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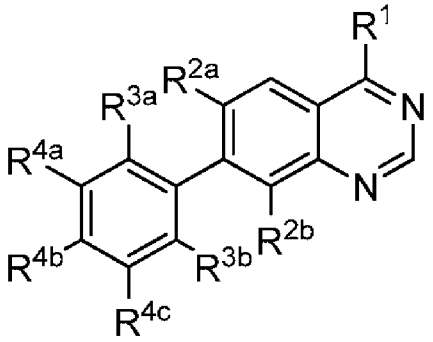
(54) Title: METHODS FOR PREPARATION OF QUINAZOLINE DERIVATIVES



(I)

(57) Abstract: Methods for preparing compounds having the following structure (I): (Formula (I)) or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein R^1, R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, R^{4b} and R^{4c}, are as defined herein are provided. Related compounds and methods for making the same are also provided.

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METHODS FOR PREPARATION OF QUINAZOLINE DERIVATIVES

BACKGROUND

Technical Field

The present invention generally relates to methods and compounds for preparing quinazoline and quinazoline derivatives using chemo and/or regioselective metalation reactions.

Background

The heterocyclyl fused ring scaffold of quinazoline has drawn interest in the field of pharmaceutical chemistry because of the diverse range of biological properties exhibited by compounds derived from such a substrate. Quinazoline scaffolds containing various substitution patterns are considered to be of important synthetic chemical as well as physiological importance. The range of biological activity exhibited by this class of compounds, and derivatives thereof, is wide and diverse, showing anticancer, antifungal, and antibacterial activity among many others. (Asif, M. Int. J. Med. Chem. 2014, 395637, 1-27). Accordingly, because of the complexity of functionalization and substitution patterns associated with pharmaceuticals, a synthetic method for selective functionalization of quinazoline scaffolds for use in synthesis of quinazoline derivatives is very valuable.

Given recent advancements in organometallic chemistry, functionalization via organometallic intermediates has become an important tool for synthesis of pharmaceutical products. Specifically, organozinc intermediates serve as an important synthetic species as they are compatible with a wide range of functional groups and afford desired products in high yields. Preparation of heteroaryl zinc intermediates is achieved by three general procedures; (1) insertion of zinc to heteroaryl iodides or bromides, (2) direct insertion of magnesium into heteroaryl halides with zinc (II) salts present, and (3) metalation with $(tmp)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$. (Knochel, P.; Schade, M. A.; Bernhardt, S.; Manolikakes, G.; Metzger, A.; Piller, F. M.; Rohbogner,

C. J.; Mosrin, M. Beilstein J. Org. Chem. 2011, 7, 1261-1277). Due to the low reactivity afforded by the carbon-zinc bond, the assistance of a transition metal catalyst is sometimes required to facilitate a reaction with an electrophile (i.e., via a Negishi cross-coupling; Wunderlich, S.H.; Knochel, P. Angew. Chem. Int. Ed. 2007, 46, 7685-7688).

Recently, heterocyclyl mixed metal bases have been developed for use in forming zinc intermediates via direct metalation. Those bases are related to the third procedure mentioned above (*i.e.*, metalation with $(tmp)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$) and have been reported to achieve chemo and regioselective metalations (Yus, M.; Foubelo, F. Handbook of Functionalized Organometallics; Knochel, P., Ed.; Wiley-VCH: Weinheim, Germany, 2005). However, this strategy has drawbacks. Specifically, only recently has this specific heterocyclyl mixed metal base been discovered so its synthetic methodology is relatively new and unpredictable (Knochel, P.; Schade, M. A.; Bernhardt, S.; Manolikakes, G.; Metzger, A.; Piller, F. M.; Rohbogner, C. J.; Mosrin, M. Beilstein J. Org. Chem. 2011, 7, 1261-1277). In some instances, high temperature and/or microwave irradiation is required to assist zinc metalation reactions that use $(tmp)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (Wunderlich, S.; Knochel, P. Org. Lett. 2008, 10(20) 4705-4707). As of yet, there does not appear to be a way to accurately predict whether a specific scaffold will require high temperature or microwave irradiation to afford zincated synthetic intermediates in a regiospecific manner. Accordingly, although it appears the use of zincated intermediates tolerates most functional groups, certain substrates, sensitive to high temperatures or microwave irradiation, may complicate the use of this reaction strategy.

There have been some reported instances of organometallic chemistry relating to a quinazoline scaffolds, and derivatives thereof. One reported instance of organometallic chemistry related to selective lithiation of quinazoline. (Plé, N.; Turck, A.; Chapouland, V.; Quéguiner, G. Tetrahedron 1997, 53, 2871). While it would initially appear to be somewhat analogous to a zincation strategy, it is also known that aryl lithium species are highly reactive, and are not compatible in the presence of sensitive functional groups like esters or ketones (Yus, M.; Foubelo, F. Handbook of

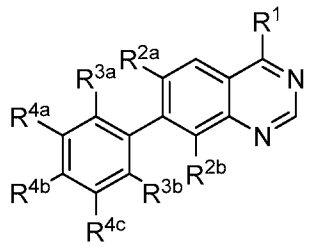
Functionalized Organometallics; Knochel, P., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Vol. 1). As such, a pathway that makes use of a lithiated quinazoline intermediate would have only limited value in a synthetic strategy. Accordingly, lithiation of quinazolines would not be an ideal candidate for a scaffold containing incompatible functional groups like esters or ketones.

While various methods exist for preparing quinazoline compounds, there remains a need in the art for an improved methods and compounds for preparation of various functionalized quinazoline scaffolds. The present disclosure provides these and other related advantages.

BRIEF DESCRIPTION

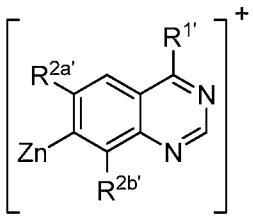
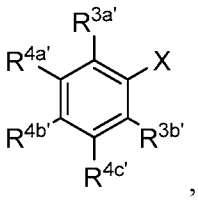
Embodiments of the present invention provide methods and compounds for preparation of aryl or heteroaryl substituted quinazoline compounds. The provided methods are efficient and amenable to large scale manufacturing of the compounds, as well as smaller scale production for research purposes. The provided methods and compounds find utility in any number of applications, including preparation of compounds for treatment of various Kras-mediated cancers as described in PCT Pub. No: WO 2015/054572, the full disclosure of which is incorporated herein by reference.

Accordingly, in one embodiment, there is provided a method for preparing a compound having the following structure (I):



(I)

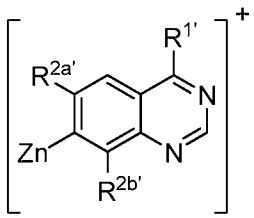
or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^1, R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, R^{4b} and R^{4c}, are as defined herein , the method comprising preparing a mixture comprising a compound of structure (II) and a compound of structure (III), the compounds of structure (II) and (III) having the following structures, respectively:

(II) and (III),

or a salt thereof, wherein $R^{1'}$, $R^{2a'}$, $R^{2b'}$, $R^{3a'}$, $R^{3b'}$, $R^{4a'}$, $R^{4b'}$, $R^{4c'}$ and X are as defined herein, thereby forming a carbon-carbon bond between the carbon bearing the Zn moiety on compound (II) and the carbon bearing the X moiety on compound (III).

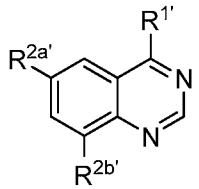
Other embodiments provide compounds useful for preparation of compounds of structure (I), for example in some embodiments is provided a compound having the following structure (II):



(II),

or a salt thereof, wherein $R^{1'}$, $R^{2a'}$ and $R^{2b'}$ are as defined herein.

Still other embodiments provide different compounds having the following structure (V):



(V),

or a salt thereof, wherein $R^{1'}$, $R^{2a'}$ and $R^{2b'}$ are as defined herein.

These and other aspects of the invention will be apparent upon reference to the following detailed description. To this end, various references are set forth herein which describe, in more detail, certain background information, procedures, compounds and/or compositions and are each hereby incorporated by reference in their entirety.

DETAILED DESCRIPTION

In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments of the invention. However, one skilled in the art will understand that the invention may be practiced without these details.

Unless the context requires otherwise, throughout the present specification and claims, the word "comprise" and variations thereof, such as, "comprises" and "comprising" are to be construed in an open, inclusive sense, that is, as "including, but not limited to".

Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. As used in the specification and claims, the singular form of "a", "an" and "the" include plural references unless the context clearly dictates otherwise.

"Halo" refers to chloro, fluoro, bromo or iodo.

"Hydroxy" or "hydroxyl" refers to the -OH radical.

"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, which is saturated or unsaturated (*i.e.*, contains one or more double and/or triple bonds), having from one to twelve carbon atoms (C_1-C_{12} alkyl), preferably one to eight carbon atoms (C_1-C_8 alkyl) or one to six carbon atoms (C_1-C_6 alkyl), and which is attached to the rest of the molecule by a single bond, *e.g.*, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), 3-methylhexyl, 2-methylhexyl, ethenyl, prop-1-enyl,

but-1-enyl, pent-1-enyl, penta-1,4-dienyl, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Alkyl includes alkenyls (one or more carbon-carbon double bonds) and alkynyls (one or more carbon-carbon triple bonds such as ethynyl and the like). Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted.

"Alkoxy" refers to a radical of the formula $-OR_a$ where R_a is an alkyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, an alkoxy group is optionally substituted.

"Aryl" refers to a hydrocarbon ring system radical comprising hydrogen, 6 to 18 carbon atoms and at least one aromatic ring. For purposes of this invention, the aryl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems. Aryl radicals include, but are not limited to, aryl radicals derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, the term "aryl" is meant to include aryl radicals that are optionally substituted.

"Carbocyclyl" refers to a stable, aromatic or non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which may include fused or bridged ring systems, having from three to fifteen carbon atoms, preferably having from three to ten carbon atoms, and which is attached to the rest of the molecule by a single bond. Carbocyclyls include aryl and cycloalkyl groups. Unless otherwise stated specifically in the specification, a carbocyclyl group is optionally substituted.

"Cycloalkyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which may include fused or bridged ring systems, having from three to fifteen carbon atoms, preferably having from three to ten carbon atoms, and which is saturated or unsaturated and attached to the rest of the molecule by a single bond. Monocyclic radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and

cyclooctyl. Polycyclic radicals include, for example, adamantyl, norbornyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, a cycloalkyl group is optionally substituted.

"Fused" refers to any ring structure described herein which is fused to an existing ring structure in the compounds of the invention. When the fused ring is a heterocyclyl ring or a heteroaryl ring, any carbon atom on the existing ring structure which becomes part of the fused heterocyclyl ring or the fused heteroaryl ring is replaced with a nitrogen atom.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. Unless stated otherwise specifically in the specification, a haloalkyl group is optionally substituted.

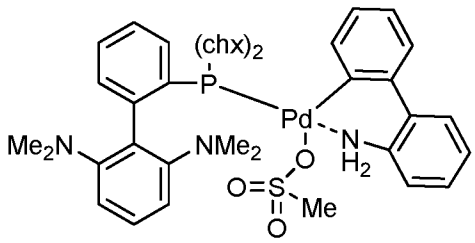
"Heterocyclyl" or "heterocyclyl ring" refers to a stable 3- to 18-membered aromatic or non-aromatic ring radical which consists of two to twelve carbon atoms and from one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Unless stated otherwise specifically in the specification, the heterocyclyl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical is optionally oxidized; the nitrogen atom is optionally quaternized; and the heterocyclyl radical is partially or fully saturated. Examples of such non-aromatic heterocyclyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification. "Unless stated otherwise specifically in the specification, a heterocyclyl group is optionally substituted.

"Heteroaryl" refers to a heterocyclyl group having a 5- to 14-membered ring system radical comprising hydrogen atoms, one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and at least one aromatic ring. For purposes of this invention, the heteroaryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e. thienyl). Unless stated otherwise specifically in the specification, a heteroaryl group is optionally substituted.

"Mixed metal heterocyclyl base" refers to a reagent comprising a basic heterocyclyl moiety and two or more metals. The reagent contains anions such that the overall complex is charge neutral. Examples of metals include, but are not limited to zinc, magnesium, and lithium. Examples of heterocycles include those defined herein. Examples of anions include, but are not limited to chloride. Examples of a "mixed metal heterocyclyl base" include, but are not limited to 2,2,6,6-

Bis(tetramethylpiperidine)zinc, magnesium chloride, lithium chloride complex, referred to herein as $(tmp)_2Zn \cdot 2\ MgCl_2 \cdot 2\ LiCl$.

Various catalysts and precatalysts are useful in certain embodiments of the invention. In some embodiments, a palladium catalyst or precatalyst is used, for example a homogenous palladium catalyst or precatalyst. One of ordinary skill in the art can determine appropriate palladium-based catalysts or precatalyst useful to implement embodiments of the invention. The palladium catalysts and/or precatalysts can be selected from those known in the art or derived by one of ordinary skill in the art. In one embodiment the precatalyst is "CPhos 3rd generation," which has the following structure:



A "protected hydroxyl" group is an oxygen moiety bearing a functionality, which can be removed to reveal a free hydroxy. One of ordinary skill in the can derive appropriate protected hydroxyl groups for use in the embodiments of the invention.

A "non-acidic substituent" is a substituent having no hydrogen atoms sufficiently acidic to be deprotonated in the presence of the mixed metal, heterocyclic bases employed in various embodiments of the invention. "Sufficiently acidic" means, at equilibrium in the presence of the mixed metal, heterocyclic bases, the hydrogen atoms will at most be 5% or less than 1% deprotonated.

The term "substituted" used herein means any of the above groups (*e.g.*, alkyl, alkoxy, aryl, carbocyclyl, cycloalkyl, haloalkyl, heterocyclyl and/or heteroaryl) wherein at least one hydrogen atom is replaced by a bond to a non-hydrogen atom such as, but not limited to: a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, and ester groups; a sulfur atom in groups such as thiol groups, thioalkyl groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines,

arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as trialkylsilyl groups, dialkylarylsilyl groups, alkyldiarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. "Substituted" also means any of the above groups in which one or more hydrogen atoms are replaced by a higher-order bond (e.g., a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; and nitrogen in groups such as imines, oximes, hydrazones, and nitriles. For example, "substituted" includes any of the above groups in which one or more hydrogen atoms are replaced with $-NR_gR_h$, $-NR_gC(=O)R_h$, $-NR_gC(=O)NR_gR_h$, $-NR_gC(=O)OR_h$, $-NR_gSO_2R_h$, $-OC(=O)NR_gR_h$, $-OR_g$, $-SR_g$, $-SOR_g$, $-SO_2R_g$, $-OSO_2R_g$, $-SO_2OR_g$, $=NSO_2R_g$, and $-SO_2NR_gR_h$. "Substituted also means any of the above groups in which one or more hydrogen atoms are replaced with $-C(=O)R_g$, $-C(=O)OR_g$, $-C(=O)NR_gR_h$, $-CH_2SO_2R_g$, $-CH_2SO_2NR_gR_h$. In the foregoing, R_g and R_h are the same or different and independently hydrogen, alkyl, alkoxy, alkylaminyl, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl. "Substituted" further means any of the above groups in which one or more hydrogen atoms are replaced by a bond to an aminyl, cyano, hydroxyl, imino, nitro, oxo, thioxo, halo, alkyl, alkoxy, alkylaminyl, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl group. In addition, each of the foregoing substituents may also be optionally substituted with one or more of the above substituents.

"Pharmaceutically acceptable salt" includes both acid and base addition salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as, but not limited to, acetic acid, 2,2-dichloroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid,

benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, propionic acid, pyroglutamic acid, pyruvic acid, salicylic acid, 4-aminosalicylic acid, sebacic acid, stearic acid, succinic acid, tartaric acid, thiocyanic acid, *p*-toluenesulfonic acid, trifluoroacetic acid, undecylenic acid, and the like.

"Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as ammonia, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, diethanolamine, ethanolamine, deanol, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, benethamine, benzathine, ethylenediamine, glucosamine, methylglucamine, theobromine, triethanolamine, tromethamine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. Particularly

preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

The invention disclosed herein is also meant to encompass all pharmaceutically acceptable compounds of structure (I) being isotopically-labelled by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. These radiolabeled compounds could be useful to help determine or measure the effectiveness of the compounds, by characterizing, for example, the site or mode of action, or binding affinity to pharmacologically important site of action. Certain isotopically-labelled compounds of structure (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence are preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of structure (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

Often crystallizations produce a solvate of the compound of the invention. As used herein, the term "solvate" refers to an aggregate that comprises one or more molecules of a compound of the invention with one or more molecules of solvent. In some embodiments, the solvent is water, in which case the solvate is a hydrate. Alternatively, in other embodiments, the solvent is an organic solvent. Thus, the compounds of the present invention may exist as a hydrate, including a monohydrate, dihydrate, hemihydrate, sesquihydrate, trihydrate, tetrahydrate and the like, as well as the corresponding solvated forms. In some aspects, the compound of the invention is a true solvate, while in other cases, the compound of the invention merely retains adventitious water or is a mixture of water plus some adventitious solvent.

