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(71) **Applicant: NATION HEALTH RESEARCH INSTITUTES**; Transfer Center (A-3160), No. 35, Keyan Road, Zhunan Town, Miaoli County, 35053 (TW).

(72) **Inventors: HSIEH, Hsing-Pang**; 35 Keyan Road, Zhunan, Miaoli County, 35053 (TW). **LEE, Kun-Hung**; 4F, No. 78, Guangming Road, Sanxia Dist., New Taipei City, 237 (TW). **LIN, Wen-Hsing**; 10F, No. 9, Ln. 51, Minquan St., Zhunan Township, Miaoli County, 350 (TW). **SHIH, Chuan**; 16032 Colleton Court, Carmel, IN 46033 (US).

(74) **Agent: TSAO, Y., Rocky**; Cesari and McKenna, LLP, One Liberty Square, Boston, MA 02109 (US).

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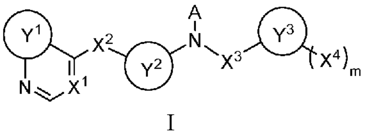
(54) Title: HETEROCYCLIC COMPOUNDS AS KINASE INHIBITORS FOR THERAPEUTIC USES



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(57) **Abstract:** Heterocyclic compounds of formula I shown below and pharmaceutical compositions containing one of such compounds: Also disclosed is a method of treating a condition modulated by the colony-stimulating factor-1 receptor with one of the heterocyclic compounds.

HETEROCYCLIC COMPOUNDS AS KINASE INHIBITORS FOR THERAPEUTIC USES

BACKGROUND

Colony-stimulating factor-1 receptor (CSF1R) is a member of tyrosine kinase class III. It plays an important role in cell proliferation, differentiation, migration, and survival. See Cannarile et al., *J. Immunother. Cancer,* 2017, 5:53. Deregulation of this tyrosine kinase is associated with various disorders and diseases, such as inflammatory disorders, neurological disorders, cardiovascular diseases, bone-related diseases, and cancers.

Recent studies have shown that CSF1R is related to differentiation of tumor-associated macrophages (TAMs). See El-Gamal et al., *J. Med. Chem.*, 2018, 61, 5450-5466. Specifically, TAMs express, on their surfaces, CSF1R, which forms a signaling axis with an active ligand, i.e., colony stimulating factor-1 (CSF1). When activated, the CSF1R/CSF1 signaling axis promotes proliferation of monocytes, differentiation of the monocytes into TAMs, and survival of the TAMs.

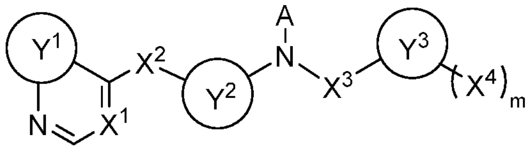
Overexpression of CSF1 in several forms of cancer has been associated with activation and recruitment of TAMs to tumor sites. TAMs modify tumor microenvironment to render it more conducive to cancer cell growth, angiogenesis, and metastasis. Further, they can cause localized immunosuppression in tumor tissues, resulting in resistance to cancer therapy. As such, inhibiting the CSF1R/CSF1 signaling axis presents an attractive avenue for treating cancers associated with overexpression of CSF1.

Thus, there is a need to provide compounds that selectively inhibit CSF1R, demonstrate favorable safety profiles, and also exhibit high *in vivo* efficacy in treating cancers associated with CSF1R.

SUMMARY

The present invention is based on unexpected discoveries that certain heterocyclic compounds effectively inhibit colony-stimulating factor-1 receptor (CSF1R).

In one aspect, this invention relates to these heterocyclic compounds and other heterocyclic compounds analogous thereto covered by formula I:



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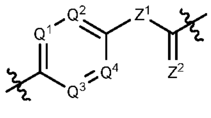
in which A is H, C_{1-6} alkyl, or ORr, Rr being H or C_{1-6} alkyl; Y^1 is phenyl substituted with $(R^1)_n$, 5-membered heteroaryl substituted with $(R^2)_o$, 5-membered heterocycloalkenyl substituted with $(R^2)_o$, or alkenyl substituted with $(R^2)_o$, in which R^1 in $(R^1)_n$, n being 0–4, is, independently, F, Cl, Br, NO_2, CN, amino, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_5-C_{15} heterocycloalkyl, aryl, heteroaryl, carbonyl, thionyl, iminyl, or spiroamino; and R^2 in $(R^2)_o$, o being 0-5, is, independently, F, Cl, Br, NO_2, CN, amino, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_5-C_{15} heterocycloalkyl, aryl, heteroaryl, carbonyl, thionyl, iminyl, spiroamino, or C_1-C_6 alkoxyl; X^1 is N or CR^3, R^3 being H, F, Cl, Br, CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl; X^2 is O, S, NH, or CH_2; Y^2 is



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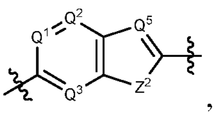

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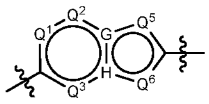

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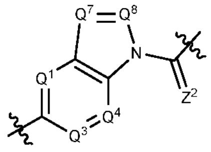

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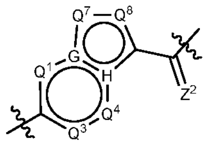


, in which each of Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, and Q^8 is, independently, N or CR^4, R^4 being H, F, Cl, Br, CN, amino, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl; Z^1 is O, S, or NRr; Z^2 is O, S, or NRr; and G and H are, respectively, C or N and N or C; X^3 is deleted, CH_2, $(CH_2)_2$, or CH(C≡CH); Y^3 is C_1-C_6 alkyl, aryl, heteroaryl, C_3-C_8 cycloalkyl, or C_5-C_6 heterocycloalkyl having one heteroatom, in which the one heteroatom is O or N; and X^4 in $(X^4)_m$, m being 0–5, is, independently, F, Cl, Br, CN, SO_2NH_2, amino, C_1-C_6 alkyl, or C_1-C_6 alkoxyl.

The term “alkyl” refers to a straight or branched monovalent hydrocarbon moiety containing 1-20 carbon atoms, e.g., methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, and *t*-butyl. The term “haloalkyl” refers to an alkyl group substituted with one or more halogen atoms. The term “alkenyl” refers to a straight or branched monovalent or bivalent hydrocarbon containing 2-20 carbon atoms and one or more double bonds, e.g., ethenyl, propenyl, propenylene, allyl, and 1,4-butadienyl. The term “alkynyl” refers to a straight or branched monovalent or bivalent hydrocarbon containing 2-20 carbon atoms and one or more triple bonds, e.g., ethynyl, ethynylene, 1-propynyl, 1- and 2-butynyl, and 1-methyl-2-butynyl. The term “aryl” refers to a monovalent 6-carbon monocyclic, 10-carbon bicyclic, 14-carbon tricyclic aromatic ring system, e.g., phenyl, naphthyl, and anthracenyl. The term “heteroaryl” refers to a monovalent aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having one or more heteroatoms (such as O, N, S, or Se), e.g., imidazolyl, pyrazoyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrazinyl, pyrimidyl, pyridazinyl, furyl, and thienyl. The term “cycloalkyl” refers to a monovalent or bivalent saturated hydrocarbon ring system having 3 to 30 carbon atoms (e.g., C_3-C_{12}), e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, 1,4-cyclohexylene, cycloheptyl, and cyclooctyl. The term “cycloalkenyl” refers to a monovalent or bivalent non-aromatic hydrocarbon ring system having 3 to 30 carbons (e.g., C_3-C_{12}) and one or more double bonds, e.g., cyclopentenyl, cyclohexenyl, and cycloheptenyl. The term "heterocycloalkyl" refers to a monovalent or bivalent nonaromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having one or more heteroatoms (such as O, N, S, or Se), e.g., piperidinyl, piperazinyl, pyrrolidinyl, dioxanyl, morpholinyl, tetrahydrofuranyl, and tetrahydropyranyl. The term "heterocycloalkenyl" refers to a monovalent or bivalent nonaromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having one or more heteroatoms (such as O, N, S, or Se) and one or more double bonds. The term “amino” refers to a –NRR′ moiety, in which R and R′ are, independently, H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, aralkyl, or heteroarakyl. The term “carbonyl” refers to a –C(O)R moiety, in which R is H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, alkoxyl, amino, aryl, or heteroaryl. The term “thionyl” refers to a –S(O)R moiety, in which R is H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, alkoxyl, amino, aryl, or heteroaryl. The term “iminyl” refers to a –C(NR)R′, in which R is H or C_1-C_6 alkyl and R′ is H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, alkoxyl, amino, aryl, or heteroaryl. The term “spiroamino” refers to a monovalent 7-11 membered bicyclic spiro moiety containing one N or a monovalent 10-16 membered tricyclic spiro moiety containing one N.

In addition, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, and alkoxyl can be substituted or unsubstituted. Possible substituents include, but are not limited to, D, CN, NO_2, halo, C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_2-

C_{20} alkynyl, C_1-C_{10} alkoxyl, C_3-C_{30} cycloalkyl, C_3-C_{30} cycloalkenyl, C_3-C_{30} heterocycloalkyl, C_3-C_{30} heterocycloalkenyl, aryl, aryloxyl, heteroaryl, heteroaryloxyl, amino, halo, oxo (O=), thioxo (S=), thio, silyl, C_1-C_{10} alkylthio, arylthio, C_1-C_{10} alkylsulfonyl, arylsulfonyl, acylamino, aminoacyl, aminothioacyl, amidino, mercapto, amido, thioureido, thiocyanato, sulfonamido, guanidine, ureido, acyl, thioacyl, acyloxy, carbamido, carbamyl, carboxyl, and carboxylic ester.

The compounds of formula I include the compounds themselves, as well as their salts, their stereoisomers, their solvates, their tautomers, their deuterated analogues, and their prodrugs, if applicable. A salt, for example, can be formed between an anion and a positively charged group (e.g., ammonium) on a heterocyclic compound of this invention. Suitable anions include chloride, bromide, iodide, sulfate, bisulfate, sulfamate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, glutamate, glucuronate, glutarate, malate, maleate, succinate, fumarate, tartrate, tosylate, salicylate, lactate, naphthalenesulfonate, and acetate. Likewise, a salt can also be formed between a cation and a negatively charged group (e.g., carboxylate) on a heterocyclic compound. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion. The salts of the heterocyclic compounds of this invention can also contain quaternary nitrogen atoms. Examples of prodrugs include esters and other pharmaceutically acceptable derivatives, which, upon administration to a subject, are capable of providing active heterocyclic compounds. A solvate refers to a complex formed between an active heterocyclic compound and a pharmaceutically acceptable solvent, e.g., water, ethanol, isopropanol, ethyl acetate, acetic acid, and ethanolamine.

An additional aspect of this invention relates to a pharmaceutical composition containing one or more of the heterocyclic compounds covered by formula I. The pharmaceutical composition can be used for treatment of a CSF1R modulated condition.

Also within the scope of this invention is a method of treating a CSF1R modulated condition, e.g., a cancer, an inflammatory disorder, a bone disorder, or an autoimmune disease. The method includes administering to a subject in need thereof an effective amount of one or more of the above-described heterocyclic compounds.

The term “treatment” or “treating” refers to administering one or more heterocyclic compounds of this invention to a subject who has a CSF1R modulated condition, a symptom of such a condition, or a predisposition toward it, with the purpose of conferring a therapeutic or prophylactic effect. “An effective amount” refers to the amount of an active compound that is required to confer such effect. Effective doses will vary, as recognized by those skilled in the art, depending on the types of disease treated, route of administration, excipient usage, and the possibility of co-usage with other therapeutic treatment.

A pharmaceutical composition of this invention can be administered parenterally, orally, nasally, rectally, topically, or buccally. The term “parenteral” as used herein refers to subcutaneous, intracutaneous, intravenous, intraperitoneal, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional, or intracranial injection, as well as any suitable infusion technique.

A sterile injectable composition can be a solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are mannitol, water, Ringer’s solution, and isotonic sodium chloride solution. In addition, fixed oils are conventionally employed as a solvent or suspending medium (e.g., synthetic mono- or di-glycerides). Fatty acids, such as oleic acid and its glyceride derivatives, are useful in preparation of injectables, as are natural pharmaceutically acceptable oils, such as olive oil and castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions can also contain a long chain alcohol diluent or dispersant, carboxymethyl cellulose, or similar dispersing agents. Other commonly used surfactants such as Tweens and Spans or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms can also be used for the purpose of formulation.

A composition for oral administration can be any orally acceptable dosage form including capsules, tablets, emulsions and aqueous suspensions, dispersions, and solutions. In the case of tablets, commonly used carriers include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions or emulsions are administered orally, the active ingredient can be suspended or dissolved in an oily phase combined with emulsifying or suspending agents. If desired, certain sweetening, flavoring, or coloring agents can be added.

A nasal composition can be prepared according to techniques well known in the art of pharmaceutical formulation. For example, such a composition can be prepared as a solution in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

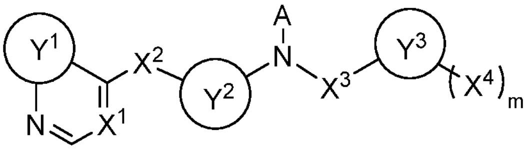
A pharmaceutical composition of this invention can also be administered in the form of a suppository for rectal administration.

The carrier in a pharmaceutical composition must be “acceptable” in the sense that it is compatible with the active ingredient of the composition and, preferably, capable of stabilizing the active ingredient, and not deleterious to the subject to be treated. One or more solubilizing agents can be utilized as pharmaceutical excipients for delivery of an active heterocyclic compound of this invention. Examples of other carriers include colloidal silicon oxide, magnesium stearate, cellulose, sodium lauryl sulfate, and D&C Yellow #10.

The details of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the following detailed description of several embodiments, and also from the appending claims.

DETAILED DESCRIPTION

Disclosed first in detail are heterocyclic compounds of formula I:



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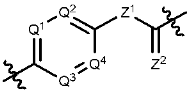
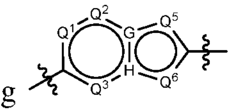
A, Y^1, X^1, X^2, Y^2, X^3, Y^3, X^4, and m are defined in the SUMMARY section above.

In one embodiment, the compounds of formula I have Y^1 being phenyl substituted with $(R^1)_n$, 5-membered heteroaryl substituted with $(R^2)_o$, or 5-membered heterocycloalkenyl substituted with $(R^2)_o$, in which R^1 in $(R^1)_n$ is, independently, F, Cl, Br, NO_2, CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_5-C_{15} heterocycloalkyl, aryl, heteroaryl, carbonyl, thionyl, iminyl, or spiroamino; and R^2 in $(R^2)_o$ is, independently, F, Cl, Br, NO_2, CN, amino, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_5-C_{15} heterocycloalkyl, aryl, heteroaryl, carbonyl, thionyl, iminyl, spiroamino, or C_1-C_6 alkoxyl.

In one subset of this embodiment, the compounds of formula I have Y^2 being



, Y^3 being pyridyl, and R^1 being C_5-C_{15} heterocycloalkyl.

In another embodiment, the compounds of formula I have Y^2 being 

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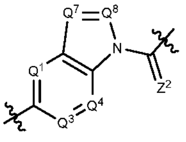
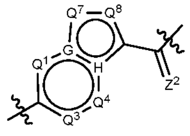
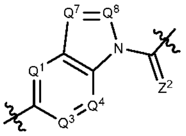


, or 

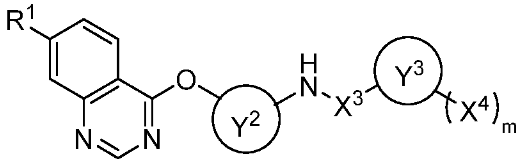
, in which Z^2 is O or NRr.

In one subset of this embodiment, the compounds of formula I have Y^2 being



, Y^3 being pyridyl, and R^1 being amino.

In still another embodiment, the compounds of formula I are those covered by formula Ia:



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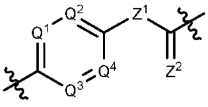
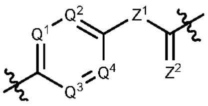
in which R^1 is amino or C_5-C_{15} heterocycloalkyl.

