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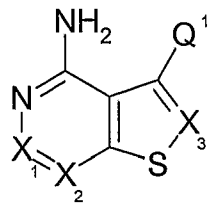
(54) Title: 6,6-BICYCLIC RING SUBSTITUTED SULFUR CONTAINING HETEROBICYCLIC PROTEIN KINASE INHIBITORS



(I)

(57) Abstract: Compounds of the formula (I) and pharmaceutically acceptable salts thereof, wherein X_1, X_2, X_3, and Q^1 are defined herein, 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.

TITLE OF THE INVENTION

6,6-BICYCLIC RING SUBSTITUTED SULFUR CONTAINING HETEROBICYCLIC PROTEIN KINASE INHIBITORS

This application claims the benefit of U.S. Application No. 60/706,324 filed August 8, 2005, which is herein incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[1] The present invention is directed to novel sulfur-containing heterobicyclic compounds, their salts, compositions comprising them, and combined treatment of patients with those compounds and an epidermal growth factor receptor (EGFR) kinase inhibitor. In particular, the present invention is directed to novel sulfur-containing 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 IGF-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 selectivity. 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. Thienopyrimidines and isothiazolopyrimidines (International Patent Publication No. WO 2003/080625) have been described as inhibitors of the tyrosine kinases KDR and Tie-2 and thereby inhibiting angiogenesis. Thienopyridines and furopyridines (International Patent Publication No. WO 2005/010009; US Patent Application Publication No. US 2005043347; International Patent Publication No. WO 2004/100947) have been described as inhibitors of the tyrosine kinases KDR and Lck. 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 that 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.

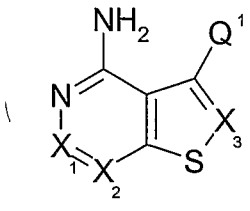
[17] IGF-1R performs important roles in cell division, development, and metabolism, and in its activated state, plays a role in oncogenesis and suppression of apoptosis. IGF-1R is known to be overexpressed in a number of cancer cell lines (IGF-1R overexpression is linked to acromegaly and to cancer of 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.

[19] **SUMMARY OF THE INVENTION**

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

[21]

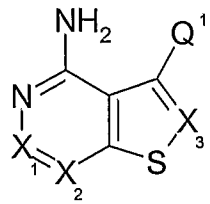


I

[22] 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.

[23] **DETAILED DESCRIPTION OF THE INVENTION**

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

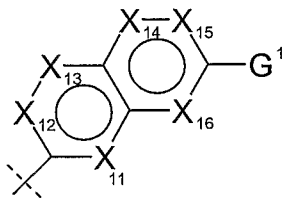


I

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

[26] X_1, X_2, and X_3 are each independently N or C–$(E^1)_{aa}$;

[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] 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–$C_{0\text{-}10}$alkyl, heterocyclyl–$C_{2\text{-}10}$alkenyl, or heterocyclyl–$C_{2\text{-}10}$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;

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

[32] or E^1, E^{11}, G^1, or G^{41} optionally independently is aryl–$C_{0\text{-}10}$alkyl, aryl–$C_{2\text{-}10}$alkenyl, aryl–$C_{2\text{-}10}$alkynyl, hetaryl–$C_{0\text{-}10}$alkyl, hetaryl–$C_{2\text{-}10}$alkenyl, or hetaryl–$C_{2\text{-}10}$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;

[33] R^2, R^{2a}, R^3, R^{3a}, R^{222}, R^{222a}, R^{333}, and R^{333a} 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;

[34] or in the case of $-NR^2R^3(R^{2a})_{j1}$ or $-NR^{222}R^{333}(R^{222a})_{j1a}$ or $-NR^{222}R^{333}(R^{222a})_{j2a}$, then R^2 and R^3, or R^{222} and R^{333}, 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}, are attached;

[35] 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 $-CH(R^7)N(C(O)R^8)P(OR^{7a})-$;

[36] 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;

[37] 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;

[38] 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;

[39] 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;

[40] 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;

[41] 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;

[42] 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;

[43] 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;

[44] 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;

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

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

[47]

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

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

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

[51] In a fourth 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 and X_2 are C–$(E^1)_{aa}$; and the other variables are described as above for Formula I.

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

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

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

[55] In an eighth aspect of the present invention, a compound is represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein X_1, X_2, and X_3 are N; and the other variables are described as above for Formula I.

[56]

[57] The following embodiments refer to all of the eight aspects above:

[58] 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.

[59] 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.

[60] 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.

[61] 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.

[62] 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.

[63] 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.

[64] 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.

[65] 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.

[66] 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.

[67] 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.

[68] 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.

[69] 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.

[70] 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.

[71] 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.

[72] 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.

[73] 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.

[74] 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.

[75] 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.

[76] 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.

[77] 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.

[78] 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.

[79] 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.

[80] 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.

[81] 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.

[82] 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.

[83] 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.

[84] 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.

[85] 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.

[86] 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.

[87] 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.

[88] 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.

[89] 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.

[90] 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.

[91] 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.

[92] 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.

[93] 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.

[94] 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.

[95] 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.

[96] 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.

[97] 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.

[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_{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.

[99]

[100] Advantageous embodiments of the above aspects include:

[101] 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.

[102] 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.

[103] 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.

[104] 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.

[105] 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.

[106]

[107] The compounds of the present invention include compounds represented by Formula I above, or a pharmaceutically acceptable salt thereof, wherein 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};

[108] 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; and

[109] wherein X_1, X_2, and X_3 are C–$(E^1)_{aa}$; or

[110] wherein X_1 is N; X_2 and X_3 are C–$(E^1)_{aa}$; or

[111] wherein X_2 is N; X_1 and X_3 are C–$(E^1)_{aa}$; or

[112] wherein X_3 is N; X_1 and X_2 are C–$(E^1)_{aa}$; or

[113] wherein X_1 and X_2 are N; X_3 is C–$(E^1)_{aa}$; or

[114] wherein X_1 and X_3 are N; X_2 is C–$(E^1)_{aa}$; or

[115] wherein X_2 and X_3 are N; X_1 is C–$(E^1)_{aa}$; or

[116] wherein X_1, X_2, and X_3 are N; or

[117] wherein any one of $X_{11\text{-}16}$ is N; or

[118] wherein any two of $X_{11\text{-}16}$ is N; or

[119] wherein any three of $X_{11\text{-}16}$ is N; or

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

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

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

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

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

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

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

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

[128] wherein G^1 is $-OR^2$, $-NR^2R^3(R^{2a})_{j1}$, $-S(O)_{j1}R^2$, $C_{0\text{-}10}$alkyl, cyclo$C_{3\text{-}8}$alkyl, heterocyclyl–$C_{0\text{-}10}$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–$C_{0\text{-}10}$alkyl or hetaryl–$C_{0\text{-}10}$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

[129] wherein G^1 is C_{0-10}alkyl, cycloC_{3-8}alkyl, or 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

[130] wherein 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

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

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

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

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

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

[136] wherein E^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

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

[138] wherein E^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

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

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

[141] wherein E^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

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

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

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

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

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

[147] 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}; or

[148] 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, $-OR^{2221}$, or $-NR^{2221}R^{3331}(R^{222a1})_{j4a}$ 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

[149] wherein G^{11} is oxo, $-OR^{21}$, $-NR^{21}R^{31}(R^{2a1})_{j4}$, $-CO_2R^{21}$, $-C(=O)NR^{21}R^{31}$, C_{0-10}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

[150] wherein G^{11} is oxo, $-OR^{21}$, $-NR^{21}R^{31}(R^{2a1})_{j4}$, $-CO_2R^{21}$, $-C(=O)NR^{21}R^{31}$, C_{0-10}alkyl, heterocyclyl–C_{0-10}alkyl, any of which is optionally substituted with one or more independent halo, oxo, $-OR^{2221}$, or $-NR^{2221}R^{3331}(R^{222a1})_{j4a}$ 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

[151] 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}; or

[152] wherein E^1 is C_{0-10}alkyl, 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

[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 any one of $X_{11\text{-}16}$ is N; or

[155] wherein any two of $X_{11\text{-}16}$ is N; or

[156] wherein any three of $X_{11\text{-}16}$ is N; or

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

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

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

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

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

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

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

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

[165] 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

[166] wherein G^1 is C_{0-10}alkyl, cycloC_{3-8}alkyl, or 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

[167] wherein 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

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

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

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

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

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

[173] wherein E^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

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

[175] wherein E^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

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

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

[178] wherein E^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

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

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

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

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

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

[184] 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}; or

[185] 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, $-OR^{2221}$, or $-NR^{2221}R^{3331}(R^{222a1})_{j4a}$ 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

[186] wherein G^{11} is oxo, $-OR^{21}$, $-NR^{21}R^{31}(R^{2a1})_{j4}$, $-CO_2R^{21}$, $-C(=O)NR^{21}R^{31}$, C_{0-10}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

[187] wherein G^{11} is oxo, $-OR^{21}$, $-NR^{21}R^{31}(R^{2a1})_{j4}$, $-CO_2R^{21}$, $-C(=O)NR^{21}R^{31}$, C_{0-10}alkyl, heterocyclyl–C_{0-10}alkyl, any of which is optionally substituted with one or more independent halo, oxo, $-OR^{2221}$, or $-NR^{2221}R^{3331}(R^{222a1})_{j4a}$ 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

[188] 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}; or

[189] wherein E^1 is C_{0-10}alkyl, 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

[190] 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

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

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

[193] wherein any three of $X_{11\text{-}16}$ is N; or

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

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

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

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

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

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

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

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

[202] wherein G^1 is $-OR^2$, $-NR^2R^3(R^{2a})_{j1}$, $-S(O)_{j1}R^2$, $C_{0\text{-}10}$alkyl, cyclo$C_{3\text{-}8}$alkyl, heterocyclyl–$C_{0\text{-}10}$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–$C_{0\text{-}10}$alkyl or hetaryl–$C_{0\text{-}10}$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

[203] wherein G^1 is $C_{0\text{-}10}$alkyl, cyclo$C_{3\text{-}8}$alkyl, or heterocyclyl–$C_{0\text{-}10}$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–$C_{0\text{-}10}$alkyl or hetaryl–$C_{0\text{-}10}$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

[204] wherein 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

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

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

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

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

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

[210] wherein E^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

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

[212] wherein E^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

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

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

[215] wherein E^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

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

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

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

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

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

[221] 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}; or

[222] 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, $-OR^{2221}$, or $-NR^{2221}R^{3331}(R^{222a1})_{j4a}$ 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

[223] wherein G^{11} is oxo, $-OR^{21}$, $-NR^{21}R^{31}(R^{2a1})_{j4}$, $-CO_2R^{21}$, $-C(=O)NR^{21}R^{31}$, C_{0-10}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

[224] wherein G^{11} is oxo, $-OR^{21}$, $-NR^{21}R^{31}(R^{2a1})_{j4}$, $-CO_2R^{21}$, $-C(=O)NR^{21}R^{31}$, C_{0-10}alkyl, heterocyclyl–C_{0-10}alkyl, any of which is optionally substituted with one or more independent halo, oxo, $-OR^{2221}$, or $-NR^{2221}R^{3331}(R^{222a1})_{j4a}$ 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

[225] 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}; or

[226] wherein E^1 is C_{0-10}alkyl, 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

[227] 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

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

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

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

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

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

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

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

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

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

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

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

[239] 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

[240] wherein G^1 is C_{0-10}alkyl, cycloC_{3-8}alkyl, or 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

[241] wherein 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

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

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

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

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

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

[247] wherein E^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

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

[249] wherein E^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

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

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

[252] wherein E^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

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

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

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

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

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

[258] 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}; or

[259] 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, $-OR^{2221}$, or $-NR^{2221}R^{3331}(R^{222a1})_{j4a}$ 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

[260] wherein G^{11} is oxo, $-OR^{21}$, $-NR^{21}R^{31}(R^{2a1})_{j4}$, $-CO_2R^{21}$, $-C(=O)NR^{21}R^{31}$, C_{0-10}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

[261] wherein G^{11} is oxo, $-OR^{21}$, $-NR^{21}R^{31}(R^{2a1})_{j4}$, $-CO_2R^{21}$, $-C(=O)NR^{21}R^{31}$, C_{0-10}alkyl, heterocyclyl–C_{0-10}alkyl, any of which is optionally substituted with one or more independent halo, oxo, $-OR^{2221}$, or $-NR^{2221}R^{3331}(R^{222a1})_{j4a}$ 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

[262] 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}; or

[263] wherein E^1 is C_{0-10}alkyl, 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

[264] 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

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

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

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

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

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

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

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

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

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

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

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

[276] 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

[277] wherein G^1 is C_{0-10}alkyl, cycloC_{3-8}alkyl, or 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

[278] wherein 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

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

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

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

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

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

[284] wherein E^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

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

[286] wherein E^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

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

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

[289] wherein E^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

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

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

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

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

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

[295] 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}; or

[296] 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, $-OR^{2221}$, or $-NR^{2221}R^{3331}(R^{222a1})_{j4a}$ 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

[297] wherein G^{11} is oxo, $-OR^{21}$, $-NR^{21}R^{31}(R^{2a1})_{j4}$, $-CO_2R^{21}$, $-C(=O)NR^{21}R^{31}$, C_{0-10}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

[298] wherein G^{11} is oxo, $-OR^{21}$, $-NR^{21}R^{31}(R^{2a1})_{j4}$, $-CO_2R^{21}$, $-C(=O)NR^{21}R^{31}$, C_{0-10}alkyl, heterocyclyl–C_{0-10}alkyl, any of which is optionally substituted with one or more independent halo, oxo, $-OR^{2221}$, or $-NR^{2221}R^{3331}(R^{222a1})_{j4a}$ 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

[299] 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}; or

[300] wherein E^1 is C_{0-10}alkyl, 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

[301] 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; and

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

[303]

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

[305] wherein X_1, X_2, and X_3 are C–$(E^1)_{aa}$; or

[306] wherein X_1 is N and wherein X_2 and X_3 are C–$(E^1)_{aa}$; or

[307] wherein X_2 is N and wherein X_1 and X_3 are C–$(E^1)_{aa}$; or

[308] wherein X_3 is N and wherein X_1 and X_2 are C–$(E^1)_{aa}$; or

[309] wherein X_1 and X_2 are N and X_3 is C–$(E^1)_{aa}$; or

[310] wherein X_1 and X_3 are N and X_2 is C–$(E^1)_{aa}$; or

[311] wherein X_2 and X_3 are N and X_1 is C–$(E^1)_{aa}$; or

[312] wherein X_1, X_2, and X_3 are N; or

[313] wherein X_1, X_2, and X_3 are C–$(E^1)_{aa}$; and wherein any one, two, or three of $X_{11\text{-}16}$ is N; or

[314] wherein X_1, X_2, and X_3 are C–$(E^1)_{aa}$; and wherein any one of X_{11}, X_{14}, X_{15}, or X_{16} is N; or