"Optional" or "optionally" means that the subsequently described event or circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

It will also be appreciated by those skilled in the art that in the processes for preparing the compounds described herein the functional groups of intermediate compounds may need to be protected by suitable protecting groups. Such functional groups include, but are not limited to, hydroxy, amino, mercapto and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl or diarylalkylsilyl (for example, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, and the like. Suitable protecting groups for amino, amidino and guanidino include *t*-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for mercapto include -C(O)-R" (where R" is alkyl, aryl or arylalkyl), *p*-methoxybenzyl, trityl and the like. Suitable protecting groups for carboxylic acid include alkyl, aryl or arylalkyl esters. Protecting groups are optionally added or removed in accordance with standard techniques, which are known to one skilled in the art and as described herein. The use of protecting groups is described in detail in Green, T.W. and P.G.M. Wutz, *Protective Groups in Organic Synthesis* (1999), 3rd Ed., Wiley. As one of skill in the

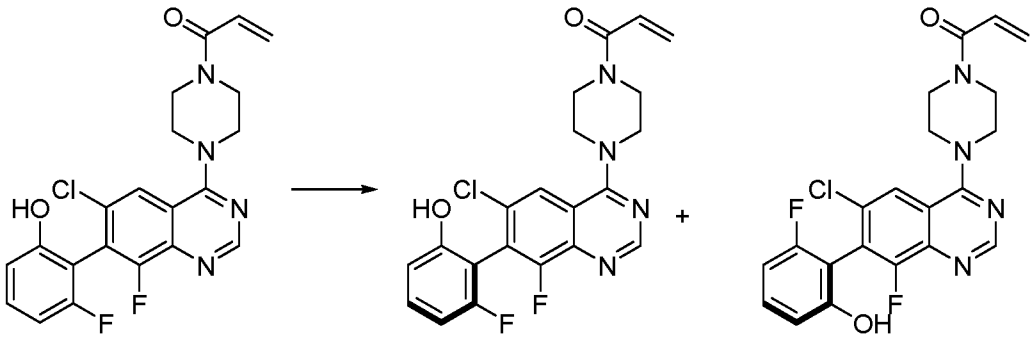
art would appreciate, the protecting group may also be a polymer resin such as a Wang resin, Rink resin or a 2-chlorotrityl-chloride resin.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The compounds of the invention, or their pharmaceutically acceptable salts may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that are defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Accordingly, certain embodiments of the methods comprise enriching a racemic mixture to obtain an enriched or substantially pure (e.g., greater than 95% or greater than 99%) enantiomer. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

The present invention includes all manner of rotamers and conformationally restricted states of a compound of the invention. Atropisomers, which are stereoisomers arising because of hindered rotation about a single bond, where energy differences due to steric strain or other contributors create a barrier to rotation that is high enough to allow for isolation of individual conformers, are also included. As an example, certain compounds of the invention may exist as mixtures of

atropisomers or purified or enriched for the presence of one atropisomer. Non-limiting examples of compounds which exist as atropisomers include the following compounds:



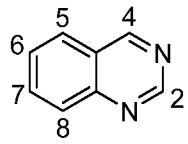
A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present invention contemplates various stereoisomers and mixtures thereof and includes "enantiomers", which refers to two stereoisomers whose molecules are nonsuperimposeable mirror images of one another.

A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule. The present invention includes tautomers of any said compounds.

The chemical naming protocol and structure diagrams used herein are a modified form of the I.U.P.A.C. nomenclature system, using the ACD/Name Version 9.07 software program and/or ChemDraw Ultra Version 14.0 software naming program (CambridgeSoft). For complex chemical names employed herein, a substituent group is typically named before the group to which it attaches. For example, cyclopropylethyl comprises an ethyl backbone with a cyclopropyl substituent. Except as described below, all bonds are identified in the chemical structure diagrams herein, except for all bonds on some carbon atoms, which are assumed to be bonded to sufficient hydrogen atoms to complete the valency.

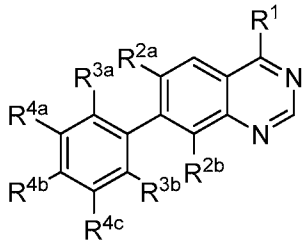
Embodiments of the invention are directed to preparation of various compounds comprising a quinazoline moiety. The presently described metalation reactions for forming a carbon-carbon bond between a quinazoline core and an aryl or heteroaryl substituent have not previously been reported. Surprisingly, the present

inventors have discovered that the disclosed metalations (and subsequent carbon-carbon bond formation) proceeds in a regiospecific manner at carbon 7 of the quinazoline (see below structure), although other metalation sites are available (e.g., carbons 2 and 5). Further, and in contrast to other methods for forming the desired carbon-carbon bond (e.g., Suzuki coupling), the present inventors have discovered that the present metalation reactions are highly efficient despite steric hindrance at the site of carbon-carbon bond formation. For example, in certain embodiments a carbon-carbon bond is formed between carbon 7 of a quinazoline and carbon 1 of an aryl or heteroaryl moiety (e.g., phenyl), while the quinazoline has non-hydrogen substituents at the 6 and 7 positions, and the aryl or heteroaryl has non-hydrogen substituents at the 2 and 6 positions (i.e., both carbons adjacent the newly formed carbon-carbon bond are substituted with non-hydrogen substituents).



quinazoline

Accordingly, in various embodiments is provided a method for preparing a compound having the following structure (I):



(I)

or a pharmaceutically acceptable salt, tautomer, prodrug or stereoisomer thereof, wherein:

R^1 is a non-hydrogen substituent;

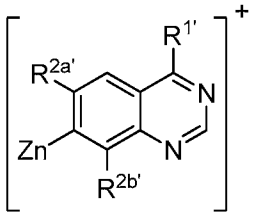
R^{2a} and R^{2b} are each independently halo, hydroxyl, protected hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy;

R^{3a} and R^{3b} are each independently halo, hydroxyl, protected hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy; or R^{3a} joins with R^{4a} to form a

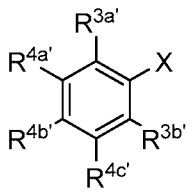
carbocyclyl or heterocyclic ring, and R^{3b} is halo, hydroxyl, protected hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy; and

R^{4a}, R^{4b} and R^{4c} are each independently H or a non-hydrogen substituent; or R^{4a} joins with R^{3a} to form a carbocyclyl or heterocyclic ring, and R^{4b} and R^{4c} are each independently H or a non-hydrogen substituent;

wherein the method comprises preparing a mixture comprising a compound of structure (II) and a compound of structure (III), the compounds of structure (II) and (III) having the following structures, respectively:



and



,

(II) (III)

or a salt thereof, wherein:

$R^{1'}$ is a non-hydrogen, non-acidic substituent;

$R^{2a'}$ and $R^{2b'}$ are each independently halo, protected hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy;

$R^{3a'}$ and $R^{3b'}$ are each independently halo, protected hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy; or $R^{3a'}$ joins with $R^{4a'}$ to form a carbocyclyl or heterocyclic ring, and $R^{3b'}$ is halo, protected hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy;

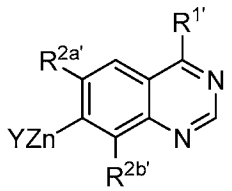
$R^{4a'}$, $R^{4b'}$ and $R^{4c'}$ are each independently H or a non-hydrogen substituent; or $R^{4a'}$ joins with $R^{3a'}$ to form a carbocyclyl or heterocyclic ring, and $R^{4b'}$ and $R^{4c'}$ are each independently H or a non-hydrogen substituent; and

X is a leaving group,

thereby forming a carbon-carbon bond between the carbon bearing the Zn moiety on compound (II) and the carbon bearing the X moiety on compound (III).

For ease of illustration, the compound of structure (II) is often illustrated in a cationic form throughout the description of the methods and compounds herein. It will be apparent to one of ordinary skill in the art that the compound of structure (II)

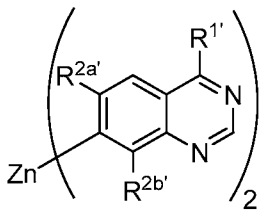
will be associated with a counter ion, and the compounds of structure (II) in their associated form are also included within the scope of the methods and compounds described herein. For example, the compounds of structure (II) may be associated with a counter ion and represented as follows (II′):



(II′)

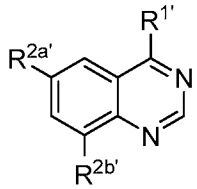
wherein Y is a counter ion, such as halogen (*e.g.*, Cl, Br or I).

In other aspects, the compound of structure (II) forms a pseudo-dimer and can be represented as follows (II″):



(II″)

In some embodiments, the compound of structure (II) is prepared by reaction of a mixed-metal, heterocyclic base with a compound having the following structure (IV):



(IV)

In various other embodiments, the heterocyclyl base comprises Zn, Mg and/or Li.

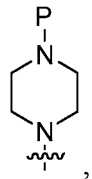
In some different embodiments, the mixed metal, heterocyclic base comprises a piperidinyl heterocycle. For example, in some embodiments the mixed

metal, heterocyclic base comprises a 2,2,6,6-Bis(tetramethylpiperidine)zinc, magnesium chloride, lithium chloride complex ($(tmp)_2Zn \cdot 2\ MgCl_2 \cdot 2\ LiCl$).

In other embodiments, the mixture comprising a compound of structure (II) and a compound of structure (III) further comprises a metal catalyst or metal precatalyst. For example, in some embodiments the metal is palladium. In other embodiments, the metal precatalyst is CPhos 3rd generation.

Various different solvents can be used for the disclosed transformations. In some embodiments, the mixture comprising a compound of structure (II) and a compound of structure (III) comprises a polar, aprotic solvent. For example, in some embodiments the solvent is tetrahydrofuran.

In some other different embodiments, R^1 and $R^{1'}$ are each independently C_1-C_6 alkyl, carbocyclyl or heterocyclyl. In some exemplary embodiments, R^1 and $R^{1'}$ are each independently heterocyclyl. For example, in some embodiments the heterocyclyl is piperazinyl. In some more embodiments, R^1 and $R^{1'}$ each have the following structure:



,

wherein P is a nitrogen protecting group, such as butyloxycarbonyl (Boc).

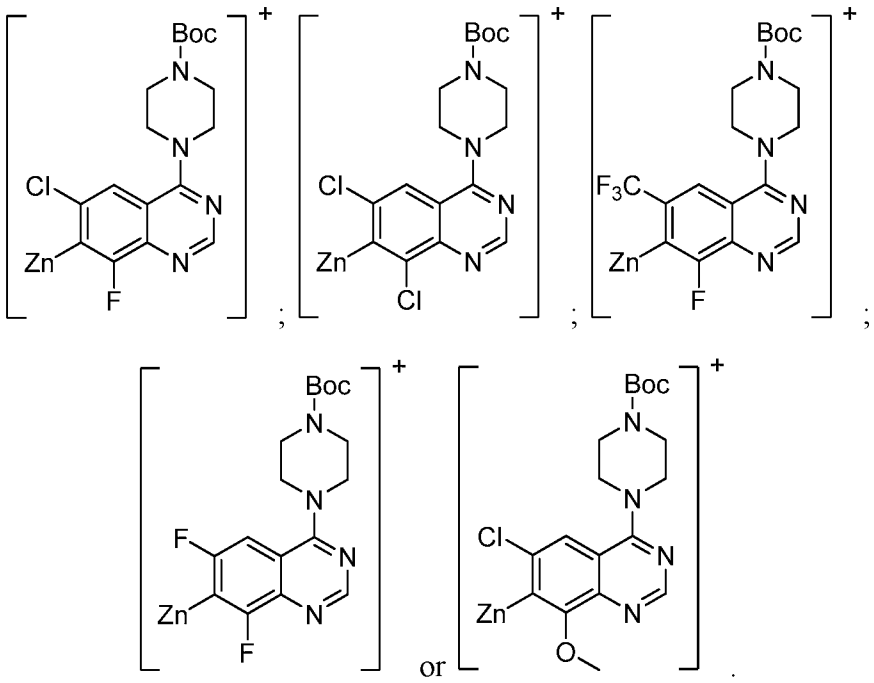
In other embodiments, R^{2a} and R^{2b} are each independently halo. In some other embodiments, $R^{2a'}$ and $R^{2b'}$ are each independently halo.

In some other different embodiments, R^{3a} and R^{3b} are each independently halo, hydroxyl or C_1-C_6 alkoxy, and in other embodiments, $R^{3a'}$ and $R^{3b'}$ are each independently halo or C_1-C_6 alkoxy.

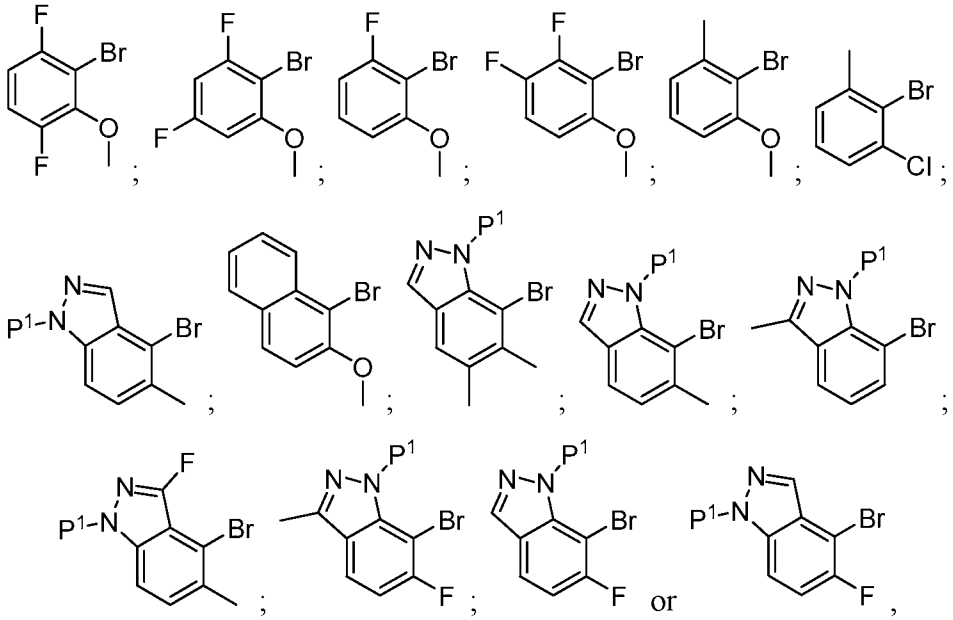
In yet other embodiments, R^{4a}, R^{4b} and R^{4c} are each independently H. In other different embodiments, $R^{4a'}$, $R^{4b'}$ and $R^{4c'}$ are each independently H.

In various embodiments of the foregoing, X is halo, for example bromo.

In some embodiments, the compound of structure (II) has one of the following structures:

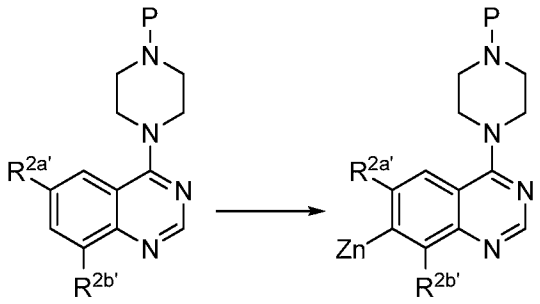


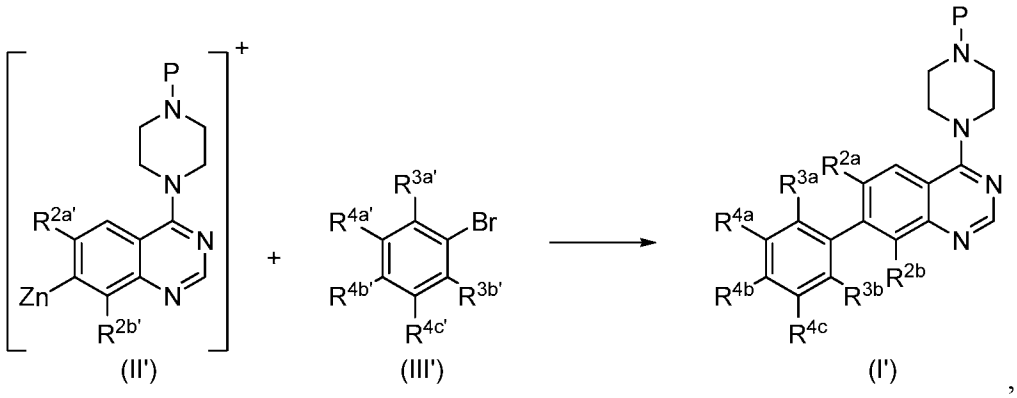
In yet other embodiments, the compound of structure (III) has one of the following structures:



wherein P^1 is nitrogen protecting group, such as butyloxycarbonyl.

