

ALKYNE SUBSTITUTED QUINAZOLINE DERIVATIVES AND USES THEREOF**CROSS-REFERENCE TO RELATED APPLICATIONS**

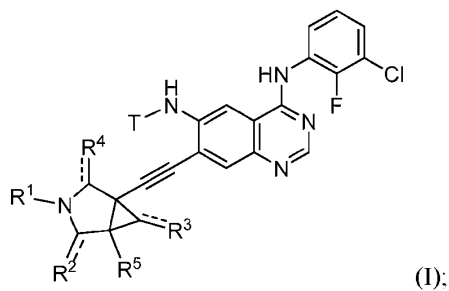
[001] This application claims priority to and the benefit of U.S. Provisional Application No. 63/612,552, filed on December 20, 2023, which is incorporated by reference herein in its entirety for all purposes.

BACKGROUND

[002] Mutations affecting either the intracellular catalytic domain or extracellular ligand binding domain of an ErbB receptor can generate oncogenic activity (the ErbB protein family consists of 4 members including ErbB-1, also named epidermal growth factor receptor (EGFR) and Erb-2, also named HER2 in humans). ErbB inhibitors are a known treatment for a number of cancers. However, not every patient is responsive satisfactorily to this treatment. Thus, there is a long-felt need in the art for new therapies that are able to address the variable responsiveness of cancer patients to known therapies. The present disclosure provides compositions and methods for preventing or treating cancer in patients with these oncogenic mutations.

SUMMARY

[003] In some aspects, the present disclosure provides a compound (e.g., an isolated compound) of Formula (I):



or a pharmaceutically acceptable salt thereof.

[004] In some aspects, the present disclosure provides a pharmaceutical composition comprising a compound disclosed herein, and a pharmaceutically acceptable excipient.

[005] In some aspects, the present disclosure provides a method of inhibiting an oncogenic variant of an ErbB receptor, comprising administering to the subject in need thereof a compound disclosed herein (e.g., in a therapeutically effective amount).

[006] In some aspects, the present disclosure provides a method of preventing or treating cancer, comprising administering to the subject in need thereof a compound disclosed herein (e.g., in a therapeutically effective amount).

[007] In some aspects, the present disclosure provides a compound disclosed herein for use in the inhibition of an oncogenic variant of an ErbB receptor.

[008] In some aspects, the present disclosure provides a compound disclosed herein for use in the prevention or treatment of cancer.

[009] In some aspects, the present disclosure provides use of a compound disclosed herein in the manufacture of a medicament for inhibiting an oncogenic variant of an ErbB receptor.

[010] In some aspects, the present disclosure provides use of a compound disclosed herein in the manufacture of a medicament for preventing or treating cancer.

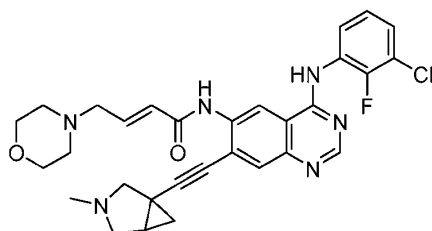
[011] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents and other references mentioned herein are incorporated by reference. The references cited herein are not admitted to be prior art to the claimed invention. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods and examples are illustrative only and are not intended to be limiting. In the case of conflict between the chemical structures and names of the compounds disclosed herein, the chemical structures will control.

[012] Other features and advantages of the disclosure will be apparent from the following detailed description and claims.

DETAILED DESCRIPTION

Compounds of the Present Disclosure

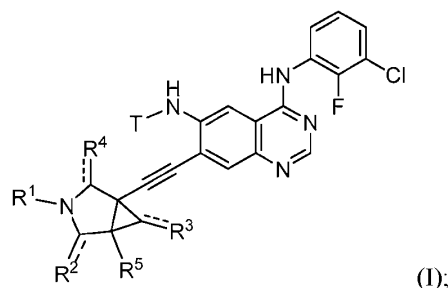
[013] Without wishing to be bound by theory, it is understood that compounds disclosed herein may be metabolites of Compound A:



(Compound A).

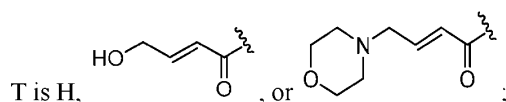
[014] In some embodiments, a compound disclosed herein may be a metabolite of Compound A in human, rat, or dog. In some embodiments, a compound disclosed herein may be a metabolite of Compound A in human.

[015] In some aspects, the present disclosure provides a compound (e.g., an isolated compound) of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

each $\equiv$ independently denotes a single bond or a double bond, as valency permits;



R¹ is H or C₁-C₆ alkyl;

R² is H, -OH, or oxo;

R³ is H, -OH, or oxo;

R⁴ is H, -OH, or oxo; and

R⁵ is H or -OH;

provided that the compound is not Compound A or a pharmaceutically acceptable salt thereof.

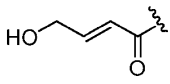
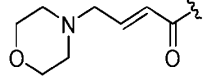
Isolated Compounds

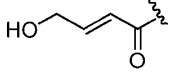
[016] In some embodiments, the compound is an isolated compound.

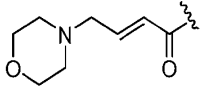
[017] In some embodiments, the compound has a purity of about 80% or higher, about 85% or higher, about 90% or higher, about 91% or higher, about 92% or higher, about 93% or higher, about 94% or higher, about 95% or higher, about 96% or higher, about 97% or higher, about 98% or higher, about 99% or higher, about 99.1% or higher, about 99.2% or higher, about 99.3% or higher, about 99.4% or higher, about 99.5% or higher, about 99.6% or higher, about 99.7% or higher, about 99.8% or higher, or about 99.9% or higher (e.g., as measured by HPLC).

Variables T , R^1 , R^2 , R^3 , R^4 , and R^5

[018] In some embodiments, T is H.

[019] In some embodiments, T is , or .

[020] In some embodiments, T is .

[021] In some embodiments, T is .

[022] In some embodiments, R^1 is H.

[023] In some embodiments, R^1 is C₁-C₆ alkyl.

[024] In some embodiments, R^1 is methyl, ethyl, or propyl.

[025] In some embodiments, R^1 is methyl.

[026] In some embodiments, R^2 is H.

[027] In some embodiments, R^2 is -OH.

[028] In some embodiments, R^2 is oxo.

[029] In some embodiments, R^3 is H.

[030] In some embodiments, R^3 is -OH.

[031] In some embodiments, R^3 is oxo.

[032] In some embodiments, R^4 is H.

[033] In some embodiments, R^4 is -OH.

[034] In some embodiments, R^4 is oxo.

[035] In some embodiments, R^5 is H.

[036] In some embodiments, R^5 is -OH.

Exemplary Embodiments of the Compounds

[037] In some embodiments, at least one of R^2 , R^3 , and R^4 is oxo.

[038] In some embodiments, when R^1 is C₁-C₆ alkyl (e.g., methyl), then at least one of R^2 , R^3 , and R^4 is oxo.

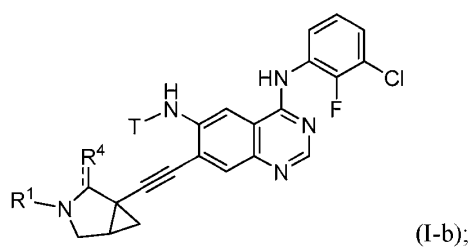
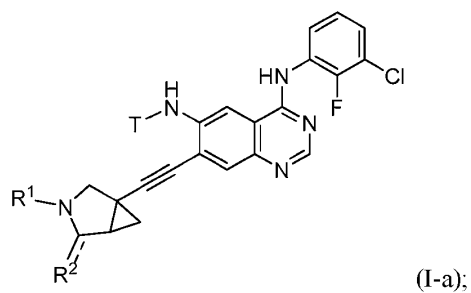
[039] In some embodiments, when R^1 is C₁-C₆ alkyl (e.g., methyl), then R^2 is oxo.

[040] In some embodiments, when R^1 is C₁-C₆ alkyl (e.g., methyl), then R^3 is oxo.

[041] In some embodiments, when R^1 is C₁-C₆ alkyl (e.g., methyl), then R^4 is oxo.

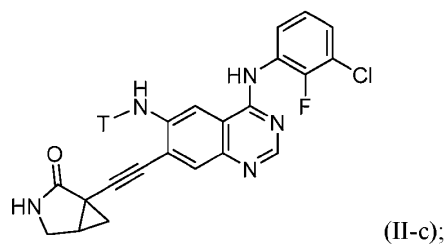
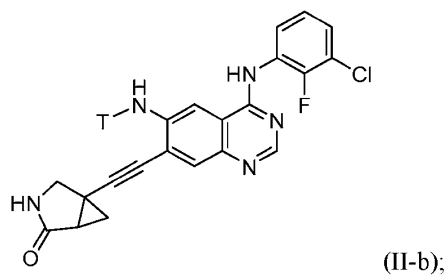
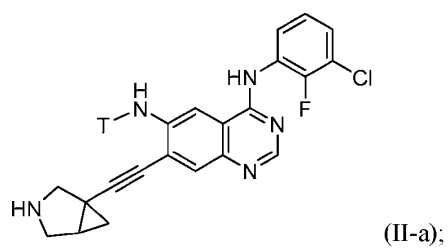
[042] In some embodiments, when R^2 , R^3 , and R^4 are each H, then R^1 is H.

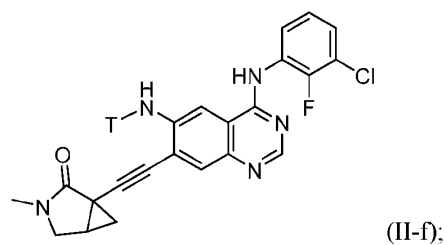
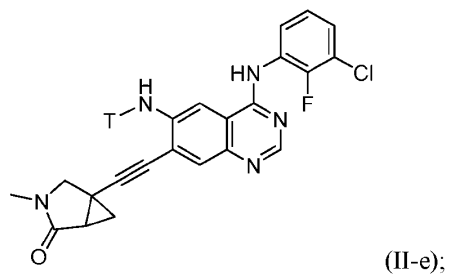
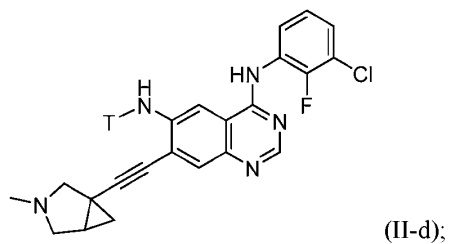
[043] In some embodiments, the compound is of Formula (I-a) or (I-b):



or a pharmaceutically acceptable salt thereof.

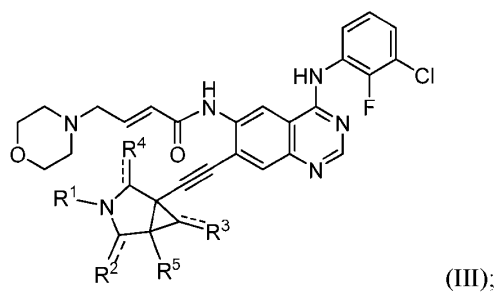
[044] In some embodiments, the compound is of Formula (II-a), (II-b), (II-c), (II-d), (II-e), or (II-f):





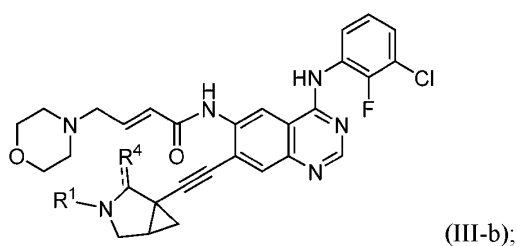
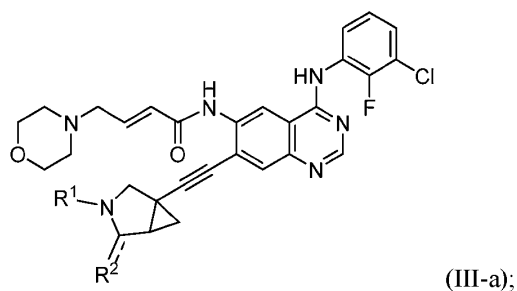
or a pharmaceutically acceptable salt thereof.

[045] In some embodiments, the compound is of Formula (III):



or a pharmaceutically acceptable salt thereof.

[046] In some embodiments, the compound is of Formula (III-a) or (III-b):



or a pharmaceutically acceptable salt thereof.

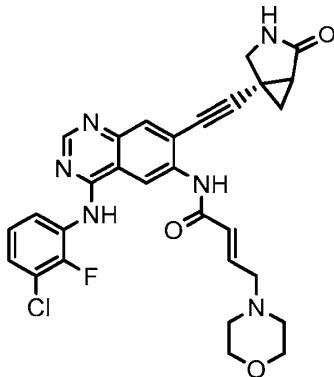
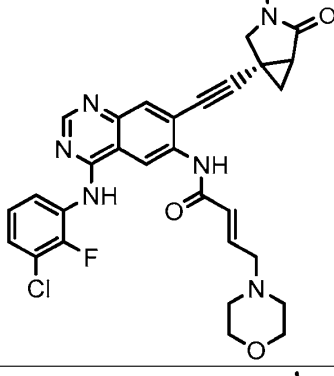
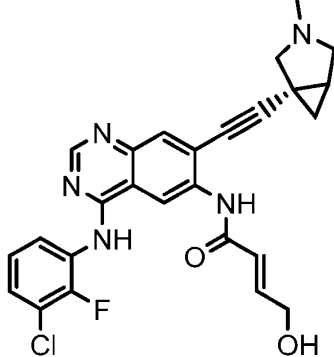
[047] In some embodiments, the compound is selected from the compounds described in Table I, and pharmaceutically acceptable salts thereof.

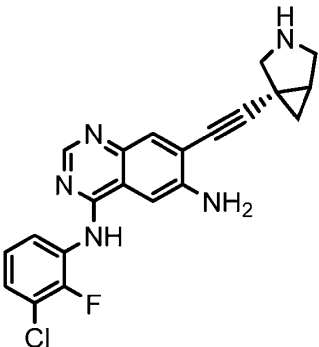
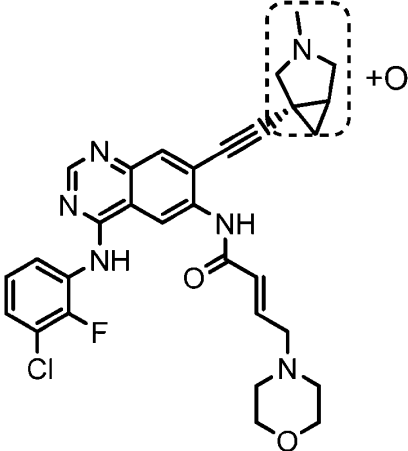
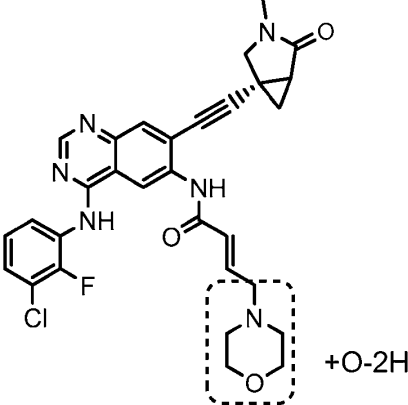
[048] In some embodiments, the compound is selected from the compounds described in Table I.

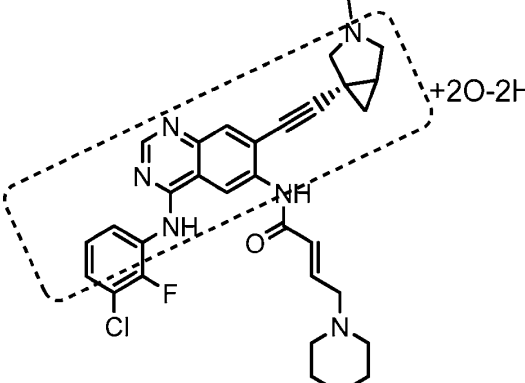
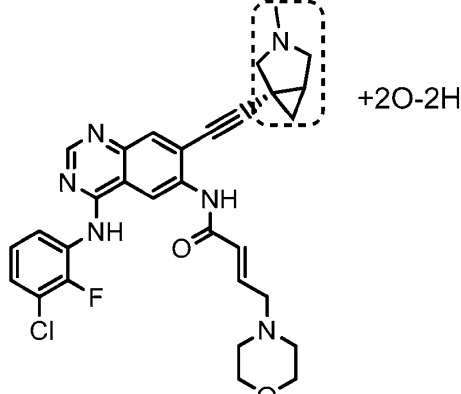
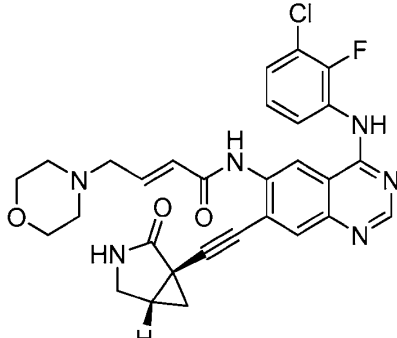
[049] It is understood that, when a portion of the compound structure is marked by a circle and “+” and/or “-” one or more atoms, such presentation intends to cover each and all derivatives of the structure in which the marked portion is further modified by adding (“+”) and/or removing (“-”) the one or more atoms.

Table I

Compound No.	Structure
1	

Compound No.	Structure
2	
3	
4	

Compound No.	Structure
5	
6	
7	

Compound No.	Structure
8	
9	
10	

[050] In some aspects, the present disclosure provides a compound being an isotopic derivative (e.g., isotopically labeled compound) of any one of the compounds disclosed herein.

[051] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table I, or a pharmaceutically acceptable salt thereof.

[052] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table I.

[053] It is understood that the isotopic derivative can be prepared using any of a variety of art-recognized techniques. For example, the isotopic derivative can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples described herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[054] In some embodiments, the isotopic derivative is a deuterium labeled compound.

[055] In some embodiments, the isotopic derivative is a deuterium labeled compound of any one of the compounds of the Formulae disclosed herein.

[056] In some embodiments, the isotopic derivative is a deuterium labeled compound of any one of the compounds described in Table I, or a pharmaceutically acceptable salt thereof.

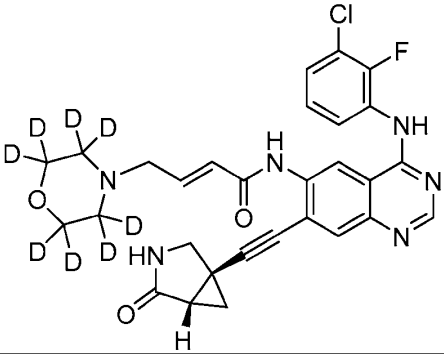
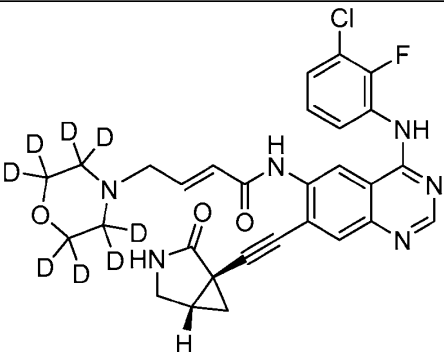
[057] In some embodiments, the isotopic derivative is a deuterium labeled compound of any one of the compounds described in Table I.

[058] In some embodiments, the isotopic derivative is selected from the compounds described in Table D-I, and pharmaceutically acceptable salts thereof.

[059] In some embodiments, the isotopic derivative is selected from the compounds described in Table D-I.

Table D-I

Compound No.	Structure
D1	
D2	

Compound No.	Structure
D3	
D4	

[060] It is understood that the deuterium labeled compound comprises a deuterium atom having an abundance of deuterium that is substantially greater than the natural abundance of deuterium, which is 0.015%.

[061] In some embodiments, the deuterium labeled compound has a deuterium enrichment factor for each deuterium atom of at least 3500 (52.5% deuterium incorporation at each deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation). As used herein, the term “deuterium enrichment factor” means the ratio between the deuterium abundance and the natural abundance of a deuterium.

[062] It is understood that the deuterium labeled compound can be prepared using any of a variety of art-recognized techniques. For example, the deuterium labeled compound can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the

Examples described herein, by substituting a deuterium labeled reagent for a non-deuterium labeled reagent.

[063] A compound of the present disclosure or a pharmaceutically acceptable salt or solvate thereof that contains the aforementioned deuterium atom(s) is within the scope of the disclosure. Further, substitution with deuterium (*i.e.*, ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability, e.g., increased *in vivo* half-life or reduced dosage requirements.

[064] For the avoidance of doubt it is to be understood that, where in this specification a group is qualified by “described herein”, the said group encompasses the first occurring and broadest definition as well as each and all of the particular definitions for that group.

[065] It will be understood that the compounds of the present disclosure and any pharmaceutically acceptable salts thereof, comprise stereoisomers, mixtures of stereoisomers, polymorphs of all isomeric forms of said compounds.

[066] As used herein, the term “isomerism” means compounds that have identical molecular formulae but differ in the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers.” Stereoisomers that are not mirror images of one another are termed “diastereoisomers,” and stereoisomers that are non-superimposable mirror images of each other are termed “enantiomers” or sometimes optical isomers. A mixture containing equal amounts of individual enantiomeric forms of opposite chirality is termed a “racemic mixture.”

[067] As used herein, the term “chiral center” refers to a carbon atom bonded to four nonidentical substituents.

[068] As used herein, the term “chiral isomer” means a compound with at least one chiral center. Compounds with more than one chiral center may exist either as an individual diastereomer or as a mixture of diastereomers, termed “diastereomeric mixture.” When one chiral center is present, a stereoisomer may be characterized by the absolute configuration (R or S) of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The substituents attached to the chiral center under consideration are ranked in accordance with the *Sequence Rule* of Cahn, Ingold and Prelog. (Cahn *et al.*, *Angew. Chem. Inter. Edit.* 1966, 5, 385; errata 511; Cahn *et al.*, *Angew. Chem.* 1966, 78, 413; Cahn and Ingold, *J. Chem. Soc.* 1951 (London), 612; Cahn *et al.*, *Experientia* 1956, 12, 81; Cahn, *J. Chem. Educ.* 1964, 41, 116).

[069] As used herein, the term “geometric isomer” means the diastereomers that owe their existence to hindered rotation about double bonds or a cycloalkyl linker (e.g., 1,3-cyclobutyl). These configurations are differentiated in their names by the prefixes *cis* and *trans*, or *Z* and *E*,

which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules.

[070] It is to be understood that the compounds of the present disclosure may be depicted as different chiral isomers or geometric isomers. It is also to be understood that when compounds have chiral isomeric or geometric isomeric forms, all isomeric forms are intended to be included in the scope of the present disclosure, and the naming of the compounds does not exclude any isomeric forms, it being understood that not all isomers may have the same level of activity.

