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[57]	Abstract:	Cyclic ether pyrazol-4-yl-heterocyclyl-carboxamide compounds of Formula I, including stereoisomers, geometric isomers, tautomers, and pharmaceutically acceptable salts thereof, wherein R2 is a cyclic ether and X is thiazolyl, pyrazinyl, pyridinyl, or pyrimidinyl, are useful for inhibiting Pim kinase, and for treating disorders such as cancer mediated by Pim kinase. Methods of using compounds of Formula I for in vitro, in situ, and in vivo diagnosis, prevention or treatment of such disorders in mammalian cells, or associated pathological conditions, are disclosed.		

carbon, sp triple bond, wherein the alkynylene radical may be optionally substituted independently with one or more substituents described herein. Examples include, but are not limited to, ethynylene (-C≡C-), propynylene (propargylene, -CH_2C≡C-), and the like.

The terms "carbocycle", "carbocyclyl", "carbocyclic ring" and "cycloalkyl" refer to a monovalent non-aromatic, saturated or partially unsaturated ring having 3 to 12 carbon atoms (C_3–C_{12}) as a monocyclic ring or 7 to 12 carbon atoms as a bicyclic ring. Bicyclic carbocycles having 7 to 12 atoms can be arranged, for example, as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, and bicyclic carbocycles having 9 or 10 ring atoms can be arranged as a bicyclo [5,6] or [6,6] system, or as bridged systems such as bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane and bicyclo[3.2.2]nonane. Spiro moieties are also included within the scope of this definition. Examples of monocyclic carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, cyclododecyl, and the like. Carbocyclyl groups are optionally substituted independently with one or more substituents described herein.

"Aryl" means a monovalent aromatic hydrocarbon radical of 6-20 carbon atoms (C_6–C_{20}) derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Some aryl groups are represented in the exemplary structures as "Ar". Aryl includes bicyclic radicals comprising an aromatic ring fused to a saturated, partially unsaturated ring, or aromatic carbocyclic ring. Typical aryl groups include, but are not limited to, radicals derived from benzene (phenyl), substituted benzenes, naphthalene, anthracene, biphenyl, indenyl, indanyl, 1,2-dihydronaphthalene, 1,2,3,4-tetrahydronaphthyl, and the like. Aryl groups are optionally substituted independently with one or more substituents described herein.

"Arylene" means a divalent aromatic hydrocarbon radical of 6-20 carbon atoms (C_6–C_{20}) derived by the removal of two hydrogen atom from a two carbon atoms of a parent aromatic ring system. Some arylene groups are represented in the exemplary structures as "Ar". Arylene includes bicyclic radicals comprising an aromatic ring fused to a saturated, partially unsaturated ring, or aromatic carbocyclic ring. Typical arylene groups include, but are not limited to, radicals derived from benzene (phenylene), substituted benzenes, naphthalene, anthracene, biphenylene, indenylene, indanylene, 1,2-dihydronaphthalene, 1,2,3,4-tetrahydronaphthyl, and the like. Arylene groups are optionally substituted with one or more substituents described herein.

The terms "heterocycle," "heterocyclyl" and "heterocyclic ring" are used interchangeably herein and refer to a saturated or a partially unsaturated (i.e., having one or more double and/or triple bonds within the ring) carbocyclic radical of 3 to about 20 ring atoms in which at least one ring atom is a heteroatom selected from nitrogen, oxygen, phosphorus and sulfur, the remaining ring atoms being C, where one or more ring atoms is optionally substituted independently with one or more substituents described below. A heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 4 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 6 heteroatoms selected from N, O, P, and S), for example: a bicyclo [4,5], [5,5], [5,6], or [6,6] system. Heterocycles are described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and J. Am. Chem. Soc. (1960) 82:5566. "Heterocyclyl" also includes radicals where heterocycle radicals are fused with a saturated, partially unsaturated ring, or aromatic carbocyclic or heterocyclic ring. Examples of heterocyclic rings include, but are not limited to, morpholin-4-yl, piperidin-1-yl, piperazinyl, piperazin-4-yl-2-one, piperazin-4-yl-3-one, pyrrolidin-1-yl, thiomorpholin-4-yl, S-dioxothiomorpholin-4-yl, azocan-1-yl, azetidin-1-yl, octahydropyrido[1,2-a]pyrazin-2-yl, [1,4]diazepan-1-yl, pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, homopiperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinylimidazolinyl, imidazolidinyl, 3-azabicyco[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, azabicyclo[2.2.2]hexanyl, 3H-indolyl quinolizinyl and N-pyridyl ureas. Spiro moieties are also included within the scope of this definition. Examples of a heterocyclic group wherein 2 ring atoms are substituted with oxo (=O) moieties are pyrimidinonyl and 1,1-dioxo-thiomorpholinyl. The heterocycle groups herein are optionally substituted independently with one or more substituents described herein.

The term "heteroaryl" refers to a monovalent aromatic radical of 5-, 6-, or 7-membered rings, and includes fused ring systems (at least one of which is aromatic) of 5-20 atoms, containing one or more heteroatoms independently selected from nitrogen, oxygen,

and sulfur. Examples of heteroaryl groups are pyridinyl (including, for example, 2-hydroxypyridinyl), imidazolyl, imidazopyridinyl, pyrimidinyl (including, for example, 4-hydroxypyrimidinyl), pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxadiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, triazolyl, thiadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. Heteroaryl groups are optionally substituted independently with one or more substituents described herein.

The heterocycle or heteroaryl groups may be carbon (carbon-linked), or nitrogen (nitrogen-linked) bonded where such is possible. By way of example and not limitation, carbon bonded heterocycles or heteroaryls are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline.

By way of example and not limitation, nitrogen bonded heterocycles or heteroaryls are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline.

The terms "treat" and "treatment" refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder, such as the development or spread of cancer. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with

the condition or disorder as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented.

The phrase "therapeutically effective amount" means an amount of a compound of the present invention that (i) treats or prevents the particular disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition, or disorder described herein. In the case of cancer, the therapeutically effective amount of the drug may reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. To the extent the drug may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic. For cancer therapy, efficacy can be measured, for example, by assessing the time to disease progression (TTP) and/or determining the response rate (RR).

The terms "cancer" refers to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. A "tumor" comprises one or more cancerous cells. Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include squamous cell cancer (*e.g.,* epithelial squamous cell cancer), lung cancer including small- cell lung cancer, non-small cell lung cancer ("NSCLC"), adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, as well as head and neck cancer.

A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer, regardless of mechanism of action. Classes of chemotherapeutic agents include, but are not limited to: alkylating agents, antimetabolites, spindle poison plant alkaloids, cytotoxic/antitumor antibiotics, topoisomerase inhibitors, antibodies, photosensitizers, and kinase inhibitors. Chemotherapeutic agents include compounds used in "targeted therapy" and conventional chemotherapy. Examples of chemotherapeutic agents include: erlotinib

(TARCEVA®, Genentech/OSI Pharm.), docetaxel (TAXOTERE®, Sanofi-Aventis), 5-FU (fluorouracil, 5-fluorouracil, CAS No. 51-21-8), gemcitabine (GEMZAR®, Lilly), PD-0325901 (CAS No. 391210-10-9, Pfizer), cisplatin (cis-diamine, dichloroplatinum(II), CAS No. 15663-27-1), carboplatin (CAS No. 41575-94-4), paclitaxel (TAXOL®, Bristol-Myers Squibb Oncology, Princeton, N.J.), trastuzumab (HERCEPTIN®, Genentech), temozolomide (4-methyl-5-oxo- 2,3,4,6,8-pentazabicyclo [4.3.0] nona-2,7,9-triene- 9-carboxamide, CAS No. 85622-93-1, TEMODAR®, TEMODAL®, Schering Plough), tamoxifen ((*Z*)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]-*N*,*N*-dimethylethanamine, NOLVADEX®, ISTUBAL®, VALODEX®), and doxorubicin (ADRIAMYCIN®), Akti-1/2, HPPD, and rapamycin.

More examples of chemotherapeutic agents include: oxaliplatin (ELOXATIN®, Sanofi), bortezomib (VELCADE®, Millennium Pharm.), sutent (SUNITINIB®, SU11248, Pfizer), letrozole (FEMARA®, Novartis), imatinib mesylate (GLEEVEC®, Novartis), XL-518 (MEK inhibitor, Exelixis, WO 2007/044515), ARRY-886 (MEK inhibitor, AZD6244, Array BioPharma, Astra Zeneca), SF-1126 (PI3K inhibitor, Semafore Pharmaceuticals), BEZ-235 (PI3K inhibitor, Novartis), XL-147 (PI3K inhibitor, Exelixis), PTK787/ZK 222584 (Novartis), fulvestrant (FASLODEX®, AstraZeneca), leucovorin (folinic acid), rapamycin (sirolimus, RAPAMUNE®, Wyeth), a rapamycin analog, mTOR inhibitor such as everolimus, a MEK inhibitor (GDC-0973), a Bcl-2 inhibitor such as navitoclax, (ABT-263) or ABT-199), lapatinib (TYKERB®, GSK572016, Glaxo Smith Kline), lonafarnib (SARASAR™, SCH 66336, Schering Plough), sorafenib (NEXAVAR®, BAY43-9006, Bayer Labs), gefitinib (IRESSA®, AstraZeneca), irinotecan (CAMPTOSAR®, CPT-11, Pfizer), tipifarnib (ZARNESTRA™, Johnson & Johnson), ABRAXANE™ (Cremophor-free), albumin-engineered nanoparticle formulations of paclitaxel (American Pharmaceutical Partners, Schaumberg, Il), vandetanib (rINN, ZD6474, ZACTIMA®, AstraZeneca), chloranmbucil, AG1478, AG1571 (SU 5271; Sugen), temsirolimus (TORISEL®, Wyeth), pazopanib (GlaxoSmithKline), canfosfamide (TELCYTA®, Telik), thiotepa and cyclosphosphamide (CYTOXAN®, NEOSAR®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analog topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogs); cryptophycins (particularly

cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogs, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, calicheamicin gamma1I, calicheamicin omega1I (Angew Chem. Intl. Ed. Engl. (1994) 33:183-186); dynemicin, dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, nemorubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; 6-

thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; vinorelbine (NAVELBINE®); novantrone; teniposide; edatrexate; daunomycin; aminopterin; capecitabine (XELODA®, Roche); ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; and pharmaceutically acceptable salts, acids and derivatives of any of the above.

Also included in the definition of "chemotherapeutic agent" are: (i) anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX®; tamoxifen citrate), raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and FARESTON® (toremifine citrate); (ii) aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, MEGASE® (megestrol acetate), AROMASIN® (exemestane; Pfizer), formestanie, fadrozole, RIVISOR® (vorozole), FEMARA® (letrozole; Novartis), and ARIMIDEX® (anastrozole; AstraZeneca); (iii) anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); (iv) protein kinase inhibitors such as MEK inhibitors (WO 2007/044515); (v) lipid kinase inhibitors; (vi) antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, for example, PKC-alpha, Raf and H-Ras, such as oblimersen (GENASENSE®, Genta Inc.); (vii) ribozymes such as VEGF expression inhibitors (e.g., ANGIOZYME®) and HER2 expression inhibitors; (viii) vaccines such as gene therapy vaccines, for example, ALLOVECTIN®, LEUVECTIN®, and VAXID®; PROLEUKIN® rIL-2; topoisomerase 1 inhibitors such as LURTOTECAN®; ABARELIX® rmRH; (ix) anti-angiogenic agents such as bevacizumab (AVASTIN®, Genentech); and pharmaceutically acceptable salts, acids and derivatives of any of the above.

Also included in the definition of "chemotherapeutic agent" are therapeutic antibodies such as alemtuzumab (CAMPATH®), bevacizumab (AVASTIN®, Genentech); cetuximab (ERBITUX®, Imclone); panitumumab (VECTIBIX®, Amgen), rituximab (RITUXAN®, Genentech/Biogen Idec), pertuzumab (OMNITARG™, 2C4, Genentech), trastuzumab (HERCEPTIN®, Genentech), and tositumomab (BEXXAR®, Corixa, GlaxoSmithKline).

Humanized monoclonal antibodies with therapeutic potential as chemotherapeutic agents in combination with the Formula I compounds of the invention include: alemtuzumab, apolizumab, aselizumab, atlizumab, bapineuzumab, bevacizumab, bivatuzumab mertansine, cantuzumab mertansine, cedelizumab, certolizumab pegol, cidfusituzumab, cidtuzumab, daclizumab, eculizumab, efalizumab, epratuzumab, erlizumab, felvizumab, fontolizumab, gemtuzumab ozogamicin, inotuzumab ozogamicin, ipilimumab, labetuzumab, lebrikizumab, lintuzumab, matuzumab, mepolizumab, motavizumab, motovizumab, natalizumab, nimotuzumab, nolovizumab, numavizumab, ocrelizumab, omalizumab, palivizumab, pascolizumab, pecfusituzumab, pectuzumab, pertuzumab, pexelizumab, ralivizumab, ranibizumab, reslivizumab, reslizumab, resyvizumab, rovelizumab, ruplizumab, sibrotuzumab, siplizumab, sontuzumab, tacatuzumab tetraxetan, tadocizumab, talizumab, tefibazumab, tocilizumab, toralizumab, trastuzumab, tucotuzumab celmoleukin, tucusituzumab, umavizumab, urtoxazumab, and visilizumab.

A "metabolite" is a product produced through metabolism in the body of a specified compound or salt thereof. Metabolites of a compound may be identified using routine techniques known in the art and their activities determined using tests such as those described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered compound. Accordingly, the invention includes metabolites of compounds of the invention, including compounds produced by a process comprising contacting a Formula I compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof.

The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities.

Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., *McGraw-Hill Dictionary of Chemical Terms* (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. The compounds of the invention may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or *R* and *S,* are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity. Enantiomers may be separated from a racemic mixture by a chiral separation method, such as supercritical fluid chromatography (SFC). Assignment of configuration at chiral centers in separated enantiomers may be tentative, and depicted in Table 1 structures for illustrative purposes, while stereochemical determination awaits, such as x-ray crystallographic data.

The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

The term "pharmaceutically acceptable salts" denotes salts which are not biologically or otherwise undesirable. Pharmaceutically acceptable salts include both acid and base addition salts. The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

The term "pharmaceutically acceptable acid addition salt" denotes those pharmaceutically acceptable salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid, and organic acids selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid "mesylate", ethanesulfonic acid, p-toluenesulfonic acid, and salicyclic acid.

The term "pharmaceutically acceptable base addition salt" denotes those pharmaceutically acceptable salts formed with an organic or inorganic base. Examples of acceptable inorganic bases include sodium, potassium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, and aluminum salts. Salts derived from pharmaceutically acceptable organic nontoxic bases includes salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, and polyamine resins

A "solvate" refers to an association or complex of one or more solvent molecules and a compound of the invention. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethylacetate, acetic acid, and ethanolamine.

The term "EC_{50}" is the half maximal effective concentration" and denotes the plasma concentration of a particular compound required for obtaining 50% of the maximum of a particular effect in vivo.

The term "Ki" is the inhibition constant and denotes the absolute binding affinity of a particular inhibitor to a receptor. It is measured using competition binding assays and is equal to the concentration where the particular inhibitor would occupy 50% of the receptors if no competing ligand (e.g. a radioligand) was present. Ki values can be converted logarithmically to pKi values (-log Ki), in which higher values indicate exponentially greater potency.

The term "IC_{50}" is the half maximal inhibitory concentration and denotes the concentration of a particular compound required for obtaining 50% inhibition of a biological process in vitro. IC_{50} values can be converted logarithmically to pIC_{50} values (-log IC_{50}), in which higher values indicate exponentially greater potency. The IC_{50} value is not an absolute value but depends on experimental conditions e.g. concentrations employed, and can be converted to an absolute inhibition constant (Ki) using the Cheng-Prusoff equation (Biochem. Pharmacol. (1973) 22:3099).

The terms "compound of this invention," and "compounds of the present invention" and "compounds of Formula I" include compounds of Formulas I and stereoisomers, geometric isomers, tautomers, solvates, metabolites, and pharmaceutically acceptable salts and prodrugs thereof.

Any formula or structure given herein, including Formula I compounds, is also intended to represent hydrates, solvates, and polymorphs of such compounds, and mixtures thereof.

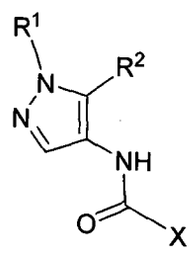
Any formula or structure given herein, including Formula I compounds, is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as, but not limited to 2H (deuterium, D), 3H (tritium), 11C, 13C, 14C, 15N, 18F, 31P, 32P, 35S, 36Cl, and 125I. Various isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as 3H, 13C, and 14C are incorporated. Such isotopically labelled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. Deuterium labelled or substituted therapeutic compounds of the invention may have

improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism, and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements. An 18F labeled compound may be useful for PET or SPECT studies. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. Further, substitution with heavier isotopes, particularly deuterium (i.e., 2H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent in the compound of the formula (I). The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this invention any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the compounds of this invention any atom specifically designated as a deuterium (D) is meant to represent deuterium.

CYCLIC ETHER PYRAZOL-4-YL-HETEROCYCLYL-CARBOXAMIDE COMPOUNDS

The present invention provides cyclic ether pyrazol-4-yl-heterocyclyl-carboxamide compounds of Formula I, including Formulas Ia-i, and pharmaceutical formulations thereof, which are potentially useful in the treatment of diseases, conditions and/or disorders modulated by Pim kinases.

Formula I compounds have the structure:

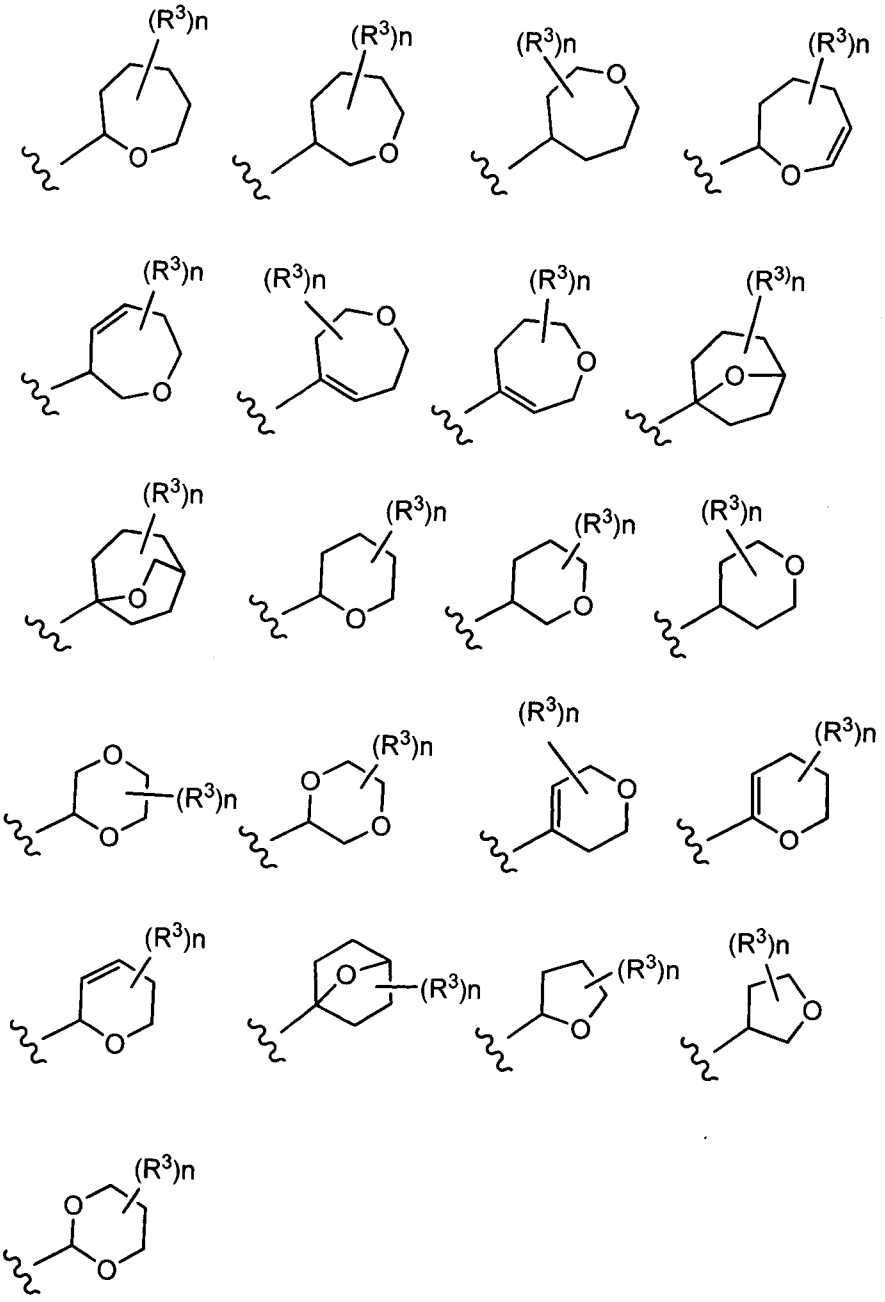


I

and stereoisomers, geometric isomers, tautomers, or pharmaceutically acceptable salts thereof, wherein:

R^1 is selected from H, C_1–C_{12} alkyl, C_2–C_{12} alkenyl, C_2–C_{12} alkynyl, C_6–C_{20} aryl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_1–C_{20} heteroaryl, and –(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl);

R^2 is selected from the structures:



where the wavy line indicates the site of attachment;

R^3 is independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2CH(CH_3)_2$, $-CH{=}CH_2$, $-CH{=}C(CH_3)_2$, $=CH_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2CH_2NH_2$, $-CH_2CHCH_2NH_2$, $-CH_2CH(CH_3)NH_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$, $-CH(OH)CH(CH_3)_2$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2SO_2CH_3$, $-CN$, $-CO_2H$, $-COCH_3$, $-COCH_2NH_2$, $-CO_2CH_3$, –

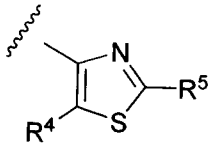
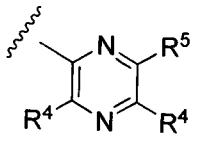
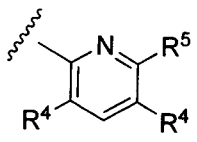
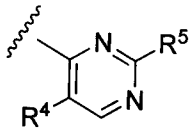
$CO_2C(CH_3)_3$, $-COCH(OH)CH_3$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-C(CH_3)_2CONH_2$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCH_2CHF_2$, $-NHCH_2CF_3$, $-NHCH_2CH_2OH$, $-NHCOCH_3$, $-N(CH_3)COCH_3$, $-NHC(O)OCH_2CH_3$, $-NHC(O)OCH_2Cl_3$, $-NHC(O)OC_6H_5$, $-NHS(O)_2CH_3$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, =O, $-OH$, $-OCH_3$, $-OCHF_2$, $-OCH_2F$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-OCH_2CH(CH_3)_2$, $-OC(CH_3)_3$, $-S(O)_2N(CH_3)_2$, $-SCH_3$, $-CH_2OCH_3$, $-S(O)_2CH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, azetidinyl, azepanyl, oxetanyl, oxetan-3-ylmethylamino, (3-methyloxetan-3-yl)methylamino, pyrrolidinyl, piperazinyl, piperidinyl, (piperidin-4-yl)ethyl), pyranyl, (piperidin-4-ylmethyl), morpholinomethyl, and morpholino;

or where two geminal R^3 groups form a spiro ring selected from a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl, azetidinyl, azepanyl, oxetanyl, pyrrolidinyl, piperazinyl, or piperidinyl ring, where the spiro ring is optionally substituted with one or more groups independently selected from –F, –OH, =O, $-CH_3$, $-NH_2$, $-CH_2F$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2NH_2$, and $-CF_3$;

or where two vicinal R^3 groups form a five-membered or six-membered heterocyclyl fused ring, where the heterocyclyl fused ring is optionally substituted with one or more groups independently selected from –F, –OH, =O, $-CH_3$, $-NH_2$, $-CH_2F$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2NH_2$, and $-CF_3$;

n is 0, 1, 2, 3, 4, 5, or 6;

X is selected from the structures:

where the wavy line indicates the site of attachment;

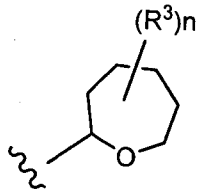
R^4 is independently H, F, $-CH_3$, or $-NH_2$; and

R^5 is selected from H, Cl, Br, C_1–C_{12} alkyl, –O–(C_1–C_{12} alkyl), –(C_1–C_{12} alkylene)–(C_3–C_{12} carbocyclyl), –(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl), –(C_2–C_8 alkenylene)–(C_3–C_{12} carbocyclyl), –(C_2–C_8 alkenylene)–(C_2–C_{20} heterocyclyl), C_6–C_{20} aryl, –(C_6–C_{20} arylene)–(C_2–C_{20} heterocyclyl), –(C_6–C_{20} arylene)–(C_6–C_{20} arylene), –(C_6–C_{20} arylene)–(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl), –(C_6–C_{20} arylene)–O–(C_2–C_{20} heterocyclyl), –(C_6–C_{20} arylene)–O–(C_1–C_{12} alkyl), C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_1–C_{20} heteroaryl, –(C_1–C_{20} heteroaryl)–(C_2–C_{20} heterocyclyl), and –(C_1–C_{20} heteroaryl)–(C_1–C_{12} alkyl); where alkyl, alkenyl, alkynyl, alkylene, carbocyclyl,

heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2CHCH_2NH_2$, $-CH_2CH(CH_3)NH_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH(CH_2OH)_2$, $-C(CH_2OH)_3$, $-CH(CH_3)OH$, $-C(CH_3)_2OH$, $-CH(OH)CH(CH_3)_2$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2SO_2CH_3$, $-CN$, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CO_2H$, $-COCH_3$, $-COCH(CH_3)_2$, $-CO_2CH_3$, $-CO_2C(CH_3)_3$, $-COCH(OH)CH_3$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-C(CH_3)_2CONH_2$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCOCH_3$, $-N(CH_3)COCH_3$, $-NHS(O)_2CH_3$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, $=O$, $-OH$, $-OCH_3$, $-OCF_3$, $-OCH(CH_3)_2$, $-S(O)_2N(CH_3)_2$, $-SCH_3$, $-CH_2OCH_3$, $-S(O)_2CH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, azetidinyl, azepanyl, oxetanyl, phenyl, pyrrolidinyl, piperazinyl, piperidinyl, (piperidin-4-yl)ethyl), pyranyl, (piperidin-4-ylmethyl), morpholinomethyl, and morpholino.

Exemplary embodiments of Formula I compounds include wherein R^1 is H, C_1–C_{12} alkyl including $-CH_3$, $-CH_2CH_3$, $-CH_2CHF_2$, and $-CH_2CF_3$, C_3–C_{12} carbocyclyl, or $-(C_1$–C_{12} alkylene)–(C_2–C_{20} heterocyclyl) including oxetan-3-ylmethyl.

