

SUBSTITUTED TRICYCLIC COMPOUNDS AS KRAS DEGRADERS

This application claims a benefit of Indian provisional application number 202341067839, filed on October 10, 2023, and Indian provisional application number 202441054021, filed on July 15, 2024, the specifications of which are hereby incorporated by
5 reference in their entirety.

FIELD OF THE INVENTION

The present invention relates to substituted tricyclic compounds or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof which are useful as KRAS degraders and for the treatment of diseases or conditions or disorders dependent upon KRAS. The present
10 invention also relates to a method of preparation of the substituted tricyclic compounds and pharmaceutical compositions comprising said compounds.

BACKGROUND OF THE INVENTION

Cancer is one of the leading causes of death worldwide. The treatment of cancer is gradually changing from an organ-centred to a pathway-centred approach. Cancer cells often
15 have an addiction to the signals that are generated by the cancer-causing genes. Consequently, targeted cancer drugs that selectively inhibit the products of activated oncogenes can have dramatic effects on cancer cell viability.

RAS is a family of related proteins which are ubiquitously expressed in all cell lineages and organs. All RAS protein family members (the key human members of which are KRAS,
20 NRAS, and HRAS) belong to a class of protein called small GTPase and are involved in cellular signal transduction).

RAS represents a group of closely related monomeric globular proteins comprised of 189 amino acids (21 kDa molecular mass) which is associated with the plasma membrane, and which binds either GDP or GTP. RAS acts as a molecular switch. When RAS contains bound
25 GDP, it is in the resting or off position and is “inactive”. In response to exposure of the cell to certain growth promoting stimuli, RAS is induced to exchange its bound GDP for a GTP. When GTP bound, RAS is “switched on” and is able to interact with and activate other proteins (its “downstream targets”). The RAS protein itself has a very low intrinsic ability to hydrolyze GTP back to GDP, to turn into the ‘off’ state. Switching RAS off requires extrinsic proteins
30 termed GTPase- activating proteins (GAPs) that interact with RAS and accelerate the conversion of GTP to GDP. consequently, in RAS which affects its ability to interact with GAP

or to convert GTP back to GDP will result in a prolonged activation of the protein and consequently a prolonged growth signal to the cell. Because these signals result in cell growth and cell division, an overactive RAS signalling may ultimately lead to cancer.

Activating mutations in the RAS oncogenes (KRAS, NRAS, or HRAS) are found in
5 approximately 30% of all human tumours. Although mutation of any one of the three RAS
isoforms (KRAS, NRAS, or HRAS) has been shown to lead to oncogenic transformation,
KRAS mutations are by far the most common in human cancer. Oncogenic KRAS mutations
occur in 90% of pancreatic, 45% of colorectal and 35% of lung carcinomas (Bos J L., Bos J L.
RAS oncogenes in human cancer: a review. *Cancer Res.* 1989 Sep 1;49(17):4682-9. Erratum
10 in: *Cancer Res* 1990 Feb 15;50(4):1352 and Downward J., Downward J. Targeting RAS
signalling pathways in cancer therapy. *Nat Rev Cancer.* 2003 Jan;3(1):11-22).

The well-known role of KRAS in malignancy and the discovery of these frequent
mutations in KRAS in various tumour types, made KRAS a highly attractive target of the
pharmaceutical industry for cancer therapy. Notwithstanding thirty years of large-scale
15 discovery efforts to develop inhibitors of KRAS for treating cancer.

Compounds that inhibit KRAS activity are still highly desirable and under
investigation, including those that disrupt effectors such as guanine nucleotide exchange
factors (Sun Q, Burke JP, Phan J, Burns MC, Olejniczak ET, Waterson AG, Lee T, Rossanese
OW, Fesik SW. Discovery of small molecules that bind to KRAS and inhibit Sos-mediated
20 activation. *Angew Chem Int Ed Engl.* 2012 Jun 18;51(25):6140-3) as well advances in the
covalent targeting of an allosteric pocket of KRAS G12C (Ostrem JM, Peters U, Sos ML, Wells
JA, Shokat KM). KRAS (G12C) inhibitors allosterically control GTP affinity and effector
interactions (*Nature* 2013 Nov 28; 503(7477):548-51). Clearly there is a continued interest in
developing inhibitors of KRAS, particularly inhibitors of activating KRAS mutants, especially
25 KRAS G12D.

In recent years, use of the ubiquitin proteasome pathway to specifically degrade protein
substrates with the help of proteolysis-targeting chimeras (PROTAC) has become more
impactful than the inhibition. PROTAC which is a compound with two hetero functional
ligands linked by a linker: one ligand targets the target protein of interest (POI), while the other
30 ligand specifically recruits E3 ligase. When PROTAC binds to E3 ligase and the protein of
interest to form a ternary complex, by hijacking the E3 ligase, PROTAC presents POI with a
favourable spatial position to facilitate its ubiquitination, and subsequently the ubiquitinated

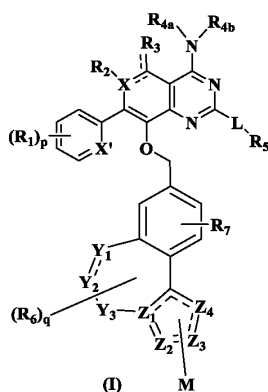
target protein is recognized by the proteasome and degraded, thereby selectively reducing the level of the target protein within the cell. The advantage of PROTAC technology, compared with the research and development methods of traditional small molecule inhibitors, is that they can catalyse multiple rounds of degradation of target proteins, and complete removal of proteins will also produce more potent efficacy.

Least progress has been made in this field, and hence there is a need for potent therapeutic compounds for the treatment of KRAS mutant cancers, as well as to provide therapeutically effective pharmaceutical compositions for use in these KRAS mutant cancers. That is, there remains a need for compounds that are KRAS degraders useful as therapeutic agents.

SUMMARY OF THE INVENTION:

Provided herein are substituted tricyclic compounds and pharmaceutical compositions thereof that are useful as KRAS degraders and for treating diseases or conditions or disorders that are dependent upon or mediated by KRAS.

In one aspect, the present application provides a compound of formula (I):



or a pharmaceutically acceptable salt or stereoisomer or a tautomer thereof;

wherein,

R₁ at each occurrence, independently is hydrogen, (C₁-C₆)alkyl, hydroxy, halo, amino, halo(C₁-C₆)alkyl, and/or two R₁ adjacent to each other together with the C atoms to which they are attached form a phenyl or 5- to 6-membered heterocyclyl; wherein the phenyl and heterocyclyl are unsubstituted or substituted with 1, 2 or 3 substituents each independently

selected from the group consisting of (C₁-C₆)alkyl, (C₂-C₄)alkynyl, halo, hydroxy, halo(C₁-C₆)alkyl, amino, and cyano;

p is 1, 2, 3, or 4;

X and X', independently, is C or N;

5 R₂ is hydrogen, cyclopropyl or absent;

R₃ is hydrogen or oxo;

R_{4a} and R_{4b}, independently, is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 5- to 10-membered heteroaryl(C₁-C₆)alkyl or 4- to 7-membered heterocycloalkyl, wherein the cycloalkyl and heteroarylalkyl are unsubstituted or substituted with 1, 2 or 3 substituents each
10 independently selected from the group consisting of halo, (C₁-C₆)alkyl and amino; and/or

R_{4a} and R_{4b} together with the nitrogen to which they are attached form a 4- to 14-membered heterocyclyl optionally containing one or two additional heteroatoms selected from the group consisting of nitrogen, oxygen, and sulphur; wherein the heterocyclyl is unsubstituted or substituted with 1, 2 or 3 groups each independently selected from the group consisting of (C₁-
15 C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy, cyano and -C(O)-R_{4c}; wherein said alkyl is unsubstituted or substituted independently with one or more of halo, hydroxy, amino, cyano or (C₃-C₆)cycloalkyl; and/or

R_{4c} is hydrogen, amino, (C₁-C₆)alkylamino, 4- to 7-membered heterocycloalkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkyl or (C₁-C₆)alkylamino(C₁-C₆)alkyl; wherein the heterocycloalkyl
20 and cycloalkyl are unsubstituted or substituted with 1, 2 or 3 groups each independently selected from the group consisting of halo, hydroxy and (C₁-C₆)alkyl;

L is -O-(CH₂)_m*, or -C(O)-*, -C(O)-NH-*; wherein asterisk mark represents the point of attachment with R₅;

R₅ is (C₁-C₆)alkyl, (C₁-C₆)alkoxy, -(CH₂)_m-NR_cR_d, 5- to 14-membered
25 heterocycloalkyl or (C₃-C₆)cycloalkyl; wherein the heterocycloalkyl and cycloalkyl are unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkyl, halo, amino, and -(CH₂)_mNR_yR_z;

m is 0, 1, 2 or 3;

R_c and R_d , independently, is hydrogen or (C₁-C₆)alkyl; or R_c and R_d together with the N atom to which they are attached, form a 4- to 7-membered heterocycloalkyl;

R_y and R_z , independently is hydrogen or (C₁-C₆)alkyl; or R_y and R_z together with the N atom to which they are attached, form a 4- to 7-membered heterocycloalkyl; wherein the
5 heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkyl, halo and (C₂-C₄)acyl;

R_6 at each occurrence, independently, is hydrogen, amino, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or hydroxy; or two R_6 on the same carbon represent an oxo group;

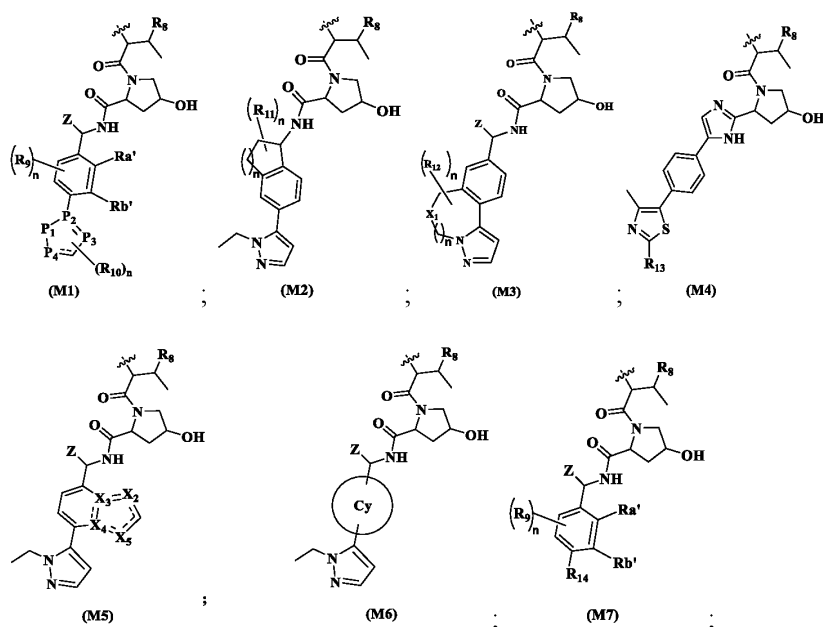
q is 1, 2 or 3;

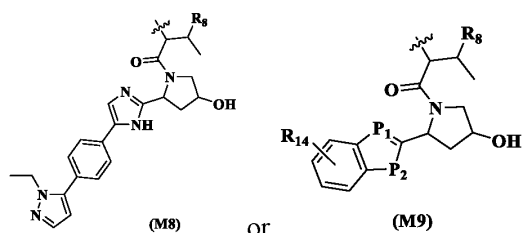
10 Y_1 , Y_2 and Y_3 , independently, is a bond, C, N, or O; wherein not more than one of Y_1 , Y_2 or Y_3 is a bond;

Z_1 , Z_2 , Z_3 and Z_4 independently, is a C, CR₇, NR₇, or N; wherein at least two of Z_1 , Z_2 , Z_3 and Z_4 are N;

R_7 and $R_{7'}$ independently, is hydrogen, halo, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₁-
15 C₆)alkoxy, or halo(C₁-C₆)alkoxy;

M is M1, M2, M3, M4, M5, M6, M7, M8 or M9;





wherein,

R_8 is (C_1-C_6) alkyl, hydroxy, halo, or amino;

5 Z is hydrogen, (C_1-C_6) alkyl, halo or $-CH_2OH$;

$R_{a'}$ and $R_{b'}$ independently, is hydrogen, halo or (C_1-C_6) alkyl; or $R_{a'}$ and $R_{b'}$ together with the C atoms to which they are attached form a 5 to 6 membered heterocyclyl ring optionally containing one or two hetero atoms independently selected from the group consisting of O, S, and N;

10 R_9 at each occurrence, independently, is hydrogen, 4- to 8-membered heterocycloalkyl, -O-heterocycloalkyl, -O- (C_1-C_6) alkyl;

 wherein heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo or (C_1-C_6) alkyl;

15 wherein the alkyl in -O- (C_1-C_6) alkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C_1-C_6) alkylamino or 5- to 8-membered heterocycloalkyl; wherein the heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo, or (C_1-C_6) alkyl;

20 P_1 , P_2 , P_3 and P_4 , independently, is C, N or S; wherein at least one of P_1 , P_2 , P_3 and P_4 , is N;

R_{10} is hydrogen, (C_1-C_6) alkyl, (C_2-C_4) alkynyl, hydroxy, 3- to 7-membered heterocycloalkyl, or (C_3-C_6) cycloalkyl;

25 wherein the alkyl and alkynyl is unsubstituted or substituted with halo, cycloalkyl, $-NH-(CO)-NH_2$, $-NR_mR_n$, or 4 to 6 membered heterocycloalkyl; wherein

the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkyl, hydroxy, halo or amino;

5 wherein 3- to 7-membered heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo, hydroxy or (C₁-C₆)alkyl;

R_m and R_n are independently hydrogen or (C₁-C₆)alkyl;

R₁₁ at each occurrence, independently, is hydrogen, hydroxy or (C₁-C₆)alkyl; wherein the alkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected
10 from the group consisting of halo or hydroxy;

R₁₂ at each occurrence, independently, is hydrogen or amino;

X₁ is C or N;

R₁₃ is hydrogen or (C₁-C₆)alkyl;

X₂, X₃, X₄ and X₅, each independently is C, CH or N; wherein one of X₃ or X₄ is always
15 N and the other is C;

R₁₄ at each occurrence, independently is hydrogen, halo, hydroxy, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl or (C₂-C₆)alkynyl;

Cy is (C₃-C₁₀)cycloalkyl or 3- to 10-membered heterocycloalkyl;

a dotted line [-----] indicates a bond or absent; and

20 n is 1, 2 or 3.

In another aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, and a pharmaceutically acceptable carrier or an excipient.

In another aspect, the present invention provides a pharmaceutical composition
25 comprising a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof for treating diseases or conditions or disorders that are dependent upon or mediated by KRAS.

In another aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof for treating diseases or conditions or disorders that have altered KRAS including mutations and overexpression.

5 In another aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer for treating diseases or conditions or disorders wherein degradation of KRAS proteins provide a benefit. For example, cancer.

10 In another aspect, the present invention provides a method of degrading a target protein in a subject comprising, administering to the subject in need thereof, a therapeutically effective amount of the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

15 In another aspect, the present invention provides a method of treating a condition or a disease or a disorder dependent upon KRAS in a subject comprising, administering to the subject in need thereof, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof. The conditions or disease or disorder of interest is treatable by degradation of KRAS, for example, a cancer.

20 In another aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, for use as a medicament.

In another aspect, the present invention provides a use of a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, in the manufacture of a medicament for the treatment of a disease or disorder dependent upon KRAS; wherein the disease or disorder is cancer.

25 BRIEF DESCRIPTION OF THE DRAWINGS

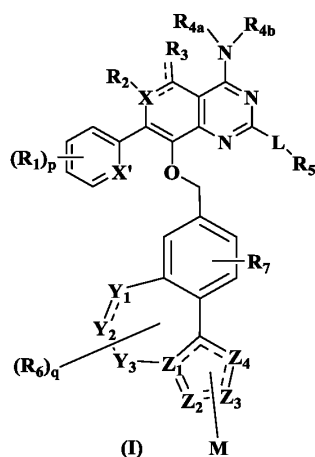
FIG.1 illustrates the change in tumor volume in mice that received the compound 1d (10 mg/kg or 30 mg/kg) and compound 12d (10 mg/kg or 30 mg/kg) at various treatment days.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides substituted tricyclic compounds, referred as a compound of formula (I), which are useful as KRAS degraders and for the treatment of diseases or conditions or disorders dependent upon or mediated by KRAS. The present invention further provides a pharmaceutical composition comprising compound or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof as therapeutic agents.

Each embodiment is provided by way of explanation of the invention and not by way of limitation of the invention. In fact, it will be apparent to those skilled in the art that various modifications and variations can be made to the compounds, compositions and methods described herein without departing from the scope of the invention. For instance, features illustrated or described as part of one embodiment can be applied to another embodiment to yield a still further embodiment. Thus, it is intended that the present invention includes such modifications and variations and their equivalents. Other objects, features and aspects of the present invention are disclosed in or are obvious from, the following detailed description. It is to be understood by one of ordinary skill in the art that the present discussion is a description of exemplary embodiments only and is not to be construed as limiting the broader aspects of the present invention.

In one embodiment, the present invention provides a compound of formula (I),



or a pharmaceutically acceptable salt or stereoisomer or a tautomer thereof;

wherein,

R₁ at each occurrence, independently is hydrogen, (C₁-C₆)alkyl, hydroxy, halo, amino, halo(C₁-C₆)alkyl, and/or two R₁ adjacent to each other together with the C atoms to which they are attached form a phenyl or 5- to 6-membered heterocyclyl; wherein the phenyl and heterocyclyl are unsubstituted or substituted with 1, 2 or 3 substituents each independently
 5 selected from the group consisting of (C₁-C₆)alkyl, (C₂-C₄)alkynyl, halo, hydroxy, halo(C₁-C₆)alkyl, amino, and cyano;

p is 1, 2, 3, or 4;

X and X', independently, is C or N;

R₂ is hydrogen, cyclopropyl or absent;

10 R₃ is hydrogen or oxo;

R_{4a} and R_{4b}, independently, is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 5- to 10-membered heteroaryl(C₁-C₆)alkyl or 4- to 7-membered heterocycloalkyl, wherein the cycloalkyl and heteroarylalkyl are unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo, (C₁-C₆)alkyl and amino; and/or

15 R_{4a} and R_{4b} together with the nitrogen to which they are attached form a 4- to 14-membered heterocyclyl optionally containing one or two additional heteroatoms selected from the group consisting of nitrogen, oxygen, and sulphur; wherein the heterocyclyl is unsubstituted or substituted with 1, 2 or 3 groups each independently selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy, cyano and -C(O)-R_{4c}; wherein said alkyl is unsubstituted
 20 or substituted independently with one or more of halo, hydroxy, amino, cyano or (C₃-C₆)cycloalkyl; and/or

R_{4c} is hydrogen, amino, (C₁-C₆)alkylamino, 4- to 7-membered heterocycloalkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkyl or (C₁-C₆)alkylamino(C₁-C₆)alkyl; wherein the heterocycloalkyl and cycloalkyl are unsubstituted or substituted with 1, 2 or 3 groups each independently
 25 selected from the group consisting of halo, hydroxy and (C₁-C₆)alkyl;

L is -O-(CH₂)_m*, or -C(O)-*, -C(O)-NH-*; wherein asterisk mark represents the point of attachment with R₅;

R₅ is (C₁-C₆)alkyl, (C₁-C₆)alkoxy, -(CH₂)_m-NR_cR_d, 5- to 14-membered heterocycloalkyl or (C₃-C₆)cycloalkyl; wherein the heterocycloalkyl and cycloalkyl are

unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkyl, halo, amino, and -(CH₂)_mNR_yR_z;

m is 0, 1, 2 or 3;

5 R_c and R_d, independently, is hydrogen or (C₁-C₆)alkyl; or R_c and R_d together with the N atom to which they are attached, form a 4- to 7-membered heterocycloalkyl;

R_y and R_z, independently is hydrogen or (C₁-C₆)alkyl; or R_y and R_z together with the N atom to which they are attached, form a 4- to 7-membered heterocycloalkyl; wherein the heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkyl, halo and (C₂-C₄)acyl;

10 R₆ at each occurrence, independently, is hydrogen, amino, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or hydroxy; or two R₆ on the same carbon represent an oxo group;

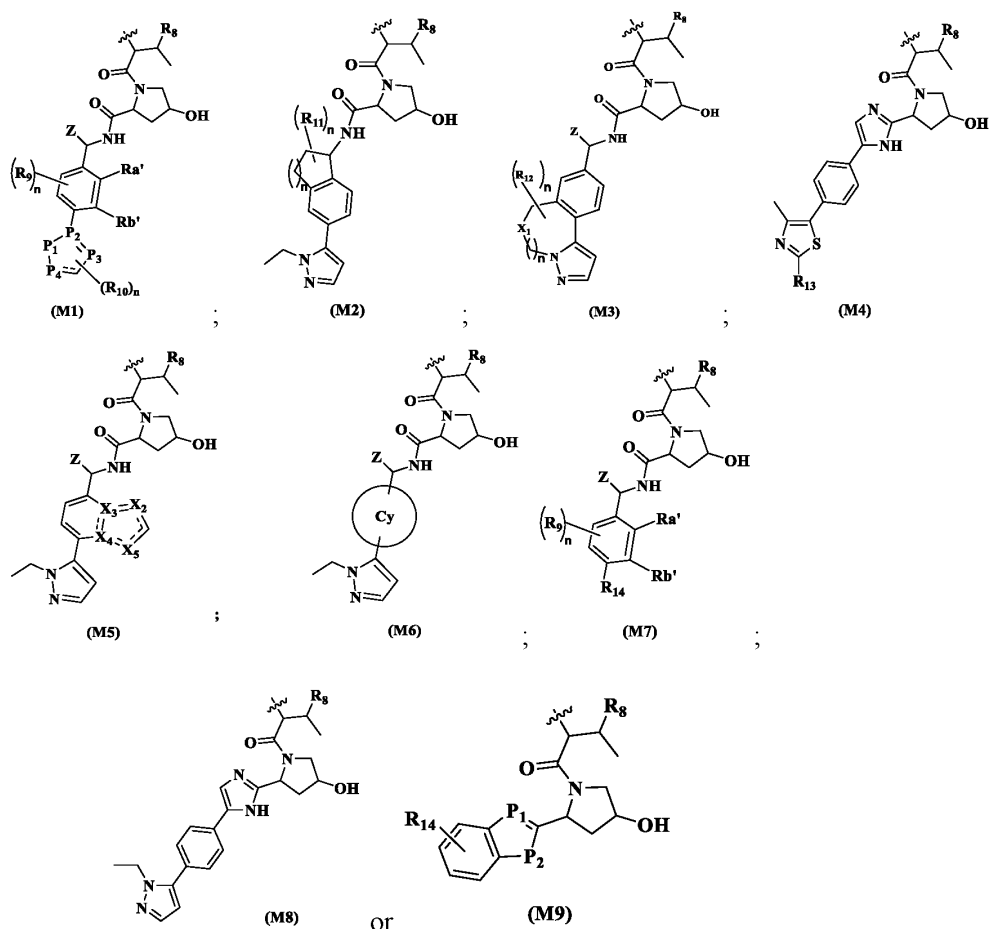
q is 1, 2 or 3;

Y₁, Y₂ and Y₃, independently, is a bond, C, N, or O; wherein not more than one of Y₁, Y₂ or Y₃ is a bond;

15 Z₁, Z₂, Z₃ and Z₄ independently, is a C, CR₇, NR₇, or N; wherein at least two of Z₁, Z₂, Z₃ and Z₄ are N;

R₇ and R_{7'} independently, is hydrogen, halo, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₁-C₆)alkoxy, or halo(C₁-C₆)alkoxy;

M is M1, M2, M3, M4, M5, M6, M7, M8 or M9;



wherein,

5 R_8 is (C₁-C₆)alkyl, hydroxy, halo or amino;

Z is hydrogen, (C₁-C₆)alkyl, halo or -CH₂OH;

$R_{a'}$ and $R_{b'}$ independently, is hydrogen, halo or (C₁-C₆)alkyl; or $R_{a'}$ and $R_{b'}$ together with the C atoms to which they are attached form a 5 to 6 membered heterocyclyl ring optionally containing one or two hetero atoms independently selected from the group consisting of O, S, and N;

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R_9 at each occurrence, independently, is hydrogen, 4- to 8-membered heterocycloalkyl, -O-heterocycloalkyl, -O-(C₁-C₆)alkyl;

wherein heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo or (C₁-C₆)alkyl;

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wherein the alkyl in -O-(C₁-C₆)alkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkylamino or 5- to 8-membered heterocycloalkyl; wherein the heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo, or (C₁-C₆)alkyl;

P₁, P₂, P₃ and P₄, independently, is C, N or S; wherein at least one of P₁, P₂, P₃ and P₄, is N;

R₁₀ is hydrogen, (C₁-C₆)alkyl, (C₂-C₄)alkynyl, hydroxy, 3- to 7-membered heterocycloalkyl or (C₃-C₆)cycloalkyl;

wherein the alkyl and alkynyl is unsubstituted or substituted with halo, cycloalkyl, -NH-(CO)-NH₂, -NR_mR_n, or 4 to 6 membered heterocycloalkyl; wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkyl, hydroxy, halo or amino;

wherein 3- to 7-membered heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo, hydroxy or (C₁-C₆)alkyl;

R_m and R_n are independently hydrogen or (C₁-C₆)alkyl;

R₁₁ at each occurrence, independently, is hydrogen, hydroxy or (C₁-C₆)alkyl; wherein the alkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo or hydroxy;

R₁₂ at each occurrence, independently, is hydrogen or amino;

X₁ is C or N;

R₁₃ is hydrogen or (C₁-C₆)alkyl;

X₂, X₃, X₄ and X₅, each independently is C, CH or N; wherein one of X₃ or X₄ is always N and the other is C;

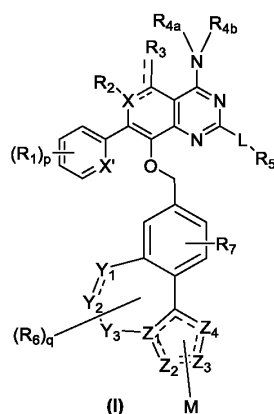
R₁₄ at each occurrence, independently is hydrogen, halo, hydroxy, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl or (C₂-C₆)alkynyl;

Cy is (C₃-C₁₀)cycloalkyl or 3- to 10-membered heterocycloalkyl;

a dotted line [-----] indicates a bond or absent; and

n is 1, 2 or 3.

In one embodiment, the present invention provides a compound of formula (I),



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or a pharmaceutically acceptable salt or stereoisomer or a tautomer thereof;

wherein,

R₁ at each occurrence, independently is hydrogen, (C₁-C₆)alkyl, hydroxy, halo, amino or halo(C₁-C₆)alkyl, and/or two R₁ adjacent to each other together with the C atoms to which they are attached form a phenyl or 5- to 6-membered heterocyclyl; wherein the phenyl and heterocyclyl are unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkyl, (C₂-C₄)alkynyl, halo, hydroxy, halo(C₁-C₆)alkyl, amino, and cyano;

p is 1, 2, 3, or 4;

15 X and X', independently, is C or N;

R₂ is hydrogen, cyclopropyl or absent;

R₃ is hydrogen or oxo;

R_{4a} and R_{4b}, independently, is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 5- to 10-membered heteroaryl(C₁-C₆)alkyl or 4- to 7-membered heterocycloalkyl, wherein the cycloalkyl and heteroarylalkyl are unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo, (C₁-C₆)alkyl and amino; and/or

20

R_{4a} and R_{4b} together with the nitrogen to which they are attached form a 4- to 14-membered heterocyclyl optionally containing one or two additional heteroatoms selected from the group consisting of nitrogen, oxygen, and sulphur; wherein the heterocyclyl is unsubstituted or substituted with 1, 2 or 3 groups each independently selected from the group consisting of
 5 (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy, cyano and -C(O)- R_{4c} ; wherein said alkyl is unsubstituted or substituted independently with one or more of hydrogen, halo, hydroxy, amino, cyano or (C₃-C₆)cycloalkyl; and/or

R_{4c} is hydrogen, amino, (C₁-C₆)alkylamino, 4- to 7-membered heterocycloalkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkyl or (C₁-C₆)alkylamino(C₁-C₆)alkyl; wherein the heterocycloalkyl
 10 and cycloalkyl are unsubstituted or substituted with 1, 2 or 3 groups each independently selected from the group consisting of halo, hydroxy and (C₁-C₆)alkyl;

L is -O-(CH₂)_m*, or -C(O)-NH-*, wherein asterisk mark represents the point of attachment with R_5 ;

R_5 is (C₁-C₆)alkyl, (C₁-C₆)alkoxy, -(CH₂)_m-NR_cR_d, 5- to 14-membered
 15 heterocycloalkyl or (C₃-C₆)cycloalkyl; wherein the heterocycloalkyl and cycloalkyl are unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkyl, halo, amino and -(CH₂)_mNR_yR_z;

m is 0, 1, 2 or 3;

R_c and R_d , independently, is hydrogen or (C₁-C₆)alkyl;

R_y and R_z , independently is hydrogen or (C₁-C₆)alkyl; or R_y and R_z together with the N
 20 atom to which they are attached, form a 4- to 7-membered heterocycloalkyl; wherein the heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkyl, halo and (C₂-C₄)acyl;

R_6 at each occurrence, independently, is hydrogen, amino, (C₁-C₆)alkyl, (C₁-C₆)alkoxy
 25 or hydroxy; or two R_6 on the same carbon represent an oxo group;

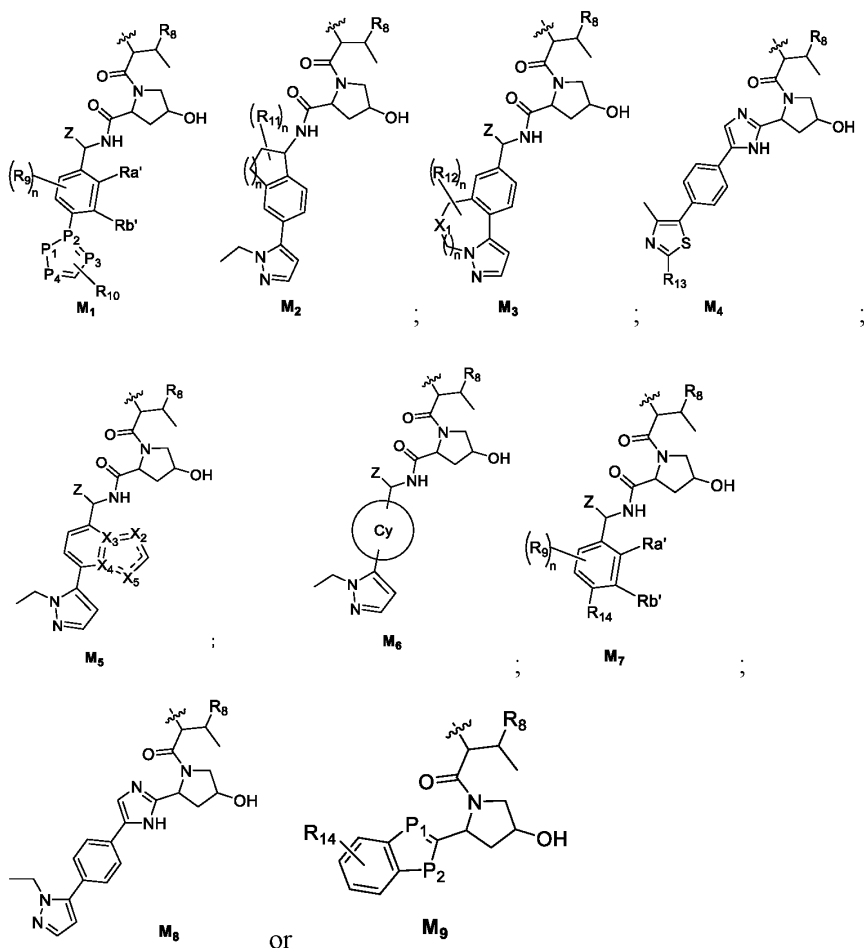
q is 1, 2 or 3;

Y_1 , Y_2 and Y_3 , independently, is a bond, C, N, or O; wherein not more than one of Y_1 ,
 Y_2 or Y_3 is a bond;

Z_1 , Z_2 , Z_3 and Z_4 independently, is a C, CR₇, NR₇, or N; wherein at least two of Z_1 , Z_2 ,
 30 Z_3 and Z_4 are N;

R_7 and $R_{7'}$ independently, is hydrogen, halo, (C_1-C_6) alkyl, halo (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or halo (C_1-C_6) alkoxy;

M is M1, M2, M3, M4, M5, M6, M7, M8 or M9;



wherein,

R_8 is (C_1-C_6) alkyl, hydroxy, halo or amino;

Z is hydrogen, (C_1-C_6) alkyl, halo or $-CH_2OH$;

10 $R_{a'}$ and $R_{b'}$ independently, is hydrogen, halo or (C_1-C_6) alkyl; or $R_{a'}$ and $R_{b'}$ together with the C atoms to which they are attached form a 5 to 6 membered heterocyclyl ring optionally containing one or two hetero atoms independently selected from the group consisting of O, S and N;

R₉ at each occurrence, independently, is hydrogen, 4- to 8-membered heterocycloalkyl, -O-heterocycloalkyl or -O-(C₁-C₆)alkyl;

5 wherein 4- to 8-membered heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo or (C₁-C₆)alkyl;

10 wherein the alkyl in -O-(C₁-C₆)alkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkylamino or 5- to 8-membered heterocycloalkyl; wherein the heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo, or (C₁-C₆)alkyl;

P₁, P₂, P₃ and P₄, independently, is C, N or S; wherein at least one of P₁, P₂, P₃ and P₄, is N;

R₁₀ is hydrogen, (C₁-C₆)alkyl, (C₂-C₄)alkynyl, hydroxy, 3- to 7-membered heterocycloalkyl or (C₃-C₆)cycloalkyl;

15 wherein the alkyl and alkynyl is unsubstituted or substituted with halo, cycloalkyl, NH-(CO)-NH₂, NR_mR_n or 5 to 6 membered heterocycloalkyl; wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkyl, hydroxy, halo or amino;

20 wherein 3- to 7-membered heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo, hydroxy or (C₁-C₆)alkyl;

R_m and R_n are independently hydrogen or (C₁-C₆)alkyl;

25 R₁₁ at each occurrence, independently, is hydrogen, hydroxy or (C₁-C₆)alkyl; wherein the alkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo or hydroxy;

R₁₂ at each occurrence, independently, is hydrogen or amino;

X₁ is C or N;

R₁₃ is hydrogen or (C₁-C₆)alkyl;

X₂, X₃, X₄ and X₅, each independently is C, CH or N; wherein one of X₃ or X₄ is always N and the other is C;

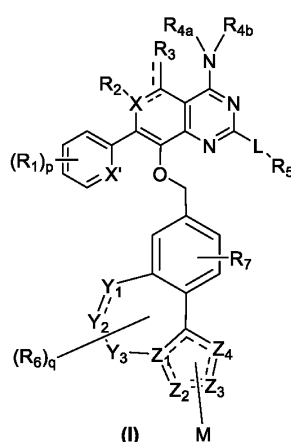
R₁₄ at each occurrence, independently is hydrogen, halo, hydroxy, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl or (C₂-C₆)alkynyl;

5 Cy is (C₃-C₁₀)cycloalkyl or 3- to 10-membered heterocycloalkyl;

a dotted line [-----] indicates a bond or absent; and

n is 1, 2 or 3.

In one embodiment, the present invention provides a compound of formula (I),



10 or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof;

wherein,

R₁ at each occurrence, independently is hydrogen, (C₁-C₆)alkyl, hydroxy, halo, amino or halo(C₁-C₆) alkyl, and/or two R₁ adjacent to each other together with the C atoms to which they are attached form a phenyl or 5- to 6-membered heterocyclyl; wherein the phenyl and
 15 heterocyclyl are unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkyl, (C₂-C₄)alkyne, halo, hydroxy, halo(C₁-C₆)alkyl, amino and cyano;

p is 1, 2, 3 or 4;

X and X', independently, is C or N;

20 R₂ is hydrogen, cyclopropyl or absent;

R₃ is hydrogen or an oxo;

R_{4a} and R_{4b}, independently, is hydrogen, (C₁-C₆)alkyl or 4- to 7-membered heterocyloalkyl; or R_{4a} and R_{4b} together with the nitrogen to which they are attached form a 5- to 14-membered heterocyclyl optionally containing one or two additional heteroatoms selected
5 from the group consisting of nitrogen, oxygen, and sulphur; wherein the heterocyclyl is unsubstituted or substituted with 1, 2 or 3 groups each independently selected from the group consisting of (C₁-C₆)alkyl, hydroxy and -C(O)-amino(C₁-C₆)alkyl;

L is -O-(CH₂)_m- or -C(O)-NH-;

R₅ is (C₁-C₆)alkyl, -(CH₂)_mNR_cR_d, 5- to 14-membered heterocycloalkyl or (C₃-
10 C₆)cycloalkyl; wherein the heterocycloalkyl and cycloalkyl are unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkyl, halo, amino and -(CH₂)_mNR_yR_z;

m is 0, 1, 2 or 3;

R_c and R_d, independently, is hydrogen or (C₁-C₆)alkyl;

15 R_y and R_z, independently is hydrogen or (C₁-C₆)alkyl; or R_y and R_z together with the N atom to which they are attached, form a 4- to 7-membered heterocycloalkyl; wherein the heterocycloalkyl is unsubstituted or substituted with (C₁-C₆)alkyl, halo or (C₂-C₄)acyl;

R₆ at each occurrence, independently, is hydrogen, amino, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or hydroxy; or two R₆ on the same carbon represent an oxo group;

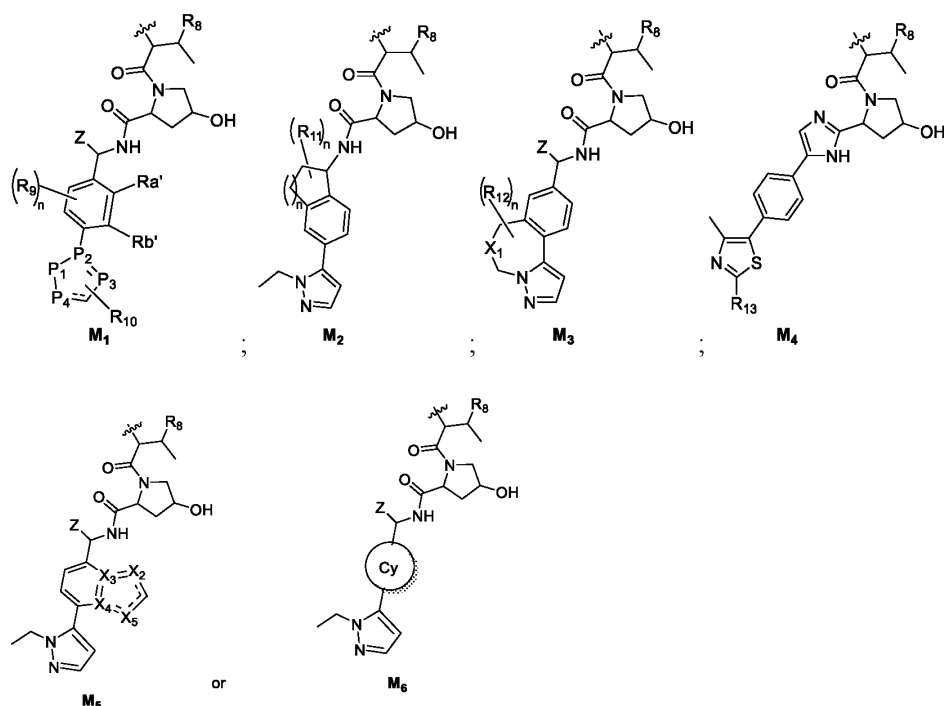
20 q is 1, 2 or 3;

Y₁, Y₂ and Y₃, independently, is a bond, C, N or O; wherein not more than one of Y₁, Y₂ or Y₃ is a bond;

Z₁, Z₂, Z₃ and Z₄ independently, is a C, CR₇, NR₇ or N; wherein at least two of Z₁, Z₂, Z₃ and Z₄ are N;

25 R₇ and R₇, independently, is hydrogen, halo, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₁-C₆)alkoxy or halo(C₁-C₆)alkoxy;

M is M₁, M₂, M₃, M₄ M₅ or M₆;



wherein,

R₈ is (C₁-C₆)alkyl, hydroxy, halo or amino;

5 **Z** is hydrogen, (C₁-C₆)alkyl, halo or CH₂OH;

R_{a'} and **R_{b'}** independently, is hydrogen, halo or (C₁-C₆)alkyl; or **R_{a'}** and **R_{b'}** together with the C atoms to which they are attached form a 5 to 6 membered heterocyclyl ring optionally containing one or two hetero atoms independently selected from the group consisting of O, S and N;

10 **R₉** at each occurrence, independently, is hydrogen, 4- to 8-membered heterocycloalkyl, -O- heterocycloalkyl or -O-(C₁-C₆)alkyl; wherein the alkyl is unsubstituted or substituted with amino(C₁-C₆)alkyl or 5 to 8 membered heterocycloalkyl; wherein the heterocycloalkyl at each occurrence is unsubstituted or substituted with halo or (C₁-C₆)alkyl;

15 **P₁**, **P₂**, **P₃** and **P₄**, independently, is C, N or S; wherein at least one of **P₁**, **P₂**, **P₃** and **P₄**, is N;

R₁₀ is hydrogen, (C₁-C₆)alkyl, (C₂-C₄)alkynyl, hydroxy, 3- to 7-membered heterocycloalkyl or (C₃-C₆)cycloalkyl; wherein the alkyl and alkynyl is unsubstituted or substituted with halo, cycloalkyl, NH-(CO)-NH₂, NR_mR_n or 5 to 6 membered heterocycloalkyl;

wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with (C₁-C₆)alkyl, hydroxy, halo or amino;

R_m and R_n are independently hydrogen or (C₁-C₆)alkyl;

R₁₁ at each occurrence, independently, is hydrogen, hydroxy or (C₁-C₆)alkyl; wherein the
5 alkyl is unsubstituted or substituted with halo or hydroxy;

R₁₂ at each occurrence, independently, is hydrogen or amino;

X₁ is C or N;

R₁₃ is hydrogen or (C₁-C₆)alkyl;

X₂, X₃, X₄ and X₅, each independently is C, CH or N; wherein one of X₃ or X₄ is always
10 N and the other is C;

Cy is (C₃-C₁₀)cycloalkyl or 3- to 10-membered heterocycloalkyl;

a dotted line [-----] indicates a bond or absent; and

n is 1, 2 or 3.

In one embodiment, R₁ at each occurrence, independently is (C₁-C₆)alkyl, halo(C₁-C₆)
15 alkyl, hydroxy, halo or amino.

In one embodiment, R₁ at each occurrence is (C₁-C₆)alkyl, amino, hydroxy or halo.

In one embodiment, R₁ at each occurrence, independently is -CH₃, -CH₂-CH₃, -CH₂-CH₂-
CH₃, -CH(CH₃)₂ or -CH₂-CH₂-CH₂-CH₃.

In one embodiment, R₁ is methyl, hydroxy, amino or fluoro.

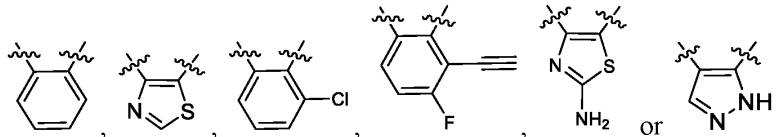
In one embodiment, R₁ at each occurrence, independently is -CHF₂ or -CF₃.
20

In one embodiment, R₁ at each occurrence, independently is -CH₃, -CF₃ or -NH₂.

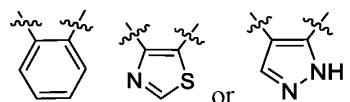
In one embodiment, R₁ at each occurrence, independently is -CH₃, -OH or F.

In one embodiment, two R₁ adjacent to each other together with the C atoms to which
they are attached form a phenyl or 5- to 6-membered heterocyclyl; wherein the phenyl and
25 heterocyclyl are unsubstituted or substituted with 1, 2 or 3 substituents each independently
selected from (C₁-C₆)alkyl, (C₂-C₄)alkynyl, halo and amino.

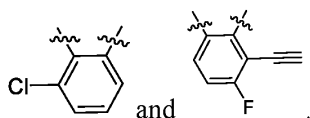
In one embodiment, two R₁ adjacent to each other together with the C atoms to which

they are attached form a  , or .

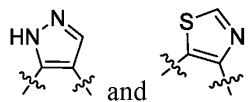
In one embodiment, two R₁ adjacent to each other together with the C atoms to which

they are attached form a  or .

- 5 In one embodiment, two R₁ adjacent to each other together with the C atoms to which they are attached form a substituted phenyl selected from the group consisting of formula:



In one embodiment, R₁ at each occurrence, independently is two R₁ adjacent to each other together with the C atoms to which they are attached form a unsubstituted 5- to 6-membered

- 10 heterocyclyl selected from the group consisting of formula:  and .

In one embodiment, p is 1, 2, 3, or 4.

In one embodiment, X and X', independently, is C or N.

In one embodiment, X is C and X' is N.

In one embodiment, X is N and X' is C.

- 15 In one embodiment, X and X' both are C or N.

In one embodiment, R₂ is hydrogen, cyclopropyl or absent.

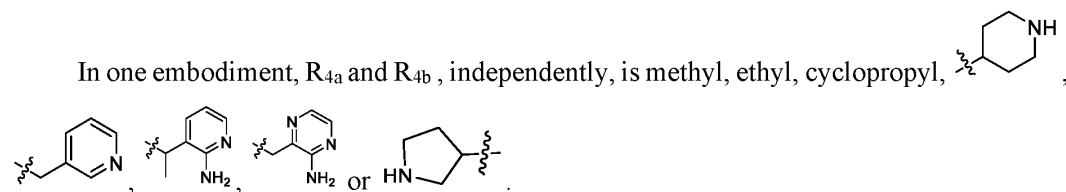
In one embodiment, R₂ is cyclopropyl or absent.

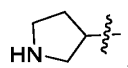
In one embodiment, R₃ is hydrogen.

In one embodiment, R₃ is oxo.

- 20 In one embodiment, R_{4a} and R_{4b}, independently, is (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 5- to 10-membered heteroaryl(C₁-C₆)alkyl or 4- to 7-membered heterocycloalkyl.