[071] It is to be understood that the structures and other compounds discussed in this disclosure include all atropic isomers thereof. It is also to be understood that not all atropic isomers may have the same level of activity.

[072] As used herein, the term “atropic isomers” are a type of stereoisomer in which the atoms of two isomers are arranged differently in space. Atropic isomers owe their existence to a restricted rotation caused by hindrance of rotation of large groups about a central bond. Such atropic isomers typically exist as a mixture, however as a result of recent advances in chromatography techniques, it has been possible to separate mixtures of two atropic isomers in select cases.

[073] As used herein, the term “tautomer” is one of two or more structural isomers that exist in equilibrium and is readily converted from one isomeric form to another. This conversion results in the formal migration of a hydrogen atom accompanied by a switch of adjacent conjugated double bonds. Tautomers exist as a mixture of a tautomeric set in solution. In solutions where tautomerization is possible, a chemical equilibrium of the tautomers will be reached. The exact ratio of the tautomers depends on several factors, including temperature, solvent and pH. The concept of tautomers that are interconvertible by tautomerisations is called tautomerism. Of the various types of tautomerism that are possible, two are commonly observed. In keto-enol tautomerism a simultaneous shift of electrons and a hydrogen atom occurs. Ring-chain tautomerism arises as a result of the aldehyde group (-CHO) in a sugar chain molecule reacting with one of the hydroxy groups (-OH) in the same molecule to give it a cyclic (ring-shaped) form as exhibited by glucose.

[074] It is to be understood that the compounds of the present disclosure may be depicted as different tautomers. It should also be understood that when compounds have tautomeric forms, all tautomeric forms are intended to be included in the scope of the present disclosure, and the naming of the compounds does not exclude any tautomer form. It will be understood that certain tautomers may have a higher level of activity than others.

[075] Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed “isomers”. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers”. Stereoisomers that are not mirror images of one another are termed “diastereomers” and those that are non-superimposable mirror images of each other are termed “enantiomers”. When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a “racemic mixture”.

[076] The compounds of this disclosure may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)-stereoisomers or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of “Advanced Organic Chemistry”, 4th edition J. March, John Wiley and Sons, New York, 2001), for example by synthesis from optically active starting materials or by resolution of a racemic form. Some of the compounds of the disclosure may have geometric isomeric centers (E- and Z- isomers). It is to be understood that the present disclosure encompasses all optical, diastereoisomers and geometric isomers and mixtures thereof that possess inflammasome inhibitory activity.

[077] The present disclosure also encompasses compounds of the disclosure as defined herein which comprise one or more isotopic substitutions.

[078] It is to be understood that the compounds of any Formula described herein include the compounds themselves, as well as their salts, and their solvates, if applicable. A salt, for example, can be formed between an anion and a positively charged group (e.g., amino) on a substituted compound disclosed herein. Suitable anions include chloride, bromide, iodide, sulfate, bisulfate, sulfamate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, glutamate, glucuronate, glutarate, malate, maleate, succinate, fumarate, tartrate, tosylate, salicylate, lactate, naphthalenesulfonate, and acetate (e.g., trifluoroacetate).

[079] It is to be understood that the compounds of the present disclosure, for example, the salts of the compounds, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates

with other solvent molecules. Nonlimiting examples of hydrates include monohydrates, dihydrates, etc. Nonlimiting examples of solvates include ethanol solvates, acetone solvates, etc.

[080] As used herein, the term “solvate” means solvent addition forms that contain either stoichiometric or non-stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate; and if the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one molecule of the substance in which the water retains its molecular state as H₂O.

[081] As used herein, the term “analog” refers to a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group, or the replacement of one functional group by another functional group). Thus, an analog is a compound that is similar or comparable in function and appearance, but not in structure or origin to the reference compound.

[082] As used herein, the term “derivative” refers to compounds that have a common core structure and are substituted with various groups as described herein.

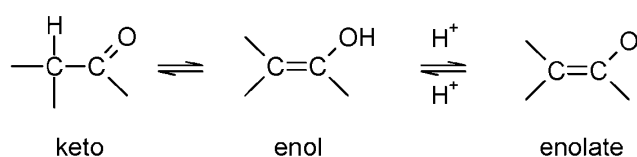
[083] As used herein, the term “bioisostere” refers to a compound resulting from the exchange of an atom or of a group of atoms with another, broadly similar, atom or group of atoms. The objective of a bioisosteric replacement is to create a new compound with similar biological properties to the parent compound. The bioisosteric replacement may be physicochemically or topologically based. Examples of carboxylic acid bioisosteres include, but are not limited to, acyl sulfonamides, tetrazoles, sulfonates and phosphonates. See, *e.g.*, Patani and LaVoie, *Chem. Rev.* 96, 3147-3176, 1996.

[084] It is also to be understood that certain compounds of the present disclosure may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. A suitable pharmaceutically acceptable solvate is, for example, a hydrate such as hemi-hydrate, a monohydrate, a di-hydrate or a tri-hydrate. It is to be understood that the disclosure encompasses all such solvated forms that possess inflammasome inhibitory activity.

[085] It is also to be understood that certain compounds of the present disclosure may exhibit polymorphism, and that the disclosure encompasses all such forms, or mixtures thereof, which possess inflammasome inhibitory activity. It is generally known that crystalline materials may be analysed using conventional techniques such as X-Ray Powder Diffraction analysis, Differential Scanning Calorimetry, Thermal Gravimetric Analysis, Diffuse Reflectance Infrared Fourier Transform (DRIFT) spectroscopy, Near Infrared (NIR) spectroscopy, solution and/or

solid state nuclear magnetic resonance spectroscopy. The water content of such crystalline materials may be determined by Karl Fischer analysis.

[086] Compounds of the present disclosure may exist in a number of different tautomeric forms and references to compounds of the present disclosure include all such forms. For the avoidance of doubt, where a compound can exist in one of several tautomeric forms, and only one is specifically described or shown, all others are nevertheless embraced by the Formulae disclosed. Examples of tautomeric forms include keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, and nitro/aci-nitro.



[087] Compounds of the present disclosure containing an amine function may also form N-oxides. A reference herein to a compound disclosed herein that contains an amine function also includes the N-oxide. Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidized to form an N-oxide. Particular examples of N-oxides are the N-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocycle. N-oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a peracid (e.g. a peroxycarboxylic acid), see for example Advanced Organic Chemistry, by Jerry March, 4th Edition, Wiley Interscience, pages. More particularly, N-oxides can be made by the procedure of L. W. Deady (Syn. Comm. 1977, 7, 509-514) in which the amine compound is reacted with meta-chloroperoxybenzoic acid (mCPBA), for example, in an inert solvent such as dichloromethane.

[088] The compounds of the present disclosure may be administered in the form of a prodrug which is broken down in the human or animal body to release a compound of the disclosure. A prodrug may be used to alter the physical properties and/or the pharmacokinetic properties of a compound of the disclosure. A prodrug can be formed when the compound of the disclosure contains a suitable group or substituent to which a property-modifying group can be attached. Examples of prodrugs include derivatives containing *in vivo* cleavable alkyl or acyl substituents at the sulfonylurea group in a compound of the any one of the Formulae disclosed herein.

[089] Accordingly, the present disclosure includes those compounds of the present disclosure as defined hereinbefore when made available by organic synthesis and when made available within the human or animal body by way of cleavage of a prodrug thereof. Accordingly, the

present disclosure includes those compounds of the present disclosure that are produced by organic synthetic means and also such compounds that are produced in the human or animal body by way of metabolism of a precursor compound, that is a compound of the present disclosure may be a synthetically-produced compound or a metabolically-produced compound.

[090] A suitable pharmaceutically acceptable prodrug of a compound of the present disclosure is one that is based on reasonable medical judgment as being suitable for administration to the human or animal body without undesirable pharmacological activities and without undue toxicity. Various forms of prodrug have been described, for example in the following documents: a) *Methods in Enzymology*, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985); b) *Design of Pro-drugs*, edited by H. Bundgaard, (Elsevier, 1985); c) *A Textbook of Drug Design and Development*, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 “Design and Application of Pro-drugs”, by H. Bundgaard p. 113-191 (1991); d) H. Bundgaard, *Advanced Drug Delivery Reviews*, 8, 1-38 (1992); e) H. Bundgaard, et al., *Journal of Pharmaceutical Sciences*, 77, 285 (1988); f) N. Kakeya, et al., *Chem. Pharm. Bull.*, 32, 692 (1984); g) T. Higuchi and V. Stella, “Pro-Drugs as Novel Delivery Systems”, A.C.S. Symposium Series, Volume 14; and h) E. Roche (editor), “Bioreversible Carriers in Drug Design”, Pergamon Press, 1987.

[091] A suitable pharmaceutically acceptable prodrug of a compound of the present disclosure that possesses a hydroxy group is, for example, an *in vivo* cleavable ester or ether thereof. An *in vivo* cleavable ester or ether of a compound of the present disclosure containing a hydroxy group is, for example, a pharmaceutically acceptable ester or ether which is cleaved in the human or animal body to produce the parent hydroxy compound. Suitable pharmaceutically acceptable ester forming groups for a hydroxy group include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters). Further suitable pharmaceutically acceptable ester forming groups for a hydroxy group include C₁-C₁₀ alkanoyl groups such as acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups, C₁-C₁₀ alkoxycarbonyl groups such as ethoxycarbonyl, N,N-(C₁-C₆ alkyl)₂carbamoyl, 2-dialkylaminoacetyl and 2-carboxyacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, N-alkylaminomethyl, N,N-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(C₁-C₄ alkyl)piperazin-1-ylmethyl. Suitable pharmaceutically acceptable ether forming groups for a hydroxy group include α -acyloxyalkyl groups such as acetoxymethyl and pivaloyloxymethyl groups.

[092] A suitable pharmaceutically acceptable prodrug of a compound of the present disclosure that possesses a carboxy group is, for example, an *in vivo* cleavable amide thereof, for example an amide formed with an amine such as ammonia, a C₁-4alkylamine such as methylamine, a (C₁-

C₄ alkyl)₂amine such as dimethylamine, N-ethyl-N-methylamine or diethylamine, a C₁-C₄ alkoxy-C₂-C₄ alkylamine such as 2-methoxyethylamine, a phenyl-C₁-C₄ alkylamine such as benzylamine and amino acids such as glycine or an ester thereof.

[093] A suitable pharmaceutically acceptable prodrug of a compound of the present disclosure that possesses an amino group is, for example, an *in vivo* cleavable amide derivative thereof. Suitable pharmaceutically acceptable amides from an amino group include, for example an amide formed with C₁-C₁₀ alkanoyl groups such as an acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, N-alkylaminomethyl, N,N-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl, and 4-(C₁-C₄ alkyl)piperazin-1-ylmethyl.

[094] The *in vivo* effects of a compound of the present disclosure may be exerted in part by one or more metabolites that are formed within the human or animal body after administration of a compound of the present disclosure. As stated hereinbefore, the *in vivo* effects of a compound of the present disclosure may also be exerted by way of metabolism of a precursor compound (a prodrug).

Methods of Preparing the Compounds

[095] In some aspects, the present disclosure features a method of preparing a compound described herein.

[096] The compound disclosed herein can be prepared by any suitable technique known in the art. Particular processes for the preparation of these compounds are described further in the accompanying examples.

Pharmaceutical Compositions

[097] In some aspects, the present disclosure features pharmaceutical compositions comprising a compound disclosed herein, and one or more pharmaceutically acceptable carriers or excipients.

[098] The pharmaceutical compositions containing active compounds of the present disclosure may be manufactured in a manner that is generally known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of the active compounds into preparations that can be used

pharmaceutically. Of course, the appropriate formulation is dependent upon the route of administration chosen.

[0099] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol and sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0100] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0101] Oral compositions generally include an inert diluent or an edible pharmaceutically acceptable carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible

binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0102] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser, which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

[0103] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[0104] The active compounds can be prepared with pharmaceutically acceptable carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art.

[0105] It may be especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the disclosure are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved.

[0106] In therapeutic applications, the dosages of the pharmaceutical compositions used in accordance with the disclosure vary depending on the agent, the age, weight, and clinical condition of the recipient patient, and the experience and judgment of the clinician or practitioner administering the therapy, among other factors affecting the selected dosage. Generally, the

dose should be sufficient to result in slowing, and preferably regressing, the symptoms of the disease and also preferably causing complete regression of the disease.

[0107] It is understood that the pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

Methods of Use

[0108] In some aspects, the present disclosure provides a method of inhibiting an oncogenic variant of an ErbB receptor, comprising administering to the subject in need thereof a compound disclosed herein (e.g., in a therapeutically effective amount).

[0109] In some aspects, the present disclosure provides a method of preventing or treating cancer, comprising administering to the subject in need thereof a compound disclosed herein (e.g., in a therapeutically effective amount).

[0110] In some aspects, the present disclosure provides a method of treating cancer, comprising administering to the subject in need thereof a compound disclosed herein (e.g., in a therapeutically effective amount).

[0111] In some aspects, the present disclosure provides a compound disclosed herein for use in the inhibition of an oncogenic variant of an ErbB receptor.

[0112] In some aspects, the present disclosure provides a compound disclosed herein for use in the prevention or treatment of cancer.

[0113] In some aspects, the present disclosure provides a compound disclosed herein for use in the treatment of cancer.

[0114] In some aspects, the present disclosure provides use of a compound disclosed herein in the manufacture of a medicament for inhibiting an oncogenic variant of an ErbB receptor.

[0115] In some aspects, the present disclosure provides use of a compound disclosed herein in the manufacture of a medicament for preventing or treating cancer.

[0116] In some aspects, the present disclosure provides use of a compound disclosed herein in the manufacture of a medicament for treating cancer.

Suitable Subjects and Diseases

[0117] In some embodiments, the subject is a mammal.

[0118] In some embodiments, the subject is a human.

[0119] In some embodiments, the subject is a mouse.

[0120] In some embodiments, cancer is a solid tumor.

[0121] In some embodiments, the cancer is a bladder cancer, a breast cancer, a cervical cancer, a colorectal cancer, an endometrial cancer, a gastric cancer, a glioblastoma (GBM), a head and neck cancer, a lung cancer, a non-small cell lung cancer (NSCLC), or any subtype thereof.

[0122] In some embodiments, the cancer is glioblastoma (GBM) or any subtype thereof. In some embodiments, the cancer is glioblastoma.

[0123] In some embodiments, the cancer is glioblastoma and the cancer is characterized by overexpression of EGFR.

[0124] In some embodiments, the cancer is methylated glioblastoma. In some embodiments, the cancer is unmethylated glioblastoma.

[0125] In some embodiments, the cancer is recurrent glioblastoma.

[0126] In some embodiments, the cancer is relapsed glioblastoma.

[0127] In some embodiments, the cancer is glioblastoma and the cancer, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR.

[0128] In some embodiments, the cancer is relapsed glioblastoma and the cancer, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR.

[0129] In some embodiments, the cancer is recurrent glioblastoma and the cancer, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR.

[0130] In some embodiments, the cancer is non-small cell lung cancer (NSCLC) or any subtype thereof.

[0131] In some embodiments, the cancer is non-small cell lung cancer (NSCLC).

[0132] In some embodiments, the cancer is recurrent non-small cell lung cancer (NSCLC).

[0133] In some embodiments, the cancer is relapsed non-small cell lung cancer (NSCLC).

[0134] In some embodiments, the cancer is NSCLC and the cancer, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR.

[0135] In some embodiments, the cancer is recurrent NSCLC and the cancer, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR.

[0136] In some embodiments, the cancer is relapsed NSCLC and the cancer, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR.

[0137] In some embodiments, the cancer is advanced or metastatic NSCLC .

[0138] In some embodiments, the cancer is advanced or metastatic NSCLC and the cancer, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR.

[0139] In some embodiments, the cancer is NSCLC, wherein the cancer has metastasized to the central nervous system (CNS).

[0140] In some embodiments, the cancer is advanced or metastatic NSCLC, wherein the cancer, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR, and wherein the cancer has metastasized to the central nervous system (CNS).

[0141] In some embodiments, the cancer is advanced or metastatic NSCLC, wherein the cancer, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR, and wherein the cancer has not metastasized to the central nervous system (CNS).

[0142] In some embodiments, the cancer is NSCLC, wherein the cancer has not metastasized to cerebrospinal fluid (CSF).

[0143] In some embodiments, the cancer is NSCLC, wherein the cancer has metastasized to cerebrospinal fluid (CSF).

[0144] In some embodiments, the cancer is glioblastoma, wherein the cancer has not metastasized to cerebrospinal fluid (CSF).

[0145] In some embodiments, the cancer is glioblastoma, wherein the cancer has metastasized to cerebrospinal fluid (CSF).

[0146] In some embodiments, the cancer is NSCLC, wherein the cancer has not metastasized to the brain.

[0147] In some embodiments, the cancer is NSCLC, wherein the cancer has metastasized to the brain.

[0148] In some embodiments, the subject has a central nervous system (CNS) disease.

[0149] In some embodiments, the subject does not have any CNS disease.

[0150] In some embodiments, the subject has a leptomeningeal disease.

[0151] In some embodiments, the subject does not have any leptomeningeal disease.

[0152] In some embodiments, the cancer is NSCLC and the subject has leptomeningeal disease.

[0153] In some embodiments, the cancer is glioblastoma and the subject has leptomeningeal disease.

[0154] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of an ErbB receptor.

[0155] It is understood that an oncogenic variant of an ErbB receptor is an ErbB receptor protein that comprises at least one oncogenic mutation and that is produced as the result of the expression of a gene encoding the ErbB receptor that comprises at least one oncogenic mutation.

[0156] As would be appreciated by the skilled artisan, in the context of a gene (*e.g.* a gene encoding an ErbB receptor), an oncogenic mutation can include, but is not limited to a mutation that results in the substitution of one amino acid for another at a specific position within an ErbB receptor, a mutation that results in an insertion of one or more amino acids between two positions

within an ErbB receptor, a mutation that results in the deletion of one more amino acids between two positions within an ErbB receptor, and mutation that results in a fusion of an ErbB receptor or portion thereof, with another protein, or portion thereof. As would be appreciated by the skilled artisan, in the context of a gene, an oncogenic mutation can include, but is not limited to, a missense mutation, a nonsynonymous mutation, an insertion of one or more nucleotides, a deletion of one or more nucleotides, an inversion and a deletion-insertion.

[0157] As would be appreciated by the skilled artisan, in the context of a protein (*e.g.* an ErbB receptor), an oncogenic mutation can include, but is not limited to, the substitution of one amino acid for another at a specific position within an ErbB receptor, an insertion of one or more amino acids between two positions within an ErbB receptor, a deletion of one more amino acids between two positions within an ErbB receptor, and a fusion of an ErbB receptor, or portion thereof, with another protein, or portion thereof.

[0158] In some embodiments, the oncogenic variant of the ErbB receptor comprises an allosteric mutation.

[0159] In some embodiments, the oncogenic variant of an ErbB receptor is an allosteric variant of the ErbB receptor.

[0160] In some embodiments, the ErbB receptor is an epidermal growth factor receptor (EGFR) or a human epidermal growth factor receptor 2 (HER2) receptor.

[0161] In some embodiments, the ErbB receptor is an epidermal growth factor receptor (EGFR).

[0162] In some embodiments, the ErbB receptor is a HER2 receptor.

[0163] In some embodiments, the ErbB receptor is a HER3 receptor.

[0164] In some embodiments, the ErbB receptor is a HER4 receptor.

[0165] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of an epidermal growth factor receptor (EGFR).

[0166] In some embodiments, the oncogenic variant of EGFR is an allosteric variant of EGFR.

[0167] In some embodiments, the oncogenic variant of EGFR comprises an allosteric mutation.

[0168] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of a HER2 receptor.

[0169] In some embodiments, the oncogenic variant of the HER2 receptor is an allosteric variant of the HER2 receptor.

[0170] In some embodiments, the oncogenic variant of the HER2 receptor comprises an allosteric mutation.

[0171] In some embodiments, the oncogenic variant of an EGFR comprises an EGFR variant III (EGFR-Viii) mutation.

[0172] In some embodiments, the oncogenic variant of EGFR comprises an EGFR variant II (EGFR-Vii) mutation.

[0173] In some embodiments, the oncogenic variant of EGFR comprises an EGFR variant VI (EGFR-Vvi) mutation.

Definitions

[0174] Unless explicitly indicated otherwise, the terms “approximately” and “about” are synonymous. In some embodiments, “approximately” and “about” refer to the recited amount, value, dose, or duration $\pm 20\%$, $\pm 15\%$, $\pm 10\%$, $\pm 8\%$, $\pm 6\%$, $\pm 5\%$, $\pm 4\%$, $\pm 2\%$, $\pm 1\%$, or $\pm 0.5\%$. In some embodiments, “approximately” and “about” refer to the listed amount or duration $\pm 10\%$, $\pm 8\%$, $\pm 6\%$, $\pm 5\%$, $\pm 4\%$, or $\pm 2\%$. In some embodiments, “approximately” and “about” refer to the listed amount, value, dose, or duration $\pm 5\%$. In some embodiments, “approximately” and “about” refer to the listed amount, value, dose, or duration $\pm 2\%$. In some embodiments, “approximately” and “about” refer to the listed amount, value, dose, or duration $\pm 1\%$.

[0175] As used herein, the expressions “one or more of A, B, or C,” “one or more A, B, or C,” “one or more of A, B, and C,” “one or more A, B, and C,” “selected from the group consisting of A, B, and C,” “selected from A, B, and C”, and the like are used interchangeably and all refer to a selection from a group consisting of A, B, and/or C, i.e., one or more As, one or more Bs, one or more Cs, or any combination thereof, unless indicated otherwise.

[0176] It is understood that, throughout the description, where compositions are described as having, including, or comprising specific components, it is contemplated that compositions also consist essentially of, or consist of, the recited components. Similarly, where methods or processes are described as having, including, or comprising specific process steps, the processes also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions is immaterial so long as the invention remains operable. Moreover, two or more steps or actions can be conducted simultaneously.

[0177] It is understood that compounds of the present disclosure can be prepared in a variety of ways using commercially available starting materials, compounds known in the literature, or from readily prepared intermediates, by employing standard synthetic methods and procedures either known to those skilled in the art, or which will be apparent to the skilled artisan in light of the teachings herein. Standard synthetic methods and procedures for the preparation of

organic molecules and functional group transformations and manipulations can be obtained from the relevant scientific literature or from standard textbooks in the field. Although not limited to any one or several sources, classic texts such as Smith, M. B., March, J., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th edition, John Wiley & Sons: New York, 2001; Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons: New York, 1999; R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), incorporated by reference herein, are useful and recognized reference textbooks of organic synthesis known to those in the art.