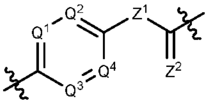
In one subset of this embodiment, the compounds of formula Ia have Y^2 being

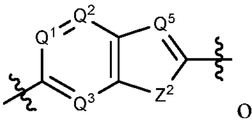
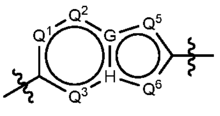
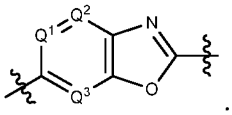


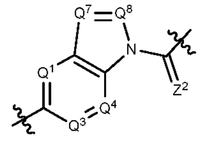
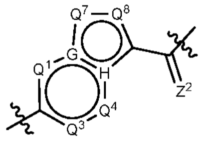
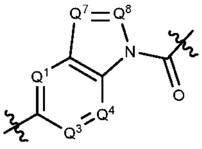
; Y^3 being pyridyl; X^3 being CH_2; X^4 being CH_3, CH_2F, CHF_2, CF_3, or OCH_3; m being 1; and R^1 preferably being amino.

In another subset, the compounds have Y^2 being 

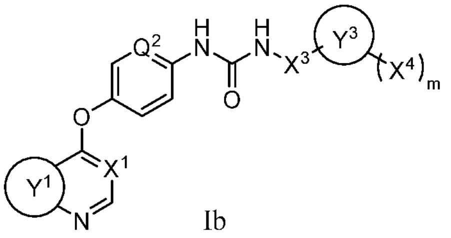
; Y^3 being phenyl; X^3 being CH_2; each of X^4 being, independently, F, Cl, Br, CN, SO_2NH_2, CH_3, CH_2F, CHF_2, CF_3, OCF_3, C_1-C_6 alkoxyl, or amino; and m being 0–2.

In a third subset, the compounds have Y^2 being ; Y^3 being phenyl; X^3 being deleted; each of X^4 being, independently, F, Cl, Br, CN, SO_2NH_2, CH_3, CH_2F, CHF_2, CF_3, OCF_3, C_1-C_6 alkoxyl, or amino; and m being 0–2.

Formula Ia includes compounds in which Y^2 is  or , Y^3 is phenyl or pyridyl, and X^3 is CH_2. As an example, Y^2 is .

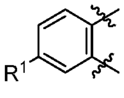
Formula Ia further includes compounds in which Y^2 is  or , Y^3 is phenyl or pyridyl, and X^3 is CH_2. For instance, Y^2 is .

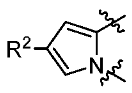
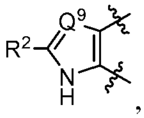
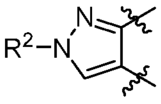
In a fourth embodiment, the heterocyclic compounds of this invention are covered by formula Ib:

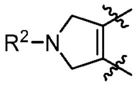
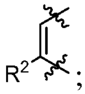


Ib

.

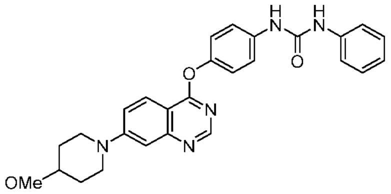
A subset of compounds of formula Ib have Y^1 being , Y^3 being phenyl or pyridyl; and X^3 being deleted or CH_2.

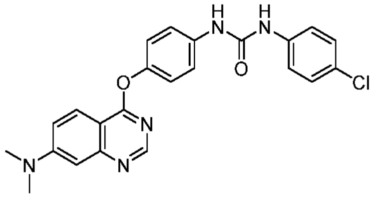
In a different subset, compounds of formula Ib have Y^1 being , , or ; Y^3 being phenyl or pyridyl; and X^3 being deleted or CH_2, in which Q^9 is N or CR^5, R^5 being H, F, Cl, Br, CN, amino, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl.

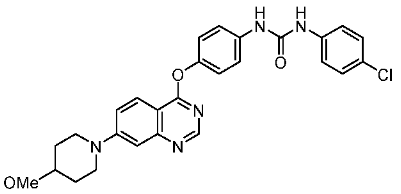
In another subset, compounds of this formula have Y^1 being  or ; Y^3 being phenyl or pyridyl; and X^3 being deleted or CH_2.

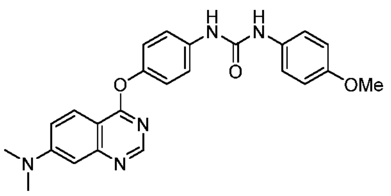
Typically, the compounds of formula Ib have each of X^4 being, independently, CH_3, CH_2F, CHF_2, CF_3, or OCH_3 and m being 0–2.

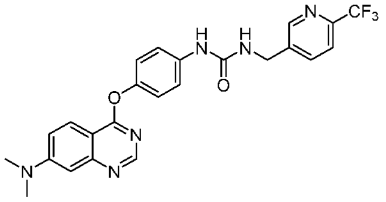
Exemplary compounds of formula I include, but are not limited to, the following compounds:

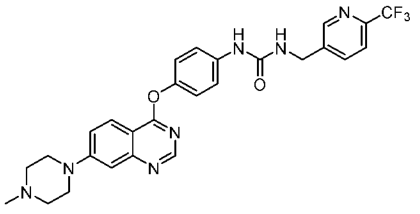


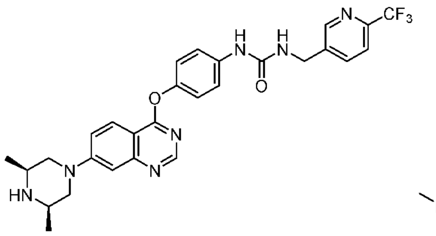


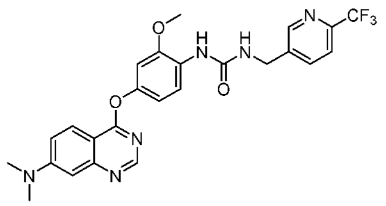


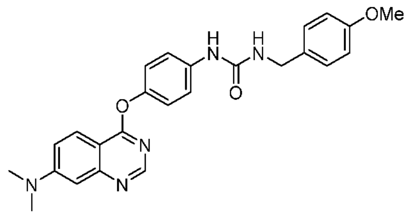


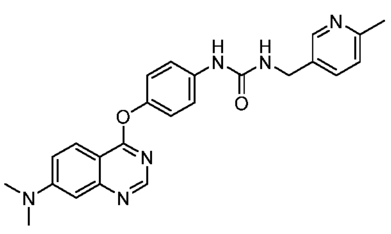


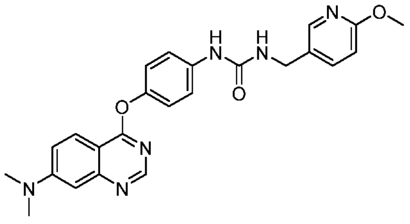


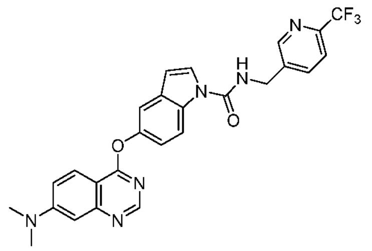


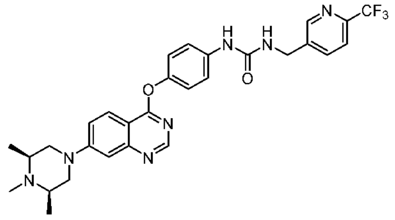


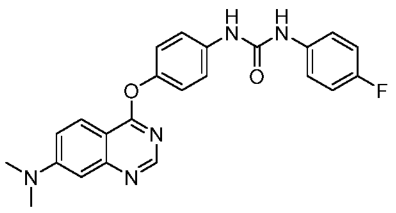


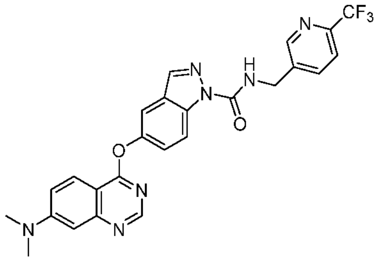


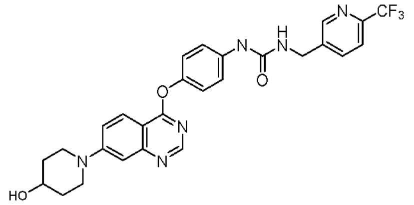


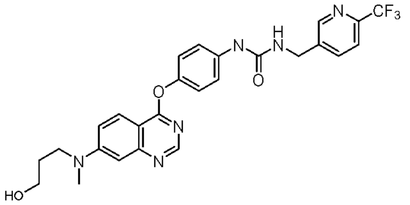


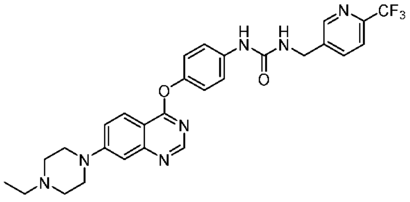












The compounds of formula I can be prepared according to methods well known in the field. See, for example, R. Larock, Comprehensive Organic Transformations (2nd Ed., VCH Publishers 1999); P. G. M. Wuts and T. W. Greene, Greene's Protective Groups in Organic Synthesis (4th Ed., John Wiley and Sons 2007); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis (John Wiley and Sons 1994); L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis (2nd ed., John Wiley and Sons 2009); and G. J. Yu *et al., J. Med. Chem.* 2008, *51*, 6044-6054.

Also within the scope of this invention is a pharmaceutical composition containing one or more of the heterocyclic compounds of formula I. The pharmaceutical composition is used for treating a CSF1R modulated condition.

In certain embodiments, the pharmaceutical composition further contains one of the following therapeutic agents: an anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory agent, and an immunosuppressive agent.

In other embodiments, the pharmaceutical composition further contains one of the following therapeutic agents: an alkylating agent, e.g., adozelesin, altretamine, bizelesin, busulfan, carboplatin, carboquone, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, estramustine, fotemustine, hepsulfam, ifosfamide, improsulfan, irofulven, lomustine, mechlorethamine, melphalan, oxaliplatin, piposulfan, semustine, streptozocin, temozolomide, thiotepa, and treosulfan; an antibody, e.g., alemtuzumab, bevacizumab, cetuximab, galiximab, gemtuzumab, nivolumab, panitumumab, pembrolizumab, pertuzumab, rituximab, tositumomab, trastuzumab, and 90 Y ibritumomab tiuxetan; a targeted signal transduction inhibitor, e.g., bortezomib, geldanamycin, and rapamycin; a kinase inhibitor, e.g., erlotinib, gefitinib, flavopiridol, imatinib mesylate, lapatinib, sorafenib, sunitinib malate, AEE-788, AG-013736, AMG 706, AMN107, BMS-354825, BMS-599626, 7-hydroxystaurosporine, vemurafenib, dabrafenib, trametinib, cobimetinib, selumetinib, and vatalanib; a taxane, e.g., DJ-927, docetaxel, TPI 287, paclitaxel, and DHA-paclitaxel; a retinoid, e.g., alitretinoin, bexarotene, fenretinide, isotretinoin, and tretinoin; an alkaloid, e.g., etoposide, homoharringtonine, teniposide, vinblastine, vincristine, vindesine, and vinorelbine; an antibiotic, e.g., bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, menogaril, mitomycin, mitoxantrone, neocarzinostatin, pentostatin, and plicamycin; an antiangiogenic agent, e.g., AE-941, ABT-510, 2-methoxyestradiol, lenalidomide, and thalidomide; a topoisomerase inhibitor, e.g., amsacrine, edotecarin, exatecan, irinotecan, 7-ethyl-10-hydroxy-camptothecin, rubitecan, topotecan, and 9-aminocamptothecin; an antimetabolite, e.g., azacitidine, capecitabine, cladribine, clofarabine, cytarabine, decitabine, floxuridine, fludarabine, 5-fluorouracil, ftorafur, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, nelarabine, pemetrexed, raltitrexed, thioguanine, and trimetrexate; a hormone or hormone antagonist, e.g., anastrozole, androgens, buserelin, diethylstilbestrol, exemestane, flutamide, fulvestrant, goserelin, idoxifene, letrozole, leuprolide, magestrol, raloxifene, tamoxifen, and toremifene; a biological response modifier, e.g., imiquimod, interferon-α, and interleukin-2; an indoleamine 2,3-dioxygenase inhibitor; a chemotherapeutic agent, e.g., 3-amino-2-carboxyaldehyde thiosemicarbazone, altrasentan, aminoglutethimide, anagrelide, asparaginase, bryostatin-1, cilengitide, elesclomol, eribulin mesylate, ixabepilone, lonidamine, masoprocol, mitoguanazone, oblimersen, sulindac, testolactone, and tiazofurin; a mammalian target of rapamycin inhibitor; a phosphoinositide 3-kinase inhibitor; a cyclin-dependent kinase 4 inhibitor; a protein kinase B inhibitor; a heat shock protein 90 inhibitor; a farnesyltransferase inhibitor; an aromatase inhibitor (such as anastrozole, letrozole, and exemestane); a mitogen-activated protein kinase kinase inhibitor; a tyrosine kinase inhibitor; an epidermal growth factor receptor inhibitor; a programmed cell death protein 1 inhibitor; a programmed death-ligand 1 inhibitor; or an interleukin 8 receptor beta inhibitor.

Still within the scope of this invention is a method of treating a CSF1R modulated condition using one or more of the above-described heterocyclic compounds. For example, the condition can be a cancer, e.g., acute myeloid leukemia, bladder cancer, breast cancer, cervical cancer, colon cancer, gastric cancer, gastrointestinal stromal tumor, glioblastoma multiforme, hepatocellular carcinoma, Hodgkin’s lymphoma, kidney cancer, liver cancer, lung cancer, melanoma, metastatic tumor, ovarian cancer, pancreatic cancer, pigmented villondular synovitis, prostate cancer, tenosynovial giant cell tumors, endometrial cancer, multiple myeloma, myelocytic leukemia, bone cancer, renal cancer, brain cancer, myeloproliferative disorder, esophageal cancer, squamous cell carcinoma, uveal melanoma, follicular lymphoma, colorectal cancer, head and neck cancer, astrocytoma, and pulmonary adenocarcinoma; an inflammatory disorder or an autoimmune disease, e.g., psoriatic arthritis, arthritis, asthma, thyroiditis, glomerular nephritis, atherosclerosis, psoriasis, Sjogren's syndrome, rheumatoid arthritis, systemic lupus erythematosis, cutaneous lupus erythematosus, Crohn's disease, ulcerative colitis, type I diabetes, multiple sclerosis, human immunodeficiency virus encephalitis, Alzheimer's disease, amyotrophic lateral sclerosis, and epilepsy; or a bone disorder, e.g., osteoporosis, osteoarthritis, periodontitis, periprosthetic osteolysis, and Paget’s disease.

Without further elaboration, it is believed that one skilled in the art can, based on the above description, utilize the present invention to its fullest extent. The following specific examples are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. All publications cited herein are incorporated by reference in their entirety.

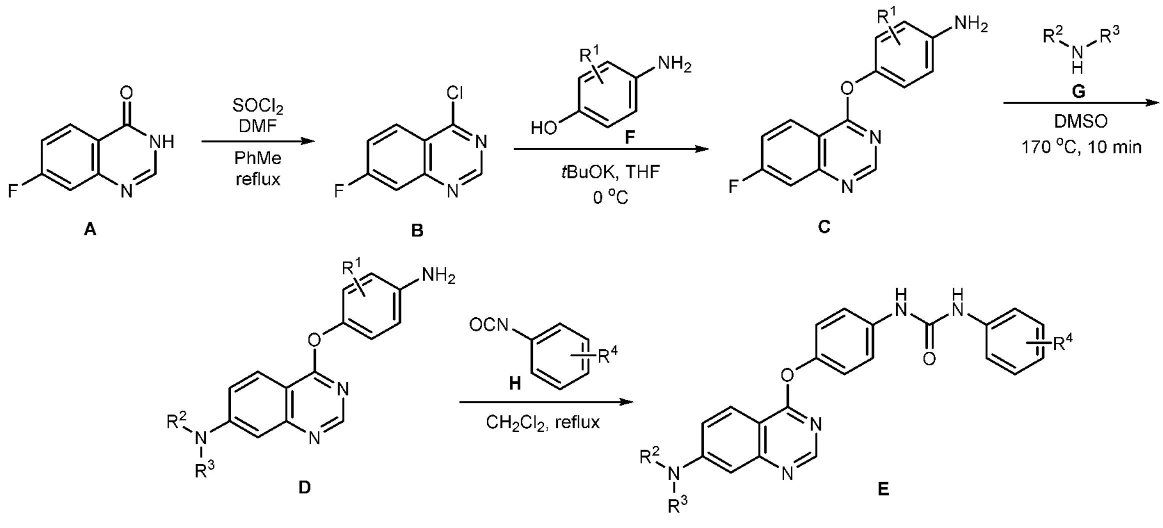
EXAMPLE 1: Synthesis of heterocyclic compounds

Exemplary compounds of this invention, shown in Table 1 below, were prepared by procedures shown in Scheme 1, Scheme 2, Scheme 3, or Scheme 4. Table 1 includes mass spectral data for the compounds.