Exemplary embodiments of Formula I compounds include wherein R^2 has the structure:



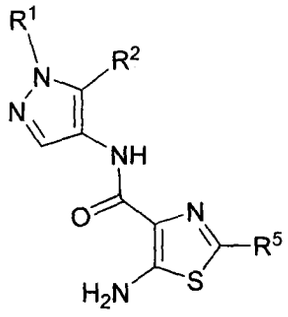
Exemplary embodiments of Formula I compounds include wherein R^3 is independently selected from F, Cl, $-OH$, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCH_2CHF_2$, $-NHCH_2CF_3$, $-CH_2NHCH_3$, and $-OCH_3$; and n is 1, 2, or 3.

Exemplary embodiments of Formula I compounds include wherein R^4 is $-NH_2$.

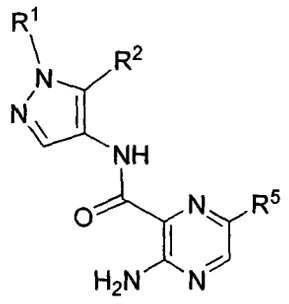
In a particular embodiments of Formula R^4 is –H.

Exemplary embodiments of Formula I compounds include wherein R^5 is C_6–C_{20} aryl including phenyl substituted with one or more F.

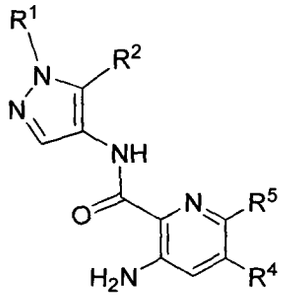
Exemplary embodiments of Formula I compounds include the structures of Formula Ia-d:



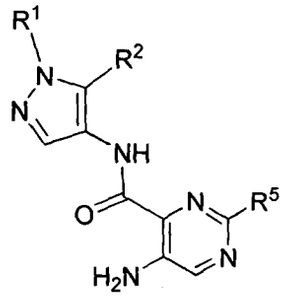
Ia



Ib



Ic



Id

BIOLOGICAL EVALUATION

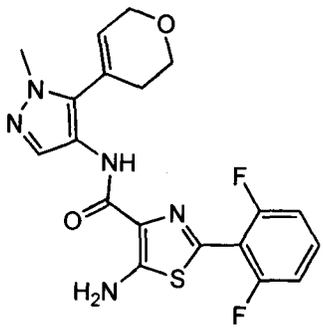
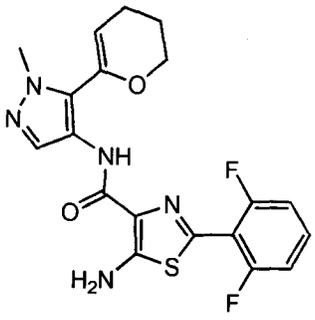
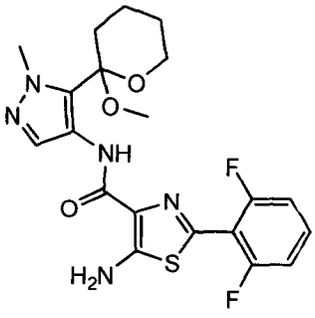
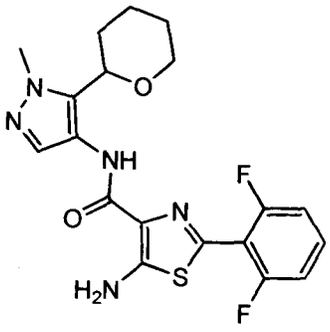
Determination of the Pim kinase activity of a Formula I compound is possible by a number of direct and indirect detection methods. Certain exemplary compounds described herein were assayed for their Pim kinase binding activity, including isoforms Pim-1, Pim-2, and Pim-3, (Example 901) and *in vitro* activity against tumor cells (Example 902). Certain exemplary compounds of the invention had Pim binding activity IC_{50} values less than about 1 micromolar (μM). Certain compounds of the invention had tumor cell-based activity EC_{50} values less than about 1 micromolar (μM), for example against cell line BaF3, a murine interleukin-3 dependent pro-B cell line, useful as a model system for assessing both the potency and downstream signaling of kinase oncogenes ("Ba/F3 cells and their use in kinase drug discovery", Warmuth, M, et al, (January 2007) Current Opinion in Oncology, Vol 19(1):55-60), and against MM1.S, a multiple myeloma cell line, useful as a model system for assessing the efficacy of Pim inhibitors in the treatment of multiple myeloma patients (Greenstein et al (2003) Exper. Hematol. 31(4):271-282). Formula I compounds having $Ki/IC_{50}/EC_{50}$ of less than 1 μM in assays described in Examples 901 and 902, may be useful therapeutically as Pim kinase inhibitors (Pim-1, Pim-2 and/or Pim-3).

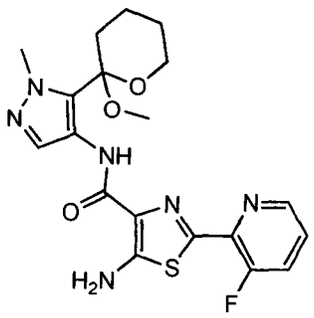
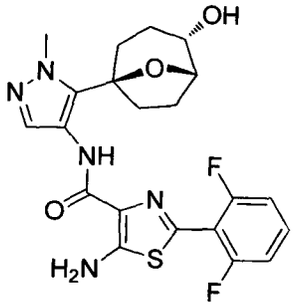
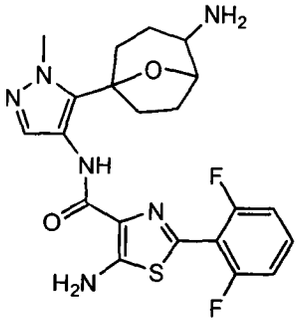
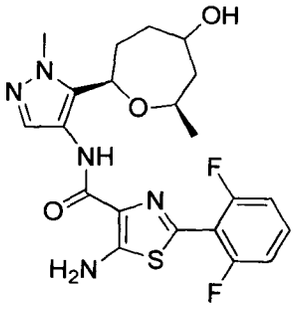
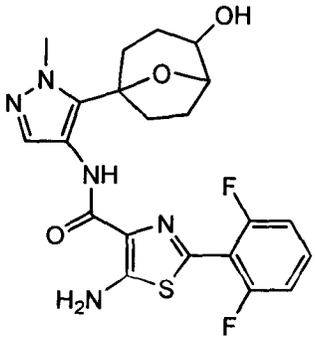
hERG (the human *Ether-à-go-go*-Related Gene) is a gene (*KCNH2*) that codes for a protein known as $K_v11.1$, the alpha subunit of a potassium ion channel. This ion channel (sometimes simply denoted as 'hERG') is best known for its contribution to the electrical activity of the heart that coordinates the heart's beating (i.e., the hERG channel mediates the repolarizing I_{Kr} current in the cardiac action potential). When this channel's ability to conduct electrical current across the cell membrane is inhibited or compromised, either by

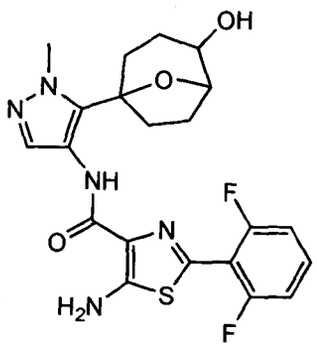
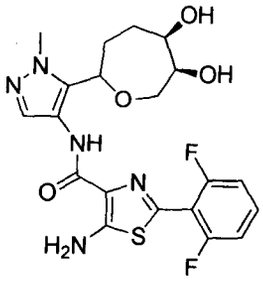
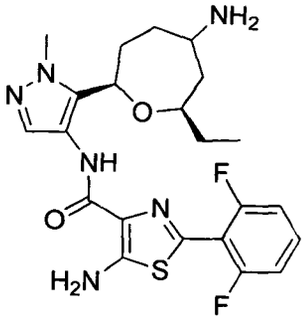
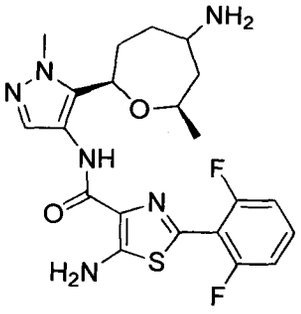
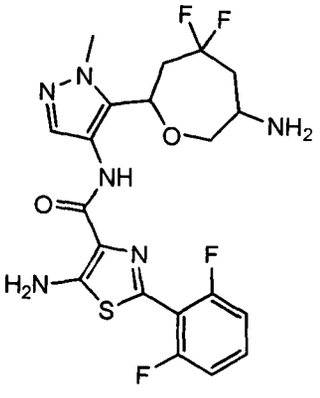
application of drugs or by rare mutations in some families (Hedley PL et al. (2009) Human Mutation 30 (11): 1486-511), it can result in a potentially fatal disorder called long QT syndrome; a number of clinically successful drugs in the market have had the tendency to inhibit hERG, and create a concomitant risk of sudden death, as a side-effect, which has made hERG inhibition an important antitarget that must be avoided during drug development (Sanguinetti MC, Tristani-Firouzi M (March 2006) Nature 440(7083): 463-9). hERG has also been associated with modulating the functions of some cells of the nervous system (Chiesa N et al (June 1997) J. Physiol. (Lond.). 501 (Pt 2) (2): 313-8; Overholt JL, et al (2000) Adv. Exp. Med. Biol. 475: 241-8) and with establishing and maintaining cancer-like features in leukemic cells. hERG assays were conducted according to Example 903.

Exemplary Formula I compounds in Tables 1a, 1b, and 1c were made, characterized, and tested for inhibition of Pim kinase according to the methods of this invention, and have the following structures and corresponding names (ChemBioDraw Ultra, Version 11.0, CambridgeSoft Corp., Cambridge MA). Some compounds with chiral atoms in Table 1 have not been fully characterized as to stereochemistry. A tentative assignment of stereochemistry or stereochemical relationship to other groups may be depicted in the structures. Means of separation of stereoisomers and characterization data are given in the Examples.

Table 1a.

No.	Structure	IUPAC Name	PIM1 LC3K (KI) uM
101		5-amino-2-(2,6-difluorophenyl)-N-[5-(3,6-dihydro-2H-pyran-4-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000485
102		5-amino-2-(2,6-difluorophenyl)-N-[5-(3,4-dihydro-2H-pyran-6-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000408
103		5-amino-2-(2,6-difluorophenyl)-N-[5-(2-methoxytetrahydropyran-2-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000209
104		5-amino-2-(2,6-difluorophenyl)-N-(1-methyl-5-tetrahydropyran-2-yl-pyrazol-4-yl)thiazole-4-carboxamide	0.000424

105		5-amino-2-(3-fluoro-2-pyridyl)-N-[5-(2-methoxytetrahydropyran-2-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000118
106		5-amino-2-(2,6-difluorophenyl)-N-(5-((1S,4S,5S)-4-hydroxy-8-oxabicyclo[3.2.1]octan-1-yl)-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000032
107		5-amino-N-[5-(2-amino-8-oxabicyclo[3.2.1]octan-5-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000008
108		5-amino-2-(2,6-difluorophenyl)-N-(5-((2R,7R)-5-hydroxy-7-methyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000049
109		5-amino-2-(2,6-difluorophenyl)-N-[5-(2-hydroxy-8-oxabicyclo[3.2.1]octan-5-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000034

110		5-amino-2-(2,6-difluorophenyl)-N-[5-(2-hydroxy-8-oxabicyclo[3.2.1]octan-5-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000017
111		5-amino-2-(2,6-difluorophenyl)-N-(5-((5R,6S)-5,6-dihydroxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000425
112		5-amino-N-(5-((2R,7R)-5-amino-7-ethyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000502
113		5-amino-N-(5-((2R,7R)-5-amino-7-methyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000019
114		5-amino-N-[5-(6-amino-4,4-difluoro-oxepan-2-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000032

CYCLIC ETHER PYRAZOL-4-YL-HETEROCYCLYL-CARBOXAMIDE COMPOUNDS AND METHODS OF USE

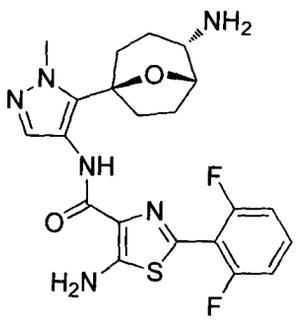
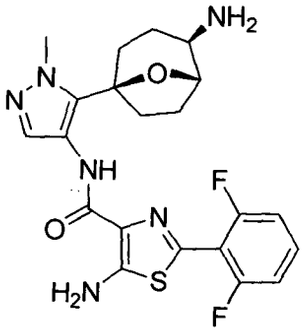
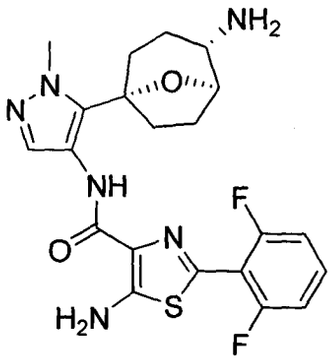
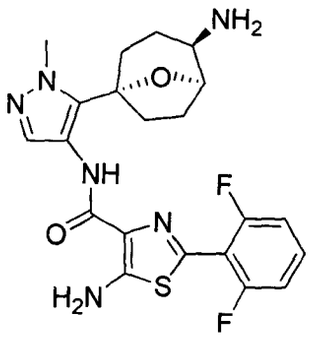
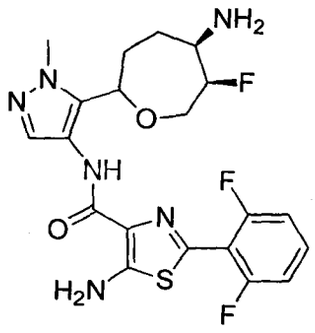
FIELD OF THE INVENTION

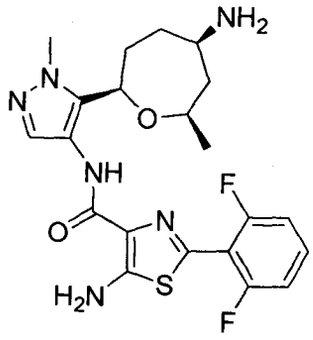
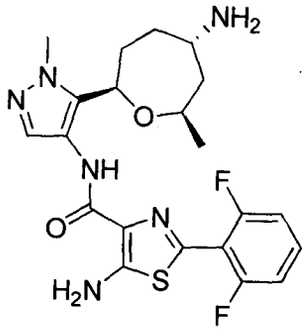
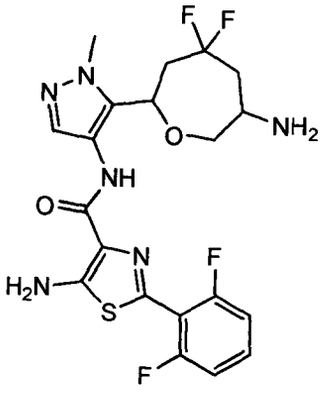
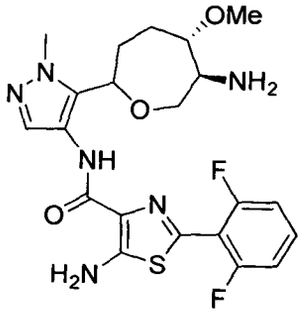
The invention relates generally to cyclic ether pyrazol-4-yl-heterocyclyl-carboxamide compounds for treating disorders mediated by Pim kinase (Pim-1, Pim-2, and/or Pim-3) inhibitors, thus useful as cancer therapeutics. The invention also relates to compositions, more specifically pharmaceutical compositions comprising these compunds and methods of using the same, either alone or in combination, to treat various forms of cancer and hyperproliferative disorders, as well as methods of using the compounds for *in vitro*, *in situ*, and *in vivo* diagnosis or treatment of mammalian cells, or associated pathological conditions.

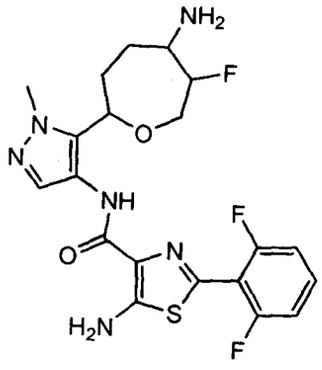
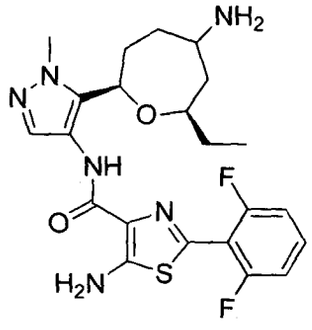
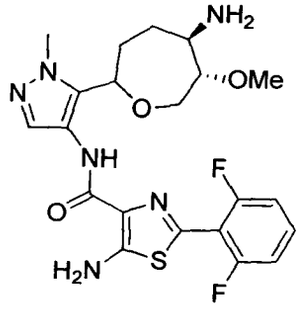
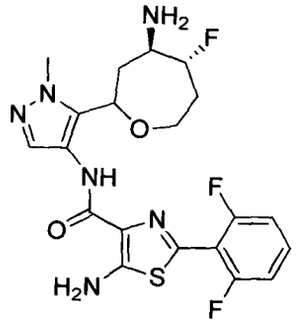
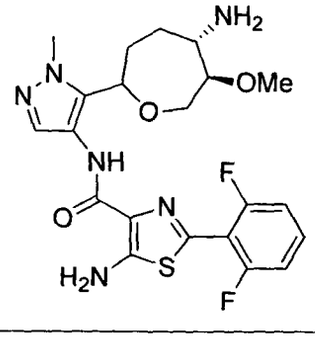
BACKGROUND OF THE INVENTION

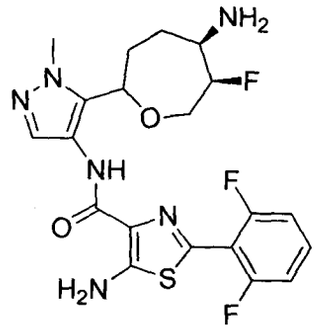
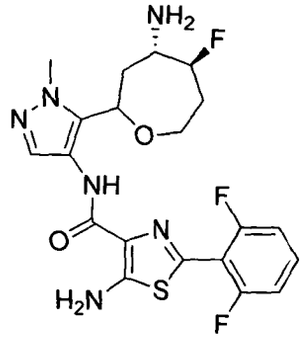
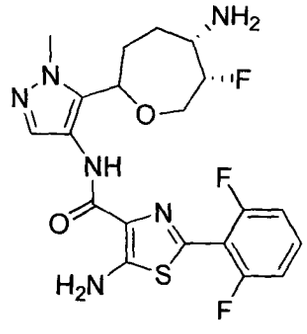
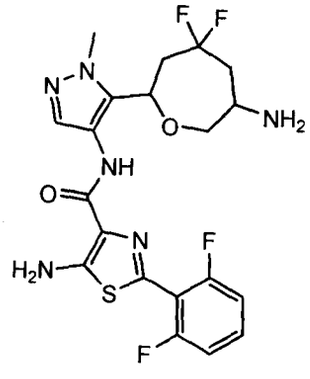
Pim kinases are family of three highly-related serine and threonine protein kinases encoded by the genes Pim-1, Pim-2, and Pim-3. The gene names are derived from the phrase Proviral Insertion, Moloney, frequent integration sites for murine moloney virus wherein the insertions lead to overexpression of Pim kinases and either *de novo* T-cell lymphomas, or dramatic acceleration of tumorigenesis in a transgenic Myc-driven lymphoma model (Cuypers et al. (1984) Cell, vol. 37 (1) pp. 141-50; Selten et al. (1985) EMBO J. vol. 4 (7) pp. 1793-8; van der Lugt et al. (1995) EMBO J. vol. 14 (11) pp. 2536-44; Mikkers et al. (2002) Nature Genetics, vol. 32 (1) pp. 153-9; van Lohuizen et al. (1991) Cell, vol. 65 (5) pp. 737-52). These experiments reveal synergy with the oncogene c-Myc, and suggest that inhibition of the Pim kinases may have therapeutic benefit.

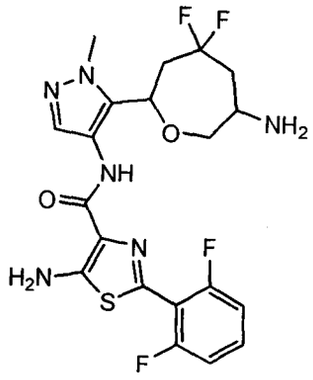
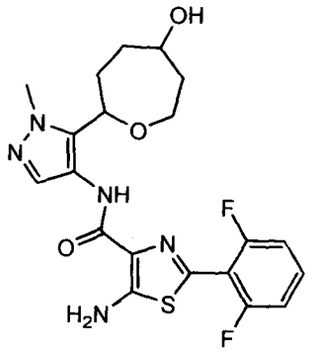
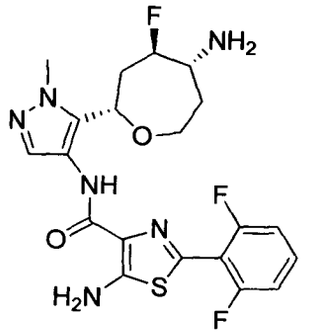
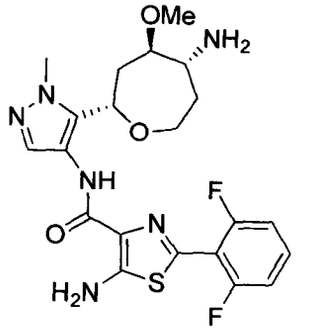
Mouse genetics suggests that antagonizing Pim kinases may have an acceptable safety profile; a Pim 1 -/-; Pim-2 -/-, Pim-3 -/- mouse knockout is viable although slightly smaller than wild type littermates (Mikkers et al. (2004) Mol Cell Biol vol. 24 (13) pp. 6104-154). The three genes give rise to six protein isoforms including a protein kinase domain, and apparently without recognizable regulatory domains. All six isoforms are constitutively active protein kinases that do not require post-translational modification for activity, thus Pim kinases are regulated primarily at the transcriptional level (Qian et al. (2005) J Biol Chem, vol. 280 (7) pp. 6130-7). Pim kinase expression is highly inducible by cytokines and growth factors receptors and Pims are direct transcriptional targets of the Stat proteins, including Stat3 and Stat5. Pim-1, for example, is required for the gp130-mediated Stat3 proliferation signal (Aksoy et al. (2007) Stem Cells, vol. 25 (12) pp. 2996-3004;

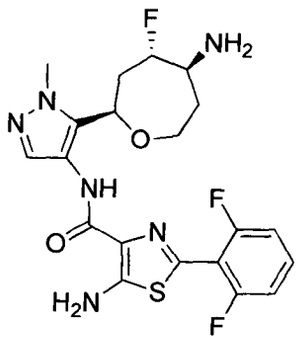
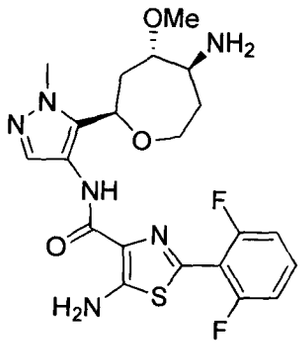
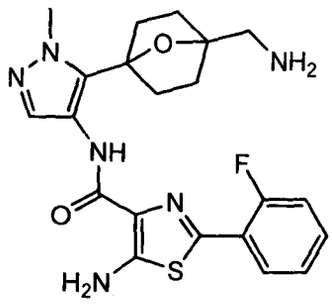
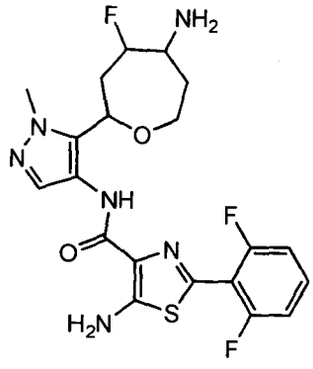
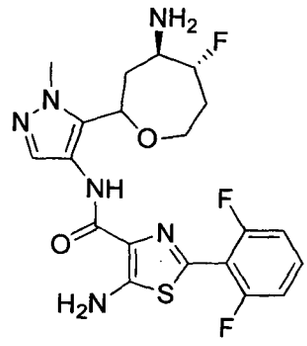
115		5-amino-N-(5-((1S,4S,5S)-4-amino-8-oxabicyclo[3.2.1]octan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000006
116		5-amino-N-(5-((1S,4R,5S)-4-amino-8-oxabicyclo[3.2.1]octan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000072
117		5-amino-N-(5-((1R,4S,5R)-4-amino-8-oxabicyclo[3.2.1]octan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000002
118		5-amino-N-(5-((1R,4R,5R)-4-amino-8-oxabicyclo[3.2.1]octan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000009
119		5-amino-N-(5-((5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000021

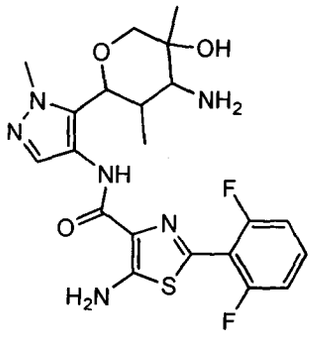
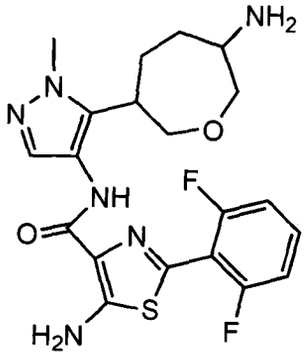
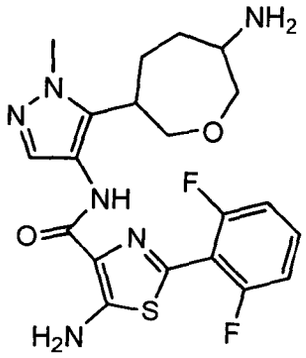
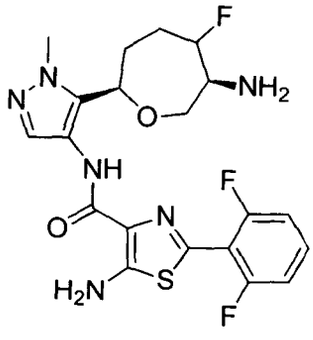
120		5-amino-N-(5-((2R,5R,7R)-5-amino-7-methyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000081
121		5-amino-N-(5-((2R,5S,7R)-5-amino-7-methyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000003
122		5-amino-N-[5-(6-amino-4,4-difluoro-oxepan-2-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000014
123		5-amino-N-(5-((5S,6S)-6-amino-5-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000125