In one embodiment, R_{4a} and R_{4b} , independently, is (C₁-C₆)alkyl or 4- to 7-membered heterocyloalkyl.



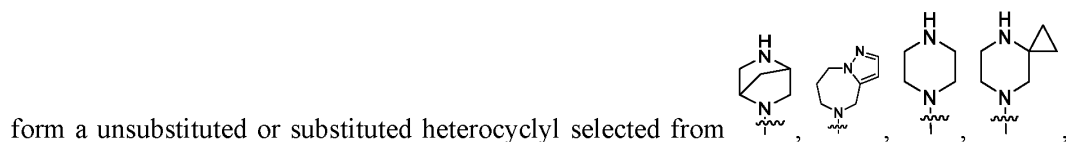
5 In one embodiment, R_{4a} and R_{4b} , independently, is methyl or .

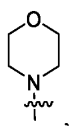
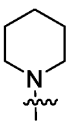
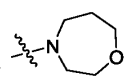
In one embodiment, R_{4a} and R_{4b} together with the nitrogen to which they are attached form a 4- to 14-membered heterocyclyl optionally containing additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur.

10 In one embodiment, the 4- to 14-heterocyclyl is optionally substituted with 1, 2 or 3 groups each independently selected from (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy and -C(O)- R_{4c} ; wherein said alkyl is substituted independently with one or more of halo, hydroxy or (C₃-C₆)cycloalkyl.

15 In one embodiment, R_{4a} and R_{4b} together with the nitrogen to which they are attached form a 4- to 14-membered heterocyclyl optionally containing one or two additional nitrogen, wherein the heterocyclyl is unsubstituted.

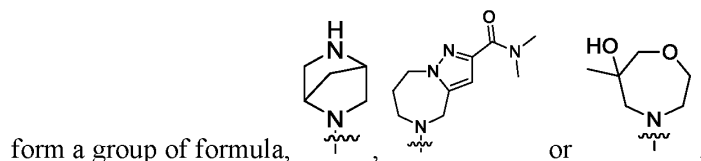
In one embodiment, R_{4a} and R_{4b} together with the nitrogen to which they are attached

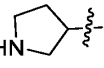


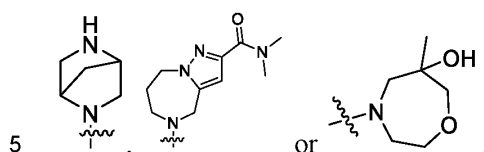
,  or  wherein; the heterocyclyl is unsubstituted or substituted with 1, 2 or 3 groups each independently selected from (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy and -C(O)- R_{4c} ; wherein said alkyl is substituted independently with one or more of halo, hydroxy or (C₃-C₆)cycloalkyl.

20

In one embodiment, R_{4a} and R_{4b} together with the nitrogen to which they are attached



In one embodiment R_{4a} and R_{4b} , independently, is methyl or ; or together with the nitrogen to which they are attached form a moiety selected from the group consisting of



In one embodiment, R_{4c} is amino, (C_1-C_6) alkylamino, unsubstituted or substituted 4- to 7-membered heterocycloalkyl, (C_3-C_6) cycloalkyl, (C_1-C_6) alkyl or (C_1-C_6) alkylamino (C_1-C_6) alkyl; wherein the heterocycloalkyl and cycloalkyl are unsubstituted or substituted with 1, 2 or 3 groups each independently selected from the group consisting of halo, hydroxy and (C_1-C_6) alkyl.

In one embodiment, R_{4c} is amino, (C_1-C_6) alkylamino, (C_1-C_6) alkyl or unsubstituted or substituted 4- to 7-membered heterocycloalkyl; wherein the heterocycloalkyl is substituted with (C_1-C_6) alkyl.

In one embodiment, L is $-O-$, $-O-(CH_2)_m-$, $-C(O)-$ or $-C(O)-NH-$; wherein asterisk mark represents the point of attachment with R_5 .

In one embodiment, L is $-O-$, $-O-(CH_2)_m-$ or $-C(O)-NH-$; wherein asterisk mark represents the point of attachment with R_5 .

In one embodiment, L is $-O-(CH_2)_m-$ or $-C(O)-NH-$; wherein asterisk mark represents the point of attachment with R_5 .

In one embodiment, L is $-O-(CH_2)_m-$; wherein asterisk mark represents the point of attachment with R_5 .

In one embodiment, wherein L is $-O-$ or $-O-CH_2-$ wherein asterisk mark represent the point of attachment with R_5 .

In one embodiment, L is $-C(O)-NH-$; wherein asterisk mark represents the point of attachment with R_5 .

In one embodiment, R₅ is (C₁-C₆)alkyl, -(CH₂)_m-NR_cR_d, 5- to 14-membered heterocycloalkyl or (C₃-C₆)cycloalkyl, wherein the heterocycloalkyl and cycloalkyl are unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkyl, halo, amino and -(CH₂)_mNR_yR_z.

5 In one embodiment, R₅ is (C₁-C₆)alkoxy, -(CH₂)_mNR_cR_d or 5- to 14-membered heterocycloalkyl; wherein the heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from (C₁-C₆)alkyl, halo, amino and -(CH₂)_m-NR_yR_z.

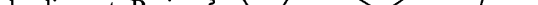
In one embodiment, R₅ is 5- to 14-membered heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently
10 selected from (C₁-C₆)alkyl, halo and -(CH₂)_mNR_yR_z.

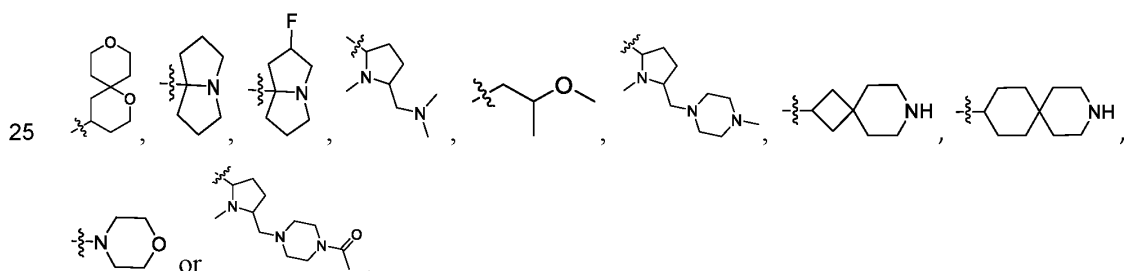
In one embodiment, R₅ is (C₃-C₆)cycloalkyl, wherein the cycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkyl, halo, amino and -(CH₂)_mNR_zR_z.

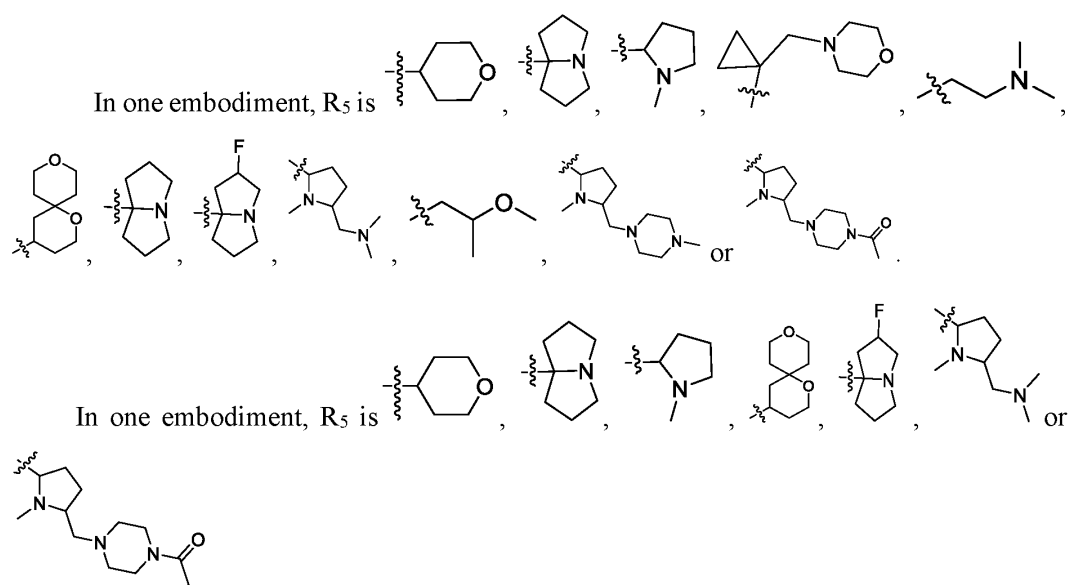
In one embodiment, R_c and R_d are (C₁-C₆)alkyl; or R_c and R_d together with the N atom
15 to which they are attached, form a 4- to 7-membered heterocycloalkyl.

R_y and R_z, independently is hydrogen or (C₁-C₆)alkyl; or R_y and R_z together with the N atom to which they are attached, form a 4- to 7-membered heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from (C₁-C₆)alkyl, halo or (C₂-C₄)acyl.

20 In one embodiment, R_y and R_z is (C₁-C₆)alkyl; or R_y and R_z together with the N atom to which they are attached, form a 4- to 7-membered heterocycloalkyl; wherein the heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from (C₁-C₆)alkyl and (C₂-C₄)acyl.

In one embodiment, R₅ is 





5 In one embodiment, m is 0, 1, 2 or 3. In one embodiment, R₆ at each occurrence, independently, is hydrogen, amino, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or hydroxy; or two R₆ on the same carbon represent an oxo group.

In one embodiment, R₆ is amino, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or hydroxy; or two R₆ on the same carbon represent an oxo group.

10 In one embodiment, R₆ is amino, methyl, methoxy, hydroxy or oxo.

In one embodiment, two R₆ on the same carbon represent an oxo group.

In one embodiment q is 1, 2 or 3.

In one embodiment Y₁, Y₂ and Y₃, independently, is a bond, C, N, or O, wherein not more than one of Y₁, Y₂ or Y₃ is a bond.

15 In one embodiment Y_1 , Y_2 and Y_3 , are independently, is C or N.

In one embodiment Y₁, Y₂ and Y₃, are independently, is C or O.

In one embodiment Z_1, Z_2, Z_3 and Z_4 are independently, is a C, CR₇, NR₇, or N, wherein at least two of Z_1, Z_2, Z_3 and Z_4 are N.

In one embodiment Z_1, Z_2, Z_3 and Z_4 independently, is a C or N.

20 In one embodiment Z_1 , Z_2 , Z_3 and Z_4 independently, is N, wherein two of Z_1 , Z_2 , Z_3 and Z_4 are N.

In one embodiment Z_1 , Z_2 , Z_3 and Z_4 independently, is N, wherein three of Z_1 , Z_2 , Z_3 and Z_4 are N.

In one embodiment R₇ and R_{7'} independently, is hydrogen, halo, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₁-C₆)alkoxy or halo(C₁-C₆)alkoxy.

5 In one embodiment, R₇ and R_{7'} are independently, is halo, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₁-C₆)alkoxy or halo(C₁-C₆)alkoxy.

In one embodiment, R₇ and R_{7'} is halo, methyl, trifluoromethyl, methoxy or -O-CF₃.

In one embodiment, R₇ and R_{7'} independently, is F, Cl or Br.

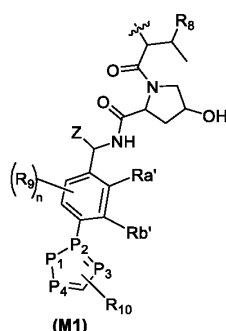
In one embodiment, R₇ and R_{7'} independently, is CHF₂ or CF₃.

10 In one embodiment, R₇ and R_{7'} independently, is CH₃, -CH₂-CH₃, -CH₂-CH₂-CH₃, -CH(CH₃)₂ or -CH₂-CH₂-CH₂-CH₃.

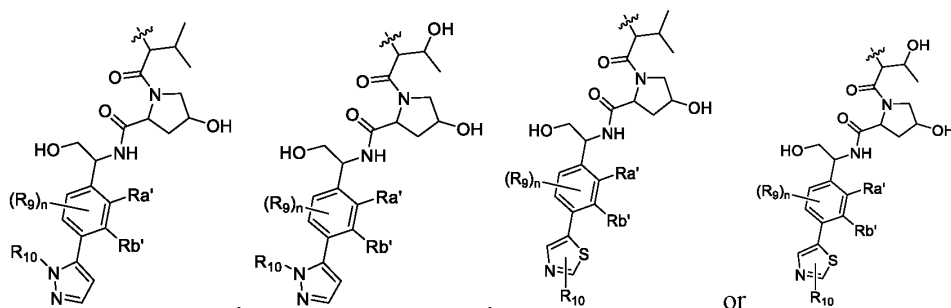
In one embodiment, R₇ and R_{7'} independently is methoxy.

In one embodiment, R₇ and R_{7'} independently is -OCF₃.

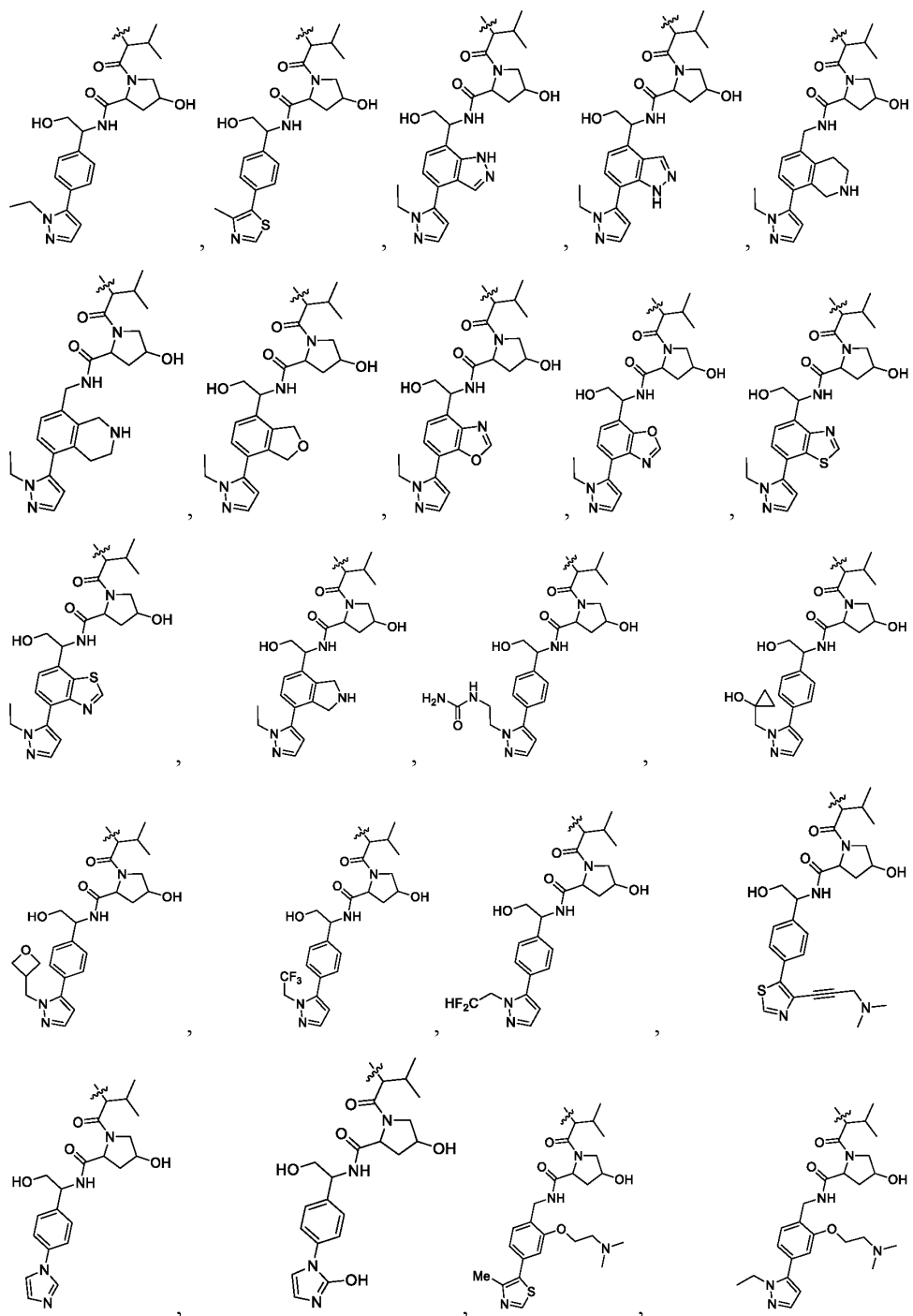
In one embodiment, M is M1

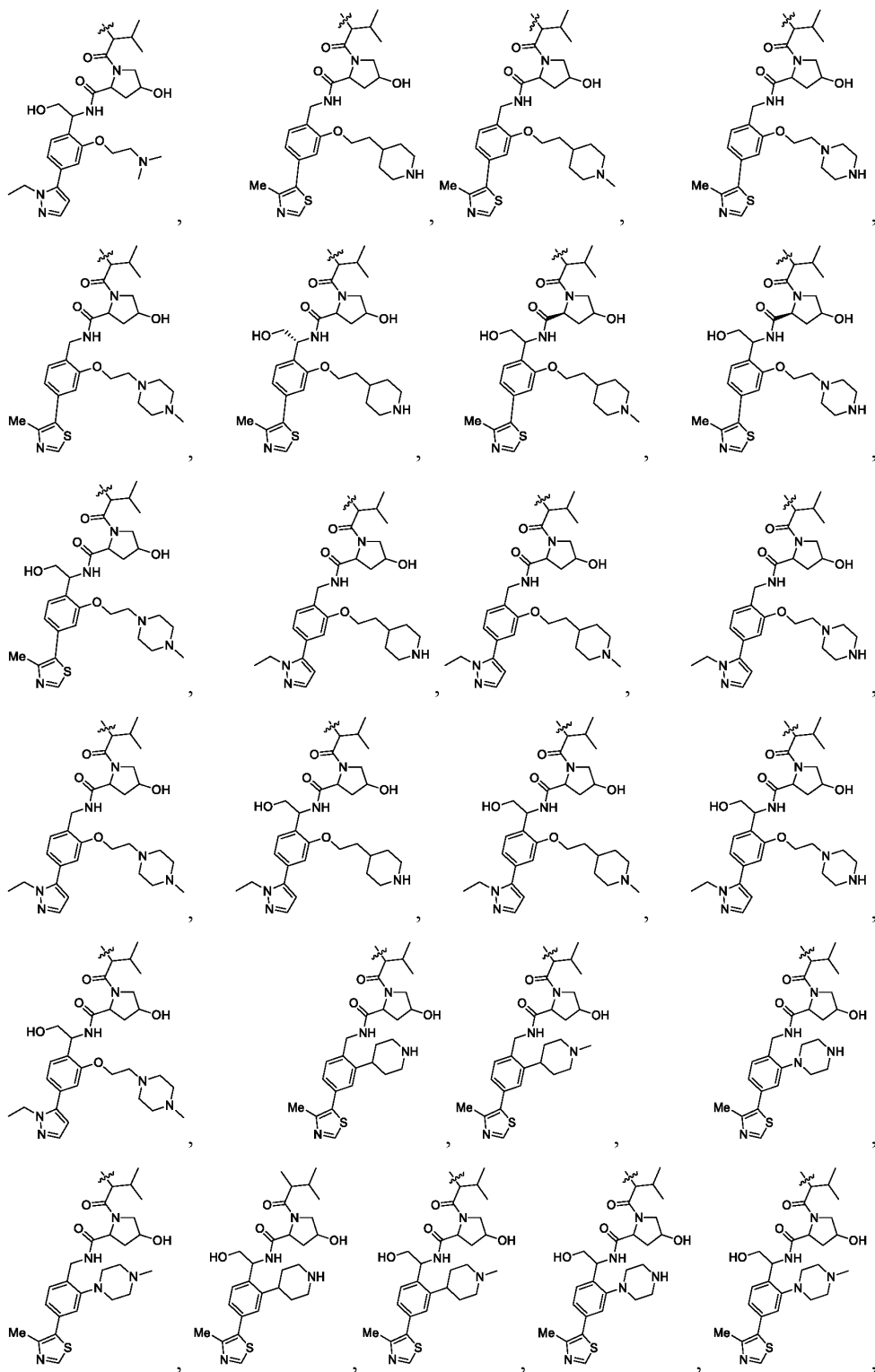


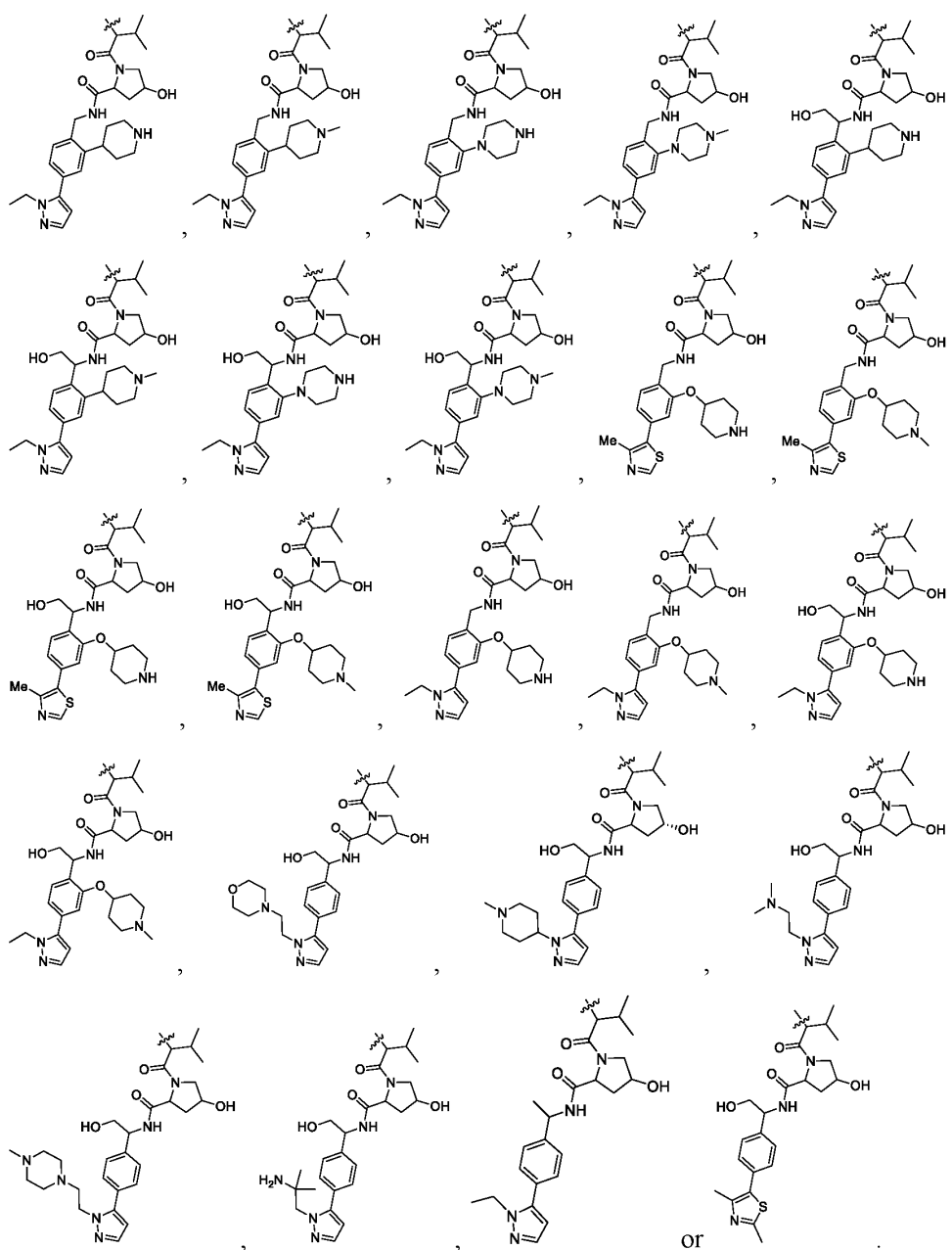
In one embodiment, M1 is



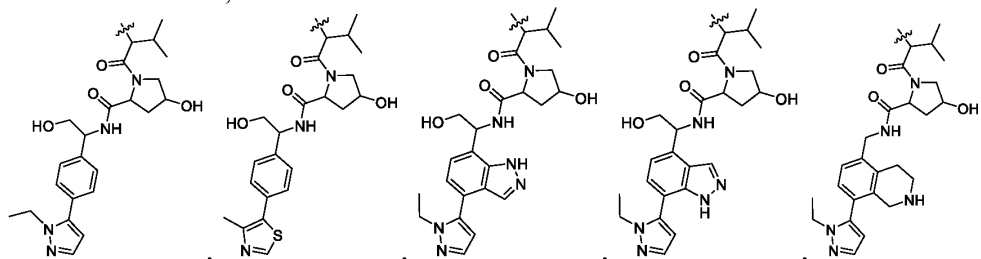
In one embodiment, M1 is

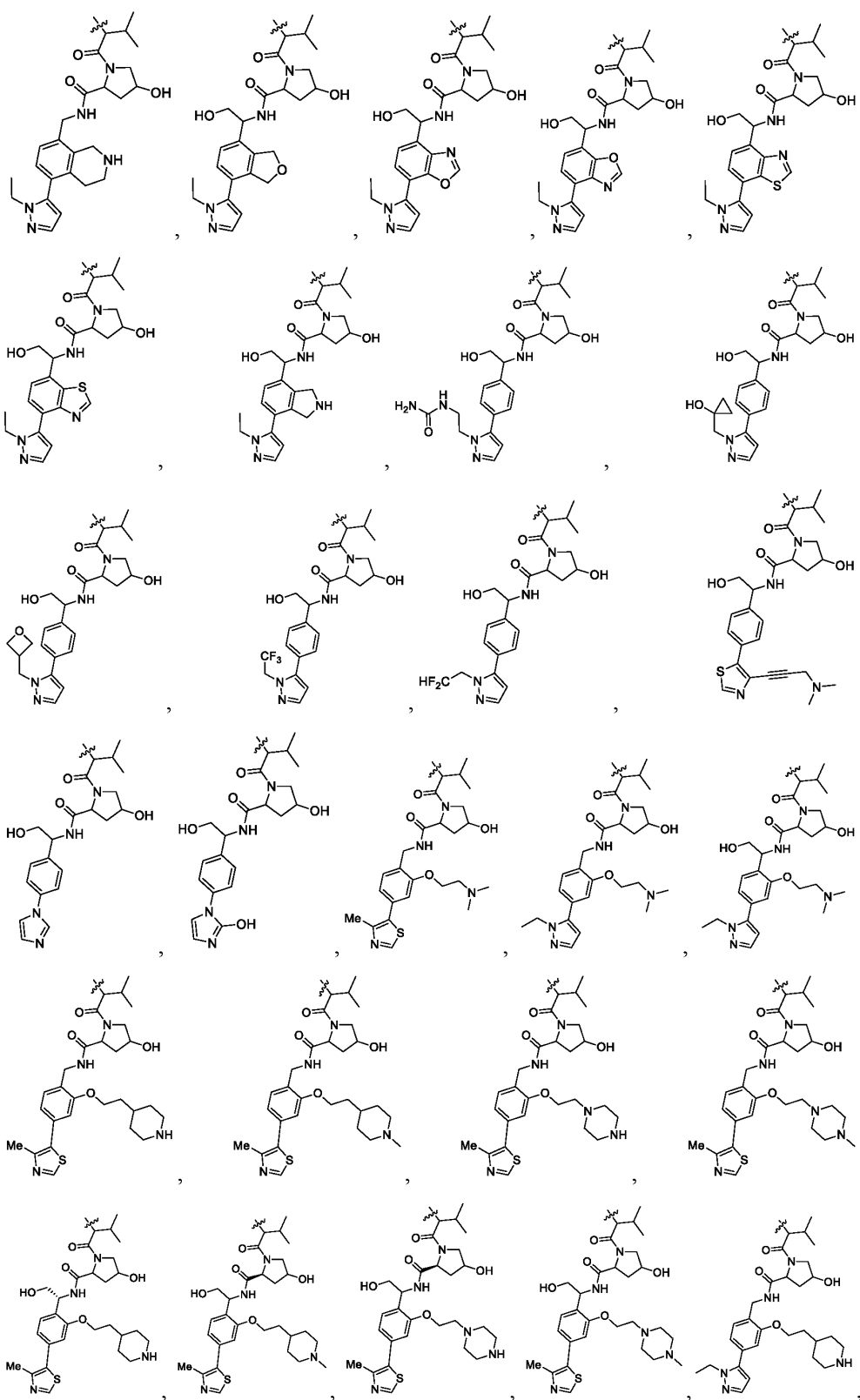


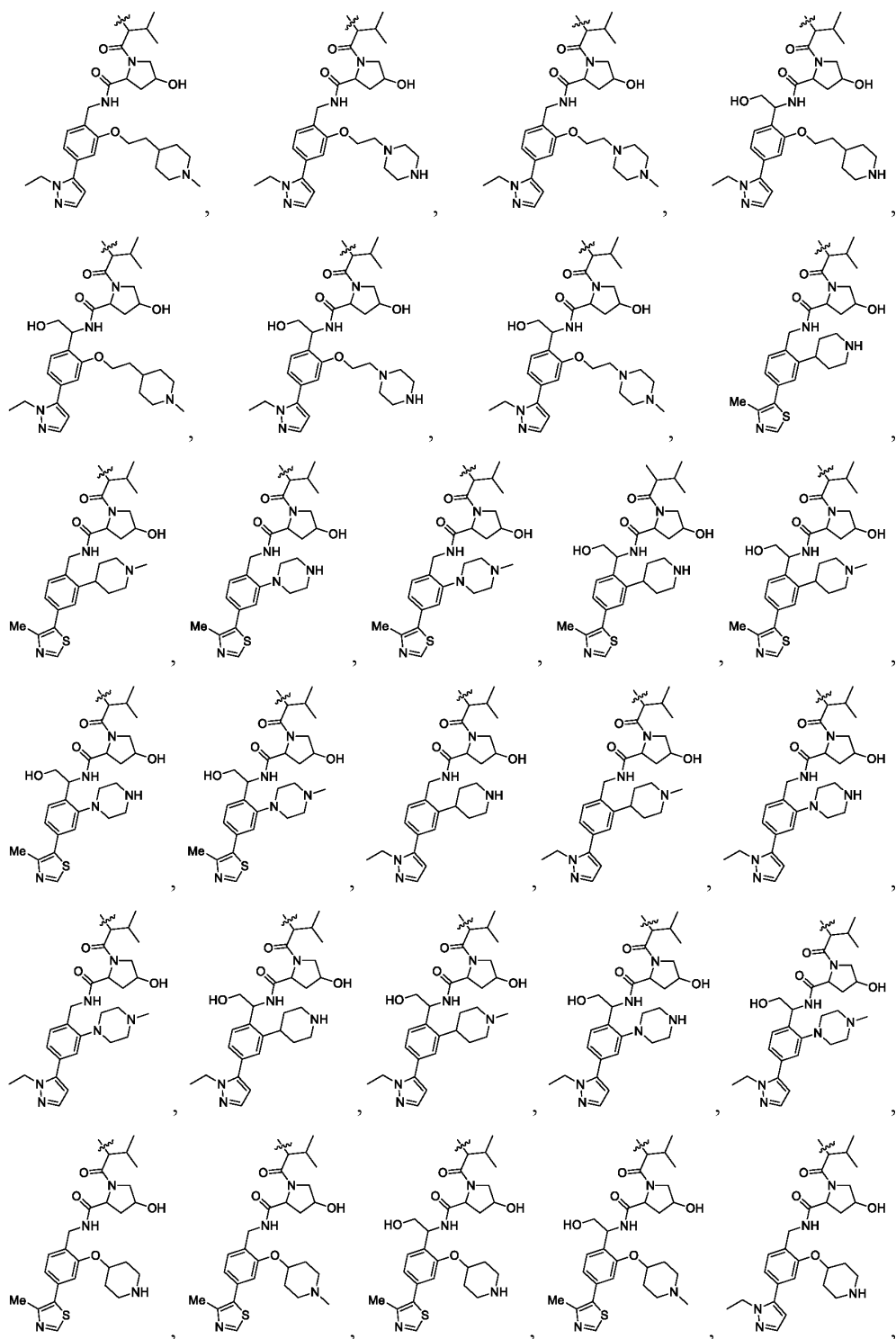


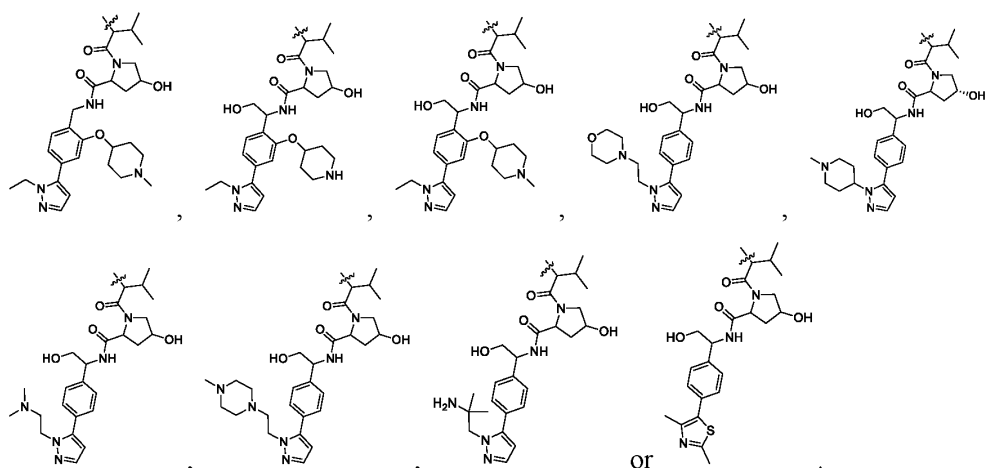


In one embodiment, M1 is

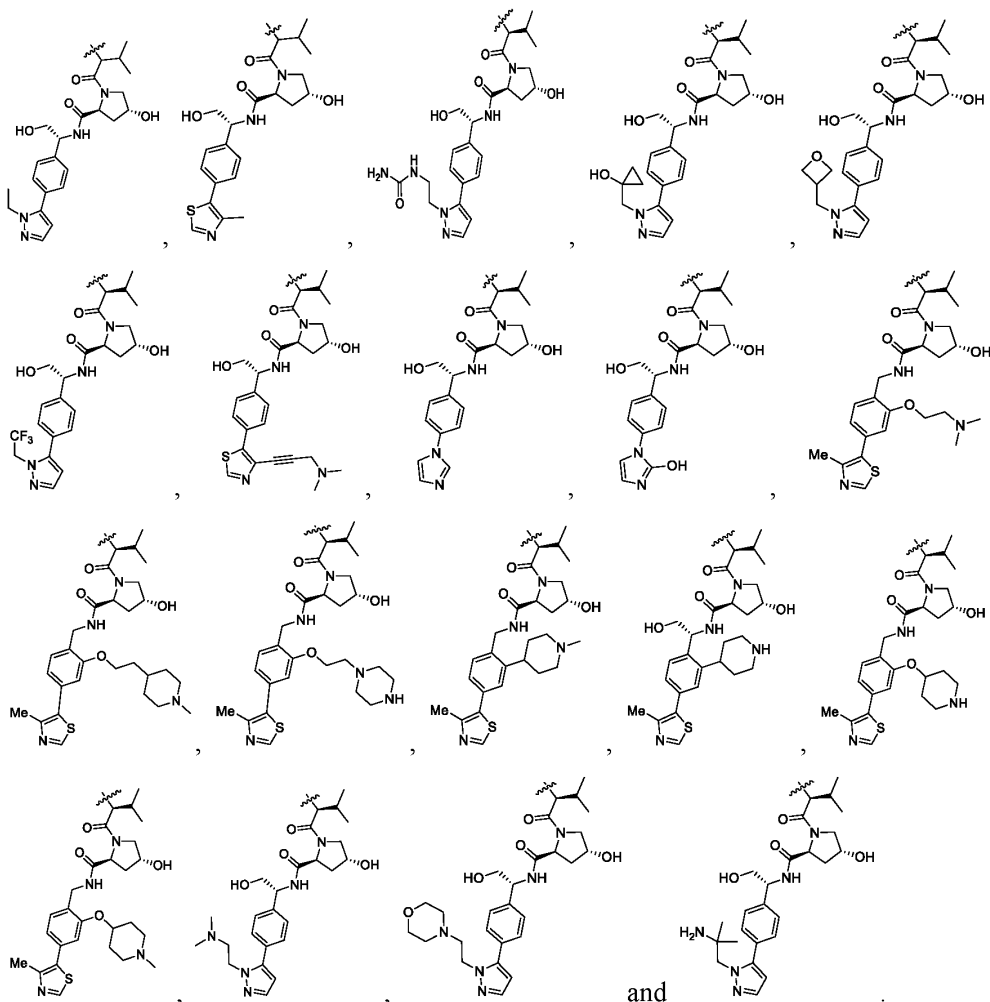








In one embodiment, M1 has formula selected from the group consisting of



In one embodiment, R₈ is (C₁-C₆)alkyl, hydroxy, halo, or amino.

In one embodiment, R₈ is (C₁-C₆)alkyl.

In one embodiment, Z is hydrogen, (C₁-C₆)alkyl, halo or -CH₂OH.

In one embodiment, Z is hydrogen or -CH₂OH.

In one embodiment, R_a and R_b independently, is hydrogen.

- 5 In one embodiment, R_a and R_b together with the C atoms to which they are attached form a 5 to 6 membered heterocyclyl ring optionally containing one or two hetero atoms independently selected from the group consisting of O, S, and N.

In one embodiment, R₉ at each occurrence, independently, is hydrogen, 4- to 8-membered heterocycloalkyl, -O- heterocycloalkyl, -O-(C₁-C₆)alkyl, wherein the alkyl is unsubstituted or
10 substituted with amino(C₁-C₆)alkyl or 5 to 8 membered heterocycloalkyl, wherein the heterocycloalkyl at each occurrence is unsubstituted or substituted with halo, or (C₁-C₆)alkyl.

In one embodiment, R₉ at each occurrence, independently is 4- to 8-membered heterocycloalkyl, wherein the heterocycloalkyl at each occurrence is unsubstituted or substituted with halo, or (C₁-C₆)alkyl.

- 15 In one embodiment, R₉ at each occurrence, independently is 6-membered heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted.

In one embodiment, R₉ at each occurrence, independently is 6-membered heterocycloalkyl, wherein the heterocycloalkyl is substituted with methyl.

- In one embodiment, R₉ at each occurrence, independently is -O-heterocycloalkyl,
20 wherein the heterocycloalkyl is unsubstituted.

In one embodiment, R₉ at each occurrence, independently is -O-heterocycloalkyl, wherein the heterocycloalkyl is substituted with methyl.

- In one embodiment, R₉ at each occurrence, independently is -O-(C₁-C₆)alkyl, wherein the alkyl is unsubstituted or substituted with amino(C₁-C₆)alkyl or 5 to 8 membered
25 heterocycloalkyl, wherein the heterocycloalkyl at each occurrence is unsubstituted or substituted with halo, or (C₁-C₆)alkyl.

In one embodiment, R₉ at each occurrence, independently is -O-(C₁-C₆)alkyl, wherein the alkyl is substituted with amino(C₁-C₆)alkyl.

In one embodiment, R₉ at each occurrence, independently is -O-(C₁-C₆)alkyl, wherein the alkyl is substituted with 5 to 8 membered heterocycloalkyl, wherein the heterocycloalkyl at each occurrence is unsubstituted or substituted with halo, or (C₁-C₆)alkyl.

In one embodiment, R₉ at each occurrence, independently is -O-(C₁-C₆)alkyl, wherein
5 the alkyl is substituted with 5 to 8 membered heterocycloalkyl, wherein the heterocycloalkyl is substituted with (C₁-C₆)alkyl.

In one embodiment, R₉ at each occurrence, independently is -O-(C₁-C₆)alkyl, wherein the alkyl is substituted with 6 membered heterocycloalkyl, wherein the heterocycloalkyl is substituted with (C₁-C₆)alkyl.

10 In one embodiment, P₁, P₂, P₃ and P₄, independently, is C, N or S, wherein at least one of P₁, P₂, P₃ and P₄, is N.

In one embodiment, P₁, P₂, P₃ and P₄, independently, is C, N or S, wherein two of P₁, P₂, P₃ and P₄, is N.

In one embodiment, P₁, P₂, P₃ and P₄, independently, is C or N.

15 In one embodiment, R₁₀ is hydrogen, (C₁-C₆)alkyl, (C₂-C₄)alkynyl, hydroxy, 3- to 7-membered heterocycloalkyl, or (C₃-C₆)cycloalkyl, wherein the alkyl and alkynyl is unsubstituted or substituted with halo, cycloalkyl, -NH-(CO)-NH₂, NR_mR_n, or 5 to 6 membered heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with (C₁-C₆)alkyl, hydroxy, halo or amino; and

20 R_m and R_n are independently hydrogen or (C₁-C₆)alkyl.

In one embodiment, R₁₀ is (C₁-C₆)alkyl.

In one embodiment, R₁₀ is -CH₃, -CH₂-CH₃, -CH₂-CH₂-CH₃, -CH(CH₃)₂ or -CH₂-CH₂-CH₂-CH₃.

In one embodiment, R₁₀ is hydroxy.

25 In one embodiment, R₁₀ is (C₁-C₆)alkyl, wherein the alkyl is substituted with -NH-(CO)-NH₂.

In one embodiment, R₁₀ is (C₁-C₆)alkyl, wherein the alkyl is substituted with halo.

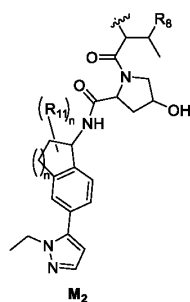
In one embodiment, R₁₀ is (C₁-C₆)alkyl, wherein the alkyl is substituted with cycloalkyl, wherein the cycloalkyl is substituted with hydroxy.

In one embodiment, R_{10} is (C₁-C₆)alkyl, wherein the alkyl is substituted with 5 to 6 membered heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted with (C₁-C₆)alkyl, hydroxy, halo or amino.

In one embodiment, R_{10} is (C₁-C)alkyl, wherein alkyl is substituted with NR_mR_n .

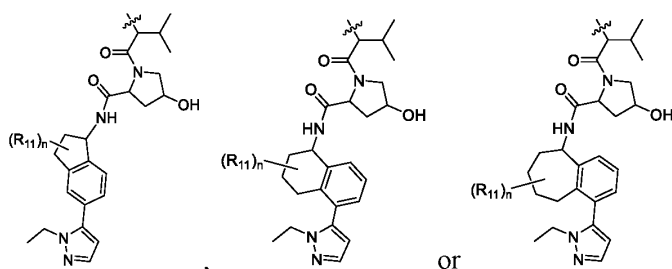
5 In one embodiment, R_{10} is (C₂-C₄)alkynyl, wherein alkynyl is substituted with NR_mR_n .

In one embodiment, R_m and R_n are independently hydrogen or (C₁-C₆)alkyl.

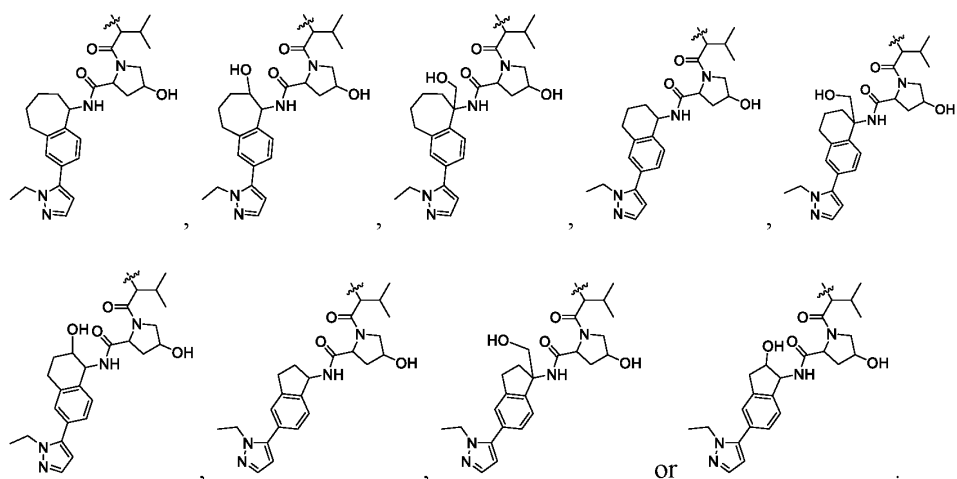


In one embodiment, M is M2

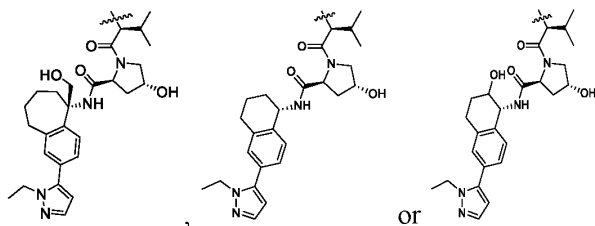
In one embodiment, M2 is



10 In one embodiment, M2 is



In one embodiment, M_2 has formula selected from the group consisting of



In one embodiment, R_{11} at each occurrence, independently, is hydrogen, hydroxy or (C₁-C₆)alkyl, wherein the alkyl is unsubstituted or substituted with halo or hydroxy.

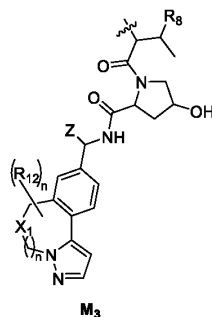
5 In one embodiment, R_{11} at each occurrence, independently is hydroxy.

In one embodiment, R_{11} at each occurrence, independently is (C₁-C₆)alkyl, wherein the alkyl is unsubstituted or substituted with hydroxy.

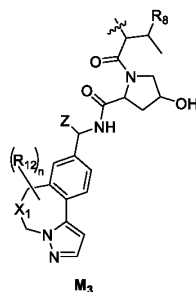
In one embodiment, R_{11} at each occurrence, independently is methyl or ethyl, wherein the methyl or ethyl is substituted with -OH.

