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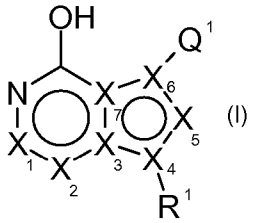
(54) Title: IMIDAZOPYRAZINOL DERIVATIVES FOR THE TREATMENT OF CANCERS



(I)

(57) Abstract: Compounds of the formula (I) and pharmaceutically acceptable salts thereof, wherein X_1, X_2, X_3, X_4, X_5, X_6, X_7, R^1, and Q^1 are defined herein, inhibit the IGF-IR enzyme and are useful for the treatment and/or prevention of hyperproliferative diseases such as cancer, inflammation, psoriasis, allergy/asthma, disease and conditions of the immune system, disease and conditions of the central nervous system.

IMIDAZOPYRAZINOL DERIVATIVES FOR THE TREATMENT OF CANCERS

BACKGROUND OF THE INVENTION

[1] The present invention is directed to novel heterobicyclic compounds, their salts, and compositions comprising them. In particular, the present invention is directed to novel heterobicyclic compounds that inhibit the activity of tyrosine kinase enzymes in animals, including humans, for the treatment and/or prevention of various diseases and conditions such as cancer.

[2] Protein tyrosine kinases (PTKs) are enzymes that catalyse the phosphorylation of specific tyrosine residues in various cellular proteins involved in regulation of cell proliferation, activation, or differentiation (Schlessinger and Ullrich, 1992, *Neuron* 9:383-391). Aberrant, excessive, or uncontrolled PTK activity has been shown to result in uncontrolled cell growth and has been observed in diseases such as benign and malignant proliferative disorders, as well as having been observed in diseases resulting from an inappropriate activation of the immune system (e.g., autoimmune disorders), allograft rejection, and graft vs. host disease. In addition, endothelial-cell specific receptor PTKs such as KDR and Tie-2 mediate the angiogenic process, and are thus involved in supporting the progression of cancers and other diseases involving inappropriate vascularization (e.g., diabetic retinopathy, choroidal neovascularization due to age-related macular degeneration, psoriasis, arthritis, retinopathy of prematurity, infantile hemangiomas).

[3] Tyrosine kinases can be of the receptor-type (having extracellular, transmembrane and intracellular domains) or the non-receptor type (being wholly intracellular). The Receptor Tyrosine Kinases (RTKs) comprise a large family of transmembrane receptors with at least nineteen distinct RTK subfamilies having diverse biological activities. The RTK family includes receptors that are crucial for the growth and differentiation of a variety of cell types (Yarden and Ullrich, *Ann. Rev. Biochem.* 57:433-478, 1988; Ullrich and Schlessinger, *Cell* 61:243-254, 1990). The intrinsic function of RTKs is activated upon ligand binding, which results in phosphorylation of the receptor and multiple cellular substrates, and subsequently results in a variety of cellular responses (Ullrich & Schlessinger, 1990, *Cell* 61:203-212). Thus, RTK mediated signal transduction is initiated by extracellular interaction with a specific growth factor (ligand), typically followed by receptor

dimerization, stimulation of the intrinsic protein tyrosine kinase activity and receptor trans-phosphorylation. Binding sites are thereby created for intracellular signal transduction molecules and lead to the formation of complexes with a spectrum of cytoplasmic signaling molecules that facilitate a corresponding cellular response such as cell division, differentiation, metabolic effects, and changes in the extracellular microenvironment (Schlessinger and Ullrich, 1992, *Neuron* 9:1-20).

[4] Malignant cells are associated with the loss of control over one or more cell cycle elements. These elements range from cell surface receptors to the regulators of transcription and translation, including the insulin-like growth factors, insulin growth factor-I (IGF-l) and insulin growth factor-2 (IGF-2) (M.J. Ellis, "The Insulin-Like Growth Factor Network and Breast Cancer", Breast Cancer, Molecular Genetics, Pathogenesis and Therapeutics, Humana Press 1999). The insulin growth factor system consists of families of ligands, insulin growth factor binding proteins, and receptors.

[5] A major physiological role of the IGF-l system is the promotion of normal growth and regeneration. Overexpressed IGF-1R (type 1 insulin-like growth factor receptor) can initiate mitogenesis and promote ligand-dependent neoplastic transformation. Furthermore, IGF-1R plays an important role in the establishment and maintenance of the malignant phenotype.

[6] IGF-1R exists as a heterodimer, with several disulfide bridges. The tyrosine kinase catalytic site and the ATP binding site are located on the cytoplasmic portion of the beta subunit. Unlike the epidermal growth factor (EGF) receptor, no mutant oncogenic forms of the IGF-1R have been identified. However, several oncogenes have been demonstrated to affect IGF-1 and IGF-1R expression. The correlation between a reduction of IGF-1R expression and resistance to transformation has been seen. Exposure of cells to the mRNA antisense to IGF-1R RNA prevents soft agar growth of several human tumor cell lines.

[7] Apoptosis is a ubiquitous physiological process used to eliminate damaged or unwanted cells in multicellular organisms. Misregulation of apoptosis is believed to be involved in the pathogenesis of many human diseases. The failure of apoptotic cell death has been implicated in various cancers, as well as autoimmune disorders. Conversely, increased apoptosis is associated with a variety of diseases involving cell loss such as neurodegenerative disorders and AIDS. As such, regulators of apoptosis have become an important therapeutic target. It is now established that a major mode of tumor survival is escape from apoptosis. IGF-1R abrogates progression into apoptosis, both *in vivo* and *in*

vitro. It has also been shown that a decrease in the level of IGF-1R below wild-type levels causes apoptosis of tumor cells *in vivo*. The ability of IGF-1R disruption to cause apoptosis appears to be diminished in normal, non-tumorigenic cells.

[8] Inappropriately high protein kinase activity has been implicated in many diseases resulting from abnormal cellular function. This might arise either directly or indirectly by a failure of the proper control mechanisms for the kinase, related to mutation, over-expression or inappropriate activation of the enzyme; or by an over- or underproduction of cytokines or growth factors participating in the transduction of signals upstream or downstream of the kinase. In all of these instances, selective inhibition of the action of the kinase might be expected to have a beneficial effect.

[9] IGF-1R is a transmembrane RTK that binds primarily to IGF-1 but also to lGF-II and insulin with lower affinity. Binding of IGF-1 to its receptor results in receptor oligomerization, activation of tyrosine kinase, intermolecular receptor autophosphorylation and phosphorylation of cellular substrates (major substrates are IRS1 and Shc). The ligand-activated IGF-1R induces mitogenic activity in normal cells and plays an important role in abnormal growth.

[10] The IGF-1 pathway in human tumor development has an important role: 1) IGF-1R overexpression is frequently found in various tumors (breast, colon, lung, sarcoma) and is often associated with an aggressive phenotype. 2) High circulating IGF1 concentrations are strongly correlated with prostate, lung and breast cancer risk. Furthermore, IGF-1R is required for establishment and maintenance of the transformed phenotype *in vitro* and *in vivo* (Baserga R. *Exp. Cell. Res*., 1999, 253, 1-6). The kinase activity of IGF-1R is essential for the transforming activity of several oncogenes: EGFR, PDGFR, SV40 T antigen, activated Ras, Raf, and v-Src. The expression of IGF-1R in normal fibroblasts induces neoplastic phenotypes, which can then form tumors *in vivo*. IGF-1R expression plays an important role in anchorage-independent growth. IGF-1R has also been shown to protect cells from chemotherapy-, radiation-, and cytokine-induced apoptosis. Conversely, inhibition of endogenous IGF-1R by dominant negative IGF-1R, triple helix formation or antisense expression vector has been shown to repress transforming activity *in vitro* and tumor growth in animal models.

[11] Many of the tyrosine kinases, whether an RTK or non-receptor tyrosine kinase, have been found to be involved in cellular signaling pathways involved in numerous disorders, including cancer, psoriasis, fibrosis, atherosclerosis, restenosis, auto-immune

disease, allergy, asthma, transplantation rejection, inflammation, thrombosis, nervous system diseases, and other hyperproliferative disorders or hyper-immune responses. It is desirable to provide novel inhibitors of kinases involved in mediating or maintaining disease states to treat such diseases.

[12] The identification of effective small compounds that specifically inhibit signal transduction and cellular proliferation, by modulating the activity of receptor and non-receptor tyrosine and serine/threonine kinases, to regulate and modulate abnormal or inappropriate cell proliferation, differentiation, or metabolism is therefore desirable. In particular, the identification of methods and compounds that specifically inhibit the function of a tyrosine kinase essential for angiogenic processes or for the formation of vascular hyperpermeability leading to edema, ascites, effusions, exudates, macromolecular extravasation, matrix deposition, and their associated disorders would be beneficial.

[13] It has been recognized that inhibitors of protein-tyrosine kinases are useful as selective inhibitors of the growth of mammalian cancer cells. For example, Gleevec™ (also known as imatinib mesylate, or STI571), a 2-phenylpyrimidine tyrosine kinase inhibitor that inhibits the kinase activity of the BCR-ABL fusion gene product, was recently approved by the U.S. Food and Drug Administration for the treatment of CML. This compound, in addition to inhibiting BCR-ABL kinase, also inhibits KIT kinase and PDGF receptor kinase, although it is not effective against all mutant isoforms of KIT kinase. In recent clinical studies on the use of Gleevec™ to treat patients with GIST, a disease in which KIT kinase is involved in transformation of the cells, many of the patients showed marked clinical improvement. Other kinase inhibitors show even greater selectively. For example, the 4-anilinoquinazoline compound Tarceva™ inhibits only EGF receptor kinase with high potency, although it can inhibit the signal transduction of other receptor kinases, probably because such receptors heterodimerize with the EGF receptor.

[14] In view of the importance of PTKs to the control, regulation, and modulation of cell proliferation and the diseases and disorders associated with abnormal cell proliferation, many attempts have been made to identify small molecule tyrosine kinase inhibitors. Bis-, mono-cyclic, bicyclic or heterocyclic aryl compounds (International Patent Publication No. WO 92/20642) and vinylene-azaindole derivatives (International Patent Publication No. WO 94/14808) have been described generally as tyrosine kinase inhibitors. Styryl compounds (U.S. Patent No. 5,217,999), styryl-substituted pyridyl compounds (U.S. Patent No. 5,302,606), certain quinazoline derivatives (EP Application No. 0566266 A1;

Expert Opin. Ther. Pat. (1998), 8(4): 475-478), selenoindoles and selenides (International Patent Publication No. WO 94/03427), tricyclic polyhydroxylic compounds (International Patent Publication No. WO 92/21660) and benzylphosphonic acid compounds (International Patent Publication No. WO 91/15495) have been described as compounds for use as tyrosine kinase inhibitors for use in the treatment of cancer. Anilinocinnolines (PCT WO97/34876) and quinazoline derivative compounds (International Patent Publication No. WO 97/22596; International Patent Publication No. WO97/42187) have been described as inhibitors of angiogenesis and vascular permeability. Bis(indolylmaleimide) compounds have been described as inhibiting particular PKC serine/threonine kinase isoforms whose signal transducing function is associated with altered vascular permeability in VEGF-related diseases (International Patent Publication Nos. WO 97/40830 and WO 97/40831).

[15] International Patent Publication Nos. WO 03/018021 and WO 03/018022 describe pyrimidines for treating IGF-1R related disorders, International Patent Publication Nos. WO 02/102804 and WO 02/102805 describe cyclolignans and cyclolignans as IGF-1R inhibitors, International Patent Publication No. WO 02/092599 describes pyrrolopyrimidines for the treatment of a disease which responds to an inhibition of the IGF-1R tyrosine kinase, International Patent Publication No. WO 01/72751 describes pyrrolopyrimidines as tyrosine kinase inhibitors. International Patent Publication No. WO 00/71129 describes pyrrolotriazine inhibitors of kinases. International Patent Publication No. WO 97/28161 describes pyrrolo [2,3-d]pyrimidines and their use as tyrosine kinase inhibitors.

[16] Parrizas, et al. describes tyrphostins with *in vitro* and *in vivo* IGF-1R inhibitory activity (Endocrinology, 138:1427-1433 (1997)), and International Patent Publication No. WO 00/35455 describes heteroaryl-aryl ureas as IGF-1R inhibitors. International Patent Publication No. WO 03/048133 describes pyrimidine derivatives as modulators of IGF-1R. International Patent Publication No. WO 03/024967 describes chemical compounds with inhibitory effects towards kinase proteins. International Patent Publication No. WO 03/068265 describes methods and compositions for treating hyperproliferative conditions. International Patent Publication No. WO 00/17203 describes pyrrolopyrimidines as protein kinase inhibitors. Japanese Patent Publication No. JP 07/133280 describes a cephem compound, its production and antimicrobial composition. A. Albert et al., *Journal of the Chemical Society*, 11: 1540-1547 (1970) describes pteridine studies and pteridines unsubstituted in the 4-position, a synthesis from pyrazines via 3,4-dhydropteridines. A. Albert et al., *Chem. Biol. Pteridines Proc. Int. Symp., 4th*, 4: 1-5 (1969)

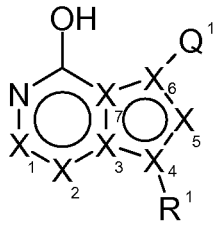
describes a synthesis of pteridines (unsubstituted in the 4-position) from pyrazines, via 3-4-dihydropteridines.

[17] IGF-1R performs important roles in cell division, development, and metabolism, and in its activated state, plays a role in oncogenesis and suppression of apoptosis. IGF-1R is known to be overexpressed in a number of cancer cell lines (IGF-1R overexpression is linked to acromegaly and to cancer of the prostate). By contrast, down-regulation of IGF-1R expression has been shown to result in the inhibition of tumorigenesis and an increased apoptosis of tumor cells.

[18] Although the anticancer compounds described above have made a significant contribution to the art, there is a continuing need in this field of art to improve anticancer pharmaceuticals with better selectivity or potentcy, reduced toxicity, or fewer side effects.

SUMMARY OF THE INVENTION

[19] The present invention relates to compounds of Formula I:

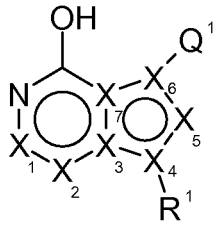


I

[20] or a pharmaceutically acceptable salt thereof. The compounds of Formula I inhibit the IGF-1R enzyme and are useful for the treatment and/or prevention of hyperproliferative diseases such as cancer, inflammation, psoriasis, allergy/asthma, disease and conditions of the immune system, disease and conditions of the central nervous system.

DETAILED DESCRIPTION OF THE INVENTION

[21] The present invention relates to a compound of Formula I:



I

[22] or a pharmaceutically acceptable salt thereof, wherein:

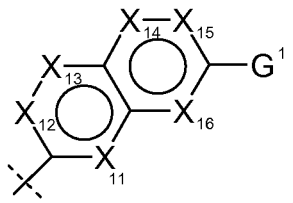
[23] X_1, and X_2 are each independently N or C–$(E^1)_{aa}$;

[24] X_5 is N, C–$(E^1)_{aa}$, or N–$(E^1)_{aa}$;

[25] X_3, X_4, X_6, and X_7 are each independently N or C;

[26] wherein at least one of X_3, X_4, X_5, X_6, and X_7 is independently N or N–$(E^1)_{aa}$;

[27] Q^1 is



;

[28] X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, and X_{16} are each independently N, C–$(E^{11})_{bb}$, or N^+–O^-;

[29] wherein at least one of X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, and X_{16} is N or N^+–O^-;

[30] R^1 is absent, C_{0-10}alkyl, cycloC_{3-10}alkyl, bicycloC_{5-10}alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl, heterobicycloC_{5-10}alkyl, spiroalkyl, or heterospiroalkyl, any of which is optionally substituted by one or more independent G^{11} substituents;

[31] E^1, E^{11}, G^1, and G^{41} are each independently halo, $–CF_3$, $–OCF_3$, $–OR^2$, $–NR^2R^3(R^{2a})_{j1}$, $–C(=O)R^2$, $–CO_2R^2$, $–CONR^2R^3$, $–NO_2$, –CN, $–S(O)_{j1}R^2$, $–SO_2NR^2R^3$, $–NR^2C(=O)R^3$, $–NR^2C(=O)OR^3$, $–NR^2C(=O)NR^3R^{2a}$, $–NR^2S(O)_{j1}R^3$, $–C(=S)OR^2$, $–C(=O)SR^2$, $–NR^2C(=NR^3)NR^{2a}R^{3a}$, $–NR^2C(=NR^3)OR^{2a}$, $–NR^2C(=NR^3)SR^{2a}$, $–OC(=O)OR^2$, $–OC(=O)NR^2R^3$, $–OC(=O)SR^2$, $–SC(=O)OR^2$, $–SC(=O)NR^2R^3$, C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl–C_{0-10}alkyl, heterocyclyl–C_{2-10}alkenyl, or heterocyclyl–C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $–CF_3$, $–OCF_3$, $–OR^{222}$, $–NR^{222}R^{333}(R^{222a})_{j1a}$, $–C(=O)R^{222}$, $–CO_2R^{222}$, $–C(=O)NR^{222}R^{333}$, $–NO_2$, –CN, $–S(=O)_{j1a}R^{222}$, $–SO_2NR^{222}R^{333}$, $–NR^{222}C(=O)R^{333}$, $–NR^{222}C(=O)OR^{333}$, $–NR^{222}C(=O)NR^{333}R^{222a}$, $–NR^{222}S(O)_{j1a}R^{333}$, $–C(=S)OR^{222}$, $–C(=O)SR^{222}$, $–NR^{222}C(=NR^{333})NR^{222a}R^{333a}$, $–NR^{222}C(=NR^{333})OR^{222a}$, $–NR^{222}C(=NR^{333})SR^{222a}$, $–OC(=O)OR^{222}$, $–OC(=O)NR^{222}R^{333}$, $–OC(=O)SR^{222}$, $–SC(=O)OR^{222}$, or $–SC(=O)NR^{222}R^{333}$ substituents;

[32] or E^1, E^{11}, or G^1 optionally is $–(W^1)_n–(Y^1)_m–R^4$;

[33] or E^1, E^{11}, G^1, or G^{41} optionally independently is aryl–C_{0-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, hetaryl–C_{0-10}alkyl, hetaryl–C_{2-10}alkenyl, or hetaryl–C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $–CF_3$, $–OCF_3$, $–OR^{222}$, $–NR^{222}R^{333}(R^{222a})_{j2a}$, $–C(O)R^{222}$, $–CO_2R^{222}$, $–C(=O)NR^{222}R^{333}$, $–NO_2$, –CN, $–S(O)_{j2a}R^{222}$, $–SO_2NR^{222}R^{333}$, $–NR^{222}C(=O)R^{333}$, $–NR^{222}C(=O)OR^{333}$, $–NR^{222}C(=O)NR^{333}R^{222a}$, $–NR^{222}S(O)_{j2a}R^{333}$, $–C(=S)OR^{222}$, $–C(=O)SR^{222}$, $–NR^{222}C(=NR^{333})NR^{222a}R^{333a}$, $–NR^{222}C(=NR^{333})OR^{222a}$, $–NR^{222}C(=NR^{333})SR^{222a}$,

$-OC(=O)OR^{222}$, $-OC(=O)NR^{222}R^{333}$, $-OC(=O)SR^{222}$, $-SC(=O)OR^{222}$, or $-SC(=O)NR^{222}R^{333}$ substituents;

[34] G^{11} is halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{21}$, $-NR^{21}R^{31}(R^{2a1})_{j4}$, $-C(O)R^{21}$, $-CO_2R^{21}$, $-C(=O)NR^{21}R^{31}$, $-NO_2$, $-CN$, $-S(O)_{j4}R^{21}$, $-SO_2NR^{21}R^{31}$, $NR^{21}(C=O)R^{31}$, $NR^{21}C(=O)OR^{31}$, $NR^{21}C(=O)NR^{31}R^{2a1}$, $NR^{21}S(O)_{j4}R^{31}$, $-C(=S)OR^{21}$, $-C(=O)SR^{21}$, $-NR^{21}C(=NR^{31})NR^{2a1}R^{3a1}$, $-NR^{21}C(=NR^{31})OR^{2a1}$, $-NR^{21}C(=NR^{31})SR^{2a1}$, $-OC(=O)OR^{21}$, $-OC(=O)NR^{21}R^{31}$, $-OC(=O)SR^{21}$, $-SC(=O)OR^{21}$, $-SC(=O)NR^{21}R^{31}$, $-P(O)OR^{21}OR^{31}$, C_{1-10}alkylidene, C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl–C_{0-10}alkyl, heterocyclyl–C_{2-10}alkenyl, or heterocyclyl–C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{2221}$, $-NR^{2221}R^{3331}(R^{222a1})_{j4a}$, $-C(O)R^{2221}$, $-CO_2R^{2221}$, $-C(=O)NR^{2221}R^{3331}$, $-NO_2$, $-CN$, $-S(O)_{j4a}R^{2221}$, $-SO_2NR^{2221}R^{3331}$, $-NR^{2221}C(=O)R^{3331}$, $-NR^{2221}C(=O)OR^{3331}$, $-NR^{2221}C(=O)NR^{3331}R^{222a1}$, $-NR^{2221}S(O)_{j4a}R^{3331}$, $-C(=S)OR^{2221}$, $-C(=O)SR^{2221}$, $-NR^{2221}C(=NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}C(=NR^{3331})OR^{222a1}$, $-NR^{2221}C(=NR^{3331})SR^{222a1}$, $-OC(=O)OR^{2221}$, $-OC(=O)NR^{2221}R^{3331}$, $-OC(=O)SR^{2221}$, $-SC(=O)OR^{2221}$, $-P(O)OR^{2221}OR^{3331}$, or $-SC(=O)NR^{2221}R^{3331}$ substituents;

[35] or G^{11} is aryl–C_{0-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, hetaryl–C_{0-10}alkyl, hetaryl–C_{2-10}alkenyl, or hetaryl–C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{2221}$, $-NR^{2221}R^{3331}(R^{222a1})_{j5a}$, $-C(O)R^{2221}$, $-CO_2R^{2221}$, $-C(=O)NR^{2221}R^{3331}$, $-NO_2$, $-CN$, $-S(O)_{j5a}R^{2221}$, $-SO_2NR^{2221}R^{3331}$, $-NR^{2221}C(=O)R^{3331}$, $-NR^{2221}C(=O)OR^{3331}$, $-NR^{2221}C(=O)NR^{3331}R^{222a1}$, $-NR^{2221}S(O)_{j5a}R^{3331}$, $-C(=S)OR^{2221}$, $-C(=O)SR^{2221}$, $-NR^{2221}C(=NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}C(=NR^{3331})OR^{222a1}$, $-NR^{2221}C(=NR^{3331})SR^{222a1}$, $-OC(=O)OR^{2221}$, $-OC(=O)NR^{2221}R^{3331}$, $-OC(=O)SR^{2221}$, $-SC(=O)OR^{2221}$, $-P(O)OR^{2221}OR^{3331}$, or $-SC(=O)NR^{2221}R^{3331}$ substituents;