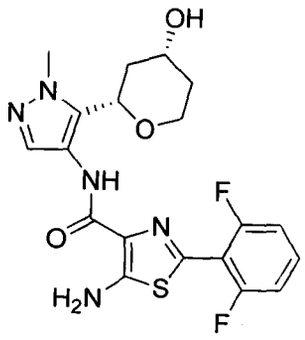
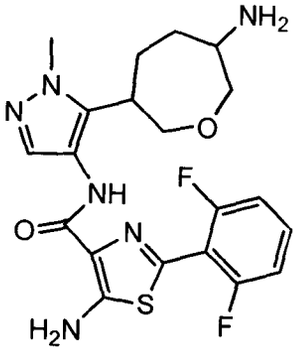
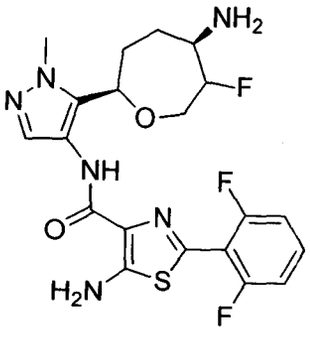
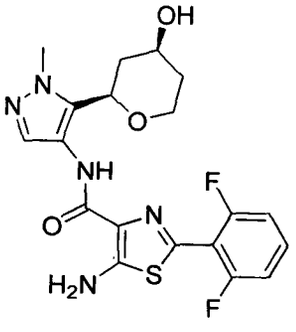
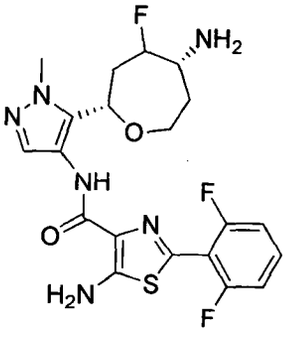
124		5-amino-N-[5-(5-amino-6-fluoro-oxepan-2-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000015
125		5-amino-N-(5-((2R,7R)-5-amino-7-ethyloxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.0035
126		5-amino-N-(5-((5R,6S)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000026
127		5-amino-N-(5-((4R,5R)-4-amino-5-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000112
128		5-amino-N-(5-((5S,6R)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000476

129		5-amino-N-(5-((5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000006
130		5-amino-N-(5-((4S,5S)-4-amino-5-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000358
131		5-amino-N-(5-((5S,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.00027
132		5-amino-N-[5-(6-amino-4,4-difluoro-oxepan-2-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000014

133		5-amino-N-[5-(6-amino-4,4-difluoro-oxepan-2-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000076
134		5-amino-2-(2,6-difluorophenyl)-N-[5-(5-hydroxyoxepan-2-yl)-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000054
135		5-amino-N-[5-(5-amino-4-fluoro-oxepan-2-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.00001
136		5-amino-N-(5-((2S,4R,5R)-5-amino-4-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000057

137		5-amino-N-(5-((2R,4S,5S)-5-amino-4-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000099
138		5-amino-N-(5-((2R,4S,5S)-5-amino-4-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.00187
139		5-amino-N-[5-[1-(aminomethyl)-7-oxabicyclo[2.2.1]heptan-4-yl]-1-methyl-pyrazol-4-yl]-2-(2-fluorophenyl)thiazole-4-carboxamide	0.000053
140		5-amino-N-(5-(5-amino-4-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000469
141		5-amino-N-(5-((4R,5R)-4-amino-5-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.00007

142		5-amino-N-[5-(4-amino-5-hydroxy-3,5-dimethyl-tetrahydropyran-2-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000441
143		5-amino-N-[5-(6-aminooxepan-3-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000194
144		5-amino-N-[5-(6-aminooxepan-3-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.00145
145		5-Amino-*N*-[5-[6-amino-5-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000351

146		5-amino-2-(2,6-difluorophenyl)-N-(5-((2S,4R)-4-hydroxytetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000095
147		5-amino-N-[5-(6-aminooxepan-3-yl)-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000141
148		5-Amino-*N*-[5-[5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000079
149		5-amino-2-(2,6-difluorophenyl)-N-(5-((2R,4S)-4-hydroxytetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000174
150		5-Amino-*N*-[5-[(2*S*,5*R*)-5-amino-4-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000105

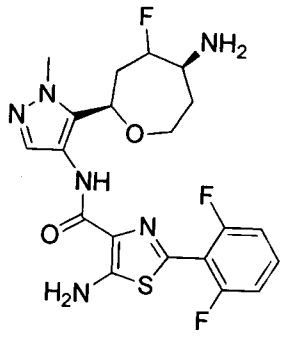
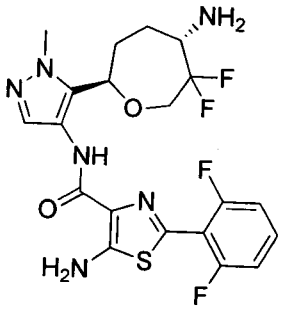
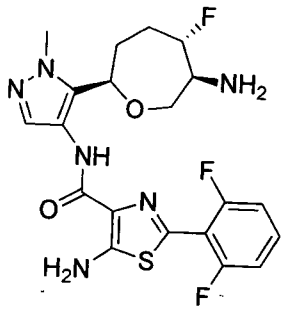
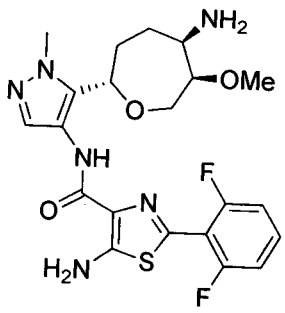
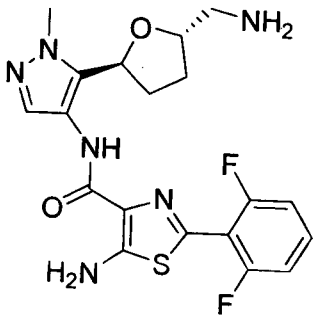
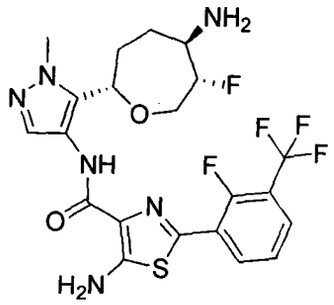
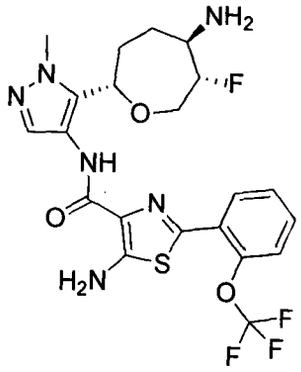
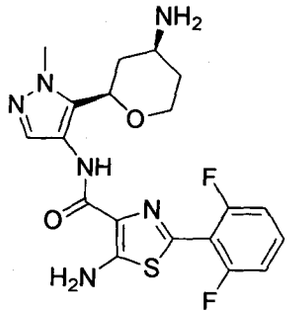
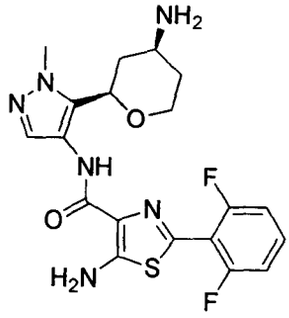
151		5-Amino-*N*-[5-[(2*R*,5*S*)-5-amino-4-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000068
152		5-Amino-*N*-[5-[(5-amino-6,6-difluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000031
153		5-Amino-*N*-[5-[(2*R*,5*S*,6*S*)-6-amino-5-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000114
154		5-Amino-*N*-[5-[(2*S*,5*R*,6*R*)-5-amino-6-methoxy-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.0000080
155		5-Amino-*N*-[5-[5-(aminomethyl)tetrahydrofuran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000104

Table 1b.

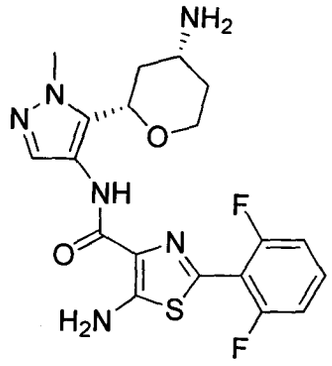
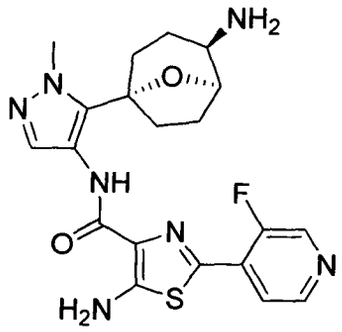
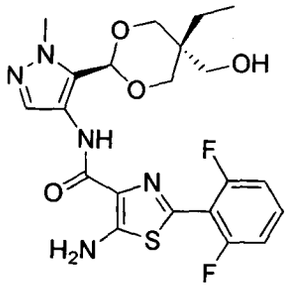
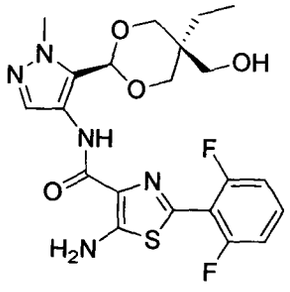
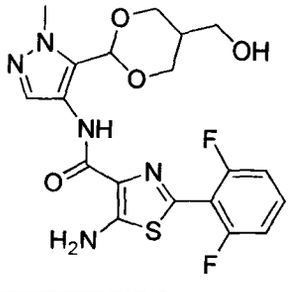
No.	Structure	IUPAC Name	PIM1 LC3K (KI) μM
156		5-amino-N-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.000107
157		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethoxy)phenyl)thiazole-4-carboxamide	0.000965
158		Amino-*N*-[5-[4-aminotetrahydropyran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000032
159		5-Amino-*N*-[5-[(2*R*,4*S*)-4-aminotetrahydropyran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000019

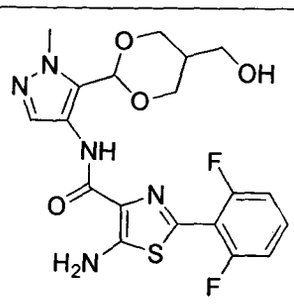
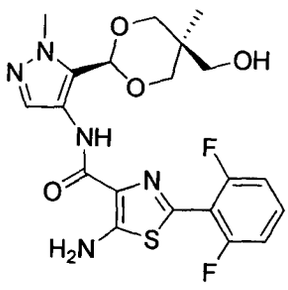
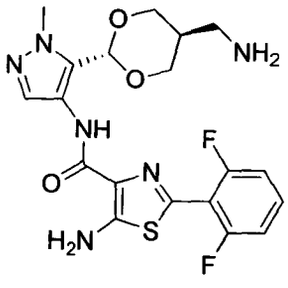
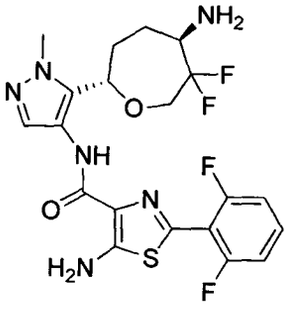
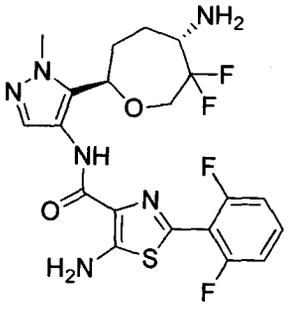
Hirano et al. (2000) Oncogene vol. 19 (21) pp. 2548-56; Shirogane et al. (1999) Immunity vol. 11 (6) pp. 709-19).

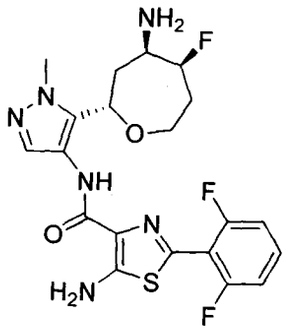
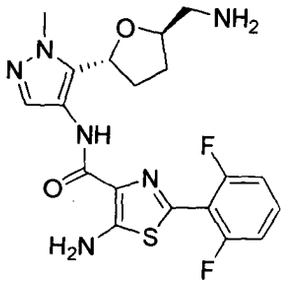
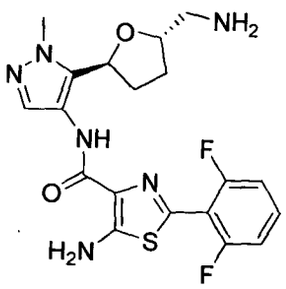
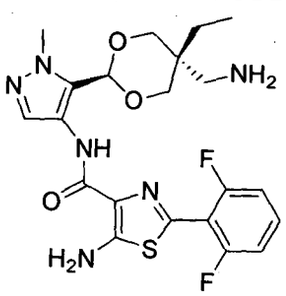
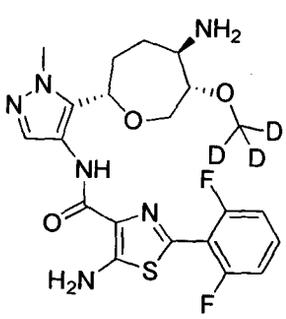
Pim kinases function in cellular proliferation and survival pathways parallel to the PI3k/Akt/mTOR signaling axis (Hammerman et al. (2005) Blood vol. 105 (11) pp. 4477-83). Indeed, several of the phosphorylation targets of the PI3k axis including Bad and eIF4E-BP1 are cell growth and apoptosis regulators and are also phosphorylation targets of the Pim kinases (Fox et al. (2003) Genes Dev vol. 17 (15) pp. 1841-54; Macdonald et al. (2006) Cell Biol vol. 7 pp. 1; Aho et al. (2004) FEBS Letters vol. 571 (1-3) pp. 43-9; Tamburini et al. (2009) Blood vol. 114 (8) pp. 1618-27). Pim kinase may affect cell survival since phosphorylation of Bad increases Bcl-2 activity and therefore promotes cell survival. Likewise, phosphorylation of eIF4E-BP1 by mTOR or Pim kinases causes depression of eIF4E, promoting mRNA translation and cellular growth. In addition, Pim-1 has been recognized to promote cell cycle progression through phosphorylation of CDC25A, p21, and Cdc25C (Mochizuki et al. (1999) J Biol Chemvol. 274 (26) pp. 18659-66; Bachmann et al. (2006) Int J Biochem Cell Biol vol. 38 (3) pp. 430-43; Wang et al. (2002) Biochim Biophys Acta vol. 1593 (1) pp. 45-55.

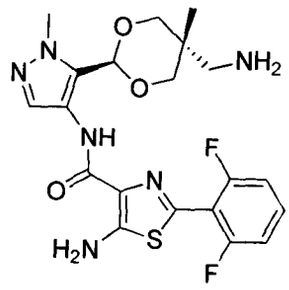
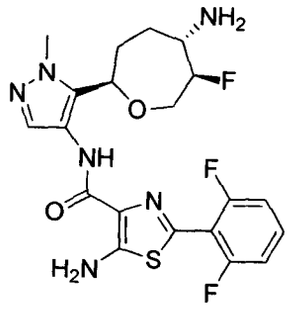
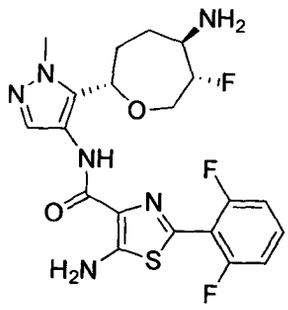
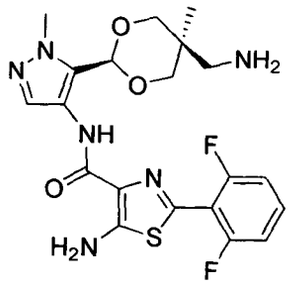
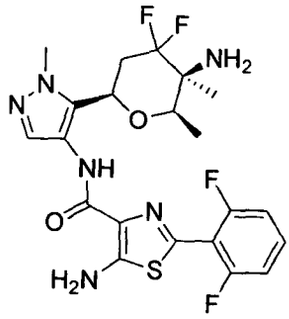
Pim kinases show synergy in transgenic mouse models with c-Myc-driven and Akt-driven tumors (Verbeek et al. (1991) Mol Cell Biol vol. 11 (2) pp. 1176-9; Allen et al. Oncogene (1997) vol. 15 (10) pp. 1133-41; Hammerman et al. (2005) Blood vol. 105 (11) pp. 4477-83). Pim Kinases are involved in transforming activity of oncogenes identified in acute myeloid leukemia (AML) including Flt3-ITD, BCR-abl, and Tel-Jak2. Expression of these oncogenes in BaF3 cells results in upregulation of Pim-1 and Pim-2 expression, resulting in IL-3 independent growth, and subsequent Pim inhibition results in apoptosis and cell growth arrest (Adam et al. (2006) Cancer Research 66 (7):3828-35). Pim overexpression and dysregulation has also been noted as a frequent event in many hematopoietic cancers, including leukemias and lymphoma (Amson et al. (1989) Proc Natl Acad Sci USA 86 (22):8857-61); Cohen et al. (2004) Leuk Lymphoma 45 (5):951-5; Hüttmann et al. (2006) Leukemia 20 (10):1774-82) as well as multiple myeloma (Claudio et al. (2002) Blood 100 (6):2175-86. Multiple myeloma (MM) is a clonal B-lymphocyte malignancy, which is characterized by the accumulation of terminally differentiated antibody-producing cells in the bone marrow.

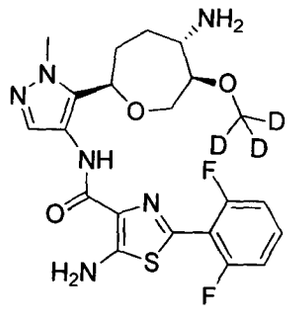
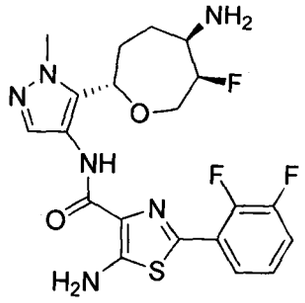
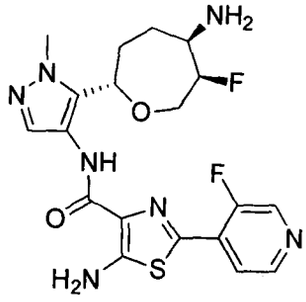
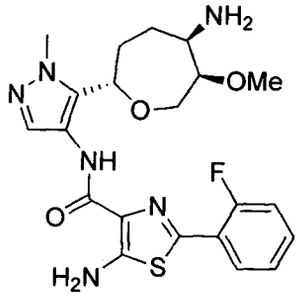
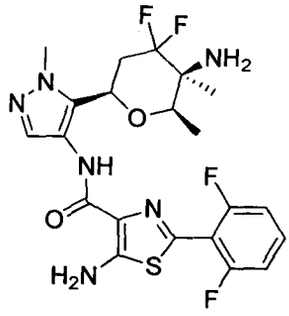
Pim 1 has been shown to be overexpressed and correlated to prostate cancer progression (Cibull et al. (2006) J Clin Pathol 59 (3):285-8; Dhanasekaran et al. (2001) Nature vol. 412 (6849):822-6). Pim 1 expression increases in mouse models with disease

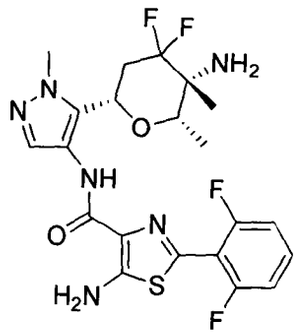
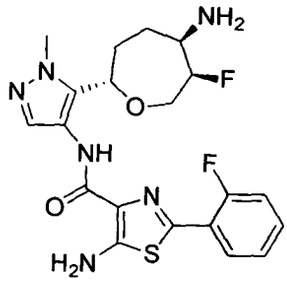
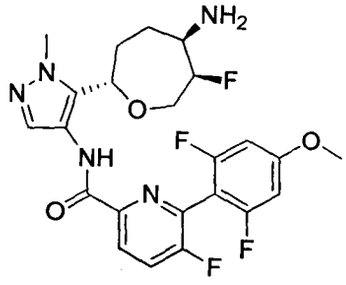
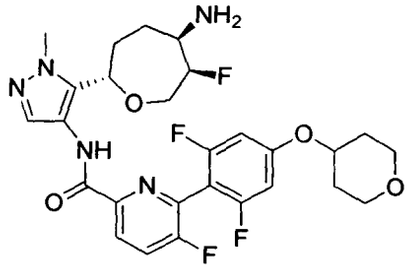
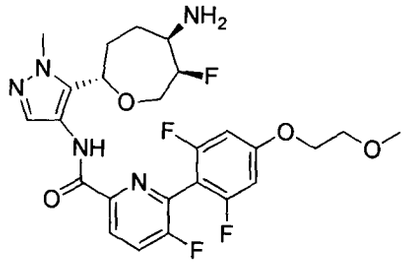
160		5-Amino-*N*-[5-[(2*S*,4*R*)-4-aminotetrahydropyran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000248
161		5-Amino-*N*-[5-[2-amino-8-oxabicyclo[3.2.1]octan-5-yl]-1-methyl-pyrazol-4-yl]-2-(3-fluoro-4-pyridyl)thiazole-4-carboxamide	0.000013
162		5-Amino-2-(2,6-difluorophenyl)-*N*-[5-[5-ethyl-5-(hydroxymethyl)-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000025
163		5-Amino-2-(2,6-difluorophenyl)-*N*-[5-[5-ethyl-5-(hydroxymethyl)-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.00126
164		5-Amino-2-(2,6-difluorophenyl)-*N*-[5-[5-(hydroxymethyl)-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000105

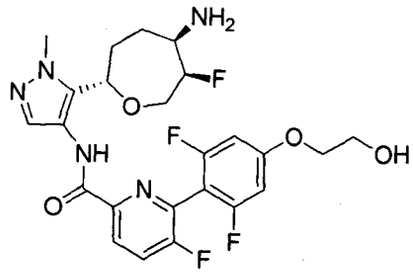
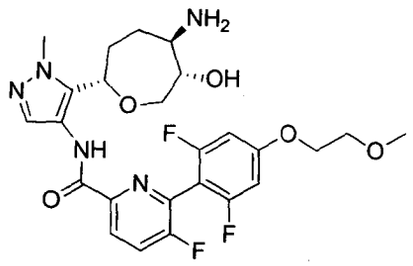
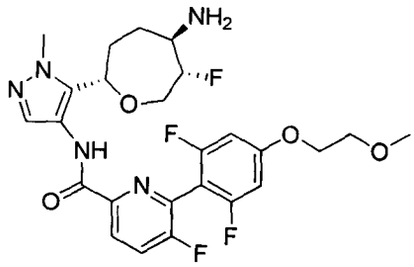
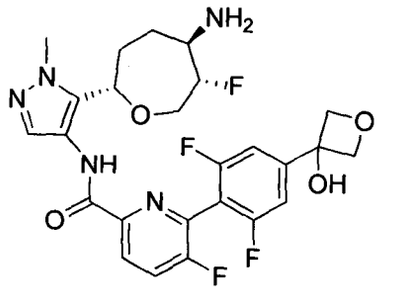
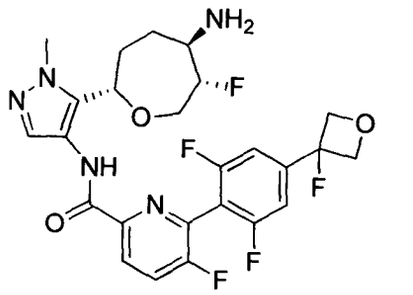
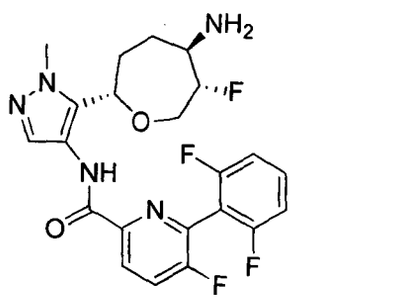
165		5-Amino-2-(2,6-difluorophenyl)-*N*-[5-[5-(hydroxymethyl)-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000647
166		5-Amino-2-(2,6-difluorophenyl)-*N*-[5-[5-(hydroxymethyl)- 5-methyl-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000514
167		5-Amino-*N*-[5-[5-(aminomethyl)-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000029
168		5-Amino-*N*-[5-[(2*S*,5*R*)-5-amino-6,6-difluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000013
169		5-Amino-*N*-[5-[(2*R*,5*S*)-5-amino-6,6-difluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000341

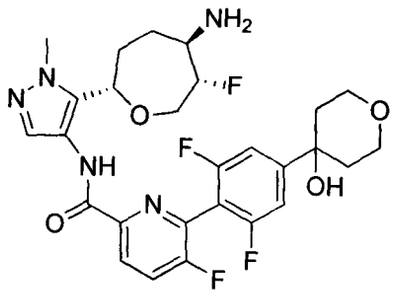
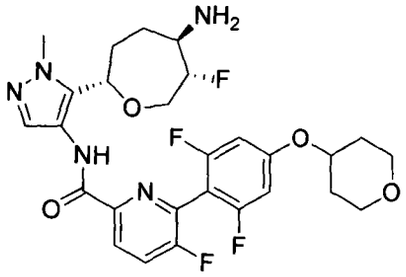
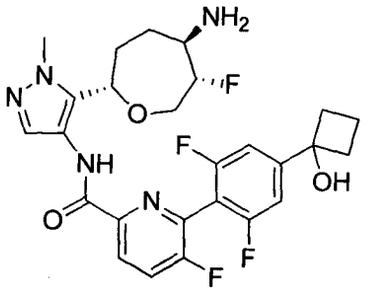
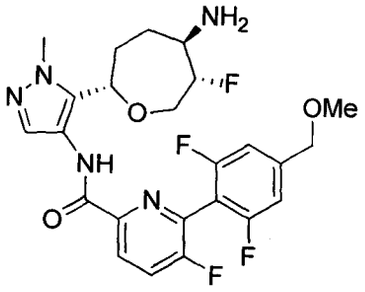
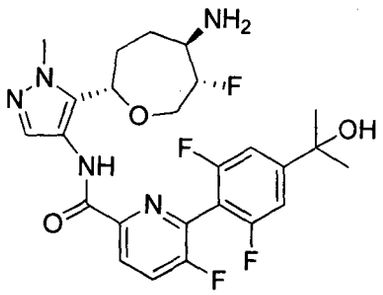
170		5-Amino-*N*-[5-[4-amino-5-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000126
171		5-Amino-*N*-[5-[(2*R*,5*R*)-5-(aminomethyl)tetrahydrofuran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000027
172		5-Amino-*N*-[5-[(2*S*,5*S*)-5-(aminomethyl)tetrahydrofuran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.00015
173		5-Amino-*N*-[5-[5-(aminomethyl)-5-ethyl-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000015
174		5-Amino-*N*-[5-[(2*S*,5*R*,6*S*)-5-amino-6-(trideuteriomethoxy)oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000135