[0178] It is to be understood that, unless otherwise stated, any description of a method of treatment or prevention includes use of a compound disclosed herein to provide such treatment or prevention as is described herein. It is to be further understood, unless otherwise stated, any description of a method of treatment or prevention includes use of a compound disclosed herein to prepare a medicament to treat or prevent such condition. The treatment or prevention includes treatment or prevention of human or non-human animals including rodents and other disease models.

[0179] It is to be understood that, unless otherwise stated, any description of a method of treatment includes use of a compound disclosed herein to provide such treatment as is described herein. It is to be further understood, unless otherwise stated, any description of a method of treatment includes use of a compound disclosed herein to prepare a medicament to treat such condition. The treatment includes treatment of human or non-human animals including rodents and other disease models.

[0180] As used herein, the term "subject" refers to a subject having a disease or having an increased risk of developing the disease. A "subject" includes a mammal. The mammal can be *e.g.*, a human or appropriate non-human mammal, such as primate, mouse, rat, dog, cat, cow, horse, goat, camel, sheep or a pig. The subject can also be a bird or fowl. In one embodiment, the mammal is a human.

[0181] In some embodiments, the term "subject in need thereof" can be one who has been previously diagnosed or identified as having a disease or disorder disclosed herein. A subject in need thereof can also be one who is suffering from a disease or disorder disclosed herein. Alternatively, a subject in need thereof can be one who has an increased risk of developing such disease or disorder relative to the population at large (*i.e.*, a subject who is predisposed to developing such disorder relative to the population at large). A subject in need thereof can have

a refractory or resistant a disease or disorder disclosed herein (i.e., a disease or disorder disclosed herein that does not respond or has not yet responded to treatment). The subject in need thereof may be resistant at start of treatment or may become resistant during treatment. In some embodiments, the subject in need thereof received and failed all known effective therapies for a disease or disorder disclosed herein. In some embodiments, the subject in need thereof received at least one prior therapy.

[0182] As used herein, the term “treating” or “treat” describes the management and care of a patient for the purpose of combating a disease, condition, or disorder and includes the administration of a compound of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof, to alleviate the symptoms or complications of a disease, condition or disorder, or to eliminate the disease, condition or disorder. The term “treat” can also include treatment of a cell *in vitro* or an animal model.

[0183] It is to be understood that a compound disclosed herein can or may also be used to prevent a relevant disease, condition or disorder, or used to identify suitable candidates for such purposes.

[0184] As used herein, the term “preventing,” “prevent,” or “protecting against” describes reducing or eliminating the onset of the symptoms or complications of such disease, condition or disorder.

[0185] As used herein, “stable” refers to a polymorph that maintains purity, appearance, and/or analytical parameters over a defined time and temperature as compared to the polymorph as isolated. In some embodiments, the “stable” polymorph exhibits less than about 10%, about 9%, about 8%, about 7%, about 6%, about 5%, about 4%, about 3%, about 2%, about 1%, about 0.9%, about 0.8%, about 0.7%, about 0.6%, about 0.5%, about 0.4%, about 0.3%, about 0.2%, or about 0.1% impurity over a set period of time (e.g., 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, one week, two weeks, three weeks, one month, two months, three months, or four months).

[0186] As used herein, the term “pharmaceutical composition” is a formulation containing the compounds of the present disclosure in a form suitable for administration to a subject. In one embodiment, the pharmaceutical composition is in bulk or in unit dosage form. The unit dosage form is any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single pump on an aerosol inhaler or a vial. The quantity of active ingredient (e.g., a formulation of the disclosed compound or salt, hydrate, solvate or isomer thereof) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of

administration. A variety of routes are contemplated, including oral, pulmonary, rectal, parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, inhalational, buccal, sublingual, intrapleural, intrathecal, intranasal, and the like. Dosage forms for the topical or transdermal administration of a compound of this disclosure include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. In one embodiment, the active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that are required.

[0187] As used herein, the term “pharmaceutically acceptable” refers to those compounds, anions, cations, materials, compositions, carriers, 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.

[0188] As used herein, the term “pharmaceutically acceptable excipient” means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A “pharmaceutically acceptable excipient” as used in the specification and claims includes both one and more than one such excipient.

[0189] As used herein, the term “therapeutically effective amount”, refers to an amount of a pharmaceutical agent to treat, ameliorate, or prevent an identified disease or condition, or to exhibit a detectable therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician.

[0190] It is understood that, for the compounds of the present disclosure being capable of further forming salts, all of these forms are also contemplated within the scope of the claimed disclosure.

[0191] As used herein, the term “pharmaceutically acceptable salts” refer to derivatives of the compounds of the present disclosure wherein the parent compound is modified by making acid or base salts thereof. In some embodiments, the pharmaceutically acceptable salt of a compound is also a prodrug of the compound. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent

compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, 1,2-ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, toluene sulfonic, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, etc.

[0192] Other examples of pharmaceutically acceptable salts include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present disclosure also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. In the salt form, it is understood that the ratio of the compound to the cation or anion of the salt can be 1:1, or any ration other than 1:1, *e.g.*, 3:1, 2:1, 1:2, or 1:3.

[0193] It is understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same salt.

[0194] The compounds, or pharmaceutically acceptable salts thereof, are administered orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperitoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally and parenterally. In one embodiment, the compound is administered orally. One skilled in the art will recognize the advantages of certain routes of administration.

[0195] The dosage regimen utilizing the compounds is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to

prevent, counter, or arrest the progress of the condition.

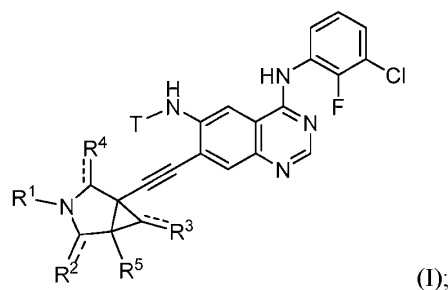
[0196] Techniques for formulation and administration of the disclosed compounds of the disclosure can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995). In an embodiment, the compounds described herein, and the pharmaceutically acceptable salts thereof, are used in pharmaceutical preparations in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The compounds will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein.

[0197] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present disclosure are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present disclosure. The examples do not limit the claimed disclosure. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present disclosure.

All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. Citation of publications and patent documents is not intended as an admission that any is pertinent prior art, nor does it constitute any admission as to the contents or date of the same. The invention having now been described by way of written description, those of skill in the art will recognize that the invention can be practiced in a variety of embodiments and that the foregoing description and examples below are for purposes of illustration and not limitation of the claims that follow.

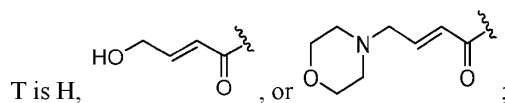
EXEMPLARY EMBODIMENTS

[0198] **Exemplary Embodiment No. 1.** A compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

each $\equiv$ independently denotes a single bond or a double bond, as valency permits:



R¹ is H or C₁-C₆ alkyl;

R² is H, -OH, or oxo;

R³ is H, -OH, or oxo;

R⁴ is H, -OH, or oxo; and

R⁵ is H or -OH;

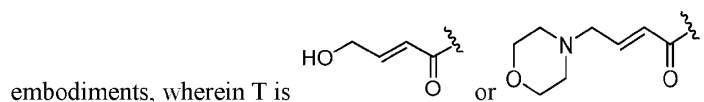
provided that the compound is not Compound A or a pharmaceutically acceptable salt thereof.

[0199] **Exemplary Embodiment No. 2.** The compound of Exemplary Embodiment No. 1, wherein the compound is an isolated compound.

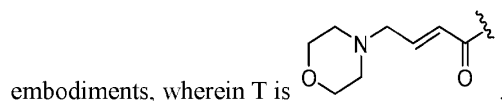
[0200] **Exemplary Embodiment No. 3.** The compound of any one of the preceding embodiments, wherein the compound has a purity of about 80% or higher, about 85% or higher, about 90% or higher, about 91% or higher, about 92% or higher, about 93% or higher, about 94% or higher, about 95% or higher, about 96% or higher, about 97% or higher, about 98% or higher, about 99% or higher, about 99.1% or higher, about 99.2% or higher, about 99.3% or higher, about 99.4% or higher, about 99.5% or higher, about 99.6% or higher, about 99.7% or higher, about 99.8% or higher, or about 99.9% or higher.

[0201] **Exemplary Embodiment No. 4.** The compound of any one of the preceding embodiments, wherein T is H.

[0202] **Exemplary Embodiment No. 5.** The compound of any one of the preceding



[0203] **Exemplary Embodiment No. 6.** The compound of any one of the preceding



[0204] **Exemplary Embodiment No. 7.** The compound of any one of the preceding embodiments, wherein R¹ is H.

[0205] **Exemplary Embodiment No. 8.** The compound of any one of the preceding embodiments, wherein R¹ is methyl.

[0206] **Exemplary Embodiment No. 9.** The compound of any one of the preceding embodiments, wherein R² is H.

- [0207] **Exemplary Embodiment No. 10.** The compound of any one of the preceding embodiments, wherein R^2 is -OH.
- [0208] **Exemplary Embodiment No. 11.** The compound of any one of the preceding embodiments, wherein R^2 is oxo.
- [0209] **Exemplary Embodiment No. 12.** The compound of any one of the preceding embodiments, wherein R^3 is H.
- [0210] **Exemplary Embodiment No. 13.** The compound of any one of the preceding embodiments, wherein R^3 is -OH.
- [0211] **Exemplary Embodiment No. 14.** The compound of any one of the preceding embodiments, wherein R^3 is oxo.
- [0212] **Exemplary Embodiment No. 15.** The compound of any one of the preceding embodiments, wherein R^4 is H.
- [0213] **Exemplary Embodiment No. 16.** The compound of any one of the preceding embodiments, wherein R^4 is -OH.
- [0214] **Exemplary Embodiment No. 17.** The compound of any one of the preceding embodiments, wherein R^4 is oxo.
- [0215] **Exemplary Embodiment No. 18.** The compound of any one of the preceding embodiments, wherein R^5 is H.
- [0216] **Exemplary Embodiment No. 19.** The compound of any one of the preceding embodiments, wherein R^5 is -OH.
- [0217] **Exemplary Embodiment No. 20.** The compound of any one of the preceding embodiments, wherein the compound is of Formula (I-a) or (I-b) or a pharmaceutically acceptable salt thereof.
- [0218] **Exemplary Embodiment No. 21.** The compound of any one of the preceding embodiments, wherein the compound is of Formula (II-a), (II-b), (II-c), (II-d), (II-e), or (II-f), or a pharmaceutically acceptable salt thereof.
- [0219] **Exemplary Embodiment No. 22.** The compound of any one of the preceding embodiments, wherein the compound is of Formula (III) or a pharmaceutically acceptable salt thereof.
- [0220] **Exemplary Embodiment No. 23.** The compound of any one of the preceding embodiments, wherein the compound is of Formula (III-a) or (III-b) or a pharmaceutically acceptable salt thereof.

[0221] **Exemplary Embodiment No. 24.** The compound of any one of the preceding embodiments, wherein the compound is selected from the compounds described in Table I, and pharmaceutically acceptable salts thereof.

[0222] **Exemplary Embodiment No. 25.** An isotopic derivative of the compound of any one of the preceding embodiments.

[0223] **Exemplary Embodiment No. 26.** The isotopic derivative of Exemplary Embodiment No. 25, being selected from the compounds described in Table D-I, and pharmaceutically acceptable salts thereof.

[0224] **Exemplary Embodiment No. 27.** A pharmaceutical composition comprising the compound of any one of the preceding embodiments, and one or more pharmaceutically acceptable carriers or excipients.

[0225] **Exemplary Embodiment No. 28.** A method of inhibiting an oncogenic variant of an ErbB receptor, comprising administering to the subject in need thereof the compound of any one of the preceding embodiments.

[0226] **Exemplary Embodiment No. 29.** A method of preventing or treating cancer, comprising administering to the subject in need thereof the compound of any one of the preceding embodiments.

[0227] **Exemplary Embodiment No. 30.** The compound of any one of the preceding embodiments for use in the inhibition of an oncogenic variant of an ErbB receptor.

[0228] **Exemplary Embodiment No. 31.** The compound of any one of the preceding embodiments for use in the prevention or treatment of cancer.

[0229] **Exemplary Embodiment No. 32.** Use of the compound of any one of the preceding embodiments in the manufacture of a medicament for inhibiting an oncogenic variant of an ErbB receptor.

[0230] **Exemplary Embodiment No. 33.** Use of the compound of any one of the preceding embodiments in the manufacture of a medicament for preventing or treating cancer.

[0231] **Exemplary Embodiment No. 34.** The method, compound, or use of any one of the preceding embodiments, wherein the subject is a human.

[0232] **Exemplary Embodiment No. 35.** The method, compound, or use of any one of the preceding embodiments, wherein the cancer is a solid tumor.

[0233] **Exemplary Embodiment No. 36.** The method, compound, or use of any one of the preceding embodiments, wherein cancer is a bladder cancer, a breast cancer, a cervical cancer, a colorectal cancer, an endometrial cancer, a gastric cancer, a glioblastoma (GBM), a head and neck cancer, a lung cancer, a non-small cell lung cancer (NSCLC), or any subtype thereof.

EXAMPLES

[0234] It is understood that the experimental values described in the present application are approximate and subject to instrumental variations.

Example 1. Metabolic Profile of Compound A

[0235] The *in vivo* metabolism of Compound A was investigated by analyzing rat, dog, and human plasma samples. The samples analyzed and compared were from subjects following administration of Compound A.

[0236] Plasma samples from each subject were pooled. An aliquot of the pooled sample was extracted with three volumes of Methanol/ACN, vortexed and centrifuged for 5 min at 13,000 rpm. The supernatant was transferred to a 96 well plate and partially dried under nitrogen for analysis.

[0237] **UPLC Conditions:** A Waters AQUITY I-class UPLC system consisting of a binary solvent manager and a sample manager was operated under the following conditions:

- Solvent A: 0.1% formic acid in water
- Solvent B: 0.1% formic acid in ACN
- Seal Wash: 50% MeOH
- Column: Phenomenex Biphenyl, 2.6 μ m, 2.1 x 100 mm
- Column Temperature: 40°C
- Strong Wash: 85:15 ACN:Isopropanol
- Weak Wash: Water
- Injection Volume: 2-5 μ L
- Gradient:

Time (min)	Flow (mL/min)	%A	%B
0.0	0.4	95	95
0.1	0.2	95	95
2.0	0.4	95	95
18.0	0.4	85	15
26.0	0.4	30	70
26.3	0.6	5	95
28.5	0.6	5	95
28.6	0.4	95	5
30.0	0.4	95	5

[0238] **HRMS Conditions:** A Waters Xevo G2-XS QToF high resolution mass spectrometer was operated under the following conditions:

- Ionization Mode: Positive
- Capillary Voltage: 1.2 KV
- Sampling Conc: 25 V
- Desolvation Temp: 500 °C
- Source Offset: 80 V
- Source Temp: 115 °C
- Cone Gas: 5 L/hr
- Desolvation Gas: 500 L/hr
- MS Mass Range: 180 to 850 amu
- MS/MS Mass Range: 50 to 850 amu
- Lockspray Solution: 0.2 µg/mL Leucine Enkephalin in 50/50 ACN/H₂O
- Lock Mass Used: 556.2771 and m/z 278.1139
- Mass Resolution: >20,000 (FWHM) at m/z 500
- Collision Energy: Energy Ramp from 20 to 40 V applied
- Calibration Residual Error: < 2 mDa

[0239] **PDA Conditions:** A Waters ACQUITY PDA was operated under the following conditions:

- Sampling Rate: 5 points/second
- Filter Time Constant: 0.8000 second
- Range: 210-400 (nm)
- Resolution: 1.2 (nm)
- Processing Wavelength: 270-290 (nm)

[0240] **Processing of LC/HRMS Data:** The UPLC-MS full scan data was processed using manual and automated methods to identify both expected and unanticipated metabolites. A separate UPLC/HRMS/MS acquisition was conducted based on this metabolite list, to generate product ion spectra for each metabolite. The metabolite structures were proposed by comparison of the metabolite high-resolution product ion spectra with the high-resolution product ions spectrum of Compound A.

[0241] **Observations:** Nine metabolites were identified in human plasma. Table A summarizing the metabolites observed.

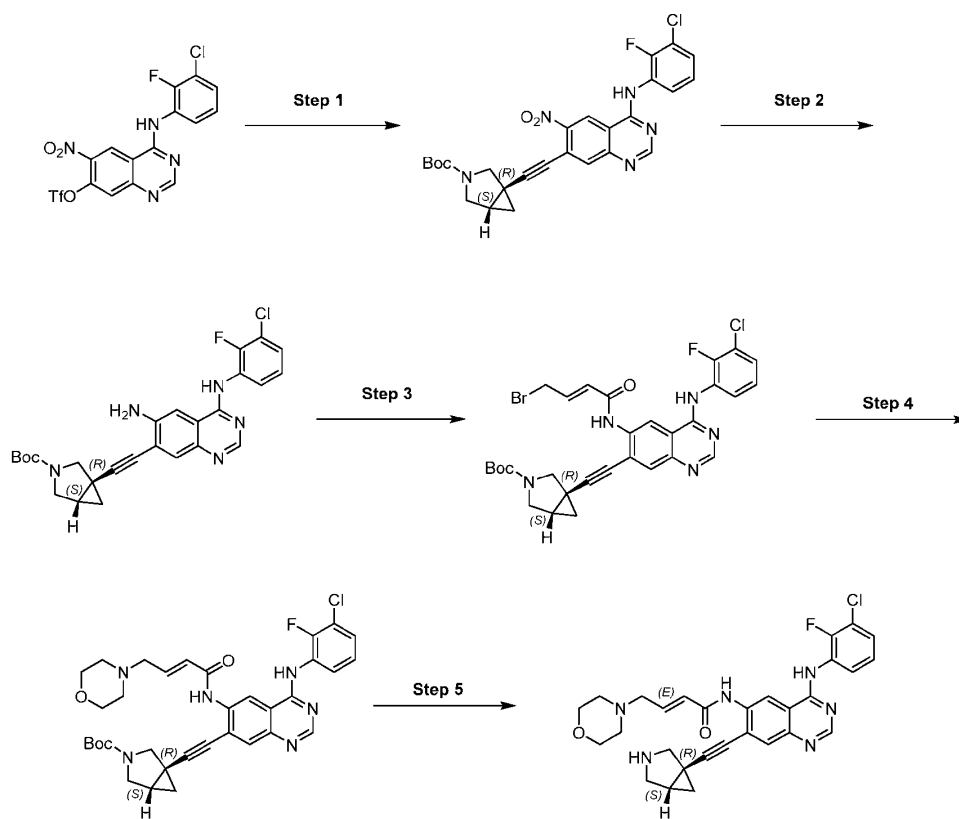
Table A

Compound No.	Mass (m/z)	Human	Rat	Dog
A	561	6.45%	17.4%	14.1%

1	547	2.35%	19.1%	29.1%
2	561	3.99%	-	22.3%
3	575	81.1%	-	18.9%
4	492	3.16%	56.1%	4.66%
5	394	0.04%	3.79%	4.09%
6	577	0.12%	-	1.84%
7	589	0.43%	-	1.11%
8	591	0.25%	-	0.98%
9	591	2.07%	3.62%	2.91%

Example 2. Synthesis of Exemplary Compounds

[0242] **Preparation of (E)-N-(7-(((1R,5S)-3-azabicyclo[3.1.0]hexan-1-yl)ethynyl)-4-((3-chloro-2-fluorophenyl)amino)quinazolin-6-yl)-4-morpholinobut-2-enamide (Compound No. 1):**



[0243] **Step 1.** Synthesis of *tert*-butyl (1R,5S)-1-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate. To a solution of [4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl] trifluoromethanesulfonate (28 g, 60 mmol) and

tert-butyl (*1R,5S*)-1-ethynyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (13.7 g, 66 mmol) in *N,N*-dimethylformamide (260 mL) was added palladium triphenylphosphane (6.93 g, 6.00 mmol), triethylamine (18.2 g, 180 mmol, 25 mL) and copper iodide (2.28 g, 12.0 mmol). The mixture was stirred at 25 °C for 4 hr under nitrogen atmosphere. The reaction mixture was diluted with water (400 mL) and extracted with ethyl acetate (400 mL x 3). The combined organic layers were washed with brine (1000 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate=100/1 to 1/5) to give *tert*-butyl (*1R,5S*)-1-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (30 g, 57.3 mmol, 95%) as a brown solid. *m/z* ES+ [M+H]⁺ 524.3.

[0244] **Step 2.** Synthesis of *tert*-butyl (*1R,5S*)-1-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate. To a solution of *tert*-butyl (*1R,5S*)-1-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (30 g, 57.3 mmol) in methanol (370 mL) and water (74 mL) was added iron powder (15.2 g, 272 mmol) and ammonium chloride (28.1 g, 525 mmol). The mixture was stirred at 80 °C for 1 hr. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl (*1R,5S*)-1-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (28 g, 56.7 mmol, 99%) as a yellow solid. *m/z* ES+ [M+H]⁺ 494.2.

