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(12) **CORRECTED EUROPEAN PATENT SPECIFICATION**

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Corrections, see

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Claims EN	**1, 3, 5**
Claims FR	**1, 2, 3, 5, 6, 8**

Numerous spelling errors of minor importance

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C07D 401/14 $^{(2006.01)}$
C07D 405/12 $^{(2006.01)}$
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C07D 471/04 $^{(2006.01)}$
C07D 493/10 $^{(2006.01)}$
C07D 495/04 $^{(2006.01)}$
C07D 498/04 $^{(2006.01)}$
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(54) **Compounds and methods of use**
VERBINDUNGEN UND ANWENDUNGSVERFAHREN
COMPOSÉS ET PROCÉDÉS D'UTILISATION

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US-A1- 2007 244 116

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

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EP 2 532 657 B9

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Description

FIELD OF THE INVENTION

[0001] Provided herein are novel compounds that are useful in the treatment of hyperproliferative diseases, such as cancers, in mammals. In particular, the invention relates to compounds that inhibit the protein tyrosine kinase activity, resulting in the inhibition of inter- and/or intra-cellular signaling. Provided also herein are methods of using such compounds in the treatment of hyperproliferative diseases in mammals, especially humans, and pharmaceutical compositions containing such compounds.

BACKGROUND OF THE INVENTION

[0002] Protein kinases represent a large family of proteins, which play a pivotal role in the regulation of a wide variety of cellular processes, maintaining control over cellular function. Protein tyrosine kinases may be classified as growth factor receptor (e.g. VEGFR, EGFR, PDGFR, FGFR and erbB2) or non-receptor (*e.g.* c-src and bcr-abl) kinases. The receptor type tyrosine kinases make up about 20 different subfamilies. The non-receptor type tyrosine kinases make up numerous subfamilies. Receptor tyrosine kinases are large enzymes that span the cell membrane and possess an extracellular binding domain for growth factors, a transmembrane domain, and an intracellular portion that functions as a kinase to phosphorylate a specific tyrosine residue in proteins and hence to influence cell proliferation. Aberrant or inappropriate protein kinase activity can contribute to the rise of disease states associated with such aberrant kinase activity.

[0003] A partial list of such kinases include abl, AATK, ALK, Akt, axl, bmx, bcr-abl, Blk, Brk, Btk, csk, c-kit, c-Met, c-src, c-fins, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDK10, cRaf1, CSF1R, CSK, DDR1, DDR2, EPHA, EPHB, EGFR, ErbB2, ErbB3, ErbB4, Erk, Fak, fes, FER, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, flt-1, Fps, Frk, Fyn, GSG2, GSK, Hck, ILK, INSRR, IRAK4, ITK, IGF-1R, INS-R, Jak, KSR1, KDR, LMTK2, LMTK3, LTK, Lck, Lyn, MATK, MERTK, MLTK, MST1R, MUSK, NPR1, NTRK, MEK, PLK4, PTK, p38, PDGFR, PIK, PKC, PYK2, RET, ROR1, ROR2, RYK, ros, Ron, SGK493, SRC, SRMS, STYK1, SYK, TEC, TEK, TEX14, TNK1, TNK2, TNNI3K, TXK, TYK2, TYRO3, tie, tie2, TRK, Yes, and Zap70. Inhibition of such kinases has become an important therapeutic target. Certain diseases are known to be associated with deregulated angiogenesis, for example, ocular neovascularisation, such as retinopathies (including diabetic retinopathy); age-related macular degeneration; psoriasis; hemangioblastoma; hemangioma; arteriosclerosis; inflammatory diseases, such as a rheumatoid or rheumatic inflammatory disease, especially arthritis (including rheumatoid arthritis); or other chronic inflammatory disorders, such as chronic asthma; arterial or post-transplantational atherosclerosis; endometriosis; and neoplastic diseases, for example so-called solid tumors and liquid tumors (such as leukemias).

[0004] Angiogenesis is an important component of certain normal physiological processes such as embryogenesis and wound healing, but aberrant angiogenesis contributes to some pathological disorders and in particular to tumor growth. VEGF-A (vascular endothelial growth factor A) is a key factor promoting neovascularization (angiogenesis) of tumors. VEGF induces endothelial cell proliferation and migration by signaling through two high affinity receptors, the fms-like tyrosine kinase receptor, flt-1, and the kinase insert domain-containing receptor, KDR. These signaling responses are critically dependent upon receptor dimerization and activation of intrinsic receptor tyrosine kinase (RTK) activity. The binding of VEGF as a disulfide-linked homodimer stimulates receptor dimerization and activation of the RTK domain. The kinase activity autophosphorylates cytoplasmic receptor tyrosine residues, which then serve as binding sites for molecules involved in the propagation of a signaling cascade.

[0005] Disruption of VEGF receptor signaling is a highly attractive therapeutic target in cancer, as angiogenesis is a prerequisite for all solid tumor growth, and that the mature endothelium remains relatively quiescent (with the exception of the female reproductive system and wound healing). A number of experiment approaches to inhibiting VEGF signaling have been examined, including use of neutralizing antibodies receptor antagonists, small molecule antagonists, antisense constructs and dominant negative strategies ("Molecular basis for sunitinib efficacy and future clinical development "Nature Review Drug Discovery, 2007, 6, 734; Angiogenesis: "an organizing principle for drug discovery?" Nature Review Drug Discovery, 2007, 6, 273).

[0006] Hepatocyte growth factor (HGF), also known as scatter factor, is a multifunctional growth factor that enhances transformation and tumor development by inducing mitogenesis and cell motility. In order to produce cellular effects, HGF must bind to its receptor, c-Met, a receptor tyrosine kinase. c-Met is overexpressed in a significant percentage of various types of human cancers and is often amplified during the transition between primary tumors and metastasis. c-Met is also implicated in atherosclerosis and lung fibrosis ("Molecular cancer therapy: can our expectation be MET." Euro. J. Cancer, 2008, 44, 641 - 651). Invasive growth of certain cancer cells is drastically enhanced by tumor-stromal interactions involving the HOF/c-Met (HGF receptor) pathway. Binding of HGF to c-Met leads to receptor phosphorylation and activation of Ras/mitogen-activated protein kinase (MAPK) signaling pathway, thereby enhancing malignant behaviors of cancer cells. Moreover, stimulation of the HGF/c-Met pathway itself can lead to the induction of VEGF expression, itself contributing directly to angiogenic activity ("From Tpr-Met to Met, tumorigenesis and tubes." Oncogene. 2007, 26, 1276; "Targeting the c-Met Signaling Pathway in Cancer." Clin. Cancer Res. 2006, 12, 3657; "Drug development of MET inhibitors: targeting oncogene addiction and expedience." Nature Review Drug Discovery, 2008, 7, 504).

[0007] Insulin-like growth factor 1 receptor (IGF1R) is an integral membrane tyrosine kinase receptor that binds insulin-like growth factor (IGF) with high affinity. IGF1R plays a critical role in transformation events and human cancer. It is highly over-expressed in most malignant tissues where it functions as an anti-apototic agent by enhancing cell survival through the PI3K pathway, and also the p53 pathway. IGF1R has been linked to various disease states, such as breast and ovarian cancer, metastatic uveal melanoma, macular degeneration, and intrauterine growth retardation and poor postnatal growth, among others ("IGF1R signaling and its inhibition." Endocrine-Related Cancer, 2006,13, S33-S43; "The new kid on the block(ade) of the IGF-1 receptor." Cancer Cell, 2004, 5, 201.).

[0008] Anti-tumor approaches that target VEGF/VEGFR, HGF/c-Met and/or IGF/IGF1R signaling may circumvent the ability of tumor cells to overcome VEGFR, HGFR or IGF1R inhibition alone and may represent improved cancer therapeutics. Here we describe small molecules that are potent inhibitors of protein tyrosine kinase activity, such as that of, for example, the VEGF receptor KDR, the HGF receptor c-Met, and/or the IGF receptor IGF1R, among others.

[0009] From WO 2006/116713 A1 substituted amide derivatives are known as protein kinase inhibitors. From US 2004/242603 A1 quinoline derivatives and quinazoline derivatives are known which have antitumor activity. From US 2007/244116 A1 c-MET modulators are known for modulating protein kinase enzymatic activity for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration and chemoinvasion.

[0010] WO 2007/059257 discloses type I receptor tyrosine kinase inhibitors and their use in the treatment of hyperproliferative disorders in mammals.

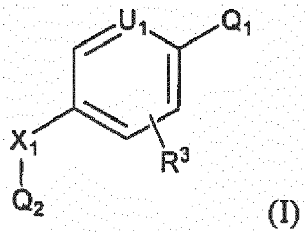
[0011] WO 2007/084875 pertains to compounds for use as medicaments for inbhibiting tyrosine kinase reducing effects in warm-blooded animals such as humans.

SUMMARY OF THE INVENTION

[0012] A compound according to independent claims 1 and 16, a pharmaceutical composition according to independent claim 11 and a method according to independent claim 14 are provided. The dependent claims provide advantageous embodiments.

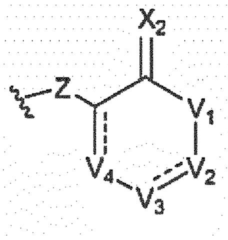
[0013] The compounds disclosed herein may be inhibitors of protein tyrosine kinase activity. Some of the compounds disclosed herein are multiple function inhibitors, capable of inhibiting, for example, VEGF, HGF and/or IGF receptor signaling. Accordingly, provided herein are new inhibitors of protein tyrosine kinase receptor signaling, such as for example, VEGF receptor signaling, HGF receptor signaling, and/or IGF receptor signaling, including the VEGF receptor KDR, the HGF receptor c-Met, and/or IGF1R.

[0014] Specifically, it has been found that compounds disclosed herein, and pharmaceutically acceptable compositions thereof, are effective as inhibitors of receptor tyrosine kinases, especially c-Met, KDR and/or IGF1R. In one aspect, provided herein are compounds having Formula (I) as shown below:

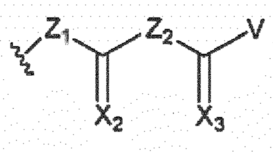


or a stereoisomer, a geometric isomer, a tautomer, an N-oxide, a hydrate, a solvate, a pharmaceutically acceptable salt thereof, wherein

Q_1 is formula (IIa) or (IIb):

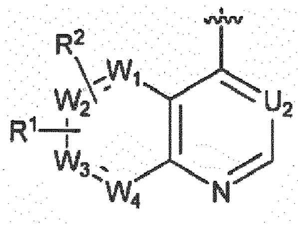


(IIa), or



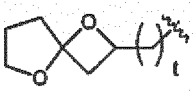
(IIb);

Q$_2$ is Formula (III):



(III);

R^1 is selected from



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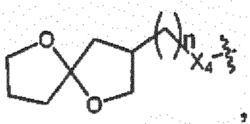

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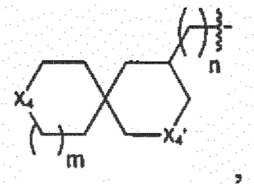

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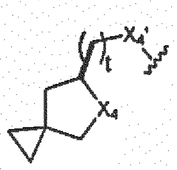

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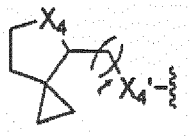

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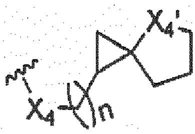

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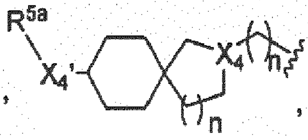

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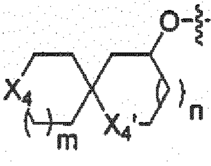

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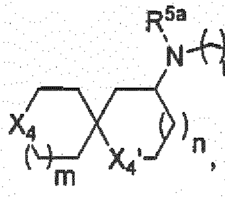

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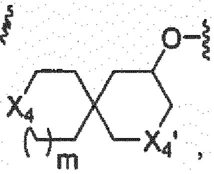

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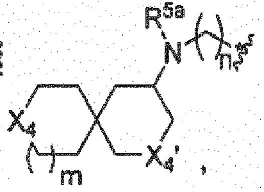

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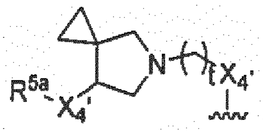

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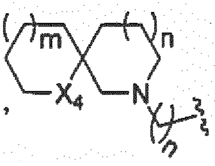

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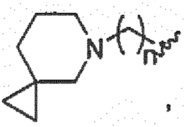

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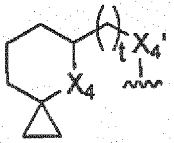

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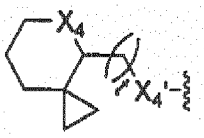

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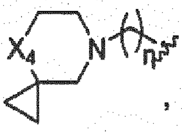

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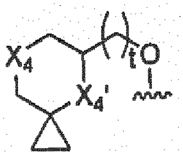

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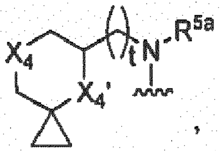

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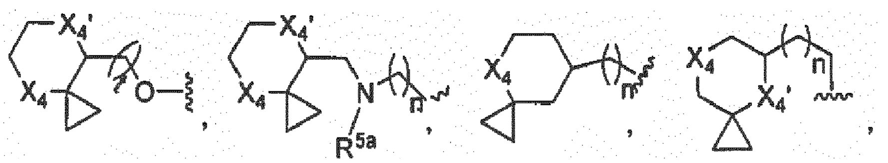
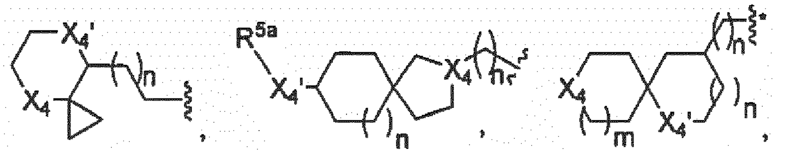
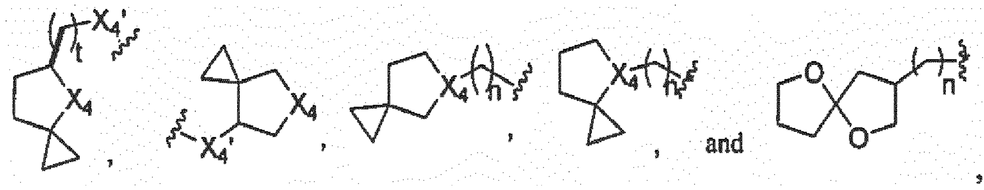






wherein each of X_4 and X_4' is independently $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2; each of m and n is independently 0, 1 or 2; and t is 1,2 or 3;

R^2 is H, halo, cyano(CN), $R^{5a}R^5N$-C_{1-6} alkoxy, C_{1-6} alkoxy, C_{1-6} hydroxyalkoxy, C_{1-6} aminoalkoxy, C_{1-6} hydroxy-substituted aminoalkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylamino C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkoxy, C_{4-10} heterocyclyloxy C_{1-6} alkoxy, C_{5-12} fused bicyclyl, C_{5-12} fused bicyclyl C_{1-6} aliphatic, C_{5-12} fused heterobicyclyl C_{1-6} aliphatic, C_{5-12} fused bicycloxy, C_{5-12} fused bicyclylamino, C_{5-12} fused bicycloxo C_{1-6} alkoxy, C_{5-12} fused bicyclylamino C_{1-6} alkoxy, C_{5-12} fused bicyclyl-C(=O)-, C_{5-12} fused bicyclyl-C(=O)O-, C_{5-12} fused heterobicyclyl-C(=O)-, C_{5-12} fused heterobicyclyl-C(=O)O-, C_{5-12} fused bicyclylamino-C(=O)-, C_{5-12} fused heterobicyclylamino-C(=O)-, C_{5-12} fused bicyclyl-C(=O)NR^5-, C_{5-12} fused heterobicyclyl-C(=O)NR^5-, C_{5-12} spiro bicyclyl, C_{5-12} spiro bicycloxy, C_{5-12} spiro bicyclylamino, C_{5-12} spiro bicycloxo C_{1-6} alkoxy, C_{5-12} spiro bicyclylamino C_{1-6} alkoxy, C_{5-12} fused heterobicyclyl, C_{5-12} fused hetembicycloxy, C_{5-12} fused heterobicyclylamino, C_{5-12} fused heterobicycloxo C_{1-6} alkoxy, C_{5-12} fused heterobicyclylamino C_{1-6} alkoxy, C_{5-12} spiro bicyclyl, C_{5-12} spiro heterobicyclyl, C_{5-12} spiro bicyclyl C_{1-6} aliphatic, C_{5-12} spiro heterobicyclyl C_{1-6} aliphatic, C_{5-12} spiro heterobicycloxo C_{1-6} alkoxy, C_{5-12} spiro heterobicyclylamino C_{1-6} alkoxy, C_{5-12} spiro bicyclyl -C(=O)-, C_{5-12} spiro bicyclyl-C(=O)O-, C_{5-12} spiro heterobicyclyl-C(=O)-, C_{5-12} spiro heterobicyclyl-C(=O)O-, C_{5-12} spiro bicyclylamino-C(=O)-, C_{5-12} spiro heterobicyclylamino-C(=O)-, C_{5-12} spiro bicyclyl-C(=O)NR^5-, or C_{5-12} spiro heterobicyclyl-C(=O)NR^5-, C_{6-10} aryl, C_{1-10} heteroaryl, C_{6-10} aryl C_{1-6} aliphatic or C_{1-10} heteroaryl C_{1-6} aliphatic;

wherein R^3 is independently H, F, Cl, Br, -CN, C_{1-3} aliphatic, C_{1-3} alkoxy, or C_{1-3} haloalkyl;

each of U_1 and U_2 is independently CR^4 or N;

V is NR^5R^{5a}, OR^5;

V_1 is O or NR^5;

each of V_2, V_3 and V_4 is independently CR^4R^{4a}, NR^5, CR^4 or N, with the proviso that only one of V_2, V_3, and V_4 is NR^5 or N, or V_2 and V_3 or V_3 and V_4 combine to become CR^4R^{4a}, NR^5, O, CR^4 or N, with the proviso that the resulted structure is stable;

each of W_1, W_2, W_3 and W_4 is independently CR^4R^{4a}, NR^5, CR^4 or N, or W_1 and W_2 or W_3 and W_4 combine to become CR^4R^{4a}, NR^5, O or S;

X_1 is $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2, where m is 0, 1 or 2;

each of X_2 and X_3 is independently O, S or NR^5;

Z is -NR^5C(=O)-$(CR^4R^{4a})_p$-, -NR^5C(=S)-$(CR^4R^{4a})_p$-, -NR^{5a}-$(CR^4R^{4a})p^-$, -NR^5-$(CR^4R^{4a})_p$C(=O)-,

$-NR^5-(CR^4R^{4a})_pC(=S)-$, $-NR^5S(=O)_r-$, $-NR^5S(=O)_r(CR^4R^{4a})_p-$, $-C(=O)NR^5(CR^4R^{4a})_p-$ or $-NR^5-(CR^4R^{4a})_pS(=O)_r-$, where p is 0,1,2 or 3 and r is 1 or 2;

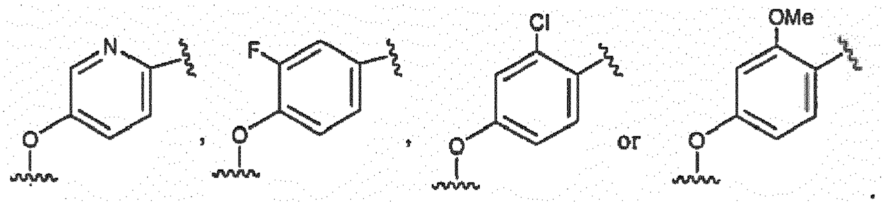
each of Z_1 and Z_2 is independently NR^5 or CR^4R^{4a};

each of R^4 and R^{4a} is independently H, F, Cl, Br, I, -CN, hydroxyl, $-NR^{5a}R^5$, with the proviso that where R^4 and R^{4a} are bonded to the same carbon atom, R^4 and R^{4a}, together with the carbon atom they are attached to, optionally form a 3-8 membered carbocyclic or heterocyclic ring;

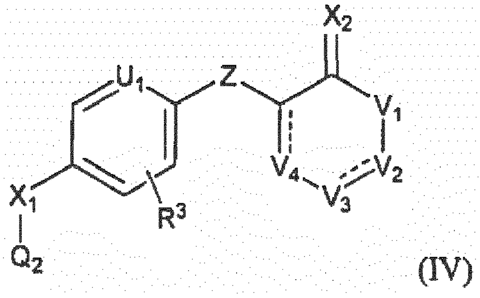
each of R^5 and R^{5a} is independently H, $R^6R^{6a}NC(=O)-$, $R^6OC(=O)-$, $R^6C(=O)-$, $R^6R^{6a}NS(=O)-$, $R^6OS(=O)$, $R^6S(=O)-$, $R^6R^{6a}NSO_2-$, R^6OSO_2-, R^6SO_2-, with the proviso that where R^5 and R^{5a} are bonded to the same nitrogen atom, R^5 and R^{5a}, together with the nitrogen atom they are attached to, optionally form a 3-8 membered ring, including spiro and fused bicyclic rings;

each of R^6 and R^{6a} is H.

[0015] In an embodiment, Z of formula (IIa) is -NHC(=O)-, Z_1 of formula (IIb) is NH; and the substructure defined by X_2, U_1 and R^3 of Formula I is:

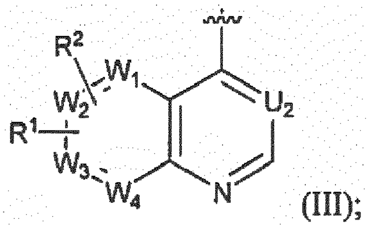


[0016] In an embodiment the compound further has Formula (IV):

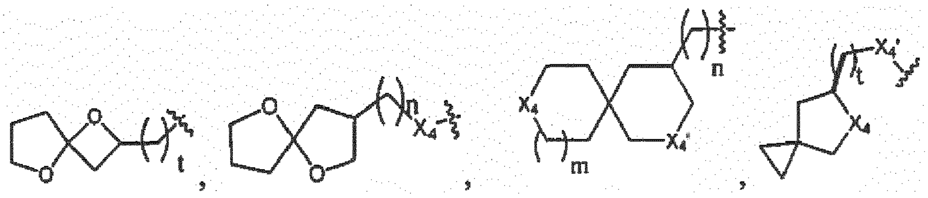


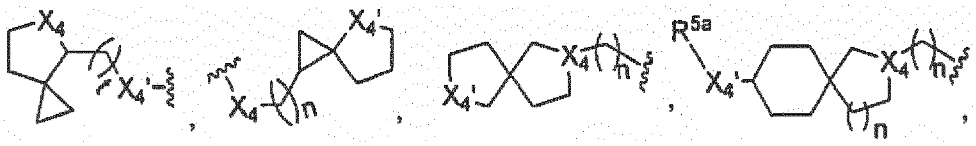
or a stereoisomer, a geometric isomer, a tautomer, an N-oxide, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof, wherein:

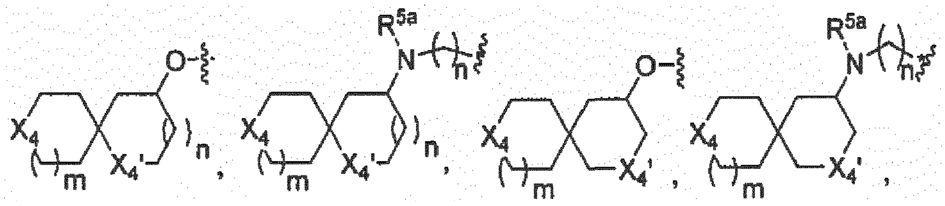
Q_2 has formula (III):

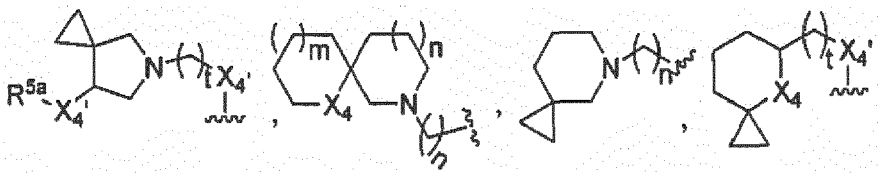


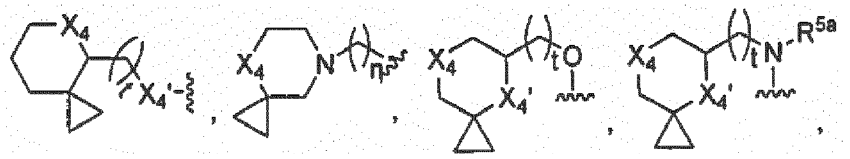
R^1 is selected from

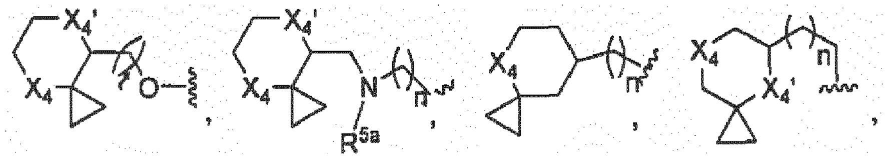


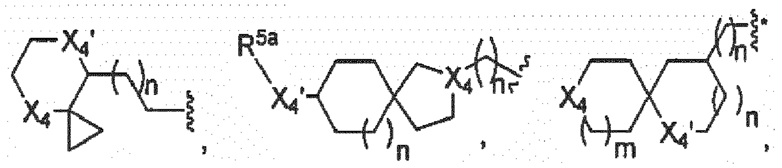


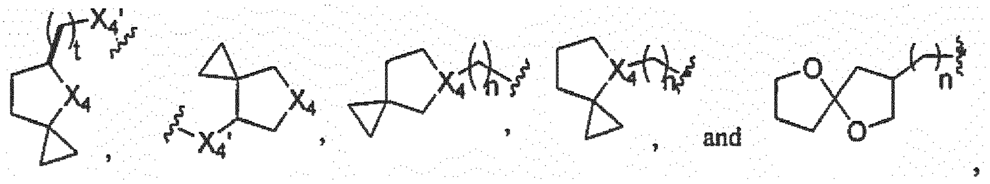












wherein each of X_4 and X_4' is independently $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2; each of m and n is independently 0,1 or 2; and t is 1, 2 or 3;

R^2 is H, halo, cyano(CN), $R^{5a}R^5N$-C_{1-6} alkoxy, C_{1-6} alkoxy, C_{1-6} hydroxyalkoxy, C_{1-6} aminoalkoxy, C_{1-6} hydroxy-substituted aminoalkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylamino C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkoxy, C_{4-10} heterocyclyloxy C_{1-6} alkoxy, C_{5-12} fused bicyclyle, C_{5-12} fused bicyclyl C_{1-6} aliphatic, C_{5-12} fused heterobicyclyl C_{1-6} aliphatic, C_{5-12} fused bicycloxy, C_{5-12} fused bicyclylamino, C_{5-12} fused bicycloxo C_{1-6} alkoxy, C_{5-12} fused bicyclylamino C_{1-6} alkoxy, C_{5-12} fused bicyclyl-C(=O)-, C_{5-12} fused bicyclyl-C(=O)O-, C_{5-12} fused heterobicyclyl-C(=O)-, C_{5-12} fused heterobicyclyl-C(=O)O-, C_{5-12} fused bicyclylamino-C(=O)-, C_{5-12} fused heterobicyclylamino-C(=O)-, C_{5-12} fused bicyclyl-C(=O)NR^5-, C_{5-12} fused heterobicyclyl-C(=O)NR^5-, C_{5-12} spiro bicyclyl, C_{5-12} spiro bicycloxy, C_{5-12} spiro bicyclylamino, C_{5-12} spiro bicycloxo C_{1-6} alkoxy, C_{5-12} spiro bicyclylamino C_{1-6} alkoxy, C_{5-12} fused heterobicyclyl, C_{5-12} fused heterobicycloxy, C_{5-12} fused heterobicyclylamino, C_{5-12} fused heterobicycloxo C_{1-6} alkoxy, C_{5-12} fused heterobicyclylamino C_{1-6} alkoxy, C_{5-12} spiro bicyclyl, C_{5-12} spiro heterobicyclyl, C_{5-12} spiro bicyclyl C_{1-6} aliphatic, C_{5-12} spiro heterobicyclyl C_{1-6} aliphatic, C_{5-12} spiro hetembicycloxo C_{1-6} alkoxy, C_{5-12} spiro heterobicyclylamino C_{1-6-} alkoxy, C_{5-12} spiro bicyclyl -C(=O)-, C_{5-12} spiro bicyclyl-C(=O)O-, C_{5-12} spiro heterobicyclyl-C(=O)-, C_{5-12} spiro heterobicyclyl-C(=O)O-, C_{5-12} spiro bicyclylamino-C(=O)-, C_{5-12} spiro heterobicyclylamino-C(=O)-, C_{5-12} spiro bicyclyl-C(=O)NR^5-, or C_{5-12} spiro heterobicyclyl-C(=O)NR^5-, C_{6-10} aryl, C_{1-10} heteroaryl, C_{6-10} aryl C_{1-6} aliphatic or C_{1-10} heteroaryl C_{1-6} aliphatic;

wherein R^3 is independently H, F, Cl, Br, -CN, C_{1-3} aliphatic, C_{1-3} alkoxy, or C_{1-3} haloalkyl;

each of U_1 and U_2 is independently CR^4 or N;

V is NR^5R^{5a}, OR^5;

V_1 is O or NR^5;

each of V_2, V_3 and V_4 is independently CR^4R^{4a}, NR^5, CR^4 or N, with the proviso that only one of V_2, V_3, and V_4 is NR^5 or N, or V_2 and V_3 or V_3 and V_4 combine to become CR^4R^{4a}, NR^7, O, CR^4 or N, with the proviso that the resulted structure is stable;

each of W_1, W_2, W_3 and W_4 is independently CR^4R^{4a}, NR^5, CR^4 or N, or W_1 and W_2 or W_3 and W_4 combine to become CR^4R^{4a}, NR^5, O or S;

X_1 is $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2, where m is 0, 1 or 2;

X_2 is independently O, S or NR^5;

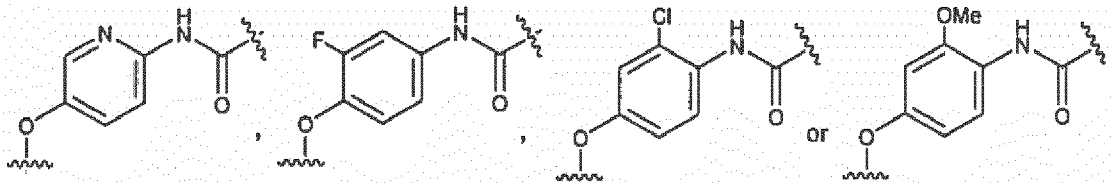
Z is $-NR^5C(=O)-(CR^4R^{4a})_p-$, $-NR^5C(=S)-(CR^4R^{4a})_p-$, $-NR^{5a}-(CR^4R^{4a})_p-$, $-NR^5-(CR^4R^{4a})_pC(=O)-$, $-NR^5-(CR^4R^{4a})_pC(=S)-$, $-NR^5S(=O)_r-$, $-NR^5S(=O)_r(CR^4R^{4a})_p-$,$-C(=O)NR^5(CR^4R^{4a})_p-$ or $-NR^5(CR^4R^{4a})_pS(=O)_r-$, where p is 0,1,2 or 3 and r is 1 or 2;

each of R^4 and R^{4a} is independently H, F, Cl, Br, I, -CN, hydroxyl, $-NR^{5a}R^5$, with the proviso that where R^4 and R^{4a} are bonded to the same carbon atom, R^4 and R^{4a}, together with the carbon atom they are attached to, optionally form a substituted or unsubstituted 3-8 membered carbocyclic or heterocyclic ring;

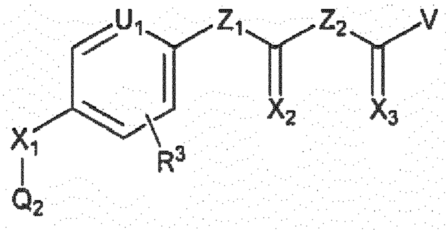
each of R^5 and R^{5a} is independently H, $R^6R^{6a}NC(=O)-$, $R^6OC(=O)-$, $R^6C(=O)-$, $R^6R^{6a}NS(=O)-$, $R^6OS(=O)-$, $R^6S(=O)-$, $R^6R^{6a}NSO_2-$, R^6OSO_2-, R^6SO_2-, with the proviso that where R^5 and R^{5a} are bonded to the same nitrogen atom, R^5 and R^{5a}, together with the nitrogen atom they are attached to, optionally form a 3-8 membered ring, including spiro and fused bicyclic rings;

each of R^6 and R^{6a} is independently H;

wherein each of $R^{5a}R^5N-$, $-C(=O)NR^5R^{5a}$, $-OC(=O)NR^5R^{5a}$, $-OC(=O)OR^5$,$-NR^5C(=O)NR^5R^{5a}$, $-NR^5C(=O)OR^{5a}$, $-NR^5C(=O)-R^{5a}$, $R^5R^{5a}N-O_2S-$, R^5O_2S-, $R^5O_2SR^{5a}N-$, OR^7, NR^5, CR^4R^{4a}, CR^4, $(CR^4R^{4a})_m$, $-NR^5C(O)-(CR^4R^{4a})_p-$, $-NR^5C(=S)-(CR^4R^{4a})_p-$, $-NR^{5a}-(CR^4R^{4a})_p-$, $-NR^5CR^4R^{4a})_pC(=O)-$, $-NR^5-(CR^4R^{4a})_pC(=S)-$, $-NR^5S(O)_{r,}-NR^5S(=O)(CR^4R^{4a})_p-$, $-C(=O)NR^5-(CR^4R^{4a})_p-$, $-NR^5-(CR^4R^{4a})_p-S(=O)_r-$, $R^{5a}R^5N$-alkyl, $R^5(S=O)$-alkyl, $R^5R^{5a}N-(C=O)$-alkyl, $R^{5a}R^5N$-alkoxy, $R^5(S=O)$-alkoxy, $R^5R^{5a}N-(C=O)$-alkoxy, $R^6R^{6a}NC(=O)-$, $R^6OC(=O)-$, $R^6C(=O)-$, $R^6R^{6a}NS(=O)-$, $R^6OS(=O)-$, $R^6S(=O)-$, $R^6R^{6a}NSO_2-$, R^6OSO_2-, R^6SO_2-, hydroxy-substituted cyclopropylalkoxy, $R^5S(=O)_2O$-substituted cyclopropylalkoxy. Preferably, Z is -NHC(=O)-; or wherein the substructure defined by X_1, Z, U_1 and R^3 is



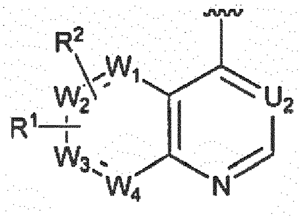
[0017] In certain embodiments, the compound has Formula V:



(V)

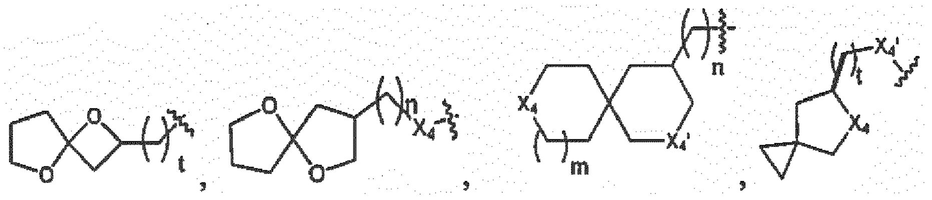
or a stereoisomer, a geometric isomer, a tautomer, an N-oxide, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof, wherein:

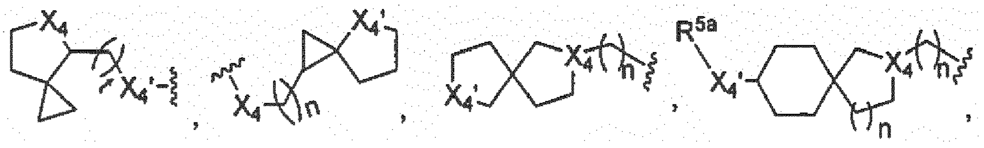
Q_2 has Formula (III):

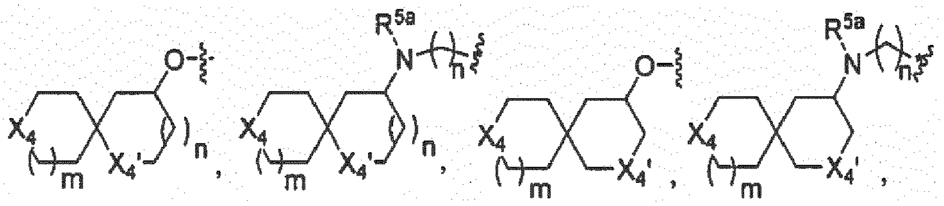


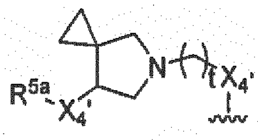
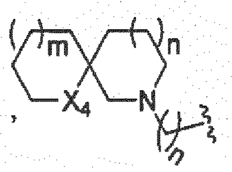
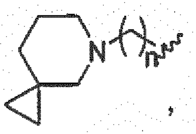
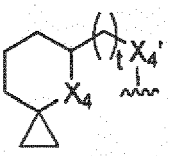
(III);

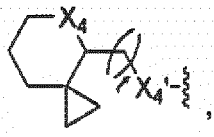
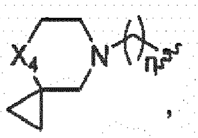
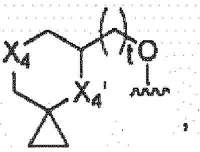
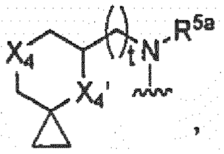
R^1 is selected from

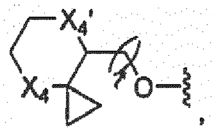
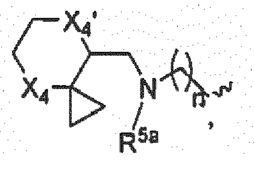
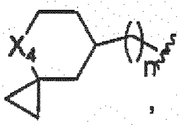
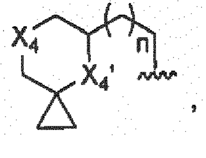


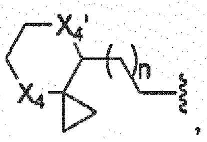
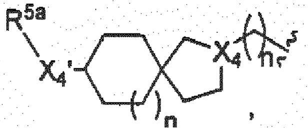
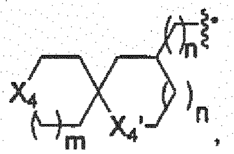


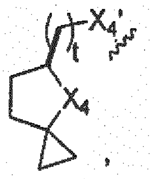
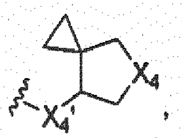
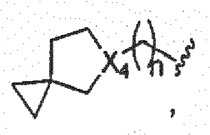
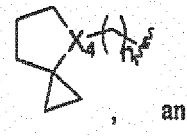
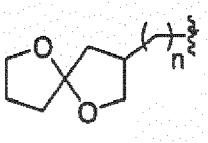


,
,
,
,

,
,
,
,

,
,
,
,

,
,
,

,
,
,
, and
,

wherein each of X_4 and X_4' is independently $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2; each of m and n is independently 0, 1 or 2; and t is 1,2 or 3;

R^2 is H, halo, cyano(CN), $R^{5a}R^5N$-C_{1-6} alkoxy, C_{1-6} alkoxy, C_{1-6} hydroxyalkoxy, C_{1-6} aminoalkoxy, C_{1-6} hydroxy-substituted aminoalkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylamino C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkoxy, C_{4-10} heterocyclyloxy C_{1-6} alkoxy, C_{5-12} fused bicyclyl, C_{5-12} fused bicyclyl C_{1-6} aliphatic, C_{5-12} fused heterobicyclyl C_{1-6} aliphatic, C_{5-12} fused bicycloxy, C_{5-12} fused bicyclylamino, C_{5-12} fused bicycloxo C_{1-6} alkoxy, C_{5-12} fused bicyclylamino C_{1-6} alkoxy, C_{5-12} fused bicyclyl-C(=O)-, C_{5-12} fused bicyclyl-C(=O)O-, C_{5-12} fused heterobicyclyl-C(=O)-, C_{5-12} fused heterobicyclyl-C(=O)O-, C_{5-12} fused bicyclylamino-C(=O)-, C_{5-12} fused heterobicyclylamino-C(=O)-, C_{5-12} fused bicyclyl-C(=O)NR^5-, C_{5-12} fused heterobicyclyl-C(=O)NR^5-, C_{5-12} spiro bicyclyl, C_{5-12} spiro bicycloxy, C_{5-12} spiro bicyclylamino, C_{5-12} spiro bicycloxo C_{1-6} alkoxy, C_{5-12} spiro bicyclylamino C_{1-6} alkoxy, C_{5-12} fused heterobicyclyl, C_{5-12} fused heterobicycloxy, C_{5-12} fused heterobicyclylamino, C_{5-12} fused heterobicycloxo C_{1-6} alkoxy, C_{5-12} fused heterobicyclylamino C_{1-6} alkoxy, C_{5-12} spiro bicyclyl, C_{5-12} spiro heterobicyclyl, C_{5-12} spiro bicyclyl C_{1-6} aliphatic, C_{5-12} spiro heterobicyclyl C_{1-6} aliphatic, C_{5-12} spiro heterobicycloxo C_{1-6} alkoxy, C_{5-12} spiro heterobicyclylamino C_{1-6} alkoxy, C_{5-12} spiro bicyclyl -C(=O)-, C_{5-12} spiro bicyclyl-C(=O)O-, C_{5-12} spiro heterobicyclyl-C(=O)-, C_{5-12} spiro heterobicyclyl-C(=O)O-, C_{5-12} spiro bicyclylamino-C(=O)-, C_{5-12} spiro heterobicyclylamino-C(=O)-, C_{5-12} spiro bicyclyl-C(=O)NR^5-, or C_{5-12} spiro heterobicyclyl-C(=O)NR^5-, C_{6-10} aryl, C_{1-10} heteroaryl, C_{6-10} aryl C_{1-6} aliphatic or C_{1-10} heteroaryl C_{1-6} aliphatic;

wherein R^3 is independently H, F, Cl, Br, -CN, C_{1-3} aliphatic, C_{1-3} alkoxy, or C_{1-3} haloalkyl;

each of U_1 and U_2 is independently CR^4 or N;

V is NR^5R^{5a}, OR^5;

each of W_1, W_2, W_3 and W_4 is independently CR^4R^{4a}, NR^5, CR^4 or N, or W_1 and W_2 or W_3 and W_4 combine to become CR^4R^{4a}, NR^5, O or S;

X_1 is $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2, where m is 0, 1 or 2;

each of X_2 and X_3 is independently O, S or NR^5;

each of Z_1 and Z_2 is independently NR^5 or CR^4R^{4a};

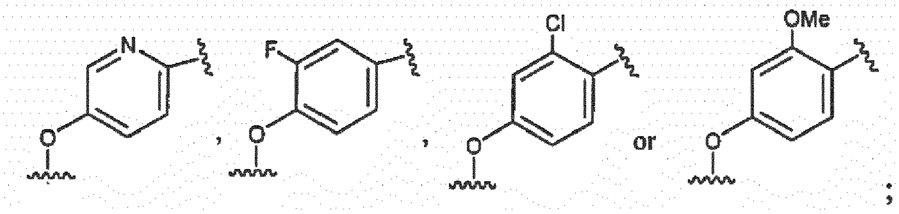
each of R^4 and R^{4a} is independently H, F, Cl, Br, I, -CN, hydroxyl, $-NR^{5a}R^5$, with the proviso that where R^4 and R^{4a} are bonded to the same carbon atom, R^4 and R^{4a}, together with the carbon atom they are attached to, optionally form a substituted or unsubstituted 3-8 membered carbocyclic or heterocyclic ring;

each of R^5 and R^{5a} is independently H, $R^6R^{6a}NC(=O)-$, $R^6OC(=O)-$, $R^6C(=O)-$, $R^6R^{6a}S(=O)-$, $R^6OS(O)-$, $R^6S(=O)-$, $R^6R^{6a}NSO_2-$, R^6OSO_2-, R^6SO_2-, with the proviso that where R^5 and R^{5a} are bonded to the same nitrogen atom, R^5 and R^{5a}, together with the nitrogen atom they are attached to, optionally form a substituted or unsubstituted 3-8 membered ring, including spiro and fused bicyclic rings;

each of R^6 and R^{6a} is independently H;

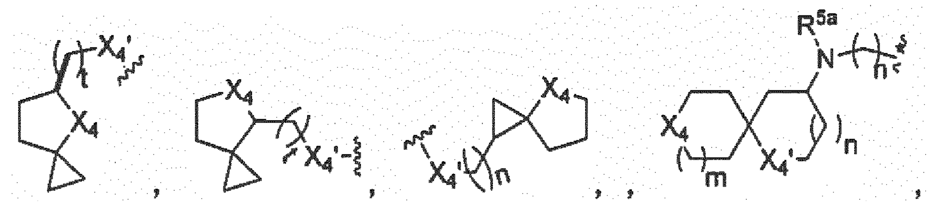
wherein each of $R^{5a}R^5N-$, $-C(=O)NR^5R^{5a}$, $-OC(=O)NR^5R^{5a}$, $-OC(=O)OR^5$,$-NR^5C(=O)NR^5R^{5a}$, $-NR^5C(=O)OR^{5a}$, $-NR^5C(=O)-R^{5a}$, $R^5R^{5a}O_2S-$, R^5O_2S-, $R^5O_2SR^{5a}N-$, OR^5, $-NR^5$, CR^4R^{4a}, CR^4, $(CR^4R^{4a})_m$, $-NR^5C(O)-(CR^4R^{4a})_p-$, $-NR^5C(=S)-(CR^4R^{4a})_p-$, $-NR^{5a}-(CR^4R^{4a})_p-$, $-NR^5-(CR^4R^{4a})_pC(=O)-$, $-NR^5-(CR^4R^{4a})_pC(=S)-$, $-NR^5S(O)_r-$,$-NR^5S(=O)(CR^4R^{4a})_p-$, $-C(=O)NR^5-(CR^4R^{4a})_p-$, $-NR^5-(CR^4R^{4a})_p-S(=O)_r-$, $R^{5a}R^5N$-alkyl, $R^5(S=O)$-alkyl, $R^5R^{5a}N-(C=O)$-alkyl, $R^{5a}R^5N$-alkoxy, $R^5(S=O)$-alkoxy, $R^5R^{5a}N-(C=O)$-alkoxy, $R^6R^{6a}NC(=O)-$, $R^6OC(=O)-$, $R^6C(=O)-$, $R^6R^{6a}NS(=O)-$, $R^6OS(=O)-$, $R^6S(=O)-$, $R^6R^{6a}NSO_2-$, R^6OSO_2-, R^6SO_2-, hydroxy-substituted cyclopropylalkoxy, $R^5S(=O)_2O$-substituted cyclopropylalkoxy.

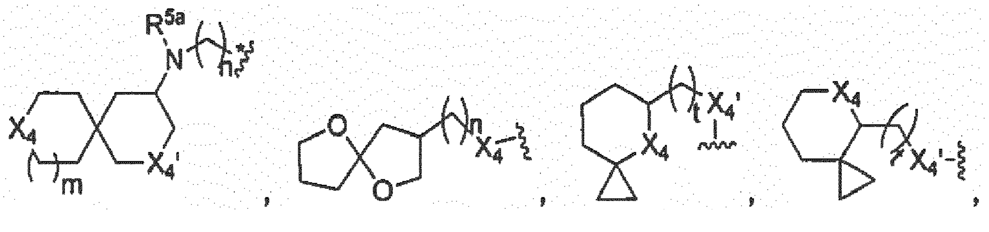
[0018] Preferably, the substructure defined by X_1, U_1 and R^3 is

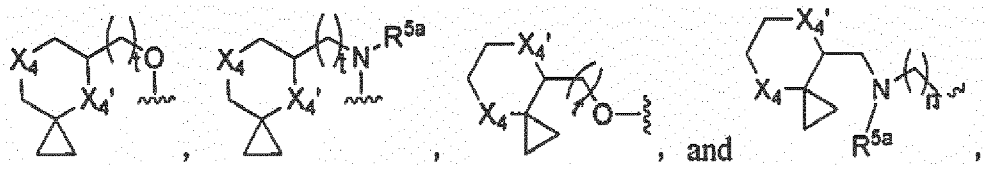


and/or

wherein R^1 is one of the following structures:

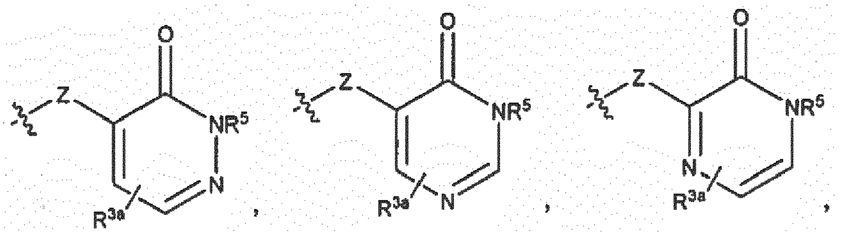


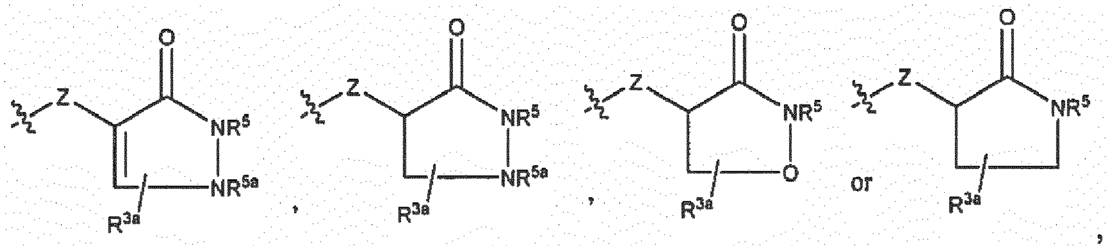




wherein each of X_4 and X_4' is independently $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2; each of m and n is independently 0, 1 or 2; and t is 1, 2 or 3.

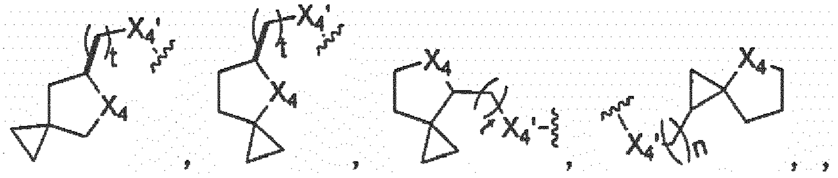
[0019] In other embodiments, Q_1 in Formula I or the substructure defined by X_2, V_1, V_2, V_3, V_4 and Z of Formula (IV) is

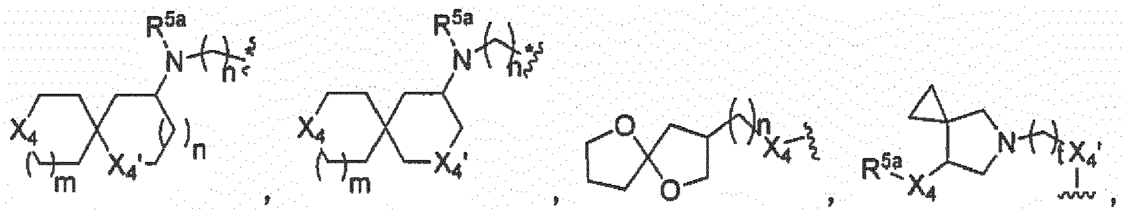


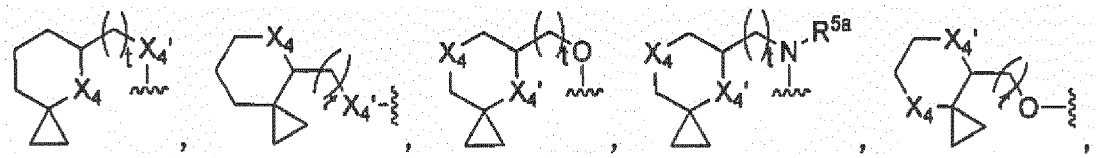


wherein R^{3a} is H, F, Cl, Br, I, -CN, hydroxyl, $R^{5a}R^5N$-, $R^{5a}R^5N$-aliphatic.

[0020] In some embodiments, R^1 is one of the following structures:







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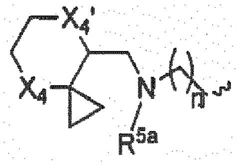
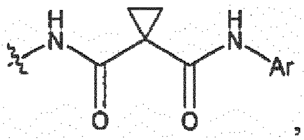


,

wherein each of X_4 and X_4' is independently $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2; each of m and n is independently 0, 1 or 2; and t is 1,2 or 3.

[0021] In certain embodiments, Q_1 in Formula (I) or the substructure defined by Z_1, Z_2, X_2, X_3 and V of Formula (V) is



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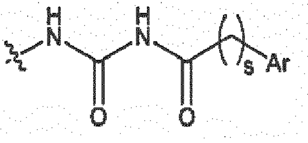

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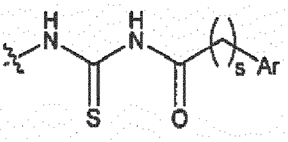
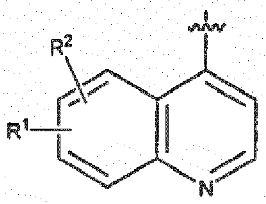


wherein Ar is substituted or unsubstituted aryl or heteroaryl; and s is 0 or 1

[0022] In certain embodiments, Q_2 is



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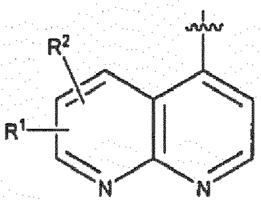

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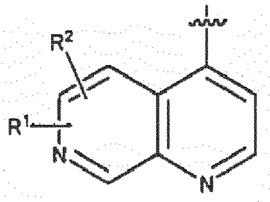

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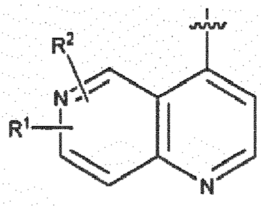

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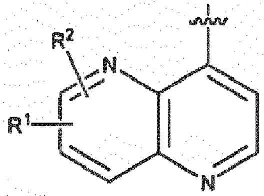

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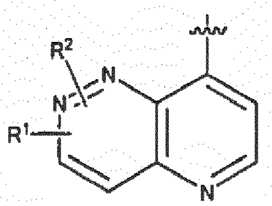

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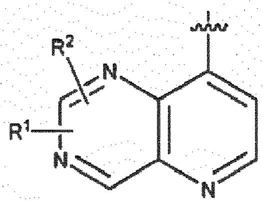

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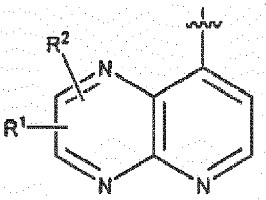

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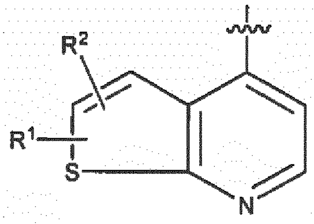

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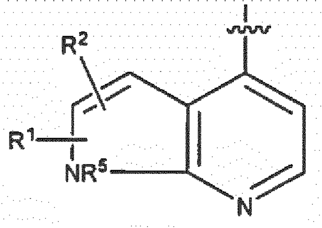

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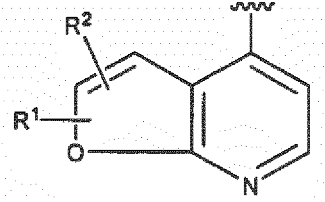

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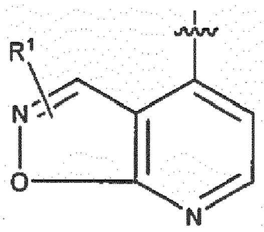

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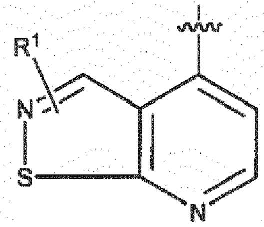

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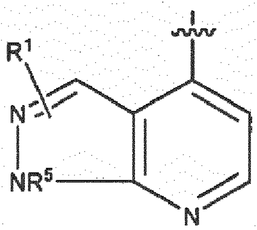

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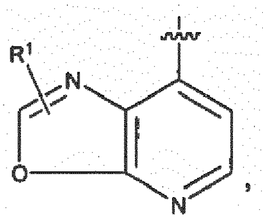
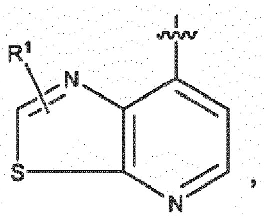
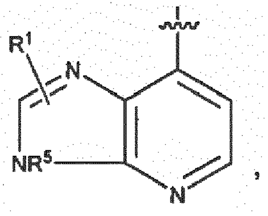
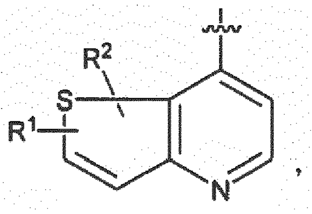
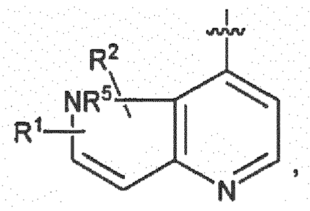
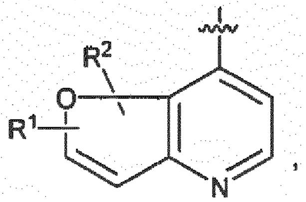
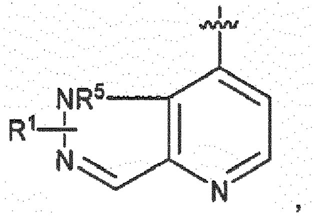
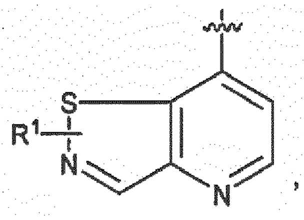
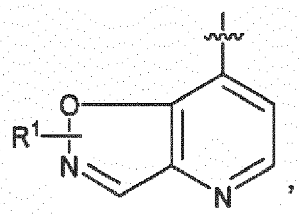
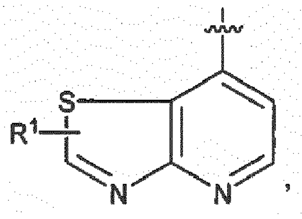
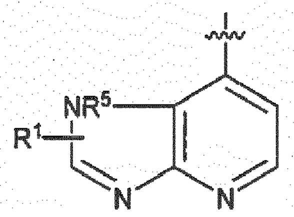

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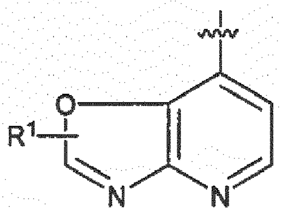
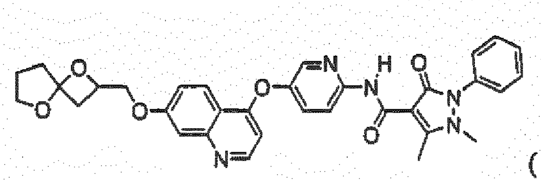


wherein X_1 is O or NR^5.

[0023] The present invention further provides a pharmaceutical composition comprising a compound disclosed herein above, and a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof, and optionally a therapeutic agent selected from a chemotherapeutic agent, an anti-proliferative agent, an agent for treating atherosclerosis, an agent for treating lung fibrosis, and combinations thereof; wherein the additional therapeutic agent is optionally adriamycin, rapamycin, temsirolimus, everolimus, ixabepilone, gemcitabin, cyclophosphamide, dexamethasone, etoposide, fluorouracil, imatinib mesylate, dasatinib, nilotinib, erlotinib, lapatinib, iressa, sorafenib, sunitinib, an interferon, carboplatin, topotecan, taxol, vinblastine, vincristine, temozolomide, tositumomab, trabectedin, bevacizumab, trastuzumab, cetuximab, panitumumab or a combination thereofAccording to a further aspect, the compound disclosed herein above or the pharmaceutical composition is for use in preventing, managing, treating or lessening the severity of a proliferative disorder. The proliferative disorder preferably is metastatic cancer, colon cancer, gastric adenocarcinoma, bladder cancer, breast cancer, kidney cancer, liver cancer, lung cancer, thyroid cancer, cancer of the head and neck, prostate cancer, pancreatic cancer, cancer of the CNS, glioblastoma, or a myeloproliferative disorder, atherosclerosis or lung fibrosis

[0024] According to a further aspect, the present invention provides a method of inhibiting or modulating protein kinase activity in a biological sample comprising contacting a biological sample with the compound disclosed herein above or the pharmaceutical composition disclosed herein above. Preferably, the protein kinases are receptor tyrosine kinases, and the receptor tyrosine kinases are KDR, c-Met or IGF1R

[0025] Also provided in accordance with the present invention is a compound having one of the following structures:



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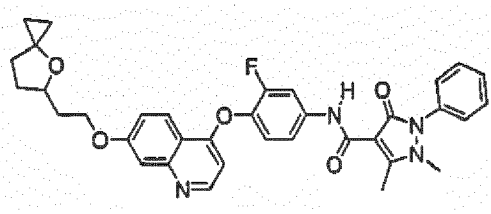

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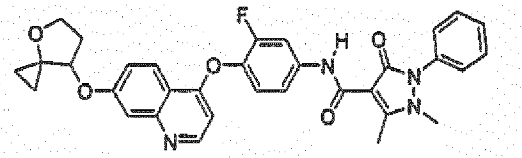

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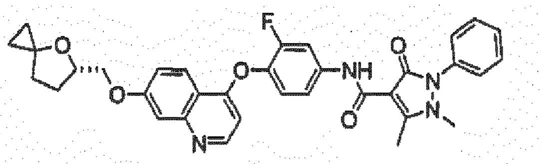

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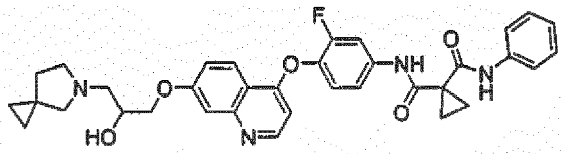

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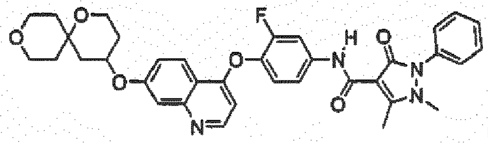

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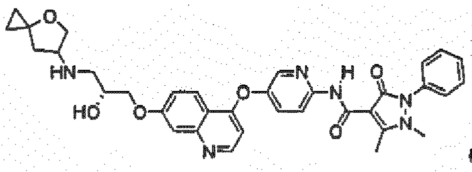

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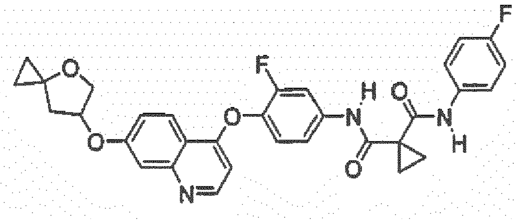

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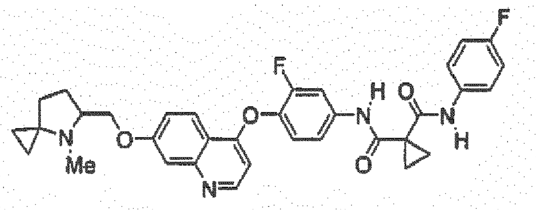

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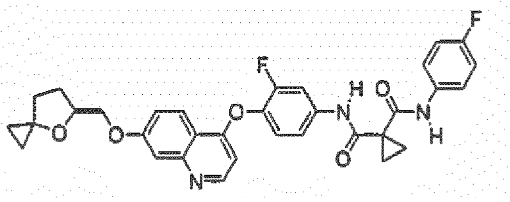

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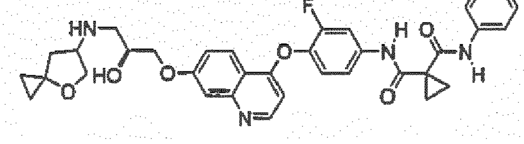

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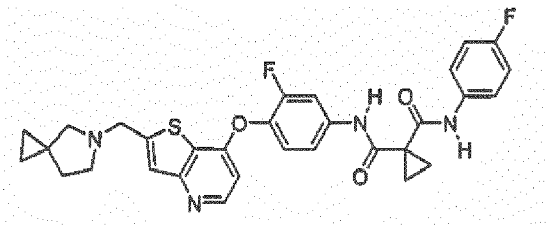

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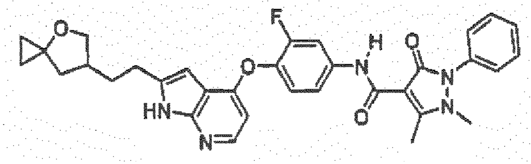

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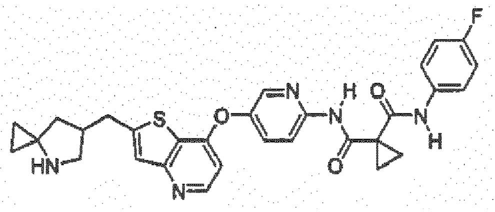

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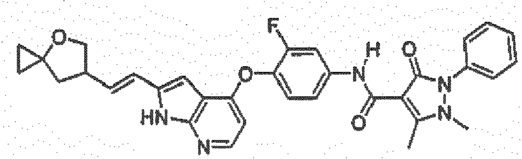

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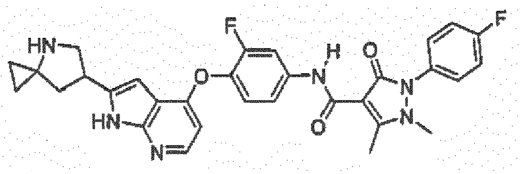

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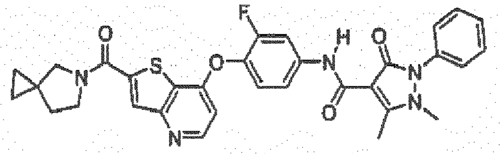

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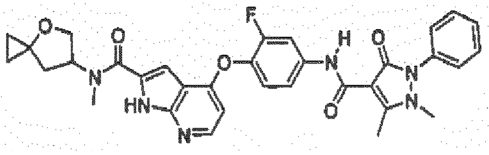

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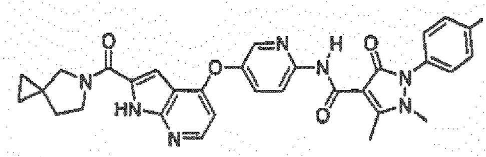

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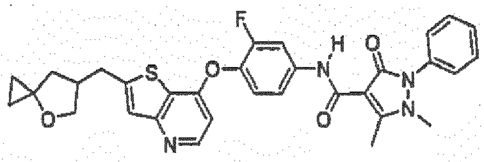

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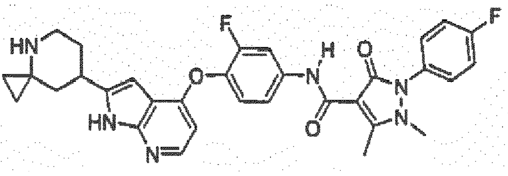

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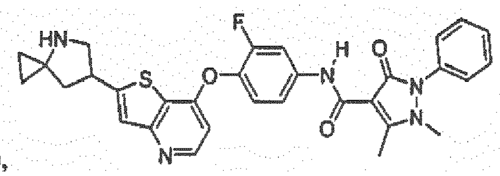

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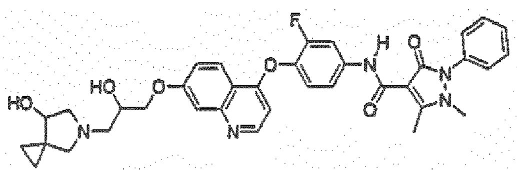

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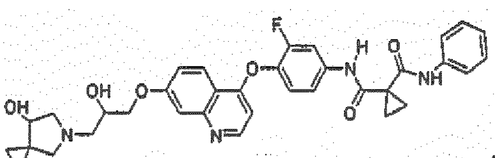

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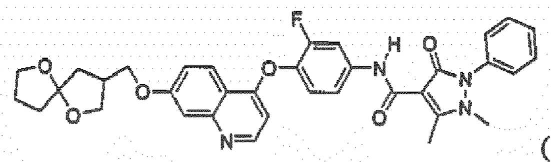

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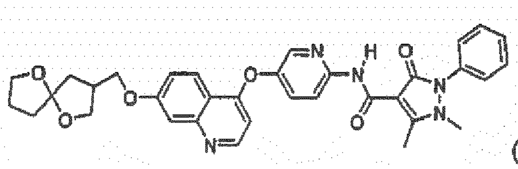

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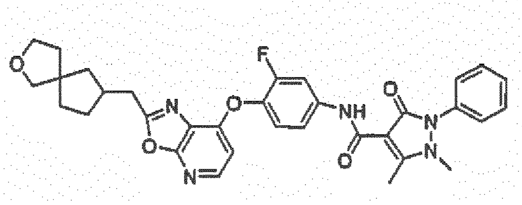

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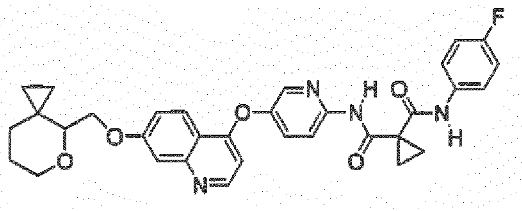

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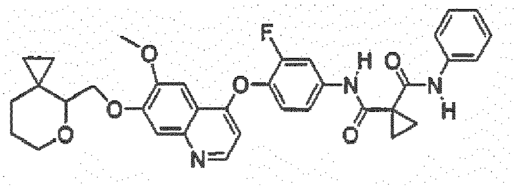

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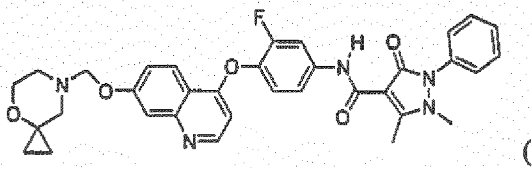

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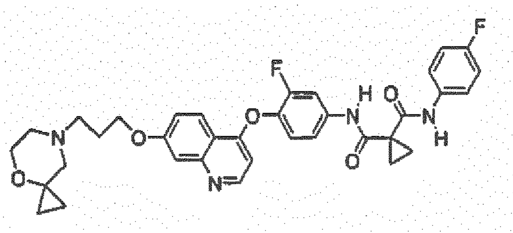

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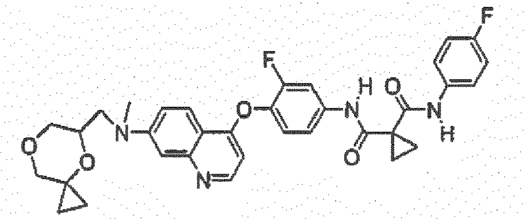

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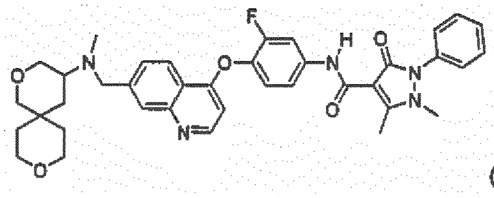

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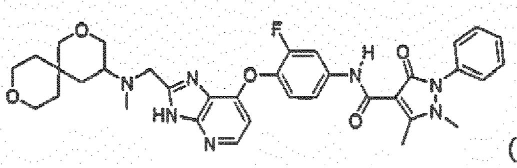

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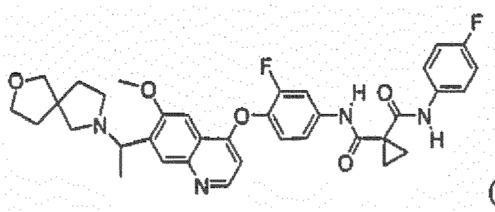

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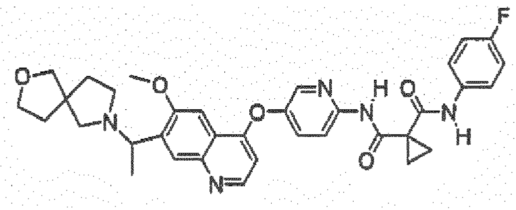

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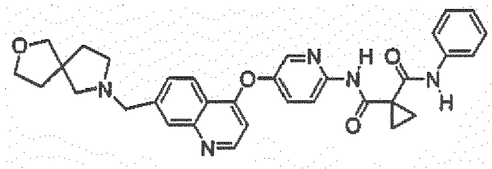

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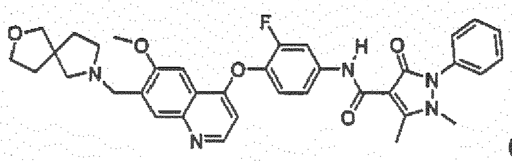

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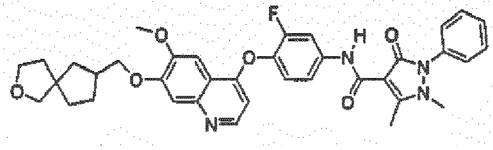

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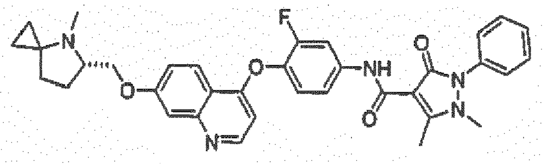

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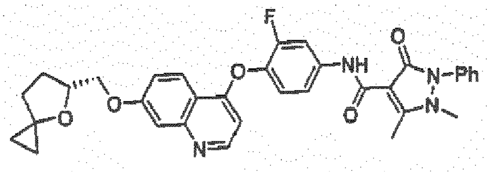
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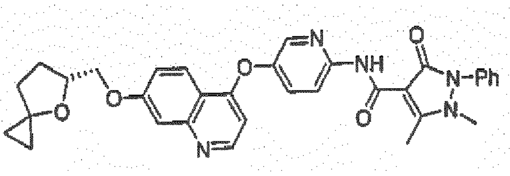
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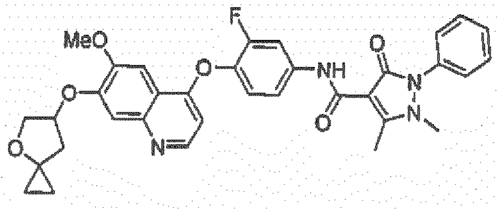
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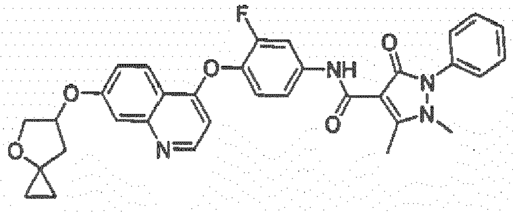
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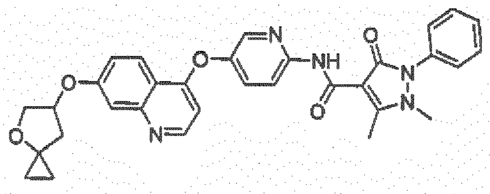
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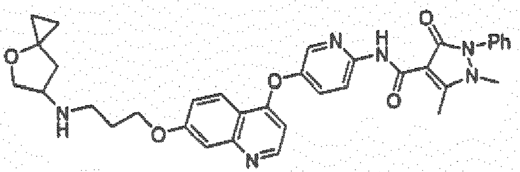
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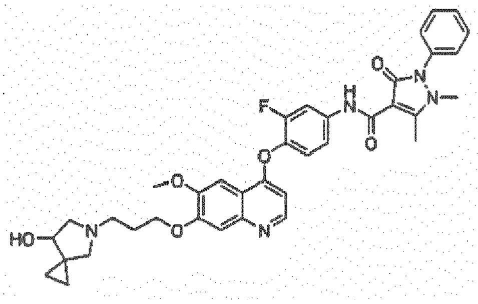
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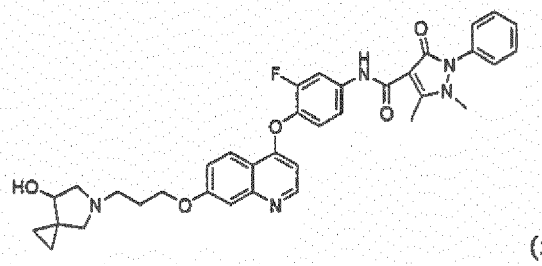
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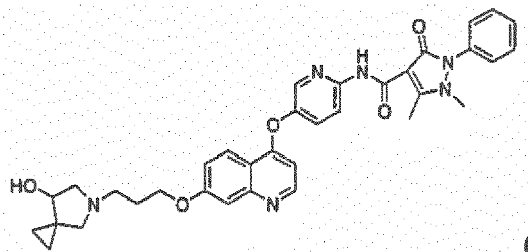
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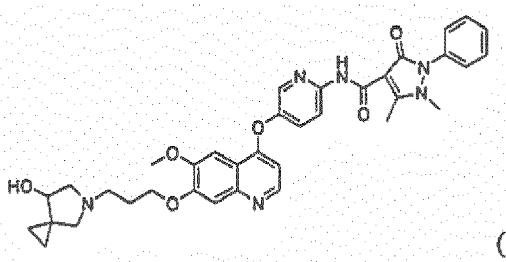
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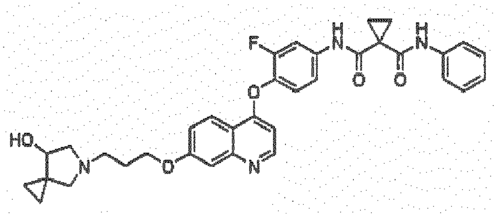
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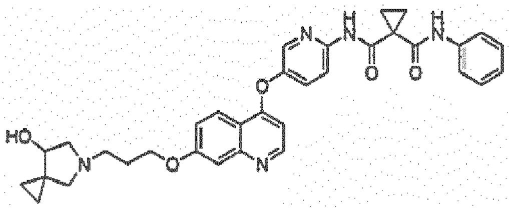
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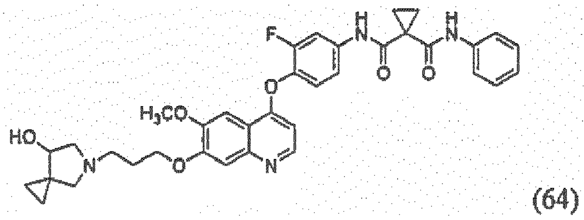
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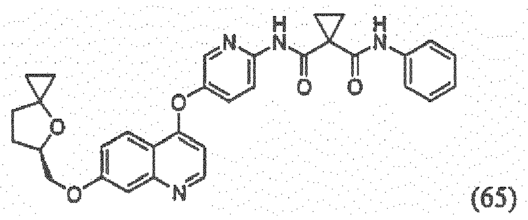
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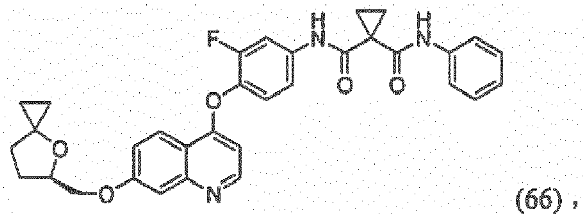
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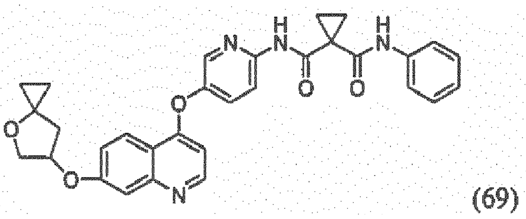
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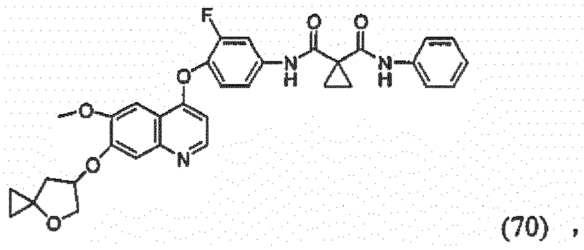
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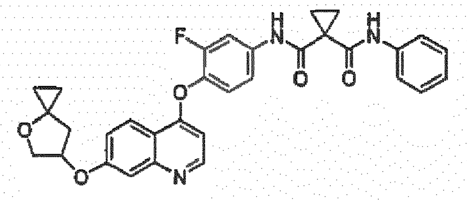
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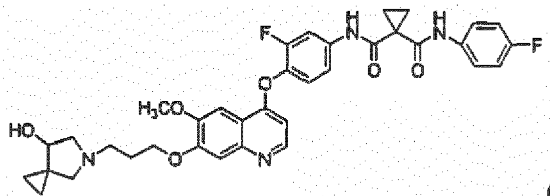
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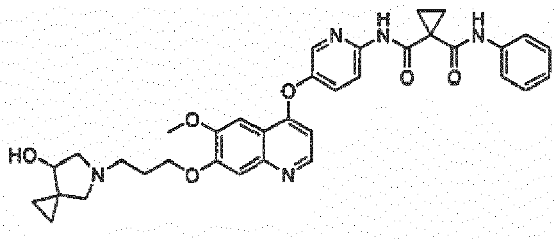

and (78),

or a stereoisomer, a geometric isomer, a tautomer, an N-oxide, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof.