[315] wherein X_1, X_2, and X_3 are C–$(E^1)_{aa}$; and wherein any two of X_{11}, X_{14}, X_{15}, or X_{16} is N; or

[316] wherein X_1, X_2, and X_3 are C–$(E^1)_{aa}$; and wherein X_{11} or X_{16} is N; or

[317] wherein X_1 is N and wherein X_2 and X_3 are C–$(E^1)_{aa}$; and wherein any one, two, or three of $X_{11\text{-}16}$ is N; or

[318] wherein X_1 is N and wherein X_2 and X_3 are C–$(E^1)_{aa}$; and wherein any one of X_{11}, X_{14}, X_{15}, or X_{16} is N; or

[319] wherein X_1 is N and wherein X_2 and X_3 are C–$(E^1)_{aa}$; and wherein any two of X_{11}, X_{14}, X_{15}, or X_{16} is N; or

[320] wherein X_1 is N and wherein X_2 and X_3 are C–$(E^1)_{aa}$; and wherein X_{11} or X_{16} is N; or

[321] wherein X_2 is N and wherein X_1 and X_3 are C–$(E^1)_{aa}$; and wherein any one, two, or three of $X_{11\text{-}16}$ is N; or

[322] wherein X_2 is N and wherein X_1 and X_3 are C–$(E^1)_{aa}$; and wherein any one of X_{11}, X_{14}, X_{15}, or X_{16} is N; or

[323] wherein X_2 is N and wherein X_1 and X_3 are C–$(E^1)_{aa}$; and wherein any two of X_{11}, X_{14}, X_{15}, or X_{16} is N; or

[324] wherein X_2 is N and wherein X_1 and X_3 are C–$(E^1)_{aa}$; and wherein X_{11} or X_{16} is N; or

[325] wherein X_3 is N and wherein X_1 and X_2 are C–$(E^1)_{aa}$; and wherein any one, two, or three of $X_{11\text{-}16}$ is N; or

[326] wherein X_3 is N and wherein X_1 and X_2 are C–$(E^1)_{aa}$; and wherein any one of X_{11}, X_{14}, X_{15}, or X_{16} is N; or

[327] wherein X_3 is N and wherein X_1 and X_2 are C–$(E^1)_{aa}$; and wherein any two of X_{11}, X_{14}, X_{15}, or X_{16} is N; or

[328] wherein X_3 is N and wherein X_1 and X_2 are C–$(E^1)_{aa}$; and wherein X_{11} or X_{16} is N; or

[329] wherein X_1 and X_2 are N and X_3 is C–$(E^1)_{aa}$; and wherein any one, two, or three of $X_{11\text{-}16}$ is N; or

[330] wherein X_1 and X_2 are N and X_3 is C–$(E^1)_{aa}$; and wherein any one of X_{11}, X_{14}, X_{15}, or X_{16} is N; or

[331] wherein X_1 and X_2 are N and X_3 is C–$(E^1)_{aa}$; and wherein any two of X_{11}, X_{14}, X_{15}, or X_{16} is N; or

[332] wherein X_1 and X_2 are N and X_3 is C–$(E^1)_{aa}$; and wherein X_{11} or X_{16} is N.

[333] wherein X_1 and X_3 are N and X_2 is C–$(E^1)_{aa}$; and wherein any one, two, or three of $X_{11\text{-}16}$ is N; or

[334] wherein X_1 and X_3 are N and X_2 is C–$(E^1)_{aa}$; and wherein any one of X_{11}, X_{14}, X_{15}, or X_{16} is N; or

[335] wherein X_1 and X_3 are N and X_2 is C–$(E^1)_{aa}$: and wherein any two of X_{11}, X_{14}, X_{15}, or X_{16} is N; or

[336] wherein X_1 and X_3 are N and X_2 is C–$(E^1)_{aa}$: and wherein X_{11} or X_{16} is N; or

[337] wherein X_2 and X_3 are N and X_1 is C–$(E^1)_{aa}$; and wherein any one, two, or three of $X_{11\text{-}16}$ is N; or

[338] wherein X_2 and X_3 are N and X_1 is C–$(E^1)_{aa}$; and wherein any one of X_{11}, X_{14}, X_{15}, or X_{16} is N; or

[339] wherein X_2 and X_3 are N and X_1 is C–$(E^1)_{aa}$; and wherein any two of X_{11}, X_{14}, X_{15}, or X_{16} is N; or

[340] wherein X_2 and X_3 are N and X_1 is C–$(E^1)_{aa}$; and wherein X_{11} or X_{16} is N.

[341] wherein X_1, X_2, and X_3 are N; and wherein any one, two, or three of $X_{11\text{-}16}$ is N; or

[342] wherein X_1, X_2, and X_3 are N; and wherein any one of X_{11}, X_{14}, X_{15}, or X_{16} is N; or

[343] wherein X_1, X_2, and X_3 are N; and wherein any two of X_{11}, X_{14}, X_{15}, or X_{16} is N; or

[344] wherein X_1, X_2, and X_3 are N; and wherein X_{11} or X_{16} is N; or

[345] wherein X_1, X_2, and X_3 are C–$(E^1)_{aa}$; and wherein G^1 is $-OR^2$, $-NR^2R^3(R^{2a})_{j1}$, $-S(O)_{j1}R^2$, $C_{0\text{-}10}$alkyl, cyclo$C_{3\text{-}8}$alkyl, heterocyclyl–$C_{0\text{-}10}$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–$C_{0\text{-}10}$alkyl or hetaryl–$C_{0\text{-}10}$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

[346] wherein X_1 is N and wherein X_2 and X_3 are $C-(E^1)_{aa}$; and 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

[347] wherein X_2 is N and wherein X_1 and X_3 are $C-(E^1)_{aa}$; and 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

[348] wherein X_3 is N and wherein X_1 and X_2 are $C-(E^1)_{aa}$; and 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

[349] wherein X_1 and X_2 are N and X_3 is C–$(E^1)_{aa}$; and 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

[350] wherein X_1 and X_3 are N and X_2 is C–$(E^1)_{aa}$; and 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

[351] wherein X_2 and X_3 are N and X_1 is $C-(E^1)_{aa}$; and 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

[352] wherein X_1, X_2, and X_3 are N; and 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

[353] wherein X_1, X_2, and X_3 are $C-(E^1)_{aa}$; and wherein any one, two, or three of X_{11-16} is N; and 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

[354] wherein X_1 is N and wherein X_2 and X_3 are C–$(E^1)_{aa}$; and wherein any one, two, or three of X_{11-16} is N; and 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

[355] wherein X_2 is N and wherein X_1 and X_3 are C–$(E^1)_{aa}$; and wherein any one, two, or three of X_{11-16} is N; and 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

[356] wherein X_3 is N and wherein X_1 and X_2 are $C-(E^1)_{aa}$; and wherein any one, two, or three of X_{11-16} is N; and 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

[357] wherein X_1 and X_2 are N and X_3 is $C-(E^1)_{aa}$; and wherein any one, two, or three of X_{11-16} is N; and 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

[358] wherein X_1 and X_3 are N and X_2 is $C-(E^1)_{aa}$; and wherein any one, two, or three of X_{11-16} is N; and 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

[359] wherein X_2 and X_3 are N and X_1 is C–$(E^1)_{aa}$; and wherein any one, two, or three of X_{11-16} is N; and 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

[360] wherein X_1, X_2, and X_3 are N; and wherein any one, two, or three of X_{11-16} is N; and 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; and

[361] wherein, in each case, the other variables are as defined as above for Formula 1.

[362] The present invention includes 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 or a pharmaceutically acceptable salt thereof.

[363] The present invention includes 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 or a pharmaceutically acceptable salt thereof wherein said protein kinase is IGF-IR.

[364] The present invention includes 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 or a pharmaceutically acceptable salt thereof wherein the condition mediated by protein kinase activity is a hyperproliferative disorder.

[365] The present invention includes 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 or a pharmaceutically acceptable salt thereof wherein the activity of said protein kinase influences angiogenesis, vascular permeability, immune response, cellular apoptosis, tumor growth, or inflammation.

[366] The present invention includes 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 or a pharmaceutically acceptable salt thereof wherein the protein kinase is a protein serine/threonine kinase or a protein tyrosine kinase.

[367] The present invention includes 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 or a pharmaceutically acceptable salt thereof wherein the condition mediated by protein kinase activity is one or more ulcers; or one or more ulcers caused by a bacterial or fungal infection; or Mooren ulcers; or one or more ulcers which are a symptom of ulcerative colitis.

[368] The present invention includes 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 or a pharmaceutically acceptable salt thereof wherein the condition mediated by protein kinase activity is Lyme disease, sepsis or infection by Herpes simplex, Herpes Zoster, human immunodeficiency virus, parapoxvirus, protozoa, toxoplasmosis, von Hippel Lindau disease, pemphigoid, psoriasis, Paget's disease, polycystic kidney

disease, 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, ischemia, ovarian hyperstimulation syndrome, preeclainpsia, menometrorrhagia, endometriosis, chronic inflammation, systemic lupus, glomerulonephritis, synovitis, inflammatory bowel disease, Crohn's disease, glomerulonephritis, rheumatoid arthritis and osteoarthritis, multiple sclerosis, graft rejection, sickle cell anaemia, an ocular condition, Crow-Fukase (POEMS) syndrome, or a diabetic condition.

[369] The present invention includes 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 or a pharmaceutically acceptable salt thereof wherein the condition mediated by protein kinase activity is an ocular condition 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.

[370] The present invention includes 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 or a pharmaceutically acceptable salt thereof wherein the condition mediated by protein kinase activity is a cardiovascular condition.

[371] The present invention includes 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 or a pharmaceutically acceptable salt thereof wherein the condition mediated by protein kinase activity is a cardiovascular condition wherein the condition mediated by protein kinase activity is atherosclerosis, restenosis, ischemia/reperfusion injury, vascular occlusion, venous malformation, or carotid obstructive disease.

[372] The present invention includes 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 or a pharmaceutically acceptable salt thereof wherein the condition mediated by protein kinase activity is cancer.

[373] The present invention includes 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 or a pharmaceutically acceptable salt thereof wherein the condition mediated by protein kinase activity is cancer wherein the cancer is a solid tumor, a sarcoma, fibrosarcoma, osteoma, melanoma, retinoblastoma, a rhabdomyosarcoma, glioblastoma, neuroblastoma, teratocarcinoma, an hematopoietic malignancy, malignant ascites, Kaposi's sarcoma, Hodgkin's disease, lymphoma, myeloma, or leukemia.

[374] The present invention includes 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 or a pharmaceutically acceptable salt thereof wherein the condition mediated by protein kinase activity is a diabetic condition wherein the diabetic condition is insulin-dependent diabetes mellitus glaucoma, diabetic retinopathy, or microangiopathy.

[375] The present invention includes 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 or a pharmaceutically acceptable salt thereof 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.

[376] The present invention includes a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[377] The present invention includes 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 comprising a therapeutically effective amount of a compound of Formula 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[378] The present invention includes 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.

[379] The present invention includes a method 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.

[380] 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.

[381] 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.

[382] 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.

[383] The present invention includes a pharmaceutical composition comprising an EGFR kinase inhibitor and the compound of Formula 1 in a pharmaceutically acceptable carrier. The present invention includes a pharmaceutical composition comprising an EGFR kinase inhibitor and the compound of Formula 1 in a pharmaceutically acceptable carrier wherein the EGFR kinase inhibitor is erlotinib. The present invention includes a pharmaceutical composition comprising an EGFR kinase inhibitor and the compound of Formula 1 in a pharmaceutically acceptable carrier wherein the EGFR kinase inhibitor is erlotinib present as a hydrochloride salt. The present invention includes a pharmaceutical composition comprising an EGFR kinase inhibitor and the compound of Formula 1 in a pharmaceutically acceptable carrier additionally comprising one or more other anti-cancer agents. The present invention includes a pharmaceutical composition comprising an EGFR kinase inhibitor and the compound of Formula 1 in a pharmaceutically acceptable carrier wherein the EGFR kinase inhibitor is erlotinib, additionally comprising one or more other anti-cancer agents.

[384] The present invention includes a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of an EGFR kinase inhibitor and the compound of Formula 1. The present invention includes a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of the EGFR kinase inhibitor erlotinib and the compound of Formula 1. The present invention includes a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of an EGFR kinase inhibitor and the compound of Formula 1 wherein the patient is a human that is being treated for cancer. The present invention includes a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of the EGFR kinase inhibitor erlotinib and the compound of Formula 1 wherein the patient is a human that is being treated for cancer. The present invention includes a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of an EGFR kinase inhibitor and the compound of Formula 1 wherein the EGFR kinase inhibitor and the compound of Formula 1 are co-administered to the patient in the same or different formulations. The present invention includes a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially

a therapeutically effective amount of the EGFR kinase inhibitor erlotinib and the compound of Formula 1 wherein the erlotinib and the compound of Formula 1 are co-administered to the patient in the same or different formulations. The present invention includes a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of an EGFR kinase inhibitor and the compound of Formula 1 wherein the EGFR kinase inhibitor and the compound of Formula 1 are co-administered to the patient by the same or different routes. The present invention includes a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of the EGFR kinase inhibitor erlotinib and the compound of Formula 1 wherein the erlotinib and the compound of Formula 1 are co-administered to the patient by the same or different routes. The present invention includes a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of an EGFR kinase inhibitor and the compound of Formula 1 wherein the EGFR kinase inhibitor or the compound of Formula 1 are administered to the patient by parenteral or oral administration. The present invention includes a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of the EGFR kinase inhibitor erlotinib and the compound of Formula 1 wherein the erlotinib or the compound of Formula 1 are administered to the patient by parenteral or oral administration.

[385] The present invention includes a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of an EGFR kinase inhibitor and the compound of Formula 1, additionally comprising one or more other anti-cancer agents. The present invention includes a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of the EGFR kinase inhibitor erlotinib and the compound of Formula 1, additionally comprising one or more other anti-cancer agents. The present invention includes a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of an EGFR kinase inhibitor and the compound of Formula 1, additionally comprising one or more other anti-cancer agents, wherein the other anti-cancer agents are one or more agents selected from an alkylating agent, cyclophosphamide, chlorambucil, cisplatin, busulfan, melphalan, carmustine, streptozotocin, triethylenemelamine, mitomycin C, an anti-metabolite, methotrexate, etoposide, 6-mercaptopurine, 6-thiocguanine, cytarabine, 5-fluorouracil, raltitrexed, capecitabine, dacarbazine, an antibiotic, actinomycin D, doxorubicin, daunorubicin, bleomycin, mithramycin, an alkaloid, vinblastine, paclitaxel, a glucocorticoid, dexamethasone, a corticosteroid, prednisone, a nucleoside enzyme inhibitors, hydroxyurea, an amino acid depleting enzyme, asparaginase, folinic acid, leucovorin, and a folic acid derivative.