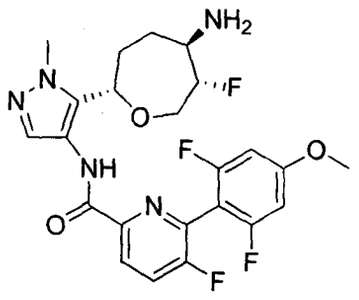
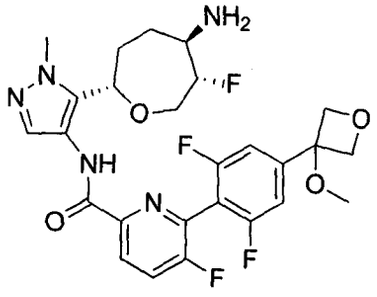
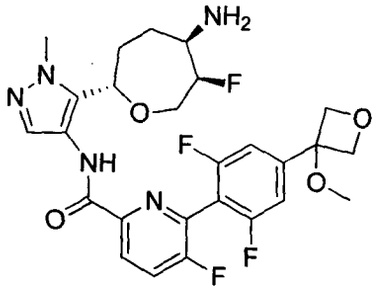
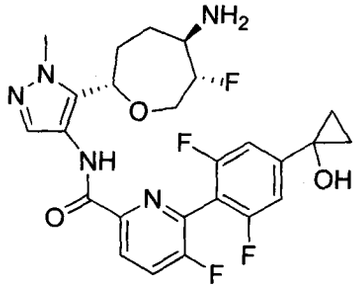
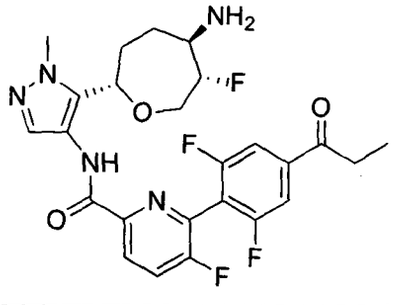
175		5-Amino-*N*-[5-[5-(aminomethyl)-5-methyl-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000036
176		5-Amino-*N*-[5-[(2*R*,5*S*,6*R*)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000595
177		5-Amino-*N*-[5-[(2*S*,5*R*,6*S*)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.00000342
178		5-Amino-*N*-[5-[5-(aminomethyl)-5-methyl-1,3-dioxan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000155
179		5-Amino-*N*-[5-[5-amino-4,4-difluoro-5,6-dimethyl-tetrahydropyran-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000456

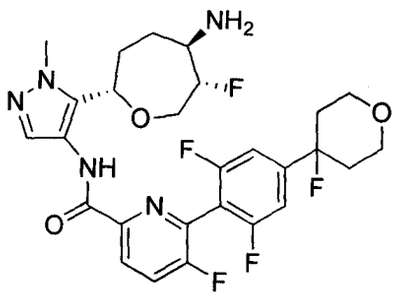
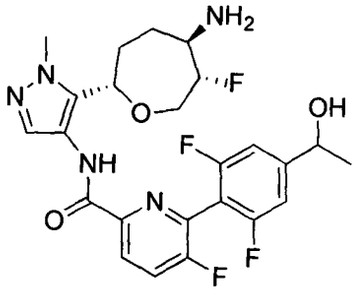
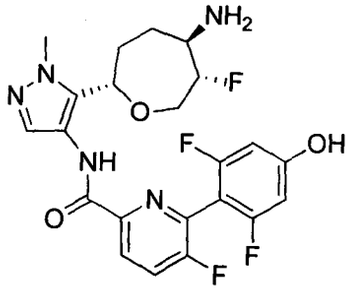
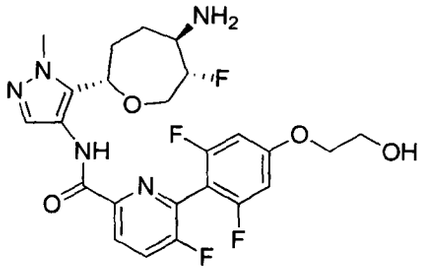
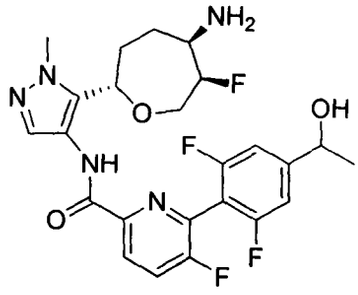
180		5-Amino-*N*-[5-[(2*R*,5*S*,6*R*)-5-amino-6-(trideuteriomethoxy)oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000017
181		5-Amino-*N*-[5-[(2*S*,5*R*,6*R*)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,3-difluorophenyl)thiazole-4-carboxamide	0.000004
182		5-Amino-*N*-[5-[(2*S*,5*R*,6*R*)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(3-fluoro-4-pyridyl)thiazole-4-carboxamide	0.000051
183		5-Amino-*N*-[5-[(2*S*,5*R*,6*R*)-5-amino-6-methoxy-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2-fluorophenyl)thiazole-4-carboxamide	0.0000143
184		5-Amino-*N*-(5-((2*R*,5*S*,6*R*)-5-amino-4,4-difluoro-5,6-dimethyltetrahydro-2*H*-pyran-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000484

185		5-Amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-4,4-difluoro-5,6-dimethyltetrahydro-2*H*-pyran-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.00435
186		5-Amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-2-(2-fluorophenyl)thiazole-4-carboxamide	0.000007
187		*N*-(5-((2*S*,5*R*,6*R*)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-6-(2,6-difluoro-4-methoxyphenyl)-5-fluoropicolinamide	0.000027
188		*N*-(5-((2*S*,5*R*,6*R*)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-6-(2,6-difluoro-4-((tetrahydro-2*H*-pyran-4-yl)oxy)phenyl)-5-fluoropicolinamide	0.00003
189		*N*-(5-((2*S*,5*R*,6*R*)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-5-fluoropicolinamide	0.000025

190		*N*-(5-((2*S*,5*R*,6*R*)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-hydroxyethoxy)phenyl)-5-fluoropicolinamide	0.000014
191		*N*-(5-((2*S*,5*R*,6*S*)-5-Amino-6-hydroxyoxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-5-fluoropicolinamide	0.000056
192		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-methoxyethoxy)phenyl)-5-fluoropicolinamide	0.000023
193		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(3-hydroxyoxetan-3-yl)phenyl)-5-fluoropicolinamide	0.000034
194		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(3-fluorooxetan-3-yl)phenyl)-5-fluoropicolinamide	0.000022
195		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide	0.000025

196		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(4-hydroxytetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinamide	0.000006
197		*N*-(5-((2*S*,5*R*,6*S*)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-6-(2,6-difluoro-4-((tetrahydro-2*H*-pyran-4-yl)oxy)phenyl)-5-fluoropicolinamide	0.000018
198		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-hydroxycyclobutyl)phenyl)-5-fluoropicolinamide	0.000021
199		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(methoxymethyl)phenyl)-5-fluoropicolinamide	0.000031
200		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-hydroxypropan-2-yl)phenyl)-5-fluoropicolinamide	0.000011

201		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-methoxyphenyl)-5-fluoropicolinamide	0.000019
202		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(3-methoxyoxetan-3-yl)phenyl)-5-fluoropicolinamide	0.000056
203		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(3-methoxyoxetan-3-yl)phenyl)-5-fluoropicolinamide	0.000119
204		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-hydroxycyclopropyl)phenyl)-5-fluoropicolinamide	0.000001
205		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-propionylphenyl)-5-fluoropicolinamide	0.000034

206		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(4-fluorotetrahydro-2H-pyran-4-yl)phenyl)-5-fluoropicolinamide	0.000016
207		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-hydroxyethyl)phenyl)-5-fluoropicolinamide	0.000017
208		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-hydroxyphenyl)-5-fluoropicolinamide	0.000012
209		*N*-(5-((2*S*,5*R*,6*S*)-5-Amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-hydroxyethoxy)phenyl)-5-fluoropicolinamide	0.000016
210		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-hydroxyethyl)phenyl)-5-fluoropicolinamide	0.000053

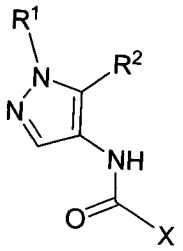
progression (Kim et al. (2002) Proc Natl Acad Sci USA 99 (5):2884-9). Pim-1 has been reported to be the most highly overexpressed mRNA in the subset of human prostate tumor samples which have a c-Myc-driven gene signature (Ellwood-Yen et al. (2003) Cancer Cell 4(3):223-38). Pim-3 has been also been shown to be overexpressed and to have a functional role in pancreatic cancer and hepatocellular carcinoma (Li et al. (2006) Cancer Research 66 (13):6741-7; Fujii et al. (2005) Int J Cancer 114 (2):209-18.

Beyond oncology therapeutic and diagnostic applications, Pim kinases could play an important role in normal immune system function and Pim inhibition could be therapeutic for a number of different immunologic pathologies including tumorigensis (Nawijn et al (2011) Nature Rev. 11:23-34), inflammation, autoimmune conditions, allergy, and immune suppression for organ transplantation (Aho et al. (2005) Immunology 116 (1):82-8).

SUMMARY OF THE INVENTION

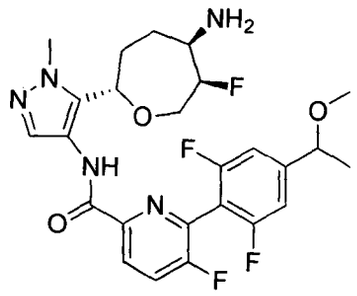
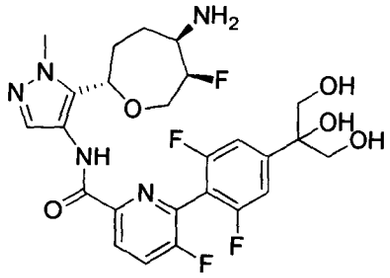
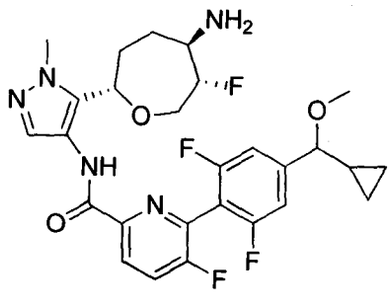
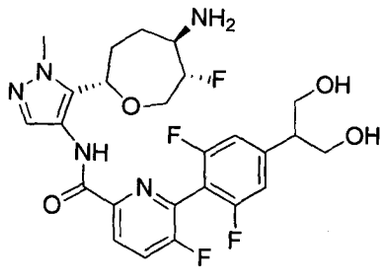
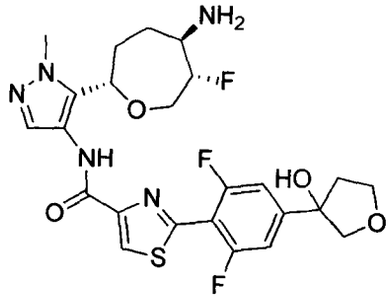
The invention relates to cyclic ether pyrazol-4-yl-heterocyclyl-carboxamide compounds for treating disorders mediated by Pim kinase (Pim-1, Pim-2, and/or Pim-3) inhibitors Formula I compounds.

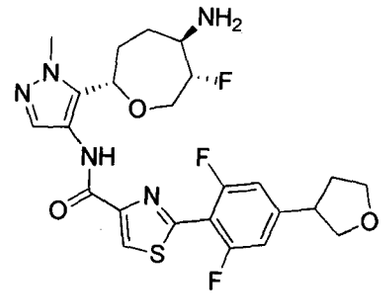
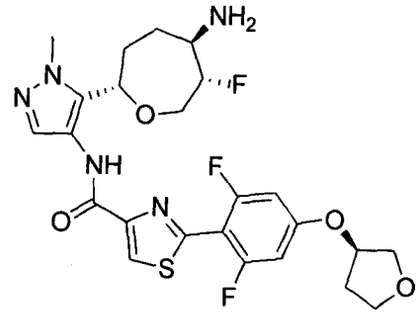
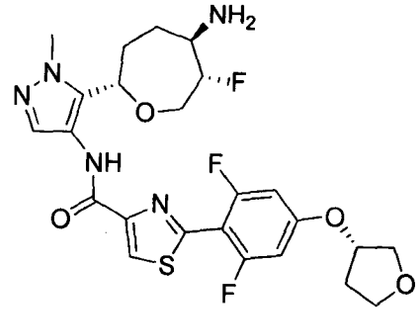
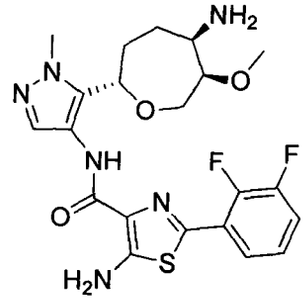
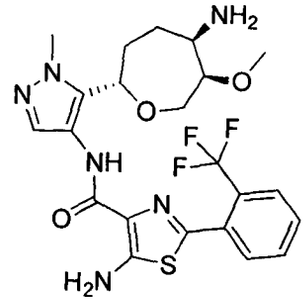
Formula I compounds have the structure:

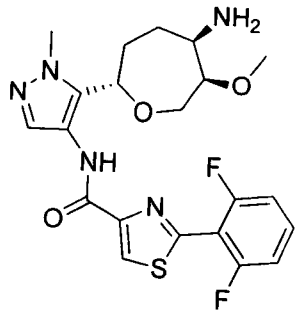
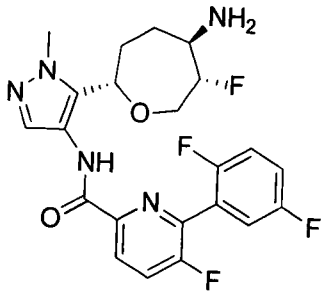
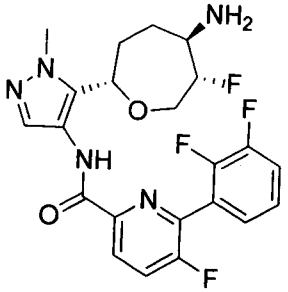
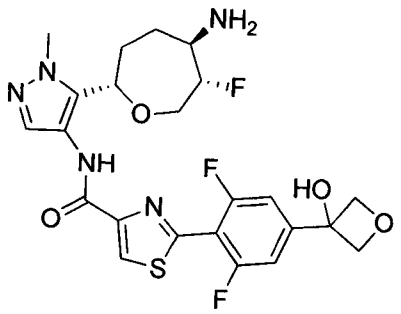
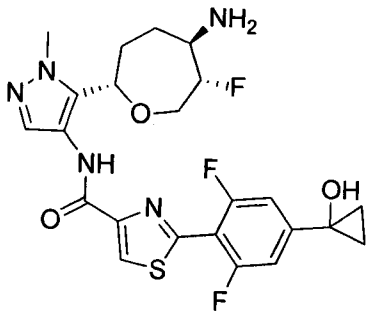


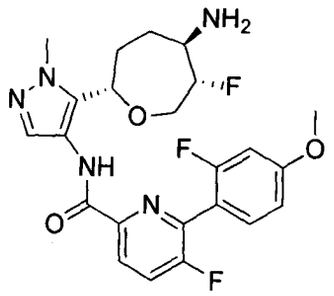
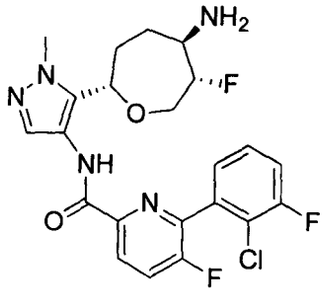
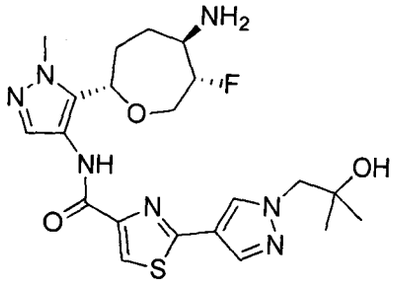
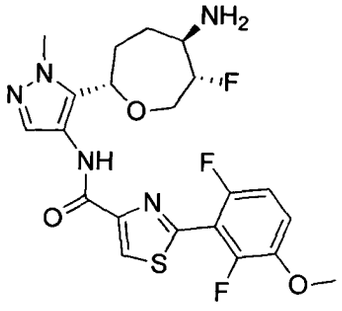
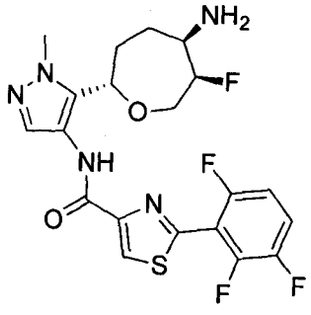
I

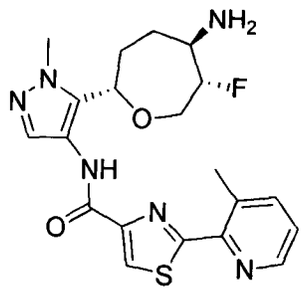
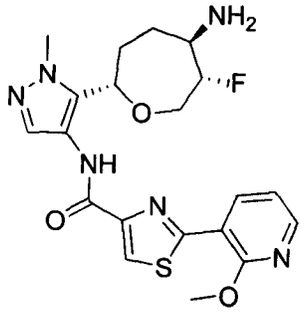
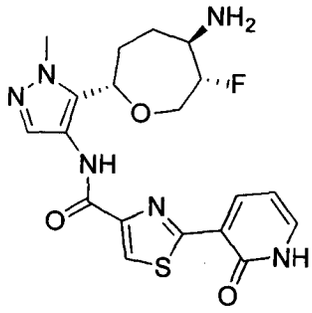
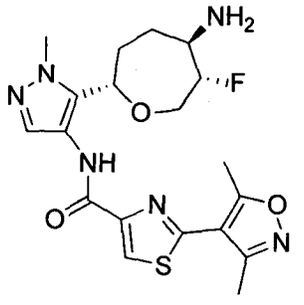
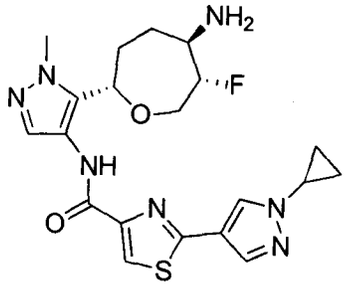
where R^2 is selected from the structures:

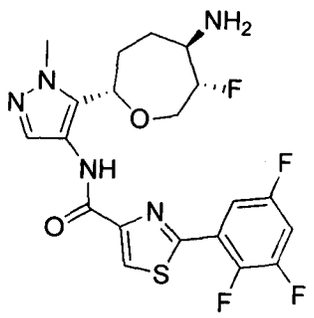
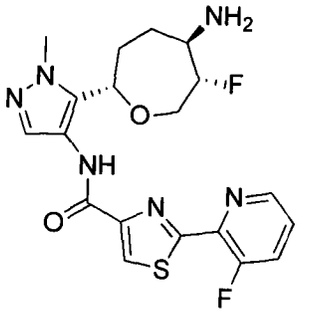
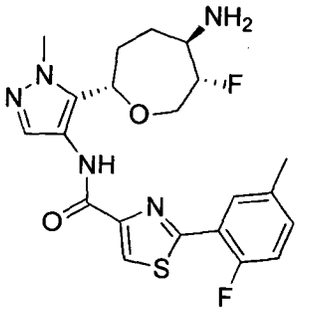
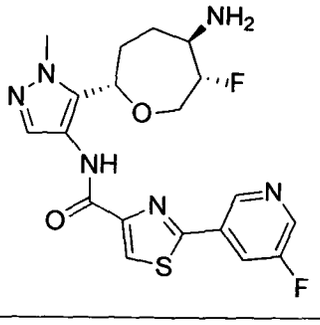
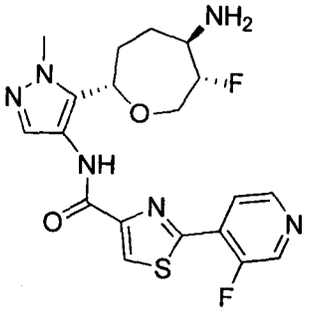
211		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-methoxyethyl)phenyl)-5-fluoropicolinamide	0.000037
212		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1,2,3-trihydroxypropan-2-yl)phenyl)-5-fluoropicolinamide	0.000162
213		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(4-(cyclopropyl(methoxy)methyl)-2,6-difluorophenyl)-5-fluoropicolinamide	0.000078
214		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(4-(1,3-dihydroxypropan-2-yl)-2,6-difluorophenyl)-5-fluoropicolinamide	0.000075
215		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(3-hydroxytetrahydrofuran-3-yl)phenyl)thiazole-4-carboxamide	0.00000762

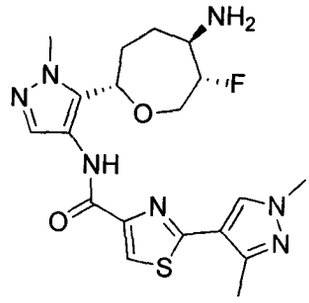
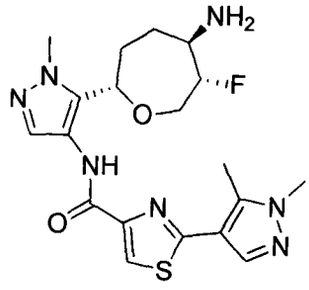
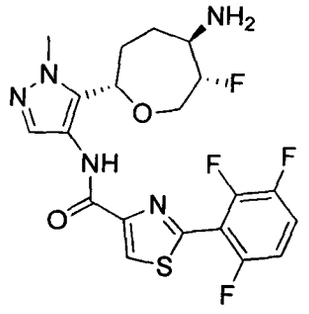
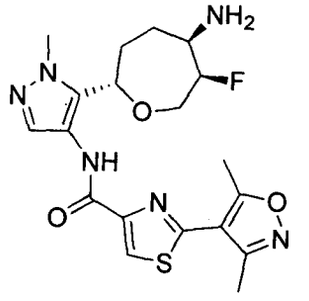
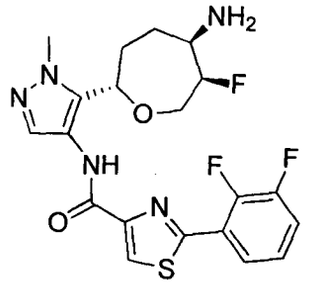
216		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(tetrahydrofuran-3-yl)phenyl)thiazole-4-carboxamide	0.000011+
217		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(((*R*)-tetrahydrofuran-3-yl)oxy)phenyl)thiazole-4-carboxamide	0.000003
218		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(((*S*)-tetrahydrofuran-3-yl)oxy)phenyl)thiazole-4-carboxamide	0.00000224
219		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluorophenyl)thiazole-4-carboxamide	0.00005
220		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.000083

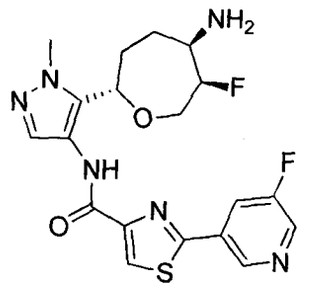
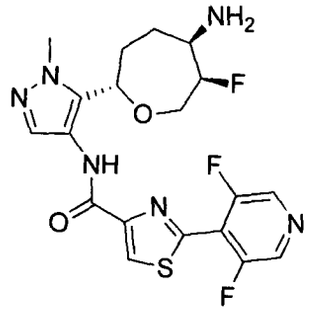
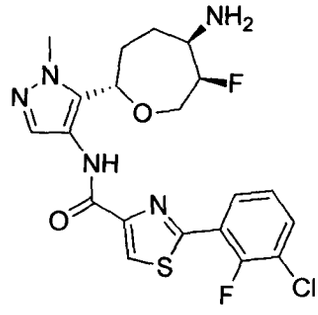
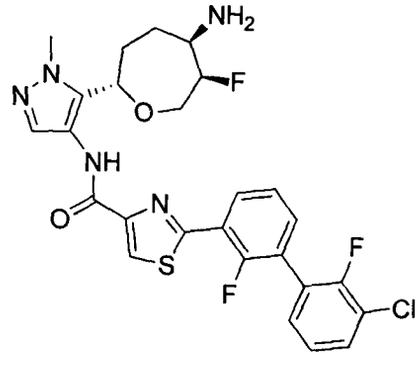
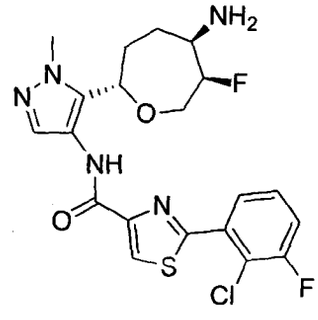
221		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000066
222		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,5-difluorophenyl)-5-fluoropicolinamide	0.000161
223		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,3-difluorophenyl)-5-fluoropicolinamide	0.000083
224		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(3-hydroxyoxetan-3-yl)phenyl)thiazole-4-carboxamide	0.000035
225		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(1-hydroxycyclopropyl)phenyl)thiazole-4-carboxamide	0.000028

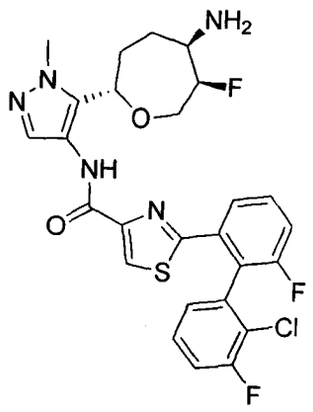
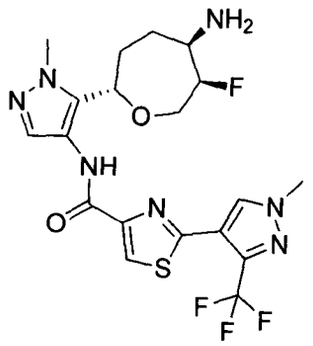
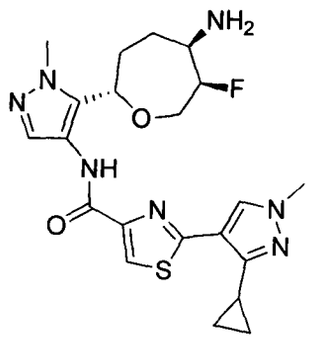
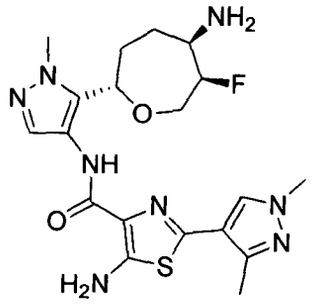
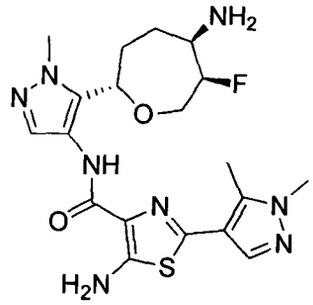
226		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-5-fluoro-6-(2-fluoro-4-methoxyphenyl)picolinamide	0.000036
227		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2-chloro-3-fluorophenyl)-5-fluoropicolinamide	0.00057
228		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000124
229		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-3-methoxyphenyl)thiazole-4-carboxamide	0.000001
230		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide	0.000031