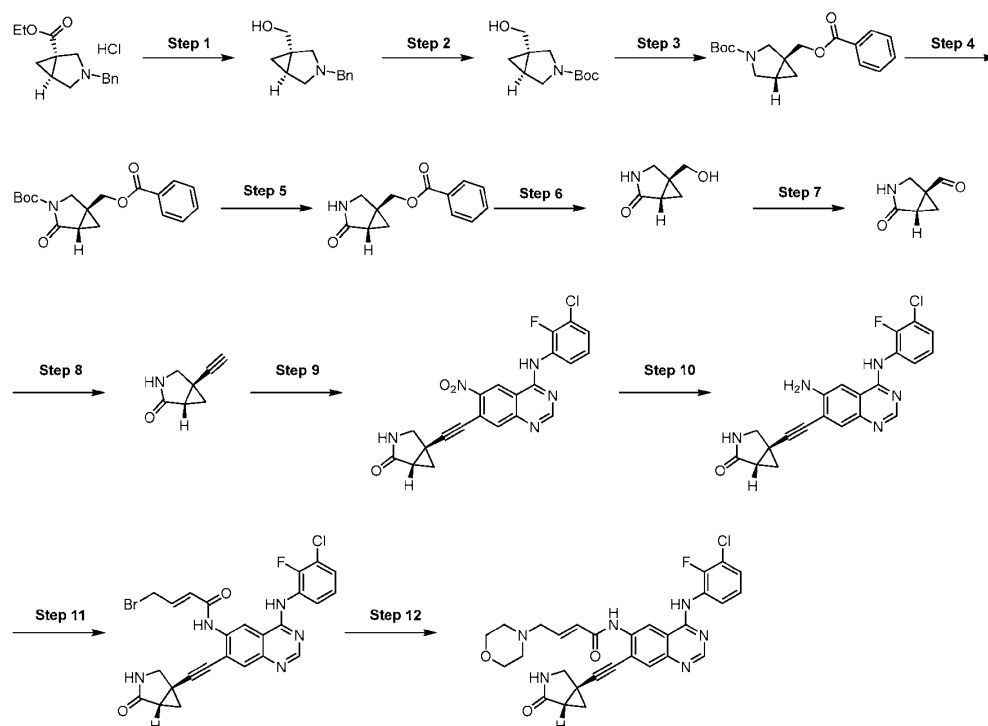
[0245] **Step 3.** Synthesis of *tert*-butyl (*1R,5S*)-1-[2-[6-[[*E*]-4-bromobut-2-enoyl]amino]-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate. A solution of *tert*-butyl (*1R,5S*)-1-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (10 g, 20.2 mmol) and (*E*)-4-bromobut-2-enoic acid (5.01 g, 30.4 mmol) in *N,N*-dimethylformamide (50 mL) and anhydrous tetrahydrofuran (50 mL) was degassed and purged with nitrogen for 3 times, then added diisopropylethylamine (10.5 g, 81.0 mmol, 14 mL) and 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (25.8 g, 40.5 mmol, 24 mL, 50% purity) slowly at 0 °C and then the mixture was stirred at 25 °C for 2 hr under nitrogen atmosphere. The reaction mixture was diluted with water (800 mL) and extracted with ethyl acetate (800 mL x 3). The combined organic layers were washed with brine (500 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give *tert*-butyl (*1R,5S*)-1-[2-[6-[[*E*]-4-bromobut-2-enoyl]amino]-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-

azabicyclo[3.1.0]hexane-3-carboxylate (10 g, 15.6 mmol, 77%) as a brown solid. m/z ES+ $[M+H]^+$ 642.3.

[0246] **Step 4.** Synthesis of *tert*-butyl (*1R,5S*)-1-[2-[4-(3-chloro-2-fluoro-anilino)-6-[[*(E)*]-4-morpholinobut-2-enoyl]amino]quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate. To a solution of *tert*-butyl (*1R,5S*)-1-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitroquinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (30 g, 57.3 mmol) in methanol (370 mL) and water (74 mL) was added iron powder (15.2 g, 272 mmol) and ammonium chloride (28.1 g, 525 mmol). The mixture was stirred at 80 °C for 1 hr. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl (*1R,5S*)-1-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (28 g, 56.7 mmol, 99%) as a yellow solid. m/z ES+ $[M+H]^+$ 494.2.

[0247] **Step 5.** Synthesis of (*E*)-*N*-[7-[2-[(*1R,5S*)-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]-4-(3-chloro-2-fluoro-anilino)quinazolin-6-yl]-4-morpholino-but-2-enamide. To a solution of *tert*-butyl (*1R,5S*)-1-[2-[4-(3-chloro-2-fluoro-anilino)-6-[[*(E)*]-4-morpholinobut-2-enoyl]amino]quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (17 g, 26.3 mmol) in dichloromethane (170 mL) was added trifluoroacetic acid (47.6 g, 417 mmol). The mixture was stirred at 25 °C for 0.5 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC(column: Kromasil Eternity XT 250x80mmx10um; mobile phase: [water(ammonium hydroxide)-acetonitrile]; gradient: 25%-55% B over 20 min) to give (*E*)-*N*-[7-[2-[(*1R,5S*)-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]-4-(3-chloro-2-fluoro-anilino)quinazolin-6-yl]-4-morpholino-but-2-enamide (10.0 g, 18.0 mmol, 69%) as a light yellow solid. 1H NMR (400 MHz, CD_3OD): δ 8.72 (s, 1H), 8.45 (br. s, 1H), 7.83 (s, 1H), 7.62 - 7.52 (m, 1H), 7.47 - 7.37 (m, 1H), 7.28 - 7.19 (m, 1H), 7.09 - 6.97 (m, 1H), 6.45 (d, J = 15.2 Hz, 1H), 3.79 - 3.72 (m, 4H), 3.30 - 3.26 (m, 2H), 3.24 - 3.17 (m, 1H), 3.07 - 2.98 (m, 3H), 2.61 - 2.52 (m, 4H), 2.04 - 1.98 (m, 1H), 1.25 - 1.16 (m, 1H), 1.10 - 1.04 (m, 1H); m/z ES+ $[M+H]^+$ 547.2.

[0248] **Preparation of (*E*)-*N*-(4-((3-Chloro-2-fluorophenyl)amino)-7-(((*1R,5S*)-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl)ethynyl)quinazolin-6-yl)-4-morpholinobut-2-enamide (Compound No. 2)**



[0249] **Step 1.** Synthesis of [(1*S*,5*S*)-3-benzyl-3-azabicyclo[3.1.0]hexan-1-yl]methanol. To a solution of ethyl [(1*S*,5*S*)-3-benzyl-3-azabicyclo[3.1.0]hexane-1-carboxylate (10.0 g, 40.8 mmol) in anhydrous tetrahydrofuran (60 mL) was added lithium aluminum hydride (2.5 M, 20 mL) at 25 °C under nitrogen atmosphere. The mixture was stirred at 25 °C for 2 hr under nitrogen atmosphere. On completion, the reaction mixture was quenched by sequentially adding water (2.5 mL), sodium hydroxide (15%, 2.5 mL), and water (8.5 mL) at 0 °C and warmed to 25 °C. Then anhydrous sodium sulfate (6.5 g) was added. The mixture was stirred at 25 °C for 0.5 hr, filtered and filtrate was concentrated under reduced pressure to give [(1*S*,5*S*)-3-benzyl-3-azabicyclo[3.1.0]hexan-1-yl]methanol (7.40 g, 35.7 mmol, 88%) as an off-yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 7.29 - 7.20 (m, 5H), 3.73 - 3.55 (m, 4H), 3.01 (d, *J* = 8.4 Hz, 1H), 2.93 (d, *J* = 8.4 Hz, 1H), 2.43 - 2.38 (m, 2H), 1.43 - 1.21 (m, 1H), 1.11 (t, *J* = 4.0 Hz, 1H), 0.47 - 0.42 (m, 1H).

[0250] **Step 2.** Synthesis of *tert*-butyl [(1*S*,5*S*)-1-(hydroxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate. To a solution of palladium on carbon (1 g, 940 μmol, 10% purity) in methanol (74 mL) was added [(1*S*,5*S*)-3-benzyl-3-azabicyclo[3.1.0]hexan-1-yl]methanol (7.40 g, 36.4 mmol) and *tert*-butyl (2-methylpropan-2-yl)oxycarbonyl carbonate (9.53 g, 43.7 mmol) under

nitrogen atmosphere. The suspension was degassed and purged with molecular hydrogen 3 times. Then the mixture was stirred under hydrogen (50 Psi) at 35 °C for 12 hr. On completion, the mixture was filtered and filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate=10/1 to 1/1) to give *tert*-butyl (1*S*,5*S*)-1-(hydroxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (6.80 g, 30.3 mmol, 83%) as an off-yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 3.77 - 3.47 (m, 4H), 3.45 - 3.34 (m, 2H), 1.76 - 1.36 (m, 10H), 0.80 - 0.75 (m, 1H), 0.53 - 0.44 (m, 1H).

[0251] **Step 3.** Synthesis of *tert*-butyl (1*S*,5*S*)-1-(benzoyloxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate. To a solution of *tert*-butyl (1*S*,5*S*)-1-(hydroxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (6.30 g, 29.5 mmol), benzoic acid (3.61 g, 29.5 mmol) in dichloromethane (63 mL) was added 3-(ethyliminomethyleneamino)-*N,N*-dimethyl-propan-1-amine hydrochloride (8.49 g, 44.3 mmol) and 4-dimethylaminopyridine (5.41 g, 44.3 mmol). The mixture was stirred at 40 °C for 12 hr. On completion, the reaction mixture was diluted with water (50 mL) and extracted with dichloromethane (40 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate=1/0 to 3/1) to give *tert*-butyl (1*S*,5*S*)-1-(benzoyloxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (9.30 g, 26.7 mmol, 90%) as an off-white oil. ¹H NMR (400 MHz, CDCl₃): δ 8.05 (br. d, *J* = 7.2 Hz, 2H), 7.66 - 7.54 (m, 1H), 7.50 - 7.36 (m, 2H), 4.44 - 4.30 (m, 2H), 3.90 - 3.51 (m, 2H), 3.43 (br. s, 2H), 1.55 (br. s, 1H), 1.45 (s, 9H), 0.93 - 0.90 (m, 1H), 0.60 (br. s, 1H); *m/z* ES+ [M+H]⁺ 318.2.

[0252] **Step 4.** Synthesis of *tert*-butyl (1*S*,5*S*)-1-(benzoyloxymethyl)-4-oxo-3-azabicyclo[3.1.0]hexane-3-carboxylate. A solution of *tert*-butyl (1*S*,5*S*)-1-(benzoyloxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (9.90 g, 31.2 mmol) in ethyl acetate (315 mL) was treated with a solution of sodium periodate (26.7 g, 125 mmol) in water (315 mL) and trichlororuthenium (194 mg, 936 μmol). The mixture was stirred at 20 °C for 6 hr then treated with 2-propanol (315 mL) and stirred for 0.5 hr. On completion, the reaction mixture was quenched by added saturated sodium sulfite solution (500 mL), diluted with water (900 mL) and extracted with ethyl acetate (900 mL × 3). The combined organic layers were washed with brine (500 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate=6/1 to 2/1) to give *tert*-butyl (1*S*,5*S*)-1-(benzoyloxymethyl)-4-oxo-3-azabicyclo[3.1.0]hexane-3-carboxylate (6.20 g, 18.3 mmol, 59%) as a yellow oil. ¹H

NMR (400 MHz, CDCl₃): δ 8.04 (d, J = 7.2 Hz, 2H), 7.63 - 7.56 (m, 1H), 7.51 - 7.42 (m, 2H), 4.53 - 4.45 (m, 1H), 4.42 - 4.32 (m, 1H), 3.94 - 3.74 (m, 2H), 2.13 (dd, J = 3.2, 8.8 Hz, 1H), 1.51 (s, 9H), 1.42 (dd, J = 5.2, 9.2 Hz, 1H), 1.16 - 1.09 (m, 1H).

[0253] **Step 5.** Synthesis of [(*1S,5S*)-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]methyl benzoate. To a solution of *tert*-butyl (*1S,5S*)-1-(benzyloxymethyl)-4-oxo-3-azabicyclo[3.1.0]hexane-3-carboxylate (3.60 g, 10.9 mmol) in dichloromethane (43.2 mL) was added trifluoroacetic acid (16.6 g, 145 mmol). The mixture was stirred at 25 °C for 0.25 hr. On completion, the reaction mixture was concentrated under reduced pressure to the crude product [(*1S,5S*)-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]methyl benzoate (2.50 g, 10.3 mmol, 95%) as an off-yellow oil. m/z ES⁺ [M+H]⁺ 232.1.

[0254] **Step 6.** Synthesis of (*1S,5S*)-5-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-2-one. To a solution of [(*1S,5S*)-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]methyl benzoate (660 mg, 2.85 mmol) in anhydrous tetrahydrofuran (7.0 mL) was added sodium hydroxide (2 M, 3.6 mL). The mixture was stirred at 25 °C for 1 hr. On completion, the reaction mixture was concentrated under reduced pressure to give a residue. Added formic acid to adjust pH = 7, then added tetrahydrofuran (30 mL), filtered and filtrate was concentrated under reduced pressure to give a residue. The crude product was triturated with petroleum ether at 25 °C for 0.5 hr to give (*1S,5S*)-5-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-2-one (360 mg, 2.55 mmol, 89%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.97 - 7.90 (m, 1H), 7.64 - 7.56 (m, 1H), 7.52 - 7.45 (m, 1H), 3.54 (d, J = 11.6 Hz, 1H), 3.41 (d, J = 11.6 Hz, 1H), 3.32 (d, J = 10.4 Hz, 1H), 3.14 (d, J = 10.4 Hz, 1H), 1.50 (td, J = 1.6, 8.8 Hz, 1H), 1.07 (dd, J = 4.0, 8.8 Hz, 1H), 0.63 (t, J = 3.6 Hz, 1H).

[0255] **Step 7.** Synthesis of (*1S,5S*)-4-oxo-3-azabicyclo[3.1.0]hexane-1-carbaldehyde. To a solution of (*1S,5S*)-5-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-2-one (360 mg, 2.83 mmol) in dichloromethane (2.00 mL) and anhydrous tetrahydrofuran (8.00 mL) was added (1,1,1-triacetoxy)-1,1-dihydro-1,2-benziodoxol-3(1H)-one (1.80 g, 4.25 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 hr. On completion, the mixture was filtered and extracted with dichloromethane (10 mL x 3) and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate=3/1 to 0/1) to give (*1S,5S*)-4-oxo-3-azabicyclo[3.1.0]hexane-1-carbaldehyde (300 mg, 2.16 mmol, 76%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.91 (s, 1H), 7.55 - 7.39 (m, 1H), 3.75 (d, J = 10.8 Hz, 1H), 3.18 (d, J = 10.8 Hz, 1H), 2.48 - 2.42 (m, 1H), 1.98 (dd, J = 4.8, 9.2 Hz, 1H), 1.36 (t, J = 4.8 Hz, 1H).

[0256] **Step 8.** Synthesis of (*1S,5R*)-5-ethynyl-3-azabicyclo[3.1.0]hexan-2-one. To a solution of (*1S,5S*)-4-oxo-3-azabicyclo[3.1.0]hexane-1-carbaldehyde (375 mg, 3.00 mmol) and

potassium carbonate (1.24 g, 8.99 mmol) in methanol (4 mL) was added 1-diazo-1-dimethoxyphosphoryl-propan-2-one (518 mg, 2.70 mmol) dropwise at 10 °C ~ 20 °C. The mixture was stirred at 25 °C for 12 hr. On completion, the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (15 mL × 5). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate = 3/1 to 1/1) to give (*1S,5R*)-5-ethynyl-3-azabicyclo[3.1.0]hexan-2-one (252 mg, 1.87 mmol, 62%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 6.09 (br. s, 1H), 3.61 - 3.55 (m, 1H), 3.54 - 3.50 (m, 1H), 2.17 - 2.13 (m, 1H), 2.13 (s, 1H), 1.55 (dd, *J* = 4.8, 8.8 Hz, 1H), 1.10 (t, *J* = 4.4 Hz, 1H).

[0257] **Step 9.** Synthesis of (*1S,5R*)-5-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexan-2-one. To a solution of [4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl] trifluoromethanesulfonate (880 mg, 1.89 mmol) and (*1S,5R*)-5-ethynyl-3-azabicyclo[3.1.0]hexan-2-one (251 mg, 2.07 mmol) in *N,N*-dimethylformamide (9 mL) was added palladium triphenylphosphane (218 mg, 189 μmol), triethylamine (572 mg, 5.66 mmol) and iodocopper (71.8 mg, 377 μmol). The mixture was stirred at 25 °C for 1.5 hr under nitrogen atmosphere. On completion, the reaction mixture was diluted with water (40 mL) and extracted with ethyl acetate (25 mL × 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate=3/1 to 0/1) to give (*1S,5R*)-5-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexan-2-one (700 mg, 1.60 mmol, 85%) as a yellow solid. *m/z* ES+ [M+H]⁺ 438.1.

[0258] **Step 10.** Synthesis of (*1S,5R*)-5-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexan-2-one. To a solution of (*1S,5R*)-5-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexan-2-one (700 mg, 1.60 mmol) in methanol (7 mL) and water (1.4 mL) was added iron (424 mg, 7.59 mmol) and ammonium chloride (784 mg, 14.7 mmol). The mixture was stirred at 80 °C for 1 hr. On completion, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was dissolved with methylene chloride (100 mL), diluted with water (50 mL) and extracted with methylene chloride (100 mL × 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give (*1S,5R*)-5-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexan-2-one (580 mg, 1.38 mmol, 86%) as a yellow solid. ¹H

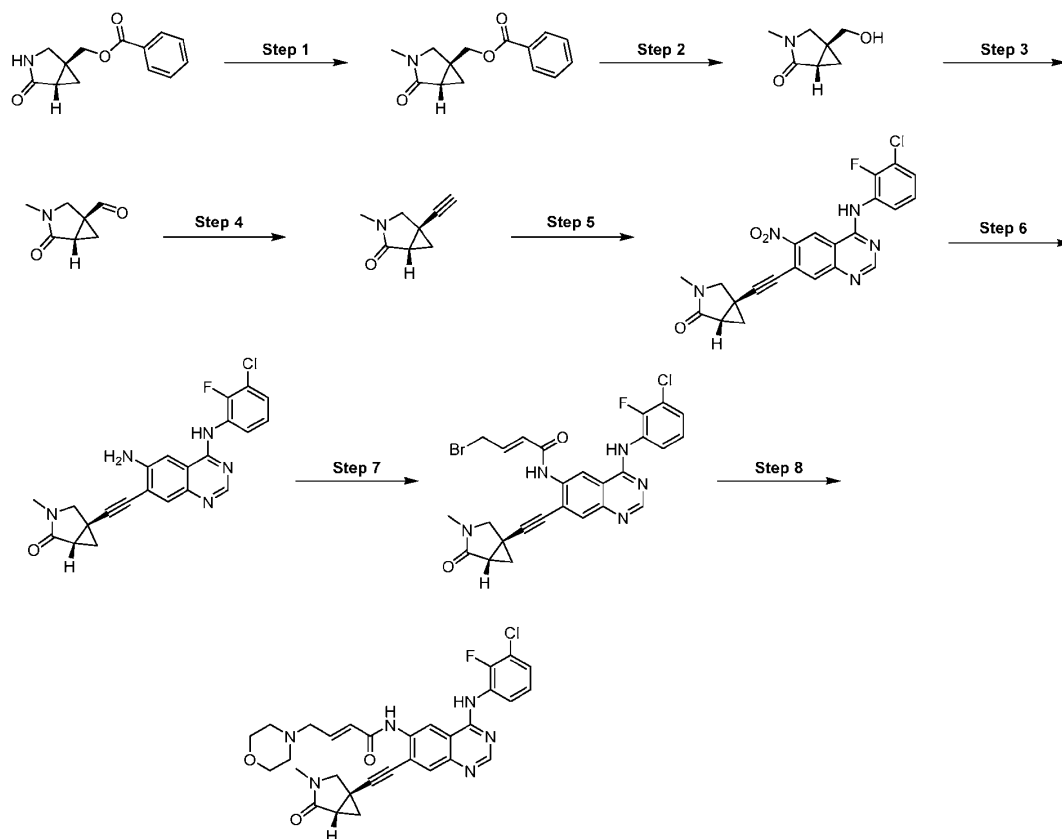
NMR (400 MHz, DMSO-*d*₆): δ 9.58 (s, 1H), 8.24 (s, 1H), 7.64 (s, 1H), 7.53 (br. t, *J* = 6.8 Hz, 1H), 7.48 - 7.42 (m, 2H), 7.38 (s, 1H), 7.25 (br. t, *J* = 8.0 Hz, 1H), 5.77 (br. s, 2H), 3.66 - 3.58 (m, 1H), 3.51 (br. d, *J* = 10.4 Hz, 1H), 2.31 (br. d, *J* = 5.2 Hz, 1H), 1.73 (br. dd, *J* = 4.0, 8.8 Hz, 1H), 1.16 - 1.11 (m, 1H); *m/z* ES+ [M+H]⁺ 408.2.

[0259] **Step 11.** Synthesis of (*E*)-4-bromo-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*1R,5S*)-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]but-2-enamide. To a solution of (*1S,5R*)-5-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexan-2-one (280 mg, 687 μ mol) and (*E*)-4-bromobut-2-enoic acid (170 mg, 1.03 mmol) in *N,N*-dimethylformamide (1.4 mL) and anhydrous tetrahydrofuran (1.4 mL) was added diisopropylethylamine (355 mg, 2.75 mmol) and 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (874 mg, 1.37 mmol) at 0 °C under nitrogen atmosphere. The mixture was stirred at 25 °C for 2 hr under nitrogen atmosphere. On completion, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (7 mL $\times$ 3). The combined organic layers were washed with brine (5 mL $\times$ 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give (*E*)-4-bromo-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*1R,5S*)-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]but-2-enamide (380 mg, crude) as a brown solid. *m/z* ES+ [M+H]⁺ 556.1.

[0260] **Step 12.** Synthesis of (*E*)-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*1R,5S*)-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]-4-morpholino-but-2-enamide. To a solution of (*E*)-4-bromo-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*1R,5S*)-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]but-2-enamide (380 mg, 685 μ mol) in diisopropylethylamine (0.5 mL) was added morpholine (239 mg, 2.74 mmol). The mixture was stirred at 25 °C for 12 hr. On completion, the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: YMC Triart C18 150*25mm*5 μ m; mobile phase: [water(hydrochloride)-acetonitrile]; gradient: 15%-45% B over 10 min). Then purified by prep-HPLC (column: Waters Xbridge 150*25mm*5 μ m; mobile phase: [water (ammonia hydroxide v/v)-acetonitrile]; gradient: 24%-54% B over 10 min) to give (*E*)-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*1R,5S*)-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]-4-morpholino-but-2-enamide (85.6 mg, 153 μ mol, 22%) as a light yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 9.19 (s, 1H), 8.74 (s, 1H), 8.38 - 8.32 (m, 1H), 8.09 (s, 1H), 8.00 (s, 1H), 7.79 - 7.76 (m, 1H), 7.25 - 7.18 (m, 2H), 7.17 - 7.05 (m, 1H), 6.23 (d, *J* = 14.8 Hz, 1H), 5.30 (br. s, 1H), 3.82 - 3.72 (m, 6H), 3.30 (d, *J* = 5.2 Hz, 2H), 2.62 - 2.51 (m, 4H),

2.42 (br. dd, $J = 4.0, 8.8$ Hz, 1H), 1.81 (dd, $J = 4.8, 8.8$ Hz, 1H), 1.41 (t, $J = 4.4$ Hz, 1H); m/z ES⁺ [M+H]⁺ 561.2.

[0261] **Preparation of (*E*)-*N*-(4-((3-chloro-2-fluorophenyl)amino)-7-(((1*R*,5*S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl)ethynyl)quinazolin-6-yl)-4-morpholinobut-2-enamide (Compound No. 3).**



[0262] **Step 1.** Synthesis of [(1*S*,5*S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]methyl benzoate. To a solution of [(1*S*,5*S*)-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]methyl benzoate (600 mg, 2.59 mmol) in *N,N*-dimethylformamide (6 mL) was added iodomethane (441 mg, 3.11 mmol) and cesium carbonate (2.54 g, 7.78 mmol) at 0 °C. The mixture was stirred at 25 °C for 12 hr under nitrogen atmosphere. On completion, the reaction mixture was filtered, washed with acetonitrile (6 mL) and combined filtrate was added water (12 mL) and lyophilized to give [(1*S*,5*S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]methyl benzoate (636 mg, 2.59 mmol, 100%) as a yellow solid. m/z ES⁺ [M+H]⁺ 246.1.