All chemicals and solvents were purchased from commercial suppliers and used as received. All reactions were carried out under an atmosphere of dry nitrogen unless specified otherwise. Reactions were monitored by thin layer chromatography using Merck 60 F254 silica gel glass backed plates (5 × 10 cm) and zones were detected visually under ultraviolet irradiation (254 nm) or by spraying with phosphomolybdic acid reagent (Aldrich) followed by heating at 80°C. Microwave reactions were performed in the CEM Discover SP System.

Flash column chromatography was performed by using Merck Kieselgel 60, No. 9385, 230-400 mesh ASTM silica gel as the stationary phase. Proton nuclear magnetic resonance (^{1}H NMR) spectra were measured on a Varian Mercury-300 or Varian Mercury-400 spectrometer. Chemical shifts were recorded in parts per million (ppm) on the delta (δ) scale relative to the resonance of the solvent peak. The following abbreviations were used to describe coupling: s = singlet; d = doublet; t = triplet; q = quartet; quin = quintet; ABq = AB quartet; AA'XX' = second order AA'XX' pattern; app. = apparent; br = broad; and m = multiplet.

Liquid chromatography mass spectrometry (LCMS) data was obtained with an Agilent MSD-1100 ESI-MS/MS, an Agilent 1200 series LC/MSD VL, or a Waters Acquity UPLC-ESI-MS/MS system.



Scheme 1

Among the listed reagents and solvents in Scheme 1, SOCl$_2$ is thionylchloride, DMF is dimethylformamide, PhMe is toluene, *t*BuOK is potassium tert-butoxide, THF is tetrahydrofuran, DMSO is dimethylsulfoxide, and CH$_2$Cl$_2$ is methylene chloride.

4-Chloro-7-fluoroquinazoline (B). To a suspension of 7-fluoroquinazolin-4-ol compound A (6.32 g, 38.5 mmol) in dry PhMe (30 mL), SOCl$_2$ (22 mL, 7.7 eq.) and DMF (2.6 mL) were added. The resulting mixture was refluxed for 10 h. The mixture was then cooled to room temperature, quenched with water (200 mL), and extracted with ethyl acetate (EtOAc; 170 mL). The combined organic extracts were washed with water (300 mL) and brine (30 mL), dried over sodium sulfate (Na$_2$SO$_4$), and concentrated to afford compound B (6.08 g, 86%) as a yellow solid. LCMS (ESI) m/z calculated for C$_8$H$_4$ClFN$_2$: 182, 184; found: 183, 185 $[M+H]^+$. ^{1}H-NMR (400 MHz, CDCl$_3$) δ 9.04 (s, 1H), 8.33 (dd, J = 9.2 Hz, $^4J_{F,H}$ = 6.0 Hz, 1H), 7.71 (dd, $^3J_{F,H}$ = 9.2 Hz, J = 2.4 Hz, 1H), 7.52 (ddd, J = 9.2, 2.4 Hz, $^3J_{F,H}$ = 8.4 Hz, 1H).

4-((7-fluoroquinazolin-4-yl)oxy)aniline (C). A mixture of 4-aminophenol F (3.05 g, 28.0 mmol) and *t*-BuOK (3.14 g, 28.0 mmol) in dry THF (100 mL) was stirred for 20 min at

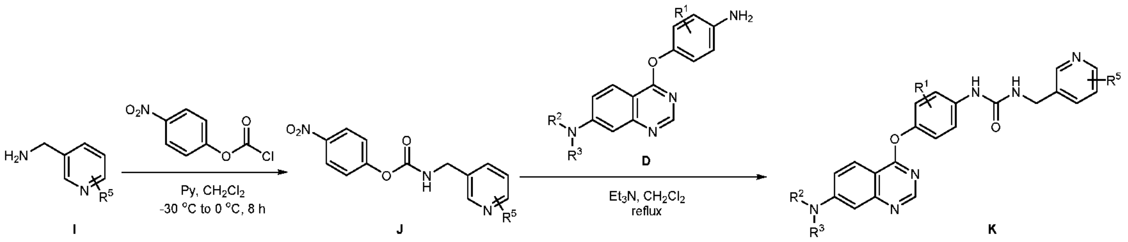
0 °C. Subsequently, compound B (4.44 g, 24.3 mmol) was added slowly in small portions. The reaction mixture was then stirred for 3 h at 0 °C, during which a suspension was formed. Afterwards, the suspension was filtered through a pad of celite, The pad was rinsed with THF. THF in the filtrate was removed by evaporation to give a crude residue. The residue was suspended in methanol (MeOH) and sonicated to form a solid. The solid was collected via filtration and dried to afford the titled product C (5.47 g, 88%) as an off-white solid. LCMS (ESI) m/z calculated for $C_{14}H_{10}BrN_3O$: 255; found: 256 $[M+H]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.40 (dd, $J = 9.2$ Hz, $^4J_{F,H} = 6.0$ Hz, 1H), 7.61 (dd, $^3J_{F,H} = 9.2$ Hz, $J = 2.4$ Hz, 1H), 7.40 (ddd, $J = 9.2$, 2.4 Hz, $^3J_{F,H} = 8.8$ Hz, 1H), 7.04 (AA'XX', $J_{AX} = 8.8$ Hz, $J_{AX'} = 0$ Hz, 2H), 6.77 (AA'XX', $J_{AX} = 8.8$ Hz, $J_{AX'} = 0$ Hz, 2H), 3.71 (br, 2H).

4-(4-aminophenoxy)-*N*,*N*-dimethylquinazolin-7-amine (D). To a solution of compound C (600 mg, 2.35 mmol) in DMSO (7.1 mL), 2 M dimethlyamine in THF (3 eq., 3.53 mL) was added. The mixture was then irradiated in microwave for 10 min at 170 °C. After compound C was consumed, the reaction mixture was diluted with EtOAc (30 mL) and 2% sodium carbonate (Na_2CO_3) solution (80 mL), and extracted with EtOAc (50 mL). The combined organic extracts were sequentially washed with 2% Na_2CO_3 solution (160 mL), water (200 mL), and brine (20 mL), dried over Na_2SO_4, and concentrated. The crude residue was suspended in MeOH. Particles in the supension were collected via filtration and dried to afford the titled product D (207 mg, 32%) as a pale yellow solid. LCMS (ESI) m/z calculated for $C_{16}H_{16}N_4O$: 280; found: 281 $[M+H]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.58 (s, 1H), 8.15 (d, $J = 9.2$ Hz, 1H), 7.12 (dd, $J = 9.2$ Hz, $J = 2.7$ Hz, 1H), 7.03 (AA'XX', $J_{AX} = 9.0$ Hz, $J_{AX'} = 0$ Hz, $J_{AA'} = 2.9$ Hz, $J_{XX'} = 2.9$ Hz, 2H), 6.96 (d, $J = 2.7$ Hz, 1H), 6.75 (AA'XX', $J_{AX} = 9.0$ Hz, $J_{AX'} = 0$ Hz, $J_{AA'} = 2.9$ Hz, $J_{XX'} = 2.9$ Hz, 2H), 3.67 (br, 2H), 3.15 (s, 6H).

1-(4-((7-(dimethylamino)quinazolin-4-yl)oxy)phenyl)-3-phenylurea (compound 4, E**).** To a solution of compound D (165 mg, 0.588 mmol) in CH_2Cl_2 (15 mL), compound H (108 µL, 0.883 mmol) was added. The mixture was refluxed for 10 h, during which a suspension was formed. Particles in the suspension were collected via filtration and rinsed with excess CH_2Cl_2 to afford the titled product E (214 mg, 91%) as a white solid. LCMS (ESI) m/z calculated for $C_{23}H_{21}N_5O_2$: 399; found: 400 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.77 (br s, 1H), 8.71 (br s, 1H), 8.45 (s, 1H), 8.11 (d, $J = 9.6$ Hz, 1H), 7.52 (AA'XX', $J_{AX} = 8.8$ Hz, $J_{AX'} = 0$ Hz, $J_{AA'} = 2.6$ Hz, $J_{XX'} = 2.6$ Hz, 2H), 7.47 (d, $J = 5.6$ Hz, 2H), 7.32–7.27 (m, 3H), 7.19 (AA'XX', $J_{AX} =$

8.8 Hz, $J_{AX'}$ = 0 Hz, $J_{AA'}$ = 2.6 Hz, $J_{XX'}$ = 2.6 Hz, 2H), 6.97 (t, J = 7.2 Hz, 1H), 6.88 (d, J = 2.4 Hz, 1H), 3.12 (s, 6H).

Compounds 1, 2, 3, 5, 6, 7, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 52, and 106 were prepared in a manner similar to compound 4, with appropriate amines G and isocyanates H.



Scheme 2

Among the listed reagents and solvents in Scheme 2, Py is pyridine, and Et_3N is triethylamine.

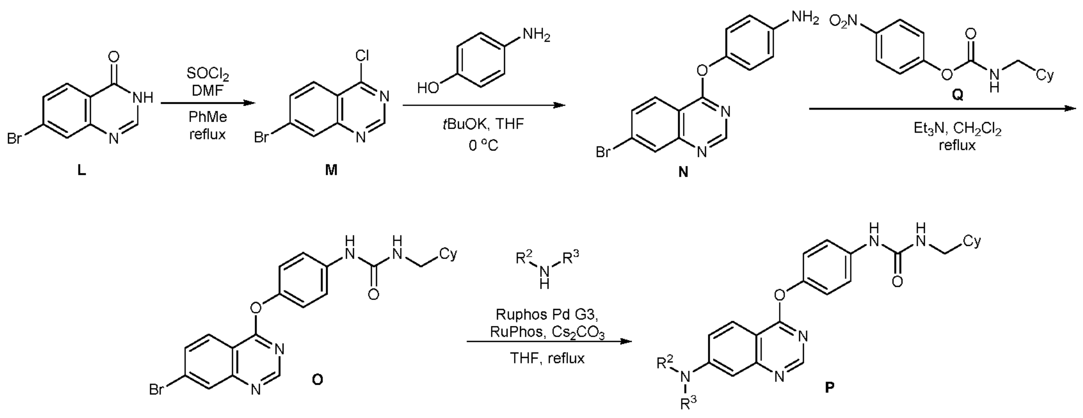
4-nitrophenyl ((6-(trifluoromethyl)pyridin-3-yl)methyl)carbamate (J). To a -30 °C solution of (6-(trifluoromethyl)pyridin-3-yl)methanamine I (2.69 g, 15.3 mmol) and Py (1.23 mL, 15.3 mmol) in CH_2Cl_2 (50 mL), 4-nitrophenyl chloroformate (3.85 g, 19.1 mmol) was slowly added. The reaction mixture was stirred for 8 h and allowed to slowly warm to 0 °C. Subsequently, water (50 mL) was added to the reaction mixture. The mixture was then stirred for 20 min, during which a suspension was formed. Particles in the suspension were removed by filtering the reaction mixture through a pad of celite. The filtrate was washed with 2% sodium bisulfate solution (20 mL), 2% sodium bicarbonate solution (40 mL), water (20 mL), and brine (3 mL), dried over Na_2SO_4, and concentrated. The crude residue was purified by column chromatography to afford the titled product J (3.33 g, quant.) as a white solid. LCMS (ESI) m/z calculated for $C_{14}H_{10}F_3N_3O_4$: 341; found: 342 $[M+H]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.73 (d, J = 1.4 Hz, 1H), 8.26 (AA'XX', J_{AX} = 9.2 Hz, $J_{AX'}$ = 0 Hz, $J_{AA'}$ = 2.6 Hz, $J_{XX'}$ = 2.6 Hz, 2H), 7.91 (dd, J = 8.0, 1.4 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.33 (AA'XX', J_{AX} = 9.2 Hz, $J_{AX'}$ = 0 Hz, $J_{AA'}$ = 2.6 Hz, $J_{XX'}$ = 2.6 Hz, 2H), 5.68 (br t, 1H), 4.58 (d, J = 6.4 Hz, 2H).

1-(4-((7-(dimethylamino)quinazolin-4-yl)oxy)phenyl)-3-((6-(trifluoromethyl)pyridin-3-yl)methyl)urea (compound 27, K). To a solution of compound J (2.19 g, 6.43 mmol) and compound D (1.06 g, 3.78 mmol) in CH_2Cl_2 (95 mL), Et_3N (1.05 mL) was added. The reaction mixture was refluxed for 4 d, during which a suspension was formed. Particles in the suspension were collected via filtration and rinsed with excess CH_2Cl_2 to afford the titled product K (1.33 g, 73%) as a white solid. LCMS (ESI) m/z calculated for $C_{24}H_{21}F_3N_6O_2$: 482; found: 483 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.83 (s, 1H), 8.72 (d, J = 1.2 Hz, 1H), 8.43 (s, 1H), 8.10 (d, J = 9.2 Hz, 1H), 8.00 (dd, J = 8.4, 1.2 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.47 (AA’XX’, J_{AX} = 8.8 Hz, $J_{AX'}$ = 0 Hz, $J_{AA'}$ = 2.6 Hz, $J_{XX'}$ = 2.6 Hz, 2H), 7.29 (d, J = 9.2, 2.4 Hz, 1H), 7.13 (AA’XX’, J_{AX} = 8.8 Hz, $J_{AX'}$ = 0 Hz, $J_{AA'}$ = 2.6 Hz, $J_{XX'}$ = 2.6 Hz, 2H), 6.87 (d, J = 2.4 Hz, 1H), 6.84 (t, J = 6.0 Hz, 1H), 4.44 (d, J = 6.0 Hz, 2H), 3.12 (s, 6H).

1-(4-((7-(dimethylamino)quinazolin-4-yl)oxy)phenyl)-3-((6-methylpyridin-3-yl)methyl)urea (compound 65, K) LCMS (ESI) m/z calculated for $C_{24}H_{21}F_3N_6O_2$: 428; found: 429 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.43 (s, 1H), 8.39 (d, J = 2.4 Hz, 1H), 8.10 (d, J = 9.2 Hz, 1H), 7.61 (dd, J = 8.0, 2.4 Hz, 1H), 7.46 (AA’XX’, J_{AX} = 8.8 Hz, 2H), 7.29 (dd, J = 9.2, 2.4 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.13 (AA’XX’, J_{AX} = 8.8 Hz, 2H), 6.87 (d, J = 2.4 Hz, 1H), 6.67 (t, J = 6.0 Hz, 1H), 4.28 (d, J = 6.0 Hz, 1H), 3.12 (s, 6H), 2.44 (s, 3H).

1-(4-((7-(dimethylamino)quinazolin-4-yl)oxy)phenyl)-3-((6-methylpyridin-3-yl)methyl)urea (compound 66, K) LCMS (ESI) m/z calculated for $C_{24}H_{21}F_3N_6O_2$: 444; found: 445 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.43 (s, 1H), 8.39 (d, J = 2.4 Hz, 1H), 8.10 (d, J = 9.2 Hz, 1H), 7.61 (dd, J = 8.0, 2.4 Hz, 1H), 7.46 (AA’XX’, J_{AX} = 8.8 Hz, 2H), 7.29 (dd, J = 9.2, 2.4 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.13 (AA’XX’, J_{AX} = 8.8 Hz, 2H), 6.87 (d, J = 2.4 Hz, 1H), 6.67 (t, J = 6.0 Hz, 1H), 4.28 (d, J = 6.0 Hz, 1H), 3.12 (s, 6H), 2.44 (s, 3H).

Compounds 23, 24, 25, 28, 30, 33, 36, 39, 40, 42, 43, 44, 49, 50, 51, 54, 55, 56, 57, 58, 59, 60, 63, 65, 66, 87, 90, 91, 92, 96, and 101 were prepared in a manner similar to compound 27 with appropriate amines H and anilines D.