[36] or G^{11} is C, taken together with the carbon to which it is attached forms a C=C double bond which is substituted with R^5 and G^{111};

[37] R^2, R^{2a}, R^3, R^{3a}, R^{222}, R^{222a}, R^{333}, R^{333a}, R^{21}, R^{2a1}, R^{31}, R^{3a1}, R^{2221}, R^{222a1}, R^{3331}, and R^{333a1} are each independently C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl,

C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl–C_{0-10}alkyl, heterocyclyl–C_{2-10}alkenyl, heterocyclyl–C_{2-10}alkynyl, aryl–C_{0-10}alkyl, aryl–C_{2-10}alkenyl, or aryl–C_{2-10}alkynyl, hetaryl–C_{0-10}alkyl, hetaryl–C_{2-10}alkenyl, or hetaryl–C_{2-10}alkynyl, any of which is optionally substituted by one or more independent G^{111} substituents;

[38] or in the case of $–NR^2R^3(R^{2a})_{j1}$ or $–NR^{222}R^{333}(R^{222a})_{j1a}$ or $–NR^{222}R^{333}(R^{222a})_{j2a}$ or $–NR^{21}R^{31}(R^{2a1})_{j4}$ or $–NR^{2221}R^{3331}(R^{222a1})_{j4a}$ or $–NR^{2221}R^{3331}(R^{222a1})_{j5a}$, then R^2 and R^3, or R^{222} and R^{333}, or R^{2221} and R^{3331}, respectfully, are optionally taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring, wherein said ring is optionally substituted by one or more independent G^{1111} substituents and wherein said ring optionally includes one or more heteroatoms other than the nitrogen to which R^2 and R^3, or R^{222} and R^{333}, or R^{2221} and R^{3331} are attached;

[39] W^1 and Y^1 are each independently –O–, $–NR^7–$, $–S(O)_{j7}–$, $–CR^5R^6–$, $–N(C(O)OR^7)–$, $–N(C(O)R^7)–$, $–N(SO_2R^7)–$, $–CH_2O–$, $–CH_2S–$, $–CH_2N(R^7)–$, $–CH(NR^7)–$, $–CH_2N(C(O)R^7)–$, $–CH_2N(C(O)OR^7)–$, $–CH_2N(SO_2R^7)–$, $–CH(NHR^7)–$, $–CH(NHC(O)R^7)–$, $–CH(NHSO_2R^7)–$, $–CH(NHC(O)OR^7)–$, $–CH(OC(O)R^7)–$, $–CH(OC(O)NHR^7)–$, –CH=CH–, –C≡C–, $–C(=NOR^7)–$, –C(O)–, $–CH(OR^7)–$, $–C(O)N(R^7)–$, $–N(R^7)C(O)–$, $–N(R^7)S(O)–$, $–N(R^7)S(O)_2–$ $–OC(O)N(R^7)–$, $–N(R^7)C(O)N(R^8)–$, $–NR^7C(O)O–$, $–S(O)N(R^7)–$, $–S(O)_2N(R^7)–$, $–N(C(O)R^7)S(O)–$, $–N(C(O)R^7)S(O)_2–$, $–N(R^7)S(O)N(R^8)–$, $–N(R^7)S(O)_2N(R^8)–$, $–C(O)N(R^7)C(O)–$, $–S(O)N(R^7)C(O)–$, $–S(O)_2N(R^7)C(O)–$, $–OS(O)N(R^7)–$, $–OS(O)_2N(R^7)–$, $–N(R^7)S(O)O–$, $–N(R^7)S(O)_2O–$, $–N(R^7)S(O)C(O)–$, $–N(R^7)S(O)_2C(O)–$, $–SON(C(O)R^7)–$, $–SO_2N(C(O)R^7)–$, $–N(R^7)SON(R^8)–$, $–N(R^7)SO_2N(R^8)–$, –C(O)O–, $–N(R^7)P(OR^8)O–$, $–N(R^7)P(OR^8)–$, $–N(R^7)P(O)(OR^8)O–$, $–N(R^7)P(O)(OR^8)–$, $–N(C(O)R^7)P(OR^8)O–$, $–N(C(O)R^7)P(OR^8)–$, $–N(C(O)R^7)P(O)(OR^8)O–$, $–N(C(O)R^7)P(OR^8)–$, $–CH(R^7)S(O)–$, $–CH(R^7)S(O)_2–$, $–CH(R^7)N(C(O)OR^8)–$, $–CH(R^7)N(C(O)R^8)–$, $–CH(R^7)N(SO_2R^8)–$, $–CH(R^7)O–$, $–CH(R^7)S–$, $–CH(R^7)N(R^8)–$, $–CH(R^7)N(C(O)R^8)–$, $–CH(R^7)N(C(O)OR^8)–$, $–CH(R^7)N(SO_2R^8)–$, $–CH(R^7)C(=NOR^8)–$, $–CH(R^7)C(O)–$, $–CH(R^7)CH(OR^8)–$, $–CH(R^7)C(O)N(R^8)–$, $–CH(R^7)N(R^8)C(O)–$, $–CH(R^7)N(R^8)S(O)–$, $–CH(R^7)N(R^8)S(O)_2–$,

–CH(R^7)OC(O)N(R^8)–, –CH(R^7)N(R^8)C(O)N(R^{7a})–, –CH(R^7)NR^8C(O)O–, –CH(R^7)S(O)N(R^8)–, –CH(R^7)S(O)$_2$N(R^8)–, –CH(R^7)N(C(O)R^8)S(O)–, –CH(R^7)N(C(O)R^8)S(O)–, –CH(R^7)N(R^8)S(O)N(R^{7a})–, –CH(R^7)N(R^8)S(O)$_2$N(R^{7a})–, –CH(R^7)C(O)N(R^8)C(O)–, –CH(R^7)S(O)N(R^8)C(O)–, –CH(R^7)S(O)$_2$N(R^8)C(O)–, –CH(R^7)OS(O)N(R^8)–, –CH(R^7)OS(O)$_2$N(R^8)–, –CH(R^7)N(R^8)S(O)O–, –CH(R^7)N(R^8)S(O)$_2$O–, –CH(R^7)N(R^8)S(O)C(O)–, –CH(R^7)N(R^8)S(O)$_2$C(O)–, –CH(R^7)SON(C(O)R^8)–, –CH(R^7)SO$_2$N(C(O)R^8)–, –CH(R^7)N(R^8)SON(R^{7a})–, –CH(R^7)N(R^8)SO$_2$N(R^{7a})–, –CH(R^7)C(O)O–, –CH(R^7)N(R^8)P(OR^{7a})O–, –CH(R^7)N(R^8)P(OR^{7a})–, –CH(R^7)N(R^8)P(O)(OR^{7a})O–, –CH(R^7)N(R^8)P(O)(OR^{7a})–, –CH(R^7)N(C(O)R^8)P(OR^{7a})O–, –CH(R^7)N(C(O)R^8)P(OR^{7a})–, –CH(R^7)N(C(O)R^8)P(O)(OR^{7a})O–, or –CH(R^7)N(C(O)R^8)P(OR^{7a})–;

[40] R^5, R^6, G^{111}, and G^{1111} are each independently C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl–C_{0-10}alkyl, heterocyclyl–C_{2-10}alkenyl, heterocyclyl–C_{2-10}alkynyl, aryl–C_{0-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, hetaryl–C_{0-10}alkyl, hetaryl–C_{2-10}alkenyl, or hetaryl–C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, –CF_3, –OCF_3, –OR^{77}, –$NR^{77}R^{87}$, –C(O)R^{77}, –CO_2R^{77}, –$CONR^{77}R^{87}$, –NO_2, –CN, –S(O)$_{j5a}R^{77}$, –$SO_2NR^{77}R^{87}$, –NR^{77}C(=O)R^{87}, –NR^{77}C(=O)OR^{87}, –NR^{77}C(=O)$NR^{78}R^{87}$, –NR^{77}S(O)$_{j5a}R^{87}$, –C(=S)OR^{77}, –C(=O)SR^{77}, –NR^{77}C(=NR^{87})$NR^{78}R^{88}$, –NR^{77}C(=NR^{87})OR^{78}, –NR^{77}C(=NR^{87})SR^{78}, –OC(=O)OR^{77}, –OC(=O)$NR^{77}R^{87}$, –OC(=O)SR^{77}, –SC(=O)OR^{77}, –P(O)OR^{77}OR^{87}, or –SC(=O)$NR^{77}R^{87}$ substituents;

[41] or R^5 with R^6 are optionally taken together with the carbon atom to which they are attached to form a 3-10 membered saturated or unsaturated ring, wherein said ring is optionally substituted with one or more independent R^{69} substituents and wherein said ring optionally includes one or more heteroatoms;

[42] R^7, R^{7a}, and R^8 are each independently acyl, C_{0-10}alkyl, C_{2-10}alkenyl, aryl, heteroaryl, heterocyclyl or cycloC_{3-10}alkyl, any of which is optionally substituted by one or more independent G^{111} substituents;

[43] R^4 is C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, aryl, heteroaryl, cycloC_{3-10}alkyl, heterocyclyl, cycloC_{3-8}alkenyl, or heterocycloalkenyl, any of which is optionally substituted by one or more independent G^{41} substituents;

[44] R^{69} is halo, $-OR^{78}$, $-SH$, $-NR^{78}R^{88}$, $-CO_2R^{78}$, $-C(=O)NR^{78}R^{88}$, $-NO_2$, $-CN$, $-S(O)_{j8}R^{78}$, $-SO_2NR^{78}R^{88}$, C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl–C_{0-10}alkyl, heterocyclyl–C_{2-10}alkenyl, or heterocyclyl–C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents;

[45] or R^{69} is aryl–C_{0-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, hetaryl–C_{0-10}alkyl, hetaryl–C_{2-10}alkenyl, hetaryl–C_{2-10}alkynyl, mono(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, mono(aryl)aminoC_{1-6}alkyl, di(aryl)aminoC_{1-6}alkyl, or $-N(C_{1-6}alkyl)-C_{1-6}alkyl-aryl$, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-OR^{778}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, C_{1-4}alkoxycarbonyl, $-C(=O)NR^{778}R^{888}$, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents;

[46] or in the case of $-NR^{78}R^{88}$, R^{78} and R^{88} are optionally taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring, wherein said ring is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, C_{1-10}alkoxy, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents, and wherein said ring optionally includes one or more heteroatoms other than the nitrogen to which R^{78} and R^{88} are attached;

[47] R^{77}, R^{78}, R^{87}, R^{88}, R^{778}, and R^{888} are each independently C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl–C_{0-10}alkyl, heterocyclyl–C_{2-10}alkenyl, heterocyclyl–C_{2-10}alkynyl, C_{1-10}alkylcarbonyl, C_{2-10}alkenylcarbonyl, C_{2-10}alkynylcarbonyl, C_{1-}

$_{10}$alkoxycarbonyl, C_{1-10}alkoxycarbonylC_{1-10}alkyl, monoC_{1-6}alkylaminocarbonyl, diC_{1-6}alkylaminocarbonyl, mono(aryl)aminocarbonyl, di(aryl)aminocarbonyl, or C_{1-10}alkyl(aryl)aminocarbonyl, any of which is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, C_{1-10}alkoxy, $-SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl)$, or $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$ substituents;

[48] or R^{77}, R^{78}, R^{87}, R^{88}, R^{778}, and R^{888} are each independently aryl–C_{0-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, hetaryl–C_{0-10}alkyl, hetaryl–C_{2-10}alkenyl, hetaryl–C_{2-10}alkynyl, mono(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, mono(aryl)aminoC_{1-6}alkyl, di(aryl)aminoC_{1-6}alkyl, or $-N(C_{1-6}alkyl)-C_{1-6}alkyl-aryl$, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-O(C_{0-4}alkyl)$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, C_{1-4}alkoxycarbonyl, $-CON(C_{0-4}alkyl)(C_{0-10}alkyl)$, $-SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl)$, or $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$ substituents;

[49] n, m, j1, j1a, j2a, j4, j4a, j5a, j7, and j8 are each independently 0, 1, or 2; and

[50] aa and bb are each independently 0 or 1.

[51] In an aspect of the present invention, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_3 is N; X_1, X_2, and X_5 are $C–(E^1)_{aa}$; X_4, X_6, and X_7 are C; and the other variables are described as above for Formula I.

[52] In a second aspect of the present invention, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_4 is N; X_1, X_2, and X_5 are $C–(E^1)_{aa}$; and X_3, X_6, and X_7 are C; and the other variables are described as above for Formula I.

[53] In a third aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_5 is $N–(E^1)_{aa}$; X_1 and X_2 are $C–(E^1)_{aa}$; X_3, X_4, X_6, and X_7 are C; and the other variables are described as above for Formula I.

[54] In a fourth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_6 is N; X_1, X_2, and X_5 are $C–(E^1)_{aa}$; X_3, X_4, and X_7 are C; and the other variables are described as above for Formula I.

[55] In a fifth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_7 is N; X_1, X_2, and X_5 are $C–(E^1)_{aa}$; X_3, X_4, and X_6 are C; and the other variables are described as above for Formula I.

[56] In a sixth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_1 and X_3 are N; X_2 and X_5 are C–$(E^1)_{aa}$; X_4, X_6, and X_7 are C; and the other variables are described as above for Formula I.

[57] In a seventh aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_1 and X_4 are N; X_2 and X_5 are C–$(E^1)_{aa}$; X_3, X_6, and X_7 are C; and the other variables are described as above for Formula I.

[58] In an eighth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_1 is N; X_5 is N–$(E^1)_{aa}$; X_2 is C–$(E^1)_{aa}$; X_3, X_4, X_6, and X_7 are C; and the other variables are described as above for Formula I.

[59] In a ninth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_1 and X_6 are N; X_2 and X_5 are C–$(E^1)_{aa}$; X_3, X_4, and X_7 are C; and the other variables are described as above for Formula I.

[60] In a tenth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_1 and X_7 are N; X_2 and X_5 are C–$(E^1)_{aa}$; X_3, X_4, and X_6 are C; and the other variables are described as above for Formula I.

[61] In a eleventh aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_2 and X_3 are N; X_1 and X_5 are C–$(E^1)_{aa}$; X_4, X_6, and X_7 are C; and the other variables are described as above for Formula I.

[62] In a twelfth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_2 and X_4 are N; X_1 and X_5 are C–$(E^1)_{aa}$; X_3, X_6, and X_7 are C; and the other variables are described as above for Formula I.

[63] In a thirteenth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_2 is N; X_5 is N–$(E^1)_{aa}$, X_1 is C–$(E^1)_{aa}$; X_3, X_4, X_6, and X_7 are C; and the other variables are described as above for Formula I.

[64] In a fourteenth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_2 and X_6 are N; X_1 and X_5 are C–$(E^1)_{aa}$; X_3, X_4, and X_7 are C; and the other variables are described as above for Formula I.

[65] In a fifteenth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_2 and X_7 are N; X_1 and X_5 are C–$(E^1)_{aa}$; X_3, X_4, and X_6 are C; and the other variables are described as above for Formula I.

[66] In a sixteenth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_3 and X_4 are N; X_1, X_2, and X_5 are C–$(E^1)_{aa}$; X_6 and X_7 are C; R^1 is absent; and the other variables are described as above for Formula I.

[67] In a seventeenth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_3 and X_5 are N; X_1 and X_2 are C–$(E^1)_{aa}$; X_4, X_6, and X_7 are C; and the other variables are described as above for Formula I.

[68] In an eighteenth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_4 and X_5 are N; X_1 and X_2 are C–$(E^1)_{aa}$; X_3, X_6, and X_7 are C; and the other variables are described as above for Formula I.

[69] In a nineteenth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_4 and X_6 are N; X_1, X_2, and X_5 are C–$(E^1)_{aa}$; X_3 and X_7 are C; R^1 is absent; and the other variables are described as above for Formula I.

[70] In a twentieth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_4 and X_7 are N; X_1, X_2, and X_5 are C–$(E^1)_{aa}$; X_3 and X_6 are C; R^1 is absent; and the other variables are described as above for Formula I.

[71] In a twenty-first aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_5 and X_6 are N; X_1 and X_2 are C–$(E^1)_{aa}$; X_3, X_4, and X_7 are C; and the other variables are described as above for Formula I.

[72] In a twenty-second aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_5 and X_7 are N; X_1 and X_2 are C–$(E^1)_{aa}$; X_3, X_4, and X_6 are C; and the other variables are described as above for Formula I.

[73] In a twenty-third aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_2, X_3, and X_4 are N; X_1 and X_5 are C–$(E^1)_{aa}$; X_6 and X_7 are C; R^1 is absent; and the other variables are described as above for Formula I.

[74] In a twenty-fourth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_2, X_3, and X_5 are N; X_1 is C–$(E^1)_{aa}$; X_4, X_6 and X_7 are C; and the other variables are described as above for Formula I.

[75] In a twenty-fifth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_3, X_4, and X_5 are N; X_1 and X_2 are C–$(E^1)_{aa}$; X_6 and X_7 are C; R^1 is absent; and the other variables are described as above for Formula I.

[76] In a twenty-sixth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_1, X_3, and X_4 are N; X_2 and X_5 are C–$(E^1)_{aa}$; X_6 and X_7 are C; R^1 is absent; and the other variables are described as above for Formula I.

[77] In a twenty-seventh aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_1, X_4, and X_5 are N; X_2 is C–$(E^1)_{aa}$; X_3, X_6 and X_7 are C; and the other variables are described as above for Formula I.

[78] In a twenty-eighth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_2, X_4, and X_5 are N; X_1 is C–$(E^1)_{aa}$; X_3, X_6 and X_7 are C; and the other variables are described as above for Formula I.

[79] In a twenty-ninth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_1, X_5, and X_6 are N; X_2 is C–$(E^1)_{aa}$; X_3, X_4, and X_7 are C; and the other variables are described as above for Formula I.

[80] In a thirtieth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_2, X_5, and X_6 are N; X_1 is C–$(E^1)_{aa}$; X_3, X_4, and X_7 are C; and the other variables are described as above for Formula I.

[81] In a thirty-first aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_4, X_5, and X_6 are N; X_1 and X_2 are C–$(E^1)_{aa}$; X_3 and X_7 are C; R^1 is absent; and the other variables are described as above for Formula I.

[82] In a thirty-second aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_1, X_3, and X_5 are N; X_2 is C–$(E^1)_{aa}$; X_4, X_6 and X_7 are C; and the other variables are described as above for Formula I.

[83] In a thirty-third aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_1, X_4, and X_6 are N; X_2 and X_5 are C–$(E^1)_{aa}$; X_3 and X_7 are C; R^1 is absent; and the other variables are described as above for Formula I.

[84] In a thirty-fourth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_1, X_5, and X_7 are N; X_2 is C–$(E^1)_{aa}$; X_3, X_4, and X_6 are C; and the other variables are described as above for Formula I.

[85] In a thirty-fifth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_1, X_4, and X_7 are N; X_2 and X_5 are C–$(E^1)_{aa}$; X_3 and X_6 are C; R^1 is absent; and the other variables are described as above for Formula I.

[86] In a thirty-sixth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_2, X_4, and X_6 are N; X_1 and X_5 are C–$(E^1)_{aa}$; X_3 and X_7 are C; R^1 is absent; and the other variables are described as above for Formula I.

[87] In a thirty-seventh aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_2, X_4, and X_7 are N; X_1 and X_5 are C–$(E^1)_{aa}$; X_3 and X_6 are C; R^1 is absent; and the other variables are described as above for Formula I.

[88] In a thirty-eighth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_2, X_5, and X_7 are N; X_1 is C–$(E^1)_{aa}$; X_3, X_4, and X_6 are C; and the other variables are described as above for Formula I.

[89] In a thirty-ninth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_1, X_4, X_5, and X_6 are N; X_2 is C–$(E^1)_{aa}$; X_3 and X_7 are C; R^1 is absent; and the other variables are described as above for Formula I.

[90] In a fortieth aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_2, X_4, X_5, and X_6 are N; X_1 is C–$(E^1)_{aa}$; X_3 and X_7 are C; R^1 is absent; and the other variables are described as above for Formula I.

[91] In a forty-first aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_1, X_3, X_4, and X_5 are N; X_2 is C–$(E^1)_{aa}$; X_6 and X_7 are C; R^1 is absent; and the other variables are described as above for Formula I.

[92] In a forty-second aspect of the present invention, a compound is represented by Formula I, or a salt thereof, wherein X_2, X_3, X_4, and X_5 are N; X_1 is C–$(E^1)_{aa}$; X_6 and X_7 are C; R^1 is absent; and the other variables are described as above for Formula I.