10 In one embodiment, n is 1, 2 or 3.

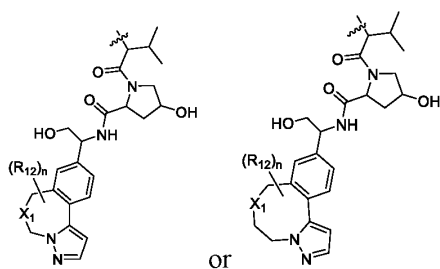
In one embodiment, M is M3



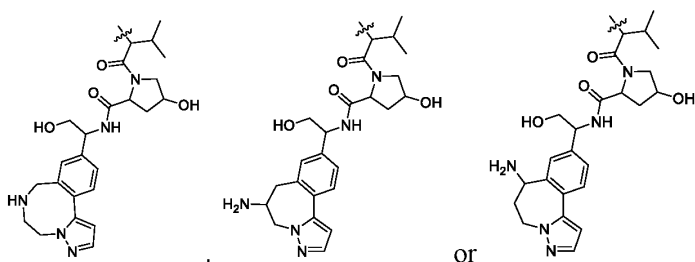
In one embodiment, M is M3



In one embodiment, M3 is



In one embodiment, M3 is



5 In one embodiment, R_{12} at each occurrence, independently, is hydrogen or amino.

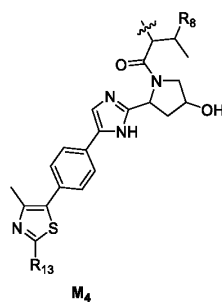
In one embodiment, n is 1, 2 or 3.

In one embodiment, X_1 is C or N.

In one embodiment, X_1 is C.

In one embodiment, X_1 is N.

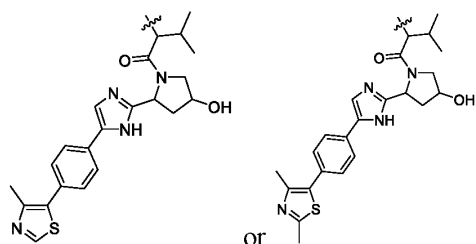
10 In one embodiment, M is M₄



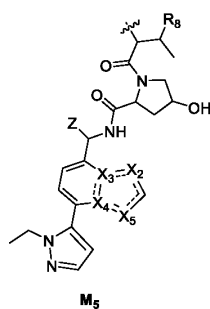
In one embodiment, R_{13} is hydrogen or (C₁-C₆)alkyl.

In one embodiment, R_{13} is methyl.

In one embodiment, M_4 is a group of formula



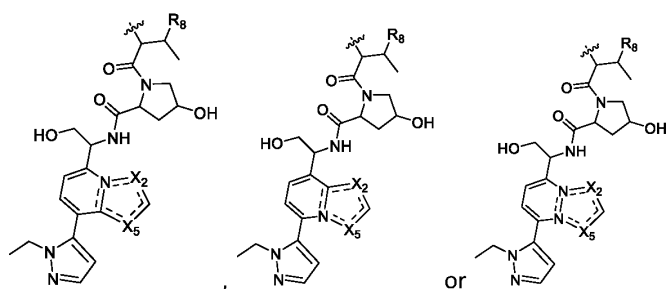
In one embodiment, M is M_5 :



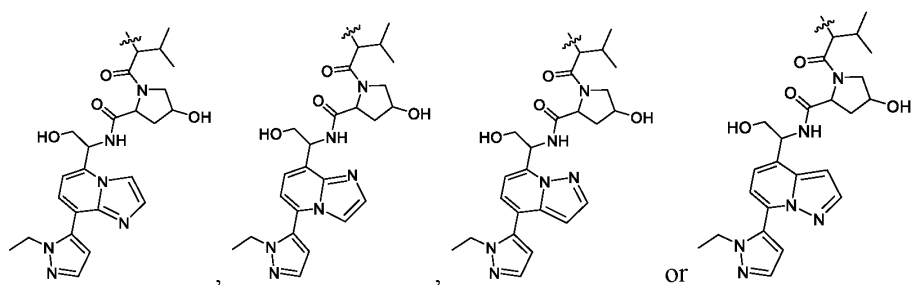
- 5 In one embodiment, X_2 , X_3 , X_4 and X_5 , each independently is C, CH or N, wherein one of X_3 or X_4 is always N and the other is C; and

a dotted line [-----] indicates a bond or absent.

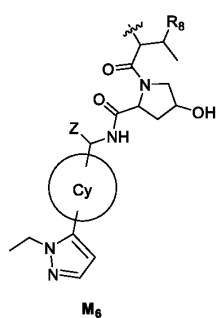
In one embodiment, M_5 is



In one embodiment, M5 is a group of formula

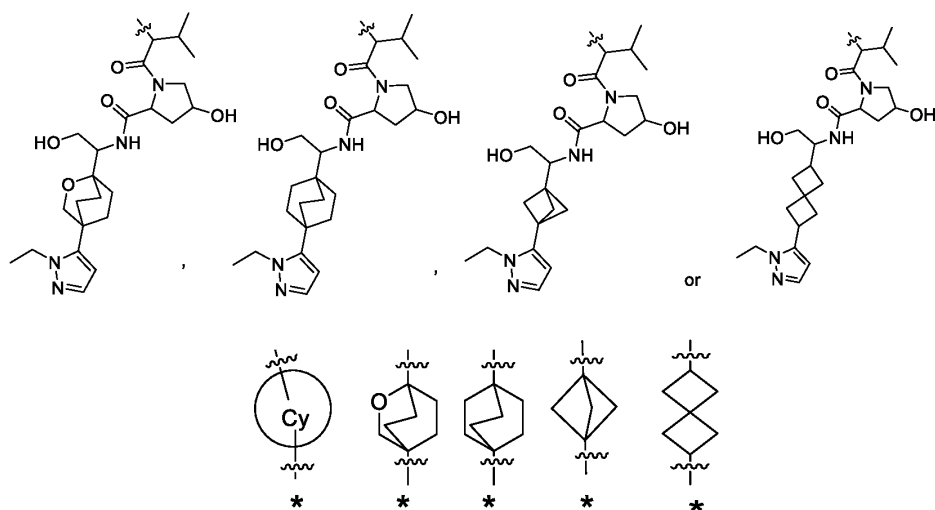


In one embodiment, M is M6,



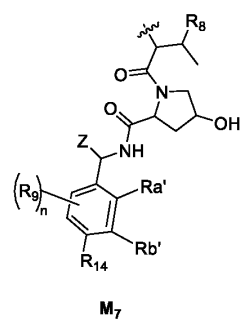
5 wherein Cy is (C₃-C₁₀)cycloalkyl or 3- to 10-membered heterocycloalkyl.

In one embodiment M6 is a group of formula

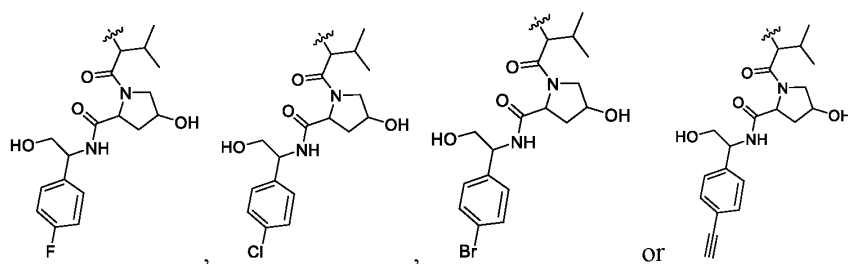


In one embodiment, is , , or ; wherein asterisk mark represents the point of attachment with pyrazole ring.

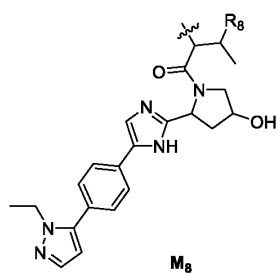
10 In one embodiment, M is M7



In one embodiment, M₇ is

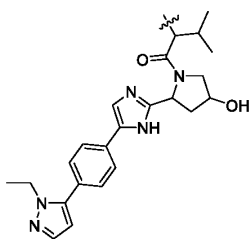


In one embodiment, M is M₈



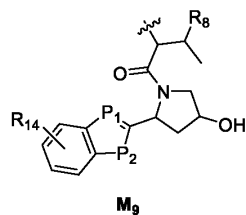
5

In another embodiment, M₈ is

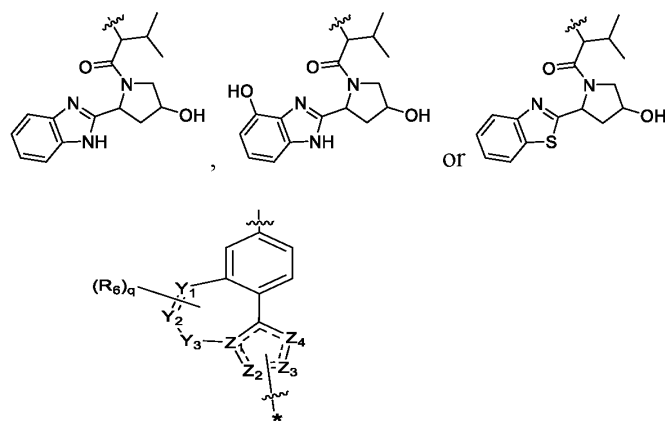


10

In one embodiment, M is M9

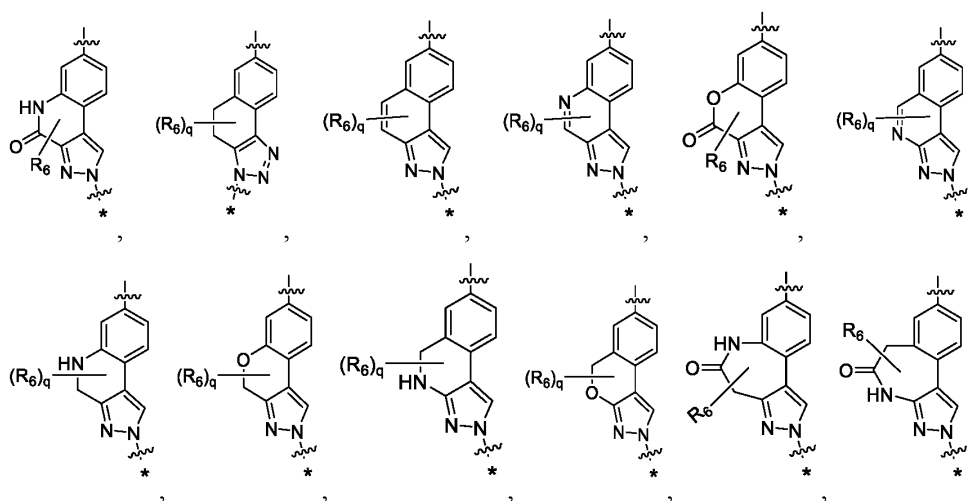


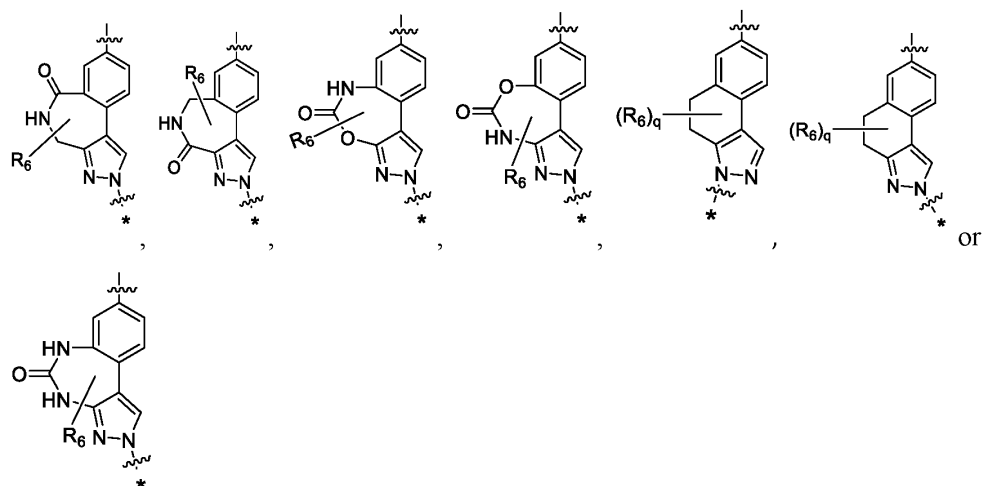
In another embodiment, M9 is



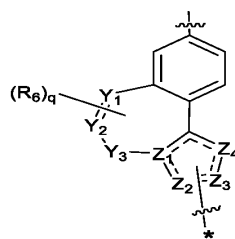
5

In one embodiment, represents



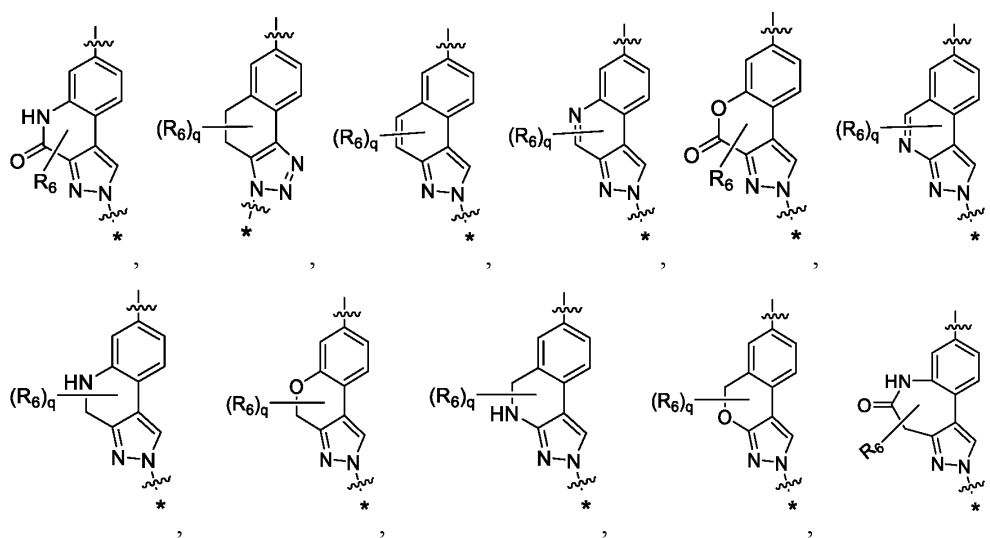


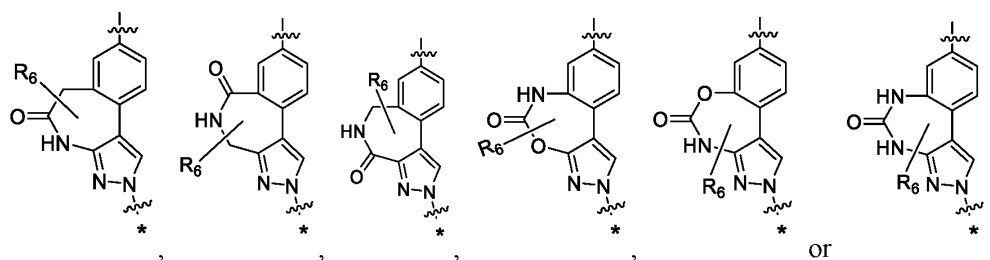
; wherein asterisk mark represents the point of attachment with M.



In one embodiment, wherein

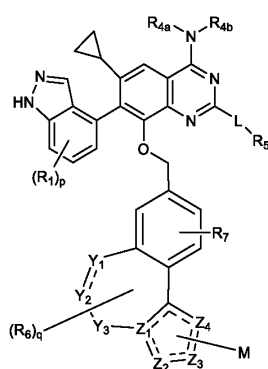
represents





wherein asterisk mark represents the point of attachment with M.

In one embodiment, the present invention provides a compound of formula (IA) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof:



Formula (IA)

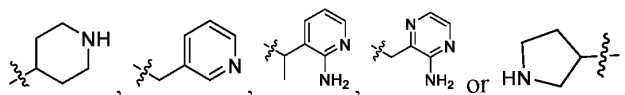
wherein R_{4a} , R_{4b} , L, R_5 , R_6 , q, Y_1 , Y_2 , Y_3 , R_7 , M and same as defined in compound of formula I.

In one embodiment, R_1 is (C_1-C_6) alkyl, hydroxy or halo.

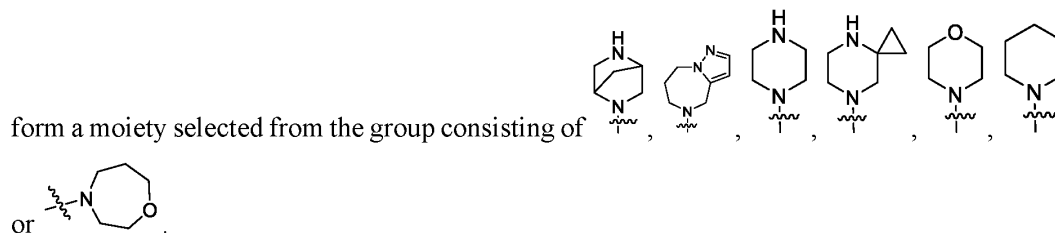
In one embodiment, R_{4a} and R_{4b} independently is (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl or 5- to 10-membered heteroaryl (C_1-C_6) alkyl.

In one embodiment, R_{4a} and R_{4b} together with the nitrogen to which they are attached form a 5- to 14-membered heterocyclyl containing one or two additional heteroatoms selected from the group consisting of nitrogen and oxygen, wherein the heterocyclyl substituted with 2 or groups each independently selected from the group consisting of (C_1-C_6) alkyl and hydroxy.

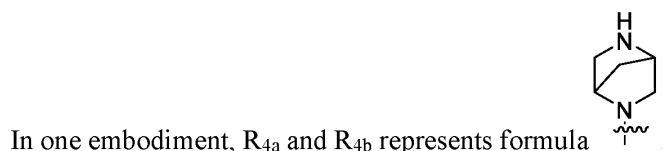
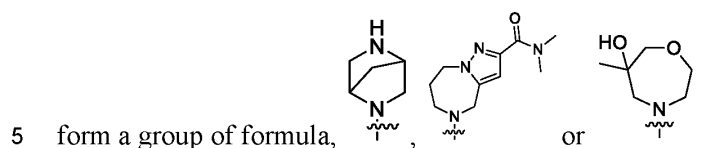
In another embodiment, R_{4a} and R_{4b} , independently, is methyl, ethyl, cyclopropyl,



In one embodiment, R_{4a} and R_{4b} together with the nitrogen to which they are attached



In one embodiment, R_{4a} and R_{4b} together with the nitrogen to which they are attached



In one embodiment, L is -O-, -C(O)-* or -O-CH₂-, wherein asterisk mark represents the point of attachment with R₅.

In one embodiment, L is -O-(CH₂)_m- or -C(O)-NH-.

10 In one embodiment, L is -O- or -O-CH₂-.

In one embodiment, L is -C(O)-NH-.

In one embodiment, R₅ is (C₁-C₆)alkyl, -(CH₂)_mNR_cR_d, 5- to 14-membered heterocycloalkyl or (C₃-C₆)cycloalkyl, wherein the heterocycloalkyl and cycloalkyl are unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the
 15 group consisting of (C₁-C₆)alkyl, halo, amino and -(CH₂)_mNR_yR_z;

m is 0, 1, 2 or 3;

R_c and R_d, independently, is hydrogen or (C₁-C₆)alkyl; and

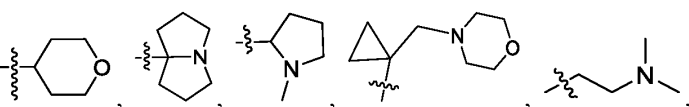
R_y and R_z, independently is hydrogen or (C₁-C₆)alkyl; or R_y and R_z together with the N atom to which they are attached, form a 4- to 7-membered heterocycloalkyl, wherein the
 20 heterocycloalkyl is unsubstituted or substituted with (C₁-C₆)alkyl, halo or (C₂-C₄)acyl.

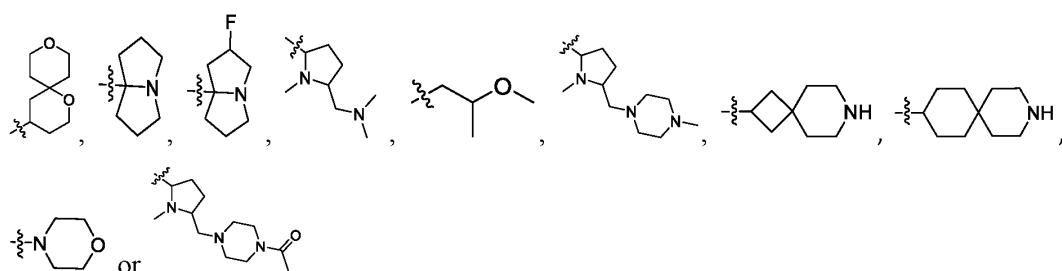
In one embodiment of the compound of formula (IA), R₅ is 5- to 14-membered heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3

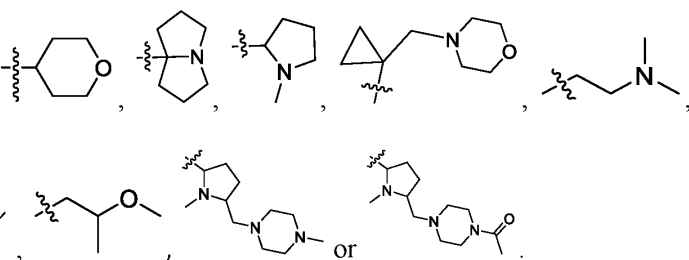
substituents each independently selected from the group consisting of (C₁-C₆)alkyl, halo, and -(CH₂)_mNR_yR_z.

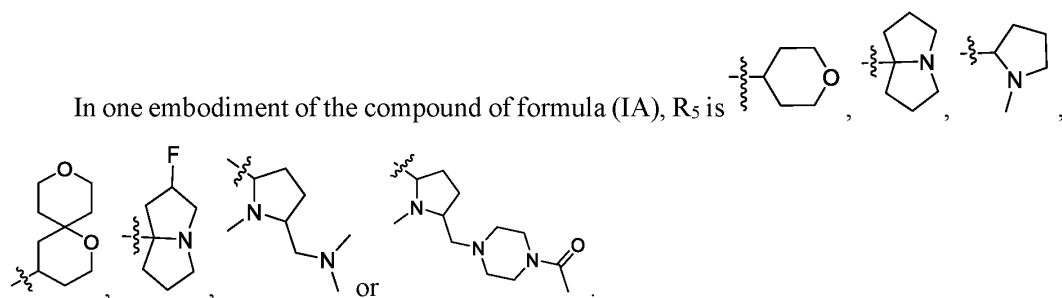
m is 0, 1, 2 or 3; and

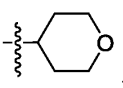
R_y and R_z, independently is hydrogen or (C₁-C₆)alkyl; or R_y and R_z together with the N atom to which they are attached, form a 4- to 7-membered heterocycloalkyl, wherein the heterocycloalkyl is unsubstituted or substituted with (C₁-C₆)alkyl, halo or (C₂-C₄)acyl.

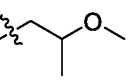
In one embodiment, R₅ is 



10 In one embodiment, R₅ is 



In one embodiment of the compound of formula (IA), R₅ is 

15 In one embodiment, R₅ is 

In one embodiment of the compound of formula (IA), R_6 at each occurrence, independently, is hydrogen, amino, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or hydroxy; or two R_6 on the same carbon represent an oxo group.

In one embodiment, R_6 is hydrogen, amino, hydroxy or two R_6 on the same carbon
5 represent an oxo group.

In one embodiment of the compound of formula (IA), R_6 is hydrogen or two R_6 on the same carbon represent an oxo group.

In one embodiment of the compound of formula (IA), R_6 is methoxy.

In one embodiment of the compound of formula (IA), R_6 at each occurrence,
10 independently is -CH₃, -CH₂-CH₃, -CH₂-CH₂-CH₃, -CH(CH₃)₂ or -CH₂-CH₂-CH₂-CH₃.

In one embodiment of the compound of formula (IA), q is 1, 2 or 3.

In one embodiment of the compound of formula (IA), Y_1 , Y_2 and Y_3 , independently, is a bond, C, N, or O, wherein not more than one of Y_1 , Y_2 or Y_3 is a bond.

In one embodiment of the compound of formula (IA), Y_1 , Y_2 and Y_3 , independently, is C
15 or N.

In one embodiment of the compound of formula (IA), Y_1 , Y_2 and Y_3 , independently, is C or O.

In one embodiment of the compound of formula (IA), R_7 is hydrogen, halo, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₁-C₆)alkoxy, or halo(C₁-C₆)alkoxy.

In one embodiment of the compound of formula (IA), R_7 is hydrogen, halo, (C₁-C₆)alkyl,
20 or halo(C₁-C₆)alkyl.

In one embodiment of the compound of formula (IA), R_7 is -F, -Cl or -Br.

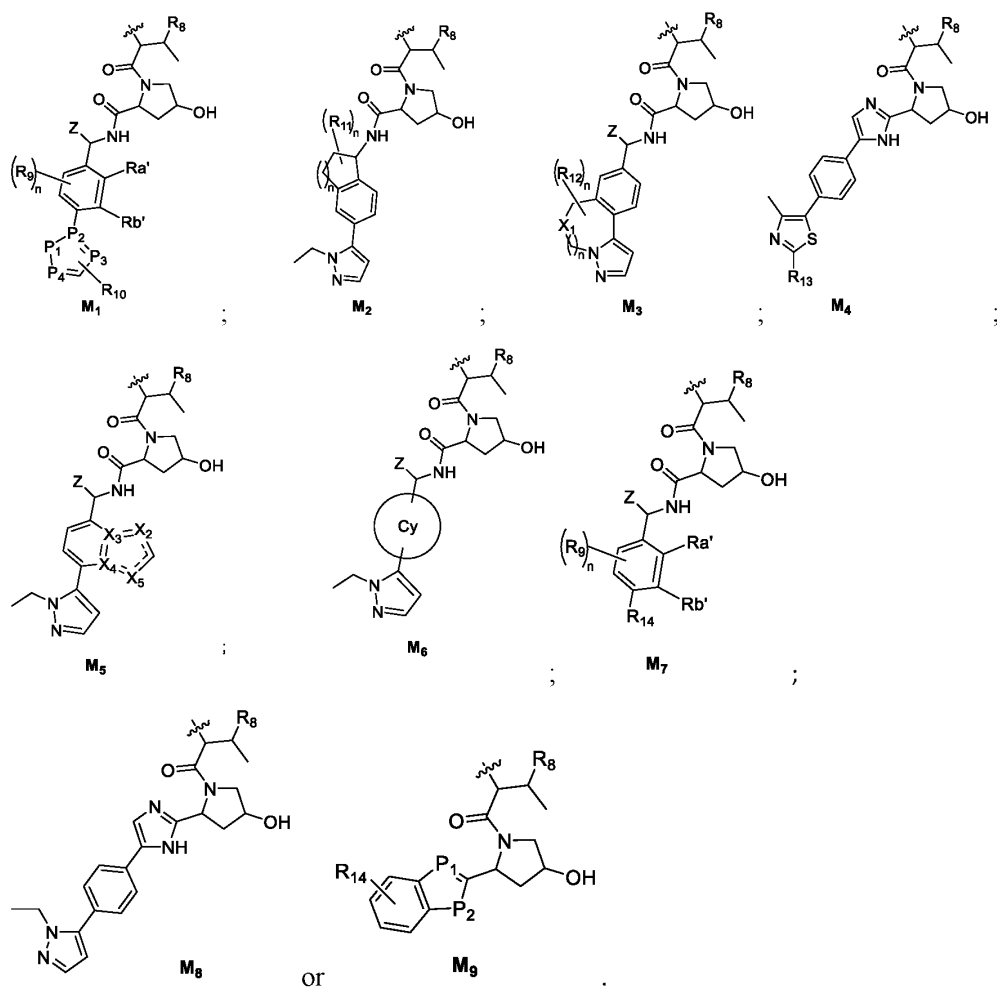
In one embodiment of the compound of formula (IA), R_7 is -CHF₂ or -CF₃.

In one embodiment of the compound of formula (IA), R_7 is -CH₃, -CH₂-CH₃, -CH₂-CH₂-
25 CH₃, -CH(CH₃)₂ or -CH₂-CH₂-CH₂-CH₃.

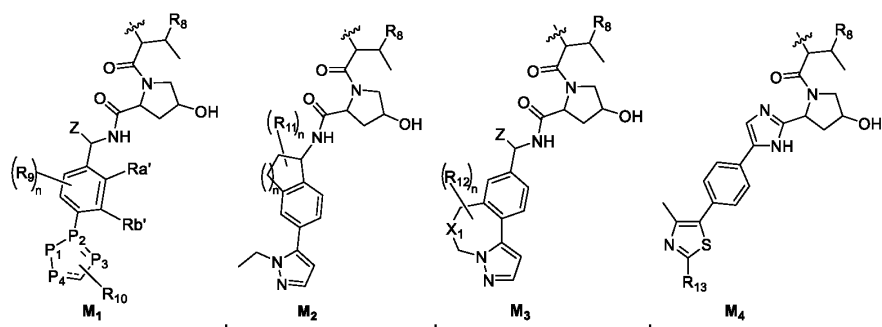
In one embodiment of the compound of formula (IA), R_7 is methoxy.

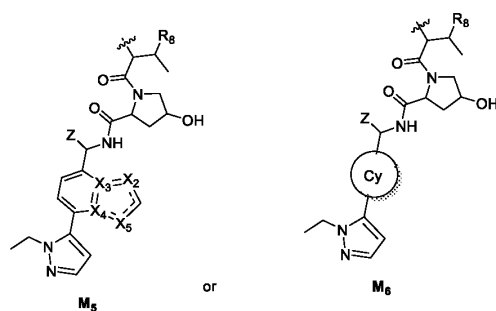
In one embodiment of the compound of formula (IA), R_7 is -OCF₃.

In one embodiment, M is M_1 , M_2 , M_3 , M_4 , M_5 , M_6 , M_7 , M_8 or M_9 ;



In one embodiment, M is M₁, M₂, M₃, M₄, M₅, or M₆.





wherein,

R₈ is (C₁-C₆)alkyl, hydroxy, halo or amino;

Z is hydrogen, (C₁-C₆)alkyl, halo or -CH₂OH;

- 5 R_a' and R_b' independently, is hydrogen, halo or (C₁-C₆)alkyl; or R_a' and R_b' together with the C atoms to which they are attached form a 5 to 6 membered heterocyclyl ring optionally containing one or two hetero atoms independently selected from the group consisting of O, S and N;

- 10 R₉ at each occurrence, independently, is hydrogen, 4- to 8-membered heterocycloalkyl, -O- heterocycloalkyl, -O-(C₁-C₆)alkyl; wherein the alkyl is unsubstituted or substituted with amino(C₁-C₆)alkyl or 5 to 8 membered heterocycloalkyl; wherein the heterocycloalkyl at each occurrence is unsubstituted or substituted with halo or (C₁-C₆)alkyl;

P₁, P₂, P₃ and P₄, independently, is C, N or S; wherein at least one of P₁, P₂, P₃ and P₄ is N;

- 15 R₁₀ is hydrogen, (C₁-C₆)alkyl, (C₂-C₄)alkynyl, hydroxy, 3- to 7-membered heterocycloalkyl, or (C₃-C₆)cycloalkyl; wherein the alkyl and alkynyl is unsubstituted or substituted with halo, cycloalkyl, -NH-(CO)-NH₂, NR_mR_n or 5 to 6 membered heterocycloalkyl; wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with (C₁-C₆)alkyl, hydroxy, halo or amino;

- 20 R_m and R_n are independently hydrogen or (C₁-C₆)alkyl;

R₁₁ at each occurrence, independently, is hydrogen, hydroxy or (C₁-C₆)alkyl; wherein the alkyl is unsubstituted or substituted with halo or hydroxy;

R₁₂ at each occurrence, independently, is hydrogen or amino;

X₁ is C or N;

R₁₃ is hydrogen or (C₁-C₆)alkyl;

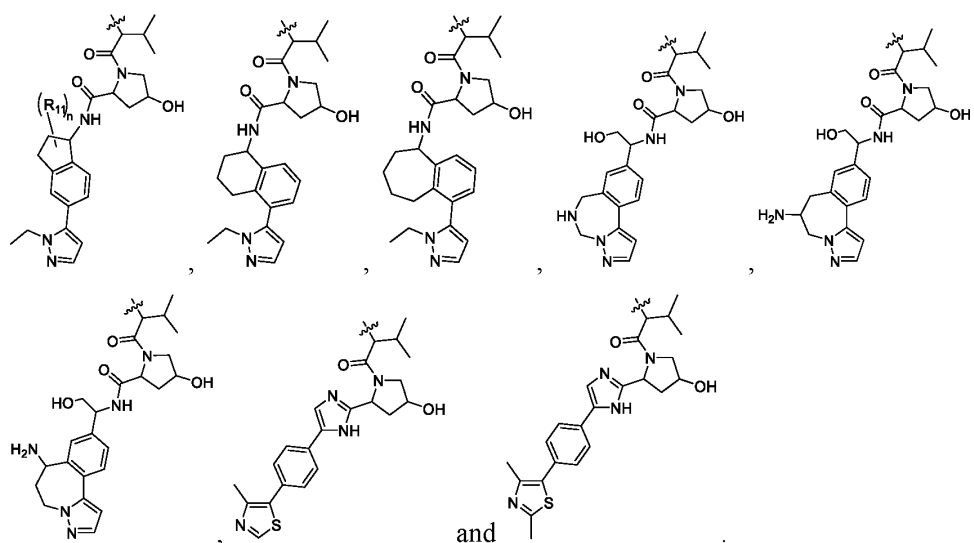
X₂, X₃, X₄ and X₅ each independently is C, CH or N; wherein one of X₃ or X₄ is always N and the other is C;

Cy is (C₃-C₁₀)cycloalkyl or 3- to 10-membered heterocycloalkyl;

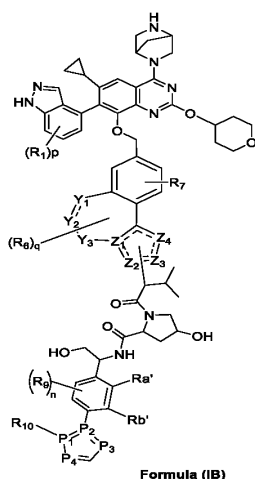
5 a dotted line [-----] indicates a bond or absent; and

n is 1, 2 or 3.

In one embodiment, M is selected from the group consisting of



10 In one embodiment, the present invention provides a compound of formula (IB) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof:



wherein R₇, R₆, q, Y₁, Y₂, Y₃, R₉, n, R_a', R_b', P₁, P₂, P₃, P₄ and R₁₀ same as defined in compound of formula I.

In one embodiment, R₁ is (C₁-C₆)alkyl, hydroxy or halo.

In one embodiment of the compound of formula (IB), R₇ is hydrogen, halo, (C₁-C₆)alkyl,
5 halo(C₁-C₆)alkyl, (C₁-C₆)alkoxy, or halo(C₁-C₆)alkoxy.

In one embodiment of the compound of formula (IB), R₇ is F, Cl or Br.

In one embodiment of the compound of formula (IB), R₇ is -CHF₂ or -CF₃.

In one embodiment of the compound of formula (IB), R₇ is -CH₃, -CH₂-CH₃, -CH₂-CH₂-CH₃, -CH(CH₃)₂ or -CH₂-CH₂-CH₂-CH₃.

10 In one embodiment of the compound of formula (IB), R₇ is methoxy.

In one embodiment of the compound of formula (IB), R₇ is -OCF₃.

In one embodiment of the compound of formula (IB), R₆ at each occurrence, independently, is hydrogen, amino, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or hydroxy; or two R₆ on the same carbon represent an oxo group.

15 In one embodiment of the compound of formula (IB), R₆ is hydrogen, amino, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or hydroxy; or two R₆ on the same carbon represent an oxo group.

In one embodiment, R₆ is hydrogen, amino, hydroxy or two R₆ on the same carbon represent an oxo group.

In one embodiment of the compound of formula (IB), two R₆ on the same carbon
20 represent an oxo group.

In one embodiment of the compound of formula (IB), R₆ is methoxy.

In one embodiment of the compound of formula (IB), R₆ at each occurrence, independently is -CH₃, -CH₂-CH₃, -CH₂-CH₂-CH₃, -CH(CH₃)₂ or -CH₂-CH₂-CH₂-CH₃.

In one embodiment of the compound of formula (IB), q is 1, 2 or 3.

25 In one embodiment of the compound of formula (IB), Y₁, Y₂ and Y₃, independently, is a bond, C, N, or O, wherein not more than one of Y₁, Y₂ or Y₃ is a bond.

In one embodiment of the compound of formula (IB), Y₁, Y₂ and Y₃, independently, is C or N.

In one embodiment of the compound of formula (IB), Y_1 , Y_2 and Y_3 , independently, is C or O.

In one embodiment of the compound of formula (IB), R_9 is hydrogen or (C_1-C_6) alkyl.

In one embodiment of the compound of formula (IB), n is 0, 1, 2 or 3.

5 In one embodiment, $R_{a'}$ and $R_{b'}$ together with the C atoms to which they are attached form 5- to 6-membered heterocycloalkyl or heteroaryl.

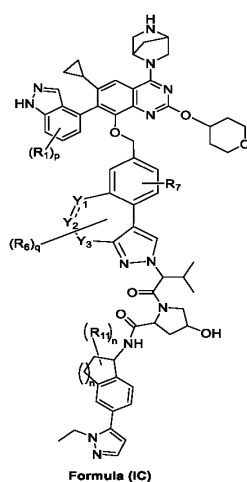
In one embodiment of the compound of formula (IB), $R_{a'}$ and $R_{b'}$ together with the C atoms to which they are attached form a 5 to 6 membered heterocyclyl ring optionally containing one or two hetero atoms independently selected from the group consisting of O, S,
10 and N;

In one embodiment of the compound of formula (IB), P_1 , P_2 , P_3 and P_4 , independently, is C, N or S, wherein at least one of P_1 , P_2 , P_3 and P_4 is N.

In one embodiment of the compound of formula (IB), R_{10} is hydrogen, (C_1-C_6) alkyl, (C_2-C_4) alkynyl, hydroxy, 3- to 7-membered heterocycloalkyl, or (C_3-C_6) cycloalkyl, wherein the
15 alkyl and alkynyl is unsubstituted or substituted with halo, cycloalkyl, $NH-(CO)-NH_2$, NR_mR_n , or 5 to 6 membered heterocycloalkyl, wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with (C_1-C_6) alkyl, hydroxy, halo or amino.

In one embodiment of the compound of formula (IB), R_{10} is hydrogen, or (C_1-C_6) alkyl.

In one embodiment, the present invention provides a compound of formula (IC) or a
20 pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof:



wherein R₇, R₆, q, Y₁, Y₂, Y₃, R₁₁ and n same as defined in compound of formula I.

In one embodiment of the compound of formula (IC), R₇ is hydrogen, halo, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₁-C₆)alkoxy, or halo(C₁-C₆)alkoxy.

In one embodiment of the compound of formula (IC), R₇ is F, Cl or Br.

5 In one embodiment of the compound of formula (IC), R₇ is -CHF₂ or -CF₃.

In one embodiment of the compound of formula (IC), R₇ is -CH₃, -CH₂-CH₃, -CH₂-CH₂-CH₃, -CH(CH₃)₂ or -CH₂-CH₂-CH₂-CH₃.

In one embodiment of the compound of formula (IC), R₇ is methoxy.

In one embodiment of the compound of formula (IC), R₇ is -OCF₃.

10 In one embodiment of the compound of formula (IC), R₆ at each occurrence, independently, is hydrogen, amino, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or hydroxy; or two R₆ on the same carbon represent an oxo group.

In one embodiment of the compound of formula (IC), R₆ is hydrogen.

In one embodiment of the compound of formula (IC), two R₆ on the same carbon
15 represent an oxo group.

In one embodiment of the compound of formula (IC), R₆ is methoxy.

In one embodiment of the compound of formula (IC), R₆ at each occurrence, independently is -CH₃, -CH₂-CH₃, -CH₂-CH₂-CH₃, -CH(CH₃)₂ or -CH₂-CH₂-CH₂-CH₃.

In one embodiment of the compound of formula (IC), q is 1, 2 or 3.

20 In one embodiment of the compound of formula (IC), Y₁, Y₂ and Y₃, independently, is a bond, C, N, or O, wherein not more than one of Y₁, Y₂ or Y₃ is a bond.

In one embodiment of the compound of formula (IC), Y₁, Y₂ and Y₃, independently, is C or N.

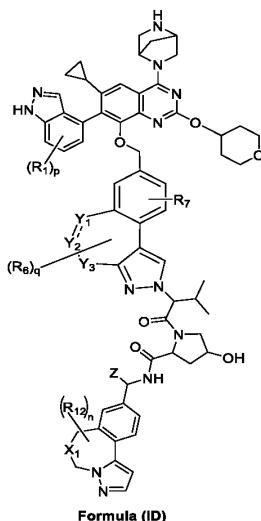
In one embodiment of the compound of formula (IC), Y₁, Y₂ and Y₃, independently, is C
25 or O.

In one embodiment of the compound of formula (IC), the compound of R₁₁ at each occurrence, independently, is hydrogen, hydroxy or (C₁-C₆)alkyl, wherein the alkyl is unsubstituted or substituted with halo or hydroxy.

a dotted line [-----] indicates a bond or absent.

n is 1, 2 or 3.

In one embodiment, the present invention provides a compound of formula (ID) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof:



wherein R₇, R₆, q, Y₁, Y₂, Y₃, Z, R₁₂, n and X₁, and same as defined in compound of formula (I).

In one embodiment of the compound of formula (IC), R₇ is hydrogen, halo, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₁-C₆)alkoxy, or halo(C₁-C₆)alkoxy.

10 In one embodiment of the compound of formula (ID), R₇ is F, Cl or Br.

In one embodiment of the compound of formula (ID), R₇ is -CHF₂ or -CF₃.

In one embodiment of the compound of formula (ID), R₇ is -CH₃, -CH₂-CH₃, -CH₂-CH₂-CH₃, -CH(CH₃)₂ or -CH₂-CH₂-CH₂-CH₃.

In one embodiment of the compound of formula (ID), R₇ is methoxy.

15 In one embodiment of the compound of formula (ID), R₇ is -OCF₃.

In one embodiment of the compound of formula (ID), R₆ at each occurrence, independently, is hydrogen, amino, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or hydroxy; or two R₆ on the same carbon represent an oxo group.

In one embodiment of the compound of formula (ID), two R₆ on the same carbon
20 represent an oxo group.

In one embodiment of the compound of formula (IE), R₇ is hydrogen, halo, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₁-C₆)alkoxy, or halo(C₁-C₆)alkoxy.

In one embodiment of the compound of formula (IE), R₇ is F, Cl or Br.

In one embodiment of the compound of formula (IE), R₇ is -CHF₂ or -CF₃.

5 In one embodiment of the compound of formula (IE), R₇ is -CF₃.

In one embodiment of the compound of formula (IE), R₇ is -CH₃, -CH₂-CH₃, -CH₂-CH₂-CH₃, -CH(CH₃)₂ or -CH₂-CH₂-CH₂-CH₃.

In one embodiment of the compound of formula (IE), R₇ is methoxy.

In one embodiment of the compound of formula (IE), R₇ is -OCF₃.

10 In one embodiment of the compound of formula (IE), R₆ at each occurrence, independently, is hydrogen, amino, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or hydroxy; or two R₆ on the same carbon represent an oxo group.

In one embodiment of the compound of formula (IE), two R₆ on the same carbon represent an oxo group.

15 In one embodiment of the compound of formula (IE), R₆ is methoxy.

In one embodiment of the compound of formula (IE), R₆ at each occurrence, independently is -CH₃, -CH₂-CH₃, -CH₂-CH₂-CH₃, -CH(CH₃)₂ or -CH₂-CH₂-CH₂-CH₃.

In one embodiment of the compound of formula (IE), q is 1, 2 or 3.

In one embodiment of the compound of formula (IE), Y₁, Y₂ and Y₃, independently, is a
20 bond, C, N, or O, wherein not more than one of Y₁, Y₂ or Y₃ is a bond.

In one embodiment of the compound of formula (IE), Y₁, Y₂ and Y₃, independently, is C or N.

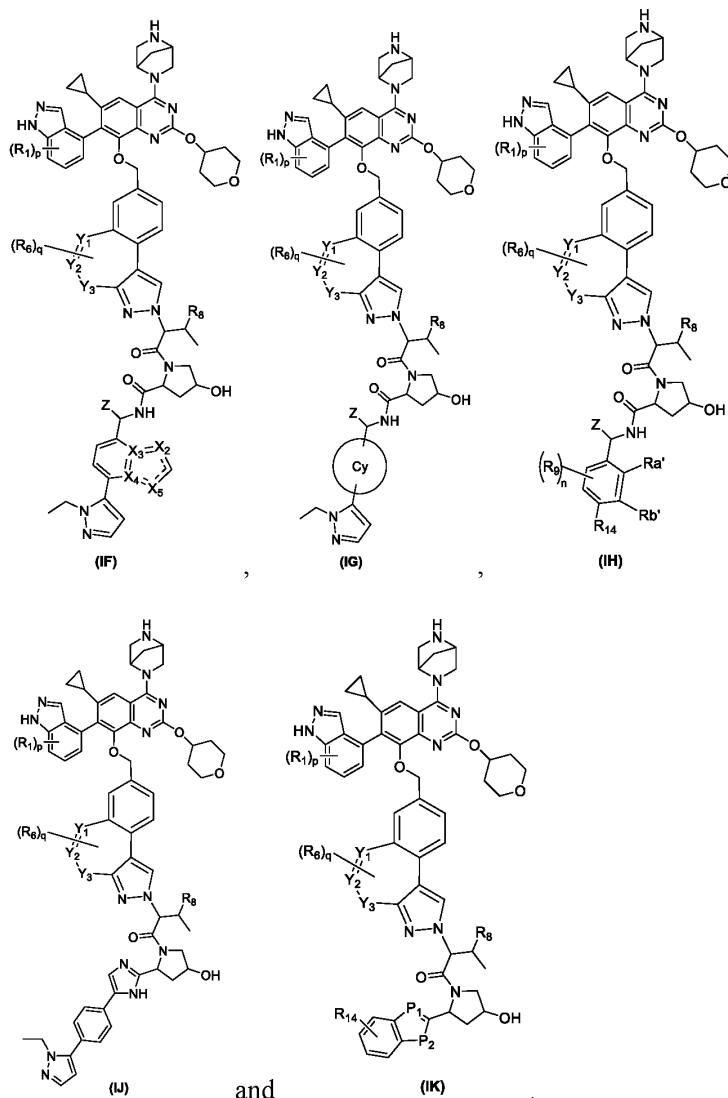
In one embodiment of the compound of formula (IE), Y₁, Y₂ and Y₃, independently, is C or O.