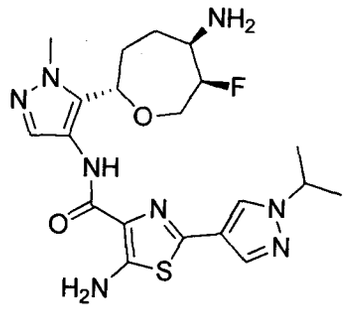
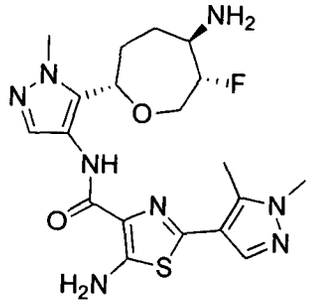
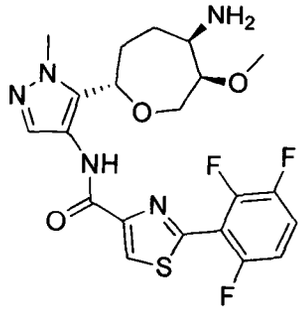
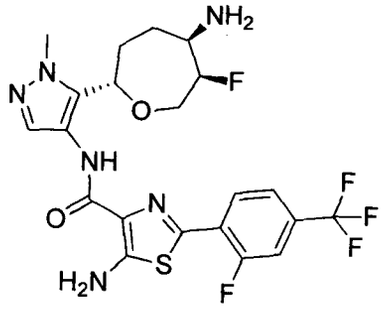
231		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-methylpyridin-2-yl)thiazole-4-carboxamide	0.000045
232		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-methoxypyridin-3-yl)thiazole-4-carboxamide	0.00111
233		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-oxo-1,2-dihydropyridin-3-yl)thiazole-4-carboxamide	0.000103
234		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3,5-dimethylisoxazol-4-yl)thiazole-4-carboxamide	0.000068
235		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-cyclopropyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000068

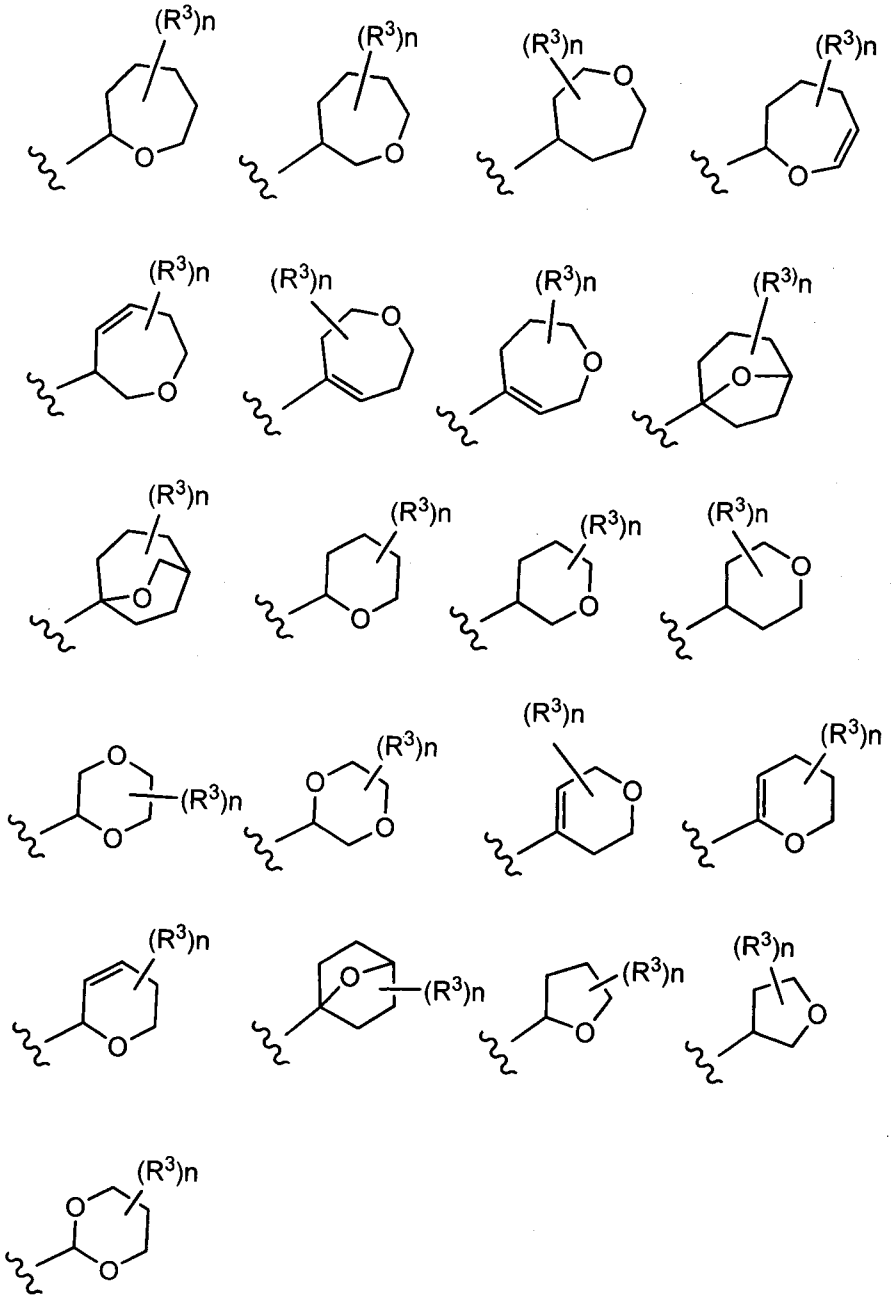
236		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,5-trifluorophenyl)thiazole-4-carboxamide	0.000255
237		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-fluoropyridin-2-yl)thiazole-4-carboxamide	0.000107
238		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-5-methylphenyl)thiazole-4-carboxamide	0.000048
239		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-fluoropyridin-3-yl)thiazole-4-carboxamide	0.00266
240		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-fluoropyridin-4-yl)thiazole-4-carboxamide	0.00034

241		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1,3-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000283
242		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1,5-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000218
243		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide	0.000047
244		N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3,5-dimethylisoxazol-4-yl)thiazole-4-carboxamide	0.00598
245		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluorophenyl)thiazole-4-carboxamide	0.000104

246		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-fluoropyridin-3-yl)thiazole-4-carboxamide	0.00576
247		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3,5-difluoropyridin-4-yl)thiazole-4-carboxamide	0.000112
248		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-chloro-2-fluorophenyl)thiazole-4-carboxamide	0.000064
249		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3'-chloro-2,2'-difluoro-[1,1'-biphenyl]-3-yl)thiazole-4-carboxamide	0.000533
250		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-3-fluorophenyl)thiazole-4-carboxamide	0.000132

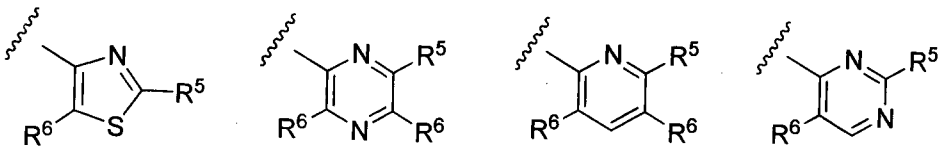
251		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2'-chloro-3',6-difluoro-[1,1'-biphenyl]-2-yl)thiazole-4-carboxamide	0.63
252		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000281
253		N-(5-((2S,5R,6R)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-cyclopropyl-1-methyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000253
254		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1,3-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000026
255		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1,5-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000007

256		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-isopropyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000093
257		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1,5-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000025
258		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide	0.000145
259		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-4-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.00001
260		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide	0.000004

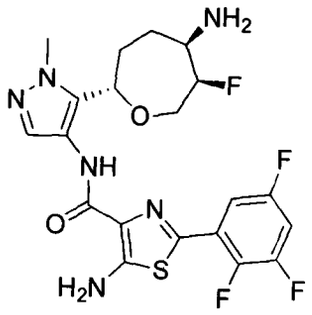
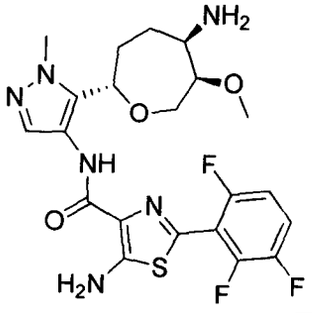
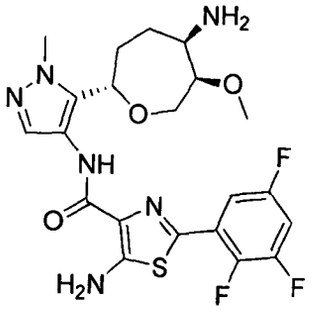
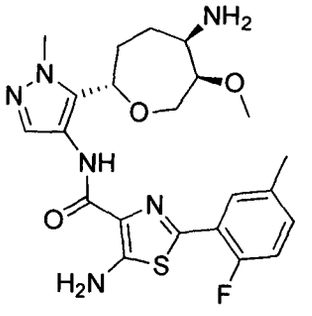
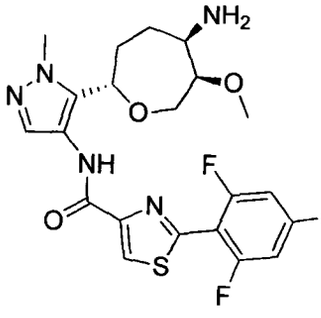


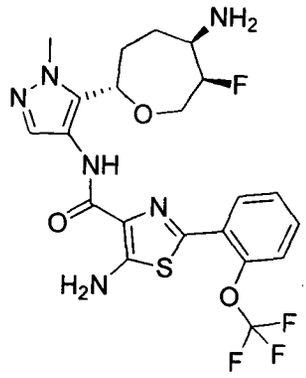
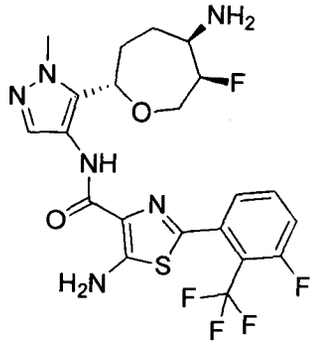
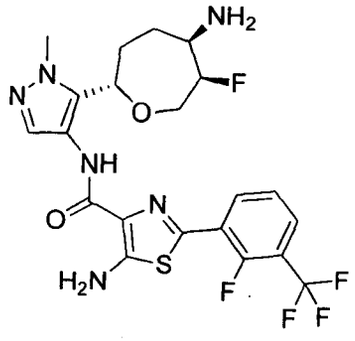
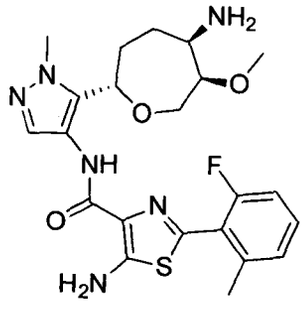
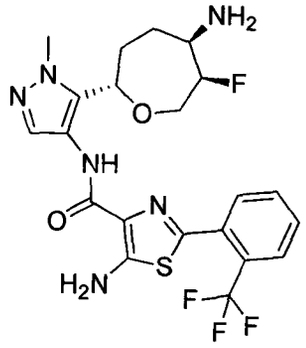
where the wavy line indicates the site of attachment and the dashed line indicates an optional double bond;

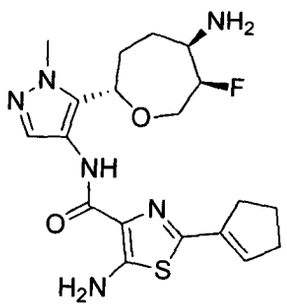
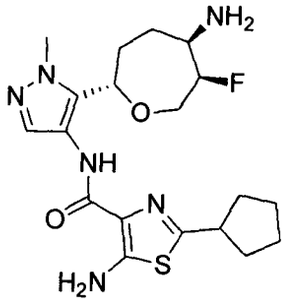
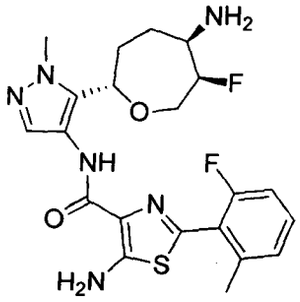
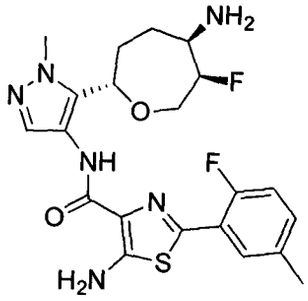
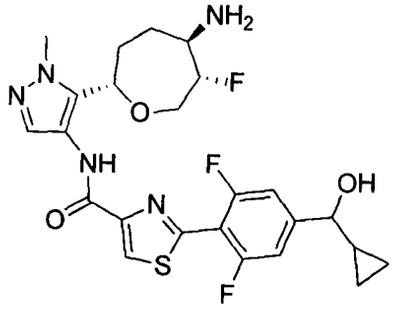
X is selected from the structures:

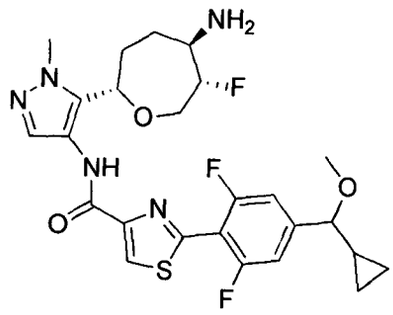
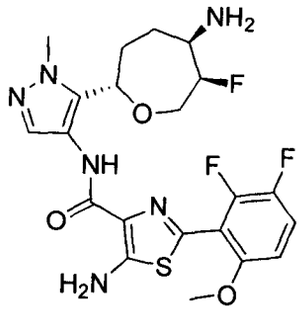
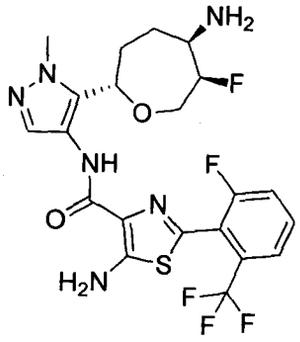
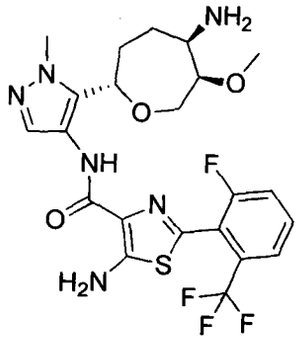
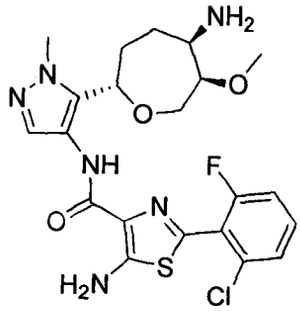


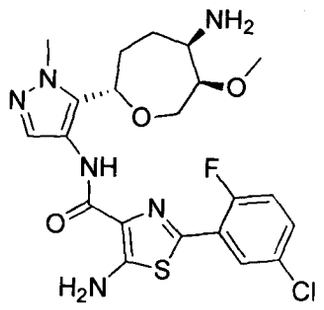
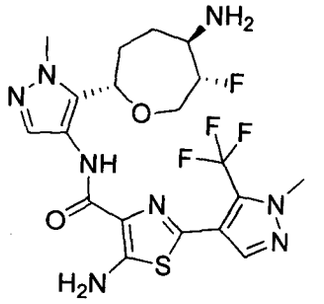
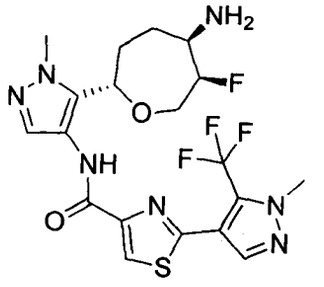
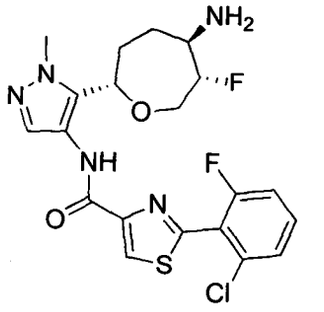
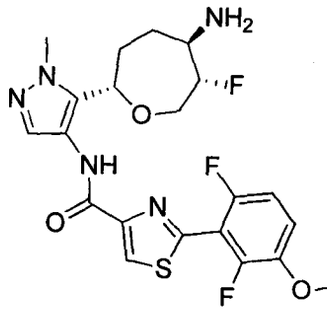
and stereoisomers, geometric isomers, tautomers, and pharmaceutically acceptable salts thereof. The various substituents, including R^1, R^2, R^3, R^4, R^5, R^6, R^7, and X are as defined herein.

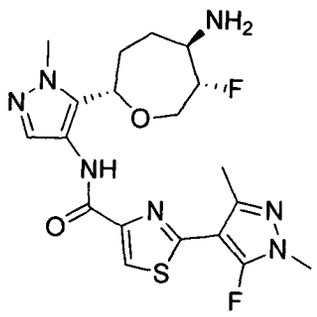
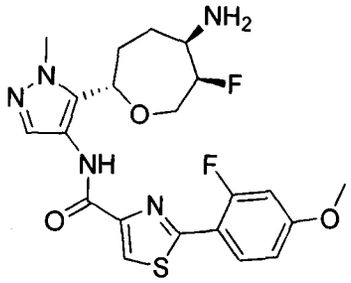
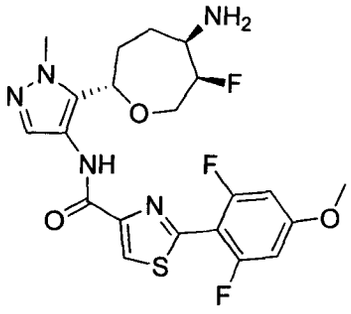
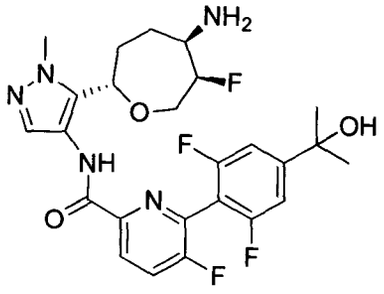
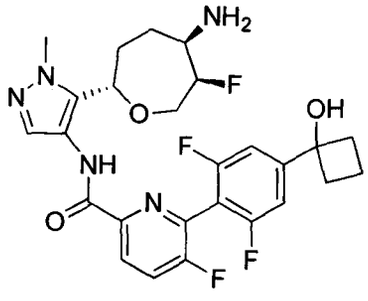
261		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,5-trifluorophenyl)thiazole-4-carboxamide	0.000037
262		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide	0.00001
263		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,5-trifluorophenyl)thiazole-4-carboxamide	0.000127
264		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-5-methylphenyl)thiazole-4-carboxamide	0.00002
265		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-methoxyphenyl)thiazole-4-carboxamide	0.000034

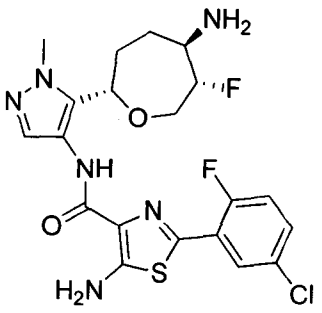
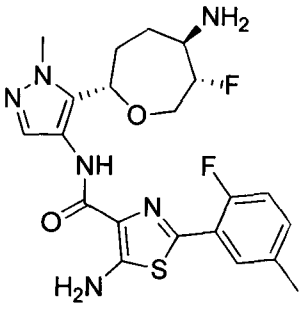
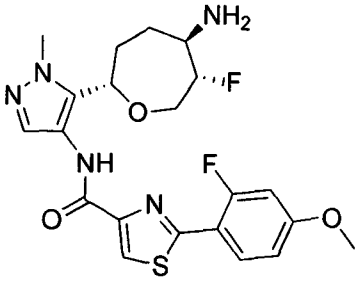
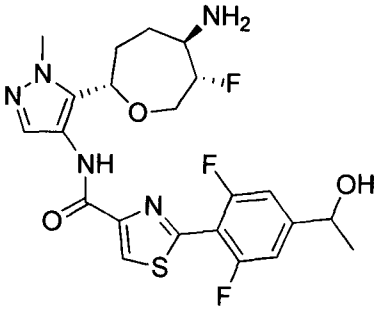
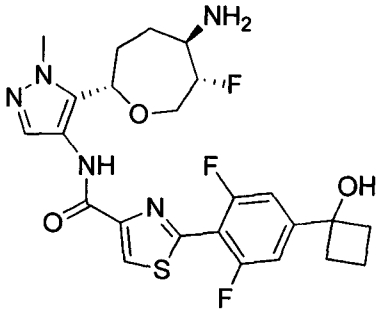
266		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethoxy)phenyl)thiazole-4-carboxamide	0.000155
267		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-fluoro-2-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.000098
268		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.000028
269		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-methylphenyl)thiazole-4-carboxamide	0.000052
270		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.000053

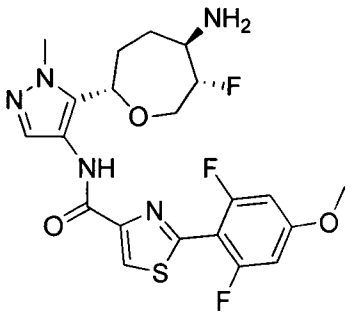
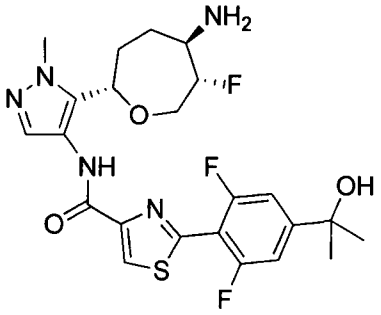
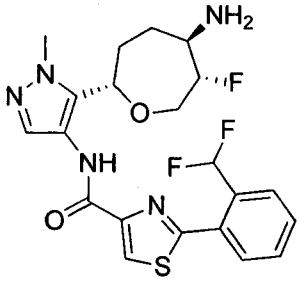
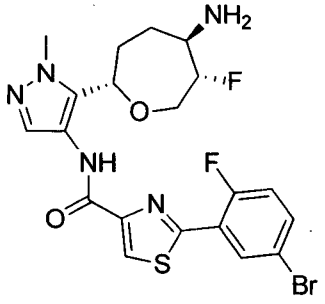
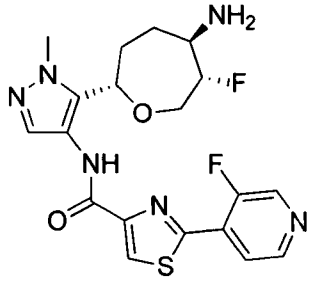
271		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(cyclopent-1-en-1-yl)thiazole-4-carboxamide	0.000062
272		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-cyclopentylthiazole-4-carboxamide	0.000992
273		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-methylphenyl)thiazole-4-carboxamide	0.000007
274		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-5-methylphenyl)thiazole-4-carboxamide	0.00002
275		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-(cyclopropyl(hydroxy)methyl)-2,6-difluorophenyl)thiazole-4-carboxamide	0.000037

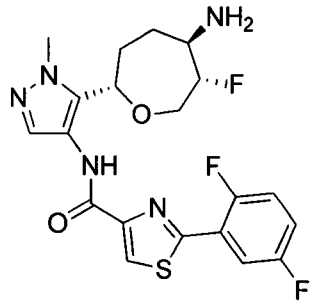
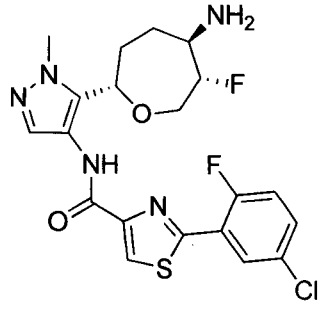
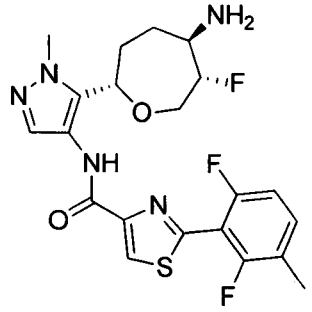
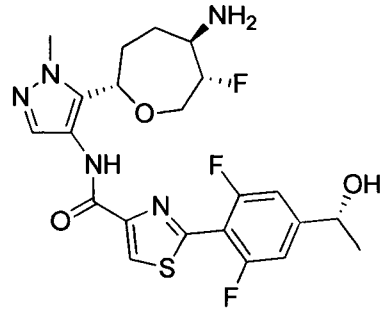
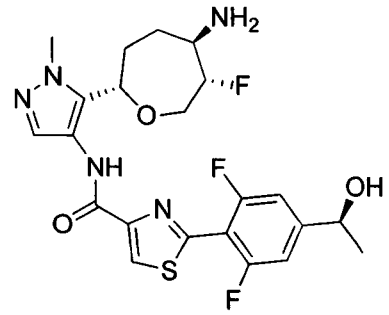
276		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-(cyclopropyl(methoxy)methyl)-2,6-difluorophenyl)thiazole-4-carboxamide	0.000084
277		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluoro-6-methoxyphenyl)thiazole-4-carboxamide	0.000143
278		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.000061
279		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.000083
280		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-6-fluorophenyl)thiazole-4-carboxamide	0.000014

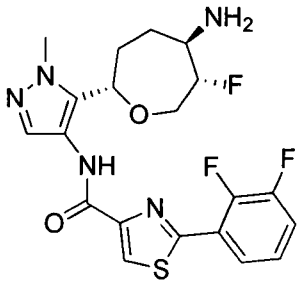
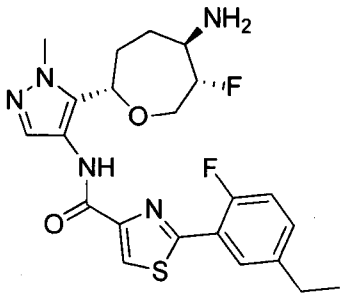
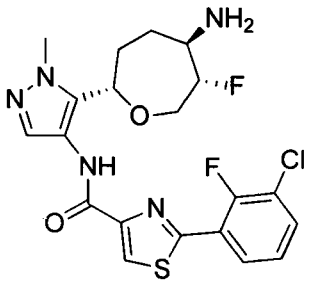
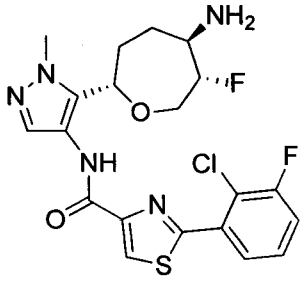
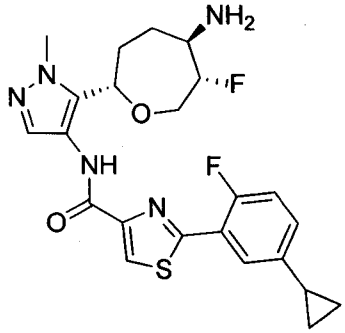
281		5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-chloro-2-fluorophenyl)thiazole-4-carboxamide	0.000007
282		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000058
283		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)thiazole-4-carboxamide	0.000171
284		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-6-fluorophenyl)thiazole-4-carboxamide	0.00022
285		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-ethoxy-2,6-difluorophenyl)thiazole-4-carboxamide	0.000001

286		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-fluoro-1,3-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide	
287		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-4-methoxyphenyl)thiazole-4-carboxamide	0.000053
288		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-methoxyphenyl)thiazole-4-carboxamide	0.000035
289		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(2-hydroxypropan-2-yl)phenyl)-5-fluoropicolinamide	0.00008
290		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-(1-hydroxycyclobutyl)phenyl)-5-fluoropicolinamide	0.000131

291		5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-chloro-2-fluorophenyl)thiazole-4-carboxamide	0.000018
292		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-5-methylphenyl)thiazole-4-carboxamide	0.000024
293		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-4-methoxyphenyl)thiazole-4-carboxamide	0.000059
294		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(1-hydroxyethyl)phenyl)thiazole-4-carboxamide	0.000029
295		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(1-hydroxycyclobutyl)phenyl)thiazole-4-carboxamide	0.000027

296		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-methoxyphenyl)thiazole-4-carboxamide	0.000031
297		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(2-hydroxypropan-2-yl)phenyl)thiazole-4-carboxamide	0.000021
298		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(difluoromethyl)phenyl)thiazole-4-carboxamide	0.000783
299		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-bromo-2-fluorophenyl)thiazole-4-carboxamide	0.000023
300		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-fluoropyridin-4-yl)thiazole-4-carboxamide	0.000134

301		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,5-difluorophenyl)thiazole-4-carboxamide	0.000058
302		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-chloro-2-fluorophenyl)thiazole-4-carboxamide	0.000031
303		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-3-methylphenyl)thiazole-4-carboxamide	0.000013
304		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-((*R*)-1-hydroxyethyl)phenyl)thiazole-4-carboxamide	0.000014
305		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-((*S*)-1-hydroxyethyl)phenyl)thiazole-4-carboxamide	0.000008

306		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluorophenyl)thiazole-4-carboxamide	0.000044
307		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-ethyl-2-fluorophenyl)thiazole-4-carboxamide	0.000081
308		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-chloro-2-fluorophenyl)thiazole-4-carboxamide	0.000054
309		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-3-fluorophenyl)thiazole-4-carboxamide	0.000274
310		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-cyclopropyl-2-fluorophenyl)thiazole-4-carboxamide	0.000093

One aspect of the invention is a pharmaceutical composition comprised of a Formula I compound and a pharmaceutically acceptable carrier, glidant, diluent, or excipient. The pharmaceutical composition may further comprise a chemotherapeutic agent.