[386] The present invention includes a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of the EGFR kinase inhibitor erlotinib and the compound of Formula 1, additionally comprising one or more other anti-cancer agents, wherein the other anti-cancer agents are one or more agents selected from an alkylating agent, cyclophosphamide, chlorambucil, cisplatin, busulfan, melphalan, carmustine, streptozotocin, triethylenemelamine, mitomycin C, an anti-metabolite, methotrexate, etoposide, 6-mercaptopurine, 6-thiocguanine, cytarabine, 5-fluorouracil, raltitrexed, capecitabine, dacarbazine, an antibiotic, actinomycin D, doxorubicin, daunorubicin, bleomycin, mithramycin, an alkaloid, vinblastine, paclitaxel, a glucocorticoid, dexamethasone, a corticosteroid, prednisone, a nucleoside enzyme inhibitors, hydroxyurea, an amino acid depleting enzyme, asparaginase, folinic acid, leucovorin, and a folic acid derivative.

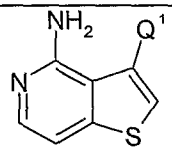
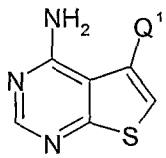
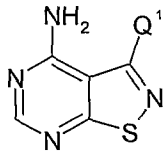
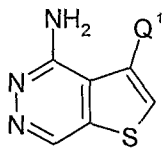
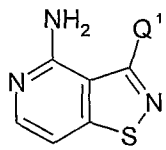
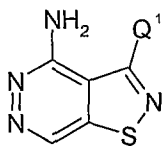
[387] The present invention includes a method of preparing a pharmaceutical composition useful for treating tumors or tumor metastases in a patient, comprising combining the compound of Formula 1 with an EGFR kinase inhibitor. The present invention includes a method of preparing a pharmaceutical composition useful for treating tumors or tumor metastases in a patient, comprising combining the compound of Formula 1 with an EGFR kinase inhibitor wherein the EGFR kinase inhibitor is erlotinib. The present invention includes a method of preparing a pharmaceutical composition useful for treating tumors or tumor metastases in a patient, comprising combining the compound of Formula 1 with an EGFR kinase inhibitor, further comprising combining a pharmaceutically acceptable carrier with the compound of Formula 1 and erlotinib.

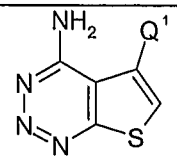
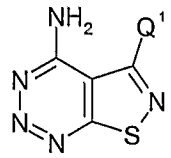
[388] The present invention includes a pharmaceutical composition comprising an EGFR kinase inhibitor and the compound of Formula 1 in a pharmaceutically acceptable carrier, additionally comprising one or more other anti-cancer agents. The present invention includes a pharmaceutical composition comprising an EGFR kinase inhibitor and the compound of Formula 1 in a pharmaceutically acceptable carrier wherein the EGFR kinase inhibitor is erlotinib, additionally comprising one or more other anti-cancer agents. The present invention includes a pharmaceutical composition comprising an EGFR kinase inhibitor and the compound of Formula 1 in a pharmaceutically acceptable carrier, additionally comprising one or more other anti-cancer agents, wherein said other anti-cancer agent is a member selected from the group consisting of alkylating drugs, antimetabolites, microtubule inhibitors, podophyllotoxins, antibiotics, nitrosoureas, hormone therapies, kinase inhibitors, activators of tumor cell apoptosis, and antiangiogenic agents. The present invention includes a pharmaceutical composition comprising an EGFR kinase inhibitor and the compound of Formula 1 in a pharmaceutically acceptable carrier wherein the EGFR kinase inhibitor is erlotinib, additionally comprising one or more other anti-cancer agents, wherein said other anti-cancer agent is a member selected from the group consisting of alkylating drugs, antimetabolites, microtubule inhibitors, podophyllotoxins, antibiotics, nitrosoureas, hormone therapies, kinase inhibitors, activators of tumor cell apoptosis, and antiangiogenic agents.

[389] The present invention includes a method for the treatment of cancer, comprising administering to a subject in need of such treatment (i) an effective or sub-therapeutic first amount of the EGFR kinase inhibitor erlotinib, or a pharmaceutically acceptable salt thereof; and (ii) an effective or sub-therapeutic second amount of the compound of Formula 1.

[390] The present invention includes a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of an EGFR kinase inhibitor and the compound of Formula 1, wherein the tumors or tumor metastases to be treated are colorectal tumors or tumor metastases. The present invention includes a method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of the EGFR kinase inhibitor erlotinib and the compound of Formula 1, wherein the tumors or tumor metastases to be treated are colorectal tumors or tumor metastases.

[391] The present invention includes the following core structures wherein said core structures contain between one and four N and the Q^1 substituent is as defined above:

Structure	Name of unsubstituted core with NH_2 group	Abbreviation used herein
	Thieno[3,2-*c*]pyridin-4-ylamine	I-A
	Thieno[2,3-*d*]pyrimidin-4-ylamine	I-B
	Isothiazolo[5,4-*d*]-pyrimidin-4-ylamine	I-C
	Thieno[2,3-*d*]pyridazin-4-ylamine	I-D
	Isothiazolo[4,5-*c*]pyridin-4-ylamine	I-E
	Isothiazolo[4,5-*d*]pyridazin-4-ylamine	I-F

Structure	Name of unsubstituted core with NH_2 group	Abbreviation used herein
	Thieno[2,3-*d*][1,2,3]triazin-4-ylamine	I-G
	1-Thia-2,5,6,7-tetraazainden-4-ylamine	I-H

[392]

[393] The compounds of the present invention include:

[394] 3-(2-Phenylquinolin-7-yl)-thieno[3,2-*c*]pyridin-4-ylamine;

[395] 3-(2-Pyridin-2-ylquinolin-7-yl)-thieno[3,2-*c*]pyridin-4-ylamine;

[396] 3-(4-Methyl-2-phenylquinolin-7-yl)-thieno[3,2-*c*]pyridin-4-ylamine;

[397] 3-(8-Fluoro-2-phenylquinolin-7-yl)-thieno[3,2-*c*]pyridin-4-ylamine;

[398] 3-(8-Fluoro-4-methyl-2-phenylquinolin-7-yl)-thieno[3,2-*c*]pyridin-4-ylamine;

[399] 3-(4-Methyl-2-pyridin-2-ylquinolin-7-yl)-thieno[3,2-*c*]pyridin-4-ylamine;

[400] 3-(8-Fluoro-2-pyridin-2-ylquinolin-7-yl)-thieno[3,2-*c*]pyridin-4-ylamine;

[401] 3-(7-Phenyl-[1,8]naphthyridin-2-yl)-thieno[3,2-*c*]pyridin-4-ylamine;

[402] 3-(5-Methyl-7-phenyl-[1,8]naphthyridin-2-yl)-thieno[3,2-*c*]pyridin-4-ylamine;

[403] 5-(2-Phenylquinolin-7-yl)-thieno[2,3-*d*]pyrimidin-4-ylamine;

[404] 5-(2-Pyridin-2-ylquinolin-7-yl)-thieno[2,3-*d*]pyrimidin-4-ylamine;

[405] 5-(4-Methyl-2-phenylquinolin-7-yl)-thieno[2,3-*d*]pyrimidin-4-ylamine;

[406] 5-(8-Fluoro-2-phenylquinolin-7-yl)-thieno[2,3-*d*]pyrimidin-4-ylamine;

[407] 5-(8-Fluoro-4-methyl-2-phenylquinolin-7-yl)-thieno[2,3-*d*]pyrimidin-4-ylamine;

[408] 5-(4-Methyl-2-pyridin-2-ylquinolin-7-yl)-thieno[2,3-*d*]pyrimidin-4-ylamine;

[409] 5-(8-Fluoro-2-pyridin-2-ylquinolin-7-yl)-thieno[2,3-*d*]pyrimidin-4-ylamine;

[410] 5-(7-Phenyl-[1,8]naphthyridin-2-yl)-thieno[2,3-*d*]pyrimidin-4-ylamine;

[411] 5-(5-Methyl-7-phenyl-[1,8]naphthyridin-2-yl)-thieno[2,3-*d*]pyrimidin-4-ylamine;

[412] 3-(2-Phenylquinolin-7-yl)-isothiazolo[5,4-*d*]pyrimidin-4-ylamine;

[413] 3-(2-Pyridin-2-ylquinolin-7-yl)-isothiazolo[5,4-*d*]pyrimidin-4-ylamine;

[414] 3-(4-Methyl-2-phenylquinolin-7-yl)-isothiazolo[5,4-*d*]pyrimidin-4-ylamine;

[415] 3-(8-Fluoro-2-phenylquinolin-7-yl)-isothiazolo[5,4-*d*]pyrimidin-4-ylamine;

[416] 3-(8-Fluoro-4-methyl-2-phenylquinolin-7-yl)-isothiazolo[5,4-*d*]pyrimidin-4-ylamine;

[417] 3-(4-Methyl-2-pyridin-2-ylquinolin-7-yl)-isothiazolo[5,4-*d*]pyrimidin-4-ylamine;

[418] 3-(8-Fluoro-2-pyridin-2-ylquinolin-7-yl)-isothiazolo[5,4-*d*]pyrimidin-4-ylamine;

[419] 3-(7-Phenyl-[1,8]naphthyridin-2-yl)-isothiazolo[5,4-*d*]pyrimidin-4-ylamine;

[420] 3-(5-Methyl-7-phenyl-[1,8]naphthyridin-2-yl)-isothiazolo[5,4-*d*]pyrimidin-4-ylamine; or a pharmaceutically acceptable salt thereof.

[421] The compounds of the present invention include:

[422] 5-(4-Methoxy-2-phenyl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine,

[423] 5-(2,4-Diphenyl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine,

[424] 5-(4-Oxazol-2-yl-2-phenyl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine,

[425] 5-(2-Phenyl-4-thiazol-2-yl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine,

[426] 5-(8-Fluoro-2,4-diphenyl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine,

[427] 5-(8-Fluoro-4-oxazol-2-yl-2-phenyl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine,

[428] 5-(8-Fluoro-2-phenyl-4-thiazol-2-yl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine,

[429] 5-[2-(2-Fluoro-phenyl)-quinolin-7-yl]-thieno[2,3-d]pyrimidin-4-ylamine,

[430] 5-(2-Furan-2-yl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine,

[431] [7-(4-Amino-thieno[2,3-d]pyrimidin-5-yl)-2-phenyl-quinolin-4-yl]-dimethyl-amine,

[432] 7-(4-Amino-thieno[2,3-d]pyrimidin-5-yl)-2-phenyl-quinoline-4-carboxylic acid ethylamide, or a pharmaceutically acceptable salt thereof.

[433]

[434] 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.

[435] 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.

[436] 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.

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

[438] 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.

[439] The term "acyl" refers to the structure –C(=O)–R, in which R is a general substituent variable such as, for example E^1 described above. Examples include, but are not limited to,

(bi)(cyclo)alkylketo, (cyclo)alkenylketo, alkynylketo, arylketo, hetarylketo, heterocyclylketo, heterobicycloalkylketo, spiroalkylketo, and the like.

[440] 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.

[441] 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.

[442] 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.

[443] 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.

[444] 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.

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

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

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

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

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

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

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

[452] 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.

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

[454] 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.

[455] 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.

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

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

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

[459] 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.

[460] 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, indolyl, benzofuranyl, and benzothienyl. The heterocyclic ring may be optionally substituted with one or more substituents.

[461] 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.

[462] 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.

[463] 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.

[464] 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.

[465] 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.

[466] 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.

[467] 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.

[468] 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.

[469] 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.

[470] 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.

[471] 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.

[472] 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.

[473] 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.

[474] 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.

[475] 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.

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

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

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

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

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

[481] 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.

[482] 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.

[483] 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.

[484] 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.

[485] 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.

[486] 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.

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

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

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

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

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

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

[493] 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.

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

[495] 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.

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

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

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

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

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

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

[502] 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.

[503] 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.

[504] 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.

[505] 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.

[506] 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.

[507] 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.

[508] 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.

[509] 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.

[510] 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.

[511] 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.

[512] 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.

[513] 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.

[514] 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 substituted onto an aryl or heteroaryl ring.

[515] 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.

[516] 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.

[517] It is well known to someone skilled in the art that certain structural elements can give rise to tautomers. Examples include, but are not limited to, keto-enol and imino-enamino tautomers. The present invention includes all tautomers of Formula I and pharmaceutically acceptable salts thereof. Further, mixtures of tautomers are also included.

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

[519] 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).

[520] 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).

[521] 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 salts. 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.

[522] 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.

[523] 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.

[524] 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.

[525] 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.

[526] 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.

[527] 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.

[528] 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.

[529] 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.

[530] 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.

[531] 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.

[532] 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.

[533] 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.

[534] 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.

[535] 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.

[536] 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.

[537] Anti-angiogenic agents include, for example: VEGFR inhibitors, such as SU-5416 and SU-6668 (Sugen Inc. of South San Francisco, Calif., USA), or as described in, for example International Application Nos. WO 99/24440, WO 99/62890, WO 95/21613, WO 99/61422, WO 98/50356, WO 99/10349, WO 97/32856, WO 97/22596, WO 98/54093, WO 98/02438, WO 99/16755, and WO 98/02437, and U.S. Patent Nos. 5,883,113, 5,886,020, 5,792,783, 5,834,504 and 6,235,764; VEGF inhibitors such as IM862 (Cytran Inc. of Kirkland, Wash., USA); angiozyme, a synthetic ribozyme from Ribozyme (Boulder, Colo.) and Chiron (Emeryville, Calif.); and antibodies to VEGF, such as bevacizumab (e.g. Avastin™, Genentech, South San Francisco, CA), a recombinant humanized antibody to VEGF; integrin receptor antagonists and integrin antagonists, such as to $\alpha_v\beta_3$, $\alpha_v\beta_5$ and $\alpha_v\beta_6$ integrins, and subtypes thereof, e.g. cilengitide (EMD 121974), or the anti-integrin antibodies, such as for example $\alpha_v\beta_3$ specific humanized antibodies (e.g. Vitaxin®); factors such as IFN-alpha (U.S. Patent Nos. 41530,901, 4,503,035, and 5,231,176); angiostatin and plasminogen fragments (e.g. kringle 1-4, kringle 5, kringle 1-3 (O'Reilly, M. S. et al. (1994) Cell 79:315-328; Cao et al. (1996) J. Biol. Chem. 271: 29461-29467; Cao et al. (1997) J. Biol. Chem. 272:22924-22928); endostatin (O'Reilly, M. S. et al. (1997) Cell 88:277; and International Patent Publication No. WO 97/15666); thrombospondin (TSP-1; Frazier, (1991) Curr. Opin. Cell Biol. 3:792); platelet factor 4 (PF4); plasminogen activator/urokinase inhibitors; urokinase receptor antagonists; heparinases; fumagillin analogs such as TNP-4701; suramin and suramin analogs; angiostatic steroids; bFGF antagonists; flk-1 and flt-1 antagonists; anti-angiogenesis agents such as MMP-2 (matrix-metalloprotienase 2) inhibitors and MMP-9 (matrix-metalloprotienase 9) inhibitors. Examples of useful matrix metalloproteinase inhibitors are described in International Patent Publication Nos. WO 96/33172, WO 96/27583, WO 98/07697, WO 98/03516, WO 98/34918, WO 98/34915, WO

98/33768, WO 98/30566, WO 90/05719, WO 99/52910, WO 99/52889, WO 99/29667, and WO 99/07675, European Patent Publication Nos. 818,442, 780,386, 1,004,578, 606,046, and 931,788; Great Britain Patent Publication No. 9912961, and U.S. patent Nos. 5,863,949 and 5,861,510. Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or MMP-9 relative to the other matrix-metalloproteinases (i.e. MMP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13).