[93] The following embodiments refer to all of the forty-two aspects above:

[94] In an embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{11}, X_{12}, and X_{13} are N; X_{14}, X_{15}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[95] In another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{11}, X_{12}, and X_{14} are N; X_{13}, X_{15}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[96] In yet another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{11}, X_{12},

and X_{15} are N; X_{13}, X_{14}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[97] In another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{11}, X_{12}, and X_{16} are N; X_{13}, X_{14}, and X_{15} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[98] In still another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{11}, X_{13}, and X_{14} are N; X_{12}, X_{15}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[99] In yet still another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{11}, X_{13}, and X_{15} are N; X_{12}, X_{14}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[100] In another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{11}, X_{13}, and X_{16} are N; X_{12}, X_{14}, and X_{15} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[101] In still another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{11}, X_{14}, and X_{15} are N; X_{12}, X_{13}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[102] In still another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{11}, X_{14}, and X_{16} are N; X_{12}, X_{13}, and X_{15} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[103] In yet another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{11}, X_{15}, and X_{16} are N; X_{12}, X_{13}, and X_{14} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[104] In yet still another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{12}, X_{13},

and X_{14} are N; X_{11}, X_{15}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[105] In still yet another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{12}, X_{13}, and X_{15} are N; X_{11}, X_{14}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[106] In another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{12}, X_{13}, and X_{16} are N; X_{11}, X_{14}, and X_{15} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[107] In yet another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{12}, X_{14}, and X_{15} are N; X_{11}, X_{13}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[108] In still another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{12}, X_{14}, and X_{16} are N; X_{11}, X_{13}, and X_{15} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[109] In yet still another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{12}, X_{15}, and X_{16} are N; X_{11}, X_{13}, and X_{14} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[110] In still another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{13}, X_{14}, and X_{15} are N; X_{11}, X_{12}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[111] In another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{13}, X_{14}, and X_{16} are N; X_{11}, X_{12}, and X_{15} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[112] In another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{14}, X_{15},

and X_{16} are N; X_{11}, X_{12}, and X_{13} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[113] In yet another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{13}, X_{15}, and X_{16} are N; X_{11}, X_{12}, and X_{14} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[114] In yet still another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{11} and X_{12} are N; X_{13}, X_{14}, X_{15}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[115] In another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{11} and X_{13} are N; X_{12}, X_{14}, X_{15}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[116] In still another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{11} and X_{14} are N; X_{12}, X_{13}, X_{15}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[117] In still yet another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{11} and X_{15} are N; X_{12}, X_{13}, X_{14}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[118] In yet another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{11} and X_{16} are N; X_{12}, X_{13}, X_{14}, and X_{15} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[119] In still another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{12} and X_{13} are N; X_{11}, X_{14}, X_{15}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[120] In another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{12} and X_{14}

are N; X_{11}, X_{13}, X_{15}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[121] In still another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{12} and X_{15} are N; X_{11}, X_{13}, X_{14}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[122] In still yet another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{12} and X_{16} are N; X_{11}, X_{13}, X_{14}, and X_{15} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[123] In still another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{13} and X_{14} are N; X_{11}, X_{12}, X_{15}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[124] In yet still another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{13} and X_{15} are N; X_{11}, X_{12}, X_{14}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[125] In another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{13} and X_{16} are N; X_{11}, X_{12}, X_{14}, and X_{15} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[126] In still another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{14} and X_{15} are N; X_{11}, X_{12}, X_{13}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[127] In still another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{14} and X_{16} are N; X_{11}, X_{12}, X_{13}, and X_{15} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[128] In another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{15} and X_{16}

are N; X_{11}, X_{12}, X_{13}, and X_{14} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[129] In another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{11} is N; X_{12}, X_{13}, X_{14}, X_{15}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[130] In yet another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{12} is N; X_{11}, X_{13}, X_{14}, X_{15}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[131] In still another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{13} is N; X_{11}, X_{12}, X_{14}, X_{15}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[132] In yet still another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{14} is N; X_{11}, X_{12}, X_{13}, X_{15}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[133] In still another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{15} is N; X_{11}, X_{12}, X_{13}, X_{14}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[134] In still another embodiment of each of the above aspects, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{16} is N; X_{11}, X_{12}, X_{13}, X_{14}, and X_{15} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[135] Advantageous embodiments of the above aspects include:

[136] An embodiment of each of the above aspects, wherein a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{11} and X_{16} are N; X_{12}, X_{13}, X_{14}, and X_{15} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[137] An embodiment of each of the above aspects, wherein a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{14} and X_{16} are N; X_{11}, X_{12}, X_{13}, and X_{15} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[138] An embodiment of each of the above aspects, wherein a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{15} and X_{16} are N; X_{11}, X_{12}, X_{13}, and X_{14} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[139] An embodiment of each of the above aspects, wherein a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{11} is N; X_{12}, X_{13}, X_{14}, X_{15}, and X_{16} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[140] An embodiment of each of the above aspects, wherein a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_{16} is N; X_{11}, X_{12}, X_{13}, X_{14}, and X_{15} are C–$(E^{11})_{bb}$; and the other variables are as described in each of the above aspects.

[141] The compounds of the present invention include compounds represented by Formula I above, or a pharmaceutically acceptable salt thereof, and

[142] wherein any one of X_{11-16} is N; or

[143] wherein any two of X_{11-16} is N; or

[144] wherein any three of X_{11-16} is N; or

[145] wherein any one of X_{11}, X_{14}, X_{15}, or X_{16} is N; or

[146] wherein any two of X_{11}, X_{14}, X_{15}, or X_{16} is N; or

[147] wherein any two of X_{14}, X_{15}, or X_{16} is N; or

[148] wherein X_{16} is N; or

[149] wherein X_{14} and X_{16} are N; or

[150] wherein X_{15} and X_{16} are N; or

[151] wherein X_{11} and X_{16} are N; or

[152] wherein X_{11} is N; or

[153] wherein G^1 is $–OR^2$, $–NR^2R^3(R^{2a})_{j1}$, $–S(O)_{j1}R^2$, C_{0-10}alkyl, cycloC_{3-8}alkyl, heterocyclyl–C_{0-10}alkyl, any of which is optionally substituted with one or more independent halo, oxo, $–CF_3$, $–OCF_3$, $–OR^{222}$, $–NR^{222}R^{333}(R^{222a})_{j1a}$, $–C(=O)R^{222}$, $–CO_2R^{222}$,

$-C(=O)NR^{222}R^{333}$, $-NO_2$, $-CN$, $-S(=O)_{j1a}R^{222}$, $-SO_2NR^{222}R^{333}$, $-NR^{222}C(=O)R^{333}$, $-NR^{222}C(=O)OR^{333}$, $-NR^{222}C(=O)NR^{333}R^{222a}$, $-NR^{222}S(O)_{j1a}R^{333}$, $-C(=S)OR^{222}$, $-C(=O)SR^{222}$, $-NR^{222}C(=NR^{333})NR^{222a}R^{333a}$, $-NR^{222}C(=NR^{333})OR^{222a}$, $-NR^{222}C(=NR^{333})SR^{222a}$, $-OC(=O)OR^{222}$, $-OC(=O)NR^{222}R^{333}$, $-OC(=O)SR^{222}$, $-SC(=O)OR^{222}$, or $-SC(=O)NR^{222}R^{333}$ substituents; or G^1 is aryl–C_{0-10}alkyl or hetaryl–C_{0-10}alkyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{222}$, $-NR^{222}R^{333}(R^{222a})_{j2a}$, $-C(O)R^{222}$, $-CO_2R^{222}$, $-C(=O)NR^{222}R^{333}$, $-NO_2$, $-CN$, $-S(O)_{j2a}R^{222}$, $-SO_2NR^{222}R^{333}$, $-NR^{222}C(=O)R^{333}$, $-NR^{222}C(=O)OR^{333}$, $-NR^{222}C(=O)NR^{333}R^{222a}$, $-NR^{222}S(O)_{j2a}R^{333}$, $-C(=S)OR^{222}$, $-C(=O)SR^{222}$, $-NR^{222}C(=NR^{333})NR^{222a}R^{333a}$, $-NR^{222}C(=NR^{333})OR^{222a}$, $-NR^{222}C(=NR^{333})SR^{222a}$, $-OC(=O)OR^{222}$, $-OC(=O)NR^{222}R^{333}$, $-OC(=O)SR^{222}$, $-SC(=O)OR^{222}$, or $-SC(=O)NR^{222}R^{333}$ substituents; or

[154] wherein R^1 is cycloC_{3-10}alkyl, bicycloC_{5-10}alkyl, aryl, heteroaralkyl, heterocyclyl, heterobicycloC_{5-10}alkyl, spiroalkyl, or heterospiroalkyl any of which is optionally substituted by one or more independent G^{11} substituents; or

[155] wherein R^1 is C_{0-10}alkyl, heteroaralkyl, or aralkyl, any of which is optionally substituted by one or more independent G^{11} substituents; or

[156] wherein R^1 is cycloC_{3-10}alkyl, bicycloC_{5-10}alkyl, spiroalkyl, or heterospiroalkyl any of which is optionally substituted by one or more independent G^{11} substituents; or

[157] wherein R^1 is heterocyclyl or heterobicycloC_{5-10}alkyl, of which is optionally substituted by one or more independent G^{11} substituents; or

[158] wherein R^1 is aryl or heteroaryl, any of which is optionally substituted by one or more independent G^{11} substituents; or

[159] wherein R^1 is C_{0-10}alkyl, cycloC_{3-10}alkyl, bicycloC_{5-10}alkyl, aralkyl, heteroaralkyl, heterocyclyl, heterobicycloC_{5-10}alkyl, spiroalkyl, or heterospiroalkyl any of which is optionally substituted by one or more independent G^{11} substituents; or

[160] wherein G^{11} is oxo, $-OCF_3$, $-OR^{21}$, $-NR^{21}R^{31}(R^{2a1})_{j4}$, $-C(O)R^{21}$, $-CO_2R^{21}$, $-C(=O)NR^{21}R^{31}$, $-CN$, $-SO_2NR^{21}R^{31}$, $-NR^{21}(C=O)R^{31}$, $-NR^{21}C(=O)OR^{31}$, $-NR^{21}C(=O)NR^{31}R^{2a1}$, $-NR^{21}S(O)_{j4}R^{31}$, $-OC(=O)NR^{21}R^{31}$, C_{0-10}alkyl, C_{1-10}alkoxyC_{1-10}alkyl, cycloC_{3-8}alkylC_{1-10}alkyl, heterocyclyl–C_{0-10}alkyl, any of which is optionally substituted with one or more independent halo, oxo, $-CF_3$, $-OCF_3$, $-OR^{2221}$, $-NR^{2221}R^{3331}(R^{222a1})_{j4a}$,

$-C(O)R^{2221}$, $-CO_2R^{2221}$, $-C(=O)NR^{2221}R^{3331}$, $-NO_2$, $-CN$, $-S(O)_{j4a}R^{2221}$, $-SO_2NR^{2221}R^{3331}$, $-NR^{2221}C(=O)R^{3331}$, $-NR^{2221}C(=O)OR^{3331}$, $-NR^{2221}C(=O)NR^{3331}R^{222a1}$, $-NR^{2221}S(O)_{j4a}R^{3331}$, $-C(=S)OR^{2221}$, $-C(=O)SR^{2221}$, $-NR^{2221}C(=NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}C(=NR^{3331})OR^{222a1}$, $-NR^{2221}C(=NR^{3331})SR^{222a1}$, $-OC(=O)OR^{2221}$, $-OC(=O)NR^{2221}R^{3331}$, $-OC(=O)SR^{2221}$, $-SC(=O)OR^{2221}$, $-P(O)OR^{2221}OR^{3331}$, or $-SC(=O)NR^{2221}R^{3331}$ substituents; or G^{11} is hetaryl–C_{0-10}alkyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{2221}$, $-NR^{2221}R^{3331}(R^{222a1})_{j5a}$, $-C(O)R^{2221}$, $-CO_2R^{2221}$, $-C(=O)NR^{2221}R^{3331}$, $-NO_2$, $-CN$, $-S(O)_{j5a}R^{2221}$, $-SO_2NR^{2221}R^{3331}$, $-NR^{2221}C(=O)R^{3331}$, $-NR^{2221}C(=O)OR^{3331}$, $-NR^{2221}C(=O)NR^{3331}R^{222a1}$, $-NR^{2221}S(O)_{j5a}R^{3331}$, $-C(=S)OR^{2221}$, $-C(=O)SR^{2221}$, $-NR^{2221}C(=NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}C(=NR^{3331})OR^{222a1}$, $-NR^{2221}C(=NR^{3331})SR^{222a1}$, $-OC(=O)OR^{2221}$, $-OC(=O)NR^{2221}R^{3331}$, $-OC(=O)SR^{2221}$, $-SC(=O)OR^{2221}$, $-P(O)OR^{2221}OR^{3331}$, or $-SC(=O)NR^{2221}R^{3331}$ substituents; or G^{11} is C, taken together with the carbon to which it is attached forms a C=C double bond which is substituted with R^5 and G^{111}; and

[161] wherein, in each case, the other variables are as defined above for Formula I.

[162] A method of inhibiting protein kinase activity according to the present invention comprises administering a compound of Formula I, or a pharmaceutically acceptable salt thereof. The method includes wherein the protein kinase is IGF-IR. The method includes wherein the activity of the protein kinase affects hyperproliferative disorders. The method includes wherein the activity of the protein kinase influences angiogenesis, vascular permeability, immune response, cellular apoptosis, tumor growth, or inflammation.

[163] A method of the present invention of treating a patient having a condition which is mediated by protein kinase activity, comprises administering to the patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof. The method includes wherein the protein kinase is IGF-IR. The method includes wherein the condition mediated by protein kinase activity is a hyperproliferative disorder. The method includes wherein the activity of the protein kinase influences angiogenesis, vascular permeability, immune response, cellular apoptosis, tumor growth, or inflammation. The method includes wherein the protein kinase is a protein serine/threonine kinase or a protein tyrosine kinase. The method includes wherein the condition mediated by protein kinase activity is one or more ulcers. The method includes

wherein the ulcer or ulcers are caused by a bacterial or fungal infection; or the ulcer or ulcers are Mooren ulcers; or the ulcer or ulcers are a symptom of ulcerative colitis. The method includes wherein the condition mediated by protein kinase activity is Lyme disease, sepsis or infection by Herpes simplex, Herpes Zoster, human immunodeficiency virus, parapoxvirus, protozoa, or toxoplasmosis. The method includes wherein the condition mediated by protein kinase activity is von Hippel Lindau disease, pemphigoid, psoriasis, Paget's disease, or polycystic kidney disease. The method includes wherein the condition mediated by protein kinase activity is fibrosis, sarcoidosis, cirrhosis, thyroiditis, hyperviscosity syndrome, Osler-Weber-Rendu disease, chronic occlusive pulmonary disease, asthma, exudtaes, ascites, pleural effusions, pulmonary edema, cerebral edema or edema following burns, trauma, radiation, stroke, hypoxia, or ischemia. The method includes wherein the condition mediated by protein kinase activity is ovarian hyperstimulation syndrome, preeclainpsia, menometrorrhagia, or endometriosis. The method includes wherein the condition mediated by protein kinase-activity is chronic inflammation, systemic lupus, glomerulonephritis, synovitis, inflammatory bowel disease, Crohn's disease, glomerulonephritis, rheumatoid arthritis and osteoarthritis, multiple sclerosis, or graft rejection. The method includes wherein the condition mediated by protein kinase activity is sickle cell anaemia. The method includes wherein the condition mediated by protein kinase activity is an ocular condition. The method includes wherein the ocular condition is ocular or macular edema, ocular neovascular disease, seleritis, radial keratotomy, uveitis, vitritis, myopia, optic pits, chronic retinal detachment, post-laser treatment complications, conjunctivitis, Stargardt's disease, Eales disease, retinopathy, or macular degeneration. The method includes wherein the condition mediated by protein kinase activity is a cardiovascular condition. The method includes wherein the condition mediated by protein kinase activity is atherosclerosis, restenosis, ischemia/reperfusion injury, vascular occlusion, venous malformation, or carotid obstructive disease. The method includes wherein the condition mediated by protein kinase activity is cancer. The method includes wherein the cancer is a solid tumor, a sarcoma, fibrosarcoma, osteoma, melanoma, retinoblastoma, a rhabdomyosarcoma, glioblastoma, neuroblastoma, teratocarcinoma, an hematopoietic malignancy, or malignant ascites. The method includes wherein the cancer is Kaposi's sarcoma, Hodgkin's disease, lymphoma, myeloma, or leukemia. Further, the method includes wherein the condition mediated by protein kinase activity is Crow-Fukase (POEMS) syndrome or a diabetic condition. The method includes wherein the diabetic condition is insulin-dependent diabetes mellitus

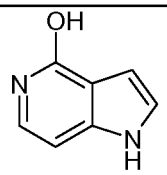
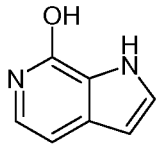
glaucoma, diabetic retinopathy, or microangiopathy. The method also includes wherein the protein kinase activity is involved in T cell activation, B cell activation, mast cell degranulation, monocyte activation, signal transduction, apoptosis, the potentiation of an inflammatory response or a combination thereof.

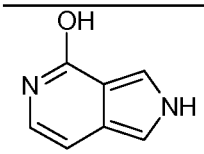
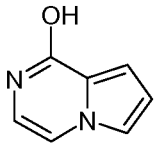
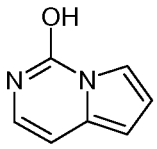
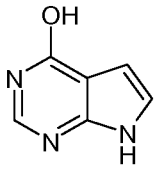
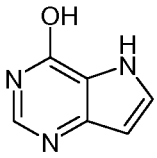
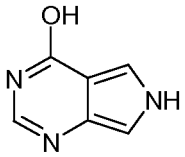
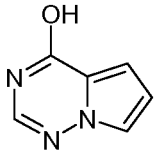
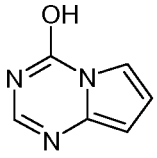
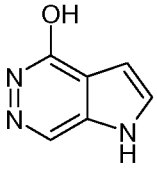
[164] The present invention includes the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of a disease which responds to an inhibition of the IGF-IR-dependent cell proliferation.

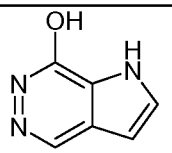
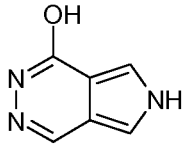
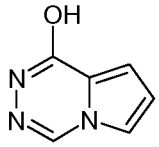
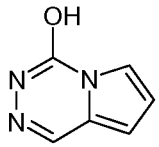
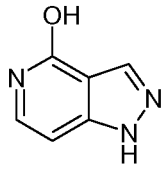
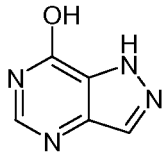
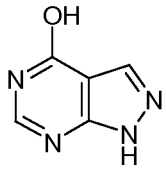
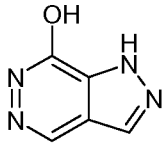
[165] The present invention includes the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of a disease which responds to an inhibition of the IGF-IR tyrosine kinase.

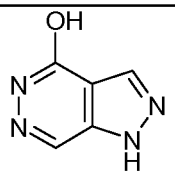
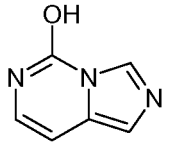
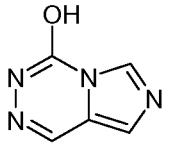
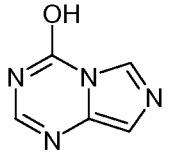
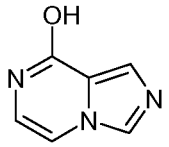
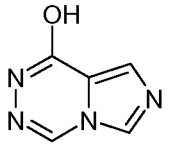
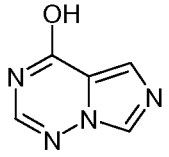
[166] The present invention includes a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. The invention includes a method of inhibiting protein kinase activity that comprises administering such pharmaceutical composition. The invention includes a method of treating a patient having a condition which is mediated by protein kinase activity by administering to the patient a therapeutically effective amount of such pharmaceutical composition.

[167] The following include core structures of the present invention wherein at least one of $X_3 - X_7$ is optionally substituted N and the core structure can have Q^1 and R^1 substituents as defined above (the substituent is hydrogen where hydrogen is specified):

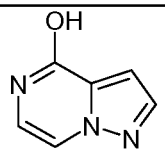
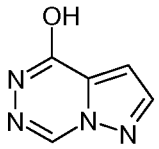
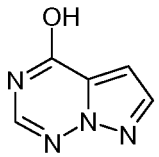
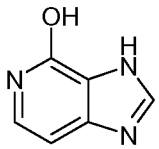
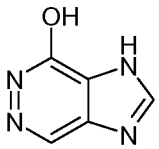
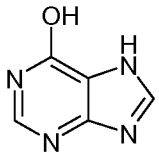
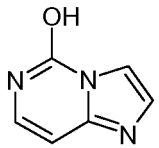
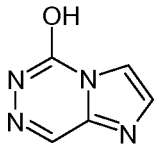
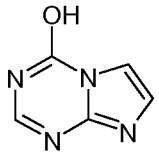
Structure	Name of unsubstituted core with OH group
	1*H*-Pyrrolo[3,2-*c*]pyridin-4-ol
	1*H*-Pyrrolo[2,3-*c*]pyridin-7-ol

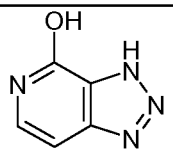
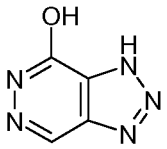
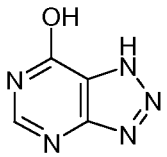
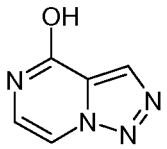
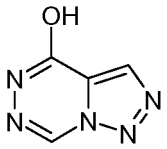
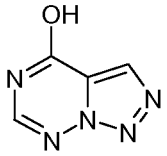
Structure	Name of unsubstituted core with OH group
	2*H*-Pyrrolo[3,4-*c*]pyridin-4-ol
	Pyrrolo[1,2-*a*]-pyrazin-1-ol
	Pyrrolo[1,2-*c*]-pyrimidin-1-ol
	7*H*-Pyrrolo[2,3-*d*]pyrimidin-4-ol
	5*H*-Pyrrolo[3,2-*d*]pyrimidin-4-ol
	6*H*-Pyrrolo[3,4-*d*]pyrimidin-4-ol
	Pyrrolo[2,1-*f*]-[1,2,4]triazin-4-ol
	Pyrrolo[1,2-*a*]-[1,3,5]triazin-4-ol
	1*H*-Pyrrolo[2,3-*d*]pyridazin-4-ol

Structure	Name of unsubstituted core with OH group
	1*H*-Pyrrolo[2,3-*d*]pyridazin-7-ol
	6*H*-Pyrrolo[3,4-*d*]pyridazin-1-ol
	Pyrrolo[1,2-*d*]-[1,2,4]triazin-1-ol
	Pyrrolo[1,2-*d*]-[1,2,4]triazin-4-ol
	1*H*-Pyrazolo[4,3-*c*]pyridin-4-ol
	1*H*-Pyrazolo[3,4-*c*]pyridin-7-ol
	1*H*-Pyrazolo[4,3-*d*]pyrimidin-7-ol
	1*H*-Pyrazolo[3,4-*d*]pyrimidin-4-ol
	1*H*-Pyrazolo[3,4-*d*]pyridazin-7-ol

Structure	Name of unsubstituted core with OH group
	1*H*-Pyrazolo[3,4-*d*]pyridazin-4-ol
	Imidazo[1,5-*c*]-pyrimidin-5-ol
	Imidazo[1,5-*d*]-[1,2,4]triazin-4-ol
	Imidazo[1,5-*a*]-[1,3,5]triazin-4-ol
	Imidazo[1,5-*a*]-pyrazin-8-ol
	Imidazo[1,5-*d*]-[1,2,4]triazin-1-ol
	Imidazo[5,1-*f*]-[1,2,4]triazin-4-ol

[168] The following include core structures of the present invention wherein R^1 is absent, at least one of $X_3 - X_7$ is optionally substituted N and the core structure can have Q^1 substituent as defined above (the substituent is hydrogen where hydrogen is specified):

Structure	Name of unsubstituted core with OH group
	Pyrazolo[1,5-*a*]-pyrazin-4-ol
	Pyrazolo[1,5-*d*]-[1,2,4]triazin-4-ol
	1,5,7,7a-Tetraaza-inden-4-ol
	3*H*-Imidazo[4,5-*c*]-pyridin-4-ol
	3*H*-Imidazo[4,5-*d*]-pyridazin-4-ol
	7*H*-Purin-6-ol
	Imidazo[1,2-*c*]-pyrimidin-5-ol
	Imidazo[1,2-*d*]-[1,2,4]triazin-5-ol
	Imidazo[1,2-*a*]-[1,3,5]triazin-4-ol

Structure	Name of unsubstituted core with OH group
	3*H*-[1,2,3]-Triazolo[4,5-*c*]-pyridin-4-ol
	3*H*-[1,2,3]-Triazolo[4,5-*d*]-pyridazin-4-ol
	1*H*-[1,2,3]-Triazolo[4,5-*d*]-pyrimidin-7-ol
	[1,2,3]Triazolo[1,5-*a*]pyrazin-4-ol
	1,2,5,6,7a-Pentaazainden-4-ol
	1,2,5,7,7a-Pentaazainden-4-ol

[169] The compounds of the present invention include:

[170] 1-(2-Phenyl-quinolin-7-yl)-3-piperidin-4-ylmethyl-imidazo[1,5-a]pyrazin-8-ol

[171] 3-Cyclobutyl-1-(2-phenyl-quinolin-7-yl)-imidazo[1,5-a]pyrazin-8-ol

[172] 3-(3-Hydroxymethyl-cyclobutyl)-1-(2-phenyl-quinolin-7-yl)-imidazo[1,5-a]pyrazin-8-ol

[173] 3-[3-(4-Methyl-piperazin-1-yl)-cyclobutyl]-1-(2-phenyl-quinolin-7-yl)-imidazo[1,5-a]pyrazin-8-ol

[174] 3-(3-Morpholin-4-yl-cyclobutyl)-1-(2-phenyl-quinolin-7-yl)-imidazo[1,5-a]pyrazin-8-ol

[175] 3-{3-[(2,4-Dimethoxy-benzyl)-methyl-amino]-cyclobutyl}-1-(2-phenyl-quinolin-7-yl)-7H-imidazo[1,5-a]pyrazin-8-ol

[176] Unless otherwise stated, the connections of compound name moieties are at the rightmost recited moiety. That is, the substituent name starts with a terminal moiety, continues with any bridging moieties, and ends with the connecting moiety. For example, hetarylthioC_{1-4}alkyl has a heteroaryl group connected through a thio sulfur to a C_{1-4} alkyl that connects to the chemical species bearing the substituent.