[0026] The foregoing merely summarizes certain aspects disclosed herein and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS AND GENERAL TERMINOLOGY

[0027] Reference will now be made in detail to certain embodiments disclosed herein, examples of which are illustrated in the accompanying structures and formulas. 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 disclosed herein. Described herein is in no way limited to the methods and materials.

[0028] As used herein, the following definitions shall be applied unless otherwise indicated. For purposes disclosed herein, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, and the Handbook of Chemistry and Physics, 75th Ed. 1994. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry" by Michael B. Smith and Jerry March, John Wiley & Sons, New York: 2007.

[0029] As described herein, compounds may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species disclosed herein. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted". In general, the term "substituted" whether it is preceded by the term "optionally" or not, refers to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group. When more than one position in a given structure can be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at each position.

[0030] The term "aliphatic" or "aliphatic group" as used herein, refers to a straight-chain (*i.e.*, unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation. Unless otherwise specified, aliphatic groups contain 1-20 carbon atoms. Aliphatic groups may contain 1-10 carbon atoms. Aliphatic groups may also contain 1-8 carbon atoms. Alternatively, aliphatic groups may contain 1-6 carbon atoms, or 1-4 carbon atoms. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, or alkynyl groups.

[0031] The term "alkyl" as used herein refers to a saturated linear or branched-chain monovalent hydrocarbon radical of one to twenty carbon atoms, wherein the alkyl radical may be optionally substituted independently with one or more substituents described below. Further examples of aliphatic 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 ($-CH(CH_3)CH_2CH_2CH_3$), 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 terms "alkyl" and the prefix "alk-" as used herein, are inclusive of both straight chain and branched saturated carbon chain. The term "alkylene", as used herein, represents a saturated divalent hydrocarbon group derived from a straight or branched chain saturated hydrocarbon by the removal of two hydrogen atoms, and is exemplified by methylene, ethylene, isopropylene, and the like.

[0032] The term "alkenyl" refers to linear or branched-chain monovalent hydrocarbon radical of two to twelve carbon atoms 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.

[0033] The term "alkynyl" refers to a linear or branched monovalent hydrocarbon radical of two to twelve carbon atoms 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 ($-C\equiv CH$), propynyl (propargyl, $-CH_2C\equiv CH$), and the like.

[0034] The term "cycloaliphatic" (or "carbocycle", "carbocyclyl", "carbocyclic ring" and "cycloalkyl") refers to a monovalent or multivalent non-aromatic, saturated or partially unsaturated ring having 3 to 12 carbon atoms 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. Suitable cycloaliphatic groups include, but are not limited to, cycloalkyl, cycloalkenyl, and cycloalkynyl. Further examples of cycloaliphatic groups include 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.

[0035] The term "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" as used interchangeably herein refers to a monocyclic, bicyclic, or tricyclic ring system in which one or more ring members are an independently selected heteroatom and that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. One or more ring atoms are optionally substituted independently with one or more substituents described below. The "heterocycle", "heterocyclyl", "heterocycloaliphatic" or "heterocyclic" group may be a monocycle having 3 to 7 ring members (*e.g.*, 1 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P or S, wherein the S or P is optionally substituted with one or more oxo to provide the group SO or SO_2, PO or PO_2, with the proviso that when the ring is a 3-membered ring, there is only one heteroatom) or a bicycle having 7 to 10 ring members (*e.g.*, 4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P or S, wherein the S or P is optionally substituted with one or more oxo to provide the group SO or SO_2, PO or PO_2).

[0036] The heterocyclyl may be a carbon radical or heteroatom radical. "Heterocyclyl" also includes radicals where heterocycle radicals are fused with a saturated, partially unsaturated ring, or heterocyclic ring. Examples of heterocyclic rings include, but are not limited to, pyrrolidinyl, tetrahydrofliranyl, 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, 1,2,3,4-tetrahydroisoquinolinyl, 3-azabicyco[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, azabicyclo[2.2.2]hexanyl, 3H-indolyl quinolizinyl and N-pyridyl ureas. Some non-limiting examples of a heterocyclic ring include 1,1-dioxo-thiomorpholinyl and heterocyclic group wherein 2 carbon atoms on the ring are substituted with oxo (=O) moieties are pyrimidindionyl. The heterocyclic groups herein are optionally substituted independently with one or more substituents described herein.

[0037] The term "heterocyclylalkyl" refers to heterocyclic-substituted alkyl radical. The term "heterocyclylalkoxy" refers to hetercyclic-substituted alkoxy radical wherein oxygen atom serves as the attaching point to the rest of the molecule. The term "hetemcyclylalkylamino" refers to heterocyclic-substituted alkylamino radical wherein nitrogen atom serves as the attaching point to the rest of the molecule. The term "heterocyclyloxy" refers to heterocyclic-substituted oxygen radical wherein oxygen atom serves as the attaching point to the rest of the molecule. The terms "heterocyclylamino" and "heterocyclylalkylamino" refers to heterocyclic-substituted nitrogen radical and heterocyclic- and alkyl-substituted nitrogen radical wherein nitrogen atom serves as the attaching point to the rest of the molecule.

[0038] The term "heteroatom" refers to one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon, including any oxidized form of nitrogen, sulfur, or phosphorus; the quatemized form of any basic nitrogen; or a substitutable nitrogen of a heterocyclic ring, for example, N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR (as in N-substituted pyrrolidinyl).

[0039] The term "halogen" refers to F, Cl, Br or I.

[0040] The term "unsaturated" as used herein, refers to that a moiety has one or more units of unsaturation.

[0041] The term "alkoxy," as used herein, refers to an alkyl group, as previously defined, attached to the principal carbon chain through an oxygen ("alkoxy") atom.

[0042] The terms "haloalkyl", "haloalkenyl" or "haloalkoxy" refers to alkyl, alkenyl, or alkoxy, as the case may be, substituted with one or more halogen atoms.

[0043] The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy" or "aryloxyalkyl" refers to monocyclic, bicyclic, and tricyclic carbocyclic ring systems having a total of six to fourteen ring members, wherein at least one ring in the system is aromatic, wherein each ring in the system contains 3 to 7 ring members and that has a single point of attachment to the rest of the molecule. The term "aryl" may be used interchangeably with the term "aryl ring". Some non-limiting examples of aryl rings include phenyl, naphthyl, and anthracene.

[0044] The term "heteroaryl" used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy" refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, wherein each ring in the system contains 3 to 7 ring members and that has a single point of attachment to the rest of the molecule. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic".

[0045] Some non-limiting examples of suitable heteroaryl rings include the following monocycles: 2-furanyl, 3-furanyl, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, N-pyrrolyl, 2-pyrrolyl, 3- pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, pyridazinyl (e.g., 3-pyridazinyl), 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, tetrazolyl (*e.g.*, 5- tetrazolyl), triazolyl (*e.g.*, 2-triazolyl and 5-triazolyl), 2-thienyl, 3-thienyl, pyrazolyl (*e.g.*, 2-pyrezolyl), isothiazolyl, 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl,1,2,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, pyrazinyl, 1,3,5- triazinyl, and the following bicycles: benzimidazolyl, benzofuryl, benzothiophenyl, indolyl (*e.g.,* 2-indolyl), purinyl, quinolinyl (*e.g.*, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl), or isoquinolinyl (*e.g.*, 1-isoquinolinyl, 3-isoquinolinyl, or 4-isoquinolinyl).

[0046] The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, refers to respectively divalent radicals $-SO_2-$. The term "alkylsulfonyl", refers to a sulfonyl radical substituted with an alkyl radical, forming a alkylsulfonyl ($-SO_2CH_3$).

[0047] The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" refer to a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2NH_2$).

[0048] The term "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", refers to $-CO_2H$. The term "carbonyl", whether used alone or with other terms, such as "aminocarbonyl" or "carbonyloxy", refers to -(C=O)-.

[0049] The term "aralkyl" refers to aryl-substituted alkyl radicals. Aralkyl radicals may be "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms, or aralkyl radicals may be "phenylalkylenyl" attached to alkyl portions having one to three carbon atoms. Some non-limiting examples of such radicals include benzyl, diphenylmethyl and phenylethyl. The aryl in said aralkyl can be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

[0050] The term "alkylthio" refers to radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Alkylthio radicals may be lower alkylthio radicals having one to three carbon atoms. Some non-limiting examples of "alkylthio" include methylthio (CH_3S-).

[0051] The term "haloalkylthio" refers to radicals containing a haloalkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Haloalkylthio radicals may be lower haloalkylthio radicals having one to three carbon atoms. Some non-limiting examples of "haloalkylthio" include trifluoromethylthio.

[0052] The term "alkylamino" refers to "N-alkylamino" and "N,N-dialkylamino" where amino groups are independently substituted with one alkyl radical or with two alkyl radicals, respectively. In other embidiments, alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Alkylamino radicals may be lower alkylamino radicals having one to three carbon atoms. Some non-limiting examples of suitable alkylamino radicals include mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino, and the like.

[0053] The term "arylamino" refers to amino groups, which have been substituted with one or two aryl radicals. Some non-limiting examples of arylamino include N-phenylamino. The arylamino radicals may include substituted on the aryl ring portion of the radical.

[0054] The term "heteroarylamino" refers to amino groups, which have been substituted with one or two heteroaryl radicals. Some non-limiting examples of heteroarylamino include N-thienylamino. The "heteroarylamino" radicals may include substituted on the heteroaryl ring portion of the radical.

[0055] The term "aminoalkyl" refers to linear or branched alkyl radicals having one to about ten carbon atoms any one of which includes substituted with one or more amino radicals. Aminoalkyl radicals may be "lower aminoalkyl" radicals having one to six carbon atoms and one or more amino radicals. Some non-limiting examples of such radicals include aminomethyl, aminoethyl, aminopropyl, aminobutyl or aminohexyl.

[0056] The term "alkylaminoalkyl" refers to alkyl radicals substituted with alkylamino radicals. Alkylaminoalkyl radicals may be "lower alkylaminoalkyl" radicals having alkyl radicals of one to six carbon atoms, or lower alkylaminoalkyl radicals having alkyl radicals of one to three carbon atoms. Some non-limiting examples of suitable alkylaminoalkyl radicals include mono or dialkyl substituted, such as N-methylaminomethyl, N,N-dimethyl-aminoethyl, N,N-diethylaminomethyl, and the like.

[0057] The term "alkylaminoalkoxy" refers to alkoxy radicals substituted with alkylamino radicals. Some non-limiting examples of suitable alkylaminoalkoxy radicals include mono or dialkyl substituted, such as N-methylaminoethoxy, N,N-dimethylaminoethoxy, N,N-diethylaminoethoxy, and the like.

[0058] The term "alkylaminoalkoxyalkoxy" refers to alkoxy radicals substituted with alkylaminoalkoxy radicals. Some non-limiting examples of suitable alkylaminoalkoxyalkoxy radicals include mono or dialkyl substituted, such as N-methylaminomethoxyethoxy, N-methylaminoethoxyethoxy, N,N-dimethylaminoethoxyethoxy, N,N-diethylaminomethoxymethoxy, and the like.

[0059] The term "carboxyalkyl" refers to linear or branched alkyl radicals having one to about ten carbon atoms any one of which maybe substituted with one or more carboxy radicals. Some non-limiting examples of such radicals include carboxymethyl, carboxypropyl, and the like.

[0060] The term "aryloxy" refers to optionally substituted aryl radicals, as defined above, attached to an oxygen atom. Some non-limiting examples of such radicals include phenoxy.

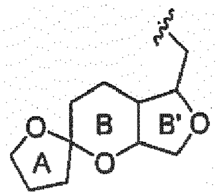
[0061] The term "heteroaryloxy" refers to optionally substituted heteroaryl radicals, as defined above, attached to an oxygen atom.

[0062] The term "heteroarylalkoxy" refers to oxy-containing heteroarylalkyl radicals attached through an oxygen atom to other radicals.

[0063] The term "cycloalkylalkyl" refers to cycloalkyl-substituted alkyl radicals. Some non-limiting examples of such radicals include cyclohexylmethyl. The cycloalkyl in the radicals may be additionally substituted with halo, alkyl, alkoxy or hydroxy.

[0064] The terms "fused bicyclic", "fused cyclic", "fused bicyclyl" and "fused cyclyl" refer to saturated bridged ring system, which refers to a bicyclic ring system that is not aromatic. Such a system may contain isolated or conjugated unsaturation, but not aromatic or heteroaromatic rings in its core structure (but may have aromatic substitution thereon). Each cyclic ring in a fused bicyclyl can be either a carbocyclic or a heteroalicyclic. Some non-limiting examples of fused bicyclic ring system include hexahydro-furo[3,2-b]furan, 2,3,3a,4,7,7a-hexahydro-1H-indene, 7-azebicyclo[2.2.1]heptene, and 1,2,3,4,4a,5,8,8a-octahydro-naphthalene.

[0065] The terms "spirocyclyl", "spirocyclic", "spiro bicyclyl" or "spiro bicyclic" refer to a ring originating from a particular annular carbon of another ring. For example, as depicted below, a saturated bridged ring system (ring B and B') is termed as "fused bicyclic", whereas ring A and ring B share an atom between the two saturated ring system, which terms as a "spirocyclyl" or "spiro bicyclyl". Each cyclic ring in a spirocyclyl can be either a carbocyclic or a heteroalicyclic.



[0066] As described herein, a bond drawn from a substituent to the center of one ring within a ring system (as shown below) represents substitution of the substituent at any substitutable position on the rings to which it is attached. For example, Figure a represents possible substitution in any of the positions on the B ring shown in Figure b.

Figure a Figure b

[0067] As described herein, a dot line drawn together with a bond within a ring system (as shown in Figure c) represents either a double bond or a single bond. For example, structure in Figure c represents any structures selected from Figure d.

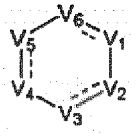


Figure c

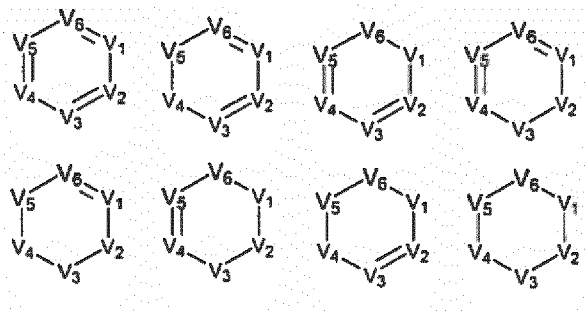


Figure d

[0068] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (*e.g.*, enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, or geometric (or conformational) mixtures of the present compounds are within the scope disclosed herein.

[0069] The term "prodrug" as used herein, represents a compound that is transformed in vivo into a compound of Formula (I). Such a transformation can be affected, for example, by hydrolysis in blood or enzymatic transformation of the prodrug form to the parent form in blood or tissue. Prodrugs of the compounds disclosed herein may be, for example, esters. Esters that may be utilized as prodrugs are phenyl esters, aliphatic (C_1-C_{24}) esters, acyloxymethyl esters, carbonates, carbamates, and amino acid esters. For example, a compound disclosed herein that contains an OH group may be acylated at this position in its prodrug form. Other prodrug forms include phosphates, such as, for example those phosphates resulting from the phosphonation of an OH group on the parent compound. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, J. Rautio et al, Prodrugs: Design and Clinical Applications, Nature Review Drug Discovery, 2008, 7, 255-270, and S. J. Hecker et al, Prodrugs of Phosphates and Phosphonates, Journal of Medicinal Chemistry, 2008, 51, 2328-2345.

[0070] 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.

[0071] 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 disclosed herein may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. 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 *l* 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.

[0072] The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. Some non-limiting examples of 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.

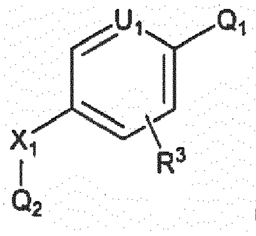
[0073] A "pharmaceutically acceptable salt" as used herein, refers to organic or inorganic salts of a compound disclosed herein. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19,1977. Examples of pharmaceutically acceptable, nontoxic acid addition salts include, but are not limited to, salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}\ alkyl)_4$ salts. Also disclosed is the quatemization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil- soluble or dispersable products may be obtained by such quatemization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, C_{1-8} sulfonate or aryl sulfonate.

[0074] A "solvate" refers to an association or complex of one or more solvent molecules and a compound disclosed herein. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, and ethanolamine. The term "hydrate" refers to the complex where the solvent molecule is water.

[0075] The term "protecting group" or "Pg" refers to a substituent that is commonly employed to block or protect a particular functionality while reacting other functional groups on the compound. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Some non-limiting examples of suitable amino-protecting groups include acetyl, trifluomacetyl, t-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Some non-limiting examples of suitable hydroxy-protecting groups include acetyl and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Some non-limiting examples of common carboxy-protecting groups include $-CH_2CH_2SO_2Ph$, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl) ethoxy methyl, 2-(p-toluenesulfonyl)ethyl, 2-(p-nitrophenylsulfonyl)ethyl, 2-(diphenyl phosphino)-ethyl, nitroethyl, and the like. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991**;** and P. J. Kocienski, Protecting Groups, Thieme, Stuttgart, 2005**.**

DESCRIPTION OF COMPOUNDS OF THE INVENTION

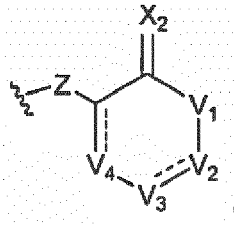
[0076] Disclosed herein are heterocyclic compounds, and pharmaceutical formulations thereof, that are potentially useful in the treatment of diseases, conditions and/or disorders modulated by protein kinases, especially KDR, c-Met receptor and/or IGF receptor. More specifically, provided herein are compounds of Formula (I):



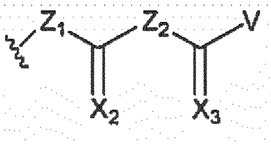
(I),

or a stereoisomer, a geometric isomer, a tautomer, an N-oxide, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof, wherein

Q_1 is formula (IIa) or **(IIb):**

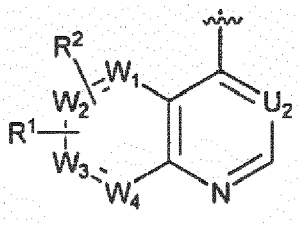


(IIa), or



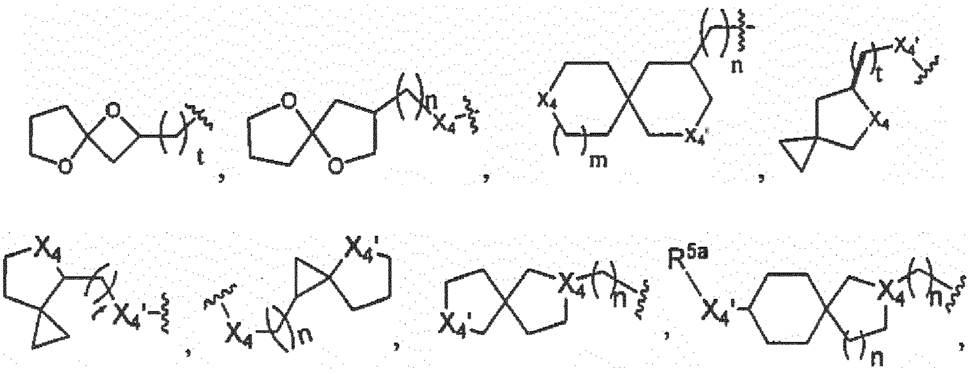
(IIb);

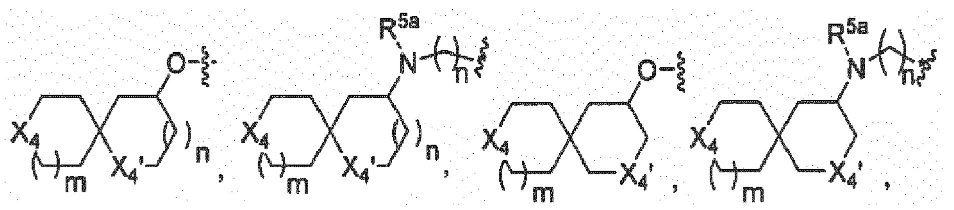
Q_2 is formula (III):

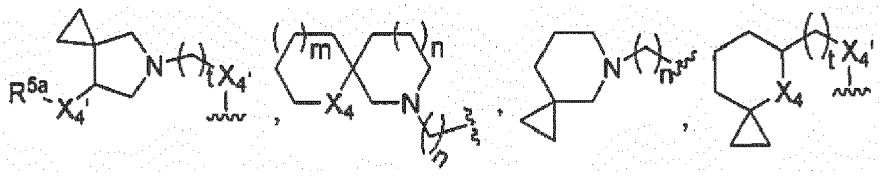


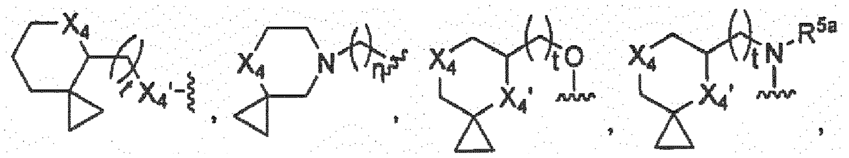
(III);

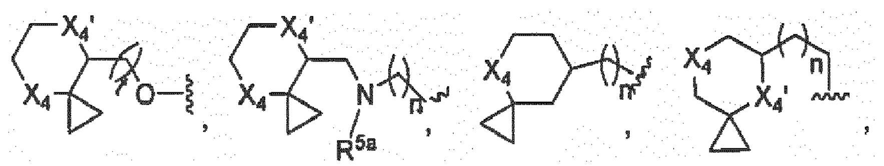
R^1 is selected from

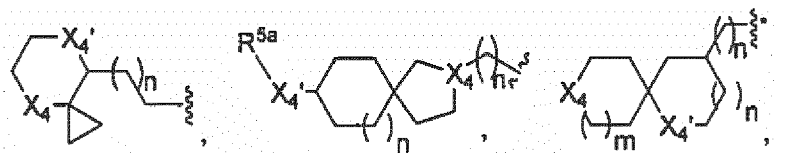


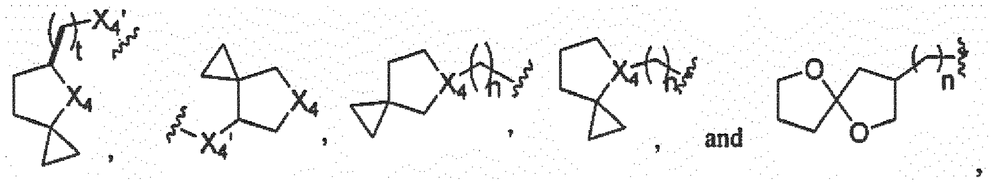












wherein each of X_4 and X_4' is independently $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2 ; each of m and n is independently 0, 1 or 2; and t is 1,2 or 3;

R^2 is H, halo, cyano(CN), $R^{5a}R^5N$-C_{1-6} alkoxy, optionally substituted C_{1-6} alkoxy, C_{1-6} hydroxyalkoxy, C_{1-6} aminoalkoxy, C_{1-6} hydroxy-substituted aminoalkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylamino C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alcoxy, C_{4-10} heterocyclyloxy C_{1-6} alkoxy, C_{5-12} fused bicyclyl, C_{5-12} fused bicyclyl C_{1-6} aliphatic, C_{5-12} fused heterobicyclyl C_{1-6} aliphatic, C_{5-12} fused bicycloxy, C_{5-12} fused bicyclylamino, C_{5-12} fused bicycloxo C_{1-6} alkoxy, C_{5-12} fused bicyclylamino C_{1-6} alkoxy, C_{5-12} fused bicyclyl-C(=O)-, C_{5-12} fused bicyclyl-C(=O)O-, C_{5-12} fused heterobicyclyl-C(=O)-, C_{5-12} fused heterobicyclyl-C(=O)O-, C_{5-12} fused bicyclylamino-C(=O)-, C_{5-12} fused heterobicyclylamino-C(=O)-, C_{5-12} fused bicyclyl-C(=O)NR^5-, C_{5-12} fused heterobicyclyl-C(=O)NR^5-, C_{5-12} spiro bicyclyl, C_{5-12} spiro bicycloxy, C_{5-12} spiro bicyclylamino, C_{5-12} spiro bicycloxo C_{1-6} alkoxy, C_{5-12} spiro bicyclylamino C_{1-6} alcoxy, C_{5-12} fused heterobicyclyl, C_{5-12} fused heterobicycloxy, C_{5-12} fused heterobicyclylamino, C_{5-12} fused heterobicycloxo C_{1-6} alkoxy, C_{5-12} fused heterobicyclylamino C_{1-6} alkoxy, C_{5-12} spiro bicyclyl, C_{5-12} spiro heterobicyclyl-, C_{5-12} spiro bicyclyl C_{1-6} aliphatic, C_{5-12} spiro hetembicyclyl C_{1-6} aliphatic, C_{5-12} spiro heterobicycloxo C_{1-6} alkoxy, C_{5-12} spiro heterobicyclylamino C_{1-6} alkoxy, C_{5-12} spiro bicyclyl -C(=O)-, C_{5-12} spiro bicyclyl-C(=O)O-, C_{5-12} spiro heterobicyclyl-C(=O)-, C_{5-12} spiro heterobicyclyl-C(=O)O-, C_{5-12} spiro bicyclylamino-C(=O)-, C_{5-12} spiro hetembicyclylamino-C(=O)-, C_{5-12} spiro bicyclyl-C(=O)NR^5-, or C_{5-12} spiro heterobicyclyl-C(=O)NR^5-, C_{6-10} aryl, C_{1-10} heteroaryl, C_{6-10} aryl C_{1-6} aliphatic or C_{1-10} heteroaryl C_{1-6}aliphatic;

wherein R^3 is independently H, F, Cl, Br, -CN, C_{1-3} aliphatic, C_{1-3} alkoxy, or C_{1-3} haloalkyl;

each of U_1 and U_2 is independently CR^4 or N;

V is NR^5R^{5a}, OR^5;

V_1 is O orNR^5;

each of V_2, V_3 and V_4 is independently CR^4R^{4a}, NR^5, CR^4 or N, with the proviso that only one of V_2, V_3, and V_4 is NR^5 or N, or V_2 and V_3 or V_3 and V_4 combine to become CR^4R^{4a}, NR^5, O, CR^4 or N, with the proviso that the resulted structure is stable;

each of W_1, W_2, W_3 and W_4 is independently CR^4R^{4a}, NR^5, CR^4 or N, or W_1 and W_2 or W_3 and W_4 combine to become CR^4R^{4a}, NR^5, O or S;

X_1 is $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2, where m is 0, 1 or 2;

each of X_2 and X_3 is independently O, S or NR^5;

Z is $-NR^5C(=O)-(CR^4R^{4a})_p-$, $-NR^5C(=S)-(CR^4R^{4a})_p-$, $-NR^{5a}-(CR^4R^{4a})_p-$, $-NR^5-(CR^4R^{4a})_pC(=O)-$, $-NR^5-(CR^4R^{4a})_pC(=S)-$, $-NR^5S(=O)_r-$, $-NR^5S(=O)_r(CR^4R^{4a})_p-$, $- C(=O)NR^5(CR^4R^{4a})_p-$ or $NR^5-(CR^4R^{4a})_pS(=O)_r-$, where p is 0,1,2 or 3 and r is 1 or 2;

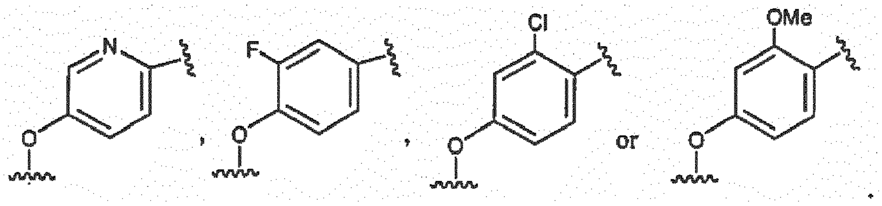
each of Z_1 and Z_2 is independently NR^5 or CR^4R^{4a};

each of R^4 and R^{4a} is independently H, F, Cl, Br, I, -CN, hydroxyl, $-NR^{5a}R^5$, with the proviso that where R^4 and R^{4a} are bonded to the same carbon atom, R^4 and R^{4a}, together with the carbon atom they are attached to, optionally form a 3-8 membered carbocyclic or heterocyclic ring;

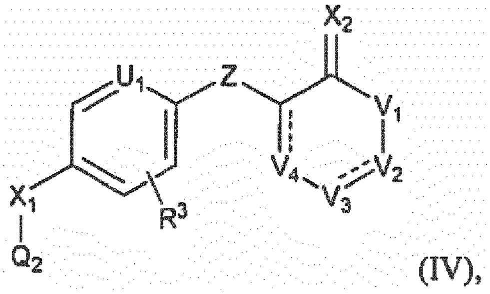
each of R^5 and R^{5a} is independently H, $R^6R^{6a}NC(=O)-$, $R^6OC(=O)-$, $R^6C(=O)-$, $R^6R^{6a}NS(=O)-$, $R^6OS(=O)-$, $R^6S(=O)-$, $R^6R^{6a}NSO_2-$, R^6OS_2-, R^6SO_2-, with the proviso that where R^5 and R^{5a} are bonded to the same nitrogen atom, R^5 and R^{5a}, together with the nitrogen atom they are attached to, optionally form a 3-8 membered ring, including spiro and fused bicyclic rings;

each of R^6 and R^{6a} is H.

[0077] In certain embodiments, Z of Formula (IIa) is -NHC(=O)-, Z_1 of formula (IIb) is NH; and the substructure defined by X_1, U_1 and R^3 of Formula I is:



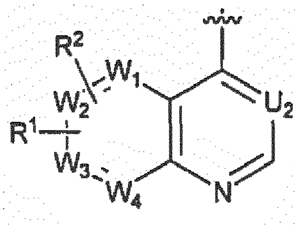
[0078] In some embodiments, the compounds have Formula (IV):



(IV),

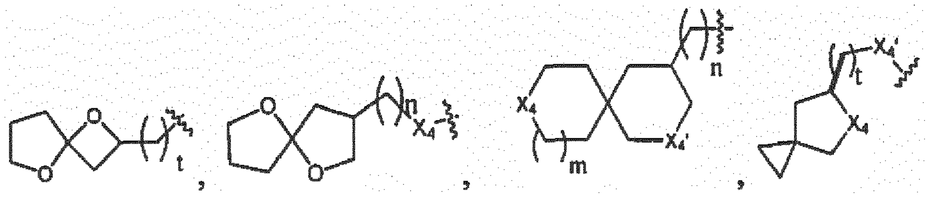
or a stereoisomer, a geometric isomer, a tautomer, an N-oxide, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof, wherein:

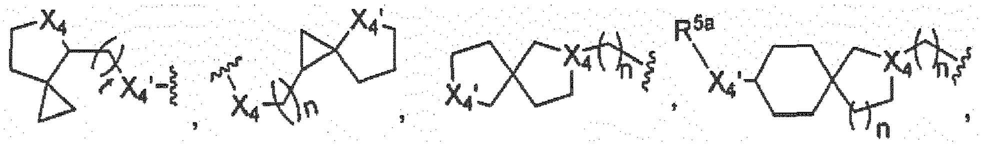
Q_2 has formula (III):

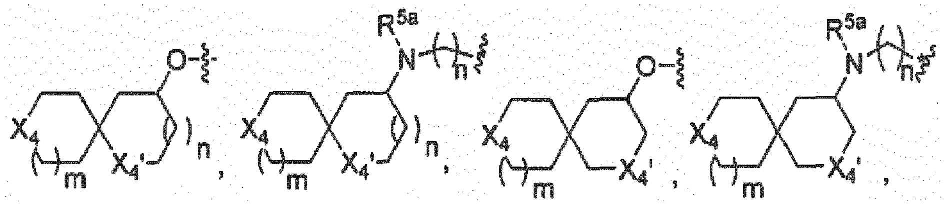


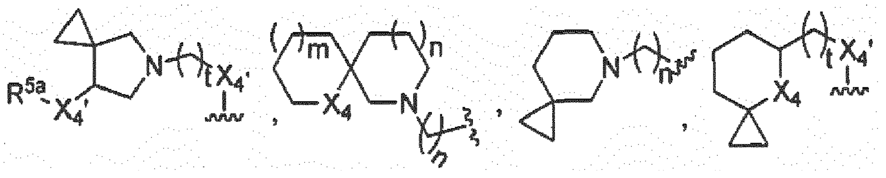
(III);

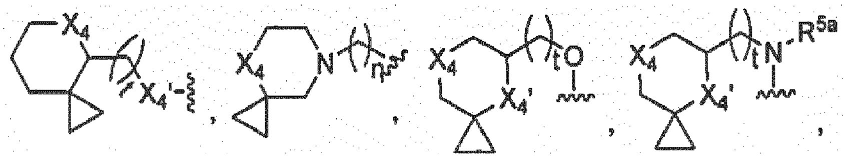
R^1 is selected from

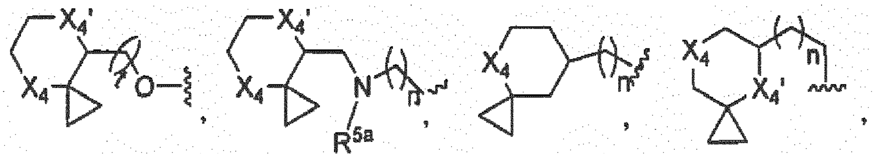


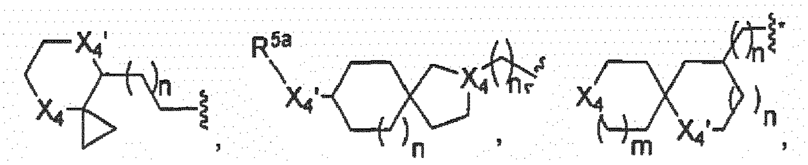


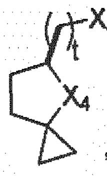
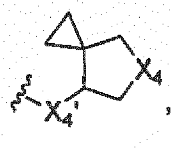
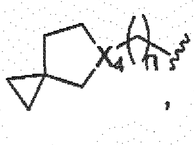
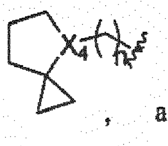
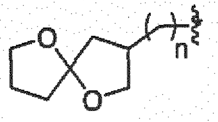










,
,
,
, and
,

wherein each of X_4 and X_4' is independently $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2; each of m and n is independently 0, 1 or 2; and t is 1, 2 or 3;

R^2 is H, halo, cyano(CN), $R^{5a}R^5N$-C_{1-6} alkoxy, C_{1-6} alkoxy, C_{1-6} hydroxyalkoxy, C_{1-6} aminoalkoxy, C_{1-6} hydroxy-substituted aminoalkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylamino C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkoxy, C_{4-10} heterocyclyloxy C_{1-6} alkoxy, C_{5-12} fused bicyclyl, C_{5-12} fused bicyclyl C_{1-6} aliphatic, C_{5-12} fused heterobicyclyl C_{1-6} aliphatic, C_{5-12} fused bicycloxy, C_{5-12} fused bicyclylamino, C_{5-12} fused bicycloxo C_{1-6} alkoxy, C_{5-12} fused bicyclylamino C_{1-6} alkoxy, C_{5-12} fused bicyclyl-C(=O)-, C_{5-12} fused bicyclyl-C(=O)O-, C_{5-12} fused heterobicyclyl-C(=O)-, C_{5-12} fused heterobicyclyl-C(=O)O-, C_{5-12} fused bicyclylamino-C(=O)-, C_{5-12} fused heterobicyclylamino-C(=O)-, C_{5-12} fused bicyclyl-C(=O)NR^5-, C_{5-12} fused heterobicyclyl-C(=O)NR^5-, C_{5-12} spiro bicyclyl, C_{5-12} spiro bicycloxy, C_{5-12} spiro bicyclylamino, C_{5-12} spiro bicycloxo C_{1-6} alkoxy, C_{5-12} spiro bicyclylamino C_{1-6} alkoxy, C_{5-12} fused heterobicyclyl, C_{5-12} fused heterobicycloxy, C_{5-12} fused heterobicyclylamino, C_{5-12} fused heterobicycloxo C_{1-6} alkoxy, C_{5-12} fused heterobicyclylamino C_{1-6} alkoxy, C_{5-12} spiro bicyclyl, C_{5-12} spiro heterobicyclyl, C_{5-12} spiro bicyclyl C_{1-6} aliphatic, C_{5-12} spiro heterobicyclyl C_{1-6} aliphatic, C_{5-12} spiro heterobicycloxo C_{1-6} alkoxy, C_{5-12} spiro heterobicyclylamino C_{1-6}- alkoxy, C_{5-12} spiro bicyclyl -C(=O)-, C_{5-12} spiro bicyclyl-C(=O)O-, C_{5-12} spiro heterobicyclyl-C(=O)-, C_{5-12} spiro heterobicyclyl-C(=O)O-, C_{5-12} spiro bicyclylamino-C(=O)-, C_{5-12} spiro heterobicyclylamino-C(=O)-, C_{5-12} spiro bicyclyl-C(=O)NR^5-, or C_{5-12} spiro heterobicyclyl-C(=O)NR^5-, C_{6-10} aryl, C_{1-10} heteroaryl, C_{6-10} aryl C_{1-6}aliphatic or C_{1-10} heteroaryl C_{1-6} aliphatic;

wherein R^3 is independently H, F, Cl, Br, -CN, C_{1-3} aliphatic, C_{1-3} alkoxy, or C_{1-3} haloalkyl;

each of U_1 and U_2 is independently CR^4 or N;

V is NR^5R^{5a}, OR^5;

V_1 is O or NR^5;

each of V_2, V_3 and V_4 is independently CR^4R^{4a}, NR^5, CR^4 or N, with the proviso that only one of V_2, V_3, and V_4 is NR^5 or N, or V_2 and V_3 or V_3 and V_4 combine to become CR^4R^{4a}, NR^5, O, CR^4 or N, with the proviso that the resulted structure is stable;

each of W_1, W_2, W_3 and W_4 is independently CR^4R^{4a}, NR^5, CR^4 or N, or W_1 and W_2 or W_3 and W_4 combine to become CR^4R^{4a}, NR^5, O or S;

X_1 is $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2, where m is 0, 1 or 2;

X_2 is independently O, S or NR^5;

Z is $-NR^5C(=O)-(CR^4R^{4a})_p-$, $-NR^5C(=S)-(CR^4R^{4a})_p-$, $-NR^{5a}-(CR^4R^{4a})_p-$, $-NR^5-(CR^4R^{4b})_pC(=O)-$, $-NR^5-(CR^4R^{4a})_pC(=S)-$, $-NR^5S(=O)_r-$, $-NR^5S(=O)_r(CR^4R^{4a})_p-$, $-\ C(=O)NR^5(CR^4R^{4a})_p-$ or $-NR^5(CR^4R^{4a})_pS(=O)_r-$, where p is 0, 1, 2 or 3 and r is 1 or 2;

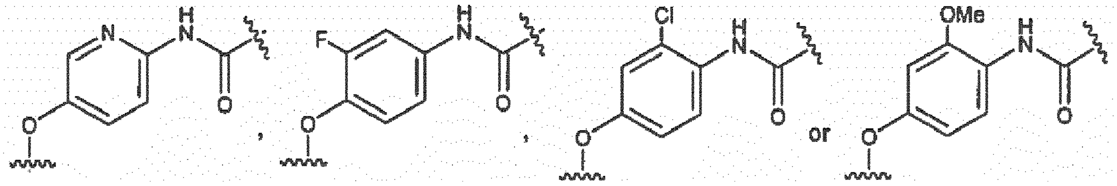
each of R^4 and R^{4a} is independently H, F, Cl, Br, I, -CN, hydroxyl, $-NR^{5a}R^5$, with the proviso that where R^4 and R^{4a} are bonded to the same carbon atom, R^4 and R^{4a}, together with the carbon atom they are attached to, optionally form a substituted or unsubstituted 3-8 membered carbocyclic or heterocyclic ring;

each of R^5 and R^{5a} is independently H, $R^6R^{6a}NC(=O)$-, $R^6OC(=O)$-, $R^6C(=O)$-, $R^6R^{6a}NS(=O)$-, $R^6OS(=O)$-, $R^6S(=O)$-, $R^6R^{6a}NSO_2$-, R^6OSO_2-, R^6SO_2-, with the proviso that where R^5 and R^{5a} are bonded to the same nitrogen atom, R^5 and R^{5a}, together with the nitrogen atom they are attached to, optionally form a 3-8 membered ring, including spiro and fused bicyclic rings;

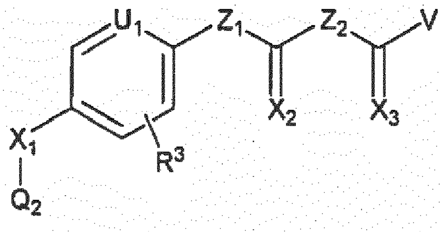
each of R^6 and R^{6a} is independently H;

wherein each of $R^{5a}R^5N$-, $-C(=O)NR^5R^{5a}$, $-OC(=O)NR^5R^{5a}$, $-OC(=O)OR^5$, - $NR^5C(=O)NR^5R^{5a}$, $-NR^5C(=O)OR^{5a}$, $-NR^5C(=O)-R^{5a}$, $R^5R^{5a}N-O_2S$-, R^5O_2S-, $R^5O_2SR^{5a}N$-, OR^5, NR^5, CR^4R^{4a}, CR^4, $(CR^4R^{4a})_m$, $-NR^5C(O)-(CR^4R^{4a})_p$-, $NR^5C(=S)-(CR^4R^{4a})_p$-, $-NR^{5a}-(CR^4R^{4a})_p$-, $NR^5-(CR^4R^{4a})_pC(=O)$-, $NR^5-(CR^4R^{4a})_pC(=S)$-, $-NR^5S(O)_r$-,$-NR^5S(=O)(CR^4R^{4a})_p$-, $-C(=O)NR^5-(CR^4R^{4a})_p$-, $-NR^5$ $-(CR^4R^{4a})_p-S(=O)_r$-, $R^{5a}R^5N$-alkyl, $R^5(S=O)$-alkyl, $R^5R^{5a}N-(C=O)$-alkyl, $R^{5a}R^5N$-alkoxy, $R^5(S=O)$-alkoxy, $R^5R^{5a}N-(C=O)$-alkoxy, $R^6R^{6a}NC(=O)$-, $R^6OC(=O)$-, $R^6C(=O)$-, $R^6R^{6a}NS(=O)$-, $R^6OS(=O)$-, $R^6S(=O)$-, $R^6R^{6a}NSO_2$-, R^6OSO_2-, R^6SO_2-, hydroxy-substituted cyclopropylalkoxy, $R^5S(=O)_2O$-substituted cyclopropylalkoxy.

[0079] Preferably, Z is -NHC(=O)-; or the substructure defined by X_1, Z, U_1 and R^3 is



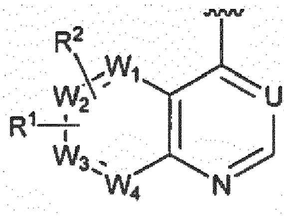
[0080] In some embodiments, the compounds have Formula V:



(V)

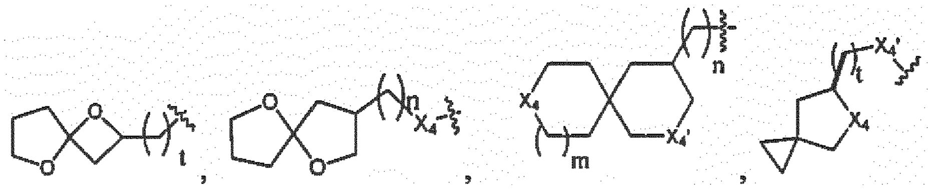
or a stereoisomer, a geometric isomer, a tautomer, an N-oxide, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof, wherein:

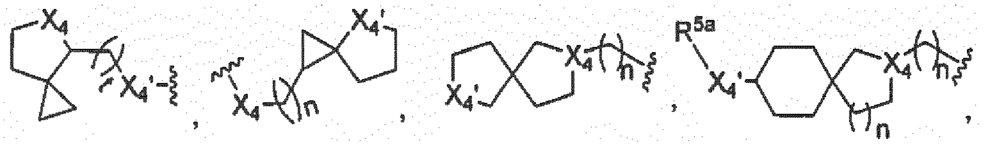
Q_2 has Formula (III):

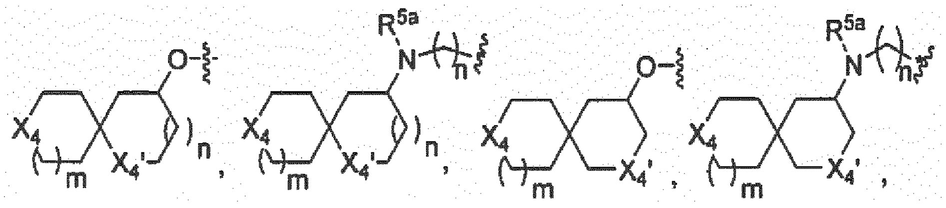


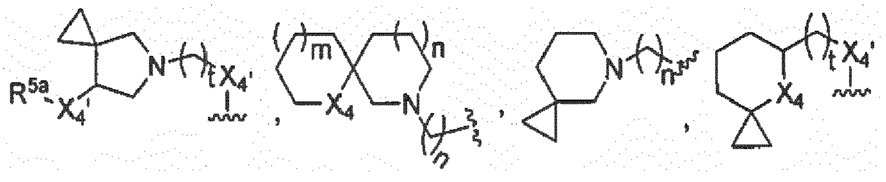
(III);

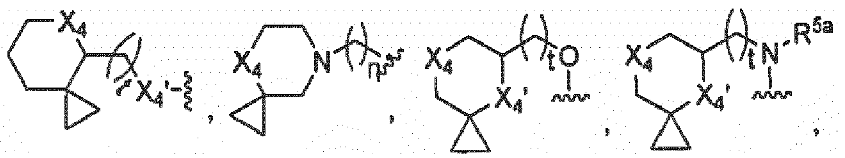
R^1 is selected from

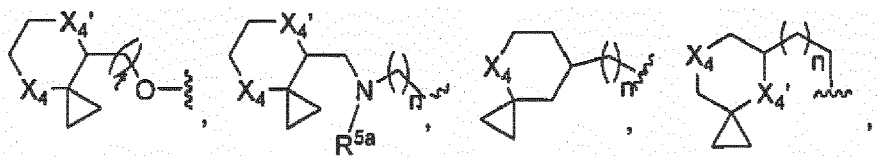


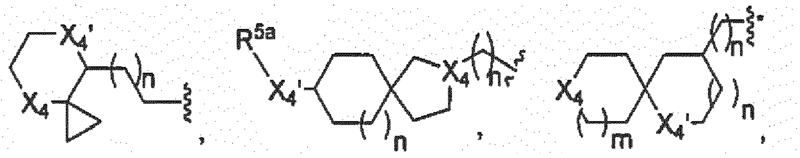


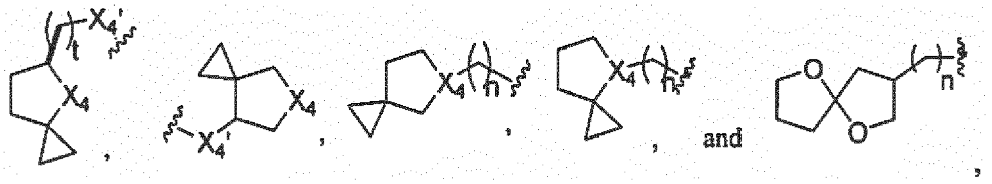












wherein each of X_4 and X_4' is independently $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2; each of m and n is independently 0, 1 or 2; and t is 1,2 or 3;

R^2 is H, halo, cyano(CN), $R^{5a}R^5N$-C_{1-6}, alkoxy, C_{1-6} alkoxy, C_{1-6} hydroxyalkoxy, C_{1-6} aminoalkoxy, C_{1-6} hydroxy-substituted aminoalkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylamino C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkoxy, C_{4-10} heterocyclyloxy C_{1-6} alkoxy, C_{5-12} fused bicyclyl, C_{5-12} fused bicyclyl C_{1-6} aliphatic, C_{5-12} fused heterobicyclyl C_{1-6} aliphatic, C_{5-12} fused bicycloxy, C_{5-12} fused bicyclylamino, C_{5-12} fused bicycloxo C_{1-6} alkoxy, C_{5-12} fused bicyclylamino C_{1-6} alkoxy, C_{5-12} fused bicyclyl-C(=O)-, C_{5-12} fused bicyclyl-C(-O)O-, C_{5-12} fused heterobicyclyl-C(=O)-, C_{5-12} fused heterobicyclyl-C(=O)O-, C_{5-12} fused bicyclylamino-C(=O)-, C_{5-12} fused heterobicyclylamino-C(=O)-, C_{5-12} fused bicyclyl-C(=O)NR^5-, C_{5-12} fused heterobicyclyl-C(=O)NR^5-, C_{5-12} spiro bicyclyl, C_{5-12} spiro bicycloxy, C_{5-12} spiro bicyclylamino, C_{5-12} spiro bicycloxo C_{1-6} alkoxy, C_{5-12} spiro bicyclylamino C_{1-6} alkoxy, C_{5-12} fused hetembicyclyl, C_{5-12} fused heterobicycloxy, C_{5-12} fused heterobicyclylamino, C_{5-12} fused heterobicycloxo C_{1-6} alkoxy, C_{5-12} fused heterobicyclylamino C_{1-6} alkoxy, C_{5-12} spiro bicyclyl, C_{5-12} spiro heterobicyclyl, C_{5-12} spiro bicyclyl C_{1-6} aliphatic, C_{5-12} spiro heterobicyclyl C_{1-6} aliphatic, C_{5-12} spiro heterobicycloxo C_{1-6} alkoxy, C_{5-12} spiro heterobicyclylamino C_{1-6} alkoxy, C_{5-12} spiro bicyclyl -C(=O)-, C_{5-12} spiro bicyclyl-C(=O)O-, C_{5-12} spiro heterobicyclyl-C(=O)-, C_{5-12} spiro heterobicyclyl,-C(=O)O-, C_{5-12} spiro bicyclylamino-C(=O)-, C_{5-12} spiro heterobicyclylamino-C(=O)-, C_{5-12} spiro bicyclyl-C(=O)NR^5-, or C_{5-12} spiro beterobicyclyl-C(=O)NR^5-, C_{6-10} aryl, C_{1-10} heteroaryl, C_{6-10} aryl C_{1-6} aliphatic or C_{1-10} heteroaryl C_{1-6} aliphatic;

wherein R^3 is independently H, F, Cl, Br, -CN, C_{1-3} aliphatic, C_{1-3} alkoxy, or C_{1-3} haloalkyl;

each of U_1 and U_2 is independently CR^4 or N;

V is NR^5R^{5a}, OR^5;

each of W_1, W_2, W_3 and W_4 is independently CR^4R^{4a}, NR^5, CR^4 or N, or W_1 and W_2 or W_3 and W_4 combine to become CR^4R^{4a}, NR^5, O or S;

X_1 is $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2, where m is 0, 1 or 2;

each of X_2 and X_3 is independently O, S or NR^5;

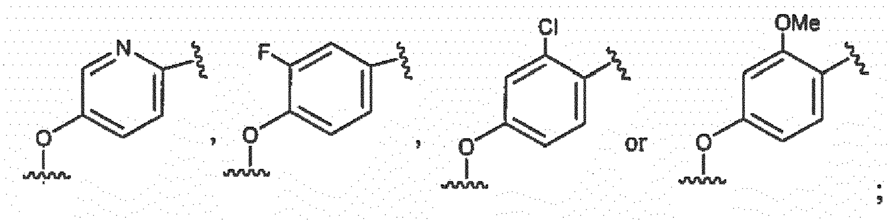
each of Z_1 and Z_2 is independently NR^5 or CR^4R^{4a};

each of R^4 and R^{4a} is independently H, F, Cl, Br, I, -CN, hydroxyl, $-NR^{5a}R^5$, with the proviso that where R^4 and R^{4a} are bonded to the same carbon atom, R^4 and R^{4a}, together with the carbon atom they are attached to, optionally form a substituted or unsubstituted 3-8 membered carbocyclic or heterocyclic ring;

each of R^5 and R^{5a} is independently H, $R^6R^{6a}NC(=O)$-, $R^6OC(=O)$-, $R^6C(=O)$-, $R^6R^{6a}NS(=O)$-, $R^6OS(=O)$-, $R^6S(=O)$-, $R^6R^{6a}NSO_2$-, R^6OSO_2-, R^6SO_2-, with the proviso that where R^5 and R^{5a} are bonded to the same nitrogen atom, R^5 and R^{5a}, together with the nitrogen atom they are attached to, optionally form a substituted or unsubstituted 3-8 membered ring, including spiro and fused bicyclic rings;

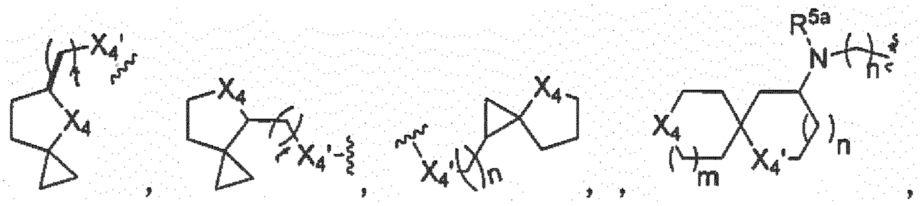
each of R^6 and R^{6a} is independently H;

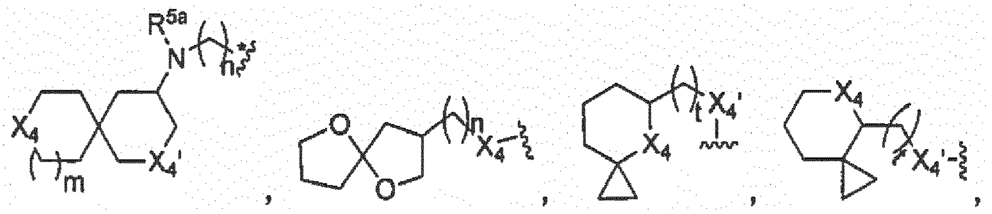
wherein each of $R^{5a}R^5N$-, $-C(=O)NR^5R^{5a}$, $-OC(=O)NR^5R^{5a}$, $-OC(=O)OR^5$, - $NR^5C(=O)NR^5R^{5a}$, $-NR^5C(=O)OR^{5a}$, $NR^5C(=O)-R^{5a}$, $R^5R^{5a}N-O_2S$-, R^5O_2S-, $R^5O_2SR^{5a}N$-, OR^5, NR^5, CR^4R^{4a}, CR^4, $(CR^4R^{4a})_m$, $-NR^5C(O)-(CR^4R^{4a})_p$-, $-NR^5C(=S)-(CR^4R^{4a})_p$-, $-NR^{5a}-(CR^4R^{4a})_p$-, $-NR^5-(CR^4R^{4a})_pC(=O)$-, $-NR^5-(CR^4R^{4a})_pC(=S)$-, $-NR^5S(O)_r$-,$-NR^5S(=O)(CR^4R^{4a})_p$-, $-C(=O)NR^5-(CR^4R^{4a})_p$-, $NR^5-(CR^4R^{4a})_p-S(=O)_r$-, $R^{5a}R^5N$-alkyl, $R^5(S=O)$-alkyl, $R^5R^{5a}N-(C=O)$-alkyl, $R^{5a}R^5N$-alkoxy, $R^5(S=O)$-alkoxy, $R^5R^{5a}N-(C=O)$-alkoxy, $R^6R^{6a}NC(=O)$-, $R^6OC(=O)$-, $R^6C(=O)$-, $R^6R^{6a}NS(=O)$-, $R^6OS(=O)$-, $R^6S(=O)$-, $R^6R^{6a}NSO_2$-, R^6OSO_2-, R^6SO_2-, hydroxy-substituted cyclopropylalkoxy, $R^5S(=O)_2O$-substituted cyclopropylalkoxy. Preferably, according to some embodiments, the substructure defined by X_1, U_1 and R^3 is

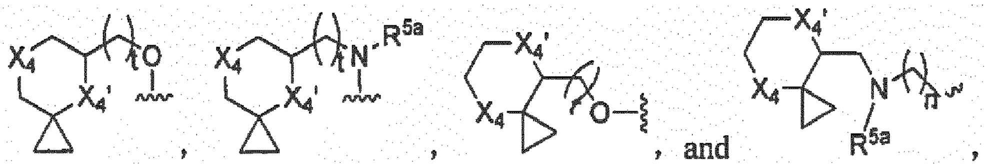


and/or

wherein R^1 is one of the following structures:

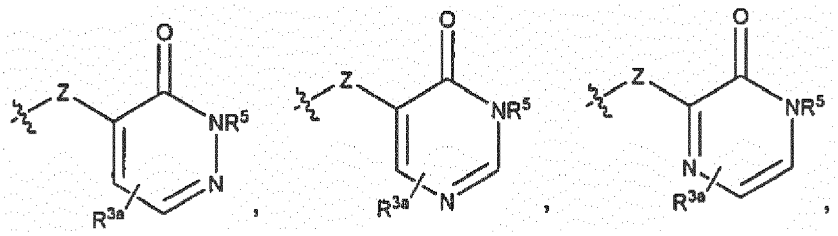


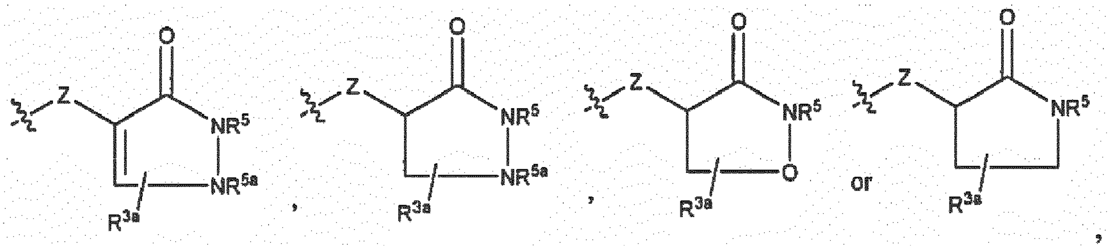




wherein each of X_4 and X_4' is independently $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2; each of m and n is independently 0,1 or 2; and t is 1,2 or 3

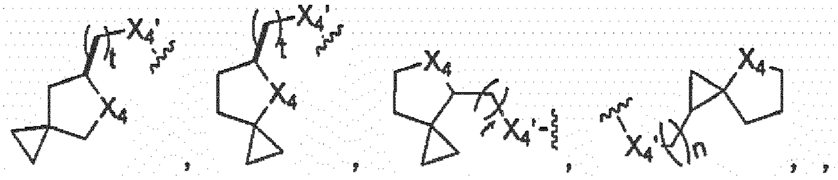
[0081] In another embodiment, Q_1 in Formula 1 or the substructure defined by X_2, V_1, V_2, V_3, V_4 and Z of Formula (IV) is

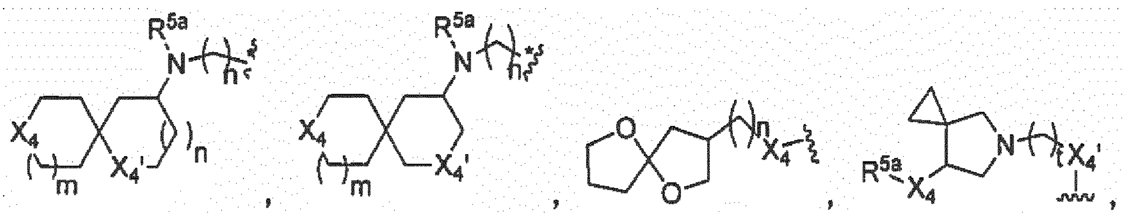


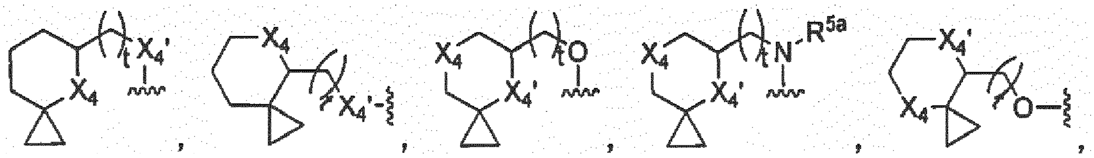


wherein R^{3a} is H, F, Cl, Br, I, -CN, hydroxyl, $R^{5a}R^5N$-, $R^{5a}R^5N$-aliphatic.