[538] In the context of this invention, additional other cytotoxic, chemotherapeutic or anti-cancer agents, or compounds that enhance the effects of such agents, include, for example: alkylating agents or agents with an alkylating action, such as cyclophosphamide (CTX; e.g. cytoxan®), chlorambucil (CHL; e.g. leukeran®), cisplatin (CisP; e.g. platinol®), oxaliplatin (e.g. Eloxatin™), busulfan (e.g. myleran®), melphalan, carmustine (BCNU), streptozotocin, triethylenemelamine (TEM), mitomycin C, and the like; anti-metabolites, such as methotrexate (MTX), etoposide (VP16; e.g. vepesid®), 6-mercaptopurine (6MP), 6-thiocguanine (6TG), cytarabine (Ara-C), 5-fluorouracil (5-FU), capecitabine (e.g.Xeloda®), dacarbazine (DTIC), and the like; antibiotics, such as actinomycin D, doxorubicin (DXR; e.g. adriamycin®), daunorubicin (daunomycin), bleomycin, mithramycin and the like; alkaloids, such as vinca alkaloids such as vincristine (VCR), vinblastine, and the like; and other antitumor agents, such as paclitaxel (e.g. taxol®) and pactitaxel derivatives, the cytostatic agents, glucocorticoids such as dexamethasone (DEX; e.g. decadron®) and corticosteroids such as prednisone, nucleoside enzyme inhibitors such as hydroxyurea, amino acid depleting enzymes such as asparaginase, leucovorin, folinic acid, raltitrexed, and other folic acid derivatives, and similar, diverse antitumor agents. The following agents may also be used as additional agents: arnifostine (e.g. ethyol®), dactinomycin, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, lornustine (CCNU), doxorubicin lipo (e.g. doxil®), gemcitabine (e.g. gemzar®), daunorubicin lipo (e.g. daunoxome®), procarbazine, mitomycin, docetaxel (e.g. taxotere®), aldesleukin, carboplatin, cladribine, camptothecin, 10-hydroxy 7-ethyl-camptothecin (SN38), floxuridine, fludarabine, ifosfamide, idarubicin, mesna, interferon alpha, interferon beta, mitoxantrone, topotecan, leuprolide, megestrol, melphalan, mercaptopurine, plicamycin, mitotane, pegaspargase, pentostatin, pipobroman, plicamycin, tamoxifen, teniposide, testolactone, thioguanine, thiotepa, uracil mustard, vinorelbine, chlorambucil.

[539]

[540] **BIOLOGICAL ASSAY**

[541] 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 assay and its 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**

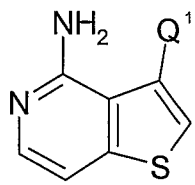
[542] The IGF-1R inhibitory of a compound of Formula I can be shown in a tyrosine kinase assay using purified GST fusion protein containing the cytoplasmic kinase domain of human IGF-1R expressed in Sf9 cells. This assay is carried out in a final volume of 90μL containing 1-100nM (depending on the specific 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 3×250μL 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.

[543] All **EXAMPLES** showed inhibition of IGF-1R. The following examples showed efficacy and activity by inhibiting IGF-1R in the biochemical assay with IC_{50} values less than 20μM to less than 50nM. Preferably the IC_{50} value is less than 5μM. Advantageously, the IC_{50} value is less than 1μM. More advantageously, the IC_{50} value is less than 200nM. Even more advantageously, the IC_{50} value is less than 100nM. Still more advantageously, the IC_{50} value is less than 50nM.

[544] The most preferred **EXAMPLES** are selective towards IGF-1R.

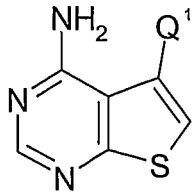
[545]

[546] Compound of Formula I-AA is equal to compound of Formula I wherein X_1, X_2, and X_3 = CH:



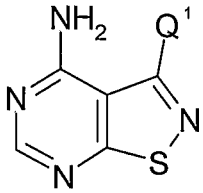
I-AA

[547] Compound of Formula I-BB is equal to compound of Formula I wherein X_1 and X_3 = CH, and X_2 = N:



I-BB

[548] Compound of Formula I-CC is equal to compound of Formula I wherein X_1 = CH, and X_2 and X_3 = N:



I-CC

EXPERIMENTAL

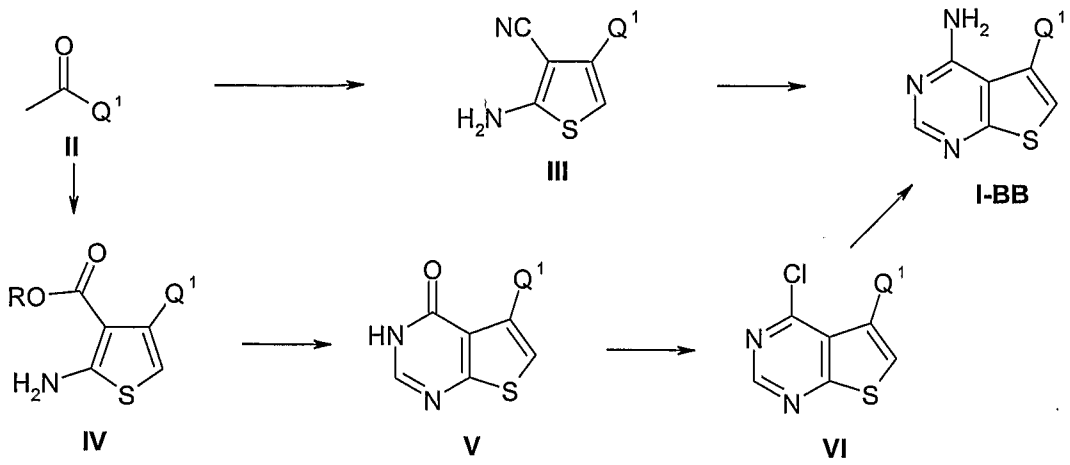
[549] In **Scheme 1 – Scheme 3** below showing how to synthesize compounds of this invention, the following abbreviations are used: Me for methyl, Et for ethyl, ^{i}Pr or ^{i}Pr for isopropyl, n-Bu for *n*-butyl, t-Bu for *tert*-butyl, Ac for acetyl, Ph for phenyl, 4Cl-Ph or (4Cl)Ph for 4-chlorophenyl, 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-PPh_3 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.

[550] Accordingly, the following are compounds that are useful as intermediates in the formation of IGF-1R inhibiting **EXAMPLES**.

[551] 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.

[552] Scheme 1 shows a method that can be used to prepare compounds of Formula **I-BB**, wherein Q^1 is as previously defined and R is alkyl such as methyl, ethyl, and the like:

[553] **Scheme 1**



[554]

[555] The starting methyl ketones Q^1–C(=O)–CH_3 of Formula II can be prepared by methods known to someone skilled in the art. For example, an aldehyde Q^1–CHO may be reacted with a methyl transfer reagent such as methyllithium or a methyl Grignard reagent, followed by oxidation of the resulting secondary alcohol Q^1–CH(–OH)–CH_3 to the methyl ketone of Formula II. Alternatively, an ester Q^1–CO_2R (where R is alkyl, etc.) or carboxylic acid Q^1–CO_2H may be converted to a methoxymethyl amide Q^1–C(=O)–N(CH_3)–OMe or the like followed by reaction with methyllithium or a methyl Grignard reagent, or a nitrile Q^1–CN may be reacted with a methyl Grignard reagent to yield a methyl ketone of Formula II. Further methods for the preparation of compounds of Formula II may be found in: Larock, R. C. *Comprehensive Organic Transformations,* 2nd ed.; Wiley and Sons: New York, 1999, pp. 1199–1620.

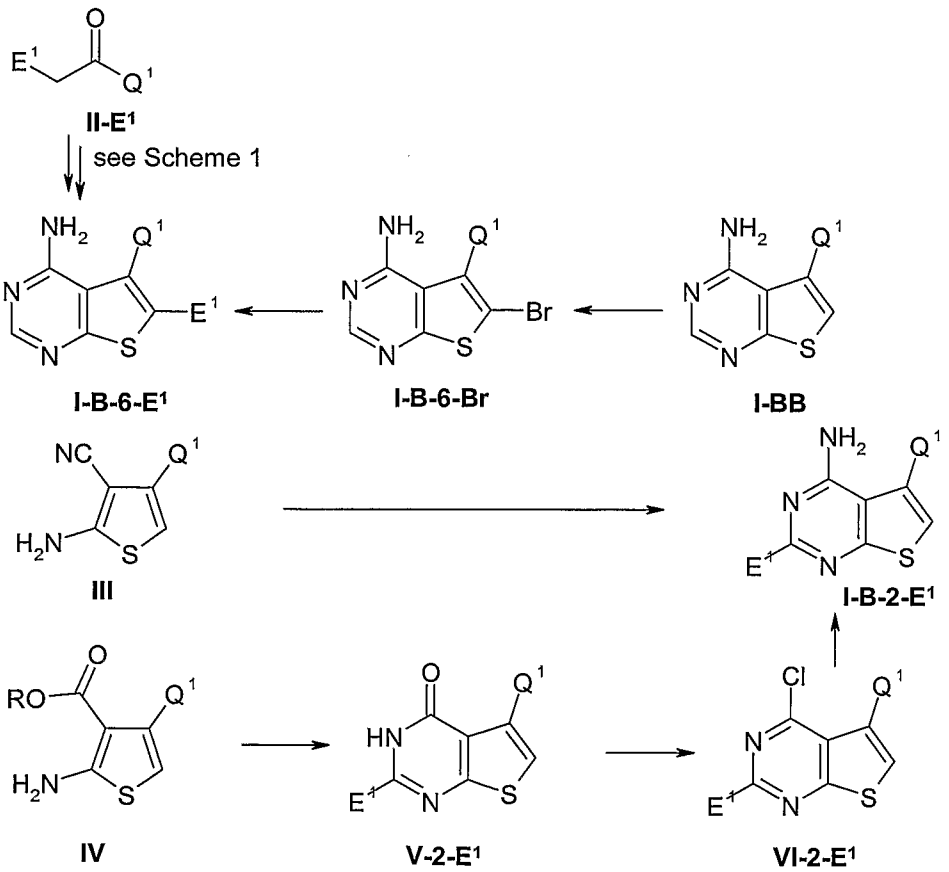
[556] The aminocyanopyrroles of Formula III can be prepared from compounds of Formula II by reaction with sulfur and malononitrile in a typical solvent in the presence of a typical amine base. Typical amine bases include, but are not limited to, morpholine, diethylamine, diisopropylamine, and triethylamine. Typical solvents include, but are not limited to, alcohols such as methanol, ethanol, isopropanol; amides such as DMF and formamide. The reaction is typically conducted at temperatures of, but not limited to, about 25 °C to about 90 °C. Alternatively, compounds of Formula II may be reacted first with malononitrile in the presence of ammonium acetate and acetic acid in benzene or toluene and then reacted with sulfur and an amine base as described above. The compounds of Formula I-BB can be prepared from compounds of Formula III by cyclization under typical cyclization conditions. These conditions include, but are not limited to, heating with formamide neat to about 150–180 °C; heating with formamidine acetate or a trialkylorthoformate followed by treatment with ammonia.

[557] In an alternative synthesis, compounds of Formula II are reacted with sulfur and an alkyl cyanoacetate in a typical solvent in the presence of a typical amine base to give compounds of Formula IV. Typical amine bases include, but are not limited to, morpholine, diethylamine, diisopropylamine, and triethylamine. Typical solvents include, but are not limited to, alcohols such as methanol, ethanol, isopropanol; amides such as DMF and formamide. The reaction is typically

conducted at temperatures of, but not limited to, about 25 °C to about 90 °C. Alternatively, compounds of Formula II may be reacted first with an alkyl cyanoacetate in the presence of ammonium acetate and acetic acid in benzene or toluene and then reacted with sulfur and an amine base as described above. Compounds of Formula V can be prepared from compounds of Formula IV thus obtained by cyclization under typical cyclization conditions. These conditions include, but are not limited to, heating with formamidine acetate in an alcoholic solvent to about reflux temperature of said solvent; heating with a mixture of formamide, DMF, and formic acid to about 80–180 °C, preferably to about 140–160 °C. Compounds of Formula VI may be prepared from compounds of Formula V by chlorination using typical chlorinating reagents including, but not limited to, $POCl_3$ (either neat or in solution) or the Vilsmeier reagent (in solution of a suitable solvent such as DMF). The compounds of Formula I-BB can then be prepared from compounds of Formula VI by reaction with ammonia in a typical solvent under typical reaction conditions. Typical solvents include, but are 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. The preferred solvent is isopropanol. The reaction can be carried out at temperatures between about 20 °C and about 120 °C, preferably between 80°C and about 100°C.