The invention includes a method of treating a disease or disorder which method comprises administering a therapeutically effective amount of a Formula I compound to a patient with a disease or disorder selected from cancer, immune disorders, cardiovascular disease, viral infection, inflammation, metabolism/endocrine function disorders and neurological disorders, and mediated by Pim kinase. The method includes further administering an additional therapeutic agent selected from a chemotherapeutic agent, an anti-inflammatory agent, an immunomodulatory agent, a neurotropic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, and an agent for treating immunodeficiency disorders.

The invention includes use of a Formula I compound in the manufacture of a medicament for the treatment of cancer, immune disorders, cardiovascular disease, viral infection, inflammation, metabolism/endocrine function disorders and neurological disorders, wherein the medicament mediates Pim kinase.

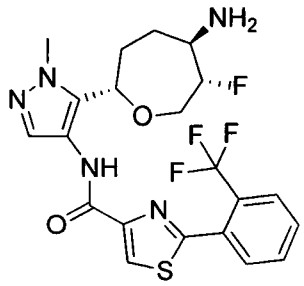
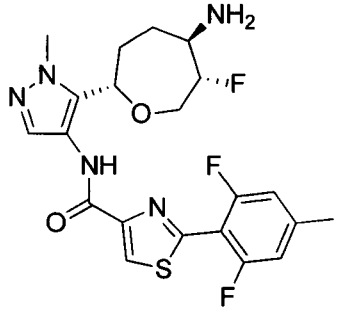
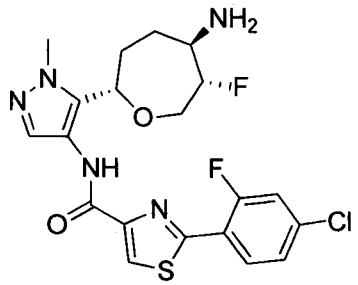
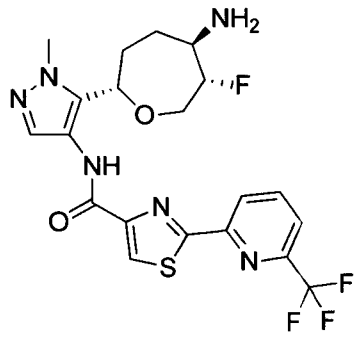
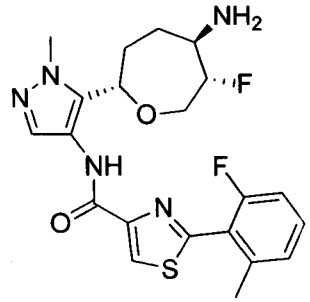
The invention includes a kit for treating a condition mediated by Pim kinase, comprising: a) a first pharmaceutical composition comprising a Formula I compound; and b) instructions for use.

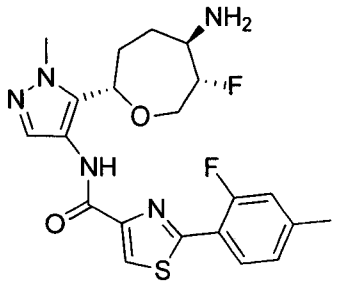
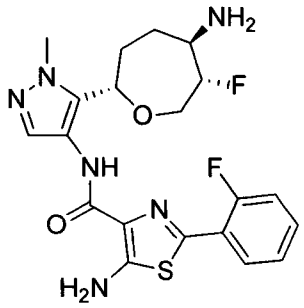
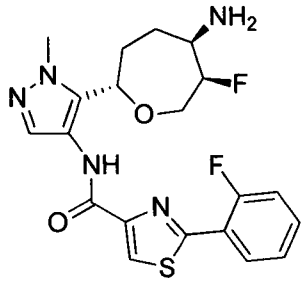
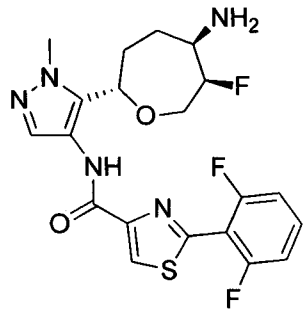
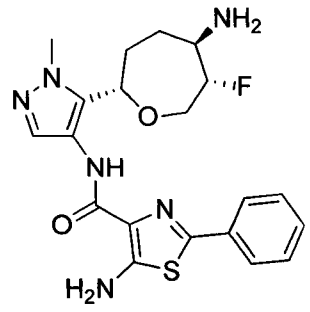
The invention includes a Formula I compound for use as a medicament, and for use in treating a disease or disorder selected from cancer, immune disorders, cardiovascular disease, viral infection, inflammation, metabolism/endocrine function disorders and neurological disorders, and mediated by Pim kinase.

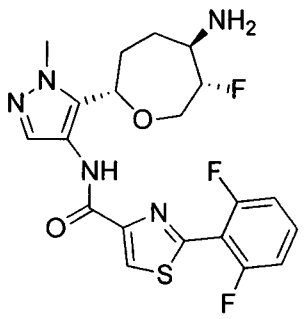
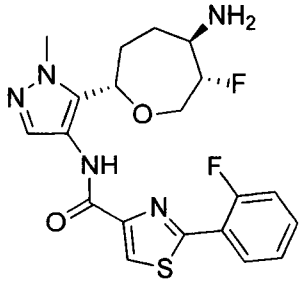
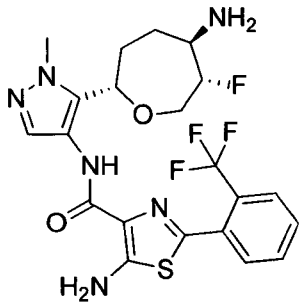
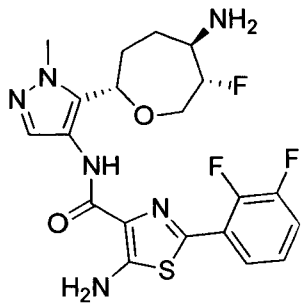
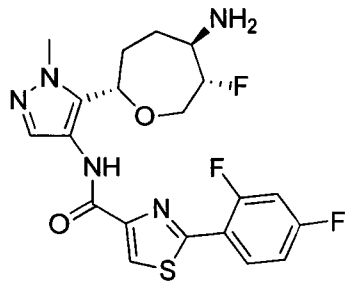
The invention includes methods of making a Formula I compound.

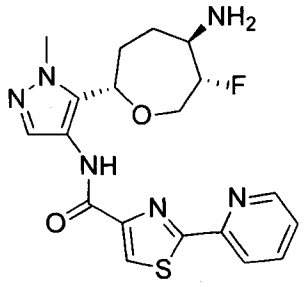
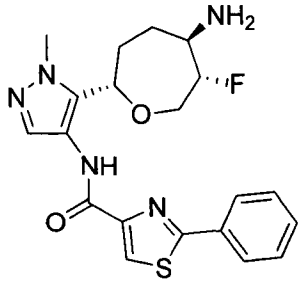
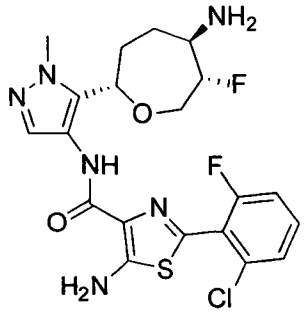
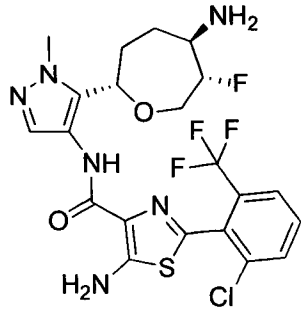
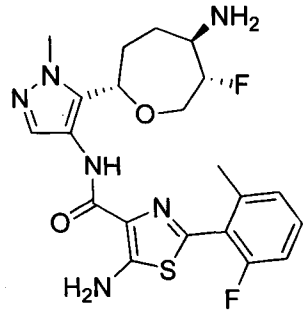
DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

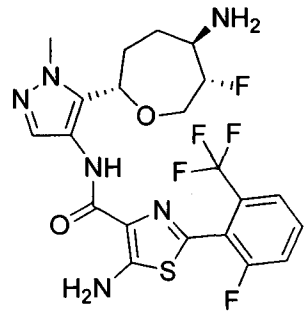
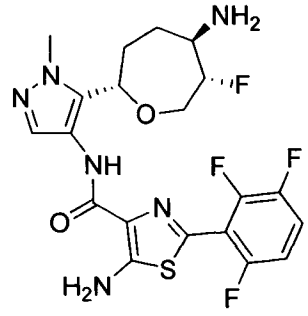
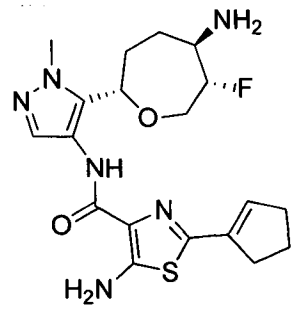
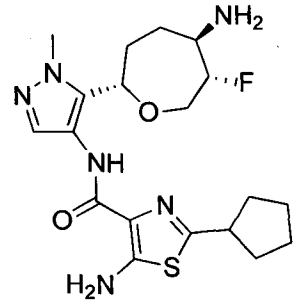
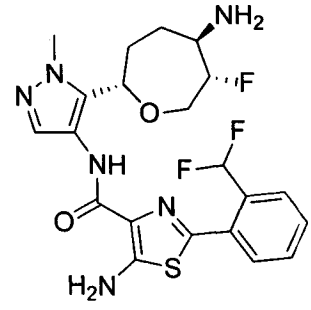
Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents which may be included within the scope of the present invention as defined by the claims. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The

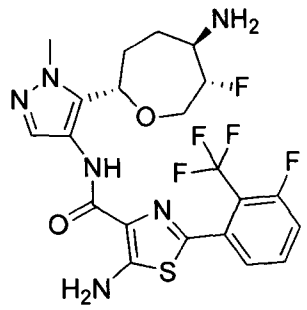
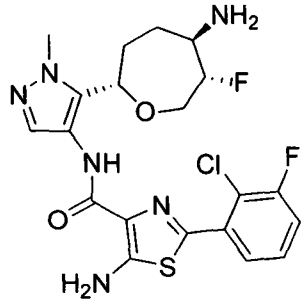
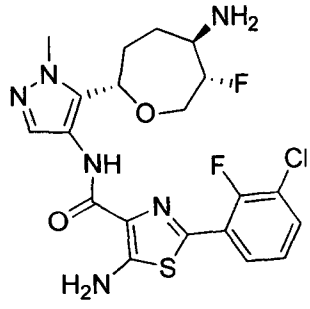
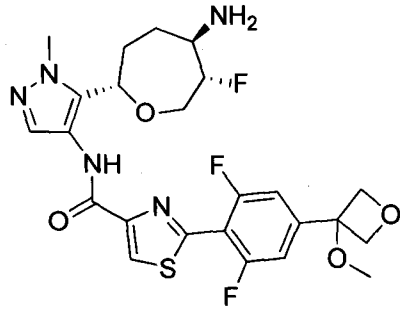
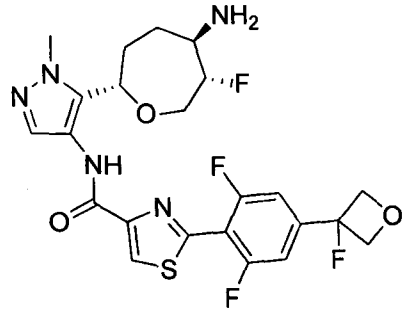
311		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.00165
312		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-methylphenyl)thiazole-4-carboxamide	0.000003
313		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-chloro-2-fluorophenyl)thiazole-4-carboxamide	0.000002
314		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)thiazole-4-carboxamide	0.00208
315		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-methylphenyl)thiazole-4-carboxamide	0.000091

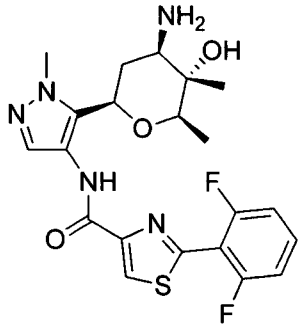
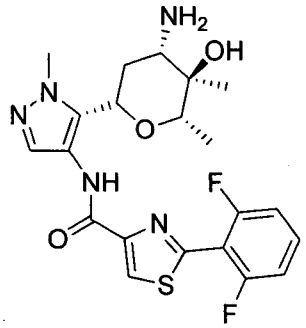
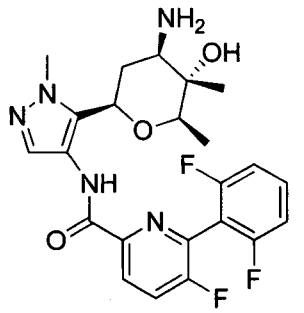
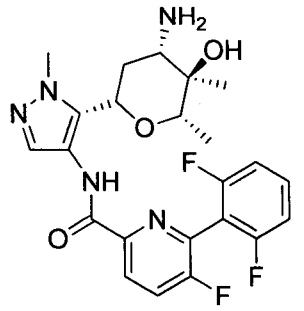
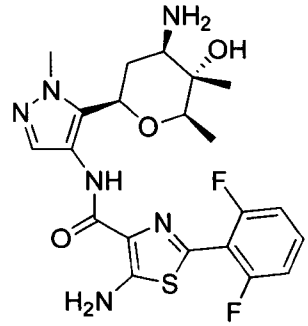
316		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-4-methylphenyl)thiazole-4-carboxamide	
317		5-amino-N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluorophenyl)thiazole-4-carboxamide	0.00000509
318		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluorophenyl)thiazole-4-carboxamide	0.000098
319		*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000038
320		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-phenylthiazole-4-carboxamide	0.000036

321		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.0000137
322		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluorophenyl)thiazole-4-carboxamide	0.000072
323		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.000283
324		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluorophenyl)thiazole-4-carboxamide	0.000019
325		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,4-difluorophenyl)thiazole-4-carboxamide	0.00005

326		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(pyridin-2-yl)thiazole-4-carboxamide	0.000031
327		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-phenylthiazole-4-carboxamide	0.000021
328		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-6-fluorophenyl)thiazole-4-carboxamide	0.000036
329		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-6-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.000071
330		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-methylphenyl)thiazole-4-carboxamide	0.000016

331		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.000104
332		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide	0.000003
333		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(cyclopent-1-en-1-yl)thiazole-4-carboxamide	0.00003
334		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-cyclopentylthiazole-4-carboxamide	0.000453
335		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(difluoromethyl)phenyl)thiazole-4-carboxamide	0.000092

336		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-fluoro-2-(trifluoromethyl)phenyl)thiazole-4-carboxamide	0.000188
337		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-chloro-3-fluorophenyl)thiazole-4-carboxamide	0.000015
338		5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-chloro-2-fluorophenyl)thiazole-4-carboxamide	0.000007
339		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(3-methoxyoxetan-3-yl)phenyl)thiazole-4-carboxamide	0.000014
340		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-(3-fluorooxetan-3-yl)phenyl)thiazole-4-carboxamide	0.000010

341		*N*-(5-((2*R*,4*R*,5*S*,6*R*)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.0000030
342		*N*-(5-((2*S*,4*S*,5*R*,6*S*)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.0023
343		*N*-(5-((2*R*,4*R*,5*S*,6*R*)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide	
344		*N*-(5-((2*S*,4*S*,5*R*,6*S*)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide	
345		5-amino-*N*-(5-((2*R*,4*R*,5*S*,6*R*)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	

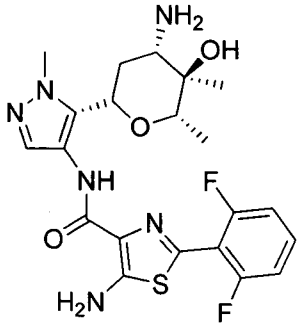
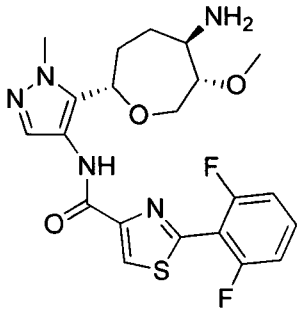
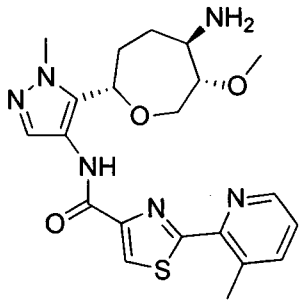
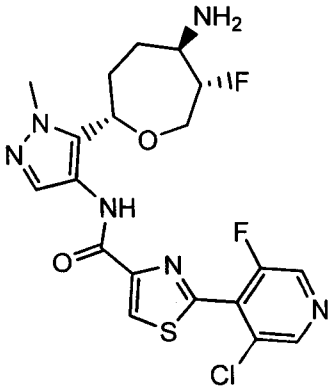
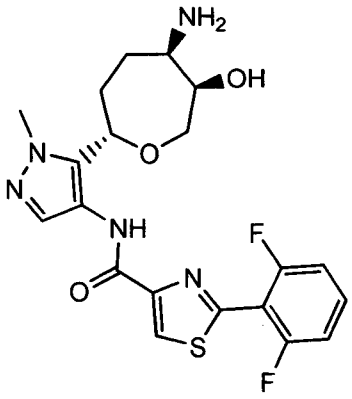
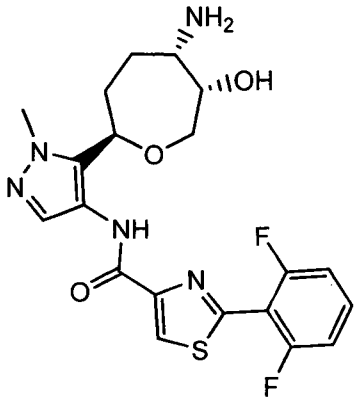
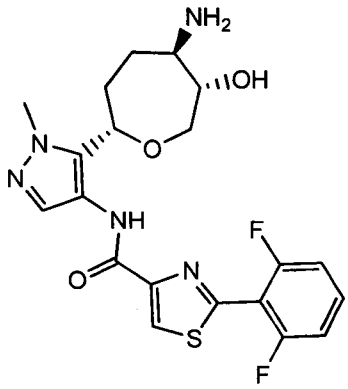
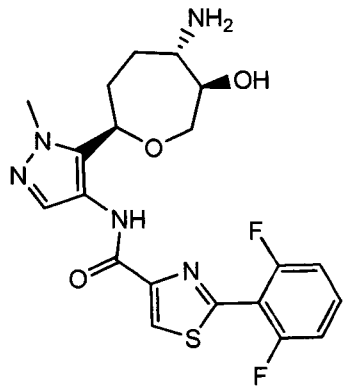
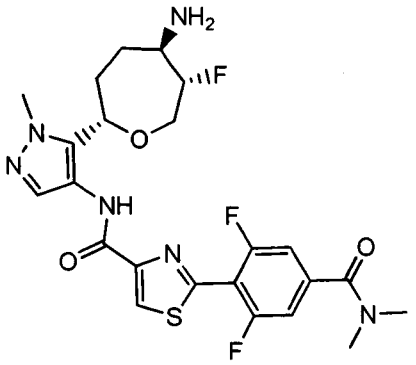
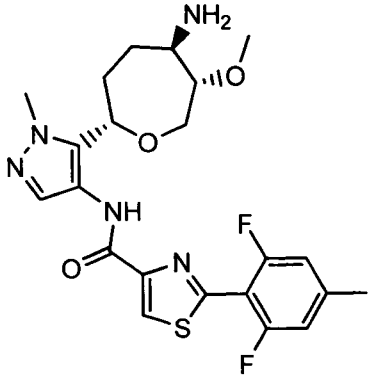
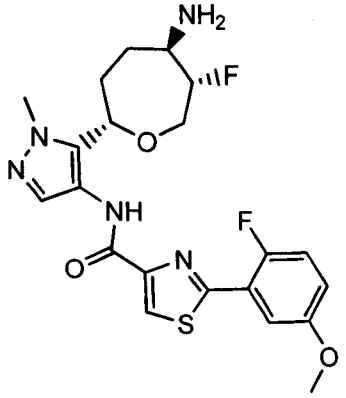
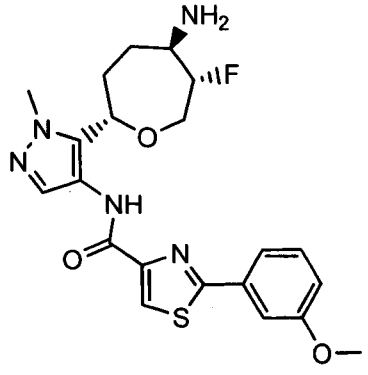
346		5-amino-*N*-(5-((2*S*,4*S*,5*R*,6*S*)-4-amino-5-hydroxy-5,6-dimethyltetrahydro-2H-pyran-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	
347		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000014
348		*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-methylpyridin-2-yl)thiazole-4-carboxamide	0.000014

Table 1c

No.	Structure	IUPAC Name	PIM1 LC3K (KI) μM
349		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-chloro-5-fluoropyridin-4-yl)thiazole-4-carboxamide	0.00312

350		N-(5-((2S,5R,6R)-5-amino-6-hydroxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	>0.667
351		N-(5-((2R,5S,6S)-5-amino-6-hydroxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000076
352		N-(5-((2S,5R,6S)-5-amino-6-hydroxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000174
353		N-(5-((2R,5S,6R)-5-amino-6-hydroxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	0.000111

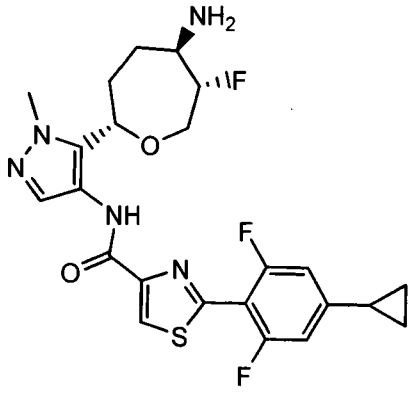
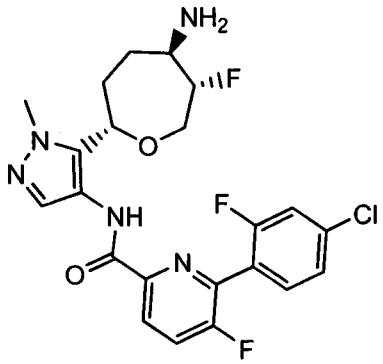
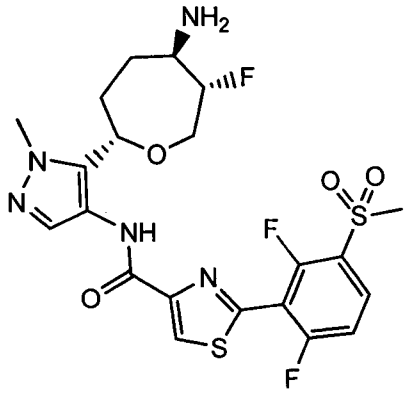
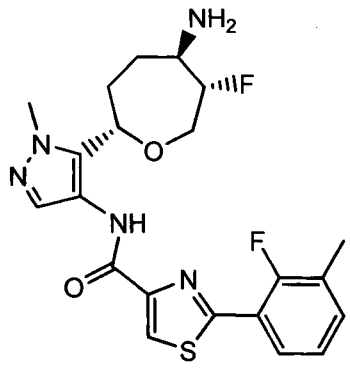
354		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-(dimethylcarbamoyl)-2,6-difluorophenyl)thiazole-4-carboxamide	0.000083
355		N-(5-((2S,5R,6S)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-methylphenyl)thiazole-4-carboxamide	0.000035
356		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-5-methoxyphenyl)thiazole-4-carboxamide	0.000053
357		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-methoxyphenyl)thiazole-4-carboxamide	0.000035

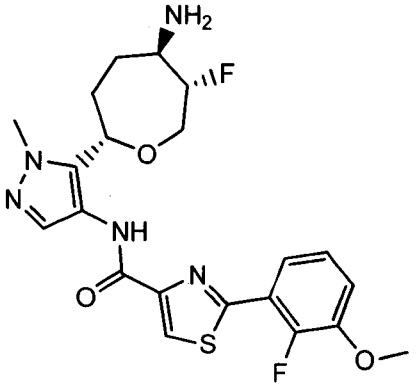
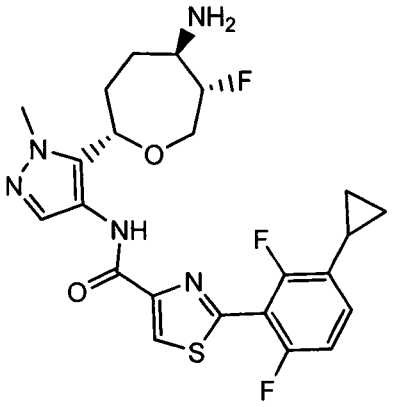
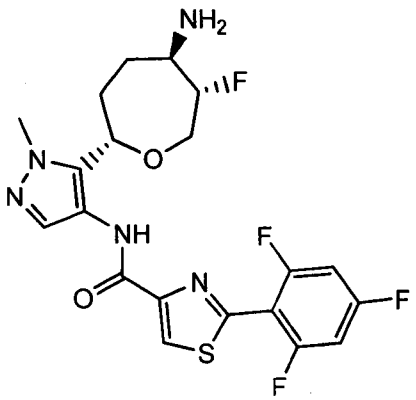
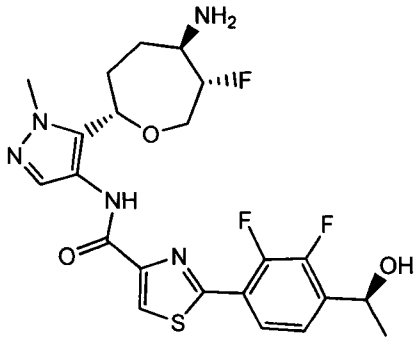
present invention is in no way limited to the methods and materials described. In the event that one or more of the incorporated literature, patents, and similar materials differs from or contradicts this application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. The nomenclature used in this Application is based on IUPAC systematic nomenclature, unless indicated otherwise.