[0263] **Step 2.** Synthesis of (*1S,5S*)-5-(hydroxymethyl)-3-methyl-3-azabicyclo[3.1.0]hexan-2-one. To a solution of [(*1S,5S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]methyl benzoate (636 mg, 2.59 mmol) in anhydrous tetrahydrofuran (7 mL) was added sodium hydroxide (2 M, 2.6 mL) at 0 °C. The mixture was stirred at 25 °C for 2 hr. On completion, the reaction mixture was acidified with formic acid (200 μ L) to pH = 6 at 0 °C and then concentrated under reduced pressure at below 30 °C. The resulting mixture was diluted with anhydrous tetrahydrofuran (40 mL) and stirred at 25 °C for 15 minutes and then filtered and the filtrate was concentrated to give (*1S,5S*)-5-(hydroxymethyl)-3-methyl-3-azabicyclo[3.1.0]hexan-2-one (366 mg, 2.59 mmol, 100%) as a brown oil. ^1H NMR (400 MHz, CDCl_3): δ 3.86 - 3.74 (m, 1H), 3.71 - 3.57 (m, 2H), 3.40 - 3.32 (m, 1H), 2.78 (s, 3H), 1.94 - 1.82 (m, 1H), 1.20 (dd, J = 4.8, 8.8 Hz, 1H), 0.91 - 0.80 (m, 1H).

[0264] **Step 3.** Synthesis of (*1S,5S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexane-1-carbaldehyde. To a solution of (*1S,5S*)-5-(hydroxymethyl)-3-methyl-3-azabicyclo[3.1.0]hexan-2-one (366 mg, 2.59 mmol) in dichloromethane (2 mL) and anhydrous tetrahydrofuran (8 mL) was added (1,1,1-triacetoxy)-1,1-dihydro-1,2-benziodoxol-3(1H)-one (1.65 g, 3.89 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 hr under nitrogen atmosphere. On completion, the reaction mixture was diluted with tetrahydrofuran (40 mL), filtered and washed with tetrahydrofuran (20 mL) and then filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate = 100/1 to 0/1) to give (*1S,5S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexane-1-carbaldehyde (180 mg, 1.16 mmol, 44%) as a white solid. ^1H NMR (400 MHz, CDCl_3): δ 8.93 (d, J = 3.6 Hz, 1H), 4.02 (dd, J = 3.2, 10.8 Hz, 1H), 3.30 - 3.21 (m, 1H), 2.76 (d, J = 3.2 Hz, 3H), 2.51 - 2.51 (m, 1H), 1.97 - 1.87 (m, 1H), 1.43 - 1.33 (m, 1H).

[0265] **Step 4.** Synthesis of (*1S,5R*)-5-ethynyl-3-methyl-3-azabicyclo[3.1.0]hexan-2-one. To a solution of (*1S,5S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexane-1-carbaldehyde (180 mg, 1.29 mmol) in methanol (5 mL) was added potassium carbonate (536 mg, 3.88 mmol) and 1-diazo-1-dimethoxyphosphoryl-propan-2-one (248 mg, 1.29 mmol) at 0 °C. The mixture was stirred at 25 °C for 12 hr under nitrogen atmosphere. On completion, the reaction mixture was partitioned between water (10 mL) and ethyl acetate (30 mL). The organic phase was separated and washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate = 100/1 to 0/1) to give (*1S,5R*)-5-ethynyl-3-methyl-3-azabicyclo[3.1.0]hexan-2-one (120 mg, 799 μ mol, 61%) as a brown oil. ^1H NMR (400 MHz,

CDCl_3): δ 3.59 (d, $J = 10.0$ Hz, 1H), 3.47 (d, $J = 10.0$ Hz, 1H), 2.76 (s, 3H), 2.30 - 2.21 (m, 1H), 2.11 (s, 1H), 1.53 (d, $J = 4.4$ Hz, 1H), 1.03 (t, $J = 4.4$ Hz, 1H).

[0266] **Step 5.** Synthesis of *(1S,5R)*-5-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl]ethynyl]-3-methyl-3-azabicyclo[3.1.0]hexan-2-one. To a solution of *(1S,5R)*-5-ethynyl-3-methyl-3-azabicyclo[3.1.0]hexan-2-one (120 mg, 887 μmol) and [4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl] trifluoromethanesulfonate (414 mg, 887 μmol) in *N,N*-dimethylformamide (4 mL) was added palladium triphenylphosphane (102 mg, 88.7 μmol), copper iodide (33.8 mg, 177 μmol) and triethylamine (269 mg, 2.66 mmol). The mixture was stirred at 25 °C for 1.5 hr under nitrogen atmosphere. On completion, the reaction mixture was partitioned between water (20 mL) and ethyl acetate (60 mL). The organic phase was separated, washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate/methanol = 100/1/0 to 0/10/1) to give *(1S,5R)*-5-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl]ethynyl]-3-methyl-3-azabicyclo[3.1.0]hexan-2-one (270 mg, 579 μmol , 65%) as a yellow solid. m/z ES+ $[\text{M}+\text{H}]^+$ 452.0.

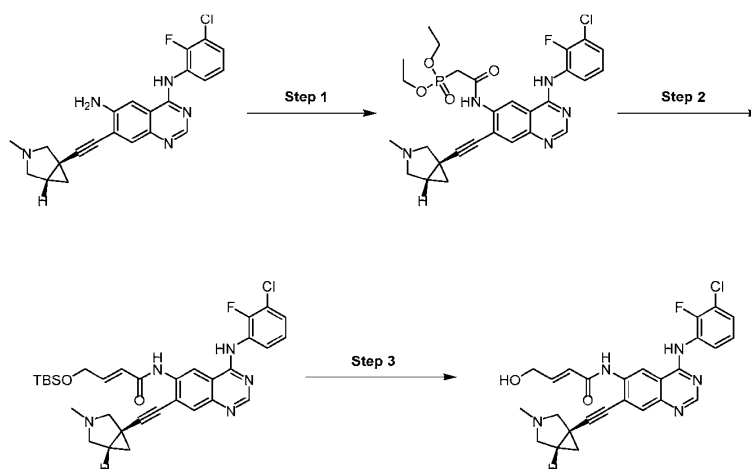
[0267] **Step 6.** Synthesis of *(1S,5R)*-5-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-methyl-3-azabicyclo[3.1.0]hexan-2-one. To a solution of *(1S,5R)*-5-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl]ethynyl]-3-methyl-3-azabicyclo[3.1.0]hexan-2-one (270 mg, 597 μmol) in methanol (5 mL) and water (1 mL) was added iron (158 mg, 2.84 mmol) and ammonium chloride (293 mg, 5.48 mmol). The mixture was stirred at 80 °C for 1 hr under nitrogen atmosphere. On completion, the reaction mixture was filtered, washed with methanol (3 $\times$ 20 mL) and then filtrates were concentrated under reduced pressure. The residue was diluted with dichloromethane (50 mL), basified with ammonium hydroxide to pH = 8, and then washed with water (10 mL) and brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give *(1S,5R)*-5-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-methyl-3-azabicyclo[3.1.0]hexan-2-one (252 mg, 591 μmol , 98%) as a yellow solid. m/z ES+ $[\text{M}+\text{H}]^+$ 422.1.

[0268] **Step 7.** Synthesis of *(E)*-4-bromo-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*1R,5S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]but-2-enamide. To a solution of *(1S,5R)*-5-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-methyl-3-azabicyclo[3.1.0]hexan-2-one (252 mg, 597 μmol) and *(E)*-4-bromobut-2-enoic acid (147 mg, 896 μmol) in *N,N*-dimethylformamide (2 mL) and anhydrous tetrahydrofuran (2 mL) was added diisopropylethylamine (386 mg, 2.99 mmol) and 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (950 mg, 1.49 mmol, 50% purity) at 0 °C. The mixture was

stirred at 25 °C for 12 hr under nitrogen atmosphere. On completion, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (7 mL × 3). The combined organic layers were washed with brine (5 mL × 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give (*E*)-4-bromo-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*1R,5S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]but-2-enamide (339 mg, 512 μmol, 85%) as a yellow solid. *m/z* ES+ [M+H]⁺ 570.1.

[0269] **Step 8.** Synthesis of (*E*)-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*1R,5S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]-4-morpholino-but-2-enamide. To a solution of (*E*)-4-bromo-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*1R,5S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]but-2-enamide (339 mg, 595 μmol) in *N,N*-dimethylformamide (2 mL) and anhydrous tetrahydrofuran (2 mL) was added diisopropylethylamine (385 mg, 2.98 mmol) and morpholine (207 mg, 2.38 mmol) at 0 °C. The mixture was stirred at 25 °C for 12 hr under nitrogen atmosphere. On completion, the reaction mixture was partitioned between water (20 mL) and ethyl acetate (60 mL). The organic phase was separated, washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by reverse-phase HPLC (column: YMC Triart C18 150*25mm*5um; mobile phase: [water(hydrogen chloride)-acetonitrile]; gradient: 17%-47% B over 10 min) and the separation fractions were collected and cooled to 0 °C and basified with ammonium hydroxide to pH = 8, then extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give the title compound which was purified with by reverse-phase HPLC (column: Waters Xbridge 150*25mm*5um; mobile phase: [water (ammonia hydroxide v/v)-acetonitrile]; gradient: 25%-55% B over 10 min) to give (*E*)-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*1R,5S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]-4-morpholino-but-2-enamide (144 mg, 251 μmol, 42%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 9.18 (s, 1H), 8.73 (s, 1H), 8.37 - 8.26 (m, 1H), 8.05 (s, 1H), 7.99 (s, 1H), 7.83 (s, 1H), 7.24 - 7.13 (m, 2H), 7.08 (td, *J* = 6.0, 15.2 Hz, 1H), 6.19 (d, *J* = 15.2 Hz, 1H), 3.83 - 3.71 (m, 5H), 3.66 (dd, *J* = 1.6, 10.4 Hz, 1H), 3.27 (dd, *J* = 1.2, 6.0 Hz, 2H), 2.85 (s, 3H), 2.60 - 2.52 (m, 4H), 2.49 (ddd, *J* = 1.6, 4.0, 8.8 Hz, 1H), 1.78 - 1.73 (m, 1H), 1.32 (t, *J* = 4.4 Hz, 1H); *m/z* ES+ [M+H]⁺ 575.2.

[0270] **Preparation of (*E*)-*N*-(4-((3-chloro-2-fluorophenyl)amino)-7-(((*1R,5S*)-3-methyl-3-azabicyclo[3.1.0]hexan-1-yl)ethynyl)quinazolin-6-yl)-4-hydroxybut-2-enamide (Compound No. 4)**



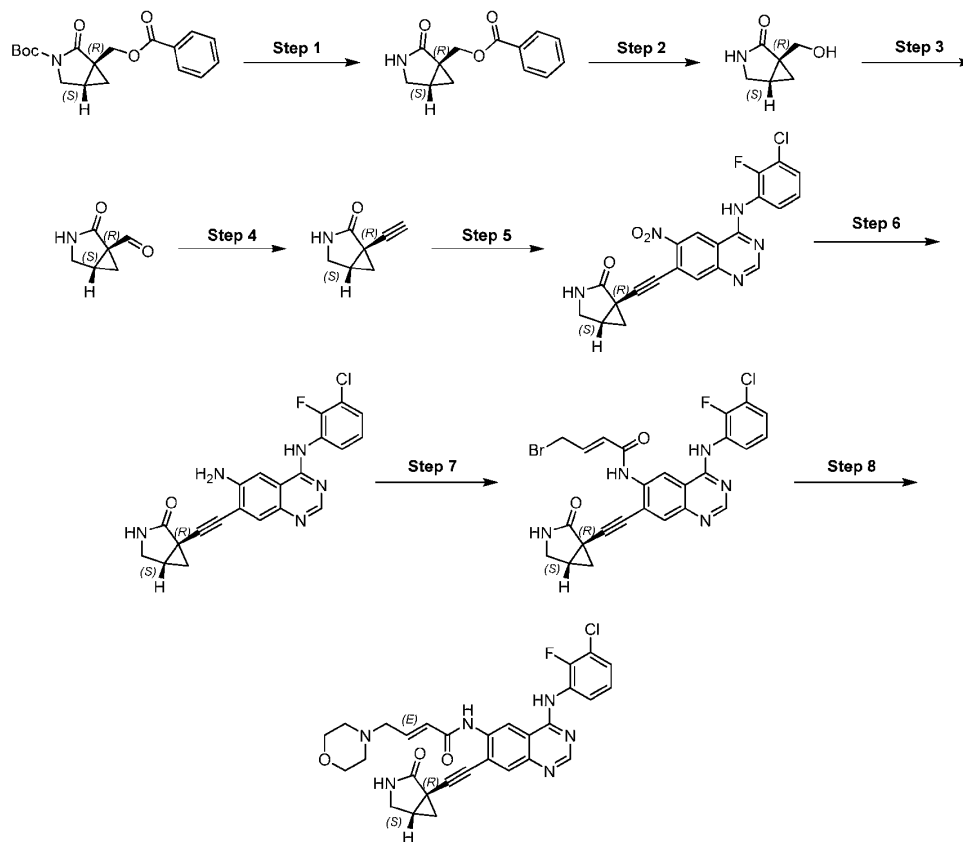
[0271] **Step 1.** Synthesis of *N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*1R,5S*)-3-methyl-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]-2-diethoxyphosphoryl-acetamide. To a solution of *N*-(3-chloro-2-fluoro-phenyl)-7-[2-[(*1R,5S*)-3-methyl-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-4,6-diamine (2 g, 4.90 mmol) and 2-diethoxyphosphorylacetic acid (4.81 g, 24.5 mmol, 3.9 mL) in *N,N*-dimethylformamide (40 mL) was added triethylamine (14.8 g, 147 mmol, 20 mL) and [dimethylamino(triazolo[4,5-*b*]pyridin-3-yl)oxy)methylene]-dimethylammonium hexafluorophosphate (9.32 g, 24.5 mmol). The mixture was stirred at 25 °C for 2 hr. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (150 mL × 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by reverse-phase HPLC (0.1% ammonium hydroxide condition) to give *N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*1R,5S*)-3-methyl-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]-2-diethoxyphosphoryl-acetamide (2.3 g, 3.85 mmol, 78%) as a white solid. *m/z* ES+ [M+H]⁺ 586.3

[0272] **Step 2.** Synthesis of (*E*)-4-[*tert*-butyl(dimethyl)silyl]oxy-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*1R,5S*)-3-methyl-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]but-2-enamide. To a mixture of *N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*1R,5S*)-3-methyl-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]-2-diethoxyphosphoryl-acetamide (2.2 g, 3.75 mmol) in ethanol (192 mL) was added lithium chloride (6.37 g, 150 mmol, 3.1 mL) and 45_w% potassium hydroxide (9.36 g, 75.0 mmol, 11 mL). The mixture was stirred at 20 °C for 10 min. Then, 2-[*tert*-butyl(dimethyl)silyl]oxyacetaldehyde (9.82 g, 56.3 mmol, 11 mL) was added dropwise into the mixture at 20 °C. The mixture was stirred at 20 °C for 50 min. The reaction mixture was diluted with water (200 mL) and extracted with ethyl acetate (250 mL ×

3). The combined organic layers were washed with brine (250 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase HPLC (0.1% formic acid condition) to give (*E*)-4-[*tert*-butyl(dimethyl)silyl]oxy-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*1R,5S*)-3-methyl-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]but-2-enamide (1.2 g, 1.98 mmol, 53%) as a white solid. *m/z* ES⁺ [M+H]⁺ 606.3.

[0273] **Step 3.** Synthesis of (*E*)-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*1R,5S*)-3-methyl-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]-4-hydroxy-but-2-enamide. To a solution of (*E*)-4-[*tert*-butyl(dimethyl)silyl]oxy-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*1R,5S*)-3-methyl-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]but-2-enamide (1.2 g, 1.98 mmol) in dichloromethane (4 mL) was added hydrochloric acid/dioxane (2 M, 4.5 mL). The mixture was stirred at 25 °C for 0.1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase HPLC (column: Phenomenex luna C18 150*25mm*10um; mobile phase: [water(formic acid)-ACN]; gradient: 3%-36% B over 11 min) to give (*E*)-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*1R,5S*)-3-methyl-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]-4-hydroxy-but-2-enamide (600 mg, 1.21 mmol, 61%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.25 - 9.89 (m, 1H), 9.74 (br. s, 1H), 8.68 (s, 1H), 8.47 (br. s, 1H), 8.16 (s, 1H), 7.85 - 7.73 (m, 1H), 7.50 (br. s, 2H), 7.32 - 7.24 (m, 1H), 7.00 - 6.93 (m, 1H), 6.48 (br. d, *J* = 15.2 Hz, 1H), 4.22 (br. s, 2H), 3.13 (d, *J* = 8.4 Hz, 1H), 2.94 (d, *J* = 9.2 Hz, 1H), 2.49 - 2.41 (m, 2H), 2.27 (s, 3H), 1.99 - 1.91 (m, 1H), 1.41 - 1.35 (m, 1H), 1.09 - 1.01 (m, 1H); *m/z* ES⁺ [M+H]⁺ 492.2.

[0274] **Preparation of (*E*)-*N*-(4-((3-chloro-2-fluorophenyl)amino)-7-(((1*R*,5*S*)-2-oxo-3-azabicyclo[3.1.0]hexan-1-yl)ethynyl)quinazolin-6-yl)-4-morpholinobut-2-enamide (Compound No. 10).**



[0275] **Step 1.** Synthesis of [(1*R*,5*S*)-2-oxo-3-azabicyclo[3.1.0]hexan-1-yl]methyl benzoate. To a solution of *tert*-butyl (1*R*,5*S*)-1-(benzoyloxymethyl)-2-oxo-3-azabicyclo [3.1.0] hexane-3-carboxylate (1.8 g, 5.43 mmol) in dichloromethane (18 mL) was added trifluoroacetic acid (6.91 g, 60.6 mmol, 4.5 mL). The mixture was stirred at 25 °C for 15 min. The reaction mixture was concentrated under reduced pressure to give [(1*R*,5*S*)-2-oxo-3-azabicyclo[3.1.0]hexan-1-yl]methyl benzoate (1.26 g, 5.45 mmol, 100%) as a brown oil.

[0276] **Step 2.** Synthesis of (1*R*,5*S*)-1-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-2-one. To a solution of [(1*R*,5*S*)-2-oxo-3-azabicyclo[3.1.0]hexan-1-yl]methyl benzoate (1.26 g, 5.45 mmol) in anhydrous tetrahydrofuran (13 mL) was added sodium hydroxide (2 M, 6.8 mL). The mixture was stirred at 25 °C for 2 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was washed with dichloromethane (30 mL) and washed with anhydrous tetrahydrofuran (30 mL). The filtrate was concentrated under reduced pressure to give a residue and the residue was washed with petroleum ether (30 mL × 3) to give (1*R*,5*S*)-1-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-2-one (690 mg, 5.43 mmol, 99%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 7.12 (br. s, 1H), 4.91 - 4.25 (m, 1H), 3.94 (d, *J* = 11.6 Hz, 1H), 3.31 - 3.25 (m, 1H), 3.21 (d, *J* = 11.6 Hz, 1H), 3.08 (d, *J* = 10.4 Hz, 1H), 1.96 - 1.83 (m, 1H), 1.08 - 0.96 (m, 1H), 0.59 - 0.37 (m, 1H).

[0277] **Step 3.** Synthesis of (*1R,5S*)-2-oxo-3-azabicyclo[3.1.0]hexane-1-carbaldehyde. To a solution of (*1R,5S*)-1-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-2-one (690 mg, 5.43 mmol) in dichloromethane (4 mL) and anhydrous tetrahydrofuran (16 mL) was added (1,1-diacetoxy-3-oxo-1,2-benziodoxol-1-yl) acetate (3.45 g, 8.14 mmol, 2.5 mL) at 0 °C. The mixture was stirred at 25 °C for 12 hr. The reaction mixture filtered and the filtrate concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide petroleum ether/ethyl acetate = 100/1 to 1/2) to give compound (*1R,5S*)-2-oxo-3-azabicyclo[3.1.0]hexane-1-carbaldehyde (400 mg, 3.20 mmol, 59%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.88 (s, 1H), 7.53 (br. s, 1H), 3.42 - 3.36 (m, 1H), 3.19 (d, *J* = 10.4 Hz, 1H), 2.64 - 2.56 (m, 1H), 1.83 - 1.74 (m, 1H), 1.35 - 1.28 (m, 1H).

[0278] **Step 4.** Synthesis of (*1R,5S*)-1-ethynyl-3-azabicyclo[3.1.0]hexan-2-one. To a solution of (*1R,5S*)-2-oxo-3-azabicyclo[3.1.0]hexane-1-carbaldehyde (300 mg, 2.40 mmol) and potassium carbonate (994 mg, 7.19 mmol) in methanol (3 mL) was added 1-diazo-1-dimethoxyphosphoryl-propan-2-one (460 mg, 2.40 mmol) dropwise at 0 °C. The mixture was stirred at 25 °C for 12 hr. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL × 5). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate = 100/1 to 1/2) to give (*1R,5S*)-1-ethynyl-3-azabicyclo[3.1.0]hexan-2-one (250 mg, 2.06 mmol, 86.0%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 6.66 (br. s, 1H), 3.64 - 3.46 (m, 1H), 3.26 (d, *J* = 10.4 Hz, 1H), 2.43 - 2.27 (m, 1H), 2.19 (s, 1H), 1.58 - 1.46 (m, 1H), 1.22 - 1.06 (m, 1H).