[0082] In another embodiment, R^1 is one of the following structures:







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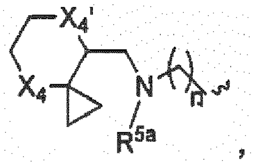
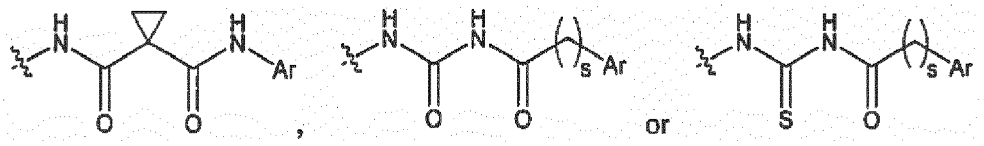


wherein each of X_4 and X_4' is independently $(CR^4R^{4a})_m$, NR^3, O, S, S=O or SO_2; each of m and n is independently 0,1 or 2; and t is 1,2 or 3.

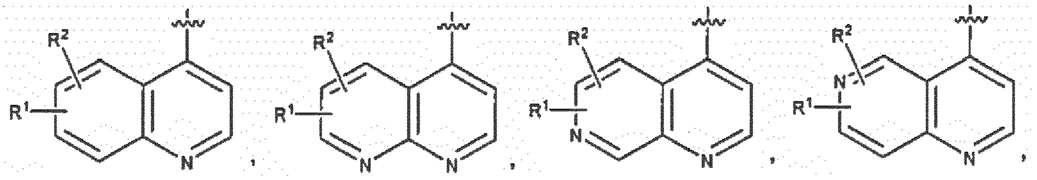
[0083] In another embodiment, Q_1 in Formula (I) or the substructure defined by Z_1, Z_2, X_2, X_3 and V of Formula (V) is

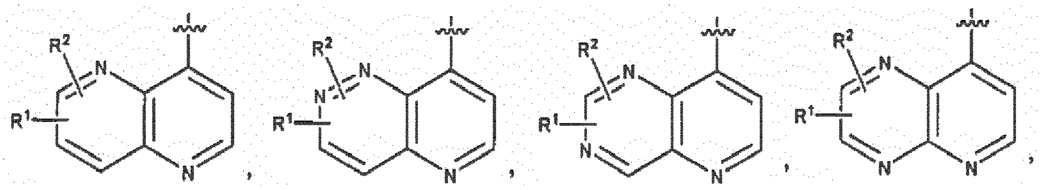


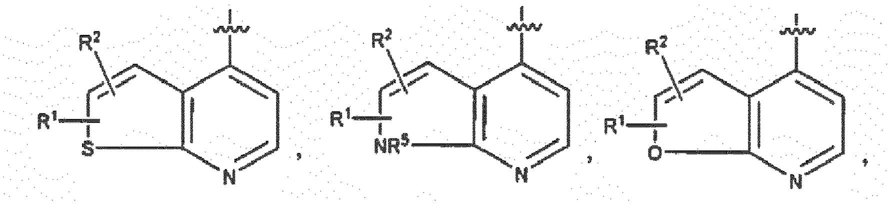
wherein Ar is substituted or unsubstituted aryl or heteroaryl; and s is 0 or 1.

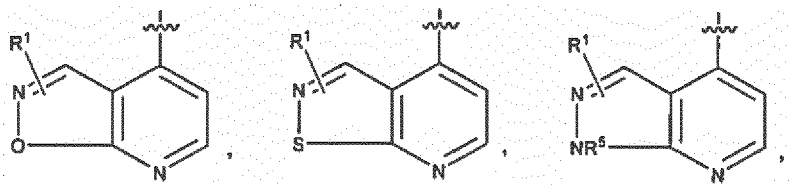
[0084] In another embodiment,

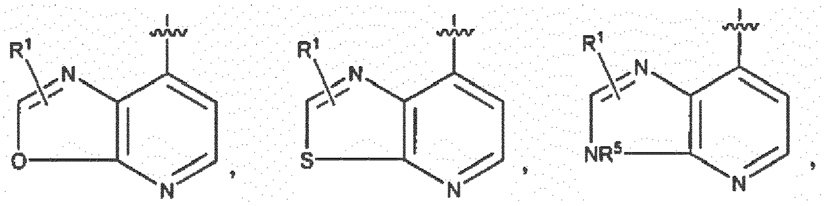
Q_2 is

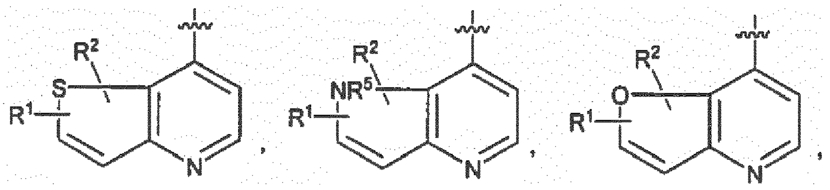


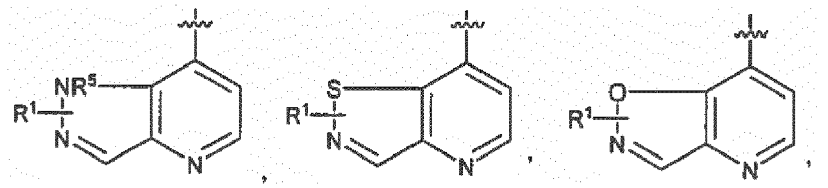


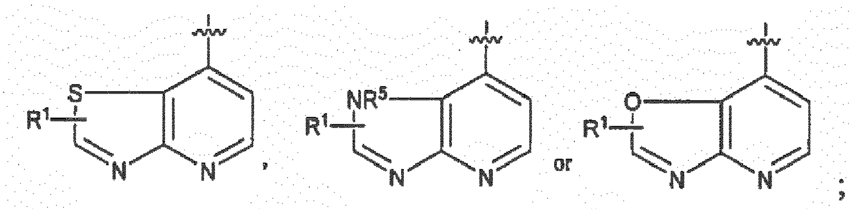












or

wherein X_1 is O or NR^5.

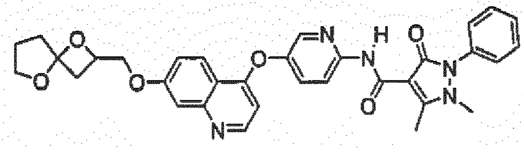
[0085] Provided herein is also a pharmaceutical composition comprising a compound disclosed herein above and a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof, and optionally a therapeutic agent selected from a chemotherapeutic agent, an anti-proliferative agent, an agent for treating atherosclerosis, an agent for treating lung fibrosis, and combinations thereof, wherein the additional therapeutic agent is optionally adriamycin, rapamycin, temsirolimus, everolimus, ixabepilone, gemcitabin, cyclophosphamide, dexamethasone, etoposide, fluorouracil, imatinib mesylate, dasatinib, nilotinib, erlotinib, lapatinib, iressa, sorafenib, sunitinib, an interferon, carboplatin, topotecan, taxol, vinblastine, vincristine, temozolomide, tositumomab, trabectedin, bevacizumab, trastuzumab, cetuximab, panitumumab or a combination thereof.

[0086] Also provided herein is the compound disclosed herein above or the pharmaceutical composition disclosed herein for use in preventing, managing, treating or lessening the severity of a proliferative disorder.

[0087] According to some embodiments, the proliferative disorder is metastatic cancer, colon cancer, gastric adenocarcinoma, bladder cancer, breast cancer, kidney cancer, liver cancer, lung cancer, thyroid cancer, cancer of the head and neck, prostate cancer, pancreatic cancer, cancer of the CNS, glioblastoma, or a myeloproliferative disorder, atherosclerosis or lung fibrosis.

[0088] The present invention also provides a method of inhibiting or modulating protein kinase activity in a biological sample comprising contacting a biological sample with the compound disclosed herein above or the pharmaceutical composition disclosed herein. Preferably, according to one embodiment, the protein kinases are receptor tyrosine kinases, and wherein the receptor tyrosine kinases are KDR, c-Met or IGF1R.

The present invention also provides a compound having one of the following structures: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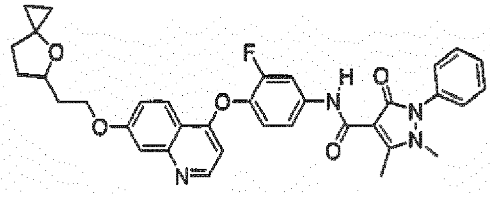
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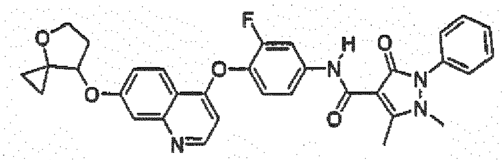
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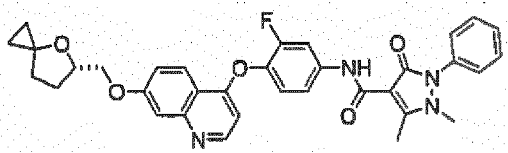
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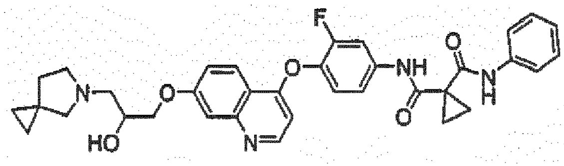
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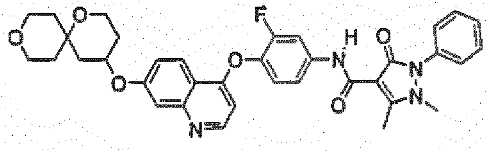
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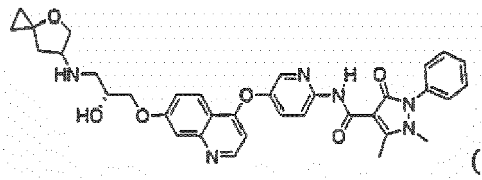
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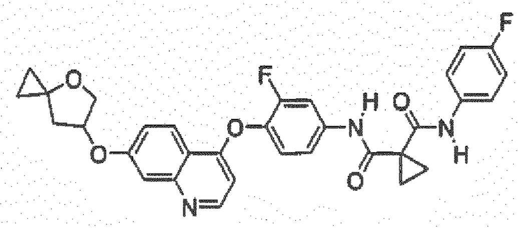
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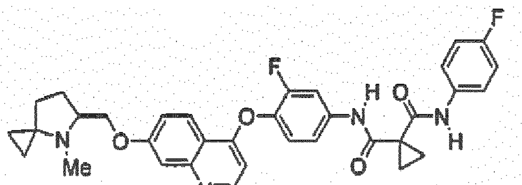
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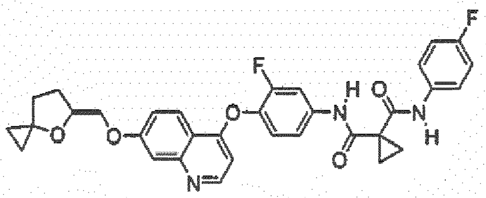
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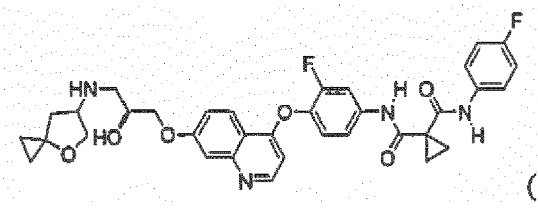
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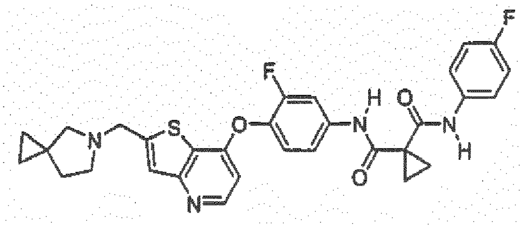

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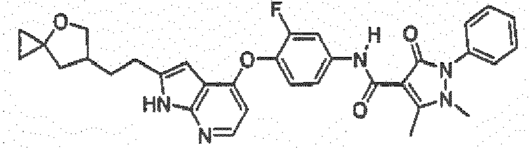

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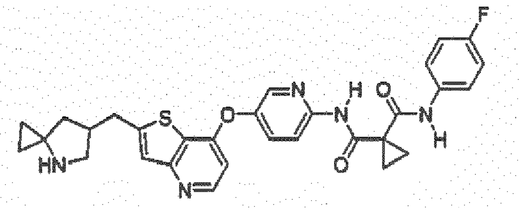

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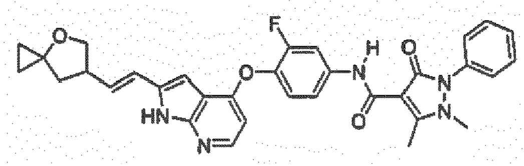

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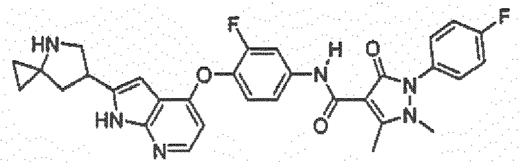

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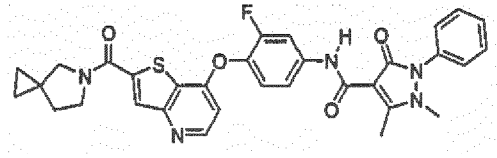

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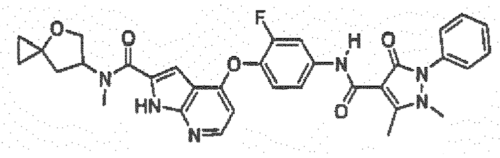

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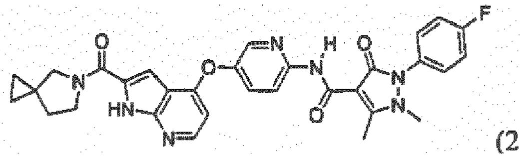

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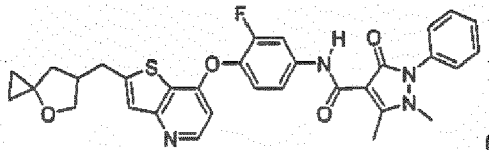

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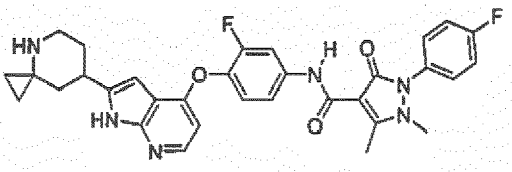

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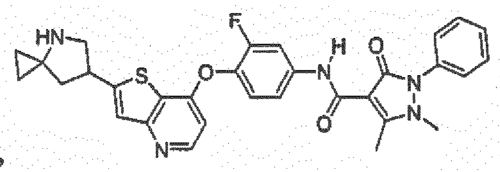

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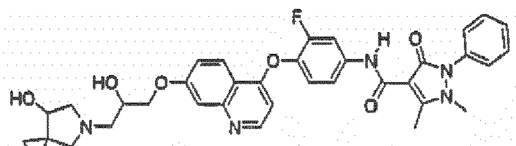

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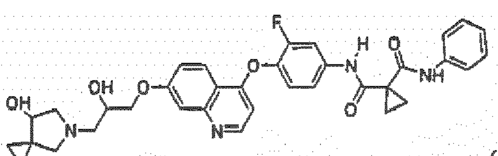

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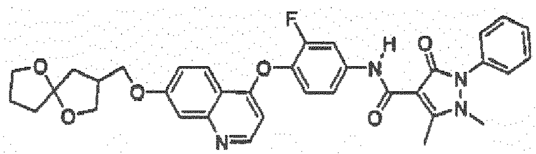

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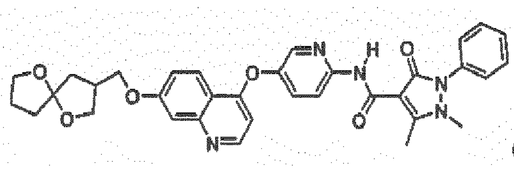

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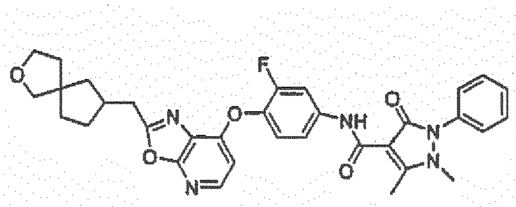

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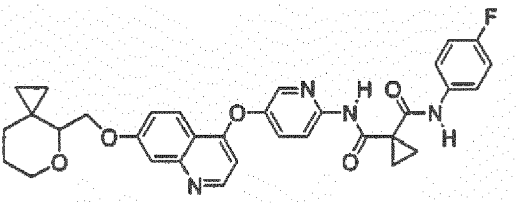

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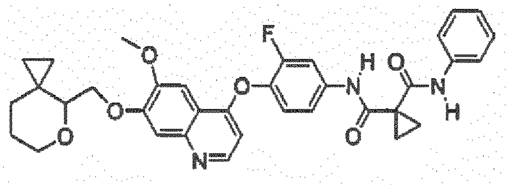

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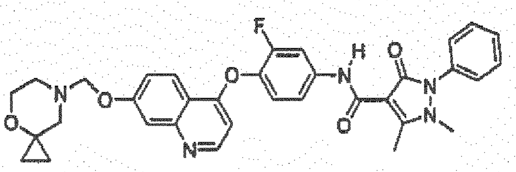

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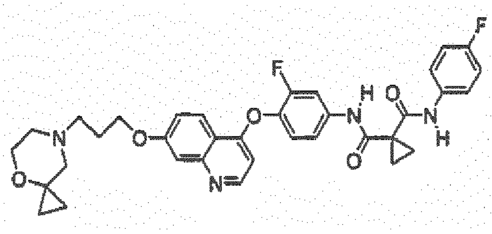

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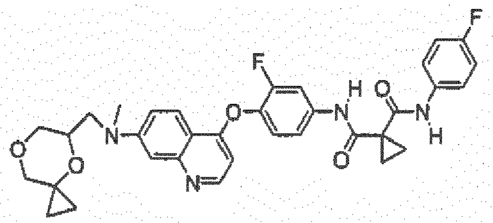

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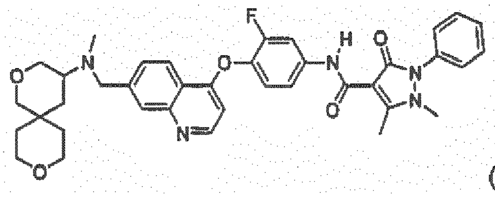

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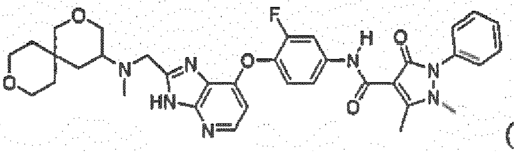

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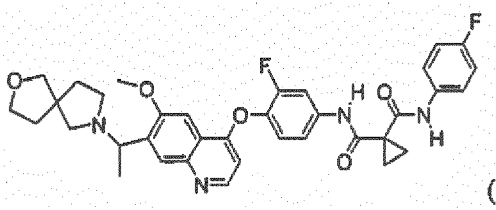

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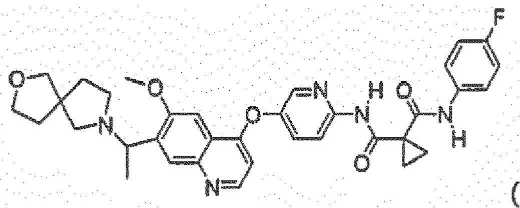

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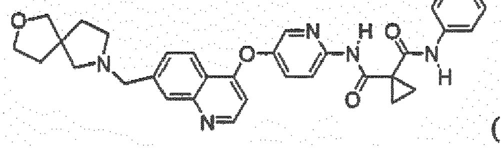

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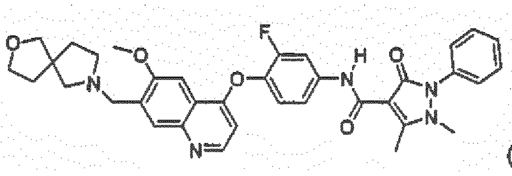

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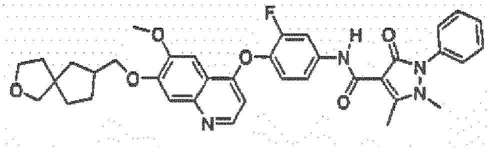

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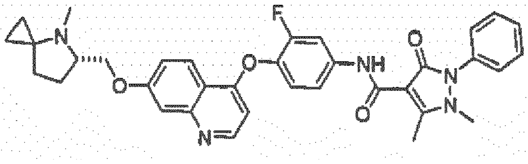

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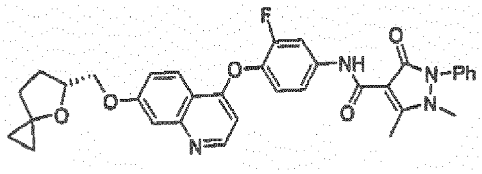
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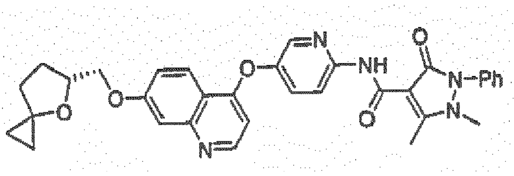
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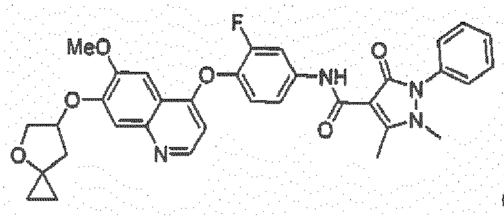
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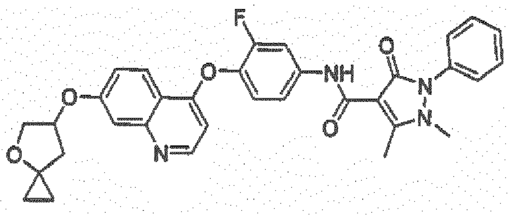
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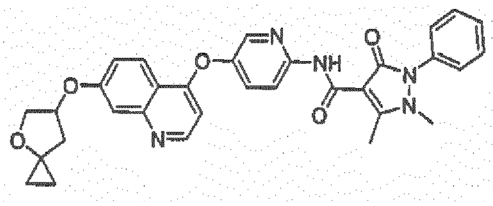
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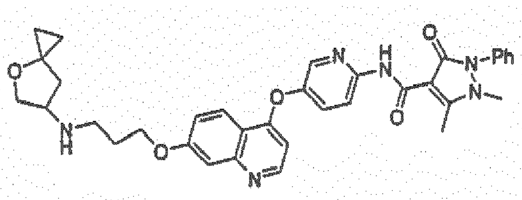
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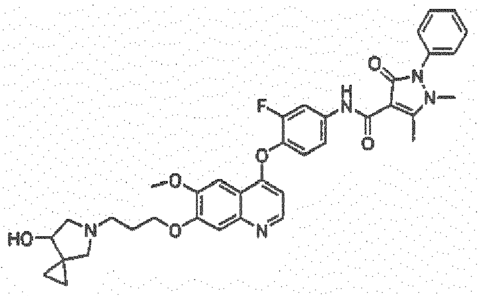
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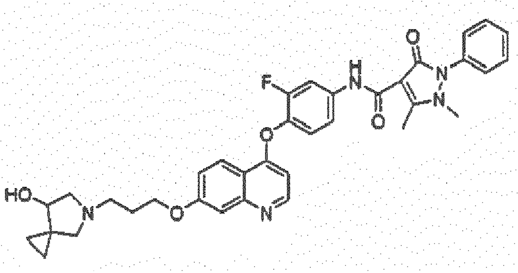
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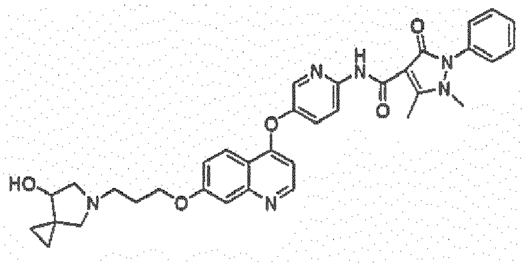
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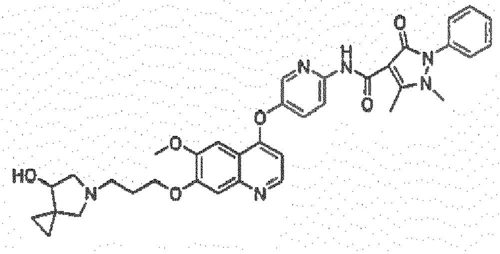
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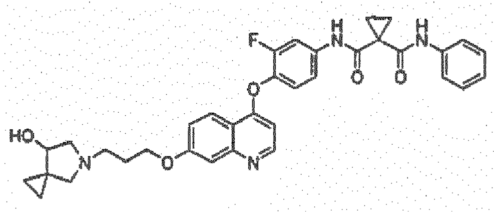
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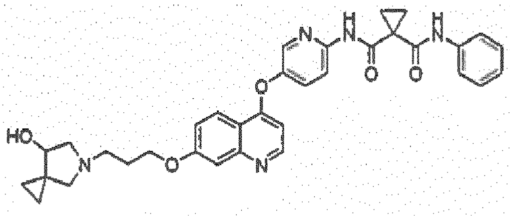
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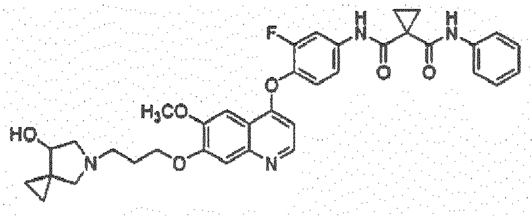
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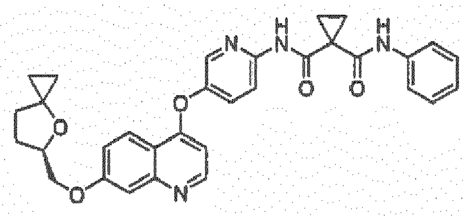
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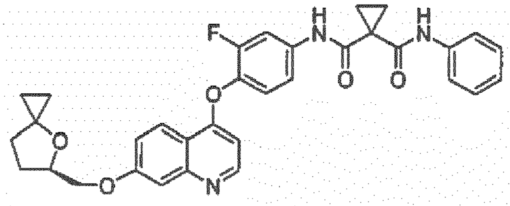
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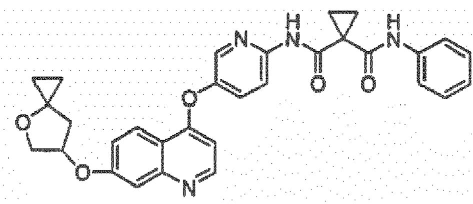
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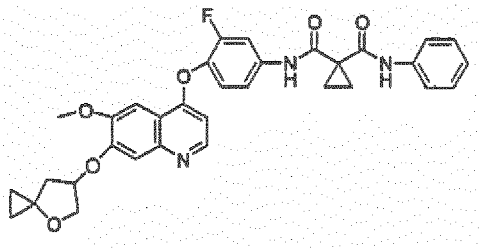
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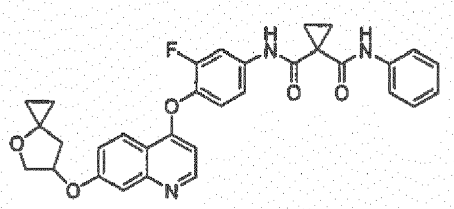
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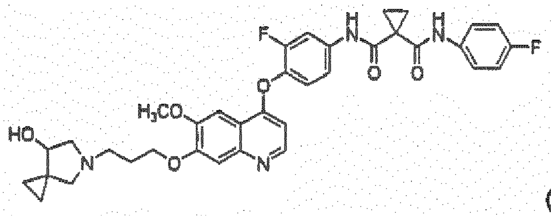
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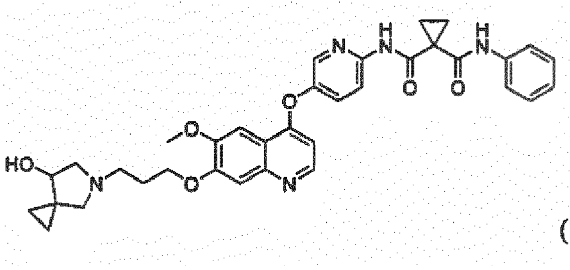

(78),

or a stereoisomer, a geometric isomer, a tautomer, an N-oxide, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof

[0089] The compounds disclosed herein also include salts of such compounds which are not necessarily pharmaceutically acceptable salts, and which may be useful as intermediates for preparing and/or purifying compounds of Formula (I), (IV) or (V) and/or for separating enantiomers of compounds of Formula (I), (IV) or (V).

[0090] If the compound disclosed herein is a base, the desired salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, and the like.

[0091] If the compound disclosed herein is an acid, the desired salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, and the like. Illustrative examples of suitable salts include, but are not limited to, organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, lithium, and the like.

COMPOSITION, FORMULATIONS AND ADMINSTRATION OF COMPOUNDS OF THE INVENTION

[0092] The amount of the compound in the compositions disclosed herein is such that is effective to detectably inhibit a protein kinase in a biological sample or in a patient.

[0093] It will also be appreciated that certain of the compounds disclosed herein can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. Some non-limiting examples of the pharmaceutically acceptable derivative include pharmaceutically acceptable prodrugs, salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[0094] As described above, the pharmaceutically acceptable compositions disclosed herein additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. In Remington: The Science and Practice of Pharmacy, 21st edition, 2005, ed. D.B. Troy, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan,1988-1999, Marcel Dekker, New York, are disclosed various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof.

[0095] Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols such as propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants.

[0096] The compositions disclosed herein may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrastemal, intrathecal, intraocular, intrahepatic, intralesional and intracranial injection or infusion techniques. The compositions may be administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions disclosed herein include aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3- butanediol. Among the acceptable vehicles and solvents that include water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[0097] For this purpose, any bland fixed oil includes synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as *Tweens, Spans* and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[0098] The pharmaceutically acceptable compositions disclosed herein include orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[0099] Alternatively, the pharmaceutically acceptable compositions disclosed herein include administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols. The pharmaceutically acceptable compositions disclosed herein also include administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[0100] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used. For topical applications, the pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds disclosed herein include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[0101] For ophthalmic use, the pharmaceutically acceptable compositions may be formulated, *e.g.*, as micronized suspensions in isotonic, pH adjusted sterile saline or other aqueous solution, or, as solutions in isotonic, pH adjusted sterile saline or other aqueous solution, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum. The pharmaceutically acceptable compositions disclosed herein may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[0102] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0103] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0104] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use. In order to prolong the effect of a compound disclosed herein, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, dissolving or suspending the compound in an oil vehicle accomplishes delayed absorption of a parenterally administered compound form.

[0105] Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Some non-limiting examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[0106] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds disclosed herein with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0107] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia; c) humectants such as glycerol; d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates and sodium carbonate; e) solution retarding agents such as paraffin; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate; h) absorbents such as kaolin and bentonite clay; and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0108] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0109] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain pacifying agents and can also be of a composition that they release the active ingredient(s) only, or, in a certain part of the intestinal tract, optionally, in a delayed manner. Some non-limiting examples of embedding compositions that can be used include polymeric substances and waxes.

[0110] Dosage forms for topical or transdermal administration of a compound disclosed herein include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, eardrops, and eye drops are also envisioned. Additionally, contemplated herein is the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[0111] The compounds disclosed herein are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions disclosed herein will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts.

[0112] The amount of the compounds disclosed herein that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. The compositions should be formulated so that a dosage of between 0.01- 300 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

[0113] Compounds disclosed herein can be administered as the sole pharmaceutical agent or in combination with one or more other additional therapeutic (pharmaceutical) agents where the combination causes no unacceptable adverse effects. This may be of particular relevance for the treatment of hyper-proliferative diseases such as cancer. In this instance, the compound disclosed herein can be combined with known cytotoxic agents, signal transduction inhibitors, or with other anti-cancer agents, as well as with admixtures and combinations thereof. As used herein, additional therapeutic agents that are normally administered to treat a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated". As used herein, "additional therapeutic agents" refers to include chemotherapeutic agents and other anti-proliferative agents.

[0114] For example, chemotherapeutic agents or other antiproliferative agents may be combined with the compounds disclosed herein to treat proliferative disease or cancer. Examples of chemotherapeutic agents or other antiproliferative agents include HDAC inhibitors including, but are not limited to, SAHA, MS-275, MGO 103, and those described in WO 2006/010264, WO 03/024448, WO 2004/069823, US 2006/0058298, US 2005/0288282, WO 00/71703, WO 01/38322, WO 01/70675, WO 03/006652, WO 2004/035525, WO 2005/030705, WO 2005/092899, and demethylating agents including, but not limited to, 5-aza-dC, Vidaza and Decitabine and those described in US 6268137, US 5578716, US 5919772, US 6054439, US 6184211, US 6020318, US 6066625, US 6506735, US 6221849, US 6953783, US 11393380.

[0115] Also, chemotherapeutic agents or other anti-proliferative agents may be combined with the compounds disclosed herein to treat proliferative diseases and cancer. Examples of known chemotherapeutic agents include, but are not limited to, for example, other therapies or anticancer agents that may be used in combination with the inventive anticancer agents disclosed herein and include surgery, radiotherapy (in but a few examples, gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes, to name a few), endocrine therapy, taxanes (taxol, taxotere etc), platinum derivatives, biologic response modifiers (interferons, interleukins, and tumor necrosis factor (TNF), TRAIL receptor targeting, agents, to name a few), hyperthermia and cryotherapy, agents to attenuate any adverse effects (*e.g.*, antiemetics), and other approved chemotherapeutic drugs, including, but not limited to, alkylating drugs (mechlorethamine, chlorambucil, Cyclophosphamide, Melphalan, Ifosfamide), antimetabolites (Methotrexate, Pemetrexed etc), purine antagonists and pyrimidine antagonists (6-Mercaptopurine, 5-Fluorouracil, Cytarabile, Gemcitabine), spindle poisons (Vinblastine, Vincristine, Vinorelbine, Paclitaxel), podophyllotoxins (Etoposide, Irinotecan, Topotecan), antibiotics (Doxorubicin, Bleomycin, Mitomycin), nitrosoureas (Carmustine, Lomustine), inorganic ions (Cisplatin, Carboplatin), Cell cycle inhibitors (KSP mitotic kinesin inhibitors, CENP-E and CDK inhibitors), enzymes (Asparaginase), and hormones (Tamoxifen, Leuprolide, Flutamide, and Megestrol), Gleevec(TM), adriamycin, dexamethasone, and cyclophosphamide. Antiangiogenic agents (Avastin and others). Kinase inhibitors (Imatinib (Gleevec), Sutent, Nexavar, Erbitux, Herceptin, Tarceva, Iressa and others). Agents inhibiting or activating cancer pathways such as the mTOR, HIF (hypoxia induced factor) pathways and others. For a more comprehensive discussion of updated cancer therapies see, http://www.nci.nih.gov/, a list of the FDA approved oncology drugs at http://www.fda.gov/cder/cancer/druglist-rame.htm, and The Merck Manual, Eighteenth Ed. 2006.

[0116] The compounds disclosed herein can be combined with cytotoxic anti-cancer agents. Examples of such agents can be found in the 13th Edition of the Merck Index (2001). These agents include, by no way of limitation, asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, or vindesine.

[0117] Other cytotoxic drugs suitable for use with the compounds disclosed herein include, but are not limited to, those compounds acknowledged to be used in the treatment of neoplastic diseases, such as those for example in Goodman and Gilman's The Pharmacological Basis of Therapeutics (Ninth Edition, 1996, McGraw-Hill). These agents include, by no way of limitation, aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2', 2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, or vinorelbine.

[0118] Other cytotoxic anti-cancer agents suitable for use in combination with the compounds disclosed herein also include newly discovered cytotoxic principles, some examples of cytotoxic principles include, but are not limited to, oxaliplatin, gemcitabine, capecitabine, epothilone and its natural or synthetic derivatives, temozolomide (Quinn et al., J. Clin. Oncology, 2003, 21(4), 646-651), tositumomab (Bexxar), trabedectin (Vidal et al., Proceedings of the American Society for Clinical Oncology, 2004, 23, abstract, 3181), and the inhibitors of the kinesin spindle protein Eg5 (Wood et al., Curr. Opin. Pharmacol. 2001, 1, 370-377).

[0119] The compounds disclosed herein can be combined with other signal transduction inhibitors. Of particular interest are signal transduction inhibitors which target the EGFR family, such as EGFR, HER-2, and HER-4 (Raymond et al., Drugs, 2000, 60 (Suppl.1), 15-23; Harari et al., Oncogene, 2000, 19 (53), 6102-6114), and their respective ligands. Examples of such agents include, by no way of limitation, antibody therapies such as Herceptin (trastuzumab), Erbitux (cetuximab), Vectibix (panitumumab), and pertuzumab. Examples of such therapies also include, by no way of limitation, small-molecule kinase inhibitors such as Iressa (Gefitinib), Tarceva (Erlotinib), Tykerb (Lapatinib) Canertinib (CI1033), AEE788 (Traxler et al., Cancer Research, 2004, 64, 4931-4941).

[0120] The compounds disclosed herein can be combined with other signal transduction inhibitors targeting receptor kinases of the split-kinase domain families (VEGFR, FGFR, PDGFR, flt-3, c-kit, c-fins, and the like), and their respective ligands. These agents include, by no way of limitation, antibodies such as Avastin (bevacizumab). These agents also include, by no way of limitation, small-molecule inhibitors such as Gleevec/Imanitib, Sprycel (Dasatinib), Tasigna (Nilotinib), Nexavar (Sorafenib), CHIR-265, Pazopanib (GW-786034), Recentin (Cediranib/AZD2171), Zactima (Vandetanib), Vatalanib (PTK787/ZK222584), Telatinib (BAY-579352), BMS-690514, BMS582664 (Brivanib), BMS540215, Axitinib (AG-013736). Motesanib (AMG706), Sutent (Sunitinib), ZD6474 (Hennequin et al., 92nd AACR Meeting, New Orleans, Mar. 24-28, 2001, abstract, 3152), Tivozanib (KRN-951) (Taguchi et al., 95th AACR Meeting, Orlando, Fla, 2004, abstract, 2575), CP-547, 632 (Beebe et al., Cancer Res. 2003, 63, 7301-7309), CP-673, 451 (Roberts et al., Proceedings of the American Association of Cancer Research, 2004, 45, abstract, 3989), CHIR-258 (Lee et al., Proceedings of the American Association of Cancer Research, 2004, 45, abstract, 2130), MLN-518 (Shen et al., Blood, 2003,102,11, abstract, 476).

[0121] The compounds disclosed herein can be combined with inhibitors of histone deacetylase. Examples of such agents include, by no way of limitation, suberoylanilide hydroxamic acid (SAHA), LAQ-824 (Ottmann et al., Proceedings of the American Society for Clinical Oncology, 2004, 23, abstract, 3024), LBH-589 (Beck et al., Proceedings of the American Society for Clinical Oncology, 2004, 23, abstract, 3025), MS-275 (Ryan et al., Proceedings of the American Association of Cancer Research, 2004, 45, abstract, 2452), FR-901228 (Piekarz et al., Proceedings of the American Society for Clinical Oncology, 2004, 23, abstract, 3028) and MGCDOI03 (US 6897220).

[0122] The compounds disclosed herein can be combined with other anti-cancer agents such as proteasome inhibitors, and m-TOR inhibitors. These include, by no way of limitation, bortezomib (Mackay et al., Proceedings of the American Society for Clinical Oncology, 2004, 23, Abstract, 3109), and sirolimus (rapamycin), everolimus, temsirolimus (CCI-779) (Wu et al., Proceedings of the American Association of Cancer Research, 2004, 45, abstract, 3849). The compounds disclosed herein can be combined with other anti-cancer agents such as topoisomerase inhibitors, including but not limited to camptothecin.

[0123] Those additional agents may be administered separately from the compound-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with the compound disclosed herein in a single composition. If administered as part of a multiple dosage regimen, the two active agents may be submitted simultaneously, sequentially or within a period of time from one another which would result in the desired activity of the agents.

[0124] The amount of both the compound and the additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Normally, the amount of additional therapeutic agent present in the compositions disclosed herein will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. The amount of additional therapeutic agent in the presently disclosed compositions may range from about 50 % to 100 % of the amount normally present in a composition comprising that agent as the only therapeutically active agent. In those compositions which comprise an additional therapeutic agent, that additional therapeutic agent and the compound disclosed herein may act synergistically.

USES OF THE COMPOUNDS AND COMPOSITIONS OF THE INVENTION

[0125] The invention features pharmaceutical compositions as defined above. The amount of compound in the compositions disclosed herein is such that is effective to detectably inhibit a protein kinase, such as VEGFR/KDR, IGF/IGF1R and/or c-Met inhibitory activity. The compounds disclosed herein are useful in therapy as antineoplasia agents or to minimize deleterious effects of VEGF, IGF and/or HGF.

[0126] Compounds disclosed herein would be useful for, but not limited to, the prevention or treatment of proliferative diseases, conditions, or disorders in a patient by administering to the patient a compound or a composition disclosed herein in an effective amount. Such diseases, conditions, or disorders include cancer, particularly metastatic cancer, atherosclerosis, and lung fibrosis.

[0127] Compounds disclosed herein would be useful for the treatment of neoplasia including cancer and metastasis, including, but not limited to: carcinoma such as cancer of the bladder, breast, colon, kidney, liver, lung (including small cell lung cancer), esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin (including squamous cell carcinoma); hematopoietic tumors of lymphoid lineage (including leukemia, acute lymphocitic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma); hematopoietic tumors of myeloid lineage (including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyclocytic leukemia); tumors of mesenchymal origin (including fibrosarcoma and rhabdomyosarcoma, and other sarcomas, *e.g.* soft tissue and bone); tumors of the central and peripheral nervous system (including astrocytoma, neuroblastoma, glioma and schwannomas); and other tumors (including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma).

[0128] The compounds also would be useful for treatment of ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, retrolental fibroplasia and neovascular glaucoma; retinal ischemia; vitreous hemorrhage; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemaginomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis. The compounds are also useful for the treatment of edema, and conditions of vascular hyperpermeability.

[0129] The compounds disclosed herein are also useful in the treatment of diabetic conditions such as diabetic retinopathy and microangiopathy. The compounds disclosed herein are also useful in the reduction of blood flow in a tumor in a subject. The compounds disclosed herein are also useful in the reduction of metastasis of a tumor in a subject.

[0130] Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. Animals may include horses, dogs, and cats. As used herein, the compounds disclosed herein include the pharmaceutically acceptable derivatives thereof.

[0131] Where the plural form is used for compounds, salts, and the like, this is taken to refer to also a single compound, salt, and the like.

[0132] The treatment method not forming part of the present invention that includes administering a compound or composition disclosed herein can further include administering to the patient an additional therapeutic agent (combination therapy) selected from: a chemotherapeutic or anti-pmliferative agent, or an anti-inflammatory agent, wherein the additional therapeutic agent is appropriate for the disease being treated and the additional therapeutic agent is administered together with a compound or composition disclosed herein as a single dosage form or separately from the compound or composition as part of a multiple dosage form. The additional therapeutic agent may be administered at the same time as a compound disclosed herein or at a different time. In the latter case, administration may be staggered by, for example, 6 hours, 12 hours, 1 day, 2 days, 3 days, 1 week, 2 weeks, 3 weeks, 1 month, or 2 months.

[0133] Also disclosed but not forming part of the present invention is a method of inhibiting the growth of a cell that expresses VEGFR, IGF1R or c-Met, that includes contacting the cell with a compound or composition disclosed herein, thereby causing inhibition of growth of the cell. Examples of a cell whose growth can be inhibited include: a breast cancer cell, a colorectal cancer cell, a lung cancer cell, a papillary carcinoma cell, a prostate cancer cell, a lymphoma cell, a colon cancer cell, a pancreatic cancer cell, an ovarian cancer cell, a cervical cancer cell, a central nervous system cancer cell, an osteogenic sarcoma cell, a renal carcinoma cell, a hepatocellular carcinoma cell, a bladder cancer cell, a gastric carcinoma cell, a head and neck squamous carcinoma cell, a melanoma cell, or a leukemia cell.

[0134] Also disclosed but not forming part of the present invention is a method of inhibiting VEGFR, IGF1R or c-Met kinase activity in a biological sample that includes contacting the biological sample with a compound or composition disclosed herein. The term "biological sample" as used herein, means a sample outside a living organism and includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof. Inhibition of kinase activity, particularly VEGFR, IGF1R or c-Met kinase activity, in a biological sample is useful for a variety of purposes known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

[0135] An "effective amount" or "effective dose" of the compound or pharmaceutically acceptable composition is that amount effective for treating or lessening the severity of one or more of the aforementioned disorders. The compounds and compositions, according to the method disclosed herein, may be administered using any amount and any route of administration effective for treating or lessening the severity of the disorder or disease. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. A compound or composition can also be administered with one or more other therapeutic agents, as discussed above.

[0136] The compounds disclosed herein or pharmaceutical compositions thereof may also be used for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Vascular stents, for example, have been used to overcome restenosis (re-narrowing of the vessel wall after injury). However, patients using stents or other implantable devices risk clot formation or platelet activation. These unwanted effects may be prevented or mitigated by pre-coating the device with a pharmaceutically acceptable composition comprising a compound disclosed herein.

[0137] Suitable coatings and the general preparation of coated implantable devices are described in U.S. Patent Nos. 6099562, 5886026, and 5304121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccarides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics into the composition. Implantable devices coated with a compound disclosed herein are also disclosed herein. The compounds may also be coated on implantable medical devices, such as beads, or co-formulated with a polymer or other molecule, to provide a "drug depot" thus permitting the drug to be released over a longer time period than administration of an aqueous solution of the drug.

GENERAL SYNTHETIC PROCEDURES

[0138] Generally, the compounds disclosed herein may be prepared by methods described herein, wherein the substituents are as defined for formulas (I), (IV) or (V), above, except where further noted. The following non-limiting schemes and examples are presented to further exemplify the invention.

[0139] Persons skilled in the art will recognize that the chemical reactions described may be readily adapted to prepare a number of other compounds disclosed herein, and alternative methods for preparing the compounds disclosed herein are deemed to be within the scope disclosed herein. For example, the synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, and/or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds disclosed herein.

[0140] In the examples described below, unless otherwise indicated all temperatures are set forth in degrees Celsius. Reagents were purchased from commercial suppliers such as Aldrich Chemical Company, Arco Chemical Company and Alfa Chemical Company, and were used without further purification unless otherwise indicated. Common solvents were purchased from commercial suppliers such as Shantou XiLong Chemical Factory, Guangdong Guanghua Reagent Chemical Factory Co. Ltd., Guangzhou Reagent Chemical Factory, Tianjin YuYu Fine Chemical Ltd., Qingdao Tenglong Reagent Chemical Ltd., and Qingdao Ocean Chemical Factory.

[0141] Anhydrous THF, dioxane, toluene, and ether were obtained by refluxing the solvent with sodium. Anhydrous CH_2Cl_2 and $CHCl_3$ were obtained by refluxing the solvent with CaH_2. EtOAc, PE, hexane, DMA and DMF were treated with anhydrous Na_2SO_4 prior use.

[0142] The reactions set forth below were done generally under a positive pressure of nitrogen or argon or with a drying tube (unless otherwise stated) in anhydrous solvents, and the reaction flasks were typically fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried.

[0143] Column chromatography was conducted using a silica gel column. Silica gel (300 - 400 mesh) was purchased from Qingdao Ocean Chemical Factory. ^1H NMR spectra were recorded with a Bruker 400 MHz spectrometer at ambient temperature. ^1H NMR spectra were obtained as $CDCl_3$, d_6-DMSO, CD_3OD or d_6-acetone solutions (reported in ppm), using TMS (0 ppm) or chloroform (7.25 ppm) as the reference standard. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz).

[0144] Low-resolution mass spectral (MS) data were determined on an Agilent 1200 Series LCMS (Zorbax SB-C18, 2.1 × 30 mm, 4 micorn, 10 min, 0.6 mL/min flow rate, 5 to 95 % (0.1 % formic acid in CH_3CN) in (0.1 % formic acid in H_2O) with UV detection at 210/254 nm and a low resonance electrospray mode (ESI).

[0145] Purities of compounds were assessed by Agilent 1100 Series high performance liquid chromatography (HPLC) with UV detection at 210 nm and 254 nm (Zorbax SB-C18, 2.1 × 30 mm, 4 micorn,10 min, 0.6 mL/min flow rate, 5 to 95 % (0.1 % formic acid in CH_3CN) in (0.1 % formic acid in H_2O). Column was operated at 40 °C.

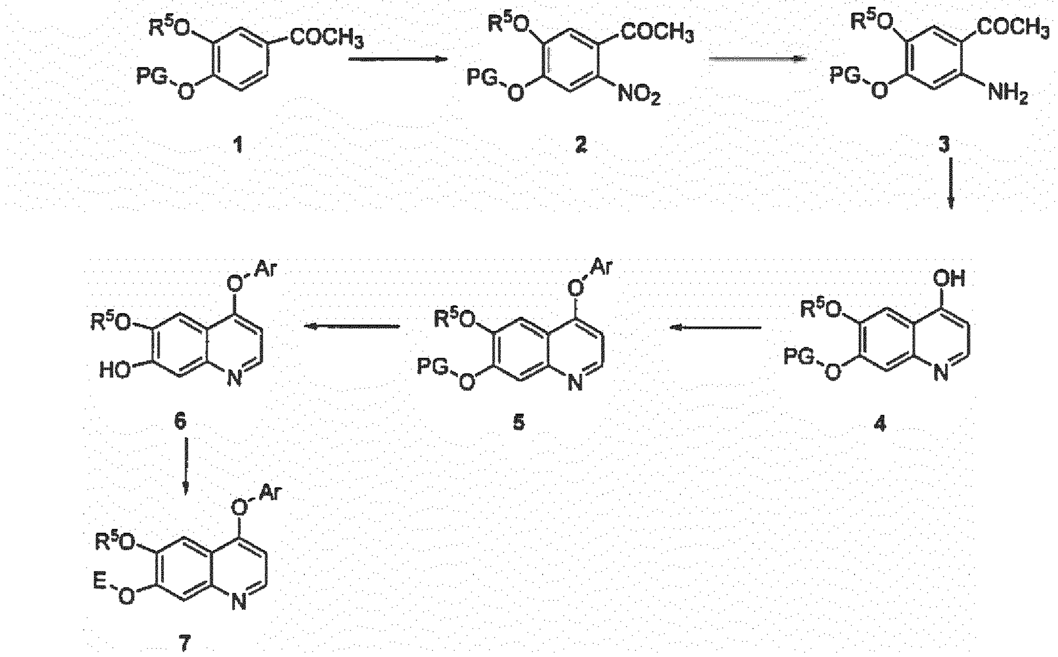
[0146] The following abbreviations are used throughout the specification:

HOAc	acetic acid
MeCN, CH_3CN	acetonitrile
NH_3	ammonia
NH_4Cl	ammonium chloride
HBTU	O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
PyBop	benzotriazol-1-yl-oxy-tripyrrolidino-phosphonium hexafluorophosphate
$Pd_2(dba)_3$	bis(dibenzylideneacetone) palladium
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
TEAC	bis(tetra-ethylammonium)carbonate
BBr_3	boron tribromide
BSA	bovine serum albumin
Br_2	bromine
BOC, Boc	tert-butyloxycarbonyl
Cs_2CO_3	cesium carbonate
$CHCl_3$	chloroform
$CDCl_3$	chloroform deuterated
Cu	copper

CuI copper(I) iodide
Et_2O diethyl ether
DBU 1,8-diazabicyclo[5,4,0]undec-7-ene
DIBAL diisobutylaluminum hydride
DIAD diisopropyl azodicarboxylate
DIEA diisopropylethylamine
DEAD dimethyl azodicarboxylate
DMF dimethylformamide
DMAP 4-dimethylaminopyridine
DMSO dimethylsulfoxide
EDC, EDCI 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride dppa diphenylphosphoryl azide
EtOAc ethyl acetate
FBS fetal bovine serum g gram h hour
HBr hydrobromic acid
HCl hydrochloric acid
HOBt 1-hydroxybenzotriazole hydrate
H_2 hydrogen
H_2O_2 hydrogen peroxide
Fe iron
LiHMDS lithium bis(trimethylsilyl)-amide
LDA lithium diisopropylamide
MCPBA meta-chloroperbenzoic acid
$MgSO_4$ magnesium sulfate
MeOH, CH_3OH methanol
MeI methyl iodide
CH_2Cl_2, DCM methylene chloride
NMP N-methylpyrrolidinone
mL, ml milliliter
N_2 nitrogen
Pd/C palladium on carbon
$Pd(OAc)_2$ palladium acetate
$Pd(OH)_2$ palladium hydroxide
$Pd(PPh_3)_4$ palladium tetrakis triphenylphosphine
$Pd(dppf)Cl_2$ 1,1-bis(diphenylphosphino)ferrocene palladium chloride
PE petroleum ether (60 - 90 °C)
PBS phosphate buffered saline
$POCl_3$ phosphorous oxychloride
K_2CO_3 potassium carbonate
KOH potassium hydroxide
RT, rt room temperature
Rt retention time
$NaHCO_3$ sodium bicarbonate
$NaBH_4$ sodium borohydride
$NaBH_3CN$ sodium cyanoborohydride
NaOtBu sodium tert-butoxide
NaOH sodium hydroxide
$NaClO_2$ sodium chlorite
NaCl sodium chloride
NaH_2PO_4 sodium dihydric phosphate
NaH sodium hydride
NaI sodium iodide
Na_2SO_4 sodium sulfate
TBTU O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate
THF tetrahydrofuran
Et_3N, TEA triethylamine
TFA trifluoroacetic acid
$P(t-bu)_3$ tri(tert-butyl)phosphine
NBS N-bromosuccinimide

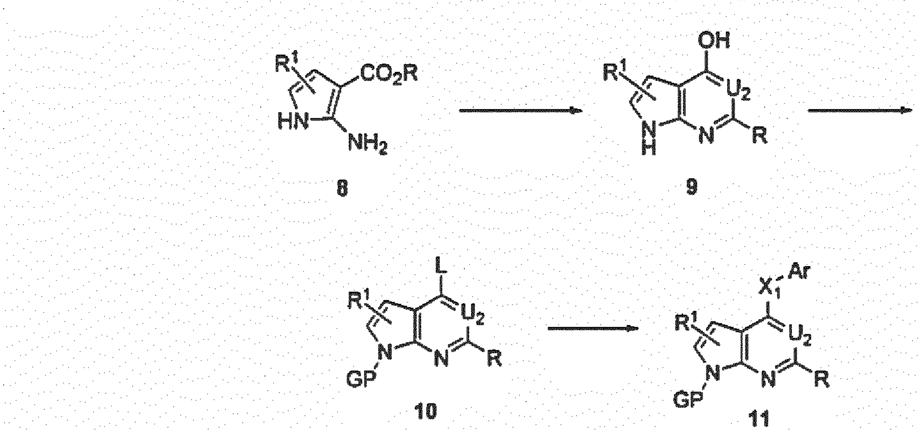
TBAI Tetrabutylammonium iodide
H2O water

Scheme 1



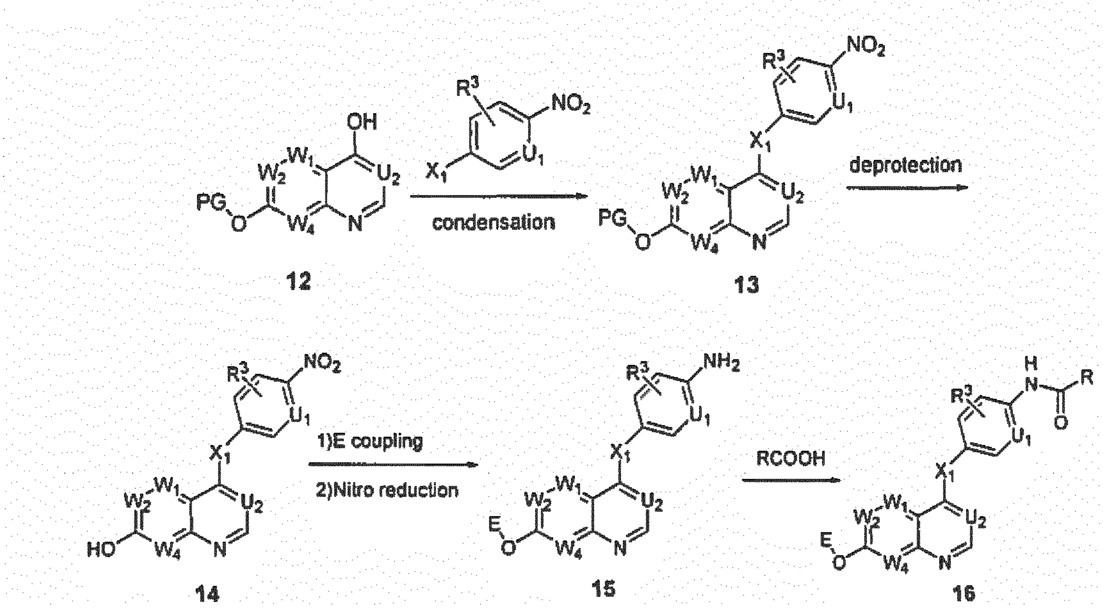
[0147] Substituted compounds **7**, where W_1, W_2, W_3 and W_4 are CH, X_1 is O; R^1 (*i.e.* EO-), R^5, and PG are as defined above, can be prepared by the process illustrated in Scheme 1. The substituted aryl **1** is nitrated to give compound **2** by a suitable nitration reagent such as HNO_3 at appropriate temperature such as 0 °C. The NO_2 group is then reduced by a reducing reagent such as Fe or Zn powder, or under hydrogenation condition in the presence of Pd catalyst such as Pd/C. Aniline **3** is condensed with a formate such as ethyl formate under basic condition to give substituted quinoline **4**. Coupling of **4** with appropriate aryl derivatives yields substituted diaryl ethers **5**. The protecting group PG is removed to provide compound **6**, which is condensed with E-L (L = a suitable leaving group such as OMs, Cl, Br or I; E = aliphatic, heterocyclic aliphatic, fused heterobicyclic aliphatic, spiro heterobicyclic aliphatic, cyclic aliphatic, fused bicyclic aliphatic, spiro bicyclic aliphatic, heterocyclic, fused heterobicyclic, spiro heterobicyclic, cyclic, fused bicyclic, spiro bicyclic, etc.) to afford desired kinase inhibitor **7**.

Scheme 2



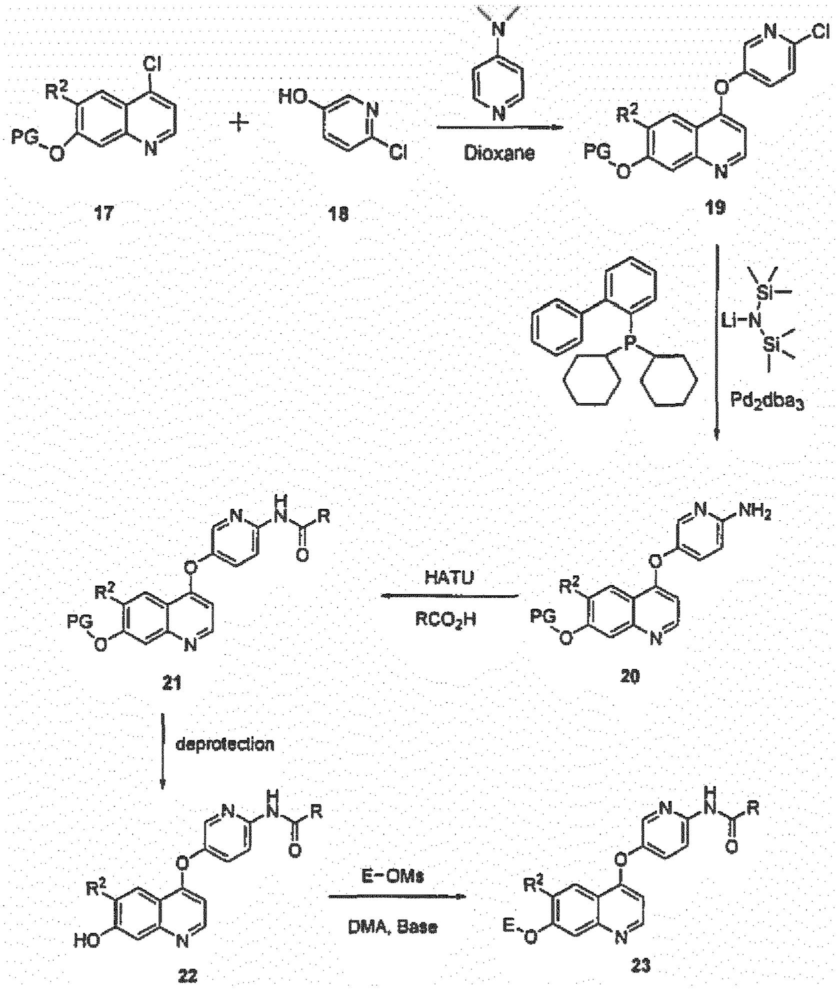
[0148] Alternatively, substituted indole/azaindole analogs **11** can be synthesized through the procedure depicted in Scheme 2. Where R^1, X_1, U_2 and PG are as defined above, R is H, $R^{5a}R^5N$-, aliphatic, alkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkoxy or heterocyclylalkoxy. Substituted 2-aminopyrazole **8** is first transformed to **9** in a similar fashion as described in Scheme 1. The OH group is then replaced with a good leaving group L, such as Cl, F or OMs. L in compound **10** is converted to a kinase inhibitor **11** in the presence of base such as Cs_2CO_3, NaOH, DMAP, or lutidine in a solvent such as dioxane, toluene, or DMA, etc. preferably at elevated temperature.

Scheme 3



[0149] Alternatively, substituted kinase inhibitor **16** can be prepared using a process as demonstrated in Scheme 3. Where W_1, W_2, W_3, W_4, R^1 (*i.e.* EO-), R^3, U_1, U_2, X_1 and PG are as defined above. Condensation of **12** with a nitro-aryl derivative gives compound **13.** Deprotection removes the protecting group PG leading to compound **14.** Attachment of E group through a coupling process followed by the reduction of nitro group affords compound **15.** Coupling of aniline **15** with an acid in the presence of coupling reagent such as EDCI or HATU furnishes desired kinase inhibitor **16.**

Scheme 4



[0150] Alternatively, kinase inhibitors can be obtained through the process as described in Scheme 4. Where R^1 (*i.e.* EO-), R^2 and PG are as defined above. Thus, compound **20** is prepared through Pd catalyzed amination of 2-chloropyridine derivative **19.** Coupling of aniline **20** with an acid followed by the removal of protecting group PG gives compound **22.** An appropriate group such as spiro or bicyclic moiety is appended to the quinoline portion to yield compound **23.** In the above structures, R is structures defined by V_1, V_2, V_3, and V_4 in Formula (IIa), or structures defined by Z_1, Z_2, X_2, and X_3 in Fomular (IIb).

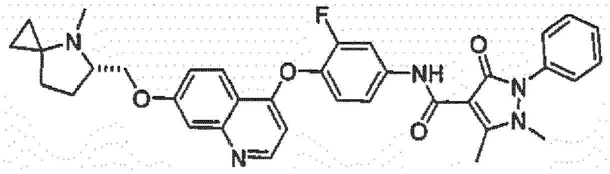
EXAMPLES

[0151] Examples 4, 5, 9,10, 23, 25, and 27 do not form part of the present invention.

Example 1

N-(4-(7-(((5S)-4-methyl-4-azaspiro[2.4]heptane-5-yl)methoxy)quinolin-4-yloxy)-3-fluorophenyl)-2.3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide

[0152]



Step1) (S)-5-((tetrahydro-2H-pyran-2-yloxy)methyl)pyrrolidin-2-one

[0153] To a mixture of (S)-5-(hydroxymethyl)pyrrolidin-2-one (1.0 g, 8.7 mmol, Aldrich) and DHP (1.46 g, 17.4 mmol, Alfa) in 20 mL of dichloromethane was added PPTS (0.437 g, 1.74 mmol, Aldrich) in portions. The reaction mixture was stirred at rt for 4 hrs, and was quenched with 20 mL of saturated $NaHCO_3$ aqueous solution. The resulted mixture was extracted with dichloromethane (25 mL×2). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by a silica gel column chromatography (EtOAc) to give the title compound (as a diastereomer mixture) as colorless oil (0.9 g, 52 %).
MS (ESI, pos. ion) m/z: 199.9 (M+1);
^1H NMR (400MHz, $CDCl_3$): δ1.69 - 1.88 (m, 6H), 2.25 - 2.28 (m, 2H), 2.32 - 2.35 (m, 2H), 3.23 (m, 1H), 3.48 - 3.55 (m, 2H), 3.78 - 3.85 (m, 2H), 4.58 (m, 1H).

Step2) (S)-1-methyl-5-((tetrahydro-2H-pyran-2-yloxy)methyl)pyrrolidin-2-one

[0154] To a mixture of NaH (0.48 g, 12 mmol, 60 % mineral oil, Aldrich) in 15 mL of DMF was added a solution of (S)-5-((tetrahydro-2H-pyran-2-yloxy)methyl) pyrrolidin-2-one (2 g,10 mmol) in 5 mL of DMF via a syringe at -40 °C. The reaction was stirred at -40 °C for 1 hr. CH_3I (0.9 mL, 12 mmol, *Shanghai* Jingchun Reagent Ltd.) was added dropwise via a syringe. The reaction was continued to stir at -40 °C for 4 hrs, and was quenched with 10 mL of saturated $NaHSO_3$ aqueous solution. The mixture was extracted with ethyl acetate (50 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by a silica gel column chromatography (EtOAc) to give the desired product as colorless oil (1.98 g, 92 %).
MS (ESI, pos. ion) m/z: 214.0 (M+1);
1H NMR (400MHz, CDCl3): δ1.69 - 1.88 (m, 6H), 1.93 - 2.17 (m, 2H), 2.33 - 2.47 (m, 2H), 2.90 (3H, s), 3.40 - 3.52 (m, 2H), 3.80 - 3.90 (m, 2H), 3.78 (m, 1H), 4.60 (m, 1H).

Step3) (5S)-4-methyl-5-((tetrahydro-2H-pyran-2-yloxy)methyl)-4-azaspiro[2.4]heptane

[0155] To a mixture of (S)-1-methyl-5-((tetrahydro-2H-pyran-2-yloxy)methyl)-pyrrolidin-2-one (0.6 g, 2.82 mmol) in 20 mL of THF was added $Ti(Oi\text{-}Pr)_4$ (2.56 mL, 8.45 mmol, d = 0.937 g/L, Aldrich) via a syringe under nitrogen at rt. After stirring at rt for 30 min, EtMgBr (5.63 mL, 16.9 mmol, 3M ether solution, Aldrich) was added via a syringe pump over 3 hrs. The reaction was continued to stir at rt overnight, and then quenched with a mixture of 20 mL of water and 30 mL of ethyl acetate. After stirring for 20 min, the mixture was filtered through a celite pad. The filtrate was extracted with ethyl acetate (30 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by a silica gel column chromatography (50:1 (v/v) CH_2Cl_2/ CH_3OH) to afford (5S)-4-methyl-5-((tetrahydro-2H-pyran-2-yloxy)methyl)-4-azaspiro[2.4]heptane as pale yellow oil (64 mg, 10 %).
MS (ESI, pos. ion) m/z: 226.0 (M+1);
^1H NMR (400MHz, $CDCl_3$): 50.23 (m, 1H), 0.46 (m, 1H), 0.63 (m, 1H), 0.86 (m, 1H), 1.58 - 1.90 (m, 10H), 2.13 (s, 3H), 2.85 (m, 1H), 3.37 - 3.50 (m, 2H), 3.72 - 3.89 (m, 2H), 4.62 (m, 1H).

Step4) (5S)-4-methyl-5-(hydroxymethyl)-4-azaspiro[2.4]heptane

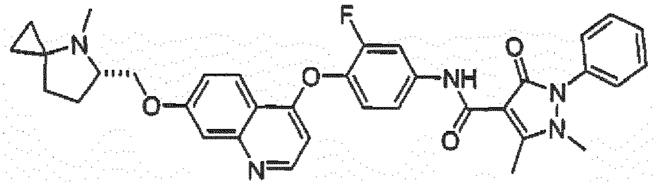
[0156] To a mixture of (5S)-4-methyl-5-((tetrahydro-2H-pyran-2-yloxy)methyl)-4-azaspiro[2.4]heptane (64 mg, 0.284 mmol) in 10 mL of methanol was added 4-methylbenzenesulfonic acid (97.8 mg, 0.568 mmol, Aldrich). The reaction mixture was stirred at 50 °C overnight, and then concentrated *in vacuo.* The residue was treated with 10 mL of saturated Na_2CO_3 aqueous solution, and extracted with dichloromethane (20 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to give the desired product as yellow oil (32 mg, 80 %).
MS (ESI, pos. ion) m/z: 142.0 (M+1).

Step5) ((5S)-4-methyl-4-azaspiro[2.4]heptane-5-yl)methyl methanesulfonate

[0157] A mixture of (5S)-4-methyl-5-(hydroxymethyl)-4-azaspiro[2.4]heptane (0.2 g, 1.42 mmol) and triethylamine (0.287g, 2.84 mmol, *Shantou* Xilong chemical factory) in 5 mL of dichloromethane was stirred at 0 °C for 30 min. To the mixture was added methanesulfonyl chloride (0.325 g, 2.84 mmol, *Shanghai* Haiqu chemical. Ltd.) via a syringe. The reaction mixture was stirred at 0 °C for 4 hrs and quenched with a mixture of 5 mL of saturated Na_2CO_3 aqueous solution and 5 mL of water. The resulted mixture was extracted with dichloromethane (20 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to give ((5S)-4-methyl-4-azaspiro[2.4]heptane-5-yl)methyl methanesulfonate as yellow oil (150 mg, 48 %).

Step6) N-(4-(7-(((5S)-4-methyl-4-azaspiro[2.4]heptane-5-yl)methoxy)quinolin-4-yloxy)-3-fluorophenyl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide

[0158]

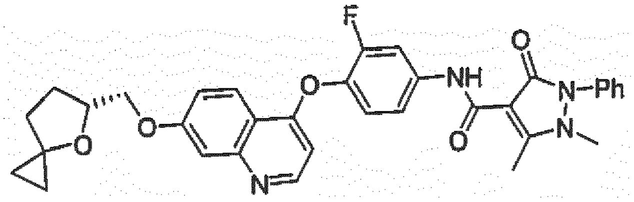


[0159] To a mixture of ((5S)-4-methyl-4-azaspiro[2.4]heptane-5-yl)methyl methanesulfonate (150 mg, 0.685 mmol) and N-(4-(7-hydroxyquinolin-4-yloxy)-3-fluorophenyl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide (331.5 mg, 0.685 mmol) in 8 mL of N,N-dimethylacetamide was added cesium carbonate (893 mg, 2.74 mmol, Aladdin). After stirring at 40 °C for 3 days, the reaction mixture was concentrated *in vacuo* and the residue was chromatographed with a silica gel column (50:1 1 (v/v) CH_2Cl_2 / CH_3OH) to give the desired product as a pale yellow solid (25 mg, 6 %).
MS (ESI, pos. ion) m/z: 304.5 [(M/2)+1]; LC-MS Rt : 3.402 min;
^{1}H NMR (400MHz, $CDCl_3$): δ0.32 (m,1H), 0.52 (m, 1H), 0.71 (m,1H), 0.92 (m, 1H), 1.52 (m, 2H), 1.85 (m, 2H), 3.19 (m, 1H), 2.26 (s, 3H), 2.80 (s, 3H), 3.37 (s, 3H), 4.11 (m, 1H), 4.22 (m, 1H), 6.40 (d, J=5.2Hz, 1H), 7.16 (t, J=8.4Hz, 1H), 7.30 (m, 1H), 7.36 (m, 2H), 7.41 (m, 1H), 7.48 (m, 2H), 7.56 (m, 2H), 7.91 (dd, J=12Hz, 1H), 8.26 (d, J=9Hz, 1H), 8.58 (d, J=5Hz, 1H), 10.88 (s, 1H).