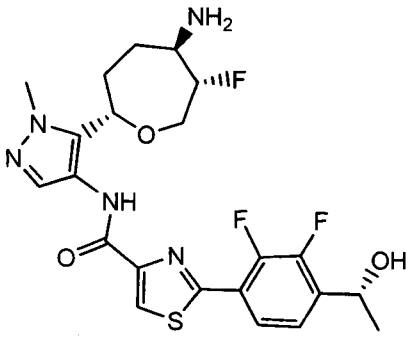
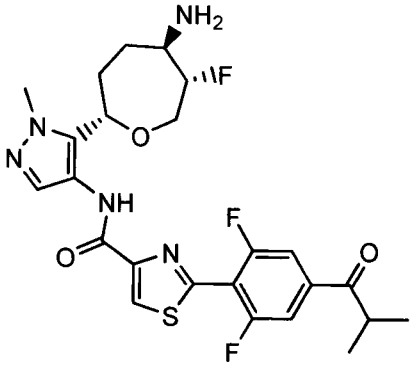
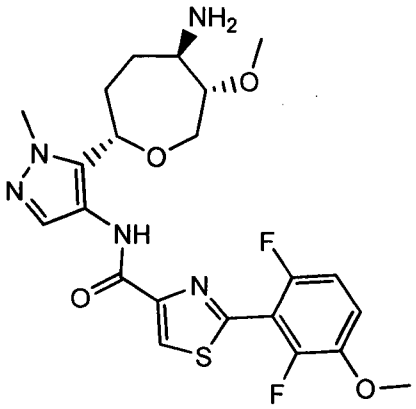
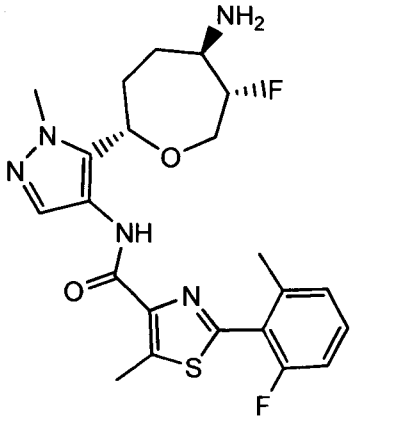
DEFINITIONS

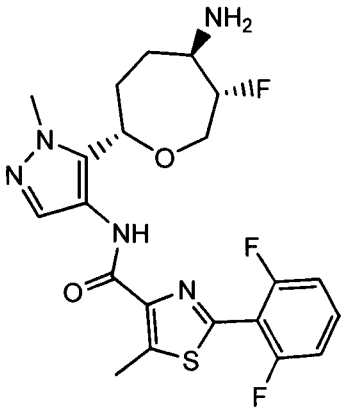
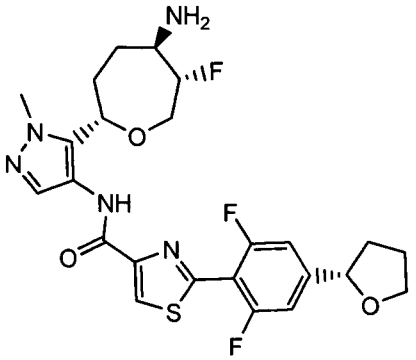
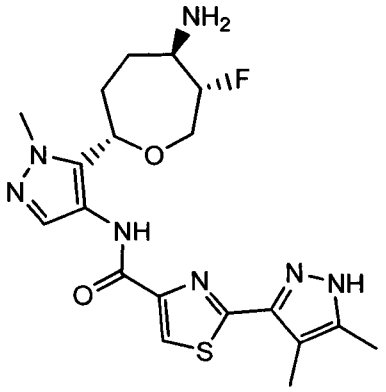
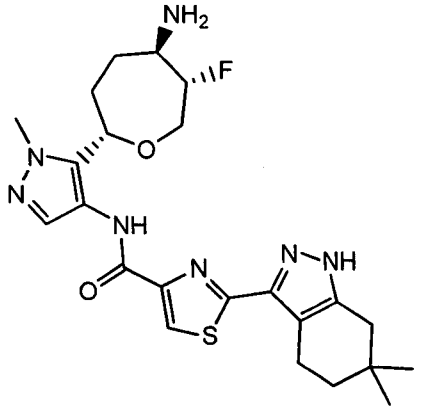
When indicating the number of substituents, the term "one or more" refers to the range from one substituent to the highest possible number of substitution, i.e. replacement of one hydrogen up to replacement of all hydrogens by substituents. The term "substituent" denotes an atom or a group of atoms replacing a hydrogen atom on the parent molecule. The term "substituted" denotes that a specified group bears one or more substituents. Where any group may carry multiple substituents and a variety of possible substituents is provided, the substituents are independently selected and need not to be the same. The term "unsubstituted" means that the specified group bears no substituents. The term "optionally substituted" means that the specified group is unsubstituted or substituted by one or more substituents, independently chosen from the group of possible substituents. When indicating the number of substituents, the term "one or more" means from one substituent to the highest possible number of substitution, i.e. replacement of one hydrogen up to replacement of all hydrogens by substituents.

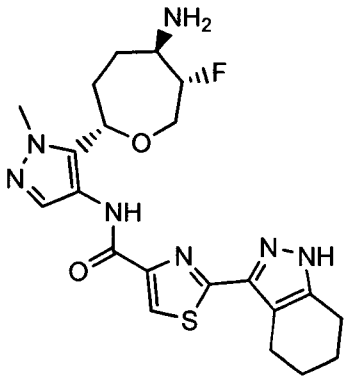
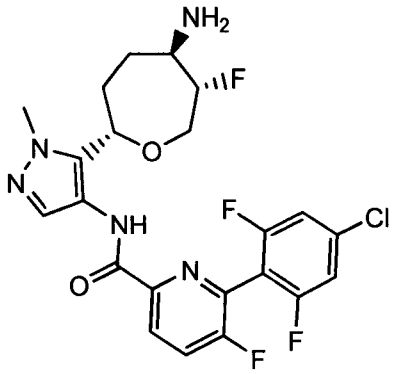
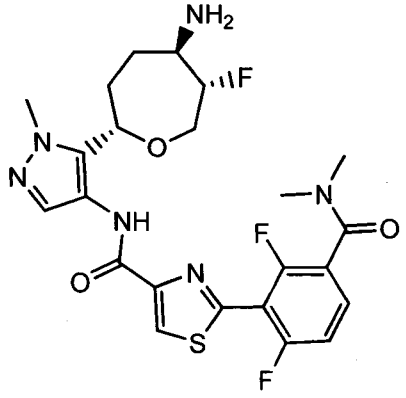
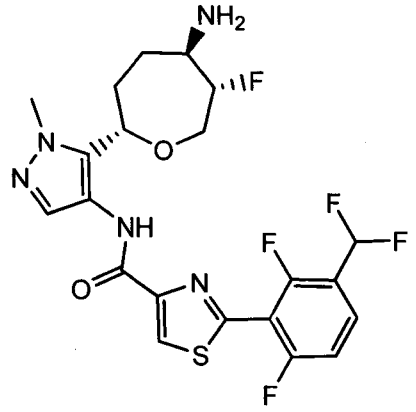
The term "alkyl" as used herein refers to a saturated linear or branched-chain monovalent hydrocarbon radical of one to twelve carbon atoms (C_1–C_{12}), wherein the alkyl radical may be optionally substituted independently with one or more substituents described below. In another embodiment, an alkyl radical is one to eight carbon atoms (C_1–C_8), or one to six carbon atoms (C_1–C_6). Examples of alkyl groups include, but are not limited to, methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl (-

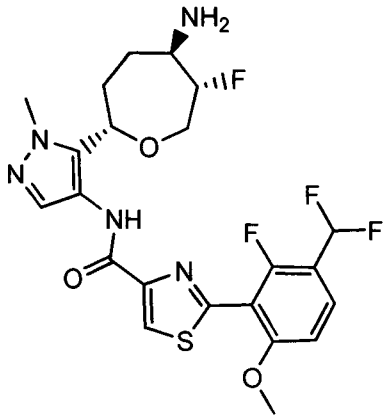
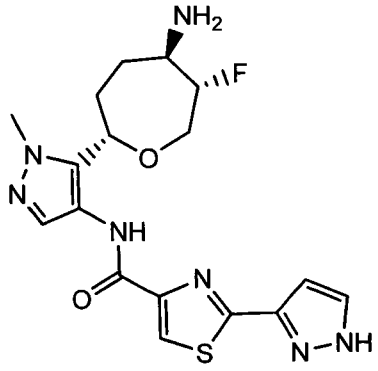
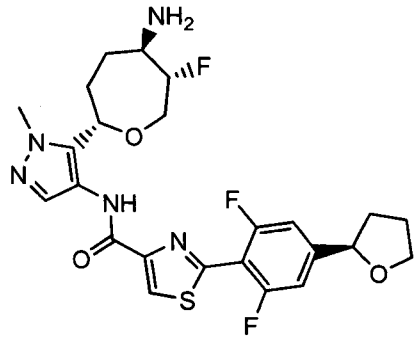
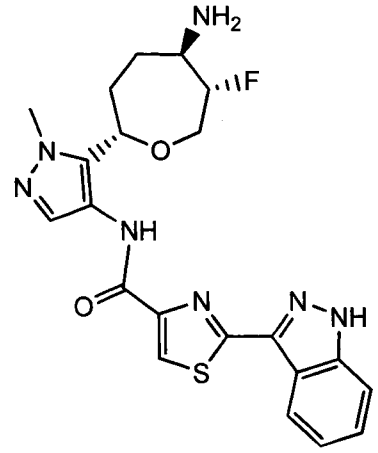
358		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-cyclopropyl-2,6-difluorophenyl)thiazole-4-carboxamide	0.000009
359		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(4-chloro-2-fluorophenyl)-5-fluoropicolinamide	0.000007
360		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluoro-3-methylsulfonyl-phenyl)thiazole-4-carboxamide	0.00185
361		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2-fluoro-3-methyl-phenyl)thiazole-4-carboxamide	0.000068

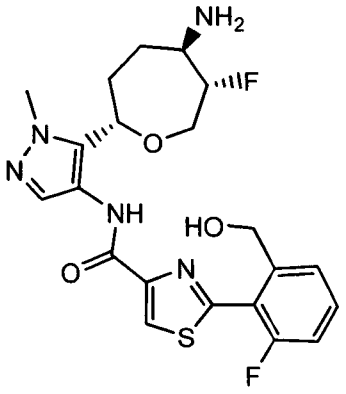
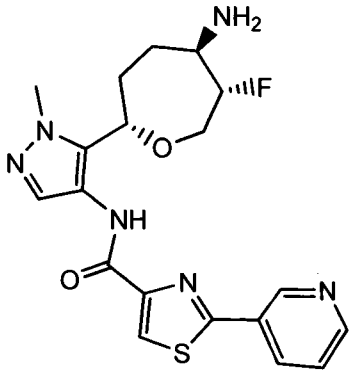
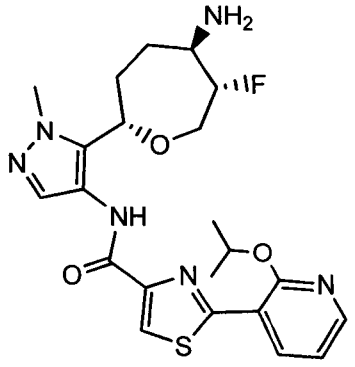
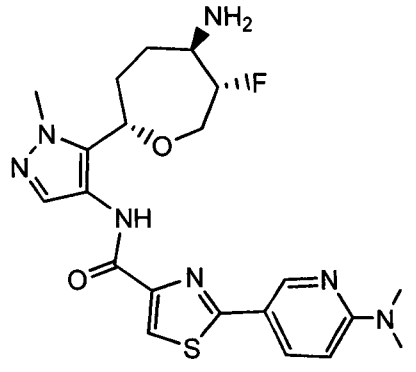
362		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-3-methoxyphenyl)thiazole-4-carboxamide	0.000036
363		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-cyclopropyl-2,6-difluorophenyl)thiazole-4-carboxamide	0.000034
364		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,4,6-trifluorophenyl)thiazole-4-carboxamide	0.000039
365		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluoro-4-((S)-1-hydroxyethyl)phenyl)thiazole-4-carboxamide	0.000069

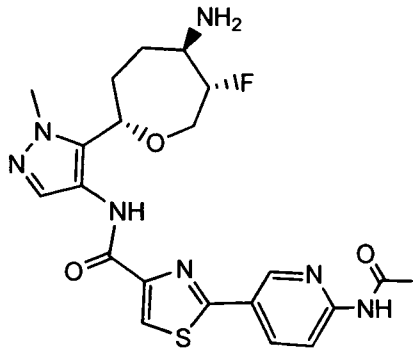
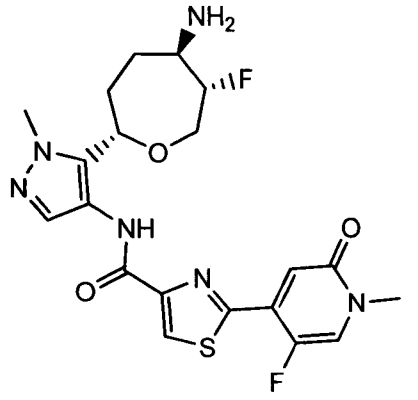
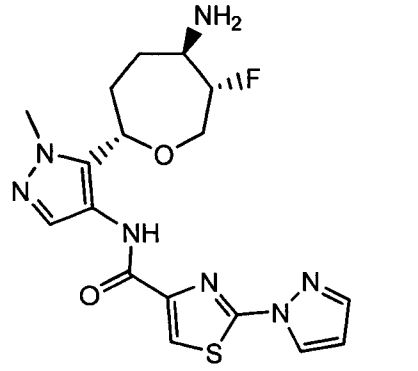
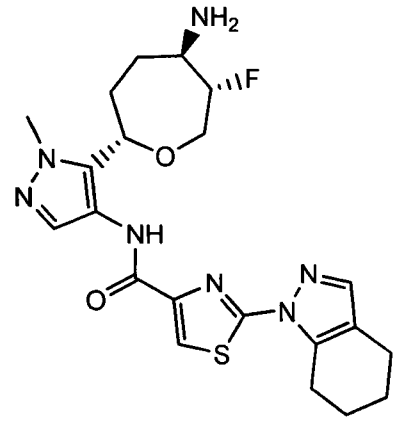
366		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3-difluoro-4-((R)-1-hydroxyethyl)phenyl)thiazole-4-carboxamide	0.00014
367		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-isobutyrylphenyl)thiazole-4-carboxamide	0.000061
368		N-(5-((2S,5R,6S)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-3-methoxyphenyl)thiazole-4-carboxamide	0.000030
369		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2-fluoro-6-methyl-phenyl)-5-methyl-thiazole-4-carboxamide	0.00359

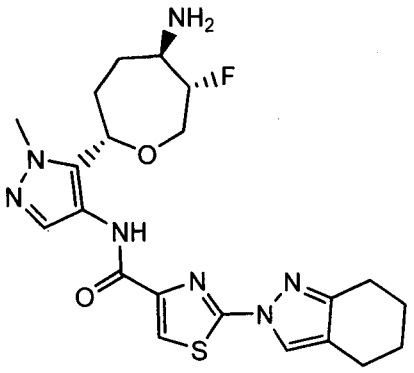
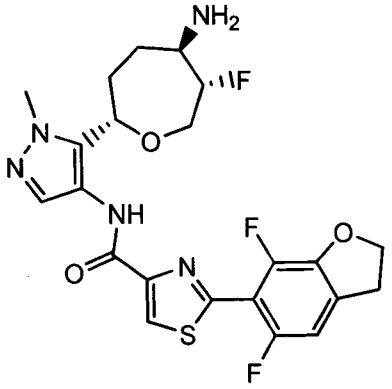
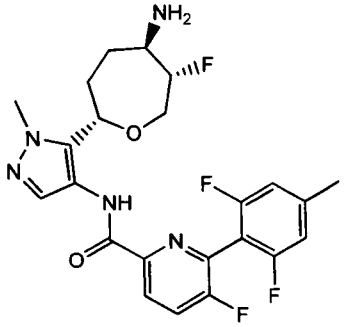
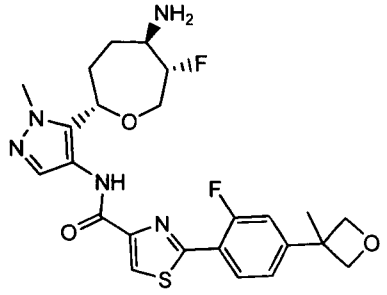
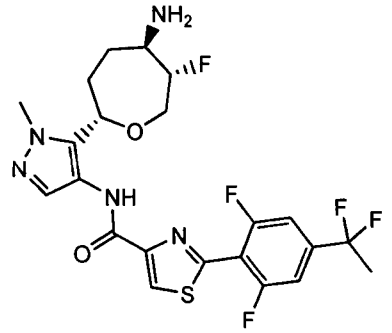
370		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2,6-difluorophenyl)-5-methyl-thiazole-4-carboxamide	0.000382
371		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-((S)-tetrahydrofuran-2-yl)phenyl)thiazole-4-carboxamide	0.000057
372		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4,5-dimethyl-1H-pyrazol-3-yl)thiazole-4-carboxamide	0.000064
373		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(6,6-dimethyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)thiazole-4-carboxamide	0.0000090

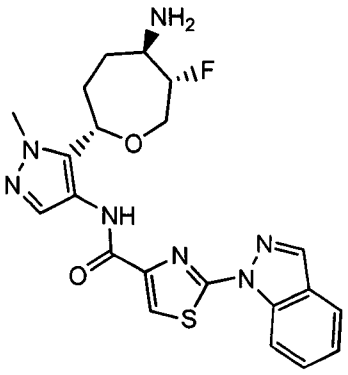
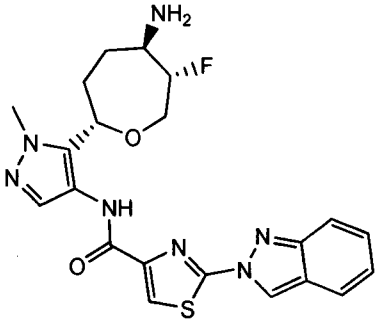
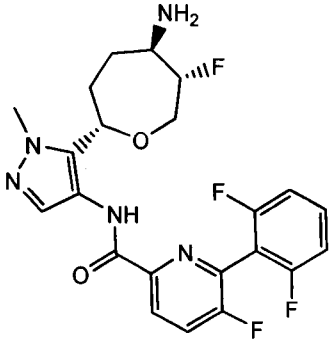
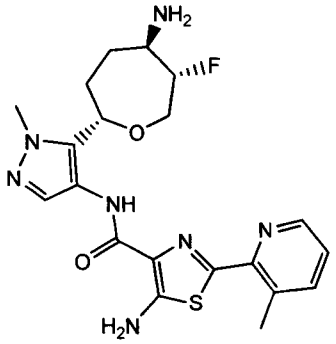
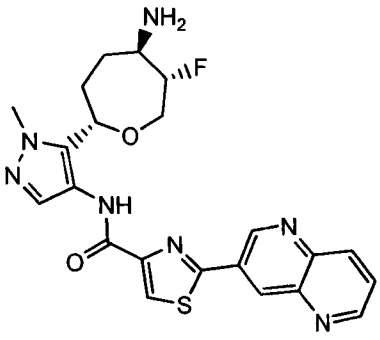
374		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4,5,6,7-tetrahydro-1H-indazol-3-yl)thiazole-4-carboxamide	0.000023
375		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(4-chloro-2,6-difluorophenyl)-5-fluoropicolinamide	0.000036
376		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-[3-(dimethylcarbamoyl)-2,6-difluoro-phenyl]thiazole-4-carboxamide	0.000727
377		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-[3-(difluoromethyl)-2,6-difluoro-phenyl]thiazole-4-carboxamide	0.000031

378		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-[3-(difluoromethyl)-2-fluoro-6-methoxy-phenyl]thiazole-4-carboxamide	0.00148
379		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(1H-pyrazol-3-yl)thiazole-4-carboxamide	0.000129
380		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-((R)-tetrahydrofuran-2-yl)phenyl)thiazole-4-carboxamide	0.000071
381		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1H-indazol-3-yl)thiazole-4-carboxamide	0.000022

382		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-[2-fluoro-6-(hydroxymethyl)phenyl]thiazole-4-carboxamide	0.0072
383		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(3-pyridyl)thiazole-4-carboxamide	0.000991
384		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(2-isopropoxy-3-pyridyl)thiazole-4-carboxamide	0.0097
385		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-[6-(dimethylamino)-3-pyridyl]thiazole-4-carboxamide	0.0002

386		2-(6-acetamido-3-pyridyl)-N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]thiazole-4-carboxamide	0.000389
387		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)thiazole-4-carboxamide	0.000954
388		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1H-pyrazol-1-yl)thiazole-4-carboxamide	0.000157
389		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4,5,6,7-tetrahydro-1H-indazol-1-yl)thiazole-4-carboxamide	0.000020

390		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4,5,6,7-tetrahydro-2H-indazol-2-yl)thiazole-4-carboxamide	0.000267
391		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(5,7-difluoro-2,3-dihydrobenzofuran-6-yl)thiazole-4-carboxamide	0.000024
392		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-6-(2,6-difluoro-4-methylphenyl)-5-fluoropicolinamide	0.000041
393		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-4-(3-methyloxetan-3-yl)phenyl)thiazole-4-carboxamide	0.000003
394		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(4-(1,1-difluoroethyl)-2,6-difluorophenyl)thiazole-4-carboxamide	0.000018

395		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1H-indazol-1-yl)thiazole-4-carboxamide	0.000085
396		N-(5-((2S,5R,6S)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2H-indazol-2-yl)thiazole-4-carboxamide	0.000002
397		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-6-(2,6-difluorophenyl)-5-fluoro-pyridine-2-carboxamide	0.000016
398		5-amino-N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(3-methyl-2-pyridyl)thiazole-4-carboxamide	0.0000040
399		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(1,5-naphthyridin-3-yl)thiazole-4-carboxamide	0.00021

$CH(CH_3)CH_2CH_2CH_3$), 3-pentyl (-$CH(CH_2CH_3)_2$), 2-methyl-2-butyl (-$C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl (-$CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl (-$CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl (-$CH_2CH(CH_3)CH_2CH_3$), 1-hexyl (-$CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl (-$CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl (-$CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl (-$C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl (-$CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl (-$CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl (-$C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl (-$CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl (-$C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl (-$CH(CH_3)C(CH_3)_3$, 1-heptyl, 1-octyl, and the like.

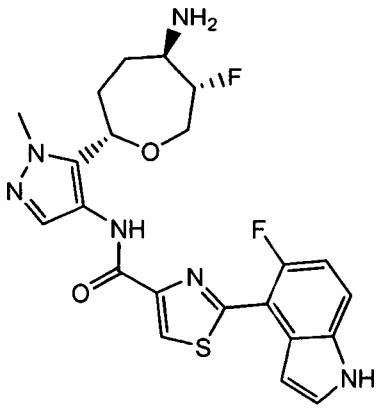
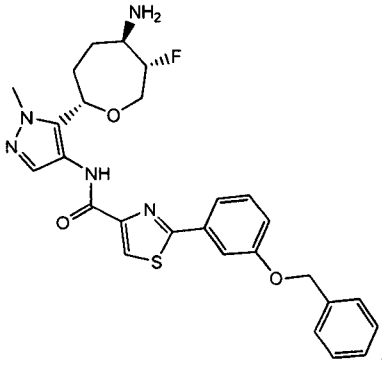
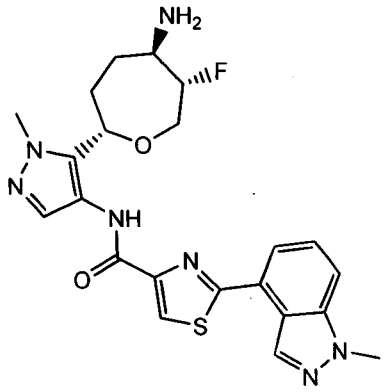
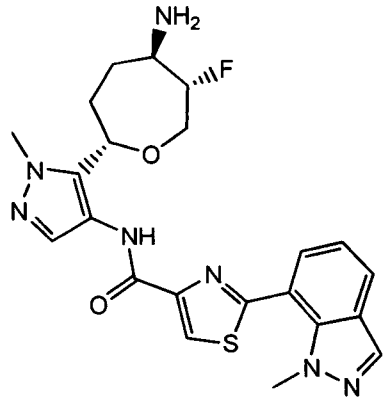
The term "alkylene" as used herein refers to a saturated linear or branched-chain divalent hydrocarbon radical of one to twelve carbon atoms (C_1–C_{12}), wherein the alkylene radical may be optionally substituted independently with one or more substituents described below. In another embodiment, an alkylene radical is one to eight carbon atoms (C_1–C_8), or one to six carbon atoms (C_1–C_6). Examples of alkylene groups include, but are not limited to, methylene (-CH_2-), ethylene (-CH_2CH_2-), propylene (-$CH_2CH_2CH_2$-), and the like.