25 In one embodiment of the compound of formula (IE), R₈ is hydrogen or (C₁-C₆)alkyl.

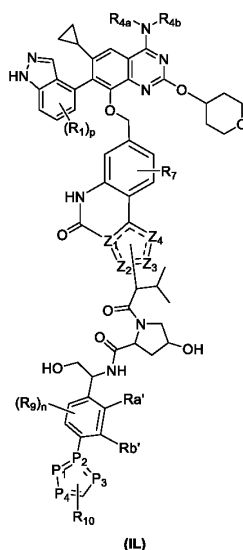
In one embodiment of the compound of formula (IE), R₁₃ is hydrogen or (C₁-C₆)alkyl.

a dotted line [-----] indicates a bond or absent.

In one embodiment, present invention provides a compound of formula (IF), (IG), (IH), (IJ) and (IK) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof:



In one embodiment, the present invention provides a compound of formula (II):



or a pharmaceutically acceptable salt or stereoisomer or a tautomer thereof;

wherein,

5 R₁ at each occurrence, independently is hydrogen, (C₁-C₆)alkyl, hydroxy, halo, amino
or halo(C₁-C₆) alkyl, and/or two R₁ adjacent to each other together with the C atoms to which
they are attached form a phenyl or 5- to 6-membered heterocyclyl; wherein the phenyl and
heterocyclyl are unsubstituted or substituted with 1, 2 or 3 substituents each independently
selected from the group consisting of (C₁-C₆)alkyl, (C₂-C₄)alkyne, halo, hydroxy, halo(C₁-
10 C₆)alkyl, amino, and cyano;

p is 1, 2, 3, or 4;

R_{4a} and R_{4b}, independently, is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 5- to 10-membered heteroaryl(C₁-C₆)alkyl or 4- to 7-membered heterocycloalkyl, wherein the cycloalkyl and heteroarylalkyl are unsubstituted or substituted with 1, 2 or 3 substituents each
15 independently selected from the group consisting of halo, alkyl and amino; and/or

R_{4a} and R_{4b} together with the nitrogen to which they are attached form a 4- to 14-membered heterocyclyl optionally containing one or two additional heteroatoms selected from the group consisting of nitrogen, oxygen, and sulphur; wherein the heterocyclyl is unsubstituted or substituted with 1, 2 or 3 groups each independently selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy, cyano and -C(O)-R_{4c}; wherein said alkyl is

substituted independently with one or more of hydrogen, halo, hydroxy, amino, cyano or (C₃-C₆)cycloalkyl; and/or

R_{4c} is hydrogen, amino, (C₁-C₆)alkylamino, 4- to 7-membered heterocycloalkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkyl or (C₁-C₆)alkylamino(C₁-C₆)alkyl; wherein the heterocycloalkyl
 5 and cycloalkyl are unsubstituted or substituted with 1, 2 or 3 groups each independently selected from the group consisting of halo, hydroxy and (C₁-C₆)alkyl;

R₇ is hydrogen, halo, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₁-C₆)alkoxy, or halo(C₁-C₆)alkoxy;

R_a' and R_b' independently, is hydrogen, halo or (C₁-C₆)alkyl; or R_a' and R_b' together
 10 with the C atoms to which they are attached form a 5 to 6 membered heterocyclyl ring optionally containing one or two hetero atoms independently selected from the group consisting of O, S, and N;

R₉ at each occurrence, independently, is hydrogen, 4- to 8-membered heterocycloalkyl, -O-heterocycloalkyl, -O-(C₁-C₆)alkyl;

15 wherein 4- to 8-membered heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo or (C₁-C₆)alkyl;

wherein the alkyl in -O-(C₁-C₆)alkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkylamino or 5- to 8-membered heterocycloalkyl; wherein the heterocycloalkyl
 20 is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo, or (C₁-C₆)alkyl;

P₁, P₂, P₃ and P₄, independently, is C, N or S; wherein at least one of P₁, P₂, P₃ and P₄, is N;

R₁₀ is hydrogen, (C₁-C₆)alkyl, (C₂-C₄)alkynyl, hydroxy, 3- to 7-membered
 25 heterocycloalkyl, or (C₃-C₆)cycloalkyl;

wherein the alkyl and alkynyl is unsubstituted or substituted with halo, cycloalkyl, NH-(CO)-NH₂, NR_mR_n, or 5 to 6 membered heterocycloalkyl; wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkyl, hydroxy, halo or amino;

Wherein; 3- to 7-membered heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo, hydroxy or (C₁-C₆)alkyl;

R_m and R_n are independently hydrogen or (C₁-C₆)alkyl; and

5 n is 1, 2 or 3.

PHARMACEUTICAL COMPOSITIONS:

In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

10 In another embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, and at least one pharmaceutically acceptable carrier excipient.

Illustrative pharmaceutical compositions are tablets and gelatin capsules comprising one or more compounds of the present disclosure and a pharmaceutically acceptable carrier, such as, but not limited to, a) a diluent, example, purified water, triglyceride oils, such as hydrogenated or partially hydrogenated vegetable oil or mixtures thereof, corn oil, olive oil, sunflower oil, safflower oil, fish oils, such as EPA or DHA or their esters or triglycerides or mixtures thereof, omega-3 fatty acids or derivatives thereof, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, sodium, saccharin, glucose and/or glycine; b) a lubricant, 15 example, silica, talcum, stearic acid, its magnesium or calcium salt, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and/or polyethylene glycol; for tablets also; c) a binder, example, magnesium aluminium silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, magnesium carbonate, natural sugars such as glucose or beta- lactose, corn sweeteners, natural and 20 synthetic gums such as acacia, tragacanth or sodium alginate, waxes and/or polyvinylpyrrolidone, if desired; d) a disintegrant, example, starches, agar, methyl cellulose, bentonite, xanthan gum, alginic acid or its sodium salt or effervescent mixtures; e) absorbent, colorant, flavourant and sweetener; f) an emulsifier or dispersing agent, such as Tween 80, Labrasol, HPMC, DOSS, caproyl 909, labrafac, labrafil, peceol, transcitol, capmul MCM, 25 capmul PG-12, captex 355, gelucire, vitamin E TGPS or other acceptable emulsifier; and/or g) an agent that enhances absorption of the compound such as cyclodextrin, hydroxypropyl-cyclodextrin, PEG400, PEG200.

In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, for use in degrading a target protein in a subject, wherein the target protein is KRAS.

5 In one embodiment, the subject is afflicted with a disease or disorder dependent upon at least one of KRAS, wherein the disease or disorder is cancer.

In one embodiment, the subject is afflicted with a disease or disorder dependent upon KRAS G12A, KRAS G12C, KRAS G12D, KRAS G12R, KRAS G12S, KRAS G12V, KRAS G13D or KRAS Q61H.

10 In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, for use in treating or preventing cancers selected from the group consisting of biliary tract malignancies, colon cancer, liver cancer, colorectal cancer, non-small cell lung cancer, small-cell lung cancer, pancreatic cancer, appendiceal cancer, melanoma,
15 acute myeloid leukemia, small bowel cancer, ampullary cancer, germ cell cancer, cervical cancer, cancer of unknown primary origin, endometrial cancer, esophagogastric cancer, GI neuroendocrine cancer, ovarian cancer, sex cord stromal tumor cancer, hepatobiliary cancer, bladder cancer, lung cancer, prostate cancer, breast cancer, cervical carcinomas, testicular carcinomas, gastric cancer, head and neck cancer, hepatocellular cancer, laryngeal cancer, oral
20 cancer, thyroid carcinomas, sarcomas, cardiac cancer, angiosarcoma, rhabdomyosarcoma, liposarcoma, myxoma, rhabdomyoma, fibroma, lipoma, teratoma, bronchogenic carcinoma, undifferentiated small cell cancer, adenocarcinoma, alveolar carcinoma, bronchiolar carcinoma, bronchial adenoma, lymphoma, chondromatous hamartoma, mesothelioma, gastrointestinal cancer, squamous cell carcinoma, leiomyosarcoma, stomach cancer,
25 carcinoma, pancreas cancer, ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, VIPoma, adenocarcinoma, Kaposi's sarcoma, leiomyoma, hemangioma, neurofibroma, tubular adenoma, villous adenoma, hamartoma, genitourinary tract cancer, Wilm's tumor, nephroblastoma, leukemia, urethra cancer, transitional cell carcinoma, testis cancer, seminoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma,
30 interstitial cell carcinoma, fibroadenoma, adenomatoid tumors, hepatoma, hepatocellular carcinoma, cholangiocarcinoma, hepatoblastoma, hepatocellular adenoma, gall bladder carcinoma, ampullary carcinoma, bone cancer, osteogenic sarcoma, osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant

lymphoma, reticulum cell sarcoma, multiple myeloma, malignant giant cell tumor chordoma, osteochondroma, osteochondrogenous exostoses, benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma, giant cell tumors, nervous system cancer, skull cancer, granuloma, xanthoma, osteitis deformans, meningioma, meningiosarcoma, gliomatosis, brain
5 cancer, astrocytoma, medulloblastoma, glioma, ependymoma, germinoma, pinealoma, glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors, spinal cord neurofibroma, neurofibromatosis type 1, gynecological cancer, uterus cancer, endometrial carcinoma, uterine carcinoma, uterine corpus endometrial carcinoma, pre-tumor cervical dysplasia, ovarian carcinoma, serous cystadenocarcinoma, mucinous
10 cystadenocarcinoma, granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma, intraepithelial carcinoma, clear cell carcinoma, botryoid sarcoma, embryonal rhabdomyosarcoma, fallopian tubes carcinoma, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, myelodysplastic syndrome, Hodgkin's disease, non-Hodgkin's lymphoma, malignant
15 melanoma, basal cell carcinoma, moles dysplastic nevi, dermatofibroma, keloids and neuroblastoma.

METHODS and/or USES:

In one embodiment, the present invention provides, a method of degrading a target protein in a subject comprising administering to a subject in need thereof, a therapeutically
20 effective amount of the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

In one embodiment, the present invention provides a method of degrading a target protein is KRAS.

In one embodiment, the present invention provides a method of degrading a target protein
25 is KRAS G12A, KRAS G12C, KRAS G12D, KRAS G12R, KRAS G12S, KRAS G12V, KRAS G13D or KRAS Q61H.

In one embodiment, the present invention provides a method of treating or delaying progression of a disease or disorder dependent upon KRAS in a subject comprising administering to the subject, in need thereof, a therapeutically effective amount of a compound
30 of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

In one embodiment, the present invention provides a method for treating diseases or disorders dependent upon KRAS in a subject comprising administering to the subject in need

thereof a therapeutically effective amount of a compound formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

In one embodiment, diseases or disorders that are dependent upon KRAS, include cancer.

In one embodiment, the present invention provides a method of inhibiting tumour growth
5 in a subject afflicted with cancer comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof to the subject, in need thereof.

In any one of the preceding embodiments, cancer is selected from the group consisting of biliary tract malignancies, colon cancer, liver cancer, colorectal cancer, non-small cell lung
10 cancer, small-cell lung cancer, pancreatic cancer, appendiceal cancer, melanoma, acute myeloid leukemia, small bowel cancer, ampullary cancer, germ cell cancer, cervical cancer, cancer of unknown primary origin, endometrial cancer, esophagogastric cancer, GI neuroendocrine cancer, ovarian cancer, sex cord stromal tumor cancer, hepatobiliary cancer, bladder cancer, lung cancer, prostate cancer, breast cancer, cervical carcinomas, testicular
15 carcinomas, gastric cancer, head and neck cancer, hepatocellular cancer, laryngeal cancer, oral cancer, thyroid carcinomas, sarcomas, cardiac cancer, angiosarcoma, rhabdomyosarcoma, liposarcoma, myxoma, rhabdomyoma, fibroma, lipoma, teratoma, bronchogenic carcinoma, undifferentiated small cell cancer, adenocarcinoma, alveolar carcinoma, bronchiolar carcinoma, bronchial adenoma, lymphoma, chondromatous hamartoma, mesothelioma,
20 gastrointestinal cancer, squamous cell carcinoma, leiomyosarcoma, stomach cancer, carcinoma, pancreas cancer, ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, VIPoma, adenocarcinoma, Kaposi's sarcoma, leiomyoma, hemangioma, neurofibroma, tubular adenoma, villous adenoma, hamartoma, genitourinary tract cancer, Wilm's tumor, nephroblastoma, leukemia, urethra cancer, transitional cell carcinoma, testis
25 cancer, seminoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroadenoma, adenomatoid tumors, hepatoma, hepatocellular carcinoma, cholangiocarcinoma, hepatoblastoma, hepatocellular adenoma, gall bladder carcinoma, ampullary carcinoma, bone cancer, osteogenic sarcoma, osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant
30 lymphoma, reticulum cell sarcoma, multiple myeloma, malignant giant cell tumor chordoma, osteochondroma, osteochondrogenous exostoses, benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma, giant cell tumors, nervous system cancer, skull cancer, granuloma, xanthoma, osteitis deformans, meningioma, meningiosarcoma, gliomatosis, brain

cancer, astrocytoma, medulloblastoma, glioma, ependymoma, germinoma, pinealoma, glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors, spinal cord neurofibroma, neurofibromatosis type 1, gynecological cancer, uterus cancer, endometrial carcinoma, uterine carcinoma, uterine corpus endometrial carcinoma, pre-tumor
5 cervical dysplasia, ovarian carcinoma, serous cystadenocarcinoma, mucinous cystadenocarcinoma, granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma, intraepithelial carcinoma, clear cell carcinoma, botryoid sarcoma, embryonal rhabdomyosarcoma, fallopian tubes carcinoma, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases,
10 myelodysplastic syndrome, Hodgkin's disease, non-Hodgkin's lymphoma, malignant melanoma, basal cell carcinoma, moles dysplastic nevi, dermatofibroma, keloids and neuroblastoma.

In one embodiment, the cancer dependent upon KRAS is lung cancer and non-small cell lung cancer.

15 In one embodiment, the cancer dependent upon KRAS is pancreatic cancer.

In one embodiment, the present invention provides a compound of (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, for use as a medicament.

In one embodiment, the present invention provides a compound of formula (I) or a
20 pharmaceutical acceptable salt or a stereoisomer or a tautomer thereof, for use in the treatment of a disease or disorder dependent upon KRAS.

In one embodiment, the present invention provides a compound of formula (I) or a pharmaceutical acceptable salt or a stereoisomer or a tautomer thereof, for use in the treatment of a disease or disorder dependent upon KRAS G12A, KRAS G12C, KRAS G12D, KRAS
25 G12R, KRAS G12S, KRAS G12V, KRAS G13D or KRAS Q61H.

In one embodiment, a disease or disorder dependent upon KRAS is cancer.

In one embodiment, the present invention provides use of compound of formula (I) or a pharmaceutical acceptable salt or a stereoisomer or a tautomer thereof, in the manufacture of a medicament for the treatment of a disease or disorder dependent upon KRAS.

30 In one embodiment, the present invention provides a compound represented by formula (I) or a pharmaceutical acceptable salt or a stereoisomer or a tautomer thereof, for use in the

treatment of a disease or disorder dependent upon KRAS, wherein the disease or disorder dependent upon KRAS is cancer.

In one embodiment, the disease or disorder is cancer selected from the group consisting of biliary tract malignancies, colon cancer, liver cancer, colorectal cancer, non-small cell lung
 5 cancer, small-cell lung cancer, pancreatic cancer, appendiceal cancer, melanoma, acute myeloid leukemia, small bowel cancer, ampullary cancer, germ cell cancer, cervical cancer, cancer of unknown primary origin, endometrial cancer, esophagogastric cancer, GI neuroendocrine cancer, ovarian cancer, sex cord stromal tumor cancer, hepatobiliary cancer, bladder cancer, lung cancer, prostate cancer, breast cancer, cervical carcinomas, testicular
 10 carcinomas, gastric cancer, head and neck cancer, hepatocellular cancer, laryngeal cancer, oral cancer, thyroid carcinomas, sarcomas, cardiac cancer, angiosarcoma, rhabdomyosarcoma, liposarcoma, myxoma, rhabdomyoma, fibroma, lipoma, teratoma, bronchogenic carcinoma, undifferentiated small cell cancer, adenocarcinoma, alveolar carcinoma, bronchiolar carcinoma, bronchial adenoma, lymphoma, chondromatous hamartoma, mesothelioma,
 15 gastrointestinal cancer, squamous cell carcinoma, leiomyosarcoma, stomach cancer, carcinoma, pancreas cancer, ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, VIPoma, adenocarcinoma, Kaposi's sarcoma, leiomyoma, hemangioma, neurofibroma, tubular adenoma, villous adenoma, hamartoma, genitourinary tract cancer, Wilm's tumor, nephroblastoma, leukemia, urethra cancer, transitional cell carcinoma, testis
 20 cancer, seminoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroadenoma, adenomatoid tumors, hepatoma, hepatocellular carcinoma, cholangiocarcinoma, hepatoblastoma, hepatocellular adenoma, gall bladder carcinoma, ampullary carcinoma, bone cancer, osteogenic sarcoma, osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant
 25 lymphoma, reticulum cell sarcoma, multiple myeloma, malignant giant cell tumor chordoma, osteochondroma, osteochondrogenous exostoses, benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma, giant cell tumors, nervous system cancer, skull cancer, granuloma, xanthoma, osteitis deformans, meningioma, meningiosarcoma, gliomatosis, brain cancer, astrocytoma, medulloblastoma, glioma, ependymoma, germinoma, pinealoma,
 30 glioblastoma multiforme, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors, spinal cord neurofibroma, neurofibromatosis type 1, gynecological cancer, uterus cancer, endometrial carcinoma, uterine carcinoma, uterine corpus endometrial carcinoma, pre-tumor cervical dysplasia, ovarian carcinoma, serous cystadenocarcinoma, mucinous

cystadenocarcinoma, granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma, intraepithelial carcinoma, clear cell carcinoma, botryoid sarcoma, embryonal rhabdomyosarcoma, fallopian tubes carcinoma, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, 5 myelodysplastic syndrome, Hodgkin's disease, non-Hodgkin's lymphoma, malignant melanoma, basal cell carcinoma, moles dysplastic nevi, dermatofibroma, keloids and neuroblastoma.

In one embodiment, the present invention provides a process for the preparation of compound of formula (I).

10 In one embodiment, the present invention provides a method for degrading KRAS protein, comprising contacting a compound of formula or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof with KRAS protein.

In one embodiment, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof for use as a drug for 15 treating or preventing a KRAS- mediated disease or condition.

In one embodiment, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof for use as a drug for KRAS- mediated disease or condition.

The present invention provides a method for treating or preventing a disease or condition 20 regulated by KRAS (e.g., cancer), comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

The present invention provides a method for treating or preventing a disease or condition regulated by KRAS mutations, wherein the KRAS mutation is in the region selected from 25 KRAS G12C, KRAS G12D, KRAS G12H, KRAS G12V, KRAS G12S, KRAS G13C, KRAS G13D, KRAS Q61, KRAS Q61K and KRAS Q61H, or pan-KRAS degrader comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

In one embodiment, the compounds of the present disclosure are KRAS degraders.

30 In one embodiment, the compounds of the present disclosure are pan-KRAS degraders as the compounds target more than one KRAS mutation.

Definitions:

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in art to which the subject matter herein belongs. As used in the specification and the appended claims, unless specified to the contrary,
5 the following terms have the meaning indicated in order to facilitate the understanding of the present invention.

The singular forms “a”, “an” and “the” encompass plural references unless the context clearly indicates otherwise.

As used herein, the terms “optional” or “optionally” mean that the subsequently
10 described event or circumstance may occur or may not occur and that the description includes instances where the event or circumstance occurs as well as instances in which it does not. For example, “optionally substituted alkyl” refers to an event or circumstance where the alkyl is substituted as well as the event or circumstance where the alkyl is not substituted. The term “optionally substituted alkyl” can also be referred to as ‘unsubstituted or substituted alkyl’
15 group, wherein the substituent(s) are as stated therein.

As used herein, the term “unsubstituted” means that there is no substituent or that the only substituents are hydrogen.

As used herein, the term “substituted” refers to moieties having substituents replacing hydrogen on one or more carbons of the backbone. It will be understood that “substitution” or
20 “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent and that the substitution results in a stable compound, example, which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term “substituted” is contemplated to include all permissible substituents of organic compounds. In a broad aspect,
25 the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described
30 herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxy carbonyl, a formyl or an acyl), a thiocarbonyl (such as a thioester, a thioacetate or a

thioformate), an alkoxy, an oxo, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heteroaryl, a heterocyclyl, an aralkyl or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that substituents can themselves be substituted, if appropriate.

As used herein, the term “alkyl” refers to saturated aliphatic groups, including but not limited to C₁-C₁₀ straight-chain alkyl groups or C₃-C₁₀ branched-chain alkyl groups. Preferably, “alkyl” group refers to C₁-C₆ straight-chain alkyl groups or C₃-C₆ branched-chain alkyl groups. In one embodiment, the “alkyl” group refers to C₁-C₄ alkyl groups. Examples of “alkyl” include, but are not limited to, methyl, ethyl, 1-propyl, 2-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, 1-pentyl, 2-pentyl, 3-pentyl, neo-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 1-octyl, 2-octyl, 3-octyl and 4-octyl. Accordingly, examples of “alkyl” include, but are not limited to, -CH₃, -CH₂CH₃, -CH(CH₃)CH₃, -CH₂CH₂CH₂CH₃, -CH(CH₃)CH₂CH₂CH₃ and -CH₂CH(CH₃)CH₂CH₃. The “alkyl” group may be optionally substituted. In one embodiment, the term “optionally substituted alkyl” can also be referred to as ‘unsubstituted or substituted alkyl’ group, wherein the substituent(s) are as stated therein.

As used herein, the term “alkynyl” refers to straight or branched carbon chains with one or more triple bonds wherein the number atoms are in the range 2 to 6.

As used herein, the term “acyl” refers to the general formula RCO-. The carbon atom is double bonded to an oxygen atom, and the R group is a chain of carbon and hydrogen atoms. Examples of “acyl” groups include but are not limited to -C(O)-CH₃, -C(O)-C₂H₅, -C(O)-CH(CH₃)₂ and the like.

As used herein, the term “halogen” is used herein interchangeably with the term “halogen” to mean F, Cl, Br or I atoms.

As used herein, the term “cyano” as used herein refers to -CN group.

As used herein, the term “oxo” as used herein refers to -O- or =O.

As used herein, the term “amino” is art-recognized and refers to -NR_xR_y, wherein R_x and R_y independently absent, H or (C₁-C₆)alkyl. Exemplary amino includes an -NH₂ group, -NH-, and -N R_x - group.

As used herein, the term “alkylamino” refers to an amino group substituted with one or more “alkyl” group, wherein the alkyl group and amino group is as defined above. Examples of “alkylamino” groups include but are not limited to -NHCH₃, -NHCH₂CH₃, -N(CH₃)₂, -N(CH₃)(CH₂CH₃) and the like.

5 As used herein, the term “haloalkoxy” means alkoxy substituted with one or more halogen atoms, wherein the halo and alkoxy groups are as defined above. The term “halo” is used herein interchangeably with the term “halogen” means F, Cl, Br or I.

As used herein, the term “hydroxy” or “hydroxyl” alone or in combination with other term(s), is art-recognized and refers to -OH.

10 As used herein, the term “alkoxy” refers to the group -O-alkyl, where alkyl groups are as defined above. Exemplary C₁-C₁₀ alkoxy group include but are not limited to methoxy, ethoxy, n-propoxy, n-butoxy or t-butoxy. In one embodiment, the “alkoxy” group refers to C₁-C₆ alkoxy groups. In another embodiment, the “alkoxy” group refers to C₁-C₄ alkoxy groups. An alkoxy group can be optionally substituted with one or more suitable groups. In some
15 embodiments, alkoxy group can be unsubstituted or substituted with one or more substituents, wherein the substituents are described herein.

As used herein, the term “haloalkyl” refers to alkyl substituted with one or more halogen atoms, wherein the halogen and alkyl groups are as defined above. Preferably (C₁-C₆) alkyl substituted with one or more halogen atoms. Examples of “haloalkyl” include but are not
20 limited to fluoromethyl, difluoromethyl, chloromethyl, trifluoromethyl and 2,2,2-trifluoroethyl.

As used herein, the term “cycloalkyl” means C₃-C₁₀ saturated cyclic hydrocarbon ring. A cycloalkyl may be a single ring, which typically contains from 3 to 8 carbon ring atoms. Examples of single ring cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A cycloalkyl may alternatively be polycyclic or spiro
25 or bicyclo or contain more than one ring. Examples of polycyclic cycloalkyls include bridged, fused and spirocyclic carbocyclis. Accordingly, examples of ‘cycloalkylenyl include, but not limited to, cyclopropylenyl, cyclobutylenyl, cyclopentylenyl, cyclohexylenyl, bicyclo[2.2.2]octane, spiro[3.3]heptane, and cycloheptylenyl.

30 As used herein, the term “heterocycloalkyl” refers to a non-aromatic, saturated or partially saturated, monocyclic or polycyclic ring system of 3 to 15 member having at least one heteroatom or heterogroup selected from the group consisting of O, N, S, S(O), S(O)₂, NH and

C(O) with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. The term “heterocycloalkyl” also refers to the bridged or spiro or fused bicyclic ring system having at least one heteroatom or heterogroup selected from the group consisting of O, N, S, S(O), S(O)₂, NH and C(O). Examples of “heterocycloalkyl” include, but are not limited to azetidiny, oxetanyl, imidazolidiny, pyrrolidiny, oxazolidiny, thiazolidiny, pyrazolidiny, tetrahydrofuranyl, piperidiny, piperaziny, tetrahydropyranyl, morpholiny, thiomorpholiny, 1,4-dioxanyl, dioxidothiomorpholiny, oxapiperaziny, oxapiperidiny, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiophenyl, dihydropyranyl, indoliny, indolinylmethyl, aza-bicyclooctanyl, azociny, chromanyl, xanthenyl, 2-oxabicyclo[2.2.2]octanyl, and N-oxides thereof. Attachment of a heterocycloalkyl substituent can occur via either a carbon atom or a heteroatom. A heterocycloalkyl group can be optionally substituted with one or more suitable groups by one or more aforesaid groups. Preferably “heterocycloalkyl” refers to 5- to 6-membered ring selected from the group consisting of azetidiny, oxetanyl, imidazolidiny, pyrrolidiny, oxazolidiny, thiazolidiny, pyrazolidiny, tetrahydrofuranyl, piperidiny, piperaziny, tetrahydropyranyl, morpholiny, thiomorpholiny, 1,4-dioxanyl, and N-oxides thereof. More preferably, “heterocycloalkyl” includes azetidiny, pyrrolidiny, morpholiny and piperidiny. All heterocycloalkyl are optionally substituted by one or more aforesaid groups.

As used herein, the term “heteroaryl” refers to an aromatic heterocyclic ring system containing 5 to 20 ring atoms, suitably 5 to 10 ring atoms, which may be a single ring (monocyclic) or multiple rings (bicyclic, tricyclic or polycyclic) fused together or linked covalently. Preferably, “heteroaryl” is a 5- to 6-membered ring. The rings may contain from 1 to 4 heteroatoms selected from the group consisting of N, O and S, wherein the N or S atom is optionally oxidized or the N atom is optionally quarternized. Any suitable ring position of the heteroaryl moiety may be covalently linked to the defined chemical structure.

Examples of heteroaryl include, but are not limited to: furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, cinnoliny, isoxazolyl, thiazolyl, isothiazolyl, 1H-tetrazolyl, oxadiazolyl, triazolyl, pyridyl, pyrimidinyl, pyraziny, pyridaziny, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzofuranyl, benzothienyl, benzotriazinyl, phthalazinyl, thianthrene, dibenzofuranyl, dibenzothienyl, benzimidazolyl, indolyl, isoindolyl, indazolyl, quinoliny, isoquinoliny, quinazoliny, quinoxaliny, puriny, pteridiny, 9H-carbazolyl, α -carboline, indoliziny, benzoisothiazolyl, benzoxazolyl, pyrrolopyridyl, pyrazolopyrimidyl, furopyridiny, puriny, benzothiadiaazolyl, benzooxadiazolyl, benzotriazolyl, benzotriadiaazolyl,

carbazolyl, dibenzothienyl, acridinyl and the like. Preferably “heteroaryl” refers to 5- to 6-membered ring selected from the group consisting of furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, cinnolinyl, isoxazolyl, thiazolyl, isothiazolyl, 1H-tetrazolyl, oxadiazolyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl and pyridazinyl. More preferably, pyrazolyl, pyridyl, 5 oxazolyl, and furanyl. All heteroaryls are optionally substituted by one or more aforesaid groups. As used herein, the term ‘compound(s)’ comprise(s) the compound(s) disclosed in the present invention.

As used herein, the term “heteroarylalkyl” refers to alkyl substituted with one or more heteroaryl groups, wherein the heteroaryl and alkyl groups are as defined above. Preferably 10 (C₁-C₆) alkyl substituted with one or more heteroaryl groups. Examples of “heteroarylalkyl” include but are not limited to -CH₂-Pyridine, -CH₂-Pyrazine, -CH₂-CH₂-Pyridine etc.

As used herein, the term “heterocyclyl” refers to heterocycloalkyl or heteroaryl.

As used herein, the term “aryl” is optionally substituted monocyclic, bicyclic or polycyclic aromatic hydrocarbon ring system of about 6 to 14 carbon atoms. Examples of a C₆- 15 C₁₄ aryl group include, but are not limited to phenyl, naphthyl, biphenyl, anthryl, fluorenyl, indanyl, biphenylenyl and acenaphthyl. Aryl group can be unsubstituted or substituted with one or more suitable groups.

The term “acyl” refers to a group R-CO- wherein R is an optionally substituted alkyl group defined above. Examples of ‘acyl’ groups are, but not limited to, CH₃CO-, CH₃CH₂CO- 20 , CH₃CH₂CH₂CO- or (CH₃)₂CHCO-.

The term “heteroatom” as used herein designates a sulfur, nitrogen or oxygen atom.

As used herein, the term ‘compound(s)’ comprises the compounds disclosed in the present invention.

As used herein, the term “salt/salts” refers to the salts derived from appropriate bases 25 include alkali metal (example, sodium and potassium), alkaline earth metal (example, magnesium), ammonium and N⁺(C₁-C₄ alkyl)₄ salts.

As used herein, the term “comprises” or “comprising” is generally used in the sense of include, that is to say permitting the presence of one or more features or components.

As used herein, the term “or” means “and/or” unless stated otherwise.

30 As used herein, the term “including” as well as other forms, such as “include”, “includes” and “included” is not limiting.

As used herein, the term “composition” is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By “pharmaceutically acceptable” it is meant the carrier, diluent or excipient must be compatible
5 with the other ingredients of the formulation and not deleterious to the recipient thereof.

As used herein, the term “pharmaceutical composition” refers to a composition(s) containing a therapeutically effective amount of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

The pharmaceutical composition(s) usually contain(s) about 1% to 99%, for example,
10 about 5% to 75% or from about 10% to about 30% by weight of the compound of formula (I) or (II) or pharmaceutically acceptable salts thereof. The amount of the compound of formula (I) or pharmaceutically acceptable salts thereof in the pharmaceutical composition(s) can range from about 1 mg to about 1000 mg or from about 2.5 mg to about 500 mg or from about 5 mg to about 250 mg or in any range falling within the broader range of 1 mg to 1000 mg or higher
15 or lower than the aforementioned range.

As used herein, “pharmaceutically acceptable carrier, diluent or excipient” includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, surfactant or emulsifier that has been
20 approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

As used herein, the term “administer”, “administering,” or “administration” as used in this disclosure refers to either directly administering one or more disclosed compounds or a pharmaceutically acceptable salt of one or more disclosed compounds or a composition
25 comprising one or more disclosed compounds to a subject or administering a prodrug derivative or analog of the compound or a pharmaceutically acceptable salt of the compound or composition to the subject, which can form an equivalent amount of active compound within the subject’s body.

As used herein, the term “carrier” as used in this disclosure, encompasses carriers,
30 excipients and diluents and means a material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting

a pharmaceutical agent from one organ or portion of the body to another organ or portion of the body of a subject.

As used herein, the term “treat”, “treating” and “treatment” refer to a method of alleviating or abrogating a disease and/or its attendant symptoms.

5 As used herein, the term “prevent”, “preventing” and “prevention” refer to a method of preventing the onset of a disease and/or its attendant symptoms or barring a subject from acquiring a disease. As used herein, “prevent”, “preventing” and “prevention” also include delaying the onset of a disease and/or its attendant symptoms and reducing a subject’s risk of acquiring a disease.

10 As used herein, the term “subject” that may be interchangeable with ‘patient’, refers to an animal, preferably a mammal and most preferably a human.

As used herein, the term, “therapeutically effective amount” refers to an amount of a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, or a composition comprising the compound of formula (I) or a pharmaceutically
15 acceptable salt or a stereoisomer or a tautomer thereof, effective in producing the desired therapeutic response in a particular patient suffering from a diseases or disorder, in particular their use in diseases or disorder associated with cancer. Particularly, the term “therapeutically effective amount” includes the amount of the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer or a tautomer hereof, when administered, that induces a
20 positive modification in the disease or disorder to be treated or is sufficient to prevent development of or alleviate to some extent, one or more of the symptoms of the disease or disorder being treated in a subject. In respect of the therapeutic amount of the compound, the amount of the compound used for the treatment of a subject is low enough to avoid undue or severe side effects, within the scope of sound medical judgment can also be considered. The
25 therapeutically effective amount of the compound or composition will be varied with the particular condition being treated, the severity of the condition being treated or prevented, the duration of the treatment, the nature of concurrent therapy, the age and physical condition of the end user, the specific compound or composition employed the particular pharmaceutically acceptable carrier utilized.

30 As used herein, the term “pharmaceutically acceptable salt” refers to a product obtained by reaction of the compound of the present invention with a suitable acid or a base. Pharmaceutically acceptable salts of the compounds of this invention include those derived

from suitable inorganic bases such as Li, Na, K, Ca, Mg, Fe, Cu, Al, Zn and Mn salts; Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, pantothenate, 5 bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, 4-methylbenzenesulfonate or p-toluenesulfonate salts and the like. Certain compounds of the invention (compound of formula (I)) can form pharmaceutically acceptable salts with various organic bases such as lysine, arginine, guanidine, diethanolamine or 10 metformin. Suitable base salts include, but are not limited to, aluminium, calcium, lithium, magnesium, potassium, sodium or zinc salts.

“Pharmaceutically acceptable” means that, which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary as well as human 15 pharmaceutical use.

The present invention also provides methods for formulating the disclosed compounds as for pharmaceutical administration.

In a preferred embodiment, when such pharmaceutical compositions are for human administration, particularly for invasive routes of administration (i.e., routes, such as injection 20 or implantation, that circumvent transport or diffusion through an epithelial barrier), the aqueous solution is pyrogen-free or substantially pyrogen-free. The excipients can be chosen, for example, to effect delayed release of an agent or to selectively target one or more cells, tissues or organs. The pharmaceutical composition can be in dosage unit form such as tablet, capsule (including sprinkle capsule and gelatin capsule), granule, lyophile for reconstitution, 25 powder, solution, syrup, suppository, injection or the like. The composition can also be present in a transdermal delivery system, example, a skin patch. The composition can also be present in a solution suitable for topical administration, such as an eye drop.

The term “cancer” is used throughout the specification to refer to the pathological process that results in the formation and growth of a cancerous or malignant neoplasm, i.e., abnormal 30 tissue that grows by cellular proliferation, often more rapidly than normal and continues to grow after the stimuli that initiated the new growth cease. Malignant neoplasms show partial or complete lack of structural organization and functional coordination with the normal tissue

and most invade surrounding tissues, metastasize to several sites and are likely to recur after attempted removal and to cause the death of the patient unless adequately treated. As used herein, the term neoplasia is used to describe all cancerous disease states and embraces or encompasses the pathological process associated with malignant hematogenous, ascitic and
5 solid tumours.

Exemplary cancers which may be treated by the present compounds include biliary tract malignancies, bladder cancer, breast cancer, colon cancer, colorectal cancer, cervical cancer, endometrial cancer, liver cancer, lung cancer, non-small cell lung cancer, myeloid leukemia or pancreatic cancer.

10 The term “stereoisomers” refers to any enantiomers, diastereoisomers or geometrical isomers of the compound of formula (I), wherever they are chiral or when they bear one or more double bonds. When the compounds of the formula (I) and related formulae are chiral, they can exist in racemic or in optically active form. It should be understood that the invention encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric and
15 epimeric forms, as well as d-Isomers and l-Isomers and mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centres or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers
20 on chiral chromatographic columns or any other appropriate method known in the art. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art. Additionally, the compounds of the present invention may exist as geometric Isomers. The present invention includes all cis, trans, syn, anti, entgegen I and zusammen (Z) Isomers as well as the appropriate mixtures thereof.

25 The term “tautomer” refers to compounds in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. Compounds of the present invention, free form and salts thereof, may exist in multiple tautomeric forms. It is understood that all tautomeric forms, insofar as they may exist, are included within the invention. For example, pyridine or pyridyl can be optionally
30 substituted by oxo to form a respective pyridone or pyridon-yl and may include its tautomeric form such as a respective hydroxy-pyridine or hydroxy-pyridyl, provided said tautomeric form may be obtainable.

The term “enantiomers” refers to a pair of stereoisomers which are non-superimposable mirror images of one another. The term “enantiomer” refers to a single member of this pair of stereoisomers. The term “racemic” refers to a 1:1 mixture of a pair of enantiomers. The disclosure includes enantiomers of the compounds described herein. Each compound herein
5 disclosed includes all the enantiomers that conform to the general structure of the compound. The compounds may be in a racemic or enantiomerically pure form or any other form in terms of stereochemistry. In some embodiments the compounds are the (S)-enantiomer.

The term “diastereomers” refers to the set of stereoisomers which cannot be made superimposable by rotation around single bonds. For example, cis- and trans- double bonds,
10 endo- and exo- substitution on bicyclic ring systems and compounds containing multiple stereogenic centres with different relative configurations are considered to be diastereomers.

The term “diastereomer” refers to any member of this set of compounds. In some examples presented, the synthetic route may produce a single diastereomer or a mixture of diastereomers. The disclosure includes diastereomers of the compounds described herein.

15 The compounds of the present invention may be used as single drug or as a pharmaceutical composition in which the compound is mixed with various pharmacologically acceptable materials.

The compounds of the invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared using procedures well known
20 in the pharmaceutical art and comprise at least one compound of the invention. The pharmaceutical composition of the present patent application comprises one or more compounds described herein and one or more pharmaceutically acceptable excipients. Typically, the pharmaceutically acceptable excipients are approved by regulatory authorities or are generally regarded as safe for human or animal use. The pharmaceutically acceptable
25 excipients include, but are not limited to, carriers, diluents, glidants and lubricants, preservatives, buffering agents, chelating agents, polymers, gelling agents, viscosifying agents and solvents.

The pharmaceutical composition can be administered by oral, parenteral or inhalation routes. Examples of the parenteral administration include administration by injection,
30 percutaneous, transmucosal, transnasal and transpulmonary administrations.

Examples of suitable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin,

magnesium carbonate, sugar, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid, lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, fatty acid esters and polyoxyethylene.

The pharmaceutical composition may also include one or more pharmaceutically acceptable auxiliary agents, wetting agents, suspending agents, preserving agents, buffers, sweetening agents, flavouring agents, colorants or any combination of the foregoing.

The pharmaceutical compositions may be in conventional forms, for example, tablets, capsules, solutions, suspensions, injectables or products for topical application. Further, the pharmaceutical composition of the present invention may be formulated so as to provide desired release profile.

Administration of the compounds of the invention, in pure form or in an appropriate pharmaceutical composition, can be carried out using any of the accepted routes of administration of pharmaceutical compositions. The route of administration may be any route which effectively transports the active compound of the patent application to the appropriate or desired site of action. Suitable routes of administration include, but are not limited to oral, nasal, buccal, dermal, intradermal, transdermal, parenteral, rectal, subcutaneous, intravenous, intraurethral, intramuscular or topical.

Solid oral formulations include, but are not limited to, tablets, capsules (soft or hard gelatin), dragees (containing the active ingredient in powder or pellet form), troches and lozenges.

Liquid formulations include, but are not limited to, syrups, emulsions and sterile injectable liquids, such as suspensions or solutions.

Topical dosage forms of the compounds include ointments, pastes, creams, lotions, powders, solutions, eye or ear drops, impregnated dressings and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration.

The pharmaceutical compositions of the present patent application may be prepared by conventional techniques known in literature.

Suitable doses of the compounds for use in treating the diseases or disorders described herein can be determined by those skilled in the relevant art. Therapeutic doses are generally identified through a dose ranging study in humans based on preliminary evidence derived from the animal studies. Doses must be sufficient to result in a desired therapeutic benefit without

causing unwanted side effects. Mode of administration, dosage forms and suitable pharmaceutical excipients can also be well used and adjusted by those skilled in the art. All changes and modifications are envisioned within the scope of the present patent application.

According to one embodiment, the compounds of the present invention can also contain
5 unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the present invention also embraces isotopically labelled variants of the present invention which are identical to those recited herein, but for the fact that one or more atoms of the compound are replaced by an atom having the atomic mass or mass number different from the predominant atomic mass or mass number usually found in nature for the
10 atom. All isotopes of any particular atom or element as specified are contemplated within the scope of the compounds of the invention and their uses. Exemplary isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine and iodine, such as 2H ("D"), 3H , 11C , 13C , 14C , 13N , 15N , 15O , 17O , 18O , 32P , 33P , 35S , 18F , 36Cl , 123I and 125I . Isotopically labelled
15 compounds of the present inventions can generally be prepared by following procedures analogous to those disclosed in the schemes and/or in the examples herein below, by substituting an isotopically labelled reagent for a non-isotopically labelled reagent.

EXPERIMENTAL:

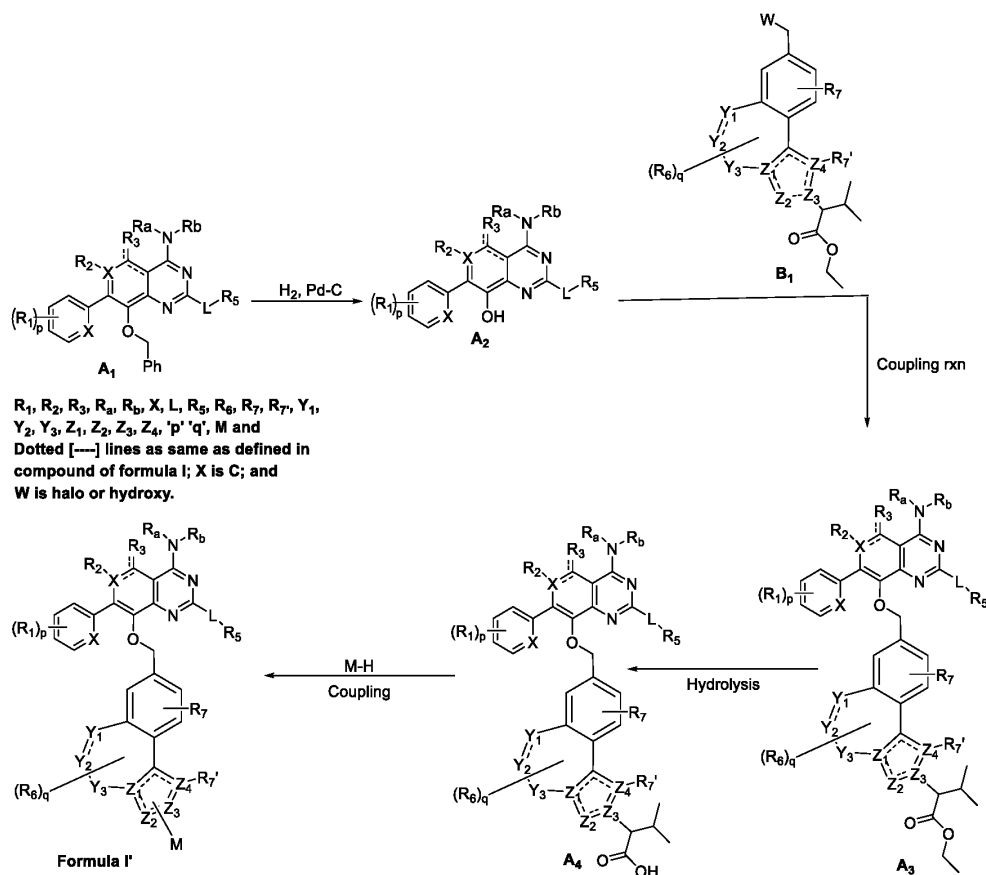
The following general guidelines apply to all experimental procedures described here.
20 Unless otherwise stated, reactions were performed under positive pressure of nitrogen, and temperatures described are external temperatures (oil bath temperature). Reagents and solvents received from vendors were used as such without any further drying or purification. Molarities mentioned here for reagents in solutions are approximate, as they were not verified by a prior titration with a standard. All reactions were stirred with a magnetic stir bar. Cooling to negative
25 temperatures was achieved with acetone / dry ice or ice / salt baths. Magnesium sulfate and sodium sulfate were used as solvent drying agent after reaction work up and are interchangeable. Removal of solvents under reduced pressure/vacuum was conducted using a rotary evaporator. The specifics of the processes for preparing compounds of the present disclosure are detailed in the experimental section.

ABBREVIATIONS:

The abbreviations used in the entire specification is summarized below with their meaning.