[177] As used herein, for example, "C_{0-4}alkyl" is used to mean an alkyl having 0-4 carbons - that is, 0, 1, 2, 3, or 4 carbons in a straight or branched configuration. An alkyl having no carbon is hydrogen when the alkyl is a terminal group. An alkyl having no carbon is a direct bond when the alkyl is a bridging (connecting) group. Further, C_0alkyl includes being a substituted bond – that is, for example, -X-Y-Z is –C(O)-C_{2-4}alkyl when X is C_0alkyl, Y is C_0alkyl, and Z is -C(O)-C_{2-4}alkyl.

[178] In all embodiments of this invention, the term "alkyl" includes both branched and straight chain alkyl groups. Typical alkyl groups are methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, isopentyl, *n*-hexyl, *n*-heptyl, isooctyl, nonyl, decyl, undecyl, dodecyl, tetradecyl, hexadecyl, octadecyl, eicosyl, and the like.

[179] The term "halo" refers to fluoro, chloro, bromo, or iodo.

[180] The term "haloalkyl" refers to an alkyl group substituted with one or more halo groups, for example chloromethyl, 2-bromoethyl, 3-iodopropyl, trifluoromethyl, perfluoropropyl, 8-chlorononyl, and the like.

[181] The term "acyl" refers to the structure –C(=O)–R, in which R is a general substituent variable such as, for example R^1 described above. Examples include, but are not limited to, (bi)(cyclo)alkylketo, (cyclo)alkenylketo, alkynylketo, arylketo, hetarylketo, heterocyclylketo, heterobicycloalkylketo, spiroalkylketo.

[182] Unless otherwise specified, the term "cycloalkyl" refers to a 3-8 carbon cyclic aliphatic ring structure, optionally substituted with for example, alkyl, hydroxy, oxo, and halo, such as cyclopropyl, methylcyclopropyl, cyclobutyl, cyclopentyl, 2-hydroxycyclopentyl, cyclohexyl, 4-chlorocyclohexyl, cycloheptyl, cyclooctyl, and the like.

[183] The term "bicycloalkyl" refers to a structure consisting of two cycloalkyl moieties that have two or more atoms in common. If the cycloalkyl moieties have exactly two atoms in common they are said to be "fused". Examples include, but are not limited to, bicyclo[3.1.0]hexyl, perhydronaphthyl, and the like. If the cycloalkyl moieties have more

than two atoms in common they are said to be "bridged". Examples include, but are not limited to, bicyclo[2.2.1]heptyl ("norbornyl"), bicyclo[2.2.2]octyl, and the like.

[184] The term "spiroalkyl" refers to a structure consisting of two cycloalkyl moieties that have exactly one atom in common. Examples include, but are not limited to, spiro[4.5]decyl, spiro[2.3]hexyl, and the like.

[185] The term "heterobicycloalkyl" refers to a bicycloalkyl structure in which at least one carbon atom is replaced with a heteroatom independently selected from oxygen, nitrogen, and sulfur.

[186] The term "heterospiroalkyl" refers to a spiroalkyl structure in which at least one carbon atom is replaced with a heteroatom independently selected from oxygen, nitrogen, and sulfur.

[187] The term "alkylcarbonyloxyalkyl" refers to an ester moiety, for example acetoxymethyl, *n*-butyryloxyethyl, and the like.

[188] The term "alkynylcarbonyl" refers to an alkynylketo functionality, for example propynoyl and the like.

[189] The term "hydroxyalkyl" refers to an alkyl group substituted with one or more hydroxy groups, for example hydroxymethyl, 2,3-dihydroxybutyl, and the like.

[190] The term "alkylsulfonylalkyl" refers to an alkyl group substituted with an alkylsulfonyl moiety, for example mesylmethyl, isopropylsulfonylethyl, and the like.

[191] The term "alkylsulfonyl" refers to a sulfonyl moiety substituted with an alkyl group, for example mesyl, *n*-propylsulfonyl, and the like.

[192] The term "acetylaminoalkyl" refers to an alkyl group substituted with an amide moiety, for example acetylaminomethyl and the like.

[193] The term "acetylaminoalkenyl" refers to an alkenyl group substituted with an amide moiety, for example 2-(acetylamino)vinyl and the like.

[194] The term "alkenyl" refers to an ethylenically unsaturated hydrocarbon group, straight or branched chain, having 1 or 2 ethylenic bonds, for example vinyl, allyl, 1-butenyl, 2-butenyl, isopropenyl, 2-pentenyl, and the like.

[195] The term "haloalkenyl" refers to an alkenyl group substituted with one or more halo groups.

[196] Unless otherwise specified, the term "cycloalkenyl" refers to a cyclic aliphatic 3 to 8 ring structure, optionally substituted with alkyl, hydroxy and halo, having 1 or 2

ethylenic bonds such as methylcyclopropenyl, trifluoromethylcyclopropenyl, cyclopentenyl, cyclohexenyl, 1,4-cyclohexadienyl, and the like.

[197] The term "alkynyl" refers to an unsaturated hydrocarbon group, straight or branched, having at least one acetylenic bond, for example ethynyl, propargyl, and the like.

[198] The term, "haloalkynyl" refers to an alkynyl group substituted with one or more independent halo groups.

[199] The term "alkylcarbonyl" refers to an alkylketo functionality, for example acetyl, *n*-butyryl, and the like.

[200] The term "alkenylcarbonyl" refers to an alkenylketo functionality, for example, propenoyl and the like.

[201] The term “aryl” refers to phenyl or naphthyl which may be optionally substituted. Examples of aryl include, but are not limited to, phenyl, 4-chlorophenyl, 4-fluorophenyl, 4-bromophenyl, 3-nitrophenyl, 2-methoxyphenyl, 2-methylphenyl, 3-methyphenyl, 4-methylphenyl, 4-ethylphenyl, 2-methyl-3-methoxyphenyl, 2,4-dibromophenyl, 3,5-difluorophenyl, 3,5-dimethylphenyl, 2,4,6-trichlorophenyl, 4-methoxyphenyl, naphthyl, 2-chloronaphthyl, 2,4-dimethoxyphenyl, 4-(trifluoromethyl)phenyl, and 2-iodo-4-methylphenyl.

[202] The terms "heteroaryl" or “hetaryl” or “heteroar-“ or “hetar-“ refer to a substituted or unsubstituted 5- or 6-membered unsaturated ring containing one, two, three, or four independently selected heteroatoms, preferably one or two heteroatoms independently selected from oxygen, nitrogen, and sulfur or to a bicyclic unsaturated ring system containing up to 10 atoms including at least one heteroatom selected from oxygen, nitrogen, and sulfur. Examples of hetaryls include, but are not limited to, 2-, 3- or 4-pyridinyl, pyrazinyl, 2-, 4-, or 5-pyrimidinyl, pyridazinyl, triazolyl, tetrazolyl, imidazolyl, 2- or 3-thienyl, 2- or 3-furyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, quinolyl, isoquinolyl, benzimidazolyl, benzotriazolyl, benzofuranyl, and benzothienyl. The heterocyclic ring may be optionally substituted with one or more substituents.

[203] The terms “aryl–alkyl” or "arylalkyl" or “aralkyl” are used to describe a group wherein the alkyl chain can be branched or straight chain forming a bridging portion with the terminal aryl, as defined above, of the aryl–alkyl moiety. Examples of aryl–alkyl groups include, but are not limited to, optionally substituted benzyl, phenethyl, phenpropyl and phenbutyl such as 4-chlorobenzyl, 2,4-dibromobenzyl, 2-methylbenzyl, 2-(3-

fluorophenyl)ethyl, 2-(4-methylphenyl)ethyl, 2-(4-(trifluoromethyl)phenyl)ethyl, 2-(2-methoxyphenyl)ethyl, 2-(3-nitrophenyl)ethyl, 2-(2,4-dichlorophenyl)ethyl, 2-(3,5-dimethoxyphenyl)ethyl, 3-phenylpropyl, 3-(3-chlorophenyl)propyl, 3-(2-methylphenyl)propyl, 3-(4-methoxyphenyl)propyl, 3-(4-(trifluoromethyl)phenyl)propyl, 3-(2,4-dichlorophenyl)propyl, 4-phenylbutyl, 4-(4-chlorophenyl)butyl, 4-(2-methylphenyl)butyl, 4-(2,4-dichlorophenyl)butyl, 4-(2-methoxphenyl)butyl, and 10-phenyldecyl.

[204] The terms "aryl–cycloalkyl" or "arylcycloalkyl" are used to describe a group wherein the terminal aryl group is attached to a cycloalkyl group, for example phenylcyclopentyl and the like.

[205] The terms “aryl–alkenyl” or "arylalkenyl" or “aralkenyl” are used to describe a group wherein the alkenyl chain can be branched or straight chain forming a bridging portion of the aralkenyl moiety with the terminal aryl portion, as defined above, for example styryl (2-phenylvinyl), phenpropenyl, and the like.

[206] The terms “aryl–alkynyl” or "arylalkynyl" or “aralkynyl” are used to describe a group wherein the alkynyl chain can be branched or straight chain forming a bridging portion of the aryl–alkynyl moiety with the terminal aryl portion, as defined above, for example 3-phenyl-1-propynyl, and the like.

[207] The terms “aryl–oxy” or "aryloxy" or “aroxy” are used to describe a terminal aryl group attached to a bridging oxygen atom. Typical aryl–oxy groups include phenoxy, 3,4-dichlorophenoxy, and the like.

[208] The terms “aryl–oxyalkyl” or "aryloxyalkyl" or “aroxyalkyl” are used to describe a group wherein an alkyl group is substituted with a terminal aryl–oxy group, for example pentafluorophenoxymethyl and the like.

[209] The term “heterocycloalkenyl” refers to a cycloalkenyl structure in which at least one carbon atom is replaced with a heteroatom selected from oxygen, nitrogen, and sulfur.

[210] The terms “hetaryl–oxy” or "heteroaryl–oxy" or “hetaryloxy” or “heteroaryloxy” or “hetaroxy” or “heteroaroxy” are used to describe a terminal hetaryl group attached to a bridging oxygen atom. Typical hetaryl–oxy groups include 4,6-dimethoxypyrimidin-2-yloxy and the like.

[211] The terms “hetarylalkyl” or "heteroarylalkyl" or “hetaryl–alkyl” or “heteroaryl–alkyl” or “hetaralkyl” or “heteroaralkyl” are used to describe a group wherein the alkyl chain can be branched or straight chain forming a bridging portion of the heteroaralkyl moiety with the terminal heteroaryl portion, as defined above, for example 3-furylmethyl, thenyl, furfuryl, and the like.

[212] The terms “hetarylalkenyl” or "heteroarylalkenyl" or “hetaryl–alkenyl” or “heteroaryl–alkenyl” or “hetaralkenyl” or heteroaralkenyl” are used to describe a group wherein the alkenyl chain can be branched or straight chain forming a bridging portion of the heteroaralkenyl moiety with the terminal heteroaryl portion, as defined above, for example 3-(4-pyridyl)-1-propenyl.

[213] The terms “hetarylalkynyl” or "heteroarylalkynyl" or “hetaryl–alkynyl” or “heteroaryl–alkynyl” or “hetaralkynyl” or “heteroaralkynyl” are used to describe a group wherein the alkynyl chain can be branched or straight chain forming a bridging portion of the heteroaralkynyl moiety with the heteroaryl portion, as defined above, for example 4-(2-thienyl)-1-butynyl.

[214] The term "heterocyclyl" or “hetcyclyl” refers to a substituted or unsubstituted 4-, 5-, or 6-membered saturated or partially unsaturated ring containing one, two, or three heteroatoms, preferably one or two heteroatoms independently selected from oxygen, nitrogen and sulfur; or to a bicyclic ring system containing up to 10 atoms including at least one heteroatom independently selected from oxygen, nitrogen, and sulfur wherein the ring containing the heteroatom is saturated. Examples of heterocyclyls include, but are not limited to, tetrahydrofuranyl, tetrahydrofuryl, pyrrolidinyl, piperidinyl, 4-pyranyl, tetrahydropyranyl, thiolanyl, morpholinyl, piperazinyl, dioxolanyl, dioxanyl, indolinyl, and 5-methyl-6-chromanyl.

[215] The terms "heterocyclylalkyl" or "heterocyclyl–alkyl" or “hetcyclylalkyl” or “hetcyclyl-alkyl” are used to describe a group wherein the alkyl chain can be branched or straight chain forming a bridging portion of the heterocyclylalkyl moiety with the terminal heterocyclyl portion, as defined above, for example 3-piperidinylmethyl and the like.

[216] The terms "heterocyclylalkenyl" or "heterocyclyl–alkenyl" or “hetcyclylalkenyl” or “hetcyclyl-alkenyl” are used to describe a group wherein the alkenyl chain can be branched or straight chain forming a bridging portion of the heterocyclylalkenyl

moiety with the terminal heterocyclyl portion, as defined above, for example 2-morpholinyl-1-propenyl and the like.

[217] The terms "heterocyclylalkynyl" or "heterocyclyl–alkynyl" or "hetcyclylalkynyl" or "hetcyclyl–alkynyl" are used to describe a group wherein the alkynyl chain can be branched or straight chain forming a bridging portion of the heterocyclylalkynyl moiety with the terminal heterocyclyl portion, as defined above, for example 2-pyrrolidinyl-1-butynyl and the like.

[218] The term "carboxylalkyl" refers to a terminal carboxyl (–COOH) group attached to branched or straight chain alkyl groups as defined above.

[219] The term "carboxylalkenyl" refers to a terminal carboxyl (–COOH) group attached to branched or straight chain alkenyl groups as defined above.

[220] The term "carboxylalkynyl" refers to a terminal carboxyl (–COOH) group attached to branched or straight chain alkynyl groups as defined above.

[221] The term "carboxylcycloalkyl" refers to a terminal carboxyl (–COOH) group attached to a cyclic aliphatic ring structure as defined above.

[222] The term "carboxylcycloalkenyl" refers to a terminal carboxyl (–COOH) group attached to a cyclic aliphatic ring structure having ethylenic bonds as defined above.

[223] The terms "cycloalkylalkyl" or "cycloalkyl–alkyl" refer to a terminal cycloalkyl group as defined above attached to an alkyl group, for example cyclopropylmethyl, cyclohexylethyl, and the like.

[224] The terms "cycloalkylalkenyl" or "cycloalkyl–alkenyl" refer to a terminal cycloalkyl group as defined above attached to an alkenyl group, for example cyclohexylvinyl, cycloheptylallyl, and the like.

[225] The terms "cycloalkylalkynyl" or "cycloalkyl–alkynyl" refer to a terminal cycloalkyl group as defined above attached to an alkynyl group, for example cyclopropylpropargyl, 4-cyclopentyl-2-butynyl, and the like.

[226] The terms "cycloalkenylalkyl" or "cycloalkenyl–alkyl" refer to a terminal cycloalkenyl group as defined above attached to an alkyl group, for example 2-(cyclopenten-1-yl)ethyl and the like.

[227] The terms "cycloalkenylalkenyl" or "cycloalkenyl–alkenyl" refer to terminal a cycloalkenyl group as defined above attached to an alkenyl group, for example 1-(cyclohexen-3-yl)allyl and the like.

[228] The terms "cycloalkenylalkynyl" or "cycloalkenyl–alkynyl" refer to terminal a cycloalkenyl group as defined above attached to an alkynyl group, for example 1-(cyclohexen-3-yl)propargyl and the like.

[229] The term "carboxylcycloalkylalkyl" refers to a terminal carboxyl (–COOH) group attached to the cycloalkyl ring portion of a cycloalkylalkyl group as defined above.

[230] The term "carboxylcycloalkylalkenyl" refers to a terminal carboxyl (–COOH) group attached to the cycloalkyl ring portion of a cycloalkylalkenyl group as defined above.

[231] The term "carboxylcycloalkylalkynyl" refers to a terminal carboxyl (–COOH) group attached to the cycloalkyl ring portion of a cycloalkylalkynyl group as defined above.

[232] The term "carboxylcycloalkenylalkyl" refers to a terminal carboxyl (–COOH) group attached to the cycloalkenyl ring portion of a cycloalkenylalkyl group as defined above.

[233] The term "carboxylcycloalkenylalkenyl" refers to a terminal carboxyl (–COOH) group attached to the cycloalkenyl ring portion of a cycloalkenylalkenyl group as defined above.

[234] The term "carboxylcycloalkenylalkynyl" refers to a terminal carboxyl (–COOH) group attached to the cycloalkenyl ring portion of a cycloalkenylalkynyl group as defined above.

[235] The term "alkoxy" includes both branched and straight chain terminal alkyl groups attached to a bridging oxygen atom. Typical alkoxy groups include methoxy, ethoxy, *n*-propoxy, isopropoxy, *tert*-butoxy and the like.

[236] The term "haloalkoxy" refers to an alkoxy group substituted with one or more halo groups, for example chloromethoxy, trifluoromethoxy, difluoromethoxy, perfluoroisobutoxy, and the like.

[237] The term "alkoxyalkoxyalkyl" refers to an alkyl group substituted with an alkoxy moiety which is in turn is substituted with a second alkoxy moiety, for example methoxymethoxymethyl, isopropoxymethoxyethyl, and the like.

[238] The term "alkylthio" includes both branched and straight chain alkyl groups attached to a bridging sulfur atom, for example methylthio and the like.

[239] The term "haloalkylthio" refers to an alkylthio group substituted with one or more halo groups, for example trifluoromethylthio and the like.

[240] The term "alkoxyalkyl" refers to an alkyl group substituted with an alkoxy group, for example isopropoxymethyl and the like.

[241] The term "alkoxyalkenyl" refers to an alkenyl group substituted with an alkoxy group, for example 3-methoxyallyl and the like.

[242] The term "alkoxyalkynyl" refers to an alkynyl group substituted with an alkoxy group, for example 3-methoxypropargyl.

[243] The term "alkoxycarbonylalkyl" refers to a straight chain or branched alkyl substituted with an alkoxycarbonyl, for example ethoxycarbonylmethyl, 2-(methoxycarbonyl)propyl and the like.

[244] The term "alkoxycarbonylalkenyl" refers to a straight chain or branched alkenyl as defined above substituted with an alkoxycarbonyl, for example 4-(ethoxycarbonyl)-2-butenyl and the like.

[245] The term "alkoxycarbonylalkynyl" refers to a straight chain or branched alkynyl as defined above substituted with an alkoxycarbonyl, for example 4-(ethoxycarbonyl)-2-butynyl and the like.

[246] The term "haloalkoxyalkyl" refers to a straight chain or branched alkyl as defined above substituted with a haloalkoxy, for example 2-chloroethoxymethyl, trifluoromethoxymethyl and the like.

[247] The term "haloalkoxyalkenyl" refers to a straight chain or branched alkenyl as defined above substituted with a haloalkoxy, for example 4-(chloromethoxy)-2-butenyl and the like.

[248] The term "haloalkoxyalkynyl" refers to a straight chain or branched alkynyl as defined above substituted with a haloalkoxy, for example 4-(2-fluoroethoxy)-2-butynyl and the like.

[249] The term "alkylthioalkyl" refers to a straight chain or branched alkyl as defined above substituted with an alkylthio group, for example methylthiomethyl, 3-(isobutylthio)heptyl, and the like.

[250] The term "alkylthioalkenyl" refers to a straight chain or branched alkenyl as defined above substituted with an alkylthio group, for example 4-(methylthio)-2-butenyl and the like.

[251] The term "alkylthioalkynyl" refers to a straight chain or branched alkynyl as defined above substituted with an alkylthio group, for example 4-(ethylthio)-2-butynyl and the like.

[252] The term "haloalkylthioalkyl" refers to a straight chain or branched alkyl as defined above substituted with an haloalkylthio group, for example 2-chloroethylthiomethyl, trifluoromethylthiomethyl and the like.

[253] The term "haloalkylthioalkenyl" refers to a straight chain or branched alkenyl as defined above substituted with an haloalkylthio group, for example 4-(chloromethylthio)-2-butenyl and the like.