Scheme 3

Among the listed reagents, solvents and catalysts in Scheme 3, $SOCl_2$ is thionylchloride, RuPhos Pd G3 is (2-dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)[2-2′-amino-1,1′-biphenyl]] palladium(II) methanesulfonate, RuPhos is 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl, and Cs_2CO_3 is cesium carbonate.

4-Chloro-7-bromoquinazoline (M). To a suspension of 7-bromoquinazolin-4-ol L (1.17 g, 5.20 mmol) in dry PhMe (6 mL), $SOCl_2$ (6 mL) and DMF (0.6 mL) were added. The resulting mixture was stirred at 95 °C for 9 h, cooled to room temperature, quenched with water (100 mL), and extracted with EtOAc (70 mL). The combined organic extracts were washed with water (200 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated to afford the titled product M (1.26 g, 99%) as a yellow solid. LCMS (ESI) m/z calculated for $C_8H_4BrClN_2$: 242, 244, 246; found: 243, 245, 247 $[M+H]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.05 (s, 1H), 8.28 (d, J = 1.8 Hz, 1H), 8.15 (d, J = 9.0 Hz, 1H), 7.84 (dd, J = 9.0, 1.8 Hz, 1H).

4-((7-Bromoquinazolin-4-yl)oxy)aniline (N). A mixture of 4-aminophenol (0.678 g, 6.21 mmol) and *t*-BuOK (0.668 g, 5.95 mmol) in dry THF (15 mL) at 0 °C was stirred for 20 min. Subsequently, 4-chloro-7-bromoquinazoline M (1.26 g, 5.17 mmol) was added slowly in small portions. The reaction mixture was then stirred for 3 h at 0 °C, during which a suspension was formed. The suspension was filtered through a pad of celite. The pad was rinsed with THF (20 mL), and the resulting filtrate was evaporated to give a crude solid. The crude solid was suspended in MeOH (6 mL) and sonicated. Particles in the suspension were collected via filtration and dried to afford the titled product N (1.461 g, 89%) as an off-white solid. LCMS (ESI) m/z calculated for $C_{14}H_{10}BrN_3O$: 315, 317; found: 316, 318 $[M+H]^+$.

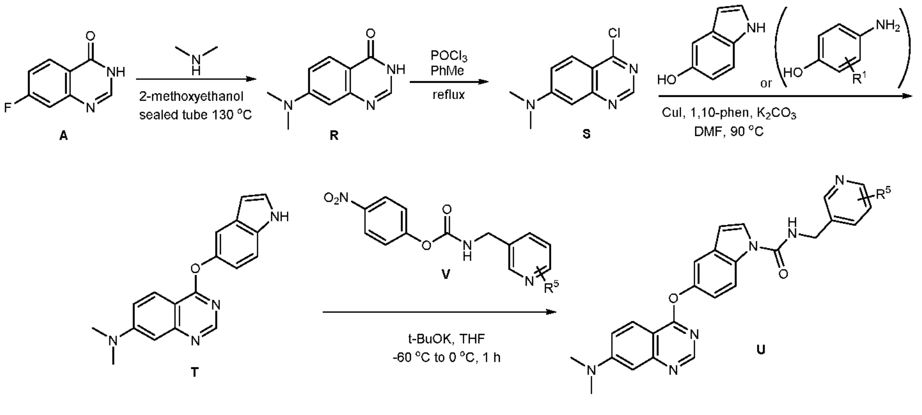
1-(4-((7-Bromoquinazolin-4-yl)oxy)phenyl)-3-((6-(trifluoromethyl)pyridin-3-yl)methyl)urea (O; compound 31). To a solution of 4-((7-Bromoquinazolin-4-yl)oxy)aniline N (305 mg, 0.964 mmol) and compound Q (461 mg, 1.35 mmol) in CH_2Cl_2 (6 mL), Et_3N (0.27 mL) was added. The resulting mixture was refluxed for 1.5 d, during which a suspension was formed. Particles in the suspension was collected via filtration and rinsed with excess CH_2Cl_2 to afford the titled product O (462 mg, 93%) as a white solid. LCMS (ESI) m/z calculated for $C_{22}H_{15}BrF_3N_5O_2$: 517, 519; found: 518, 520 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.87 (s, 1H), 8.74 (s, 1H), 8.72 (br s, 1H), 8.30 (d, J = 8.8 Hz, 1H), 8.24 (d, J

= 2.0 Hz, 1H), 8.00 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.93 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.50 (AA'XX', J_{AX} = 9.0 Hz, $J_{AX'}$ = 0 Hz, 2H), 7.21 (AA'XX', J_{AX} = 9.0 Hz, $J_{AX'}$ = 0 Hz, 2H), 6.86 (t, *J* = 6.0 Hz, 1H), 4.44 (d, *J* = 6.0 Hz, 2H).

1-(4-((7-(3,5-Dimethylpiperazin-1-yl)quinazolin-4-yl)oxy)phenyl)-3-((6-(trifluoromethyl)pyridin-3-yl)methyl)urea (P; compound 34)**.** Freshly-distilled THF (4 mL) was purged with argon for 20 min, after which compound O (50 mg, 0.097 mmol), Cs_2CO_3 (47 mg, 0.15 mmol), *cis*-2,6-dimethylpiperazine (17 mg, 0.15 mmol), Ruphos (4.1 mg, 0.009 mmol), and Ruphos Pd G3 (4.1 mg, 0.005 mmol) were added to form a suspension. The resulting mixture was stirred under argon for 5 min. Subsequently, the reaction mixture was refluxed overnight. The resulting pale-yellow solution was filtered through a pad of celite and the filtrate was concentrated to give a residue. The residue was purified by column chromatography to afford the titled product P (49 mg, 92%) as a white solid. LCMS (ESI) m/z calculated for $C_{28}H_{28}F_3N_7O_2$: 551; found: 552 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.85 (s, 1H), 8.72 (d, *J* = 1.6 Hz, 1H), 8.46 (s, 1H), 8.09 (d, *J* = 9.2 Hz, 1H), 8.00 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.51 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.47 (AA'XX', J_{AX} = 9.2 Hz, $J_{AX'}$ = 0 Hz, 2H), 7.17–7.13 (m, 3H), 6.85 (t, *J* = 5.6 Hz, 1H), 4.44 (d, *J* = 5.6 Hz, 2H), 3.91–3.88 (m, 2H), 2.87–2.82 (m, 2H), 2.39–2.33 (m, 2H), 1.06 (d, *J* = 6.4 Hz, 6H).

1-(4-((7-(4-hydroxypiperidin-1-yl)quinazolin-4-yl)oxy)phenyl)-3-((6-(trifluoromethyl)pyridin-3-yl)methyl)urea (P; compound 30)**.** Similar to compound 34, compound 30 was prepared from compound 31 and was obtained as a white solid. LCMS (ESI) m/z calculated for $C_{28}H_{28}F_3N_7O_2$: 538; found: 539 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.82 (br s, 1H), 8.72 (d, *J* = 1.2 Hz, 1H), 8.45 (s, 1H), 8.08 (d, *J* = 9.2 Hz, 1H), 8.00 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.51–7.45 (m, 3H), 7.15–7.11 (m, 3H), 6.84 (t, *J* = 6.0 Hz, 1H), 4.76 (d, *J* = 4.0 Hz, 2H), 4.44 (d, *J* = 6.0 Hz, 2H), 3.87–3.81 (m, 2H), 3.77–3.72 (m, 1H), 3.21–3.14 (m, 1H), 1.87–1.83 (m, 2H), 1.51–1.43 (m, 2H).

Compounds 24, 96 ,97, 98 ,99, 100 were prepared analogously to compound 34.



Scheme 4

Among the listed reagents, solvents, and catalysts listed in Scheme 3, $POCl_3$ is phosphoryl chloride, CuI is copper iodide, 1,10-phen is 1,10-phenanthroline, K_2CO_3 is potassium carbonate, and *t*BuOH is tert-butanol.

7-(Dimethylamino)quinazolin-4(3*H*)-one (R). A solution of 7-fluoroquinazolin-4(3*H*)-one A (1.65 g, 10.1 mmol) and dimethylamine (2M in THF, 20 mL, 40.2 mmol) in 2-methoxyethanol (60 mL) in a 250 mL sealed tube was stirred at 130 °C for 1 d, during which a solid was formed. Subsequently, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was suspended in MeOH (8 mL) and filtered to afford the titled product R (1.5 g, 79%) as a brown solid. LCMS (ESI) m/z calculated for $C_{10}H_{11}N_3O$: 189; found: 190 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.69 (br, 1H), 7.91 (s, 1H), 7.88 (d, $J = 9.0$ Hz, 1H), 6.93 (dd, $J = 9.0$, 2.4 Hz, 1H), 6.98 (d, $J = 2.4$ Hz, 1H), 3.04 (s, 6H).

4-Chloro-*N*,*N*-dimethylquinazolin-7-amine (S). To a suspension of 7-(dimethylamino)quinazolin-4(3*H*)-one R (910 mg, 4.81 mmol) in dry PhMe (10 mL), $POCl_3$ (4 mL) was added, after which the resulting mixture was stirred at 95 °C for 12 h. The reaction mixture was the cooled to 0 °C, quenched with ice water (100 mL), and neutralized with saturated sodium carbonate solution until the color of the solution turned from bright orange to pale yellow. Subsequently, the reaction mixture was extracted with EtOAc (170 mL), and the organic extract was washed with water (200 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated to afford the titled product S (948 mg, 95%) as a yellow solid. LCMS (ESI) m/z calculated for $C_{10}H_{10}ClN_3$: 207, 209; found: 208, 210 $[M+H]^+$. ^{1}H-NMR (300 MHz, $CDCl_3$):

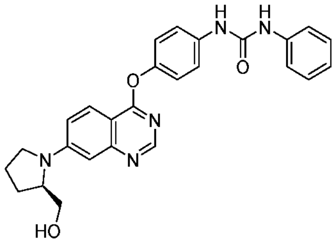
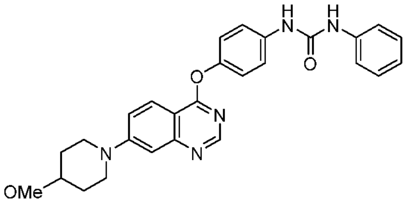
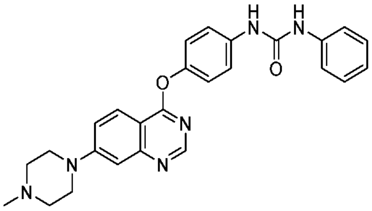
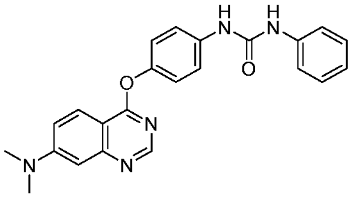
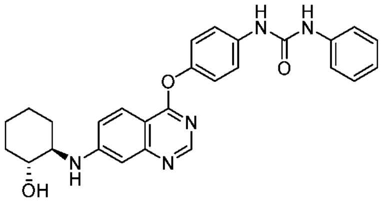
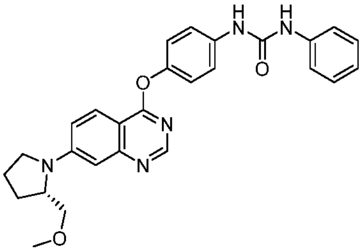
δ 8.77 (s, 1H), 8.03 (d, J = 9.3 Hz, 1H), 7.20 (dd, J = 9.3, 2.7 Hz, 1H), 6.96 (d, J = 2.7 Hz, 1H), 3.18 (s, 1H).

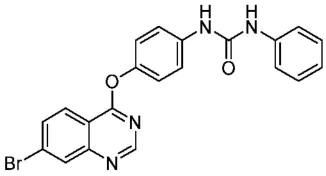
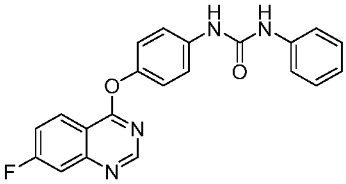
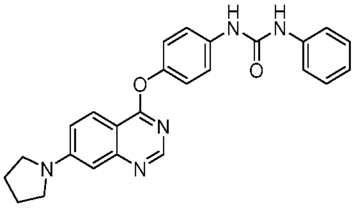
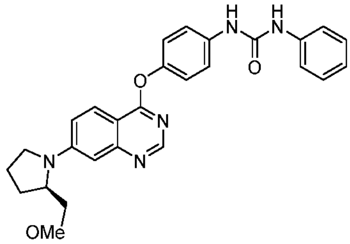
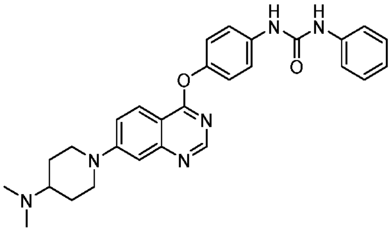
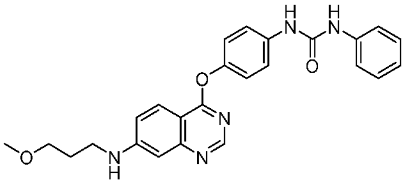
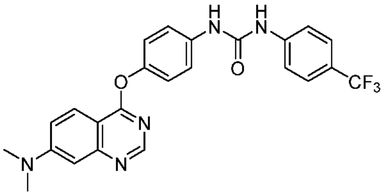
4-((1*H*-indol-5-yl)oxy)-*N*,*N*-dimethylquinazolin-7-amine (T). DMF (4 mL) was purged with argon. Subsequently, 4-Chloro-*N*,*N*-dimethylquinazolin-7-amine **S** (322 mg, 1.55 mmol), 5-hydroxyindole (413 mg, 3.10 mmol), K_2CO_3 (429 mg, 3.10 mmol), CuI (29.5 mg, 0.155 mmol), and 1,10-phen (27.9 mg, 0.155 mmol) were added to form a reaction mixture, which was stirred at 90 °C for 3 h under argon. The reaction mixture was then diluted with EtOAc (15 mL) and water (15 mL), and filtered through a pad of celite. The filtrate was extracted with EtOAc (60 mL), and the organic extract was washed with water (120 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was suspended in MeOH and particles were collected by filtration to afford the titled product T (381 mg, 81%) as a white solid. LCMS (ESI) m/z calculated for $C_{18}H_{16}N_4O$: 304; found: 305 $[M+H]^+$.

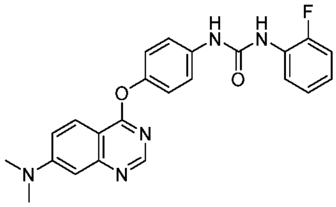
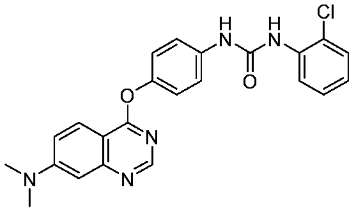
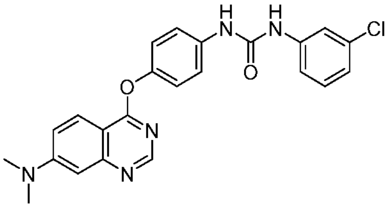
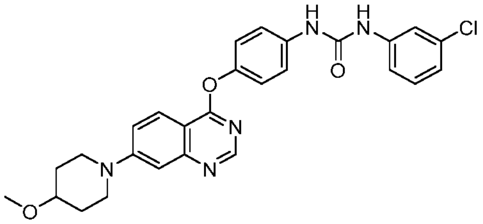
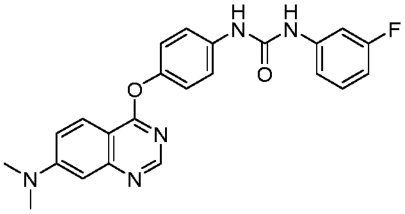
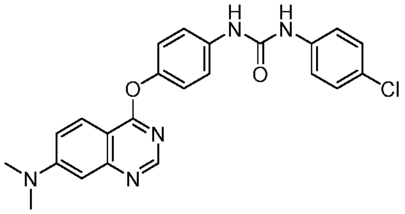
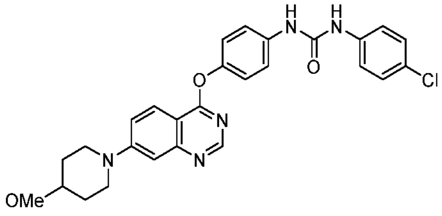
5-((7-(dimethylamino)quinazolin-4-yl)oxy)-N-((6-(trifluoromethyl)pyridin-3-yl)methyl)-1H-indole-1-carboxamide (U; compound 67). To a solution of 4-(4-amino-3-methoxyphenoxy)-*N*,*N*-dimethylquinazolin-7-amine T (170 mg, 0.95 mmol) in dry THF (5 mL), NaH (60% in oil, 112 mg, 2.79 mmol) was added. The resulting mixture was stirred at room temperature for 20 min. Subsequently, the mixture was cooled to -60 °C, and 4-nitrophenyl ((6-(trifluoromethyl)pyridin-3-yl)methyl)carbamate V (574 mg, 1.68 mmol) was added in 3 portions. The mixture was then slowly warmed to 0 °C, stirred for 1 h, and quenched with saturated ammonium chloride solution. The solvent was removed under reduced pressure and the resulting residue was diluted with EtOAc (35 mL), washed with water (80 mL) and brine (3 mL), dried over Na_2SO_4, and concentrated. The crude residue was purified by column chromatography to afford the titled product U (171 mg, 65%) as a white solid. LCMS (ESI) m/z calculated for $C_{26}H_{21}F_3N_6O_2$: 506; found: 507 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.94 (t, J = 5.6 Hz, 1H), 8.82 (d, J = 1.6 Hz, 1H), 8.41 (s, 1H), 8.27 (d, J = 8.8 Hz, 1H), 8.15 (d, J = 9.2 Hz, 1H), 8.10 (dd, J = 8.0, 1.6 Hz, 1H), 7.96 (d, J = 3.6 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 2.4 Hz, 1H), 7.31 (dd, J = 9.2, 2.4 Hz, 1H) 7.16 (dd, J = 8.8, 2.4 Hz, 1H), 6.88 (d, J = 2.4 Hz, 1H), 6.74 (d, J = 3.6 Hz, 1H), 4.64 (d, J = 5.6 Hz, 2H), 3.13 (s, 6H).