[0279] **Step 5.** Synthesis of (*1R,5S*)-1-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexan-2-one. To a solution of [4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl] trifluoromethanesulfonate (700 mg, 1.50 mmol) and (*1R,5S*)-1-ethynyl-3-azabicyclo[3.1.0]hexan-2-one (200 mg, 1.65 mmol) in *N,N*-dimethylformamide (7 mL) was added palladium triphenylphosphane (173 mg, 150 μmol), triethylamine (455 mg, 4.50 mmol, 626 μL) and copper iodide (57.1 mg, 300 μmol). The mixture was stirred at 25 °C for 4 hr under nitrogen atmosphere. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a

residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate = 100/1 to 0/1) to give (*IR,5S*)-1-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexan-2-one (800 mg, crude) as a brown solid. *m/z* ES+ [M+H]⁺ 438.1

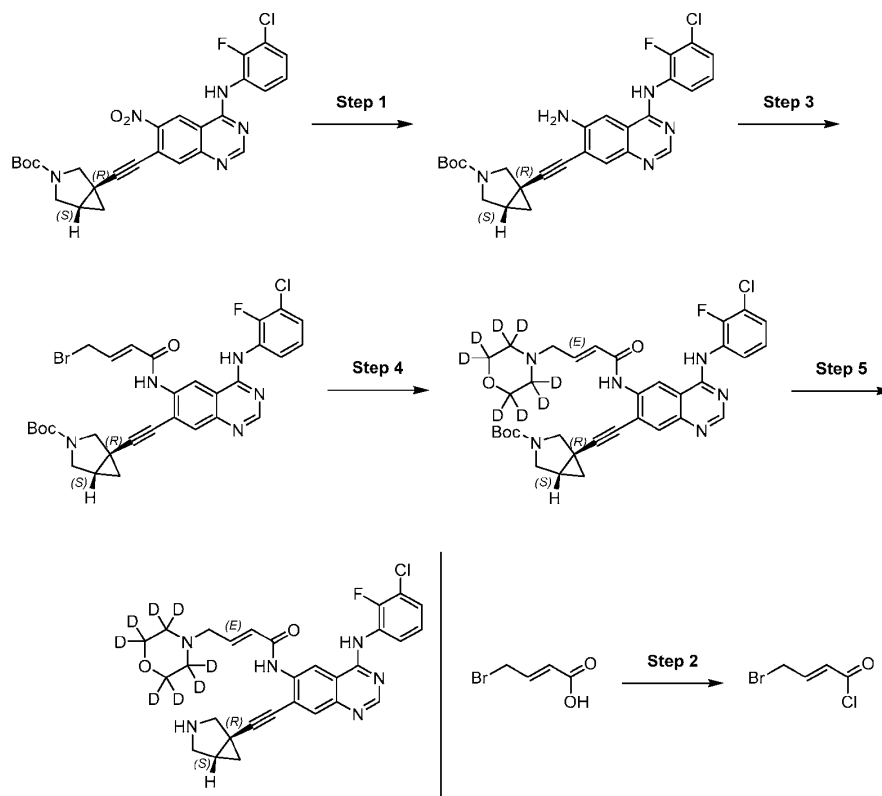
[0280] **Step 6.** Synthesis of (*IR,5S*)-1-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexan-2-one. To a solution of (*IR,5S*)-1-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexan-2-one (700 mg, 1.60 mmol) in methanol (7 mL) and water (1.4 mL) was added iron (424 mg, 7.59 mmol) and ammonium chloride (784 mg, 14.6 mmol). The mixture was stirred at 80 °C for 0.5 hr under nitrogen atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue then diluted with water (100 mL) and extracted with dichloromethane (150 mL × 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give (*IR,5S*)-1-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexan-2-one (600 mg, 1.47 mmol, 92.0%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.58 (s, 1H), 8.25 (s, 1H), 7.60 (s, 1H), 7.57 - 7.52 (m, 2H), 7.48 - 7.44 (m, 1H), 7.41 (s, 1H), 7.30 - 7.23 (m, 1H), 5.81 - 5.75 (m, 2H), 3.53 - 3.47 (m, 1H), 3.18 (s, 1H), 2.66 - 2.60 (m, 1H), 1.75 - 1.69 (m, 1H), 1.23 - 1.19 (m, 1H).

[0281] **Step 7.** Synthesis of (*E*)-4-bromo-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*IR,5S*)-2-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]but-2-enamide. A solution of (*IR,5S*)-1-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexan-2-one (300 mg, 735 μmol) and (*E*)-4-bromobut-2-enoic acid (182 mg, 1.10 mmol) in *N,N*-dimethylformamide (1.5 mL) and anhydrous tetrahydrofuran (1.5 mL) was degassed and purged with nitrogen for 3 times, then added diisopropylethylamine (380 mg, 2.94 mmol, 512 μL) and 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (468 mg, 1.47 mmol, 437 μL) slowly at 0 °C and then the mixture was stirred at 25 °C for 2 hr under nitrogen atmosphere. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give (*E*)-4-bromo-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*IR,5S*)-2-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]but-2-enamide (320 mg, 576 μmol, 78.4%) as a brown oil. *m/z* ES+ [M+H]⁺ 556.2.

[0282] **Step 8.** Synthesis of (*E*)-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*IR,5S*)-2-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]-4-morpholino-but-2-enamide. To a

solution of (*E*)-4-bromo-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*1R,5S*)-2-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]but-2-enamide (320 mg, 576 μ mol) in dichloromethane (3.2 mL) was added diisopropylethylamine (298 mg, 2.31 mmol, 401 μ L) and morpholine (201 mg, 2.31 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 hr. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC (column: YMC Triart C18 150x25mmx5um; mobile phase: [water(hydrochloride)-acetonitrile]; gradient: 16%-46% B over 10 min). Then purified by prep-HPLC (column: Waters Xbridge 150x25mmx 5um; mobile phase: [water (ammonia hydroxide v/v)-acetonitrile]; gradient: 25%-55% B over 10 min) to give (*E*)-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(*1R,5S*)-2-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]-quinazolin-6-yl]-4-morpholino-but-2-enamide (101 mg, 180 μ mol, 31%) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.33 - 9.95 (m, 1H), 9.60 (br. s, 1H), 8.89 (s, 1H), 8.58 - 8.19 (m, 1H), 7.85 - 7.70 (m, 1H), 7.59 (s, 1H), 7.46 (br. s, 2H), 7.32 - 7.20 (m, 1H), 6.89 - 6.78 (m, 1H), 6.57 (br. d, *J* = 15.6 Hz, 1H), 3.66 - 3.59 (m, 4H), 3.54 - 3.48 (m, 1H), 3.22 (d, *J* = 10.4 Hz, 1H), 3.17 (br. d, *J* = 5.2 Hz, 2H), 2.64 - 2.59 (m, 1H), 2.42 (br. s, 4H), 1.73 - 1.64 (m, 1H), 1.28 - 1.24 (m, 1H); *m/z* ES⁺ [M+H]⁺ 561.2.

[0283] **Preparation of (*E*)-*N*-(7-(((1*R*,5*S*)-3-azabicyclo[3.1.0]hexan-1-yl)ethynyl)-4-((3-chloro-2-fluorophenyl)amino)quinazolin-6-yl)-4-(morpholino-d8)but-2-enamide (Compound No. D1)**



[0284] **Step 1.** Synthesis of *tert*-butyl (1*R*,5*S*)-1-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate. To a solution of *tert*-butyl (1*R*,5*S*)-1-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (1.00 g, 1.91 mmol) in methanol (10 mL) and water (2 mL) was added ammonium chloride (936 mg, 17.5 mmol) and iron (506 mg, 9.07 mmol). The mixture was stirred at 80 °C for 1 hr. On completion, the mixture was filtered and washed with ethyl acetate (15 mL x 3), then the filtrate was adjusted to pH ~ 8 with potassium carbonate. The organic phase was separated, washed with brine (15 mL x 3), dried over with anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate = 100/1 to 1/1) to give *tert*-butyl (1*R*,5*S*)-1-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]-hexane-3-carboxylate (630 mg, 1.15 mmol, 60%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 8.69 - 8.56 (m, 2H), 7.87 (s, 1H), 7.49 - 7.35 (m, 1H), 7.20 - 7.12 (m, 2H), 6.98 (s, 1H), 4.59 (br. s, 2H), 3.97 - 3.82 (m, 1H), 3.75 - 3.59 (m, 1H), 3.56 (br. d, *J* = 10.4 Hz, 2H), 2.05 - 1.99 (m, 1H), 1.48 (s, 9H), 1.41 - 1.34 (m, 1H), 0.96 (t, *J* = 5.2 Hz, 1H); *m/z* ES⁺ [M+H]⁺ 494.1.

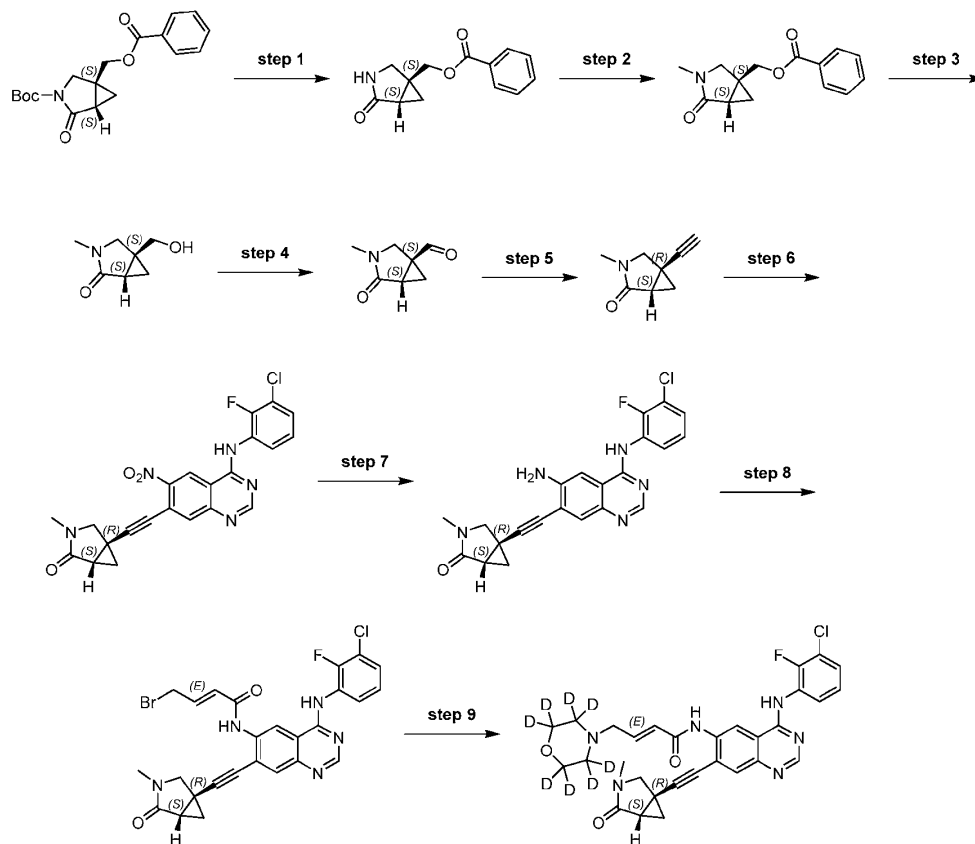
[0285] **Step 2.** Synthesis of (*E*)-4-bromobut-2-enoyl chloride. To a solution of (*E*)-4-bromobut-2-enoic acid (1 g, 6.06 mmol) and oxalyl dichloride (1.54 g, 12.1 mmol) in dichloromethane (10 mL) was added one drop of *N,N*-dimethylformamide. The mixture was stirred at 0 °C for 1 hr. On completion, the reaction mixture was concentrated under reduced pressure to give (*E*)-4-bromobut-2-enoyl chloride (800 mg, crude) as a yellow oil.

[0286] **Step 3.** Synthesis of *tert*-butyl (1*R*,5*S*)-1-[2-[6-[(*E*)-4-bromobut-2-enoyl]amino]-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate. To a solution of *tert*-butyl (1*R*,5*S*)-1-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (600 mg, 1.21 mmol) in dichloromethane (6 mL) was added triethylamine (368 mg, 3.64 mmol) and a mixture of (*E*)-4-bromobut-2-enoyl chloride (334 mg, 1.82 mmol) in dichloromethane (1.5 mL) at 0 °C. The mixture was stirred at 0 °C for 1 hr. On completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate = 100/1 to 1/1) to give *tert*-butyl (1*R*,5*S*)-1-[2-[6-[(*E*)-4-bromobut-2-enoyl]amino]-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (200 mg, 312 μmol, 26%) as a yellow solid. *m/z* ES+ [M+H]⁺ 642.1.

[0287] **Step 4.** Synthesis of *tert*-butyl (1*R*,5*S*)-1-[2-[4-(3-chloro-2-fluoro-anilino)-6-[(*E*)-4-(2,2,3,3,5,5,6,6-octadeuteriomorpholin-4-yl)but-2-enoyl]amino]quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate. To a solution of 2,2,3,3,5,5,6,6-octadeuteriomorpholine (139 mg, 1.06 mmol) in dichloromethane (2 mL) was added triethylamine (134 mg, 1.33 mmol), then the mixture was added into *tert*-butyl (1*R*,5*S*)-1-[2-[6-[(*E*)-4-bromobut-2-enoyl]amino]-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (170 mg, 265 μmol). The mixture was stirred at 25 °C for 1 hr. On completion, the reaction mixture was concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase HPLC (0.1% ammonium hydroxide) to give *tert*-butyl (1*R*,5*S*)-1-[2-[4-(3-chloro-2-fluoro-anilino)-6-[(*E*)-4-(2,2,3,3,5,5,6,6-octadeuteriomorpholin-4-yl)but-2-enoyl]amino]quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (140 mg, 213 μmol, 80%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 9.25 - 9.18 (m, 1H), 8.75 (s, 1H), 8.44 - 8.35 (m, 1H), 8.20 (br. s, 1H), 7.98 (br. d, *J* = 4.4 Hz, 1H), 7.71 (br. s, 1H), 7.24 - 7.16 (m, 2H), 7.14 - 7.04 (m, 1H), 6.28 - 6.16 (m, 1H), 4.04 - 3.87 (m, 1H), 3.80 - 3.65 (m, 1H), 3.58 (br. d, *J* = 10.8 Hz, 2H), 3.36 - 3.21 (m, 2H), 2.10 (dd, *J* = 4.4, 8.0 Hz, 1H), 1.50 (s, 9H), 1.43 - 1.40 (m, 1H), 1.06 (br. s, 1H); *m/z* ES+ [M+H]⁺ 655.3.

[0288] **Step 5.** Synthesis of (*E*)-*N*-[7-[2-[(1*R*,5*S*)-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]-4-(3-chloro-2-fluoro-anilino)quinazolin-6-yl]-4-(2,2,3,3,5,5,6,6-octadeuteriomorpholin-4-yl)but-2-enamide. To a solution of *tert*-butyl (1*R*,5*S*)-1-[2-[4-(3-chloro-2-fluoro-anilino)-6-[[(*E*)-4-(2,2,3,3,5,5,6,6-octadeuteriomorpholin-4-yl)but-2-enoyl]amino]quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (120 mg, 183 μ mol) in dichloromethane (1.2 mL) was added trifluoroacetic acid (368 mg, 3.23 mmol). The mixture was stirred at 25 °C for 0.5 hr. On completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm*10um; mobile phase: [water(formic acid)- acetonitrile]; gradient: 4%-24% B over 25 min) and then lyophilized to give a residue. The residue was diluted with water (5 mL) and washed with sodium bicarbonate solution (1 N) until pH = 7 and then extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge 150*25mm*10um; mobile phase: [water(ammonium bicarbonate)- acetonitrile]; gradient: 22%-52% B over 10 min) to give (*E*)-*N*-[7-[2-[(1*R*,5*S*)-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]-4-(3-chloro-2-fluoro-anilino)quinazolin-6-yl]-4-(2,2,3,3,5,5,6,6-octadeuteriomorpholin-4-yl)but-2-enamide (60 mg, 108 μ mol, 39%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.05 (br. s, 1H), 9.75 (s, 1H), 8.67 (s, 1H), 8.47 (s, 1H), 7.79 (s, 1H), 7.55 - 7.42 (m, 2H), 7.28 (br. t, *J* = 7.6 Hz, 1H), 6.80 (td, *J* = 5.6, 15.2 Hz, 1H), 6.44 (br. d, *J* = 15.2 Hz, 1H), 3.16 (br. d, *J* = 5.2 Hz, 2H), 3.04 (d, *J* = 10.8 Hz, 1H), 2.86 - 2.81 (m, 3H), 1.88 (br. dd, *J* = 5.6, 7.2 Hz, 1H), 1.07 - 1.02 (m, 2H); *m/z* ES+ [M+H]⁺ 555.3.

[0289] **Preparation of (*E*)-*N*-(4-((3-chloro-2-fluorophenyl)amino)-7-(((1*R*,5*S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl)ethynyl)quinazolin-6-yl)-4-(morpholino-*d*8)but-2-enamide (Compound No. D2)**



[0290] **Step 1.** Synthesis of [(1*S*,5*S*)-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]methyl benzoate. To a solution of *tert*-butyl (1*S*,5*S*)-1-(benzoyloxymethyl)-4-oxo-3-azabicyclo[3.1.0]hexane-3-carboxylate (15 g, 45.3 mmol) in dichloromethane (40 mL) was added trifluoroacetic acid (25.8 g, 226 mmol). The mixture was stirred at 25 °C for 0.1 hr. The reaction mixture was concentrated under reduced pressure to give [(1*S*,5*S*)-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]methyl benzoate (10 g, crude) as a white solid. *m/z* ES+ [M+H]⁺ 232.0.

[0291] **Step 2.** Synthesis of [(1*S*,5*S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]methyl benzoate. To a solution of [(1*S*,5*S*)-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]methyl benzoate (4.5 g, 19.4 mmol) in *N,N*-dimethylformamide (30 mL) was added iodomethane (3.31 g, 23.3 mmol) and cesium carbonate (31.7 g, 97.3 mmol) at 0 °C. The mixture was stirred at 25 °C for 12 hr under nitrogen. On completion, the reaction mixture was filtered, washed with acetonitrile (30 mL) and added water (120 mL) and then lyophilized to give [(1*S*,5*S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]methyl benzoate (4.5 g, crude) as a white solid. *m/z* ES+ [M+H]⁺ 246.1.

[0292] **Step 3.** Synthesis of (1*S*,5*S*)-5-(hydroxymethyl)-3-methyl-3-azabicyclo[3.1.0]hexan-2-one. To a solution of [(1*S*,5*S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]methyl benzoate (4.5 g, 18.3 mmol) in anhydrous tetrahydrofuran (40 mL) was added sodium hydroxide (2 M, 23 mL) at 0 °C. The mixture was stirred at 25 °C for 2 hr. On completion, the reaction mixture was adjusted to pH = 6 with formic acid at 0 °C, and concentrated under reduced pressure. The mixture was diluted with tetrahydrofuran (40 mL) and stirred at 25 °C for 15 min and then filtered and concentrated to give (1*S*,5*S*)-5-(hydroxymethyl)-3-methyl-3-azabicyclo[3.1.0]hexan-2-one (3 g, crude) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 3.80 (d, *J* = 12.0 Hz, 1H), 3.64 - 3.56 (m, 2H), 3.37 - 3.33 (m, 1H), 2.75 (s, 3H), 1.90 - 1.84 (m, 1H), 1.21 - 1.15 (m, 1H), 0.85 - 0.79 (m, 1H).

[0293] **Step 4.** Synthesis of (1*S*,5*S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexane-1-carbaldehyde. To a solution of (1*S*,5*S*)-5-(hydroxymethyl)-3-methyl-3-azabicyclo[3.1.0]hexan-2-one (3 g, 21.2 mmol) in anhydrous tetrahydrofuran (30 mL) and dichloromethane (8 mL) was added Dess-Martin periodinane (13.5 g, 31.9 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 hr under nitrogen. On completion, the reaction mixture was diluted with tetrahydrofuran (40 mL), filtered, washed with tetrahydrofuran (20 mL) and then concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate = 10/1 to 0/1) to give (1*S*,5*S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexane-1-carbaldehyde (1.1 g, 7.91 mmol, 37%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 8.96 (s, 1H), 4.07 (d, *J* = 10.8 Hz, 1H), 3.33 - 3.27 (m, 1H), 2.81 (s, 3H), 2.61 - 2.53 (m, 1H), 2.00 - 1.93 (m, 1H), 1.45 - 1.39 (m, 1H).

[0294] **Step 5.** Synthesis of (1*S*,5*R*)-5-ethynyl-3-methyl-3-azabicyclo[3.1.0]hexan-2-one. To a solution of (1*S*,5*S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexane-1-carbaldehyde (1.1 g, 7.91 mmol) in methanol (10 mL) was added potassium carbonate (3.28 g, 23.7 mmol) and 1-diazo-1-dimethoxyphosphoryl-propan-2-one (1.52 g, 7.91 mmol) at 0 °C. The mixture was stirred at 25 °C for 12 hr under nitrogen atmosphere. On completion, the reaction mixture was partitioned between water (10 mL) and ethyl acetate (30 mL). The organic phase was separated, washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate = 10/1 to 0/1) to give (1*S*,5*R*)-5-ethynyl-3-methyl-3-azabicyclo[3.1.0]hexan-2-one (460 mg, 3.40 mmol, 43%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 3.63 - 3.53 (m, 1H), 3.50 - 3.41 (m, 1H), 2.75 (s, 3H), 2.29 - 2.21 (m, 1H), 2.11 (s, 1H), 1.57 - 1.48 (m, 1H), 1.08 - 0.96 (m, 1H).

[0295] **Step 6.** Synthesis of (1*S*,5*R*)-5-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl]ethynyl]-3-methyl-3-azabicyclo[3.1.0]hexan-2-one. To a solution of (1*S*,5*R*)-5-ethynyl-3-methyl-3-azabicyclo[3.1.0]hexan-2-one (460 mg, 3.40 mmol) and [4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl] trifluoromethanesulfonate (1.59 g, 3.40 mmol) in *N,N*-dimethylformamide (4 mL) was added palladium triphenylphosphane (125 mg, 340 μ mol), copper iodide (129 mg, 680 μ mol) and triethylamine (1.03 g, 10.2 mmol). The mixture was stirred at 25 °C for 1.5 hr under nitrogen atmosphere. On completion, the reaction mixture was partitioned between water (20 mL) and ethyl acetate (60 mL). The organic phase was separated, washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, ethyl acetate/ methanol = 10/1) to give (1*S*,5*R*)-5-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl]ethynyl]-3-methyl-3-azabicyclo[3.1.0]hexan-2-one (1.4 g, 2.79 mmol, 82%) as a white solid. *m/z* ES+ [M+H]⁺ 452.1.