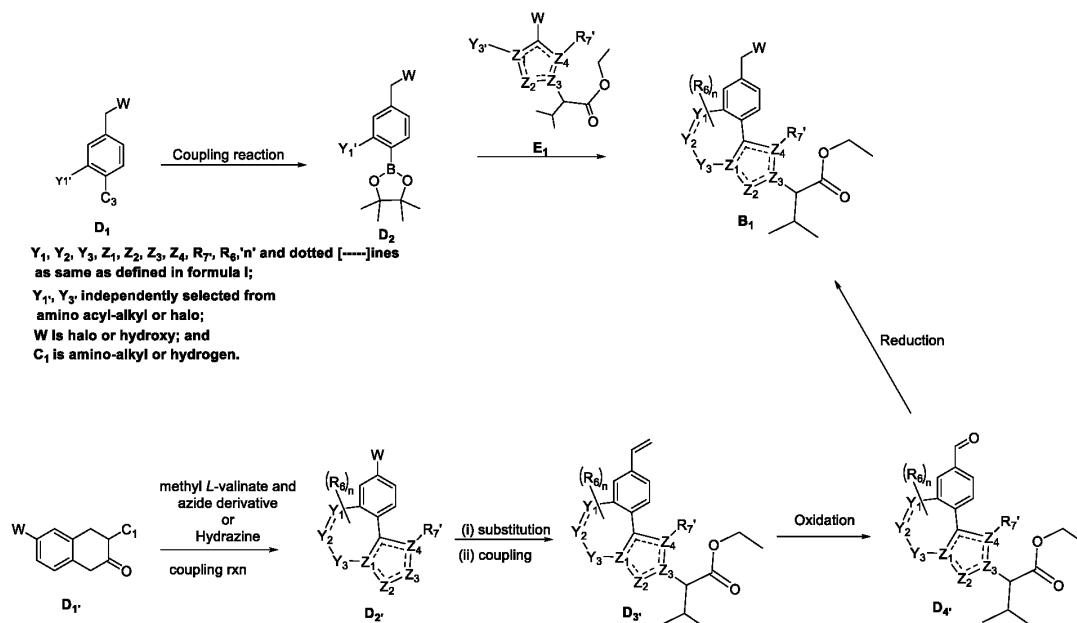
DMF-*N,N*-Dimethylformamide; ACN-Acetonitrile; EtOAc-Ethyl acetate; THF-
 5 Tetrahydrofuran; DCM-Dichloromethane; MeOH-Methanol; EtOH-Ethanol; DMSO-dimethyl sulfoxide; THF- Tetrahydrofuran; MeI-Methyl iodide; EtI-Ethyl iodide; TEA (or) Et₃N-Triethylamine; DIPEA- *N,N*-Diisopropylethylamine; KO^tBu-potassium tertiary butoxide; K₂CO₃-Potassium carbonate; Cs₂CO₃-cesium carbonate; K₃PO₄ - Potassium phosphate; LiOH-Lithium hydroxide; NH₃-Ammonia; NaOAc-Sodium acetate; KOAc-Potassium acetate;
 10 NH₄OH-Ammonium hydroxide; NH₄Cl-Ammonium chloride; NIS- N-Iodosuccinimide, CDI-1,1 carbonyl diimidazole, DDQ - 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone; POCl₃-Phosphoryl chloride, PBr₃- Phosphorus tribromide; N₂H₄-hydrazine monohydrate; NaBH₄ - sodium borohydride; NaIO₄- sodium periodate; OsO₄ - osmium tetroxide DABCO- 1,4-Diazabicyclo[2.2.2]octane, HATU-1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-
 15 *b*]pyridinium 3-oxide hexafluorophosphate; RuPhos-2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl; TFA-Trifluoroacetic acid; AcOH-Acetic acid; RT/rt-Room temperature; *P*-TSA- *para*-toluene sulfonic acid monohydrate; Ruphos-Pd-G3 - (2-Dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)] palladium (II) methanesulfonate; Pd-C- Palladium on carbon; Pd(dppf)Cl₂·DCM-[1,1'-
 20 Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane; LiAlH₄- Lithium aluminum hydride; B₂pin₂-bis(pinacolato)diboron; DMF-DMA- *N,N*-Dimethylformamide dimethyl acetal; BnOH- benzyl alcohol; MW- microwave; TLC-Thin layer chromatography; LCMS-Liquid chromatography-mass spectrometry; HPLC- High-performance liquid chromatography; CD₃OD- Deuterated methanol; DMSO-*d*₆-Deuterated
 25 dimethyl sulfoxide; CDCl₃-Deuterated chloroform; NMR-Nuclear magnetic resonance; s-Singlet; d-Doublet; t-Triplet; q-Quartet; app. quint-Apparent quintet; dd-doublet of doublets; td-Triplet of doublets; SM-starting material; Int-Intermediate.

GENERAL SCHEME – I:



The general scheme for the synthesis of compound represented by formula (I') is depicted in the above scheme. The compound of formula (A₂) can be obtained by the reduction reaction of a compound of formula (A₁). The compound of formula (A₂) upon further reaction with a compound of formula (B₁) in a suitable solvent can result in a compound of formula (A₃) which can undergo hydrolysis in the presence of a base to yield a compound of formula (A₄). The compound of formula (A₄) can be coupled with a pyrrolidine nitrogen of M in the presence of a solvent to yield compound of formula (I').

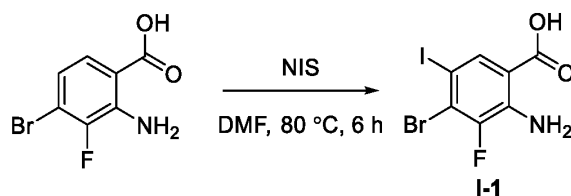
GENERAL SCHEME – II:



The general scheme for the synthesis of compound represented by formula (B₁) is depicted in the above scheme. The compound of formula (D₂) can be obtained from a compound of formula (D₁). The compound of formula (D₂), upon further reaction with a compound of formula (E₁) in the presence of a suitable solvent can yield a compound of formula (B₁). Alternatively, the compound of formula (D₂) can undergo substitution and coupling to give a compound of formula (D₃). The compound of formula (D₃) can undergo oxidation in the presence of a suitable solvent and reagent to yield a compound of formula (D₄), which can further undergo reduction in the presence of a suitable reagent and solvent to yield the compound of formula (B₁).

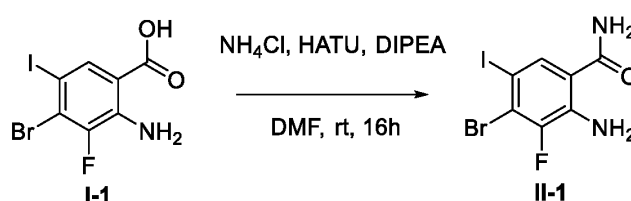
PREPARATION OF INTERMEDIATES (I-1 to XXIV-1)

Synthesis of 2-amino-4-bromo-3-fluoro-5-iodobenzoic acid (I-1):



To a stirred solution of 2-amino-4-bromo-3-fluorobenzoic acid (40.0 g, 0.017 mol, 1.0 equiv.) in DMF (200 mL) was added NIS (46.14 g, 0.02 mol, 1.2 equiv.) at room temperature and the reaction mixture was subsequently stirred at 80 °C for 6 h. The reaction mixture was allowed to cool to room temperature, then poured into ice water (100 mL) and stirred for 30 min. The resulting solid was filtered from the aqueous phase and dried under high vacuum to give acid title compound **I-1** (62.0 g), which was sufficiently pure to perform the next reaction. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.30 (bs, 1H), 7.99 (d, *J* = 2.0 Hz, 1H), 6.7 (bs, 2 H); LC-MS: *m/z* 357.7 (M-H)⁺.

Synthesis of 2-amino-4-bromo-3-fluoro-5-iodobenzamide (**II-1**):

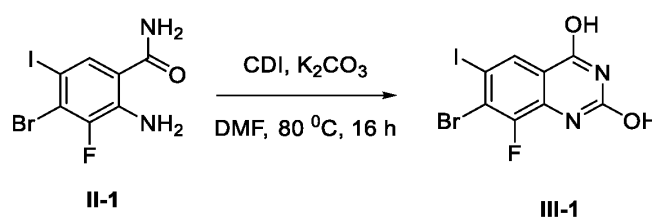


10

To a stirred solution of ammonium chloride (2.95 g, 0.055 mol, 2.0 equiv.) and DIPEA (10.8 g, 0.08 mol, 3.0 equiv.) in DMF (0.1 L) was added 2-amino-4-bromo-3-fluoro-5-iodobenzamide (**II-1**) (10.0 g, 0.028 mol, 1.0 equiv.) and HATU (12.0 g, 0.033 mol, 1.2 equiv.) at room temperature. The mixture was stirred at room temperature for 16 h. The reaction mixture was poured into ice water and stirred for 30 min. The solid was filtered from the aqueous phase and dried under a high vacuum to afford iodobenzamide **II-1** (10.0 g) which was sufficiently pure to perform the next reaction. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.03 (bs, 2H), 7.94 (s, 1H), 6.85 (s, 2H); LC-MS: *m/z* 358.60 (M-H)⁺.

15

Synthesis of 7-bromo-8-fluoro-6-iodoquinazoline-2,4-diol (**III-1**):

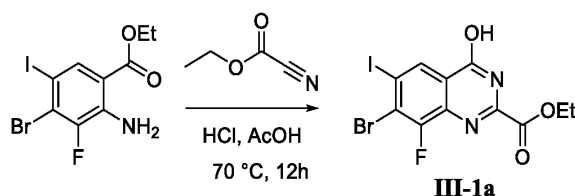


20

To a stirred solution of 2-amino-4-bromo-3-fluoro-5-iodobenzamide (**II-1**) (30.0 g, 0.083 mol, 1.0 equiv.) in DMF (150 mL) was added potassium carbonate (40.0 g, 0.29 mol, 3 equiv.) and 1,1-carbonyl diimidazole (54.0 g, 0.33 mol, 4 equiv.) at room temperature. Then the reaction mixture was heated to 80 °C and stirred for 16 h. The reaction mixture was allowed to cool to

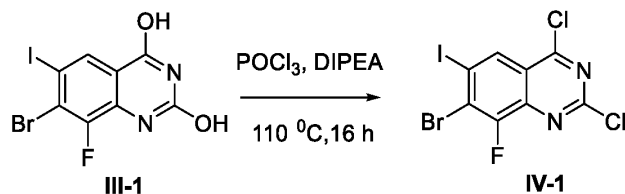
room temperature, then poured into ice water and stirred for 30 min. The solid was filtered from the aqueous phase and dried under high vacuum to provide the title dihydroxy compound **III-1** (30.0 g) which was sufficiently pure to perform the next reaction. LC-MS: m/z 382.75 (M-H)⁺.

5 Synthesis of ethyl 7-bromo-8-fluoro-4-hydroxy-6-iodoquinazoline-2-carboxylate (**III-1a**)



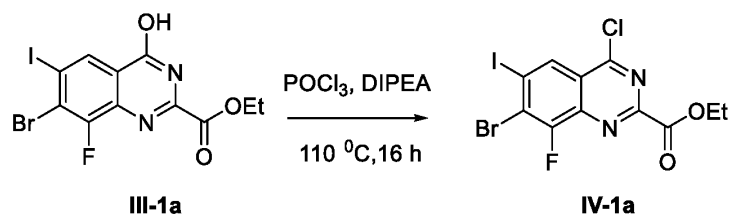
To a stirred solution of ethyl 2-amino-4-bromo-3-fluoro-5-iodobenzoate (27.0 g, 69.59 mmol, 1.0 equiv.) in acetic acid (150 mL) was added ethyl carbonocyanidate (27.58 g, 278.37mmol, 4 equiv.) followed by the addition of concentrated HCl (1 mL) and the reaction mixture was
 10 stirred for 16 h at 70 °C. The mixture was allowed to cool to room temperature and quenched with ice-cold water. The obtained solid filtered and dried to get titled crude product (12.1g) which was proceeded to next step without purification; LC-MS: m/z 440.75 (M-H)⁺.

Synthesis of 7-bromo-2,4-dichloro-8-fluoro-6-iodoquinazoline (**IV-1**):



To a stirred solution of 7-bromo-8-fluoro-6-iodoquinazoline-2,4-diol (**III-1**) (60.0 g, 0.155 mol, 1.0 equiv.) in POCl₃ (0.6 L) was added DIPEA (54.0 g, 0.13 mol, 2.2 equiv.) carefully at 0 °C. The mixture was allowed to reach room temperature and was then heated to 110 °C for 16 h. The reaction mixture was allowed to cool to room temperature, then concentrated under reduced pressure to remove the POCl₃. The crude oil was poured into ice
 20 cold water carefully and stirred for 10 min. The solid was filtered from the aqueous phase and dried under high vacuum to give a crude title compound **IV-1** (65.0 g) which was sufficiently pure to perform the next reaction. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.67 (d, *J* = 1.6 Hz, 1H); LC-MS: m/z 424.3 (M+H)⁺

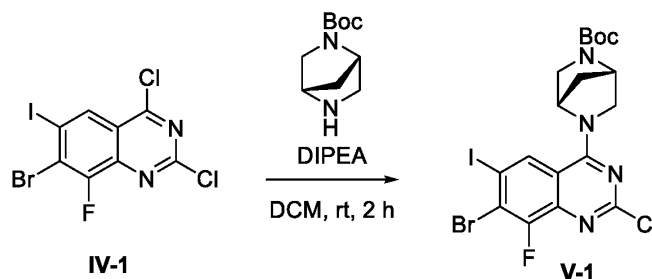
Synthesis of Ethyl 7-bromo-4-chloro-8-fluoro-6-iodoquinazoline-2-carboxylate (IV-1a):



The above intermediate **IV-1a** was prepared using procedure similar to the one described in the synthesis of **Intermediate IV-1** using POCl₃ as chlorinating agent; LC-MS: *m/z* 459.6

5 (M+H)⁺

Synthesis of *tert*-butyl (1*S*,4*S*)-5-(7-bromo-2-chloro-8-fluoro-6-iodoquinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (V-1):

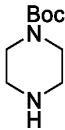
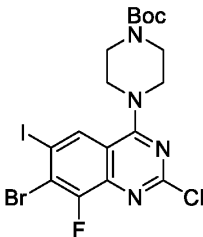
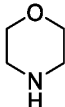
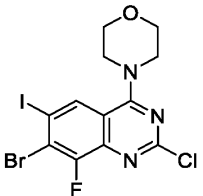
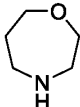
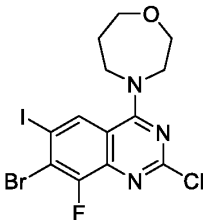
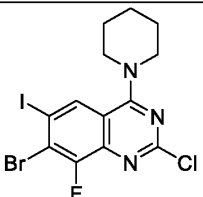
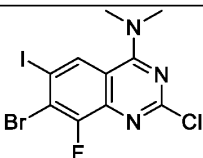


To a stirred solution of 7-bromo-2,4-dichloro-8-fluoro-6-iodoquinazoline (**IV-1**)
 10 (27.0 g, 0.06 mol, 1.0 equiv.) in DCM (280 mL) was added DIPEA (34.0 g, 0.25 mol, 4.0 equiv.) followed by *tert*-butyl (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (13.0 g, 0.07 mol, 1.05 equiv.) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was concentrated under reduced pressure. The crude material was poured into ice water and stirred for 10 min. The crude solid was filtered from the
 15 aqueous phase and dried under a high vacuum. The crude compound was suspended in 0.15 L of 5% ethyl acetate in hexane and stirred for 2 h. The solid was then filtered and dried under high vacuum to give a crude title compound **V-1** (37.0 g) which was sufficiently pure to perform the next reaction. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.37 (d, *J* = 6.4 Hz, 1H), 5.20 (d, *J* = 18.4 Hz, 1H), 4.57 (d, *J* = 16.8 Hz, 1H), 4.40- 4.30 (bs, 1H), 3.90- 3.70 (bs, 1H), 3.60- 3.40
 20 (m, 2H), 2.05- 1.90 (m, 2H), 1.39 (d, *J* = 13.6 Hz, 9H); LC-MS: *m/z* 584.90 (M+H)⁺.

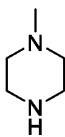
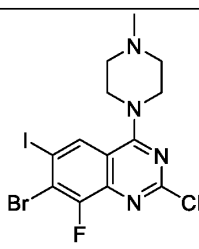
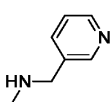
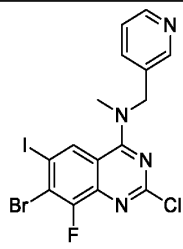
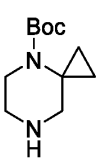
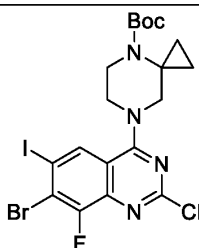
The intermediates listed below in **Table-1** were prepared by procedures similar to the one described in the synthesis of **Intermediate V-1** with 7-bromo-2,4-dichloro-8-fluoro-6-

iodoquinazoline (IV-1) and appropriate amine (SM-2) with appropriate variations in reagents, solvents and reaction conditions. The characterization data of the intermediates are summarized herein the below table.

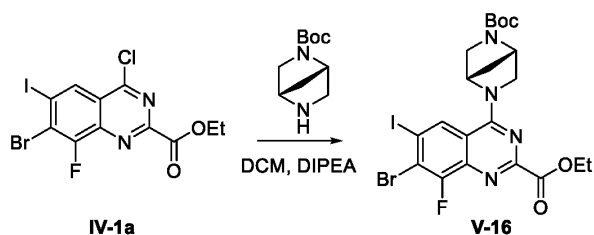
Table-1

Int-No	Amine used	Intermediate Structure	Analytical Data
V-2			LC-MS: m/z 573.9 $[M+H]^+$
V-3			1H NMR (400 MHz, DMSO- d_6): δ 8.2 (t, J = 2.0 Hz, 1H), 3.97-3.946 (m, 4H), 3.90-3.87 (5, 4H); LC-MS: m/z 472.4 $[M+H]^+$
V-4			LC-MS: m/z 487.80 $[M+H]^+$
V-5			LC-MS: m/z 471.75 $[M+H]^+$
V-6			LC-MS: m/z 431 $[M+H]^+$

V-7			LC-MS: m/z 459.80 [M+H] ⁺
V-8			LC-MS: m/z 501.0[M+H] ⁺
V-9			LC-MS: m/z 517.9 (M+H) ⁺ .
V-10			¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 8.43 (d, J = 1.6 Hz, 1H), 4.61-4.55 (m, 1H), 4.10 (d, J = 11.6 Hz, 2H), 3.25 (s, 3H), 2.85 (bs, 2H), 1.83-1.69 (m, 4H), 1.41 (d, J = 10.8 Hz, 9H); LC-MS: m/z 599.6 [M+H] ⁺
V-11			LC-MS: m/z 584.80[M+H] ⁺
V-12			LC-MS: m/z 456.1 [M+H] ⁺

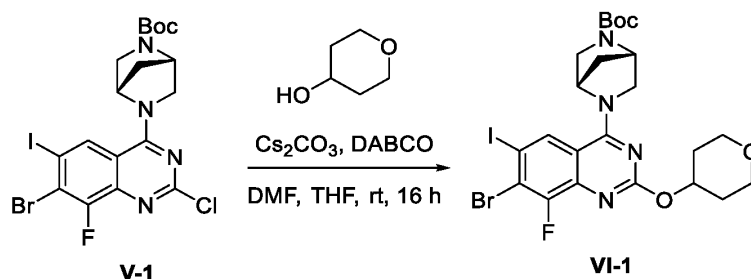
V-13			LC-MS: m/z 485.6 $[M+H]^+$
V-14			LC-MS: m/z 507.6 $[M+H]^+$
V-15			LC-MS: m/z 598.9 $[M+H]^+$

Synthesis of ethyl 7-bromo-4-((1S,4S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-8-fluoro-6-iodoquinazoline-2-carboxylate (V-16):



5 The above reaction was carried out by a procedure similar to the one described in the procedure of **Intermediate V-1** with ethyl 7-bromo-4-chloro-8-fluoro-6-iodoquinazoline-2-carboxylate (**IV-1a**) and tert-butyl (1S,4S)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate to get desired intermediate **V-16**; LC-MS: m/z 621.4 $[M+H]^+$

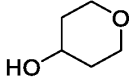
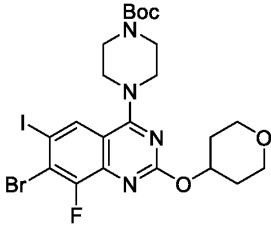
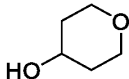
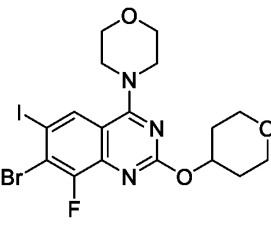
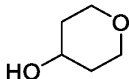
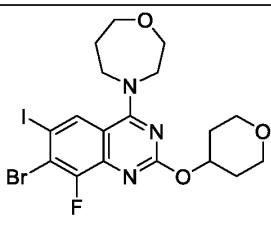
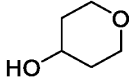
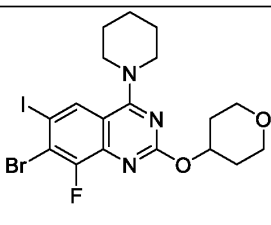
Synthesis of *tert*-butyl (1*S*,4*S*)-5-(7-bromo-8-fluoro-6-iodo-2-((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (VI-1):

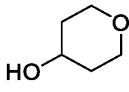
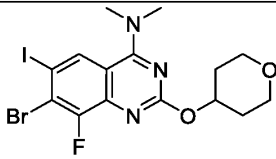
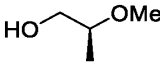
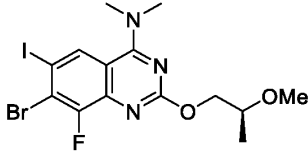
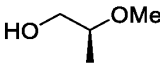
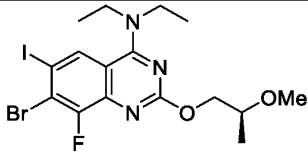
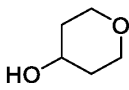
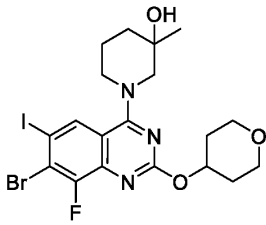
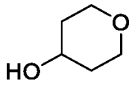
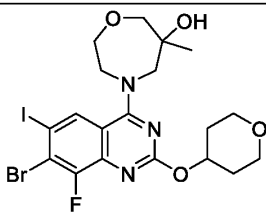
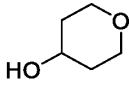
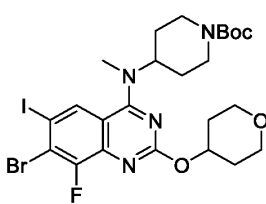


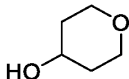
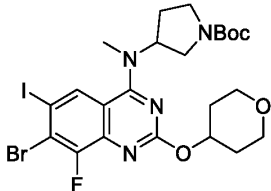
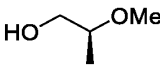
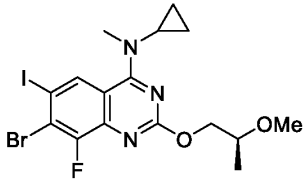
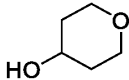
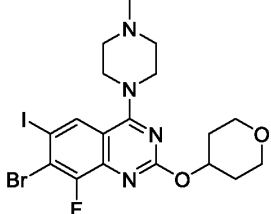
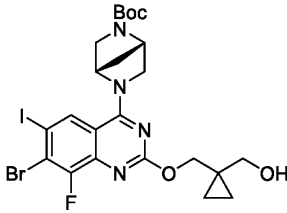
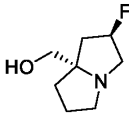
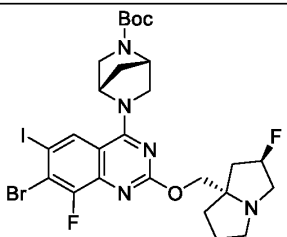
To a stirred solution of *tert*-butyl (1*S*,4*S*)-5-(7-bromo-2-chloro-8-fluoro-6-iodoquinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**V-1**) (15.0 g, 0.025 mol, 1.0 equiv.) in 120 mL of THF and DMF (3:5) was added DABCO (0.58 g, 0.005 mol, 0.20 equiv.), followed by tetrahydro 4-hydroxypyranol (7.87 g, 0.077 mol, 3.0 equiv.) and cesium carbonate (25.0 g, 0.077 mol, 3.0 equiv.) and stirred for 16 hours at room temperature. The reaction mixture was poured into ice-cold water and stirred for 5 hours. The solid formed was filtered from the aqueous phase and dried under a high vacuum. The crude compound was suspended in 0.15 L of 5% ethyl acetate in hexane solution and stirred for 15 minutes, and the solid was filtered and dried under high vacuum to give a crude title compound **VI-1** (15.0 g) which was sufficiently pure to perform the next reaction. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.28 (d, *J* = 6.0 Hz, 1H), 5.20- 5.10 (m, 2H), 4.55 (d, *J* = 17.6 Hz, 1H), 4.30- 4.20 (bs, 1H), 3.90- 3.80 (m, 2H), 3.80- 3.70 (m, 1H), 3.60- 3.30 (m, 4H), 2.10- 1.90 (m, 4H), 1.75- 1.60 (m, 2H), 1.35 (d, *J* = 8.8 Hz, 9H); LC-MS: *m/z* 649.0 (M+H)⁺.

The intermediates listed below in **Table-2** were prepared by procedures similar to the one described in the synthesis of **Intermediate VI-1** with chloro quinazoline (SM-1) and appropriate alcohol (SM-2) with appropriate variations in reagents, solvents and reaction conditions. The characterization data of the intermediates are summarized herein the below table.

Table-2

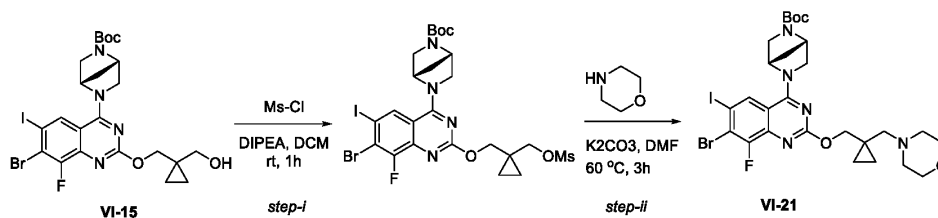
Int-No.	SM1	SM2	Intermediate Structure	Analytical Data
VI-2	V-2			LC-MS: m/z 638.80 [M+H] ⁺
VI-3	V-3			¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 8.13 (d, J = 2.0 Hz, 1H), 5.35 (m, J = 4.4 Hz, 1H), 4.06-4.03 (m, 2H), 3.89 (q, J = 4 Hz, 4H), 3.82 (q, J = 3.6 Hz, 4H), 3.66-3.60 (m, 2H), 2.18-2.14 (m, 2H), 1.94-1.87 (m, 2H); LC-MS: m/z 538.15[M+H]
VI-4	V-4			LC-MS: m/z 553.70 [M+H] ⁺
VI-5	V-5			LC-MS: m/z 535.9[M+H] ⁺

VI-6	V-6			LC-MS: m/z 497[M+H] ⁺
VI-7	V-6			LC-MS: m/z 484.10[M+H] ⁺
VI-8	V-7			LC-MS: m/z 511.90 [M+H] ⁺
VI-9	V-8			LC-MS: m/z 567.10[M+H] ⁺
VI-10	V-9			LC-MS: m/z 517.9 (M+H) ⁺ .
VI-11	V-10			¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 8.33 (d, <i>J</i> = 1.6 Hz, 1H), 5.19-5.12 (m, 1H), 4.53 (m, 1H), 4.17-4.09 (m, 2H), 3.91-3.86 (m, 2H), 3.52-3.46 (m, 2H), 3.21 (s, 3H), 2.89 (bs, 2H), 2.06-1.99 (m, 2H), 1.82-1.64 (m,

				6H), 1.39 (s, 9H); LC-MS: m/z 665.2[M+H] ⁺
VI-12	V-11			LC-MS: m/z 650.90[M+H] ⁺
VI-13	V-12			LC-MS: m/z 512.5 [M+H] ⁺
VI-14	V-13			LC-MS: m/z 551.3 [M+H] ⁺
VI-15	V-1			LC-MS: m/z 649.6 [M+H] ⁺
VI-16	V-1			LC-MS: m/z 706.8 [M+H] ⁺

VI-17	V-1		LC-MS: m/z 664.1 [M+H] ⁺
VI-18	V-14		LC-MS: m/z 573.4 [M+H] ⁺
VI-19	V-15		LC-MS: m/z 664.9 [M+H] ⁺
VI-20	V-2		LC-MS: m/z 625.2 [M+H] ⁺

Synthesis of tert-butyl (1S,4S)-5-(7-bromo-8-fluoro-6-iodo-2-((1-(morpholinomethyl)cyclopropyl)methoxy)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (VI-21)



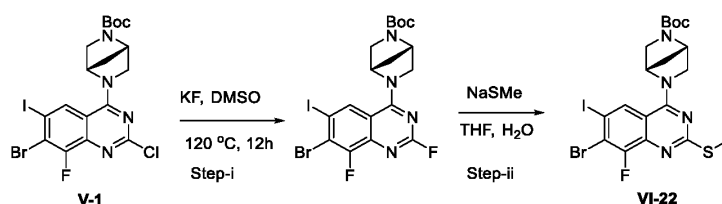
Step-i: Synthesis of tert-butyl (1S,4S)-5-(7-bromo-8-fluoro-6-iodo-2-(((methylsulfonyl)oxy)methyl)cyclopropyl)methoxyquinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

To a solution of tert-butyl (1S,4S)-5-(7-bromo-8-fluoro-2-((1-
5 (hydroxymethyl)cyclopropyl)methoxy)-6-iodoquinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**VI-15**) (4.0g, 6.16 mmol, 1.0 eq) in DCM (40 mL) was added DIPEA (3.98 g, 30.80 mmol, 5.0 eq) and the reaction mixture was stirred at room temperature for 5 min. Then methanesulfonic anhydride (1.41g, 12.31mmol, 2.0 eq) was added to the reaction mixture at 0 °C and stirred at room temperature for 1 h. After completion of
10 reaction, the reaction mixture was diluted with water and extracted with DCM (40 mL x 3). The combined organic phase was washed with brine (40 mL), dried over Na₂SO₄ and concentrated to give tert-butyl (1S,4S)-5-(7-bromo-8-fluoro-6-iodo-2-(((methylsulfonyl)oxy)methyl)cyclopropyl)methoxyquinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (4.50g, crude) as a yellow solid, which was directly
15 used in the next step without purification; LC-MS: *m/z* 728.90 [M+H]⁺

Step-ii; Synthesis of tert-butyl (1S,4S)-5-(7-bromo-8-fluoro-6-iodo-2-((1-(morpholinomethyl)cyclopropyl)methoxy)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

To a stirred solution of tert-butyl (1S,4S)-5-(7-bromo-8-fluoro-6-iodo-2-((1-
20 (((methylsulfonyl)oxy)methyl)cyclopropyl)methoxy)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (4.2 g, 5.774mmol, 1.0 equiv.) in 40 mL of DMF was added morpholine (0.654g, 7.50 mmol, 1.3equiv.), potassium carbonate (2.394 g, 17.32 mmol, 3.0 equiv.) and potassium iodide(0.096g, 0.57mmol, 0.1equiv.) and stirred for 2 hours at 60 °C. The reaction mixture was cooled to room temperature and poured into ice-cold water,
25 The mixture was diluted and extracted with EtOAc (30 mL x 3). The combined organic phase was washed with brine (40 mL), dried over Na₂SO₄ and concentrated to give a residue. The crude was purified by combi-flash column chromatography using 30% ethyl acetate in hexane to afford the compound **VI-21** (1.7 g) LC-MS: *m/z* 718.05 [M+H]⁺.

Synthesis of tert-butyl (1S,4S)-5-(7-bromo-8-fluoro-6-iodo-2-(methylthio)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (VI-22):



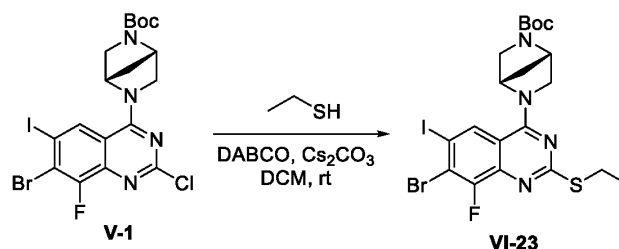
Step-i: Synthesis of tert-butyl (1S,4S)-5-(7-bromo-2,8-difluoro-6-iodoquinazolin-4-yl)-2,5-diazabicyclo [2.2.1] heptane-2-carboxylate

To a mixture of tert-butyl (1S,4S)-5-(7-bromo-2-chloro-8-fluoro-6-iodoquinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (V-1) (1.0 g, 1.71 mmol) in DMSO (5 mL) was added KF (0.99 g, 17.13 mmol) and the reaction mixture was stirred at 120 °C for 12 h. After the completion of reaction, the mixture was quenched with ice cold water and the product was extracted with ethyl acetate (3 X 15 mL). Combined organic layers were washed with brine and dried over anhydrous sodium sulphate. The filtered organic layer was concentrated to a give crude product. Crude product was purified by Combiflash using 10%-30% ethyl acetate in hexane to get titled compound as off white solid (0.81 g, 83%), LC-MS: m/z 568.90 [M+H]⁺

Step-ii: Synthesis of tert-butyl (1S,4S)-5-(7-bromo-8-fluoro-6-iodo-2-(methylthio)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

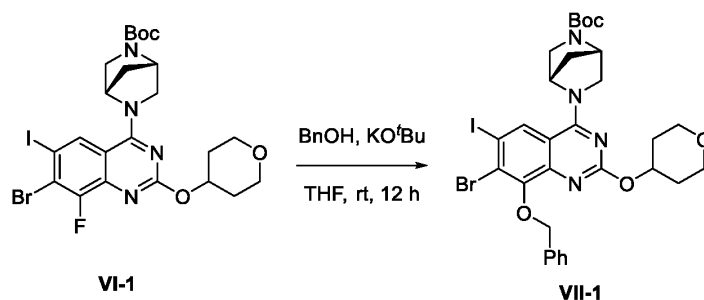
To a solution of tert-butyl (1S,4S)-5-(7-bromo-2,8-difluoro-6-iodoquinazolin-4-yl)-2,5-diazabicyclo [2.2.1] heptane-2-carboxylate (0.8 g, 1.41 mmol, 1.0 eq.) in THF (5 mL) was added NaSMe (0.198 g, 2.82 mmol, 2.0 eq.) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. After the completion of reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (20 mLx3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by Combiflash, eluting with 10%-20% ethyl acetate in hexane to get titled compound (VI-22) as off white solid (0.38 g, 45%), LC-MS: m/z 594.95 [M+H]⁺

Synthesis of *tert*-butyl (1*S*,4*S*)-5-(7-bromo-2-(ethylthio)-8-fluoro-6-iodoquinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (VI-23)



5 To a stirred solution of *tert*-butyl (1*S*,4*S*)-5-(7-bromo-2-chloro-8-fluoro-6-iodoquinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**V-1**) (15.0 g, 0.025 mol, 1.0 equiv.) in 120 mL of THF and DMF (3:5) was added DABCO (0.58 g, 0.005 mol, 0.20 equiv.), followed by the addition of ethanethiol (4.80 g, 0.077 mol, 3.0 equiv.) and cesium carbonate (25.0 g, 0.077 mol, 3.0 equiv.) and stirred for 16 hours at room temperature. After
10 the completion of reaction, the mixture was quenched with ice cold water and the product was extracted with ethyl acetate, combined organic layers were washed with brine and dried over anhydrous sodium sulphate. The filtered organic layer was concentrated to give crude product. The crude was purified by Combiflash, eluting with 10%-20% ethyl acetate in hexane to get titled compound as off white solid **VI-23** (9.40 g, 60%); LC-MS: m/z 609.90 [M+H]⁺

15 Synthesis of *tert*-butyl (1*S*,4*S*)-5-(8-(benzyloxy)-7-bromo-6-iodo-2-((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (VII-1):

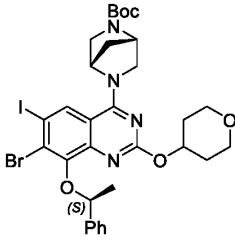
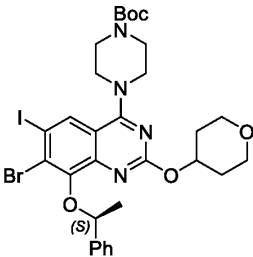


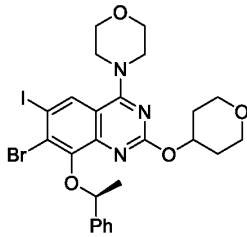
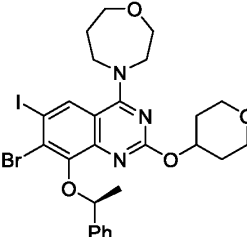
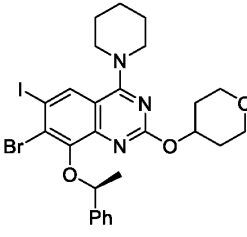
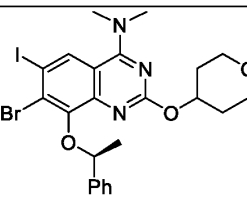
To a stirred solution of benzyl alcohol (7.25 g, 0.066 mol, 1.5 equiv.) in THF (150 mL) was added potassium tertiary butoxide (7.5 g, 0.066 mol, 1.5 equiv.) at 0 °C, and the
20 reaction mixture was stirred for 10 min, followed by the addition of starting material *tert*-butyl (1*S*,4*S*)-5-(7-bromo-8-fluoro-6-iodo-2-((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-4-yl)-2,5-

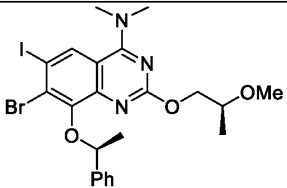
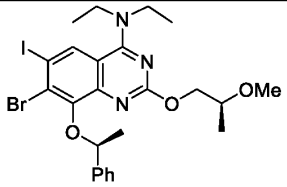
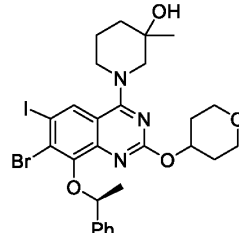
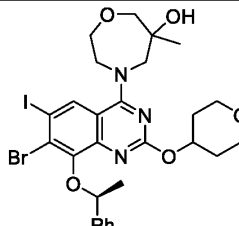
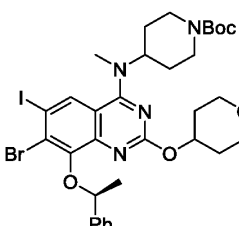
diazabicyclo[2.2.1]heptane-2-carboxylate (**VI-1**) (29.0 g, 0.044 mol, 1.0 equiv.). The mixture was allowed to warm to room temperature and stirred for 12 hours. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (200 mL) and poured into ice cold ammonium chloride solution (100 mL) and stirred for 0.5 h. The organic layer was collected, dried over anhydrous sodium sulphate, and concentrated under reduced pressure afforded the titled crude compound **VII-1** (32.0 g) which was sufficiently pure to perform next step. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.26 (d, *J* = 8.4 Hz, 1H), 7.58 (dd, *J* = 8.4 Hz, 1.2 Hz, 2H), 7.46- 7.30 (m, 3H), 5.30- 5.10 (m, 4H), 4.54 (d, *J* = 20.0 Hz, 1H), 4.30- 4.20 (bs, 1H), 4.03 (d, *J* = 7.2 Hz, 2H), 3.85- 3.82 (m, 1H), 3.50- 3.40 (m, 2H), 2.10- 1.90 (m, 5H), 1.80- 1.60 (m, 2H), 1.38 (d, *J* = 14.0 Hz, 9H); LC-MS: *m/z* 739.0 (M+H)⁺.

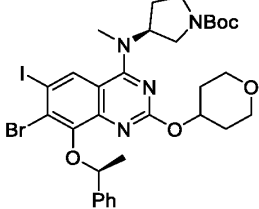
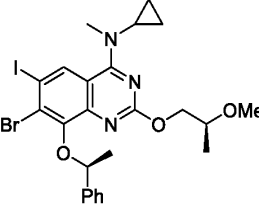
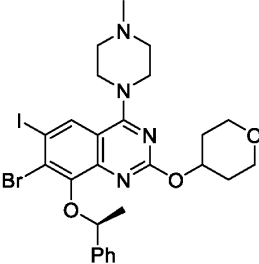
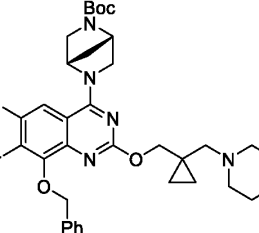
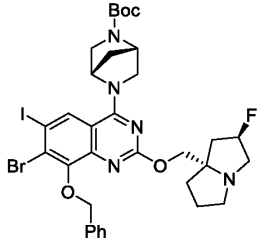
The intermediates listed below in **Table-3** were prepared by procedures similar to the one described in the synthesis of **Intermediate VII-1** with fluoro quinazoline (SM-1) and (*S*)-1-phenylethan-1-ol or benzyl alcohol (SM-2) with appropriate variations in reagents, solvents and reaction conditions. The characterization data of the intermediates are summarized herein the below table.

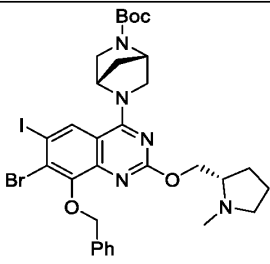
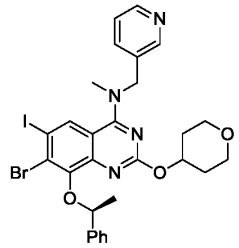
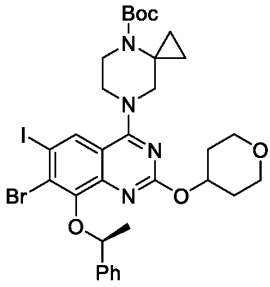
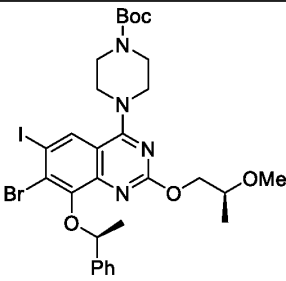
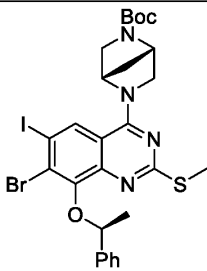
Table-3

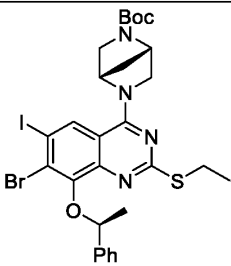
Int-No	SM-1	SM-2	Intermediate Structure	Analytical Data
VII-2	VI-1			LC-MS: <i>m/z</i> 751.80 (M+H) ⁺
VII-3	VI-2			LC-MS: <i>m/z</i> 739.5(M+H) ⁺ .

VII-4	VI-3			¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 8.20 (s, 1H), 7.55-7.41 (m, 2H), 7.40-7.36 (m, 2H), 7.34-7.30(m, 1H), 6.25 (q, <i>J</i> = 6.4 Hz, 1H), 5.08 (m, 1H), 4.48 (m, 1H), 4.10-4.02 (m, 1H), 3.88-3.81 (m, 2H), 3.31-3.26 (m, 2H), 3.14 (s, 3H), 2.53-2.50 (m, 2H), 2.00-1.99 (m, 2H), 1.79-1.64 (m, 6H), 1.52 (d, <i>J</i> = 6.4 Hz, 3H),; LC-MS: <i>m/z</i> 640.3[M+H] ⁺
VII-5	VI-4			LC-MS: <i>m/z</i> 656.0 [M+H] ⁺
VII-6	VI-5			LC-MS: <i>m/z</i> 638.05[M+H] ⁺
VII-7	VI-6			LC-MS: <i>m/z</i> 599[M+H] ⁺

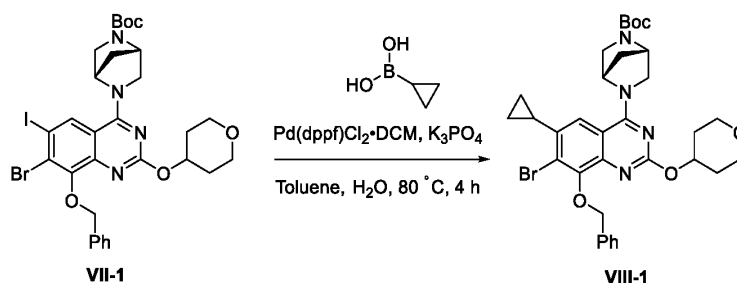
VII-8	VI-7			LC-MS: m/z 586.10[M+H] ⁺
VII-9	VI-8			LC-MS: m/z 616.00 [M+H] ⁺
VII-10	VI-9			LC-MS: m/z 669.0[M+H] ⁺
VII-11	VI-10			LC-MS: m/z 685.65 (M+H) ⁺ .
VII-12	VI-11			¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 8.20 (s, 1H), 7.55-7.41 (m, 2H), 7.40-7.36 (m, 2H), 7.34-7.30(m, 1H), 6.25 (q, <i>J</i> = 6.4 Hz, 1H), 5.08 (m, 1H), 4.48 (m, 1H), 4.10-4.02 (m, 2H), 3.88-3.81 (m, 2H), 3.31-3.26 (m, 2H), 3.14 (s, 3H), 2.53-2.50 (m, 2H), 2.00-1.99 (m, 2H), 1.79-1.64 (m,

				6H), 1.52 (d, $J = 6.4$ Hz, 3H), 1.43 (s, 9H); LC-MS: m/z 767.3[M+H] ⁺
VII-13	VI-12			LC-MS: m/z 754.1[M+H] ⁺
VII-14	VI-13			LC-MS: m/z 614.0[M+H] ⁺
VII-15	VI-14			LC-MS: m/z 653.40 [M+H] ⁺
VII-16	VI-21			LC-MS: m/z 806.50[M+H] ⁺
VII-17	VI-16			LC-MS: m/z 796.05 [M+H] ⁺

VII-18	VI-17			LC-MS: m/z 752.2 [M+H] ⁺
VII-19	VI-18			LC-MS: m/z 675.40 [M+H] ⁺
VII-20	VI-19			LC-MS: m/z 767.05[M+H] ⁺
VII-21	VI-20			LC-MS: m/z 727.60[M+H] ⁺
VII-22	VI-22			LC-MS: m/z 699.00[M+H] ⁺

VII-23	VI-23			LC-MS: m/z 711.90[M+H] ⁺
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Synthesis of *tert*-butyl (1*S*,4*S*)-5-(8-(benzyloxy)-7-bromo-6-cyclopropyl-2-((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**VIII-1**):



5

A mixture of *tert*-butyl (1*S*,4*S*)-5-(8-(benzyloxy)-7-bromo-6-iodo-2-((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**VII-1**) (17.0 g, 0.023 mol, 1.0 equiv.), cyclopropyl boronic acid (11.8 g, 0.14 mol, 6.0 equiv.) and potassium phosphate (12.2 g, 0.06 mol, 2.5 equiv.) in 170 mL of toluene and water (4:1) was transferred to a sealed tube and degassed with argon for 30 min. Pd(dppf)Cl₂·DCM was added to the reaction mixture, which was then degassed for another 5 min. The reaction mixture was then heated at 80 °C for 4 h. The reaction mixture was allowed to cool to room temperature, then diluted with ethyl acetate (0.25 L) and filtered through a pad of Celite®. The organic layer was separated from the aqueous layer and dried over anhydrous sodium sulphate, then concentrated under reduced pressure to get crude product. The crude was purified by combi-flash column chromatography using 30% ethyl acetate in hexane to afford the titled compound of **VIII-1** (14.0 g) along with des-bromo compound (49%); LC-MS: m/z 653.1 (M+H)⁺.