[558] Scheme 1a shows how compounds of Formula **I-B-2-E^1** and **I-B-6-E^1** (= compounds of Formula **I-B** that are substituted at C-2 and C-6, respectively) can be prepared, wherein Q^1 and E^1 are as previously defined, and R is alkyl such as methyl, ethyl, and the like:

Scheme 1a



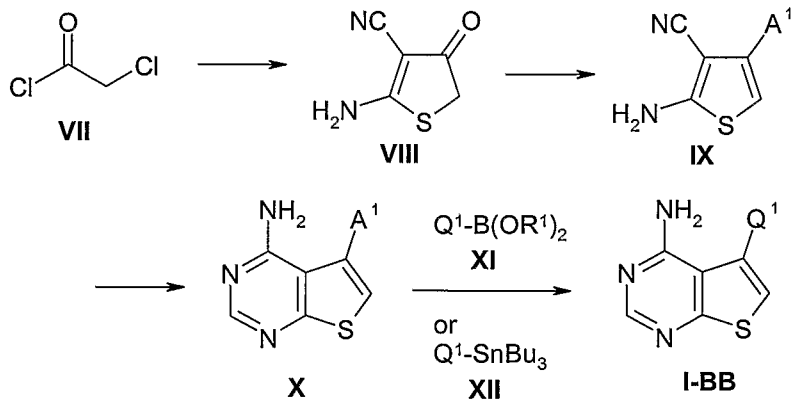
[559]

[560] Compounds of Formula I-B-6-E^1 may be prepared using the reactions described in Scheme 1 but using a substituted methyl ketone Q^1–C(=O)–CH_2–E^1 of Formula II-E^1 instead. Someone skilled in the art will appreciate that many methods for the preparation of methyl ketones of Formula II can be adapted for the preparation of substituted methyl ketones of Formula II-E^1. Alternatively, compounds of Formula I-BB may be reacted with a brominating agent such as Br_2 or NBS to give the 6-bromo compound of Formula I-B-6-Br, which can be further reacted to give compounds of Formula I-B-6-E^1 by, e.g., Suzuki or Stille coupling with a boronic acid derivative or a trialkyltin derivative, respectively.

[561] Compounds of Formula I-B-2-E^1 may be prepared from compounds of Formula III or IV under similar conditions as described above for the preparation of compounds of Formula I-BB, but replacing formamidine acetate or a trialkyl formate in the cyclization step with a substituted amidine E^1–C(=NH)–NH_2·HOAc or substituted trialkyl formate E^1–$C(OR)_3$.

[562] Scheme 1b shows an alternative method of preparing compounds of Formula **I-BB**, wherein Q^1 is as previously defined, A^1 is halogen such as Cl, Br, or I, and $B(OR^1)_2$ is a suitable boronic acid/ester wherein R^1 is $C_{0\text{-}10}$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:

Scheme 1b



[563]

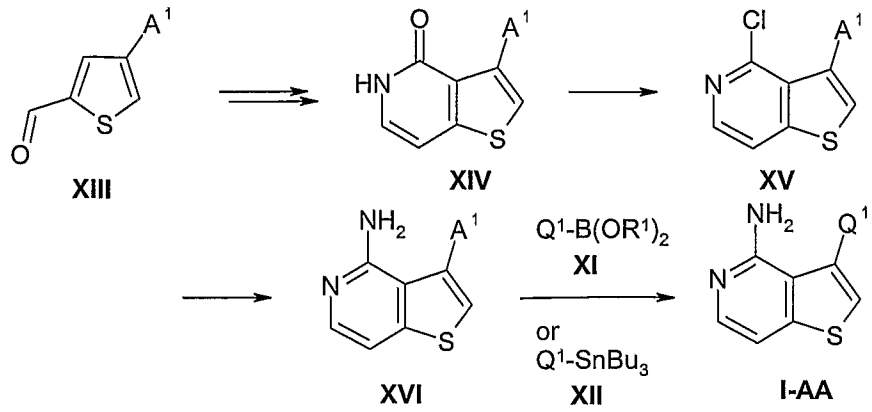
[564] In this method, chloroacetyl chloride (Formula VII) is reacted with a sulfide such as Na_2S or $(NH_4)_2S$, or the like, and malononitrile in the presence of an amine base such as triethylamine or tributylamine in a solvent such as DMF to give a compound of Formula VIII. The reaction is typically conducted at about –10 °C to about 30 °C. Compounds of Formula IX may be prepared from compounds of Formula VIII by halogenation with reagents such as PPh_3·I_2, PPh_3·Br_2, $POCl_3$, $POBr_3$, and the like. Cyclization of compounds of Formula IX to give compounds of Formula X can be accomplished by methods described above for the conversion of compounds of Formula III to compounds of Formula I-BB. Finally, compounds of Formula I-BB can be prepared from compounds of Formula X by Suzuki coupling with a boronate derivate Q^1–$B(OR^1)_2$ (compound of Formula XI) or

by Stille coupling with a trialkyltin derivative Q^1–$SnBu_3$ (compound of Formula XII), respectively, under typical coupling conditions well known to someone skilled in the art.

[565] The compounds of Formula XI (Q^1–$B(OR^1)_2$) of Scheme 1b may be prepared from compounds of Formula Q^1–A^{11} (wherein A^{11} is chloro, bromo, iodo, triflate, and the like) by reacting with a suitable metal catalyst and a suitable boronating agent under suitable reaction conditions. Suitable metal catalyst agents include, but are not limited to, $Pd(OAc)_2$ in the presence of 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride; $Pd(Cl)_2$dppf, optionally in the presence of additional dppf. Suitable boronating agents include, but are not limited to, *bis*(pinacolato)diboron. Suitable reaction conditions for use in the above process include, but are not limited to, heating a mixture of the metal catalyst agent, KOAc, and *bis*(pinacolato)diboron in a suitable solvent such as, but not limited to, THF, 1,4-dioxane, DMSO. The above process may be carried out at temperatures between about 20°C and about 120°C. Preferably, the reaction is carried out at 60°C to 80°C. The above process to produce compounds of the present invention is preferably carried out at about atmospheric pressure although higher or lower pressures were used if desired. Preferably, 2–3 equivalents of KOAc, 1–1.5 equivalents of *bis*(pinacolato)diboron, 0.03–1 equivalent of metal catalyst agent are used although higher or lower amounts were used if desired. Additionally, other suitable reaction conditions for the conversion of Q^1–A^{11} to Q^1–$B(OR^1)_2$ can be found in the literature which involve a variety of Q^1–A^{11} or aryl/heteroarylhalides and a variety of conditions (Biooganic & Medicinal Chemistry Letters, 2003, 12(22), 4001; Biooganic & Medicinal Chemistry Letters, 2003, 13(18), 3059; Chemical Communications (Cambridge, UK), 2003, 23, 2924; Synthesis, 2002, 17, 2503; Angewandte Chemie, International Ed., 2002, 41(16), 3056; Journal of the American Chemical Society, 2002, 124(3), 390; Organic Letters, 2002, 4(4), 541; Tetrahedron, 2001, 57(49), 9813; Journal of Organic Chemistry, 2000, 65(1), 164; Journal of Organic Chemistry, 1997, 62(19), 6458; Journal of Organometallic Chemistry, 1983, 259(3), 269). In some cases, compounds of Formula Q^1–A^{11} and XI (Q^1–$B(OR^1)_2$) are commercially available or synthesized according to literature procedures. In cases where neither are available, compounds of Formula Q^1–A^{11} and XI (Q^1–$B(OR^1)_2$) were synthesized via procedures described in the experimental section herein.

[566] Scheme 2 shows a method that can be used to prepare compounds of Formula **I-AA**, wherein Q^1 is as previously defined, A^1 is halogen such as Cl, Br, or I, and $B(OR^1)_2$ is a suitable boronic acid/ester wherein R^1 is $C_{0\text{-}10}$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:

[567] **Scheme 2**

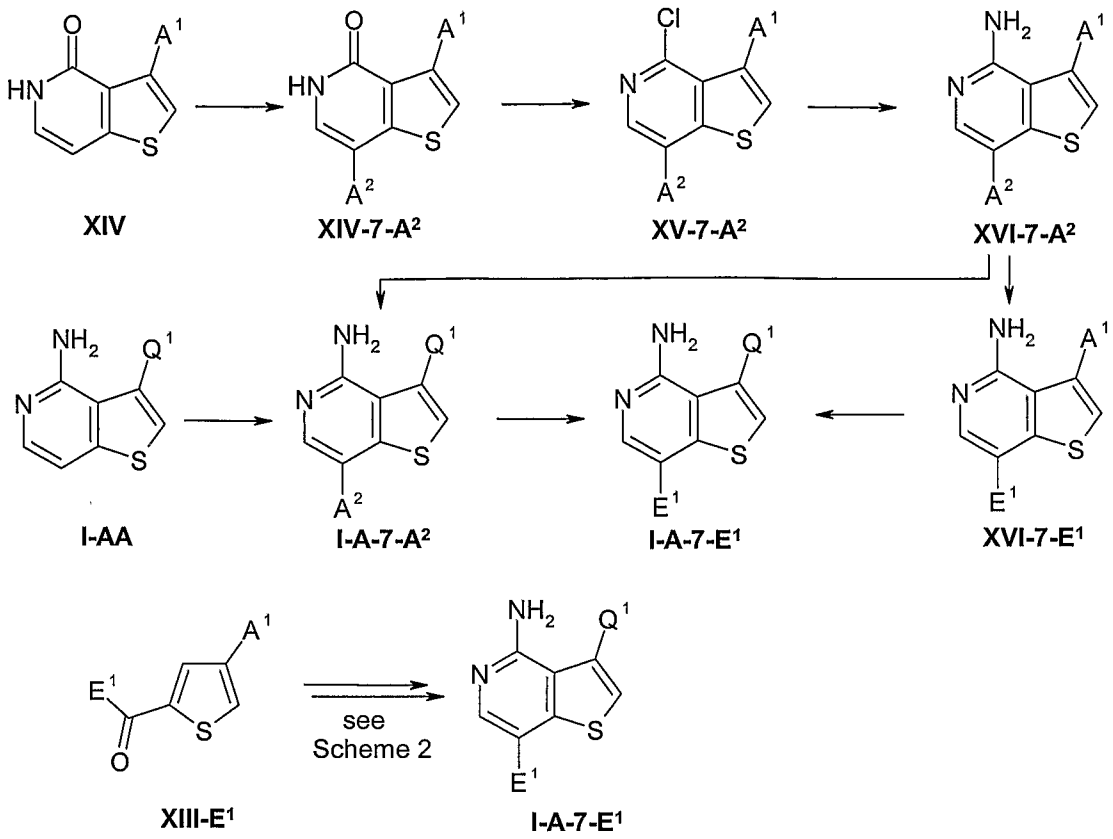


[568]

[569] The starting aldehydes of Formula XIII are known in the literature, commercially available, or can be prepared by methods known to someone skilled in the art. The compounds of Formula XIV can be prepared from the aldehydes of Formula XIII in a known four-step sequence consisting of Knoevenagel condensation with malonic acid and subsequent decarboxylation, conversion of the resulting acid to its acyl azide, thermal rearrangement of said azide to give an isocyanate, and thermal cyclization of this isocyanate to give compounds of Formula XIV. This type of sequence has repeatedly been described in the literature, e.g., Ger. Offen. DE2059386 (1971), Ger. Offen. DE1965710 (1970), WO2004/000828A1. Compounds of Formula XV may be prepared from compounds of Formula XIV by chlorination using typical chlorinating reagents including, but not limited to, $POCl_3$ (either neat or in solution). The compounds of Formula XVI can then be prepared from compounds of Formula XV by reaction with ammonia in a typical solvent under typical reaction conditions as described above for the conversion of compounds of Formula V to compounds of Formula VI. Finally, compounds of Formula I-AA can be prepared from compounds of Formula XVI by Suzuki coupling with a boronate derivate Q^1–$B(OR^1)_2$ (compound of Formula XI) or by Stille coupling with a trialkyltin derivative Q^1–$SnBu_3$ (compound of Formula XII), respectively, under typical coupling conditions well known to someone skilled in the art. It will be appreciated by someone skilled in the art that the Suzuki or Stille coupling with a compound of Formula XI or compound of Formula XII, respectively, may be performed alternatively, at an earlier stage, with any of the compounds of Formulas XIII, XIV, or XV, if one deems appropriate.

[570] Scheme 2a shows how compounds of Formula **I-A** that are substituted at C-7 can be prepared, wherein Q^1 and E^1 are as previously defined, and A^1 and A^2 are halogen such as Cl, Br, or I:

[571] **Scheme 2a**



[572]

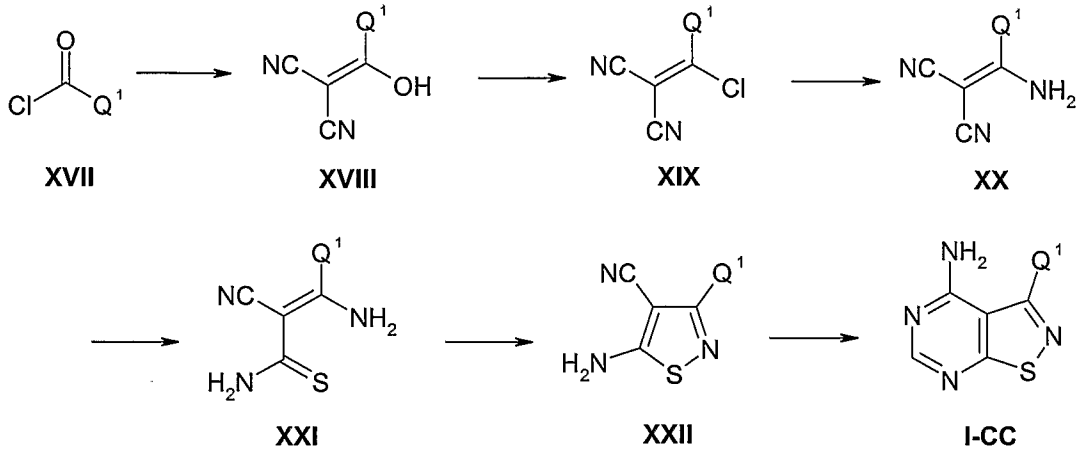
[573] Compounds of Formula I-AA may be reacted with a halogenating agent such as NCS, NBS, or NIS to give the 7-halo compound of Formula I-A-7-A^2, which can be further reacted to give compounds of Formula I-A-7-E^1 by, e.g., Suzuki or Stille coupling with a boronic acid derivative or a trialkyltin derivative, respectively, as described above. In a similar manner, compounds of Formula XIV may be reacted with a halogenating agent such as NCS, NBS, or NIS to give the 7-halo compound of Formula XIV-7-A^2. Preferably, one chooses A^1 and A^2 to be different so that the conversions of A^1 to Q^1 and of A^2 to E^1 can be accomplished selectively. The compounds of Formula XIV-7-A^2 can then be converted to compounds of Formula XV-7-A^2 and further to compounds of Formula XVI-7-A^2 in substantially the same way as described above for the conversion of compounds of Formula XIV to compounds of Formula XV and compounds of Formula XVI. Compounds of Formula XVI-7-A^2 may be converted to compounds of Formula I-A-7-A^2 by, e.g., Suzuki or Stille coupling with a boronic acid derivative of Formula XI or a trialkyltin derivative of Formula XII, respectively, as described above, and the compounds of Formula I-A-7-A^2 can be further reacted to give compounds of Formula I-A-7-E^1, as described above. Compounds of Formula XVI-7-A^2 may also be converted to compounds of Formula XVI-7-E^1, as described above, which can be further reacted to give compounds of Formula I-A-7-E^1 by, e.g., Suzuki or Stille coupling with a boronic acid derivative of Formula XI or a trialkyltin derivative of Formula XII, respectively, as described above.