[254] The term "haloalkylthioalkynyl" refers to a straight chain or branched alkynyl as defined above substituted with a haloalkylthio group, for example 4-(2-fluoroethylthio)-2-butynyl and the like.

[255] The term "dialkoxyphosphorylalkyl" refers to two straight chain or branched alkoxy groups as defined above attached to a pentavalent phosphorous atom, containing an oxo substituent, which is in turn attached to an alkyl, for example diethoxyphosphorylmethyl and the like.

[256] One in the art understands that an “oxo” requires a second bond from the atom to which the oxo is attached. Accordingly, it is understood that oxo cannot be subststituted onto an aryl or heteroaryl ring.

[257] The term "oligomer" refers to a low-molecular weight polymer, whose number average molecular weight is typically less than about 5000 g/mol, and whose degree of polymerization (average number of monomer units per chain) is greater than one and typically equal to or less than about 50.

[258] Compounds described can contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above Formula I is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of Formula I and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

[259] The invention also encompasses a pharmaceutical composition that is comprised of a compound of Formula I in combination with a pharmaceutically acceptable carrier.

[260] Preferably the composition is comprised of a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of a compound of Formula I as described above (or a pharmaceutically acceptable salt thereof).

[261] Moreover, within this preferred embodiment, the invention encompasses a pharmaceutical composition for the treatment of disease by inhibiting kinases, comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of Formula I as described above (or a pharmaceutically acceptable salt thereof).

[262] The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium slats. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N',N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylameine, trimethylamine, tripropylamine, tromethamine and the like.

[263] When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, formic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Preferred are citric, hydrobromic, formic, hydrochloric, maleic, phosphoric, sulfuric and tartaric acids. Particularly preferred are formic and hydrochloric acid.

[264] The pharmaceutical compositions of the present invention comprise a compound represented by Formula I (or a pharmaceutically acceptable salt thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[265] In practice, the compounds represented by Formula I, or a prodrug, or a metabolite, or a pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration. e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion, or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound represented by Formula I, or a pharmaceutically acceptable salt thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

[266] Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound, or a pharmaceutically acceptable salt, of Formula I. The compounds of Formula I, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

[267] The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

[268] In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

[269] A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.05mg to about 5g of the active ingredient and each cachet or capsule preferably containing from about 0.05mg to about 5g of the active ingredient.

[270] For example, a formulation intended for the oral administration to humans may contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1mg to about 2g of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg, or 1000mg.

[271] Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures

thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

[272] Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

[273] Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound represented by Formula I of this invention, or a pharmaceutically acceptable salt thereof, via conventional processing methods. As an example, a cream or ointment is prepared by admixing hydrophilic material and water, together with about 5wt% to about 10wt% of the compound, to produce a cream or ointment having a desired consistency.

[274] Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

[275] In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound described by Formula I, or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

[276] Generally, dosage levels on the order of from about 0.01mg/kg to about 150mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5mg to about 7g per patient per day. For example, inflammation, cancer, psoriasis, allergy/asthma, disease and conditions of the immune system, disease and conditions of the central nervous system (CNS), may be effectively treated by the administration of from about 0.01 to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day.

[277] It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

Biological Assays

[278] The efficacy of the Examples of the invention, compounds of Formula I, as inhibitors of insulin-like growth factor-1 receptor (IGF-1R) were demonstrated and confirmed by a number of pharmacological *in vitro* assays. The following assays and their respective methods can be carried out with the compounds according to the invention. Activity possessed by compounds of Formula I may be demonstrated *in vivo*.

***In vitro* tyrosine kinase assay**

[279] The IGF-1R inhibitory of a compound of Formula I can be shown in a tyrosine kinase assay using purified GST fusion protein containing the cytoplasmic kinase domain of human IGF-1R expressed in Sf9 cells. This assay is carried out in a final volume of 90μL containing 1-100nM (depending on the specific activity) in an Immulon-4 96-well plate (Thermo Labsystems) pre-coated with 1μg/well of substrate poly-glu-tyr (4:1 ratio) in kinase buffer (50mM Hepes, pH 7.4, 125mM NaCl, 24mM $MgCl_2$, 1mM $MnCl_2$, 1% glycerol, 200μM Na_3VO_4, and 2mM DTT). The enzymatic reaction was initiated by addition of ATP at a final concentration of 100μM. After incubation at rt for 30min, the plates were washed with 2mM Imidazole buffered saline with 0.02% Tween-20. Then the plate was incubated with anti-phosphotyrosine mouse monoclonal antibody pY-20 conjugated with horse radish peroxidase (HRP) (Calbiochem) at 167ng/mL diluted in phosphate buffered saline (PBS) containing 3% bovine serum albumin (BSA), 0.5% Tween-20 and 200μM Na_3VO_4 for 2h at

rt. Following 3X 250μL washes, the bound anti-phosphotyrosine antibody was detected by incubation with 100μL/well ABTS (Kirkegaard & Perry Labs, Inc.) for 30min at rt. The reaction was stopped by the addition of 100μL/well 1% SDS, and the phosphotyrosine dependent signal was measured by a plate reader at 405/490 nm.

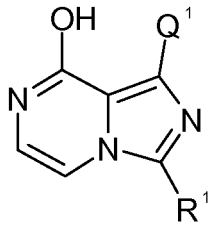
[280] All examples showed inhibition of IGF-1R. The following examples showed efficacy and activity by inhibiting IGF-1R in the biochemical and/or cellular assay with IC_{50} values less than 50 μM.

Cell-based autophosphotyrosine Assay

[281] NIH 3T3 cells stably expressing full-length human IGF-1R were seeded at $1x10^4$ cells/well in 0.1mL Dulbecco's minimal essential medium (DMEM) supplemented with 10% fetal calf serum (FCS) per well in 96-well plates. On Day 2, the medium is replaced with starvation medium (DMEM containing 0.5% FCS) for 2h and a compound was diluted in 100% dimethyl sulfoxide (DMSO), added to the cells at six final concentrations in duplicates (20, 6.6, 2.2, 0.74, 0.25 and 0.082μM), and incubated at 37°C for additional 2h. Following addition of recombinant human IGF-1 (100 ng/mL) at 37°C for 15min, the media was then removed and the cells were washed once with PBS (phosphate-buffered saline), then lysed with cold TGH buffer (1% Triton-100, 10% glycerol, 50mM Hepes [pH 7.4]) supplemented with 150mM NaCl, 1.5mM MgCl, 1mM EDTA and fresh protease and phosphatase inhibitors [10μg/mL leupeptin, 25μg/mL aprotinin, 1mM phenyl methyl sulphonyl fluoride (PMSF), and 200μM Na_3VO_4]. Cell lysates were transferred to a 96-well microlite2 plate (Corning CoStar #3922) coated with 10ng/well of IGF-1R antibody (Calbiochem, Cat#GR31L) and incubated at 4°C overnight. Following washing with TGH buffer, the plate was incubated with anti-phosphotyrosine mouse monoclonal antibody pY-20 conjugated with horse radish peroxidase (HRP) for 2h at rt. The autophosphotyrosine was then detected by addition of Super Signal ELISA Femto Maximum Sensitivity Substrate (Pierce) and chemiluminescence was read on a Wallac Victor^2 1420 Multilabel Counter. The IC_{50} curves of the compounds were plotted using an ExcelFit program.

[282] All examples showed inhibition of IGF-1R in either the biochemical or cell-based assay. The following examples showed efficacy and activity by inhibiting IGF-1R with IC_{50} values less than 50μM.

[283] Compound of Formula I-AA is equal to compound of Formula I wherein X_1 and X_2 = CH, X_3 and X_5 = N, and X_4, X_6, and X_7 = C:



I-AA

Experimental

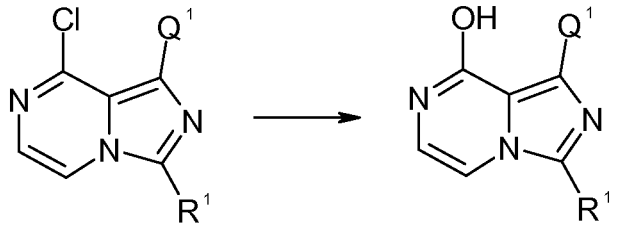
[284] In Scheme 1 – Scheme 6 below showing how to synthesize compounds of this invention, the following abbreviations are used: Me for methyl, Et for ethyl, ^{i}Pr or ^{i}Pr for isopropyl, n-Bu for *n*-butyl, t-Bu for *tert*-butyl, Ac for acetyl, Ph for phenyl, 4Cl-Ph or (4Cl)Ph for 4-chlorophenyl, 4Me-Ph or (4Me)Ph for 4-methylphenyl, (p-CH_3O)Ph for *p*-methoxyphenyl, (p-NO_2)Ph for *p*-nitrophenyl, 4Br-Ph or (4Br)Ph for 4-bromophenyl, 2-CF_3-Ph or (2CF_3)Ph for 2-trifluoromethylphenyl, DMAP for 4-(dimethylamino)pyridine, DCC for 1,3-dicyclohexylcarbodiimide, EDC for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, HOBt for 1-hydroxybenzotriazole, HOAt for 1-hydroxy-7-azabenzotriazole, TMP for tetramethylpiperidine, *n*-BuLi for *n*-butyllithium, CDI for 1,1'-carbonyldiimidazole, DEAD for diethlyl azodicarboxylate, PS-Ph3 for polystyrene triphenylphosphine, DIEA for diisopropylethylamine, DIAD for diisopropyl azodicarboxylate, DBAD for di-tert-butyl azodicarboxylate, HPFC for high performance flash chromatography, rt for room temperature, min for minute, h for hour, and Bn for benzyl.

[285] Accordingly, the following are compounds which are useful as intermediates in the formation of IGF-1R inhibiting examples.

[286] The compounds of Formula I of this invention and the intermediates used in the synthesis of the compounds of this invention were prepared according to the following methods. Method A was used when preparing compounds of Formula I-AA as shown below in Scheme 1:

Method A:

Scheme 1



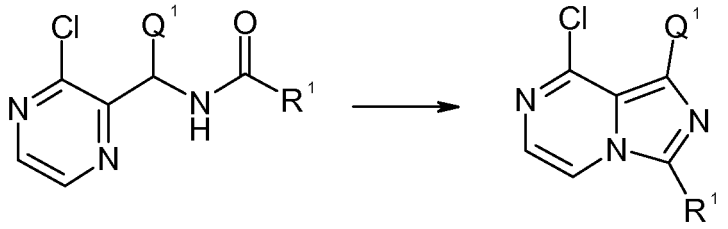
II **I-AA**

[287] where Q^1 and R^1 are as defined previously for compound of Formula I-AA.

[288] In a typical preparation of compounds of Formula I-AA, compound of Formula II was reacted under hydrolytic conditions in a suitable solvent with a suitable acid. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; alcohols such as methanol, ethanol, isopropanol, trifluoroethanol, and the like; and chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvent was a combination of tetrahydrofuran (THF) and water. Suitable acids included HCl, sulfuric acid, trifluoroacetic acid, and the like. If desired, mixtures of these acids could be used, however, the preferred acid was a HCl. The above process was carried out at temperatures between about 0°C and about 120°C. Preferably, the reaction was carried out between 20°C and about 80°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially, equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired.

[289] The compounds of Formula II of Scheme 1 were prepared as shown below in Scheme 2.

Scheme 2



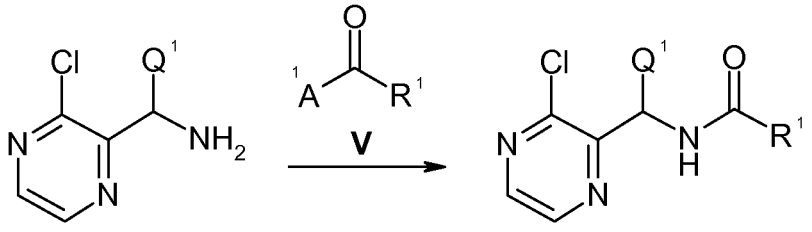
III II

[290] where Q^1 and R^1 are as defined previously for compound of Formula I-AA.

[291] In a typical preparation of a compound of Formula II, an intermediate of Formula III was treated with $POCl_3$ in a suitable solvent at a suitable reaction temperature. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; and chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used. The preferred solvent was methylene chloride. The above process was carried out at temperatures between about -78°C and about 120°C. Preferably, the reaction was carried out between 40°C and about 95°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially, equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired.

[292] The compounds of Formula III of Scheme 2 were prepared as shown below in Scheme 3:

Scheme 3



IV III

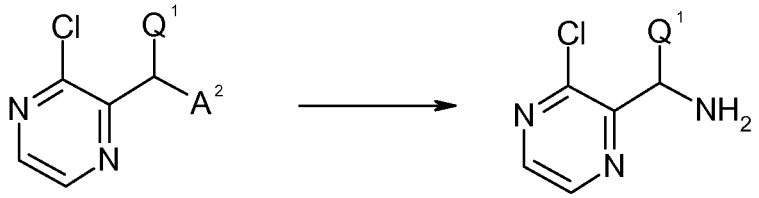
[293] where Q^1 and R^1 are as defined previously for compound of Formula I-AA and A^1 = OH, alkoxy, or a leaving group such as chloro or imidazole.

[294] In a typical preparation, of a compound of Formula III, a compound of Formula IV and compound of Formula V were reacted under suitable amide coupling conditions. Suitable conditions include but are not limited to treating compounds of Formula

IV and V (when A^1 = OH) with coupling reagents such as DCC or EDC in conjunction with DMAP, HOBt, HOAt and the like. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; halogenated solvents such as chloroform or methylene chloride. If desired, mixtures of these solvents were used, however the preferred solvent was methylene chloride. The above process was carried out at temperatures between about 0°C and about 80°C. Preferably, the reaction was carried out at about 22°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially, equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired. Alternatively, compounds of Formula IV and V (where A^1 = F, Cl, Br, I) were reacted with bases such as triethylamine or ethyldiisopropylamine and the like in conjunction with DMAP and the like. Suitable solvents for use in this process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; halogenated solvents such as chloroform or methylene chloride. If desired, mixtures of these solvents were used, however the preferred solvent was methylene chloride. The above process was carried out at temperatures between about –20°C and about 40°C. Preferably, the reaction was carried out between 0°C and 25°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially, equimolar amounts of compounds of Formula IV and V (where A^1 = F, Cl, Br, I) and base and substochiometric amounts of DMAP were preferably used although higher or lower amounts were used if desired. Additionally, other suitable reaction conditions for the conversion of a compound of Formula IV to a compound of Formaul III can be found in Larock, R. C. *Comprehensive Organic Transformations,* 2nd ed.; Wiley and Sons: New York, 1999, pp 1941-1949.

[295] The compounds of Formula IV of Scheme 3 were prepared as shown below in Scheme 4:

Scheme 4



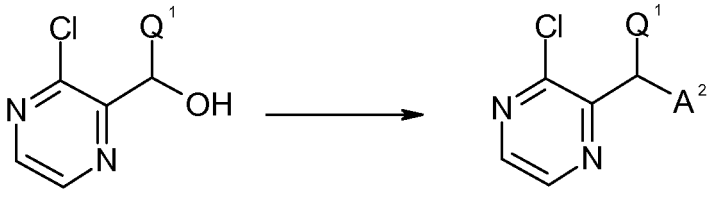
VI IV

[296] where Q^1 is as defined previously for compound of Formula I-AA and A^2 = phthalimido or N^3.

[297] In a typical preparation, of a compound of Formula IV, a compound of Formula VI is reacted under suitable reaction conditions in a suitable solvent. When A^2 = phthalimido, suitable conditions include treatment of compound of Formula VI with hydrazine in a suitable solvent. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile; halogenated solvents such as chloroform or methylene chloride; alcoholic solvents such as methanol and ethanol. If desired, mixtures of these solvents may be used, however the preferred solvent was ethanol. The above process was carried out at temperatures between about 0°C and about 80°C. Preferably, the reaction was carried out at about 22°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially, equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired.

[298] The compounds of Formula VI of Scheme 4 were prepared as shown below in Scheme 5:

Scheme 5



VII VI

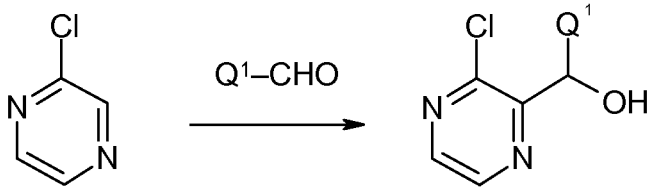
[299] where Q^1 is as defined previously for compound of Formula I-AA and A^2 = phthalimido or N^3.

[300] In a typical preparation of a compound of Formula VI (when A^2 = phthalimido), a compound of Formula VII was reacted with a phthalimide under typical

Mitsunobu conditions in a suitable solvent in the presence of suitable reactants. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like; dimethylformamide (DMF); dimethyl sulfoxide (DMSO); acetonitrile (CH_3CN); chlorinated solvents such as methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). If desired, mixtures of these solvents were used, however, the preferred solvent was THF. Suitable reactants for use in the above process included, but were not limited to, triphenylphosphine and the like, and an azodicarboxylate (DIAD, DEAD, DBAD). The preferred reactants were triphenylphosphine or resin-bound triphenylphosphine and DIAD. The above process may be carried out at temperatures between about -78°C and about 100°C. Preferably, the reaction was carried out at about 22°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially, equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired. Generally, one equivalent of triphenylphosphine, DIAD and phthalimide was used per equivalent of compound of Formula VII. Additionally, compound of Formula VII can be reacted with Ts_2O, Ms_2O, Tf_2O, TsCl, MsCl, or $SOCl_2$ in which the hydroxy group is converted to a leaving group such as its respective tosylate, mesylate, triflate, or halogen such as chloro and subsequently reacted with an amine equivalent such as $NH(Boc)_2$, phthalimide, or azide. Conversion of the amine equivalents by known methods such as by treating under acidic conditions ($NH(Boc)_2$), with hydrazine (phthalimide) as shown in Scheme 4, or with triphenylphosphine/water (azide) will afford the desired amine as shown in Scheme 4.

[301] The compounds of Formula VII of Scheme 5 were prepared from aldehydes Q1–CHO and a 2-chloropyrazine VIII as shown below in Scheme 6:

Scheme 6



VIII VII

[302] where Q^1 are as defined previously for compound of Formula I-AA.

[303] In a typical preparation, of a compound of Formula VII, a compound of Formula VIII was reacted under suitable reaction conditions in a suitable solvent with a compound of Formula Q^1–CHO. Suitable conditions included but were not limited to treating compounds of Formula VIII with a base such as lithium tetramethylpiperidide (Li-TMP) followed by treating with compounds of Formula Q^1–CHO. Lithium tetramethylpiperidide may be prepared by reacting tetramethylpiperidine with *n*-butyllithium at –78°C and warming up to 0°C. Suitable solvents for use in the above process included, but were not limited to, ethers such as tetrahydrofuran (THF), glyme, and the like. Polar solvents such as hexamethylphosphoramide (HMPA), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), and the like may be added if necessary. If desired, mixtures of these solvents were used, however, the preferred solvent was THF. The above process may be carried out at temperatures between about –80°C and about 20°C. Preferably, the reaction was carried out at –78°C to 0°C. The above process to produce compounds of the present invention was preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Substantially, equimolar amounts of reactants were preferably used although higher or lower amounts were used if desired. Q^1–CHO is either commercially available or can be prepared according to the procedures described within.

[304] It would be appreciated by those skilled in the art that in some situations, a substituent that is identical or has the same reactivity to a functional group which has been modified in one of the above processes, will have to undergo protection followed by deprotection to afford the desired product and avoid undesired side reactions. Alternatively, another of the processes described within this invention may be employed in order to avoid competing functional groups. Examples of suitable protecting groups and methods for their addition and removal may be found in the following reference: "Protective Groups in Organic Syntheses", T. W. Greene and P. G. M. Wuts, John Wiley and Sons, 1989.

[305] The following examples are intended to illustrate and not to limit the scope of the present invention.

General Experimental Information:

[306] All melting points were determined with a Mel-Temp II apparatus and are uncorrected. Commercially available anhydrous solvents and HPLC-grade solvents were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded with Varian or Bruker instruments (400 MHz for ^{1}H, 100.6 MHz for ^{13}C) at ambient temperature with TMS or the residual solvent peak as internal standards. The line positions or multiplets are given in ppm (δ) and the coupling constants (*J*) are given as absolute values in Hertz, while the multiplicities in ^{1}H NMR spectra are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), m_c (centered multiplet), br (broadened), AA'BB'. The signal multiplicities in ^{13}C NMR spectra were determined using the DEPT135 pulse sequence and are abbreviated as follows: + (CH or CH_3), – (CH_2), C_{quart} (C). LC/MS analysis was performed using a Gilson 215 autosampler and Gilson 819 autoinjector attached to a Hewlett Packard HP1100 and a MicromassZQ mass spectrometer, or a Hewlett Packard HP1050 and a Micromass Platform II mass spectrometer. Both setups used XTERRA MS C18 5μ 4.6×50mm columns with detection at 254 nm and electrospray ionization in positive mode. For mass-directed purification (MDP), a Waters / Micromass system was used.

[307] The tables below list the mobile phase gradients (solvent A: acetonitrile; solvent B: 0.01% formic acid in HPLC water) and flow rates for the analytical HPLC programs.