In some other more specific embodiments, the method comprises the following steps (a) and (b):

(a)  (IV') (II') ; and

(b)  (II') (III') (I') ,

wherein:

R^{2a}, R^{2b}, $R^{2a'}$ and $R^{2b'}$ are each independently halo;

R^{3a}, R^{3b}, $R^{3a'}$ and $R^{3b'}$ are each independently halo, protected hydroxyl or C_1-C_6 alkoxy; and

R^{4a}, R^{4b}, R^{4c}, $R^{4a'}$, $R^{4b'}$ and $R^{4c'}$ are each independently H.

In some embodiments, P is butyloxycarbonyl.

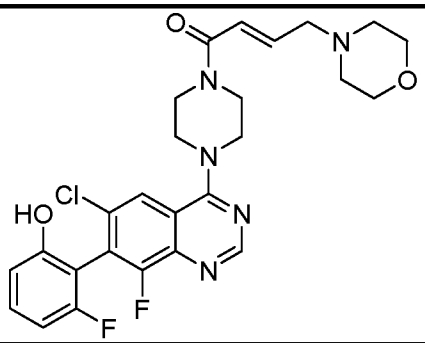
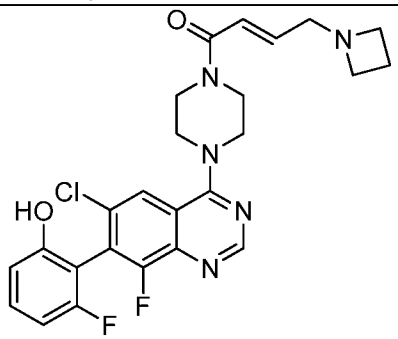
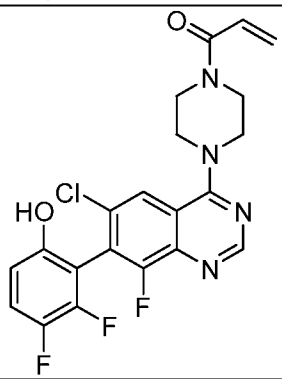
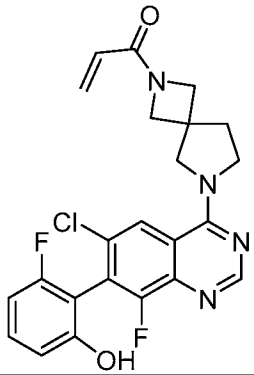
In some more embodiments, R^{2a}, R^{2b}, $R^{2a'}$ and $R^{2b'}$ are each independently chloro or fluoro. For example, in certain embodiments R^{2a} and $R^{2b'}$ are each chloro, and R^{2b} and $R^{2b'}$ are each fluoro.

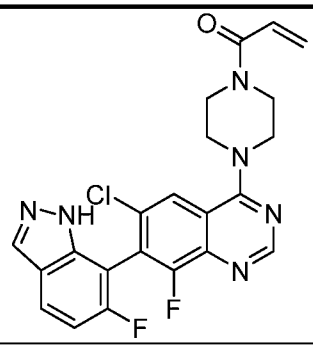
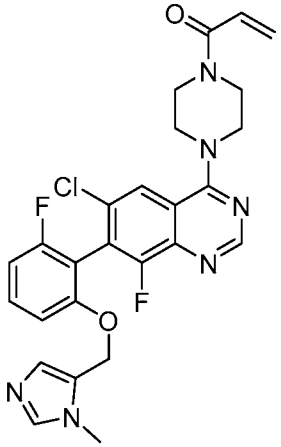
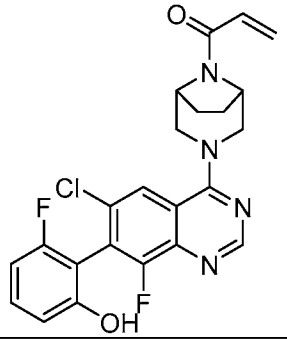
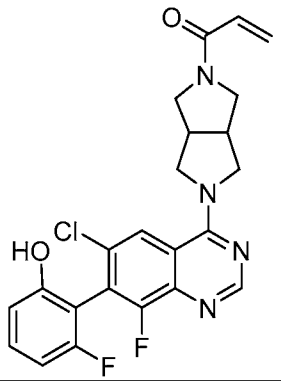
In some other embodiments of the foregoing, R^{3a}, R^{3b}, $R^{3a'}$ and $R^{3b'}$ are each independently halo or C_1-C_6 alkoxy. In some of these embodiments halo is fluoro and C_1-C_6 alkoxy is methoxy. For example, in certain embodiments R^{3a} and $R^{3a'}$ are each fluoro, and R^{3b} and $R^{3b'}$ are each methoxy.

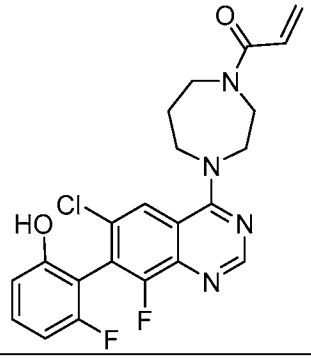
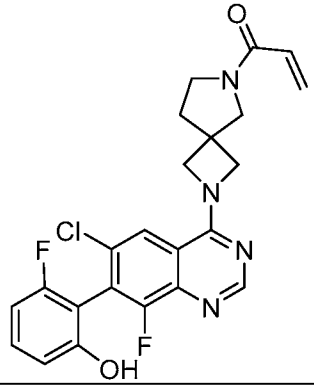
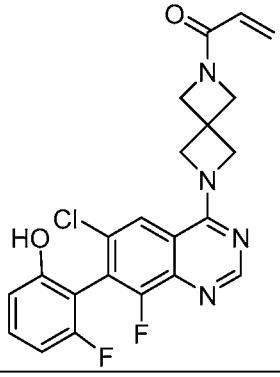
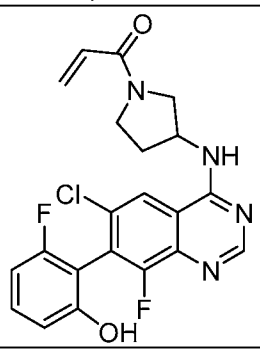
The methods disclosed herein can be used for preparation of various compounds of structure (I). In certain embodiments, the compound of structure (I) is selected from one of the compounds in Table 1.

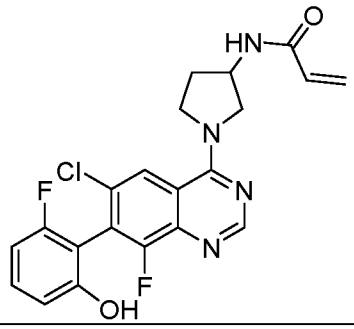
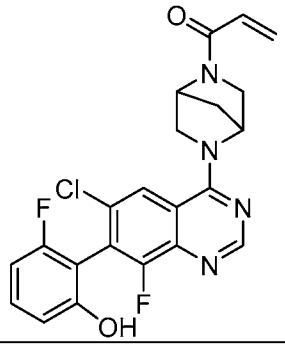
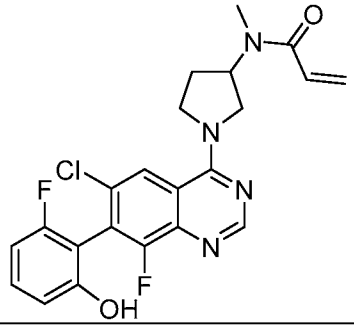
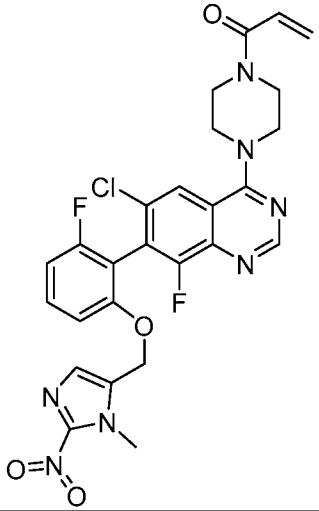
Table 1

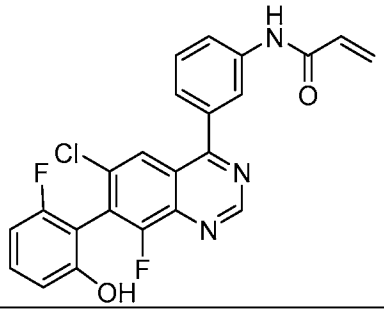
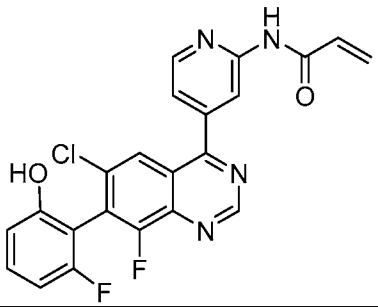
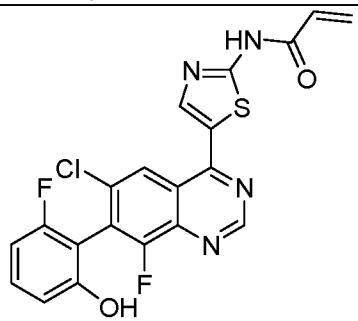
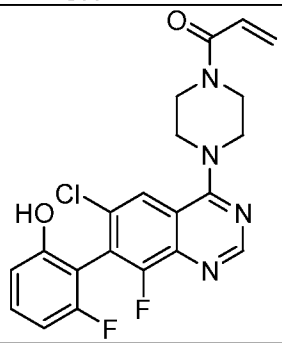
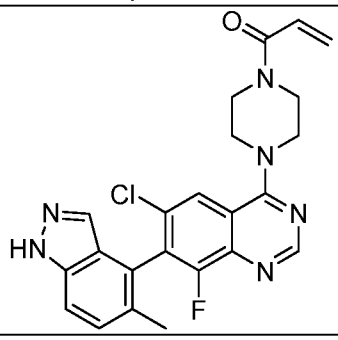
Representative Compounds of Structure I

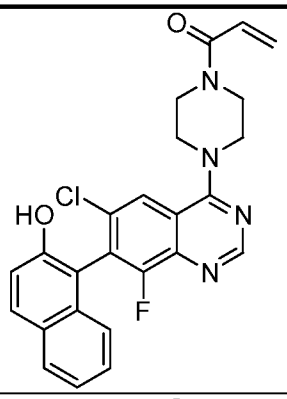
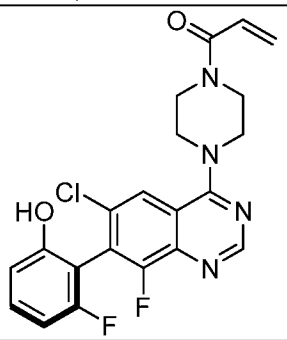
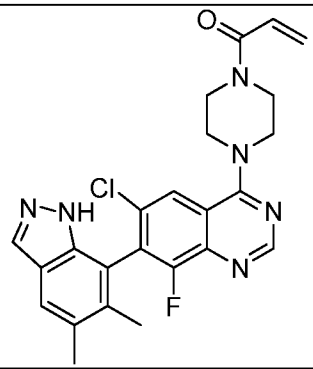
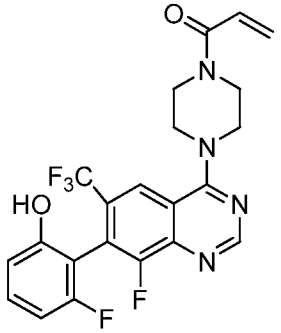
No.	Structure	Name
1		(E)-1-(4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-4-morpholinobut-2-en-1-one
2		(E)-4-(azetidin-1-yl)-1-(4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)but-2-en-1-one
3		1-(4-(6-chloro-7-(2,3-difluoro-6-hydroxyphenyl)-8-fluoroquinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one
4		1-(6-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-2,6-diazaspiro[3.4]octan-2-yl)prop-2-en-1-one

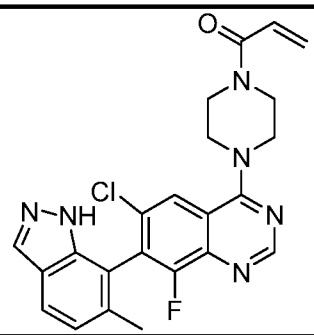
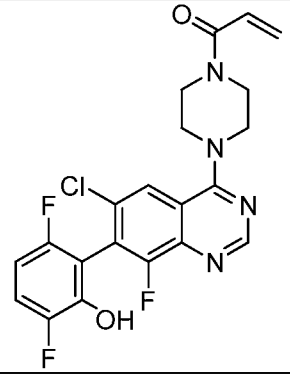
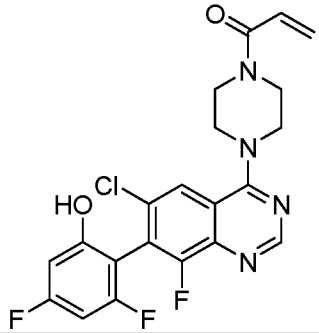
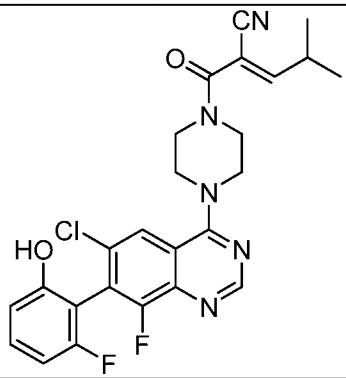
No.	Structure	Name
5		1-(4-(6-chloro-8-fluoro-7-(6-fluoro-1H-indazol-7-yl)quinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one
6		1-(4-(6-chloro-8-fluoro-7-(2-fluoro-6-((1-methyl-1H-imidazol-5-yl)methoxy)phenyl)quinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one
7		1-((1R,5S)-3-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)prop-2-en-1-one
8		1-(5-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)prop-2-en-1-one

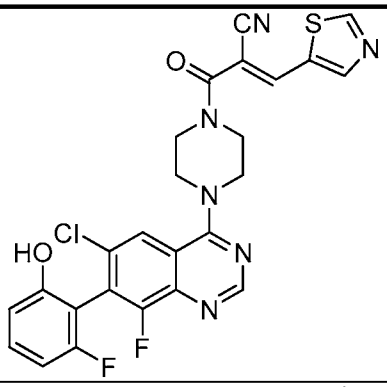
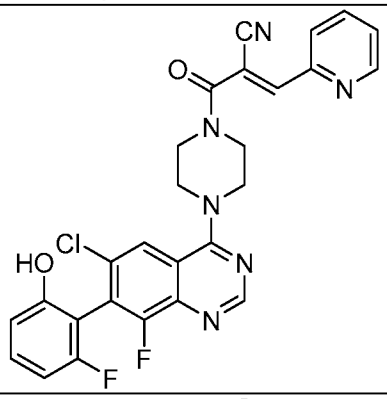
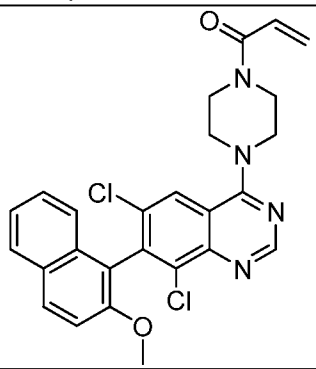
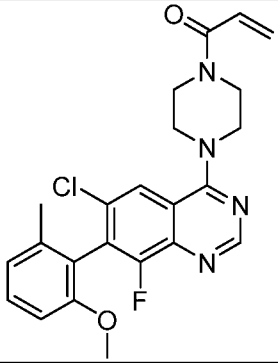
No.	Structure	Name
9		1-(4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-1,4-diazepan-1-yl)prop-2-en-1-one
10		1-(2-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-2,6-diazaspiro[3.4]octan-6-yl)prop-2-en-1-one
11		1-(6-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-2,6-diazaspiro[3.3]heptan-2-yl)prop-2-en-1-one
12		1-(3-((6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)amino)pyrrolidin-1-yl)prop-2-en-1-one