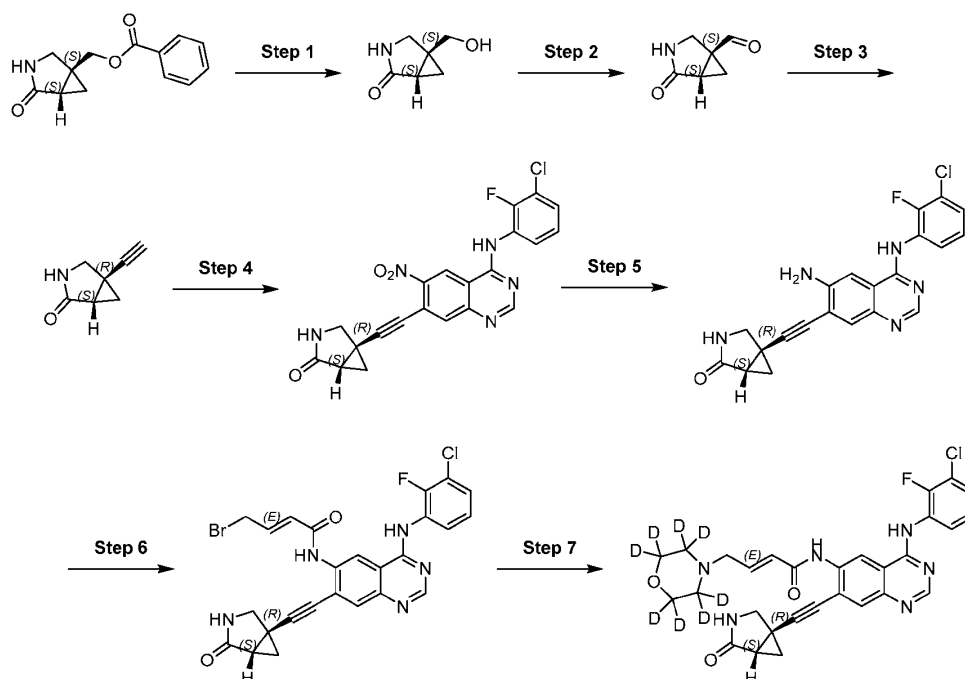
[0296] **Step 7.** Synthesis of (1*S*,5*R*)-5-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-methyl-3-azabicyclo[3.1.0]hexan-2-one. To a solution of (1*S*,5*R*)-5-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl]ethynyl]-3-methyl-3-azabicyclo[3.1.0]hexan-2-one (1.3 g, 2.88 mmol) in methanol (30 mL) and water (6 mL) was added iron powder (803 mg, 14.3 mmol) and ammonium chloride (1.54 g, 28.7 mmol). The mixture was stirred at 80 °C for 1 hr under nitrogen atmosphere. On completion, the reaction mixture was filtered, washed with methanol (10 mL x 3) and then the filtrates were concentrated under reduced pressure. The residue was diluted with dichloromethane (50 mL), basified with ammonium hydroxide to pH = 8, and then washed with water (10 mL) and brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give (1*S*,5*R*)-5-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-methyl-3-azabicyclo[3.1.0]hexan-2-one (1.14 g, crude) as a white solid. *m/z* ES+ [M+H]⁺ 422.1.

[0297] **Step 8.** Synthesis of (*E*)-4-bromo-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(1*R*,5*S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]but-2-enamide. To a solution of (1*S*,5*R*)-5-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-methyl-3-azabicyclo[3.1.0]hexan-2-one (600 mg, 1.42 mmol) and (*E*)-4-bromobut-2-enoic acid (469 mg, 2.84 mmol) in *N,N*-dimethylformamide (20 mL) and anhydrous tetrahydrofuran (20 mL) was added diisopropylethylamine (4.23 g, 32.7 mmol) and 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (5.43 g, 8.53 mmol) at 0 °C. The mixture was stirred at 25 °C for 12 hr under nitrogen atmosphere. On completion, the mixture was diluted with water (100 mL) and filtered. Then the filter was diluted with water (50 mL) and extracted

with ethyl acetate (60 mL x 6). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*40mm* 15um; mobile phase: [water(formic acid)-acetonitrile]; gradient: 30%-60% B over 10 min) to give (*E*)-4-bromo-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(1*R*,5*S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]but-2-enamide (400 mg, 703 μ mol, 49%) as a white solid. *m/z* ES+ [M+H]⁺ 570.0.

[0298] **Step 9.** Synthesis of (*E*)-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(1*R*,5*S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]-4-(2,2,3,3,5,5,6,6-octadeuteriomorpholin-4-yl)but-2-enamide. To a solution of (*E*)-4-bromo-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(1*R*,5*S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]but-2-enamide (300 mg, 527 μ mol) in *N,N*-dimethylformamide (2 mL) and anhydrous tetrahydrofuran (2 mL) was added diisopropylethylamine (545 mg, 4.22 mmol), potassium iodide (437mg, 2.64 mmol) and 2,2,3,3,5,5,6,6-octadeuteriomorpholine (208 mg, 1.58 mmol) at 0 °C. The mixture was stirred at 25 °C for 12 hr. On completion, the reaction mixture was partitioned between water (20 mL) and ethyl acetate (60 mL). The organic phase was separated, washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm*10um; mobile phase: [water(formic acid)-acetonitrile]; gradient: 7%-37% B over 10 min) to give (*E*)-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(1*R*,5*S*)-3-methyl-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]-4-(2,2,3,3,5,5,6,6-octadeuteriomorpholin-4-yl)but-2-enamide (160 mg, 275 μ mol, 52%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 9.15 (s, 1H), 8.71 (s, 1H), 8.32 - 8.21 (m, 1H), 8.18 - 8.13 (m, 1H), 7.98 (s, 1H), 7.25 - 7.04 (m, 3H), 6.36 (d, *J* = 15.2 Hz, 1H), 3.79 (d, *J* = 10.4 Hz, 1H), 3.67 (d, *J* = 10.8 Hz, 1H), 3.40 (d, *J* = 6.0 Hz, 2H), 2.85 (s, 3H), 2.52 - 2.49 (m, 1H), 1.80 - 1.72 (m, 1H), 1.36 - 1.26 (m, 1H); *m/z* ES+ [M+H]⁺ 583.3.

[0299] **Preparation of (*E*)-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(1*R*,5*S*)-4-oxo-3-azabicyclo-[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]-4-(2,2,3,3,5,5,6,6-octadeuteriomorpholin-4-yl)but-2-enamide (Compound No. D3)**



[0300] **Step 1.** Synthesis of (1*S*,5*S*)-5-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-2-one. To a mixture of [(1*S*,5*S*)-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]methyl benzoate (5.00 g, 14.4 mmol) in anhydrous tetrahydrofuran (50 mL) was added sodium hydroxide (2 M, 18 mL), the reaction was stirred at 25 °C for 12 hr. On completion, the reaction mixture was adjusted to pH = 7 with formic acid, then concentrated under reduced pressure to give a residue. The residue was diluted with anhydrous tetrahydrofuran (30 mL) and dichloromethane (30 mL), filtered and concentrated under reduced pressure to give (1*S*,5*S*)-5-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-2-one (3.2 g, crude) as a colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.08 (br. s, 1H), 3.56 (s, 1H), 3.41 (d, *J* = 12.0 Hz, 1H), 3.32 (d, *J* = 10.0 Hz, 1H), 3.15 (d, *J* = 10.0 Hz, 1H), 1.77 - 1.74 (m, 1H), 1.55 - 1.47 (m, 1H), 1.07 (dd, *J* = 4.0, 8.8 Hz, 1H), 0.63 (t, *J* = 3.6 Hz, 1H).

[0301] **Step 2.** Synthesis of (1*S*,5*S*)-4-oxo-3-azabicyclo[3.1.0]hexan-1-carbaldehyde. To a mixture of (1*S*,5*S*)-5-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-2-one (3.20 g, 25.1 mmol) in anhydrous tetrahydrofuran (32 mL) and dichloromethane (8 mL) was added Dess-Martin periodinane (16.0 g, 37.7 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 12 hr. On completion, the reaction mixture was filtered and the filtered liquor was diluted with water (80 mL) and extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate = 10/1 to 1/1) to give (1*S*,5*S*)-4-oxo-3-

azabicyclo[3.1.0]hexane-1-carbaldehyde (1.6 g, 12.7 mmol, 51%) as a pink solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.90 (s, 1H), 7.52 - 7.39 (m, 1H), 3.75 (d, *J* = 10.4 Hz, 1H), 3.18 (d, *J* = 10.4 Hz, 1H), 2.48 - 2.41 (m, 1H), 2.03 - 1.94 (m, 1H), 1.36 (t, *J* = 4.8 Hz, 1H).

[0302] **Step 3.** Synthesis of (1*S*,5*R*)-5-ethynyl-3-azabicyclo[3.1.0]hexan-2-one. To a mixture of (1*S*,5*S*)-4-oxo-3-azabicyclo[3.1.0]hexane-1-carbaldehyde (1.40 g, 11.2 mmol) and potassium carbonate (4.64 g, 33.5 mmol) in methanol (15 mL) was added 1-diazo-1-dimethoxyphosphorylpropan-2-one (2.15 g, 11.2 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 3 hr. On completion, the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (90 mL x 2). The combined organic layers were washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate = 10/1 to 1/1) to give (1*S*,5*R*)-5-ethynyl-3-azabicyclo[3.1.0]hexan-2-one (500 mg, 3.71 mmol, 33%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 5.94 (br. s, 1H), 3.56 - 3.41 (m, 2H), 2.11 - 2.07 (m, 1H), 2.06 (s, 1H), 1.49 (dd, *J* = 4.8, 8.8 Hz, 1H), 1.03 (t, *J* = 4.4 Hz, 1H).

[0303] **Step 4.** Synthesis of (1*S*,5*R*)-5-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexan-2-one. To a mixture of [4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl] trifluoromethanesulfonate (1.60 g, 3.43 mmol) and (1*S*,5*R*)-5-ethynyl-3-azabicyclo[3.1.0]hexan-2-one (456 mg, 3.77 mmol) in *N,N*-dimethylformamide (20 mL) was added palladium triphenylphosphane (396 mg, 342 μmol), cuprous iodide (130 mg, 685 μmol) and triethylamine (1.04 g, 10.2 mmol) under nitrogen, the reaction mixture was stirred at 25 °C for 4 hr under nitrogen. On completion, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL x 2). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with (petroleum ether/ethyl acetate = 3:1, 20 mL) at 25 °C for 30 min to give (1*S*,5*R*)-5-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexan-2-one (2.0 g, crude) as a yellow solid. *m/z* ES+ [M+H]⁺ 438.1.

[0304] **Step 5.** Synthesis of (1*S*,5*R*)-5-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexan-2-one. To a mixture of (1*S*,5*R*)-5-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexan-2-one (1.80 g, 4.11 mmol) in methanol (20 mL) and water (4 mL) was added iron powder (1.15 g, 20.5 mmol) and ammonium chloride (2.20 g, 41.1 mmol). The reaction mixture was stirred at 80 °C for 0.5 hr. On completion, the reaction mixture was filtered and the filtered liquor was diluted with water (60 mL) and extracted with ethyl acetate (60 mL x 2). The combined organic layers were washed

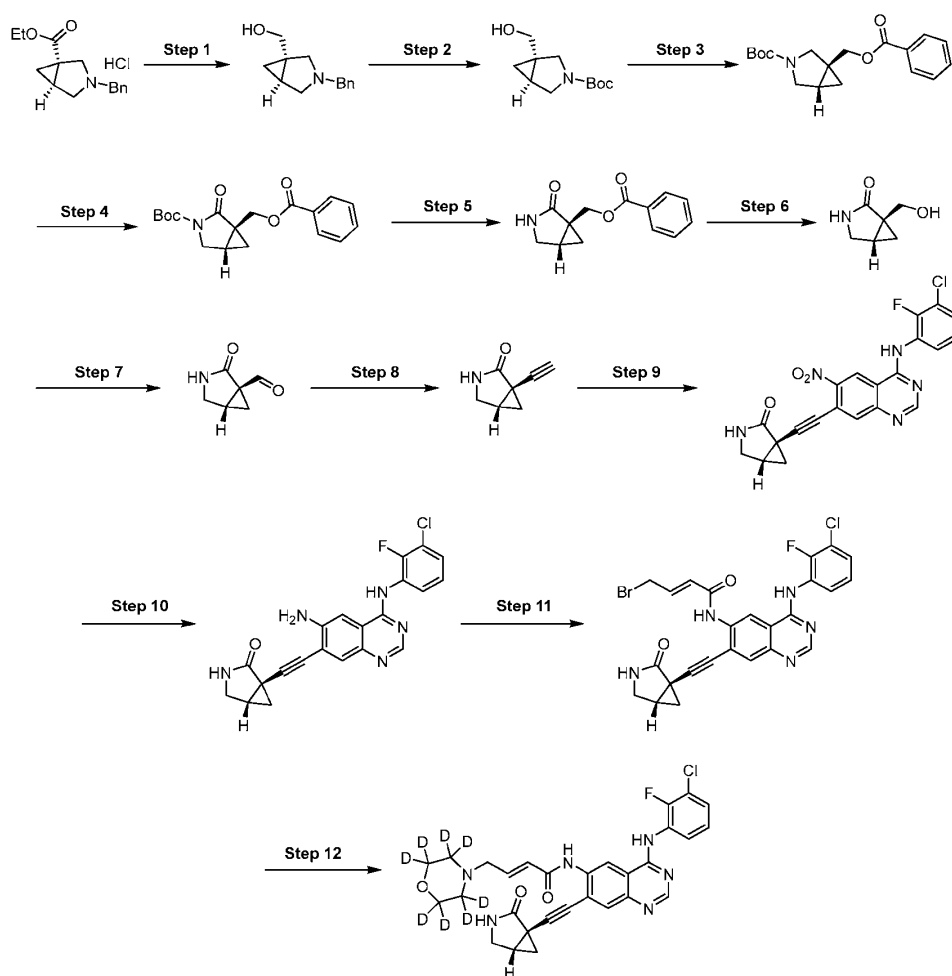
with brine (70 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase HPLC (column: Phenomenex Luna C18 150*25mm*10um; mobile phase: [water(formic acid)-acetonitrile]; gradient: 13%-43% B over 10 min) to give (1*S*,5*R*)-5-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexan-2-one (720 mg, 1.73 mmol, 42%) as a yellow solid. *m/z* ES+ [M+H]⁺ 408.1.

[0305] **Step 6.** Synthesis of (*E*)-4-bromo-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(1*R*,5*S*)-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]but-2-enamide. To a mixture of (1*S*,5*R*)-5-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexan-2-one (570 mg, 1.40 mmol) and (*E*)-4-bromobut-2-enoic acid (345 mg, 2.10 mmol) in *N,N*-dimethylformamide (4 mL) and anhydrous tetrahydrofuran (4 mL) was added diisopropylethylamine (722 mg, 5.59 mmol) and 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (1.78 g, 2.80 mmol) slowly at 0 °C under nitrogen. The reaction mixture was stirred at 25 °C for 12 hr under nitrogen. On completion, the reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (60 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give (*E*)-4-bromo-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(1*R*,5*S*)-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]but-2-enamide (530 mg, crude) as a yellow oil. *m/z* ES+ [M+H]⁺ 556.2.

[0306] **Step 7.** Synthesis of (*E*)-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(1*R*,5*S*)-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]-4-(2,2,3,3,5,5,6,6-octadeuteriomorpholin-4-yl)but-2-enamide. To a mixture of (*E*)-4-bromo-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(1*R*,5*S*)-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]but-2-enamide (500 mg, 901 μmol) in diisopropylethylamine (582 mg, 4.51 mmol) was added potassium iodide (748 mg, 4.51 mmol) and 2,2,3,3,5,5,6,6-octadeuteriomorpholine (257 mg, 1.95 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 12 hr. On completion, the reaction mixture was diluted with water (40 mL) and extracted with ethyl acetate (40 mL x 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by reversed-phase HPLC (column: Phenomenex Luna C18 150*25mm*10um; mobile phase: [water(formic acid) - acetonitrile]; gradient: 8%-38% B over 10 min) to give (*E*)-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(1*R*,5*S*)-4-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]-4-(2,2,3,3,5,5,6,6-octadeuteriomorpholin-4-yl)but-2-enamide (150 mg, 282 μmol, 29%) as an off-white solid. ¹H NMR (400 MHz, CDCl₃): δ 9.16 (s, 1H), 8.71 (s,

1H), 8.28 - 8.20 (m, 1H), 8.11 - 7.94 (m, 3H), 7.24 - 7.13 (m, 2H), 7.08 (td, $J = 6.0, 15.2$ Hz, 1H), 6.19 (d, $J = 15.2$ Hz, 1H), 5.56 (br. s, 1H), 3.83 - 3.72 (m, 2H), 3.27 (d, $J = 5.2$ Hz, 2H), 2.41 (dd, $J = 4.4, 8.8$ Hz, 1H), 1.78 (br. s, 1H), 1.40 (t, $J = 4.4$ Hz, 1H); m/z ES+ $[M+H]^+$ 569.3.

[0307] **Preparation of (E)-N-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(1R,5S)-2-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]-4-(2,2,3,3,5,5,6,6-octadeuteriomorpholin-4-yl)but-2-enamide (Compound No. D4)**



[0308] **Step 1.** Synthesis of [(1S,5S)-3-benzyl-3-azabicyclo[3.1.0]hexan-1-yl]methanol. To a solution of ethyl (1S,5S)-3-benzyl-3-azabicyclo[3.1.0]hexane-1-carboxylate (40 g, 163 mmol) in anhydrous tetrahydrofuran (240 mL) was added lithium aluminum hydride (2.5 M, 78 mL) dropwise at 25 °C under nitrogen atmosphere. The mixture was stirred at 25 °C for 2 hr under nitrogen atmosphere. The reaction mixture was quenched by sequentially added water (10 mL),

aqueous sodium hydroxide (15%, 10 mL) and water (34 mL) at 0 °C and then warmed to 25 °C. Then anhydrous sodium sulfate (26 g) was added. The mixture was stirred at 25 °C for 30 min and filtered. The filtrate was concentrated under reduced pressure to give [(1*S*,5*S*)-3-benzyl-3-azabicyclo[3.1.0]hexan-1-yl]methanol (29.5 g, 145 mmol, 89%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.23 - 7.13 (m, 5H), 3.68 - 3.49 (m, 4H), 2.95 (d, *J* = 8.4 Hz, 1H), 2.87 (d, *J* = 8.8 Hz, 1H), 2.42 - 2.28 (m, 2H), 1.19 - 1.16 (m, 1H), 1.08 - 0.97 (m, 1H), 0.46 - 0.29 (m, 1H).

[0309] **Step 2.** Synthesis of *tert*-butyl (1*S*,5*S*)-1-(hydroxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate. To a solution of palladium on activated carbon (4 g, 3.76 mmol, 10% loading) in methanol (295 mL) was added [(1*S*,5*S*)-3-benzyl-3-azabicyclo[3.1.0]hexan-1-yl]methanol (29.5 g, 145 mmol) and di-*tert*-butyl dicarbonate (38.0 g, 174 mmol) under nitrogen atmosphere. The suspension was degassed and purged with hydrogen 3 times. Then the mixture was stirred under hydrogen (50 psi) at 35 °C for 12 hr. The mixture was filtered through celite and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate = 50/1 to 1/1) to give *tert*-butyl (1*S*,5*S*)-1-(hydroxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (30 g, 140 mmol, 96%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 3.80 - 3.49 (m, 4H), 3.45 - 3.36 (m, 2H), 1.53 (s, 1H), 1.44 (s, 9H), 0.83 - 0.72 (m, 1H), 0.54 - 0.42 (m, 1H).

[0310] **Step 3.** Synthesis of *tert*-butyl (1*S*,5*S*)-1-(benzoyloxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate. To a solution of *tert*-butyl (1*S*,5*S*)-1-(hydroxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (30 g, 140 mmol) and benzoic acid (17.2 g, 140 mmol, 21.4 mL) in 1,2-dichloroethane (300 mL) was added 3-(ethyliminomethyleneamino)-*N,N*-dimethyl-propan-1-amine hydrochloride (40.4 g, 211 mmol) and 4-dimethylaminopyridine (25.7 g, 211 mmol). The mixture was stirred at 40 °C for 12 hr. The reaction mixture was diluted with water (200 mL) and extracted with dichloromethane (150 mL x 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate = 100/1 to 1/1) to give *tert*-butyl (1*S*,5*S*)-1-(benzoyloxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (40 g, 126 mmol, 90%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 8.05 (br. d, *J* = 6.8 Hz, 2H), 7.63 - 7.52 (m, 1H), 7.46 (br. s, 2H), 4.49 - 4.32 (m, 2H), 3.83 - 3.52 (m, 2H), 3.51 - 3.32 (m, 2H), 1.59 - 1.51 (m, 1H), 1.50 - 1.38 (m, 9H), 1.00 - 0.88 (m, 1H), 0.69 - 0.55 (m, 1H); *m/z* ES + [M+H]⁺ 318.1.

[0311] **Step 4.** Synthesis of *tert*-butyl (1*R*,5*S*)-1-(benzoyloxymethyl)-2-oxo-3-azabicyclo[3.1.0]hexane-3-carboxylate. To a solution of *tert*-butyl (1*S*,5*S*)-1-(benzoyloxymethyl)-3-

azabicyclo[3.1.0]hexane-3-carboxylate (40 g, 126 mmol) in ethyl acetate (1260 mL) was treated with a solution of sodium periodate (107 g, 504 mmol) in water (1260 mL) and trichlororuthenium (784 mg, 3.78 mmol). The mixture was stirred at 20 °C for 6 hr, then treated with 2-propanol (1260 mL) and stirred for 0.5 hr. The reaction mixture was quenched by adding saturated sodium sulfite solution (1000 mL), diluted with water (1800 mL) and extracted with ethyl acetate (1800 mL x 3). The combined organic layers were washed with brine (1000 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate = 100/1 to 5/1) to give *tert*-butyl (1*R*,5*S*)-1-(benzoyloxymethyl)-2-oxo-3-azabicyclo[3.1.0]hexane-3-carboxylate (7 g, 21.1 mmol, 16%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 8.07 - 7.99 (m, 2H), 7.63 - 7.53 (m, 1H), 7.50 - 7.40 (m, 2H), 4.91 (d, *J* = 12.4 Hz, 1H), 4.49 - 4.28 (m, 1H), 3.86 - 3.60 (m, 2H), 2.25 - 2.08 (m, 1H), 1.54 - 1.49 (m, 9H), 1.42 - 1.34 (m, 1H), 1.07 - 0.97 (m, 1H); *m/z* ES + [M+H]⁺ 332.2.

[0312] **Step 5.** Synthesis of [(1*R*,5*S*)-2-oxo-3-azabicyclo[3.1.0]hexan-1-yl]methyl benzoate. To a solution of *tert*-butyl (1*R*,5*S*)-1-(benzoyloxymethyl)-2-oxo-3-azabicyclo[3.1.0]hexane-3-carboxylate (3 g, 9.05 mmol) in dichloromethane (40 mL) was added trifluoroacetic acid (11.5 g, 100 mmol). The mixture was stirred at 25 °C for 15 min. The reaction mixture was concentrated under reduced pressure to give [(1*R*,5*S*)-2-oxo-3-azabicyclo[3.1.0]hexan-1-yl]methyl benzoate (2.5 g, crude) as a yellow oil.