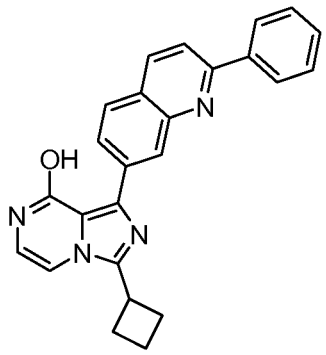
Polar_5min

Time	A%	B%	Flow Rate (mL/min) MicromassZQ	Flow Rate (mL/min) Platform II
0.00	5	95	1.3	1.3
3.00	90	10	1.3	1.3
3.50	90	10	1.3	1.3
4.00	5	95	1.3	1.3
5.00	5	95	1.3	1.3

Nonpolar_5min

Time	A%	B%	Flow Rate (mL/min) MicromassZQ	Flow Rate (mL/min) Platform II
0.00	25	75	1.3	1.3
3.00	99	1	1.3	1.3
3.50	99	1	1.3	1.3
4.00	25	75	1.3	1.3
5.00	25	75	1.3	1.3

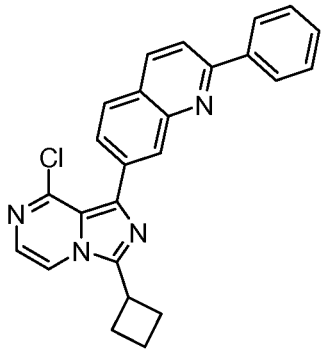
Example 1: 3-Cyclobutyl-1-(2-phenyl-quinolin-7-yl)-imidazol[1,5-a]pyrazin-8-ol



[308] 7-(8-Chloro-3-cyclobutyl-imidazol[1,5-a]pyrazin-1-yl)-2-phenyl-quinoline was dissolved in THF (2.0 mL). Water (2.0 mL) and 37% HCl (2.0 mL) were then added and the solution was heated to 60 °C. The solution was then allowed to cool to rt and stirred overnight. THF was removed *in vacuo* and the aqueous solution was treated with 5N

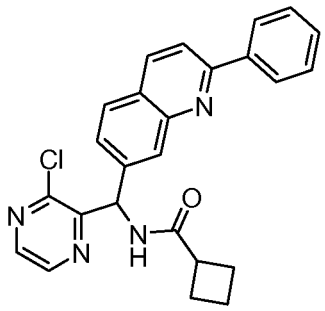
NaOH until pH10. The resultant solid was filtered and dried *in vacuo* to give the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.91–2.02 (m, 1H), 2.10 (quintuplet, 1H, J = 9.6 Hz), 3.96 (quintuplet, 1H, J = 2.4 Hz), 6.70 (dd, 1H, J = 3.2, 3.2 Hz), 7.22 (d, 1H, J = 5.6 Hz), 7.49–7.59 (m, 3H), 8.01 (d, 1H, J = 8.4 Hz), 8.12 (d, 1H, J = 4.0 Hz), 8.30 (d, 2H, J = 7.2 Hz), 8.44 (d, 1H, J = 8.8 Hz), 8.57 (d, 1H, J = 7.6 Hz), 9.10 (s, 1H), 10.70 (d, 1H, J = 2.8 Hz). MS (ES+): *m/z* 393 (100) [MH^+].

[309] 7-(8-Chloro-3-cyclobutyl-2*H*-imidazo[1,5-*a*]pyrazin-1-yl)-2-phenyl-quinoline (compound of Formula II where R^1 = cyclobutyl and Q^1 = 2-phenylquinolin-7-yl):



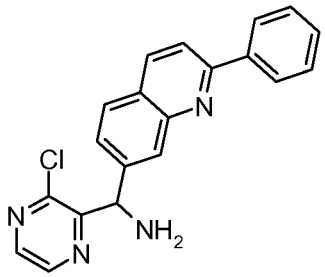
[310] A mixture of $POCl_3$ (5mL, 8g, 55mmol) and cyclobutanecarboxylic acid [(3-chloropyrazin-2-yl)-(2-phenylquinolin-7-yl)methyl]-amide (compound of Formula III where R^1 = cyclobutyl and Q^1 = 2-phenylquinolin-7-yl) [275mg of crude material from stepb), max0.583 mmol] is heated to 70°C for 21.5h. $POCl_3$ is evaporated, a cold solution of NH_3 in *i*PrOH (2M, 11mL, 22mmol) is added, the suspension is sonicated, the solid is filtered off and washed with *i*PrOH. The solid is suspended in $CHCl_3$ and filtered, and the filtrate is concentrated to obtain (over two steps from *C*-(3-chloropyrazin-2-yl)-*C*-(2-phenylquinolin-7-yl)-methylamine) of the title compound as yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.04–2.15 (m, 1H), 2.15–2.28 (m, 1H), 2.50–2.60 (m, 2H), 2.64–2.76 (m, 2H), 3.89 (quint, J = 8.4 Hz, 1H), 7.35 (d, J = 4.8 Hz, 1H), 7.44–7.50 (m, 1H), 7.51–7.57 (m, 3H), 7.89–7.93 (m, 3H), 8.17–8.22 (m, 2H), 8.27 (dd, J = 0.8, 8.8 Hz, 1H), 8.53 (d, J = 0.8 Hz, 1H). MS (ES+): *m/z* 410.9/412.9 (100/39) [MH^+]. HPLC: t_R = 3.7 min (MicromassZQ, nonpolar_5min).

[311] Cyclobutanecarboxylic acid [(3-chloro-pyrazin-2-yl)-(2-phenyl-quinolin-7-yl)-methyl]-amide (compound of Formula III where R^1 = cyclobutyl and Q^1 = 2-phenylquinolin-7-yl):



[312] To a solution of NEt(*i*Pr)$_2$ (150μL, 111mg, 0.861mmol), DMAP (5mg, 0.04mmol), and *C*-(3-chloropyrazin-2-yl)-*C*-(2-phenylquinolin-7-yl)-methylamine (compound of Formula IV where Q^1 = 2-phenylquinolin-7-yl) (202mg, 0.583mmol) in dry CH_2Cl_2 (5mL), cooled by ice/water, is added cyclobutanecarbonyl chloride (75μL, 78mg, 0.66mmol), then the cooling bath is removed, and the reaction mixture is stirred at rt for 3h. Water is added, the layers are separated, and the aqueous layer is extracted with CH_2Cl_2 (3×15mL). The combined CH_2Cl_2 layers are washed with water, saturated $NaHCO_3$ solution, and brine, dried over $MgSO_4$, filtered and concentrated to give crude material as yellow foam, which is used for the next step without purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.81–1.90 (m, 1H), 1.90–2.02 (m, 1H), 2.11–2.23 (m, 2H), 2.23–2.35 (m, 2H), 3.12 (quint, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.43–7.48 (m, 1H), 7.48–7.54 (m, 2H), 7.73 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.90 (d, *J* = 0.8 Hz, 1H), 8.07–8.12 (m, 2H), 8.19 (d, *J* = 8.4 Hz, 1H), 8.38 (d, *J* = 2.4 Hz, 1H), 8.58 (d, *J* = 2.4 Hz, 1H). MS (ES+): *m/z* 429.0/431.0 (38/13) [MH^+], 469.8/471.8 (6/2) [MH^+ + MeCN]. HPLC: t_R = 3.6 min (MicromassZQ, polar_5min).

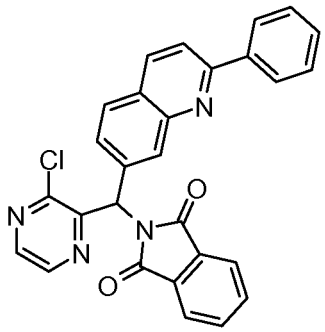
[313] *C*-(3-Chloro-pyrazin-2-yl)-*C*-(2-phenyl-quinolin-7-yl)-methylamine (compound of Formula IV where Q^1 = 2-phenylquinolin-7-yl):



[314] A solution of 2-[(3-chloropyrazin-2-yl)-(2-phenylquinolin-7-yl)-methyl]-isoindole-1,3-dione (compound of Formula VI where Q^1 = 2-phenylquinolin-7-yl and A^2 = phthalimido) (1.536g, 3.22mmol) and anhydrous hydrazine (335μL, 342mg, 10.7mmol) in

EtOH (2mL) / CH_2Cl_2 (12mL) is stirred at rt overnight. The white precipitate formed (phthalic hydrazide) is filtered off and washed with CH_2Cl_2. The combined filtrate and washings are concentrated *in vacuo*, the residue is suspended in $CDCl_3$ and filtered (0.45µM pore size), and the filtrate is concentrated *in vacuo* to obtain the title compound as yellow foam, which is used for the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.4 (brs, 2H), 5.79 (s, 1H), 7.43–7.55 (m, 3H), 7.61 (dd, *J* = 1.8, 8.6 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 1.2 Hz, 1H), 8.10–8.15 (m, 2H), 8.19 (d, *J* = 8.8 Hz, 1H), 8.31 (d, *J* = 2.4 Hz, 1H), 8.60 (d, *J* = 2.4 Hz, 1H). MS (ES+): *m/z* 347.0/349.0 (30/10) [MH^+], 330.0/332.0 (18/6) [$MH^+ - NH_3$]. HPLC: t_R = 2.1 min (MicromassZQ, polar_5min).

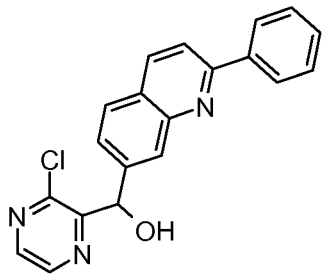
[315] 2-[(3-Chloro-pyrazin-2-yl)-(2-phenyl-quinolin-7-yl)-methyl]-isoindole-1,3-dione (compound of Formula VI where Q^1 = 2-phenylquinolin-7-yl and A^2 = phthalimido):



[316] To a suspension of (3-chloropyrazin-2-yl)-(2-phenylquinolin-7-yl)-methanol (compound of Formula VII where Q^1 = 2-phenylquinolin-7-yl) (1.215g, 3.49mmol), phthalimide (566mg, 3.85mmol), and PS–PPh_3 (loading 2.12mmol/g; 3.29g, 6.97mmol) in dry THF (40mL), cooled by ice/water, is added DIAD (830µL, 852mg, 4.22mmol). The cooling bath is removed and the flask is vortexed at rt for 1d. More phthalimide (50mg, 0.34mmol), PS–PPh_3 (300mg, 0.636mmol), and DIAD (80µL, 82mg, 0.41mmol) are added, and vortexing is continued for 2d. The resin is filtered off on a glass frit (porosity M) and washed with CH_2Cl_2. The combined filtrates and washings are concentrated *in vacuo* and chromatographed on silica gel [Jones Flashmaster, 50g / 150mL cartridge, eluting with CH_2Cl_2 (1–22) → 2% EtOAc in CH_2Cl_2 (23–38) → 5% (39–61)], mixed fractions are combined and chromatographed again [50g / 150mL cartridge, eluting with CH_2Cl_2 (1–22) → 2% EtOAc in CH_2Cl_2 (23–33) → 3% (34–55) → 5% (56–68)] to obtain the title compound as white foam. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.14 (s, 1H), 7.43–7.55 (m, 3H), 7.72–7.79 (m, 3H), 7.82–7.90 (m, 4H), 8.09 (s, 1H), 8.09–8.14 (m, 2H), 8.22 (d, *J* = 8.8 Hz, 1H), 8.40

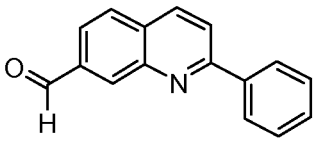
(d, J = 2.4 Hz, 1H), 8.51 (d, J = 2.4 Hz, 1H). MS (ES+): m/z 476.9/478.9 (100/38) [MH^+]. HPLC: t_R = 3.5 min (MicromassZQ, nonpolar_5min).

[317] (3-Chloropyrazin-2-yl)-(2-phenylquinolin-7-yl)-methanol (Compound of Formula VII where Q^1 = 2-phenylquinolin-7-yl):



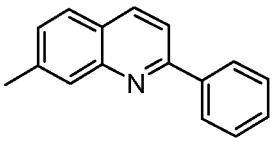
[318] To a solution of 2,2,6,6-tetramethylpiperidine (0.820mL, 0.686g, 4.86mmol) in dry THF (15mL), cooled by CO_2(s)/acetone, is added nBuLi (2.5M in hexanes; 1.95mL, 4.88mmol). The cooling bath is replaced with an ice/water bath for 15min, and then the solution is re-cooled to –78°C. After 5min, a solution of 2-chloropyrazine (VIII) (0.370mL, 0.475g, 4.14mmol) in THF (0.5mL) is added. 25min later, a solution of 2-phenylquinoline-7-carbaldehyde (compound of Formula Q^1–CHO where Q^1 = 2-phenylquinolin-7-yl) (890mg, 3.82mmol) in dry THF (7mL) is added slowly over 5min from a syringe which is then rinsed with THF (1mL), and the mixture is stirred at –78°C for 2h and then warmed up to 0°C for 0.5h. The reaction is quenched by adding citric acid (0.25M aqueous solution). The mixture is extracted with EtOAc (4×30mL), and the combined EtOAc extracts are washed with water, sodium bicarb solution, and brine and dried over $MgSO_4$. The crude material is chromatographed on silica gel [Jones Flashmaster, 50g / 150mL cartridge, eluting with CH_2Cl_2 (4×50mL, then 1–16) → 2% EtOAc in CH_2Cl_2 (17–30) → 5% (31–59) → 7% (60–85) → 10% (86–110)] to obtain the title compound as an off-white foam. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.80 (d, J = 7.6 Hz, 1H), 6.25 (d, J = 7.6 Hz, 1H), 7.43–7.56 (m, 3H), 7.58 (dd, J = 1.8, 8.2 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 8.06 (brs, 1H), 8.10–8.15 (m, 2H), 8.20 (d, J = 8.4 Hz, 1H), 8.41 (d, J = 2.4 Hz, 1H), 8.62 (d, J = 2.4 Hz, 1H). MS (ES+): m/z 348.0/350.0 (100/37) [MH^+]. HPLC: t_R = 3.3 min (MicromassZQ, polar_5min).

[319] 2-Phenylquinoline-7-carbaldehyde (compound of Formula Q^1–CHO where Q^1 = 2-phenylquinolin-7-yl):



[320] A mixture of 7-methyl-2-phenylquinoline (compound of Formula Q^1–CH_3 where Q^1 = 2-phenylquinolin-7-yl) (2.49g, 11.4mmol) and selenium dioxide (1.92g, 17.3mmol, 1.5eq.) is heated to 160°C (bath temp.) for 22h. The cooled melt is suspended in CH_2Cl_2 with the aid of sonication and filtered through Celite and then through a plug of silica gel. This effectively removes the red color and the major lower spots. The material thus obtained is crystallized from hexanes/$CHCl_3$, yielding a pale beige solid, mp. 108°C. The mother liquor is concentrated and chromatographed on silica gel [Jones Flashmaster, 50g /150mL cartridge, eluting with hexanes:CH_2Cl_2 1:1 (1–25) → 1:3 (26–53) → CH_2Cl_2 (54–73) →3% EtOAc in CH_2Cl_2 (74–85)] to obtain as pale yellow solid, mp. 109°C. ^{1}H NMR ($CDCl_3$, 400MHz): δ = 7.48–7.60 (m, 3H), 7.94 (d, *J* = 8.8 Hz, 1H), 8.01–8.05 (m, 2H), 8.18–8.23 (m, 2H), 8.29 (d, *J* = 8.8 Hz, 1H), 8.64 (s, 1H), 10.26 (s, 1H). MS (ES+): *m/z* 234.2 (100) [MH^+]. HPLC: t_R = 3.0 min (MicromassZQ, nonpolar_5min).

[321] 7-Methyl-2-phenylquinoline (compound of Formula XI where X_{11}–X_{13} = CH, E^{11} = H, and G^1 = phenyl, i.e., compound of Formula Q^1–CH_3 where Q^1 = 2-phenylquinolin-7-yl):

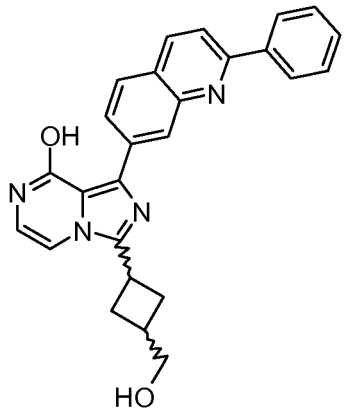


[322] To a solution of 7-methylquinoline (compound of Formula IX where X_{11}–X_{13} = CH and E^{11} = H) (1.63g, 11.4mmol) in dry THF (10mL), cooled by ice/water, is added phenyllithium (compound of Formula Li–G^1 where G^1 = phenyl) (1.9M in cyclohexane/ether 70/30, 6.0mL, 11.4mmol) dropwise over 5min. After 15min, the cooling bath is removed, and the solution is stirred at rt for 5h. The reaction is quenched by adding MeOH, and stirring is continued overnight. Water is added, the mixture is extracted with EtOAc (3×35mL), and the combined extracts are dried over $MgSO_4$. The drying agent is filtered off, and air is bubbled into the solution for 7d. The solvent is evaporated; the residue is dissolved in warm (≈50°C) EtOAc/hexanes and filtered warm. The filtrate is concentrated and dried *in vacuo* to obtain the crude title compound that is used directly for the next step. Further purification is possible by chromatography on silica gel (Jones Flashmaster, eluting with

hexanes:EtOAc 3:1 → 2:1 → 1:1). ^{1}H NMR ($CDCl_3$, 400MHz): δ = 2.58 (s, 3H), 7.31 (d, *J* = 3.7 Hz, 1H), 7.36–7.49 (m, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.96 (s, 1H), 8.16 (t, *J* = 8.0 Hz, 2H). MS (ES+): *m/z* 220.3 (100) [MH^+]. HPLC: t_R = 2.7 min (Platform II, nonpolar_5min).

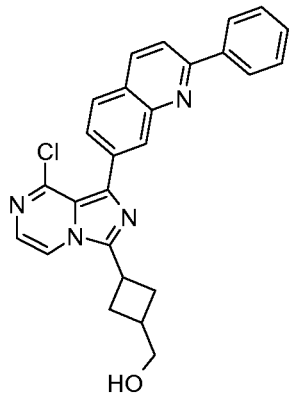
Example 2:

3-(3-Hydroxymethyl-cyclobutyl)-1-(2-phenyl-quinolin-7-yl)-imidazo[1,5-a]pyrazin-8-ol



[323] 7-[8-Chloro-3-(3-methylene cyclobutyl)imidazo[1,5-a]pyrazin-1-yl]-2-phenylquinoline (0.23 mmol, 100 mg) was dissolved in THF (2 mL) and treated with 6 N aq HCl (4 mL). The reaction mixture was heated at reflux for 4 hour and stirred at rt overnight. The reaction mixture was concentrated in vacuo and pH~10 was adjusted with 5 N aq NaOH. The desired product was extracted with DCM from the aqueous solution. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel [Jones Flashmaster, 10 g / 70 mL cartridge, eluting with 1-2% MeOH in EtOAc], yielding the title compound as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) (cis : trans: 4:1) δ 9.66-9.64 (m, 0.8H), 9.59-9.58 (m, 0.2 H), 9.14-9.13 (m, 0.2 H), 9.12-9.11 (m, 0.8H), 8.48 (dd, *J* = 1.6 Hz, 8.8 Hz, 0.2H), 8.43 (dd, *J* = 1.6 Hz, 8.8 Hz, 0.8H), 8.22-8.17 (m, 3H), 7.86-7.83 (m, 2H), 7.55-7.44 (m, 3H), 6.55-6.45 (m, 2H), 3.77 (d, *J* = 5.2 Hz, 0.4 H), 3.68 (d, *J* = 5.2 Hz, 1.6 H), 3.49-3.41 (m, 1H), 2.69-2.26 (m, 5H); MS (ES+): *m/z* 423 [MH^+]. HPLC: t_R = 2.57 min (OpenLynx, polar_5min).

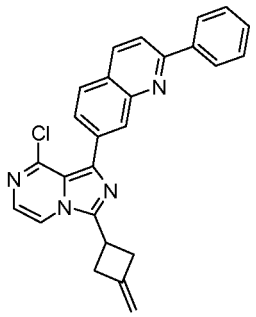
[324] {3-[8-Chloro-1-(2-phenylquinolin-7-yl)-imidazo[1,5-*a*]pyrazin-3-yl]-cyclobutyl}-methanol



[325] To a solution of 7-[8-chloro-3-(3-methylenecyclobutyl)-imidazo[1,5-*a*]pyrazin-1-yl]-2-phenylquinoline (338mg, 0.8mmol) in dry THF (5mL) was added 9-BBN (2.4mL, 1.2mmol, 0.5M in THF) dropwise at 0°C under nitrogen atmosphere. The temperature was slowly warmed to rt overnight. The mixture was cooled to 0°C, and 3mL 1N aq. NaOH and 0.6mL 30% aq. H_2O_2 were added, the resulting mixture was stirred at 0°C for 10min, then rt for 30min. The mixture was diluted with methylene chloride (30mL), washed with brine (2 × 20mL), and dried over anhydrous sodium sulfate. The filtrate was concentrated under reduced pressure, and the crude material was purified by silica gel column chromatography (eluting with hexanes:EtOAc = 50:50 → 100% ethyl acetate), to obtain the

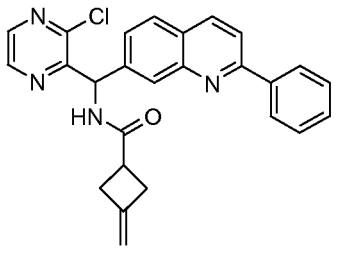
title compound as a yellow solid, a mixture of *cis* and *trans* isomers in the ratio of 5:1; MS (ES+): *m/z* 441/443 (3/1) [MH^+]; ^1H NMR ($CDCl_3$, 400MHz) δ 2.44-2.64 (m, 6H), 3.65-3.76 (m, 3H), 7.31, 7.33 (2 × d, *J* = 5.0 Hz, 1H, 1:5 ratio), 7.39-7.57 (m, 4H), 7.86-7.98 (m, 3H), 8.18 (m, 2H), 8.26 (d, *J* = 8.6 Hz, 1H), 8.51, 8.53 (2 × s, 1H, 5:1 ratio).

[326] 7-[8-Chloro-3-(3-methylenecyclobutyl)-imidazo[1,5-*a*]pyrazin-1-yl]-2-phenylquinoline



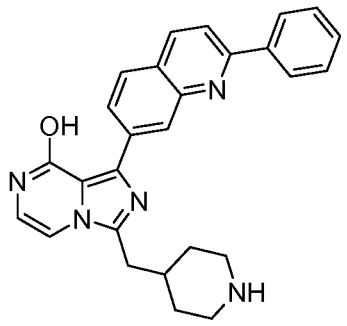
[327] *N*-[(3-Chloropyrazin-2-yl)(2-phenylquinolin-7-yl)methyl]-3 methylenecyclobutanecarboxamide (0.02 mmol, 10 g) was dissolved in 150 mL $POCl_3$ in a 250 mL rbf, charged with 0.1 mL DMF and heated to 55 °C under a consistent N_2 flow for 1 h (the reaction was vented with a needle). The excess $POCl_3$ was removed under reduced pressure and the residue was quenched with 2 N NH_3 in isopropanol (250 mL) at 0 °C and water. The aqueous layer was washed with DCM (100 mL X 2) and the combined organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (flash column) eluting with 20 – 50% EtOAc in hexane. Concentration in vacuo of the product-rich fractions afforded the desired product as yellow solid; MS (ES, Pos.): *m/z* 423 (100) [MH^+]; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.28-3.31 (m, 2H), 3.39-3.42 (m, 2H), 3.85-3.93 (m, 1H), 4.94 (p, *J* = 2.4 Hz, 2H), 7.38 (d, *J* = 4.9 Hz, 1H), 7.42-7.57 (m, 4H), 7.89-7.92 (m, 3H), 8.18-8.21 (m, 2H), 8.27 (dd, *J* = 8.6 Hz, 0.8 Hz, 1H), 8.53 (s, 1H).