Example 2

N-(4-(7-(((5R)-4-oxaspiro[2.4]heptane-5-yl)methoxyl)quinolin-4-yloxy)-3-fluorophenyl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide

[0160]



Step 1) (S)-tetrahydro-5-oxofuran-2-carboxylic acid

[0161] To a solution of L-glutamic acid (10.07 g, 0.068 mol, J&K CHEMICA) in 20 ml of concd. HCl and 40 mL H_2O was added a solution of $NaNO_2$ (7.0 g, 0.102 mol, *Shantou* Xilong chemical factory) in H_2O (20 mL) slowly at -5 °C. The mixture was continued to stir for 12 hrs at room temperature. The reaction mixture was evaporated *in vacuo* below 50 °C to give yellow oil, which was dissolved in EtOAc. The solid formed was filtered and washed with EtOAc. The filtrate and washing solution were combined, dried over Na_2SO_4. The solvent was concentrated *in vacuo* to give (S)-tetrahydro-5-oxofuran-2-carboxylic acid as pale yellow oil (8.1 g, 91.6 %)^1.
MS (ESI, pos. ion) m/z: 130.9 (M+1);
^{1}H NMR (400MHz, $CDCl_3$): δ2.27 - 2.41 (m, 1H), 2.44 - 2.65 (m, 3H), 5.09 (m,1H), 9.12 - 9.55 (m, 1H).

Step 2) (S)-5-(hydroxymethyl)-dihydrofuran-2(3H)-one

[0162] To a solution of (S)-5-oxo-tetrahydrofuran-2-carboxylic acid (0.6 g, 0.0046 mol) in 10.8 mL of THF was added $BH_3 \cdot Me_2S$ solution (2.76 mL, 0.0055 mol, 2 M in THF, Aldrich) dropwise via a syringe at -20 °C. The mixture was stirred for 12 hrs at room temperature. The reaction was then quenched with aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to furnish the crude product as light yellow oil. (S)-5-(Hydroxymethyl)-dihydrofuran-2(3H)-one was obtained as colorless oil (0.253 g, 47 %) after a silica gel column chromatography purification (100:1 (v/v) $CHCl_3$/ MeOH)^1.

MS (ESI, pos. ion) m/z: 116.9 (M+1);
^{1}H NMR (400MHz, $CDCl_3$): 82.11 - 2.15 (m, 1H), 2.20 - 2.29 (m, 1H), 2.46 - 2.51 (m, 2H), 3.63 (t, 2H), 3.83 - 3.86 (d, J=14.8Hz, 1H), 4.58 - 4.63 (m, 1H).

Step 3) (5S)-5-((tetrahydro-2H-pyran-2-yloxy)methyl)-dihydrofuran-2(3H)-one

[0163] To a mixture of (S)-5-(hydroxymethyl)-dihydrofuran-2(3H)-one (1.78 g, 0.0153 mol) and 3,4-dihydro-2H-pyran (2.62 g, 0.0312 mol, Alfa) in 40 mL of CH_2Cl_2 was added PPTS (0.391 g, 0.00156 mol, Aldrich) slowly. After stirring at rt overnight, the reaction mixture was quenched with 5 mL of water. The mixture was extracted with EtOAc (50 mL×2). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to give pale yellow oil. The crude product was purified by a silica gel column chromatography (3:1 (v/v) petroleum ether / EtOAc) to afford the title compound as colorless oil (2.7 g, 88 %).
MS (ESI, pos. ion) m/z: 200.8 (M+1);
^{1}H NMR (400MHz, $CDCl_3$): δ1.41 - 1.62 (m, 4H),1.64 - 1.75 (m, 2H), 2.11 - 2.19 (m, 1 H), 2.22 - 2.31 (m, 1H), 2.39 - 2.49 (m, 1 H), 2.51 - 2.62 (m, 1H), 3.41 - 3.48 (m, 1H), 3.58 - 3.62 (dd, J_1=3.2 Hz, J_2=14.6 Hz, 1H), 3.74 - 3.79 (m, 1H), 3.85 - 3.92 (dd, J_1=3.2 Hz, J_2=14.4 Hz, 1H), 4.55 - 4.72 (m, 2H).

Step 4) 1-((S)-3-hydroxy-4-(tetrahydro-2H-pyran-2-yloxy)butyl)cyclopropanol

[0164] To a mixture of $Ti(OiPr)_4$ (0.33 mL, 0.001 mol, Ardrich) and (5S)-5-((tetrahydro-2H-pyran-2-yloxy)methyl)-dihydrofuran-2(3H)-one (1.0 g, 0.005 mol) in 18.7 mL of THF was added a solution of 3M EtMgBr in Et_2O (4.3 mL, 0.0125 mol, Aldrich) via a syringe over 3 hrs at 15 °C. After stirring for additional one hour at 15 °C, the reaction was quenched with 20 mL of saturated NH_4Cl solution, filtered and extracted with EtOAc (50 mL×2). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by a silica gel column chromatography to afford 1-((S)-3-hydroxy-4-(tetrahydro-2H-pyran-2-yloxy)butyl)cyclopropanol as colorless oil (0.853 g, 74 %)^2.
MS (ESI, pos. ion) m/z: 253.0 (M+23);
^{1}H NMR (400MHz, $CDCl_3$): δ0.4 - 0.5 (s, 1H), 0.67 - 0.87 (m, 3H), 1.4 -1.9 (m,12H), 3.38 - 3.44 (m, 1H), 3.53 - 3.60 (m, 1H), 3.75 - 3.78 (m, 1H), 3.87 - 3.96 (m, 1H), 4.57 (d, J=2.4 Hz, 1H).

Step 5) (5R)-5-((tetrahydro-2H-pyran-2-yloxy)methyl)-4-oxaspiro[2.4]heptane

[0165] To a solution of 1-((S)-3-hydroxy-4-(tetrahydro-2H-pyran-2-yloxy)butyl)-cyclopropanol (1.73 g, 0.0075 mol) and PPh_3 (2.95 g, 0.0113 mol, Richjoint) in 32 mL of anhydrous THF at rt under N_2 was added DEAD (1.96 g, 0.0113 mol, Aladdin) dropwise via a syringe. The reaction was stirred at 60 °C for 12 hours. The solvent was concentrated *in vacuo.* The red oil was purified by a silica gel column chromatography (8:1 (v/v) n-hexane / EtOAc) to give the title compound as colorless oil (1.1 g, 64 %)^2.
MS (ESI, pos. ion) m/z: 213.0 (M+1);
^{1}H NMR (400MHz, $CDCl_3$):δ 0.4 - 0.6 (m, 2H), 0.75 - 0.95 (s, 2H), 1.4 -1.9 (m, 10H), 3.45 - 3.52 (m, 2H), 3.73 - 3.79 (m, 1H), 3.80 - 3.90 (m, 1H), 4.23 - 4.28 (m, 1H), 4.63 - 4.69 (s, 1H).

Step 6) (5R)-5-(hydroxymethyl)-4-oxaspiro[2.4]heptane

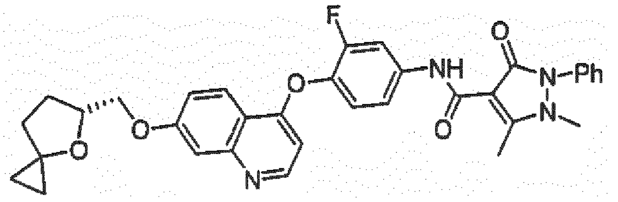
[0166] To a mixture of (5R)-5-((tetrahydro-2H-pyran-2-yloxy)methyl)-4-oxaspiro[2.4]heptane (101 mg, 0.48 mmol) in 5 mL of MeOH was added PPTS (12.1 mg, 0.048 mol, Aldrich) at room temperature. The reaction mixture was stirred at 40 °C overnight and then concentrated *in vacuo.* The residue was purified by a silica gel column chromatography (CH_2Cl_2) to give the title compound as colorless oil (55 mg, 89 %).
^{1}H NMR (400MHz, $CDCl_3$): 50.4 - 0.6 (m, 2H), 0.75 - 0.95 (m, 2H),1.84 - 1.91 (m, 1H), 1.94 -1.98 (m, 2H), 2.07 - 2.13 (m, 1H), 2.27 (s, 1H), 3.56 - 3.70 (m, 2H), 4.16 - 4.18 (m, 1H).

Step 7) ((5R)-4-oxaspiro[2.4]heptane-5-yl)methyl methanesulfonate

[0167] To a mixture of (5R)-5-(hydroxymethyl)-4-oxaspiro[2.4]heptane (116 mg, 0.9 mmol) and Et_3N (183.8 mg, 1.82 mmol, *Shantou* Xilong chemical factory) in dry CH_2Cl_2 (6 mL) at -10 °C under N_2, was added MsCl (203 mg, 1.4 mmol, *Shanghai* Haiqu chemical Ltd.) dropwise via a syringe. After stirring for 2 hrs at rt, the reaction was quenched with water ice (3 mL), and the water phases were extracted with CH_2Cl_2 (20 mL×2). The combined organic phases were dried over Na_2SO_4, and concentrated *in vacuo* to give ((5R)-4-oxaspiro[2.4]heptane-5-yl)methyl methanesulfonate as pale yellow oil.

Step 8) N-(4-(7-(((5R)-4-oxaspiro[2.4]heptane-5-yl)methoxyl)quinolin-4-yloxy)-3-fluorophenyl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide

[0168]



[0169] To a mixture of N-(4-(7-hydroxyquinolin-4-yloxy)-3-fluorophenyl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide (300 mg, 0.62 mmol) and cesium carbonate (1.0 g, 3.1 mmol, Aladdin) in N,N-dimethylacetamide (1 mL) was added ((5R)-4-oxaspiro[2.4]heptane-5-yl)methyl methanesulfonate (187.5 mg, 0.91 mmol) in 3 mL of N,N-dimethylacetamide. After stirring at 40°C for 3 days, the reaction mixture was concentrated *in vacuo* and was chromatographed with a silica gel column (1:6 (v/v) n-hexane / EtOAc) to afford the title compound as a colorless solid (220 mg, 60 %).

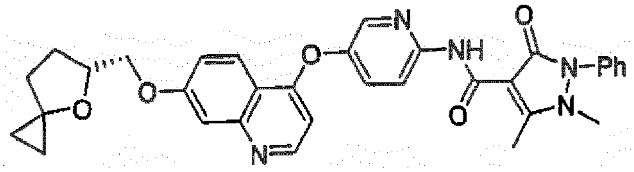
MS (ESI, pos. ion) m/z: 595.7 (M+1); LC-MS Rt: 4.17 min;

^{1}H NMR (400MHz, CDCl$_3$): δ 0.63 (m, 2H), 0.91 (m, 2H), 2.03 (d, J=5.2Hz, 3H), 2.29 (m, 1H), 2.80 (s, 3H), 3.38 (s, 3H), 4.17 (dd, J_1=16Hz, J_2=2.4Hz, 2H), 4.49 (m, 1H), 6.40 (d, J=5.2Hz, 1H), 7.16 (t, 1H), 7.26 (d, J=5.2Hz, 1H), 7.29 (d, J=2Hz, 1H), 7.38 (m, 3H), 7.48 (m, 1H), 7.56 (t, 2H), 7.90 (dd, J_1=14.8Hz, J_2=2.4Hz, 1H), 8.26 (d, J=9.2Hz, 1H), 8.58 (d, J=5.6Hz, 1H), 10.87 (s, 1H).

Example 3

N-(5-(7-(((5R)-4-oxaspiro[2,4]heptane-5-yl)methoxyl)quinolin-4-yloxy)pyridin-2-yl)2,3-dihydro-1,5-methyl-3-oxo-2 phenyl-1H-pyrazol-4-carboxamide

[0170]



[0171] The title compound was prepared according to the procedure described in Example **2** by using N-(5-(7-hydroxyquinolin-4-yloxy)pyridin-2-yl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide (280 mg, 0.69 mmol), cesium carbonate (1.17 g, 3.45 mmol, Aladdin), and ((5R)-4-oxaspiro[2.4]heptane-5-yl)methyl methanesulfonate (204 mg, 0.99 mmol) in DMA (5 mL). The title compound was purified by a silica gel column chromatography (1:8 (v/v) n-hexane / EtOAc) as a colorless solid (110 mg, 27.6 %).

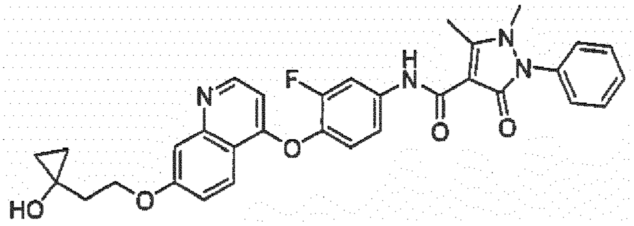
MS (ESI, pos. ion) m/z: 578.1 (M+1); LC-MS Rt: 4.11 min;

^{1}H NMR (400MHz, CDCl$_3$): δ0.55 (m, 2H), 0.92 (m, 2H), 2.03 (m, 3H), 2.31 (m, 1H), 2.81 (s, 3H), 3.38 (s, 3H), 4.18 (m, 2H), 4.52 (m, 1H), 6.43 (d, J=5.6Hz, 1H), 7.28 (d, J=2.4Hz, 1H), 7.30 (d, J=2.4Hz, 1H), 7.39 (m, 3H), 7.51 (m, 4H), 8.23 (t, 1H), 8.38 (d, J=8.8Hz, 1H), 8.60 (d, J=5.6Hz, 1H), 11.25 (s, 1H).

Reference Example 4

N-(3-fluoro-4-(7-(2-(1-hydroxycyclopropyl)ethoxy)quinolin-4-yloxy)phenyl)-1,5-dimethyl-3-oxo-2 phenyl-2.3-dihydro-1H-pyrazole-4-carboxamide

[0172]



Step 1) 3-(tetrahydro-2H-pyran-2-yloxy)propanoic acid

[0173] To a mixture of 3-hydroxypropanoic acid (7.2 g, 80 mmol, TCI, TOKYO KASEI) and DHP (13.4 g, 160 mmol, Alfa) in dichloromethane (100 mL) and THF (100 mL) was added PPTS (2 g, 8 mmol, Aldrich) in portions. The reaction mixture was stirred at rt overnight, and was quenched with 50 mL of saturated $NaHCO_3$ aqueous solution. The resulted mixture was extracted with dichloromethane (50 mL×5). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by a silica gel column chromatography (1:1 (v/v) petroleum ether / EtOAc) to give colorless oil (7.8 g, 56%).
MS (ESI, pos. ion) m/z: 196.9 (M+Na$^+$); (ESI, negative. ion) m/z: 172.8 (M-1).

Step 2) benzyl 3-(tetrahydro:2H-pyran-2-yloxy)propanoate

[0174] To a solution of 3-(tetrahydro-2H-pyran-2-yloxy) propanoic acid (1 g, 5.7 mmol) and TEA (0.863 g, 8.55 mmol, *Shantou* Xilong chemical factory) in 50 mL of CH_2Cl_2 was added BnBr (0.98 g, 5.7 mmol, Aldrich) via a syringe at 0°C. After stirring at rt overnight, the reaction mixture was quenched with 20 mL of water, and was extracted with ethyl acetate (50 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by a silica gel column chromatography (20:1 (v/v) petroleum ether / EtOAc) to give the title compound as colorless oil (270 mg, 18.6%).
MS (ESI, pos. ion) m/z: 287.0 (M+23);
^{1}H NMR (400MHz, $CDCl_3$): δ1.42 -1.79 (m, 6H), 2.65 - 2.68 (t, 2H), 3.48 - 3.80 (dd, J=12.8Hz, 2H), 3.71 - 4.01 (dd, J=12Hz, 2H), 4.61(d, 1H), 5.15 (s, 2H), 3.71 - 7.36 (m, 5H).

Step 3) 1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)cyclopropanol

[0175] To a mixture of benzyl 3-(tetrahydro-2H-pyran-2-yloxy)propanoate (150 mg, 0.568 mmol) in 2 mL of THF was added $Ti(Oi\text{-}Pr)_4$ (0.18 mL, 0.568 mmol, d= 0.955 g/L, Ardrich) via a syringe under nitrogen at rt. After stirring at 18 °C for 30 min, EtMgBr (0.48 mL, 1.42 mmol, 3M ether solution, Aldrich) was added via a syringe pump over 2 hrs. The reaction was quenched with 5 mL of water, after benzyl 3-(tetrahydro-2H-pyran-2-yloxy)propanoate was consumed completely (monitored by TLC). The mixture was filtered through a celite pad and the filtrate was extracted with ethyl acetate (30 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by a silica gel column chromatography (10:1 (v/v) petroleum ether / EtOAc) to afford 1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)cyclopropanol as colorless oil (60 mg, 57 %).
^{1}H NMR (400MHz, $CDCl_3$): δ0.46 (m, 2H), 0.75 - 0.88 (d, 2H),1.55 - 1.83 (m, 6H),1.87 - 1.90 (m, 2H), 3.55 (q, 1H), 3.69 (q, 1H), 3.88 (t, 1H), 4.06 (t, 1H), 4.66 (s, 1H).

Step 4) 1-(2-hydroxyethyl)cyclopropanol

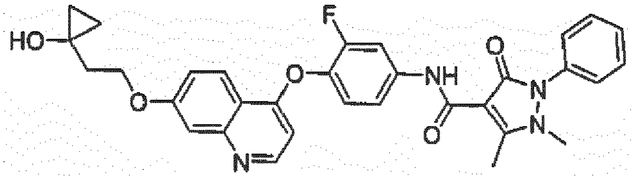
[0176] To a mixture of 1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)cyclopropanol (380 mg, 2.04 mmol) in 20 mL of methanol was added PPTS (51 mg, 0.204 mmol, Aldrich). The reaction mixture was stirred at 40 °C overnight, then treated with 10 mL of water. The resulted mixture was extracted with dichloromethane (20 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by a silica gel column chromatography (10:1 (v/v) petroleum ether / EtOAc) to give the title compound as colorless oil (170 mg, 81.7 %).
^{1}H NMR (400MHz, $CDCl_3$): δ0.55 (t, 2H), 0.85 (t, 2H), 1.85 (t, 2H), 4.02 (t, 2H).

Step 5) 2-(1-hydroxycyclopropyl)ethyl methanesulfonate

[0177] A mixture of 1-(2-hydroxyethyl)cyclopropanol (86 mg, 0.843 mmol) and triethylamine (136 mg, 1.35 mmol, *Shantou* Xilong chemical factory) in 10 mL of dichloromethane was stirred at -10 °C for 30 min. Methanesulfonyl chloride (106 mg, 0.927 mmol, *Shanghai* Haiqu chemical Ltd.) was then added via a syringe. The reaction was stirred at -10 °C for 1 hr at rt and then quenched with 1 mL ice-water. The resulted mixture was extracted with dichloromethane (20 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to afford 2-(1-hydroxycyclopropyl)ethyl methanesulfonate as yellow oil (used in the next step without further purification).

Step 6) N-(3-fluoro-4-(7-(2-(1-hydroxycyclopropyl)ethoxy)quinolin-4-yloxy)phenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H- pyrazole-4-carboxamide

[0178]

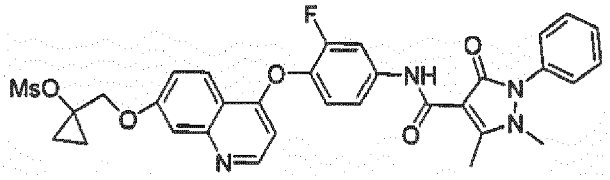


[0179] To a mixture of N-(3-fluoro-4-(7-hydroxyquinolin-4-yloxy)phenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (204 mg, 0.421 mmol) and 2-(1-hydroxycyclopropyl)ethyl methanesulfonate (152 mg, 0.843 mmol) in 8 mL of DMA was added cesium carbonate (1.37 g, 4.2 mmol, Aladdin). After stirring at 40 °C for 1 day, the reaction mixture was concentrated *in vacuo* and the residue was chromatographed with a silica gel column (50:1 (v/v) CH_2Cl_2/ CH_3OH) to afford the title compound as a white solid (60 mg, 25 %).
MS (ESI, pos. ion) m/z: 569.1 (M+1); LC-MS Rt: 3.948 min;
^1H NMR (400MHz, $CDCl_3$): δ0.57 (d, J=8 Hz, 2H), 0.86 (d, J=8 Hz, 2H), 2.14 (t, 2H), 2.80 (s, 3H), 3.37 (s, 3H), 4.43 (t, 2H), 6.41 (d, J=4 Hz, 1H), 7.14 - 7.23 (m, 2H), 7.26 - 7.35 (m, 1H), 7.37 - 7.38 (m, 2H), 7.45 - 7.50 (m, 2H), 7.50 - 7.58 (m, 2H), 7.90 - 7.93 (dd, J=2.4Hz, 1H), 8.27 (d, J=8Hz, 1H), 8.58 (d, J=8Hz, 1H), 10.89 (s, 1H).

Reference Example 5

N-(3-fluoro-4-(7-((1-cyclopropyl methanesulfonate-1-yl)methoxyl)quinolin-4-yloxy)phenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide

[0180]



Step 1) ethyl 2-(tetrahydro-2H-pyran-2-yloxy)acetate

[0181] To a mixture of ethyl 2-hydroxyacetate (2 g, 20 mmol, TCI) and 3,4-dihydro-2H-pyran (3.2 g, 40 mmol, Alfa) in 40 mL of CH_2Cl_2 was added PPTS (500 mg, 2 mmol, Aldrich) in portions at rt. The mixture was stirred at rt for 4 hours. The reaction mixture was then washed with brine, and the organic layer was separated and the combined organic phases were dried over Na_2SO_4, concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (20:1 (v/v) petroleum ether / EtOAc) to give the desired compound as colorless oil (3.01 g, 81 %).
^1H NMR (400MHz, $CDCl_3$): δ 1.25 -1.32 (m, 3H), 1.55 - 1.63 (m, 3H), 1.69 - 1.88 (m, 3H), 3.50 - 3.53 (m, 1H), 3.82 - 3.88 (m, 1H), 4.18 - 4.23 (m, 4H), 4.73 (t, J=3.2Hz, 1H).

Step 2) 1-((tetrahydro-2H-pyran-2-yloxy)methyl)cyclopropanol

[0182] To a mixture of ethyl 2-(tetrahydro-2H-pyran-2-yloxy)acetate (1 g, 5.3 mmol) and Ti(O-*i*Pr)$_4$ (1.06 mL, 3.5 mmol, Aldrich) in 18 mL of THF under N_2 was added EtMgBr (4.5 mL, 13.25 mmol, 3M ether solution, Aldrich) dropwise over 2 hrs, and the temperature must be kept at 15-20 °C. After stirring for 2 hrs, and the reaction mixture was quenched with saturated NH_4Cl aqueous solution at 0°C and extracted with EtOAc (30 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by a silica gel column chromatography (20:1 (v/v) petroleum ether / EtOAc) to afford 1-((tetrahydro-2H-pyran-2-yloxy)methyl)cyclopropanol as colorless oil (500

mg, 55 %).
^{1}H NMR (400MHz, $CDCl_3$): δ 0.51 - 0.67 (m, 2H), 0.77 - 0.85 (m, 2H), 1.55 -1.65 (m, 4H), 1.74 - 1.87 (m, 2H), 3.50 - 3.55 (m, 2H), 3.81 (d, J=11.6Hz, 1H), 3.93 - 3.98 (m, 2H), 4.64 - 4.66 (m, 1H).

Step 3) 1-(hydroxymethyl)cyclopropanol

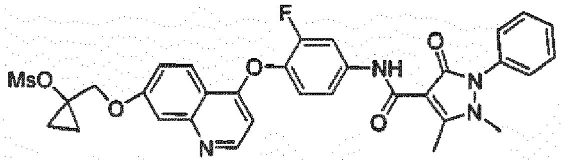
[0183] To a mixture of 1-((tetrahydro-2H-pyran-2-yloxy)methyl)cyclopropanol (420 mg, 2.44 mmol) in 30 mL of MeOH was added PPTS (61 mg, 0.244 mmol, Aldrich) at rt. The reaction mixture was stirred at rt overnight, and then concentrated and purified by a silica gel column chromatography (1:2 (v/v) petroleum ether / EtOAc) to afford 1-(hydroxymethyl)-cyclopropanol as colorless oil (209 mg, 99 %).
^{1}H NMR (400MHz, $CDCl_3$): δ 0.56 (t, J=5.6Hz, 2H), 0.82 (t, J=6Hz, 2H), 3.62 (s, 2H).

Step 4) (1-(methylsulfonyloxy)cyclopropyl)methyl methanesulfonate

[0184] To a mixture of 1-(hydroxymethyl)cyclopropanol (100 mg, 1.14 mmol) and TEA (202 mg, 1.82 mmol, *Shantou* Xilong chemical factory) in 20 mL of dry CH_2Cl_2 under N_2, was added MsCl (156 mg, 1.32 mmol, *Shanghai* Haiqu chemical Ltd.) dropwise via a syringe at -10°C. After stirring for 4 hrs at -10 °C, the mixture was washed with icewater and extracted with CH_2Cl_2 (30 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to give the desired compound as pale yellow oil (139 mg, 50%).

Step 5) N-(3-fluoro-4-(7-((1-cyclopropyl methanesulfonate-1-yl)methoxyl)-quinolin-4-yloxy)phenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide

[0185]

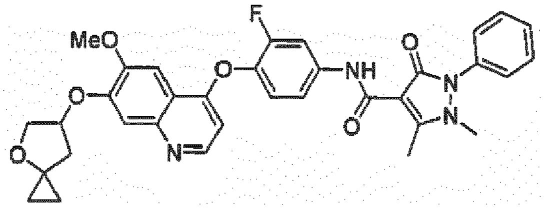


[0186] To a mixture of (1-(methylsulfonyloxy)cyclopropyl)methyl methanesulfonate (122 mg, 0.5 mmol) and N-(4-(7-hydroxyquinolin-4-yloxy)-3-fluorophenyl)-2,5-dihydro-2,3-dimethyl-5-oxo-1-phenyl-1H-pyrazole-4-carboxamide (306 mg, 0.57 mmol) in 3 mL of DMA under N_2 was added Cs_2CO_3 (926 mg, 2.84 mmol, Aladdin) at rt. The mixture was stirred at rt overnight, and then was concentrated *in vacuo.* The residue was purified by a silica gel column chromatography (5:1 (v/v) CH_2Cl_2 / EtOAc) to give the title compound as a white solid (200 mg, 55 %).
MS (ESI, pos. ion) m/z: 633.1 (M+1); LC-MS Rt: 4.178 min;
^{1}H NMR (400MHz, $CDCl_3$): δ 1.09 (t, J=7.2Hz, 2H), 1.54 (t, J=6.8Hz, 2H), 2.80 (s, 3H), 3.07(s, 3H), 3.38 (s, 3H), 4.45 (s, 2H), 6.43 (d, J=4.2Hz, 2H), 7.17 (t, J=8.8Hz, 1H), 7.27 - 7.32 (m, 2H), 7.36 - 7.40 (dd, J=0.2Hz, 3H), 7.49 (d, J=7.2Hz, 1H), 7.57 (t, J=8Hz, 2H), 7.90 - 7.94 (dd, J=2.4Hz, 1H), 8.31 (d, J=4.2Hz, 1H), 8.60 (d, J=4.2Hz, 1H).

Example 6

N-(4-(7-(4-oxaspiro[2.4]heptane-6-yloxy)-6-methoxyl-quinolin4-yloxy)-3-fluorophenyl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide

[0187]



Step 1) 4-(tetrahydro-2H-pyran-2-yloxy)-dihydrofuran-2(3H)-one

[0188] To a mixture of 4-hydroxy-dihydrofuran-2(3H)-one (10 g, 0.1 mol, Alfa) and dihydropyran (12.5 g, 0.15 mol, Alfa) in 250 mL of dry CH_2Cl_2 was added PPTS (2.5 g 0.01 mol), and the reaction mixture was strred at rt overnight. The reaction mixture was washed with brine and extracted with CH_2Cl_2 (100 mL×3), and the combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by a silica gel column chromatography (3:1 (v/v) EtOAc / n-Hexane) to give the title compound as colorless oil (15.6 g, 68%).
^1H NMR (400MHz, $CDCl_3$): δ 1.63 - 1.84 (m, 6H), 2.54 - 2.79 (m, 2H), 3.52 - 3.55 (dd, J=12Hz, 1H), 3.79 - 3.86 (m, 1H), 4.31 - 4.47 (m, 2H), 4.57 - 4.59 (t, J=4Hz, 2H).

Step2) 1-(3-hydroxy-2-(tetrahydro-2H-pyran-2-yloxy)propyl)cyclopropanol

[0189] To a solution of 4-(tetrahydro-2H-pyran-2-yloxy)-dihydrofuran-2(3H)-one (2.23 g, 12 mmol) and Ti(O*i*-Pr)$_4$ (0.68 g, 2.4 mmol, Aldrich) in 40 mL of dry THF at 15 °C under N_2 was added EtMgBr (30 mmol, 10 mL, 3M ether solution, Aldrich) dropwise via a syringe pump over 2 hrs. The temperature of the reaction was always kept below 20 °C. After stirring for 2 hrs, the reaction mixture was quenched with 30 mL of saturated NH_4Cl aqueous solution, and was extracted with ethyl acetate (50 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by a silica gel column chromatography (1:1 (v/v) EtOAc / n-hexane) to afford 1-(3-hydroxy-2-(tetrahydro-2H-pyran-2-yloxy)propyl)cyclopropanol as yellow oil (1.92 g, 73 %).[2]
^1H NMR (400MHz, $CDCl_3$): δ 0.40 - 0.53 (m, 2H), 0.71 - 0.83 (m, 2H), 1.53 - 1.67 (m, 5H), 1.81 - 1.96 (m, 3H), 3.49 - 3.72 (m, 3H), 3.98 - 4.11 (m, 2H), 4.64 - 4.73 (m, 1H).

Step3) 3-(1-hydroxycyclopropyl)-2-(tetrahydro-2H-pyran-2-yloxy)propyl methanesulfonate

[0190] To a mixture of 1-(3-hydroxy-2-(tetrahydro-2H-pyran-2-yloxy)propyl) cyclopropanol (1.0 g, 4.63 mmol) and triethylamine (1 mL, 7.4 mmol, *Shantou* Xilong chemical factory) in 30 mL of CH_2Cl_2 at 0 °C was added methanesulfonyl chloride (0.64 g, 5.6 mmol, *Shanghai* Haiqu chemical Ltd.) via a syringe. The reaction mixture was stirred at 0 °C for 1 hr and then quenched with 5 mL of ice-water. The resulted mixture was extracted with CH_2Cl_2 (50 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to furnish 3-(1-hydroxycyclopropyl)-2-(tetrahydro-2H-pyran-2-yloxy)propyl methanesulfonate as yellow oil (used in the next step immediately without further purification).

Step4) 6-(tetrahydro-2H-pyran-2-yloxy)-4-oxaspiro[2.4]heptane

[0191] A mixture of 3-(1-hydroxycyclopropyl)-2-(tetrahydro-2H-pyran-2-yloxy)propyl methanesulfonate (1.3 g, 4.63 mmol) and NaH (0.15 g, 6 mmol, Aldrich) in 20 mL of THF was stirred at rt for 4 hrs. The reaction mixture was quenched with 5 mL of methanol. The mixture was diluted with 10 mL of water and extracted with ethyl acetate (30 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (1:10 (v/v) EtOAc / petrolum ether) to give the title compound as colorless oil (380 mg, 42 %).
^1H NMR (400MHz, $CDCl_3$): δ 0.45 - 0.63 (dd, J=4.8Hz, 2H), 0.81 - 0.93 (dd, J=4.8Hz, 2H), 1.56 - 2.29 (m, 8H), 3.54 (s, 1H), 3.87 - 4.03 (m, 3H), 4.60 - 4.66 (m, 2H).

Step5) 6-hydroxy-4-oxaspiro[2.4]heptane

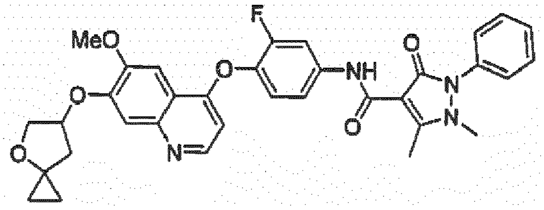
[0192] A mixture of 6-(tetrahydro-2H-pyran-2-yloxy)-4-oxaspiro[2.4]heptane (1.03 g, 5.2 mmol) and PPTS (0.26 g, 1.0 mmol, Aldrich) in methanol (40 ml) was stirred at 40°C for 5 hrs. The reaction mixture was concentrated *in vacuo,* and the residue was purified by a silica gel column chromatography (1:5 (v/v) EtOAc / petroleum ether) to afford 6-hydroxy-4-oxaspiro[2.4]heptane as colorless oil (570 mg, 97 %).
^1H NMR (400MHz, $CDCl_3$): δ 0.47 - 0.65 (m, 2H), 0.81 - 0.96 (m, 2H), 1.89 - 2.35 (m, 2H), 3.80 - 3.96 (m, 2H), 4.59 (s, 1H)

Step 6) (4-oxaspiro[2.4]heptane-6-yl)methanesulfonate

[0193] To a mixture of 6-hydroxy-4-oxaspiro[2.4]heptane (100 mg, 0.88 mmol) and triethylamine (150 mg, 1.5 mmol, *Shantou* Xilong chemical factory) in 5 mL of dichloromethane at 0 °C was added methanesulfonyl chloride (130 mg, 1 mmol, *Shanghai* Haiqu chemical Ltd.) via a syringe. The reaction mixture was stirred at 0 °C for 1 hr and was quenched with 5 mL of ice-water. The resulted mixture was extracted with CH_2Cl_2 (20 mL×3). The combined organic phases were dried over Na_2SO_4 and concentrated in *vacuo* to give the title compound as yellow oil (168 mg, 100 %).

Step7) N-(4-(7-(4-oxaspiro[2.4]heptane-6-yloxy)-6-methoxyquinolin-4-yloxy)-3-fluorophenyl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide

[0194]

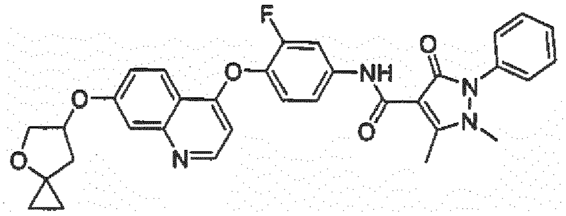


[0195] To a mixture of (4-oxaspiro[2.4]heptane-6-yl)methanesulfonate (168 mg, 0.877 mmol) and N-(4-(7-hydroxy-6-methoxyquinolin-4-yloxy)-3-fluorophenyl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide (300 mg, 0.584 mmol) in 5 mL of N,N-dimethylacetamide was added cesium carbonate (893 mg, 2.74 mmol, Aladdin). After stirring at rt for 4 hrs, the reaction was warmed to 40°C and stirred for 16 hrs. The reaction mixture was concentrated *in vacuo* and chromatographed with a silica gel column (5:1 (v/v) EtOAc / n-hexane) to afford the title compound as a white solid (65 mg, 18%).
MS (ESI, pos. ion) m/z: 611.1 [M+1]; LC-MS Rt: 4.10 min;
^{1}H NMR (400MHz, $CDCl_3$): δ 0.56 - 0.71 (m, 2H), 0.81 -1.02 (m, 2H), 2.33 (m, 1H), 2.55 (m, 1H), 2.81 (s, 3H), 3.38 (s, 3H), 4.03 (s, 3H), 4.21 (m, 2H), 5.24 (t, J=4Hz, 1H), 6.43 (d, J=4Hz, 1H), 7.15 - 7.60 (m, 9H), 7.90 - 7.94 (m, 1H), 8.48 (d, J=4Hz, 1H), 10.89 (s, 1H).

Example 7

N-(4-(7-(4-oxaspiro[2,4]heptane-6-yloxyl)quinolin-4-yloxy)-3-fluorophenyl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide

[0196]

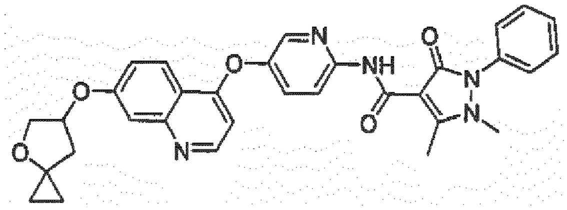


[0197] The title compound was prepared according to the procedure described in Example 6 by using (4-oxaspiro[2.4]heptane-6-yl)methanesulfonate (220 mg, 1.14 mmol), N-(4-(7-hydroxyquinolin-4-yloxy)-3-fluorophenyl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide (300 mg, 0.62 mmol), and cesium carbonate (450 mg, 2.4 mmol, Aladdin) in DMA (6 mL). The title compound was purified by a silica gel column chromatography (5:1 (v/v) EtOAc / n-hexane) and was obtained as a white solid (68 mg, 19 %).
MS (ESI, pos. ion) m/z: 581.1 [M+1]; LC-MS Rt: 4.255 min;
^{1}H NMR (400MHz, $CDCl_3$): δ 0.54 - 0.72 (m, 2H), 0.88 - 1.07 (m, 2H), 2.29 (m, 1H), 2.57 (m, 1H), 2.84 (s, 3H), 3.42 (s, 3H), 4.22 (m, 2H), 5.26 (m, 1H), 6.46 (d, J=4Hz, 1H), 7.18 - 7.63 (m, 9H), 7.96 (m, 1H), 8.33 (d, J=8Hz, 1H), 8.62 (d, J=4Hz, 1H), 10.92 (s, 1H).

Example 8

N-(5-(7-(4-oxaspiro[2.4]heptane-6-yloxy)quinolin-4-yloxy)pyridin-2-yl)-2.3-dihydro-1.5-dimethyl-3 -oxo-2-phenyl-1H-pyrazole-4-carboxamide

[0198]

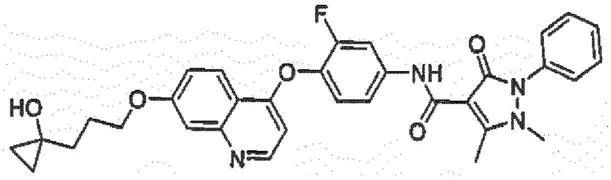


[0199] The title compound was prepared according to the procedure described in Example 6 by using (4-oxaspiro[2.4]heptane-6-yl)methanesulfonate (220 mg, 1.14 mmol), N-(5-(7-hydroxyquinolin-4-yloxy)pyridin-2-yl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide (300 mg, 0.64 mmol), and cesium carbonate (450 mg, 2.4 mmol, Aladdin) in DMA (6 mL). The title compound was purified with a silica gel column chromatography (EtOAc) to give a white solid (140 mg, 39 %).
MS (ESI, pos. ion) m/z: 564.1 [M+1]; LC-MS Rt: 4.007 min;
^{1}H NMR (400MHz, CDCl$_3$): δ 0.59 (m, 2H), 0.91 (m, 2H), 2.25 (d, J=14Hz, 1H), 2.53 (m, 1H), 2.80 (s,3H), 3.37 (s, 3H), 4.18 (m, 2H), 5.22 (t, J=4Hz, 1H), 6.44 (d, J=5Hz, 1H), 7.24 - 7.56 (m, 9H), 8.25 (m, 1H), 8.38 (d, J=9Hz, 1H), 8.60 (d, J=3Hz, 1H), 11.26 (s, 1H).

Reference Example 9

N-(3-fluoro-4-(7-(3-(1-hydroxycyclopropyl)propoxy)quinolin-4-yloxy)phenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide

[0200]



Step1) 1-(3-hydroxypropyl)cyclopropanol

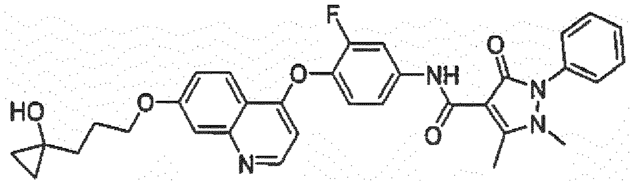
[0201] To a mixture of dihydrofuran-2(3H)-one (2.0 g, 23 mmol, Alfa) and Ti(Oi-Pr)$_4$ (1.32 g, 4.6 mmol, Aldrich) in 80 mL of dry THF at 15 °C under N$_2$ was added EtMgBr (60 mmol, 20 mL, 3M in ether solution, Aldrich) via a syringe pump over 3 hrs. The temperature was always kept below 20°C. After stirring for additional 3 hrs, the reaction mixture was quenched with 60 mL of saturated NH$_4$Cl aqueous solution, and was extracted with ethyl acetate (50 mL×3). The combined organic phases were dried over Na$_2$SO$_4$ and concentrated *in vacuo.* The orange oil residue was purified by a silica gel column chromatography (1:1 (v/v) EtOAc / n-Hexane) to afford 1-(3-hydroxypropyl) cyclopropanol as yellow oil (2.5 g, 93 %).

Step2) 3-(1-hydroxycyclopropyl)propyl methanesulfonate

[0202] A mixture of 1-(3-hydroxypropyl)cyclopropanol (140 mg, 1.2 mmol) and triethylamine (0.3 mL, 2.1mmol, *Shantou* Xilong chemical factory) in 8mL of dichloromethane was stirred at 0 °C for 10 min. To the mixture was added methanesulfonyl chloride (180 mg, 1.6 mmol, *Shanghai* Haiqu chemical Ltd.) via a syringe. The reaction mixture was stirred at 0 °C for 1 hr and then quenched with 2 mL of ice-water. The resulted mixture was extracted with dichloromethane (10 mL×3). The combined organic phases were dried over Na$_2$SO$_4$ and concentrated *in vacuo* to give 3-(1-hydroxycyclopropyl) propyl methanesulfonate as yellow oil.

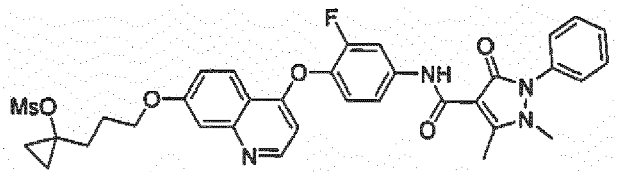
Step3) N-(3-fluoro-4-(7-(3-(1-hydroxycyclopropyl)propoxy)quinolin-4-yloxy)phenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide

[0203]



[0204] To a mixture of 3-(1-hydroxycyclopropyl)propyl methanesulfonate (240 mg, 1.2 mmol) and N-(4-(7-hydroxyquinolin-4-yloxy)-3-fluorophenyl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide (300 mg, 0.62 mmol) in 5 mL of N,N-dimethylacetamide was added cesium carbonate (470 mg, 2.4 mmol, Aladdin). After stirring at rt for 12 hrs, the reaction mixture was warmed to 40 °C and stirred for additional 6 hrs. The reaction mixture was diluted with 20 mL of water and extracted with ethyl acetate (40 mL×3). The combined organic phases were dried over Na_2SO_4, concentrated *in vacuo* and chromatographed with a silica gel column (5:1 (v/v) EtOAc / n-Hexane) to provide the title compound as a white solid (68 mg, 19 %).
MS (ESI, pos. ion) m/z: 583.1 [M+1]; LC-MS Rt: 4.129 min;
^{1}H NMR (400MHz, $CDCl_3$): δ 0.51 (m, 2H), 0.79 (m, 2H), 1.81 (t, J=8Hz, 2H), 2.15 (m, 2H), 2.81 (s, 3H), 3.38 (s, 3H), 4.24 (t, J=8Hz, 2H), 6.41 (d, J=4Hz, 1H), 7.15 - 7.59 (m, 9H), 7.91 (m, 1H), 8.27 (d, J=8Hz, 1H), 8.58 (d, J=4Hz, 1H), 10.87 (s, 1H).

[0205] N-(3-fluoro-4-(7-(3-(1-cyclopropyl-methanesulfonate-1-yl)propoxy)-quinolin-4-yloxy)phenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide was also isolated from the above reaction:

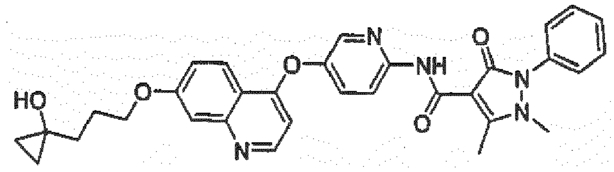


MS (ESI, pos. ion) m/z: 661.1 [M+1]; LC-MS Rt: 4.272 min;
^{1}H NMR (400MHz, $CDCl_3$): δ 0.787 (m, 2H), 1.29 (m, 2H), 2.11 (m, 4H), 2.80 (s, 3H), 3.01 (s, 3H), 3.38 (s, 3H), 4.22 (t, J=6Hz, 2H), 6.41 (d, J=5Hz, 1H), 7.14 - 7.59 (m, 9H), 7.91 (m, 1H), 8.27 (d, J=9Hz, 1H), 8.58 (d, J=5Hz, 1H), 10.88 (s, 1H).

Reference Example 10

N-(5-(7-(3-(1-hydroxycyclopropyl)propoxy)quinolin-4-yloxy)pyridin-2-yl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide

[0206]

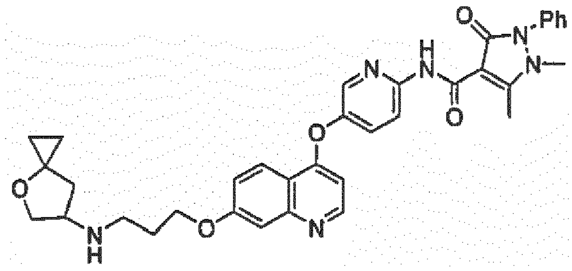


[0207] The title compound was prepared according to the procedure described in Example 9 by using N-(5-(7-hydroxyquinolin-4-yloxy)pyridin-2-yl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (277 mg, 0.593 mmol), Cs_2CO_3 (560 mg, 1.724 mmol, Aladdin), and 3-(1-hydroxycyclopropyl)propyl methanesulfonate (334 mg, 1.724 mmol) in DMA (10 mL). The title compound was purified by a silica gel column chromatography (67:30:1:2 (v/v/v/v) EtOAc / CH_2Cl_2 / CH_3OH / Et_3N) to afford the title compound as a white solid (210 mg, 62.6 %).
MS (ESI, pos. ion) m/z: 566 [M+1]; LC-MS Rt: 3.846 min;
^{1}H NMR (400MHz, $CDCl_3$): δ 0.49 - 052 (t, J=6 Hz, 2H), 0.78 - 0.81 (t, J=6 Hz, 2H), 1.26 (s, 2H), 1.79 - 1.83 (t, J=7.2 Hz, 2H), 2.13 - 2.16 (t, J=7.2 Hz, 2H), 2.81 (s, 3H), 3.38 (s, 3H), 4.23 - 4.26 (t, J=6 Hz, 2H), 6.42 - 6.44 (d, J=5.2 Hz, 1H), 7.20 - 7.23 (q, J_1=9.2 Hz, J_2=2.4 Hz, 1H), 7.37 - 7.39 (d, J=7.6Hz, 1H), 7.42 (s, 1H), 7.44 - 7.57 (m, 4H), 8.22-8.25 (m, 2H), 8.37 - 8.39 (d, J=9.2 Hz, 1H), 8.59 - 8.60 (d, J=5.2 Hz, 1H), 11.26 (s, 1H).

Example 11

N-(5-(7-((4-oxaspiro[2.4]heptane-6-yl)aminopropoxy)quinolin-4-yloxy)pyridin-2-yl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide

[0208]



Step1) (4-oxaspiro[2.4]heptane-6-yl)methanesulfonate

[0209] To a solution of 6-hydroxy-4-oxaspiro[2.4]heptane (200 mg, 1.75 mmol) and Et_3N (530.25 mg, 5.25 mmol) in dry CH_2Cl_2 (8 mL) at -10°C was added MsCl (401.7 mg, 3.5 mmol) dropwise under N_2 atmosphere. After stirring for 2 hrs, the reaction was quenched with ice-water (3 mL), extracted with CH_2Cl_2 (2×10 mL). The combined organic phases were dried over Na_2SO_4, concentrated *in vacuo* to give the title compound as pale yellow oil.

Step2) (4-oxaspiro[2.4]heptane-6-yl)aminopropanol

[0210] To a solution of (4-oxaspiro[2.4]heptane-6-yl)methanesulfonate (336 mg, 1.75 mmol) in dry THF (3 mL) was added 3-aminopropan-1-ol (656.3 mg, 8.75 mmol, TCI). The reaction was refluxed overnight. The mixture was concentrated *in vacuo* to give a brown residue, which was chromatographed with a silica gel column (8:1 (v/v) EtOAc / MeOH) to give the title compound as pale yellow oil (280 mg, 93 %).
MS (ESI, pos. ion) m/z: 171.0 (M+1).
^{1}H NMR (400MHz, $CDCl_3$): δ 0.45 (m, 1H), 0.54 (m, 1H), 0.88 (m, 2H), 1.75 (m, 2H), 1.83 (dd, J_1=4Hz, J_2=16.8Hz, 1H), 2.22 (dd, J_1=7.2Hz, J_2=20Hz, 1H), 2.40 (s, 2H), 3.58 (m, 1H), 3.72 (m, 1H), 3.83 (t, 2H), 3.96 (dd, J_1=14.8Hz, J_2=5.6Hz, 1H).

Step3) tert-butyl N-(4-oxaspiro[2.4]hetane-6-yl)hydroxypropylamino formate

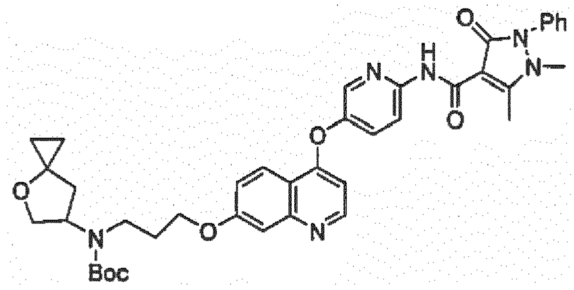
[0211] To a solution of (4-oxaspiro[2.4]heptane-6-yl)aminopropanol (361.9 mg, 2.12 mmol) and Et_3N (535.3 mg, 5.3 mmol) in CH_2Cl_2 (10 mL) at room temperature was added $(Boc)_2O$ (692 mg, 3.17 mmol). The reaction was stirred overnight and was then quenched with water (5 mL). The organic layer was separated and the water layer was extracted with 20 mL of EtOAc. The combined organic phases were dried over Na_2SO_4, concentrated *in vacuo* to give the title compound as pale yellow oil (555.8 mg, 97 %).
MS (ESI, pos. ion) m/z: 272.0 (M+1);
^{1}H NMR (400MHz, $CDCl_3$): δ 0.45 (m, 1H), 0.61 (m, 1H), 0.78 (m, 1H), 0.93 (m, 1H), 1.47 (s, 9H), 1.75 (m, 3H), 2.13 (t, 2H), 3.42 (s, 2H), 3.59 (d, J=5.2Hz, 2H), 3.76 (dd, J_1=5.6Hz, J_2=14.8Hz, 1H), 3.94 (dd, J_1=7.6Hz, J_2=16.4Hz, 1H), 4.71 (s, 1H).

Step4) (N-(4-oxaspiro[2.4]heptane-6-yl)-tert butoxycarbonylamino)propyl methanesulfonate

[0212] To a solution of tert-butyl N-(4-oxaspiro[2.4]heptane-6yl)hydroxypropylamino formate (278 mg, 1.03 mmol) and Et_3N (260 mg, 2.58 mmol) in dry CH_2Cl_2 (10 mL) at -10°C was added MsCl (234.8 mg, 2.06 mmol) dropwise under N_2 atmosphere. After stirring for 2 hrs, the reaction was quenched with ice water (3 mL). The organic phase was separated and the water layer was extracted with 15 mL of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, concentrated *in vacuo* to give the title compound as pale yellow oil.

Step5) N-(5-(7-((N-(4-oxaspiro[2.4]heptane-6-yl)-tert butoxycarbonylamino)propoxy)quinolin-4-yloxy)pyridin-2-yl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide

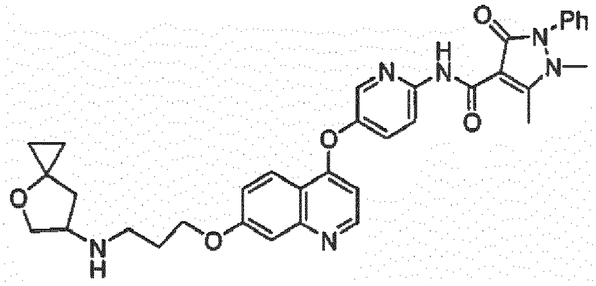
[0213]



[0214] To a solution of N-(5-(7-hydroxyquinolin4-yloxy)pyridin-2-yl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide (200.6 mg, 0.44 mmol) and cesium carbonate (684.6 mg, 2.1 mmol, Aladdin) in N,N-dimethylacetamide (1 mL) was added (N-(4-oxaspiro[2.4]heptane-6-yl)-tert butoxycarbonylamino)propyl methanesulfonate (0.63 mmol) in N,N-dimethylacetamide (5 mL). After stirring at 40°C for 2 days, the reaction mixture was concentrated *in vacuo.* The residue was chromatographed with a silica gel column (1:4 (v/v) n-hexane / EtOAc) to give the title compound as a white solid (200 mg, 62.5 %).
MS (ESI, pos. ion) m/z: 721.2 (M+1); LC-MS Rt: 4.669 min;
^{1}H NMR (400MHz, $CDCl_3$): δ 0.55 (m, 1H), 0.65 (m, 1H), 0.78 (m, 1H), 0.93 (m, 1H), 1.49 (s, 9H), 2.09 (m, 2H), 2.18 (m, 3H), 2.81 (s, 3H), 3.38 (s, 3H), 3.45 (m, 2H), 3.78 (dd, J_1=5.6Hz, J_2=14.8Hz, 1H), 3.95 (m, 1H), 4.16 (t, 2H), 6.43 (d, J=5.6Hz, 1H), 7.22 (dd, J_1=2.4Hz, J_2=11.6Hz, 1H), 7.38 (m, 3H), 7.51(m, 4H), 8.23 (d, J=4.4Hz, 1H), 8.24 (d, J=2Hz, 1H), 8.38 (d, J=9.2Hz, 1H), 8.60 (d, J=5.2Hz, 1H), 11.26 (s, 1H).

Step6) N-(5-(7-((4-oxaspiro[2.4]heptane-6-yl)aminopropoxy)quinolin-4-yloxy)pyridin-2-yl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide

[0215]

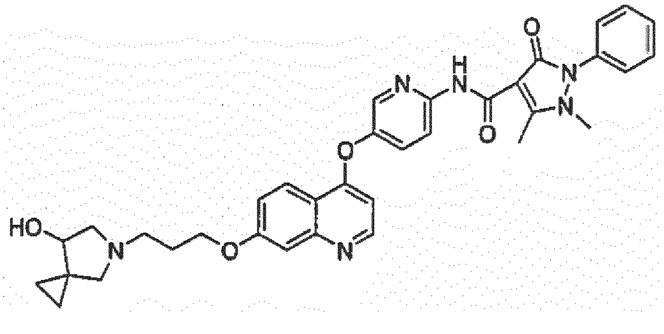


[0216] To a solution of N-(5-(7-((N-(4-oxaspiro[2.4]heptane-6-yl)-tert butoxycarbonylamino)propoxy)quinolin-4-yloxy)pyridin-2-yl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide (50 mg, 0.069 mmol) in dry THF (2 mL) was added 2 M HCl/THF (8 mmol). After stirring at room temperature for 4 hrs, 10 mL of saturated $NaHCO_3$ aqueous solution was added to quench the reaction. The mixture was extracted with EtOAc (15 mL×2). The combined organic phases were dried over Na_2SO_4, concentrated *in vacuo.* The crude product was chromatographed with a silica gel column (5:1 (v/v) EtOAc / MeOH) to give the title compound as a white solid (30 mg, 69 %).
MS (ESI, pos. ion) m/z: 621.2 (M+1); LC-MS Rt: 3.192 min;
^{1}H NMR (400MHz, $CDCl_3$): δ 0.48 (m, 1H), 0.57 (m, 1H), 0.81 (m, 1H), 0.89 (m, 1H), 1.94 (dd, J_1=4Hz, J_2=12Hz, 1H), 2.12 (m, 2H), 2.24 (dd, J_1=7.2Hz, J_2=20Hz, 1H), 2.81 (s, 3H), 2.91 (t, 2H), 3.38 (s, 3H), 3.63 (d, J=6.4Hz, 1H), 3.75 (dd, J_1=3.6Hz, J_2=12.4Hz, 1H), 4.00 (dd, J_1=6.0Hz, J_2=14.8Hz, 1H), 4.24 (t, 2H), 6.43 (d, J=5.2Hz, 1H), 7.22 (dd, J=2.4Hz, J=11.6Hz, 1H), 7.38 (m, 3H), 7.51 (m, 4H), 8.23 (d, J=2.8Hz, 1H), 8.24 (d, J=3.6Hz, 1H), 8.38 (d, J=8.8Hz, 1H), 8.60 (d, J=5.2Hz, 1H), 11.26 (s, 1H).

Example 12

N-(5-(7-(3-(7-hydroxy-5-azaspiro[2.4]heptane-5-yl)propoxy)quinolin-4-yloxy)pyridin-2-yl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide

[0217]



Step1) ethyl 1-acetylcyclopropanecarboxylate

[0218] To a solution of ethyl 3-oxobutanoate (26 g, 200 mmol) in acetone (500 mL) was added potassium carbonate (82.8 g, 600 mmol) followed by 1,2-dibromoethane (45.12 g, 240 mmol). The reaction was refluxed for 24 hrs, then the reaction mixture was filtered. The filtrate was concentrated *in vacuo,* and the residue was purified by a silica gel column chromatography (1:50(v/v)EtOAc/n-hexane) to afford the title compound as colorless oil (18.7 g, 60 %).
MS (ESI, pos. ion) m/z: 157 (M+1);
^{1}H NMR (400MHz, $CDCl_3$): δ 1.25 - 1.29 (t, J=7.2 Hz, 3H), 1.45 (s, 4H), 2.45 (s, 3H), 4.18 - 4.20 (q, 2H).

Step2) ethyl 1-(2-bromoacetyl)cyclopropanecarboxylate

[0219] To a 100 mL of round-bottomed flask was added ethyl 1-acetylcyclo-propanecarboxylate (15.6 g, 100 mmol) and NBS solid (21.36 g, 120 mmol), followed by p-toluene sulfonic acid (1.9 g, 10 mmol). After stirring at rt for 8 hrs, the reaction mixture was extracted with diethyl ether (200 mL) and washed with 80 mL of water. The organic phase was then dried over anhydrous Na_2SO_4 and concentrated *in vacuo.* The residue was purified by a silica gel column chromatography (1:30(v/v)EtOAc/n-hexane) to give the title compound as colorless oil (16.68 g, 71 %).
MS (ESI, pos. ion) m/z: 235,237 (M+1);
^{1}H NMR (400MHz, $CDCl_3$): δ 1.27 (t, J=7.2 Hz, 3H), 1.59 -1.64 (m, 4H), 4.19 - 4.24 (q, J_1=14.4 Hz, J_2=7.2 Hz, 2H), 4.49 (s, 2H).

Step3) 5-((R)-α-methylbenzyl)-4,7-dioxo-5-azaspiro[2.4]heptane

[0220] To a solution of ethyl 1-(2-bromoacetyl)cyclopropanecarboxylate (4.7g, 20 mmol) in THF (60 mL) was added (R)-α-methylbenzylamine (2.9 g, 24 mmol) and Et_3N (4.04 g, 40 mmol). After stirring at rt for 3 days, the reaction mixture was concentrated *in vacuo,* and the residue was extracted with ethyl acetate (50 mL×2) and washed with water (30 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated *in vacuo.* The residue was purified by a silica gel column chromatography (EtOAc) to afford the title compound as a light yellow solid (3.66 g, 80 %).
MS (ESI, pos. ion) m/z: 230 (M+1);
^{1}H NMR (400MHz, $CDCl_3$): δ 1.58 -1.60 (m, 4H), 1.62 - 1.63 (d, J=5.6 Hz, 3H), 3.49 - 3.53 (d, J=17.6 Hz, 1H), 3.83 - 3.88 (d, J=17.6 Hz, 1H), 5.80 - 5.82 (q, 1H), 7.26 - 7.39 (m, 5H).

Step4) 5-((R)-α-methylbenzyl)-7-hydroxy-5-azaspiro[2.4]heptane

[0221] To a suspension of $LiAlH_4$ (0.995 g, 26.2 mmol) in THF (40 mL) was added a solution of 5-((R)-α-methylbenzyl)-4,7-dioxo-5-azaspiro[2.4]heptane (3.0 g, 13.1 mmol) in THF (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 hrs, then warmed up to 50 °C and continued to stir for 6 hrs. The reaction mixture was then cooled to 0 °C and ethyl acetate (10 mL) and water (10 mL) were added. The suspension was filtered and the filtrate was concentrated *in vacuo.* The residue was purified by a silica gel column chromatography (1: 3 (v/v) 2-butanol / n-hexane) to afford the

title compound as colorless oil (2.4 g, 85 %).
MS (ESI, pos. ion) m/z: 218 (M+1);

Step5) 7-hydroxy-5-azaspiro[2.4]heptane

[0222] To a solution of 5-((R)-α-methylbenzyl)-7-hydroxy-5-azaspiro[2.4]heptane (2.4 g, 11.1 mmol) in ethanol (30 mL) was added the catalytic amount of Pd/C. The suspension was then stirred under H_2 for 3 hrs. The suspension was filtered and the filtrate was concentrated *in vacuo* to afford the desired compound as light orange oil (1.23 g, 98 %). The crude product was used for the next step without further purification.
MS (ESI, pos. ion) m/z: 114 (M+1);

Step6) 3-(7-hydroxy-5-azaspiro[2.4]heptane-5-yl)propanol

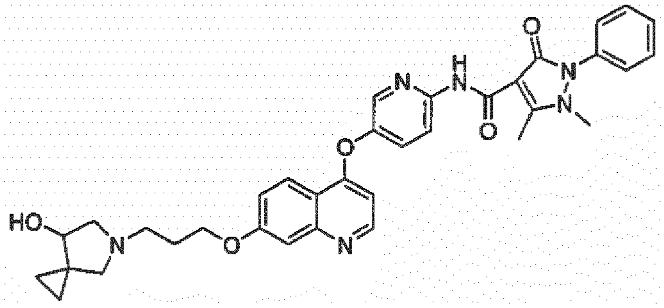
[0223] To a solution of 7-hydroxy-5-azaspiro[2.4]heptane (1.23 g, 11.0 mmol) in THF (40 mL) was added 3-bromopropanol (2.3 g, 16.65 mmol) and Et_3N (2.24 g, 22.2 mmol). The reaction mixture was stirred at rt for 12 hrs and then concentrated *in vacuo.* The residue was purified by a silica gel column chromatography (100: 50: 2(v/vlv)EtOAc /CH_3OH / Et_3N) to afford the desired compound as orange oil (1.14 g, 60 %).
MS (ESI, pos. ion) m/z: 172 (M+1); LC-MS Rt: 0.178 min;
^1H NMR (400MHz, $CDCl_3$): δ 0.59 (m, 1H), 0.62 (m, 1H), 0.70 - 0.72 (m, 1H), 0.87 - 0.92 (m, H), 1.68 - 1.74 (m, 2H), 2.39 - 2.41 (d, J=9.2Hz, 1 H), 2.70 - 2.74 (m, 2H), 2.84 - 2.87 (m, 2H), 2.88 - 2.92 (dd, J_1=10.4Hz, J_2=4.8Hz, 1H), 3.73 - 3.75 (m, 1H), 3.77 - 3.80 (t, J=5.2 Hz, 2H);

Step7) 3-(7-hydroxy-5-azaspiro[2.4]heptane-5-yl)propyl methanesulfonate

[0224] To a solution of 3-(7-hydroxy-5-azaspiro[2.4]heptane-5-yl)propanol (1.14 g, 6.67 mmol) and Et_3N (1.35 g, 13.34 mmol) in CH_2Cl_2 (20 mL) was added methanesulfonyl chloride (1.15 g, 10 mmol) dropwise at 0 °C. The reaction was then stirred at 0 °C for 3 hrs. The reaction mixture was washed with cold water (10 mL) and the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound as orange oil. The crude product was used for the next step without further purification.

Step 8) N-(5-(7-(3-(7-hydroxy-5-azaspiro[2.4]heptane-5-yl)propoxy)quinolin-4-yloxy)pyridin-2-yl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide

[0225]



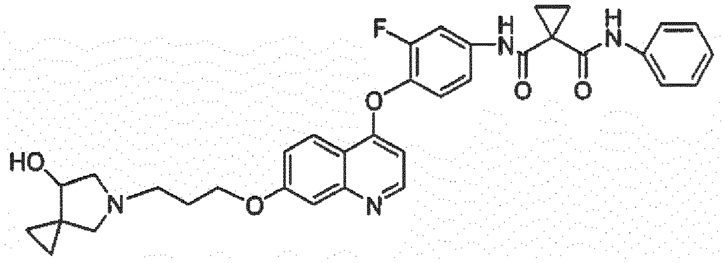
[0226] To a solution of N-(5-(7-hydroxyquinolin-4-yloxy)pyridin-2-yl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (300 mg, 0.642 mmol) in DMA (3 mL) was added 3-(7-hydroxy-5-azaspiro[2.4]heptane-5-yl)propyl methanesulfonate (240 mg, 0.963 mmol) and Cs_2CO_3 (417 mg, 1.284 mmol). The reaction was stirred at rt for 24 hrs. The solvent was removed and the residue was partioned between saturated $NaHCO_3$ aqueous solution (15 mL) and $CHCl_3$ (30 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by a silica gel column chromatography (100: 15: 1(v/v/v)EtOAc /CH_3OH / Et_3N) to afford the title compound as a white solid (259 mg, 65 %).
MS (ESI, pos. ion) m/z: 621(M+1); LC-MS Rt: 3.209 min;
^1H NMR (400MHz, $CDCl_3$): δ 0.63 (m, 1H), 0.67 (m, 1H), 0.76 - 0.79 (m, 1H), 0.96 - 0.99 (m, 1H), 2.11 - 2.14 (m, 2H), 2.47 - 2.50 (d, J=8.4 Hz, 1H), 2.80 (s, 3H), 3.00 - 3.03 (d, J=9.6 Hz, 1H), 3.06 - 3.08 (d, J=10.4 Hz, 1H), 3.37 (s, 5H), 3.76 - 3.77 (d, J=3.6 Hz, 1H), 4.23 - 4.24 (m, 2H), 6.42 - 6.43 (d, J=5.2 Hz, 1H), 7.20 - 7.23 (d, J=8.8 Hz, 1H), 7.36 - 7.38 (d, J=7.6 Hz, 2H), 7.47 - 7.49 (m, 5H), 7.53 - 7.57 (m, 2H), 8.22 - 8.24 (d, J=8.4 Hz, 2H), 8.37 - 8.39 (d, J=9.2 Hz,

1H), 8.58 - 8.59 (d, J=4.8 Hz, 1H), 11.25 (s, 1H)

Example 13

N-(4-(7-(3-(7-hydroxy-5-azaspiro[2.4]heptane-5-yl)propoxy)quinolin-4-yloxy)-3-fluorophenyl)-N-phenylcyclopropane-1,1-dicarboxamide

[0227]

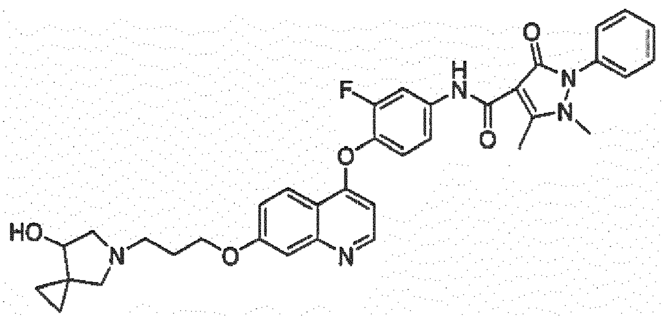


[0228] To a solution of N-(3-fluoro-4-(7-hydroxyquinolin-4-yloxy)phenyl)-N-phenylcyclopropane-1,1-dicarboxamide (240 mg, 0.525 mmol) in DMA (3 mL) was added 3-(7-hydroxy-5-azaspiro[2.4]heptane-5-yl)propyl methanesulfonate (261 mg, 1.05 mmol) and Cs_2CO_3 (512 mg, 1.575 mmol). The reaction was then stirred at rt for 24 hrs. The solvent was removed and the residue was partioned between saturated $NaHCO_3$ (10 mL) aqueous solution and $CHCl_3$ (30 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by a silica gel column chromatography (100: 15: 1(vlvlv)EtOAc / CH_3OH / Et_3N) to afford the desired compound as a white solid (170 mg , 53 %).
MS (ESI, pos. ion) m/z: 611 (M+1);
^{1}H NMR (400MHz, $CDCl_3$): 8 0.59 - 0.60 (m, 1H), 0.62 - 0.65 (m, 1H), 0.73 - 0.78 (m, 1H), 0.92 - 0.96 (m, 1H), 1.58 - 1.62 (q, J_1=8.0 Hz, J_2=4.4 Hz, 2H), 1.81 - 1.94 (m, 2H), 2.05 - 2.88 (m, 2H), 2.38 - 2.40 (d, J=8.4 Hz, 1H), 2.68 - 2.73 (m, 2H), 2.81 - 2.85 (dd, J_1=4.8 Hz, J_2=4.4 Hz, 1H), 2.90 - 2.92 (d, J=8.8 Hz, 1H), 2.96 - 2.98 (d, J=9.2 Hz, 1H), 3.74 - 3.73 (d, J=3.6 Hz, 1H), 4.21 - 4.26 (m, 2H), 6.36 - 6.38 (d, J=5.2 Hz, 1H), 7.18 - 7.24 (m, 2H), 7.26-7.29 (d, J=10.4 Hz, 1H), 7.36 - 7.40 (t, J=8 Hz, 2H), 7.48 - 7.51 (m, 2H), 7.75 - 7.79 (dd, J_1=2 Hz, J_2=2.4 Hz, 1H), 8.05 (s, 1H), 8.24 - 8.26 (d, J=9.2 Hz, 1H), 8.56 - 8.58 (d, J=5.2 Hz, 1H), 10.19 (s, 1H).