The intermediates listed below in **Table-4** were prepared by procedures similar to the one described in the synthesis of **Intermediate VIII-1** with iodo quinazoline (SM-1) and cyclopropyl boronic acid (SM-2) with appropriate variations in reagents, solvents and reaction

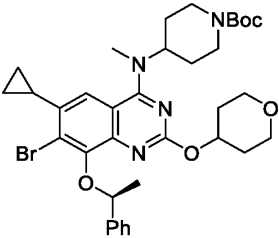
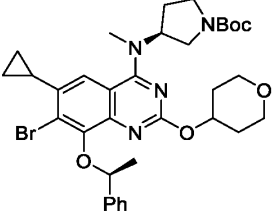
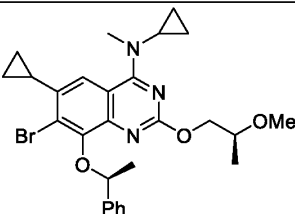
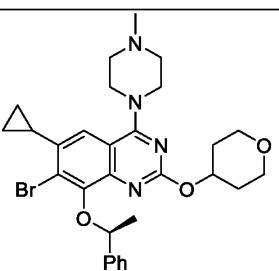
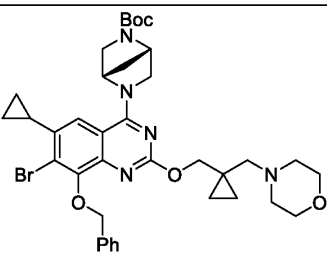
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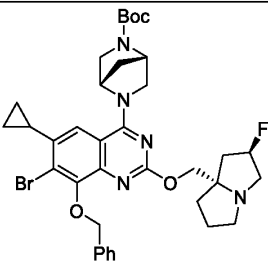
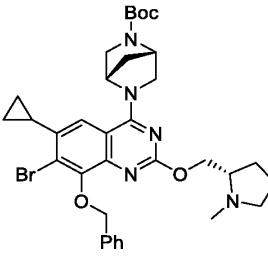
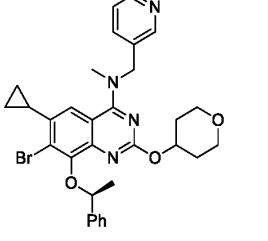
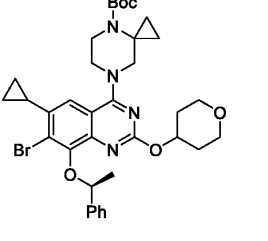
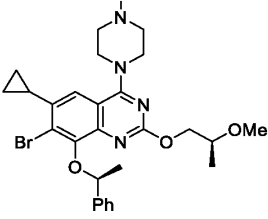
conditions. The characterization data of the intermediates are summarized herein the below table.

Table-4

Int-No	SM1	Intermediate Structure	Analytical Data
VIII-2	VII-2		LC-MS: m/z 665.80 $[M+H]^+$
VIII-3	VII-3		LC-MS: m/z 653.80 $[M+H]^+$
VIII-4	VII-4		LC-MS: m/z 554.47 $[M+H]^+$
VIII-5	VII-5		LC-MS: m/z 570.15 $[M+H]^+$

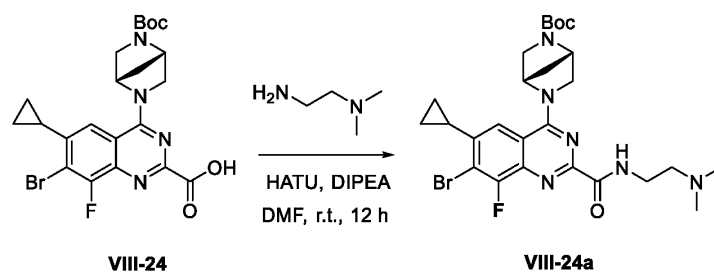
VIII-6	VII-6		LC-MS: m/z 554.15[M+H] ⁺
VIII-7	VII-7		LC-MS: m/z 512[M+H] ⁺
VIII-8	VII-8		LC-MS: m/z 500.1[M+H] ⁺
VIII-9	VII-9		LC-MS: m/z 530.15 [M+H] ⁺
VIII-10	VII-10		LC-MS: m/z 583.0[M+H] ⁺
VIII-11	VII-11		LC-MS: m/z 598.2 (M+H) ⁺ .

VIII-12	VII-12		LC-MS: m/z 681.6[M+H] ⁺
VIII-13	VII-13		LC-MS: m/z 667.6[M+H] ⁺
VIII-14	VII-14		LC-MS: m/z 528.2[M+H] ⁺
VIII-15	VII-15		LC-MS: m/z 567.15 [M+H] ⁺
VIII-16	VII-16		LC-MS: m/z 720.50[M+H] ⁺

VIII-17	VII-17		LC-MS: m/z 710.20 $[M+H]^+$
VIII-18	VII-18		LC-MS: m/z 666.4 $[M+H]^+$
VIII-19	VII-19		LC-MS: m/z 589.7 $[M+H]^+$
VIII-20	VII-20		LC-MS: m/z 681.20 $[M+H]^+$
VIII-21	VII-21		LC-MS: m/z 641.80 $[M+H]^+$

VIII-22	VII-22		LC-MS: m/z 611.10 $[M+H]^+$
VIII-23	VII-23		LC-MS: m/z 625.80 $[M+H]^+$
VIII-24	V-16		LC-MS: m/z 508.20 $[M+H]^+$

Synthesis of tert-butyl (1S,4S)-5-(7-bromo-6-cyclopropyl-2-((2-(dimethylamino)ethyl)carbamoyl)-8-fluoroquinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (VIII-24a):



5

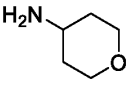
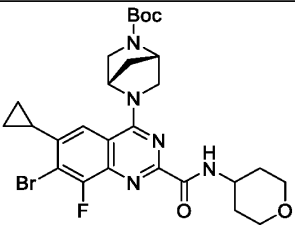
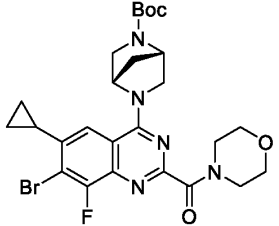
To a solution of 7-bromo-4-((1S,4S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-8-fluoroquinazoline-2-carboxylic acid (VIII-24) (8.7 g, 14.66 mmol, 1.0 equiv.) in DMF (50 mL), diisopropylethylamine (5.68 g, 43.99 mmol, 3.0 equiv.) was added at 0 °C, and the reaction mixture was stirred for 10 mins at rt. Then N1,N1-dimethylethane-1,2-diamine (1.55 g, 17.59mmol, 1.2 equiv.) followed by HATU (5.17g, 21.99

10

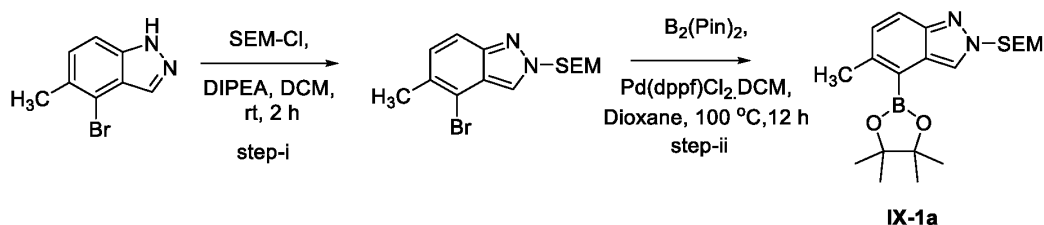
mmol, 1.5 equiv.) were added to the reaction mixture, and the reaction mixture was stirred for 12 h. The reaction mixture extracted with EtOAc (2x100 mL). Organic layers were collected and washed with brine (100 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to get the crude product which was purified by column chromatography (silica gel, 230-400 mesh, 5% MeOH in DCM) to get the pure titled compound **VIII-24a** (9.1g, 91%); LC-MS: m/z 577.7 (M+H)⁺.

The intermediates listed below in **Table-4A** were prepared by procedures similar to the one described in the synthesis of **Intermediate VIII-24a** using 7-bromo-4-((1S,4S)-5-(tert-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-6-cyclopropyl-8-fluoroquinazoline-2-carboxylic acid (SM-1) and appropriate amine (SM-2) with appropriate variations in reagents, solvents and reaction conditions. The characterization data of the intermediates are summarized herein the below table.

Table-4A

Int-No	SM-2 (Amine)	Intermediate Structure	Analytical Data
VIII-25			LC-MS: m/z 592.3[M+H] ⁺
VIII-26			LC-MS: m/z 622.95[M+H] ⁺

Synthesis of 5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole (IX-1a):



Step-i: Synthesis of 4-bromo-5-methyl-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-indazole

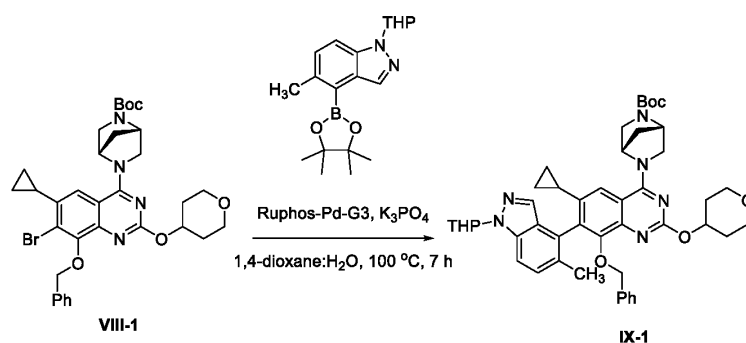
5 To a stirred solution of 4-bromo-5-methyl-1H-indazole (20 g, 0.094 mol, 1.0 equiv.) in DCM (600 mL, 30V) was added DIPEA (24.4 g, 0.188 mol, 2.0 equiv.) at room temperature, followed by addition of SEM-Cl (23.5 g, 0.141 mol, 1.5eq), and then reaction mixture was stirred for 2h at room temperature. After completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (150 mLx3). The combined
10 organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by Combi-flash, eluting with by 2-10% ethyl acetate in hexane to afford titled compound (18 g); LC-MS: *m/z* 554.00 [M+H]⁺.

Step-ii: Synthesis of 5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-indazole

15 A mixture of 4-bromo-5-methyl-2-((2-(trimethylsilyl)ethoxy)methyl)-2H-indazole (34.0 g, 0.0946 mol, 1.0 equiv.), B₂Pin₂ (48 g, 0.1892 mol, 2.0 equiv.) and potassium acetate (27.0 g, 0.2838 mol, 3.0 equiv.) in 680 mL of dioxane in 2.0 L RBF was degassed with argon for 20 min. Pd(dppf)Cl₂·DCM (3.8 g, 0.0047 mmol, 0.05 eq) was added to the reaction mixture at room temperature and subsequently heated to 100 °C and stirred for 12 h. After the
20 completion of the reaction, the mixture was filtered through a pad of celite, and the filtrate was quenched with ice cold water and extracted with ethyl acetate (40 mL x 3). The combined organic layers were dried over anhydrous Na₂SO₄, then filtered and concentrated under reduced pressure to give a residue. The residue was purified by Combi-flash, eluting with 3-10% ethyl acetate in hexane to get titled compound **IX-1a** (30 g); LC-MS: *m/z* 250.2 [M+H]⁺.

25

Synthesis of *tert*-butyl (1*S*,4*S*)-5-(8-(benzyloxy)-6-cyclopropyl-7-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-2-((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (IX-1):



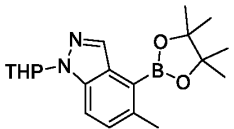
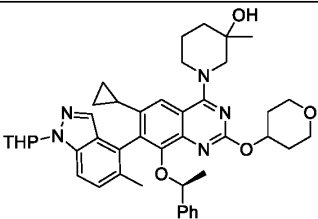
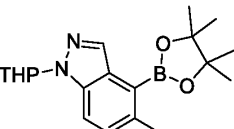
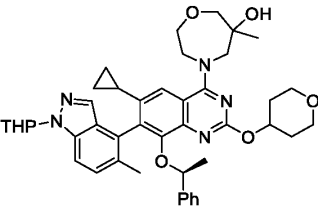
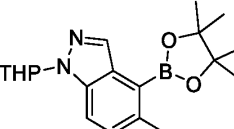
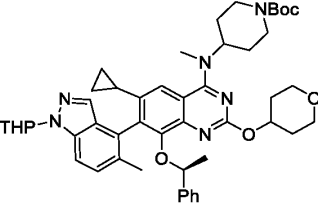
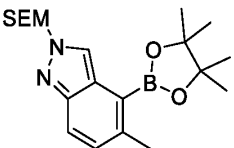
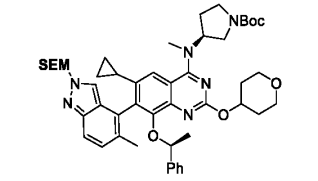
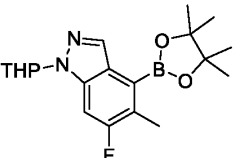
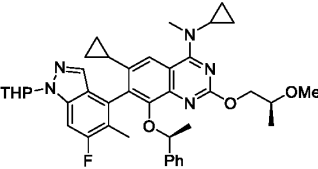
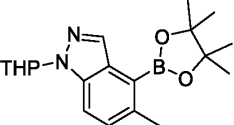
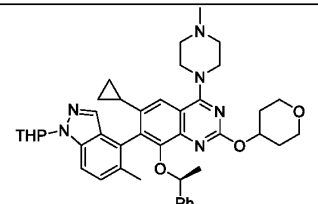
5 A mixture of *tert*-butyl (1*S*,4*S*)-5-(8-(benzyloxy)-7-bromo-6-cyclopropyl-2-((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**VIII-1**) (14.0 g, 0.021 mol, 1.0 equiv.), 5-methyl-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (8.82 g, 0.025 mol, 1.2 equiv.) and potassium phosphate (13.7 g, 0.06 mol, 3 equiv.) was dissolved in 150 mL of toluene and
10 water (4:1) using sealed tube and then degassed for 30 min with argon. Ruphos (1.0 g, 0.001 mol, 0.1equiv.) and Ruphos-Pd-G3 (1.8 g, 0.001 mol, 0.1equiv.) were added to the reaction mixture, which was degassed for another 5 min. Then the reaction mixture was heated to 100 °C for 7 h. The reaction mixture was cooled to room temperature and then diluted with ethyl acetate (0.25 L) and filtered through a pad of Celite[®]. The organic layer was separated from
15 the aqueous layer and dried over anhydrous sodium sulphate, then concentrated under reduced pressure to provide the crude product. The crude product was purified by combi-flash column chromatography using 50% ethyl acetate in hexane to provide pure titled compound **IX-1** (8.0 g; yield 46%); LC-MS: *m/z* 787.35 (M+H)⁺

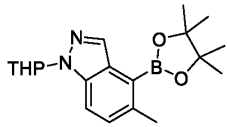
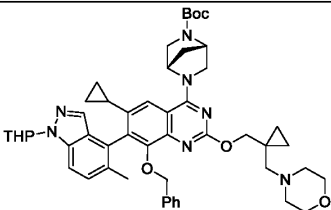
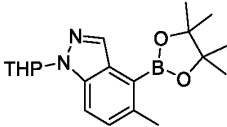
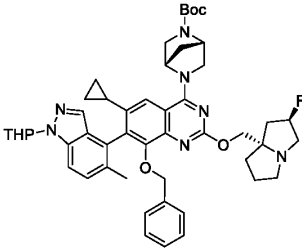
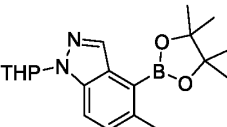
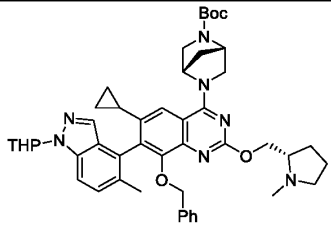
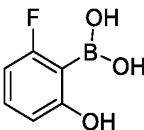
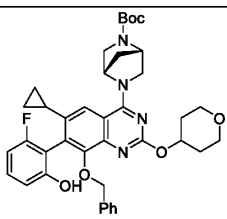
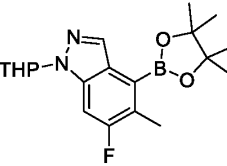
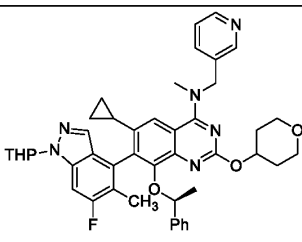
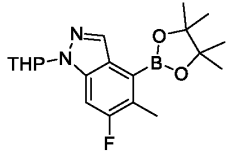
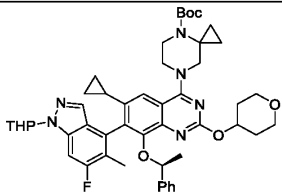
The intermediates listed below in **Table-5** were prepared by procedures similar to the
20 one described in the synthesis of **Intermediate IX-1** with bromo quinazoline (SM-1) and indazole boronated ester (SM-2) with appropriate variations in reagents, solvents and reaction conditions. The characterization data of the intermediates are summarized herein the below table.

Table-5

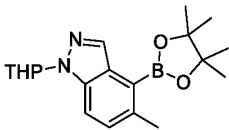
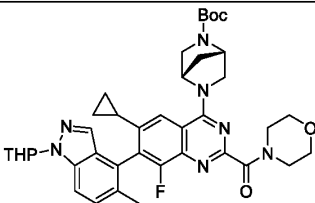
Int-No	SM1	SM2	Intermediate Structure	Analytical Data
IX-2	VIII-2			LC-MS: m/z 819.30 (M+H) ⁺
IX-3	VIII-2			LC-MS: m/z 977.20 (M+H) ⁺
IX-4	VIII-2			LC-MS: m/z 801.10 (M+H) ⁺
IX-5	VIII-3			LC-MS: m/z 808.1
IX-6	VIII-3			LC-MS: m/z 789.6[M+H] ⁺

IX-7	VIII-4			LC-MS: m/z 689.8[M+H] +
IX-8	VIII-5			LC-MS: m/z 704.35 [M+H] ⁺
IX-9	VIII-6			LC-MS: m/z 688.35[M+H] J ⁺
IX-10	VIII-7			LC-MS: m/z 648[M+H] ⁺
IX-11	VIII-8			LC-MS: m/z 654.10[M+H] J ⁺
IX-12	VIII-9			LC-MS: m/z 682.20 [M+H] ⁺

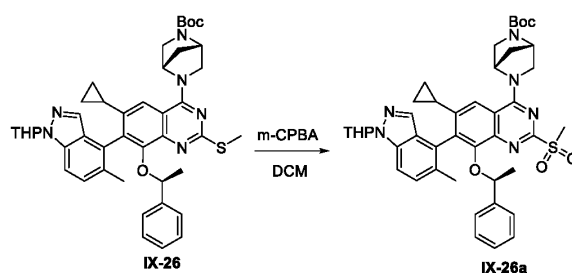
IX-13	VIII-10			LC-MS: m/z 718.0[M+H] ⁺
IX-14	VIII-11			LC-MS: m/z 534.3 (M+H) ⁺
IX-15	VIII-12			LC-MS: m/z 817.30[M+H]]
IX-16	VIII-13			LC-MS: m/z 849.60[M+H] J ⁺
IX-17	VIII-14			LC-MS: m/z 682.1[M+H] ⁺
IX-18	VIII-15			LC-MS: m/z 703.0[M+H] ⁺

IX-19	VIII-16			LC-MS: m/z 856.20 [M+H] ⁺
IX-20	VIII-17			LC-MS: m/z 844.50 [M+H] ⁺
IX-21	VIII-18			LC-MS: m/z 801.6 [M+H] ⁺
IX-22	VIII-1			LC-MS: m/z 683.4 [M+H] ⁺
IX-23	VIII-19			LC-MS: m/z 743.10 [M+H] ⁺
IX-24	VIII-20			LC-MS: m/z 833.40 [M+H] ⁺

IX-25	VIII-21			LC-MS: m/z 795.20 [M+H] ⁺
IX-26	VIII-22			LC-MS: m/z 747.35 [M+H] ⁺
IX-27	VIII-23			LC-MS: m/z 761.00 [M+H] ⁺
IX-28	VIII-23			LC-MS: m/z 923.20 (M+H) ⁺
IX-29	VIII-24a			LC-MS: m/z 713.10[M+H] J ⁺
IX-30	VIII-25			LC-MS: m/z 726.35[M+H] J ⁺

IX-31	VIII-26			LC-MS: m/z 712.0[M+H] ⁺
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Synthesis of tert-butyl (1S,4S)-5-(6-cyclopropyl-7-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-2-(methylsulfonyl)-8-((S)-1-phenylethoxy)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (IX-26a):



5

To a stirred solution of compound tert-butyl (1S,4S)-5-(6-cyclopropyl-7-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-2-(methylthio)-8-((S)-1-phenylethoxy)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**IX-26**) (460 mg, 0.616 mmol, 1 eq.) in DCM (20mL) at 0 °C under nitrogen, 3-chloroperoxybenzoic acid (319mg, 1.84 mmol, 3.0 eq.) in DCM was added slowly. The mixture was stirred at room temperature for 3h. After completion of reaction, the reaction mixture was partitioned between water (20 mL) and DCM (20 mL X 2). The layers were separated and organic layer was concentrated in vacuo and the residue obtained was purified by Combiflash, eluting with 10%-20% ethyl acetate in hexane to get titled compound **IX-26a** as off white solid (0.23 g, 44.14%), LC-MS: 779.30 [M+H]⁺.

15

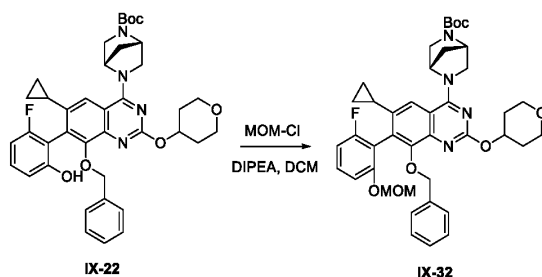
The intermediates listed below in **Table-5A** were prepared by procedures similar to the one described in the synthesis of **Intermediate IX-26a** with m-CPBA as oxidative reagent and DCM as solvent. The characterization data of the intermediates are summarized herein the below table.

20

Table-5A

Int-No	SM	Intermediate Structure	Analytical Data
IX-27a	IX-27		LC-MS: m/z 793.00 (M+H) ⁺
IX-28a	IX-28		LC-MS: m/z 955.20 (M+H) ⁺

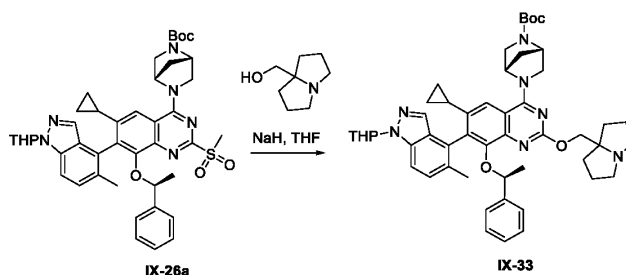
Synthesis of tert-butyl (1S,4S)-5-(8-(benzyloxy)-6-cyclopropyl-7-(2-fluoro-6-(methoxymethoxy)phenyl)-2-((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (IX-32):



To a solution of tert-butyl (1S,4S)-5-(8-(benzyloxy)-6-cyclopropyl-7-(2-fluoro-6-hydroxyphenyl)-2-((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate **IX-22** (0.90 g, 1.31 mmol, 1.0 eq.) in DCM (20mL) at 0° C were added DIPEA (0.045g, 1.97 mmol, 1.5 eq.) and MOM-Cl (0.318 g, 3.954 mmol, 3.0 eq.). The mixture was stirred at 40 °C for 2h. After completion of the reaction, the reaction was quenched with water and extracted with DCM. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The crude product was purified by combi flash (0-

20% ethyl acetate in hexanes) to provide the titled compound **IX-32** as a white solid (7.9 g, 68%); LC-MS: m/z 727.4 $[M+H]^+$

Synthesis of tert-butyl (1S,4S)-5-(6-cyclopropyl-7-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-8-((S)-1-phenylethoxy)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (IX-33**):**



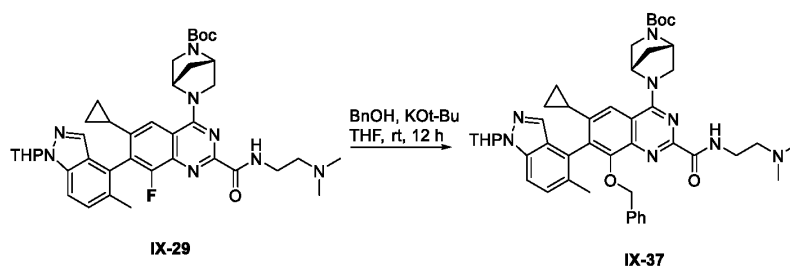
To a solution of (tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (119 mg, 0.846 mmol, 3.0 eq.) in DMF (21 mL) was added NaH (0.019 mg, 0.840 mmol, 3.0 eq.) (60% in mineral oil) at 0 °C under N_2 . The mixture was stirred at 0 °C for 10 min, then tert-butyl (1S,4S)-5-(6-cyclopropyl-7-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-2-
 10 (methylsulfonyl)-8-((S)-1-phenylethoxy)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**IX-26a**) (220 mg, 0.282 mmol, 1.0 eq.) in DMF (1 mL) was added to the above reaction mixture, and the resulting reaction mixture was stirred at 55 °C for 1 h. The reaction mixture was quenched with water and extracted with EtOAc (3 X 30 mL). The organic layer
 15 was dried over Na_2SO_4 , filtered and the residue was purified by Combiflash, eluting with 10%-20% ethyl acetate in hexane to get titled compound **IX-33** as off white solid (0.15 g.), LC-MS: 840.45 $[M+H]^+$

The intermediates listed below in **Table-5B** were prepared by procedures similar to the one described in **Intermediate IX-33** using sulfone intermediate (SM-1) with appropriate
 20 alcohol. The characterization data of the intermediates are summarized herein the below table.

Table-5B

Int-No	SM-1 (Sulfone)	SM-2 (Alcohol)	Intermediate Structure	Analytical Data
IX-34	IX-26a			LC-MS: m/z 940.50 $[M+H]^+$
IX-35	IX-27a			LC-MS: m/z 968.55 $[M+H]^+$
IX-36	IX-28a			LC-MS: m/z 951.35 $[M+H]^+$

Synthesis of tert-butyl (1S,4S)-5-(6-cyclopropyl-2-((2-(dimethylamino)ethyl)carbamoyl)-8-fluoro-7-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (IX-37):



The above intermediate **IX-37** prepared by procedures similar to the one described in the synthesis of **Intermediate VII-1** with Fluoro quinazoline amide (SM-1) and phenyl methanol (SM-2) with appropriate variations in reagents, solvents and reaction conditions; LC-MS: m/z 801.20 $[M+H]^+$.

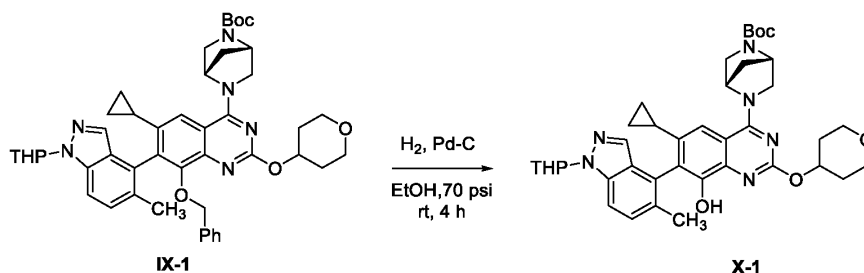
Similarly, the compounds listed in **Table-5C** also followed the same synthesis procedure as **Intermediate VII-1** with fluoro quinazoline amide (SM-1) and phenyl methanol (SM-2) with appropriate variations in reagents, solvents and reaction conditions. The characterization data of the intermediates are summarized herein the below table.

5

Table-5C

Int-No	SM-1	Intermediate Structure	Analytical Data
IX-38	IX-30		LC-MS: m/z 814.40[M+H] ⁺
IX-39	IX-31		LC-MS: m/z 800.40[M+H] ⁺

Synthesis of *tert*-butyl (1*S*,4*S*)-5-(6-cyclopropyl-8-hydroxy-7-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-2-(((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (X-1):



10

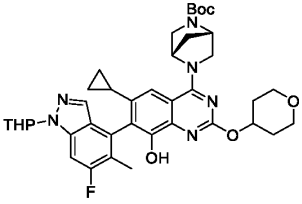
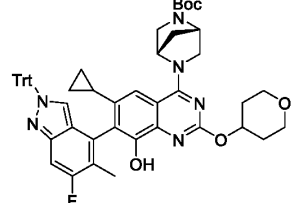
To a stirred solution of *tert*-butyl (1*S*,4*S*)-5-(8-(benzyloxy)-6-cyclopropyl-7-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-2-(((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**IX-1**) (7.0 g, 0.008 mol, 1.0 equiv.) in ethanol (0.07 L) was added Pd-C (wet 50%, 7.0 g.) at 0 °C. The reaction mixture was stirred at rt under 70 psi in hydrogen atmosphere for 4 h. The reaction mixture

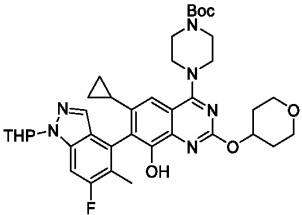
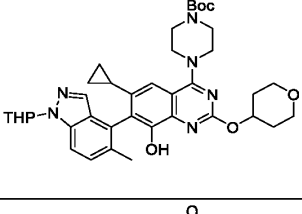
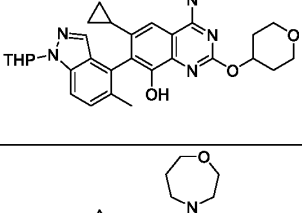
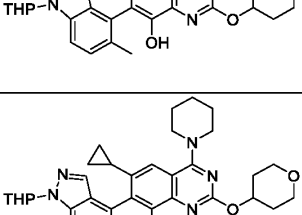
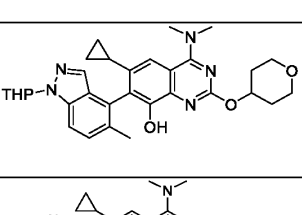
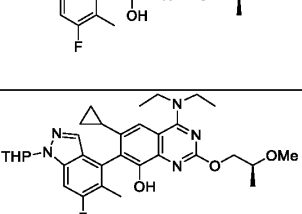
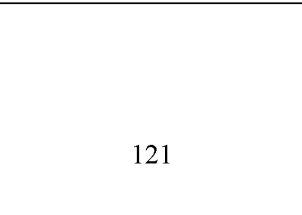
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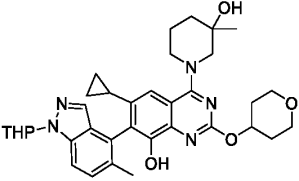
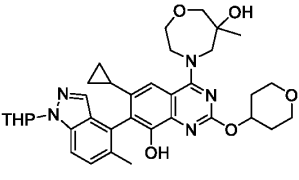
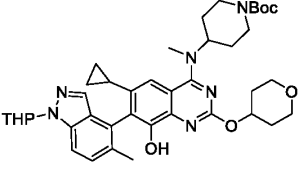
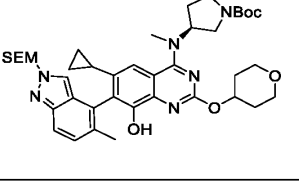
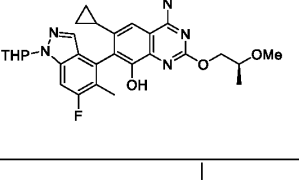
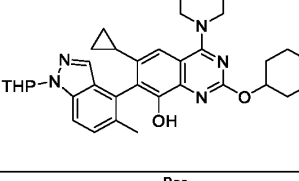
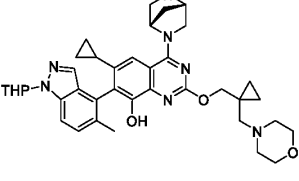
was filtered through a pad of Celite[®] and washed the Celite[®] pad with ethyl acetate (4x50 mL). The ethyl acetate was evaporated under reduced pressure to give a crude compound **X-1** (6.0 g) which was sufficiently pure to perform the next step. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.64 (d, *J* = 8.4 Hz, 1H), 7.41 (t, *J* = 4.4 Hz, 1H), 7.05 (s, 1H), 5.85 (dd, *J* = 9.6 Hz, 2.0 Hz, 1H), 5.39- 5.33 (m, 1H), 5.18 (d, *J* = 8.0 Hz, 1H), 4.55 (d, *J* = 20.0 Hz, 2H), 4.35 (d, *J* = 20.0 Hz, 2H), 3.90- 3.70 (m, 5H), 3.55- 3.40 (m, 4H), 3.17 (d, *J* = 5.2 Hz, 2H), 2.14 (d, *J* = 5.6 Hz, 3H), 2.10- 1.90 (m, 7H), 1.75- 1.55 (m, 4H), 1.39 (d, *J* = 7.6 Hz, 9H), 0.62 (m, 4H); LC-MS: *m/z* 697.30 (M+H)⁺.

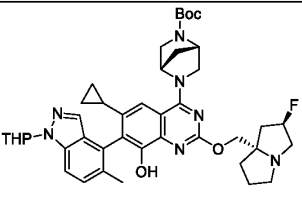
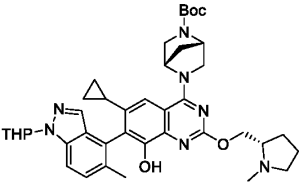
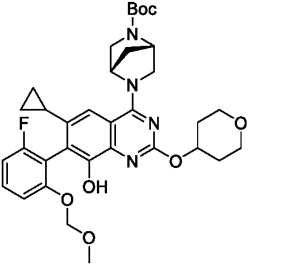
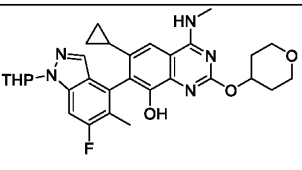
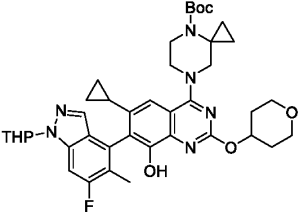
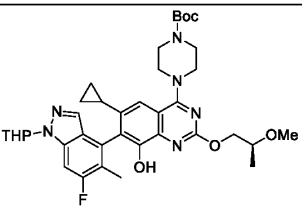
The intermediates listed below in **Table-6** were prepared by procedures similar to the one described in the synthesis of **Intermediate X-1** with Pd/C catalyst and ethanol as solvent. The characterization data of the intermediates are summarized herein the below table.

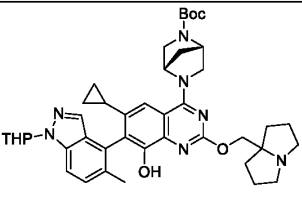
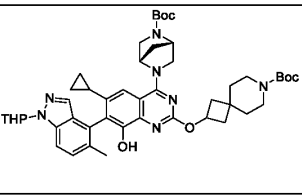
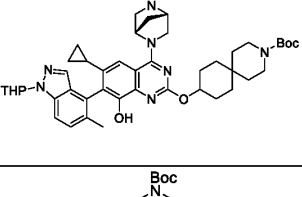
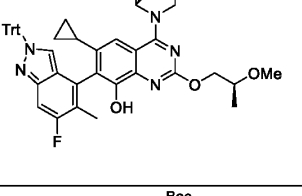
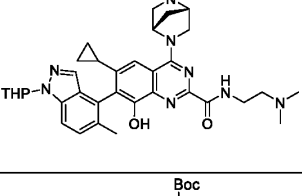
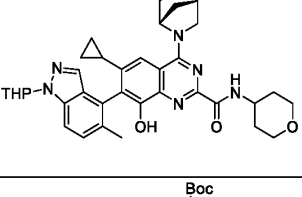
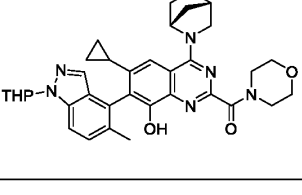
Table-6

Int-No	SM	Intermediate Structure	Analytical Data
X-2	IX-2		LC-MS: <i>m/z</i> 873.20 (M+H) ⁺
X-2a		Atropisomer-1 of X-2	LC-MS: <i>m/z</i> 873.20 (M+H) ⁺
X-2b		Atropisomer-2 of X-2	LC-MS: <i>m/z</i> 873.20 (M+H) ⁺
X-3	IX-3		LC-MS: <i>m/z</i> 873.30 (M+H) ⁺
X-3a		Atropisomer-1 of X-3	LC-MS: <i>m/z</i> 873.20 (M+H) ⁺
X-3b		Atropisomer-2 of X-3	LC-MS: <i>m/z</i> 873.20 (M+H) ⁺

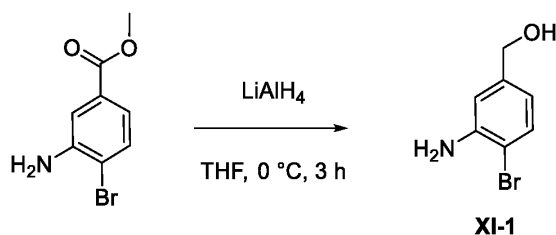
X-4	IX-5		LC-MS: m/z 703.35(M+H) ⁺ .
X-5	IX-6		LC-MS: m/z 685.55 [M+H] ⁺
X-6	IX-7		LC-MS: m/z 585.6[M+H] ⁺
X-7	IX-8		LC-MS: m/z 600.25 [M+H] ⁺
X-8	IX-9		LC-MS: m/z 584.3[M+H] ⁺
X-9	IX-10		LC-MS: m/z 544[M+H] ⁺
X-10	IX-11		LC-MS: m/z 550.1[M+H] ⁺
X-11	IX-12		LC-MS: m/z 578.25 [M+H] ⁺

X-12	IX-13		LC-MS: m/z 614.0[M+H] ⁺
X-13	IX-14		LC-MS: m/z 630.25 (M+H) ⁺ .
X-14	IX-15		LC-MS: m/z 712.8[M+H] ⁺
X-15	IX-16		LC-MS: m/z 746.1[M+H] ⁺
X-16	IX-17		LC-MS: m/z 576.50[M+H] ⁺
X-17	IX-18		LC-MS: m/z 598.40[M+H] ⁺
X-18	IX-19		LC-MS: m/z 766.20[M+H] ⁺

X-19	IX-20		LC-MS: m/z 754.35 [M+H] ⁺
X-20	IX-21		LC-MS: m/z 710.5 [M+H] ⁺
X-21	IX-32		LC-MS: m/z 637.4 [M+H] ⁺
X-22	IX-23		LC-MS: m/z 547.60 [M+H] ⁺
X-23	IX-24		LC-MS: m/z 729.35 [M+H] ⁺
X-24	IX-25		LC-MS: m/z 690.90 [M+H] ⁺

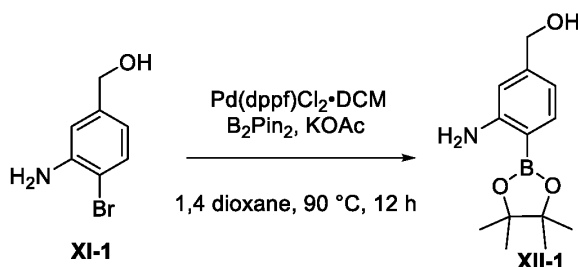
X-25	IX-33		LC-MS: m/z 736.35 $[M+H]^+$
X-26	IX-34		LC-MS: m/z 837.6 $[M+H]^+$
X-27	IX-35		LC-MS: m/z 865.6 $[M+H]^+$
X-28	IX-36		LC-MS: m/z 861.30 $[M+H]^+$
X-29	IX-37		LC-MS: m/z 711.35 $[M+H]^+$
X-30	IX-38		LC-MS: m/z 724.35 $[M+H]^+$
X-31	IX-39		LC-MS: m/z 710.20 $[M+H]^+$

Synthesis of (3-amino-4-bromophenyl) methanol (XI-1):



To a mixture of methyl 3-amino-4-bromobenzoate (5.0 g, 21.73 mmol, 1.0 equiv.) in THF (50 mL) was added LiAlH₄ (0.83 g, 17.13 mmol, 0.8 equiv.) at 0 °C, and the resulting
 5 mixture was stirred at same temperature for 2.5 h. After completion of the reaction, the reaction mixture was quenched with ice cold saturated ammonium chloride solution (50 mL), and the product was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulphate. The filtered organic layer was concentrated under reduced pressure to give crude titled compound **XI-1** (5.0 g) which was
 10 sufficiently pure to perform the next step. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.25 (d, *J* = 8.4 Hz, 1H), 6.78 (t, *J* = 0.8 Hz, 1H), 6.43 (dd, *J* = 8.0, 2.0 Hz, 1H), 5.24 (s, 2H), 5.11 (t, *J* = 6.0 Hz, 1H), 4.34 (d, *J* = 5.6 Hz, 2H); LC-MS: *m/z* 201.85 (M+H)⁺.

Synthesis of (3-amino-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (XII-1):



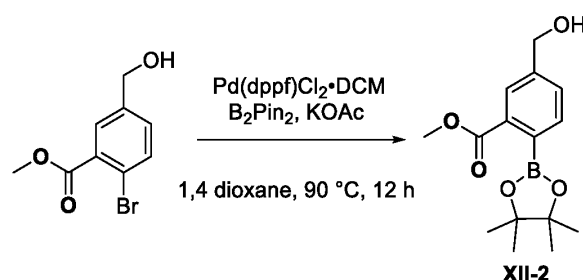
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A mixture of (3-amino-4-bromophenyl)methanol (**XI-1**) (4.1 g, 20.3 mmol, 1.0 equiv.), bis(pinacolato)diboron (6.18 g, 24.35 mmol, 1.2 equiv.) and potassium acetate (3.88 g, 40.50 mmol, 2.0 equiv.) in 1, 4 dioxane (130 mL) was degassed with argon for 15 min. Pd(dppf)Cl₂·DCM (1.26 g, 1.72 mmol, 0.008 equiv.) was added to the reaction mixture at room
 20 temperature and subsequently heated to 90 °C for 12 h. After completion of the reaction, the reaction mixture was filtered through a pad of Celite[®], and the filtrate was quenched with ice cold water and extracted with ethyl acetate (40 mL x 3). The combined organic layers were

dried over anhydrous Na_2SO_4 then filtered and concentrated under reduced pressure to give a residue. The residue was purified by Combi-flash, eluting with 60% ethyl acetate in hexane to get the title compound **XII-1** (3.4 g, 67%) as an off-white semi solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.62 (d, $J = 7.6$ Hz, 1H), 6.69- 6.64 (m, 2H), 4.62 (s, 2H), 1.32- 1.27 (m, 12H);

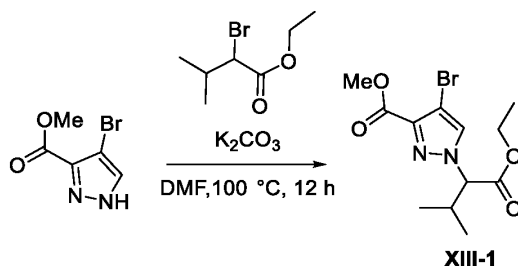
5 LC-MS: m/z 250.2 $[\text{M}+\text{H}]^+$

Synthesis of methyl 5-(hydroxymethyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (XII-2):



The above reaction was carried out according to the procedure similarly to the one described in the synthesis of **Intermediate XII-1** using methyl 2-bromo-5-(hydroxymethyl)benzoate as starting material; LC-MS: m/z 293.10 $[\text{M}+\text{H}]^+$.

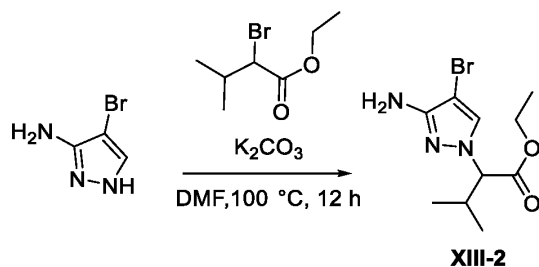
Synthesis of methyl 4-bromo-1-(1-ethoxy-3-methyl-1-oxobutan-2-yl)-1H-pyrazole-3-carboxylate (XIII-1):



To a stirred solution of methyl 4-bromo-1H-pyrazole-3-carboxylate (5.0 g, 24.38 mmol) in DMF (100 mL) was added K_2CO_3 (8.42 g, 60.97 mmol) and ethyl 2-bromo-3-methylbutanoate (6.10 g, 29.26 mmol) at room temperature. Then the reaction mixture was heated to 100 °C and stirred for 12 h. After completion of the reaction, the reaction mixture was allowed to cool to room temperature and was quenched with ice cold water (50 mL). The product was then extracted with ethyl acetate (2x500 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulphate and concentrated under reduced

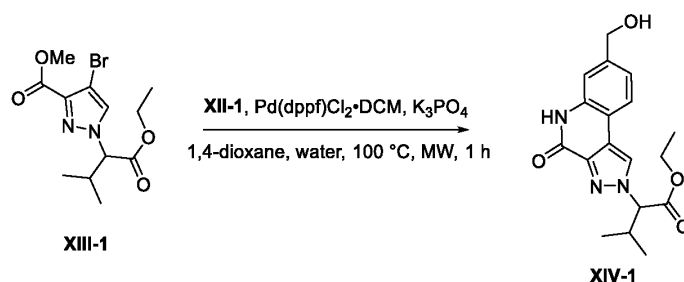
pressure to give a residue. The residue was purified by combi-flash, eluting with 40% ethyl acetate in hexane to provide the title compound **XIII-1** (7.5 g, 92%) as colorless sticky liquid; ^1H NMR (400 MHz, DMSO- d_6): δ 7.87 (s, 1H), 4.8 (d, J = 9.2 Hz, 1H), 4.32- 4.19 (m, 2H), 3.97 (s, 3H), 2.49- 2.40 (m, 1H), 1.33- 1.28 (m, 3H), 1.45 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H); LC-MS: m/z 333.1 $[\text{M}+\text{H}]^+$.