[0313] **Step 6.** Synthesis of (1*R*,5*S*)-1-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-2-one. To a solution of [(1*R*,5*S*)-2-oxo-3-azabicyclo[3.1.0]hexan-1-yl]methyl benzoate (2.5 g, 10.8 mmol) in anhydrous tetrahydrofuran (25 mL) was added sodium hydroxide (2 M, 13.5 mL). The mixture was stirred at 25 °C for 12 hr. The mixture was neutralized to pH = 7 with formic acid and then the reaction mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in anhydrous tetrahydrofuran (50 mL) and stirred at 25 °C for 0.5 hr. Then the mixture was filtered and the filtrate was concentrated under reduced pressure to give (1*R*,5*S*)-1-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-2-one (1.5 g, crude) as a colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.13 (br. s, 1H), 3.93 (d, *J* = 11.6 Hz, 1H), 3.31 - 3.27 (m, 1H), 3.22 (d, *J* = 11.6 Hz, 1H), 3.08 (d, *J* = 10.4 Hz, 1H), 1.95 - 1.84 (m, 1H), 1.08 - 0.98 (m, 1H), 0.55 - 0.41 (m, 1H).

[0314] **Step 7.** Synthesis of (1*R*,5*S*)-2-oxo-3-azabicyclo[3.1.0]hexane-1-carbaldehyde. To a solution of (1*R*,5*S*)-1-(hydroxymethyl)-3-azabicyclo[3.1.0]hexan-2-one (1.5 g, 11.8 mmol) in dichloromethane (9 mL) and anhydrous tetrahydrofuran (36 mL) was added Dess-Martin periodane (7.51 g, 17.7 mmol) at 0 °C. The mixture was stirred at 25 °C for 12 hr. The reaction

mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate = 100/1 to 1/2) to give (1*R*,5*S*)-2-oxo-3-azabicyclo[3.1.0]hexane-1-carbaldehyde (600 mg, 4.80 mmol, 40%) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.88 (s, 1H), 7.65 - 7.36 (m, 1H), 3.40 - 3.36 (m, 1H), 3.19 (d, *J* = 10.4 Hz, 1H), 2.65 - 2.55 (m, 1H), 1.82 - 1.76 (m, 1H), 1.36 - 1.28 (m, 1H).

[0315] **Step 8.** Synthesis of (1*R*,5*S*)-1-ethynyl-3-azabicyclo[3.1.0]hexan-2-one. To a solution of (1*R*,5*S*)-2-oxo-3-azabicyclo[3.1.0]hexane-1-carbaldehyde (600 mg, 4.80 mmol) and potassium carbonate (1.99 g, 14.3 mmol) in methanol (6 mL) was added 1-diazo-1-dimethoxyphosphoryl-propan-2-one (921 mg, 4.80 mmol) dropwise at 0 °C. The mixture was stirred at 25 °C for 12 hr. The reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (15 mL x 5). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate = 100/1 to 5/1) to give (1*R*,5*S*)-1-ethynyl-3-azabicyclo[3.1.0]hexan-2-one (250 mg, 2.06 mmol, 43%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 6.31 (s, 1H), 3.63 - 3.51 (m, 1H), 3.27 (d, *J* = 10.4 Hz, 1H), 2.44 - 2.30 (m, 1H), 2.19 (s, 1H), 1.59 - 1.45 (m, 1H), 1.22 - 1.07 (m, 1H).

[0316] **Step 9.** Synthesis of (1*R*,5*S*)-1-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexan-2-one. To a solution of [4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl] trifluoromethanesulfonate (1.54 g, 3.30 mmol) and (1*R*,5*S*)-1-ethynyl-3-azabicyclo[3.1.0]hexan-2-one (400 mg, 3.30 mmol) in *N,N*-dimethylformamide (15 mL) was added palladium triphenylphosphane (381 mg, 330 μmol), triethylamine (1.00 g, 9.91 mmol, 1.4 mL) and copper iodide (125 mg, 660 μmol). The mixture was stirred at 25 °C for 4 hr under nitrogen atmosphere. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate = 100/1 to 0/1) to give (1*R*,5*S*)-1-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexan-2-one (1.45 g, crude) as a brown solid. ¹H NMR (400 MHz, CDCl₃): δ 9.05 - 8.85 (m, 2H), 8.74 (br. s, 1H), 8.03 - 7.91 (m, 1H), 7.78 (br. s, 1H), 7.25 (br. d, *J* = 7.2 Hz, 1H), 7.19 - 7.12 (m, 1H), 5.86 (br. s, 1H), 3.78 - 3.67 (m, 1H), 3.38 (d, *J* = 10.4 Hz, 1H), 2.64 - 2.53 (m, 1H), 1.78 - 1.75 (m, 1H), 1.39 - 1.31 (m, 1H); *m/z* ES⁺ + [M+H]⁺ 438.1.

[0317] **Step 10.** Synthesis of (1*R*,5*S*)-1-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0] hexan-2-one. To a solution of (1*R*,5*S*)-1-[2-[4-(3-chloro-2-fluoro-anilino)-6-nitro-quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0] hexan-2-one (1.34 g, 3.06 mmol) in methanol (16 mL) and water (3.2 mL) was added iron power (811 mg, 14.5 mmol) and ammonium chloride (1.50 g, 28.0 mmol). The mixture was stirred at 80 °C for 0.5 hr under nitrogen atmosphere. The reaction mixture was diluted with water (50 mL) and extracted with dichloromethane (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give (1*R*,5*S*)-1-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0] hexan-2-one (1.2 g, 2.80 mmol, 91%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.60 (br. s, 1H), 8.25 (s, 1H), 7.60 (s, 1H), 7.54 (br. s, 2H), 7.49 - 7.38 (m, 2H), 7.30 - 7.23 (m, 1H), 5.85 - 5.71 (m, 2H), 3.56 - 3.44 (m, 1H), 3.19 (br. d, *J* = 10.4 Hz, 1H), 2.67 - 2.58 (m, 1H), 1.76 - 1.64 (m, 1H), 1.24 - 1.15 (m, 1H); *m/z* ES⁺ [M+H]⁺ 408.1.

[0318] **Step 11.** Synthesis of (*E*)-4-bromo-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(1*R*,5*S*)-2-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]but-2-enamide. To a solution of (1*R*,5*S*)-1-[2-[6-amino-4-(3-chloro-2-fluoro-anilino)quinazolin-7-yl]ethynyl]-3-azabicyclo[3.1.0]hexan-2-one (800 mg, 1.96 mmol) and (*E*)-4-bromobut-2-enoic acid (485 mg, 2.94 mmol) in *N,N*-dimethylformamide (4 mL) and anhydrous tetrahydrofuran (4 mL) was degassed and purged with nitrogen atmosphere for 3 times, then added diisopropylethylamine (1.01 g, 7.85 mmol) and 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (2.50 g, 3.92 mmol, 50% purity) slowly at 0 °C, then the mixture was stirred at 25 °C for 4 hr under nitrogen atmosphere. The reaction mixture was diluted with water (40 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give brown oil. The brown oil was purified by column chromatography (silicon dioxide, petroleum ether/ethyl acetate = 100/1 to 0/1) to give (*E*)-4-bromo-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(1*R*,5*S*)-2-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]but-2-enamide (340 mg, 588 μmol, 30%) as a white solid. *m/z* ES⁺ [M+H]⁺ 556.1.

[0319] **Step 12.** Synthesis of (*E*)-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(1*R*,5*S*)-2-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]-4-(2,2,3,3,5,5,6,6-octadeuteriomorpholin-4-yl)but-2-enamide. To a solution of (*E*)-4-bromo-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(1*R*,5*S*)-2-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]but-2-enamide (240 mg, 432 μmol) in *N,N*-dimethylformamide (4 mL) and anhydrous tetrahydrofuran (4 mL) was added diisopropylethylamine (447 mg, 3.46 mmol) and

2,2,3,3,5,5,6,6-octadeuteriomorpholine hydrochloride (170 mg, 1.30 mmol) at 0 °C. The mixture was stirred at 25 °C for 12 hr. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase HPLC (column: Waters Xbridge 150*25mm*5um; mobile phase: [water (ammonia hydroxide v/v)- acetonitrile]; gradient: 27%-57% B over 10 min) to give (*E*)-*N*-[4-(3-chloro-2-fluoro-anilino)-7-[2-[(1*R*,5*S*)-2-oxo-3-azabicyclo[3.1.0]hexan-1-yl]ethynyl]quinazolin-6-yl]-4-(2,2,3,3,5,5,6,6-octadeuteriomorpholin-4-yl)but-2-enamide (140 mg, 241 μmol, 56%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.38 - 9.91 (m, 1H), 9.68 - 9.49 (m, 1H), 8.89 (s, 1H), 8.59 - 8.22 (m, 1H), 7.89 - 7.69 (m, 1H), 7.63 - 7.56 (m, 1H), 7.55 - 7.36 (m, 2H), 7.33 - 7.19 (m, 1H), 6.90 - 6.75 (m, 1H), 6.57 (br. d, *J* = 15.6 Hz, 1H), 3.53 - 3.47 (m, 1H), 3.22 (br. d, *J* = 10.4 Hz, 1H), 3.17 (br. d, *J* = 5.2 Hz, 2H), 2.64 - 2.59 (m, 1H), 1.74 - 1.61 (m, 1H), 1.29 - 1.23 (m, 1H); *m/z* ES + [M+H]⁺ 569.3.

Example 3. Biological Activity of the Exemplary Compounds

[0320] The biological activity of the exemplary compounds of the present disclosure was assessed.

[0321] *Retroviral Production:* EGFRmutants were subcloned into pMXs-IRES-Blasticidin (RTV- 016, Cell Biolabs, San Diego, CA). Retroviral expression vector retrovirus was produced by transient transfection of HEK 293 T cells with the retroviral EGFR mutant expression vector pMXs-IRES-Blasticidin (RTV-016, Cell Biolabs), pCMV-Gag-Pol vector and pCMV-VSV-G-Envelope vector. Briefly, HEK 293T/17 cells were plated in 100mm collagen coated plate (354450, Corning Life Sciences, Tewksbury, MA) (4 X 10⁵ per plate) and incubated overnight. The next day, retroviral plasmids (3 pg of EGFR mutant, 1.0 pg of pCMV-Gag-Pol and 0.5 pg pCMV-VSV-G) were mixed in 500 μl of Optimem (31985, Life Technologies). The mixture was incubated at room temperature for 5 min and then added to Optimem containing transfection reagent Lipofectamine (11668, Invitrogen) and incubated for 20 minutes. Mixture was then added dropwise to HEK 293T cells. The next day the medium was replaced with fresh culture medium and retrovirus was harvested @ 24 and 48 hrs.

[0322] *Generation of EGFR mutant stable cell lines:* BaF3 cells (1.5E5 cells) were infected with 1 ml of viral supernatant supplemented with 8 pg/ml polybrene by centrifuging for 30 min at 1000 rpm. Cells were placed in a 37°C incubator overnight. Cells were then spun for 5 minutes to pellet the cells. Supernatant was removed and cells re-infected a fresh 1 ml of viral supernatant

supplemented with 8 µg/ml polybrene by centrifuging for 30 min at 1000 rpm. Cells were placed in 37°C incubator overnight. Cells were then maintained in RPMI containing 10% Heat Inactivated FBS, 2% L-glutamine containing 10 ng/ml IL-3. After 48 hours cells were selected for retroviral infection in 10 µg/ml Blasticidin for one week. Blasticidin resistant populations were washed twice in phosphate buffered saline before plating in media lacking IL-3 to select for IL-3 independent growth.

[0323] *Assay for cell proliferation:* BaF3 cell lines were resuspended at 1.3E5 c/ml in RPMI containing 10% Heat Inactivated FBS, 2% L-glutamine and 1% Pen/Strep and dispensed in triplicate (17.5E4 c/well) into 96 well plates. To determine the effect of drug on cell proliferation, cells incubated for 3 days in the presence of vehicle control or test drug at varying concentrations. Inhibition of cell growth was determined by luminescent quantification of intracellular ATP content using CellTiterGlo (Promega), according to the protocol provided by the manufacturer. Comparison of cell number on day 0 versus 72 hours post drug treatment was used to plot dose-response curves. The number of viable cells was determined and normalized to vehicle-treated controls. Inhibition of proliferation, relative to vehicle-treated controls was expressed as a fraction of 1 and graphed using PRISM® software (Graphpad Software, San Diego, CA). EC₅₀ values were determined with the same application.

[0324] *Cellular protein analysis:* Cell extracts were prepared by detergent lysis (RIPA, R0278, Sigma, St Louis, MO) containing 10 mM Iodoacetamide (786-228, G-Biosciences, St. Louis, MO), protease inhibitor (P8340, Sigma, St. Louis, MO) and phosphatase inhibitors (P5726, P0044, Sigma, St. Louis, MO) cocktails. The soluble protein concentration was determined by micro-BSA assay (Pierce, Rockford IL). Protein immunodetection was performed by electrophoretic transfer of SDS-PAGE separated proteins to nitrocellulose, incubation with antibody, and chemiluminescent second step detection. Nitrocellulose membranes were blocked with 5% nonfat dry milk in TBS and incubated overnight with primary antibody in 5% bovine serum albumin. The following primary antibodies from Cell Signaling Technology were used at 1:1000 dilution: phospho-EGFR[Y1173] and total EGFR. β-Actin antibody, used as a control for protein loading, was purchased from Sigma Chemicals. Horseradish peroxidase-conjugated secondary antibodies were obtained from Cell Signaling Technology and used at 1:5000 dilution. Horseradish peroxidase-conjugated secondary antibodies were incubated in nonfat dry milk for 1 hour. SuperSignal chemiluminescent reagent (Pierce Biotechnology) was used according to the manufacturer's directions and blots were imaged using the Alpha Innotech image analyzer and AlphaEaseFC software (Alpha Innotech, San Leandro CA).

[0325] The measured IC₅₀ values of compounds of the present disclosure are shown in Table B below (A represents an IC₅₀ value <10 nM; B represents an IC₅₀ value >10 nM and <100 nM; C represents an IC₅₀ value >100 nM and <500 nM; and D represents an IC₅₀ value >500 nM).

Table B

Cmpd No.	EGFR-WT (H292) IC ₅₀ (nM)	EGFR-Ex19del (Ba/F3) IC ₅₀ (nM)	Ex19del+C797S (Ba/F3) IC ₅₀ (nM)
1	C	A	A
2	D	A	B
3	D	A	A
4	D		
10	C	A	A

Example 4. Pharmacokinetic Parameters of the Exemplary Compounds

[0326] The pharmacokinetic parameters of the exemplary compounds of the present disclosure were assessed following QD oral administration of Compound A at 100 mg or 200 mg dosage levels on Days 1 and 15 in patients with NSCLC or GBM.

[0327] The measured parameters are shown in Table C.

Table C: Summary of PK Parameters for Compound A and Compounds 1-3 on Cycle 1
Day 1 and Day 15 Following QD Oral Administration of Compound A

Compound A dose			100 mg				200 mg			
Number of Patients			N = 15				N = 26			
Compound No.			A	1	3	2	A	1	3	2
Day 1	C _{max} (ng/mL)	Mean (CV%)	10.7 (35.3)	3.53 (37.7)	15.8 (33.9)	8.64 (57.9)	22.2 (50.6)	9.08 (53.9)	31.3 (56.5)	20.1 (61.4)
	T _{max} (h)	Median (min, max)	3 (1, 4)	4 (2, 24)	4 (1, 8)	3 (1, 8)	2 (1, 6)	3 (1, 24)	3 (2, 6)	2 (2, 4)
	AUC ₀₋₂₄ (ng*h/mL)	Mean (CV%)	110 (38.3)	51.0 (33.0)	166 (39.4)	92.0 (29.7)	201 (45.4)	105 (50.5)	283 (47.6)	159 (44.6)
	t _{1/2} (h)	Mean (CV%)	9.8 (37.1)	15.2 (36.2)	6.1 (29.5)	8.9 (83.9)	12.0 (31.1)	15.9 (49.2)	7.1 (23.3)	7.4 (38.0)
Day 15	C _{max} (ng/mL)	Mean (CV%)	17.3 (35.8)	11.1 (26.4)	15.8 (28.2)	9.08 (38.6)	37.3 (39.5)	26.3 (37.2)	35.1 (43.8)	26.5 (47.1)
	T _{max} (h)	Median (min, max)	2 (1, 3)	4 (2, 8)	3 (1, 4)	3 (1, 4)	2 (1, 24)	3 (2, 6)	3 (2, 4)	3 (2, 4)
	AUC ₀₋₂₄ (ng*h/mL)	Mean (CV%)	240 (52.4)	205 (28.9)	188 (25.9)	104 (26.0)	486 (44.3)	440 (37.8)	409 (50.6)	255 (49.8)
	t _{1/2} (h)	Mean (CV%)	20.5 (53.5)	34.3 (36.1)	10.9 (41.3)	12.4 (72.3)	15.4 (35.9)	31.8 (44.1)	9.7 (22.4)	9.8 (33.0)
	C _{trough} (ng/mL)	Mean (CV%)	6.73 (78.2)	7.05 (31.9)	3.50 (49.9)	1.88 (32.1)	13.3 (68.5)	14.9 (46.7)	9.51 (111)	5.65 (104)
	RA _{AUC}	Mean (CV%)	2.5 (49.3)	4.8 (45.4)	1.3 (31.7)	1.3 (35.9)	2.5 (38.3)	4.6 (38.9)	1.5 (40.5)	1.8 (34.0)

	M/P ratio C _{max}	Mean (CV%)	N/A	0.71 (35.4)	0.98 (41.3)	0.80 (33.2)	N/A	0.77 (34.3)	1.0 (54.9)	0.99 (32.5)
	M/P ratio AUC	Mean (CV%)		0.96 (31.0)	0.85 (32.2)	0.50 (27.7)		0.98 (29.5)	0.87 (49.6)	0.57 (28/7)

AUC₀₋₂₄ = area under the concentration-time curve from time 0 to 24 hours postdose; C_{max} = maximum observed concentration; C_{trough} = the concentration at the end of the dosing interval; CV = coefficient of variation; M/P ratio = metabolite to parent molar ratio; max = maximum; min = minimum; N = number of patients with intensive PK data; n = number of patients with evaluable PK parameter values; PK = pharmacokinetics; RA_{AUC} = ratio of accumulation based on AUC₀₋₂₄; t_{1/2} = half-life; T_{max} = time of first occurrence of C_{max}.

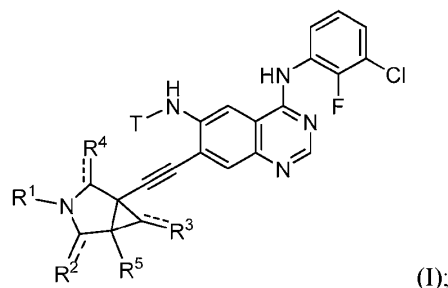
[0328] Compounds 1-3 retain potent inhibition of oncogenic EGFR mutations and selectivity versus EGFR-WT. At steady state, these 3 compounds were circulating in human plasma with a metabolite to parent molar ratio of 0.7 – 1.0 for C_{max} and 0.5 – 1.0 for AUC. The pharmacological activity index of these compounds, i.e., their contribution to in vivo pharmacological activity calculated from their in vitro EGFR mutation inhibition potency and steady state PK exposure relative to that of Compound A, was estimated to be approximately 150%, 40%, and 24% of Compound A based on C_{max}, respectively, and 132%, 53%, and 16% of Compound A based on AUC₀₋₂₄, respectively. These data suggest that all 3 compounds contribute to efficacy.

EQUIVALENTS

[0329] It is understood that the invention can be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

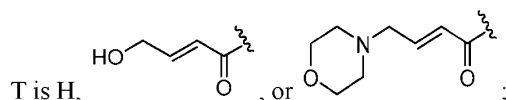
What is claimed is:

1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

each $\equiv$ independently denotes a single bond or a double bond, as valency permits;



R¹ is H or C₁-C₆ alkyl;

R² is H, -OH, or oxo;

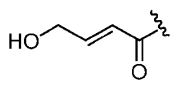
R³ is H, -OH, or oxo;

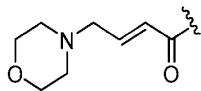
R⁴ is H, -OH, or oxo; and

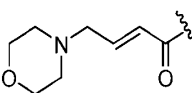
R⁵ is H or -OH;

provided that the compound is not Compound A or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein the compound is an isolated compound.
3. The compound of any one of the preceding claims, wherein the compound has a purity of about 80% or higher, about 85% or higher, about 90% or higher, about 91% or higher, about 92% or higher, about 93% or higher, about 94% or higher, about 95% or higher, about 96% or higher, about 97% or higher, about 98% or higher, about 99% or higher, about 99.1% or higher, about 99.2% or higher, about 99.3% or higher, about 99.4% or higher, about 99.5% or higher, about 99.6% or higher, about 99.7% or higher, about 99.8% or higher, or about 99.9% or higher.
4. The compound of any one of the preceding claims, wherein T is H.

5. The compound of any one of the preceding claims, wherein T is  or



6. The compound of any one of the preceding claims, wherein T is 

7. The compound of any one of the preceding claims, wherein R^1 is H.
8. The compound of any one of the preceding claims, wherein R^1 is methyl.
9. The compound of any one of the preceding claims, wherein R^2 is H.
10. The compound of any one of the preceding claims, wherein R^2 is -OH.
11. The compound of any one of the preceding claims, wherein R^2 is oxo.
12. The compound of any one of the preceding claims, wherein R^3 is H.
13. The compound of any one of the preceding claims, wherein R^3 is -OH.
14. The compound of any one of the preceding claims, wherein R^3 is oxo.
15. The compound of any one of the preceding claims, wherein R^4 is H.
16. The compound of any one of the preceding claims, wherein R^4 is -OH.
17. The compound of any one of the preceding claims, wherein R^4 is oxo.
18. The compound of any one of the preceding claims, wherein R^5 is H.
19. The compound of any one of the preceding claims, wherein R^5 is -OH.

20. The compound of any one of the preceding claims, wherein the compound is selected from the compounds described in Table I, and pharmaceutically acceptable salts thereof.
21. An isotopic derivative of the compound of any one of the preceding claims.
22. A pharmaceutical composition comprising the compound of any one of the preceding claims, and one or more pharmaceutically acceptable carriers or excipients.
23. A method of preventing or treating cancer, comprising administering to the subject in need thereof the compound of any one of the preceding claims.
24. The compound of any one of the preceding claims for use in the inhibition of an oncogenic variant of an ErbB receptor.
25. The compound of any one of the preceding claims, wherein cancer is a bladder cancer, a breast cancer, a cervical cancer, a colorectal cancer, an endometrial cancer, a gastric cancer, a glioblastoma (GBM), a head and neck cancer, a lung cancer, a non-small cell lung cancer (NSCLC), or any subtype thereof.