Example 14

N-(4-(7-(3-(7-hydroxy-5-azaspiro[2.4]heptane-5-yl)propoxy)quinolin-4-yloxy)-3-fluorophenyl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide

[0229]



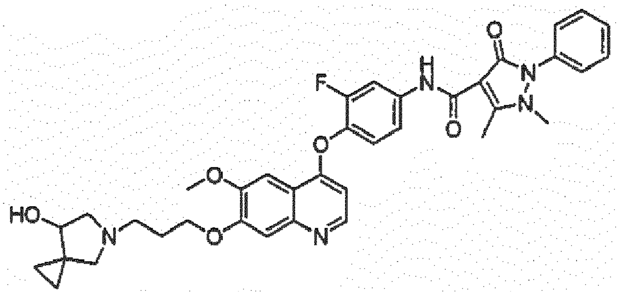
[0230] To a solution of N-(3-fluoro-4-(7-hydroxyquinolin-4-yloxy)phenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (200 mg, 0.413 mmol) in DMA (3 mL) was added 3-(7-hydroxy-5-azaspiro[2.4]heptane-5-yl)propyl methanesulfonate (154 mg, 0.619 mmol) and Cs_2CO_3 (268 mg, 0.826 mmol). The reaction was then stirred at rt for 40 hrs. The solvent was removed and the residue was partioned between saturated $NaHCO_3$ aqueous solution (10 mL) and $CHCl_3$ (25 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue

was purified by a silica gel column chromatography (100: 15: 1(v/v/v)EtOAc / CH_3OH / Et_3N) to afford a pale yellow solid (192 mg, 73 %).
MS (ESI, pos. ion) m/z: 638 (M+1); LC-MS Rt: 3.140 min;
^1H NMR (400MHz, $CDCl_3$): δ 0.63 - 0.65 (m, 1H), 0.67 - 0.69 (m, 1H), 0.76 - 0.81 (m, 1H), 0.98 - 1.02 (m, 1H), 2.08 - 2.17 (m, 2H), 2.54 - 2.57 (d, J=9.2 Hz, 1H), 2.80 (s, 3H), 2.81 (m, 2H), 2.98 - 3.02 (dd, J_1=4.8 Hz, J_2=4.4 Hz, 1H), 3.08 - 3.10 (d, J=9.2 Hz, 1H), 3.12 - 3.14 (d, J=9.6 Hz, 1H), 3.38 (s, 3H), 3.79 - 3.80 (d, J=4.8 Hz, 1H), 4.21 - 4.25 (m, 2H), 6.40 - 6.42 (d, J=5.2 Hz, 1H), 7.14 - 7.17 (d, J=8.4 Hz, 1H), 7.19 - 7.22 (dd, J_1=9.6 Hz, J_2=2.4 Hz, 1H), 7.29 - 7.31 (d, J=4.8 Hz, 1H), 7.36 - 7.37 (d, J=6 Hz, 2H), 7.47 - 7.50 (m, 2H), 7.55 - 7.59 (q, J=7.6 Hz, 2H), 7.90 - 7.94 (dd, J_1-12.4 Hz, J_2=2.4 Hz, 1H), 8.25 - 8.28 (d, J=9.2 Hz, 1H), 8.57 - 8.58 (d, J=9.2 Hz, 1H), 10.883 (s, 1H).

Example 15

N-(4-(7-(3-(7-hydroxy-5-azaspiro[2.4]heptane-5-yl)propoxy)-6-methoxyquinolin-4-yloxy)-3-fluorophenyl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide

[0231]

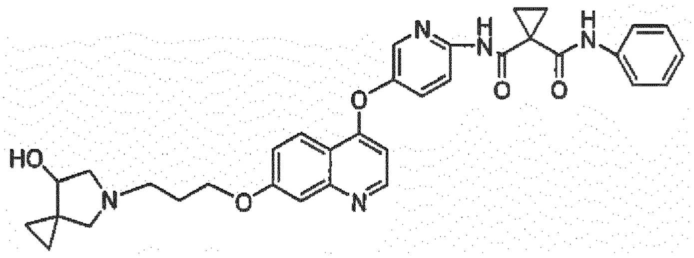


[0232] To a solution of N-(3-fluoro-4-(7-hydroxy-6-methoxyquinolin-4-yloxy)phenyl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (200 mg, 0.389 mmol) in DMA (2 mL) was added 3-(7-hydroxy-5-azaspiro[2.4]heptane-5-yl)propyl methanesulfonate (193 mg, 0.778 mmol) and Cs_2CO_3 (379 mg, 1.167 mmol). The reaction was then stirred at rt for 40 hrs. The solvent was removed and the residue was partioned between saturated $NaHCO_3$ aqueous solution (10 mL) and $CHCl_3$ (30 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and the residue was purified by a silica gel column chromatography (100: 15: 1(v/v/v)EtOAc / CH_3OH / Et_3N) to afford the desired compound as a pale yellow solid (171 mg, 66 %).
MS (ESI, pos. ion) m/z: 668 (M+1); LC-MS Rt: 3.421 min;
^1H NMR (400MHz, $CDCl_3$): δ 0.72 - 0.77 (m, 2H), 0.82 - 0.85 (m, 1H), 1.08 - 1.12 (m, 1H), 2.35 - 2.38 (m, 2H), 2.75 (m, 2H), 2.80 (s, 3H), 2.83 - 2.86 (d, J=6 Hz, 1H), 3.17 - 3.18 (m, 1H), 3.38 (s, 3H), 3.41 - 3.46 (t, J=10 Hz, 2H), 3.86 - 3.88 (d, J=4.8 Hz, 1H), 4.02 (s, 3H), 4.30 (m, 2H), 6.43 - 6.44 (d, J=5.2 Hz, 1H), 7.15 - 7.19 (t, J=8.8 Hz, 1H), 7.29 - 7.31 (d, J=8.8 Hz, 1H), 7.35 - 7.37 (d, J=7.2 Hz, 2H), 7.46 - 7.50 (m, 2H), 7.55 - 7.59 (m, 3H), 7.90 - 7.94 (dd, J_1=8.8 Hz, J_2=8.8 Hz, 1H), 8.45 - 8.47 (d, J=5.2 Hz, 1H), 10.89 (s, 1H).

Example 16

N-(5-(7-(3-(7-hydroxy-5-azaspiro[2.4]heptane-5-yl)propoxy)quinolin-4-yloxy)pyridin-2-yl)-N-phenylcyclopropane-1,1-dicarboxamide

[0233]

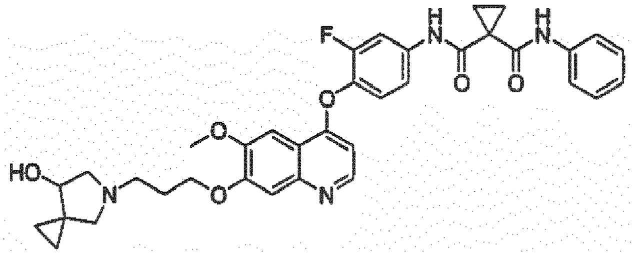


[0234] To a solution of N-(5-(7-hydroxyquinolin-4-yloxy)pyridin-2-yl)-N-phenylcyclopropane-1,1-dicarboxamide (110 mg, 0.25 mmol) in DMA (2 mL) was added 3-(7-hydroxy-5-azaspiro[2.4]heptane-5-yl)propyl methanesulfonate (125 mg, 0.50 mmol) and Cs_2CO_3 (243 mg, 0.75 mmol). The reaction was then stirred at rt for 24 hrs. The solvent was removed and the residue was partioned between saturated $NaHCO_3$ aqueous solution (10 mL) and $CHCl_3$ (30 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (100: 15: 1(v/v/v)EtOAc / CH_3OH / Et_3N) to afford the desired compound as a pale yellow solid (110 mg, 75 %).
MS (ESI, pos. ion) m/z: 594 (M+1);
^1H NMR (400MHz, $CDCl_3$): δ 0.55 (m, 1H), 0.62 (m, 1H), 0.77 (m, 1H), 0.92 - 0.96 (m, 1H), 1.66 - 1.69 (q, J_1=7.2 Hz, J_2=8.4 Hz, J_3=4.4 Hz, J_4=5.6 Hz, 2H), 1.78 - 1.81 (q, J_1=7.2 Hz, J_2=8.4 Hz, J_3=4.4 Hz, J_4=5.6 Hz, 2H), 2.04 - 2.09 (m, 2H), 2.36 - 2.38 (d, J=8.8 Hz, 1H), 2.66 - 2.72 (m, 2H), 2.79 - 2.83 (dd, J_1=J_2=10 Hz, J_3=J_4=4.8 Hz, 1H), 2.87 - 2.89 (d, J=8.8 Hz, 1 H), 2.93 - 2.95 (d, J=9.6 Hz, 1H), 3.73 - 3.74 (d, J=4.4 Hz, 1H), 4.19 - 4.25 (m, 2H), 6.38 - 6.40 (d, J=5.2 Hz, 1H), 7.11 - 7.15 (t, J_1=8.8 Hz, J_2=7.2 Hz, 1H), 7.21 - 7.24 (dd, J_1=J_2=9.2 Hz, J_3=J_4=2.8 Hz, 1H), 7.31 - 7.35 (t, J_1=J_2=7.2 Hz, 2H), 7.50 - 7.51 (d, J=2.8 Hz, 1H), 7.55 - 7.58 (m, 3H), 8.18 - 8.21 (d, J=9.2 Hz, 1H), 8.23 - 8.23 (d, J=2.4 Hz, 1H), 8.27 - 8.29 (d, J=9.2 Hz, 1H), 8.58 - 8.59 (d, J=5.2 Hz, 1H).

Example 17

N-(4-(7-(3-(7-hydroxy-5-azaspiro[2.4]heptane-5-yl)propoxy-methoxyquinolin-4-yloxyl)-3-fluorophenyl)-N-phenylcyclopropane-1,1-dicarboxamide

[0235]

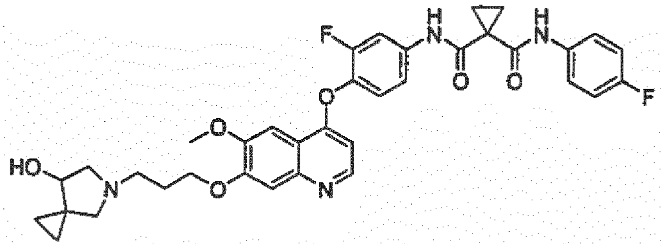


[0236] To a solution of N-(3-fluoro-4-(7-hydroxy-6-methoxyquinolin-4-yloxy)phenyl)-N-phenylcyclopropane-1,1-dicarboxamide (260 mg, 0.534 mmol) in DMA (3 mL) was added 3-(7-hydroxy-5-azaspiro[2.4]heptane-5-yl)propyl methanesulfonate (266 mg, 1.068 mmol) and Cs_2CO_3 (520 mg, 1.602 mmol). The reaction was then stirred at rt for 2 days. The solvent was removed and the residue was partioned between saturated $NaHCO_3$ aqueous solution (15 mL) and $CHCl_3$ (30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (100: 15: 1(v/v/v)EtOAc / CH_3OH / Et_3N) to afford the desired compound as a pale yellow solid (264 mg, 77 %).
MS (ESI, pos. ion) m/z: 641(M+1); LC-MS Rt: 3.439 min;
^1H NMR (400MHz, $CDCl_3$): δ 0.61 (m, 2H), 0.75 (m, 1H), 0.96 (m, 1H), 1.59 - 1.62 (q, J_1=7.2 Hz, J_2=8 Hz, J_3=4.4 Hz, J_4=5.2 Hz, 2H), 1.81 - 1.84 (q, J_1=7.6 Hz, J_2=8.4 Hz, J_3=4.4 Hz, J_4=5.2 Hz, 2H), 2.07 - 2.15 (m, 2H), 2.36 - 2.38 (d, J=8.8 Hz, 1H), 2.64 - 2.73 (m, 2H), 2.76 - 2.80 (dd, J_1=9.6 Hz, J_2=9.2 Hz, J_3=4.4 Hz, J_4=4.8 Hz, 1H), 2.92 - 2.94 (d, J=8.8 Hz, 1H), 2.99 - 3.02 (d, J=10 Hz, 1H), 3.73 - 3.74 (d, J=3.6 Hz, 1H), 4.041 (s, 3H), 4.30 - 4.32 (m, 2H), 6.38 - 6.39 (d, J=5.2 Hz, 1H), 7.19 - 7.23 (t, J_1=8.8 Hz, J_2=8 Hz, 1H), 7.30 - 7.30 (d, J=6.4 Hz, 1H), 7.36 - 7.40 (t, J_1=8.4 Hz, J_2=7.6 Hz, 2H), 7.48 - 7.50 (d, J=9.6 Hz, 2H), 7.56 (s, 1H), 7.70 (s, 1H), 7.76 - 7.80 (dd, J_1=J_2=12 Hz, J_3=J_4=2.4 Hz, 1H), 8.15 (s, 1H), 8.45 - 8.46 (d, J=5.2 Hz, 1H), 10.24 (s, 1H).

Example 18

N-(4-(7-(3-(7-hydroxy-5-azaspiro[2.4]heptane-5-yl)proproxy)-6-methoxyquinolin-4-yloxy)-3-fluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

[0237]

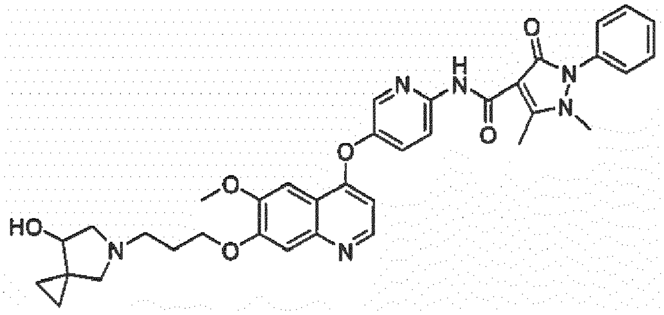


[0238] To a solution of N-(3-fluoro-4-(7-hydroxy-6-methoxyquinolin-4-yloxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (240 mg, 0.475 mmol) in DMA (3 mL) was added 3-(7-hydroxy-5-azaspiro[2.4]heptane-5-yl)propyl methanesulfonate (236 mg, 0.95 mmol) and Cs_2CO_3 (463 mg, 1.425 mmol). The reaction was then stirred at rt for 2 days. The solvent was removed and the residue was partioned between saturated $NaHCO_3$ aqueous solution (15 mL) and $CHCl_3$ (30 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated *in vacuo.* The residue was purified by a silica gel column chromatography (100: 15: 1(v/v/v)EtOAc / CH_3OH / Et_3N) to afford the desired compound as a white solid (250 mg, 80%).
MS (ESI, pos. ion) m/z: 659 (M+1);
^{1}H NMR (400MHz, $CDCl_3$): δ 0.58 - 0.66 (m, 2H), 0.74 - 0.78 (m, 1H), 0.95 - 1.00 (m, 1H), 1.62 1.65 (q, J_1=7.6 Hz, J_2=8.4 Hz, J_3=4.4 Hz, J_4=5.2 Hz, 2H), 1.79 - 1.82 (q, J_1=7.2 Hz, J_2=8.4 Hz, J_3=4.4 Hz, J_4=5.6 Hz, 2H), 2.05 - 2.16 (m, 2H), 2.39 - 2.42 (d, J=8.8 Hz, 1H), 2.68 - 2.77 (m, 2H), 2.80 - 2.83 (dd, J_1=J_2=10 Hz, J_3=J_4=4.8 Hz, 1H), 2.96 - 2.98 (d, J=8.8 Hz, 1H), 3.03 - 3.05 (d, J=10 Hz, 1H), 3.74 - 3.75 (d, J=3.6 Hz, 1H), 4.04 (s, 3H), 4.30 - 4.31 (m, 2H), 6.38 - 6.39 (d, J=5.6 Hz, 1H), 7.05 - 7.08 (d, J=6.4Hz, 2H), 7.19 - 7.23 (t, J_1=J_2=8.4 Hz, 1H), 7.27 - 7.29 (d, J=9.6 Hz, 1H), 7.41 - 7.47 (q, J_1=J_2=6.8 Hz, J_3=J_4=4.8 Hz, 1H), 7.56 (s, 1H), 7.69 (s, 1H), 7.75 - 7.78 (dd, J_1=J_2=12 Hz, J_3=J_4=2.4 Hz, 1H), 8.38 (s, 1H), 8.44 - 8.46 (d, J=5.6 Hz, 1H).

Example 19

N-(5-(7-(3-(7-hydroxy-5-azaspiro[2.4]heptane-5-yl)propoxy)-6-methoxyquinolin-4-yloxy)pyridin-2-yl)-2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazole-4-carboxamide

[0239]

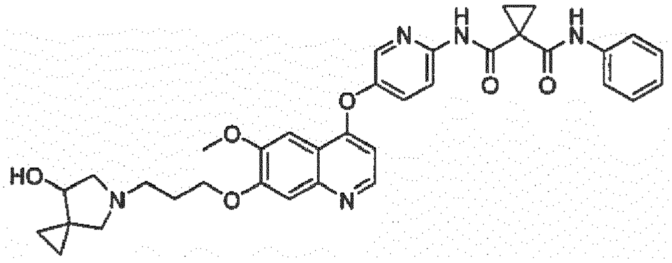


[0240] To a solution of N-(5-(7-hydroxy-6-methoxyquinolin-4-yloxy)pyridin-2-yl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (200 mg, 0.402 mmol) in DMA (4 mL) was added 3-(7-hydroxy-5-azaspiro[2.4]heptane-5-yl)propyl methanesulfonate (150 mg, 0.603 mmol) and Cs_2CO_3 (261 mg, 0.804 mmol). The reaction was then stirred at rt for 24 hrs. The solvent was removed and the residue was partioned between saturated $NaHCO_3$ aqueous solution (5 mL) and $CHCl_3$ (25 mL). The organic layer was separated, dried over anhydrous Na_2SO_4. filtered and the filtrate was concentrated *in vacuo.* The residue was purified by a silica gel column chromatography (100: 15: 1 (v/v/v)EtOAc / CH_3OH / Et_3N) to afford the desired compound as a pale yellow solid (165 mg, 63 %).
MS (ESI, pos. ion) m/z: 651(M+1); LC-MS Rt: 3.296 min;
^{1}H NMR (400MHz, $CDCl_3$): δ 0.78 (m, 1H), 0.79 (m, 1H), 0.86 (m, 1H), 0.90 (m, 1H), 1.10 (s, 3H), 1.37 (m, 2H), 1.40 (s, 2H), 1.43 (s, 2H), 2.80 (d, 3H), 3.14 (m, 2H), 3.38 (s, 3H), 4.02 (s, 3H), 4.29 (s, 1H), 6.46 (d, J=5.2 Hz, 1H), 7.36 - 7.39 (d, 2H), 7.46 - 7.57 (m, 6H), 8.24 (d, J=2.8 Hz, 1H), 8.38 (d, J=9.2 Hz, 1H), 8.49 (d, J=5.2 Hz, 1H), 11.28 (s, 1H).

Example 20

N-(5-(7-(3-(7-hydroxy-5-azaspiro[2.4]heptane-5-yl)propoxy)-6-methoxyquinolin-4-yloxy)pyridin-2-yl)-N-phenylcyclopropane-1,1-dicarboxamide

[0241]

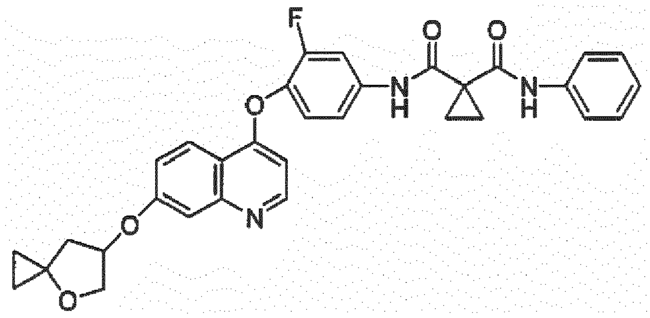


[0242] To a solution of N-(5-(7-hydroxy-6-methoxyquinolin-4-yloxy)pyridin-2-yl)-1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carboxamide (300 mg, 0.640 mmol) in DMA (4 mL) was added 3-(7-hydroxy-5-azaspiro[2.4]heptane-5-yl)propyl methanesulfonate (239 mg, 0.960 mmol) and Cs_2CO_3 (416 mg, 1.280 mmol). The reaction was then stirred at rt for 48 hrs. The solvent was removed and the residue was partioned between saturated $NaHCO_3$ aqueous solution (5 mL) and $CHCl_3$ (25 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated *in vacuo.* The residue was purified by a silica gel column chromatography (100: 15: 1 (v/v/v)EtOAc / CH_3OH / Et_3N) to afford the desired compound as a pale yellow solid (240 mg, 60 %).
MS (ESI, pos. ion) m/z: 624 (M+1);
^1H NMR (400MHz, $CDCl_3$): δ 0.71 (m, 2H), 0.85 (m, 2H), 1.25 (m, 2H), 1.42 (m, 2H), 1.69 (m, 2H), 1.79 (m, 2H), 2.23 (m, 2H), 3.12 (dd, 1H), 3.25 (m, 2H), 3.82 (d, 1H), 4.03 (s, 3H), 4.32 (m, 2H), 6.42 (d, J=5.2 Hz, 1H), 7.15 (t, J_1=8.8 Hz, J_2=7.2 Hz, 1H), 7.30 (dd, J_1=J_2=9.2 Hz, J_3=J_4=2.9 Hz, 1H), 7.37 (t, J_2=J_2=7.2 Hz, 2H), 7.52 (d, J=2.8 Hz. 1H), 7.56 (m, 4H), 8.30 (d, J=9.2 Hz, 1H), 8.49 - 8.23 (d, J=2.4 Hz, 1H), 9.41 (s, 1H).

Example 21

N-(4-(7-(4-oxaspiro[2.4]heptane-6-yloxy)quinolin-4-yloxy)-3-fluorophenyl)-N-phenylcyclopropane-1,1-dicarboxamide

[0243]



Step1) diethyl cyclopropane-1,1-dicarboxylate

[0244] To a solution of diethyl malonate (3.2 g, 20 mmol) and anhydrous potassium carbonate powder (6.9 g, 50 mmol) in DMF (50.0 mL) was added 1,2-dibromoethane (4.136 g, 22 mmol). After stirring for 2 hrs, catalytic amount of TBAI (0.738 g, 2.0 mmol) was added and the mixture was continued to stir at room temperature for 8 hrs. The reaction mixture was filtered and the solid was washed with diethyl ether 3 times. The filtrate was diluted with water (200 mL) and extracted with diethyl ether (75 mL×4). The combined organic phases were washed with 70 mL of brine, dried over Na_2SO_4 and concentrated *in vacuo.* The residue was chromatographed with a short alumina column (1: 10 (v/v) EtOAc / n-hexane) to afford the desired compound as yellow oil (3.3 g, 88.7%).
^1H NMR (400MHz, $CDCl_3$): δ 1.27 (m, J=6.8Hz, 6H), 1.42 (m, 4H), 4.18 (m, 4H).

Step2) 1-(ethoxycarbonyl)cyclopropanecarboxylic acid

[0245] To a solution of diethyl cyclopropane-1,1-dicarboxylate (4.77 g, 25.6 mmol) in ethanol (40 mL) was added KOH (1.43 g, 25.6 mmol) in H_2O (8 mL), and the reaction mixture was stirred at room temperature overnight The ethanol was removed under reduced pressure. The residue was neutralized with HCl (6 mL, 5 mol/L), then extracted with EtOAc (100 mL×3). The combined organic phases were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to give the title compound as a white solid (3.58 g, 88.4 %).
^1H NMR (400MHz, $CDCl_3$): δ 1.27 (t, J=6.7Hz, 3H), 1.83 (m, 2H), 1.86 (m, 2H), 4.25 (m, 2H).

Step3) ethyl 1-(phenyl carbamoyl)cyclopropane carboxylate

[0246] To a solution of 1-(ethoxycarbonyl)cyclopropane carboxylic acid (7.4 g, 46.84 mmol) in dry CH_2Cl_2 (70 mL) was added HATU (35.62 g, 93.67 mmol) at 0 °C. After stirring for 10 minutes, a solution of the aniline (8.71 g, 93.67 mmol) and Et_3N (9.48 g, 93.67 mmol) in dry CH_2Cl_2 (30 mL) was then added and the reaction mixture was continued to stir at 40 °C for 24 hrs. The reaction mixture was quenched with water (30 mL) and extracted with CH_2Cl_2 (100 mL×3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated *in vacuo.* The residue was chromatographed with a silica gel column (1: 5 (v/v) EtOAc / n-hexane) to afford the title compound as a pale yellow solid (9.7 g, 89 %).
^1H NMR (400MHz, $CDCl_3$): δ 1.27 (t, J=6.8Hz, 3H), 1.76 (m, 2H), 1.85 (m, 2H), 4.20 (m, 2H), 6.68 - 6.71 (m, 1H), 7.32 - 7.35 (m, 2H), 7.57 - 7.60 (m, 2H), 10.88 (s, 1H).

Step4) 1-(phenylcarbamoyl)cyclopropanecarboxylic acid

[0247] To a solution of ethyl 1-(phenol carbamoyl)cyclopropane carboxylate (13 g, 55.79 mmol) in ethanol / THF (1/1, 100 mL) was added KOH (4.69 g, 83.69 mmol) in H_2O (8 mL) and the mixture was stirred at room temperature overnight. The ethanol and THF were removed under reduced pressure. The residue was neutralized with HCl (5 mol/L, 20 mL), and extracted with EtOAc (150 mL×3). The combined organic phases were dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to afford the title compound as a white solid (10.1 g, 88.6 %).
^1H NMR (400MHz, $CDCl_3$): δ 1.77 (m, 2H), 1.84 (m, 2H), 7.10 (m, 1H), 7.3 - 7.34 (m, 2H), 7.53 - 7.55 (m, 2H), 10.61 (s, 1H).

Step5) N-(4-(7-(benzyloxy)quinolin-4-yloxy)-3-fluorophenyl)-N-phenylcyclopropane-1,1-dicarboxamide

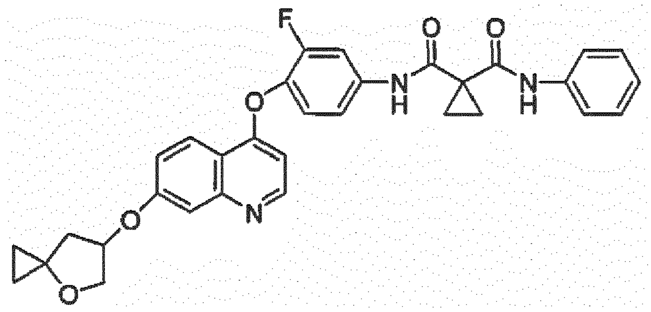
[0248] To a solution of 1-(phenylcarbamoyl)cyclopropanecarboxylic acid (1.14 g, 5.6 mmol) in dry CH_2Cl_2 (8 mL) was added HATU (2.11 g, 5.6 mmol) at 0 °C. After stirring for 10 minutes, a solution of the 4-(7-(benzyloxy)quinolin-4-yloxy)-3-fluorobenzenamine (1.0 g, 2.8 mmol) and Et_3N (0.7 g, 6.9 mmol) in dry CH_2Cl_2 (5 mL) was added. The reaction mixture was stirred at 40 °C for 24 hrs, quenched with water (10 mL), and extracted with CH_2Cl_2 (30 mL×3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated *in vacuo.* The residue was chromatographed with a silica gel column (1:1 (v/v) EtOAc / n-hexane) to afford the title compound as a white solid (1.3 g, 85 %).
MS (ESI, pos. ion) m/z: 548 (M+1); LC-MS Rt: 4.595 min;
^1H NMR (400MHz, $CDCl_3$): δ 1.60 (m, 2H), 1.83 (m, 2H), 5.25 (s, 2H), 6.45 (m, 1H), 7.28 - 7.29 (m, 1H), 7.16 - 7.24 (m, 2H), 7.34 - 7.57 (m, 10H), 7.78 - 7.81 (m, 1H), 7.99 (s, 1H), 8.30 (d, J=9.2Hz, 1H), 8.60 (d, J=6Hz, 1H), 10.29 (s, 1H).

Step6) N-(4-(7-hydroxyquinolin-4-yloxy)-3-fluorophenyl)-N-phenylcyclopropane-1,1-dicarboxamide

[0249] A solution of N-(4-(7-(benzyloxy)quinolin-4-yloxy)-3-fluorophenyl)-N-phenyl-cyclopropane-1,1-dicarboxamide (0.7 g, 1.28 mmol) and Pd/C (0.8 g) in methanol (20 mL) under H_2 was stirred at room temperature for 1.5 hrs, then the reaction mixture was filtered and washed with methanol (3×10 mL). The combined organic solvent was concentrated *in vacuo* to give N-(5-(7-hydroxy-quinolin-4-yloxy)pyridin-2-yl)-N-phenylcyclopropane-1,1-dicarboxamide as a white solid (0.53 g, 90.6 %).
MS (ESI, pos. ion) m/z: 457 (M+1); LC-MS Rt: 3.936 min;
^1H NMR (400MHz, MeOD): δ 1.66 (s, 1H), 6.81 (d, J=6.4Hz, 1H), 7.14 (t, J=7.6Hz, 1H), 7.33 (m, 3H), 7.41 - 7.48 (m, 3H), 7.55 (d, J=8Hz, 2H), 7.92 (d, J=12.8Hz, 1H), 8.49 (d, J=8.8Hz, 1H), 8.69 (d, J=6Hz, 1H).

Step7) N-(4-(7-(4-oxaspiro[2.4]heptane-6-yloxy)quinolin-4-yloxy)-3-fluorophenyl)-N-phenylcyclopropane-1,1-dicarboxamide

[0250]

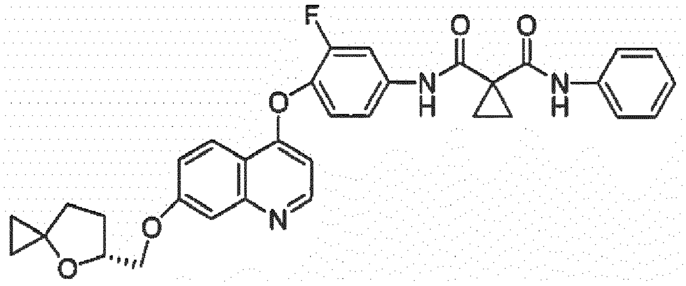


[0251] To a mixture of (4-oxaspiro[2.4]heptane-6-yl)methanesulfonate (168 mg, 0.877 mmol, from example 6) and N-(4-(7-hydroxyquinolin-4-yloxy)-3-fluorophenyl)-N-phenylcyclopropane-1,1-dicarboxamide (300 mg, 0.584 mmol) in 5 mL of N,N-dimethylacetamide was added cesium carbonate (893 mg, 2.74 mmol). After stirring at room temperature for 36 hrs, the reaction mixture was warmed up to 40°C and continued to stir for 8 hrs. The reaction mixture was concentrated *in vacuo* and the residue was chromatographed with a silica gel column (1:1 (v/v) EtOAc / n-hexane) to afford the title compound as a white solid (65 mg, 18 %).
MS (ESI, pos. ion) m/z: 554.1(M+1); LC-MS Rt: 4.354 min;
^{1}H NMR (400MHz, $CDCl_3$): δ 0.53 (m, 1H), 0.65 (m, 1H), 0.89 (m, 1H), 1.00 (m, 1H), 1.60 (m, 2H), 1.84 (m, 2H), 2.25 (m, 1H), 2.53 (m, 1H), 4.20 (m, 2H), 5.22 (m, 1H), 6.39 (d, J=5.2Hz, 1H), 7.19 (m, 2H), 7.28 (m, 2H), 7.38 (m, 2H), 7.48 (m, 2H), 7.77 (m, 1H), 7.59 (s, 1H), 8.28 (d, J=9.2Hz, 1H), 8.58 (d, J=5.2Hz, 1H).

Example 22

N-(4-(7-(((5R)-4-oxaspiro[2.4]heptane-5-yl)methoxy)quinolin-4-yloxy)-3-fluorophenyl)-N-phenylcyclopropane-1,1-dicarboxamide

[0252]

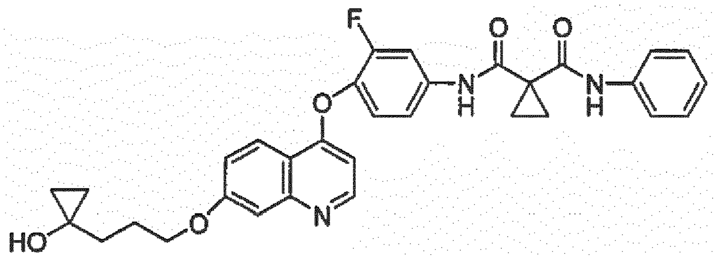


[0253] To a mixture of ((5S)-4-oxaspiro[2.4]heptane-5-yl)methyl methanesulfonate (181.2 mg, 0.877 mmol, from example 2) and N-(4-(7-hydroxyquinolin-4-yloxy)-3-fluorophenyl)-N-phenyl-cyclopropane-1,1-dicarboxamide (300 mg, 0.656 mmol) in 5 mL of N,N-dimethylacetamide was added cesium carbonate (893 mg, 2.74 mmol). After stirring at room temperature for 36 hrs, then the reaction mixture was warmed up to 40°C and stirred for 8 hrs. The reaction mixture was concentrated *in vacuo* and the residue was chromatographed with a silica gel column (1:1 (v/v) EtOAc / n-hexane) to give the title compound as a white solid (234 mg, 63%).
MS (ESI, pos. ion) m/z: 568.2 (M+1); LC-MS Rt: 4.364 min;
^{1}H NMR (400MHz, $CDCl_3$): δ0.56 (m, 2H), 0.91 (m, 2H), 1.60 (m, 4H), 1.83 (m, 2H), 2.03 (m, 2H), 4.18 (m, 2H), 4.52 (s, 1H), 6.38 (m, 1H), 7.20 (m, 2H), 7.30 (m, 1H), 7.38 (m, 3H), 7.48 (m, 2H), 7.76 (m, 1H), 8.02 (s, 1H), 8.25 (d, J=9.2Hz, 1H), 8.58 (d, J=5.2 Hz, 1H), 10.18 (s, 1H).

Reference Example 23

N-(4-(7-(3-(1-hydroxycyclopropyl)propoxy)quinolin-4-yloxy)-3-fluorophenyl)-N-phenylcyclopropane-1,1-dicarboxamide

[0254]

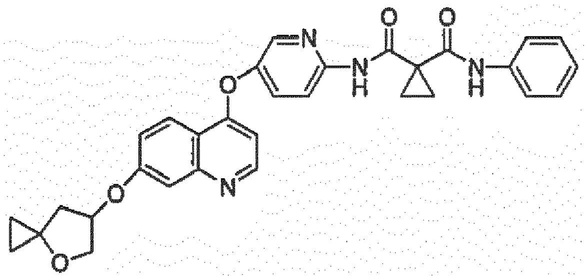


[0255] To a mixture of 3-(1-hydroxycyclopropyl)propyl methanesulfonate (170.7 mg, 0.877 mmol, from example 9) and N-(4-(7-hydroxyquinolin-4-yloxy)-3-fluorophenyl)-N-phenylcyclopropane-1,1-dicarboxamide (300 mg, 0.656 mmol) in 5 mL of N,N-dimethylacetamide was added cesium carbonate (893 mg, 2.74 mmol). After stirring at room temperature for 36 hrs, then the reaction mixture was warmed to 40°C for 8 hrs. The reaction mixture was concentrated *in vacuo* and the residue was chromatographed with a silica gel column (4:1 (v/v) EtOAc / n-hexane) to afford the title compound as a white solid (364.1 mg, 74 %).
MS (ESI, pos. ion) m/z: 556.2 (M+1); LC-MS Rt: 4.110 min;
^{1}H NMR (400MHz, $CDCl_3$): δ 0.51 (s, 2H), 0.79 (s, 2H), 1.25 (s, 2H), 1.81 (m, 4H), 2.15 (m, 2H), 3.38 (s, 3H), 4.24 (m, 2H), 6.38 (d, J=4.8Hz, 1H), 7.25 (m, 4H), 7.46 (m, 1H), 7.77 (d, J=12Hz, 1H), 7.97 (s, 1H), 8.26 (d, J=9.2Hz, 1H), 8.58 (d, J=4.8Hz, 1H), 10.18 (s, 1H).

Example 24

N-(5-(7-(4-oxaspiro[2.4]heptane-6-yloxy)quinolin-4-yloxy)pyridin-2-yl)-N-phenylcyclopropane-1,1-dicarboxamide

[0256]



Step1) N-(5-(7-(benzyloxy)quinolin-4-yloxy)pyridin-2-yl)-N-phenylcyclopropane-1,1-dicarboxamide

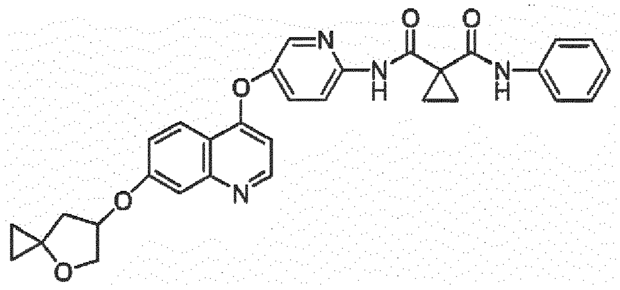
[0257] The title compound was prepared according to the procedure described in Example **21** of step 5 by using 1-(phenylcarbamoyl)cyclopropanecarboxylic acid (1.14 g, 5.6 mmol), HATU (2.11 g, 5.6 mmol), 5-(7-(benzyloxy)quinolin-4-yloxy)pyridin-2-amine (960 mg, 2.8 mmol) and DBU (868 mg, 7.0 mmol) in dry DCM (50 mL). The title compound was obtained as a white solid (1.22 g, 82 %).
MS (ESI, pos. ion) m/z: 531.1(M+1); LC-MS Rt: 4.583 min;
^{1}H NMR (400MHz, $CDCl_3$): δ 1.67 (m, 2H), 1.80 (m, 2H), 5.24 (s, 2H), 6.43 (d, J=4.8Hz, 1H), 7.14 (m, 1H), 7.34 (m, 4H), 7.41 (m, 2H), 7.43 (m, 3H), 7.51 (m, 3H), 8.24 (m, 2H), 8.30 (d, J=8.8Hz, 1H), 8.61 (d, J=5.2Hz, 1H), 9.10 (s, 1H), 9.44 (s, 1H).

Step2) N-(5-(7-hydroxyquinolin-4-yloxy)pyridin-2-yl)-N-phenylcyclopropane-1,1-dicarboxamide

[0258] A solution of N-(5-(7-(benzyloxy)quinolin-4-yloxy)pyridin-2-yl)-N-phenylcyclopropane-1,1-dicarboxamide (1.22 g, 2.3 mmol) and Pd/C (1.2 g) in methanol (30 mL) under H_2 was stirred at room temperature for 2 hrs, then the reaction mixture was filtered and washed with methanol (10 mL×3). The combined solvent was concentrated in *vacuo* to give N-(5-(7-hydroxyquinolin-4-yloxy)pyridin-2-yl)-N-phenyl-cyclopropane-1,1-dicarboxamide as a white solid (910.8 mg, 90 %).
MS (ESI, pos. ion) m/z: 441.2(M+1); LC-MS Rt: 3.508 min;
^{1}H NMR (400MHz, CD_3OD): δ1.69 (m, 4H), 6.55 (d, J=5.6Hz, 1H), 7.14 (m, 1H), 7.30 (m, 4H), 7.56 (m, 2H), 7.74 (m, 1H), 8.29 (m, 3H), 8.55 (d, J=5.6Hz, 1H).

Step3) N-(5-(7-(4-oxaspiro[2.4]heptane-6-yloxy)quinolin-4-yloxy)pyridin-2-yl)-N-phenylcyclopropane-1,1-dicarboxamide

[0259]

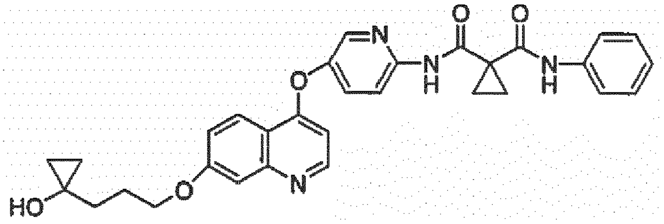


[0260] To a mixture of (4-oxaspiro[2.4]heptane-6-yl)methanesulfonate (168 mg, 0.877 mmol) and N-(5-(7-hydroxyquinolin-4-yloxy)pyridin-2-yl)-N-phenylcyclopropane-1,1-dicarboxamide (300 mg, 0.682 mmol) in 5 mL of N,N-dimethylacetamide was added cesium carbonate (893 mg, 2.74 mmol). After stirring at room temperature for 36 hrs, then the reaction mixture was warmed up to 40 °C for 8 hrs. The reaction mixture was concentrated *in vacuo* and the residue was chromatographed with a silica gel column (2:1 (v/v) EtOAc / n-hexane) to afford the tide compound as a white solid (73 mg, 20 %). MS (ESI, pos. ion) m/z: 537.1 (M+1); LC-MS Rt: 4.429 min;
^{1}H NMR (400MHz, $CDCl_3$): δ 0.60 (m, 2H), 0.95 (m, 2H), 1.70 (m, 4H), 2.40 (m, 1H), 2.54 (m, 1H), 4.19 (m, 2H), 5.23 (m, 1H), 6.42 (d, J=4.2Hz, 1H), 7.28 (m, 3H), 7.34 (m, 3H), 7.58 (m, 3H), 8.24 (m, 2H), 8.62 (d, J=5.2Hz, 1H), 9.10 (s, 1H).

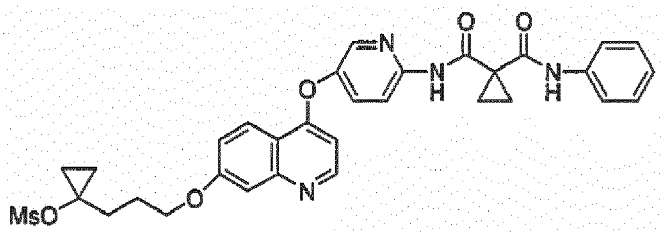
Reference Example 25

N-(5-(7-(3-(1-hydroxycyclopropyl)propoxy)quinolin-4-yloxy)pyridin-2-yl)-N-phenylcyclopropane-1,1-dicarboxamide

[0261]



[0262] The title compound was prepared according to the procedure described in Example **9** by using N-(5-(7-hydroxyquinolin-4-yloxy)pyridin-2-yl)-N-phenyl-cyclopropane-1,1-dicarboxamide (300 mg, 0.682 mmol), 3-(1-hydroxycyclopropyl)-propyl methanesulfonate (155 mg, 0.80 mmol), and Cs_2CO_3 (668 mg, 2.05 mmol) in 3 mL of DMA. The residue was purified by a silical gel column chromatography (3:1 (v/v) EtOAc / n-hexane) to give the title compound as a white solid (238.5 mg, 65 %).
MS (ESI, pos. ion) m/z: 539.2 (M+1); LC-MS Rt: 4.156 min;
^{1}H NMR (400MHz, $CDCl_3$): 50.51 (m, 2H), 0.81 (m, 2H), 1.69 (m, 2H), 1.82 (m, 4H), 2.15 (m, 2H), 4.25 (m, 2H), 6.42 (d, J=5.2Hz, 1H), 7.16 (m, 1H), 7.23 (d, J=2.8Hz, 1H), 7.36 (m, 2H), 7.44 (d, J=2.4Hz, 1H), 7.58 (m, 3H), 8.24 (m, 2H), 8.31 (d, J=8.8Hz. 1H), 8.62 (d, J=5.2Hz, 1H).

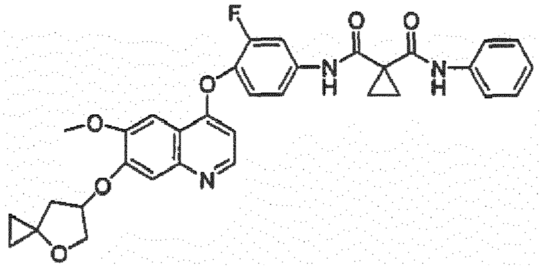


[0263] Chromatography separation also provided N-(5-(7-(3-(1-cyclopropyl methanesulfonate-1-yl)propoxy)quinolin-4-yloxy)pyridin-2-yl)-N-phenylcyclopropane-1,1-dicarboxamide as a pale yellow solid.
MS (ESI, pos. ion) m/z: 617.1 (M+1); LC-MS Rt: 4.491 min;
^{1}H NMR (400MHz, $CDCl_3$): δ0.78 (m, 2H), 1.31 (m, 2H), 1.67 (m, 2H), 1.81 (m, 2H), 2.14 (m, 4H), 3.02 (s, 3H), 4.23 (m, 2H), 6.41 (d, J=5.2Hz, 1H), 7.14 (m, 1H), 7.22 (m, 2H), 7.35 (m, 2H), 7.41 (d, J=2.4Hz, 1H), 7.58 (m, 3H), 8.22 (m, 2H), 8.30 (d, J=9.2Hz, 1H), 8.61 (d, J=5.2Hz, 1H), 9.09 (s, 1H), 9.43 (s, 1H).

Example 26

N-(4-(7-(4-oxaspiro[2.4]heptane-6-yloxy)-6-methoxyquinolin-4-yloxy)-3-fluorophenyl)-N-phenylcycloproprane-1,1-dicarboxamide

[0264]

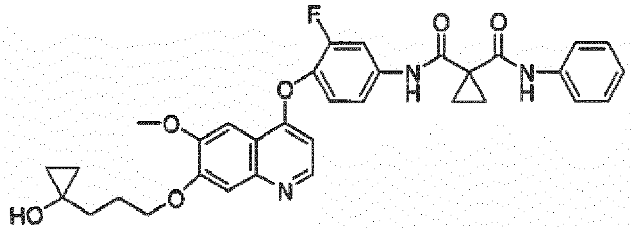


[0265] The title compound was prepared according to the procedure described in Example **24** by using (4-oxaspiro[2.4]heptane-6-yl)methanesulfonate (138 mg, 0.72 mmol), N-(4-(7-hydroxy-6-methoxyquinolin-4-yloxy)-3-fluorophenyl)-N-phenylcyclopropane-1,1-dicarboxamide (300 mg, 0.616 mmol), and Cs_2CO_3 (602.5 mg, 1.848 mmol) in 3 mL of DMA. The residue was purified by a silical gel column chromatography (2:1 (v/v) EtOAc / n-hexane). The title compound was obtained as a white solid (186.7 mg, 52 %).
MS (ESI, pos. ion) m/z: 583.9(M+1); LC-MS Rt: 4.432 min;
^{1}H NMR (400MHz, $CDCl_3$): δ0.55 (m, 1H), 0.65 (m, 1H), 0.90 (m, 1H), 1.05 (m, 1H), 1.60 (m, 2H), 1.85 (m, 2H), 4.04 (s, 3H), 4.24 (m, 2H), 5.25 (m, 1H), 6.41 (d, J=4.4Hz, 1H), 7.20 (m, 2H), 7.25 (m, 1H), 7.30 (m, 2H), 7.40 (m, 1H), 7.50 (m, 2H), 7.60 (s, 1H), 7.80 (m, 2H), 7.95 (m, 1H) 8.50 (d, J=5.2Hz, 1H), 10.25 (s, 1H).

Reference Example 27

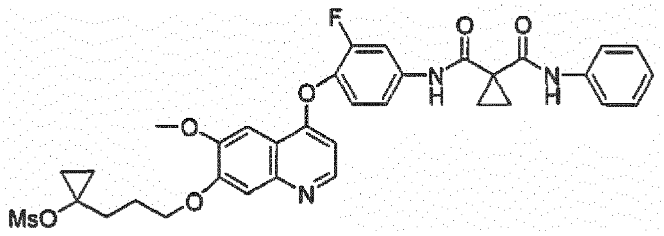
N-[4-(7-(3-(1-hydroxycyclopropyl)propoxy)-6-methoxyquinolin-4-yloxy)-3-fluorophenyl)-N-phenylcyclopropane-1,1-dicarboxamide

[0266]



[0267] The title compound was prepared according to the procedure described in Example **9** by using N-(4-(7-hydroxy-6-methoxyquinolin-4-yloxy)-3-fluorophenyl)-N-phenylcyclopropane-1,1-dicarboxamide (300 mg, 0.616 mmol),3-(1-hydroxycyclopropyl)propyl methanesulfonate (155 mg, 0.80 mmol), and Cs_2CO_3 (602.5 mg, 1.848 mmol) in 3 mL of DMA. The residue was purified by a silical gel column chromatography (6:1 (v/v) EtOAc / n-hexane). The title compound was obtained as a white solid (263 mg, 73 %).
MS (ESI, pos. ion) m/z: 586.2 (M+1); LC-MS Rt: 4.244 min;
^{1}H NMR (400MHz, $CDCl_3$): δ0.46 (s, 2H), 0.76 (m, 2H), 1.61 (m, 2H), 1.84 (m, 4H), 2.22 (t, J=6.4Hz, 2H), 4.03 (s, 3H), 4.30 (t, J=6Hz, 2H), 6.41 (m, 1H), 7.21 - 7.58 (m, 8H), 7.80 (m, 1H), 7.95 (s, 1H), 8.49 (d, J=5.2Hz, 1H), 10.24 (s, 1H).

[0268] N-(4-(7-(3-(1-cyclopropyl methanesulfonate-1-yl)propoxy)-6-methoxyquinolin-4-yloxy)-3-fluorophenyl)-N-phenylcyclopropane-1,1-dicarboxamide was obtained as a pale yellow solid.

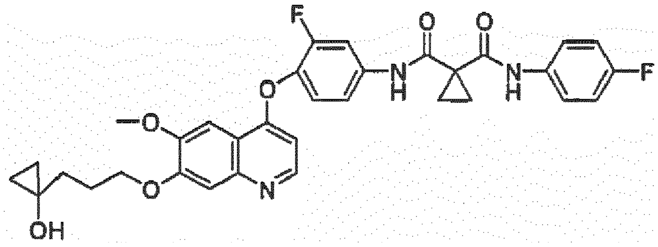


MS (ESI, pos. ion) m/z: 664.2 (M+1); LC-MS Rt: 4.563 min;
^{1}H NMR (400MHz, $CDCl_3$): δ0.78 (m, 2H), 1.30 (m, 2H), 1.60 (m, 2H), 1.85 (m, 2H), 2.11 (m, 2H), 2.25 (m, 2H), 3.06 (s, 3H), 4.03 (s, 3H), 4.28 (m, 2H), 6.41 (d, J=4.8Hz, 1H), 7.22 (m, 2H), 7.27 (m, 3H), 7.39 (m, 2H), 7.49 (d, J-8Hz, 1H), 7.57 (s, 1H), 7.79 (d, J=12Hz, 1H), 7.94 (s, 1H).

Example 28

N-(4-(7-(3-(1-hydroxycyclopropyl)propoxy)-6-methoxyquinolin-4-yloxy)-3-fluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

[0269]



[0270] The title compound was prepared according to the procedure described in Example **9** by using N-(4-(7-hydroxy-6-methoxyquinolin-4-yloxy)-3-fluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (300 mg, 0.594 mmol), 3-(1-hydroxycyclopropyl)propyl methanesulfonate (155 mg, 0.80 mmol), and Cs_2CO_3 (581 mg, 1.782 mmol) in 3 mL of DMA. The residue was purified by a silical gel column chromatography (6:1 (v/v) EtOAc / n-hexane). The title compound was obtained as a white solid (247 mg, 69 %).
MS (ESI, pos. ion) m/z: 604.2 (M+1); Rt: 4.240 min;
^{1}H NMR (400MHz, $EDCl_3$): δ0.46 (m, 2H), 0.75 (m, 2H), 1.64 (m, 2H), 1.83 (m, 4H), 2.22 (m, 2H), 4.03 (s, 3H), 4.31 (m, 2H), 6.41 (m, 1H), 7.08 (m, 2H), 7.25 (m, 1H), 7.46-7.79 (m, 5H), 8.19 (s, 1H), 8.49 (d, J=5.2Hz, 1H), 10.00 (s, 1H).

BIOLOGICAL TESTING

[0271] The efficacy of the compounds of the invention as inhibitors of receptor tyrosine kinases, such as c-Met, KDR and/or IGF1R related activity and as anti-tumor agents in xenograft animal models can be evaluated as follows.

MTT cell assay

[0272] *Preparation Instructions*: MTT ((3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) is soluble in water (10 mg/ml), ethanol (20 mg/ml) and is also soluble in buffered salt solutions and culture media (5 mg/ml).
MTT Solution: 5 mg/ml MTT in PBS. Solution must be filter sterilized after adding MTT.
MTT Solvent: 4 mM HCl, 0.1% Nondet P-40 (NP40) all in isopropanol.

Procedure:

[0273] Short 96 well assay: EACH condition was done in triplicate or more.

1. DAY ONE: Trypsinized one T-25 flask and added 5 ml of complete media to trypsinized cells. Centrifuged in a sterile 15 ml falcon tube at 500 rpm in the swinging bucked rotor (~400×g) for 5 min.
2. Removed media and resuspended cells to 1.0 ml with complete media.
3. Counted and recorded cells per ml.
4. Diluted the cells (cv=cv) to 75,000 cells per ml. Used completed media to dilute cells.
5. Added 100 μl of cells (7500 total cells) into each well and incubated overnight.
6. DAY TWO: Treated cells on day two with inhibitors. - Final volume was 100 μl per well.
7. DAY THREE: Added 20 μl of 5 mg/ml MTT to each well. Included one set of wells with MTT but no cells (control).
8. Incubated for 3.5 hours at 37 °C in culture hood.
9. Carefully removed media.
10. Added 150 μl MTT solvent.
11. Covered with tinfoil and agitate cells on orbital shaker for 15 min.
12. Read absorbance at 590 nm with a reference filter of 620 nm.

Kinase Assays

[0274] Kinase assays can be performed by measurement of incorporation of γ-^{33}P ATP into immobilized myelin basic protein (MBP). High binding white 384 well plates (Greiner) are coated with MBP (Sigma #M-1891) by incubation of 60μl/well of 20μg/ml MBP in Tris-buffered saline (TBS; 50mM Tris pH 8.0, 138mM NaCl, 2.7mM KCl) for 24 hours at 4 °C. Plates are washed 3X with 100μl TBS. Kinase reactions are carried out in a total volume of 34μl in kinase buffer (5mM Hepes pH 7.6, 15mM NaCl, 0.01% bovine gamma globulin (Sigma #I-5506), 10mM $MgCl_2$, 1mM DTT, 0.02% TritonX-100). Compound dilutions are performed in DMSO and added to assay wells to a final DMSO concentration of 1%. Each data point is measured in duplicate, and at least two duplicate assays are performed for each individual compound determination. Enzyme is added to final concentrations of 10nM or 20nM, for example. A mixture of unlabeled ATP endγ-^{33}P

ATP is added to start the reaction (2×10^{6} cpm of γ-^{33}P ATP per well (3000Ci/mmole) and either 10μM unlabeled ATP, typically. The reactions are carried out for 1 hour at room temperature with shaking. Plates are washed 7x with TBS, followed by the addition of 50μl/well scintillation fluid (Wallac). Plates are read using a Wallac Trilux counter. This is only one format of such assays, various other formats are possible, as known to one skilled in the art.

[0275] The above assay procedure can be used to determine the IC_{50} for inhibition and/or the inhibition constant, K_i. The IC_{50} is defined as the concentration of compound required to reduce the enzyme activity by 50% under the condition of the assay. Exemplary compositions have IC_{50}'s of, for example, less than about 100 μM, less than about 10μM, less than about 1μM, and further for example having IC_{50}'s of less than about 100 nM, and still further, for example, less than about 10 nM. The K_i for a compound may be determined from the IC_{50} based on three assumptions. First, only one compound molecule binds to the enzyme and there is no cooperativity. Second, the concentration of active enzyme and the compound tested are known (i.e., there are no significant amounts of impurities or inactive forms in the preparations). Third, the enzymatic rate of the enzyme-inhibitor complex is zero.

Kinase inhibition and cellular assay.

[0276] In vitro kinase assays can also be done to establish IC_{50} values against a variety of recombinant receptor and nonreceptor kinases. Optimal enzyme, ATP, and substrate (gastrin peptide) concentrations are established for each enzyme using homogeneous time-resolved fluorescence (HTRF) assays. Compouns are tested in a 10-point dose-response curve for each enzyme using an ATP concentration of two-thirds Km for each. Most assays consist of enzyme mixed with kinase reaction buffer [20 mmol/L Tris-HCl (pH 7.5), 10 mmol/L $MgCl_2$, 5 mmol/L MnCl2,100 mmol/L NaCl, 1.5 mmol/L EGTA]. A final concentration of 1 mmol/L DTT, 0.2 mmol/L $NaVO_4$, and 20 Ag/mL BSA is added before each assay. For Src, a modified kinase reaction buffer is used that included 20 mmol/L Tris-HCl (pH 7.5), 2.5 mmol/L MnCl2, 100 mmol/L NaCl, and 1.5 mmol/L EGTA. A final concentration of 1 mmol/L DTT, 0.2 mmol/L $NaVO_4$, and 20 Ag/mL BSA is added before each assay. For all assays, 5.75 mg/mL streptavidin-allophycocyanin (ProZyme, San Leandro, CA) and 0.1125 nmol/L Eu-PT66 (Perkin-Elmer Corp., Boston, MA) are added immediately before the HTRF reaction. Plates are incubated for 30 minutes at room temperature and read on a Discovery instrument (Packard Instrument Co., Downers Grove, IL).

c-Met Assay

[0277] c-Met biochemical activity can be assessed using a Luciferase-Coupled Chemilumineacent Kinase assay (LCCA) format as described above. Again, kinase activity is measured as the percent ATP remaining following the kinase reaction. Remaining ATP is detected by luciferase-luciferin-couple chemiluminescence. Specifically, the reaction is initiated by mixing test compounds, 1μM ATP, 1μM poly-EY and 10nM c-Met (baculovirus expressed human c-Met kinase domain P948-S1343) in a 20μL assay buffer (20mM Tris-HCL pH7.5, 10mM $MgCl_2$, 0.02% Triton X-100, 100mM DTT, 2mM $MnCl_2$). The mixture is incubated at ambient temperature for 2 hours after which 20μL luciferase-luciferin mix is added and the chemiluminescent signal read using a Wallac $Victor^2$ reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5μg/mL oxalic acid (pH 7.8), 5 (or 50) mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 μM AMP, 28 μg/mL luciferin and 40000 units of light/mL luciferase.

Tumor xenograft models

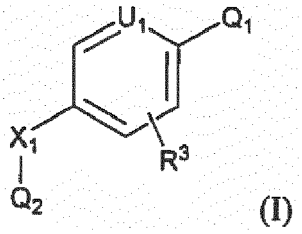
[0278] Human glioma tumor cells (U87MG cells, ATCC) are expanded in culture, harvested and injected subcutaneously into 5-8 week old female nude mice (CD1 nu/nu, Charles River Labs) (n=10). Subsequent administration of compound by oral gavage or by IP (10-100mpk/dose) begins anywhere from day 0 to day 29 post tumor cell challenge and generally continues either once or twice a day for the duration of the experiment. Progression of tumor growth is followed by three dimensional caliper measurements and recorded as a function of time. Intial statistical analysis is done by repeated measures analysis of variance (RMANOVA), followed by Scheffe post hoc testing for multiple comparisons. Vehicle alone (captisol, or the like) is the negative control.

[0279] Human gastric adenocarcinoma tumor cells (MKN45 cells, ATCC) are expanded in culture, harvested and injected subcutaneously into 5-8 week old female nude mice (CD1 nu/nu, Charles River Labs) (n=10). Subsequent administration of compound by oral gavage or by IP (10-100 mpk/dose) begins anywhere from day 0 to day 29 post tumor cell challenge and generally continues either once or twice a day for the duration of the experiment. Progression of tumor growth is followed by three dimensional caliper measurements and recorded as a function of time. Initial statistical analysis is done by repeated measures analysis of variance (RMANOVA), followed by Scheffe post hoc testing for multiple comparisons. Vehicle alone (captisol, or the like) is the negative control.

[0280] A431 cells were cultured in DMEM (low glucose) with 10% FBS and penicillin/streptomycin/glutamine. Cells are harvested by trypsinization, washed, and adjusted to a concentration of 5×10^7 /mL in serum-free medium. Animals are challenged s.c. with 1×10^7 cells in 0.2 mL over the left flank. Approximately 10 days thereafter, mice are randomized based on initial tumor volume measurements and treated with either vehicle (Ora-Plus) or test compounds. Tumor volumes and body weights are recorded twice weekly and/or on the day of sacrifice. Tumor volume is measured with a Pro-Max electronic digital caliper (Sylvac, Crissier, Switzerland) and calculated using the Formulalength (mm) × width (mm) × height (mm) and expressed in mm^3. Data are expressed as mean ±SE. Repeated measures ANOVA followed by Scheffe post hoc testing for multiple comparisons was used to evaluate the statistical significance of observed differences.

Claims

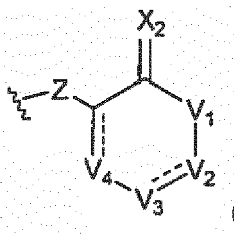
1. A compound of Formula (I):

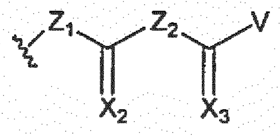


(I)

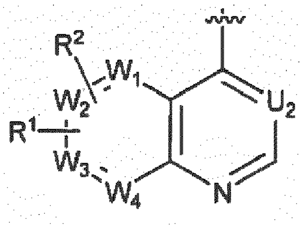
or a stereoisomer, a geometric isomer, a tautomer, an N-oxide, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof, wherein:

Q_1 is formula (IIa) or (IIb):

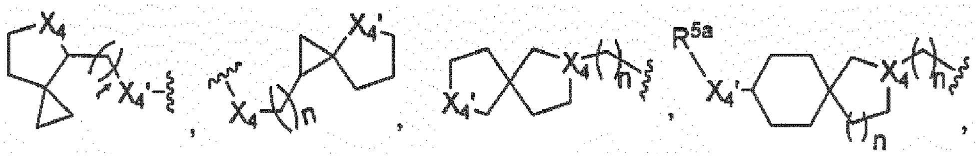

(IIa), or

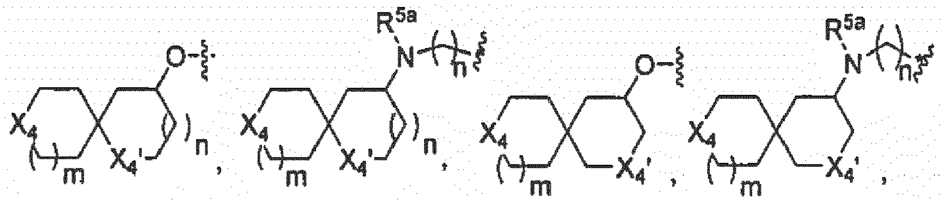

(IIb);

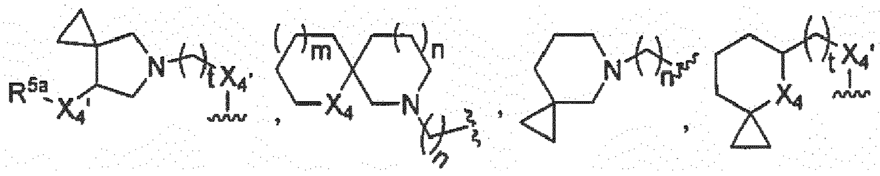
Q_2 is formula (III):

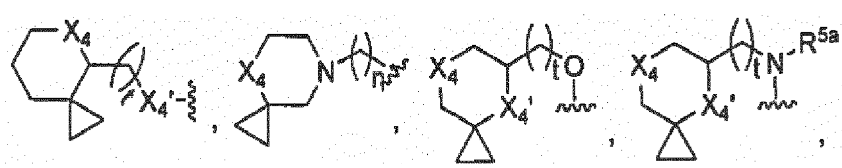

(III);

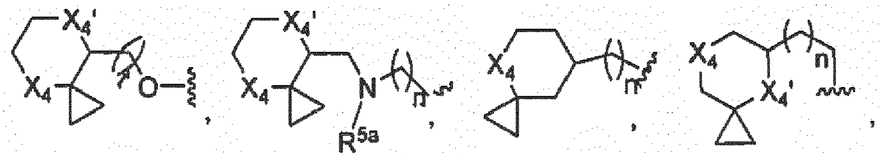
R^1 is selected from

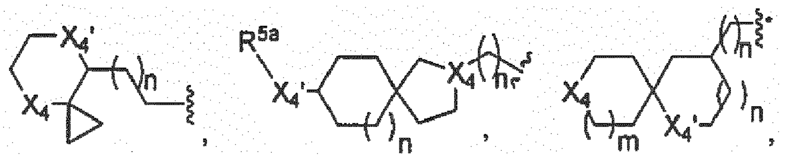


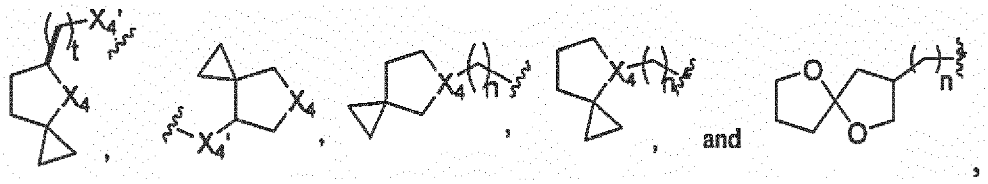












wherein each of X_4 and X_4' is independently $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2; each of m and n is independently 0,1 or 2; and t is 1, 2 or 3;

R^2 is H, halo, cyano(CN), $R^{5a}R^5N$-C_{1-6} alkoxy, C_{1-6} alkoxy, C_{1-6} hydroxyalkoxy, C_{1-6} aminoalkoxy, C_{1-6} hydroxy-substituted aminoalkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylamino C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkoxy, C_{4-10} heterocyclyloxy C_{1-6} alkoxy, C_{5-12} fused bicyclyl, C_{5-12} fused bicyclyl C_{1-6} aliphatic, C_{5-12} fused heterobicyclyl C_{1-6} aliphatic, C_{5-12} fused bicycloxy, C_{5-12} fused bicyclylamino, C_{5-12} fused bicycloxo C_{1-6} alkoxy, C_{5-12} fused bicyclylamino C_{1-6} alkoxy, C_{5-12} fused bicyclyl-C(=O)-, C_{5-12} fused bicyclyl-C(-O)O-, C_{5-12} fused heterobicyclyl-C(=O)-, C_{5-12} fused heterobicyclyl-C(=O)O-, C_{5-12} fused bicyclylamino-C(=O)-, C_{5-12} fused heterobicyclylamino-C(=O)-, C_{5-12} fused bicyclyl-C(=O)NR^5, C_{5-12} fused heterobicyclyl-C(=O)NR^5-, C_{5-12} spiro bicyclyl, C_{5-12} spiro bicycloxy, C_{5-12} spiro bicyclylamino, C_{5-12} spiro bicycloxo C_{1-6} alkoxy, C_{5-12} spiro bicyclylamino C_{1-6} alkoxy, C_{5-12} fused heterobicyclyl, C_{5-12} fused heterobicycloxy, C_{5-12} fused heterobicyclylamino, C_{5-12} fused heterobicycloxo C_{1-6} alkoxy, C_{5-12} fused heterobicyclylamino C_{1-6} alkoxy, C_{5-12} spiro bicyclyl, C_{5-12} spiro heterobicyclyl, C_{5-12} spiro bicyclyl C_{1-6} aliphatic, C_{5-12} spiro heterobicyclyl C_{1-6} aliphatic, C_{5-12} spiro heterobicycloxo C_{1-6} alkoxy, C_{5-12} spiro heterobicyclylamino C_{1-6} alkoxy, C_{5-12} spiro bicyclyl -C(=O)-, C_{5-12} spiro bicyclyl-C(=O)O-, C_{5-12} spiro heterobicyclyl-C(=O)-, C_{5-12} spiro heterobicyclyl-C(=O)O-, C_{5-12} spiro bicyclylamino-C(=O)-, C_{5-12} spiro heterobicyclylamino-C(=O)-, C_{5-12} spiro bicyclyl-C(=O)NR^5-, or C_{5-12} spiro heterobicyclyl-C(=O)NR^5-, C_{6-10} aryl, C_{1-10} heteroaryl, C_{6-10} aryl C_{1-6} aliphatic or C_{1-10} heteroaryl C_{1-6} aliphatic;

wherein R^3 is independently H, F, Cl, Br, -CN, C_{1-3} aliphatic, C_{1-3} alkoxy, or C_{1-3} haloalkyl;

each of U_1 and U_2 is independently CR^4 or N;

V is NR^5R^{5a}, OR^5;

V_1 is O or NR^5;

each of V_2, V_3 and V_4 is independently CR^4R^{4a}, NR^5, CR^4 or N, with the proviso that only one of V_2, V_3, and V_4 is NR^5 or N, or V_2 and V_3 or V_3 and V_4 combine to become CR^4R^{4a}, NR^5, O, CR^4 or N, with the proviso that the resulted structure is stable;

each of W_1, W_2, W_3 and W_4 is independently CR^4R^{4a}, NR^5, CR^4 or N, or W_1 and W_2 or W_3 and W_4 combine to become CR^4R^{4a}, NR^5, O or S;

X_1 is $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2, where m is 0, 1 or 2;

each of X_2 and X_3 is independently O, S or NR^5;

Z is -NR^5C(=O)-$(CR^4R^{4a})_p$-, -NR^5C(=S)-$(CR^4R^{4a})_p$-, -$NR^{5a}(CR^4R^{4a})_p$-, -NR^5-$(CR^4R^{4a})_p$C(=O)-, NR^5-$(CR^4R^{4a})_p$C(=S)-, -$NR^5S(=O)_r$-, -$NR^5S(=O)_r(CR^4R^{4a})_p$-,-C(=O)$NR^5(CR^4R^{4a})_p$- or -$NR^5$-$(CR^4R^{4a})_pS(=O)_r$-, where p is 0, 1, 2 or 3 and r is 1 or 2;

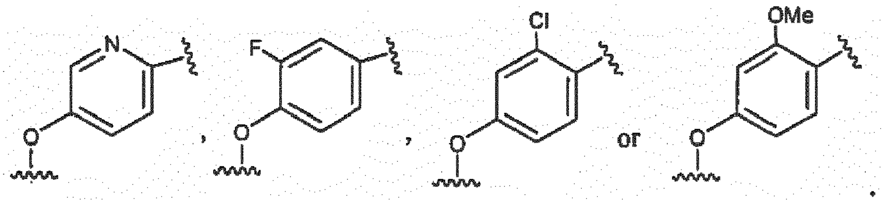
each of Z_1 and Z_2 is independently NR^5 or CR^4R^{4a};

each of R^4 and R^{4a} is independently H, F, Cl, Br, I, -CN, hydroxyl, -$NR^{5a}R^5$, with the proviso that where R^4 and R^{4a} are bonded to the same carbon atom, R^4 and R^{4a}, together with the carbon atom they are attached to, optionally form a 3-8 membered carbocyclic or heterocyclic ring;

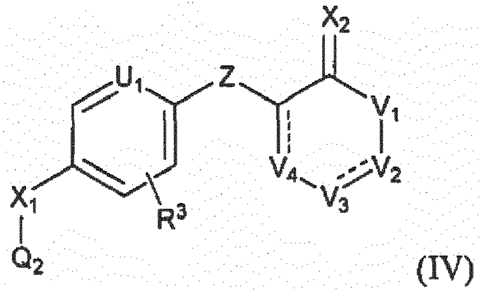
each of R^5 and R^{5a} is independently H, R^6R^{6a}NC(=O)-, R^6OC(=O)-, R^6C(=O)-, R^6R^{6a}NS(=O)-, R^6OS(=O)-, R^6S(=O)-, $R^6R^{6a}NSO_2$-, R^6OSO_2-, R^6SO_2-, with the proviso that where R^5 and R^{5a} are bonded to the same nitrogen atom, R^5 and R^{5a}, together with the nitrogen atom they are attached to, optionally form a 3-8 membered ring, including spiro and fused bicyclic rings;

each of R^6 and R^{6a} is H.