Synthesis of ethyl 2-(3-amino-4-bromo-1H-pyrazol-1-yl)-3-methylbutanoate (**XIII-2**):



The reaction was carried out according to the procedure similarly to the one described in the synthesis of Intermediate **XIII-1** using 4-bromo-1H-pyrazol-3-amine as starting material. ^1H NMR (400 MHz, CDCl₃): δ 7.46 (s, 1H), 4.33 (d, J = 9.6 Hz, 1H), 4.30- 4.18 (m, 2H), 2.45- 2.39 (m, 1H), 1.3 (t, J = 7.2 Hz, 3H), 1.02 (d, J = 6.4 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H); LC-MS: m/z 290.0 $[\text{M}+\text{H}]^+$.

Synthesis of ethyl 2-(7-(hydroxymethyl)-4-oxo-4,5-dihydro-2H-pyrazolo[3,4-c]quinolin-2-yl)-3-methylbutanoate (**XIV-1**):



15

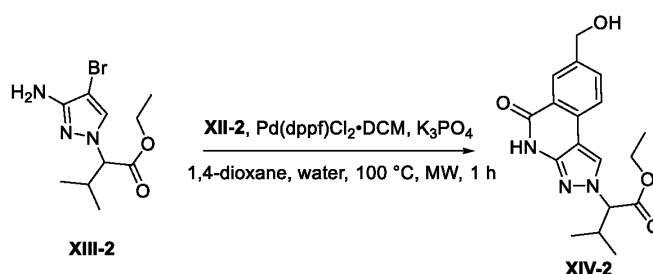
To a stirred solution of methyl 4-bromo-1-(1-methoxy-3-methyl-1-oxobutan-2-yl)-1H-pyrazole-3-carboxylate (**XIII-1**) (0.96 g, 2.89 mmol) in 1, 4 dioxane (20 mL) and water (3 mL) was added (3-amino-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (**XII-1**) (0.60 g, 2.40 mmol) and potassium phosphate (1.53 g, 7.20 mmol). The vessel was then purged with argon for 15 min. Then Pd(dppf)Cl₂·DCM (0.20 g, 0.24 mmol) was added, and the mixture was stirred at 100 °C for 1 hour under microwave irradiation. After completion of the reaction,

20

the mixture was filtered through Celite® pad and quenched with ice cold water and extracted with ethyl acetate (15 mLx3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by Combi-flash, eluting with 7% methanol in dichloromethane to afford the title compound

5 **XIV-1** (0.3 g, 36%) as light brown color solid; ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.38 (s, 1H), 8.80 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.32 (s, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 5.29 (t, *J* = 5.6 Hz, 1H), 5.10 (d, *J* = 9.6 Hz, 1H), 4.55 (d, *J* = 5.6 Hz, 2H), 4.25- 4.14 (m, 2H), 2.69- 2.63 (m, 1H), 1.24- 1.16 (m, 3H), 1.11- 1.04 (m, 3H), 0.83 (d, *J* = 8.0 Hz, 3H); LC-MS: *m/z* 344.00 [M+H]⁺.

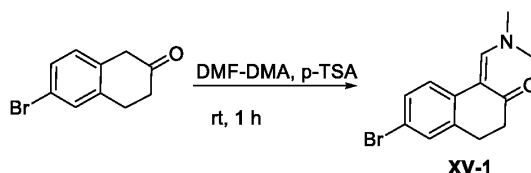
10 **Synthesis of ethyl 2-(7-(hydroxymethyl)-5-oxo-4,5-dihydro-2H-pyrazolo[3,4-c]isoquinolin-2-yl)-3-methylbutanoate (XIV-2):**



The above reaction was carried out according to the procedure similarly to the one described in the synthesis of **Intermediate XIV-1** using **XIII-2** and **XII-2** as starting materials.

15 ¹H NMR (400 MHz, CDCl₃): δ 8.93 (s, 1H), 8.40 (d, *J* = 0.8 Hz, 1H), 8.13 (s, 1H), 7.80- 7.70 (m, 2H), 4.84 (d, *J* = 5.6 Hz, 2H), 4.69 (d, *J* = 9.6 Hz, 1H), 4.31- 4.26 (m, 2H), 2.63- 2.57 (m, 1H), 1.91 (t, *J* = 6.0 Hz, 1H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.11 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 6.4 Hz, 3H); LC-MS: *m/z* 344.2 [M+H]⁺.

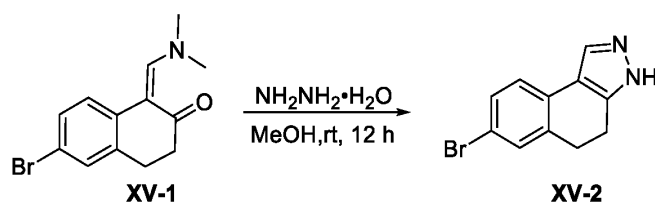
20 **Synthesis of (Z)-6-bromo-1-((dimethylamino)methylene)-3,4-dihydronaphthalen-2(1H)-one (XV-1):**



To a stirred solution of 6-bromo-3,4-dihydronaphthalen-2(1H)-one (25.0 g, 111.07 mmol, 1 equiv.) in DMF-DMA (133.47g, 120.17mmol, 10.0 equiv.) was added para-toluene

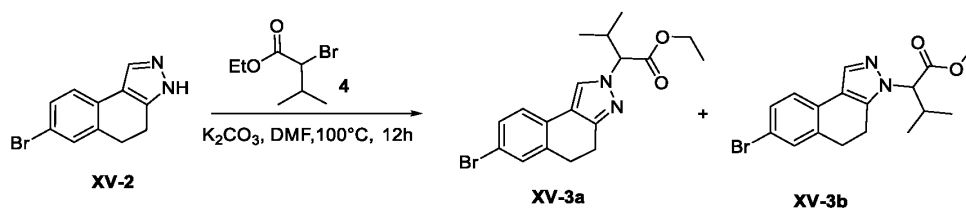
sulfonic acid monohydrate (0.423g, 2.220 mmol, 0.02 equiv.), and the reaction mixture was stirred at room temperature for 1h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to give the crude product. The crude product was purified by Combi-flash column using 50% ethyl acetate in hexane to give pure titled compound of **XV-1** (2.05 g; yield 66 %) as a pale brown solid.; ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.81 (s, 1H), 7.40- 7.20 (m, 2H), 6.75 (d, *J* = 8.0 Hz, 1H), 2.94 (s, 6H), 2.74 (d, *J* = 6.0 Hz, 2H), 2.25 (d, *J* = 6.0 Hz, 2H); LC-MS: *m/z* 282.0 [M+2H]⁺.

Synthesis of 7-bromo-4,5-dihydro-3H-benzo[e]indazole (**XV-2**):



To a stirred solution of (Z)-6-bromo-1-((dimethylamino)methylene)-3,4-dihydronaphthalen-2(1H)one (**XV-1**) (20.0 g, 71.39 mmol, 1 equiv.) in MeOH (200 mL) was added hydrazine monohydrate (8.934g, 17.840, 2.5 equiv.) The mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated under reduced pressure to give crude residue. The crude residue was purified by Combi-flash column chromatography using 50% ethyl acetate in hexane to afford pure titled compound of **XV-2** (17.5 g; yield 98 %) as brown solid; ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.64 (s, 1H), 8.09 (s, 1H), 7.43- 7.34 (m, 3H), 2.94- 2.91 (m, 2H), 2.76 (m, 2H); LC-MS: *m/z* 250.9 [M+H]⁺.

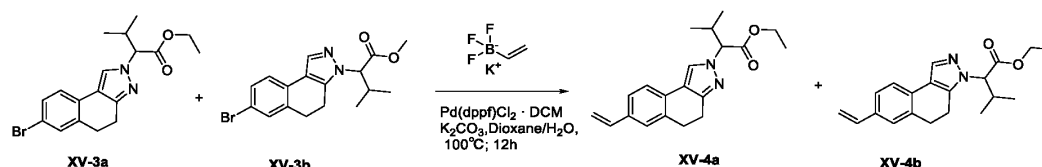
Synthesis of ethyl 2-(7-bromo-4,5-dihydro-2H-benzo[e]indazol-2-yl)-3-methylbutanoate (XV-3a**) and methyl 2-(7-bromo-4,5-dihydro-3H-benzo[e]indazol-3-yl)-3-methylbutanoate (**XV-3b**):**



The above reaction was carried out according to the procedure similar to the one described in the synthesis of **Intermediate XIII-1** using **Intermediate XV-2** as starting

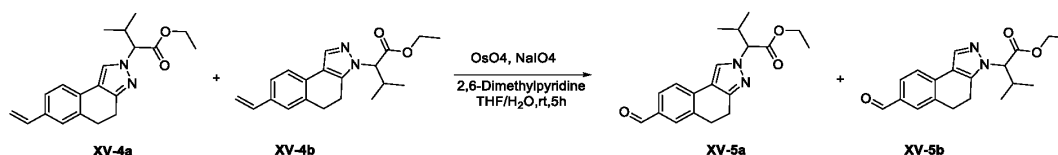
material to obtain inseparable mixture of 2:1 ratio of regio-isomers of **Intermediate XV-3a** and **Intermediate XV-3b**. LC-MS: m/z 378 $[M+H]^+$

Synthesis of ethyl 3-methyl-2-(7-vinyl-4,5-dihydro-2H-benzo[e]indazol-2-yl)butanoate (XV-4a) and ethyl 3-methyl-2-(7-vinyl-4,5-dihydro-3H-benzo[e]indazol-3-yl)butanoate (XV-4b):



In a sealed tube, ethyl 2-(7-bromo-4,5-dihydro-3H-benzo[e]indazol-3-yl)-3-methylbutanoate (**XV-3a**) (5.4 g, 14.313 mmol, 1.0 equiv.), ethyl 2-(7-bromo-4,5-dihydro-2H-benzo[e]indazol-2-yl)-3-methylbutanoate (**XV-3b**), potassium vinyl trifluoroborate (3.834g, 28.620 mmol, 2.0 equiv.) and potassium carbonate (3.956 g, 28.620 mmol, 2.0 equiv.) was taken up and dissolved in 1,4-dioxane (96 mL) and water (16 mL), after which the vessel was purged with argon for 30 min. Then $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.209 g, 0.280 mmol, 0.020 equiv.) was added, and the mixture was heated at 100 °C for 12 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a Celite® bed, after which the filtrate was diluted with water. The organic layer was then separated, dried over anhydrous sodium sulphate and concentrated under reduced pressure to give crude product. The crude product was purified by combi-flash column chromatography using 50% ethyl acetate in hexane to give inseparable mixture of titled compound **XV-4a** and **XV-4b** (6.2 g; yield 72 %) as brown semi solid. LC-MS: m/z 325.05 $[M+H]^+$.

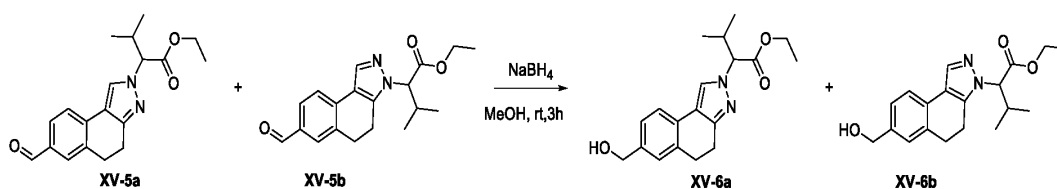
Synthesis of ethyl 2-(7-formyl-4,5-dihydro-2H-benzo[e]indazol-2-yl)-3-methylbutanoate (XV-5a) and ethyl 2-(7-formyl-4,5-dihydro-3H-benzo[e]indazol-3-yl)-3-methylbutanoate (XV-5b):



To a stirred solution of ethyl 3-methyl-2-(7-vinyl-4,5-dihydro-2H-benzo[e]indazol-2-yl)butanoate (**XV-4a**) and ethyl 3-methyl-2-(7-vinyl-4,5-dihydro-3H-benzo[e]indazol-3-yl)butanoate (**XV-4b**) (4.0 g, 12.33 mmol, 1.0 equiv.) in THF (100 mL) and water (5 mL) were

added sodium periodate (7.912 g, 36.990 mmol, 3.0 equiv.), 2,6-dimethylpyridine (1.321 g, 12.330 mmol, 1.0 equiv.) and osmium tetroxide (1.254 g, 4.930 mmol, 0.4 equiv.) at room temperature. The reaction mixture was stirred at room temperature for 5 h. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to give crude product. The crude product was purified by combi-flash column using 50% ethyl acetate in hexane to provide mixture of compound of **XV-5a** and **XV-5b** (3.8 g; yield 94%) as colorless liquid. LC-MS: m/z 327.05 $[M+H]^+$.

Synthesis of ethyl 2-(7-(hydroxymethyl)-4,5-dihydro-2H-benzo[e]indazol-2-yl)-3-methylbutanoate (XV-6a) and ethyl 2-(7-(hydroxymethyl)-4,5-dihydro-3H-benzo[e]indazol-3-yl)-3-methylbutanoate (XV-6b):



To a stirred solution of 2-(7-formyl-4,5-dihydro-3H-benzo[e]indazol-3-yl)-3-methylbutanoate (**XV-5a**) and ethyl 2-(7-formyl-4,5-dihydro-2H-benzo[e]indazol-2-yl)-3-methylbutanoate (**XV-5b**) (3.8 g, 11.64 mmol, 1.0 equiv.) in methanol (40 mL) was added sodium borohydride (0.925 g, 24.440 mmol, 2.1 equiv.) at 0°C. After stirring at 0 °C for 10 minutes, the reaction mixture was warmed to room temperature and stirred for 3 hours. After completion of the reaction, the reaction mixture was diluted with water and extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to give the crude product. The crude product was purified by chiral HPLC to afford all four isomers of titled compounds as colorless liquids.

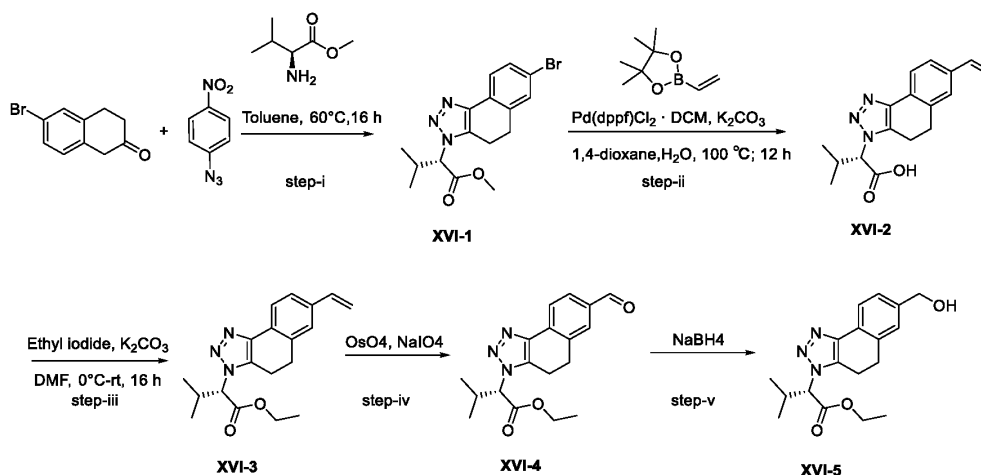
XV-6aa (isomer-1 of **XV-6a**): ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.84 (s, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.18 (s, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 5.10 (t, *J* = 6.0 Hz, 1H), 4.75 (d, *J* = 9.2 Hz, 1H), 4.44 (d, *J* = 5.6 Hz, 2H), 4.15-4.09 (m, 2H), 2.95-2.92 (m, 3H), 2.87-2.82 (m, 1H), 2.64-2.60 (m, 1H), 1.14 (t, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 6.4 Hz, 3H); LC-MS: m/z 329.05 $[M+H]^+$.

XV-6ab (isomer-2 of XV-6a): ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 7.84 (s, 1H), 7.39 (d, $J = 7.6$ Hz, 1H), 7.18 (s, 1H), 7.14 (d, $J = 7.6$ Hz, 1H), 5.10 (t, $J = 6.0$ Hz, 1H), 4.75 (d, $J = 9.2$ Hz, 1H), 4.44 (d, $J = 5.6$ Hz, 2H), 4.15- 4.09 (m, 2H), 2.95- 2.92 (m, 3H), 2.87- 2.82 (m, 1H), 2.64- 2.60 (m, 1H), 1.14 (t, $J = 7.2$ Hz, 3H), 1.02 (d, $J = 6.8$ Hz, 3H), 0.76 (d, $J = 6.4$ Hz, 3H); LC-
5 MS: m/z 329.05 $[\text{M}+\text{H}]^+$.

XV-6ba (isomer-1 of XV-6b): ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 8.13 (s, 1H), 7.42 (d, $J = 7.6$ Hz, 1H), 7.17 (s, 1H), 7.14 (d, $J = 8.0$ Hz, 1H), 5.10 (t, $J = 5.6$ Hz, 1H), 4.66 (d, $J = 9.6$ Hz, 1H), 4.45 (d, $J = 5.6$ Hz, 2H), 4.21- 4.16 (m, 2H), 2.90 (t, $J = 7.2$ Hz, 2H), 2.74 (t, $J = 7.6$ Hz, 2H), 2.55- 2.53 (m, 1H), 1.21 (t, $J = 9.2$ Hz, 3H), 0.99 (d, $J = 6.8$ Hz, 3H), 0.81 (d, $J = 6.8$ Hz, 3H); LC-MS: m/z 329.05 $[\text{M}+\text{H}]^+$.
10

XV-6bb (isomer-2 of XV-6b): ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 8.13 (s, 1H), 7.42 (d, $J = 7.6$ Hz, 1H), 7.17 (s, 1H), 7.14 (d, $J = 8.0$ Hz, 1H), 5.10 (t, $J = 5.6$ Hz, 1H), 4.66 (d, $J = 9.6$ Hz, 1H), 4.45 (d, $J = 5.6$ Hz, 2H), 4.21- 4.16 (m, 2H), 2.90 (t, $J = 7.2$ Hz, 2H), 2.74 (t, $J = 7.6$ Hz, 2H), 2.55- 2.53 (m, 1H), 1.21 (t, $J = 9.2$ Hz, 3H), 0.99 (d, $J = 6.8$ Hz, 3H), 0.81 (d, $J = 6.8$ Hz, 3H); LC-MS: m/z 329.05 $[\text{M}+\text{H}]^+$.
15

Synthesis of ethyl (S)-2-(7-(hydroxymethyl)-4,5-dihydro-3H-naphtho[1,2-d][1,2,3]triazol-3-yl)-3-methylbutanoate(XVI-5):



Step-i: Synthesis of methyl (S)-2-(7-bromo-4,5-dihydro-3H-naphtho[1,2-d][1,2,3]triazol-3-yl)-3-methylbutanoate (XVI-1)
20

To a stirred solution of 6-bromo-3,4-dihydronaphthalen-2(1H)-one (6.0 g, 26.65 mmol, 1 equiv.) in toluene (20 mL) was added methyl L-valinate (4.55 g, 34.65 mmol, 1.3

equiv.) and 1-azido-4-nitrobenzene (5.69 g, 34.65 mmol, 1.3 equiv.) at room temperature. The mixture was heated to 60 °C and stirred for 16 h. After completion of reaction, the reaction mixture was allowed to cool to room temperature and was poured into ice water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to give the crude product. The crude product was purified by combi-flash column using 10% ethyl acetate in hexane to give titled compound methyl (S)-2-(7-bromo-4,5-dihydro-3H-naphtho[1,2-d][1,2,3]triazol-3-yl)-3-methylbutanoate **XVI-1** (7.5 g; yield 77 %) as brown semi solid.; ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.67 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 1.6 Hz, 1H), 7.50 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 5.26 (d, *J* = 8.4 Hz, 1H), 3.71 (s, 3H), 3.10- 2.90 (m, 4H), 2.75- 2.65 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H); LC-MS: *m/z* 364.1 [M+H]⁺.

Step-ii: Synthesis of (S)-3-methyl-2-(7-vinyl-4,5-dihydro-3H-naphtho[1,2-d][1,2,3]triazol-3-yl)butanoic acid (XVI-2)

To a stirred solution of methyl (R)-2-(7-bromo-4,5-dihydro-3H-naphtho[1,2-d][1,2,3]triazol-3-yl)-3-methylbutanoate (**XVI-1**) (3.50 g, 9.61 mmol, 1 equiv.) in a 1,4 dioxane/water mixture (4:1) (25 mL) was added vinyl boronic acid pinacol ester (2.22 g, 14.41 mmol, 1.5 equiv.) and sodium carbonate (3.06 g, 28.82 mmol, 3 equiv.). The vessel was then purged with argon for 10 min and Pd(dppf)Cl₂·CH₂Cl₂ (0.78 g, 0.96 mmol, 0.1 equiv.) was added, and the reaction mixture was heated at 100 °C for 12 hours. The reaction mixture was poured into ice water, the pH was adjusted to 2-3, and the reaction mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to give the crude product (-SR)-3-methyl-2-(7-vinyl-4,5-dihydro-3H-naphtho[1,2-d][1,2,3]triazol-3-yl)butanoic acid (**XVI-2**) (7.0 g) as brown gummy solid; LC-MS: *m/z* 298.2 [M+H]⁺.

Step-iii: Synthesis of ethyl (S)-3-methyl-2-(7-vinyl-4,5-dihydro-3H-naphtho[1,2-d][1,2,3]triazol-3-yl)butanoate(XVI-3):

To a stirred solution of (S)-3-methyl-2-(7-vinyl-4,5-dihydro-3H-naphtho[1,2-d][1,2,3]triazol-3-yl)butanoic acid (**XVI-2**) (7.0 g, 23.54 mmol, 1.0 equiv.) in DMF was added K₂CO₃ (9.76 g, 70.62 mmol, 3.0 equiv.) at room temperature, and the reaction mixture was stirred for 5 min. Then iodoethane (7.34 g, 47.08 mmol, 2.0 equiv.) was added to the mixture at 0 °C, and the contents of the vessel were stirred for 16 hours at room temperature. The mixture was poured in ice cold water and exacted with EtOAc. The organic layer was separated,

dried over anhydrous sodium sulphate, and concentrated under reduced pressure to give the crude product. The crude product was purified by combi-flash column using 20% ethyl acetate in hexane to afford titled compound (S)-3-methyl-2-(7-vinyl-4,5-dihydro-3H-naphtho[1,2-d][1,2,3]triazol-3-yl)butanoate (**XVI-3**) (2.35 g; yield 31%) as brown solid; ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.71 (d, *J* = 8.0 Hz, 1H), 7.45 (s, 1H), 7.41 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 6.80- 6.75 (m, 1H), 5.85 (dd, *J* = 17.6 Hz, 0.80 Hz, 1H), 5.30- 5.20 (m, 2H), 4.25- 4.10 (m, 2H), 3.15- 2.90 (m, 4H), 2.75- 2.65 (m, 1H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.05 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H); LC-MS: *m/z* 326.2 [M+H]⁺.

Step-iv: Synthesis of ethyl (S)-2-(7-formyl-4,5-dihydro-3H-naphtho[1,2-d][1,2,3]triazol-3-yl)-3-methylbutanoate (XVI-4)

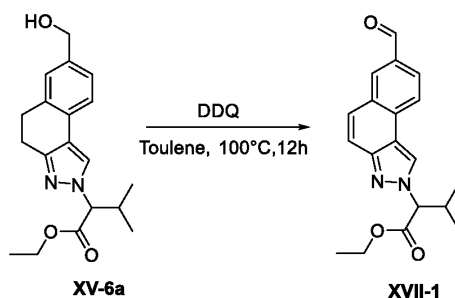
To a stirred solution of (S)-3-methyl-2-(7-vinyl-4,5-dihydro-3H-naphtho[1,2-d][1,2,3]triazol-3-yl)butanoate **XVI-3** (2.25 g, 6.91 mmol, 1.0 equiv.) in THF/water (6:1) mixture (70 mL), were added NaIO₄ (4.44 g, 20.74 mmol, 3.0 equiv.) and 2,6 dimethyl pyridine (0.74 g, 6.91 mmol, 1 equiv.) at 0 °C. After 10 min, OsO₄ (0.87 g, 3.45 mmol, 0.5 equiv.) was added to the mixture at 0 °C, and the reaction mixture was stirred for 3 h at the same temperature. After completion of reaction, the reaction mixture was poured in ice cold water and extracted with EtOAc. Then the organic layer was separated, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford crude compound ethyl (R)-2-(7-formyl-4,5-dihydro-3H-naphtho[1,2-d][1,2,3]triazol-3-yl)-3-methylbutanoate (**XVI-4**) (3.8 g) as brown solid; LC-MS: *m/z* 328.2 [M+H]⁺.

Step-v: Synthesis of ethyl (S)-2-(7-(hydroxymethyl)-4,5-dihydro-3H-naphtho[1,2-d][1,2,3]triazol-3-yl)-3-methylbutanoate (XVI-5):

To a stirred solution of (S)-2-(7-formyl-4,5-dihydro-3H-naphtho[1,2-d][1,2,3]triazol-3-yl)-3-methylbutanoate (**XVI-4**) (3.8 g, 11.6 mmol, 1.0 equiv.) in MeOH (20 mL) was added NaBH₄ (0.88 g, 23.2 mmol, 2 equiv.) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 2 hours. After completion of reaction, the reaction mixture was poured into ice-cold water and extracted with DCM. Then the organic layer was separated, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford the crude product. The crude product was purified by combi-flash column using 60% ethyl acetate in hexane to provide titled compound (ethyl (R)-2-(7-(hydroxymethyl)-4,5-dihydro-3H-naphtho[1,2-d][1,2,3]triazol-3-yl)-3-methylbutanoate (**XVI-5**) (1.65 g; yield 43%) as brown gummy solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.69 (d, *J* = 7.6 Hz, 1H), 7.30- 7.20

(m, 2H), 5.27- 5.15 (m, 2H), 4.49 (d, $J = 5.6$ Hz, 2H), 4.25- 4.10 (m, 2H), 3.15- 2.90 (m, 4H), 2.75- 2.60 (m, 1H), 1.18 (t, $J = 6.8$ Hz, 3H), 1.05 (d, $J = 6.8$ Hz, 3H), 0.85 (d, $J = 6.4$ Hz, 3H); LC-MS: m/z 330.1 $[M+H]^+$.

Synthesis of ethyl 2-(7-formyl-2H-benzo[e]indazol-2-yl)-3-methylbutanoate (XVII-1):

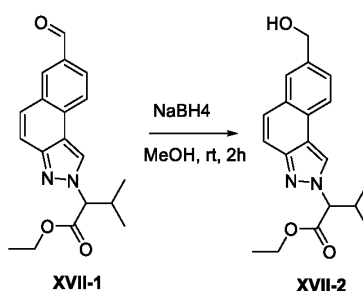


5

To a stirred solution of ethyl 2-(7-(hydroxymethyl)-4,5-dihydro-2H-benzo[e]indazol-2-yl)-3-methylbutanoate (**XV-6a**) (0.5 g, 1.52 mmol, 1 equiv.) in toluene (30 mL) was added DDQ (1.04 g, 4.56 mmol, 3.0 equiv.) at room temperature. The mixture was heated to 100 °C and stirred for 12 hours. After completion of reaction, the reaction mixture was allowed to cool to room temperature and filtered through a pad of Celite[®]. The organic layer was concentrated under reduced pressure to give the crude product. The crude product was purified by combi-
 10 flash column using 50% ethyl acetate in hexane to provide the pure compound ethyl 2-(7-formyl-2H-benzo[e]indazol-2-yl)-3-methylbutanoate (**XVII-1**) (0.27 g; yield 55 %) as pale brown semi solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.14 (s, 1H), 9.17 (s, 1H), 8.52 (s, 1H), 8.47 (d, $J = 8.4$ Hz, 1H), 8.05 (dd, $J = 8.4$ Hz, 1.6 Hz, 2H), 7.83 (d, $J = 9.2$ Hz, 1H), 7.74 (d, $J = 9.2$ Hz, 1H), 7.33 (s, 2H), 5.16 (d, $J = 9.2$ Hz, 1H), 4.22- 4.13 (m, 1H), 2.85- 2.65 (m, 1H),
 15 1.19 (t, $J = 7.2$ Hz, 3H), 1.07 (d, $J = 6.4$ Hz, 3H), 0.82 (d, $J = 6.8$ Hz, 3H); LC-MS: m/z 325.3 $[M+H]^+$.

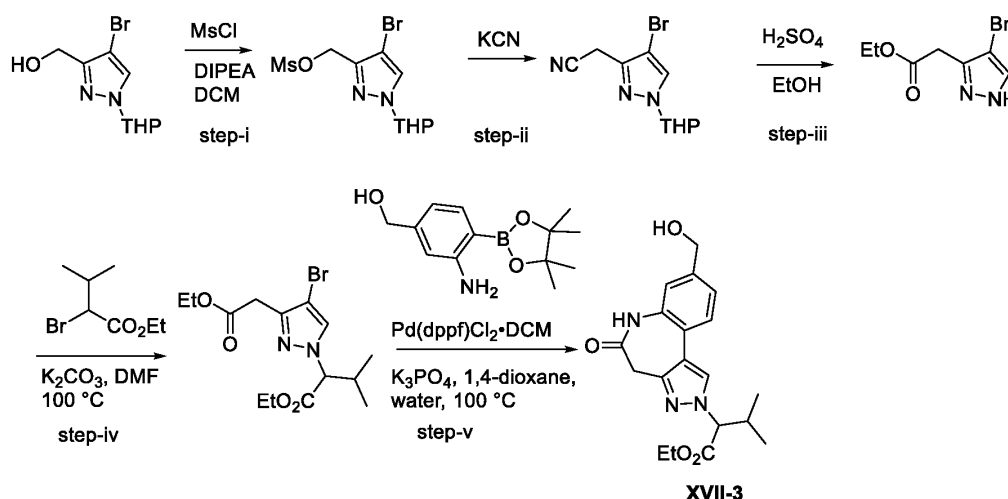
Synthesis of ethyl 2-(7-(hydroxymethyl)-2H-benzo[e]indazol-2-yl)-3-methylbutanoate (XVII-2):

20



The above reaction was carried out by a procedure similar to the one described in the step-5 of **Intermediate XVI-5** using sodium borohydride as reducing agent; LC-MS: m/z 327.2 $[M+H]^+$.

Synthesis of ethyl 2-(4-bromo-3-(2-ethoxy-2-oxoethyl)-1H-pyrazol-1-yl)-3-methylbutanoate(XVII-3):



Step-i: Synthesis of (4-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)methyl methanesulfonate

To a stirred solution of (4-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)methanol (9.4 g, 36.0 mmol, 1.0 equiv.) in DCM (100 mL) was added $DIPEA$ (13.3 g, 107.9 mmol, 3.0 equiv.) at $20^\circ C$. Methanesulfonyl chloride (8.3 g, 71.9 mmol 2.0 equiv.) was added dropwise in the reaction mixture at $0^\circ C$ and the reaction mixture was stirred at $20^\circ C$ for 4 hours. TLC showed the reaction was completed. The reaction mixture was quenched with water and extracted with DCM . The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by combi-
flash column using 60% ethyl acetate in hexane to provide titled compound (4.6 g, 37.67%), LC-MS: 341.2 $[M+H]^+$

Step-ii: Synthesis of 2-(4-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)acetonitrile

To a solution of (4-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)methyl methanesulfonate (4.1 g, 12.1 mmol, 1.0 equiv.) in DCM (80 mL) was added KCN (1.6 g, 24.17 mmol, 2.0 equiv.) and hexaoxacyclooctadecane (3.2 g, 12.1 mmol, 1.0 equiv.) at room

temperature. The mixture was stirred at rt for 3 h. The reaction mixture was diluted with ice cold water and extracted into DCM. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by combi-flash column using 30% ethyl acetate in hexane to provide titled compound (2.45g, 75.04%), LC-MS: 272.1[M+H]⁺

Step-iii: Synthesis of ethyl 2-(4-bromo-1H-pyrazol-3-yl)acetate

Concentrated sulphuric acid (5mL) was added to a stirred solution of 2-(4-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)acetonitrile (2.0 g, 7.4 mmol, 1.0 equiv.) in EtOH (20 mL) at RT. The mixture was stirred at 110 °C for 16 h. The methanol was removed in vacuo and the remaining aqueous suspension was quenched with sat aq. NaHCO₃ drop-wise to pH 8. EtOAc (50 mL) was added, and the organic layer was collected. The aqueous layer was extracted with EtOAc (50 mL) and the combined organic layers were concentrated in vacuo to afford a white solid which was triturated with diethyl ether to give a title compound (0.65 g, 37.67%);LC-MS: *m/z* 235.0 [M+H]⁺

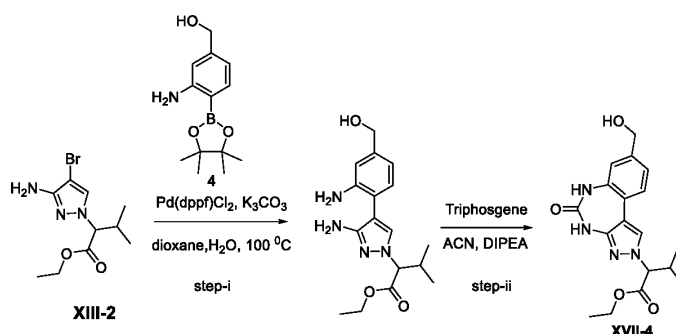
Step-iv: Synthesis of ethyl 2-(4-bromo-3-(2-ethoxy-2-oxoethyl)-1H-pyrazol-1-yl)-3-methylbutanoate

The procedure for the Step-iv was carried out similarly to the one described in the synthesis of **Intermediate XIII-1** to obtain titled compound;LC-MS: *m/z* 361.05 [M+H]⁺

Step-v: Synthesis of ethyl 2-(8-(hydroxymethyl)-5-oxo-5,6-dihydrobenzo[b]pyrazolo[4,3-d]azepin-2(4H)-yl)-3-methylbutanoate

The step-v was carried out by a procedure similar to the one described in the synthesis of **Intermediate XIV-1** to obtain titled compound **Intermediate XVII-3**; LC-MS: *m/z* 358.15 [M+H]⁺.

Synthesis of ethyl 2-(8-(hydroxymethyl)-5-oxo-5,6-dihydrobenzo[d]pyrazolo[4,3-f][1,3]diazepin-2(4H)-yl)-3-methylbutanoate (XVII-4):



Step-i: Synthesis of ethyl 2-(3-amino-4-(2-amino-4-(hydroxymethyl)phenyl)-1H-pyrazol-5-yl)-3-methylbutanoate

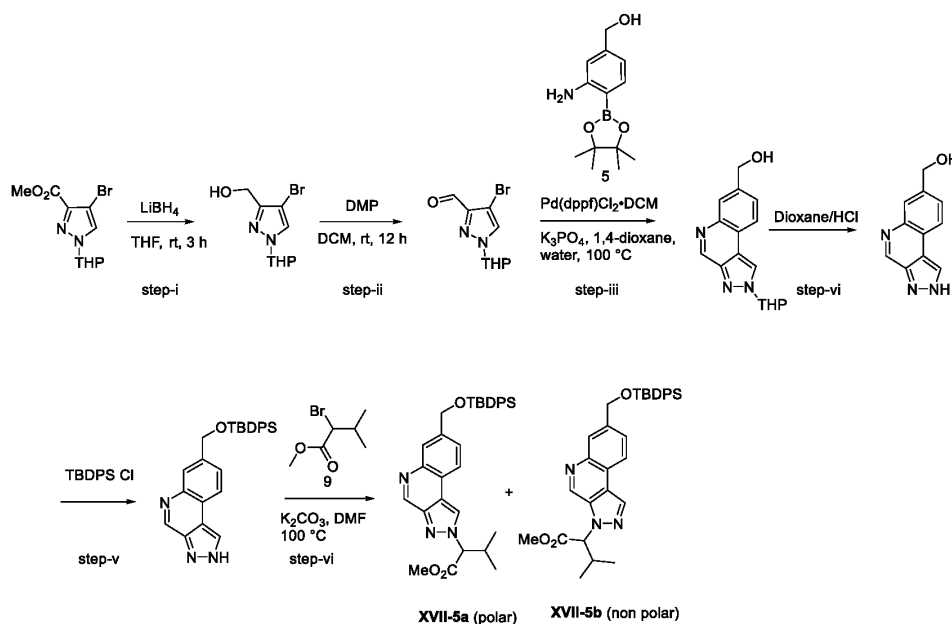
To a stirred solution of methyl 4-bromo-1-(1-methoxy-3-methyl-1-oxobutan-2-yl)-1H-pyrazole-3-carboxylate (**XIII-2**) (3.30 g, 11.37 mmol) in 1, 4 dioxane (24 mL) and water (6 mL) was added (3-amino-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (0.60 g, 2.83 mmol) and potassium phosphate (4.71 g, 34.11 mmol). The vessel was then
 10 purged with argon for 15 min. Then Pd(dppf)Cl₂·DCM (0.92 g, 1.13 mmol) was added, and the mixture was stirred at 110 °C for 1 hour under microwave irradiation. After the completion of the reaction, the mixture was filtered through Celite[®] and quenched with ice cold water and extracted with ethyl acetate (25 mLx3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The
 15 residue was purified by Combi-flash, eluting with 7% methanol in dichloromethane to afford the title compound (1.6 g, 42.33%) as light brown color solid; LC-MS: *m/z* 333.20 [M+H]⁺

Step-ii: Synthesis of ethyl 2-(8-(hydroxymethyl)-5-oxo-5,6-dihydrobenzo[d]pyrazolo[4,3-f][1,3]diazepin-2(4H)-yl)-3-methylbutanoate

To a stirred solution of ethyl 2-(3-amino-4-(2-amino-4-(hydroxymethyl)phenyl)-1H-pyrazol-1-yl)-3-methylbutanoate (0.80 g, 2.40 mmol) in ACN (10 mL) was added DIPEA (0.93 g, 7.22 mmol), followed by triphosgene (0.71 g, 2.40 mol) at 0 °C. The reaction temperature was allowed to warm to room temperature and stirred for 2 h. After completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (25 mLx3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and
 25 concentrated under reduced pressure to give a residue. The residue was purified by Combi-

flash, eluting with 5% methanol in dichloromethane to afford the title compound **XVII-4** (0.6 g, 69.55%); LC-MS: m/z 359.20 (M+H)⁺.

Synthesis of methyl 2-(7-(((tert-butyl)diphenylsilyl)oxy)methyl)-2H-pyrazolo[3,4-c]quinolin-2-yl)-3-methylbutanoate (XVII-5a) and methyl 2-(7-(((tert-butyl)diphenylsilyl)oxy)methyl)-3H-pyrazolo[3,4-c]quinolin-3-yl)-3-methylbutanoate (XVII-5b)



Step-i: Synthesis of (4-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)methanol

To a stirred solution of methyl 4-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole-3-carboxylate (7.5 g, 25.9 mmol, 1.0 equiv.) in THF (80mL) was added LiBH₄ (0.88 g, 25.9 mmol, 1.0equiv.) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 12 hours. After completion of reaction, the reaction mixture was poured into ice-cold water and extracted with EtOAc. Then the organic layer was separated, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford the crude product. The crude product was purified by combi-flash column using 50% ethyl acetate in hexane to provide titled compound (5.7 g, 84.15%), LC-MS: 263.0 [M+H]⁺.

Step-ii: Synthesis of 4-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole-3-carbaldehyde

To a stirred solution of (4-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)methanol (3.0 g, 11.5 mmol, 1.0 equiv.) in DCM (30mL) was added DMP (9.75 g, 23.0 mmol, 2equiv.) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 12 hours. After completion of reaction, the reaction mixture was poured into ice-cold water and extracted with DCM. Then the organic layer was separated, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford the crude product. The crude product was purified by combi-flash column using 50% ethyl acetate in hexane to provide titled compound (2.7 g, 90.7%), LC-MS: 260.10 [M+H]⁺.

Step-iii: Synthesis of (2-(tetrahydro-2H-pyran-2-yl)-2H-pyrazolo[3,4-c]quinolin-7-yl)methanol

The step-iii was carried out by a procedure similar to the one described in the synthesis of **Intermediate XIV-1** to obtain titled compound; LC-MS: *m/z* 284.2 [M+H]⁺.

Step-iv: Synthesis of (2H-pyrazolo[3,4-c]quinolin-7-yl)methanol

4M HCl in 1,4-dioxane (5mL) was added to stirred solution of (2-(tetrahydro-2H-pyran-2-yl)-2H-pyrazolo[3,4-c]quinolin-7-yl)methanol (0.70g, 2.5 mmol, 1.0 equiv.) in MeOH (2.0 mL) and DCM (10mL) at RT. The reaction mixture was stirred at RT for 4 h. After completion of reaction, the methanol was removed in vacuo and the remaining aqueous suspension was quenched with TEA drop-wise to pH 8. EtOAc (50 mL) was added, and the organic layer was collected. The aqueous layer was extracted with EtOAc (50 mL) and the combined organic layers were concentrated in vacuo to afford a white solid which was triturated with diethyl ether to give a title compound (0.7 g,); LC-MS: *m/z* 200.1 [M+H]⁺.

Step-v: Synthesis of 7-(((tert-butyldiphenylsilyl)oxy)methyl)-2H-pyrazolo[3,4-c]quinoline

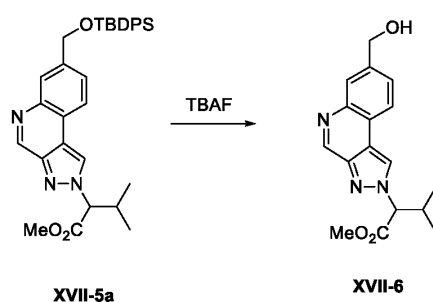
To a stirred solution of (2H-pyrazolo[3,4-c]quinolin-7-yl)methanol (0.70 g, 3.51 mmol, 1.0 equiv.) in DCM (10mL) was added imidazole (0.24 g, 68.08 mmol, 1.0 equiv) and TBDPS-Cl (0.97 g, 3.51 mmol, 1.0 equiv) at 0 °C. Reaction mixture was stirred at room temperature for 12 h. After completion of reaction, saturated aqueous NH₄Cl/H₂O was added to the reaction mixture and the aqueous phase was extracted with diethyl ether (3 200 mL), then the organic phase was washed with brine (2 *500 mL) before drying (Na₂SO₄) and

removal of solvent under reduced pressure. The crude product was purified by combi-flash column using 5% methanol in DCM provide titled compound (0.80 g, 52.02%), LC-MS: 438.2 [M+H]⁺

Step-vi: Synthesis of methyl 2-(7-(((tert-butyldiphenylsilyl)oxy)methyl)-2H-pyrazolo[3,4-c]quinolin-2-yl)-3-methylbutanoate (XVII-5a) and methyl 2-(7-(((tert-butyldiphenylsilyl)oxy)methyl)-3H-pyrazolo[3,4-c]quinolin-3-yl)-3-methylbutanoate (XVII-5b)

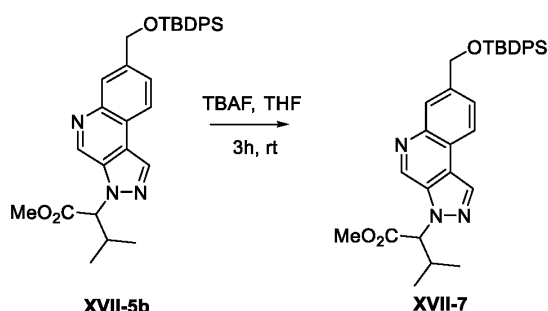
The procedure for the Step-vi was carried out similarly to the one described in the synthesis of **Intermediate XIII-1** obtain two regio-isomers **Intermediate XVII-5a** and **Intermediate XVII-5b**; LC-MS: *m/z* 566.25 [M+H]⁺.

Synthesis of methyl 2-(7-(hydroxymethyl)-2H-pyrazolo[3,4-c]quinolin-2-yl)-3-methylbutanoate (XVII-6)



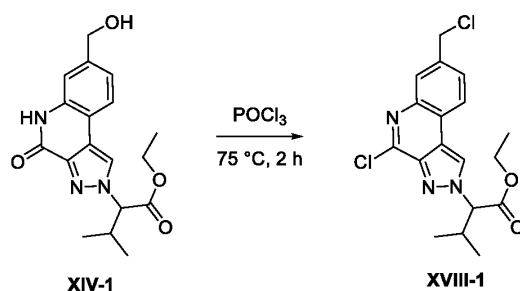
To a stirred solution of methyl 2-(7-(((tert-butyldiphenylsilyl)oxy)methyl)-2H-pyrazolo[3,4-c]quinolin-2-yl)-3-methylbutanoate (**XVII-5a**) (0.40 g, 0.7 mmol, 1.0 equiv.) in THF (10mL) was added TBAF (0.28 g, 1.1 mmol, 1.50equiv.) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 3 hours. After completion of reaction, the reaction mixture was poured into ice-cold water and extracted with DCM. Then the organic layer was separated, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford the crude product. The crude product was purified by combi-flash column using 5% methanol in DCM to provide titled compound (**XVII-6**) (0.23 g, 99.18%), LC-MS: 329.1 [M+H]⁺.

Synthesis of methyl 2-(7-(hydroxymethyl)-3H-pyrazolo[3,4-c]quinolin-3-yl)-3-methylbutanoate(XVII-7):



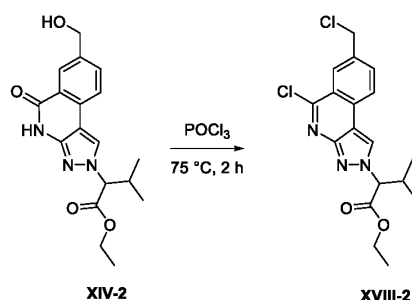
The above **Intermediate XVII-7** synthesis carried out by a procedure similar to the one described in the synthesis of **Intermediate XVII-6**; LC-MS: 329.1 [M+H]⁺.