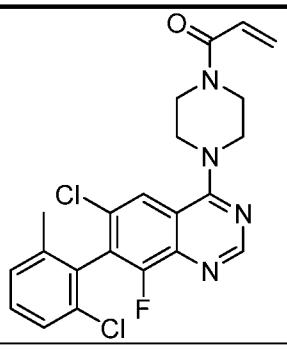
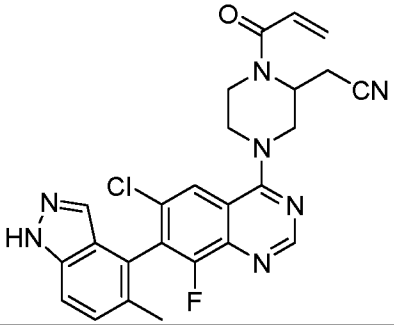
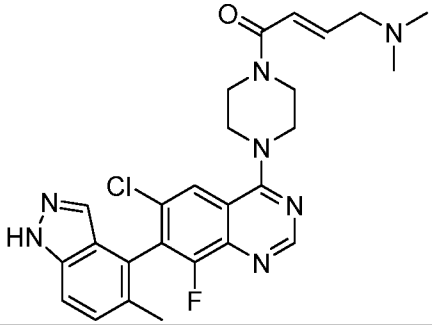
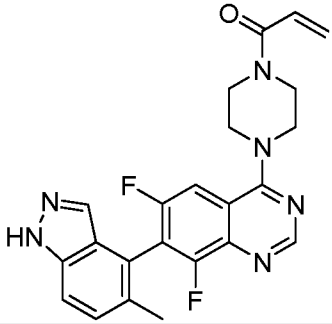
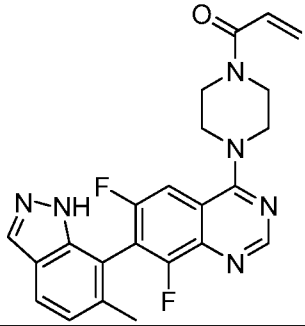
No.	Structure	Name
13		2-(4-(3-(buta-1,3-dien-2-ylamino)pyrrolidin-1-yl)-6-chloro-8-fluoroquinazolin-7-yl)-3-fluorophenol
14		1-(5-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)prop-2-en-1-one
15		N-(1-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)pyrrolidin-3-yl)-N-methylacrylamide
16		1-(4-(6-chloro-8-fluoro-7-(2-fluoro-6-((1-methyl-2-nitro-1H-imidazol-5-yl)methoxy)phenyl)quinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one

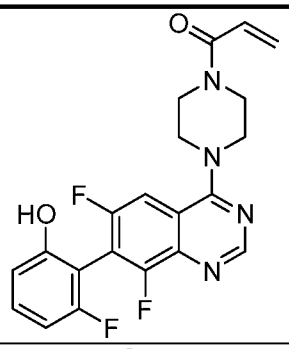
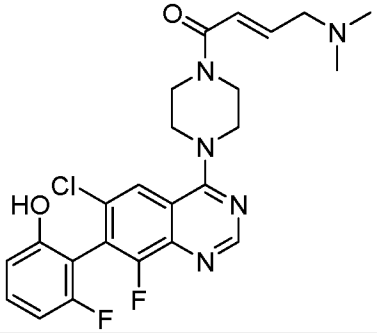
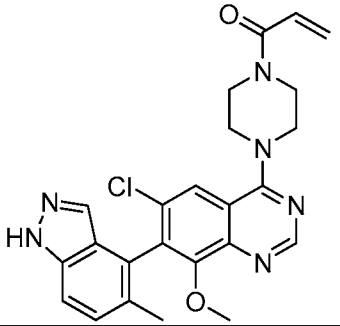
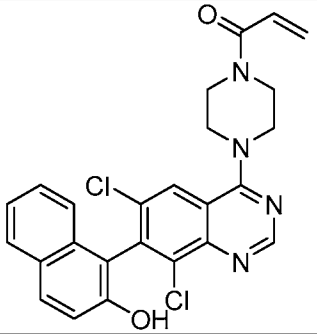
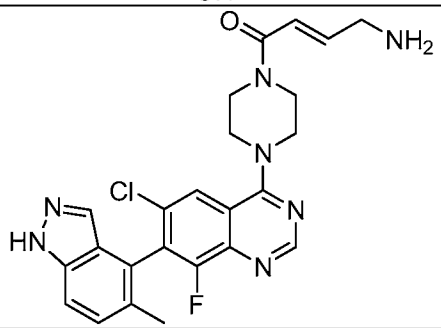
No.	Structure	Name
17		N-(3-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)phenyl)acrylamide
18		N-(4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)pyridin-2-yl)acrylamide
19		N-(5-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)thiazol-2-yl)acrylamide
20		1-(4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one
21		1-(4-(6-chloro-8-fluoro-7-(5-methyl-1H-indazol-4-yl)quinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one

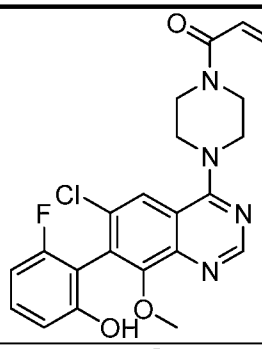
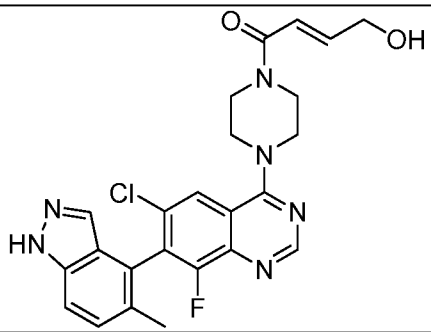
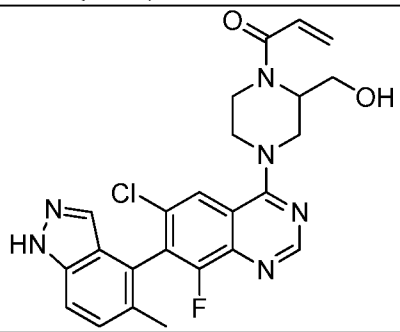
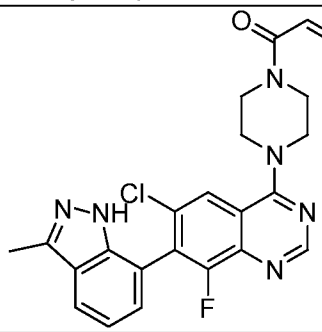
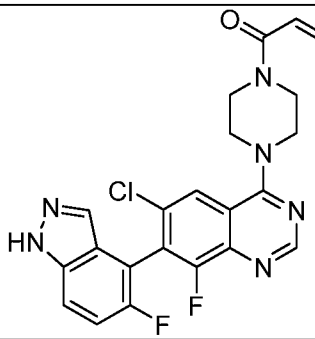
No.	Structure	Name
22		1-(4-(6-chloro-8-fluoro-7-(2-hydroxynaphthalen-1-yl)quinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one
23		(R)-1-(4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one
24		1-(4-(6-chloro-7-(5,6-dimethyl-1H-indazol-7-yl)-8-fluoroquinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one
25		1-(4-(8-fluoro-7-(2-fluoro-6-hydroxyphenyl)-6-(trifluoromethyl)quinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one

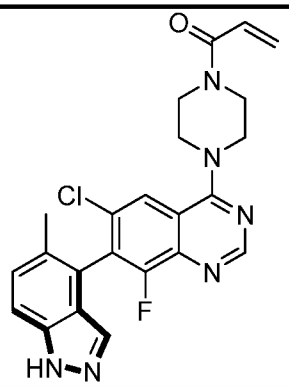
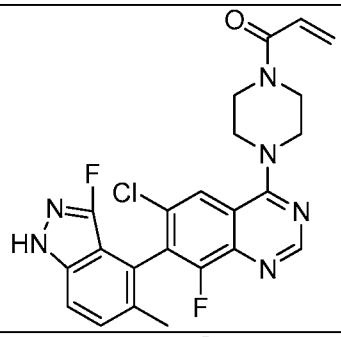
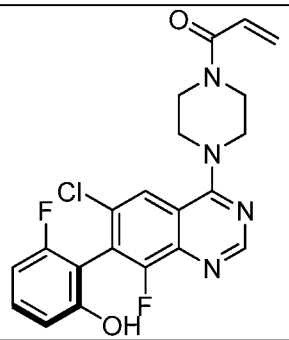
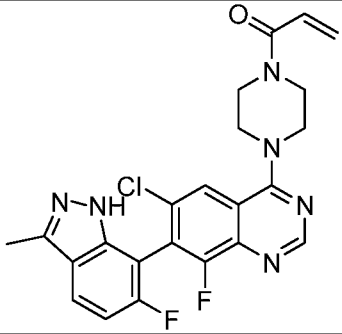
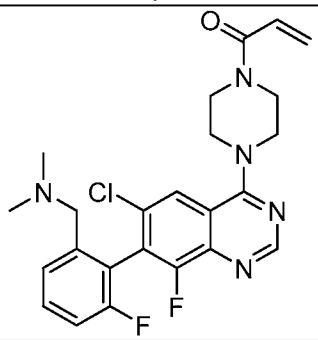
No.	Structure	Name
26		1-(4-(6-chloro-8-fluoro-7-(6-methyl-1H-indazol-7-yl)quinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one
27		1-(4-(6-chloro-7-(3,6-difluoro-2-hydroxyphenyl)-8-fluoroquinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one
28		1-(4-(6-chloro-7-(2,4-difluoro-6-hydroxyphenyl)-8-fluoroquinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one
29		(E)-2-(4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carbonyl)-4-methylpent-2-enenitrile

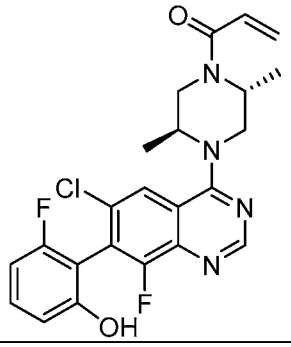
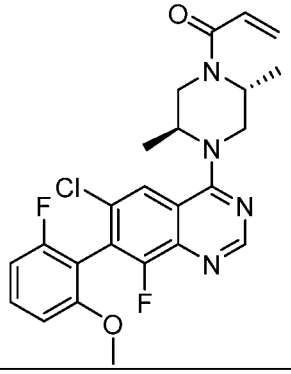
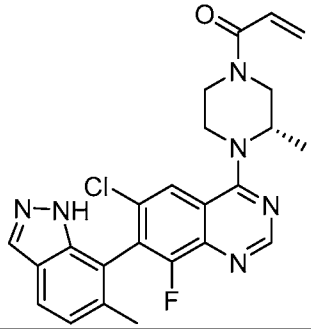
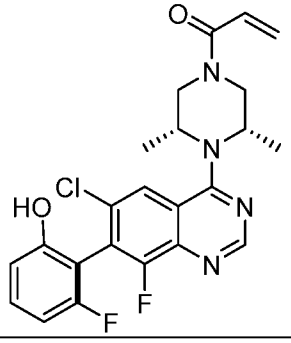
No.	Structure	Name
30		(E)-2-(4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carbonyl)-3-(thiazol-5-yl)acrylonitrile
31		(E)-2-(4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)piperazine-1-carbonyl)-3-(pyridin-2-yl)acrylonitrile
32		1-(4-(6,8-dichloro-7-(2-methoxynaphthalen-1-yl)quinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one
33		1-(4-(6-chloro-8-fluoro-7-(2-methoxy-6-methylphenyl)quinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one

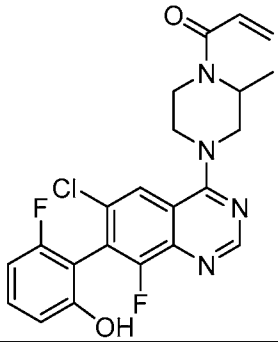
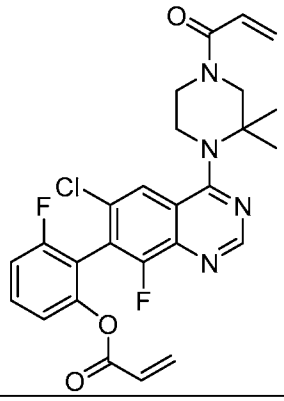
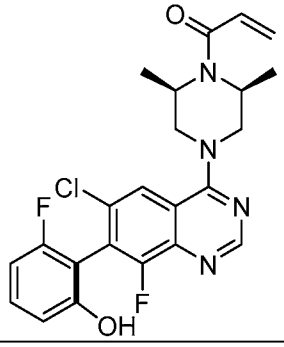
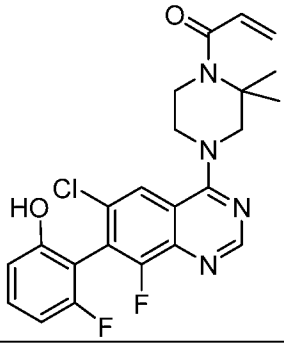
No.	Structure	Name
34		1-(4-(6-chloro-7-(2-chloro-6-methylphenyl)-8-fluoroquinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one
35		2-(1-acryloyl-4-(6-chloro-8-fluoro-7-(5-methyl-1H-indazol-4-yl)quinazolin-4-yl)piperazin-2-yl)acetonitrile
36		(E)-1-(4-(6-chloro-8-fluoro-7-(5-methyl-1H-indazol-4-yl)quinazolin-4-yl)piperazin-1-yl)-4-(dimethylamino)but-2-en-1-one
37		1-(4-(6,8-difluoro-7-(5-methyl-1H-indazol-4-yl)quinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one
38		1-(4-(6,8-difluoro-7-(6-methyl-1H-indazol-7-yl)quinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one

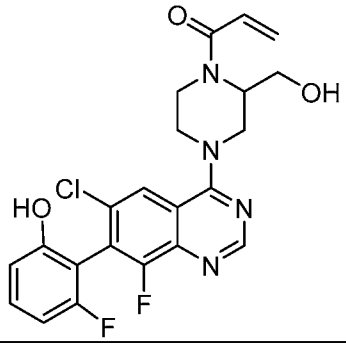
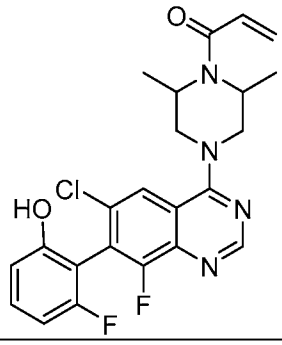
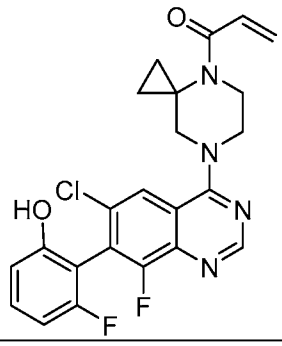
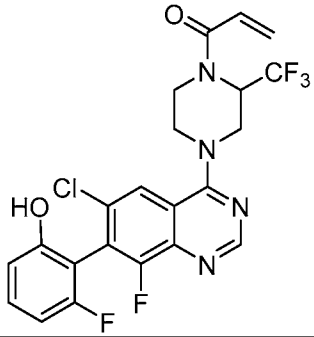
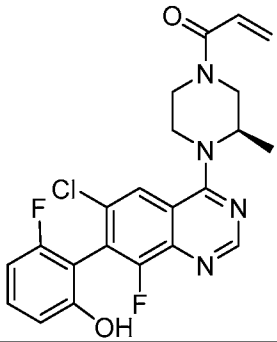
No.	Structure	Name
39		1-(4-(6,8-difluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one
40		(E)-1-(4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)-4-(dimethylamino)but-2-en-1-one
41		1-(4-(6-chloro-8-methoxy-7-(5-methyl-1H-indazol-4-yl)quinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one
42		1-(4-(6,8-dichloro-7-(2-hydroxynaphthalen-1-yl)quinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one
43		(E)-4-amino-1-(4-(6-chloro-8-fluoro-7-(5-methyl-1H-indazol-4-yl)quinazolin-4-yl)piperazin-1-yl)but-2-en-1-one

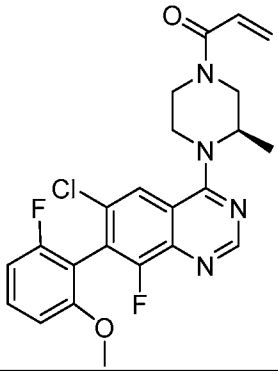
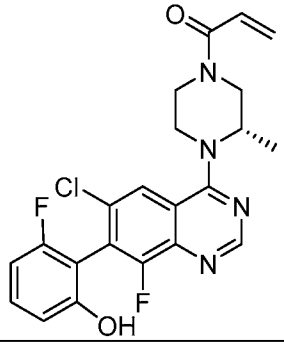
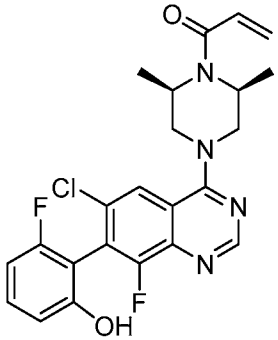
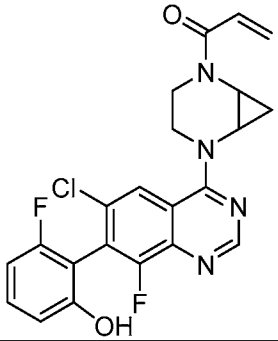
No.	Structure	Name
44		1-(4-(6-chloro-7-(2-fluoro-6-hydroxyphenyl)-8-methoxyquinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one
45		(E)-1-(4-(6-chloro-8-fluoro-7-(5-methyl-1H-indazol-4-yl)quinazolin-4-yl)piperazin-1-yl)-4-hydroxybut-2-en-1-one
46		1-(4-(6-chloro-8-fluoro-7-(5-methyl-1H-indazol-4-yl)quinazolin-4-yl)-2-(hydroxymethyl)piperazin-1-yl)prop-2-en-1-one
47		1-(4-(6-chloro-8-fluoro-7-(3-methyl-1H-indazol-7-yl)quinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one
48		1-(4-(6-chloro-8-fluoro-7-(5-fluoro-1H-indazol-4-yl)quinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one