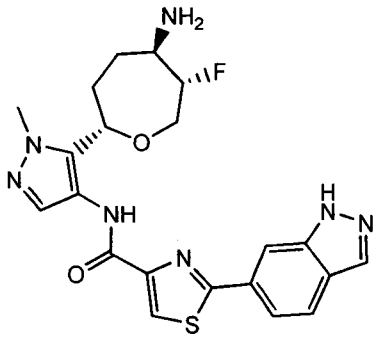
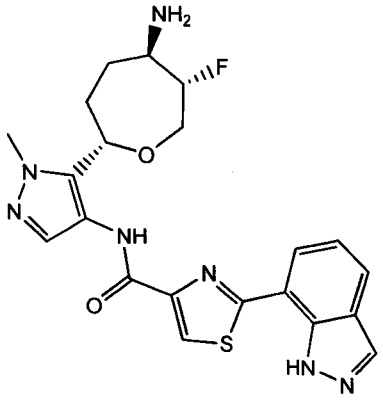
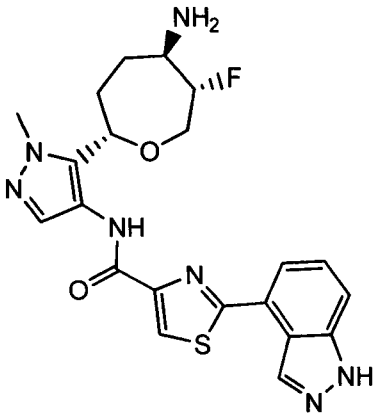
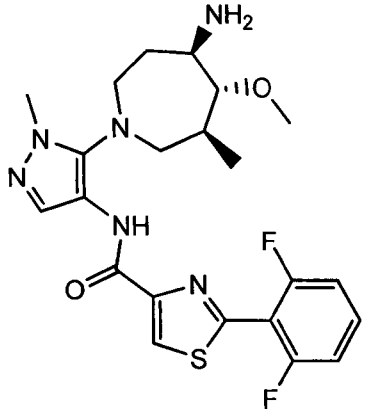
The term "alkenyl" refers to linear or branched-chain monovalent hydrocarbon radical of two to eight carbon atoms (C_2–C_8) with at least one site of unsaturation, i.e., a carbon-carbon, sp^2 double bond, wherein the alkenyl radical may be optionally substituted independently with one or more substituents described herein, and includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. Examples include, but are not limited to, ethylenyl or vinyl (-$CH=CH_2$), allyl (-$CH_2CH=CH_2$), and the like.

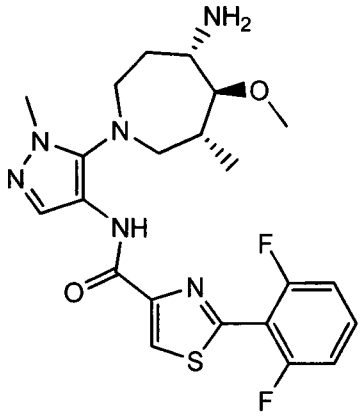
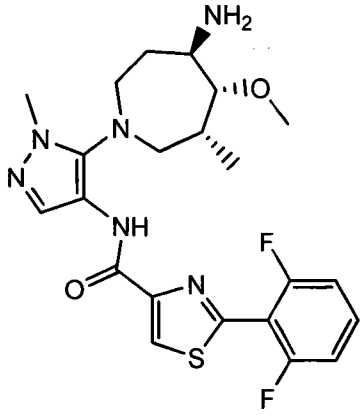
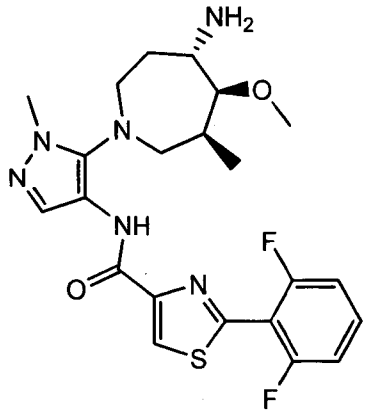
The term "alkenylene" refers to linear or branched-chain divalent hydrocarbon radical of two to eight carbon atoms (C_2–C_8) with at least one site of unsaturation, i.e., a carbon-carbon, sp^2 double bond, wherein the alkenylene radical may be optionally substituted substituted independently with one or more substituents described herein, and includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. Examples include, but are not limited to, ethylenylene or vinylene (-CH=CH-), allyl (-$CH_2CH=CH$-), and the like.

The term "alkynyl" refers to a linear or branched monovalent hydrocarbon radical of two to eight carbon atoms (C_2–C_8) with at least one site of unsaturation, i.e., a carbon-carbon, sp triple bond, wherein the alkynyl radical may be optionally substituted independently with one or more substituents described herein. Examples include, but are not limited to, ethynyl (-C≡CH), propynyl (propargyl, -$CH_2C≡CH$), and the like.

The term "alkynylene" refers to a linear or branched divalent hydrocarbon radical of two to eight carbon atoms (C_2–C_8) with at least one site of unsaturation, i.e., a carbon-

400		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(5-fluoro-1H-indol-4-yl)thiazole-4-carboxamide	0.000011
401		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(3-benzyloxyphenyl)thiazole-4-carboxamide	0.000447
402		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(1-methylindazol-4-yl)thiazole-4-carboxamide	0.000117
403		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(1-methylindazol-7-yl)thiazole-4-carboxamide	0.00591

404		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(1H-indazol-6-yl)thiazole-4-carboxamide	
405		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(1H-indazol-7-yl)thiazole-4-carboxamide	
406		N-[5-[(2S,5R,6S)-5-amino-6-fluoro-oxepan-2-yl]-1-methyl-pyrazol-4-yl]-2-(1H-indazol-4-yl)thiazole-4-carboxamide	
407		N-(5-((3S,4R,5R)-5-amino-4-methoxy-3-methylazepan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	

408		N-(5-((3R,4S,5S)-5-amino-4-methoxy-3-methylazepan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	
409		N-(5-((3R,4R,5R)-5-amino-4-methoxy-3-methylazepan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	
410		N-(5-((3S,4S,5S)-5-amino-4-methoxy-3-methylazepan-1-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide	

The present invention includes a composition (e.g., a pharmaceutical composition) comprising a compound of Formula I, and/or solvates, hydrates and/or salts thereof, and a carrier (a pharmaceutically acceptable carrier). The present invention also includes a composition (e.g., a pharmaceutical composition) comprising a compound of Formula I and/or solvates, hydrates and/or salts thereof, and a carrier (a pharmaceutically acceptable carrier), further comprising a second chemotherapeutic agent such as those described herein. The present compositions are useful for inhibiting abnormal cell growth or treating a hyperproliferative disorder such as cancer in a mammal (e.g., human). For example, the present compounds and compositions are useful for treating multiple myeloma, lymphoma,

acute myeloid leukemia, prostate cancer, breast cancer, hepatocellular carcinoma, pancreatic cancer, and/or colorectal cancer in a mammal (e.g., human).

The present invention includes a method of inhibiting abnormal cell growth or treating a hyperproliferative disorder such as cancer in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound of Formula I, and/or solvates, hydrates and/or salts thereof, or a composition thereof. For example, the present invention includes a method of treating multiple myeloma, lymphoma, acute myeloid leukemia, prostate cancer, breast cancer, hepatocellular carcinoma, pancreatic cancer, and/or colorectal cancer in a mammal (e.g., human), comprising administering to said mammal a therapeutically effective amount of a compound of Formula I, and/or solvates, hydrates and/or salts thereof) or a composition thereof.

The present invention includes a method of inhibiting abnormal cell growth or treating a hyperproliferative disorder such as cancer in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound of Formula I, and/or solvates, hydrates and/or salts thereof, or a composition thereof, in combination with a second chemotherapeutic agent such as those described herein. For example, the present invention includes a method of treating multiple myeloma, lymphoma, acute myeloid leukemia, prostate cancer, breast cancer, hepatocellular carcinoma, pancreatic cancer, and/or colorectal cancer in a mammal (e.g., human), comprising administering to said mammal a therapeutically effective amount of a compound of Formula I, and/or solvates, hydrates and/or salts thereof, or a composition thereof, in combination with a second chemotherapeutic agent such as those described herein.

The present invention includes a method of treating lymphoma in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound of Formula I, and/or solvates, hydrates and/or salts thereof, or a composition thereof, either alone or in combination with a second chemotherapeutic agent such as an anti-B-cell antibody therapeutic (e.g., RITUXAN® and/or dacetuzumab), gemcitabine, corticosteroids (e.g., prednisolone and/or dexamethasone), chemotherapy cocktails (e.g., CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) and/or ICE (isfosfamide, cytoxan, etoposide)), a combination of biologics and chemotherapy (e.g., RITUXAN®-ICE, dacetuzumab-RITUXAN®-ICE, R-Gem, and/or D-R-Gem), an Akt inhibitor, a PI3K inhibitor (e.g, GDC-0941 (Genentech) and/or GDC-0980 (Genentech)), rapamycin, a rapamycin analog, mTOR inhibitor such as everolimus or sirolimus, a MEK inhibitor (GDC-0973), and a Bcl-2 inhibitor (ABT-263 or ABT-199).

The present invention includes a method of treating multiple myeloma in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound of Formula I, and/or solvates, hydrates and/or salts thereof, or a composition thereof, either alone or in combination with a second chemotherapeutic agent such as melphalan, "Imids" (immuno-modulators, e.g., thalidomide, lenalidomide, and/or pomolidamide), corticosteroids (e.g., dexamethasone and/or prednisolone), and bortezomib or other proteasome inhibitor.

The present invention includes a method of treating multiple myeloma, chronic lymphocytic leukemia (CLL), or acute myeloid leukemia (AML) in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound of Formula I, and/or solvates, hydrates and/or salts thereof, or a composition thereof, either alone or in combination with a second chemotherapeutic agent such as cytarabine (araC), anthracyclines (e.g., daunorubicin and/or idarubicin), anti-myeloid antibody therapeutics (e.g., SGN-33), anti-myeloid antibody-drug conjugates (e.g., MYLOTARG®).

The present invention includes a method of treating chronic lymphocytic leukemia (CLL) in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound of Formula I, and/or solvates, hydrates and/or salts thereof, or a composition thereof, either alone or in combination with a second chemotherapeutic agent such as fludarabine, cyclophosphamide, anti-B-cell antibody therapeutics (e.g., RITUXAN® and/or dacetuzumab).

The present invention includes a method of treating chronic myeloid leukemia (CML) in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound of Formula I, and/or solvates, hydrates and/or salts thereof, or a composition thereof, either alone or in combination with a second chemotherapeutic agent such as a BCR-abl inhibitor (e.g., imatinib, nilotinib, and/or dasatinib).

The present invention includes a method of treating myelodysplastic diseases (MDS) and myeloproliferative disorders including polycythemia vera (PV), essential thrombocytosis (ET) or myelofibrosis (MF), in a mammal (e.g., human) comprising administering to said mammal a therapeutically effective amount of a compound of Formula I, and/or solvates, hydrates and/or salts thereof, or a composition thereof, either alone or in combination.

The present invention includes a method of using the present compounds for *in vitro*, *in situ*, and *in vivo* diagnosis or treatment of mammalian cells, organisms, or associated pathological conditions.

Administration of the compounds of the present invention (hereinafter the "active compound(s)") can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), topical, inhalation and rectal administration.

The amount of the active compound administered will be dependent on the subject being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compound and the discretion of the prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, preferably about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to 7 g/day, preferably about 0.05 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

The active compound may be applied as a sole therapy or in combination with one or more chemotherapeutic agents, for example those described herein. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of treatment.

The pharmaceutical composition may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution, suspension for parenteral injection as a sterile solution, suspension or emulsion for topical administration as an ointment or cream or for rectal administration as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound according to the invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

Exemplary parenteral administration forms include solutions or suspensions of Formula I compounds in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents. The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, tablets containing various excipients, such as citric acid may be employed together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Preferred materials, therefore, include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Ester, Pa., 15.sup.th Edition (1975).

ADMINISTRATION OF FORMULA I COMPOUNDS

The Formula I compounds of the invention may be administered by any route appropriate to the condition to be treated. Suitable routes include oral, parenteral (including subcutaneous, intramuscular, intravenous, intraarterial, intradermal, intrathecal and epidural), transdermal, rectal, nasal, topical (including buccal and sublingual), vaginal, intraperitoneal, intrapulmonary and intranasal. For local immunosuppressive treatment, the compounds may be administered by intralesional administration, including perfusing or otherwise contacting the graft with the inhibitor before transplantation. It will be appreciated that the preferred route may vary with for example the condition of the recipient. Where the compound is administered orally, it may be formulated as a pill, capsule, tablet, etc. with a pharmaceutically acceptable carrier or excipient. Where the compound is administered parenterally, it may be formulated with a pharmaceutically acceptable parenteral vehicle and in a unit dosage injectable form, as detailed below.

A dose to treat human patients may range from about 10 mg to about 1000 mg of Formula I compound. A typical dose may be about 100 mg to about 300 mg of the compound. A dose may be administered once a day (QID), twice per day (BID), or more

frequently, depending on the pharmacokinetic and pharmacodynamic properties, including absorption, distribution, metabolism, and excretion of the particular compound. In addition, toxicity factors may influence the dosage and administration regimen. When administered orally, the pill, capsule, or tablet may be ingested daily or less frequently for a specified period of time. The regimen may be repeated for a number of cycles of therapy.

METHODS OF TREATMENT WITH FORMULA I COMPOUNDS

Compounds of the present invention are useful for treating hyperproliferative diseases, conditions and/or disorders including, but not limited to, those characterized by over expression of Pim kinases, e.g. Pim-1, Pim-2 and Pim-3 kinases. Accordingly, another aspect of this invention includes methods of treating or preventing diseases or conditions that can be treated or prevented by inhibiting Pim kinase. In one embodiment, the method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of Formula I, or a stereoisomer, geometric isomer, tautomer, or pharmaceutically acceptable salt thereof. In one embodiment, a human patient is treated with a compound of Formula I and a pharmaceutically acceptable carrier, adjuvant, or vehicle, wherein said compound of Formula I is present in an amount to detectably inhibit Pim kinase activity.

Cancers which can be treated according to the methods of this invention include, but are not limited to, breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, non-small cell lung carcinoma (NSCLC), small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, Hodgkin's and leukemia.

Another aspect of this invention provides a compound of this invention for use in the treatment of the diseases or conditions described herein in a mammal, for example, a human, suffering from such disease or condition. Also provided is the use of a compound of this invention in the preparation of a medicament for the treatment of the diseases and conditions described herein in a warm-blooded animal, such as a mammal, for example a human, suffering from such disorder.

PHARMACEUTICAL FORMULATIONS

In order to use a Formula I compound for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. According to this aspect of the invention there is provided a pharmaceutical composition comprising a compound of this invention in association with a pharmaceutically acceptable diluent or carrier.

A typical formulation is prepared by mixing a Formula I compound and a carrier, diluent or excipient. Suitable carriers, diluents and excipients are well known to those skilled in the art and include materials such as carbohydrates, waxes, water soluble and/or swellable polymers, hydrophilic or hydrophobic materials, gelatin, oils, solvents, water and the like. The particular carrier, diluent or excipient used will depend upon the means and purpose for which the compound of the present invention is being applied. Solvents are generally selected based on solvents recognized by persons skilled in the art as safe (GRAS) to be administered to a mammal. In general, safe solvents are non-toxic aqueous solvents such as water and other non-toxic solvents that are soluble or miscible in water. Suitable aqueous solvents include water, ethanol, propylene glycol, polyethylene glycols (e.g., PEG 400, PEG 300), etc. and mixtures thereof. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

The formulations may be prepared using conventional dissolution and mixing procedures. For example, the bulk drug substance (i.e., compound of the present invention or stabilized form of the Formula I compound (e.g., complex with a cyclodextrin derivative or other known complexation agent) is dissolved in a suitable solvent in the presence of one or more of the excipients described above. The compound of the present invention is typically formulated into pharmaceutical dosage forms to provide an easily controllable dosage of the drug and to enable patient compliance with the prescribed regimen.

The pharmaceutical composition (or formulation) for application may be packaged in a variety of ways depending upon the method used for administering the drug. Generally, an article for distribution includes a container having deposited therein the pharmaceutical

formulation in an appropriate form. Suitable containers are well known to those skilled in the art and include materials such as bottles (plastic and glass), sachets, ampoules, plastic bags, metal cylinders, and the like. The container may also include a tamper-proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container has deposited thereon a label that describes the contents of the container. The label may also include appropriate warnings.

Pharmaceutical formulations of the compounds of the present invention may be prepared for various routes and types of administration. For example, a compound of Formula I having the desired degree of purity may optionally be mixed with pharmaceutically acceptable diluents, carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences (1980) 16th edition, Osol, A. Ed.), in the form of a lyophilized formulation, milled powder, or an aqueous solution. Formulation may be conducted by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed. The pH of the formulation depends mainly on the particular use and the concentration of compound, but may range from about 3 to about 8. Formulation in an acetate buffer at pH 5 is a suitable embodiment.

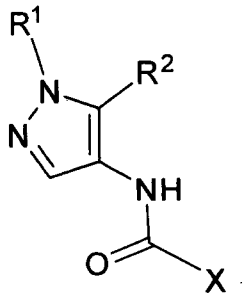
The compound of this invention for use herein is preferably sterile. In particular, formulations to be used for *in vivo* administration must be sterile. Such sterilization is readily accomplished by filtration through sterile filtration membranes.

The compound ordinarily can be stored as a solid composition, a lyophilized formulation or as an aqueous solution.

The pharmaceutical compositions of the invention comprising a Formula I compound will be formulated, dosed and administered in a fashion, i.e., amounts, concentrations, schedules, course, vehicles and route of administration, consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The "therapeutically effective amount" of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to prevent, ameliorate, or treat the coagulation factor mediated disorder. Such amount is preferably below the amount that is toxic to the host or renders the host significantly more susceptible to bleeding.

We Claim:

1. A compound selected from Formula I:

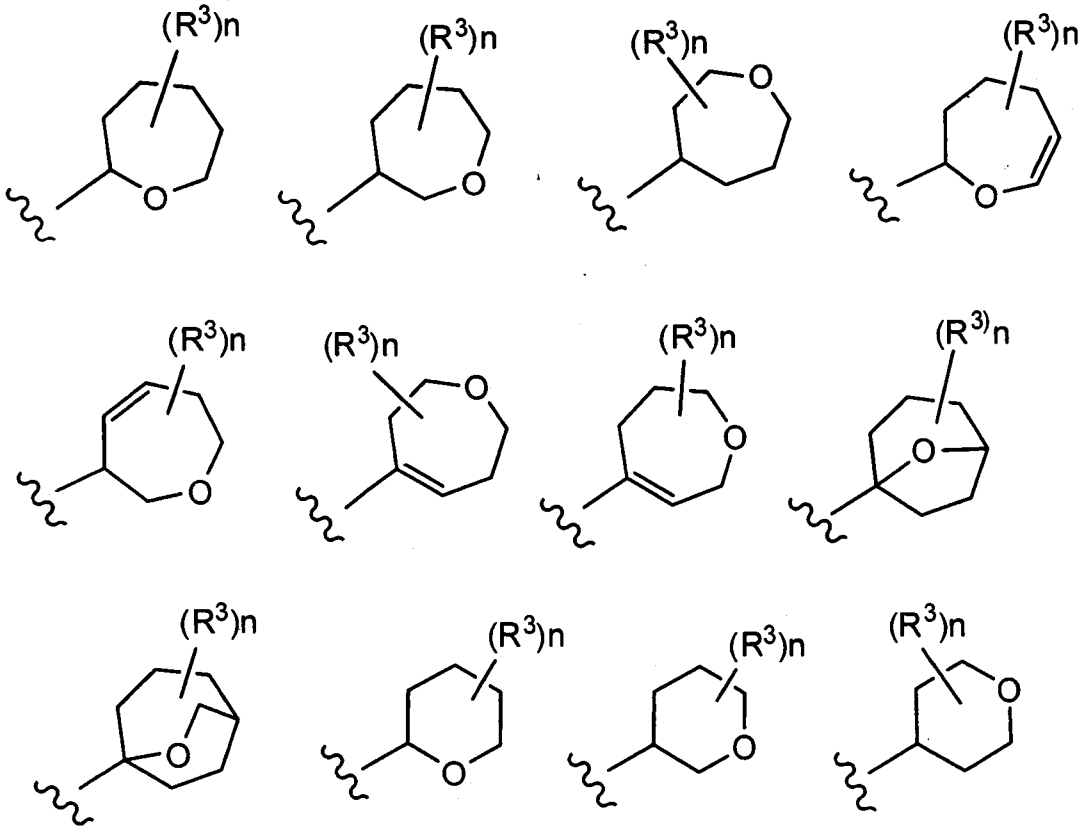


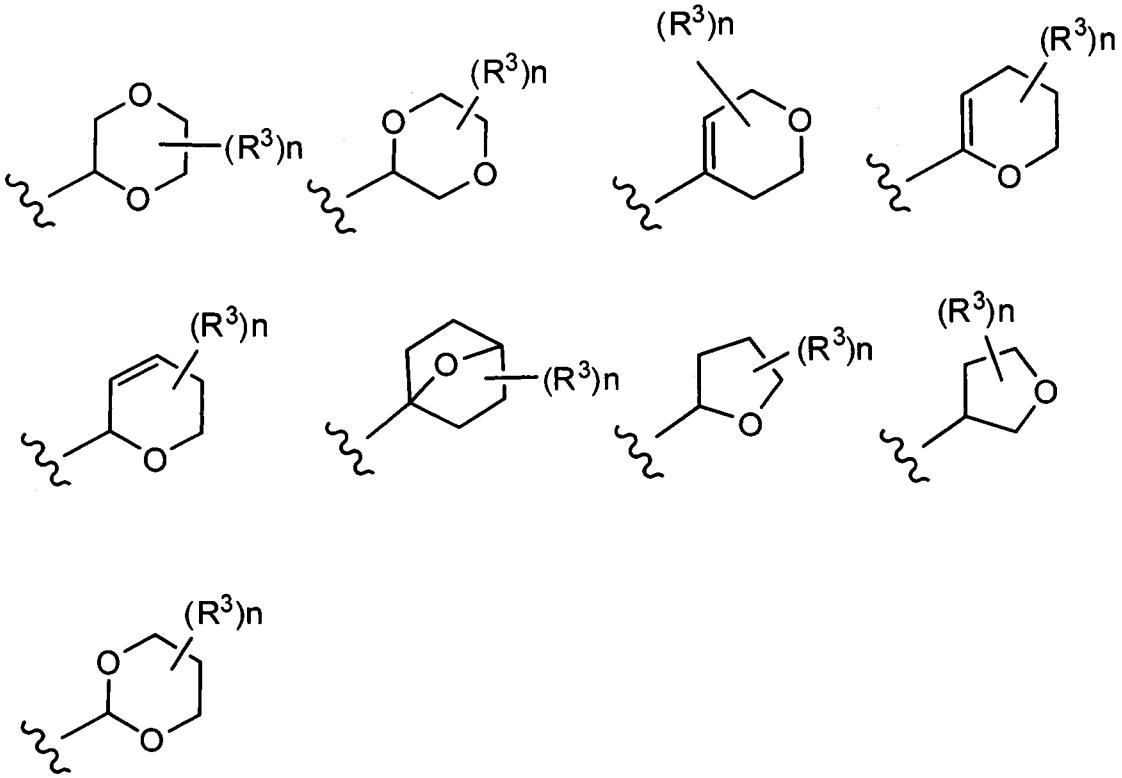
I

and stereoisomers, geometric isomers, tautomers, or pharmaceutically acceptable salts thereof, wherein:

R^1 is selected from H, C_1–C_{12} alkyl,C_2–C_{12}alkenyl, C_2–C_{12}alkynyl, C_6–C_{20} aryl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_1–C_{20} heteroaryl, and –(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl);

R^2 is selected from the structures:





where the wavy line indicates the site of attachment;

R^3 is independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2CH(CH_3)_2$, $-CH=CH_2$, $-CH=C(CH_3)_2$, $=CH_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2CH_2NH_2$, $-CH_2CHCH_2NH_2$, $-CH_2CH(CH_3)NH_2$, $-CH_2OH$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$, $-CH(OH)CH(CH_3)_2$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2SO_2CH_3$, $-CN$, $-CO_2H$, $-COCH_3$, $-COCH_2NH_2$, $-CO_2CH_3$, $-CO_2C(CH_3)_3$, $-COCH(OH)CH_3$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-C(CH_3)_2CONH_2$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCH_2CHF_2$, $-NHCH_2CF_3$, $-NHCH_2CH_2OH$, $-NHCOCH_3$, $-N(CH_3)COCH_3$, $-NHC(O)OCH_2CH_3$, $-NHC(O)OCH_2Cl_3$, $-NHC(O)OC_6H_5$, $-NHS(O)_2CH_3$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, $=O$, $-OH$, $-OCH_3$, $-OCHF_2$, $-OCH_2F$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-OCH_2CH(CH_3)_2$, $-OC(CH_3)_3$, $-S(O)_2N(CH_3)_2$, $-SCH_3$, $-CH_2OCH_3$, $-S(O)_2CH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, azetidinyl, azepanyl, oxetanyl, oxetan-3-ylmethylamino,(3-methyloxetan-3-yl)methylamino, pyrrolidinyl, piperazinyl, piperidinyl, (piperidin-4-yl)ethyl), pyranyl, (piperidin-4-ylmethyl), morpholinomethyl, and morpholino;

or where two geminal R^3 groups form a spiro ring selected from a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl, azetidinyl, azepanyl, oxetanyl, pyrrolidinyl, piperazinyl, or piperidinyl ring, where the spiro ring is optionally substituted

(1,3-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide

5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1,5-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide

5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1-isopropyl-1H-pyrazol-4-yl)thiazole-4-carboxamide

5-amino-*N*-(5-((2*S*,5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(1,5-dimethyl-1H-pyrazol-4-yl)thiazole-4-carboxamide

N-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide

5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-4-(trifluoromethyl)phenyl)thiazole-4-carboxamide

5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide

5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,5-trifluorophenyl)thiazole-4-carboxamide

5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,6-trifluorophenyl)thiazole-4-carboxamide

5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,3,5-trifluorophenyl)thiazole-4-carboxamide

5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-5-methylphenyl)thiazole-4-carboxamide

N-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2,6-difluoro-4-methoxyphenyl)thiazole-4-carboxamide

5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethoxy)phenyl)thiazole-4-carboxamide

5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(3-fluoro-2-(trifluoromethyl)phenyl)thiazole-4-carboxamide

5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)thiazole-4-carboxamide

5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-methoxyoxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-fluoro-6-methylphenyl)thiazole-4-carboxamide

5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(2-(trifluoromethyl)phenyl)thiazole-4-carboxamide

5-amino-*N*-(5-((2*S*,5*R*,6*R*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1H-pyrazol-4-yl)-2-(cyclopent-1-en-1-yl)thiazole-4-carboxamide