Synthesis of ethyl 2-(4-chloro-7-(chloromethyl)-2H-pyrazolo[3,4-c]quinolin-2-yl)-3-methylbutanoate (XVIII-1):



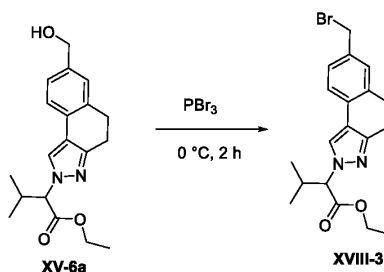
Ethyl 2-(7-(hydroxymethyl)-4-oxo-4,5-dihydro-2H-pyrazolo[3,4-c]quinolin-2-yl)-3-methylbutanoate (**XIV-1**) (0.45 g, 1.31 mmol) in POCl₃ (10 mL) was heated to 75 °C for 2 h. After completion of the reaction, the reaction mixture was allowed to cool to room temperature and was quenched with ice-cold water carefully, neutralized with sodium bicarbonate saturated solution, and extracted with ethyl acetate (15 mLx3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give the crude product. The crude product was purified by combi flash, eluting with 30% ethyl acetate in hexane to get title compound as off-white sticky solid **XVIII-1** (0.34 g, 68%); ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.7 (s, 1H), 8.09- 8.07 (m, 2H), 7.67 (dd, *J* = 8.0, 1.6 Hz, 1H), 5.17 (d, *J* = 9.6 Hz, 1H), 4.79 (s, 2H), 4.40- 4.25 (m, 2H), 2.70- 2.64 (m, 1H), 1.35 (t, *J* = 6.8 Hz, 3H), 1.15 (d, *J* = 6.8 Hz, 3H), 0.90 (dd, *J* = 4.4 Hz, 2.8 Hz, 3H); LC-MS: *m/z* 379.95 [M]⁺.

Synthesis of ethyl 2-(5-chloro-7-(chloromethyl)-2H-pyrazolo[3,4-c]isoquinolin-2-yl)-3-methylbutanoate (XVIII-2):



The above **Intermediate XVIII-2** was prepared by a procedure similar to the one described in the synthesis of **Intermediate XVIII-1** using phosphorous oxychloride as a reagent; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.08 (s, 1H), 8.46-8.43 (m, 2H), 8.02 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 5.18 (d, *J* = 8.8 Hz, 1H), 5.06 (s, 2H), 4.23- 4.14 (m, 2H), 2.71- 2.68 (m, 1H), 1.19 (t, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H); LC-MS: *m/z* 380.1 [M+H]⁺.

Synthesis of ethyl 2-(7-(bromomethyl)-4,5-dihydro-2H-benzo[e]indazol-2-yl)-3-methylbutanoate (XVIII-3):

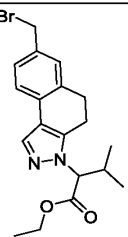
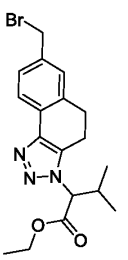
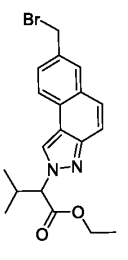


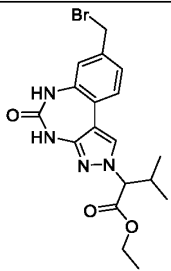
To a stirred solution of ethyl 2-(7-(hydroxymethyl)-4,5-dihydro-2H-benzo[e]indazol-2-yl)-3-methylbutanoate (**XV-6a**) (0.375 g, 1.141 mmol, 1.0 equiv.) in THF (25mL) was added phosphorus tribromide (0.371 g, 1.370 mmol, 1.2 equiv.) at 0°C. The reaction mixture was stirred at 0°C for 2 hours. After completion of reaction, the reaction mixture was concentrated under vacuum, cooled to 0 °C, neutralized with triethyl amine, and concentrated again under vacuum. The crude product was purified by flash column using 50% ethyl acetate in hexane to get titled compound (0.31 g; yield 83%) as colorless liquid (**XVIII-3**). The resulting product was directly taken into the next reaction, as the bromo compound is not stable.

The intermediates **XVIII-4** to **XVIII-8** listed in below **Table-7** were prepared by a procedure similar to the one described in the synthesis of **Intermediate XVIII-3** with appropriate starting material (SM) and appropriate variations to get the corresponding bromo product. The characterization data of the intermediates are summarized in Table-7.

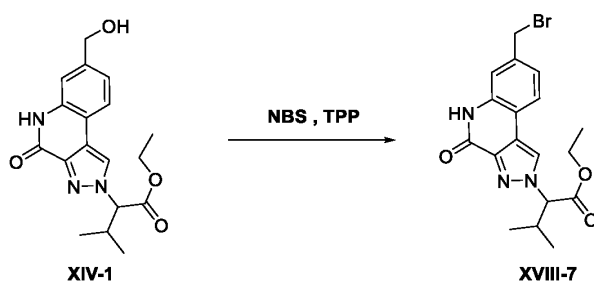
5

Table-7

Int-No	SM	Int. Structure	Analytical Data
XVIII-4	XV-6b		LC-MS: m/z 392.05[M+H] ⁺ .
XVIII-5	XVI-5		¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 7.72 (d, <i>J</i> = 8.4 Hz, 1H), 7.45- 7.35 (m, 2H), 5.22 (d, <i>J</i> = 8.8 Hz, 1H), 4.72 (s, 2H), 4.23- 4.16 (m, 2H), 3.10- 2.90 (m, 4H), 2.72- 2.65 (m, 1H), 1.18 (t, <i>J</i> = 6.8 Hz, 3H), 1.04 (d, <i>J</i> = 6.8 Hz, 3H), 0.85 (d, <i>J</i> = 6.4 Hz, 3H); LC-MS: m/z 394.1 [M++H] ⁺ .
XVIII-6	XVII-2		¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 9.00 (s, 1H), 8.28 (d, <i>J</i> = 8.4 Hz, 1H), 7.98 (dd, <i>J</i> = 1.6 Hz, 2H), 7.69- 7.63 (m, 2H), 5.1 (d, <i>J</i> = 9.6 Hz, 1H), 4.90 (s, 2H), 4.22- 4.15 (m, 1H), 2.80- 2.70 (m, 1H), 1.18 (t, <i>J</i> = 7.2 Hz, 3H), 1.05 (d, <i>J</i> = 6.4 Hz, 3H), 0.79 (d, <i>J</i> = 6.8 Hz, 3H); LC-MS: m/z 390.1 [M+H] ⁺ .

XVIII-8	XVII-4		LC-MS: m/z 422.1 $[M+H]^+$.
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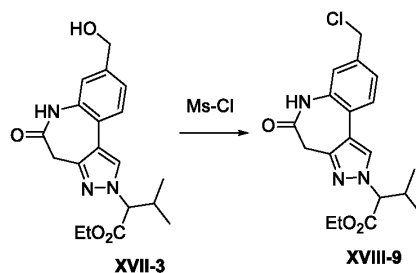
Synthesis of ethyl 2-(7-(bromomethyl)-4-oxo-4,5-dihydro-2H-pyrazolo[3,4-c]quinolin-2-yl)-3-methylbutanoate (XVIII-7):



5 To a stirred solution of ethyl 2-(7-(hydroxymethyl)-4-oxo-4,5-dihydro-2H-pyrazolo[3,4-c]quinolin-2-yl)-3-methylbutanoate (**XIV-1**) (10 g, 29.12 mmol, 1.0 equiv.) in DCM (25mL) was added N-bromo succinimide (7.7 g, 43.68 mmol, 1.5 equiv.) at 0 °C and triphenyl phosphine (11.4 g, 43.68 mmol, 1.5 eq) . The reaction mixture was stirred at 0 °C for 2 hours. After completion of reaction, the reaction mixture was concentrated under vacuum,

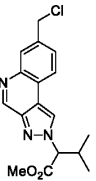
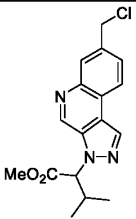
10 cooled to 0 °C, neutralized with triethyl amine, and concentrated again under vacuum. The crude product was purified by flash column using 50% ethyl acetate in hexane to get titled compound (0.31 g; yield 83%) as colorless liquid (**XVIII-7**). The resulting product was directly taken into the next reaction.

Synthesis of ethyl 2-(8-(hydroxymethyl)-5-oxo-5,6-dihydrobenzo[b]pyrazolo[4,3-d]azepin-2(4H)-yl)-3-methylbutanoate (XVIII-9):



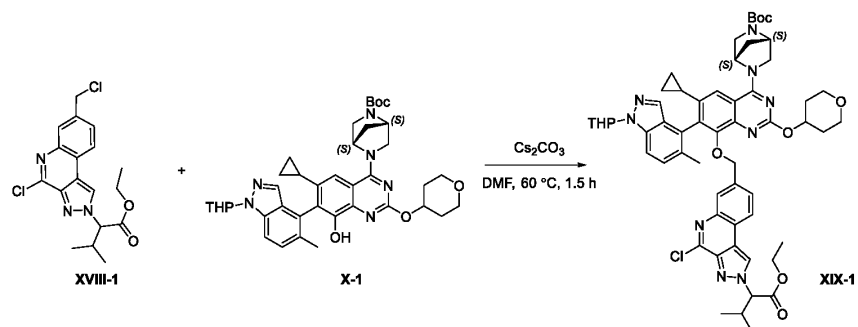
- To a solution of ethyl 2-(8-(hydroxymethyl)-5-oxo-5,6-dihydrobenzo[b]pyrazolo[4,3-d]azepin-2(4H)-yl)-3-methylbutanoate **XVII-3** (0.16 g, 0.49 mmol, 1.0 equiv.) in DCM (5mL) was added triethylamine (0.14 g, 1.34 mmol, 3.0 equiv.) at 20° C. Methanesulfonyl chloride (0.11 g, 0.94 mmol 2.1 equiv) was added dropwise at 0° C.
- 5 The reaction mixture was stirred at 20 °C. for 16 hours. TLC showed the reaction was completed. The reaction mixture was quenched with water and extracted with DCM. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by combi-flash column using 60% ethyl acetate in hexane to provide desired product **XVIII-9** (0.2 g), LC-MS: 376.10 [M+H]⁺.
- 10 The intermediates listed below in **Table-8** were prepared by a procedure similar to the one described in the synthesis of **Intermediate XVIII-9** with appropriate starting material (SM) and appropriate variations to get the corresponding choro product. The characterization data of the intermediates are summarized in Table-8.

Table-8

Int-No	SM	Int. Structure	Analytical Data
XVIII-10	XVII-6		LC-MS: <i>m/z</i> : 376.10 [M+H] ⁺ .
XVIII-11	XVII-7		LC-MS: <i>m/z</i> : 376.10 [M+H] ⁺ .

15

Synthesis of *tert*-butyl (1*S*,4*S*)-5-(8-((4-chloro-2-(1-ethoxy-3-methyl-1-oxobutan-2-yl)-2H-pyrazolo[3,4-*c*]quinolin-7-yl)methoxy)-6-cyclopropyl-7-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-2-((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**XIX-1**):



5

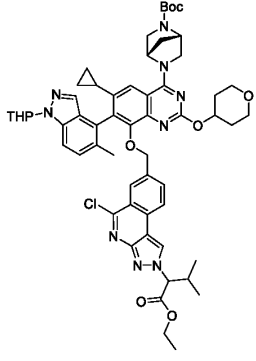
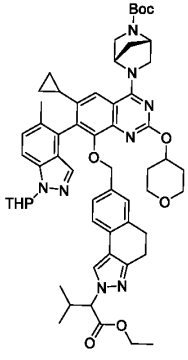
To a stirred solution of ethyl 2-(4-chloro-7-(hydroxymethyl)-2H-pyrazolo[3,4-*c*]147uinoline-2-yl)-3-methylbutanoate (**XVIII-1**) (0.33 g, 0.86 mmol) and compound (**X-1**) (0.60 g, 0.86 mmol) in DMF (10 mL) was added cesium carbonate (0.84 g, 2.58 mmol), and the resulting reaction mixture was heated to 60 °C for 1.5 h. After completion of the reaction, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (15 mLx3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give the crude product. The crude product was purified by Combi flash, eluting with 7% MeOH in DCM to get title compound as off-white sticky solid **XIX-1** (0.60 g, 67%); ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.18 (d, *J* = 2.8 Hz, 1H), 8.08- 8.04 (m, 1H), 7.67 (dd, *J* = 25.2, 8.4 Hz, 1H), 7.52- 7.39 (m, 4H), 7.21- 7.15 (m, 1H), 7.05- 6.93 (m, 1H), 5.85 5.70 (m, 1H), 5.50- 5.4 (m, 1H), 5.32 (d, *J* = 8.8 Hz, 1H), 5.30- 5.20 (m, 2H), 5.20- 5.19 (m, 1H), 4.54 (d, *J* = 23.6 Hz, 1H), 4.36- 4.15 (m, 3H), 3.17- 3.72 (m, 8H), 3.51 (s, 2H), 3.30- 3.26 (m, 3H), 2.74- 2.67 (m, 2H), 2.16 (s, 3H), 2.09- 1.95 (m, 5H), 1.75- 1.65 (m, 6H), 1.45- 1.37 (m, 9H), 1.27- 1.16 (m, 3H), 1.07- 1.05 (m, 3H), 0.87- 0.81 (m, 3H); LC-MS: *m/z* 1040.5 [M+H]⁺.

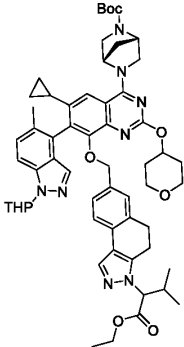
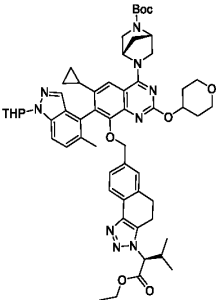
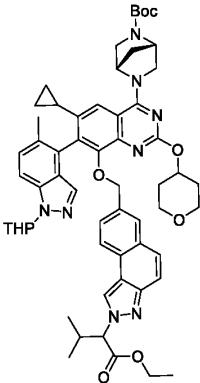
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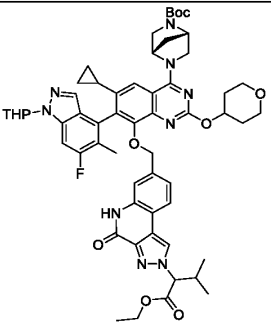
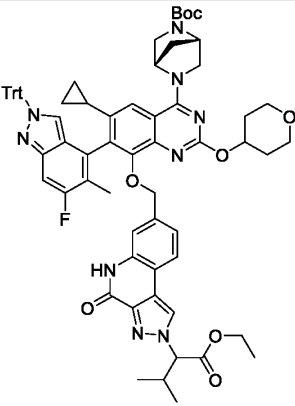
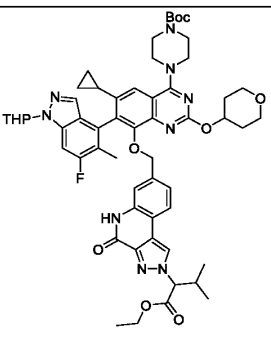
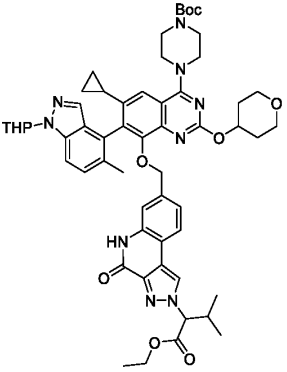
The intermediates **XIX-2 to XIX-40** listed below in **Table-9** were prepared by procedures similar to the one described in the synthesis of **Intermediate XIX-1** with appropriate benzyl halide (SM-1) and hydroxy quinazoline (SM-2) with appropriate variations. The characterization data of the intermediates are summarized in Table-9.

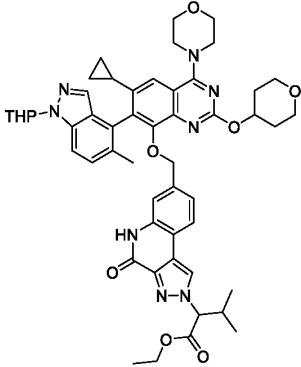
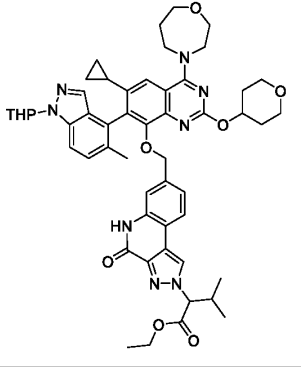
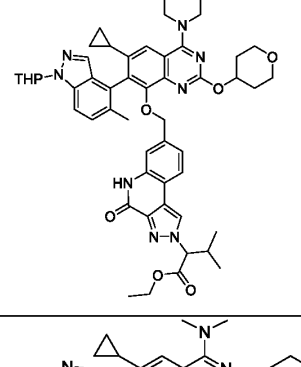
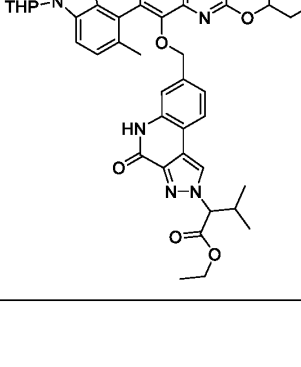
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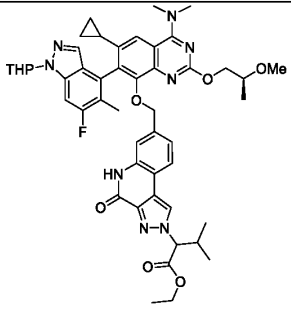
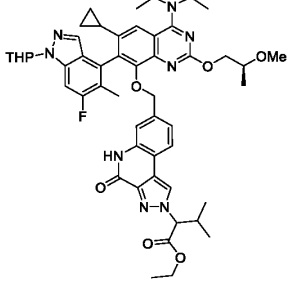
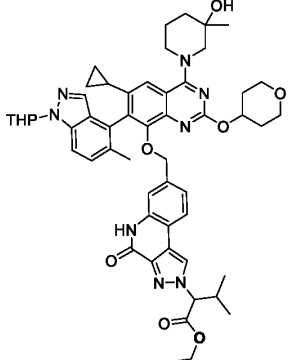
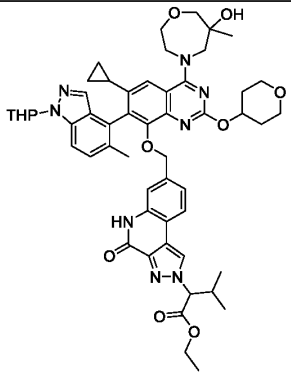
Table-9

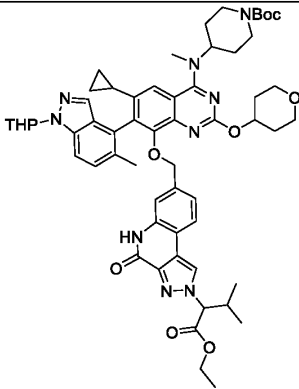
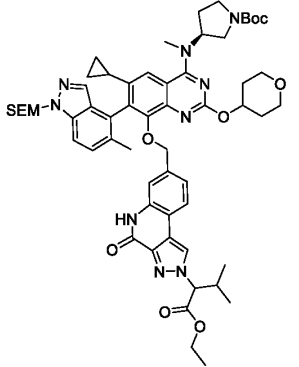
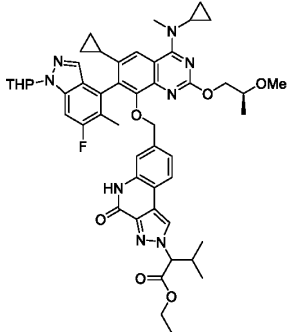
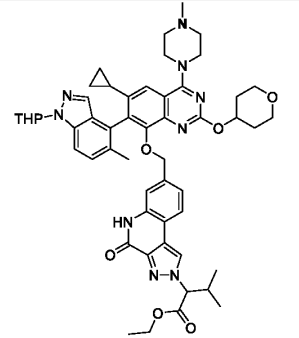
Int-No	Benzyl halide SM-1	Hydroxy Quinazoline SM-2	Intermediate Structure	Analytical Data
XIX-2	XVIII-2	X-I		LC-MS: m/z 1040.90 [M+H] ⁺ .
XIX-3	XVIII-3	X-I		¹ H NMR (400 MHz, DMSO-d ₆): δ 8.10 (q, J = 2.0 Hz, 1H), 7.72-7.69 (m, 1H), 7.51- 7.37 (m, 3H), 7.37- 7.22 (m, 1H), 6.70- 6.50 (m, 1H), 6.40- 6.28 (m, 1H), 5.92- 5.80 (m, 1H), 5.30- 5.10 (m, 4H), 5.12- 4.99 (m, 1H), 4.90- 4.70 (m, 1H), 4.70- 4.50 (m, 3H), 4.40- 4.30 (m, 1H), 4.2- 4.10 (m, 3H), 3.90- 3.80 (m, 4H), 3.80- 3.70 (m, 3H), 3.60- 3.50 (m, 3H), 3.45- 3.35 (m, 3H), 2.75- 2.65 (m, 4H), 2.45- 2.35 (m, 1H), 2.15- 2.10 (m, 4H), 2.10- 1.95 (m, 3H),

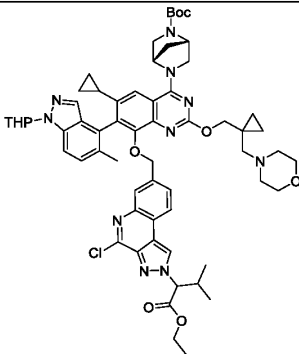
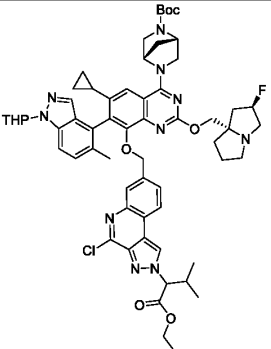
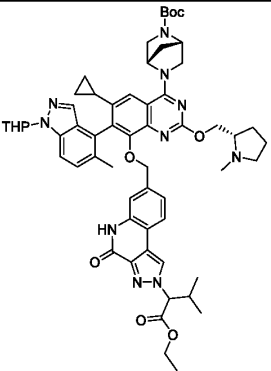
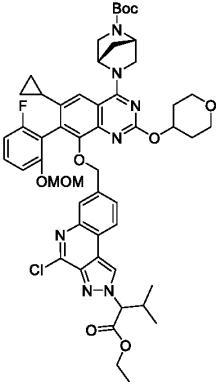
				1.95- 1.85 (m, 2H), 1.80- 1.60 (m, 3H), 1.60- 1.45 (m, 3H), 1.45- 1.25 (m, 9H), 1.24- 1.16 (m, 3H), 0.80- 0.78 (m, 3H); LC- MS: m/z 1008.5 [M+H] +.
XIX-4	XVIII-4	X-I		LC-MS: m/z 1008.5 [M+H] ⁺ .
XIX-5	XVIII-5	X-I		LC-MS: m/z 1009.5 [M+H] ⁺ .
XIX-6	XVIII-6	X-I		LC-MS: m/z 1006.1 [M+H] ⁺ .

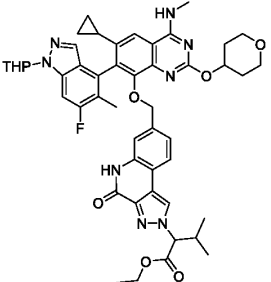
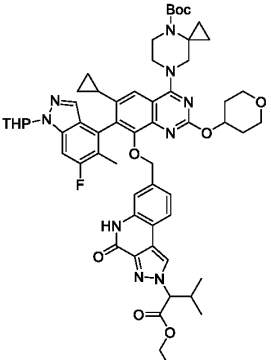
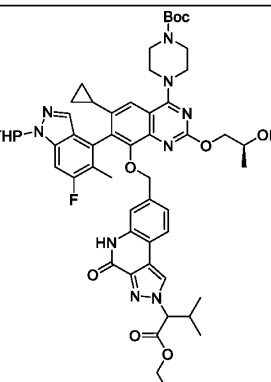
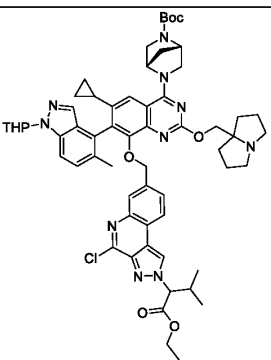
XIX-7	XVIII-7	X-2		LC-MS: m/z 1040.4 [M+H] ⁺ .
XIX-8	XVIII-7	X-3a		LC-MS: m/z 1197.70[M-H] ⁺
XIX-9	XVIII-7	X-4		LC-MS: m/z 1028.20[M+H] ⁺
XIX-10	XVIII-7	X-5		LC-MS: m/z 1010.30 [M+H] ⁺

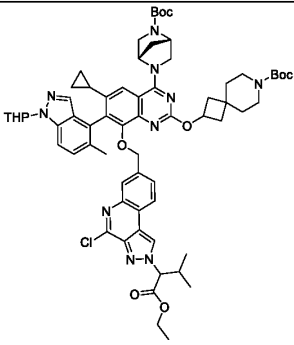
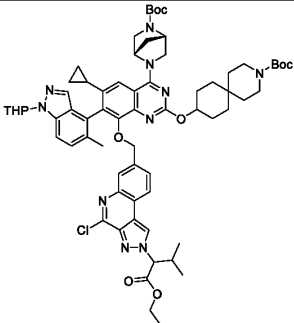
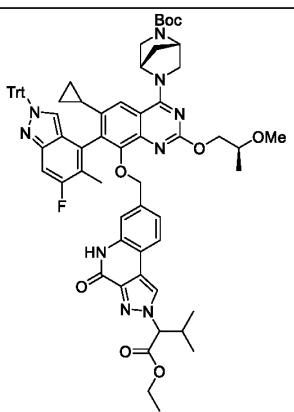
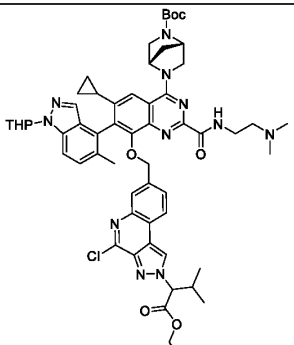
XIX-11	XVIII-7	X-6		LC-MS: m/z 911.0[M+H] ⁺
XIX-12	XVIII-7	X-7		LC-MS: m/z 925.35[M+H] ⁺
XIX-13	XVIII-7	X-8		LC-MS: m/z 909.20[M+H] ⁺
XIX-14	XVIII-7	X-9		LC-MS: m/z 869.4[M+H] ⁺

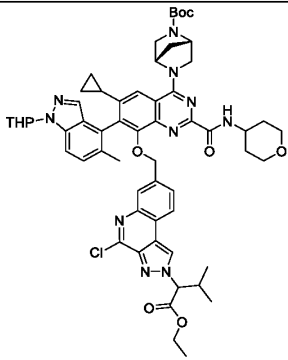
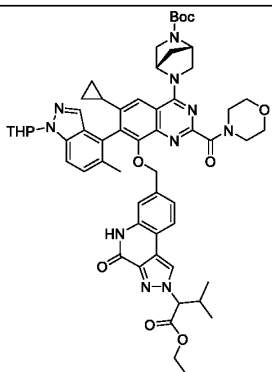
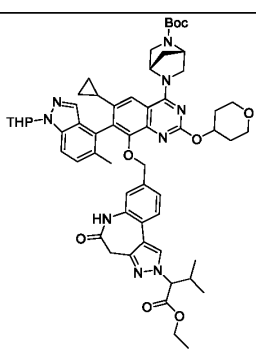
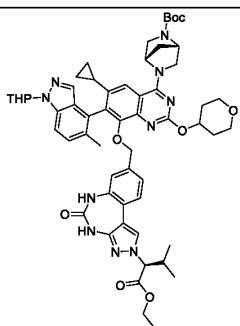
XIX-15	XVIII-7	X-10	 Chemical structure of compound X-10: A complex molecule featuring a central benzene ring substituted with a THP-protected indazole, a fluorine atom, and a methoxy group. It is linked via an ether bridge to another benzene ring, which is further substituted with a pyrazole ring and a carboxylate group. The pyrazole ring is also substituted with a methoxy group and a methyl group.	LC-MS: m/z 875.4[M+H] ⁺
XIX-16	XVIII-7	X-11	 Chemical structure of compound X-11: Similar to X-10, but with a different substitution pattern on the pyrazole ring, specifically a methyl group instead of a methoxy group.	LC-MS: m/z 903.45 [M+H] ⁺
XIX-17	XVIII-7	X-12	 Chemical structure of compound X-12: Similar to X-10, but with a different substitution pattern on the pyrazole ring, specifically a methyl group instead of a methoxy group, and a different ether bridge.	LC-MS: m/z 937[M+H] ⁺
XIX-18	XVIII-7	X-13	 Chemical structure of compound X-13: Similar to X-10, but with a different substitution pattern on the pyrazole ring, specifically a methyl group instead of a methoxy group, and a different ether bridge.	LC-MS: m/z 955.45 (M+H) ⁺ .

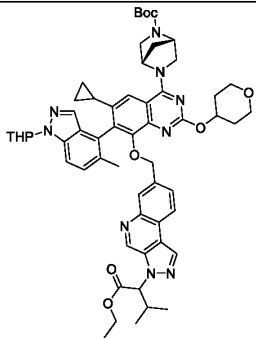
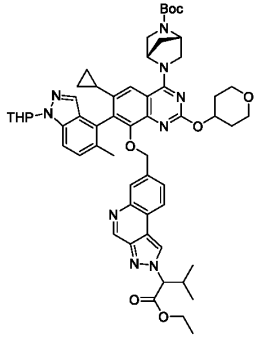
XIX-19	XVIII-7	X-14		LC-MS: m/z 1038.45[M+H] ⁺
XIX-20	XVIII-7	X-15		LC-MS: m/z 1070.8[M+H] ⁺
XIX-21	XVIII-7	X-16		LC-MS: m/z 901.3[M+H] ⁺
XIX-22	XVIII-7	X-17		LC-MS: m/z 924.2[M+H] ⁺

XIX-23	XVIII-1	X-18		LC-MS: m/z 1109.60[M+H] ⁺
XIX-24	XVIII-1	X-19		LC-MS: m/z 1096.45 [M-H] ⁺
XIX-25	XVIII-7	X-20		LC-MS: m/z 1035.45 [M+H] ⁺
XIX-26	XVIII-1	X-21		LC-MS: m/z 980.35 [M+H] ⁺

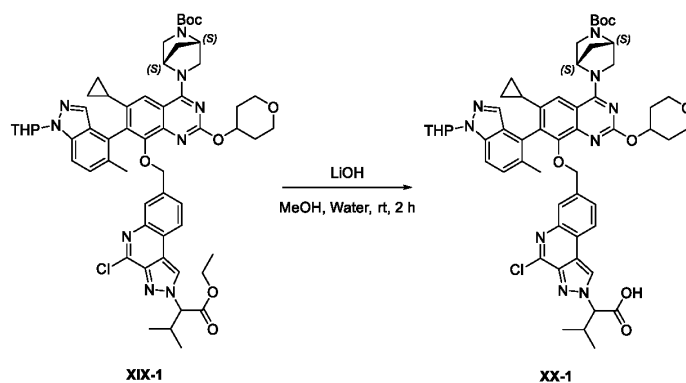
XIX-27	XVIII-7	X-22		LC-MS: m/z 873.00[M+H] ⁺
XIX-28	XVIII-7	X-23		LC-MS: m/z 1054.35[M+H] ⁺
XIX-29	XVIII-7	X-24		LC-MS: m/z 1016.20[M+H] ⁺
XIX-30	XVIII-1	X-25		LC-MS: m/z 1079.50 [M+H] ⁺

XIX-31	XVIII-1	X-26		LC-MS: m/z 1179.7 [M+H] ⁺
XIX-32	XVIII-1	X-27		LC-MS: m/z 1207.60 [M+H] ⁺
XIX-33	XVIII-7	X-28		LC-MS: m/z 1186.50[M+H] ⁺
XIX-34	XVIII-1	X-29		LC-MS: m/z 1055.7 [M+H] ⁺

XIX-35	XVIII-1	X-30		LC-MS: m/z 1067.40[M+H] ⁺
XIX-36	XVIII-7	X-31		LC-MS: m/z 1035.4[M+H] ⁺
XIX-37	XVIII-9	X-I		LC-MS: m/z 1036.40 [M+H] ⁺
XIX-38	XVIII-8	X-I		LC-MS: m/z 1038.7 [M+H] ⁺

XIX-39	XVIII-11	X-I		LC-MS: m/z 1007.7 [M+H] ⁺
XIX-40	XVIII-10	X-I		LC-MS: m/z 1007.7 [M+H] ⁺

Synthesis of 2-(7-(((4-((1*S*,4*S*)-5-(*tert*-butoxycarbonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-6-cyclopropyl-7-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-2-(((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-8-yl)oxy)methyl)-4-chloro-2H-pyrazolo[3,4-
5 c]quinolin-2-yl)-3-methylbutanoic acid (XX-1):

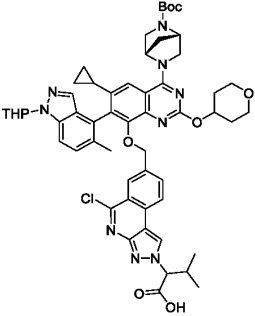
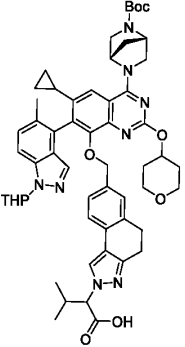


To a solution of ester (**XIX-1**) (0.60 g, 0.58 mmol) in methanol and water (5:2) mixture (7 mL) was added LiOH (0.07 g, 2.8 mmol), and the mixture was stirred for 3 h at rt. After completion of the reaction, the solvent was distilled off, and the crude mixture was acidified with 1N HCl and extracted with ethyl acetate (3x15 mL). The combined organic layers were
10 dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a light

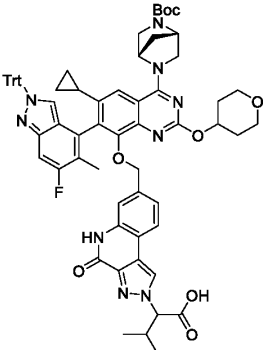
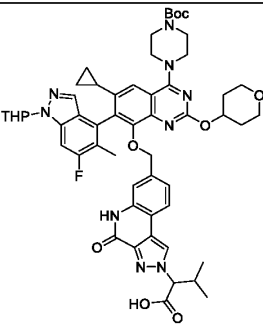
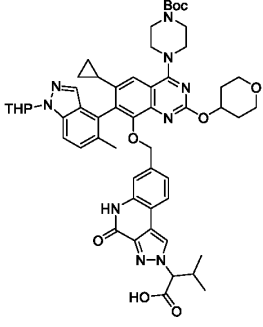
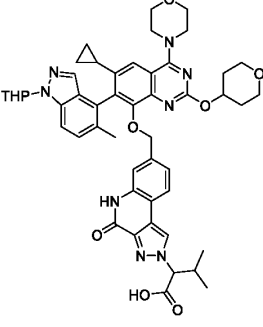
brown sticky solid (**XX-1**) (0.55 g, crude); ^1H NMR (400 MHz, DMSO- d_6): δ 13.60-13.40 (bs, 1H), 9.15 (d, $J = 3.2$ Hz, 1H), 8.06 (t, $J = 8.4$ Hz, 1H), 7.62 (dd, $J = 27.2, 8.4$ Hz, 2H), 7.51-7.39 (m, 4H), 7.21- 7.03 (m, 1H), 7.01- 6.92 (m, 1H), 5.90- 5.70 (m, 1H), 5.20 (d, $J = 8.8$ Hz, 4H), 5.10- 5.00 (m, 1H), 4.65- 4.30 (m, 3H), 3.82- 3.51 (m, 6H), 3.50 (s, 2H), 3.32- 3.20 (bs, 2H), 2.75- 2.65 (m, 1H), 2.15 (s, 3H), 2.10- 1.91 (m, 6H), 1.78- 1.50 (m, 6H), 1.45- 1.35 (bs, 9H), 1.07 (dd, $J = 6.8$ Hz, 2.0 Hz, 3H), 0.65- 0.70 (bs, 4H); LC-MS: m/z 1012.45 $[\text{M}]^+$.

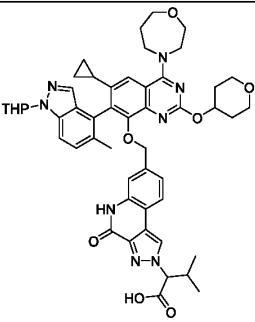
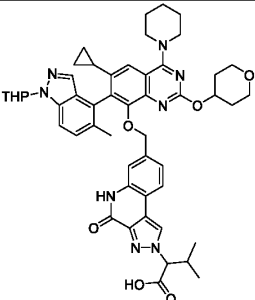
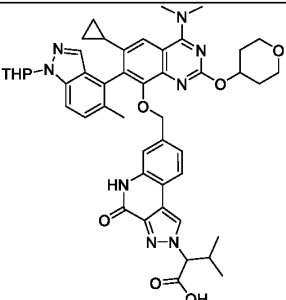
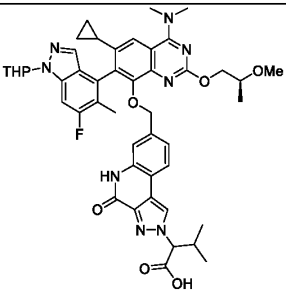
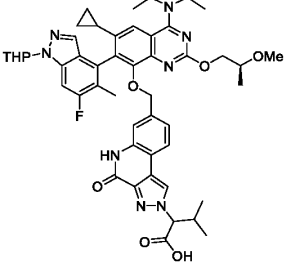
The intermediates **XX-2 to XX-40** listed in below **Table-10** were prepared by a procedure similar to the one described in the synthesis of **Intermediate XX-1** with appropriate ester (SM) compound and appropriate variations to get corresponding hydrolyzed product. The characterization data of the intermediates are summarized in Table-10.

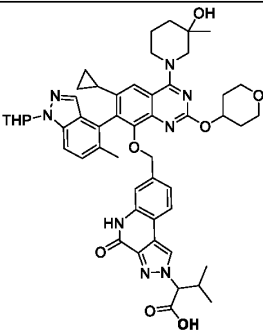
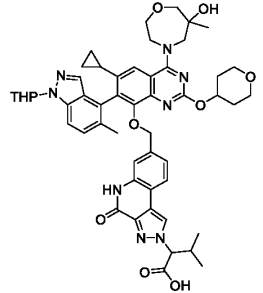
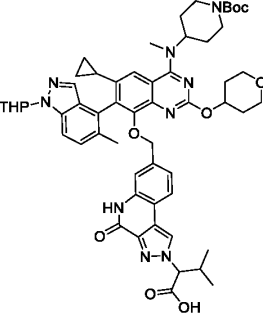
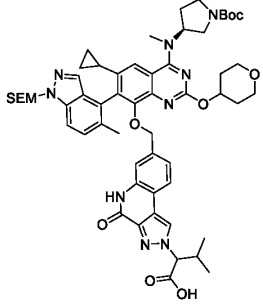
Table-10

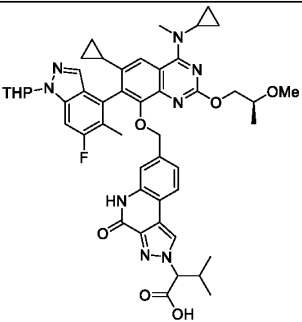
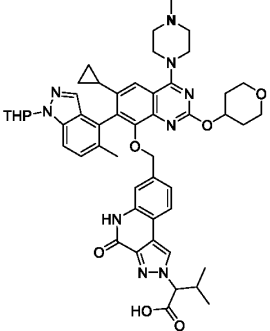
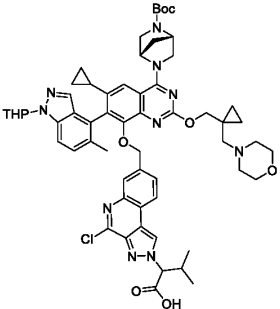
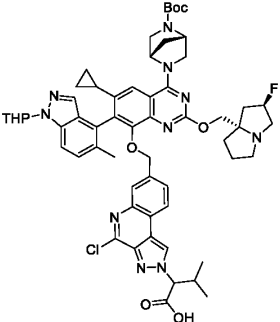
Int-No	Ester (SM)	Intermediate Structure	Analytical Data
XX-2	XIX-2		LC-MS: m/z 1013.60 $[\text{M}+\text{H}]^+$.
XX-3	XIX-3		LC-MS: m/z 980.3 $[\text{M}+\text{H}]^+$.

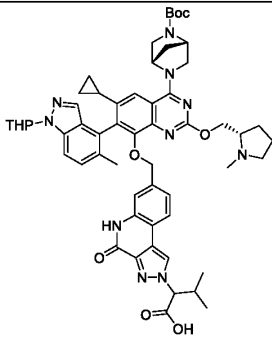
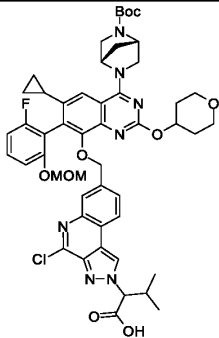
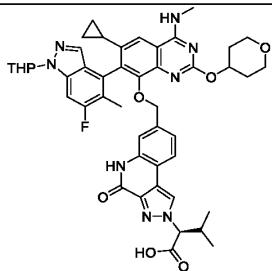
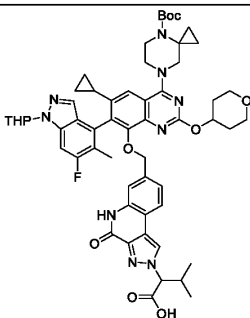
XX-4	XIX-4		LC-MS: m/z 980.3 [M+H] ⁺
XX-5	XIX-5		LC-MS: m/z 981.4 [M+H] ⁺
XX-6	XIX-6		LC-MS: m/z 978.0 [M+H] ⁺
XX-7	XIX-7		LC-MS: m/z 1012.0 [M+H] ⁺

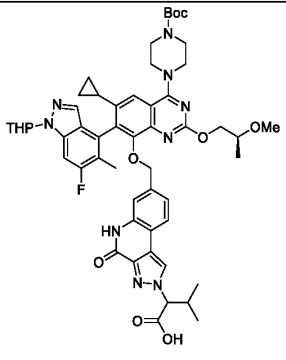
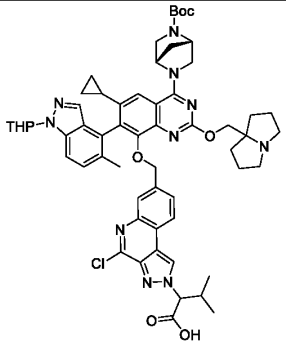
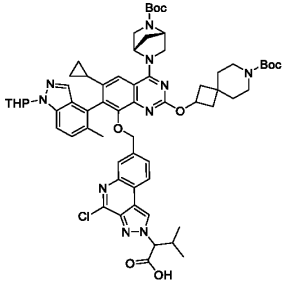
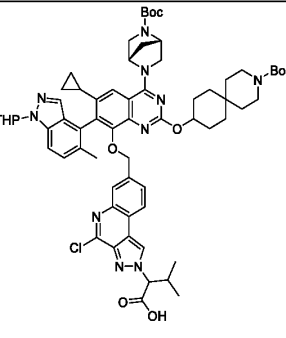
XX-8	XIX-8		LC-MS: m/z 1070.50 [M+H] ⁺
XX-9	XIX-9		LC-MS: m/z 1000.70 [M+H] ⁺
XX-10	XIX-10		LC-MS: m/z 982.35 [M+H] ⁺
XX-11	XIX-11		LC-MS: m/z 833.00 [M+H] ⁺

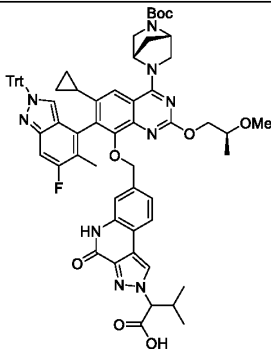
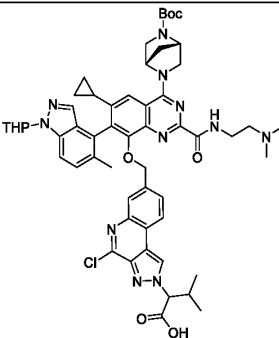
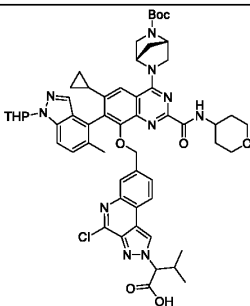
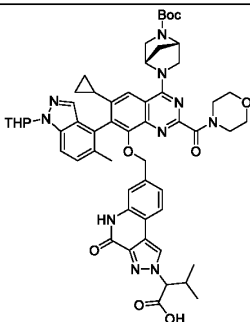
XX-12	XIX-12		LC-MS: m/z 897.50 [M+H] ⁺
XX-13	XIX-13		LC-MS: m/z 881.25 [M+H] ⁺
XX-14	XIX-14		LC-MS: m/z 841[M+H] ⁺
XX-15	XIX-15		LC-MS: m/z 846.2[M+H] ⁺
XX-16	XIX-16		LC-MS: m/z 875.40 [M+H] ⁺

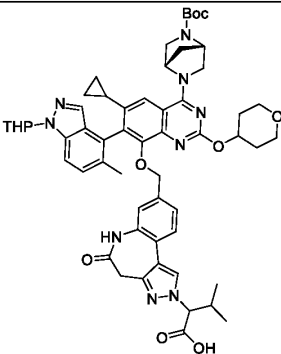
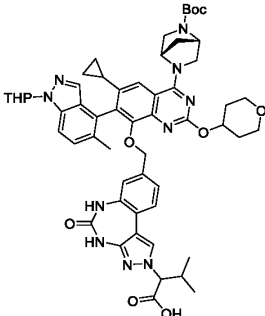
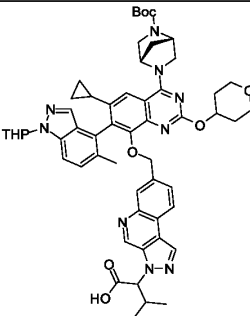
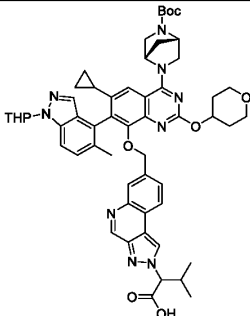
XX-17	XIX-17		LC-MS: m/z 912.0[M+H] ⁺
XX-18	XIX-18		LC-MS: m/z 927.15 (M+H) ⁺ .
XX-19	XIX-19		LC-MS: m/z 1010.15[M+H] ⁺
XX-20	XIX-20		LC-MS: m/z 1042.50[M+H] ