent is chlorambucil.

51. The use of claim 31, wherein the disorder is an inflammatory disease or immune disease.

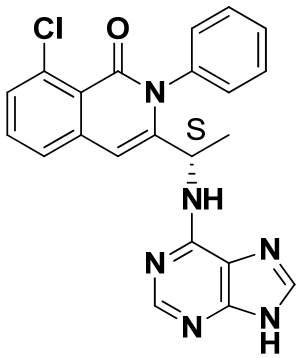
52. The use of claim 51, wherein the inflammatory disease or immune disease is rheumatoid arthritis.

53. The use of claim 31, wherein the disorder is a respiratory disease.

54. The use of claim 53, wherein the respiratory disease is asthma.

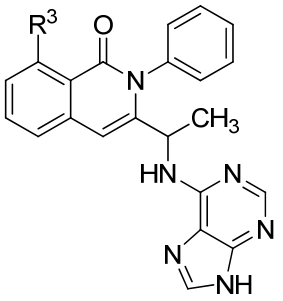
55. Use of a compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of any one of claims 12 and 13, in the manufacture of a medicament for inhibiting a phosphatidyl inositol-3 kinase (PI3 kinase) in a cell.

56. A compound of the formula:



(Compound 292).

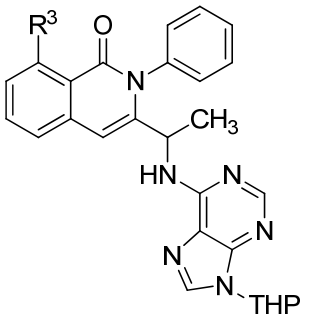
57. A process for preparing a compound of formula:



or a pharmaceutically acceptable salt thereof, wherein

R^3 is halo;

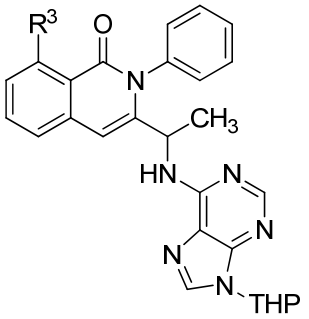
comprising deprotecting a compound of formula:



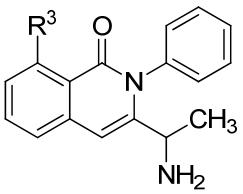
wherein the deprotection occurs in the presence of an acid.

58. The process of claim 57, wherein the acid is HCl.

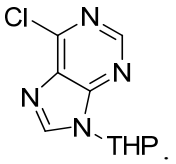
59. The process of claim 57 or claim 58, wherein the compound of formula:



is prepared by a process comprising reacting a compound of formula:

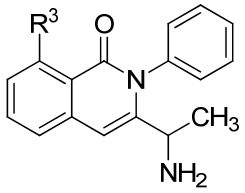


with a compound of formula:

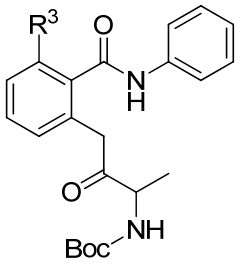


60. The process of claim 59, wherein the reaction occurs in the presence of N,N-diisopropylethylamine and n-butanol.

61. The process of claim 59 or claim 60, wherein the compound of formula:

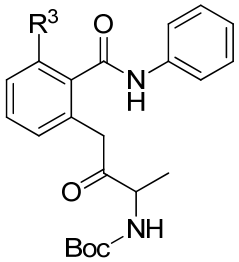


is prepared by a process comprising an intramolecular ring closure of a compound of formula:

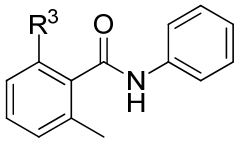


62. The process of claim 61, wherein the intramolecular ring closure occurs in the presence of hydrochloric acid and methanol.

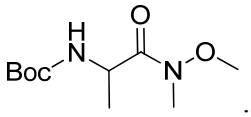
63. The process of claim 61 or claim 62, wherein the compound of formula:



is prepared by a process comprising reacting a compound of formula:

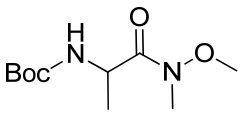


with a compound of formula:

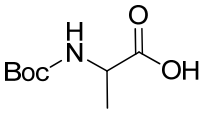


64. The process of claim 63, wherein the reaction occurs in the presence of hexamethylphosphoramide and n-butyllithium.

65. The process of claim 63 or claim 64, wherein the compound of formula:



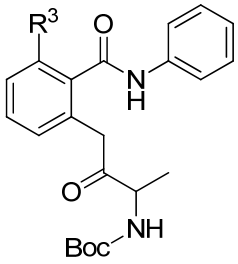
is prepared by a process comprising reacting a compound of formula:



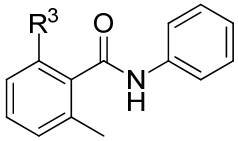
with N,O-dimethylhydroxylamine hydrochloride.

66. The process of claim 65, wherein the reaction occurs in the presence of triethylamine, hydroxybenzotriazole, and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.

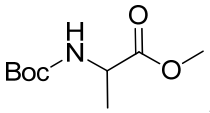
67. The process of claim 61 or claim 62, wherein the compound of formula:



is prepared by a process comprising reacting a compound of formula:

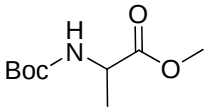


with a compound of formula:

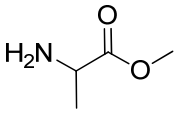


68. The process of claim 67, wherein the reaction occurs in the presence of hexamethylphosphoramide and n-butyllithium.

69. The process of claim 67 or claim 68, wherein the compound of formula:



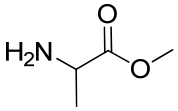
is prepared by a process comprising reacting a compound of formula:



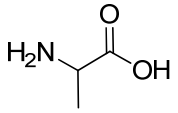
with di-tert-butyl dicarbonate.

70. The process of claim 69, wherein the reaction occurs in the presence of $NaHCO_3$.

71. The process of claim 69 or claim 70, wherein the compound of formula:



is prepared by a process comprising reacting a compound of formula:



with methanol.

72. The process of claim 71, wherein the reaction occurs in the presence of thionyl chloride.

73. The process of any one of claims 57–72, wherein R^3 is Cl.

74. A compound of any one of claims 1-11 or a pharmaceutical composition of claim 12 or 13, for use in the treatment of a disorder in a subject, wherein said disorder is one or more of cancer, bone disorder, inflammatory disease, immune disease, respiratory disease, thrombosis, or cardiac disease; or for use in the treatment of asthma, emphysema, allergy, dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, chronic obstructive pulmonary disorder (COPD), psoriasis, multiple sclerosis, disorders related to diabetic complications, lupus erythematosus, scleroderma, graft versus host disease, restenosis, or atherosclerosis in a subject; or for use in inhibiting a phosphatidyl inositol-3 kinase (PI3 kinase) in a cell.