[328] 3-Methylenecyclobutanecarboxylic acid [(3-chloropyrazin-2-yl)-(2-phenyl-quinolin-7-yl)-methyl]-amide



C-(3-Chloro-pyrazin-2-yl)-*C*-(2-phenylquinolin-7-yl)-methylamine (690mg, 1.99mmol) was dissolved in 6.0mL of CH_2Cl_2 followed by the addition of EDC (600mg, 2.98mmol) and HOBT (300mg, 1.99mmol). 3-Methylenecyclobutanecarboxylic acid (300mg, 2.59mmol) was dissolved in 1.0mL of CH_2Cl_2 and added to the homogenous reaction mixture. After 24h the reaction was concentrated *in vacuo* and dissolved in EtOAc and the organic layer was washed with sat. $NaHCO_3$. The organic layer was washed with H_2O and brine. The organic layers where combined, dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography [Jones Flashmaster, 10g cartridge, eluting with 50% EtOAc: Hex] to obtain the desired product as a white fluffy solid; ^{1}H NMR (400MHz, $CDCl_3$): δ = 2.82–2.92 (m, 2H), 2.99–3.06 (m, 2H), 4.77–4.80 (m, 2H), 6.81 (d, 1H, *J* = 7.8 Hz), 7.45–7.54 (m, 3H), 7.83–7.88 (m, 3H), 8.10 (d, 2H, *J* = 7.1 Hz), 8.22–8.23 (brm, 1H), 8.39 (d, 1H, *J* = 1.79 Hz), 8.59 (d, 1H, *J* = 2.5 Hz); MS (ES+): 440.93 (M+1), 442.91 (M+3).

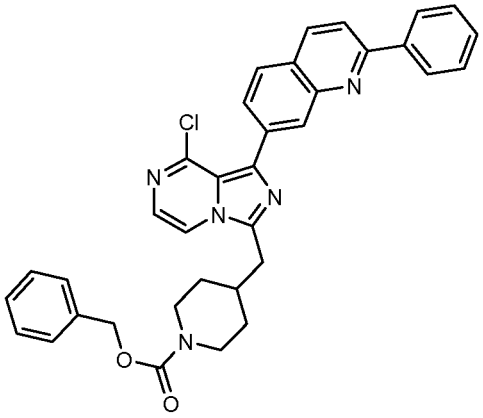
Example 3: 1-(2-Phenyl-quinolin-7-yl)-3-piperidin-4-ylmethyl-imidazo[1,5-a]pyrazin-8-ol



[329] In a 50 mL round bottom flask, benzyl 4-((8-amino-1-(2-phenylquinolin-7-yl)-imidazo-[1,5-a]pyrazin-3-yl)-methyl)-piperidine-1-carboxylate (1.94 g, 34.1 mmol) was mixed with 37% HCl (90 mL, 2.96 mol), heated and stirred for 10 min at 60°C. LC/MS showed the reaction to be completed. The solution was cooled and then washed with ether (2 x 20 mL) and methylene chloride (2 x 20 mL) respectively. The aqueous layer was extracted, basified with 5N NaOH and then washed with methylene chloride (3 x 50mL). The organic layer was extracted, combined, dried with Na_2SO_4, filtered, and concentrated *in vacuo* to give the desired product; ^{1}H NMR (*CHLOROFORM-d,* 400 MHz) δ 9.06 (1 H, s), 8.43 (1 H, d, *J =1.568*), 8.20 (3 H, m), 7.86 (2 H, dd, *J =4.72, J = 4.76*), 7.49 (3 H, m), 6.75 (1 H, d, *J =5.88*), 6.51 (1 H, d, *J =5.92*), 3.18 (2 H, d, *J =12.52*), 2.78 (2 H, d, *J =7.60*), 2.69 (2 H, t),

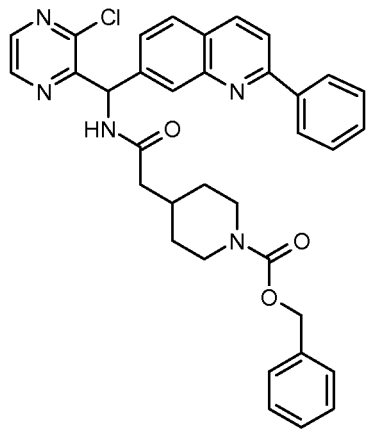
2.10 (1 H, b.s.), 1.78 (2 H, d, *J =12.68*), 1.90 (2 H, q); MS (ES+): *m/z* 436.10/437.05 (50/20) [MH^+]; HPLC: t_R = 1.97 min. (OpenLynx, polar_5min.).

[330] (4-[8-Chloro-1-(2-phenyl-quinolin-7-yl)-imidazo[1,5-a]pyrazin-3-ylmethyl]-piperidine-1-carboxylic acid benzyl ester)



[331] A solution of 4-({[(3-chloro-pyrazin-2-yl)-(2-phenyl-quinolin-7-yl)-methyl]-carbamoyl}-methyl)-piperidine-1-carboxylic acid benzyl ester in anhydrous acetonitrile (165 mL) was charged with $POCl_3$ (2.03 mL, 21.84 mmol) and DMF (2.15 mL) and heated to 55 ^oC under N_2 condition. After 2 h, LC/MS and TLC analysis showed the reaction to be completed. The reaction mixture was concentrated *in vacuo*, diluted with CH_2Cl_2, and quenched with 2N (7N NH_3) in 2-propanol to pH 9. 2-propanol was removed *in vacuo*. The crude product was purified by silica gel flash chromatography (loaded with 40% EtOAc / Hexanes, and run 50% EtOAc / Hexanes → 80% EtOAc / Hexanes), which afforded the title compound; ^1H NMR (400 MHz, *DMSO-d*) δ ppm 8.53 (1 H, d, *J*= 8.52), 8.45 (1 H, d, *J*= 5.00), 8.31 (3 H, m), 8.21 (1 H, d, *J*= 8.66), 8.08 (1 H, d, *J*= 8.47), 7.56 (3 H, m), 7.49 (1 H, d, *J*= 5.00), 7.34 (5 H, m), 5.07 (2 H, s), 4.02 (2 H, d, *J*= 12.8), 3.32 (2 H, s), 3.11 (2 H, d, *J*= 6.92), 2.82 (1 H, m), 2.13 (1 H, m), 1.73 (2 H, d, *J*= 12.26), 1.21 (2 H, m); MS (ES+): *m/z* 589.97 (5) [MH^+]; HPLC: t_R = 3.72 min (OpenLynx, polar_5min).

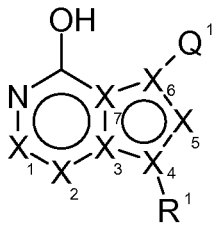
[332] (4-({[(3-Chloro-pyrazin-2-yl)-(2-phenyl-quinolin-7-yl)-methyl]-carbamoyl}-methyl)-piperidine-1-carboxylic acid benzyl ester)



[333] (3-Chloropyrazin-2-yl)(2-phenylquinolin-7-yl)-methanamine (120.00 mg, 0.35 mmol), EDC (100.64 mg, 0.53 mmol) and HOBt (47.29 mg, 0.35 mmol) were suspended in CH_2Cl_2 use CH_2Cl_2(2 mL) and charge with DIEA (122.00 μL, 0.70 mmol) followed by the addition of 1-*N*-Cbz-4-piperidineacetic acid (127.56 mg, 0.46 mmol). The reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with saturated $NaHCO_3$ (2 x 20 mL) and brine (2 x 20 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by a 10 g Jones silica gel (wetted with 50% EtOAc / Hexane, dried loaded onto silica, and run with 60% EtOAc / Hexanes → 70% EtOAc / Hexanes). The product was evaporated *in vacuo* which afforded the title compound; ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ 8.56 (1 H, d, *J*=2.47), 8.39 (1 H, d, *J*= 2.50), 8.23 (1 H, d, *J*= 4.77), 8.11 (2 H, d, *J*= 7.06), 7.85 (3 H, dd, *J*= 8.60, *J*= 8.38), 7.74 (1 H, s), 7.50 (3H, m), 7.32 (6H, m), 6.78 (1 H, d, *J*= 7.76), 5.10 (2 H, s), 4.11 (2 H, m), 2.75 (2 H, m), 2.21 (2 H, d, *J*= 7.00), 2.01 (1 H, m), 1.67 (2 H, m), 1.15 (2 H, d, *J*= 8.921); MS (ES+): *m/z* 605.96/606.98/608.93 (100/40/15) [MH^+]; HPLC: t_R = 3.33 min. (OpenLynx, nonpolar_5min.).

WHAT IS CLAIMED IS:

1. A compound represented by Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

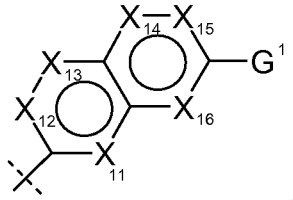
X_1, and X_2 are each independently N or C–$(E^1)_{aa}$;

X_5 is N, C–$(E^1)_{aa}$, or N–$(E^1)_{aa}$;

X_3, X_4, X_6, and X_7 are each independently N or C;

wherein at least one of X_3, X_4, X_5, X_6, and X_7 is independently N or N–$(E^1)_{aa}$;

Q^1 is



;

X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, and X_{16} are each independently N, C–$(E^{11})_{bb}$, or N^+–O^-;

wherein at least one of X_{11}, X_{12}, X_{13}, X_{14}, X_{15}, and X_{16} is N or N^+–O^-;

R^1 is absent, $C_{0\text{-}10}$alkyl, cyclo$C_{3\text{-}10}$alkyl, bicyclo$C_{5\text{-}10}$alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocyclyl, heterobicyclo$C_{5\text{-}10}$alkyl, spiroalkyl, or heterospiroalkyl, any of which is optionally substituted by one or more independent G^{11} substituents;

E^1, E^{11}, G^1, and G^{41} are each independently halo, –CF_3, –OCF_3, –OR^2, –$NR^2R^3(R^{2a})_{j1}$, –$C(=O)R^2$, –CO_2R^2, –$CONR^2R^3$, –NO_2, –CN, –$S(O)_{j1}R^2$, –$SO_2NR^2R^3$, –$NR^2C(=O)R^3$, –$NR^2C(=O)OR^3$, –$NR^2C(=O)NR^3R^{2a}$, –$NR^2S(O)_{j1}R^3$, –$C(=S)OR^2$, –$C(=O)SR^2$, –$NR^2C(=NR^3)NR^{2a}R^{3a}$, –$NR^2C(=NR^3)OR^{2a}$, –$NR^2C(=NR^3)SR^{2a}$, –$OC(=O)OR^2$, –$OC(=O)NR^2R^3$, –$OC(=O)SR^2$, –$SC(=O)OR^2$, –$SC(=O)NR^2R^3$, $C_{0\text{-}10}$alkyl, $C_{2\text{-}10}$alkenyl, $C_{2\text{-}10}$alkynyl, $C_{1\text{-}10}$alkoxy$C_{1\text{-}10}$alkyl, $C_{1\text{-}10}$alkoxy$C_{2\text{-}10}$alkenyl, $C_{1\text{-}10}$alkoxy$C_{2\text{-}10}$alkynyl, $C_{1\text{-}10}$alkylthio$C_{1\text{-}10}$alkyl, $C_{1\text{-}10}$alkylthio$C_{2\text{-}10}$alkenyl, $C_{1\text{-}10}$alkylthio$C_{2\text{-}10}$alkynyl, cyclo$C_{3\text{-}8}$alkyl, cyclo$C_{3\text{-}8}$alkenyl, cyclo$C_{3\text{-}8}$alkyl$C_{1\text{-}10}$alkyl, cyclo$C_{3\text{-}8}$alkenyl$C_{1\text{-}10}$alkyl, cyclo$C_{3\text{-}8}$alkyl$C_{2\text{-}10}$alkenyl, cyclo$C_{3\text{-}8}$alkenyl$C_{2\text{-}10}$alkenyl, cyclo$C_{3\text{-}8}$alkyl$C_{2\text{-}10}$alkynyl, cyclo$C_{3\text{-}8}$alkenyl$C_{2\text{-}$

$_{10}$alkynyl, heterocyclyl–C_{0-10}alkyl, heterocyclyl–C_{2-10}alkenyl, or heterocyclyl–C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $–CF_3$, $–OCF_3$, $–OR^{222}$, $–NR^{222}R^{333}(R^{222a})_{j1a}$, $–C(=O)R^{222}$, $–CO_2R^{222}$, $–C(=O)NR^{222}R^{333}$, $–NO_2$, –CN, $–S(=O)_{j1a}R^{222}$, $–SO_2NR^{222}R^{333}$, $–NR^{222}C(=O)R^{333}$, $–NR^{222}C(=O)OR^{333}$, $–NR^{222}C(=O)NR^{333}R^{222a}$, $–NR^{222}S(O)_{j1a}R^{333}$, $–C(=S)OR^{222}$, $–C(=O)SR^{222}$, $–NR^{222}C(=NR^{333})NR^{222a}R^{333a}$, $–NR^{222}C(=NR^{333})OR^{222a}$, $–NR^{222}C(=NR^{333})SR^{222a}$, $–OC(=O)OR^{222}$, $–OC(=O)NR^{222}R^{333}$, $–OC(=O)SR^{222}$, $–SC(=O)OR^{222}$, or $–SC(=O)NR^{222}R^{333}$ substituents;

or E^1, E^{11}, or G^1 optionally is $–(W^1)_n–(Y^1)_m–R^4$;

or E^1, E^{11}, G^1, or G^{41} optionally independently is aryl–C_{0-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, hetaryl–C_{0-10}alkyl, hetaryl–C_{2-10}alkenyl, or hetaryl–C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $–CF_3$, $–OCF_3$, $–OR^{222}$, $–NR^{222}R^{333}(R^{222a})_{j2a}$, $–C(O)R^{222}$, $–CO_2R^{222}$, $–C(=O)NR^{222}R^{333}$, $–NO_2$, –CN, $–S(O)_{j2a}R^{222}$, $–SO_2NR^{222}R^{333}$, $–NR^{222}C(=O)R^{333}$, $–NR^{222}C(=O)OR^{333}$, $–NR^{222}C(=O)NR^{333}R^{222a}$, $–NR^{222}S(O)_{j2a}R^{333}$, $–C(=S)OR^{222}$, $–C(=O)SR^{222}$, $–NR^{222}C(=NR^{333})NR^{222a}R^{333a}$, $–NR^{222}C(=NR^{333})OR^{222a}$, $–NR^{222}C(=NR^{333})SR^{222a}$, $–OC(=O)OR^{222}$, $–OC(=O)NR^{222}R^{333}$, $–OC(=O)SR^{222}$, $–SC(=O)OR^{222}$, or $–SC(=O)NR^{222}R^{333}$ substituents;

G^{11} is halo, oxo, $–CF_3$, $–OCF_3$, $–OR^{21}$, $–NR^{21}R^{31}(R^{2a1})_{j4}$, $–C(O)R^{21}$, $–CO_2R^{21}$, $–C(=O)NR^{21}R^{31}$, $–NO_2$, –CN, $–S(O)_{j4}R^{21}$, $–SO_2NR^{21}R^{31}$, $NR^{21}(C=O)R^{31}$, $NR^{21}C(=O)OR^{31}$, $NR^{21}C(=O)NR^{31}R^{2a1}$, $NR^{21}S(O)_{j4}R^{31}$, $–C(=S)OR^{21}$, $–C(=O)SR^{21}$, $–NR^{21}C(=NR^{31})NR^{2a1}R^{3a1}$, $–NR^{21}C(=NR^{31})OR^{2a1}$, $–NR^{21}C(=NR^{31})SR^{2a1}$, $–OC(=O)OR^{21}$, $–OC(=O)NR^{21}R^{31}$, $–OC(=O)SR^{21}$, $–SC(=O)OR^{21}$, $–SC(=O)NR^{21}R^{31}$, $–P(O)OR^{21}OR^{31}$, C_{1-10}alkylidene, C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl–C_{0-10}alkyl, heterocyclyl–C_{2-10}alkenyl, or heterocyclyl–C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, oxo, $–CF_3$, $–OCF_3$, $–OR^{2221}$, $–NR^{2221}R^{3331}(R^{222a1})_{j4a}$, $–C(O)R^{2221}$, $–CO_2R^{2221}$, $–C(=O)NR^{2221}R^{3331}$, $–NO_2$, –CN, $–S(O)_{j4a}R^{2221}$, $–SO_2NR^{2221}R^{3331}$, $–NR^{2221}C(=O)R^{3331}$, $–NR^{2221}C(=O)OR^{3331}$, $–NR^{2221}C(=O)NR^{3331}R^{222a1}$, $–NR^{2221}S(O)_{j4a}R^{3331}$,

$-C(=S)OR^{2221}$, $-C(=O)SR^{2221}$, $-NR^{2221}C(=NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}C(=NR^{3331})OR^{222a1}$, $-NR^{2221}C(=NR^{3331})SR^{222a1}$, $-OC(=O)OR^{2221}$, $-OC(=O)NR^{2221}R^{3331}$, $-OC(=O)SR^{2221}$, $-SC(=O)OR^{2221}$, $-P(O)OR^{2221}OR^{3331}$, or $-SC(=O)NR^{2221}R^{3331}$ substituents;

or G^{11} is aryl–C_{0-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, hetaryl–C_{0-10}alkyl, hetaryl–C_{2-10}alkenyl, or hetaryl–C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{2221}$, $-NR^{2221}R^{3331}(R^{222a1})_{j5a}$, $-C(O)R^{2221}$, $-CO_2R^{2221}$, $-C(=O)NR^{2221}R^{3331}$, $-NO_2$, $-CN$, $-S(O)_{j5a}R^{2221}$, $-SO_2NR^{2221}R^{3331}$, $-NR^{2221}C(=O)R^{3331}$, $-NR^{2221}C(=O)OR^{3331}$, $-NR^{2221}C(=O)NR^{3331}R^{222a1}$, $-NR^{2221}S(O)_{j5a}R^{3331}$, $-C(=S)OR^{2221}$, $-C(=O)SR^{2221}$, $-NR^{2221}C(=NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}C(=NR^{3331})OR^{222a1}$, $-NR^{2221}C(=NR^{3331})SR^{222a1}$, $-OC(=O)OR^{2221}$, $-OC(=O)NR^{2221}R^{3331}$, $-OC(=O)SR^{2221}$, $-SC(=O)OR^{2221}$, $-P(O)OR^{2221}OR^{3331}$, or $-SC(=O)NR^{2221}R^{3331}$ substituents;

or G^{11} is C, taken together with the carbon to which it is attached forms a C=C double bond which is substituted with R^5 and G^{111};

R^2, R^{2a}, R^3, R^{3a}, R^{222}, R^{222a}, R^{333}, R^{333a}, R^{21}, R^{2a1}, R^{31}, R^{3a1}, R^{2221}, R^{222a1}, R^{3331}, and R^{333a1} are each independently C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl–C_{0-10}alkyl, heterocyclyl–C_{2-10}alkenyl, heterocyclyl–C_{2-10}alkynyl, aryl–C_{0-10}alkyl, aryl–C_{2-10}alkenyl, or aryl–C_{2-10}alkynyl, hetaryl–C_{0-10}alkyl, hetaryl–C_{2-10}alkenyl, or hetaryl–C_{2-10}alkynyl, any of which is optionally substituted by one or more independent G^{111} substituents;

or in the case of $-NR^2R^3(R^{2a})_{j1}$ or $-NR^{222}R^{333}(R^{222a})_{j1a}$ or $-NR^{222}R^{333}(R^{222a})_{j2a}$ or $-NR^{21}R^{31}(R^{2a1})_{j4}$ or $-NR^{2221}R^{3331}(R^{222a1})_{j4a}$ or $-NR^{2221}R^{3331}(R^{222a1})_{j5a}$, then R^2 and R^3, or R^{222} and R^{333}, or R^{2221} and R^{3331}, respectfully, are optionally taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring, wherein said ring is optionally substituted by one or more independent G^{1111} substituents and wherein said ring optionally includes one or more heteroatoms other than the nitrogen to which R^2 and R^3, or R^{222} and R^{333}, or R^{2221} and R^{3331} are attached;

W^1 and Y^1 are each independently –O–, $-NR^7-$, $-S(O)_{j7}-$, $-CR^5R^6-$, $-N(C(O)OR^7)-$, $-N(C(O)R^7)-$, $-N(SO_2R^7)-$, $-CH_2O-$, $-CH_2S-$, $-CH_2N(R^7)-$, $-CH(NR^7)-$,