[574] Alternatively, compounds of Formula I-A-7-E^1 may be prepared from compounds of Formula XIII-E^1 under substantially similar conditions as described above for the conversion of

compounds of Formula XIII to compounds of Formula I-AA. The starting compounds of Formula XIII-E^1 can be prepared by methods well known to someone skilled in the art. For example, a compound of Formula XIII-E^1 where E^1 = alkyl may be prepared from compounds of Formula XIII by reaction with an alkyl lithium reagent Li–E^1 or an alkyl Grignard reagent Halogen–Mg–E^1 where E^1 = alkyl followed by oxidation of the resulting secondary alcohol to the ketone of Formula XIII–E^1.

[575] Scheme 3 shows a method that can be used to prepare compounds of Formula **I-CC**, wherein Q^1 is as previously defined.

[576] **Scheme 3**



[577]

[578] The starting acid chlorides Q^1–C(=O)–Cl of Formula XVII can be prepared by methods known to someone skilled in the art. For example, a carboxylic acid Q^1–CO_2H may be reacted with a chlorinating reagent such as, but not limited to, $SOCl_2$, PCl_3, PCl_5, $PPh_3{\cdot}CCl_4$, or the Vilsmeier reagent, either neat or in a suitable solvent such as, but not limited to, CH_2Cl_2, $CHCl_3$, of DMF. Compounds of Formula XVII can be treated with malononitrile in the presence of a typical base under typical reaction conditions to give compounds of Formula XVIII. Typical bases include, but are not limited to, NaOH and KOH. Typical reaction conditions include, but are not limited to, using a two-phase system of CH_2Cl_2 and water in the presence of a phase-transfer catalyst such as a tetrabutylammonium halide, a benzyltriethylammonium halide, and the like, at temperatures between about –5 °C and about 35 °C. Compounds of Formula XIX can be prepared from compounds of Formula XVIII by reaction with a chlorinating reagent such as PCl_5 in a typical solvent at a typical reaction temperature. Typical solvents include, but are not limited to, halogenated solvents such as CH_2Cl_2, $CHCl_3$, and CCl_4. Typical reaction temperatures range from about 0 °C to about 40 °C. Compounds of Formula XX can be prepared from compounds of Formula XIX by reaction with ammonia in a typical solvent at a typical reaction temperature. Ammonia may be used as concentrated aqueous solution, or as solution in another suitable solvent. Typical solvents include, but are not limited to, methanol, ethanol, and isopropanol. Typical reaction temperatures range from about 0 °C to about 40 °C. Compounds of Formula XXI can be prepared from compounds of Formula XX by reaction with a typical sulfur source under typical reaction conditions. Typical sulfur sources

and reaction conditions include, but are not limited to, diethyl dithiophosphate in an alcoholic solvent such as methanol or ethanol optionally containing water at about 70 °C to about 80 °C, and hydrogen sulfide gas in pyridine containing an amide base such as triethylamine at about 70 °C to about 90 °C. Compounds of Formula XXII can be prepared from compounds of Formula XXI under typical oxidative cyclization conditions. These conditions include, but are not limited to, treatment with hydrogen peroxide in water, aqueous hydrogen peroxide in an alcoholic solvent such as methanol or ethanol, or bromine in a halogenated solvent such as $CHCl_3$, at temperatures from about 0 °C to about 65 °C. Finally, cyclization of compounds of Formula XXII to give compounds of Formula I-CC can be accomplished by methods described above for the conversion of compounds of Formula III to compounds of Formula I-BB.

[579] 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.

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

[581] General Experimental Information:

[582] 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. ^1H NMR and ^{13}C NMR spectra were recorded with Varian or Bruker instruments (400 MHz for ^1H, 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 ^1H 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 / MicromassZQ system was used.

[583] 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.

[584]

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

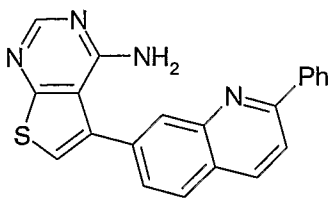
Polar_15min

Time	A%	B%	Flow Rate (mL/min) MicromassZQ	Flow Rate (mL/min) Platform II
0.00	5	95	1.3	1.3
1.00	30	70	1.3	1.3
7.50	90	10	1.3	1.3
10.00	100	0	1.3	1.3
13.00	5	95	1.3	1.3
15.00	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

[585] **EXAMPLE 1: 5-(2-Phenylquinolin-7-yl)-thieno[2,3-*d*]pyrimidin-4-ylamine**

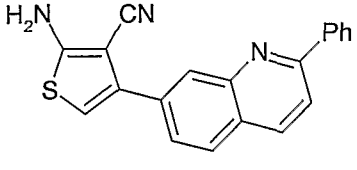


[586] *From 2-amino-4-(2-phenylquinolin-7-yl)-thiophene-3-carbonitrile:* Crude 2-amino-4-(2-phenylquinolin-7-yl)-thiophene-3-carbonitrile (440 mg) was combined with $HCONH_2$ (10 ml) in a sealed tube that was then flushed and filled with N_2. The cap was tightened and the sealed tube was heated at 180 °C for 3 h. After that time, the reaction mixture was poured into H_2O (20 ml) and extracted with EtOAc (3×20 ml). The combined EtOAc extracts were washed with H_2O (20 ml) and brine (20 ml), dried over $MgSO_4$, filtered and concentrated to give a brown foam. Purification by TLC on silica gel, eluting with 10% (150 ml), 20% (150 ml), 30% (150 ml), and 40% (200 ml) EtOAc/hexane, followed by HPLC gave the title compound as a brown solid. ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.32 (brs, 2H), 7.27 (s, 1H), 7.47–7.52 (m, 1H), 7.52–7.58 (m, 2H), 7.61 (dd, J = 1.6, 8.4 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 8.8 Hz, 1H), 8.17–8.22 (m, 2H), 8.29 (d, J = 1.6 Hz, 1H), 8.30 (d, J = 8.0 Hz, 1H), 8.49 (s, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz, DEPT135): δ = 113.76 (C_{quart}), 119.75 (+), 121.61 (+), 126.76 (C_{quart}), 127.05 (+), 127.55 (2C, +), 128.34 (+), 128.92 (2C, +), 129.74 (+), 129.82 (+), 134.38 (C_{quart}), 136.62 (+), 137.30 (C_{quart}), 139.10 (C_{quart}), 147.97 (C_{quart}), 154.03 (+) 158.06 (C_{quart}), 158.52 (C_{quart}), 168.45 (C_{quart}). MS (ES+): *m/z* 355.0 (80) [MH^+]. HPLC: t_R = 2.8 min (MicromassZQ, nonpolar_5min).

[587] *One-pot synthesis from 1-(2-phenylquinolin-7-yl)-ethanone:* The mixture of 1-(2-phenylquinolin-7-yl)-ethanone (50 mg, 0.20 mmol), malononitrile (40 mg, 0.60 mmol), sulfur (39 mg, 1.2 mmol), morpholine (0.12 ml), and formamide (1.0 ml) in a sealed tube was heated at 80 °C for 17 h under N_2. LC-MS confirmed the formation of 2-amino-4-(2-phenylquinolin-7-yl)-thiophene-3-carbonitrile (MS (ES+): *m/z* 328.1 (100) [MH^+]). The above mixture was then heated to 180 °C for 3 h. The cooled reaction mixture was poured into brine (10 ml) and extracted with EtOAc (3×15 ml). The combined organic extracts were washed with brine (10 ml), dried over $MgSO_4$, filtered, and concentrated to give a brown oil. Purification by TLC on silica gel [eluting with EtOAc/hexane (40/60)], followed by HPLC gave the title compound as an off-white solid.

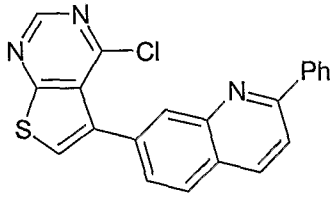
[588] *From 7-(4-chlorothieno[2,3-d]pyrimidin-5-yl)-2-phenylquinoline:* Gaseous NH_3 was bubbled into a *i*PrOH (1 ml) solution of 7-(4-chlorothieno[2,3-*d*]pyrimidin-5-yl)-2-phenylquinoline (56 mg, max. 0.084 mmol) in a sealable tube, cooled to –78 °C in a dry ice/acetone bath, for 15 min. The sealed tube was equipped with a Teflon washer, sealed and heated at 110 °C for 8 h. After that time, the excess NH_3 and the solvent were evaporated. The remaining material was purified by HPLC to give the title compound as an off-white solid.

2-Amino-4-(2-phenylquinolin-7-yl)-thiophene-3-carbonitrile



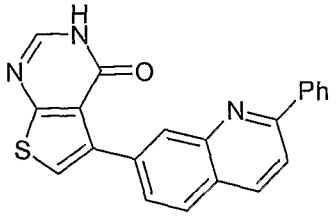
[589] A mixture of 1-(2-phenylquinolin-7-yl)-ethanone (541 mg, 2.20 mmol), malononitrile (436 mg, 6.60 mmol), sulfur (423 mg, 13.2 mmol), morpholine (1.32 ml), and EtOH (11 ml) in a sealed tube, which had been flushed and filled with N_2, was heated at 80 °C for 3 days. After that time, the reaction mixture was poured into brine (30 ml) and extracted with EtOAc (3×40 ml). The combined organic extracts were washed with brine (2×40 ml), dried over $MgSO_4$, filtered and concentrated to give a dark brown oil. Chromatography on silica gel, eluting with 15% (200 ml), 20% (300 ml), 30% (300 ml), 40% (600 ml), and 50% (250 ml) EtOAc/hexanes gave the impure title compound as brown foam. This material could be used in the next step without further purification. A sample was further purified by HPLC to give the title compound as light-brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.94 (brs, 2H), 6.57 (s, 1H), 7.46–7.56 (m, 3H), 7.77–7.80 (dd, 1H, J = 1.6 & 8.0 Hz), 7.87–7.90 (m, 2H), 8.16–8.19 (m, 2H), 8.22–8.24 (m, 1H), 8.37 (m, 1H). MS(ES+): 328.3 [MH^+]. HPLC: t_R = 3.6 min (MicromassZQ, polar_5min).

7-(4-Chlorothieno[2,3-*d*]pyrimidin-5-yl)-2-phenylquinoline



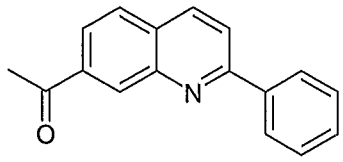
[590] A mixture of 5-(2-phenylquinolin-7-yl)-3*H*-thieno[2,3-*d*]pyrimidin-4-one (30 mg, max. 0.084 mmol, 77% purity) and $POCl_3$ (1.0 ml) was stirred at 110 °C for 1 h under N_2. The excess $POCl_3$ was removed *in vacuo*, and the residue was basified by cold NH_3 (2M in isopropanol). The precipitate that was formed was filtered off. The filtrate [crude 7-(4-chlorothieno[2,3-*d*]pyrimidin-5-yl)-2-phenylquinoline] was used without further purification for the next step. MS(ES+): 374.2 / 376.2 (M/M+2). HPLC: t_R = 6.8 min (MicromassZQ, polar_15min).

5-(2-Phenylquinolin-7-yl)-3*H*-thieno[2,3-*d*]pyrimidin-4-one



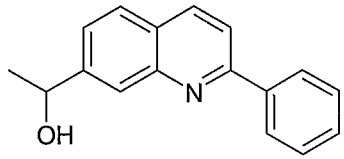
[591] Following the procedure for the one-pot synthesis of 5-(2-phenylquinolin-7-yl)-thieno[2,3-*d*]pyrimidin-4-ylamine from 1-(2-phenylquinolin-7-yl)-ethanone, but using ethyl cyanoacetate instead of malononitrile, the title compound was obtained as brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.38 (s, 1H), 7.45–7.56 (m, 3H), 7.76–7.79 (dd, 1H, J = 1.6 & 8.4 Hz), 7.86–7.91 (m, 2H), 7.98 (s, 1H), 8.15–8.18 (m, 2H), 8.25–8.27 (d, 1H, J = 8.8 Hz), 8.34 (d, 1H, J = 2.0 Hz). MS(ES+): 356.2 [MH^+]. HPLC: t_R = 4.3 min (MicromassZQ, polar_15min).

1-(2-Phenylquinolin-7-yl)-ethanone



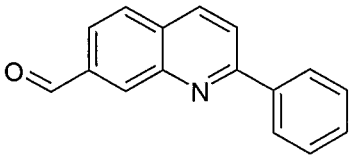
[592] Into the CH_2Cl_2 (5 ml) solution of 1-(2-phenylquinolin-7-yl)-ethanol (236 mg, 0.947 mmol) was added PCC (408 mg, 2 eq.) under N_2 at rt. After stirring for 18 h at rt, the reaction mixture was filtered through a silica pad and washed with EtOAc. After removing solvent, the title compound was obtained as brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.78 (s, 3H), 7.48–7.58 (m, 3H), 7.87–7.89 (d, 1H, J = 8.4 Hz), 7.96–7.98 (d, 1H, J = 8.8 Hz), 8.09–8.12 (dd, 1H, J = 1.6 & 8.4 Hz), 8.17–8.19 (m, 2H), 8.24–8.26 (d, 1H, J = 8.8 Hz), 8.75 (s, 1H). MS(ES+): 248.3 [MH^+]. HPLC: t_R = 3.6 min (MicromassZQ, polar_5min).

1-(2-Phenylquinolin-7-yl)-ethanol



[593] Into the THF (50 ml) solution of MeMgBr (3M in Et_2O, 5.6 mL, 1.5 eq.) was added dropwise the THF (40 ml) solution of 2-phenylquinoline-7-carbaldehyde (2625 mg, 11.25 mmol) under N_2 at rt over 20 min. After stirring at rt for 3 h, the reaction mixture was treated with saturated aqueous NH_4Cl solution (100 ml), and the organic phase was separated. The aqueous phase was extracted with EtOAc (2×100 ml). The combined organic phases were then washed with H_2O (2×100 ml) and brine (100 ml), dried over $MgSO_4$, filtered and concentrated to give the title compound as brown oil. The crude material was used for the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.60–1.62 (d, 3H, J = 6.4 Hz), 2.08 (brs, 1H), 5.11–5.14 (m, 1H), 7.44–7.60 (m, 4H), 7.81–7.83 (d, 1H, J = 8.4 Hz), 7.85–7.87 (d, 1H, J = 8.4 Hz), 8.13–8.17 (m, 3H), 8.19–8.21 (d, 1H, J = 8.4 Hz). MS(ES+): 250.3 [MH^+]. HPLC: t_R = 2.9 min (MicromassZQ, polar_5min).