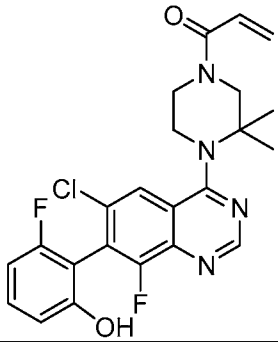
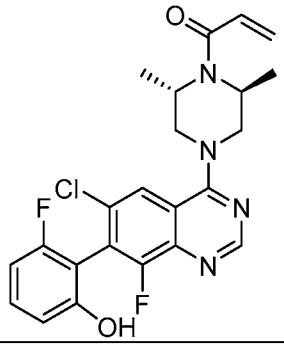
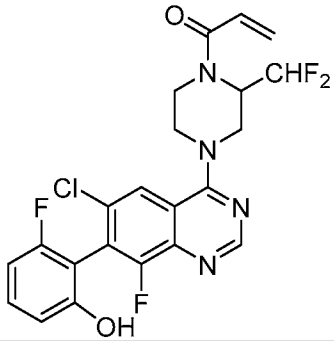
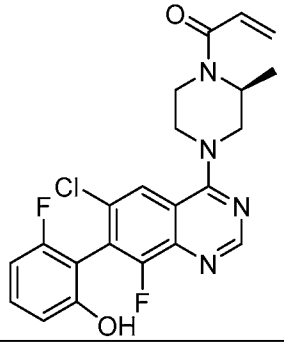
No.	Structure	Name
49		(R)-1-(4-(6-chloro-8-fluoro-7-(5-methyl-1H-indazol-4-yl)quinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one
50		1-(4-(6-chloro-8-fluoro-7-(3-fluoro-5-methyl-1H-indazol-4-yl)quinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one
51		(S)-1-(4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one
52		1-(4-(6-chloro-8-fluoro-7-(6-fluoro-3-methyl-1H-indazol-7-yl)quinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one
53		1-(4-(6-chloro-7-(2-((dimethylamino)methyl)-6-fluorophenyl)-8-fluoroquinazolin-4-yl)piperazin-1-yl)prop-2-en-1-one

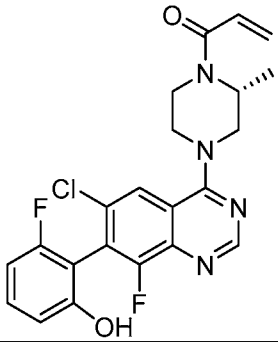
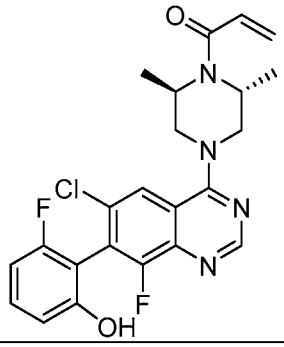
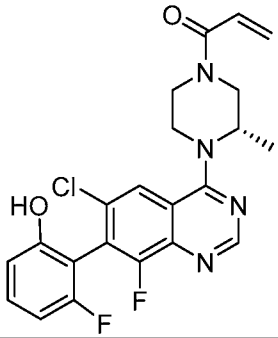
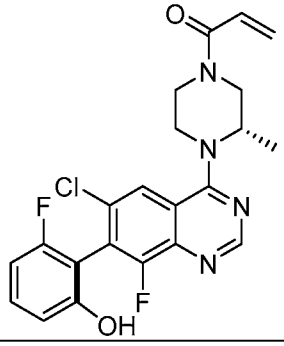
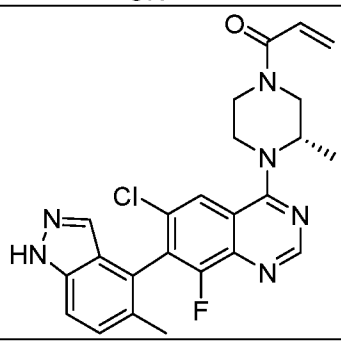
No.	Structure	Name
54		1-((2R,5S)-4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one
55		1-((2R,5S)-4-(6-chloro-8-fluoro-7-(2-fluoro-6-methoxyphenyl)quinazolin-4-yl)-2,5-dimethylpiperazin-1-yl)prop-2-en-1-one
56		1-((3S)-4-(6-chloro-8-fluoro-7-(6-methyl-1H-indazol-7-yl)quinazolin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one
57		1-((3S,5R)-4-((R)-6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-3,5-dimethylpiperazin-1-yl)prop-2-en-1-one

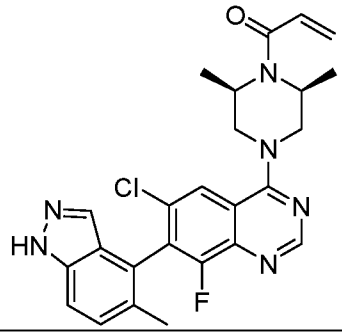
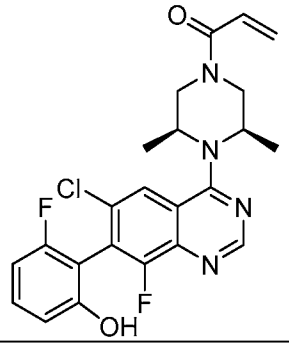
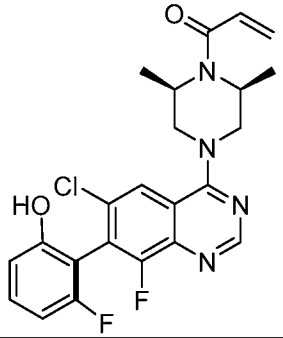
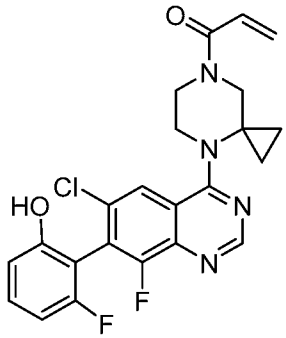
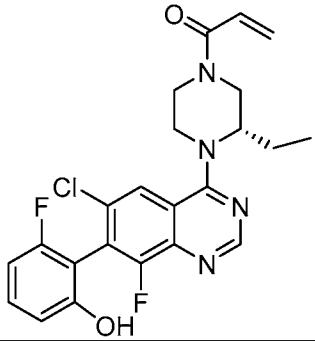
No.	Structure	Name
58		1-(4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-2-methylpiperazin-1-yl)prop-2-en-1-one
59		2-(4-(4-acryloyl-2,2-dimethylpiperazin-1-yl)-6-chloro-8-fluoroquinazolin-7-yl)-3-fluorophenyl acrylate
60		1-((2S,6R)-4-((S)-6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-2,6-dimethylpiperazin-1-yl)prop-2-en-1-one
61		1-(4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-2,2-dimethylpiperazin-1-yl)prop-2-en-1-one

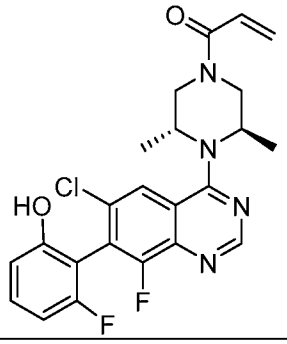
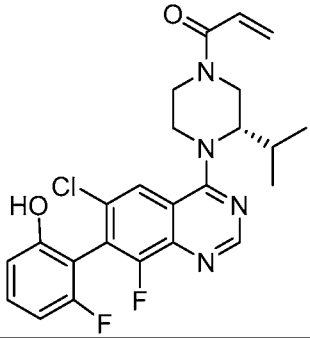
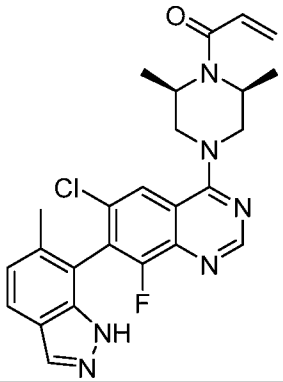
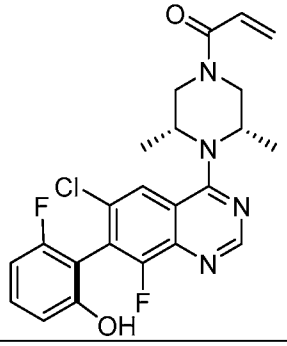
No.	Structure	Name
62		1-(4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-2-(hydroxymethyl)piperazin-1-yl)prop-2-en-1-one
63		1-(4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-2,6-dimethylpiperazin-1-yl)prop-2-en-1-one
64		1-(7-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-4,7-diazaspiro[2.5]octan-4-yl)prop-2-en-1-one
65		1-(4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-2-(trifluoromethyl)piperazin-1-yl)prop-2-en-1-one
66		1-((3R)-4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one

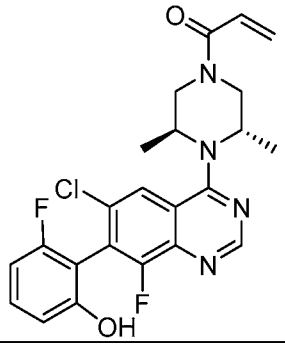
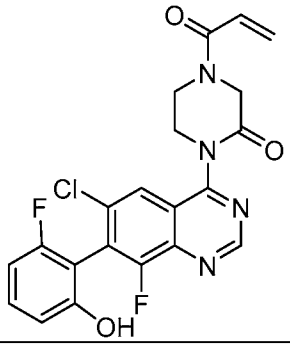
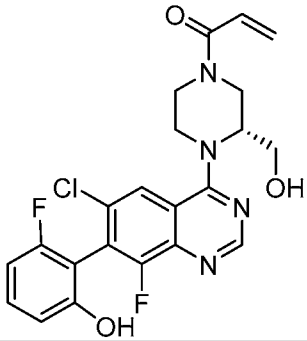
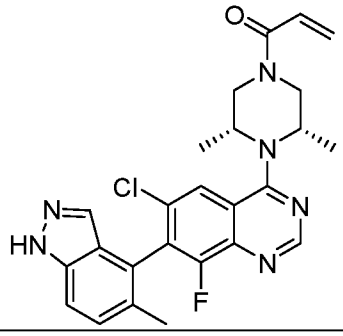
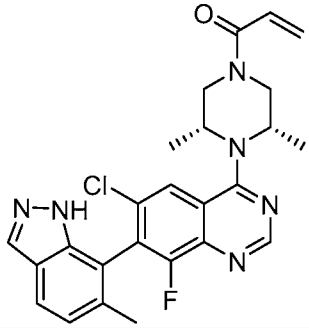
No.	Structure	Name
67		1-((3R)-4-(6-chloro-8-fluoro-7-(2-fluoro-6-methoxyphenyl)quinazolin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one
68		1-((3S)-4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one
69		1-((2S,6R)-4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-2,6-dimethylpiperazin-1-yl)prop-2-en-1-one
70		1-(5-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-2,5-diazabicyclo[4.1.0]heptan-2-yl)prop-2-en-1-one

No.	Structure	Name
71		1-(4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-3,3-dimethylpiperazin-1-yl)prop-2-en-1-one
72		1-((2S,6S)-4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-2,6-dimethylpiperazin-1-yl)prop-2-en-1-one
73		1-(4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-2-(difluoromethyl)piperazin-1-yl)prop-2-en-1-one
74		1-((2S)-4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-2-methylpiperazin-1-yl)prop-2-en-1-one

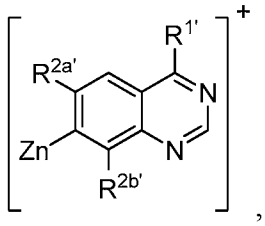
No.	Structure	Name
75		1-((2R)-4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-2-methylpiperazin-1-yl)prop-2-en-1-one
76		1-((2R,6R)-4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-2,6-dimethylpiperazin-1-yl)prop-2-en-1-one
77		1-((3S)-4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one
78		1-((S)-4-((S)-6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one
79		1-((3S)-4-(6-chloro-8-fluoro-7-(5-methyl-1H-indazol-4-yl)quinazolin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one

No.	Structure	Name
80		1-((2S,6R)-4-(6-chloro-8-fluoro-7-(5-methyl-1H-indazol-4-yl)quinazolin-4-yl)-2,6-dimethylpiperazin-1-yl)prop-2-en-1-one
81		1-((3R,5S)-4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-3,5-dimethylpiperazin-1-yl)prop-2-en-1-one
82		1-((2S,6R)-4-((R)-6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-2,6-dimethylpiperazin-1-yl)prop-2-en-1-one
83		1-(4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-4,7-diazaspiro[2.5]octan-7-yl)prop-2-en-1-one
84		1-((3S)-4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-3-ethylpiperazin-1-yl)prop-2-en-1-one

No.	Structure	Name
85		1-((3R,5R)-4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-3,5-dimethylpiperazin-1-yl)prop-2-en-1-one
86		1-((3S)-4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-3-isopropylpiperazin-1-yl)prop-2-en-1-one
87		1-((2S,6R)-4-(6-chloro-8-fluoro-7-(6-methyl-1H-indazol-7-yl)quinazolin-4-yl)-2,6-dimethylpiperazin-1-yl)prop-2-en-1-one
88		1-((3S,5R)-4-((S)-6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-3,5-dimethylpiperazin-1-yl)prop-2-en-1-one

No.	Structure	Name
89		1-((3S,5S)-4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-3,5-dimethylpiperazin-1-yl)prop-2-en-1-one
90		4-acryloyl-1-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)piperazin-2-one
91		1-((3R)-4-(6-chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-3-(hydroxymethyl)piperazin-1-yl)prop-2-en-1-one
92		1-((3S,5R)-4-(6-chloro-8-fluoro-7-(5-methyl-1H-indazol-4-yl)quinazolin-4-yl)-3,5-dimethylpiperazin-1-yl)prop-2-en-1-one
93		1-((3S,5R)-4-(6-chloro-8-fluoro-7-(6-methyl-1H-indazol-7-yl)quinazolin-4-yl)-3,5-dimethylpiperazin-1-yl)prop-2-en-1-one

The present disclosure also provides various compounds useful in embodiments of the methods. For example, in one embodiment is provided a compound having the following structure (II):



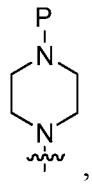
(II)

wherein:

$R^{1'}$ is a non-hydrogen, non-acidic substituent; and

$R^{2a'}$ and $R^{2b'}$ are each independently halo, protected hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy.

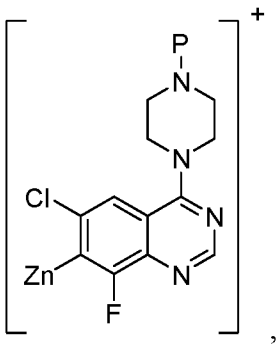
In some embodiments of the foregoing compounds, $R^{1'}$ is C_1-C_6 alkyl, carbocyclyl or heterocyclyl. For example, in some embodiments $R^{1'}$ is heterocyclyl, such as piperazinyl. In more specific embodiments $R^{1'}$ has the following structure:



wherein P is a nitrogen protecting group, such as butyloxycarbonyl (Boc).

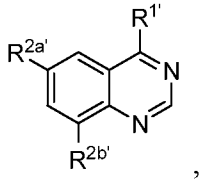
In other different embodiments, $R^{2a'}$ and $R^{2b'}$ are each independently halo. For example, in certain embodiments $R^{2a'}$ and $R^{2b'}$ are independently chloro or fluoro. In some more specific embodiments, $R^{2a'}$ is chloro and $R^{2b'}$ is fluoro.

In certain embodiments, the compound has the following structure:



wherein P is a nitrogen protecting group, such as butyloxycarbonyl.

In some other embodiments, the disclosure provides a compound having the following structure (V):



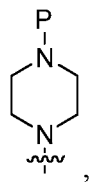
(V)

or a salt thereof, wherein:

$R^{1'}$ is heterocyclyl; and

$R^{2a'}$ and $R^{2b'}$ are each independently halo, protected hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy.

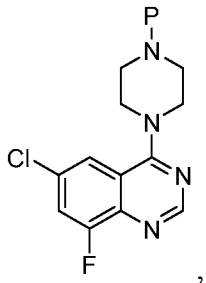
In certain embodiments of compound (V), heterocyclyl is piperazinyl. For example, in some embodiments $R^{1'}$ has the following structure:



wherein P is a nitrogen protecting group, such as butyloxycarbonyl (Boc).