2. The compound according to claim 1, wherein Z of formula (IIa) is -NHC(=O)-, Z_1 of formula (IIb) is NH; and the substructure defined by X_1, U_1 and R^3 of Formula I is:

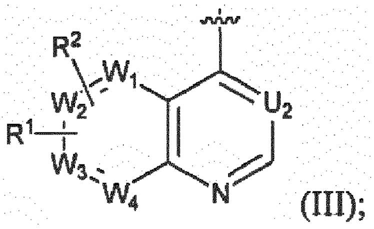


3. The compound according to claim 1 having Formula (IV):

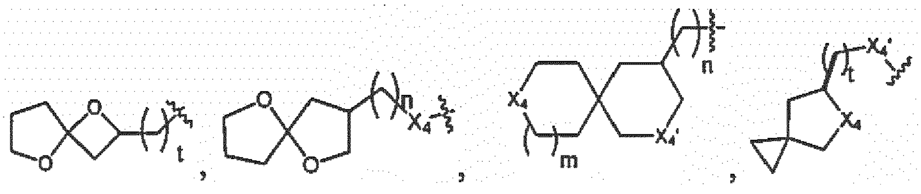


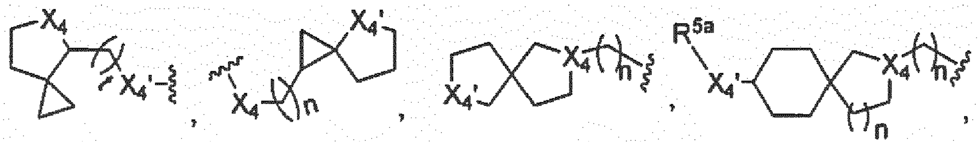
or a stereoisomer, a geometric isomer, a tautomer, an N-oxide, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof, wherein:

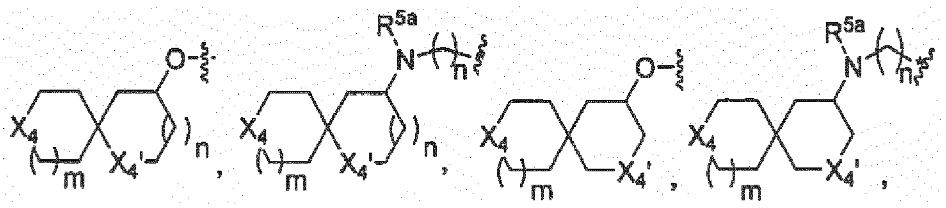
Q_2 has formula (III):

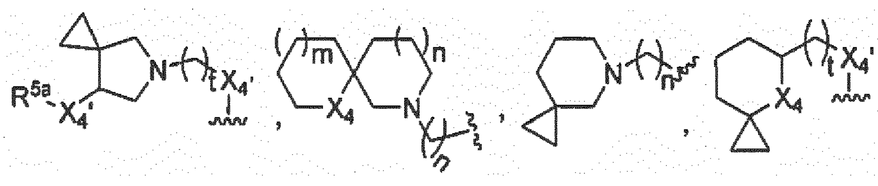


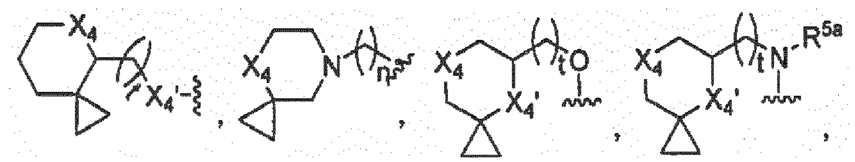
R^1 is selected from

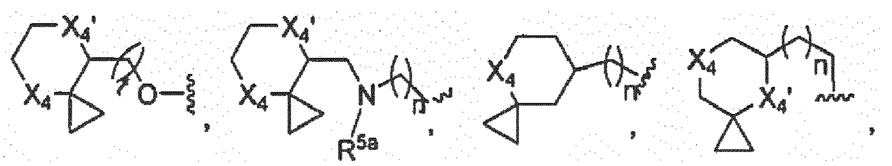


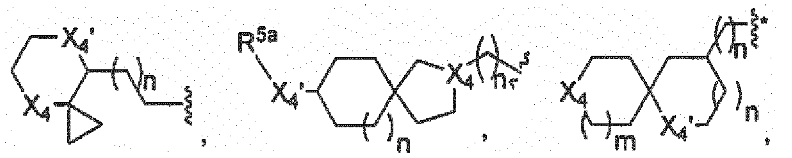


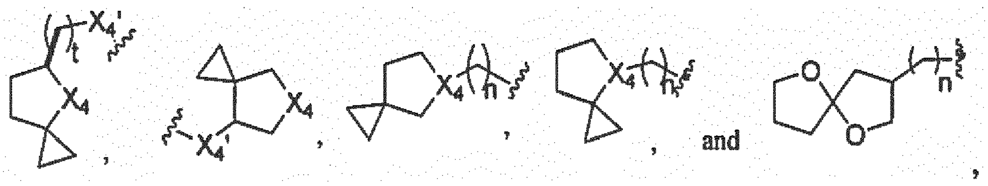












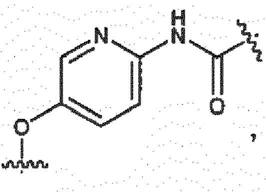
wherein each of X_4 and X_4' is independently $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2; each of m and n is independently 0, 1 or 2; and t is 1, 2 or 3;

R^2 is H, halo, cyano(CN), $R^{5a}R^5N$-C_{1-6} alkoxy, C_{1-6} alkoxy, C_{1-6} hydroxyalkoxy, C_{1-6} aminoalkoxy, C_{1-6} hydroxy-substituted aminoalkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylamino C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkoxy, C_{4-10} heterocyclyloxy C_{1-4} alkoxy, C_{5-12} fused bicyclyl, C_{5-12} fused bicyclyl C_{1-4} aliphatic, C_{5-12} fused heterobicyclyl C_{1-6} aliphatic, C_{5-12} fused bicycloxy, C_{5-12} fused bicyclylamino, C_{5-12} fused bicycloxo C_{1-6} alkoxy, C_{5-12} fused bicyclylamino C_{1-6} alkoxy, C_{5-12} fused bicyclyl-C(=O)-, C_{5-12} fused bicyclyl-C(=O)O-, C_{5-12} fused heterobicyclyl-C(=O)-, C_{5-12} fused heterobicyclyl-C(=O)O-, C_{5-12} fused bicyclylamino-C(=O)-, C_{5-12} fused heterobicyclylamino-C(=O)-, C_{5-12} fused bicyclyl-C(=O)NR^5-, C_{5-12} fused heterobicyclyl-C(=O)NR^5-, C_{5-12} spiro bicyclyl, C_{5-12} spiro bicycloxy, C_{5-12} spiro bicyclylamino, C_{5-12} spiro bicycloxo C_{1-6} alkoxy, C_{5-12} spiro bicyclylamino C_{1-6} alkoxy, C_{5-12} fused heterobicyclyl, C_{5-12} fused heterobicycloxy, C_{5-12} fused heterobicyclylamino, C_{5-12} fused heterobicycloxo C_{1-6} alkoxy, C_{5-12} fused heterobicyclylamino C_{1-6} alkoxy, C_{5-12} spiro bicyclyl, C_{5-12} spiro heterobicyclyl, C_{5-12} spiro bicyclyl C_{1-6} aliphatic, C_{5-12} spiro heterobicyclyl C_{1-6} aliphatic, C_{5-12} spiro heterobicycloxo C_{1-6} alkoxy, C_{5-12} spiro heterobicyclylamino C_{1-6-} alkoxy, C_{5-12} spiro bicyclyl -C(=O)-, C_{5-12} spiro bicyclyl-C(=O)O-, C_{5-12} spiro heterobicyclyl-C(=O)-, C_{5-12} spiro heterobicyclyl-C(=O)O-, C_{5-12} spiro bicyclylamino-C(=O)-, C_{5-12} spiro heterobicyclylamino-C(=O)-, C_{5-12} spiro bicyclyl-C(=O)NR^5-, or C_{5-12} spiro hoterobicyclyl-C(=O)NR^5-, C_{6-10} aryl, C_{1-10} heteroaryl, C_{6-10} aryl aliphatic or C_{1-10} heteroaryl C_{1-6} aliphatic;

wherein R^3 is independently H, F, Cl, Br, -CN, C_{1-3} aliphatic, C_{1-3} alkoxy, or C_{1-3} haloalkyl;

each of U_1 and U_2 is independently CR^4 or N;
V is NR^5R^{5a}, OR^5;
V_1 is O or NR^5;
each of V_2, V_3 and V_4 is independently CR^4R^{4a}, NR^5, CR^4 or N, with the proviso that only one of V_2, V_3, and V_4 is NR^5 or N, or V_2 and V_3 or V_3 and V_4 combine to become CR^4R^{4a}, NR^5, O, CR^4 or N, with the proviso that the resulted structure is stable;
each of W_1, W_2, W_3 and W_4 is independently CR^4R^{4a}, NR^5, CR^4 or N, or W_1 and W_2 or W_3 and W_4 combine to become CR^4R^{4a}, NR^5, O or S;
X_1 is $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2, where m is 0, 1 or 2;
X_2 is independently O, S or NR^5;
Z is $-NR^5C(=O)-(CR^4R^{4a})_p-$, $-NR^5C(=S)-(CR^4R^{4a})_p-$, $-NR^{5a}-(CR^4R^{4a})_p-$, $-NR^5-(CR^4R^{4a})_pC(=O)-$, $-NR^5-(CR^4R^{4a})_pC(=S)-$, $-NR^5S(=O)_r-$, $-NR^5S(=O)_r(CR^4R^{4a})_p-$, $-C(=O)NR^5(CR^4R^{4a})_p-$ or $-NR^5(CR^4R^{4a})_pS(=O)_r-$, where p is 0, 1, 2 or 3 and r is 1 or 2;
each of R^4 and R^{4a} is independently H, F, Cl, Br, I, -CN, hydroxyl, $-NR^{5a}R^5$, with the proviso that where R^4 and R^{4a} are bonded to the same carbon atom, R^4 and R^{4a}, together with the carbon atom they are attached to, optionally form a substituted or unsubstituted 3-8 membered carbocyclic or heterocyclic ring;
each of R^5 and R^{5a} is independently H, $R^6R^{6a}NC(=O)-$, $R^6OC(=O)-$, $R^6C(=O)-$, $R^6R^{6a}NS(=O)-$, $R^6OS(=O)-$, $R^6S(=O)-$, $R^6R^{6a}NSO_2-$, R^6OSO_2-, R^6SO_2-, with the proviso that where R^5 and R^{5a} are bonded to the same nitrogen atom, R^5 and R^{5a}, together with the nitrogen atom they are attached to, optionally form a 3-8 membered ring, including spiro and fused bicyclic rings;
each of R^6 and R^{6a} is independently H;
wherein each of $R^{5a}R^5N-$, $-C(=O)NR^5R^{5a}$, $-OC(=O)NR^5R^{5a}$, $-OC(=O)OR^5$, $-NR^5C(=O)NR^5R^{5a}$, $-NR^5C(=O)OR^{5a}$, $-NR^5C(=O)-R^{5a}$, $R^5R^{5a}N-O_2S-$, R^5O_2S-, $R^5O_2SR^{5a}N-$, OR^5, NR^5, CR^4R^{4a}, CR^4, $(CR^4R^{4a})_m$, $-NR^5C(O)-(CR^4R^{4a})_p-$, $-NR^5C(=S)-(CR^4R^{4a})_p-$, $-NR^{5a}-(CR^4R^{4a})_p-$, $-NR^5-(CR^4R^{4a})_pC(=O)-$, $-NR^5-(CR^4R^{4a})_pC(=S)-$, $-NR^5S(O)_r-$, $-NR^5S(=O)(CR^4R^{4a})_p-$, $-C(=O)NR^5-(CR^4R^{4a})_p-$, $-NR^5-(CR^4R^{4a})_p-S(=O)_r-$, $R^{5a}R^5N$-alkyl, $R^5(S=O)$-alkyl, $R^5R^{5a}N-(C=O)$-alkyl, $R^{5a}R^5N$-alkoxy, $R^5(S=O)$-alkoxy, $R^5R^{5a}N-(C=O)$-alkoxy, $R^6R^{6a}NC(=O)-$, $R^6OC(=O)-$, $R^6C(=O)-$, $R^6R^{6a}NS(=O)-$, $R^6OS(=O)-$, $R^6S(=O)-$, $R^6R^{6a}NSO_2-$, R^6OSO_2-, R^6SO_2-, hydroxy-substituted cyclopropylalkoxy, $R^5S(=O)_2O$-substituted cyclopropylalkoxy.

4. The compound according to claim 3, wherein Z is -NHC(=O)-; or
wherein the substructure defined by X_1, Z, U_1 and R^3 is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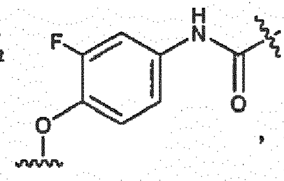
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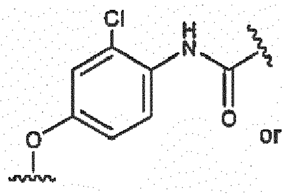
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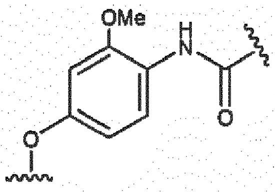
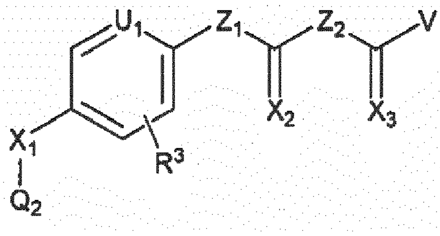
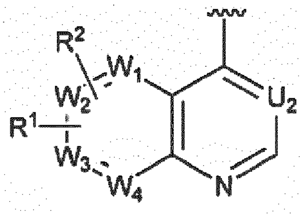

.

5. The compound according to claim 1 having Formula V:


(V)

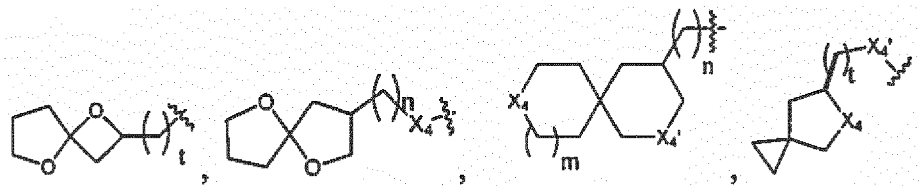
or a stereoisomer, a geometric isomer, a tautomer, an N-oxide, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof, wherein:

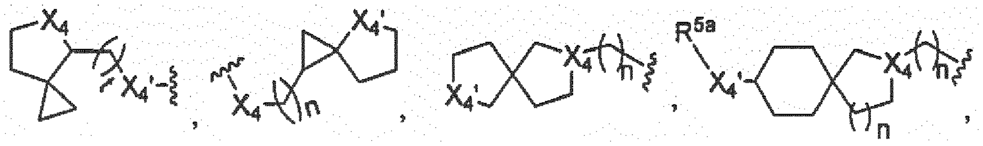
Q_2 has Formula (III):

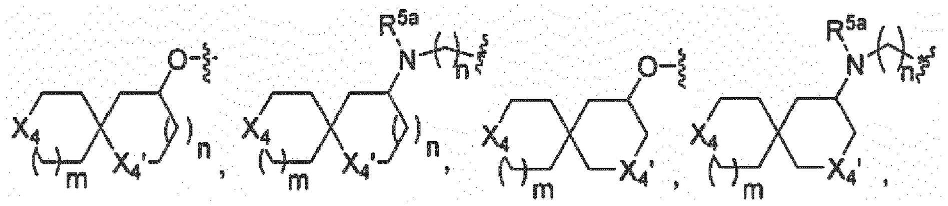


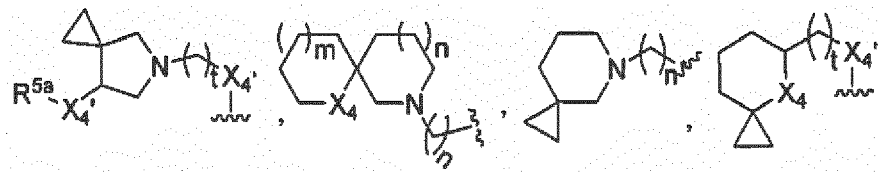
(III);

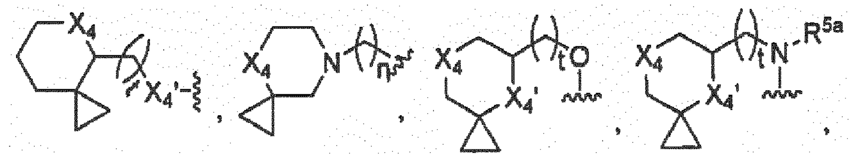
R^1 is selected from

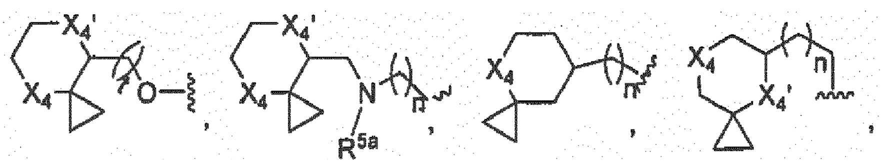


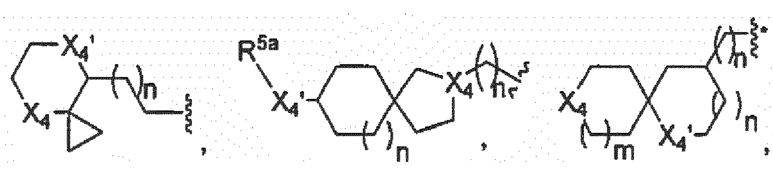


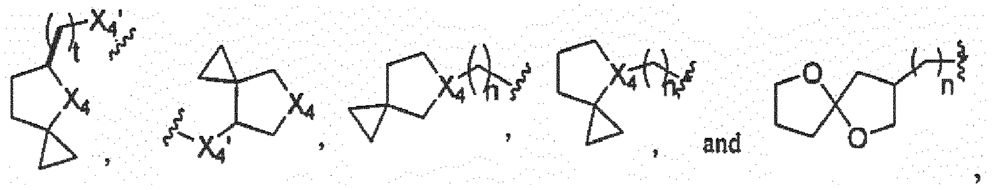












wherein each of X_4 and X_4' is independently $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2; each of m and n is independently 0, 1 or 2; and t is 1,2 or 3;

R^2 is H, halo, cyano(CN), $R^{5a}R^5N$-C_{1-6} alkoxy, C_{1-6} alkoxy, C_{1-6} hydroxyalkoxy, C_{1-6} aminoalkoxy, C_{1-6} hydroxy-substituted aminoalkoxy, C_{1-6} haloalkoxy, C_{1-6} alkylamino C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-6} alkoxy, C_{4-10} heterocyclyloxy C_{1-6} alkoxy, C_{5-12} fused bicyclyl, C_{5-12} fused bicyclyl C_{1-6} aliphatic, C_{5-12} fused heterobicyclyl C_{1-6} aliphatic, C_{5-12} fused bicycloxy, C_{5-12} fused bicyclylamino, C_{5-12} fused bicycloxo C_{1-6} alkoxy, C_{5-12} fused bicyclylamino C_{1-6} alkoxy, C_{5-12} fused bicyclyl-C(=O)-, C_{5-12} fused bicyclyl-C(=O)O-, C_{5-12} fused heterobicyclyl-C(=O)-, C_{5-12} fused heterobicyclyl-C(=O)O-, C_{5-12} fused bicyclylamino-C(=O)-, C_{5-12} fused heterobicyclylamino-C(=O)-, C_{5-12} fused bicyclyl-C(=O)NR^5-, C_{5-12} fused heterobicyclyl-C(=O)NR^5-, C_{5-12}spiro bicyclyl, C_{5-12} spiro bicycloxy, C_{5-12} spiro bicyclylamino, C_{5-12} spiro bicycloxo C_{1-6} alkoxy, C_{5-12} spiro bicyclylamino C_{1-6} alkoxy, C_{5-12} fused heterobicyclyl, C_{5-12} fused heterobicycloxy, C_{5-12} fused heterobicyclylamino, C_{5-12} fused heterobicycloxo C_{1-6} alkoxy, C_{5-12} fused heterobicyclylamino C_{1-6} alkoxy, C_{5-12} spiro bicyclyl, C_{5-12} spiro heterobicyclyl, C_{5-12} spiro bicyclyl C_{1-6} aliphatic, C_{5-12} spiro heterobicyclyl C_{1-6} aliphatic, C_{5-12} spiro heterobicycloxo C_{1-6} alkoxy, C_{5-12} spiro heterobicyclylamino C_{1-6} alkoxy, C_{5-12} spiro bicyclyl -C(=O)-, C_{5-12} spiro bicyclyl-C(=O)O-, C_{5-12} spiro heterobicyclyl-C(=O)-, C_{5-12} spiro heterobicyclyl-C(=O)O-, C_{5-12} spiro bicyclylamino-C(=O)-, C_{5-12} spiro heterobicyclylamino-C(=O)-, C_{5-12} spiro bicyclyl-C(=O)NR^5-, or C_{5-12} spiro heterobicyclyl-C(=O)NR^5-, C_{6-10} aryl, C_{1-10} heteroaryl, C_{6-10} aryl C_{1-6} aliphatic or C_{1-10} heteroaryl C_{1-6} aliphatic;

wherein R^3 is independently H, F, Cl, Br, -CN, C_{1-3} aliphatic, C_{1-3} alkoxy, or C_{1-3} haloalkyl;

each of U_1 and U_2 is independently CR^4 or N;

V is NR^5R^{5a}, OR^5;

each of W_1, W_2, W_3 and W_4 is independently CR^4R^{4a}, NR^5, CR^4 or N, or W_1 and W_2 or W_3 and W_4 combine to become CR^4R^{4a}, NR^5, O or S;

X_1 is $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2, where m is 0, 1 or 2;

each of X_2 and X_3 is independently O, S or NR^5;

each of Z_1 and Z_2 is independently NR^5 or CR^4R^{4a};

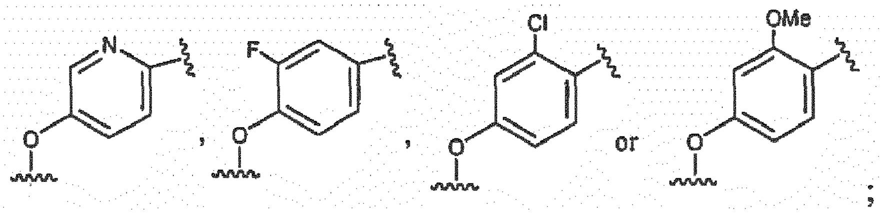
each of R^4 and R^{4a} is independently H, F, Cl, Br, I, -CN, hydroxyl, $-NR^{5a}R^5$, with the proviso that where R^4 and R^{4a} are bonded to the same carbon atom, R^4 and R^{4a}, together with the carbon atom they are attached to, optionally form a substituted or unsubstituted 3-8 membered carbocyclic or heterocyclic ring;

each of R^5 and R^{5a} is independently H, $R^6R^{6a}NC(=O)$-, $R^6OC(=O)$-, $R^6C(=O)$-, $R^6R^{6a}NS(=O)$-, $R^6OS(=O)$-, $R^6S(=O)$-, $R^6R^{6a}NSO_2$-, R^6OSO_2-, R^6SO_2-, with the proviso that where R^5 and R^{5a} are bonded to the same nitrogen atom, R^5 and R^{5a}, together with the nitrogen atom they are attached to, optionally form a substituted or unsubstituted 3-8 membered ring, including spiro and fused bicyclic rings;

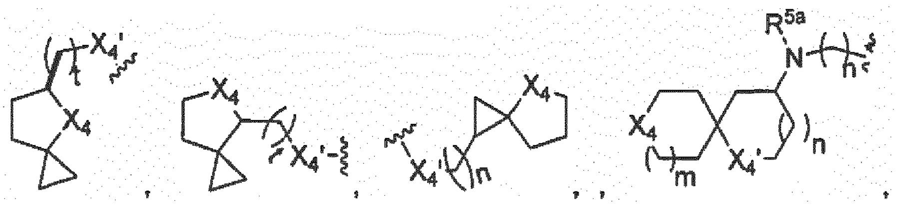
each of R^6 and R^{6a} is independently H;

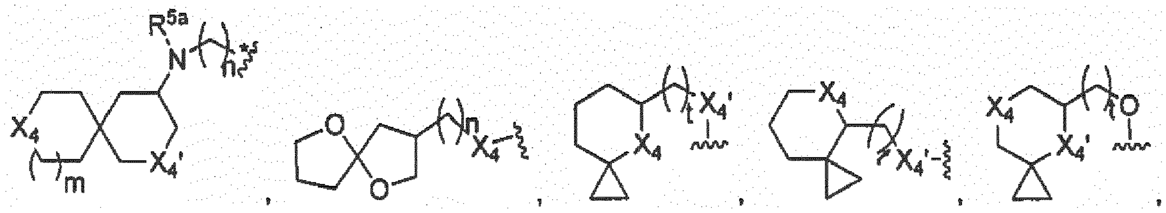
wherein each of $R^{5a}R^5N$-, $-C(=O)NR^5R^{5a}$, $-OC(=O)NR^5R^{5a}$, $-OC(=O)OR^5$,$-NR^5C(=O)NR^5R^{5a}$, $-NR^5C(=O)OR^{5a}$, $-NR^5C(=O)-R^{5a}$, R^5R^{5a}-O_2S-, R^5O_2S-, $R^5O_2SR^{5a}N$-, OR^5, NR^5, CR^4R^{4a}, CR^4, $(CR^4R^{4a})_m$, $-NR^5C(O)-(CR^4R^{4a})_p$-, $-NR^5C(=S)-(CR^4R^{4a})_p$-, $-NR^{5a}-(CR^4R^{4a})_p$-, $-NR^5-(CR^4R^{4a})_pC(=O)$-, $-NR^5-(CR^4R^{4a})_pC(=S)$, $-NR^5S(O)_r$-, - $NR^5S(=O)(CR^4R^{4a})_p$-, $-C(=O)NR^5-(CR^4R^{4a})_p$-, $-NR^5-(CR^4R^{4a})_p-S(=O)_r$, $R^{5a}R^5N$-alkyl, $R^5(S=O)$-alkyl, $R^5R^{5a}N$-(C=O)-alkyl, $R^{5a}R^5N$-alkoxy, $R^5(S=O)$-alkoxy, $R^5R^{5a}N$-(C=O)-alkoxy, $R^6R^{6a}NC(=O)$-, $R^6OC(=O)$-, $R^6C(=O)$-, $R^6R^{6a}NS(=O)$, $R^6OS(=O)$-, $R^6S(=O)$-, $R^6R^{6a}NSO_2$-, R^6OSO_2-, R^6SO_2-, hydroxy-substituted cyclopropylalkoxy, $R^5S(=O)_2O$-substituted cyclopropylalkoxy.

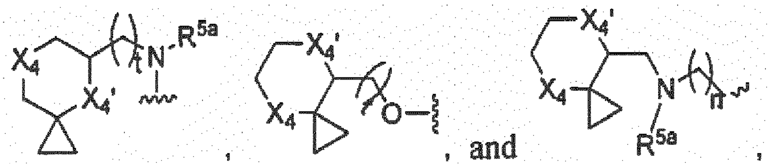
6. The compound according to claim 5, wherein the substructure defined by X_1, U_1 and R^3 is



and/or wherein R^1 is one of the following structures:

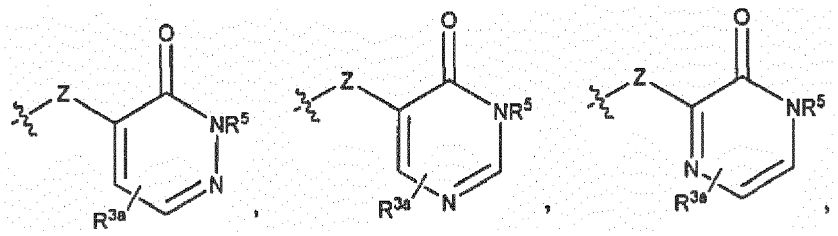


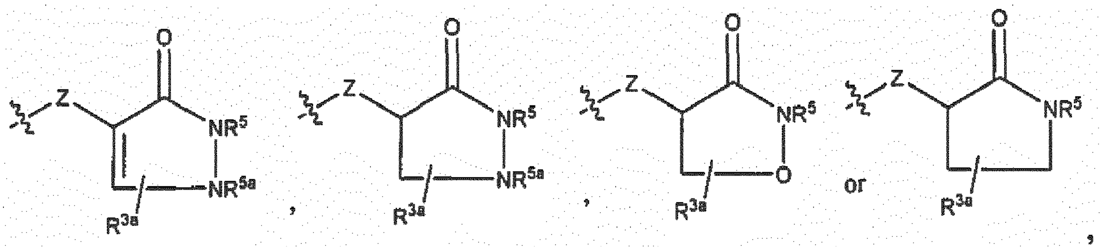




wherein each of X_4 and X_4' is independently $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2; each of m and n is independently 0, 1 or 2; and t is 1, 2 or 3.

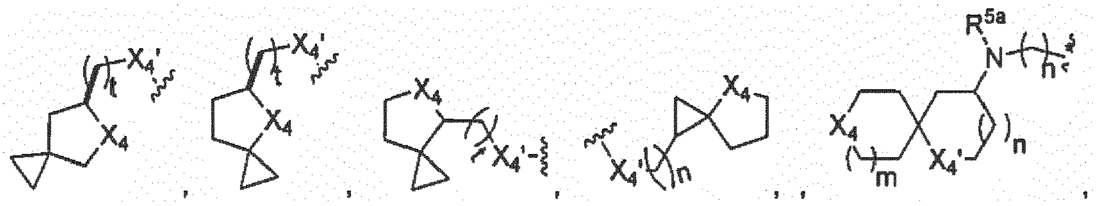
7. The compound according to claim 1 or 3, wherein Q_1 in Formula 1 or the substructure defined by X_2, V_1, V_2, V_3, V_4 and Z of Formula (IV) is

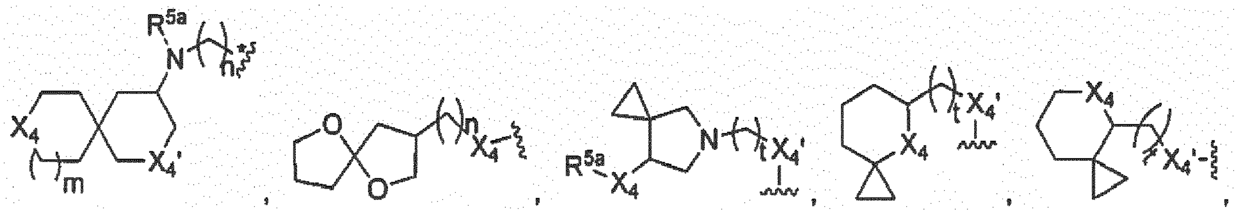


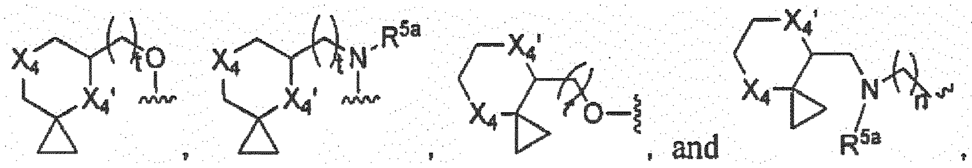


wherein R^{3a} is H, F, Cl, Br, I, -CN, hydroxyl, $R^{5a}R^5N$-, $R^{5a}R^5N$-aliphatic.

8. The compound according to claim 1 or 3 or 5, wherein R^1 is one of the following structures:

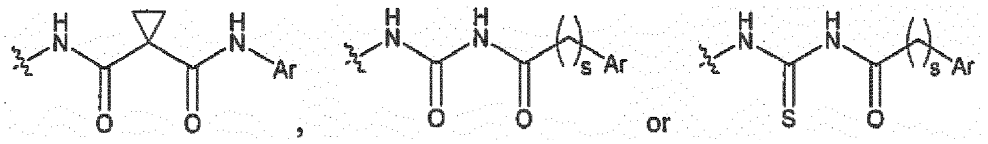






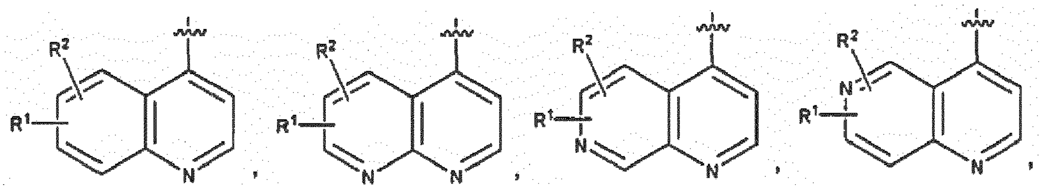
wherein each of X_4 and X_4' is independently $(CR^4R^{4a})_m$, NR^5, O, S, S=O or SO_2; each of m and n is independently 0, 1 or 2; and t is 1, 2 or 3.

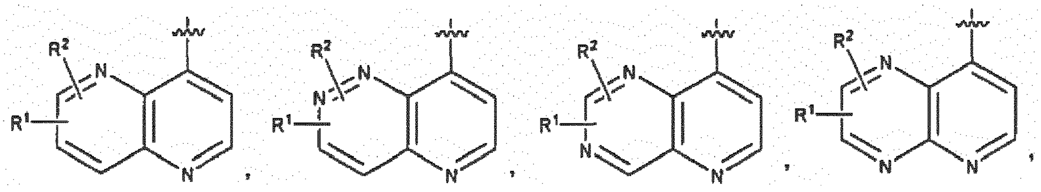
9. The compound according to claim 1 or 5, wherein Q_1 in Formula (I) or the substructure defined by Z_1, Z_2, X_2, X_3 and V of Formula (V) is

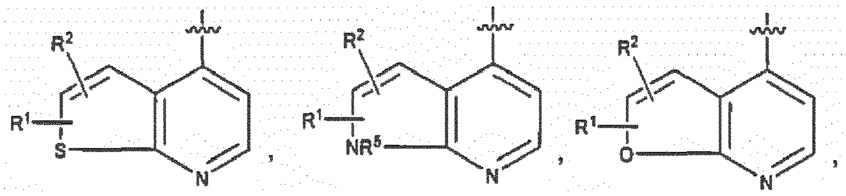


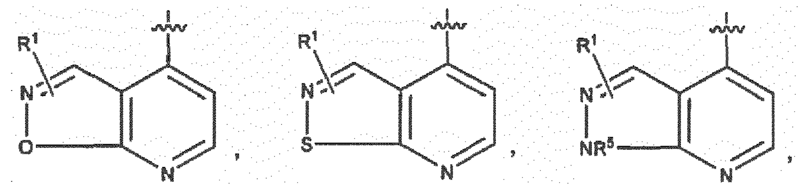
wherein Ar is substituted or unsubstituted aryl or heteroaryl; and s is 0 or 1.

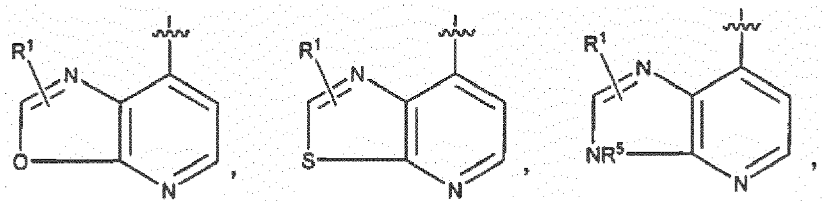
10. The compound according to any of claims 1, 3 and 5, wherein Q_2 is

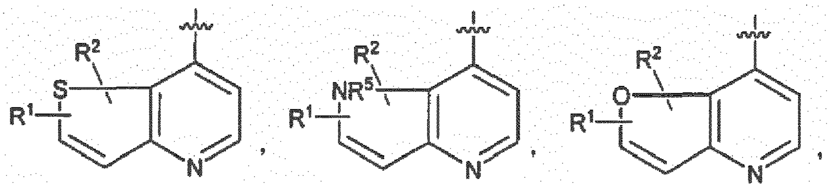


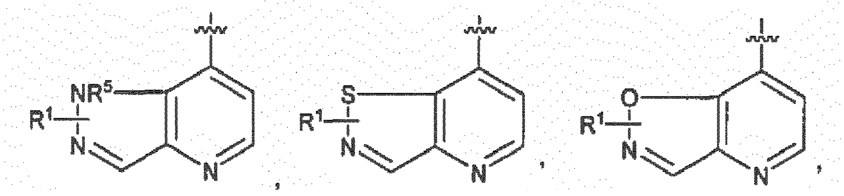


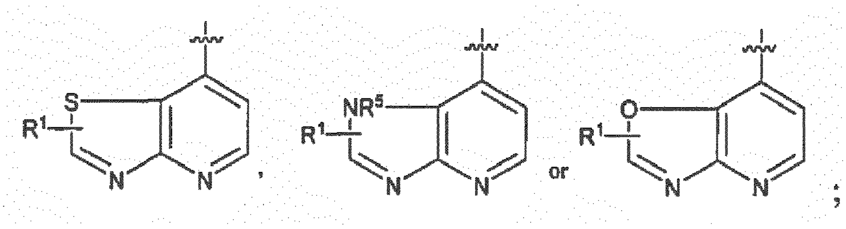












or
wherein X_1 is O or NR^5.

11. A pharmaceutical composition comprising a compound according to any one of claims 1 to 10 and a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof, and optionally a therapeutic agent selected from a chemotherapeutic agent, an anti-proliferative agent, an agent for treating atherosclerosis, an agent for treating lung fibrosis, and combinations thereof;
wherein the additional therapeutic agent is optionally adriamycin, rapamycin, temsirolimus, everolimus, ixabepilone, gemcitabin, cyclophosphamide, dexamethasone, etoposide, fluorouracil, imatinib mesylate, dasatinib, nilotinib, erlotinib, lapatinib, iressa, sorafenib, sunitinib, an interferon, carboplatin, topotecan, taxol, vinblastine, vincristine, temozolomide, tositumomab, trabectedin, bevacizumab, trastuzumab, cetuximab, panitumumab or a combination

thereof.

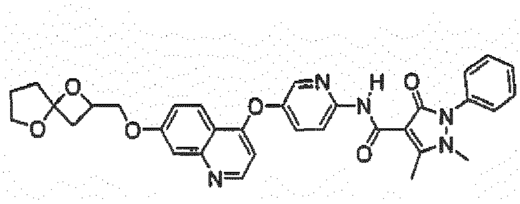
12. The compound according to any of claims 1-10 or the pharmaceutical composition according to claim 11 for use in preventing, managing, treating or lessening the severity of a proliferative disorder.

13. The compound or the pharmaceutical composition for use according to claim 12, wherein the proliferative disorder is metastatic cancer, colon cancer, gastric adenocarcinoma, bladder cancer, breast cancer, kidney cancer, liver cancer, lung cancer, thyroid cancer, cancer of the head and neck, prostate cancer, pancreatic cancer, cancer of the CNS, glioblastoma, or a myeloproliferative disorder, atherosclerosis or lung fibrosis.

14. A method of inhibiting or modulating protein kinase activity in a biological sample comprising contacting a biological sample with the compound according to any of claims 1-10 or the pharmaceutical composition according to claim 11.

15. The method according to claim 14, wherein the protein kinases are receptor tyrosine kinases, and wherein the receptor tyrosine kinases are KDR, c-Met or IGF1R.

16. A compound having one of the following structures: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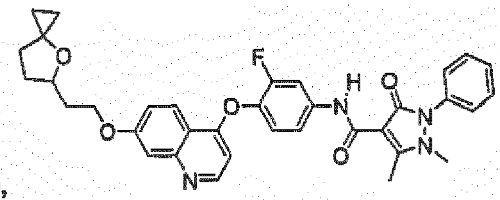
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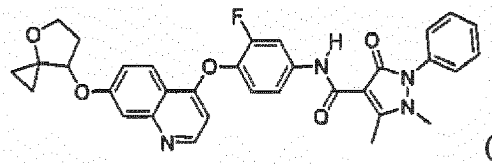
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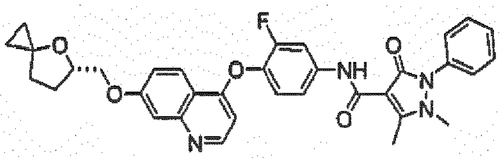
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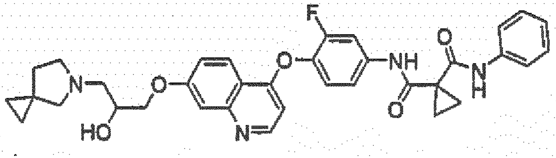
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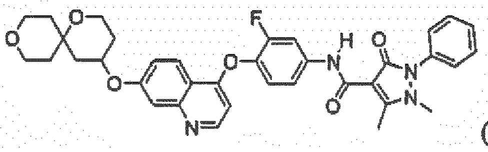
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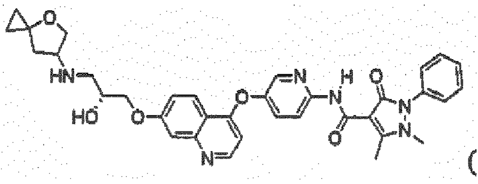
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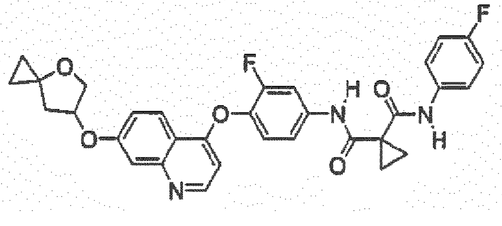
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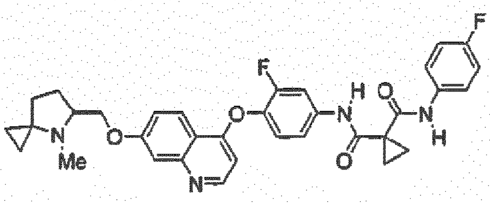
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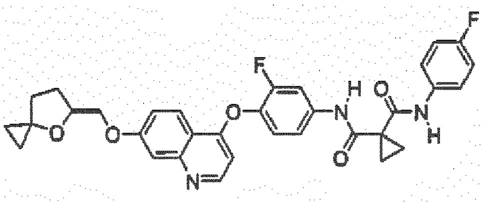
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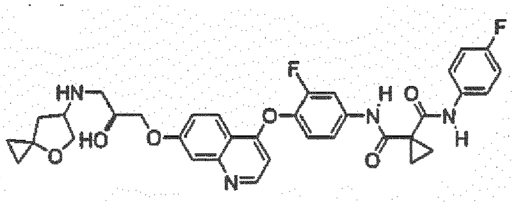
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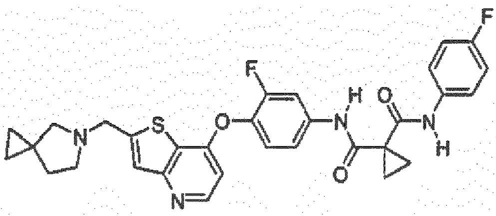
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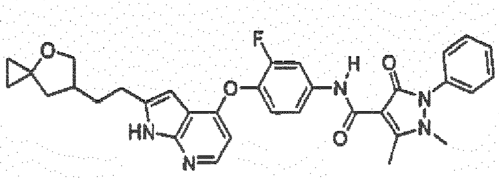
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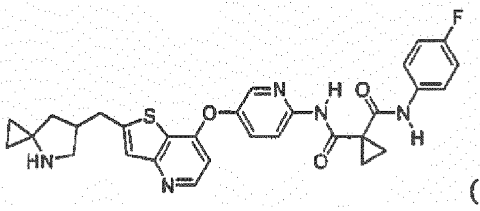
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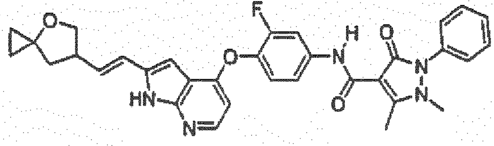
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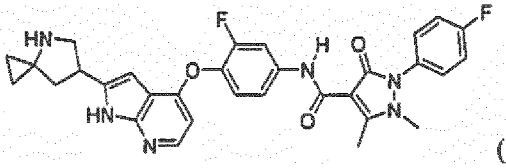
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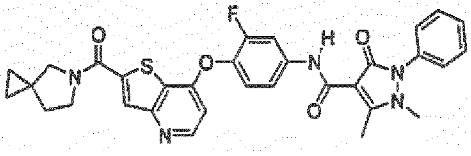
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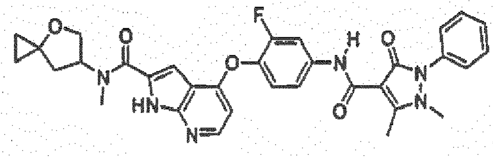
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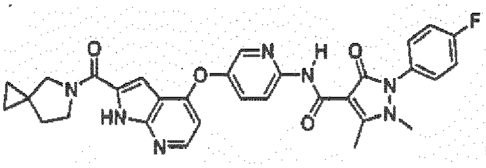
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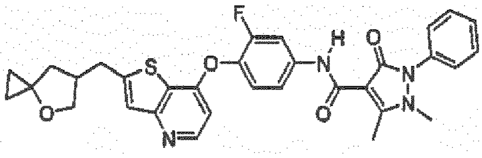
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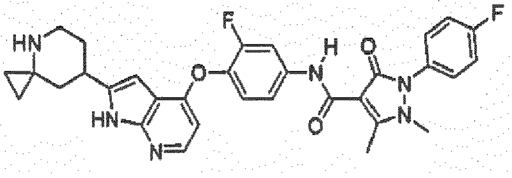
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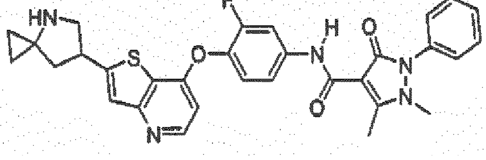
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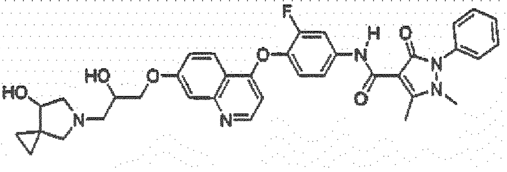
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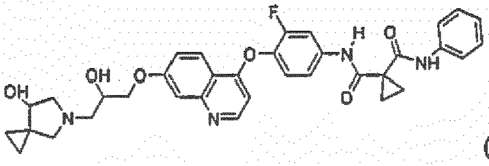
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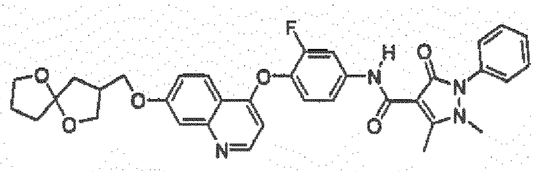
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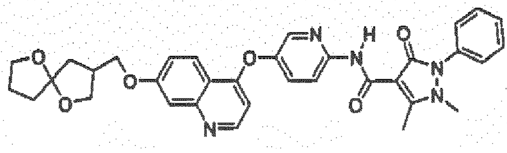
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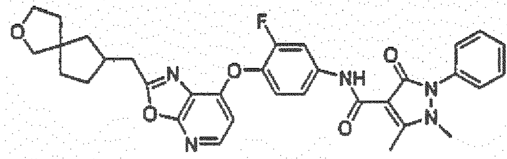
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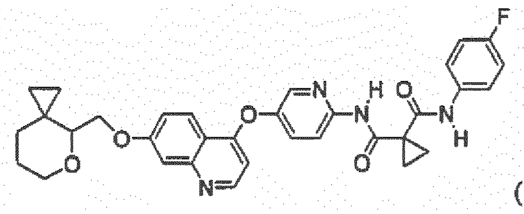
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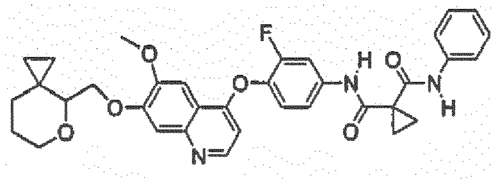
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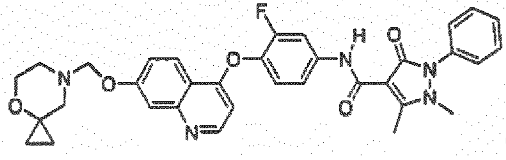
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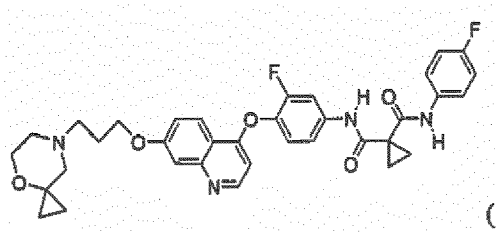
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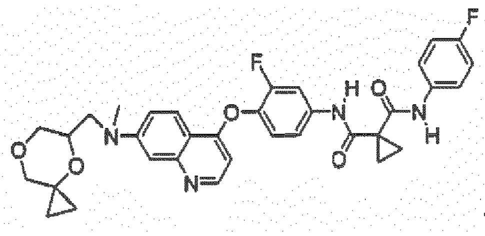
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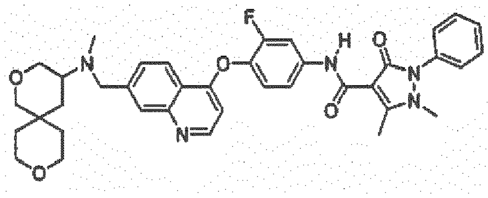
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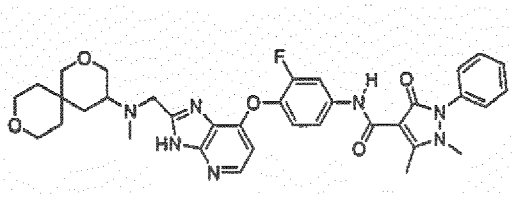
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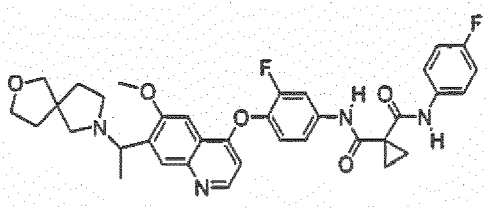
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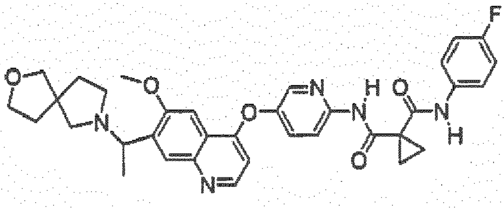
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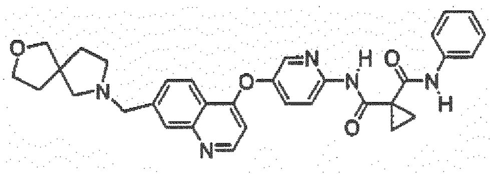
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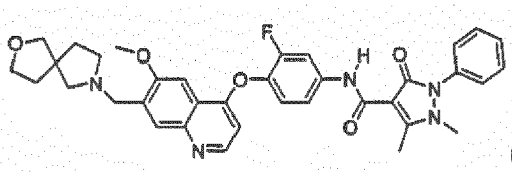
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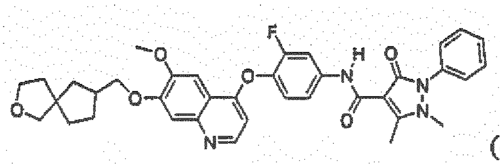
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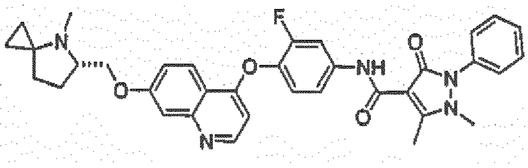
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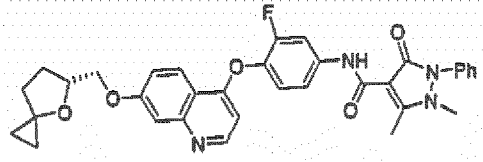
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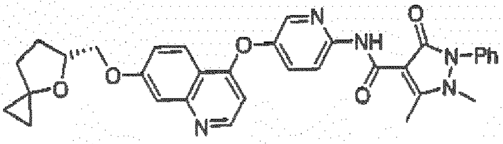
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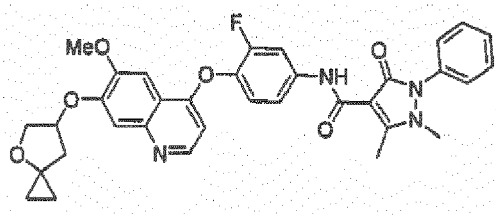
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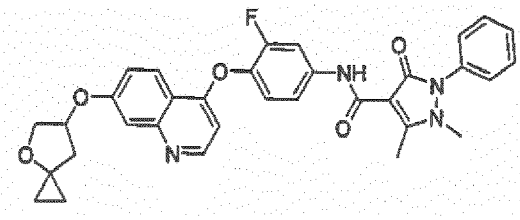
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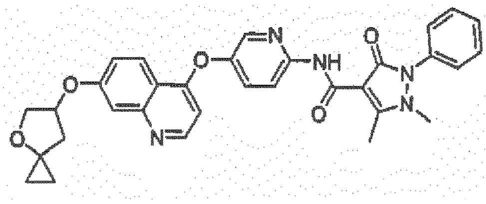
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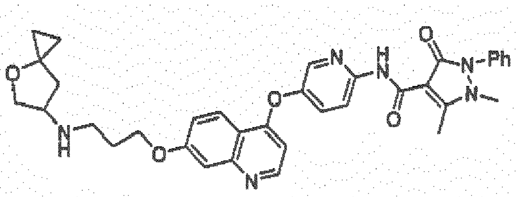
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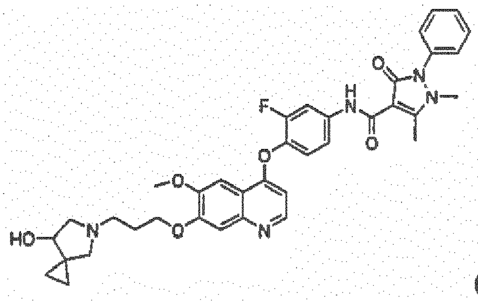
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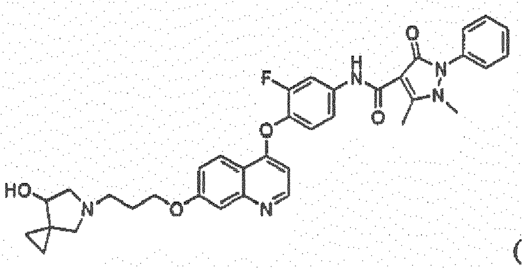
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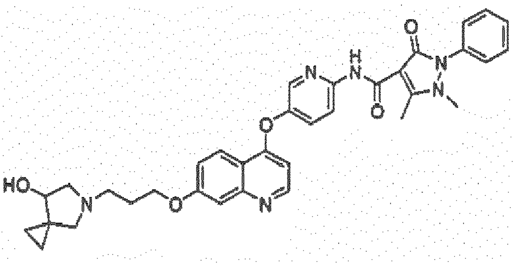
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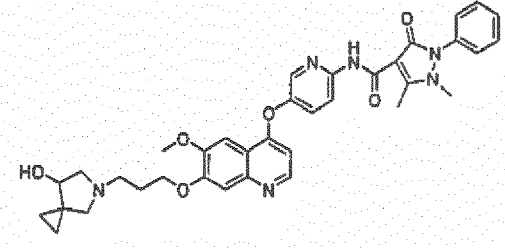
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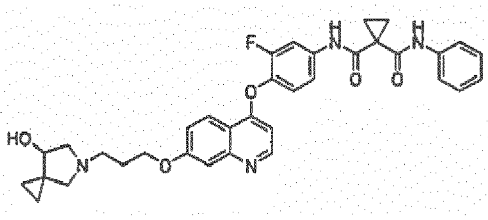
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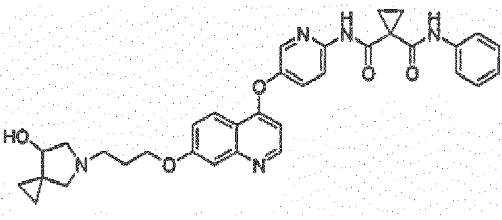
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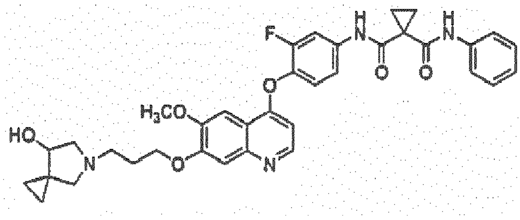

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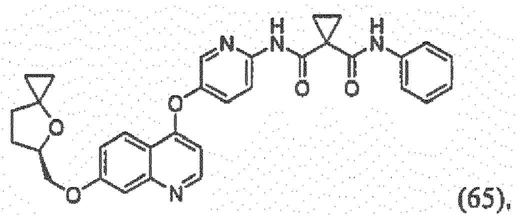

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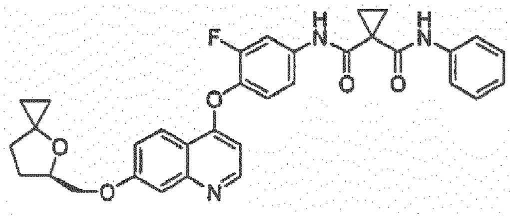

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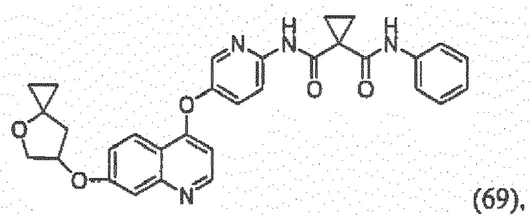

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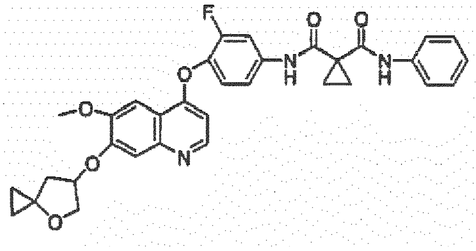

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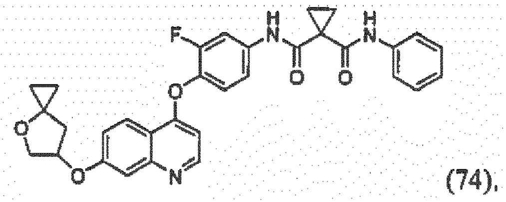

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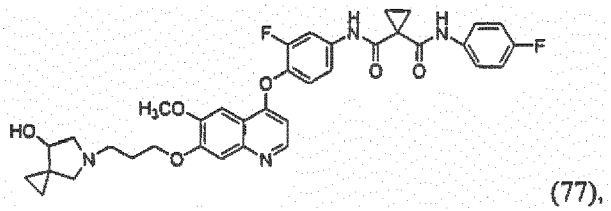
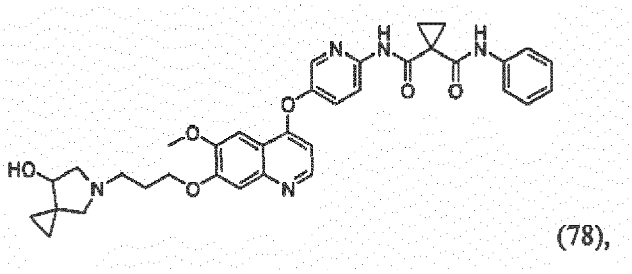


(77),

and

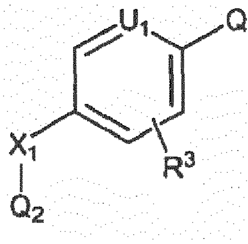


(78),

or a stereoisomer, a geometric isomer, a tautomer, an N-oxide, a hydrate, a solvate, or a pharmaceutically acceptable salt thereof.

Patentansprüche

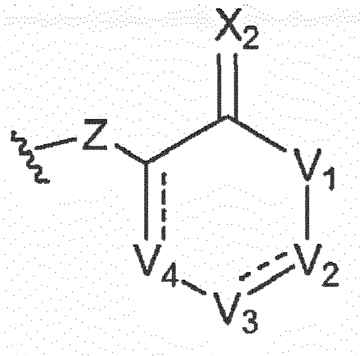
1. Verbindung der Formel (I):



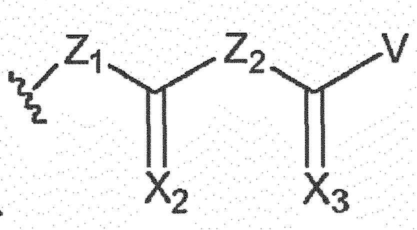
(I)

oder ein Stereoisomer, ein geometrisches Isomer, ein Tautomer, ein N-Oxid, ein Hydrat, ein Solvat oder ein pharmazeutisch verträgliches Salz davon, wobei:

Q_1 für Formel (IIa) oder (IIb) steht:

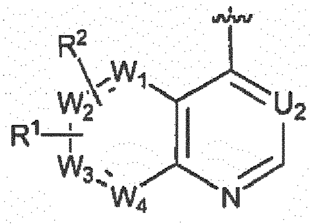


(IIa) oder



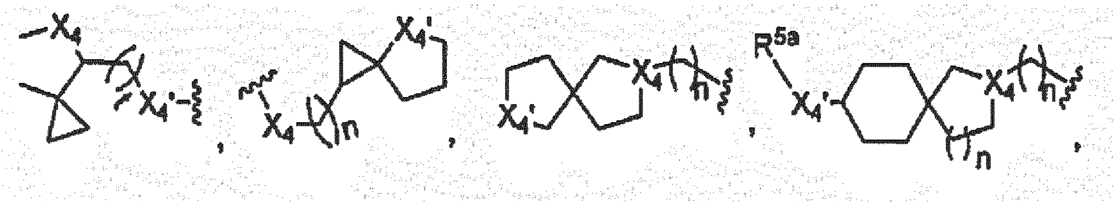
(IIb);

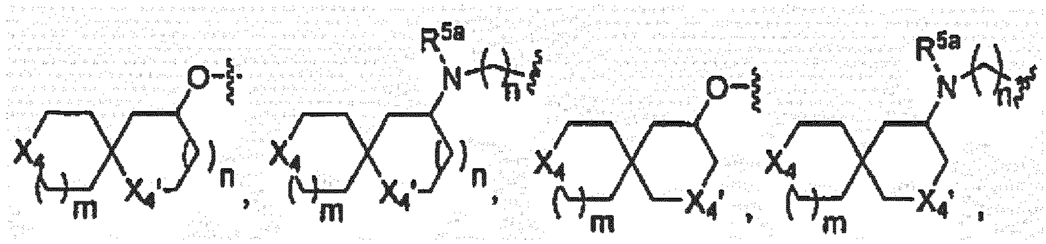
Q_2 für Formel (III) steht:

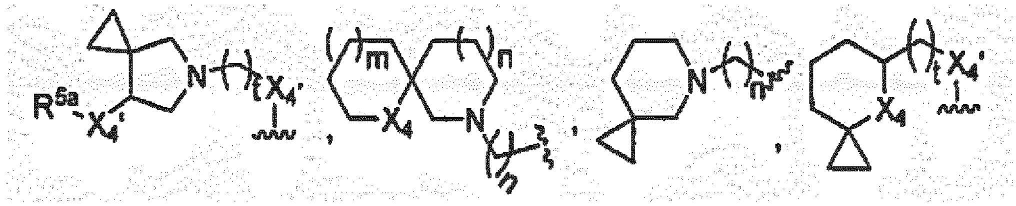


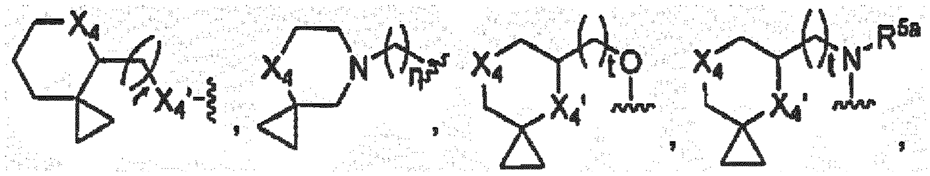
(III);

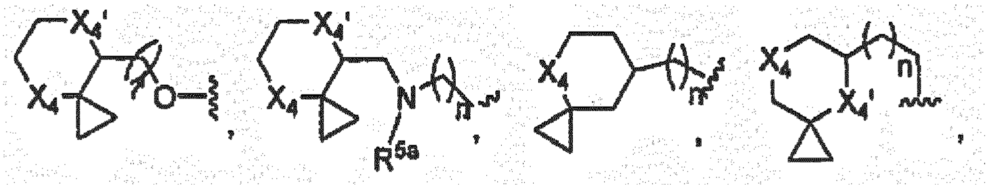
R^1 ausgewählt ist aus

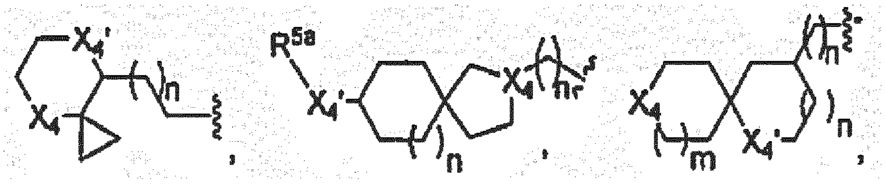


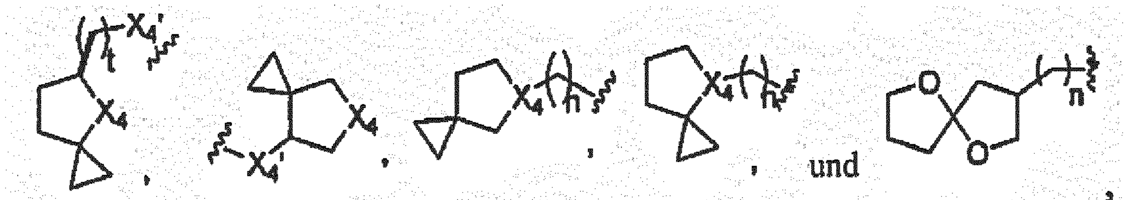












wobei jedes X_4 und X_4' unabhängig für $(CR^4R^{4a})_m$, NR^5, O, S, S=O oder SO_2 steht; jedes m und n unabhängig für 0, 1 oder 2 steht; und t für 1, 2 oder 3 steht;

R^2 für H, Halo, Cyano(CN), $R^{5a}R^5N$-C_{1-6}-Alkoxy, C_{1-6}-Alkoxy, C_{1-6}-Hydroxyalkoxy, C_{1-6}-Aminoalkoxy, C_{1-6}-Hydroxy-substituiertes Aminoalkoxy, C_{1-6}-Haloalkoxy, C_{1-6}-Alkylamino-C_{1-6}-alkoxy, C_{1-6}-Alkoxy-C_{1-6}-alkoxy, C_{4-10}-Heterocyclyloxy-C_{1-6}-alkoxy, C_{5-12}-kondensiertes Bicyclyl, C_{5-12}-kondensiertes Bicyclyl-C_{1-6}-aliphatisch, C_{5-12}-kondensiertes Heterobicyclyl-C_{1-6}-aliphatisch, C_{5-12}-kondensiertes Bicycloxy, C_{5-12}-kondensiertes Bicyclylamino, C_{5-12}-kondensiertes Bicycloxo-C_{1-6}-alkoxy, C_{5-12}-kondensiertes Bicyclylamino-C_{1-6}-alkoxy, C_{5-12}-kondensiertes Bicyclyl-C(=O)-, C_{5-12}-kondensiertes Bicyclyl-C(=O)O-, C_{5-12}-kondensiertes Heterobicyclyl-C(=O)-, C_{5-12}-kondensiertes Heterobieyclyl-C(=O)O-, C_{5-12}-kondensiertes Bicyclylamino-C(=O)-, C_{5-12}-kondensiertes Heterobicyclylamino-C(=O)-, C_{5-12}-kondensiertes Bicyclyl-C(=O)NR^5-, C_{5-12}-kondensiertes Heterobicyclyl-C(=O)NR^5-, C_{5-12}-spiro-Bicyclyl, C_{5-12}-spiro-Bicycloxy, C_{5-12}-spiro-Bicyclylamino, C_{5-12}-spiro-Bicycloxo-C$_{1-6}$-alkoxy, C$_{5-12}$-spiro-Bicyclylamino-C$_{1-6}$-alkoxy, C$_{5-12}$-kondensiertes Heterobicyclyl, C$_{5-12}$-kondensiertes Heterobicycloxy, C$_{5-12}$-kondensiertes Heterobicyclylamino, C$_{5-12}$-kondensiertes Heterobicycloxo-C$_{1-6}$-Alkoxy, C$_{5-12}$-kondensiertes Heterobicyclylamino-C$_{1-6}$-alkoxy, C$_{5-12}$-spiro-Bicyclyl, C$_{5-12}$-spiro-Heterobicyclyl, C$_{5-12}$-spiro-Bicyclyl-C$_{1-6}$-aliphatisch, C$_{5-12}$-spiro-Heterobicyclyl-C$_{1-6}$-aliphatisch, C$_{5-12}$-spiro-Heterobicycloxo-C$_{1-6}$-alkoxy, C$_{5-12}$-spiro-Heterobicyclylamino-C$_{1-6}$-alkoxy, C$_{5-12}$-spiro-Bicyclyl-C(=O)-, C$_{5-12}$-spiro-Bicyclyl-C=)O-, C$_{5-12}$-spiro-Heterobicyclyl-C(=O)-, C$_{5-12}$-spiro Heterobicyclyl-C(=O)O-, C$_{5-12}$-spiro-Bicyclylamino-C(=O)-, C$_{5-12}$-spiro-Heterobicyclylamino-C(=O)-, C$_{5-12}$-spiro-Bicyclyl-C(=O)NR^5- oder C$_{5-12}$-spiro-Heterobicyclyl-C (=O) NR^5-, C$_{6-10}$-Aryl, C$_{1-10}$-Heteroaryl, C$_{6-10}$-Aryl-C$_{1-6}$-aliphatisch oder C$_{1-10}$-Heteroaryl-C$_{1-6}$-aliphatisch steht;

wobei R^3 unabhängig für H, F, Cl, Br, -CN, C$_{1-3}$-aliphatisch, C$_{1-3}$-Alkoxy oder C$_{1-3}$-Haloalkyl steht;

jedes U$_1$ und U$_2$ unabhängig für CR^4 oder N steht;

V für NR^{5}R^{5a}, OR^5 steht;

V$_1$ für O oder NR^5 steht;

jedes V$_2$, V$_3$ und V$_4$ unabhängig für CR^{4}R^{4a}, NR^5, CR^4 oder N steht, mit der Maßgabe, dass nur eines von V$_2$, V$_3$ und V$_4$ für NR^5 oder N steht, oder V$_2$ und V$_3$ oder V$_3$ und V$_4$ kombiniert werden, um CR^{4}R^{4a}, NR^5, O, CR^4 oder N zu werden, mit der Maßgabe, dass die resultierende Struktur stabil ist;

jedes W$_1$, W$_2$, W$_3$ und W$_4$ unabhängig für CR^{4}R^{4a}, NR^5, CR^4 oder N steht, oder W$_1$ und W$_2$ oder W$_3$ und W$_4$ kombiniert werden, um CR^{4}R^{4a}, NR^5, O oder S zu werden;

X$_1$ für (CR^{4}R^{4a})$_m$, NR^5, O, S, S=O oder SO$_2$ steht, worin m für 0, 1 oder 2 steht;

jedes X$_2$ und X$_3$ unabhängig für O, S oder NR^5 steht;

Z für -NR^{5}C(=O)-(CR^{4}R^{4a})$_p$-, -NR^{5}C(=S)-(CR^{4}R^{4a})$_p$-, -NR^{5a}-(CR^{4}R^{4a})$_p$-, -NR^5-(CR^{4}R^{4a})$_p$C(=O)-, -NR^5-(CR^{4}R^{4a})$_p$C (=S)-, - NR^{5}S(=O)$_r$-, -NR^{5}S(=O)$_r$(CR^{4}R^{4a})$_p$-, -C(=O)NR^5(CR^{4}R^{4a})$_p$- oder -NR^5-(CR^{4}R^{4}a),S(=O)$_r$- steht, worin p für 0, 1, 2 oder 3 steht und r für 1 oder 2 steht;

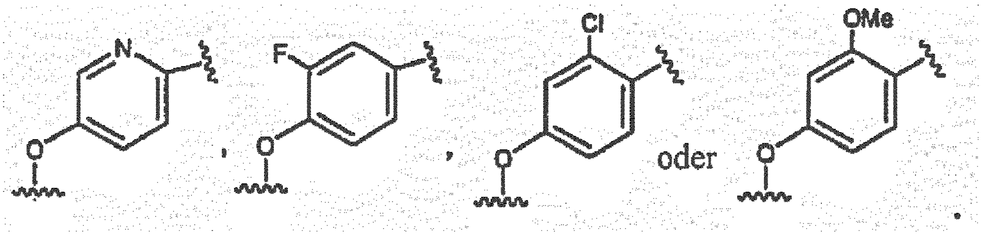
jedes Z$_1$ und Z$_2$ unabhängig für NR^5 oder CR^{4}R^{4a} steht;

jedes R^4 und R^{4a} unabhängig für H, F, Cl, Br, I, -CN, Hydroxyl, -NR^{5a}R^5 steht, mit der Maßgabe, dass, wenn R^4 und R^{4a} an das gleiche Kohlenstoffatom gebunden sind, R^4 und R^{4a} zusammen mit dem Kohlenstoffatom, an das sie angeheftet sind, optional einen 3-8-gliedrigen carbocyclischen oder heterocyclischen Ring bilden;

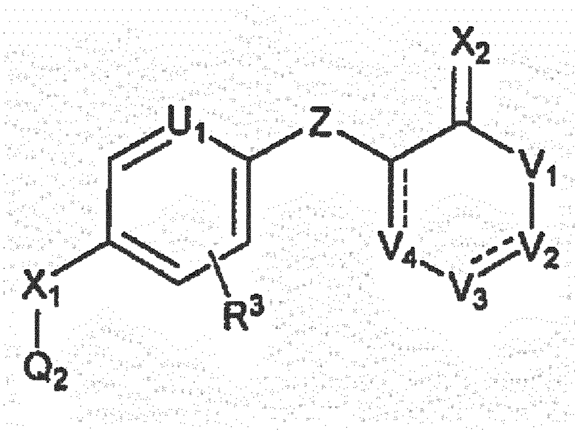
jedes R^5 und R^{5a} unabhängig für H, R^{6}R^{6a}NC(=O)-, R^{6}OC(=O)-, R^{5}C(=O)-, R^{6}R^{6a}NS(=O)-, R^{6}OS(=O)-, R^{6}S(=O)-, R^{6}R^{6a}NSO$_2$-, R^{6}OSO$_2$-, R^{6}SO$_2$- steht, mit der Maßgabe, dass wenn R^5 und R^{5a} an das gleiche Stickstoffatom gebunden sind, R^5 und R^{5a} zusammen mit dem Stickstoffatom, an das sie angeheftet sind, optional einen 3-8-gliedrigen Ring bilden, einschließlich Spiro- und kondensierte bicyclische Ringe;

jedes R^6 und R^{6a} für H steht.