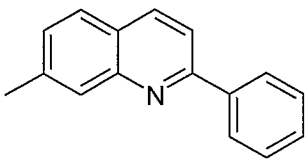
2-Phenylquinoline-7-carbaldehyde



[594] A mixture of 7-methyl-2-phenylquinoline (2.49 g, 11.4 mmol) and selenium dioxide (1.92 g, 17.3 mmol, 1.5 equiv.) was heated to 160 °C (bath temp.) for 22 h. The cooled melt was suspended in CH_2Cl_2 with the aid of sonication and filtered through Celite and then through a plug of

silica gel. This effectively removed the red color and the major lower spots. The material thus obtained was crystallized from hexanes/$CHCl_3$, yielding the title compound as pale beige solid, mp. 108 °C. The mother liquor was concentrated and chromatographed on silica gel [Jones Flashmaster, 50 g /150 mL 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)], yielding an additional batch of the title compound as pale yellow solid, mp. 109 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): 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). ^{13}C NMR ($CDCl_3$, 100.6 MHz, DEPT135): δ = 121.22 (+), 122.80 (+), 127.51 (2C, +), 128.65 (+), 128.94 (2C, +), 129.83 (+), 130.69 (C_{quart}), 135.84 (+), 136.68 (+), 137.21 (C_{quart}), 138.79 (C_{quart}), 147.91 (C_{quart}), 158.48 (C_{quart}), 192.14 (+). IR (film): ν = 3059 cm^{-1}, 3034, 2824, 2717, 1954, 1812, 1684, 1601, 1554, 1510, 1491, 1448, 1420, 1392, 1320, 1280, 1168, 1145, 1120, 1075, 1052, 1025, 971, 926, 897, 850, 812, 787, 757, 692, 673, 627. MS (ES+): *m/z* 234.2 (100) [MH^+]. HPLC: t_R = 3.0 min (MicromassZQ, nonpolar_5min).

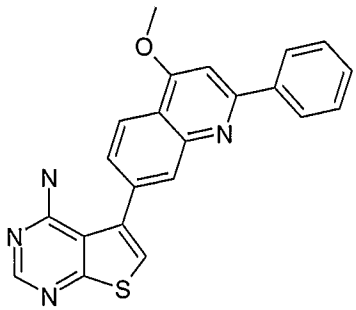
7-Methyl-2-phenylquinoline



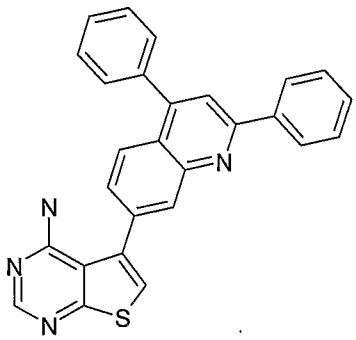
[595] To a solution of 7-methylquinoline (1.63 g, 11.4 mmol) in dry THF (10 mL), cooled by ice/water, was added phenyllithium (1.9 M in cyclohexane/ether 70/30, 6.0 mL, 11.4 mmol) dropwise over 5 min. After 15 min, the cooling bath was removed, and the solution was stirred at ambient temperature for 5 h. The reaction was quenched by adding MeOH, and stirring was continued overnight. Water was added, the mixture was extracted with EtOAc (3×35 mL), and the combined extracts were dried over $MgSO_4$. The drying agent was filtered off, and air was bubbled into the solution for 7 d. The solvent was evaporated; the residue was dissolved in warm (≈50 °C) EtOAc/hexanes and filtered warm. The filtrate was concentrated and dried *in vacuo*, giving the crude title compound that was used directly for the next step. A sample was purified further by chromatography on silica gel (Jones Flashmaster, eluting with hexanes:EtOAc 3:1 → 2:1 → 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz): 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).

[596] The following compounds are made by the methods shown above:

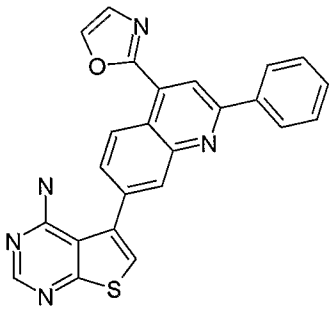
[597] **EXAMPLE 2: 5-(4-Methoxy-2-phenyl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine**



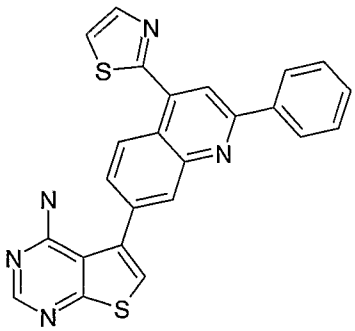
[598] **EXAMPLE 3: 5-(2,4-Diphenyl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine**



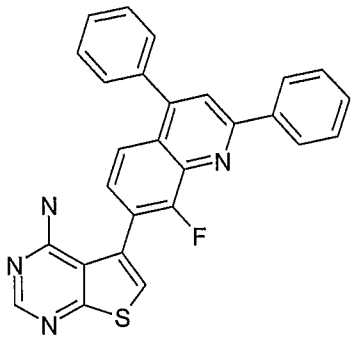
[599] **EXAMPLE 4: 5-(4-Oxazol-2-yl-2-phenyl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine**



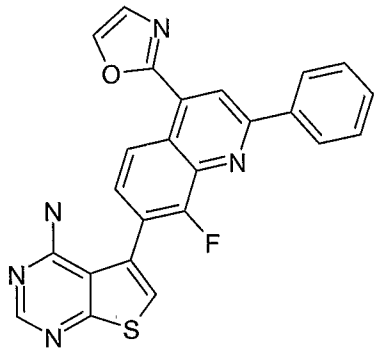
[600] **EXAMPLE 5: 5-(2-Phenyl-4-thiazol-2-yl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine**



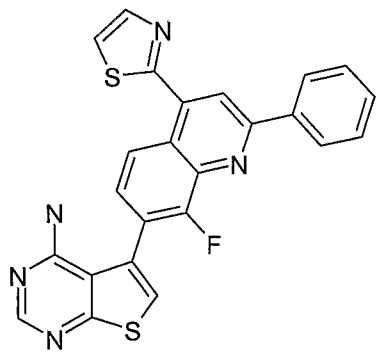
[601] **EXAMPLE 6: 5-(8-Fluoro-2,4-diphenyl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine**



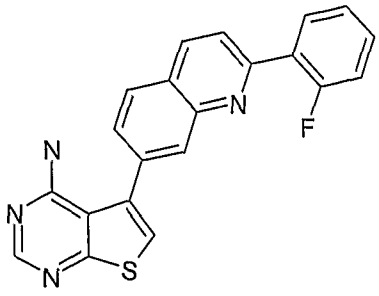
[602] **EXAMPLE 7: 5-(8-Fluoro-4-oxazol-2-yl-2-phenyl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine**



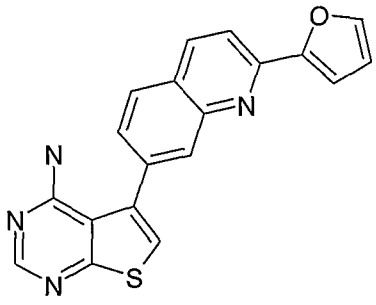
[603] **EXAMPLE 8: 5-(8-Fluoro-2-phenyl-4-thiazol-2-yl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine**



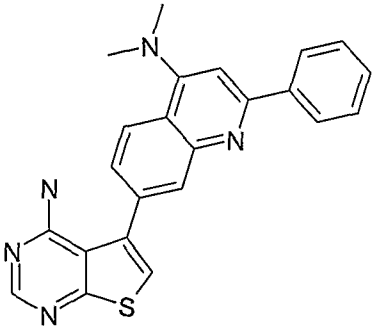
[604] **EXAMPLE 9: 5-[2-(2-Fluoro-phenyl)-quinolin-7-yl]-thieno[2,3-d]pyrimidin-4-ylamine**



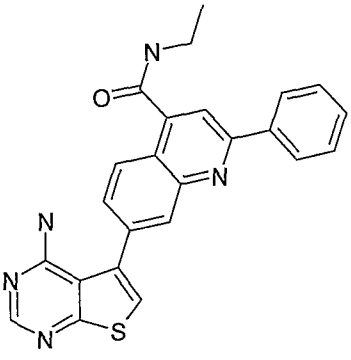
[605] **EXAMPLE 10: 5-(2-Furan-2-yl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine**



[606] **EXAMPLE 11: [7-(4-Amino-thieno[2,3-d]pyrimidin-5-yl)-2-phenyl-quinolin-4-yl]-dimethyl-amine**

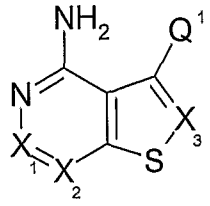


[607] **EXAMPLE 12: 7-(4-Amino-thieno[2,3-d]pyrimidin-5-yl)-2-phenyl-quinoline-4-carboxylic acid ethylamide**



WHAT IS CLAIMED IS:

Claim 1. A compound represented by Formula I:

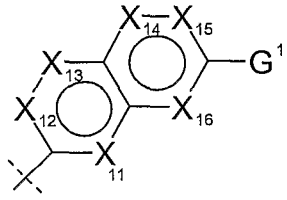


I

or a pharmaceutically acceptable salt thereof, wherein:

X_1, X_2, and X_3 are each independently N or C–$(E^1)_{aa}$;

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^-;

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–$C_{0\text{-}10}$alkyl, heterocyclyl–$C_{2\text{-}10}$alkenyl, or heterocyclyl–$C_{2\text{-}10}$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–$C_{0\text{-}10}$alkyl, aryl–$C_{2\text{-}10}$alkenyl, aryl–$C_{2\text{-}10}$alkynyl, hetaryl–$C_{0\text{-}10}$alkyl, hetaryl–$C_{2\text{-}10}$alkenyl, or hetaryl–$C_{2\text{-}10}$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;

R^2, R^{2a}, R^3, R^{3a}, R^{222}, R^{222a}, R^{333}, and R^{333a} 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 $-NR^{222}R^{333}(R^{222a})_{j2a}$, then R^2 and R^3, or R^{222} and R^{333}, 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}, 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, j5a, j7, and j8 are each independently 0, 1, or 2; and

aa and bb are each independently 0 or 1.

Claim 2. The compound of claim 1, wherein X_1, X_2, and X_3 are $C-(E^1)_{aa}$.

Claim 3. The compound of claim 1 wherein X_1 is N and wherein X_2 and X_3 are $C-(E^1)_{aa}$.

Claim 4. The compound of claim 1 wherein X_2 is N and wherein X_1 and X_3 are C–$(E^1)_{aa}$.

Claim 5. The compound of claim 1 wherein X_3 is N and wherein X_1 and X_2 are C–$(E^1)_{aa}$.

Claim 6. The compound of claim 1 wherein X_1 and X_2 are N and X_3 is C–$(E^1)_{aa}$.

Claim 7. The compound of claim 1 wherein X_1 and X_3 are N and X_2 is C–$(E^1)_{aa}$.

Claim 8. The compound of claim 1 wherein X_2 and X_3 are N and X_1 is C–$(E^1)_{aa}$.

Claim 9. The compound of claim 1 wherein X1, X_2, and X_3 are N.

Claim 10. The compound of claim 2, wherein any one, two, or three of $X_{11\text{-}16}$ is N.

Claim 11. The compound of claim 10, wherein any one of X_{11}, X_{14}, X_{15}, or X_{16} is N.

Claim 12. The compound of claim 10, wherein any two of X_{11}, X_{14}, X_{15}, or X_{16} is N.

Claim 13. The compound of claim 11, wherein X_{11} or X_{16} is N.

Claim 14. The compound of claim 3, wherein any one, two, or three of $X_{11\text{-}16}$ is N.

Claim 15. The compound of claim 14, wherein any one of X_{11}, X_{14}, X_{15}, or X_{16} is N.

Claim 16. The compound of claim 14, wherein any two of X_{11}, X_{14}, X_{15}, or X_{16} is N.

Claim 17. The compound of claim 15, wherein X_{11} or X_{16} is N.

Claim 18. The compound of claim 4, wherein any one, two, or three of $X_{11\text{-}16}$ is N.

Claim 19. The compound of claim 18, wherein any one of X_{11}, X_{14}, X_{15}, or X_{16} is N.

Claim 20. The compound of claim 18, wherein any two of X_{11}, X_{14}, X_{15}, or X_{16} is N.

Claim 21. The compound of claim 19, wherein X_{11} or X_{16} is N.

Claim 22. The compound of claim 5, wherein any one, two, or three of $X_{11\text{-}16}$ is N.

Claim 23. The compound of claim 22, wherein any one of X_{11}, X_{14}, X_{15}, or X_{16} is N.

Claim 24. The compound of claim 22, wherein any two of X_{11}, X_{14}, X_{15}, or X_{16} is N.

Claim 25. The compound of claim 23, wherein X_{11} or X_{16} is N.

Claim 26. The compound of claim 6, wherein any one, two, or three of $X_{11\text{-}16}$ is N.

Claim 27. The compound of claim 26, wherein any one of X_{11}, X_{14}, X_{15}, or X_{16} is N.

Claim 28. The compound of claim 26, wherein any two of X_{11}, X_{14}, X_{15}, or X_{16} is N.

Claim 29. The compound of claim 27, wherein X_{11} or X_{16} is N.

Claim 30. The compound of claim 7, wherein any one, two, or three of $X_{11\text{-}16}$ is N.

Claim 31. The compound of claim 30, wherein any one of X_{11}, X_{14}, X_{15}, or X_{16} is N.

Claim 32. The compound of claim 30, wherein any two of X_{11}, X_{14}, X_{15}, or X_{16} is N.

Claim 33. The compound of claim 31, wherein X_{11} or X_{16} is N.

Claim 34. The compound of claim 8, wherein any one, two, or three of X_{11-16} is N.

Claim 35. The compound of claim 34, wherein any one of X_{11}, X_{14}, X_{15}, or X_{16} is N.

Claim 36. The compound of claim 34, wherein any two of X_{11}, X_{14}, X_{15}, or X_{16} is N.

Claim 37. The compound of claim 35, wherein X_{11} or X_{16} is N.

Claim 38. The compound of claim 9, wherein any one, two, or three of X_{11-16} is N.

Claim 39. The compound of claim 38, wherein any one of X_{11}, X_{14}, X_{15}, or X_{16} is N.

Claim 40. The compound of claim 38, wherein any two of X_{11}, X_{14}, X_{15}, or X_{16} is N.

Claim 41. The compound of claim 39, wherein X_{11} or X_{16} is N.

Claim 42. The compound of claim 2, 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.

Claim 43. The compound of claim 3, 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.

Claim 44. The compound of claim 4, 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.

Claim 45. The compound of claim 5, 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.

Claim 46. The compound of claim 6, 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.

Claim 47. The compound of claim 7, 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.

Claim 48. The compound of claim 8, 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.

Claim 49. The compound of claim 9, 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.