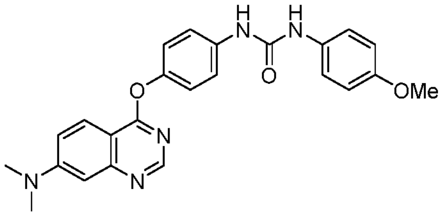
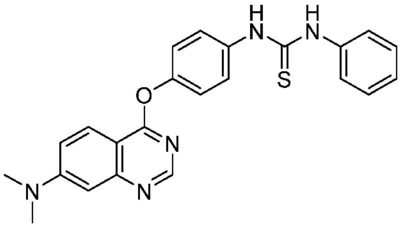
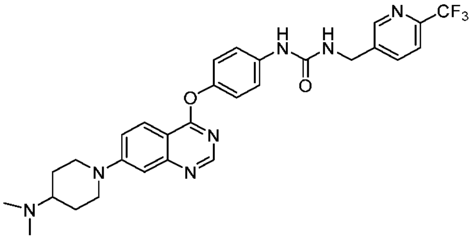
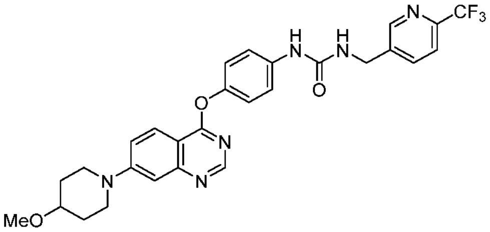
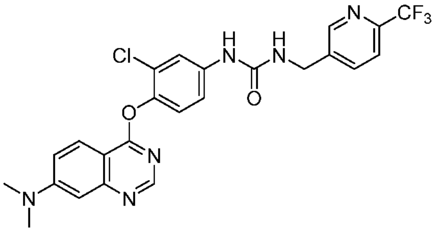
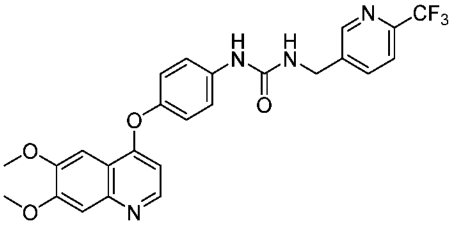
Compounds 29, 35, 38, 64, 68, 69, 83, and 89 were prepared in a manner similar to compound 67.

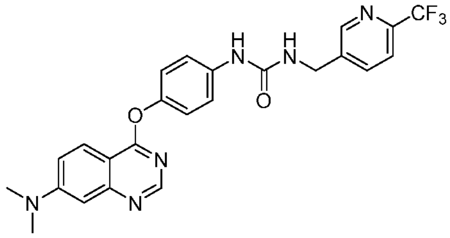
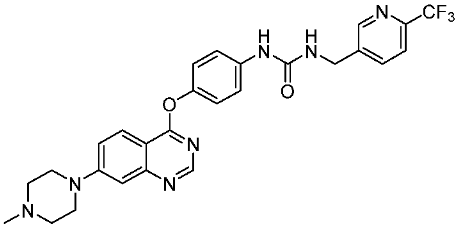
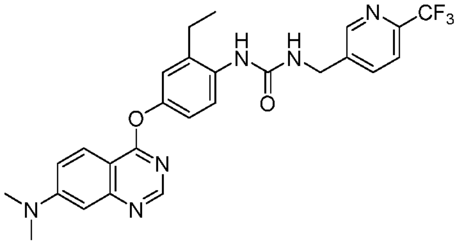
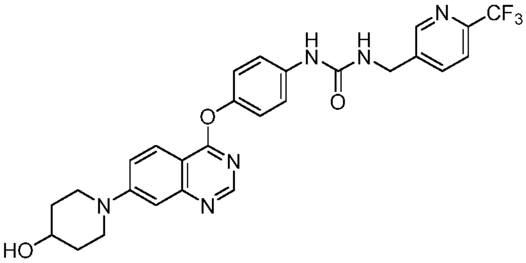
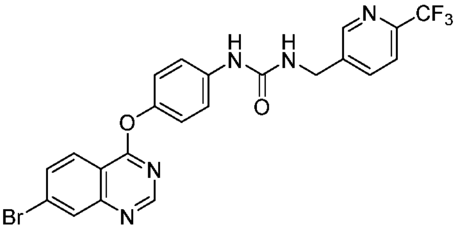
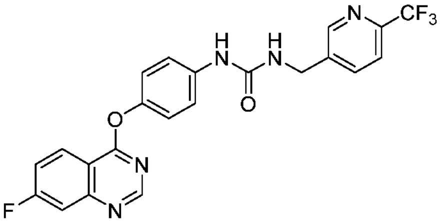
Table 1. Exemplary heterocyclic compounds

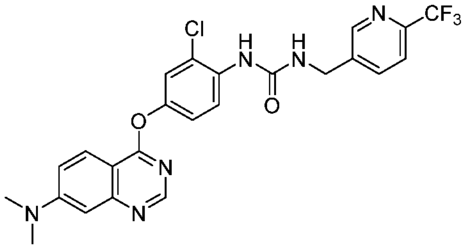
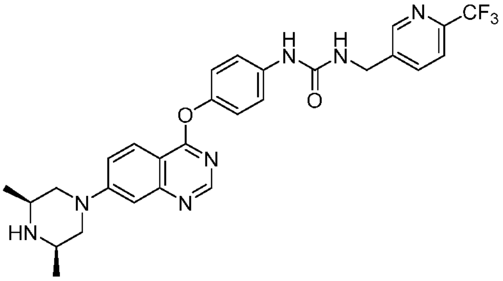
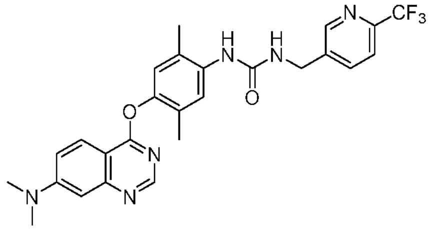
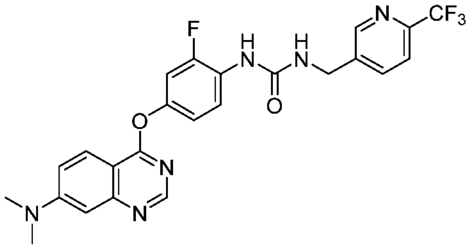
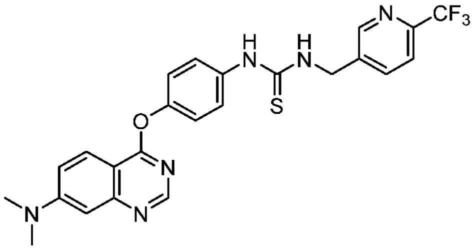
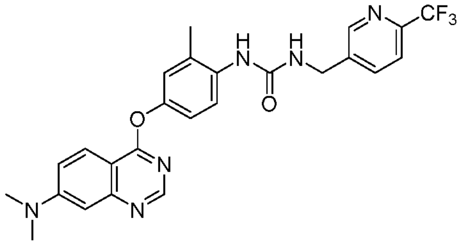
Compound	Structure	Calculated Mass	Mass $[M+H]^+$
1		455	456
2		469	470
3		454	455
4		399	400
5		469	470
6		469	470

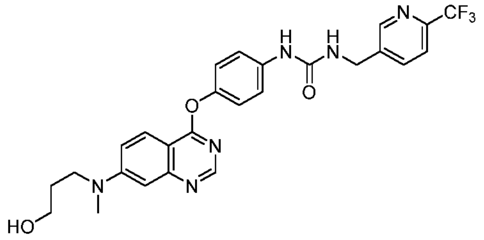
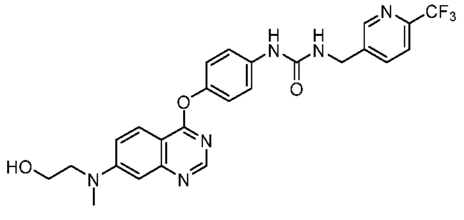
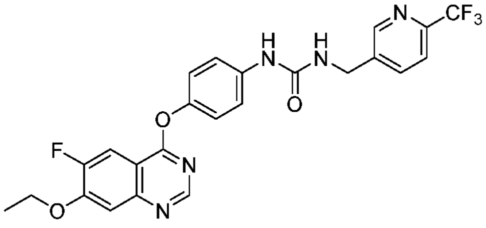
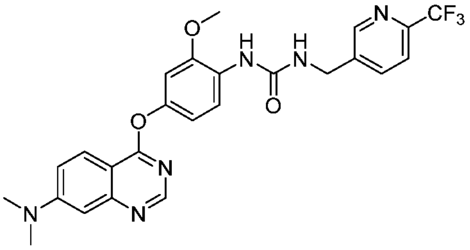
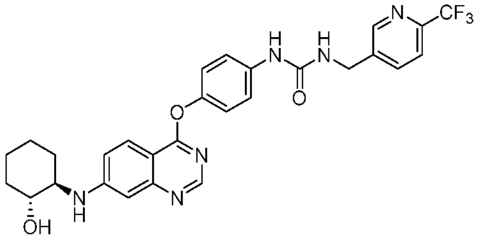
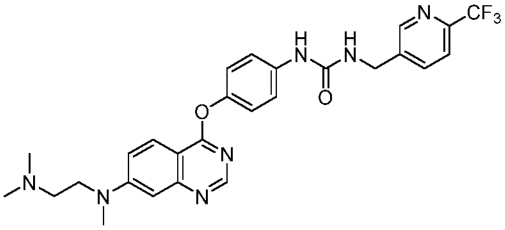
7		434	435
8		374	375
9		425	426
10		469	470
11		482	483
12		443	444
13		467	468

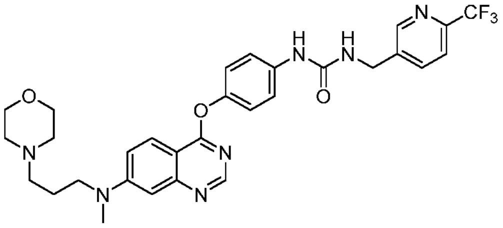
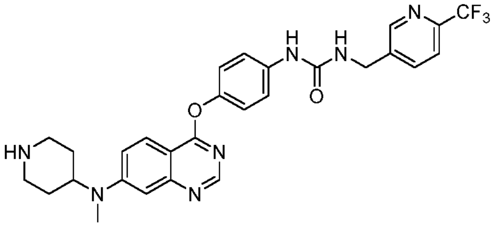
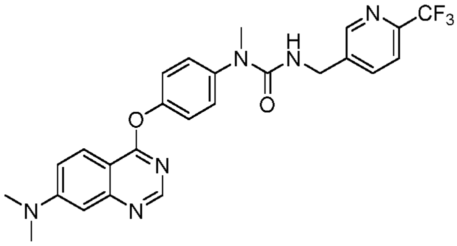
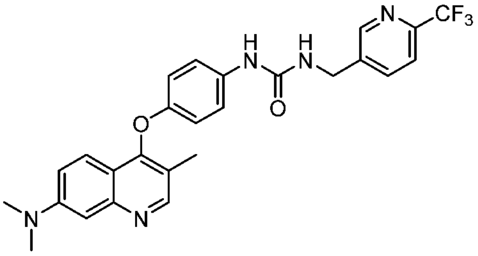
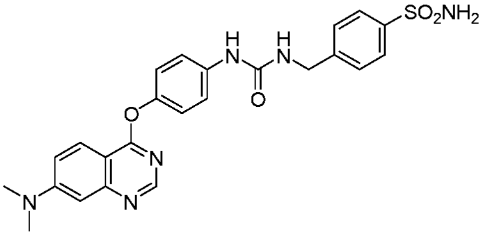
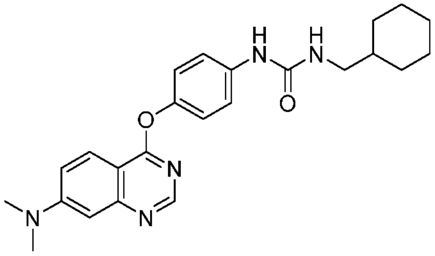
14		417	418
15		433	434
16		433	434
17		503	504
18		417	418
19		433	434
20		503	504

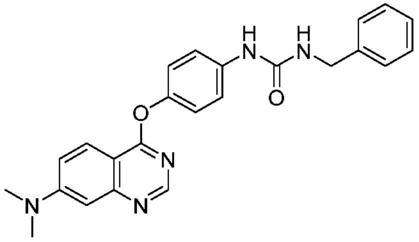
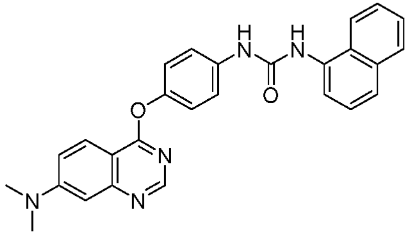
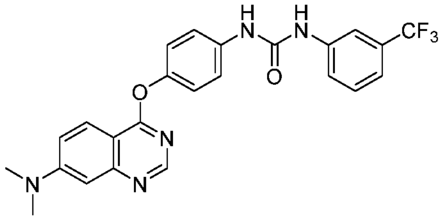
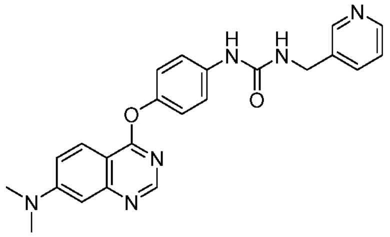
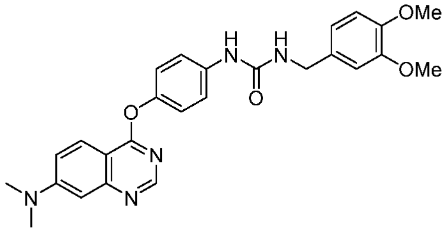
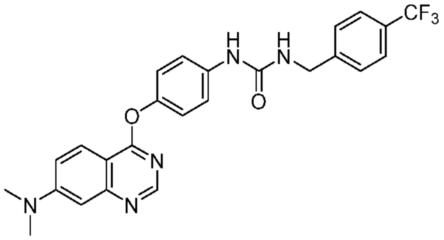
21		429	430
22		415	416
23		565	566
24		552	553
25		516	517
26		498	499