In other embodiments, $R^{2a'}$ and $R^{2b'}$ are each independently halo. In some of these embodiments, $R^{2a'}$ and $R^{2b'}$ are independently chloro or fluoro. For example, in certain embodiments $R^{2a'}$ is chloro and $R^{2b'}$ is fluoro.

In some more specific embodiments, the compound has the following structure:



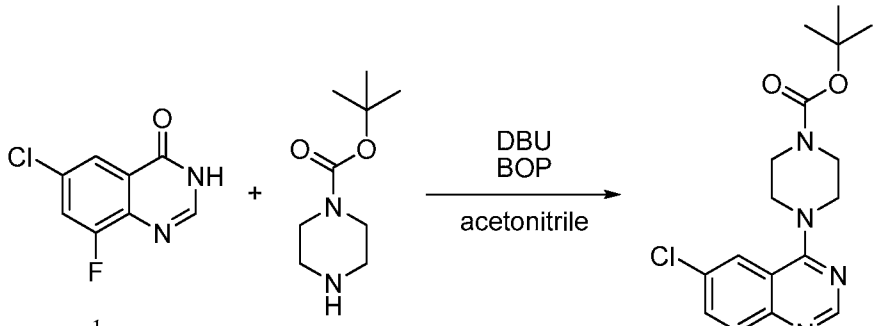
,

wherein P is a nitrogen protecting group, such as butyloxycarbonyl.

EXAMPLES

EXAMPLE 1

PREPARATION OF COMPOUND 2



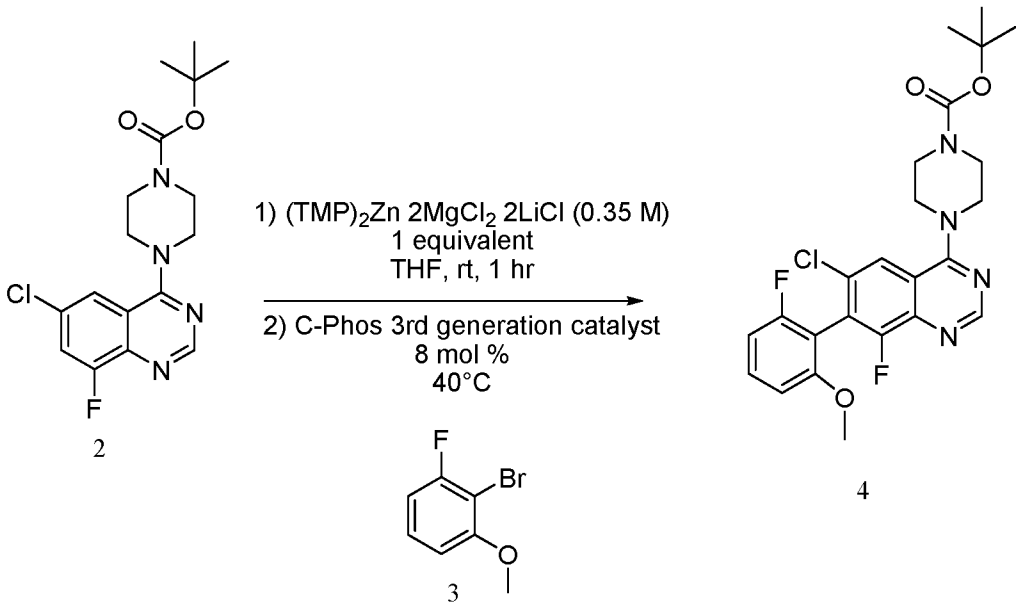
1 2

In a 4-neck, 3 L, round-bottom flask with a magnetic stir bar, compound 1 (82.47 g, 0.4153 mol, 1 equiv), BOP (201 g, 0.4544 mol, 1.1 equiv), and DBU (78.8 mL, 0.5272 mol, 1.3 equiv) were slurried in THF (2.1 L). After 30 minutes, N-Boc-piperazine (100 g, 0.5368 mol, 1.3 equiv) was added. The reaction mixture was stirred at 70 °C overnight to form a dark solution. The reaction was concentrated to one half volume via rotary evaporator, quenched with water (600 mL), then extracted with EtOAc (3 x 400 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to an oil. The dark oil was stirred in 1:1 EtOAc/Et_2O (700 mL) overnight to form solids. The solids were filtered to recover 90 g of crude 2. The impure product was slurried overnight in warm EtOAc (700 mL) then filtered to recover 10 g of starting material 1. The filtrate was then concentrated and slurried in 3:1 EtOAc/Et_2O (300/100 mL) overnight. The solids were filtered and washed with 4:1 hexane/Et_2O to recover 60 g of compound 2. All remaining impure product was combined and purified via a short plug column of silica gel with 1:4 EtOAc/hexane as eluent. All fractions containing product were combined and slurried in minimum 4:1 EtOAc/hexane (300 mL) overnight. The solids were filtered to recover another 43 g of 2 for a total combined amount of 103 g (67%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.64 (t,

J = 1.8 Hz, 1H), 7.46 (dd, J = 9.4, 2.2 Hz, 1H), 3.79–3.74 (m, 4H), 3.67-3.63 (m, 4H), 1.50 (s, 9H).

EXAMPLE 2

PREPARATION OF COMPOUND 4



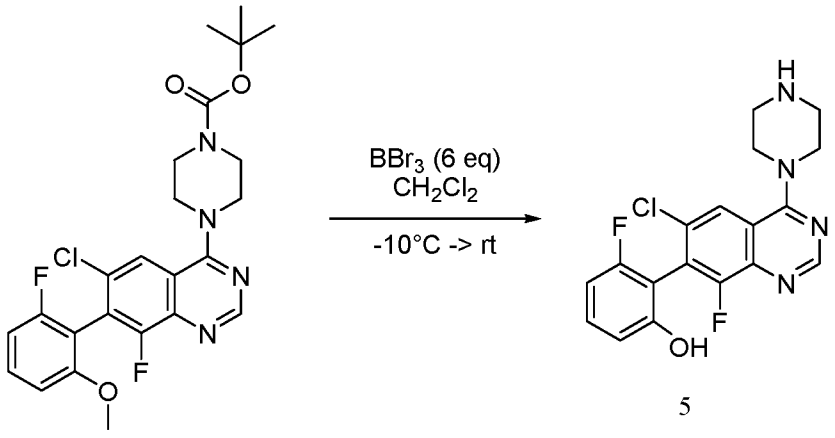
2 3 4

A dried 3 L, 3-neck flask (evacuated under vacuum and filled with N_2 three times) was fitted with mechanical stirring, temperature probe, and nitrogen inlet and charged with tert-butyl 4-(6-chloro-8-fluoroquinazolin-4-yl)piperazine-1-carboxylate 2 (100 g, 272.6 mmol) and dry THF (1 L). Bis(2,2,6,6-tetramethylpiperidinyl)zinc, lithium chloride, magnesium chloride complex ($(TMP)_2Zn$•2 $MgCl_2$•2 LiCl) (778.9 mL of a 0.35 M solution in THF/toluene, 272.6 mmol) was added via addition funnel over 10 minutes. The reaction was allowed to stir for 45 min at room temperature then degassed by bubbling nitrogen through the solution for 15 minutes. Solid 2-bromo-1-fluoro-3-methoxybenzene (55.9 g, 272.6 mmol) and CPhos 3rd generation precatalyst (17.6 g, 21.8 mmol) were added, and the mixture was heated to 40 °C for 12 h. The reaction was cooled in an ice bath and slowly quenched with 1.5 L of a 1:1 solution of saturated ammonium chloride and H_2O. The layers were separated, and the aqueous layer was extracted with DCM (800 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed under

vacuum. The residue was slurried in isopropyl alcohol (IPA, 1 L) at room temperature for 10 min then at 60 °C for 1 hour. Upon cooling to room temperature overnight, the solid was collected by vacuum filtration and washed with IPA (2 x 250 mL) yielding a pale yellow solid (64.83 g, 48.4% yield). The remaining material in the filtrate was adsorbed onto 250 g silica gel and purified by flash column chromatography (750 g silica gel column (dry loaded), stepwise gradient of 20%-40% EtOAc in hexanes). The pure fractions were concentrated, and the resulting solid was triturated with IPA (300 mL) at 60 °C for 1 hour. Upon cooling to room temperature overnight, the solid was collected by vacuum filtration and washed with IPA (2 x 100 mL) yielding a pale yellow solid (30.2 g, 22.5% yield). Total yield = 95.03 g (71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.84 – 7.76 (d, J = 1.5 Hz, 1H), 7.50 – 7.39 (m, 1H), 6.91 – 6.80 (m, 2H), 3.92 – 3.75 (m, 7H), 3.73 – 3.62 (m, 4H), 1.51 (s, 9H).

EXAMPLE 3

PREPARATION OF COMPOUND 5



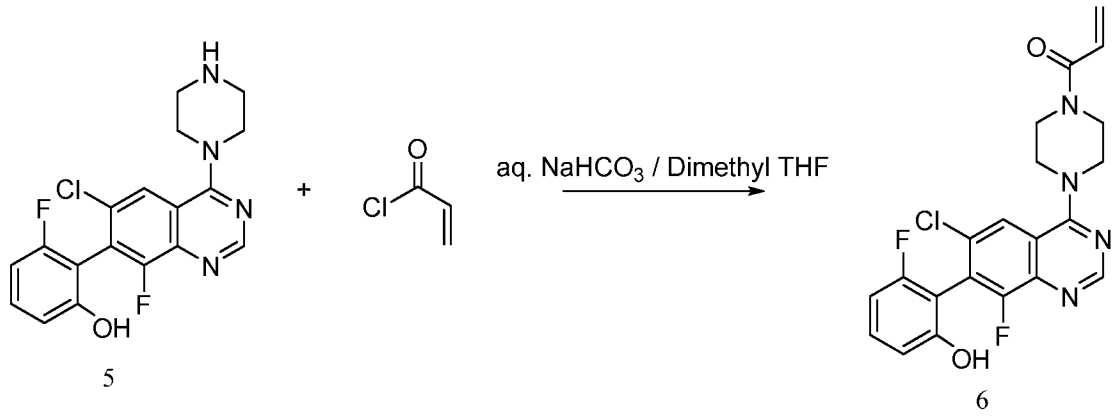
4 5

A 5 L, multi-neck, jacketed reactor with bottom valve was purged with N_2 and charged with tert-butyl 4-(6-chloro-8-fluoro-7-(2-fluoro-6-methoxyphenyl)quinazolin-4-yl)piperazine-1-carboxylate **6** and CH_2Cl_2 (1260 mL). The mixture was cooled to -10 °C. Neat BBr_3 (106 mL, 1.1 mol, 6 equiv) was added in a slow stream via syringe over 11 min causing immediate precipitation of a tan solid and an exotherm to 3 °C. After addition was complete, the reaction was warmed to room temperature, and the suspension was stirred for 19 h. HPLC analysis indicated

good conversion to the desired piperazine intermediate 5 with just a small amount of methyl ether remaining. The reaction was cooled to -10 °C and very carefully quenched with an ice/water mixture (1 kg).

EXAMPLE 4

PREPARATION OF COMPOUND 6



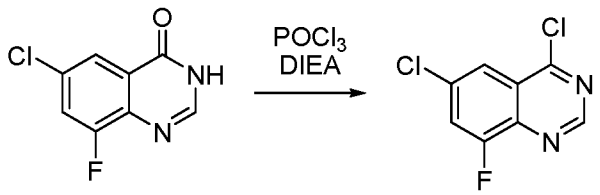
5 6

The ice and water was added very slowly at first allowing for quench to occur between additions. A maximum exothermic warming to 27 °C during the quench was observed. Additional water (1 L) was added, and the mixture was stirred 1.5 h to allow compound 5 to dissolve in the aqueous layer. The CH_2Cl_2 layer was drawn off through the reactor valve. CH_2Cl_2 (360 mL) was added; the layers were stirred for 30 min; and the CH_2Cl_2 layer was drawn off. The acidic aqueous phase was cooled to 10 °C and neutralized to pH 8 with 10 M NaOH added portion-wise, which caused precipitation of the free piperazine. Mild exothermic reaction warmed the vessel to 18 °C. The piperazine solid aggregated into a gummy material which stuck to the bottom and sides of the reactor. 2-MeTHF (1440 mL) was added, and the mixture was stirred rapidly at room temp for several minutes to dissolve most of the solid. Solid $NaHCO_3$ (77 g, 0.92 mol, 5 eq.) was added, and the reaction was allowed to stir 30 min. With stirring maintained at a rate that gave thorough mixing of the layers, the acryloyl chloride (30 mL, 0.37 mol, 2 eq.) was added at 18 °C rapidly via syringe. No exothermic reaction was observed. The acylation was allowed to proceed for 2 h. The stirring was stopped, and the layers were allowed to separate. HPLC of the organic and aqueous layers showed complete consumption of the piperazine compound 5 and good

conversion to the desired product 6. The layers were separated via the reactor valve. The aqueous layer was returned to the reactor and allowed to stir for 1 h with fresh 2-MeTHF (360 mL). Layers were again separated. The combined organic layers were dried (Na_2SO_4) and concentrated to give the crude product as a yellow-orange viscous oil that solidified upon standing overnight. Attempts to purify the product by trituration in various hot solvents were not successful. The product was purified by flash chromatography. Due to insolubility, it was necessary to dissolve the product in warm THF/DMF mixtures for loading onto the columns. The crude product was divided into 3 batches for initial columns (1.5 kg silica gel, elution with 1:1 EtOAc/hex, then 1:1 EtOAc/hex with 5% EtOH, then 1:1 EtOAc/hex with 10% EtOH). All mixed fractions were combined and re-chromatographed under the same conditions. Mixed fractions from the second round were again combined and re-chromatographed one final time. All pure fractions were combined and concentrated in vacuo to a wet, pasty solid. The material was then slurried in 5% EtOH/EtOAc at room temperature, collected by vacuum filtration, and washed with EtOAc. The product was dried in a vacuum oven overnight (house vacuum, ~10 tor, 50 °C) to provide 60.3 g (76%) of compound 6 as a colorless, light, flaky solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.70 (s, 1H), 8.04 (s, 1H), 7.43-7.32 (m, 1H), 6.90-6.78 (m, 3H), 6.18 (dd, J = 16.6, 2.2 Hz, 1H), 5.74 (dd, J = 10.4, 2.2 Hz, 1H), 3.93 (broad s, 4H), 3.88-3.70 (m, 4H).

EXAMPLE 5

PREPARATION OF COMPOUND 7



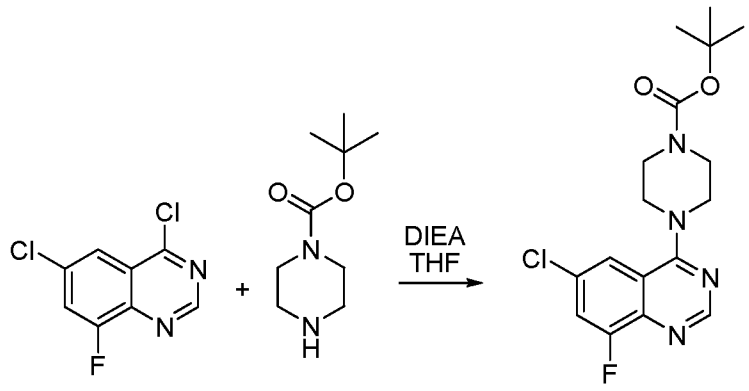
1 7

In a 1 L round-bottom flask with a magnetic stir bar, compound 1 (70 g, 0.3525 mol, 1.0 eq.) was slurried in $POCl_3$ (350 mL, 3.7663 mol, 10.7 eq.). Cautiously, DIEA (30 mL, 0.1741 mol, 0.5 eq.) was added to the mixture. The reaction mixture was heated to reflux overnight to form dark solution. HPLC analysis indicated

complete reaction. The flask was fitted with a distillation head, and approximately one half the volume of $POCl_3$ (175 mL) was distilled off. While cooling to room temperature, product precipitated from the mixture. The solids were slurried in CH_3CN (1.2 L), and the slurry was slowly added to a vigorously stirred ice/water mixture (600 mL) while maintaining the internal temperature below 10 °C. After 2 hours of stirring at 10 °C to hydrolyze the $POCl_3$, HPLC analysis showed the product also began to slowly hydrolyze to starting material 1. At this point, the precipitate was collected by vacuum filtration, washed with cold water, and dried overnight (house vacuum, ~10 torr, room temperature) to recover 46 grams (60%) of product 7. As the filtrate warmed to room temperature, a mild exothermic reaction was observed. HPLC analysis indicated the filtrate contained only 1. Compound 7 could be further isolated from the filtrate. The isolated 7 contained ca. 5% 1 and was used in the next step without further purification.