Claim 50. The compound of claim 10, 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.

Claim 51. The compound of claim 14, 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.

Claim 52. The compound of claim 18, 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.

Claim 53. The compound of claim 22, 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.

Claim 54. The compound of claim 26, 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.

Claim 55. The compound of claim 30, 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.

Claim 56. The compound of claim 34, 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.

Claim 57. The compound of claim 38, 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.

Claim 58. A compound selected from:

3-(2-Phenylquinolin-7-yl)-thieno[3,2-*c*]pyridin-4-ylamine;

3-(2-Pyridin-2-ylquinolin-7-yl)-thieno[3,2-*c*]pyridin-4-ylamine;

3-(4-Methyl-2-phenylquinolin-7-yl)-thieno[3,2-*c*]pyridin-4-ylamine;

3-(8-Fluoro-2-phenylquinolin-7-yl)-thieno[3,2-*c*]pyridin-4-ylamine;

3-(8-Fluoro-4-methyl-2-phenylquinolin-7-yl)-thieno[3,2-*c*]pyridin-4-ylamine;

3-(4-Methyl-2-pyridin-2-ylquinolin-7-yl)-thieno[3,2-*c*]pyridin-4-ylamine;

3-(8-Fluoro-2-pyridin-2-ylquinolin-7-yl)-thieno[3,2-*c*]pyridin-4-ylamine;

3-(7-Phenyl-[1,8]naphthyridin-2-yl)-thieno[3,2-*c*]pyridin-4-ylamine;

3-(5-Methyl-7-phenyl-[1,8]naphthyridin-2-yl)-thieno[3,2-*c*]pyridin-4-ylamine;

5-(2-Phenylquinolin-7-yl)-thieno[2,3-*d*]pyrimidin-4-ylamine;

5-(2-Pyridin-2-ylquinolin-7-yl)-thieno[2,3-*d*]pyrimidin-4-ylamine;

5-(4-Methyl-2-phenylquinolin-7-yl)-thieno[2,3-*d*]pyrimidin-4-ylamine;
5-(8-Fluoro-2-phenylquinolin-7-yl)-thieno[2,3-*d*]pyrimidin-4-ylamine;
5-(8-Fluoro-4-methyl-2-phenylquinolin-7-yl)-thieno[2,3-*d*]pyrimidin-4-ylamine;
5-(4-Methyl-2-pyridin-2-ylquinolin-7-yl)-thieno[2,3-*d*]pyrimidin-4-ylamine;
5-(8-Fluoro-2-pyridin-2-ylquinolin-7-yl)-thieno[2,3-*d*]pyrimidin-4-ylamine;
5-(7-Phenyl-[1,8]naphthyridin-2-yl)-thieno[2,3-*d*]pyrimidin-4-ylamine;
5-(5-Methyl-7-phenyl-[1,8]naphthyridin-2-yl)-thieno[2,3-*d*]pyrimidin-4-ylamine;
3-(2-Phenylquinolin-7-yl)-isothiazolo[5,4-*d*]pyrimidin-4-ylamine;
3-(2-Pyridin-2-ylquinolin-7-yl)-isothiazolo[5,4-*d*]pyrimidin-4-ylamine;
3-(4-Methyl-2-phenylquinolin-7-yl)-isothiazolo[5,4-*d*]pyrimidin-4-ylamine;
3-(8-Fluoro-2-phenylquinolin-7-yl)-isothiazolo[5,4-*d*]pyrimidin-4-ylamine;
3-(8-Fluoro-4-methyl-2-phenylquinolin-7-yl)-isothiazolo[5,4-*d*]pyrimidin-4-ylamine;
3-(4-Methyl-2-pyridin-2-ylquinolin-7-yl)-isothiazolo[5,4-*d*]pyrimidin-4-ylamine;
3-(8-Fluoro-2-pyridin-2-ylquinolin-7-yl)-isothiazolo[5,4-*d*]pyrimidin-4-ylamine;
3-(7-Phenyl-[1,8]naphthyridin-2-yl)-isothiazolo[5,4-*d*]pyrimidin-4-ylamine;
3-(5-Methyl-7-phenyl-[1,8]naphthyridin-2-yl)-isothiazolo[5,4-*d*]pyrimidin-4-ylamine; or a pharmaceutically acceptable salt thereof.

Claim 59. 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.

Claim 60. The method of claim 59 wherein said protein kinase is IGF-IR.

Claim 61. The method of claim 59 wherein the condition mediated by protein kinase activity is a hyperproliferative disorder.

Claim 62. The method of claim 59 wherein the activity of said protein kinase influences angiogenesis, vascular permeability, immune response, cellular apoptosis, tumor growth, or inflammation.

Claim 63. The method of claim 59 wherein the protein kinase is a protein serine/threonine kinase or a protein tyrosine kinase.

Claim 64. The method of claim 59 wherein the condition mediated by protein kinase activity is one or more ulcers; or one or more ulcers caused by a bacterial or fungal infection; or Mooren ulcers; or one or more ulcers which are a symptom of ulcerative colitis.

Claim 65. The method of claim 59 wherein the condition mediated by protein kinase activity is Lyme disease, sepsis or infection by Herpes simplex, Herpes Zoster, human immunodeficiency virus, parapoxvirus, protozoa, toxoplasmosis, von Hippel Lindau disease, pemphigoid, psoriasis, Paget's disease, polycystic kidney disease, 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, ischemia, ovarian hyperstimulation syndrome, preeclainpsia, menometrorrhagia, endometriosis, chronic inflammation, systemic lupus, glomerulonephritis, synovitis, inflammatory bowel disease, Crohn's disease, glomerulonephritis, rheumatoid arthritis and osteoarthritis, multiple sclerosis, graft rejection, sickle cell anaemia, an ocular condition, Crow-Fukase (POEMS) syndrome, or a diabetic condition.

Claim 66. The method of claim 65 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.

Claim 67. The method of claim 59 wherein the condition mediated by protein kinase activity is a cardiovascular condition.

Claim 68. The method of claim 67 wherein the condition mediated by protein kinase activity is atherosclerosis, restenosis, ischemia/reperfusion injury, vascular occlusion, venous malformation, or carotid obstructive disease.

Claim 69. The method of claim 59 wherein the condition mediated by protein kinase activity is cancer.

Claim 70. The method of claim 69 wherein the cancer is a solid tumor, a sarcoma, fibrosarcoma, osteoma, melanoma, retinoblastoma, a rhabdomyosarcoma, glioblastoma, neuroblastoma, teratocarcinoma, an hematopoietic malignancy, malignant ascites, Kaposi's sarcoma, Hodgkin's disease, lymphoma, myeloma, or leukemia.

Claim 71. The method of claim 65 wherein the diabetic condition is insulin-dependent diabetes mellitus glaucoma, diabetic retinopathy, or microangiopathy.

Claim 72. The method of claim 59 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.

Claim 73. 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.

Claim 74. 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 73.

Claim 75. A pharmaceutical composition comprising an EGFR kinase inhibitor and the compound of claim 1 in a pharmaceutically acceptable carrier.

Claim 76. The pharmaceutical composition of claim 75 wherein the EGFR kinase inhibitor is erlotinib.

Claim 77. The pharmaceutical composition of claim 76 wherein the erlotinib is present as a hydrochloride salt.

Claim 78. The pharmaceutical composition of claim 75 additionally comprising one or more other anti-cancer agents.

Claim 79. The pharmaceutical composition of claim 76 additionally comprising one or more other anti-cancer agents.

Claim 80. A method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of an EGFR kinase inhibitor and the compound of claim 1.

Claim 81. A method for treating tumors or tumor metastases in a patient, comprising administering to said patient simultaneously or sequentially a therapeutically effective amount of the EGFR kinase inhibitor erlotinib and the compound of claim 1.

Claim 82. The method of claim 80, wherein the patient is a human that is being treated for cancer.

Claim 83. The method of claim 81, wherein the patient is a human that is being treated for cancer.

Claim 84. The method of claim 80, wherein the EGFR kinase inhibitor and the compound of claim 1 are co-administered to the patient in the same or different formulations.

Claim 85. The method of claim 81, wherein the erlotinib and the compound of claim 1 are co-administered to the patient in the same or different formulations.

Claim 86. The method of claim 80, wherein the EGFR kinase inhibitor and the compound of claim 1 are co-administered to the patient by the same or different routes.

Claim 87. The method of claim 81, wherein erlotinib and the compound of claim 1 are co-administered to the patient by the same or different routes.

Claim 88. The method of claim 80, wherein the EGFR kinase inhibitor or the compound of claim 1 are administered to the patient by parenteral or oral administration.

Claim 89. The method of claim 81, wherein erlotinib or the compound of claim 1 are administered to the patient by parenteral or oral administration.

Claim 90. The method of claim 80, additionally comprising one or more other anti-cancer agents.

Claim 91. The method of claim 81, additionally comprising one or more other anti-cancer agents.

Claim 92. The method of claim 90, wherein the other anti-cancer agents are one or more agents selected from an alkylating agent, cyclophosphamide, chlorambucil, cisplatin, busulfan, melphalan, carmustine, streptozotocin, triethylenemelamine, mitomycin C, an anti-metabolite, methotrexate, etoposide, 6-mercaptopurine, 6-thiocguanine, cytarabine, 5-fluorouracil, raltitrexed, capecitabine, dacarbazine, an antibiotic, actinomycin D, doxorubicin, daunorubicin, bleomycin, mithramycin, an alkaloid, vinblastine, paclitaxel, a glucocorticoid, dexamethasone, a corticosteroid, prednisone, a nucleoside enzyme inhibitors, hydroxyurea, an amino acid depleting enzyme, asparaginase, folinic acid, leucovorin, and a folic acid derivative.

Claim 93. The method of claim 91, wherein the other anti-cancer agents are one or more agents selected from an alkylating agent, cyclophosphamide, chlorambucil, cisplatin, busulfan, melphalan, carmustine, streptozotocin, triethylenemelamine, mitomycin C, an anti-metabolite, methotrexate, etoposide, 6-mercaptopurine, 6-thiocguanine, cytarabine, 5-fluorouracil, raltitrexed,

capecitabine, dacarbazine, an antibiotic, actinomycin D, doxorubicin, daunorubicin, bleomycin, mithramycin, an alkaloid, vinblastine, paclitaxel, a glucocorticoid, dexamethasone, a corticosteroid, prednisone, a nucleoside enzyme inhibitors, hydroxyurea, an amino acid depleting enzyme, asparaginase, folinic acid, leucovorin, and a folic acid derivative.

Claim 94. A method of preparing a pharmaceutical composition useful for treating tumors or tumor metastases in a patient, comprising combining the compound of claim 1 with an EGFR kinase inhibitor.

Claim 95. The method of claim 94 wherein the EGFR kinase inhibitor is erlotinib.

Claim 96. The method of claim 94, further comprising combining a pharmaceutically acceptable carrier with the compound of claim 1 and erlotinib.

Claim 97. The composition according to claim 75, additionally comprising one or more other anti-cancer agents.

Claim 98. The composition according to claim 76, additionally comprising one or more other anti-cancer agents.

Claim 99. A composition in accordance with claim 97, wherein said other anti-cancer agent is a member selected from the group consisting of alkylating drugs, antimetabolites, microtubule inhibitors, podophyllotoxins, antibiotics, nitrosoureas, hormone therapies, kinase inhibitors, activators of tumor cell apoptosis, and antiangiogenic agents.

Claim 100. A composition in accordance with claim 98, wherein said other anti-cancer agent is a member selected from the group consisting of alkylating drugs, antimetabolites, microtubule inhibitors, podophyllotoxins, antibiotics, nitrosoureas, hormone therapies, kinase inhibitors, activators of tumor cell apoptosis, and antiangiogenic agents.

Claim 101. A method for the treatment of cancer, comprising administering to a subject in need of such treatment (i) an effective or sub-therapeutic first amount of the EGFR kinase inhibitor erlotinib, or a pharmaceutically acceptable salt thereof; and (ii) an effective or sub-therapeutic second amount of the compound of claim 1.

Claim 102. The method of claim 80, wherein the tumors or tumor metastases to be treated are colorectal tumors or tumor metastases.

Claim 103. The method of claim 81, wherein the tumors or tumor metastases to be treated are colorectal tumors or tumor metastases.

Claim 104. A compound selected from the group consisting of:

5-(4-Methoxy-2-phenyl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine,

5-(2,4-Diphenyl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine,

5-(4-Oxazol-2-yl-2-phenyl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine,

5-(2-Phenyl-4-thiazol-2-yl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine,

5-(8-Fluoro-2,4-diphenyl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine,

5-(8-Fluoro-4-oxazol-2-yl-2-phenyl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine,

5-(8-Fluoro-2-phenyl-4-thiazol-2-yl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine,

5-[2-(2-Fluoro-phenyl)-quinolin-7-yl]-thieno[2,3-d]pyrimidin-4-ylamine,

5-(2-Furan-2-yl-quinolin-7-yl)-thieno[2,3-d]pyrimidin-4-ylamine,

[7-(4-Amino-thieno[2,3-d]pyrimidin-5-yl)-2-phenyl-quinolin-4-yl]-dimethyl-amine,

7-(4-Amino-thieno[2,3-d]pyrimidin-5-yl)-2-phenyl-quinoline-4-carboxylic acid ethylamide,

or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/031433

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D495/04 A61K31/519 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

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, PAJ, BEILSTEIN Data, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/010009 A (ABBOTT LAB [US]; BETSCHMANN PATRICK [US]; BURCHAT ANDREW F [US]; CALDE) 3 February 2005 (2005-02-03) Formula I; page 12, line 6 - page 14, line 2; claims 1,23-28; example 158 page 24, lines 9-29 page 28, line 34 - page 29, line 3 page 38, line 27 - page 40, line 26 page 48, lines 3-30 ----- -/--	1,2,5, 10-13, 22-25, 42,45, 50,53, 58-103

[X] Further documents are listed in the continuation of Box C.

[X] 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 March 2007	13/03/2007

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, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rudolf, Manfred

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/031433

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/100947 A (SMITHKLINE BEECHAM CORP [US]; MIYAZAKI YASUSHI [JP]) 25 November 2004 (2004-11-25) Formula I, page 1, columns 5-7; claims 1,7; examples 16,20	1-104
A	WO 03/080625 A (ABBOTT LAB [US]) 2 October 2003 (2003-10-02) Formula I; page 20, lines 7-28; claims 1,21-25	1-104
A	ERIC DUVAL, APRIL CASE, ROSS L. STEIN, GREGORY D. CUNY: "Structure-Activity relationship study of novel tissue transglutaminase inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 15, 2005, pages 1885-1889, XP002422814 table 2	1-104

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/031433

Box 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.: 59-72,74,80-93,101-103
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 59-72,74,80-93,101-103 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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 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 all searchable claims.

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

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers 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.

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/031433

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