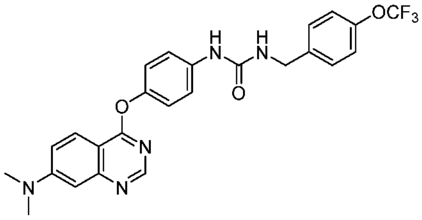
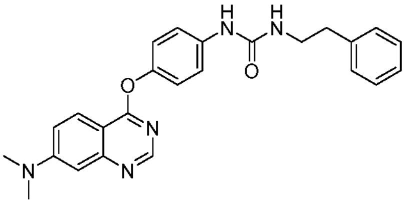
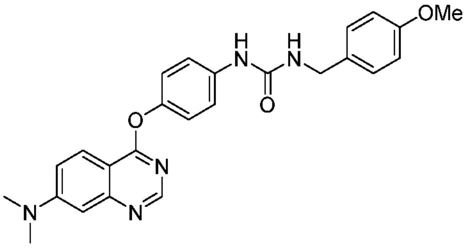
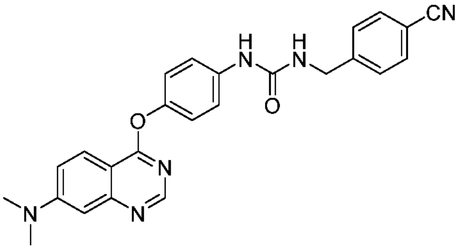
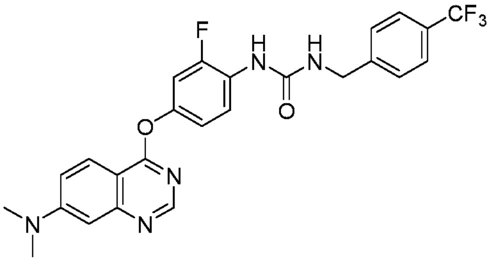
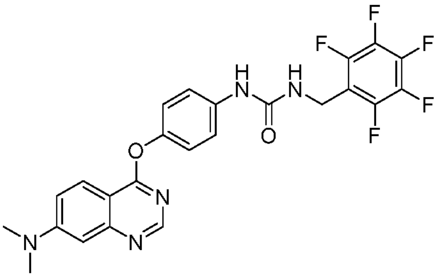
27		482	483
28		537	538
29		510	511
30		538	539
31		517	518
32		457	458

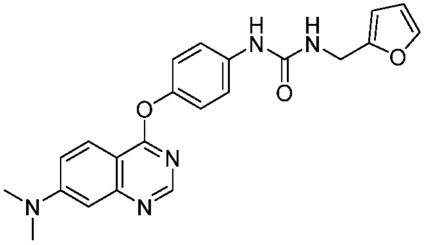
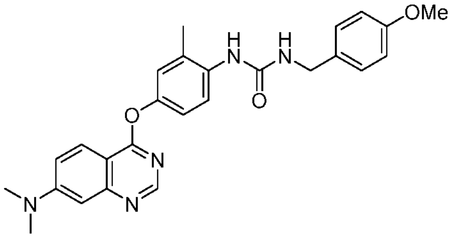
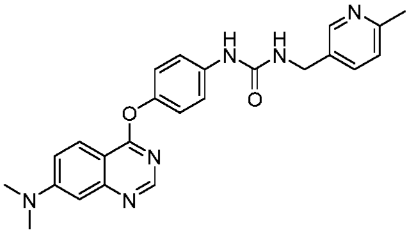
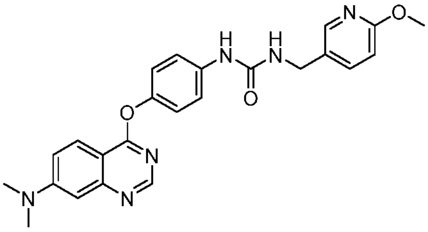
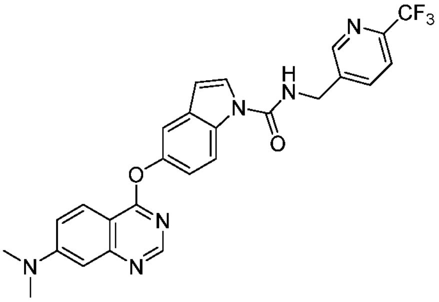
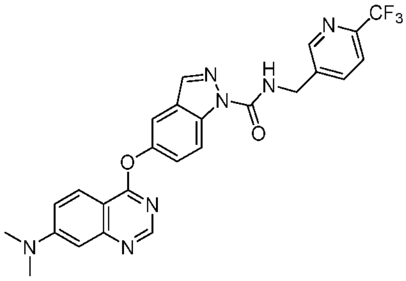
33		516	517
34		551	552
35		510	511
36		500	501
37		498	499
38		496	497

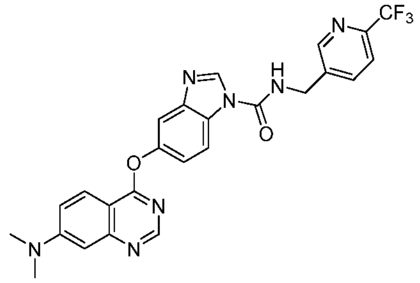
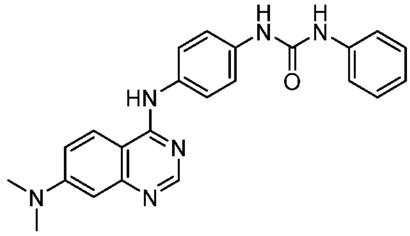
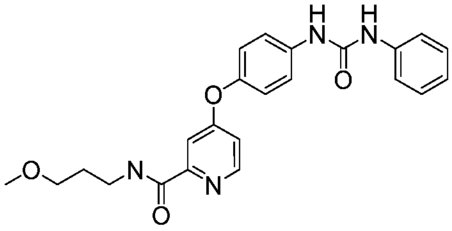
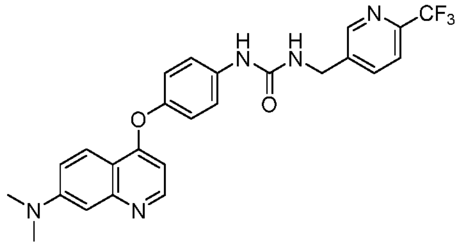
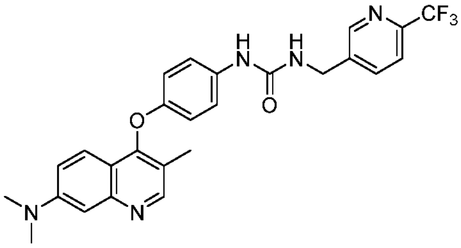
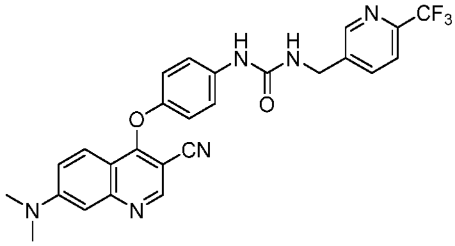
39		526	527
40		512	513
41		501	502
42		512	513
43		552	553
44		539	540

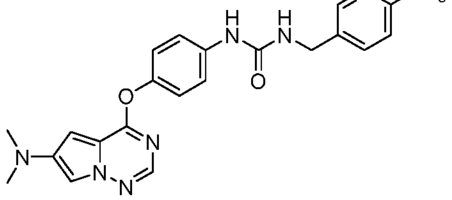
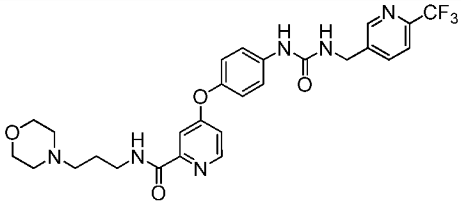
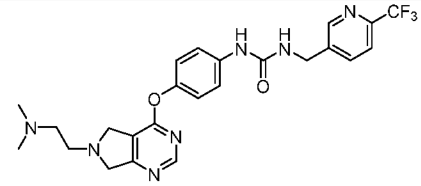
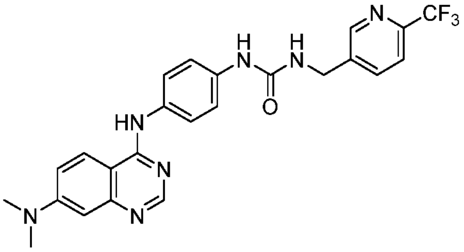
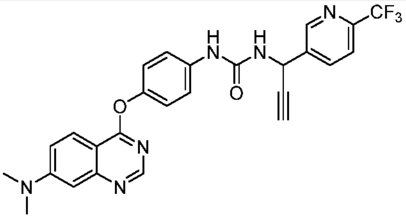
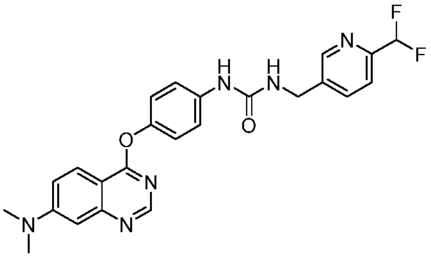
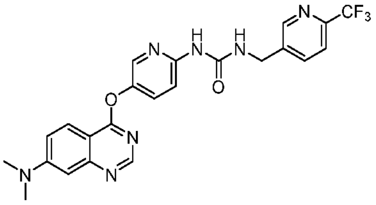
45		595	596
46		551	552
47		496	497
48		495	496
49		492	493
50		419	420

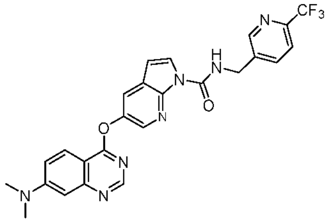
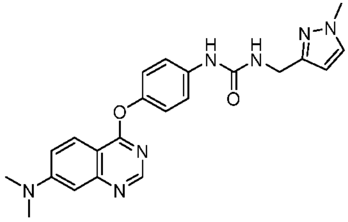
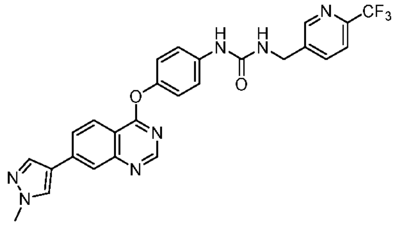
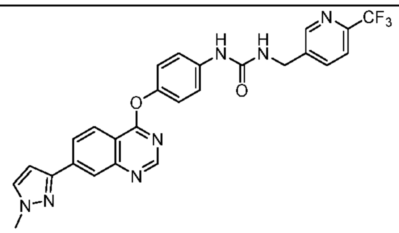
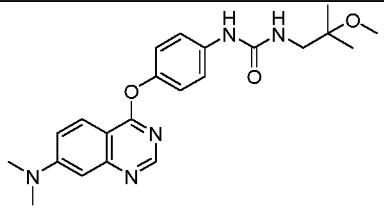
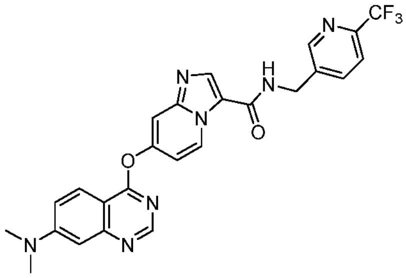
51		413	414
52		449	450
53		467	468
54		414	415
55		473	474
56		481	482

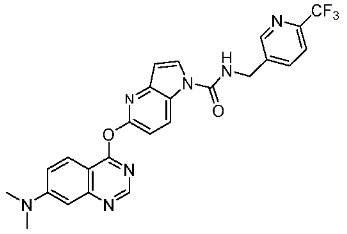
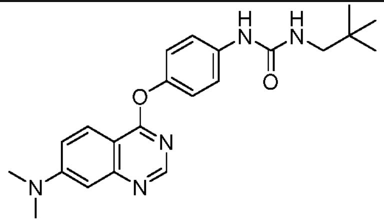
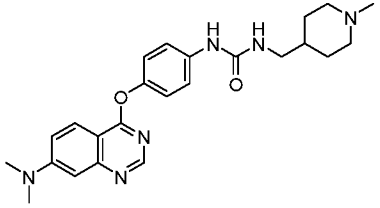
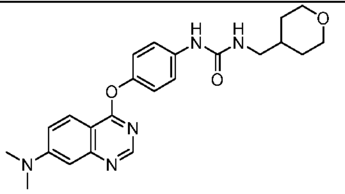
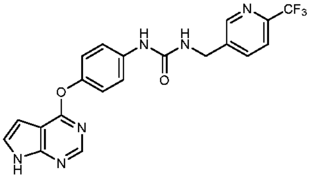
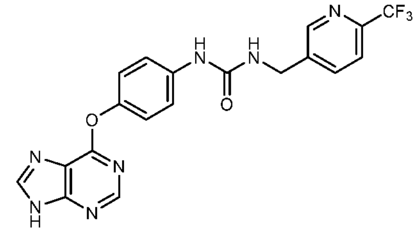
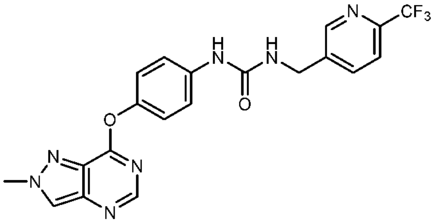
57		497	498
58		427	428
59		443	444
60		438	439
61		499	500
62		503	504

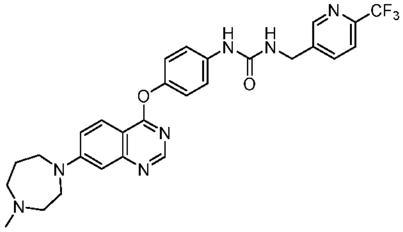
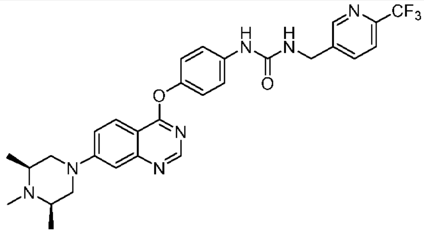
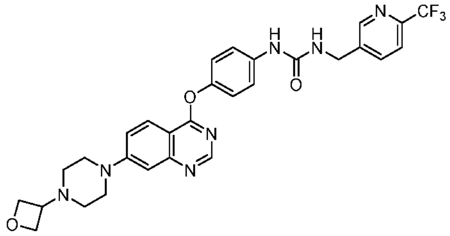
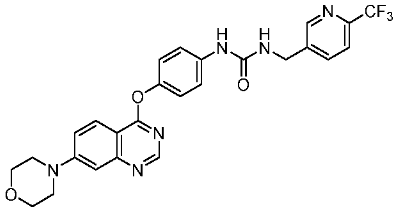
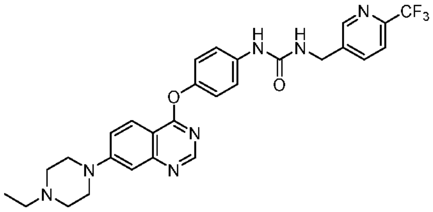
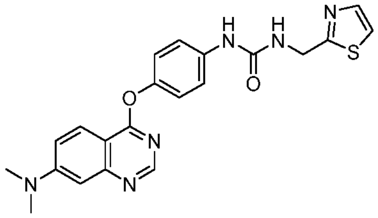
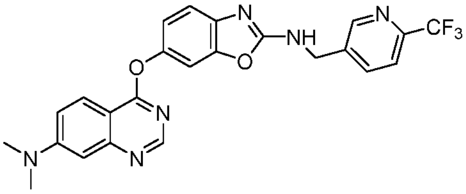
63		403	404
64		457	458
65		428	429
66		444	445
67		506	507
68		507	508

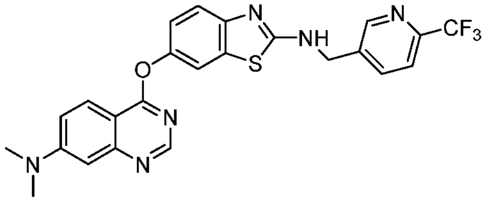
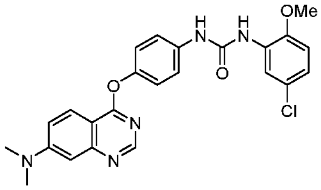
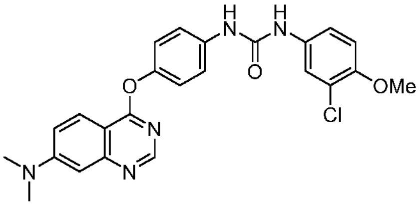
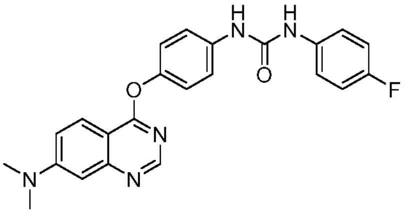
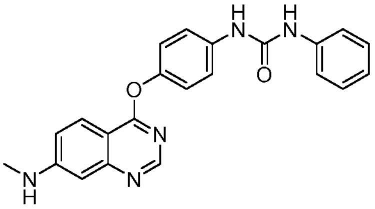
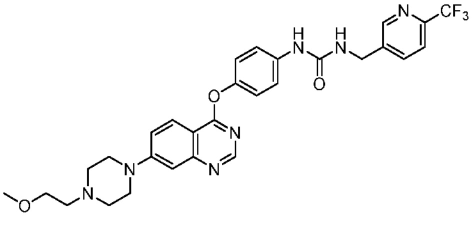
69		507	508
71		398	399
72		420	421
73		481	482
74		495	496
75		506	507

76		471	472
77		558	559
78		503	504
79		481	482
80		506	507
81		464	465
82		483	484

83		507	508
84		417	418
85		519	520
86		519	520
87		409	410
88		507	508

89		507	508
90		393	394
91		434	435
92		421	422
93		428	429
94		429	430
95		443	444

96		551	552
97		565	566
98		579	580
99		524	525
100		551	552
101		420	421
102		480	481

103		496	497
104		463 465	464 466
105		463 465	464 466
106		417	418
107		385	386
108		581	582

EXAMPLE 2: CSF1R kinase assay

A study was conducted to test certain compounds described in EXAMPLE 1 in inhibiting CSF1R kinase activity. Results from this study are shown in Table 2 below (see column 2).