EXAMPLE 6

PREPARATION OF COMPOUND 8



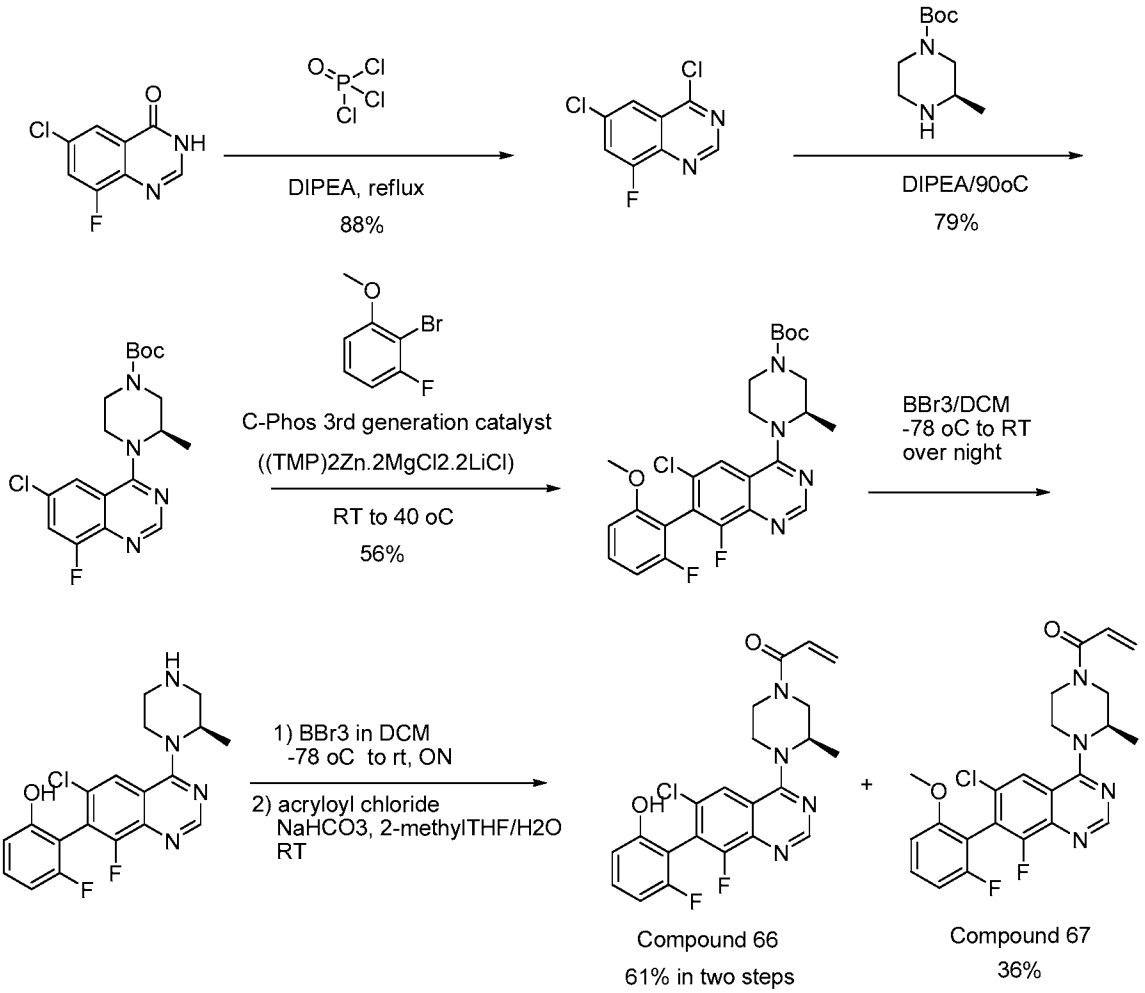
7 8

In a 1 L round-bottom flask with a magnetic stir bar, compound 7 (46 g, 0.2014 mol, 1.0 eq.) was diluted in DIEA (41.64 mL, 0.2416 mol, 1.2 equivalents) and THF (700 mL). Solid N-Boc piperazine (39.38 g, 0.2114 mol, 1.05 eq.) was slowly added in portions. A mild exothermic reaction was observed. The reaction mixture was allowed to stir at room temperature for 2 hours then was quenched with saturated NaCl solution (100 mL), water (400 mL), and EtOAc (500 mL). The layers were separated,

and the aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give a gray solid. The crude solid was stirred in 2:1 TBME/hexanes (300/150 mL) overnight. The solids were filtered then washed with hexane (250 mL) to recover 52 g of impure product. The TBME/hexanes slurry was repeated to recover 46 g (59%) of compound 8. All remaining impure material was combined and purified via silica gel chromatography (4:1 hexane/EtOAc) to recover another 11.2 g (14%) of **8** for a total combined yield of 57.2 g (74%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.64 (t, J = 1.8 Hz, 1H), 7.46 (dd, J = 9.4, 2.2 Hz, 1H), 3.79–3.74 (m, 4H), 3.67-3.63 (m, 4H), 1.50 (s, 9H).

EXAMPLE 7

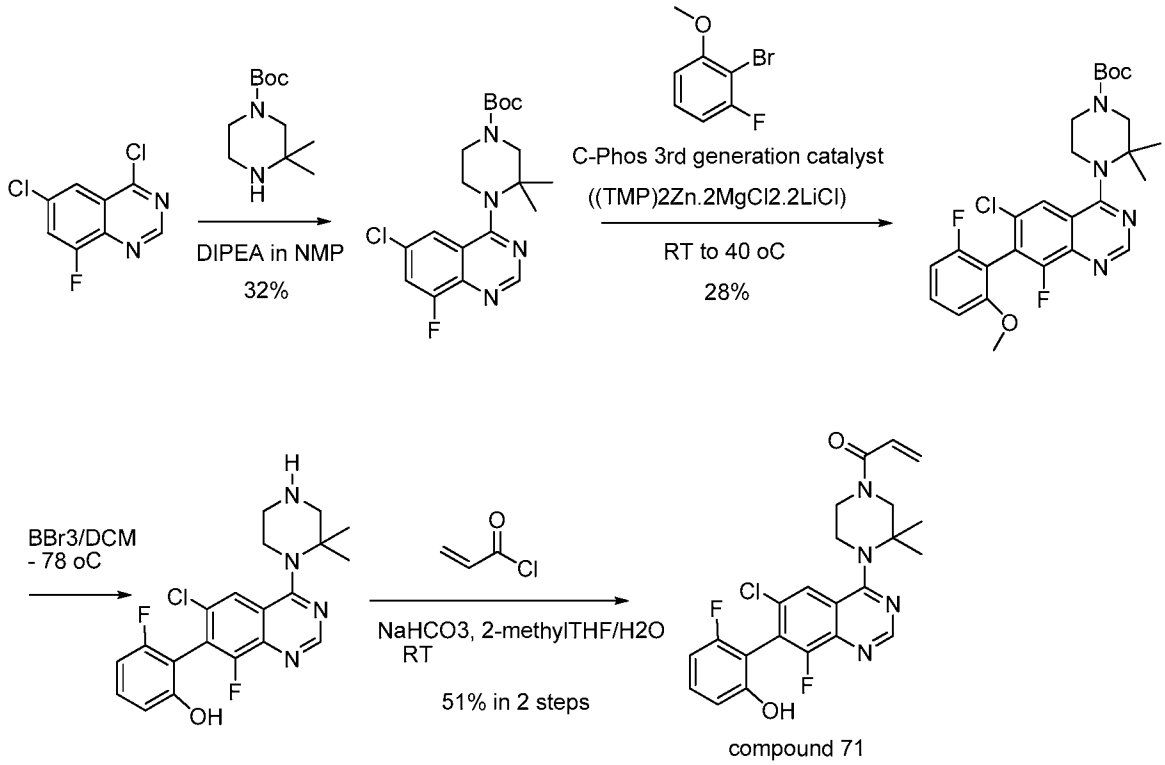
SYNTHESIS OF 1-((3R)-4-(6-CHLORO-8-FLUORO-7-(2-FLUORO-6-HYDROXYPHENYL)QUINAZOLIN-4-YL)-3-METHYLPIPERAZIN-1-YL)PROP-2-EN-1-ONE



Compounds 66 and 67 were prepared as illustrated above and according to the general procedures described in Examples 1-6.

EXAMPLE 8

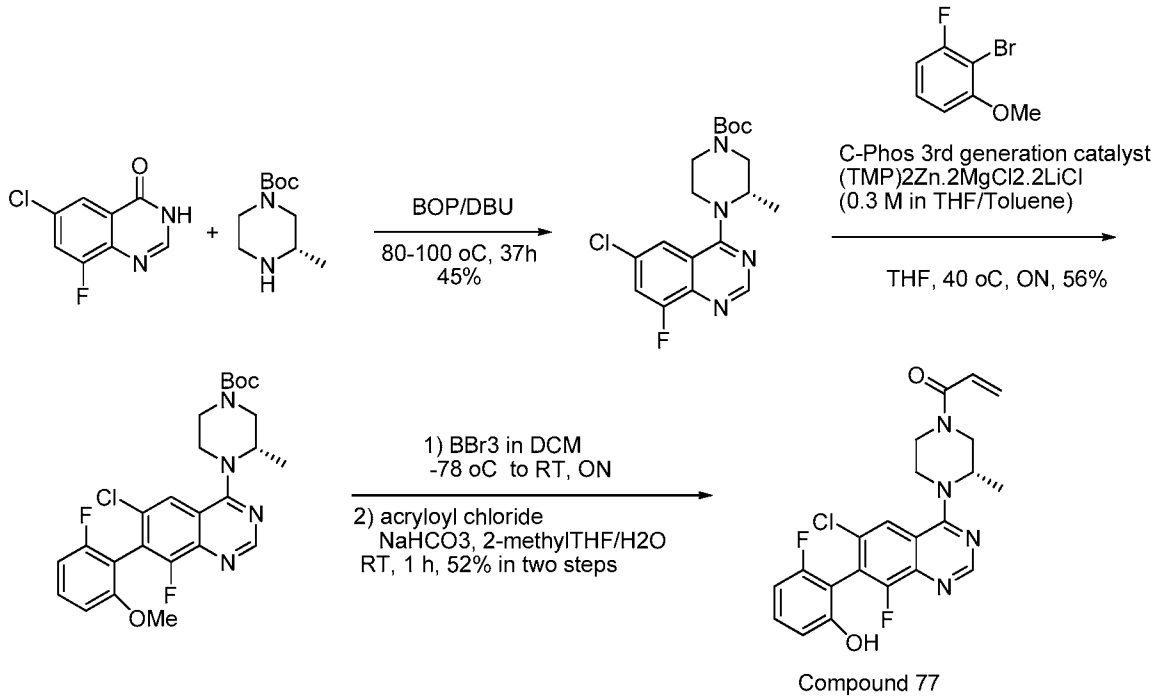
SYNTHESIS OF 1-(4-(6-CHLORO-8-FLUORO-7-(2-FLUORO-6-HYDROXYPHENYL)QUINAZOLIN-4-YL)-3,3-DIMETHYLPIPERAZIN-1-YL)PROP-2-EN-1-ONE



Compound 71 was prepared as illustrated above and according to the general procedures described in Examples 1-6.

EXAMPLE 9

SYNTHESIS OF 1-((3S)-4-(6-CHLORO-8-FLUORO-7-(2-FLUORO-6-HYDROXYPHENYL)QUINAZOLIN-4-YL)-3-METHYLPIPERAZIN-1-YL)PROP-2-EN-1-ONE



Compound 77

Compound 77 was prepared as illustrated above and described below.

tert-Butyl (S)-4-(6-chloro-8-fluoroquinazolin-4-yl)-3-methylpiperazine-1-carboxylate

To a mixture of 800 mg (4.04 mmol, 1.0 eq.) of 6-chloro-8-fluoroquinazolin-4(3H)-one and BOP (1.1 eq.) in acetonitrile, DBU (1.3 eq.) and *tert*-butyl (S)-3-methylpiperazine-1-carboxylate (1.1 eq.) were added sequentially. The resulting mixture was stirred at 80-100 °C for 37 h. The mixture was cooled down, concentrated *in vacuo* and then partitioned between water and ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (stepwise gradient of 0-10% MeOH in dichloromethane) to afford the desired product (685 mg, 45% yield).

tert-Butyl (3S)-4-(6-chloro-8-fluoro-7-(2-fluoro-6-methoxyphenyl)quinazolin-4-yl)-3-methylpiperazine-1-carboxylate

A flame dried round bottle (evacuated under vacuum and filled with N_2) was fitted with mechanical stirring, and charged with *tert*-butyl (S)-4-(6-chloro-8-fluoroquinazolin-4-yl)-3-methylpiperazine-1-carboxylate (685 mg, 1.80 mmol, 1.0 eq.) solution in dry THF. Bis(2,2,6,6-tetramethylpiperidinyl)zinc, lithium chloride, magnesium chloride complex ($(TMP)_2Zn•2\ MgCl_2•2\ LiCl$) (0.35 M solution in THF/toluene, 1.0 eq.) was dropwise added. The reaction was allowed to stir for 45 min at RT and then degassed by bubbling nitrogen through the solution for 15 min. Solid 2-bromo-1-fluoro-3-methoxybenzene (1.0 eq.) and CPhos 3rd generation precatalyst (0.1 eq.) were added, and the resulting mixture was stirred at 40 °C for 16 h. The reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate, cooled in an ice bath, and quenched with a 1:1 solution of saturated ammonium chloride and H_2O. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (stepwise gradient of 20%-30% EtOAc in hexanes) to afford the desired product (504 mg, 56% yield).

1-((3S)-4-(6-Chloro-8-fluoro-7-(2-fluoro-6-hydroxyphenyl)quinazolin-4-yl)-3-methylpiperazin-1-yl)prop-2-en-1-one

At -78 °C, BBr_3 in dichloromethane (1M, 6.0 eq.) was dropwise added into *tert*-butyl (3S)-4-(6-chloro-8-fluoro-7-(2-fluoro-6-methoxyphenyl)quinazolin-4-yl)-3-methylpiperazine-1-carboxylate (228 mg, 0.45 mmol, 1.0 eq.) solution in dichloromethane. After addition was complete, the reaction was warmed to RT, and the suspension was stirred for 19 h. The reaction was cooled to 0 °C and quenched with an ice/water. Additional water was added and the layers were separated. The water layer was collected. The organic layer was extracted with water. The combined water layer was concentrated, added 2-MeTHF and solid $NaHCO_3$ (20.0 eq.). The reaction mixture was allowed to stir for 5 min. The acryloyl chloride (2.5 eq.) was added at RT and the resulting mixture was stirred at RT for 1 h. Then 5 N NaOH (0.5 mL) was added to quench the reaction, followed by adding 1mL of 1 N HCl for neutralization. The

organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (stepwise gradient of 0-10% MeOH in dichloromethane) to afford the desired product (104 mg, 52% yield). **ESI-MS** *m/z*: 445.1 $[M + H]^+$; ^1H NMR (500 MHz, DMSO-*d*6) δ 10.27 (s, 1H), 8.70 (s, 1H), 7.94 (s, 1H), 7.39-7.34 (q, *J* = 8.5 Hz, 1H), 6.87-6.80 (m, 3H), 6.21-6.16 (m, 1H), 5.43 (dd, *J* = 10, 2.5 Hz, 1H), 4.78 (broad s, 1H), 4.40-3.96 (m, 4H), 3.70-3.61 (m, 2H), 1.30 (s, 3H).

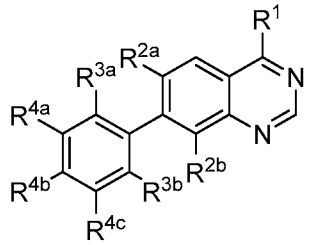
All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification or the attached Application Data Sheet are incorporated herein by reference, in their entirety to the extent not inconsistent with the present description.