$-CH_2N(C(O)R^7)-$, $-CH_2N(C(O)OR^7)-$, $-CH_2N(SO_2R^7)-$, $-CH(NHR^7)-$, $-CH(NHC(O)R^7)-$, $-CH(NHSO_2R^7)-$, $-CH(NHC(O)OR^7)-$, $-CH(OC(O)R^7)-$, $-CH(OC(O)NHR^7)-$, $-CH=CH-$, $-C\equiv C-$, $-C(=NOR^7)-$, $-C(O)-$, $-CH(OR^7)-$, $-C(O)N(R^7)-$, $-N(R^7)C(O)-$, $-N(R^7)S(O)-$, $-N(R^7)S(O)_2-$ $-OC(O)N(R^7)-$, $-N(R^7)C(O)N(R^8)-$, $-NR^7C(O)O-$, $-S(O)N(R^7)-$, $-S(O)_2N(R^7)-$, $-N(C(O)R^7)S(O)-$, $-N(C(O)R^7)S(O)_2-$, $-N(R^7)S(O)N(R^8)-$, $-N(R^7)S(O)_2N(R^8)-$, $-C(O)N(R^7)C(O)-$, $-S(O)N(R^7)C(O)-$, $-S(O)_2N(R^7)C(O)-$, $-OS(O)N(R^7)-$, $-OS(O)_2N(R^7)-$, $-N(R^7)S(O)O-$, $-N(R^7)S(O)_2O-$, $-N(R^7)S(O)C(O)-$, $-N(R^7)S(O)_2C(O)-$, $-SON(C(O)R^7)-$, $-SO_2N(C(O)R^7)-$, $-N(R^7)SON(R^8)-$, $-N(R^7)SO_2N(R^8)-$, $-C(O)O-$, $-N(R^7)P(OR^8)O-$, $-N(R^7)P(OR^8)-$, $-N(R^7)P(O)(OR^8)O-$, $-N(R^7)P(O)(OR^8)-$, $-N(C(O)R^7)P(OR^8)O-$, $-N(C(O)R^7)P(OR^8)-$, $-N(C(O)R^7)P(O)(OR^8)O-$, $-N(C(O)R^7)P(OR^8)-$, $-CH(R^7)S(O)-$, $-CH(R^7)S(O)_2-$, $-CH(R^7)N(C(O)OR^8)-$, $-CH(R^7)N(C(O)R^8)-$, $-CH(R^7)N(SO_2R^8)-$, $-CH(R^7)O-$, $-CH(R^7)S-$, $-CH(R^7)N(R^8)-$, $-CH(R^7)N(C(O)R^8)-$, $-CH(R^7)N(C(O)OR^8)-$, $-CH(R^7)N(SO_2R^8)-$, $-CH(R^7)C(=NOR^8)-$, $-CH(R^7)C(O)-$, $-CH(R^7)CH(OR^8)-$, $-CH(R^7)C(O)N(R^8)-$, $-CH(R^7)N(R^8)C(O)-$, $-CH(R^7)N(R^8)S(O)-$, $-CH(R^7)N(R^8)S(O)_2-$, $-CH(R^7)OC(O)N(R^8)-$, $-CH(R^7)N(R^8)C(O)N(R^{7a})-$, $-CH(R^7)NR^8C(O)O-$, $-CH(R^7)S(O)N(R^8)-$, $-CH(R^7)S(O)_2N(R^8)-$, $-CH(R^7)N(C(O)R^8)S(O)-$, $-CH(R^7)N(C(O)R^8)S(O)-$, $-CH(R^7)N(R^8)S(O)N(R^{7a})-$, $-CH(R^7)N(R^8)S(O)_2N(R^{7a})-$, $-CH(R^7)C(O)N(R^8)C(O)-$, $-CH(R^7)S(O)N(R^8)C(O)-$, $-CH(R^7)S(O)_2N(R^8)C(O)-$, $-CH(R^7)OS(O)N(R^8)-$, $-CH(R^7)OS(O)_2N(R^8)-$, $-CH(R^7)N(R^8)S(O)O-$, $-CH(R^7)N(R^8)S(O)_2O-$, $-CH(R^7)N(R^8)S(O)C(O)-$, $-CH(R^7)N(R^8)S(O)_2C(O)-$, $-CH(R^7)SON(C(O)R^8)-$, $-CH(R^7)SO_2N(C(O)R^8)-$, $-CH(R^7)N(R^8)SON(R^{7a})-$, $-CH(R^7)N(R^8)SO_2N(R^{7a})-$, $-CH(R^7)C(O)O-$, $-CH(R^7)N(R^8)P(OR^{7a})O-$, $-CH(R^7)N(R^8)P(OR^{7a})-$, $-CH(R^7)N(R^8)P(O)(OR^{7a})O-$, $-CH(R^7)N(R^8)P(O)(OR^{7a})-$, $-CH(R^7)N(C(O)R^8)P(OR^{7a})O-$, $-CH(R^7)N(C(O)R^8)P(OR^{7a})-$, $-CH(R^7)N(C(O)R^8)P(O)(OR^{7a})O-$, or $-CH(R^7)N(C(O)R^8)P(OR^{7a})-$;

R^5, R^6, G^{111}, and G^{1111} are each independently C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl,

heterocyclyl–C_{0-10}alkyl, heterocyclyl–C_{2-10}alkenyl, heterocyclyl–C_{2-10}alkynyl, aryl–C_{0-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, hetaryl–C_{0-10}alkyl, hetaryl–C_{2-10}alkenyl, or hetaryl–C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, $–CF_3$, $–OCF_3$, $–OR^{77}$, $–NR^{77}R^{87}$, $–C(O)R^{77}$, $–CO_2R^{77}$, $–CONR^{77}R^{87}$, $–NO_2$, –CN, $–S(O)_{j5a}R^{77}$, $–SO_2NR^{77}R^{87}$, $–NR^{77}C(=O)R^{87}$, $–NR^{77}C(=O)OR^{87}$, $–NR^{77}C(=O)NR^{78}R^{87}$, $–NR^{77}S(O)_{j5a}R^{87}$, $–C(=S)OR^{77}$, $–C(=O)SR^{77}$, $–NR^{77}C(=NR^{87})NR^{78}R^{88}$, $–NR^{77}C(=NR^{87})OR^{78}$, $–NR^{77}C(=NR^{87})SR^{78}$, $–OC(=O)OR^{77}$, $–OC(=O)NR^{77}R^{87}$, $–OC(=O)SR^{77}$, $–SC(=O)OR^{77}$, $–P(O)OR^{77}OR^{87}$, or $–SC(=O)NR^{77}R^{87}$ substituents;

or R^5 with R^6 are optionally taken together with the carbon atom to which they are attached to form a 3-10 membered saturated or unsaturated ring, wherein said ring is optionally substituted with one or more independent R^{69} substituents and wherein said ring optionally includes one or more heteroatoms;

R^7, R^{7a}, and R^8 are each independently acyl, C_{0-10}alkyl, C_{2-10}alkenyl, aryl, heteroaryl, heterocyclyl or cycloC_{3-10}alkyl, any of which is optionally substituted by one or more independent G^{111} substituents;

R^4 is C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, aryl, heteroaryl, cycloC_{3-10}alkyl, heterocyclyl, cycloC_{3-8}alkenyl, or heterocycloalkenyl, any of which is optionally substituted by one or more independent G^{41} substituents;

R^{69} is halo, $–OR^{78}$, –SH, $–NR^{78}R^{88}$, $–CO_2R^{78}$, $–C(=O)NR^{78}R^{88}$, $–NO_2$, –CN, $–S(O)_{j8}R^{78}$, $–SO_2NR^{78}R^{88}$, C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl–C_{0-10}alkyl, heterocyclyl–C_{2-10}alkenyl, or heterocyclyl–C_{2-10}alkynyl, any of which is optionally substituted with one or more independent halo, cyano, nitro, $–OR^{778}$, $–SO_2NR^{778}R^{888}$, or $–NR^{778}R^{888}$ substituents;

or R^{69} is aryl–C_{0-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, hetaryl–C_{0-10}alkyl, hetaryl–C_{2-10}alkenyl, hetaryl–C_{2-10}alkynyl, mono(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, mono(aryl)aminoC_{1-6}alkyl, di(aryl)aminoC_{1-6}alkyl, or –N(C_{1-6}alkyl)–C_{1-6}alkyl–aryl, any of which is optionally substituted with one or more

independent halo, cyano, nitro, $-OR^{778}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, C_{1-4}alkoxycarbonyl, $-C(=O)NR^{778}R^{888}$, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents;

or in the case of $-NR^{78}R^{88}$, R^{78} and R^{88} are optionally taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring, wherein said ring is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, C_{1-10}alkoxy, $-SO_2NR^{778}R^{888}$, or $-NR^{778}R^{888}$ substituents, and wherein said ring optionally includes one or more heteroatoms other than the nitrogen to which R^{78} and R^{88} are attached;

R^{77}, R^{78}, R^{87}, R^{88}, R^{778}, and R^{888} are each independently C_{0-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{1-10}alkoxyC_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, C_{1-10}alkylthioC_{1-10}alkyl, C_{1-10}alkylthioC_{2-10}alkenyl, C_{1-10}alkylthioC_{2-10}alkynyl, cycloC_{3-8}alkyl, cycloC_{3-8}alkenyl, cycloC_{3-8}alkylC_{1-10}alkyl, cycloC_{3-8}alkenylC_{1-10}alkyl, cycloC_{3-8}alkylC_{2-10}alkenyl, cycloC_{3-8}alkenylC_{2-10}alkenyl, cycloC_{3-8}alkylC_{2-10}alkynyl, cycloC_{3-8}alkenylC_{2-10}alkynyl, heterocyclyl–C_{0-10}alkyl, heterocyclyl–C_{2-10}alkenyl, heterocyclyl–C_{2-10}alkynyl, C_{1-10}alkylcarbonyl, C_{2-10}alkenylcarbonyl, C_{2-10}alkynylcarbonyl, C_{1-10}alkoxycarbonyl, C_{1-10}alkoxycarbonylC_{1-10}alkyl, monoC_{1-6}alkylaminocarbonyl, diC_{1-6}alkylaminocarbonyl, mono(aryl)aminocarbonyl, di(aryl)aminocarbonyl, or C_{1-10}alkyl(aryl)aminocarbonyl, any of which is optionally substituted with one or more independent halo, cyano, hydroxy, nitro, C_{1-10}alkoxy, $-SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl)$, or $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$ substituents;

or R^{77}, R^{78}, R^{87}, R^{88}, R^{778}, and R^{888} are each independently aryl–C_{0-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, hetaryl–C_{0-10}alkyl, hetaryl–C_{2-10}alkenyl, hetaryl–C_{2-10}alkynyl, mono(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, mono(aryl)aminoC_{1-6}alkyl, di(aryl)aminoC_{1-6}alkyl, or $-N(C_{1-6}alkyl)-C_{1-6}alkyl-aryl$, any of which is optionally substituted with one or more independent halo, cyano, nitro, $-O(C_{0-4}alkyl)$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, C_{1-4}alkoxycarbonyl, $-CON(C_{0-4}alkyl)(C_{0-10}alkyl)$, $-SO_2N(C_{0-4}alkyl)(C_{0-4}alkyl)$, or $-N(C_{0-4}alkyl)(C_{0-4}alkyl)$ substituents;

n, m, j1, j1a, j2a, j4, j4a, j5a, j7, and j8 are each independently 0, 1, or 2; and

aa and bb are each independently 0 or 1.

2. The compound of claim 1, wherein X_{11} and X_{16} are N; X_{12}, X_{13}, X_{14}, and X_{15} are $C–(E^{11})_{bb}$.

3. The compound of claim 1, wherein X_{14} and X_{16} are N; X_{11}, X_{12}, X_{13}, and X_{15} are $C–(E^{11})_{bb}$.

4. The compound of claim 1, wherein X_{15} and X_{16} are N; X_{11}, X_{12}, X_{13}, and X_{14} are $C–(E^{11})_{bb}$.

5. The compound of claim 1, wherein X_{11} is N; X_{12}, X_{13}, X_{14}, X_{15}, and X_{16} are $C–(E^{11})_{bb}$.

6. The compound of claim 1, wherein X_{16} is N; X_{11}, X_{12}, X_{13}, X_{14}, and X_{15} are $C–(E^{11})_{bb}$.

7. The compound of claim 1, wherein X_{16} is N; X_{11}, X_{12}, X_{13}, and X_{15} are C-H; X_{14} is $C-(E^{11})_{bb}$, bb is 1 and E^{11} is OR^2, C_{0-10}alkyl, aryl-C_{0-10}alkyl, hetaryl-C_{0-10}alkyl.

8. The compound of claim 1, wherein X_{16} is N; X_{12}, X_{13}, X_{14}, and X_{15} are C-H; X_{11} is $C-(E^{11})_{bb}$, bb is 1 and E^{11} is halo.

9. The compound of Claim 8, wherein E^{11} is F.

10. The compound of claim 1, wherein X_2 and X_4 are N; X_1 and X_5 are $C–(E^1)_{aa}$; and X_3, X_6, and X_7 are C.

11. The compound of claim 1, wherein X_2 and X_6 are N; X_1 and X_5 are $C–(E^1)_{aa}$; and X_3, X_4, and X_7 are C.

12. The compound of claim 1, wherein X_3 and X_5 are N; X_1 and X_2 are $C–(E^1)_{aa}$; and X_4, X_6, and X_7 are C.

13. The compound of claim 1, wherein X_2, X_3, and X_5 are N; X_1 is $C–(E^1)_{aa}$; and X_4, X_6 and X_7 are C.

14. The compound of claim 1, wherein X_2, X_4, and X_5 are N; X_1 is C–$(E^1)_{aa}$; and X_3, X_6, and X_7 are C.

15. The compound of claim 12, wherein any one of X_{11-16} is N.

16. The compound of claim 12, wherein G^1 is $–OR^2$, $–NR^2R^3(R^{2a})_{j1}$, $–S(O)_{j1}R^2$, C_{0-10}alkyl, cycloC_{3-8}alkyl, heterocyclyl–C_{0-10}alkyl, any of which is optionally substituted with one or more independent halo, oxo, $–CF_3$, $–OCF_3$, $–OR^{222}$, $–NR^{222}R^{333}(R^{222a})_{j1a}$, $–C(=O)R^{222}$, $–CO_2R^{222}$, $–C(=O)NR^{222}R^{333}$, $–NO_2$, –CN, $–S(=O)_{j1a}R^{222}$, $–SO_2NR^{222}R^{333}$, $–NR^{222}C(=O)R^{333}$, $–NR^{222}C(=O)OR^{333}$, $–NR^{222}C(=O)NR^{333}R^{222a}$, $–NR^{222}S(O)_{j1a}R^{333}$, $–C(=S)OR^{222}$, $–C(=O)SR^{222}$, $–NR^{222}C(=NR^{333})NR^{222a}R^{333a}$, $–NR^{222}C(=NR^{333})OR^{222a}$, $–NR^{222}C(=NR^{333})SR^{222a}$, $–OC(=O)OR^{222}$, $–OC(=O)NR^{222}R^{333}$, $–OC(=O)SR^{222}$, $–SC(=O)OR^{222}$, or $–SC(=O)NR^{222}R^{333}$ substituents;

or G^1 is aryl–C_{0-10}alkyl or hetaryl–C_{0-10}alkyl, any of which is optionally substituted with one or more independent halo, $–CF_3$, $–OCF_3$, $–OR^{222}$, $–NR^{222}R^{333}(R^{222a})_{j2a}$, $–C(O)R^{222}$, $–CO_2R^{222}$, $–C(=O)NR^{222}R^{333}$, $–NO_2$, –CN, $–S(O)_{j2a}R^{222}$, $–SO_2NR^{222}R^{333}$, $–NR^{222}C(=O)R^{333}$, $–NR^{222}C(=O)OR^{333}$, $–NR^{222}C(=O)NR^{333}R^{222a}$, $–NR^{222}S(O)_{j2a}R^{333}$, $–C(=S)OR^{222}$, $–C(=O)SR^{222}$, $–NR^{222}C(=NR^{333})NR^{222a}R^{333a}$, $–NR^{222}C(=NR^{333})OR^{222a}$, $–NR^{222}C(=NR^{333})SR^{222a}$, $–OC(=O)OR^{222}$, $–OC(=O)NR^{222}R^{333}$, $–OC(=O)SR^{222}$, $–SC(=O)OR^{222}$, or $–SC(=O)NR^{222}R^{333}$ substituents.

17. The compound of claim 12 wherein R^1 is cycloC_{3-10}alkyl, bicycloC_{5-10}alkyl, aryl, heteroaralkyl, heterocyclyl, heterobicycloC_{5-10}alkyl, spiroalkyl, or heterospiroalkyl any of which is optionally substituted by one or more independent G^{11} substituents.

18. The compound of claim 12 wherein G^{11} is oxo, $–OCF_3$, $–OR^{21}$, $–NR^{21}R^{31}(R^{2a1})_{j4}$, $–C(O)R^{21}$, $–CO_2R^{21}$, $–C(=O)NR^{21}R^{31}$, –CN, $–SO_2NR^{21}R^{31}$, $–NR^{21}(C=O)R^{31}$, $–NR^{21}C(=O)OR^{31}$, $–NR^{21}C(=O)NR^{31}R^{2a1}$, $–NR^{21}S(O)_{j4}R^{31}$, $–OC(=O)NR^{21}R^{31}$, C_{0-10}alkyl, C_{1-10}alkoxyC_{1-10}alkyl, cycloC_{3-8}alkylC_{1-10}alkyl, heterocyclyl–C_{0-10}alkyl, any of which is optionally substituted with one or more independent halo, oxo, $–CF_3$, $–OCF_3$, $–OR^{2221}$, $–NR^{2221}R^{3331}(R^{222a1})_{j4a}$, $–C(O)R^{2221}$, $–CO_2R^{2221}$, $–C(=O)NR^{2221}R^{3331}$, $–NO_2$, –CN,

$-S(O)_{j4a}R^{2221}$, $-SO_2NR^{2221}R^{3331}$, $-NR^{2221}C(=O)R^{3331}$, $-NR^{2221}C(=O)OR^{3331}$, $-NR^{2221}C(=O)NR^{3331}R^{222a1}$, $-NR^{2221}S(O)_{j4a}R^{3331}$, $-C(=S)OR^{2221}$, $-C(=O)SR^{2221}$, $-NR^{2221}C(=NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}C(=NR^{3331})OR^{222a1}$, $-NR^{2221}C(=NR^{3331})SR^{222a1}$, $-OC(=O)OR^{2221}$, $-OC(=O)NR^{2221}R^{3331}$, $-OC(=O)SR^{2221}$, $-SC(=O)OR^{2221}$, $-P(O)OR^{2221}OR^{3331}$, or $-SC(=O)NR^{2221}R^{3331}$ substituents;

or G^{11} is hetaryl–C_{0-10}alkyl, any of which is optionally substituted with one or more independent halo, $-CF_3$, $-OCF_3$, $-OR^{2221}$, $-NR^{2221}R^{3331}(R^{222a1})_{j5a}$, $-C(O)R^{2221}$, $-CO_2R^{2221}$, $-C(=O)NR^{2221}R^{3331}$, $-NO_2$, $-CN$, $-S(O)_{j5a}R^{2221}$, $-SO_2NR^{2221}R^{3331}$, $-NR^{2221}C(=O)R^{3331}$, $-NR^{2221}C(=O)OR^{3331}$, $-NR^{2221}C(=O)NR^{3331}R^{222a1}$, $-NR^{2221}S(O)_{j5a}R^{3331}$, $-C(=S)OR^{2221}$, $-C(=O)SR^{2221}$, $-NR^{2221}C(=NR^{3331})NR^{222a1}R^{333a1}$, $-NR^{2221}C(=NR^{3331})OR^{222a1}$, $-NR^{2221}C(=NR^{3331})SR^{222a1}$, $-OC(=O)OR^{2221}$, $-OC(=O)NR^{2221}R^{3331}$, $-OC(=O)SR^{2221}$, $-SC(=O)OR^{2221}$, $-P(O)OR^{2221}OR^{3331}$, or $-SC(=O)NR^{2221}R^{3331}$ substituents;

or G^{11} is C, taken together with the carbon to which it is attached forms a C=C double bond which is substituted with R^5 and G^{111}.

19. A compound according to claim 1 is selected from: 1-(2-Phenyl-quinolin-7-yl)-3-piperidin-4-ylmethyl-imidazo[1,5-a]pyrazin-8-ol, 3-Cyclobutyl-1-(2-phenyl-quinolin-7-yl)-imidazo[1,5-a]pyrazin-8-ol, 3-(3-Hydroxymethyl-cyclobutyl)-1-(2-phenyl-quinolin-7-yl)-imidazo[1,5-a] pyrazin-8-ol, 3-[3-(4-Methyl-piperazin-1-yl)-cyclobutyl]-1-(2-phenyl-quinolin-7-yl)-imidazo[1,5-a]pyrazin-8-ol, 3-(3-Morpholin-4-yl-cyclobutyl)-1-(2-phenyl-quinolin-7-yl)-imidazo[1,5-a]pyrazin-8-ol, 3-{3-[(2,4-Dimethoxy-benzyl)-methyl-amino]-cyclobutyl}-1-(2-phenyl-quinolin-7-yl)-7H-imidazo[1,5-a]pyrazin-8-ol or a pharmaceutically acceptable salt thereof.

20. A method of treating a patient having a condition which is mediated by protein kinase activity, said method comprising administering to the patient a therapeutically effective amount of a compound of Formula I according to claim 1 or a pharmaceutically acceptable salt thereof.

21. The method of claim 20 wherein said protein kinase is IGF-IR.

22. The method of claim 20 wherein the condition mediated by protein kinase activity is a hyperproliferative disorder.

23. The method of claim 20 wherein the protein kinase is a protein serine/threonine kinase or a protein tyrosine kinase.

24. The method of claim 20 wherein the condition mediated by protein kinase activity is cancer.

25. The method of claim 24 wherein the cancer is a solid tumor, a sarcoma, fibrosarcoma, osteoma, melanoma, retinoblastoma, a rhabdomyosarcoma, glioblastoma, neuroblastoma, teratocarcinoma, an hematopoietic malignancy, or malignant ascites.

26. The method of claim 24 wherein the cancer is Kaposi's sarcoma, Hodgkin's disease, lymphoma, myeloma, or leukemia.

27. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

28. A method of treating a patient having a condition which is mediated by protein kinase activity, said method comprising administering to the patient a therapeutically effective amount of a pharmaceutical composition according to claim 27.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/4985 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2006/084654 A1 (BECK PATRICIA A [US] ET AL DONG HAN-QING [US] ET AL) 20 April 2006 (2006-04-20) the whole document	1,6,12, 15-28
A	WO 2007/087395 A (OSI PHARM INC [US]; CREW ANDREW PHILIP [US]; WERNER DOUGLAS S [US]; TA) 2 August 2007 (2007-08-02) the whole document	1,6,12, 15-28
A	WO 2007/131991 A (GALAPAGOS N V [BE]; BRYS REGINALD CHRISTOPHE XAVIE [BE]; EDWARDS PAUL) 22 November 2007 (2007-11-22) the whole document	1,6,12, 15-28
A	WO 2006/012422 A (OSI PHARM INC [US]; CREW ANDREW PHILIP [US]; MULVIHILL MARK JOSEPH [US]) 2 February 2006 (2006-02-02) the whole document	1,6,12, 15-28

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

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 April 2009	08/04/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Fax: (+31–70) 340–3016	Fritz, Martin

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 2-5,7-11,13-14

The present claims 1-18 and 20-28 relate to an extremely large number of possible products and their use. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the products claimed, as there are only 3 specific compounds actually exemplified in the description.
The non-compliance with the substantive provisions is to such an extent, that the search had to be restricted accordinly (PCT Guidelines 9.19 and 9.23).

Consequently claims 2-5, 7-11 and 13-14 were not searched at all, and the search of claims 1,6,12,15-18 and 20-28 was restricted to those claimed compounds which appear to be supported and a generalisation of their structural formulae, namely those compounds I, wherein X3, X5 and X16 are N, X1, X2, X4, X6, X11-X15 are C, in other words quinolin-7-yl-substituted imidazo[1,5-a]pyrazin-8-ol-derivatives.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/031177

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

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

1. [X] Claims Nos.: 2-5,7-11,13-14
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/031177

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