2. Verbindung nach Anspruch 1, wobei Z der Formel (IIa) für -NHC(=O)- steht, Z$_1$ der Formel (IIb) für NH steht; und die Substruktur, definiert durch X$_1$, Z, U$_1$ und R^3 aus Formel I für Folgendes steht:



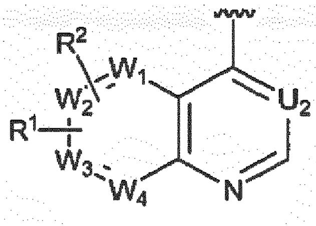
3. Verbindung nach Anspruch 1 mit der Formel (IV):



(IV)

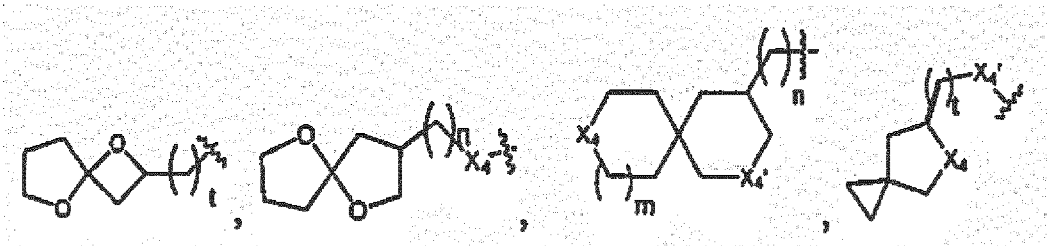
oder ein Stereoisomer, ein geometrisches Isomer, ein Tautomer, ein N-Oxid, ein Hydrat, ein Solvat oder ein pharmazeutisch verträgliches Salz davon, wobei:

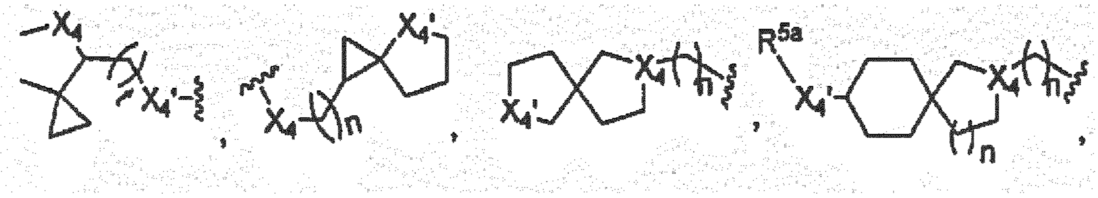
Q_2 die Formel (III) aufweist:

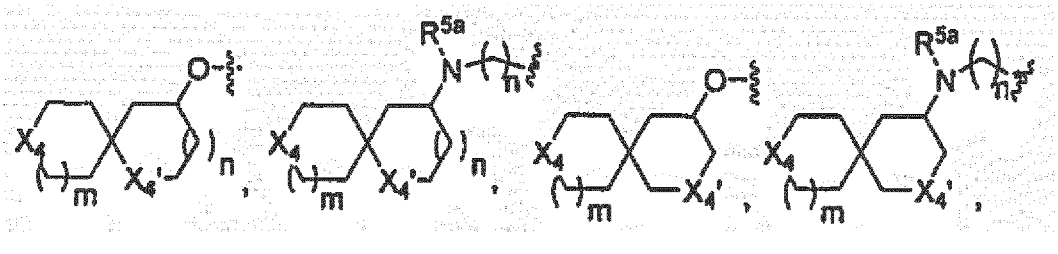


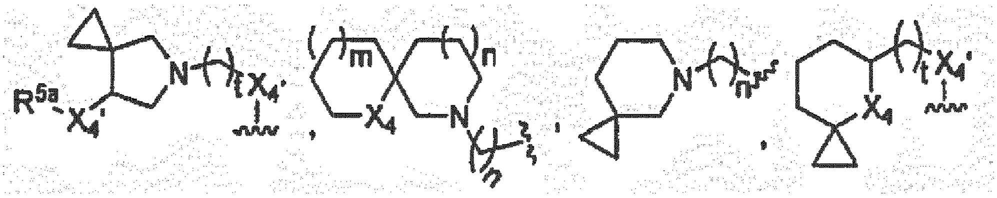
(III);

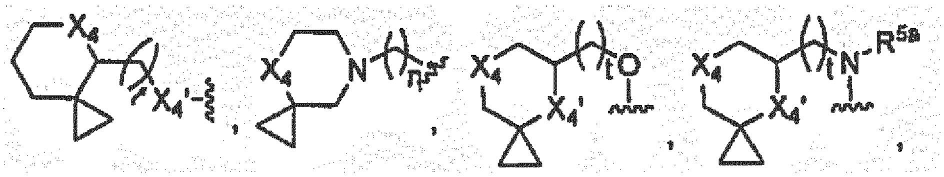
R^1 ausgewählt ist aus

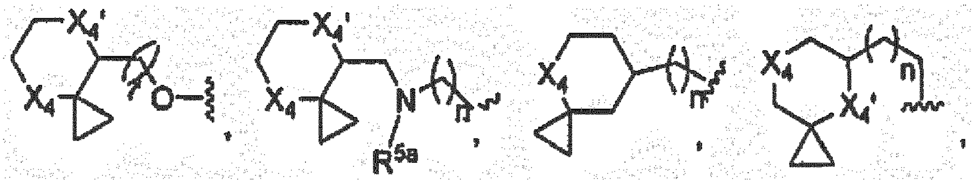


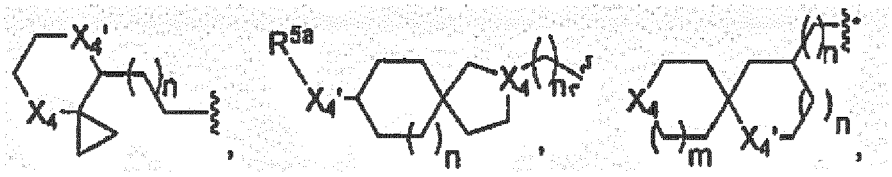


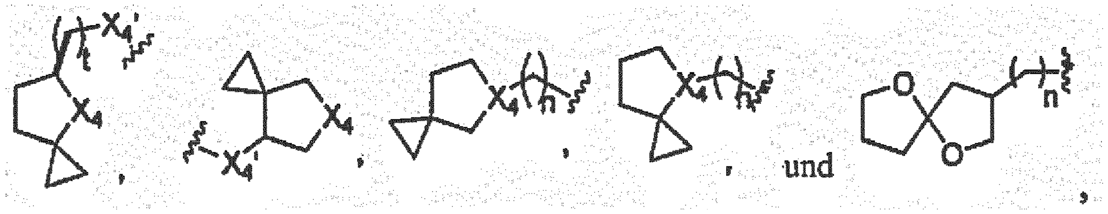












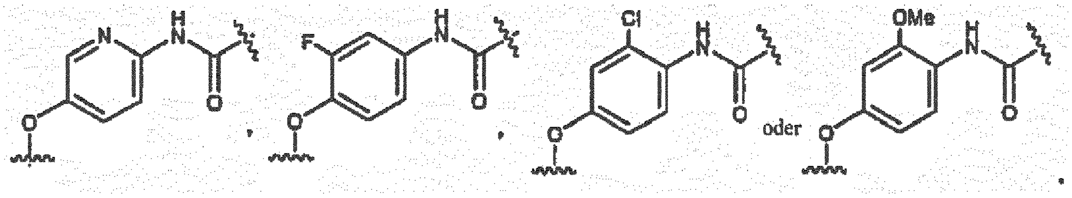
wobei jedes X_4 und X_4' unabhängig für $(CR^4R^{4a})_m$, NR^5, O, S, S=0 oder SO_2 steht; jedes m und n unabhängig für 0, 1 oder 2 steht; und t für 1, 2 oder 3 steht;

R^2 für H, Halo, Cyano(CN), $R^{5a}R^5N$-C_{1-6}-Alkoxy, C_{1-6}-Alkoxy, C_{1-6}-Hydroxyalkoxy, C_{1-6}-Aminoalkoxy, C_{1-6}-Hydroxy-substituiertes Aminoalkoxy, C_{1-6}-Haloalkoxy, C_{1-6}-Alkylamino-C_{1-6}-alkoxy, C_{1-6}-Alkoxy-C_{1-6}-alkoxy, C_{4-10}-Heterocyclyloxy-C_{1-6}-alkoxy, C_{5-12}-kondensiertes Bicyclyl, C_{5-12}-kondensiertes Bicyclyl-C_{1-6}-aliphatisch, C_{5-12}-kondensiertes Heterobieyclyl-C_{1-6}-aliphatisch, C_{5-12}-kondensiertes Bicycloxy, C_{5-12}-kondensiertes Bicyclylamino, C_{5-12}-kondensiertes Bicycloxo-C_{1-6}-alkoxy, C_{5-12}-kondensiertes Bicyclylamino-C_{1-6}-alkoxy, C_{5-12}-kotndensiertes Bicyclyl-C(=O)-, C_{5-12}-kondensiertes Bicyclyl-C(=O)O-, C_{5-12}-kondensiertes Heterobicyclyl-C(=O)-, C_{5-12}-kondensiertes Heterobicyclyl-C(=O)O-, C_{5-12}-kondensiertes Bicyclylamino-C(=O)-, C_{5-12}-kondensiertes Heterobicyclylamino-C(=O)-, C_{5-12}-kondensiertes Bicyclyl-C(=O)NR^5-, C_{5-12}-kondensiertes Heterobicyclyl-C(=O)NR^5-, C_{5-12}-spiro-Bicyclyl, C_{5-12}-spiro-Bicycloxy, C_{5-12}-spiro-Bicyclylamino, C_{5-12}-spiro-Bicycloxo-C_{1-6}-alkoxy, C_{5-12}-spiro-Bicyclylamino-C_{1-6}-alkoxy, C_{5-12}-kondensiertes Heterobicyclyl, C_{5-12}-kondensiertes Heterobicycloxy, C_{5-12}-kondensiertes Heterobicyclylamino, C_{5-12}-kondensiertes Heterobicycloxo-C_{1-6}-Alkoxy, C_{5-12}-kondensiertes Heterobicyclylamino-C_{1-6}-alkoxy, C_{5-12}-spiro-Bicyclyl, C_{5-12}-spiro-Heterobicyclyl, C_{5-12}-spiro-Bicyclyl-C_{1-6}-aliphatisch, C_{5-12}-spiro-Heterobicyclyl-C_{1-6}-aliphatisch, C_{5-12}-spiro-Heterobicycloxo-C_{1-6}-alkoxy, C_{5-12}-spiro-Heterobicyclylamino-C_{1-6}-alkoxy, C_{5-12}-spiro-Bicyclyl-C(=O)-, C_{5-12}-spiro-Bicyclyl-C(=O)O-, C_{5-12}-spiro-Heterobicyclyl-C(=0)-, C_{5-12}spiro Heterobicyclyl-C(=O)O-, C_{5-12}-spiro-Bicyclylamino-C(=O)-, C_{5-12}-spiro-Heterobicyclylamino-C(=O)-, C_{5-12}-spira-Bicyclyl-C(=O)NR^5- oder C_{5-12}-spiro-Heterobicyclyl-C(=O)NR^5-, C_{6-10}-Aryl, C_{1-10}-Heteroaryl, C_{6-10}-Aryl-C_{1-6}-aliphatisch oder C_{1-10}-Heteroaryl-C_{1-6}-aliphatisch steht;

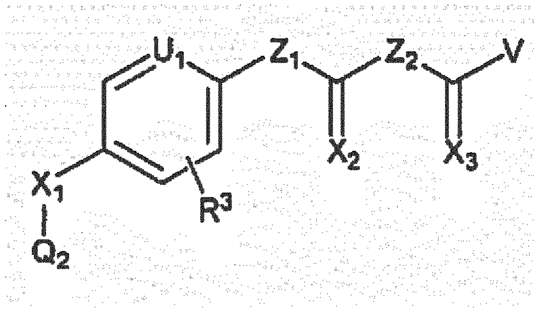
wobei R^3 unabhängig für H, F, Cl, Br, -CN, C_{1-3}-aliphatisch, C_{1-3}-Alkoxy oder C_{1-3}-Haloalkyl steht;

jedes U_1 und U_2 unabhängig für CR^4 oder N steht;
V für NR^5R^{5a}, OR^5 steht;
V_1 für O oder NR^5 steht;
jedes V_2, V_3 und V_4 unabhängig für CR^4R^{4a}, NR^5, CR^4 oder N steht, mit der Maßgabe, dass nur eines von V_2, V_3 und V_4 für NR^5 oder N steht, oder V_2 und V_3 oder V_3 und V_4 kombiniert werden, um CR^4R^{4a}, NR^S, O, CR^4 oder N zu werden, mit der Maßgabe, dass die resultierende Struktur stabil ist;
jedes W_1, W_2, W_3 und W_4 unabhängig für CR^4R^{4a}, NR^5, CR^4 oder N steht, oder W_1 und W_2 oder W_3 und W_4 kombiniert werden, um CR^4R^{4a}, NR^5, O oder S zu werden;
X_1 für $(CR^4R^{4a})_m$, NR^5, O, S, S=O oder SO_2 steht, worin m für 0, 1 oder 2 steht;
X_2 unabhängig für O, S oder NR^5 steht;
Z für $-NR^5C(=O)-(CR^4R^{4a})_p-$, $-NR^5C(=S)-(CR^4R^{4a})_p-$,$-NR^{5a}-(CR^4R^4a)_p-$, $-NR5-$ $(CR^4R^{4a})_pC(=O)-$, $-NR^5-(CR^4R^{4a})_pC(=S)-$,$-NR^5S(=O)_r-$, $-NR^5S(=O)_r(CR^4R^{4a})_p-$, $-C(=O)NR^5(CR^4R^{4a})_p-$ oder $-NR^5-(CR^4R^{4a})_pS(=O)_r-$ steht, worin p für 0, 1, 2 oder 3 steht und r für 1 oder 2 steht;
jedes R^4 und R^{4a} unabhängig für H, F, Cl, Br, I, -CN, Hydroxyl, $-NR^{5a}R^5$ steht, mit der Maßgabe, dass, wenn R^4 und R^{4a} an das gleiche Kohlenstoffatom gebunden sind, R^4 und R^{4a} zusammen mit dem Kohlenstoffatom, an das sie angeheftet sind, optional einen substituierten oder unsubstituierten 3-8-gliedrigen carbocyclischen oder heterocyclischen Ring bilden;
jedes R^5 und R^{5a} unabhängig für H, $R^6R^{6a}NC(=O)-$, $R^6OC(=O)-$, $R^6C(=O)-$, $R^5R^{6a}NS(=O)-$, $R^6OS(=O)-$, $R^6S(=O)-$, $R^6R^{6a}NSO_2-$, R^6OSO_2-, R^6SO_2- steht, mit der Maßgabe, dass wenn R^5 und R^{5a} an das gleiche Stickstoffatom gebunden sind, R^5 und R^{5a} zusammen mit dem Stickstoffatom, an das sie angeheftet sind, optional einen 3-8-gliedrigen Ring bilden, einschließlich Spiro- und kondensierte bicyclische Ringe;
jedes R^6 und R^{6a} unabhängig für H steht;
wobei jedes $R^{5a}R^5N-$, $-C (=O) NR^5R^{5a}$, $-OC(=O)NR^5R^{5a}$, $- OC(=O)OR^5$, $-NR^5C(=O)NR^5R5^a$, $-NR^5C(=O)OR^{5a}$, $-NR^5C(=O)-R^{5a}$, $R^5R^{5a}N-O_2S-$, R^5O_2S-, $R^5O_2SR^{5a}N-$, OR^5, NR^5, CR^4R^{4a}, CR^4, $(CR^4R^{4a})_m$, $-NR^5C(O)-(CR^4R^{4a})_p-$, $-NR^5C(=S)-(CR^4R^{4a})_p-$, $NR^{5a}-(CR^4R^{4a})_p-$,$-NR^5-(CR^4R^{4a})_pC(=O)-$, $-NR^5-(CR^4R^{4a})_pC(=S)-$, $- NR^5S(O)_r-$, $-NR^5S(=O)(CR^4R^{4a})_p-$, $-C(=O)NR^5-(CR^4R^{4a})_p-$, $- NR^5-(CR^4R^{4a})_p-S(=O)_r-$, $R^{5a}R^5N$-Alkyl, $R^5(S=O)$-Alkyl, $R^5R^{5a}N-(C=O)$-Alkyl, $R^{5a}R^5N$-Alkoxy, $R^5(S=O)$-Alkoxy, $R^5R^{5a}N-(C=O)$-Alkoxy, $R^6R^{6a}NC(=O)-$, $R^6OC(=O)-R^6C(=O)-$, $R^6R^{6a}NS(=O)-$, $R^6OS(=O)- R^6S(=O)-$, $R^6R^{6a}NSO2-$, R^6OSO_2-, R^6SO_2-, Hydroxy-substituiertes Cyclopropylalkoxy, $R^5S (=O)_2O$-substituiertes Cyclopropylalkoxy.

4. Verbindung nach Anspruch 3, wobei Z für -NHC(=O)-steht; oder wobei die Substruktur definiert durch X_1, Z, U_1 und R^3 für Folgendes steht:



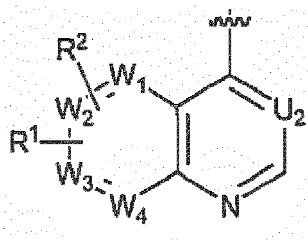
5. Verbindung nach Anspruch 1 mit der Formel V:



(V)

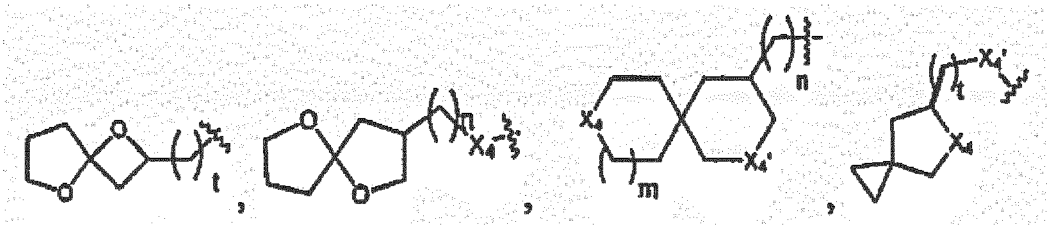
oder ein Stereoisomer, ein geometrisches Isomer, ein Tautomer, ein N-Oxid, ein Hydrat, ein Solvat oder ein pharmazeutisch verträgliches Salz davon, wobei:

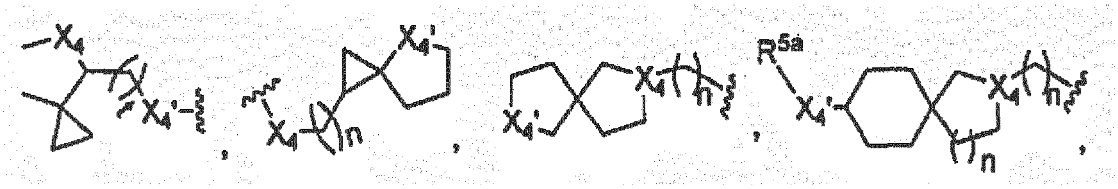
Q_2 die Formel (III) aufweist:

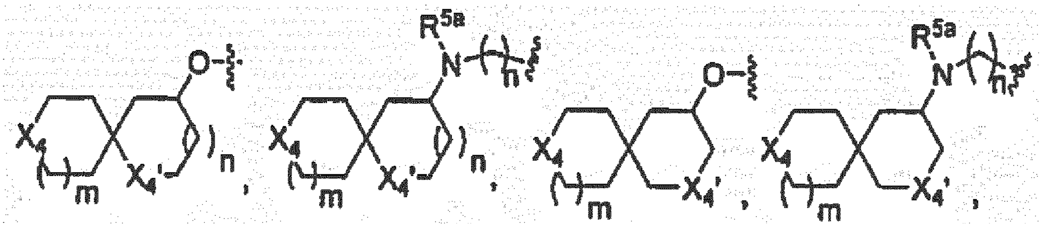


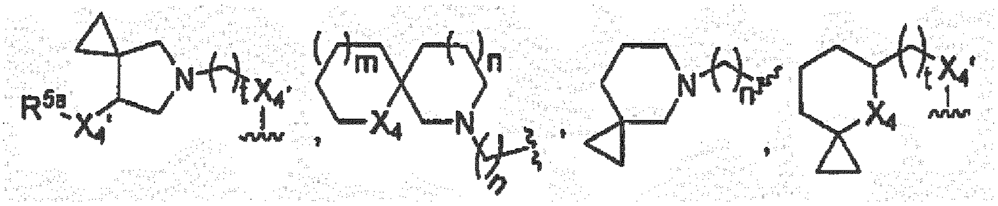
(III);

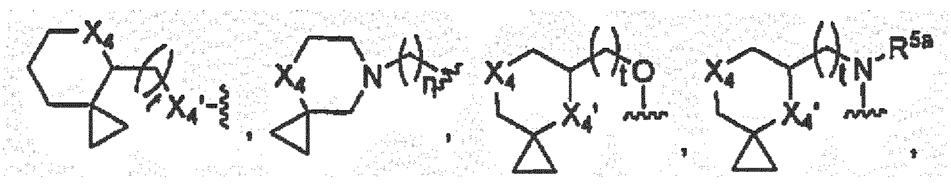
R^1 ausgewählt ist aus

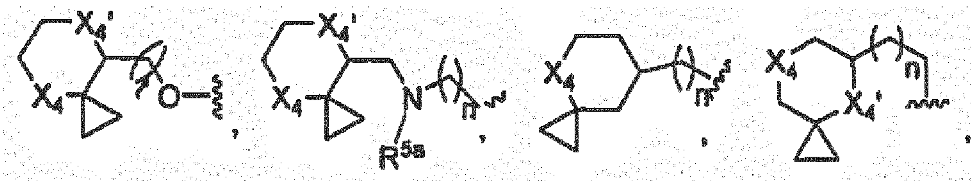


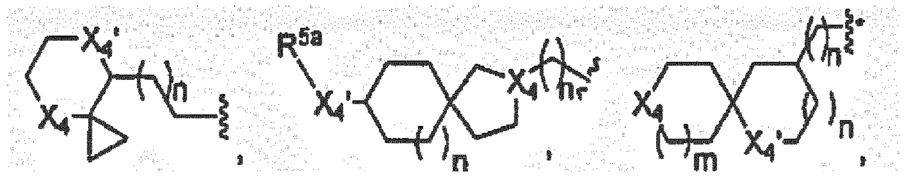


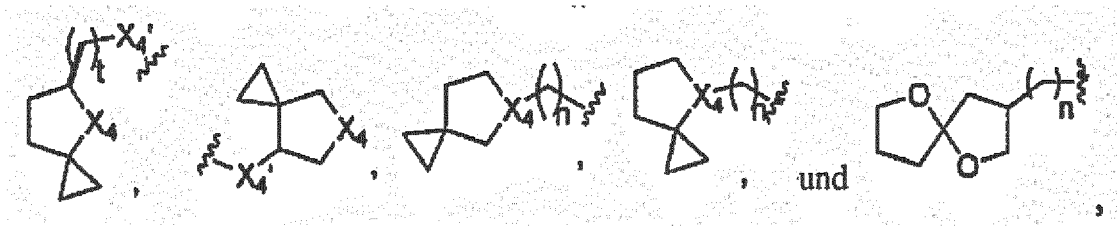












wobei jedes X_4 und $X_4{}^1$ unabhängig für $(CR^4R^{4a})_m$, NR^5, O, S, S=O oder SO_2 steht; jedes m und n unabhängig für 0, 1 oder 2 steht; und t für 1, 2 oder 3 steht;

R^2 für H, Halo, Cyano(CN), $R^{5a}R^5N$-$C_{1\text{-}6}$-Alkoxy, $C_{1\text{-}6}$-Alkoxy, $C_{1\text{-}6}$-Hydroxyalkoxy, $C_{1\text{-}6}$-Aminoalkoxy, $C_{1\text{-}6}$-Hydroxy-substituiertes Aminoalkoxy, $C_{1\text{-}6}$-Haloalkoxy, $C_{1\text{-}6}$-Alkylamino-$C_{1\text{-}6}$-alkoxy, $C_{1\text{-}6}$-Alkoxy-$C_{1\text{-}6}$-alkoxy, $C_{4\text{-}10}$-Heterocyclyloxy-$C_{1\text{-}6}$-alkoxy, $C_{5\text{-}15}$-kondensiertes Bicyclyl, $C_{5\text{-}12}$-kondensiertes Bicyclyl-$C_{1\text{-}6}$-aliphatisch, $C_{5\text{-}12}$-kondensiertes Heterobicyclyl-$C_{1\text{-}6}$-aliphatisch, $C_{5\text{-}12}$-kondensiertes Bicycloxy, $C_{5\text{-}12}$-kondensiertes Bicyclylamino, $C_{5\text{-}12}$-kondensiertes Bicycloxo-$C_{1\text{-}6}$-alkoxy, $C_{5\text{-}12}$-kondensiertes Bicyclylamino-$C_{1\text{-}6}$-alkoxy, $C_{5\text{-}12}$-kondensiertes Bicyclyl-C(=O)-, $C_{5\text{-}12}$-kondensiertes Bicyclyl-C(=O)O-, $C_{5\text{-}12}$-kondensiertes Heterobicyclyl-C(=O)-, $C_{5\text{-}12}$-kondensiertes Heterobicyclyl-C(=O)O-, $C_{5\text{-}12}$-kondensiertes Bicyclylamino-C(=O)-, $C_{5\text{-}12}$-kondensiertes Heterobicyclylamino-C(=O)-, $C_{5\text{-}12}$-kondensiertes Bicyclyl-C(=O)NR^5-, $C_{5\text{-}12}$-kondensiertes Heterobicyclyl-C(=O)NR^5-, $C_{5\text{-}12}$-spiro-Bicyclyl, $C_{5\text{-}12}$-spiro-Bicycloxy, $C_{5\text{-}12}$-spiro-Bicyclylamino, $C_{5\text{-}12}$-spiro-Bicycloxo-$C_{1\text{-}6}$-alkoxy, $C_{5\text{-}12}$-spiro-Bicyclylamino-$C_{1\text{-}6}$-alkoxy, $C_{5\text{-}12}$-kondensiertes Heterobicyclyl, $C_{5\text{-}12}$-kondensiertes Heterobicycloxy, $C_{5\text{-}12}$-kondensiertes Heterobicyclylamino, $C_{5\text{-}12}$-kondensiertes Heterobicycloxo-$C_{1\text{-}6}$-Alkoxy, $C_{5\text{-}12}$-kondensiertes Heterobicyclylamino-$C_{1\text{-}6}$-alkoxy, $C_{5\text{-}12}$-spiro-Bicyclyl, $C_{5\text{-}12}$-spiro-Heterobicyclyl, $C_{5\text{-}12}$-piro-Bicyclyl-$C_{1\text{-}6}$-aliphatisch, $C_{5\text{-}12}$-spiro-Heterobicyclyl-$C_{1\text{-}6}$-aliphatisch, $C_{5\text{-}12}$-spiro-Heterobicycloxo-$C_{1\text{-}6}$-alkoxy, $C_{5\text{-}12}$-spiro-Heterobicyclylamino-$C_{1\text{-}6}$-alkoxy, $C_{5\text{-}12}$-spiro-Bicyclyl-C(=O)-, $C_{5\text{-}12}$-spiro-Bicyclyl-C(=O)O-, $C_{5\text{-}12}$-spiro-Heterobicyclyl-C(=O)-, $C_{5\text{-}12}$-spiro Heterobicyclyl-C(=O)O-, $C_{5\text{-}12}$-spiro-Bicyclylamino-C(=O)-, $C_{5\text{-}12}$-spiro-Heterobicyclylamino-C(=O)$C_{5\text{-}12}$-spiro-Bicyclyl-C(=O)NR^5- oder $C_{5\text{-}12}$-spiro-Heterobicyclyl-C(=O)NR^5-, $C_{6\text{-}10}$-Aryl, $C_{1\text{-}10}$-Heteroaryl, $C_{6\text{-}10}$-Aryl-$C_{1\text{-}6}$-aliphatisch oder $C_{1\text{-}10}$-Heteroaryl-$C_{1\text{-}6}$-aliphatisch steht;

wobei R^3 unabhängig für H, F, Cl, Br, -CN, $C_{1\text{-}3}$-aliphatisch, $C_{1\text{-}3}$-Alkoxy oder $C_{1\text{-}3}$-Haloalkyl steht;

jedes U_1 und U_2 unabhängig für CR^4 oder N steht;

V für NR^5R^{5a}, OR^5 steht;

jedes W_1, W_2, W_3 und W_4 unabhängig für CR^4R^{4a}, NR^5, CR^4 oder N steht, oder W_1 und W_2 oder W_3 und W_4 kombiniert werden, um CR^4R^{4a}, NR^5, O oder S zu werden;

X_1 für $(CR^4R^{4a})_m$, NR^5, O, S, S=O oder SO_2 steht, worin m für 0, 1 oder 2 steht;

jedes X_2 und X_3 unabhängig für O, S oder NR^5 steht;

jedes Z_1 und Z_2 unabhängig für NR^5 oder CR^4R^{4a} steht;

jedes R^4 und R^{4a} unabhängig für H, F, Cl, Br, I, -CN, Hydroxyl, -$NR^{5a}R^5$ steht, mit der Maßgabe, dass, wenn R^4 und R^{4a} an das gleiche Kohlenstoffatom gebunden sind, R^4 und R^{4a} zusammen mit dem Kohlenstoffatom, an das sie angeheftet sind, optional einen substituierten oder unsubstituierten 3-8-gliedrigen carbocyclischen oder heterocyclischen Ring bilden;

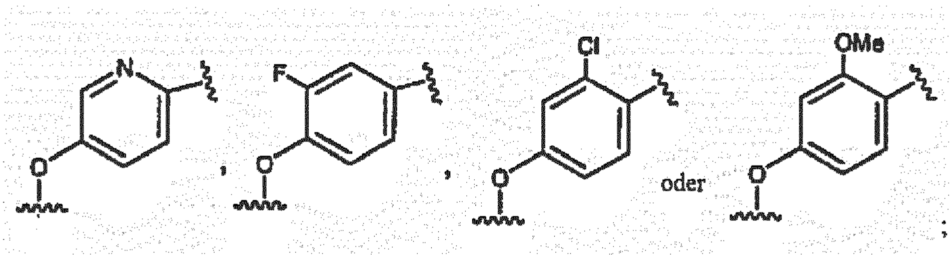
jedes R^5 und R^{5a} unabhängig für H, $R^6R^{6a}NC(=O)$-, $R^6OC(=O)$-, $R^6C(=O)$-, $R^6R^{6a}NS(=O)$-, $R^6OS(=O)$-, $R^6S(=O)$-, $R^6R^{6a}NSO_2$-, R^6OSO_2-, R^6SO_2- steht, mit der Maßgabe, dass wenn R^5 und R^{5a} an das gleiche Stickstoffatom gebunden sind, R^5 und R^{5a} zusammen mit dem Stickstoffatom, an das sie angeheftet sind, optional einen substituierten oder unsubstituierten 3-8-gliedrigen Ring bilden, einschließlich Spiro- und kondensierte bicyclische Ringe;

jedes R^6 und R^6a unabhängig für H steht;

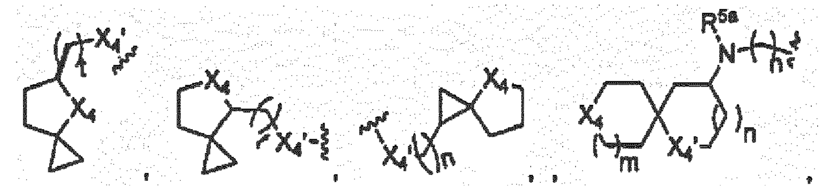
wobei jedes $R^{5a}R^5N$-, -C(=O)NR^5R^{5a}, -OC(=O)NR^5R^{5a},-OC(=O)OR^5, -$NR^5C(=O)NR^5R^{5a}$, -$NR^5C(=O)OR^{5a}$, -$NR^5C(=O)$-R^{5a}, $R^5R^{5a}N$-O_2S-, R^5O_2S-, $R^5O_2SR^{5a}N$-, OR^5, NR^5, CR^4R^{4a}, CR^4, $(CR^4R^{4a})_m$,-$NR^5C(O)$-$(CR^4R^{4a})_p$-, -$NR^5C(=S)$-$(CR^4R^{4a})_p$-, NR^{5a}-$(CR^4R^{4a})_p$-, -NR^5-$(CR^4R^{4a})_pC(=O)$-, -NR^5-$(CR^4R^{4a})_pC(=S)$-, - $NR^5S(O)_r$-, -$NR^5S(=O)(CR^4R^{4a})_p$-, -C(=O)NR^5-$(CR^4R^{4a})_p$-, - NR^5-$(CR^4R^{4a})_p$-$S(=O)_r$-,

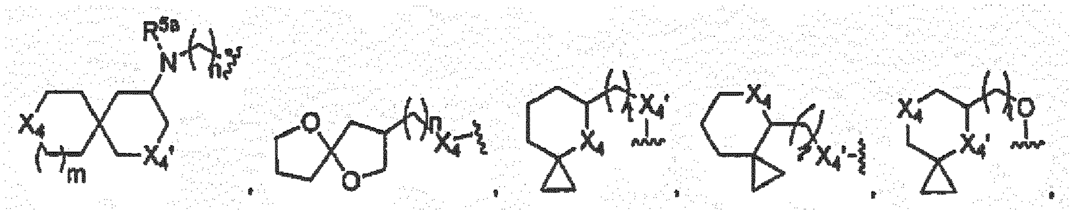
$R^{5a}R^5N$-Alkyl, R^5 (S=O)-Alkyl, $R^5R^{5a}N$- (C=O)-Alkyl, $R^{5a}R^5N$-Alkoxy, R^5(S=O)-Alkoxy, $R^5R^{5a}N$-(C=O)-alkoxy, $R^6R^{6a}NC(=O)$-, $R^6OC(=O)$-$R^6C(=O)$-, $R^6R^{6a}NS(=O)$-, $R^6OS(=O)$-$R^6S(=O)$-, $R^6R^{6a}NSO_2$-, R^6OSO_2-, R^6SO_2-, Hydroxy-substituiertes Cyclopropylalkoxy, $R^5S(=O)_2O$-substituiertes Cyclopropylalkoxy.

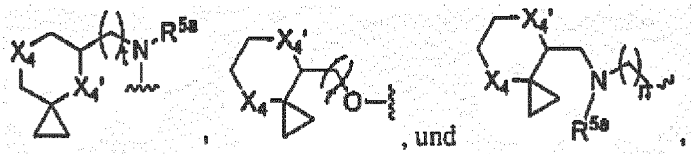
6. Verbindung nach Anspruch 5, wobei die Substruktur, definiert durch X_1, U_1 und R^3 für Folgendes steht:



und/oder wobei R^1 für eine der folgenden Strukturen steht:

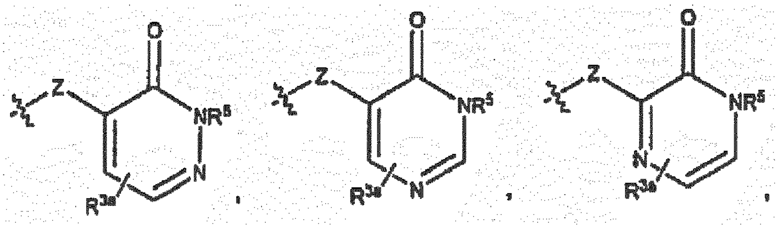


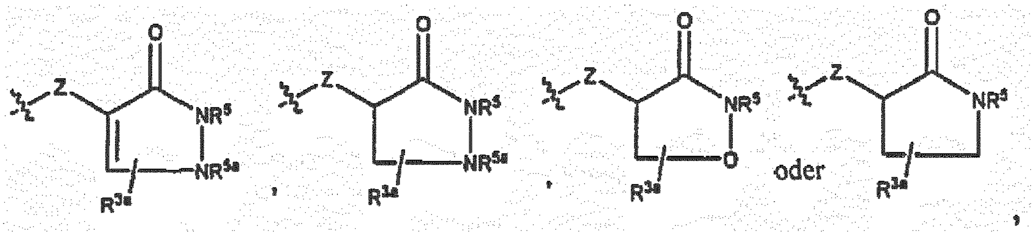




wobei jedes X_4 und X_4' unabhängig für $(CR^4R^{4a})_m$, NR^5, O, S, S=O oder SO_2 steht; jedes m und n unabhängig für 0, 1 oder 2 steht; und t für 1, 2 oder 3 steht.

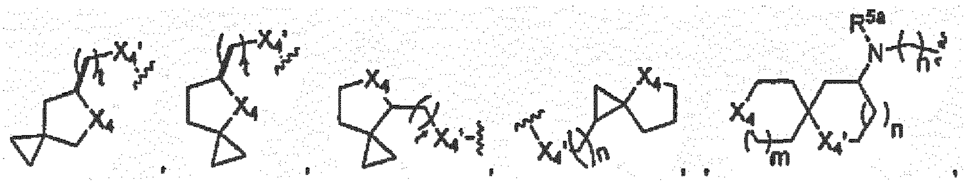
7. Verbindung nach Anspruch 1 oder 3, wobei Q_1 in Formel 1 oder der Substruktur, definiert durch X_2, V_1, V_2, V_3, V_4 und Z der Formel (IV) für Folgendes steht:

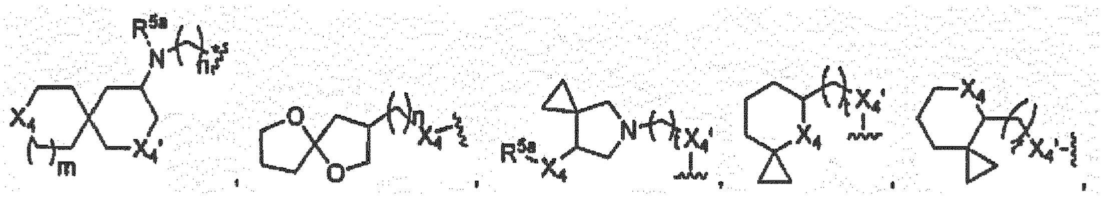


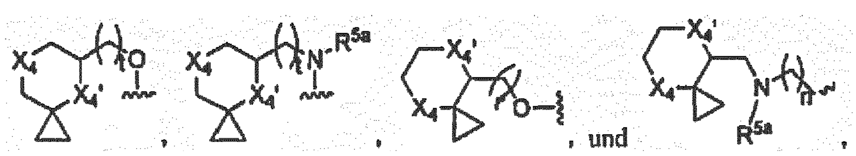


wobei R^{3a} für H, F, Cl, Br, I, -CN, Hydroxyl, $R^{5a}R^5N$-, $R^{5a}R^5N$-aliphatisch steht.

8. Verbindung nach Anspruch 1 oder 3 oder 5, wobei R^1 für eine der folgenden Strukturen steht:

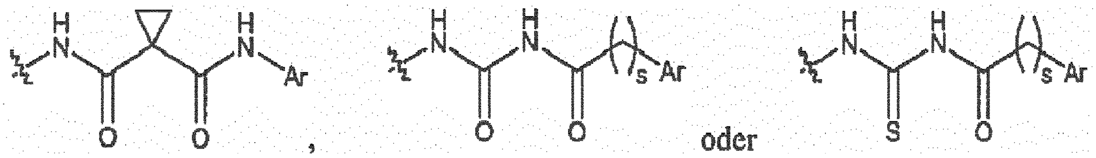






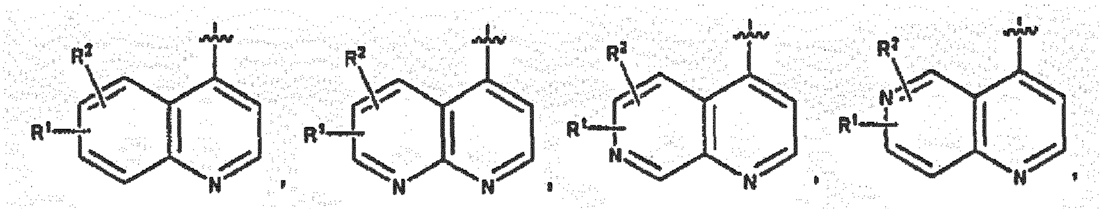
wobei jedes X_4 und X_4' unabhängig für $(CR^4R^{4a})_m$, NR^5, O, S, S=O oder SO_2 steht; jedes m und n unabhängig für 0, 1 oder 2 steht; und t für 1, 2 oder 3 steht.

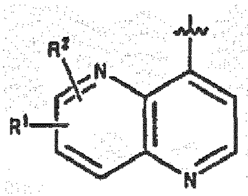
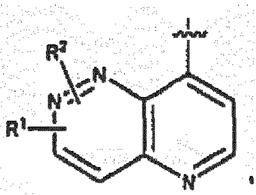
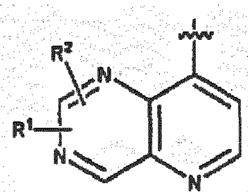
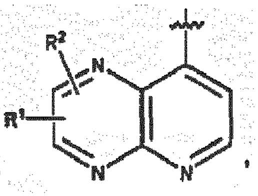
9. Verbindung nach Anspruch 1 oder 5, wobei Q_1 in Formel (I) oder die Substruktur definiert durch Z_1, Z_2, X_2, X_3 und V der Formel (V) für Folgendes steht:

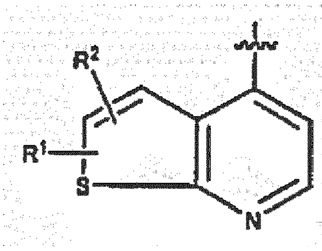
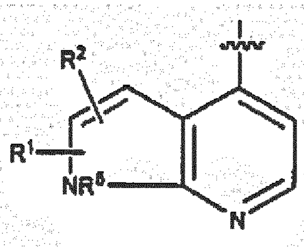
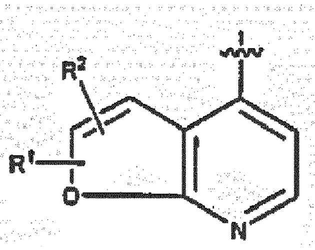


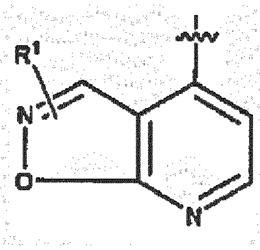
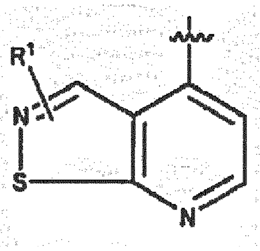
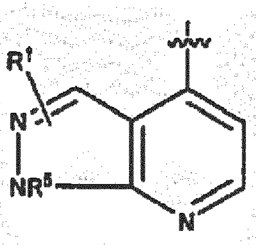
wobei Ar für substituiertes oder unsubstitutiertes Aryl oder Heteroaryl steht; und s für 0 oder 1 steht.

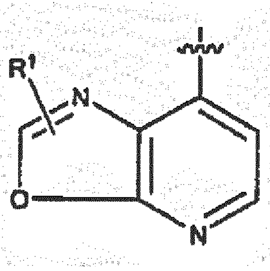
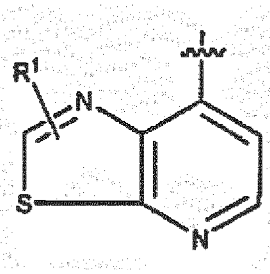
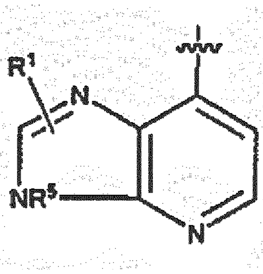
10. Verbindung nach einem der Ansprüche 1, 3 und 5, wobei Q_2 für Folgendes steht:

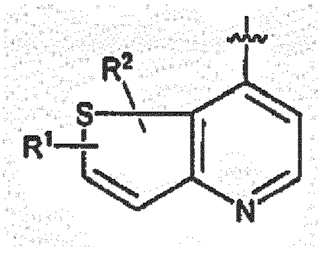
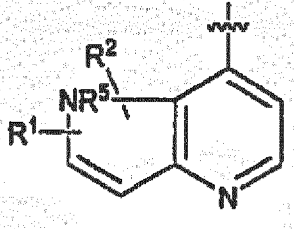
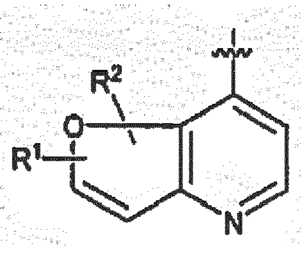


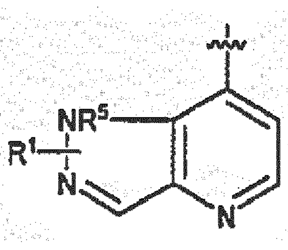
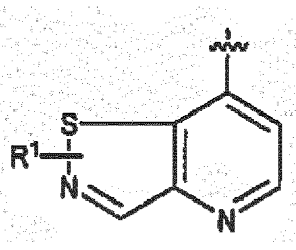
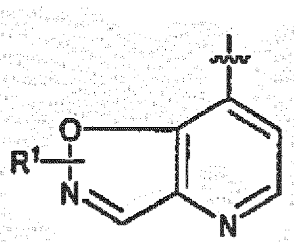

R²
R¹
N
N
,

R²
R¹
N
N
N
,

R²
R¹
N
N
N
,

R²
R¹
N
N
N
,

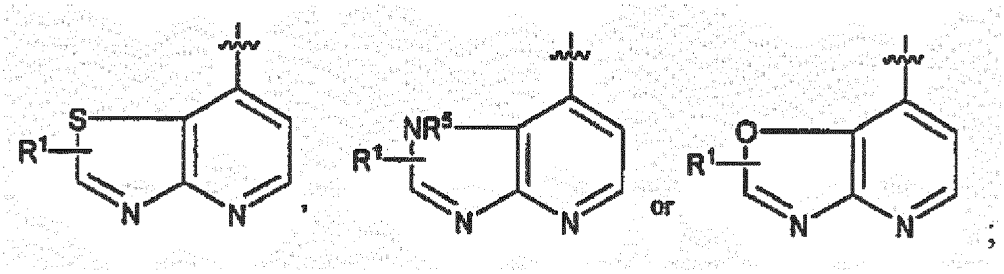

R²
R¹
S
N
,

R²
R¹
NR⁵
N
,

R²
R¹
O
N
,


R¹
N
O
N
,

R¹
N
S
N
,

R¹
N
NR⁵
N
,


R¹
N
O
N
,

R¹
N
S
N
,

R¹
N
NR⁵
N
,


R²
S
R¹
N
,

R²
NR⁵
R¹
N
,

R²
O
R¹
N
,


NR⁵
R¹
N
N
,

S
R¹
N
N
,

O
R¹
N
N
,



oder wobei X_1 für O oder NR^5 steht.

11. Pharmazeutische Zusammensetzung, umfassend eine Verbindung nach einem der Ansprüche 1 bis 10 und einen pharmazeutisch verträglichen Träger, Exzipienten, ein Verdünnungsmittel, Adjuvans, Vehikel oder eine Kombination davon, und optional ein therapeutisches Mittel, ausgewählt au einem chemotherapeutischen Mittel, einem proliferationshemmenden Mittel, einem Mittel zur Behandlung von Atherosklerose, einem Mittel zur Behandlung von Lungenfibrose und Kombinationen davon;
wobei das zusätzliche therapeutische Mittel optional Adriamycin, Rapamycin, Temsirolimus, Everolimus, Ixabepilon, Gemcitabin, Cyclophosphamid, Dexamethason, Etoposid, Fluorouracil, Imatinib-mesylat, Dasatinib, Nilotinib, Erlotinib, Lapatinib, Iressa, Sorafenib, Sunitinib, ein Interferon, Carboplatin, Topotecan, Taxol, Vinblastin, Vincristin, Temozolomid, Tositumomab, Trabedectin, Bevacizumab, Trastuzumab, Cetuximab, Panitumumab oder eine Kombination davon ist.

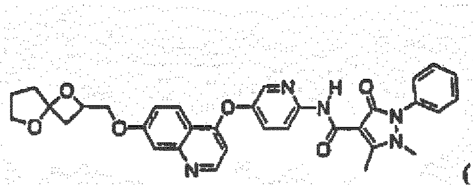
12. Verbindung nach einem der Ansprüche 1 bis 10 oder pharmazeutische Zusammensetzung nach Anspruch 11 zur Verwendung bei der Verhinderung, dem Management, der Behandlung oder der Minderung der Schwere einer proliferativen Störung.

13. Verbindung oder pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 12, wobei die proliferative Störung ein metastasierender Krebs, Kolonkrebs, Magen-Adenokarzinome, Blasenkrebs, Brustkrebs, Nierenkrebs, Leberkrebs, Lungenkrebs, Schilddrüsenkrebs, Kopf- und Halskrebs, Prostatakrebs, Bauchspeicheldrüsenkrebs, Krebs des ZNS, Glioblastom oder eine myeloproliferative Störung, Atherosklerose oder Lungenfibrose ist.

14. Verfahren zur Inhibition oder Modulation der Proteinkinaseaktivität in einer biologischen Probe, umfassend das Inkontakbringen einer biologischen Probe mit der Verbindung nach einem der Ansprüche 1 bis 10 oder der pharmazeutischen Zusammensetzung nach Anspruch 11.

15. Verfahren nach Anspruch 14, wobei die Proteinkinasen Rezeptortyrosinkinasen sind und wobei die Rezeptortyrosinkinasen KDR, c-Met oder IGF1R sind.

16. Verbindung mit einer der folgenden Strukturen: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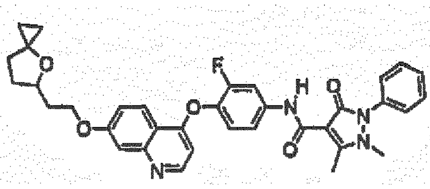
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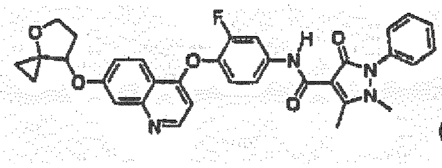
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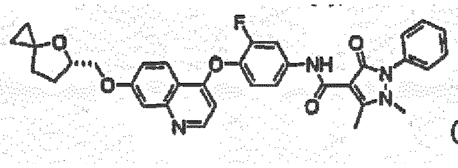
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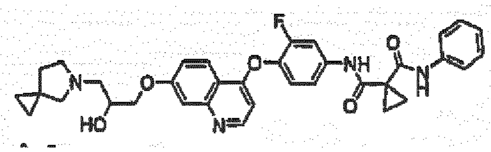
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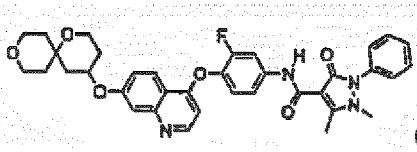
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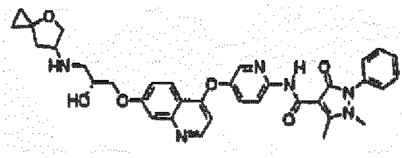
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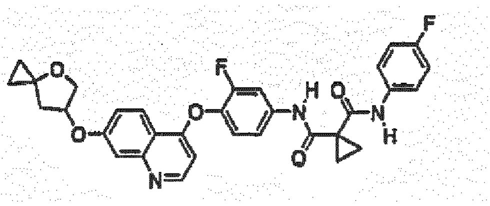
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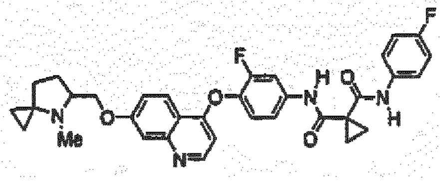
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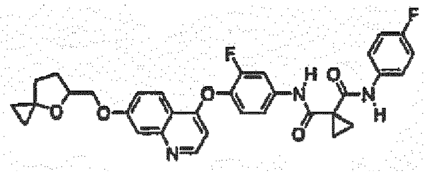
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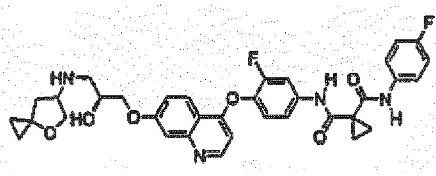
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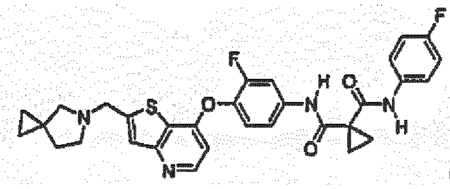
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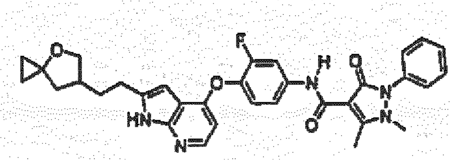
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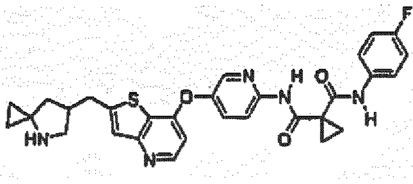
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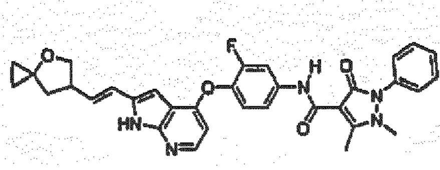
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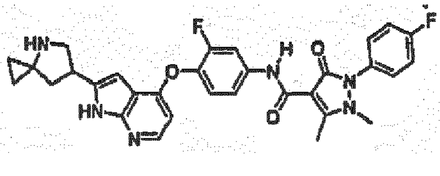
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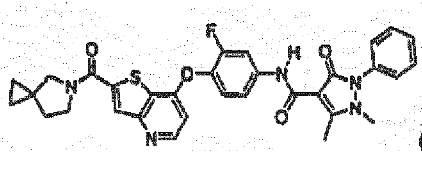
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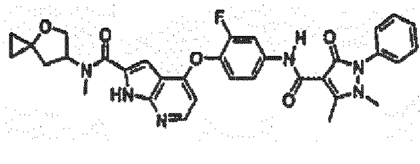
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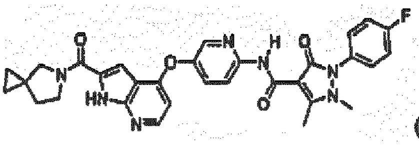
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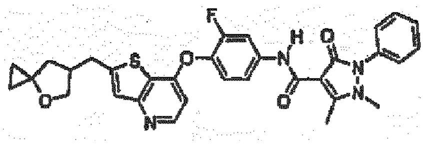
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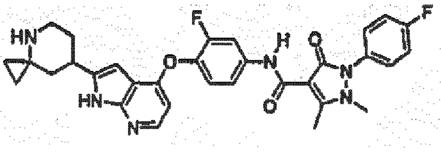
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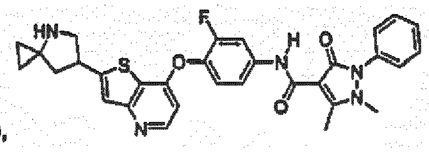
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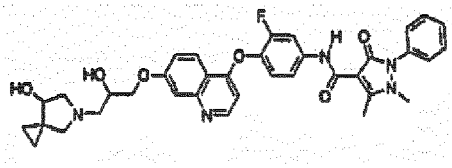
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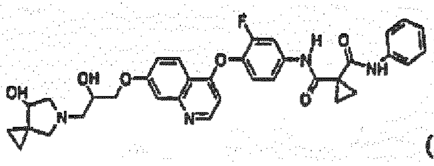
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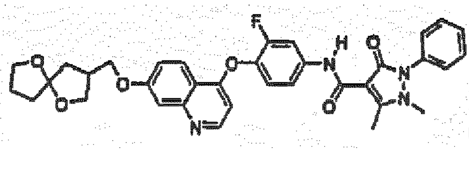
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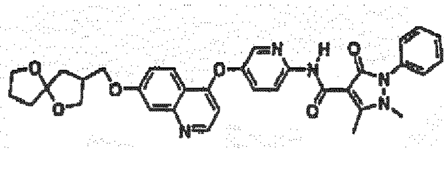
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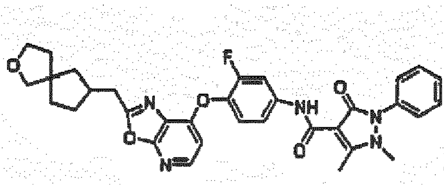
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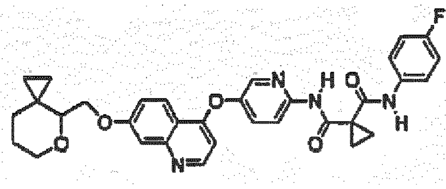
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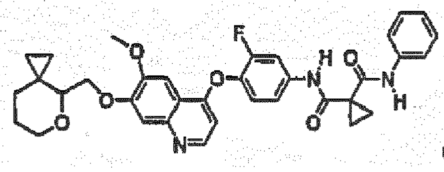
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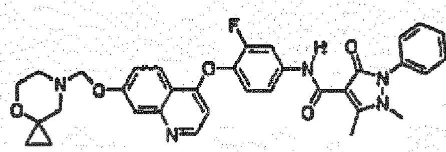
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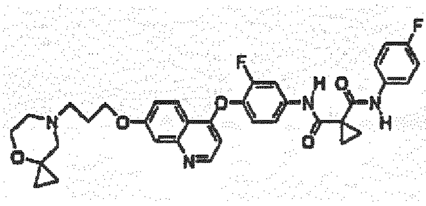
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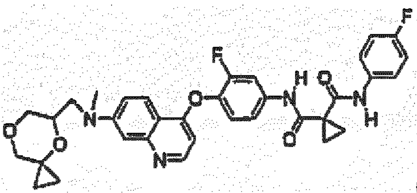
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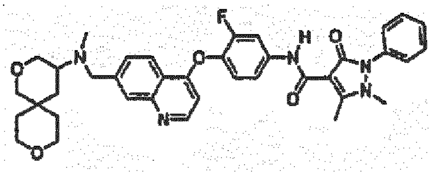
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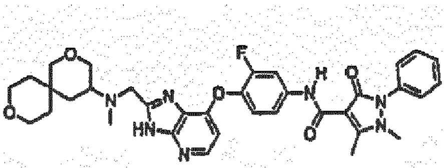
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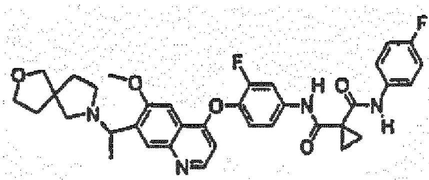
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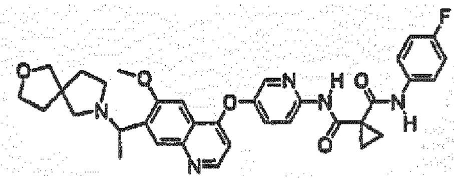
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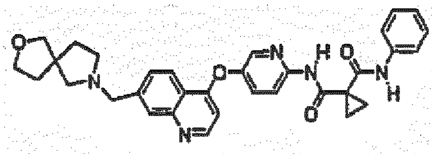
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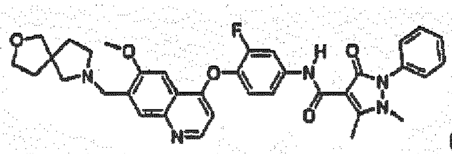
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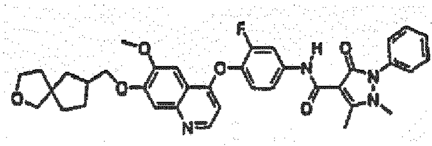
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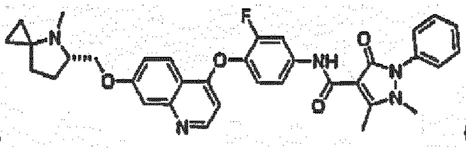
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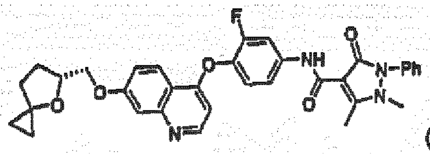
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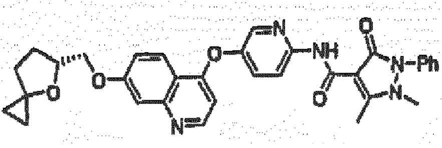
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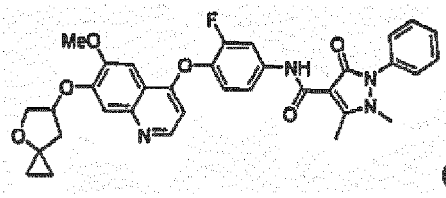
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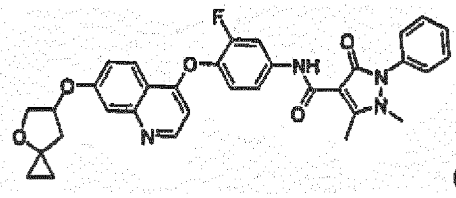
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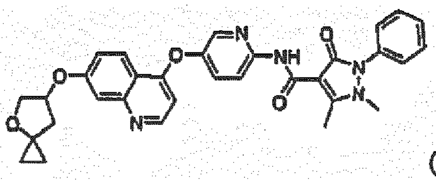
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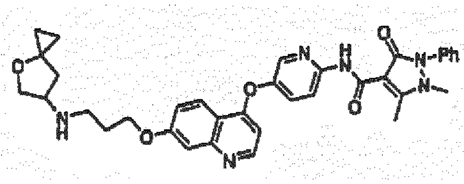
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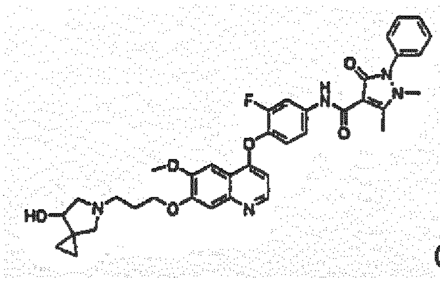
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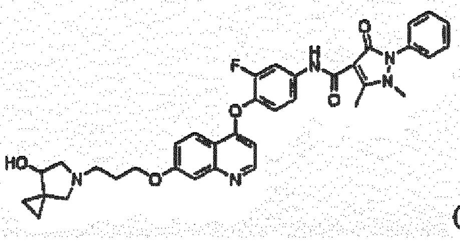
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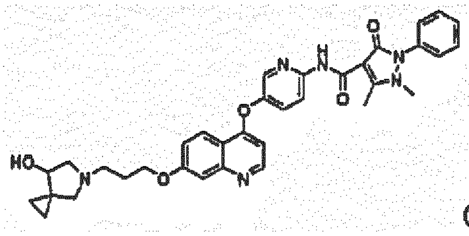
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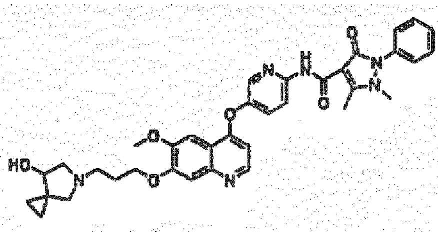
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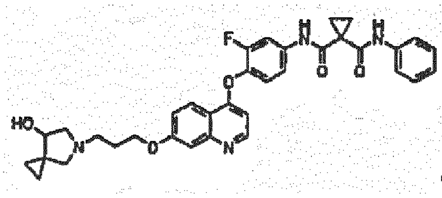

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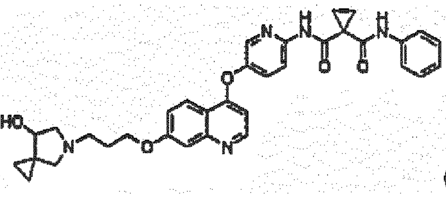

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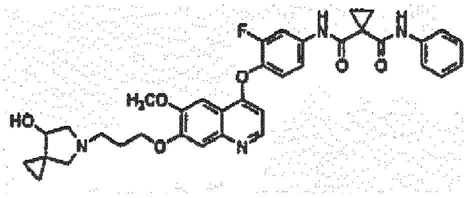

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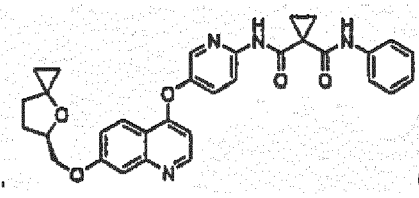

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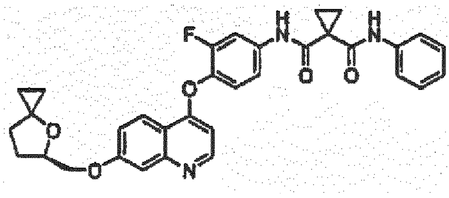

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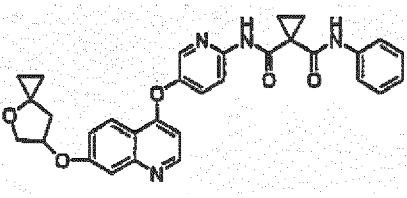

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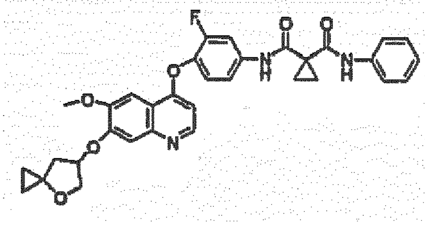

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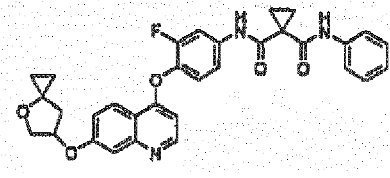

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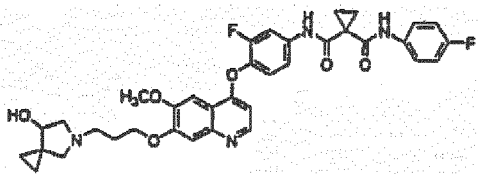
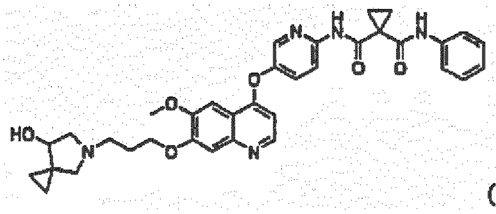


(77),

und

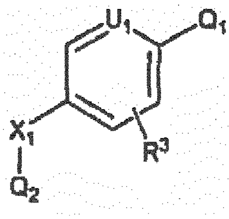


(78),

oder ein Stereoisomer, ein geometrisches Isomer, ein Tautomer, ein N-Oxid, ein Hydrat, ein Solvat oder ein pharmazeutisch verträgliches Salz davon.