Activity of CSF1R kinase was determined using a CSF1R Kinase-Glo assay. Recombinant N-terminal GST-CSF1R (CSF1R residues L534-C972) containing the CSFIR kinase domain was expressed in Sf9 insect cells and purified. The kinase assay was carried out in 96-well plates at 30 °C for 180 min with the tested compounds in a final volume of 50 µl including the following components: 25 mM Tris-HCl pH 7.4, 4 mM $MnCl_2$, 10 mM $MgCl_2$, 0.01% BSA, 0.5 mM Na_3VO_4, 0.02% Triton X-100, 40µM ATP, 2 mM DTT and 20µM poly(Glu,Tyr) 4:1 peptide, and 600 ng recombinant GST-CSF1R. Following incubation, 50 µl Kinase-Glo Plus Reagent (Promega, Madison, WI, USA) was added and the mixture was incubated at 25 °C for 20 min. A 70-µL aliquot of each reaction mixture was transferred to a black microtiter plate and luminescence was measured on Wallac Vector 1420 multilabel counter (PerkinElmer, Shelton, CT, USA). Percentage inhibition values were obtained by comparison of reaction rate with the rates in control wells (i.e., in the absence of test compound). IC_{50} values were calculated from a series of percentage inhibition values determined at a range of test compound concentrations using GraphPad Prism version 6 software (GraphPad, San Diego, CA, USA).

EXAMPLE 3: Cellular proliferation assays

Studies were conducted to evaluate *in vivo* anticancer activity of certain compounds described in EXAMPLE 1 using 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) (MTS) cell viability assays. Results from these studies are shown in Table 2 below (see columns 3 and 4).

Cell line and culture:

The cell lines M-NFS-60 (ATCC® CRL-1838™) and BaF3-CSF1R-1600 were obtained from American Type Culture Collection (ATCC, Manassas, VA, USA). The stable BaF3-CSF1R-1600 cell line expresses ETV6-CSF1R fusion protein consisting of N-terminal ETS-variant gene 6 protein (ETV6 residues M1-G337) and CSF1R tyrosine kinase (CSF1R residues L533-C972). The M-NSF-60 and BaF3-CSF1R-1600 cells were cultured in RPMI1640 medium supplemented with 10% fetal bovine serum, 0.05 mM 2-ME, 10 U/ml penicillin, and 10 g/ml streptomycin at 37 °C and 5% CO_2.

MTS cell viability assays:

M-NFS-60 and BaF3-CSF1R-1600 cells were seeded in 96-well plates at a density of 10000 cells/100 µl and 8000 cells/100 µl per well, respectively, for 16 h and treated with vehicle or various concentrations of test compounds in medium for 72 h. Viable cells were quantified using the MTS method (Promega, Madison, WI, USA) according to manufacturer's recommended protocol. The results were determined by measuring absorbance at 490 nm using a plate reader (Victor 2). The GI_{50} value was defined as the amount of compound that caused 50% reduction in cell viability in comparison with DMSO-treated (vehicle) control and was calculated using Prism GraphPad Prism version 6 software (GraphPad).

Table 2. Inhibitory activity of heterocyclic compounds in a CSF1R kinase assay and in M-NFS-60 and BaF3-CSF1R cell assays

Compound	Enzymatic Assay	Cellular Proliferation Assay	
	CSF1R enzyme IC_{50}, (nM)	M-NFS-60 (nM) GI_{50} (nM)	BaF3-CSF1R GI_{50} (nM)
1	+++	++	++
2	+++	+++	+++
3	+++	+++	+++
4	+++	+++	+++
5	+++	++	
6	+++		
7	+		
8	++		
9	+++	+++	+++
10	+++	++	++
11	+++	+++	+++
12	+++		
13	++		
14	++++	++	++++
15	++++	++	+++
16	++++	+++	+++
17	++++	+++	+++
18	++++	++	+++
19	++++	+++	++++
20	++++	+++	+++
21	++++	+++	+++
22	++		
23	+++	+++	+++
24	++++	+++	+++
25	+++	+	++
26	+++	++	+++
27	++++	+++	+++
28	+++	+++	++++
29	++		

30	++++	+++	+++
31	++	+	++
32	+++	+	++
33	+++	++	++
34	++++	++	++++
35	+		
36	+++	++	
37	++		
38	+		
39	++++	++	
40	+++	++	+++
41	+++		++
42	++++	++	+++
43	+++	++	++
44	++++	++	+++
45	++++	++	+++
47	+		
49	++++	+	++
50	+++		
51	++++	+++	+++
52	++		
53	++		
54	++		
55	+++		
56	+++	++	+++
57	++++	++	++
58	++++	++	+++
59	++++	+++	+++
60	+++		
61	++		
62	++++		++
63	+++	++	++
64	+		
65	++++	+++	+++
66	++++	+++	+++
67	+++	++	+++
68	+++	++	+++
69	+		
71	++		
72	+		
73	+++		
75	+		
77	++		
79	++++		

83	++		
84	++		
85	+++		
87	+		
89	++		
90	++		
93	+++		
97	+++	+++	+++
98	++++	+++	++++
99	++++	+++	+++
100	++++	+++	+++
101	+++	++	++
102	+++	+	++
104	+++	++	+++
105	+++	+++	+++
106	++++	++	+
107	+++		
108	+++	+++	+++

[a] ++++: $IC_{50} < 20$ nM; +++: 20 nM $< IC_{50} < 100$ nM; ++: 100 nM $< IC_{50} < 1000$ nM; +:

[b] ++++: $GI_{50} < 20$ nM; +++: 20 nM $< GI_{50} < 100$ nM; ++: 100 nM $< GI_{50} < 1000$ nM; +:

EXAMPLE 4. Kinase selectivity profile

A study was conducted to determine kinase selectivity of compounds 27 and 67. More specifically, each compound was tested for inhibitory activity of CSF1R kinase, as compared to that of seven other kinases, i.e., Aurora A, Aurora B, tyrosine-protein kinase Kit (c-Kit), fms-like tyrosine kinase 3 (FLT3), platelet-derived growth factor receptor (PDGFR) A, PDGFR B, and discoidin domain receptor tyrosine kinase 1 (DDR1). Results from this study are shown in Table 3 below.

In vitro profiling of the kinase panel was performed at Reaction Biology Corporation (www.reactionbiology.com, Malvern, PA) using the "HotSpot" assay platform. Briefly, specific kinase/substrate pairs along with required cofactors were prepared in a reaction buffer containing 20 mM Hepes pH 7.5, 10 mM $MgCl_2$, 1 mM EGTA, 0.02% Brij35, 0.02 mg/ml BSA, 0.1 mM Na_3VO_4, 2 mM DTT, and 1% DMSO. Compound 27 or 67 was added. 20 minutes later, a mixture of ATP (Sigma, St. Louis MO) and ^{33}P ATP (Perkin Elmer, Waltham MA) was added to the resulting reaction solution to give a final concentration of 10 μM. The reaction was carried out at room temperature for 120 min., followed by spotting the reaction solution onto P81 ion exchange filter paper (Whatman Inc., Piscataway, NJ). Unbound phosphate was removed by extensive washing filters in 0.75% phosphoric acid. After subtracting the background derived from a control reaction containing an inactive enzyme, kinase activity was determined as the percentage of the remaining kinase activity in a test sample compared to a vehicle (DMSO) reaction. An IC_{50} value and a dose-response curve for each compound against each kinase were obtained using Prism (Graph Pad Software). Selectivity, expressed as an IC_{50} ratio, was determined by dividing the IC_{50} value of a kinase, e.g., Aurora A, by that of CSF1R.

Table 3. Kinase selectivity profile

Compound	Kinase IC_{50} (nM)							
	CSF1R	Aurora A	Aurora B	c-Kit	FLT3	PDGFR A	PDGFR B	DDR1
27	0.534	++++	+++	++	+++	++	++	+++
67	5.69	+++	+++	+++	+++	++	+++	+

++++: IC_{50} ratio > 1000; +++: 1000 > IC_{50} ratio > 100; ++: 100 > IC_{50} ratio > 10; +: 10 > IC_{50} ratio > 1

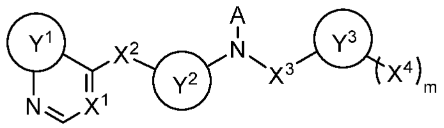
OTHER EMBODIMENTS

All of the features disclosed in this specification may be combined in any combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose. Thus, unless expressly stated otherwise, each feature disclosed is only an example of a generic series of equivalent or similar features.

Further, from the above description, one skilled in the art can easily ascertain the essential characteristics of the present invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. Thus, other embodiments are also within the claims.

WHAT IS CLAIMED IS:

1. A compound of formula I:



I

,

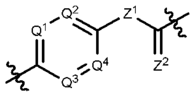
wherein

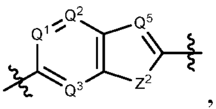
A is H, C_1-C_6 alkyl, or ORr, Rr being H or C_{1-6} alkyl;

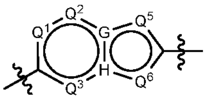
Y^1 is phenyl substituted with $(R^1)_n$, 5-membered heteroaryl substituted with $(R^2)_o$, 5-membered heterocycloalkenyl substituted with $(R^2)_o$, or alkenyl substituted with $(R^2)_o$, in which R^1 in $(R^1)_n$, n being 0–4, is, independently, F, Cl, Br, NO_2, CN, amino, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl , C_5-C_{15} heterocycloalkyl, aryl, heteroaryl, carbonyl, thionyl, iminyl, or spiroamino; and R^2 in $(R^2)_o$, o being 0-5, is, independently, F, Cl, Br, NO_2, CN, amino, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_5-C_{15} heterocycloalkyl, aryl, heteroaryl, carbonyl, thionyl, iminyl, spiroamino, or C_1-C_6 alkoxyl;

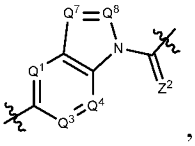
X^1 is N or CR^3, R^3 being H, F, Cl, Br, CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl;

X^2 is O, S, NH, or CH_2;

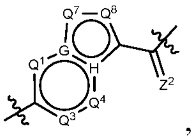
Y^2 is 

, 

, 

, 

, or



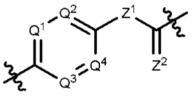
, in which each of Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, and Q^8 is, independently, N or CR^4, R^4 being H, F, Cl, Br, CN, amino, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl; Z^1 is O, S, or NRr; Z^2 is O, S, or NRr; and G and H are, respectively, C or N and N or C;

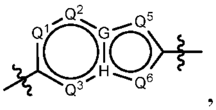
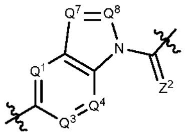
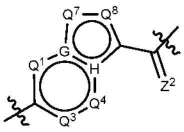
X^3 is deleted, CH_2, $(CH_2)_2$, or CH(C≡CH);

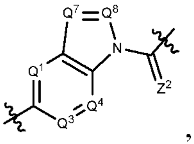
Y^3 is C_1-C_6 alkyl, aryl, heteroaryl, C_3-C_8 cycloalkyl, or C_5-C_6 heterocycloalkyl having one heteroatom, in which the one heteroatom is O or N; and

X^4 in $(X^4)_m$, m being 0–5, is, independently, F, Cl, Br, CN, SO_2NH_2, amino, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl.

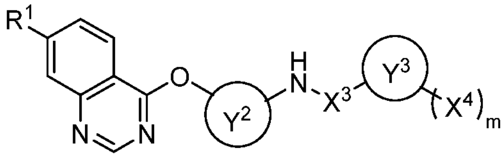
2. The compound of claim 1, wherein Y^1 is phenyl substituted with $(R^1)_n$, 5-membered heteroaryl substituted with $(R^2)_o$, or 5-membered heterocycloalkenyl substituted with $(R^2)_o$, in which R^1 in $(R^1)_n$ is, independently, F, Cl, Br, NO_2, CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_5-C_{15} heterocycloalkyl, aryl, heteroaryl, carbonyl, thionyl, iminyl, or spiroamino; and R^2 in $(R^2)_o$ is, independently, F, Cl, Br, NO_2, CN, amino, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_5-C_{15} heterocycloalkyl, aryl, heteroaryl, carbonyl, thionyl, iminyl, spiroamino, or C_1-C_6 alkoxyl.

3. The compound of claim 2, wherein Y^2 is , Y^3 is pyridyl, and R^1 is C_5-C_{15} heterocycloalkyl.

4. The compound of claim 1, wherein Y^2 is , , or , in which Z^2 is O or NRr.

5. The compound of claim 4, wherein Y^2 is , Y^3 is pyridyl, and R^1 is amino.

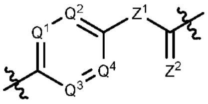
6. The compound of claim 1, wherein the compound is of formula Ia:

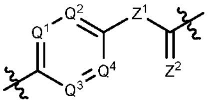


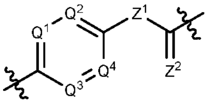
Ia

,

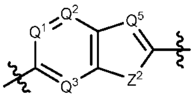
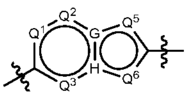
in which R^1 is amino or C_5-C_{15} heterocycloalkyl.

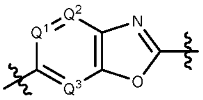
7. The compound of claim 6, wherein Y^2 is  ; Y^3 is pyridyl; X^3 is CH_2; X^4 is CH_3, CH_2F, CHF_2, CF_3, or OCH_3; and m is 1.

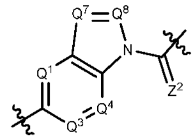
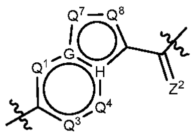
8. The compound of claim 6, wherein Y^2 is  ; Y^3 is phenyl; X^3 is CH_2; each of X^4 is, independently, F, Cl, Br, CN, SO_2NH_2, CH_3, CH_2F, CHF_2, CF_3, OCF_3, C_1-C_6 alkoxyl, or amino; and m is 0–2.

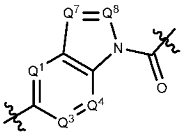
9. The compound of claim 6, wherein Y^2 is  ; Y^3 is phenyl; X^3 is deleted; each of X^4 is, independently, F, Cl, Br, CN, SO_2NH_2, CH_3, CH_2F, CHF_2, CF_3, OCF_3, C_1-C_6 alkoxyl, or amino; and m is 0–2.

10. The compound of claim 7, wherein R^1 is amino.

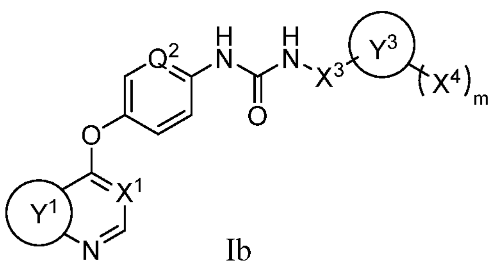
11. The compound of claim 6, wherein Y^2 is  or  , Y^3 is phenyl or pyridyl; and X^3 is CH_2.