U.S. provisional patent application Serial No. 62/265,303 filed December 9, 2015 is incorporated herein by reference, in its entirety.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

1. A method for preparing a compound having the following structure (I):



(I)

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

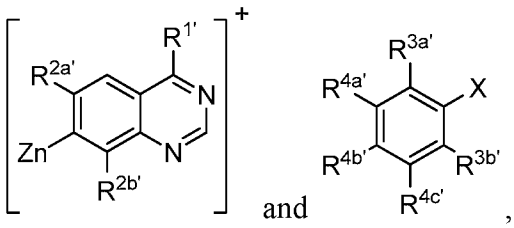
R^1 is a non-hydrogen substituent;

R^{2a} and R^{2b} are each independently halo, hydroxyl, protected hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy;

R^{3a} and R^{3b} are each independently halo, hydroxyl, protected hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy; or R^{3a} joins with R^{4a} to form a carbocyclyl or heterocyclyl ring, and R^{3b} is halo, hydroxyl, protected hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy; and

R^{4a}, R^{4b} and R^{4c} are each independently H or a non-hydrogen substituent; or R^{4a} joins with R^{3a} to form a carbocyclyl or heterocyclyl ring, and R^{4b} and R^{4c} are each independently H or a non-hydrogen substituent;

wherein the method comprises preparing a mixture comprising a compound of structure (II) and a compound of structure (III), the compounds of structure (II) and (III) having the following structures, respectively:



(II) and (III),

or a salt thereof, wherein:

$R^{1'}$ is a non-hydrogen, non-acidic substituent;

$R^{2a'}$ and $R^{2b'}$ are each independently halo, protected hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy;

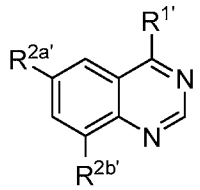
$R^{3a'}$ and $R^{3b'}$ are each independently halo, protected hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy; or $R^{3a'}$ joins with $R^{4a'}$ to form a carbocyclyl or heterocyclyl ring, and $R^{3b'}$ is halo, protected hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy;

$R^{4a'}$, $R^{4b'}$ and $R^{4c'}$ are each independently H or a non-hydrogen substituent; or $R^{4a'}$ joins with $R^{3a'}$ to form a carbocyclyl or heterocyclyl ring, and $R^{4b'}$ and $R^{4c'}$ are each independently H or a non-hydrogen substituent; and

X is a leaving group,

thereby forming a carbon-carbon bond between the carbon bearing the Zn moiety on compound (II) and the carbon bearing the X moiety on compound (III).

2. The method of claim 1, wherein the compound of structure (II) is prepared by reaction of a mixed-metal, heterocyclyl base with a compound having the following structure (IV):



(IV)

3. The method of claim 2, wherein the mixed metal, heterocyclyl base comprises Zn, Mg and Li.

4. The method of any one of claims 2 or 3, wherein the mixed metal, heterocyclyl base comprises a piperidinyl heterocycle.

5. The method of any one of claims 2-4, wherein the mixed metal, heterocyclyl base comprises a 2,2,6,6-Bis(tetramethylpiperidine)zinc, magnesium chloride, lithium chloride complex ($(tmp)_2Zn \cdot 2\ MgCl_2 \cdot 2\ LiCl$).

6. The method of any one of claims 1-5, wherein the mixture comprising a compound of structure (II) and a compound of structure (III) further comprises a metal catalyst or metal precatalyst.

7. The method of claim 6, wherein the metal is palladium.

8. The method of claim 7, wherein the metal precatalyst is CPhos 3rd generation.

9. The method of any one of claims 1-8, wherein the mixture comprising a compound of structure (II) and a compound of structure (III) comprises a polar, aprotic solvent.

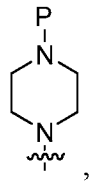
10. The method of claim 9, wherein the solvent is tetrahydrofuran.

11. The method of any one of claims 1-10, wherein R^1 and $R^{1'}$ are each independently C_1-C_6 alkyl, carbocyclyl or heterocyclyl.

12. The method of claim 11, wherein R^1 and $R^{1'}$ are each independently heterocyclyl.

13. The method of claim 12, wherein heterocyclyl is piperazinyl.

14. The method of any one of claims 1-13, wherein R^1 and $R^{1'}$ each have the following structure:



,

wherein P is a nitrogen protecting group.

15. The method of claim 14, wherein P is butyloxycarbonyl (Boc).

16. The method of any one of claims 1-15, wherein R^{2a} and R^{2b} are each independently halo.

17. The method of any one of claims 1-16, wherein $R^{2a'}$ and $R^{2b'}$ are each independently halo.

18. The method of any one of claims 1-17, wherein R^{3a} and R^{3b} are each independently halo, hydroxyl or C_1-C_6 alkoxy.

19. The method of any one of claims 1-18, wherein $R^{3a'}$ and $R^{3b'}$ are each independently halo or C_1-C_6 alkoxy.

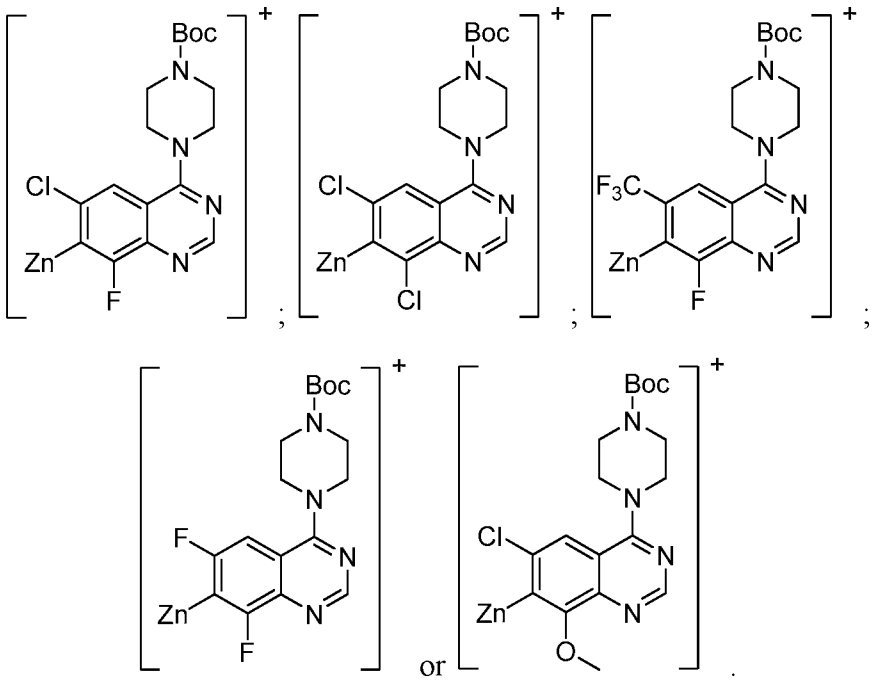
20. The method of any one of claims 1-19, wherein R^{4a}, R^{4b} and R^{4c} are each independently H.

21. The method of any one of claims 1-20, wherein $R^{4a'}$, $R^{4b'}$ and $R^{4c'}$ are each independently H.

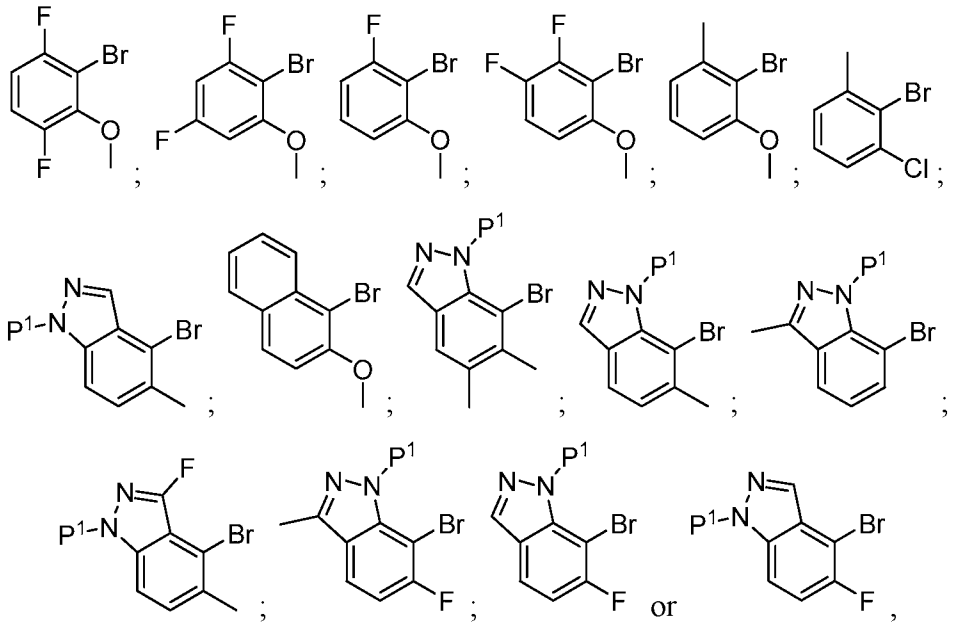
22. The method of any one of claims 1-21, wherein X is halo.

23. The method of claim 22, wherein halo is bromo.

24. The method of any one of claims 1-23, wherein the compound of structure (II) has one of the following structures:

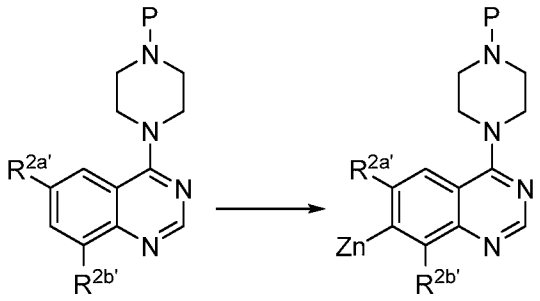


25. The method of any one of claims1-24, wherein the compound of structure (III) has one of the following structures:

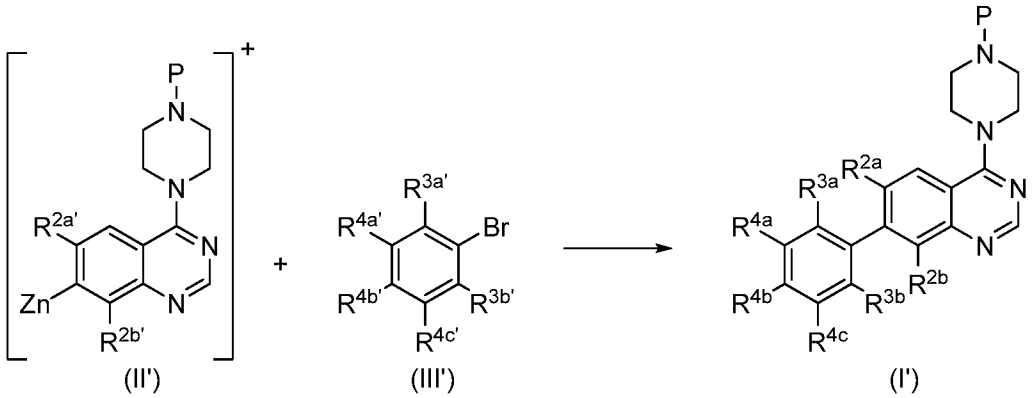


wherein P^1 is nitrogen protecting group.

26. The method of claim 1, comprising the following steps (a) and (b):

(a) 

; and

(b) 

,

wherein:

R^{2a}, R^{2b}, $R^{2a'}$ and $R^{2b'}$ are each independently halo;

R^{3a}, R^{3b}, $R^{3a'}$ and $R^{3b'}$ are each independently halo, protected hydroxyl or C_1-C_6 alkoxy; and

R^{4a}, R^{4b}, R^{4c}, $R^{4a'}$, $R^{4b'}$ and $R^{4c'}$ are each independently H.

27. The method of claim 26, wherein P is butyloxycarbonyl.

28. The method of any one of claims 26 or 27, wherein R^{2a}, R^{2b}, $R^{2a'}$ and $R^{2b'}$ are each independently chloro or fluoro.

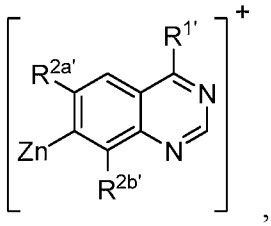
29. The method of any one of claims 26 or 27, wherein R^{2a} and $R^{2b'}$ are each chloro, and R^{2b} and $R^{2b'}$ are each fluoro.

30. The method of any one of claims 26-29, wherein R^{3a}, R^{3b}, $R^{3a'}$ and $R^{3b'}$ are each independently halo or C_1-C_6 alkoxy.

31. The method of claim 28, wherein halo is fluoro and C_1-C_6 alkoxy is methoxy.

32. The method of claim 31, wherein R^{3a} and $R^{3a'}$ are each fluoro, and R^{3b} and $R^{3b'}$ are each methoxy.

33. A compound having the following structure (II):



,

(II)

wherein:

$R^{1'}$ is a non-hydrogen, non-acidic substituent; and

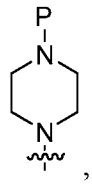
$R^{2a'}$ and $R^{2b'}$ are each independently halo, protected hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy.

34. The compound of claim 33, wherein $R^{1'}$ is C_1-C_6 alkyl, carbocyclyl or heterocyclyl.

35. The compound of claim 34, wherein $R^{1'}$ is heterocyclyl.

36. The compound of claim 35, wherein heterocyclyl is piperazinyl.

37. The compound of claim 36, wherein $R^{1'}$ has the following structure:



,

wherein P is a nitrogen protecting group.

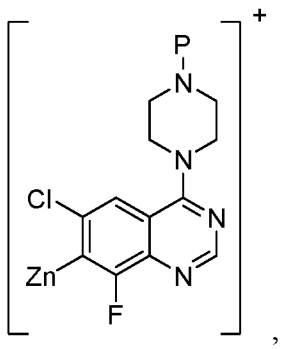
38. The compound of claim 37, wherein P is butyloxycarbonyl (Boc).

39. The compound of any one of claims 33-38, wherein $R^{2a'}$ and $R^{2b'}$ are each independently halo.

40. The compound of any one of claims 33-39, wherein $R^{2a'}$ and $R^{2b'}$ are independently chloro or fluoro.

41. The compound of any one of claims 33-40, wherein $R^{2a'}$ is chloro and $R^{2b'}$ is fluoro.

42. The compound of claim 33, having the following structure:

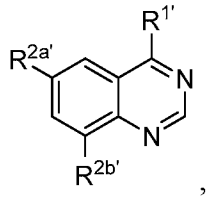


,

wherein P is a nitrogen protecting group.

43. The compound of claim 42, wherein P is butyloxycarbonyl.

44. A compound having the following structure (V):



(V)

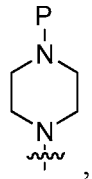
or a salt thereof, wherein:

$R^{1'}$ is heterocyclyl; and

$R^{2a'}$ and $R^{2b'}$ are each independently halo, protected hydroxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl or C_1-C_6 alkoxy.

45. The compound of claim 44, wherein heterocyclyl is piperazinyl.

46. The compound of claim 44, wherein $R^{1'}$ has the following structure:



wherein P is a nitrogen protecting group.

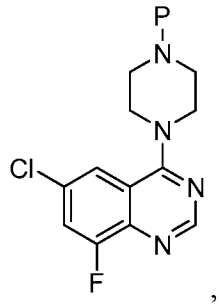
47. The compound of claim 46, wherein P is butyloxycarbonyl (Boc).

48. The compound of any one of claims 44-47, wherein $R^{2a'}$ and $R^{2b'}$ are each independently halo.

49. The compound of any one of claims 44-48, wherein $R^{2a'}$ and $R^{2b'}$ are independently chloro or fluoro.

50. The compound of any one of claims 44-49, wherein $R^{2a'}$ is chloro and $R^{2b'}$ is fluoro.

51. The compound of claim 44, having the following structure:



,

wherein P is a nitrogen protecting group.

52. The compound of claim 51, wherein P is butyloxycarbonyl.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/065786

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/00 C07D235/06 C07D403/00 C07D417/00 C07D487/00
C07F3/06
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07F

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/148922 A1 (MITSUBISHI TANABE PHARMA CORP [JP]; INOUE SHINYA [JP]; TSUBOI YASUNORI) 1 December 2011 (2011-12-01)	44,45, 47,48
A	page 352; example 348	46,49,50

X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 9 September 2015 (2015-09-09), ENAMINE LLC: XP002767505, retrieved from CHEMCATS Database accession no. 1301347730	44-46, 48,49
A	abstract	47,50-52

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 February 2017	08/03/2017

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

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/065786

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2015/054572 A1 (ARAXES PHARMA LLC [US]; LI LIANSHENG [US]; FENG JUN [US]; WU TAO [US];) 16 April 2015 (2015-04-16) cited in the application	1-5
A	page 150 - page 152	6-50

Y	PAUL KNOCHEL ET AL: "Functionalization of heterocyclic compounds using polyfunctional magnesium and zinc reagents", BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY, vol. 7, 13 September 2011 (2011-09-13), pages 1261-1277, XP055347530, DOI: 10.3762/bjoc.7.147 cited in the application	1-5
A	page 1265 - page 1266	6-50

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/065786

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011148922 A1	01-12-2011	TW 201202230 A	16-01-2012
		WO 2011148922 A1	01-12-2011
WO 2015054572 A1	16-04-2015	AU 2014331794 A1	21-04-2016
		CA 2926328 A1	16-04-2015
		EA 201690752 A1	29-07-2016
		EP 3055290 A1	17-08-2016
		JP 2016532656 A	20-10-2016
		KR 20160076519 A	30-06-2016
		PH 12016500538 A1	13-06-2016
		SG 11201602662Y A	30-05-2016
		WO 2015054572 A1	16-04-2015