Revendications

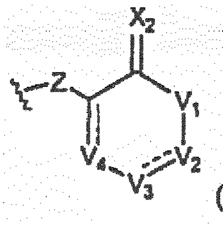
1. Composé de formule (I) :



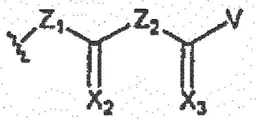
(I)

ou un stéréoisomère, un isomère géométrique, un tautomère, un N-oxyde, un hydrate, un solvate ou un sel pharmaceutiquement acceptable de celui-ci, où :

Q_1 répond à la formule (IIa) ou (IIb) :

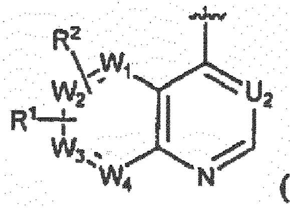


(IIa), ou



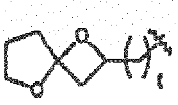
(IIb);

Q_2 répond à la formule (III) :



(III);

R^1 est sélectionné parmi :



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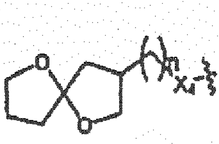

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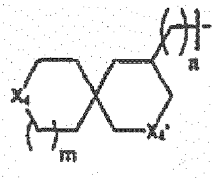

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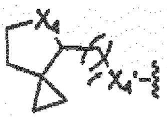

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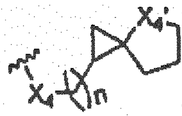

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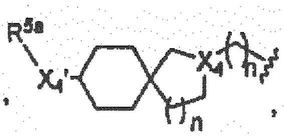

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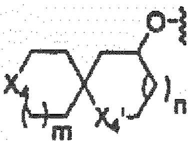

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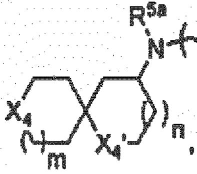

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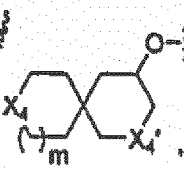

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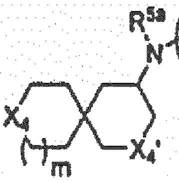

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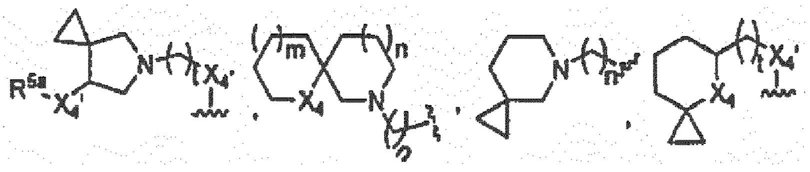
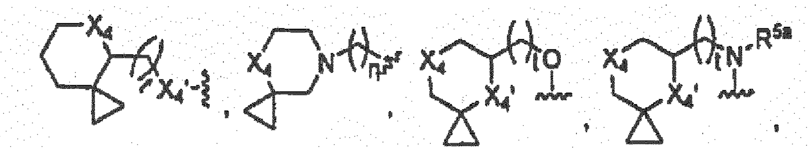
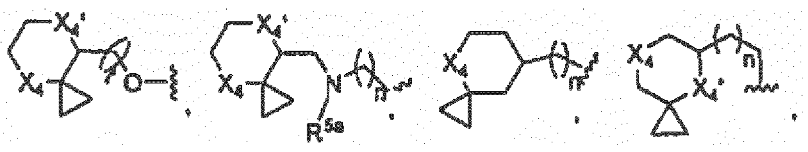
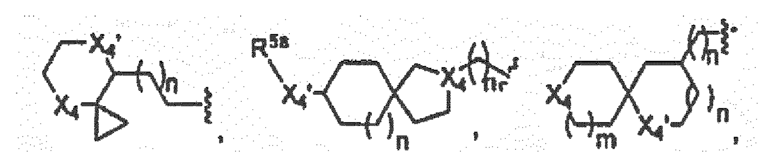
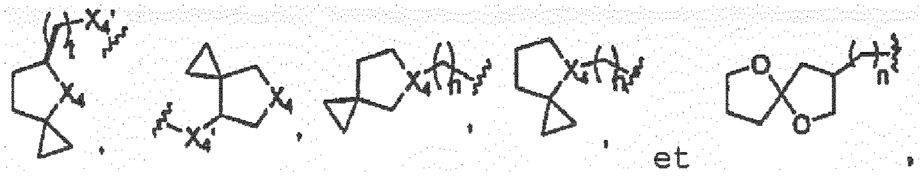










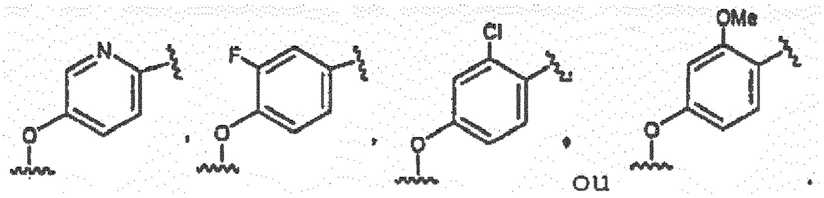
où chacun de X_4 et X_4' est indépendamment $(CR^4R^{4a})_m$, NR^5, O, S, S=O ou SO_2 ; chacun de m et n est indépendamment 0, 1 ou 2 ; et t est 1, 2 ou 3 ;

R^2 est H, un atome d'halogène, un groupe cyano (CN), $R^{5a}R^5N$-alcoxy en C_1 à C_6, alcoxy en C_1 à C_6, hydroxyalcoxy en C_1 à C_6, aminoalcoxy en C_1 à C_6, aminoalcoxy en C_1 à C_6 substitué par un groupe hydroxy, halogénoalcoxy en C_1 à C_6, (alkylamino en C_1 à C_6) alcoxy en C_1 à C_6, (alcoxy en C_1 à C_6) alcoxy en C_1 à C_6, (hétérocyclyloxy en C_4 à C_{10}) alcoxy en C_1 à C_6, bicyclyle condensé en C_5 à C_{12}, (bicyclyle condensé en C_5 à C_{12})aliphatique en C_1 à C_6, (hétérobicyclyle condensé en C_5 à C_{12})aliphatique en C_1 à C_6, bicycloxy condensé en C_5 à C_{12}, bicyclylamino condensé en C_5 à C_{12}, (bicycloxo condensé en C_5 à C_{12}) alcoxy en C_1 à C_6, (bicyclylamino condensé en C_5 à C_{12})alcoxy en C_1 à C_6, (bicyclyle condensé en C_5 à C_{12})-C(=O)-, (bicyclyle condensé en C_5 à C_{12})-C(=O)O-, (hétérobicyclyle condensé en C_5 à C_{12})-C(=O)-, (hétérobicyclyle condensé en C_5 à C_{12})-C(=O)O-, (bicyclylamino condensé en C_5 à C_{12})-C(=O)-, (hétérobicyclylamino condensé en C_5 à C_{12})-C(=O)-, (bicyclyle condensé en C_5 à C_{12}) -C (=O) NR^5-, (hétérobicyclyle condensé en C_5 à C_{12})-C(=O)NR^5-, spirobicyclyle en C_5 à C_{12}, spirobicycloxy en C_5 à C_{12}, spirobicyclylamino en C_5 à C_{12}, (spirobicycloxo en C_5 à C_{12})alcoxy en C_1 à C_6, (spirobicyclylamino en C_5 à C_{12})alcoxy en C_1 à C_6, hétérobicyclyle condensé en C_5 à C_{12}, hétérobicycloxy condensé en C_5 à C_{12}, hétérobicyclylamino condensé en C_5 à C_{12}, (hétérobicycloxo condensé en C_5 à C_{12})alcoxy en C_1 à C_6, (hétérobicyclylamino condensé en C_5 à C_{12})alcoxy en C_1 à C_6, spirobicyclyle en C_5 à C_{12}, spirohétérobicyclyle en C_5 à C_{12}, (spirobicyclyle en C_5 à C_{12})aliphatique en C_1 à C_6, (spirohétérobicyclyle en C_5 à C_{12})aliphatique en C_1 à C_6, (spirohétérobicycloxo en C_5 à C_{12})alcoxy en C_1 à C_6, (spirohétérobicyclylamino en C_5 à C_{12})alcoxy en C_1 à C_6, (spirobicyclyle en C_5 à C_{12})-C(=O)-, (spirobicyclyle en C_5 à C_{12})-C(=O)O-, (spirohétérobicyclyle en C_5 à C_{12})-C(=O)-, (spirohétérobicyclyle en C_5 à C_{12})-C(=O)O-, (spirobicyclylamino en C_5 à C_{12})-C(=O)-, (spirohétérobicyclylamino en C_5 à C_{12})-C(=O)-, (spirobicyclyle en C_5 à C_{12})-C (=O) NR^5-, ou (spirohétérobicyclyle en C_5 à C_{12})-C(=O)NR^5-, aryle en C_6 à C_{10}, hétéroaryle en C_1 à C_{10}, (aryle en C_6 à C_{10})aliphatique en C_1 à C_6 ou (hétéroaryle en C_1 à C_{10}) aliphatique en C_1 à C_6 ;

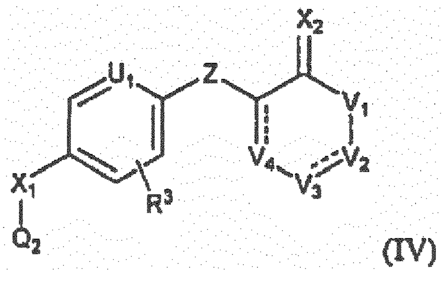
où R^3 est indépendamment H, F, Cl, Br, -CN, un groupe aliphatique en C_1 à C_3, alcoxy en C_1 à C_3 ou halogénoalkyle en C_1 à C_3 ;

chacun de U_1 et U_2 est indépendamment CR^4 ou N ;
V est NR^5R^{5a} ou OR^5 ;
V_1 est O ou NR^5 ;
chacun de V_2, V_3 et V_4 est indépendamment CR^4R^{4a}, NR^5, CR^4 ou N, à condition que seulement un de V_2, V_3 et V_4 soit NR^5 ou N, ou V_2 et V_3 ou V_3 et V_4 se combinent pour devenir CR^4R^{4a}, NR^5, O, CR^4 ou N, à condition que la structure résultante soit stable ;
chacun de W_1, W_2, W_3 et W_4 est indépendamment CR^4R^{4a}, NR^5, CR^4 ou N, ou W_1 et W_2 ou W_3 et W_4 se combinent pour devenir CR^4R^{4a}, NR^5, O ou S ;
X_1 est $(CR^4R^{4a})_m$, NR^5, O, S, S=O ou SO_2, où m est 0, 1 ou 2 ;
chacun de X_2 et X_3 est indépendamment O, S ou NR^5 ;
Z est $-NR^5C(=O)-(CR^4R^{4a})_p-$, $-NR^5C(=S)-(CR^4R^{4a})_p-$, $-NR^{5a}-(CR^4R^{4a})p-$, $-NR^5-(CR^4R^{4a})_pC(=O)-$, $-NR^5-(CR^4R^{4a})_pC(=S)-$, $-NR^5S(=O)_r-$, $-NR^5S(=O)_r(CR^4R^{4a})_p-$, $-C(=O)NR^5(CR^4R^{4a})_p-$ ou $-NR^5-(CR^4R^{4a})_pS(=O)_r-$, où p est 0, 1, 2 ou 3 et r est 1 ou 2 ;
chacun de Z_1 et Z_2 est indépendamment NR^5 ou CR^4R^{4a} ;
chacun de R^9 et R^{4a} est indépendamment H, F, Cl, Br, I, -CN, un groupe hydroxyle, $-NR^{5a}R^5$, à condition que lorsque R^4 et R^{4a} sont liés au même atome de carbone, R^4 et R^{4a}, ensemble avec l'atome de carbone auquel ils sont attachés, forment facultativement un cycle carbocyclique ou hétérocyclique de 3 à 8 éléments ;
chacun de R^5 et R^{5a} est indépendamment H, $R^6R^{6a}NC(=O)$ -, $R^6OC(=O)-$, $R^6C(=O)-$, $R^6R^{6a}NS(=O)-$, $R^6OS(=O)-$, $R^6S(=O)$ -, $R^6R^{6a}NSO_2-$, R^6OSO_2-, R^6SO_2-, à condition que lorsque R^5 et R^{5a} sont liés au même atome d'azote, R^5 et R^{5a}, ensemble avec l'atome d'azote auquel ils sont attachés, forment facultativement un cycle de 3 à 8 éléments, notamment les cycles spiro et bicycliques condensés :
chacun de R^6 et R^{6a} est H.

2. Composé selon la revendication 1, dans lequel Z de formule (IIa) est -NHC(=O)-, Z_1 de formule (IIb) est NH ; et la sous-structure définie par X_1, U_1 et R^3 de formule (I) est :



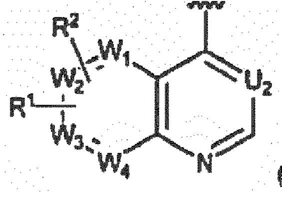
3. Composé selon la revendication 1, répondant à la formule (IV) :



(IV)

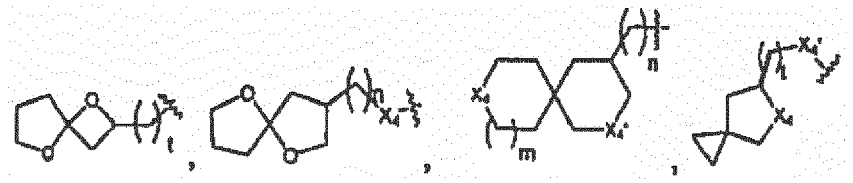
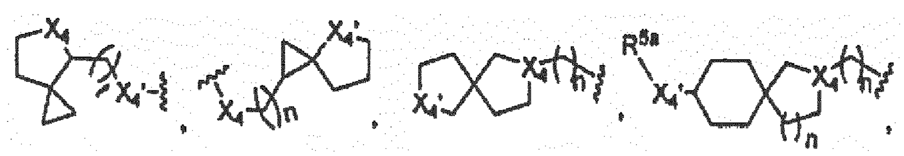
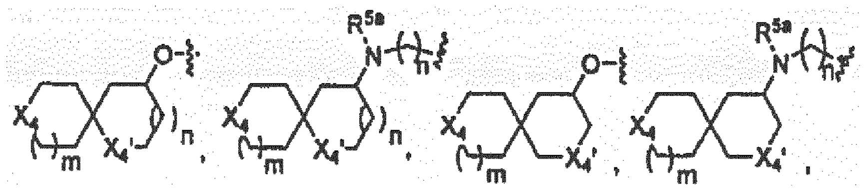
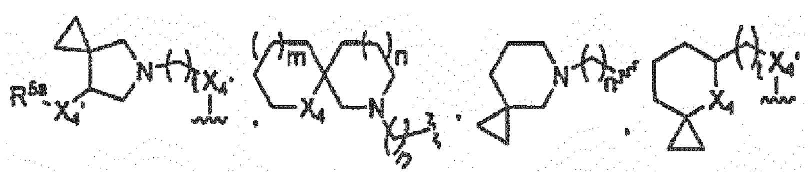
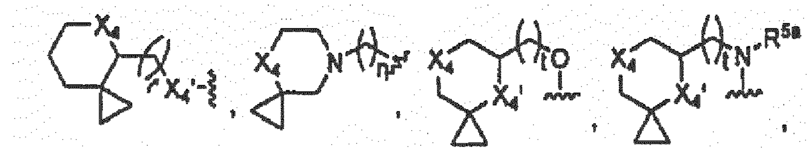
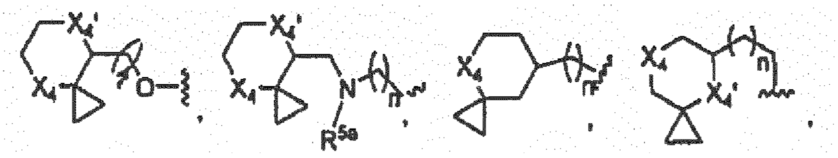
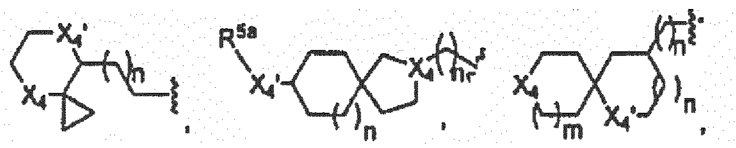
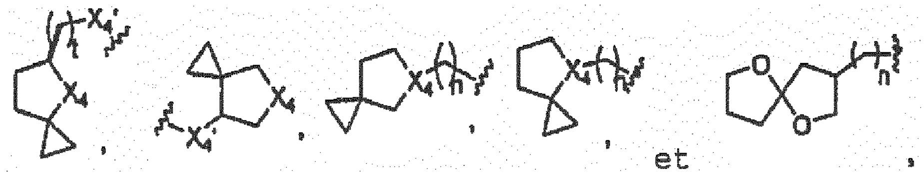
ou un stéréoisomère, un isomère géométrique, un tautomère, un N-oxyde, un hydrate, un solvate ou un sel pharmaceutiquement acceptable de celui-ci, où :

Q_2 répond à la formule (III) :



(III);

R^1 est sélectionné parmi :

où chacun de X_4 et X_4' est indépendamment $(CR^4R^{4a})_m$, NR^5, O, S, S=O ou SO_2 ; chacun de m et n est indépendamment 0, 1 ou 2 ; et t est 1, 2 ou 3 ;

R^2 est H, un atome d'halogène, un groupe cyano (CN), $R^{5a}R^5N$-alcoxy en C_1 à C_6, alcoxy en C_1 à C_6, hydroxyalcoxy en C_1 à C_6, aminoalcoxy en C_1 à C_6, aminoalcoxy en C_1 à C_6 substitué par un groupe hydroxy, halogénoalcoxy en C_1 à C_6, (alkylamino en C_1 à C_6) alcoxy en C_1 à C_6, (alcoxy en C_1 à C_6) alcoxy en C_1 à C_6, (hétérocyclyloxy en C_4 à C_{10}) alcoxy en C_1 à C_6, bicyclyle condensé en C_5 à C_{12}, (bicyclyle condensé en C_5 à C_{12}) aliphatique en C_1 à C_6, (hétérobicyclyle condensé en C_5 à C_{12}) aliphatique en C_1 à C_6, bicycloxy condensé en C_5 à C_{12}, bicyclylamino condensé en C_5 à C_{12}, (bicycloxo condensé en C_5 à C_{12}) alcoxy en C_1 à C_6, (bicyclylamino condensé en C_5 à C_{12}) alcoxy en C_1 à C_6, (bicyclyle condensé en C_5 à C_{12})-C(=O)-, (bicyclyle condensé en C_5 à C_{12}) -C(=O)O-, (hétérobicyclyle condensé en C_5 à C_{12})-C(=O)-, (hétérobicyclyle condensé en C_5 à C_{12})-C (=O) O-, (bicyclylamino condensé en C_5 à C_{12})-C(=O)-, (hétérobicyclylamino condensé en C_5 à C_{12})-C(=O)-, (bicyclyle condensé en C_5 à C_{12})-C(=O)NR^5-, (hétérobicyclyle condensé en C_5 à C_{12})-C(=O)NR^5-, spirobicyclyle en C_5 à C_{12}, spirobicycloxy en C_5 à C_{12}, spirobicyclylamino en C_5 à C_{12}, (spirobicycloxo en C_5 à C_{12}) alcoxy en C_1 à C_6, (spirobicyclylamino en C_5 à C_{12})alcoxy en C_1 à C_6, hétérobicyclyle condensé en C_5 à C_{12}, hétérobicycloxy condensé en C_5 à C_{12}, hétérobicyclylamino condensé en C_5 à C_{12}, (hétérobicycloxo condensé en C_5 à C_{12}) alcoxy en C_1 à C_6, (hétérobicyclylamino condensé en C_5 à C_{12})alcoxy en C_1 à C_6, spirobicyclyle en C_5 à C_{12}, spirohétérobicyclyle en C_5 à C_{12}, (spirobicyclyle en C_5 à C_{12}) aliphatique en C_1 à C_6, (spirohétérobicyclyle en C_5 à C_{12})aliphatique en C_1 à C_6, (spirohétérobicycloxo en C_5 à C_{12}) alcoxy en C_1 à C_6, (spirohétérobicyclylamino en C_5 à C_{12})alcoxy en C_1 à C_6, (spirobicyclyle en C_5 à C_{12})-C(=O)-, (spirobicyclyle en C_5 à C_{12})-C(=O)O-, (spirohétérobicyclyle en C_5 à C_{12})-C(=O)-, (spirohétérobicyclyle en C_5 à C_{12})-C(=O)O-, (spirobicyclylamino en C_5 à C_{12})-C(=O)-, (spirohétérobicyclylamino en C_5 à C_{12})-C(=O)-, (spirobicyclyle en C_5 à C_{12})-C(=O)NR^5-, ou (spirohétérobicyclyle en C_5 à C_{12})-C(=O) NR^5-, aryle en C_6 à C_{10}, hétéroaryle en C_1 à C_{10}, (aryle en C_6 à C_{10})aliphatique en C_1 à C_6 ou (hétéroaryle en C_1 à C_{10})aliphatique en C_1 à C_6 ;

où R^3 est indépendamment H, F, Cl, Br, -CN, un groupe aliphatique en C_1 à C_3, alcoxy en C_1 à C_3 ou halogénoalkyle en C_1 à C_3 ;

chacun de U_1 et U_2 est indépendamment CR^4 ou N ;

V est NR^5R^{5a} ou OR^5 ;

V_1 est O ou NR^5 ;

chacun de V_2, V_3 et V_4 est indépendamment CR^4R^{4a}, NR^5, CR^4 ou N, à condition que seulement un de V_2, V_3 et V_4 soit NR^5 ou N, ou V_2 et V_3 ou V_3 et V_4 se combinent pour devenir CR^4R^{4a}, NR^5, O, CR^4 ou N, à condition que la structure résultante soit stable :

chacun de W_1, W_2, W_3 et W_4 est indépendamment CR^4R^{4a}, NR^5, CR^4 ou N, ou W_1 et W_2 ou W_3 et W_4 se combinent pour devenir CR^4R^{4a}, NR^5, O ou S ;

X_1 est $(CR^4R^{4a})_m$, NR^5, O, S, S=O ou SO_2, où m est 0, 1 ou 2 ;

X_2 est indépendamment O, S ou NR^5 ;

Z est $-NR^5C(=O)-(CR^4R^{4a})_p-$, $-NR^5C(=S)-(CR^4R^{4a})_p-$, $-NR^{5a}-(CR^4R^{4a})_p-$, $-NR^5-(CR^4R^{4a})_pC(=O)-$, $-NR^5-(CR^4R^{4a})_pC(=S)-$,$-NR^5S(=O)_r-$, $-NR^5S(=O)_r(CR^4R^{4a})_p-$, $-C(=O)NR^5(CR^4R^{4a})_p-$ ou-$NR^5-(CR^4R^{4a})_pS(=O)_r-$, où p est 0, 1, 2 ou 3 et r est 1 ou 2 ;

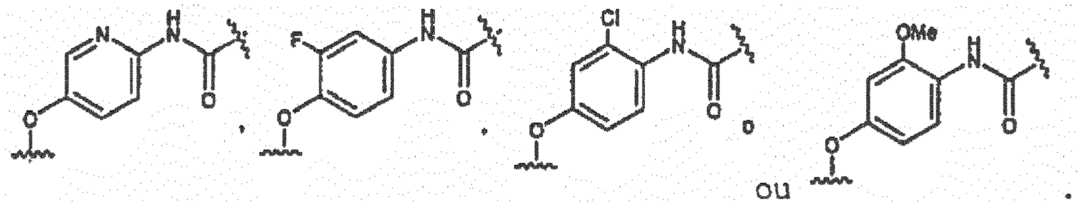
chacun de R^4 et R^{4a} est indépendamment H, F, Cl, Br, I, -CN, un groupe hydroxyle, $-NR^{5a}R^5$, à condition que lorsque R^4 et R^{4a} sont liés au même atome de carbone, R^4 et R^{4a}, ensemble avec l'atome de carbone auquel ils sont attachés, forment facultativement un cycle carbocyclique ou hétérocyclique de 3 à 8 éléments substitué ou non substitué ;

chacun de R^5 et R^{5a} est indépendamment H, $R^6R^{6a}NC(=O)-$, $R^6OC(=O)-$, $R^6C(=O)-$, $R^6R^{6a}NS(=O)-$, $R^6OS(=O)-$, $R^6S(=O)-$, $R^6R^{6a}NSO_2-$, R^6OSO_2-, R^6SO_2-, à condition que lorsque R^5 et R^{5a} sont liés au même atome d'azote, R^5 et R^{5a}, ensemble avec l'atome d'azote auquel ils sont attachés, forment facultativement un cycle de 3 à 8 éléments, notamment les cycles spiro et bicycliques condensés ;

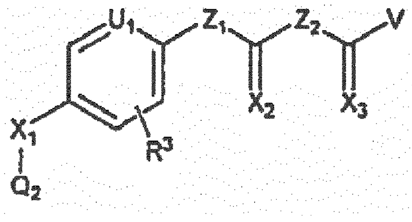
chacun de R^6 et R^{6a} est indépendamment H ;

où chacun de $R^{5a}R^5N-$, $-C(=O)NR^5R^{5a}$, $-OC(=O)NR^5R^{5a}$, - $OC(=)OR^5$, $-NR^5C(=)NR^5R^{5a}$, $-NR^5C(=)OR^{5a}$, $-NR^5C(=)-R^{5a}$, $R^5R^{5a}N-O_2S-$, R^5O_2S-, $R^5O_2SR^{5a}N-$, OR^5, NR^5, CR^4R^{4a}, CR^4, $(CR^aR^{4a})_m$, $-NR^5C(O)-(CR^4R^{4a})_p-$, $-NR^5C(=S)-(CR^4R^{4a})_p-$, $-NR^{5a}-$ $(CR^4R^{4a})_p-$, $-NR^5-$ $(CR^4R^{46})_pC(=O)-$, $-NR^5-(CR^4R^{4a})_pC(=S)-$, $-NR^5S(O)_r-$, $-NR^5S(=O)(CR^4R^{4a})_p-$, $-C(=O)NR^5-(CR^4R^{4a})_p-$, $-NR^5-(CR^4R^{4a})_p-S(=O)_r$, $R^{5a}R^5N$-alkyle, $R^5S(=O)$-alkyle, $R^5R^{5a}N-C(=O)$-alkyle, $R^{5a}R^5N$-alcoxy, $R^5S(=O)_r$-alcoxy, $R^5R^{5a}N-C(=O)$-alcoxy, $R^6R^{6a}NC(=O)-$, $R^6OC(=O)-$, $R^6C(=O)-$, $R^6R^{6a}NS(=O)-$, $R^6OS(=O)-$, $R^6S(=O)-$, $R^6R^{6a}NSO_2-$, R^6OSO_2-, R^6SO_2-, cyclopropylalcoxy substitué par un groupe hydroxy, cyclopropylalcoxy substitué par un groupe $R^5S(=O)_2O$.

4. Composé selon la revendication 3, dans lequel Z est - NHC(=O)- ; ou
dans lequel le sous-structure définie par X_1, Z, U_1 et R^3 est

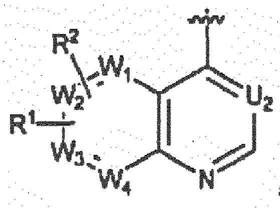


5. Composé selon la revendication 1, répondant à la formule (V) :

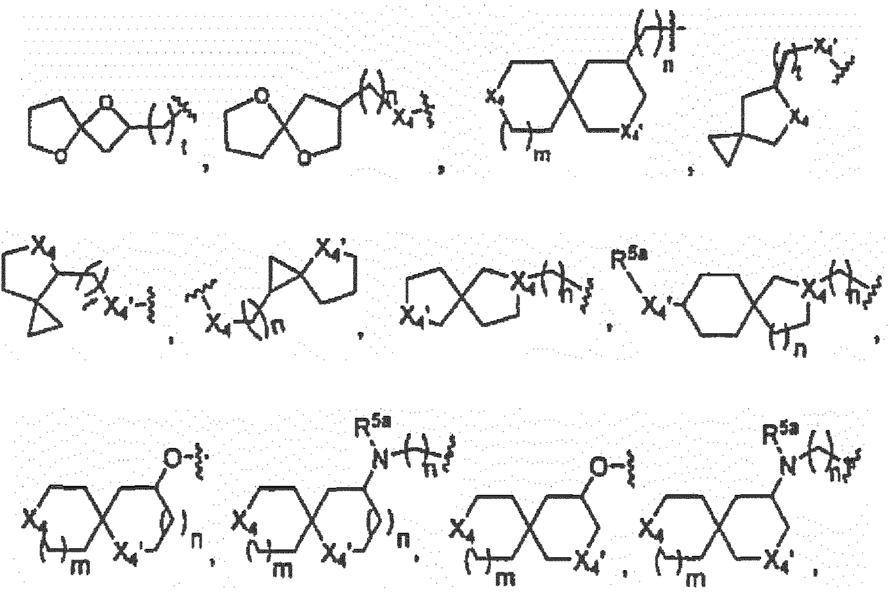

(V)

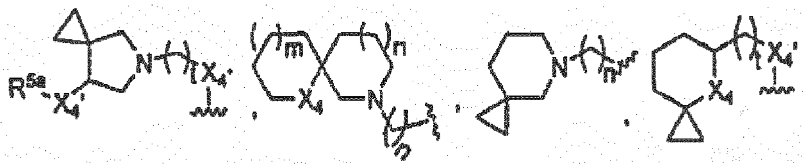
ou un stéréoisomère, un isomère géométrique, un tautomère, un N-oxyde, un hydrate, un solvate ou un sel pharmaceutiquement acceptable de celui-ci, où :

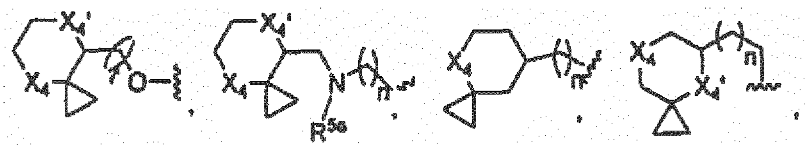
Q_2 répond à la formule (III) :

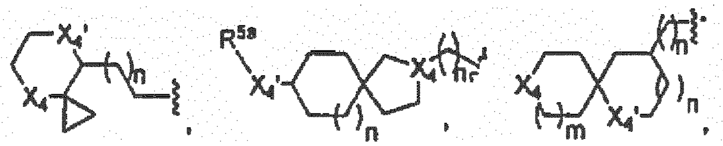

(III);

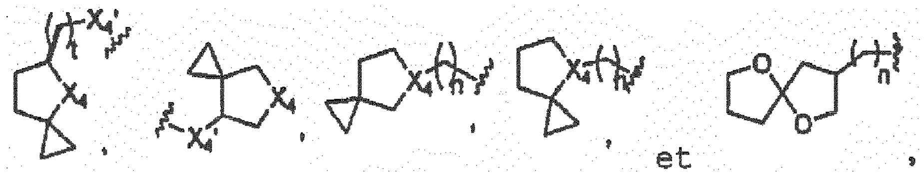
R^1 est sélectionné parmi :











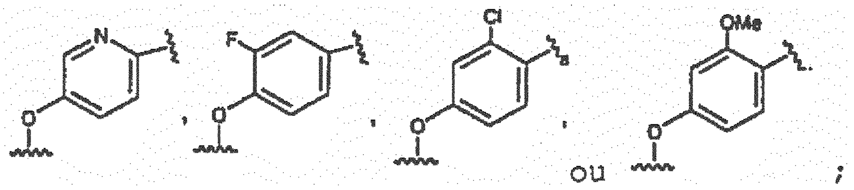
où chacun de X_4 et X_4' est indépendamment $(CR^4R^{4a})_m$, NR^5, O, S, S=O ou SO_2 ; chacun de m et n est indépendamment 0, 1 ou 2 ; et t est 1, 2 ou 3 ;

R^2 est H, un atome d'halogène, un groupe cyano (CN), $R^{5a}R^5$N-alcoxy en C_1 à C_6, alcoxy en C_1 à C_6, hydroxyalcoxy en C_1 à C_6, aminoalcoxy en C_1 à C_6, aminoalcoxy en C_1 à C_6 substitué par un groupe hydroxy, halogénoalcoxy en C_1 à C_6, (alkylamino en C_1 à C_6)alcoxy en C_1 à C_6, (alcoxy en C_1 à C_6)alcoxy en C_1 à C_6, (hétérocyclyloxy en C_4 à C_{10})alcoxy en C_1 à C_6, bicyclyle condensé en C_5 à C_{12}, (bicyclyle condensé en C_5 à C_{12})aliphatique en C_1 à C_6, (hétérobicyclyle condensé en C_5 à C_{12})aliphatique en C_1 à C_6, bicycloxy condensé en C_5 à C_{12}, bicyclylamino condensé en C_5 à C_{12}, (bicycloxo condensé en C_5 à C_{12})alcoxy en C_1 à C_6, (bicyclylamino condensé en C_5 à C_{12})alcoxy en C_1 à C_6, (bicyclyle condensé en C_5 à C_{12})-C(=O)-, (bicyclyle condensé en C_5 à C_{12})-C(=O)O-, (hétérobicyclyle condensé en C_5 à C_{12})-C(=O)-, (hétérobicyclyle condensé en C_5 à C_{12})-C(=O)O-, (bicyclylamino condensé en C_5 à C_{12})-C(=O)-, (hétérobicyclylamino condensé en C_5 à C_{12})-C(=O)-, (bicyclyle condensé en C_5 à C_{12})-C(=O)NR^5-, (hétérobicyclyle condensé en C_5 à C_{12})-C(=O)NR^5-, spirobicyclyle en C_5 à C_{12}, spirobicycloxy en C_5 à C_{12}, spirobicyclylamino en C_5 à C_{12}, (spirobicycloxo en C_5 à C_{12}) alcoxy en C_1 à C_6, (spirobicyclylamino en C_5 à C_{12})alcoxy en C_1 à C_6, hétérobicyclyle condensé en C_5 à C_{12}, hétérobicycloxy condensé en C_5 à C_{12}, hétérobicyclylamino condensé en C_5 à C_{12}, (hétérobicycloxo condensé en C_5 à C_{12})alcoxy en C_1 à C_6, (hétérobicyclylamino condensé en C_5 à C_{12})alcoxy en C_1 à C_6, spirobicyclyle en C_5 à C_{12}, spirohétérobicyclyle en C_5 à C_{12}, (spirobicyclyle en C_5 à C_{12})aliphatique en C_1 à C_6, (spirohétérobicyclyle en C_5 à C_{12})aliphatique en C_1 à C_6, (spirohétérobicycloxo en C_5 à C_{12}) alcoxy en C_1 à C_6, (spirohétérobicyclylamino en C_5 à C_{12})alcoxy en C_1 à C_6, (spirobicyclyle en C_5 à C_{12})-C(=O)-, (spirobicyclyle en C_5 à C_{12})-C(=O)O-, (spirohétérobicyclyle en C_5 à C_{12})-C(=O)-, (spirohétérobicyclyle en C_5 à C_{12})-C(=O)O-, (spirobicyclylamino en C_5 à C_{12})-C(=O)-, (spirohétérobicyclylamino en C_5 à C_{12})-C(=O)-, (spirobicyclyle en C_5 à C_{12})-C=O)NR^5-, ou (spirohétérobicyclyle en C_5 à C_{12})-C(=O)NR^5-, aryle en C_6 à C_{10}, hétéroaryle en C_1 à C_{10}, (aryle en C_6 à C_{10})aliphatique en C_1 à C_6 ou (hétéroaryle en C_1 à C_{10})aliphatique en C_1 à C_6 ;

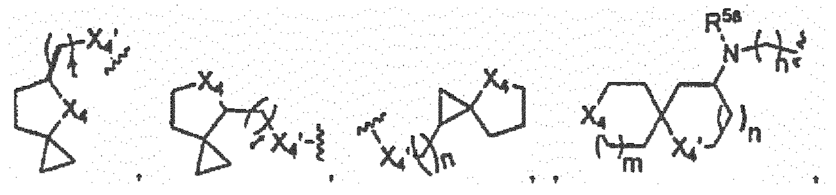
où R^3 est indépendamment H, F, Cl, Br, -CN, un groupe aliphatique en C_1 à C_3, alcoxy en C_1 à C_3 ou halogénoalkyle en C_1 à C_3 ;

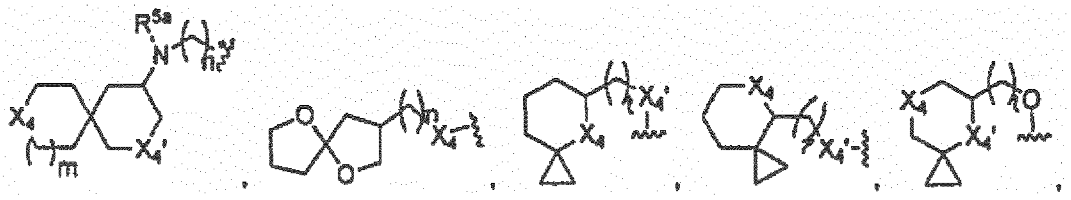
chacun de U_1 et U_2 est indépendamment CR^4 ou N ;
V est NR^5R^{5a} ou OR^5 ;
chacun de W_1, W_2, W_3 et W_4 est indépendamment CR^4R^{4a}, NR^5, CR^4 ou N, ou W_1 et W_2 ou W_3 et W_4 se combinent pour devenir CR^4R^{4a}, NR^5, O ou S ;
X_1 est $(CR^4R^{4a})_m$, NR^5, O, S, S=O ou SO_2, où m est 0, 1 ou 2 ;
chacun de X_2 et X_3 est indépendamment O, S ou NR^5 ;
chacun de Z_1 et Z_2 est indépendamment NR^5 ou CR^4R^{4a} ;
chacun de R^4 et R^{4a} est indépendamment H, F, Cl, Br, I, -CN, un groupe hydroxyle, $-NR^{5a}R^5$, à condition que lorsque R^4 et R^{4a} sont liés au même atome de carbone, R^4 et R^{4a}, ensemble avec l'atome de carbone auquel ils sont attachés, forment facultativement un cycle carbocyclique ou hétérocyclique de 3 à 8 éléments substitué ou non substitué ;
chacun de R^5 et R^{5a} est indépendamment H, $R^6R^{6a}NC(=O)-$, $R^6OC(=O)-$, $R^6C(=O)-$, $R^6R^{6a}NS(=O)-$, $R^6OS(=O)-$, $R^6S(=O)-$, $R^6R^{6a}NSO_2-$, R^6OSO_2-, R^6SO_2-, à condition que lorsque R^5 et R^{5a} sont liés au même atome d'azote, R^5 et R^{5a}, ensemble avec l'atome d'azote auquel ils sont attachés, forment facultativement un cycle de 3 à 8 éléments, notamment les cycles spiro et bicycliques condensés ;
chacun de R^6 et R^{6a} est indépendamment H ;
où chacun de $R^{5a}R^5N-$, $-C(=O)NR^5R^{5a}$, $-OC(=O)NR^5R^{5a}$, $OC(=)OR^5$, $-NR^5C(=O)NR^5R^{5a}$, $-NR^5C(=O)OR^{5a}$, $-NR^5C(=O)-R^{5a}$, $R^5R^{5a}N-O_2S-$, R^5O_2S-, $R^5O_2SR^{5a}N-$, OR^5, NR^5, CR^4R^{4a}, CR^4, $(CR^4R^{4a})_m$, $-NR^5C(O)-(CR^4R^{4a})_p-$, $-NR^5C(=S)-(CR^4R^{4a})_p-$, $-NR^{5a}-(CR^4R^{4a})_p-$, $-NR^5-(CR^4R^{4a})_pC(=O)-$, $-NR^5-(CR^4R^{4a})_pC(=S)-$, $-NR^5S(O)_r-$, $-NR^5S(=O)(CR^4R^{4a})_p-$, $-C(=O)NR^5-(CR^4R^{4a})_p-$, $-NR^5-(CR^4R^{4a})_p-S(=O)_r$, $R^{5a}R^5N$-alkyle, $R^5S(=O)$-alkyle, $R^5R^{5a}N-C(=O)$-alkyle, $R^{5a}R^5N$-alcoxy, $R^5S(=O)_r$-alcoxy, $R^5R^{5a}N-C(=O)$-alcoxy, $R^6R^{6a}NC(=O)-$, $R^6OC(=O)-$, $R^6C(=O)-$, $R^6R^{6a}NS(=O)-$, $R^6OS(=O)-$, $R^6S(=)-$, $R^6R^{6a}NSO_2-$, R^6OSO_2-, R^6SO_2-, cyclopropylalcoxy substitué par un groupe hydroxy, cyclopropylalcoxy substitué par un groupe $R^5S(=O)_2O$.

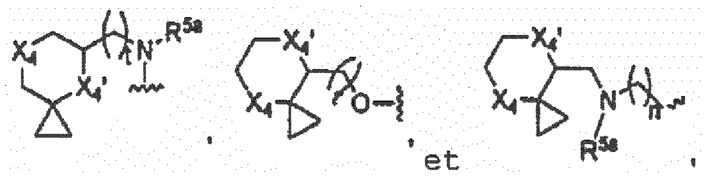
6. Composé selon la revendication 5, dans lequel la sous-structure définie par X_1, U_1 et R^3 est



et/ou où R^1 est l'une des structures suivantes :

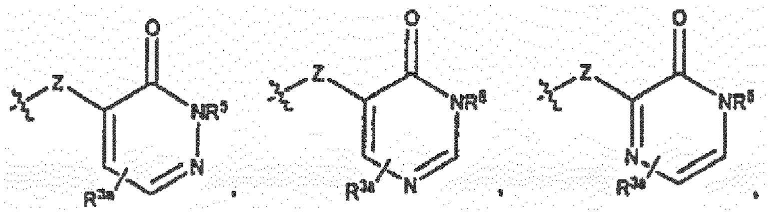


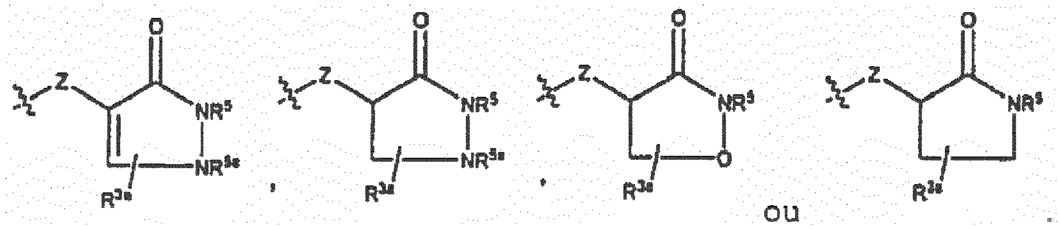




où chacun de X_4 et X_4' est indépendamment $(CR^4R^{4a})_m$, NR^5, O, S, S=O ou SO_2 ; chacun de m et n est indépendamment 0, 1 ou 2 ; et t est 1, 2 ou 3.

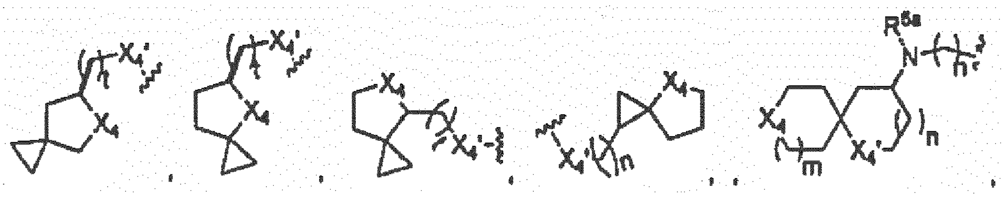
7. Composé selon la revendication 1 ou 3, dans lequel Q_1 dans la formule (I) ou dans la sous-structure définie par X_2, V_1, V_2, V_3, V_4 et Z de formule (IV) est

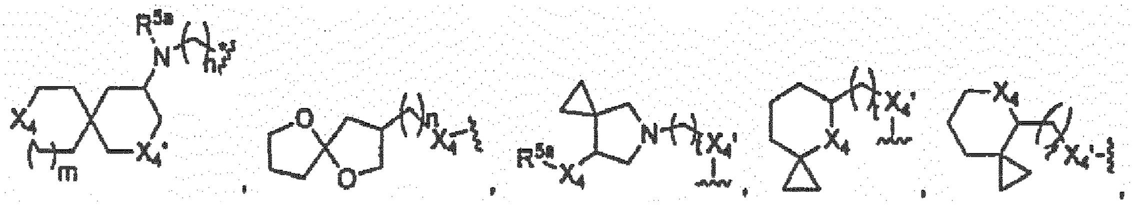


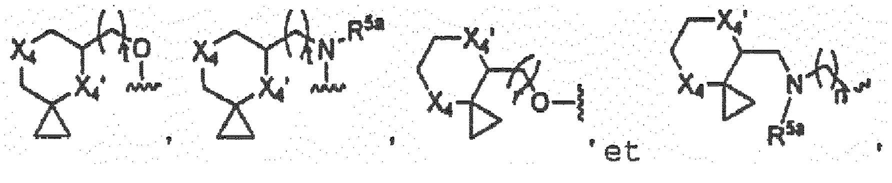


où R^{3a} est H, F, Cl, Br, I, -CN, un groupe hydroxyle, $R^{5a}R^5N$-, $R^{5a}R^5N$-aliphatique.

8. Composé selon la revendication 1 ou 3 ou 5, dans lequel R^1 est l'une des structures suivantes :

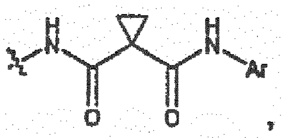


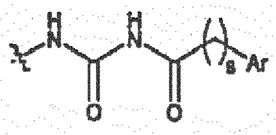




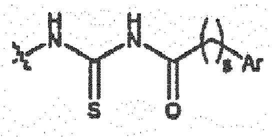
où chacun de X_4 et X_4' est indépendamment $(CR^4R^{4a})_m$, NR^5, O, S, S=O ou SO_2 ; chacun de m et n est indépendamment 0, 1 ou 2 ; et t est 1, 2 ou 3.

9. Composé selon la revendication 1 ou 5, dans lequel Q_1 dans la formule (I) ou dans la sous-structure définie par Z_1, Z_2, X_2, X_3 et V de formule (V) est



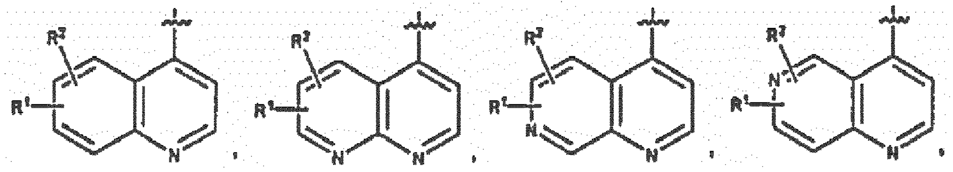


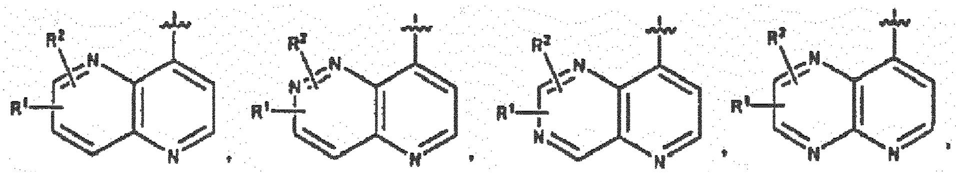
ou

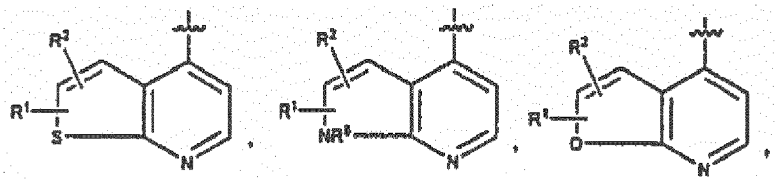


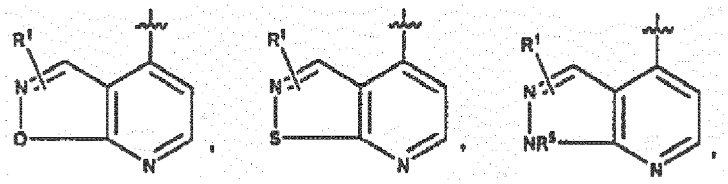
où Ar est un groupe aryle ou hétéroaryle substitué ou non substitué ; et s est 0 ou 1.

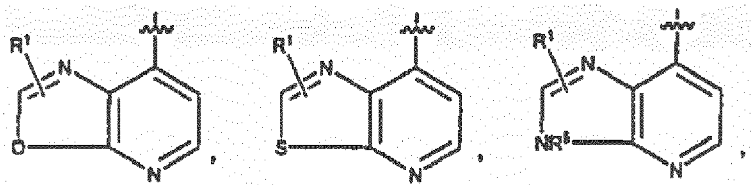
10. Composé selon l'une quelconque des revendications 1, 3 et 5, dans lequel Q_2 est

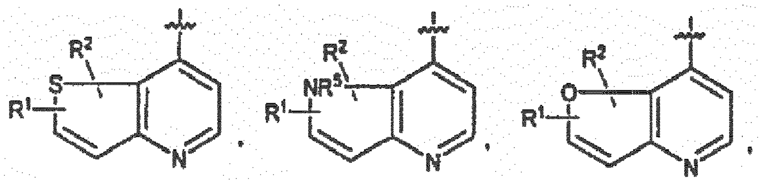


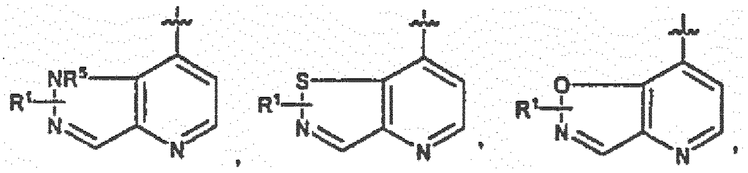


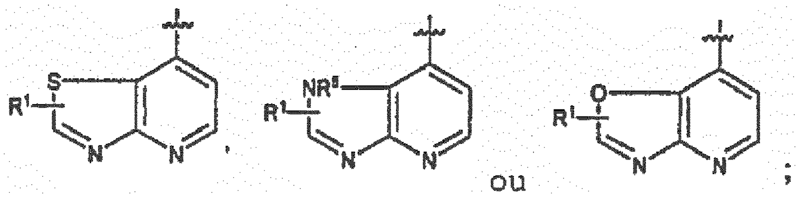












ou

où X_1 est O ou NR^5.

11. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 10 et un support, un excipient, un diluant, un adjuvant, un véhicule pharmaceutiquement acceptable ou une combinaison de ceux-ci, et facultativement un agent thérapeutique sélectionné parmi un agent chimiothérapeutique, un agent anti-prolifératif, un agent destiné au traitement de l'athérosclérose, un agent destiné au traitement de la fibrose pulmonaire et des combinaisons de ceux-ci ;
dans laquelle l'agent thérapeutique supplémentaire est facultativement l'adriamycine, la rapamycine, le temsirolimus, l'évérolimus, l'ixabépilone, la gemcitabine, le cyclophosphamide, la dexaméthasone, l'étoposide, le fluorouracile, le mésylate d'imatinib, le dasatinib, le nilotinib, l'erlotinib, le lapatinib, l'iressa, le sorafénib, le sunitinib, un interféron, le carboplatine, le topotécan, le taxol, la vinblastine, la vincristine, le témozolomide, le tositumomab, la trabectédine, le bevacizumab, le trastuzumab, le cétuximab, le panitumumab ou une combinaison de ceux-ci.

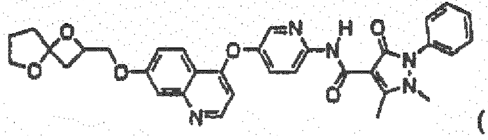
12. Composé selon l'une quelconque des revendications 1 à 10 ou composition pharmaceutique selon la revendication 11 pour une utilisation destinée à la prévention, la prise en charge, le traitement ou la réduction de la sévérité d'une maladie proliférative.

13. Composé ou composition pharmaceutique pour une utilisation selon la revendication 12, dans lequel/laquelle la maladie proliférative est un cancer métastatique, un cancer du côlon, un adénocarcinome gastrique, un cancer de la vessie, un cancer du sein, un cancer du rein, un cancer du foie, un cancer du poumon, un cancer de la thyroïde, un cancer de la tête et du cou, un cancer de la prostate, un cancer du pancréas, un cancer du système nerveux central, un glioblastome, ou un trouble myéloprolifératif, une athérosclérose ou une fibrose pulmonaire.

14. Méthode d'inhibition ou de modulation de l'activité des protéines kinases dans un échantillon biologique comprenant la mise en contact d'un échantillon biologique avec le composé selon l'une quelconque des revendications 1 à 10 ou la composition pharmaceutique selon la revendication 11.

15. Méthode selon la revendication 14, dans laquelle les protéines kinases sont des récepteurs à activité tyrosine kinase, et dans laquelle les récepteurs à activité tyrosine kinase sont KDR, c-Met ou IGF1R.

16. Composé ayant l'une des structures suivantes :



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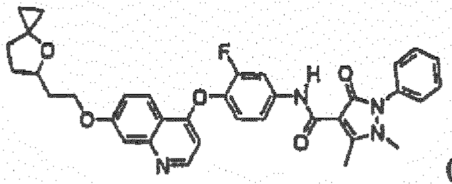

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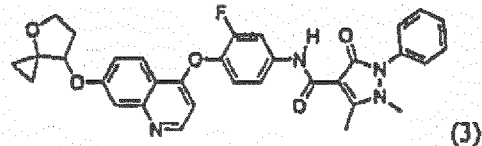

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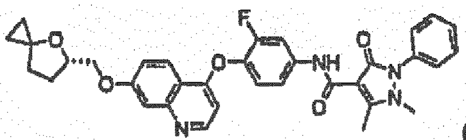

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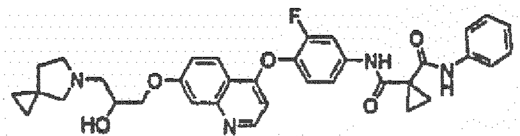

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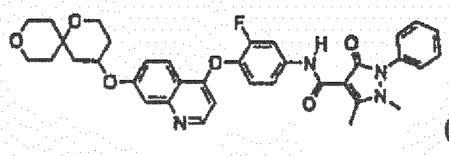

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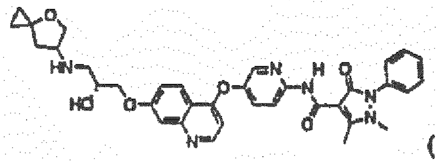

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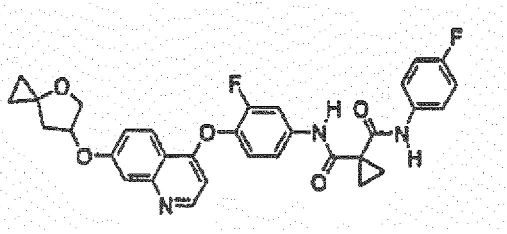

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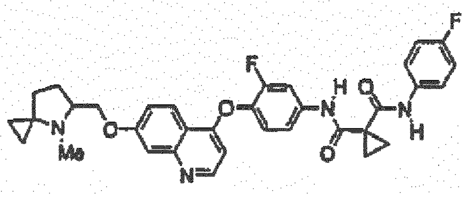

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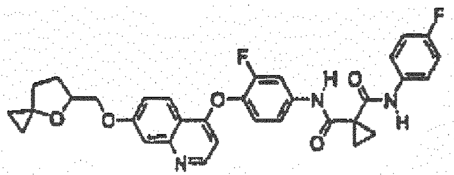

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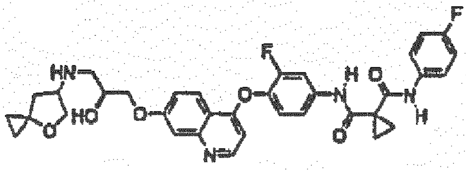

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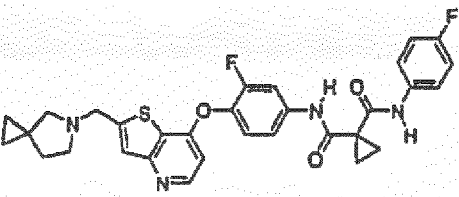

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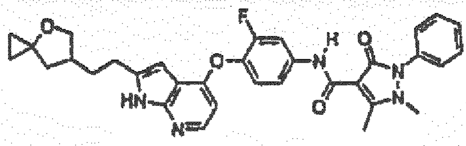

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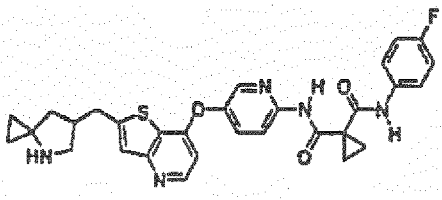

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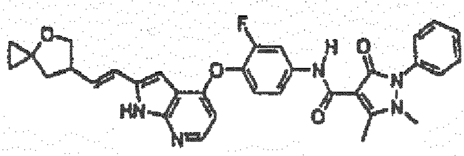

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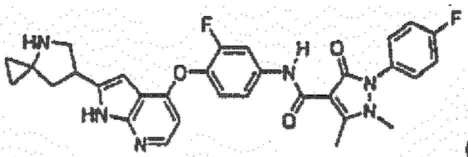

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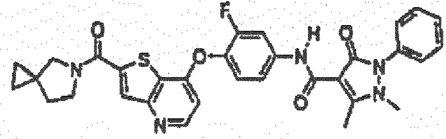

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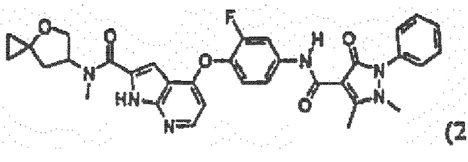

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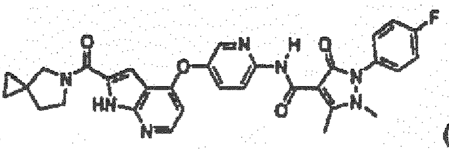

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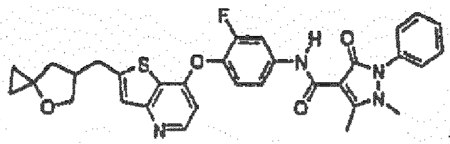
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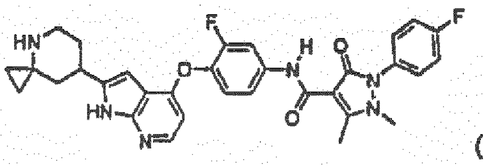
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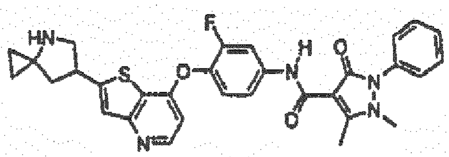
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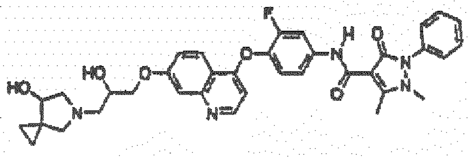
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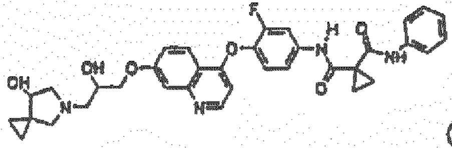
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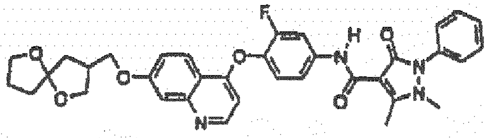
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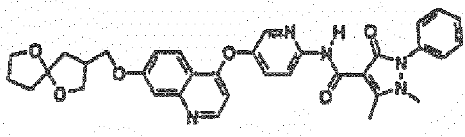
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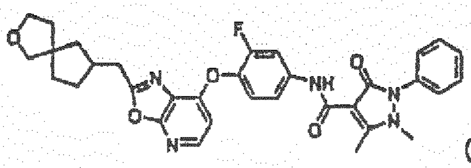
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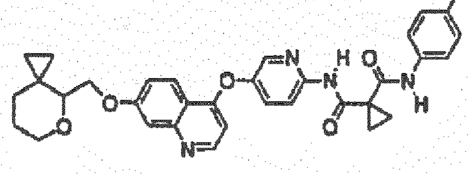

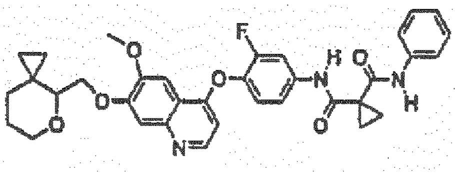
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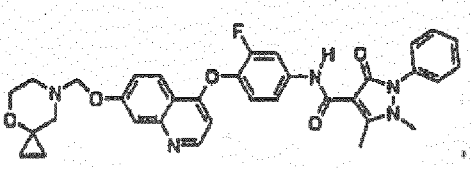

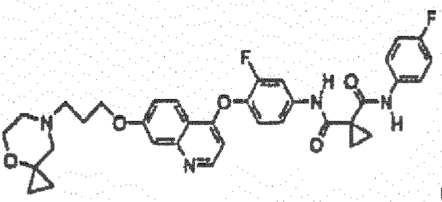
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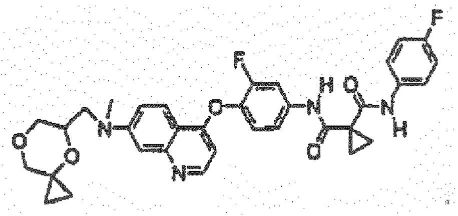

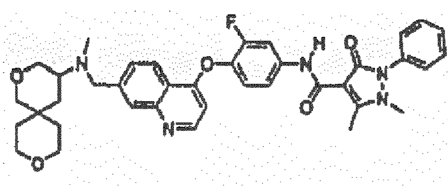
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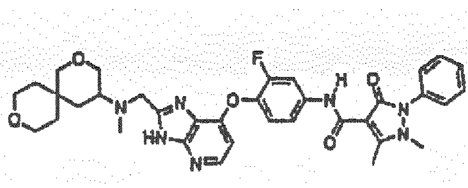
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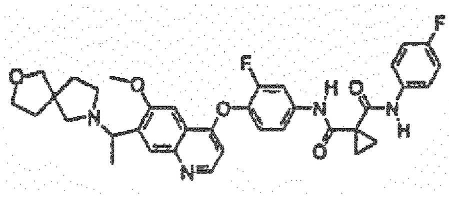
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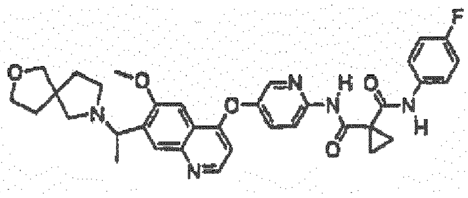
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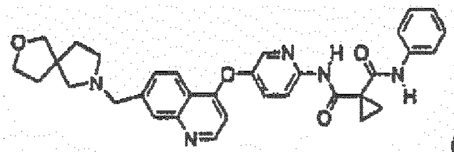
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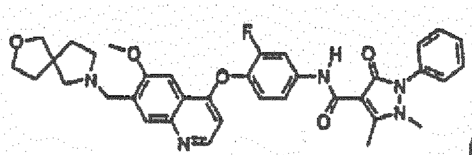
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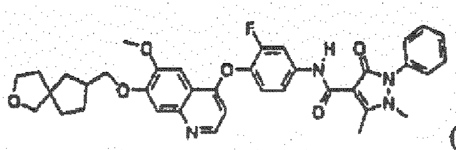
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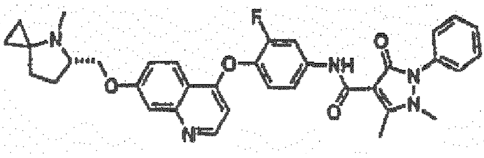
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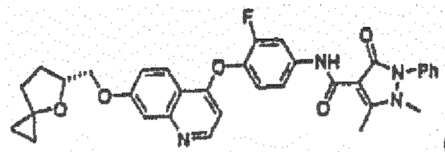
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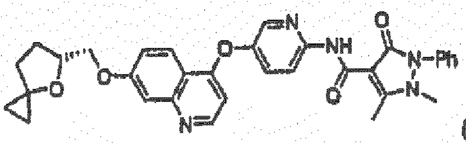
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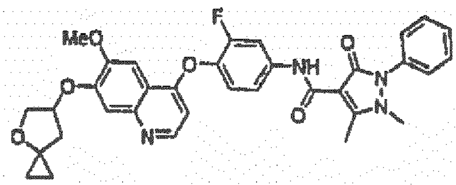
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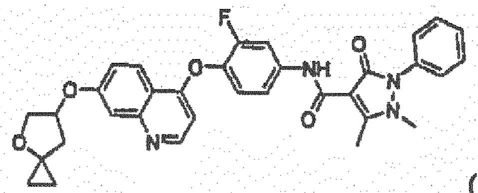
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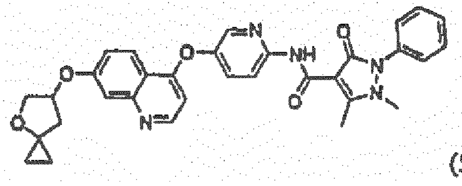
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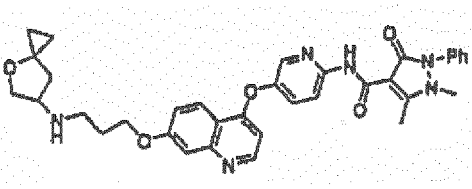
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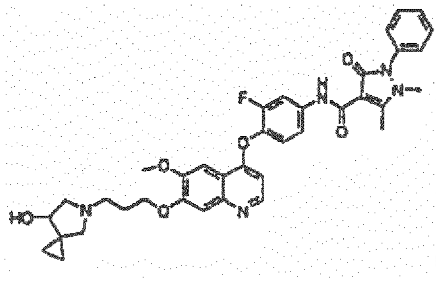
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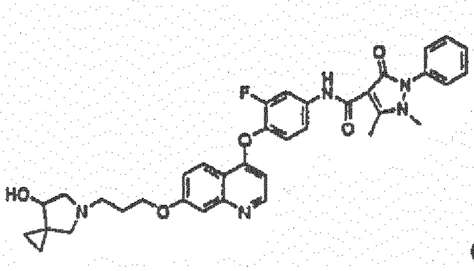
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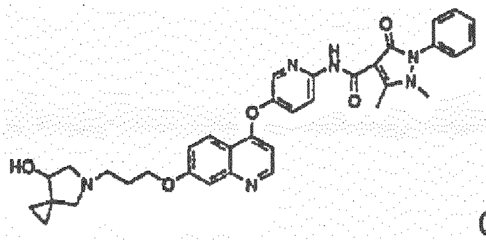

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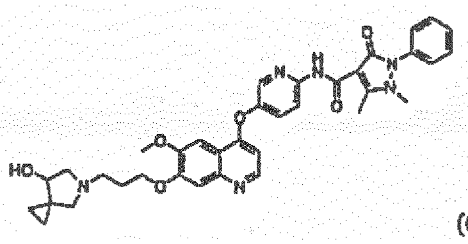

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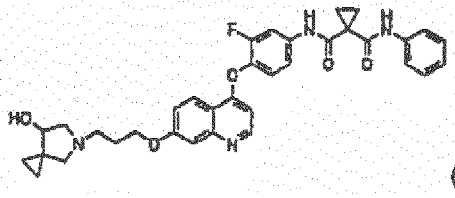

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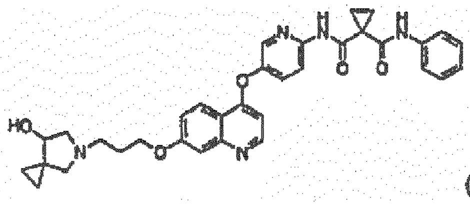

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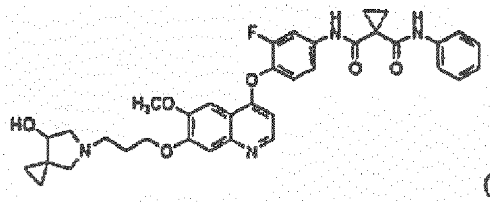

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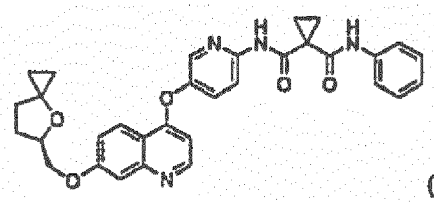

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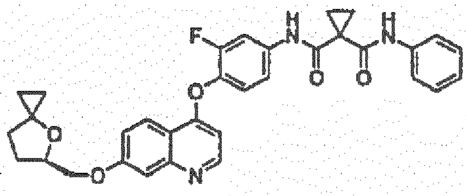

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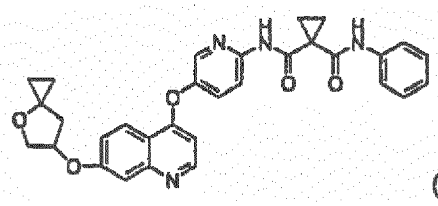

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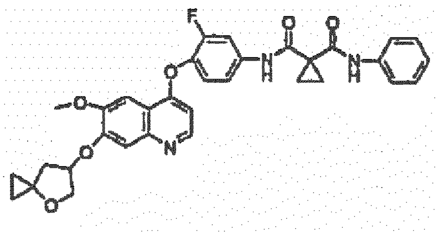

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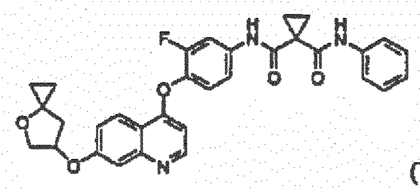

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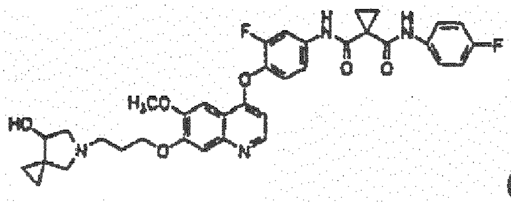

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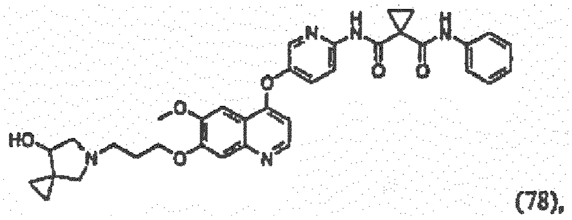

(78),

ou un stéréoisomère, un isomère géométrique, un tautomère, un N-oxyde, un hydrate, un solvate ou un sel pharmaceutiquement acceptable de celui-ci.

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