12. The compound of claim 11, wherein Y^2 is .

13. The compound of claim 6, wherein Y^2 is  or , Y^3 is phenyl or pyridyl; and X^3 is CH_2.

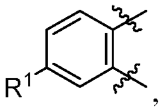
14. The compound of claim 13, wherein Y^2 is .

15. The compound of claim 1, wherein the compound is of formula Ib:

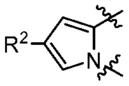
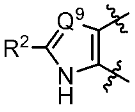
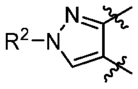


Ib

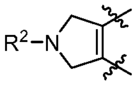
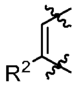
.

16. The compound of claim 15, wherein Y^1 is , Y^3 is phenyl or pyridyl; and X^3 is deleted or CH_2.

17. The compound of claim 16, wherein each of X^4 is, independently, CH_3, CH_2F, CHF_2, CF_3, or OCH3 and m is 0–2.

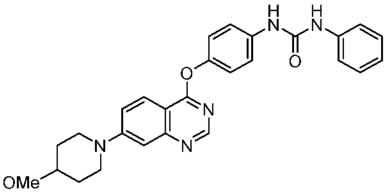
18. The compound of claim 15, wherein Y^1 is , , or ; Y^3 is phenyl or pyridyl; and X^3 is deleted or CH_2, in which Q^9 is N or CR^5, R^5 being H, F, Cl, Br, CN, amino, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl.

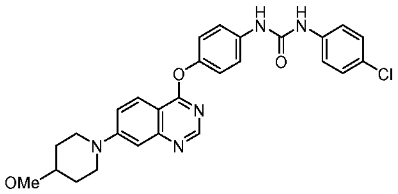
19. The compound of claim 18, wherein each of X^4 is, independently, CH_3, CH_2F, CHF_2, CF_3, or OCH3 and m is 0–2.

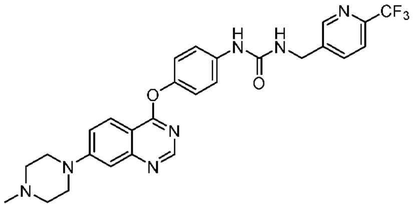
20. The compound of claim 15, wherein Y^1 is  or ; Y^3 is phenyl or pyridyl; and X^3 is deleted or CH_2.

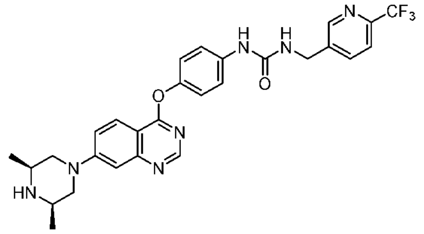
21. The compound of claim 20, wherein each of X^4 is, independently, CH_3, CH_2F, CHF_2, CF_3, or OCH_3 and m is 0–2.

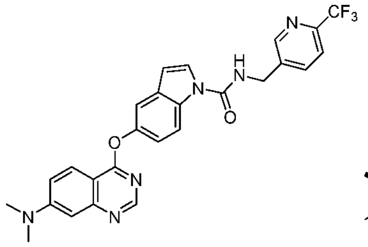
22. The compound of claim 1, wherein the compound is one of the following compounds:

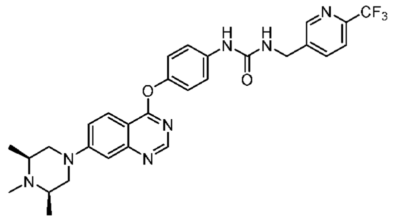


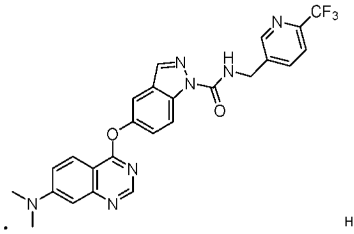


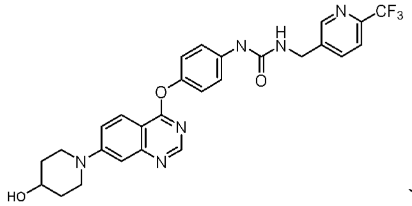


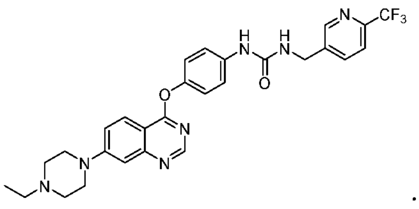




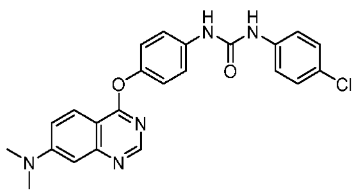


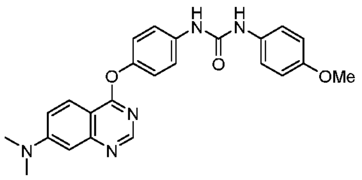


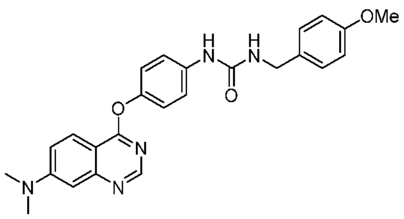


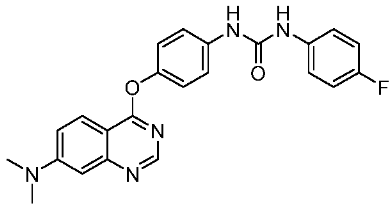


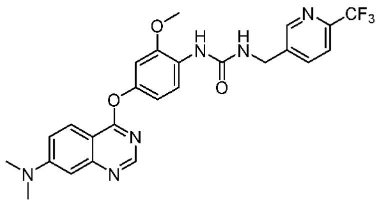
23. The compound of claim 1, wherein the compound is

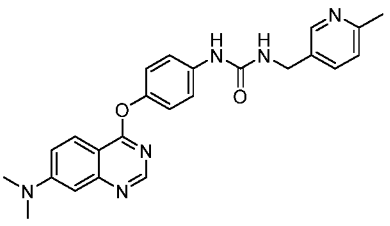


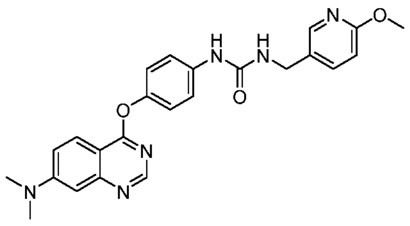


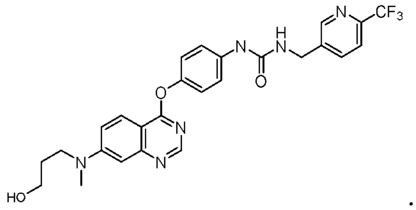




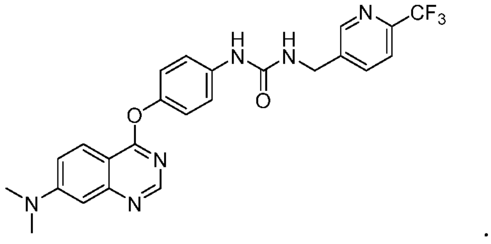








24. The compound of claim 1, wherein the compound is



25. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

26. The pharmaceutical composition of claim 25, further comprising a therapeutic agent selected from an anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory agent, or an immunosuppressive agent.

27. The pharmaceutical composition of claim 25, further comprising a therapeutic agent, the therapeutic agent being:

an alkylating agent selected from adozelesin, altretamine, bizelesin, busulfan, carboplatin, carboquone, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, estramustine, fotemustine, hepsulfam, ifosfamide, improsulfan, irofulven, lomustine, mechlorethamine, melphalan, oxaliplatin, piposulfan, semustine, streptozocin, temozolomide, thiotepa, and treosulfan;

an antibody selected from alemtuzumab, bevacizumab, cetuximab, galiximab, gemtuzumab, nivolumab, panitumumab, pembrolizumab, pertuzumab, rituximab, tositumomab, trastuzumab, and 90 Y ibritumomab tiuxetan;

a targeted signal transduction inhibitor selected from bortezomib, geldanamycin, and rapamycin;

a kinase inhibitor selected from erlotinib, gefitinib, flavopiridol, imatinib mesylate, lapatinib, sorafenib, sunitinib malate, AEE-788, AG-013736, AMG 706, AMN107, BMS-354825, BMS-599626, 7-hydroxystaurosporine, vemurafenib, dabrafenib, trametinib, cobimetinib, selumetinib, and vatalanib;

a taxane selected from DJ-927, docetaxel, TPI 287, paclitaxel, and DHA-paclitaxel;

a retinoid selected from alitretinoin, bexarotene, fenretinide, isotretinoin, and tretinoin;

an alkaloid selected from etoposide, homoharringtonine, teniposide, vinblastine, vincristine, vindesine, and vinorelbine;

an antibiotic selected from bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, menogaril, mitomycin, mitoxantrone, neocarzinostatin, pentostatin, and plicamycin;

an antiangiogenic agent selected from AE-941, ABT-510, 2-methoxyestradiol, lenalidomide, and thalidomide;

a topoisomerase inhibitor selected from amsacrine, edotecarin, exatecan, irinotecan, 7-ethyl-10-hydroxy-camptothecin, rubitecan, topotecan, and 9-aminocamptothecin;

an antimetabolite selected from the group consisting of azacitidine, capecitabine, cladribine, clofarabine, cytarabine, decitabine, floxuridine, fludarabine, 5-fluorouracil, ftorafur, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, nelarabine, pemetrexed, raltitrexed, thioguanine, and trimetrexate;

a hormone or hormone antagonist selected from the group consisting of anastrozole, androgens, buserelin, diethylstilbestrol, exemestane, flutamide, fulvestrant, goserelin, idoxifene, letrozole, leuprolide, magestrol, raloxifene, tamoxifen, and toremifene;

a biological response modifier selected from imiquimod, interferon-α, and interleukin-2;

an indoleamine 2,3-dioxygenase inhibitor;

a chemotherapeutic agent selected from 3-amino-2-carboxyaldehyde thiosemicarbazone, altrasentan, aminoglutethimide, anagrelide, asparaginase, bryostatin-1, cilengitide, elesclomol, eribulin mesylate, ixabepilone, lonidamine, masoprocol, mitoguanazone, oblimersen, sulindac, testolactone, and tiazofurin;

a mammalian target of rapamycin inhibitor;

a phosphoinositide 3-kinase inhibitor;

a cyclin-dependent kinase 4 inhibitor;

a protein kinase B inhibitor;

a heat shock protein 90 inhibitor;

a farnesyltransferase inhibitor;

an aromatase inhibitor;

a mitogen-activated protein kinase inhibitor;

a tyrosine kinase inhibitor;

an epidermal growth factor receptor inhibitor;

a programmed cell death protein 1 inhibitor;

a programmed death-ligand 1 inhibitor; or

an interleukin 8 receptor beta inhibitor.

28. A method of treating a CSF1R modulated condition, comprising administering to a subject in need thereof an effective amount of a compound of claim 1, wherein the condition is selected from a cancer, an inflammatory disorder or an autoimmune disease, and a bone disorder.

29. The method of claim 28, wherein the condition is a cancer selected from acute myeloid leukemia, bladder cancer, breast cancer, cervical cancer, colon cancer, gastric cancer, gastrointestinal stromal tumor, glioblastoma multiforme, hepatocellular carcinoma, Hodgkin’s lymphoma, kidney cancer, liver cancer, lung cancer, melanoma, metastatic tumor, ovarian cancer, pancreatic cancer, pigmented villondular synovitis, prostate cancer, tenosynovial giant cell tumors, endometrial cancer, multiple myeloma, myelocytic leukemia, bone cancer, renal cancer, brain cancer, myeloproliferative disorder, esophageal cancer, squamous cell carcinoma, uveal melanoma, follicular lymphoma, colorectal cancer, head and neck cancer, astrocytoma, and pulmonary adenocarcinoma.

30. The method of claim 28, wherein the condition is an inflammatory disorder or an autoimmune disease selected from psoriatic arthritis, arthritis, asthma, thyroiditis, glomerularnephritis, atherosclerosis, psoriasis, Sjogren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, cutaneous lupus erythematosus, Crohn's disease, ulcerative colitis, type I diabetes, multiple sclerosis, human immunodeficiency virus encephalitis, Alzheimer's disease, amyotrophic lateral sclerosis, and epilepsy.

31. The method of claim 28, wherein the condition is a bone disorder selected from osteoporosis, osteoarthritis, periodontitis, periprosthetic osteolysis, and Paget’s disease.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/27453

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 31/416; A61K 31/437; A61P 35/00 (2020.01)

CPC - A61K 31/4439; A61K 31/444; A61K 45/06; A61P 35/00

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)
See Search History document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2017/0355678 A1 (EXELIXIS INC) 14 December 2017 (14.12.2017), entire document, especially: pg 14, Table 1, Entry 23.	1-2,25-31
A	PubChem-CID-67379395, Create Date: 30 November 2012 (30.11.2012), pg 2, Fig.	1-2,25-31
A	PubChem-CID-2814130, Create Date: 19 July 2005 (19.07.2005), pg 2, Fig.	1-2,25-31
A	US 2012/0053192 A1 (ZHANG et al.) 01 March 2012 (01.03.2012), entire document, especially: pg 15, Table 7, Compound No. 19.	1-2,25-31

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent 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 06 August 2020	Date of mailing of the international search report 27 AUG 2020
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Lee Young Telephone No. PCT Helpdesk: 571-272-4300

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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

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

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

This International Searching Authority found multiple inventions in this international application, as follows:
--see attached extra sheet--

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 additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search 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.:
1-2,25-31

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

--BOX III - LACK OF UNITY--

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-31 directed to a compound of formula I or a pharmaceutically acceptable salt thereof. The compound of formula I will be searched to the extent that it encompasses the first species of claim 1, wherein A is H; Y1 is phenyl substituted with (R1)n; R1 in (R1)n, n being 0, is, F; X1 is N; X2 is O; Y2 is the first formula indicated, in which Q1 is N; Q2, Q3 and Q4 are CR4, R4 being H; Z1 is O; Z2 is O; X3 is deleted; Y3 is C1 alkyl; X4 in (X4)m, m being 0, is F. It is believed that claims 1-2 and 25-31 encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass the first species of claim 1. Applicant is invited to elect additional compounds of formula I, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of claim 1, wherein A is H; Y1 is phenyl substituted with (R1)n; R1 in (R1)n, n being 0, is, F; X1 is N; X2 is O; Y2 is the first formula indicated, in which Q1 is CR4; Q2 is N; Q3 and Q4 are CR4, R4 being H; Z1 is O; Z2 is O; X3 is deleted; Y3 is C1 alkyl; X4 in (X4)m, m being 0, is F (i.e. claims 1-2 and 25-31).

The groups of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique compound of formula I, which is not required by any other invention of Group I+.

Common technical features:

The inventions of Groups I+ share the technical feature of a compound having the structure of formula I.

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by the document entitled US 2012/0053192 A1 to Zhang et al. (hereinafter 'ZHANG').

Zhang discloses a compound of formula I: wherein A is H; Y1 is phenyl substituted with (R1)n; R1 in (R1)n, n being 1, is, F; X1 is N; X2 is O; Y2 is the first formula indicated, in which Q1, Q2, Q3 and Q4 are CR4, R4 being H; Z1 is NRr, Rr is H; Z2 is O; X3 is deleted; Y3 is aryl; X4 in (X4)m, m being 2, is Cl and C1 haloalkyl (pg 15, Table 7, Compound No. 19).

As said compound was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the inventions of Group I+.

The inventions of Group I+ thus lack unity under PCT Rule 13.

Note:
Claim 1 language lacks clarity. Specifically substructure Y2 is defined with two subgroups, Z1 and Z2, which are both defined as being selected from: O, S, or NRr, but there is no substituent Rr defined anywhere in the claim. The general formula Ib given on page 8, as well as the exemplary compounds given on pages 9 and 10 of the instant specification make it clear that the intent of the applcant was that Rr should be H. Therefore, for the purposes of the search and opinion, the occurrence of the term "Rr" was replaced by "H".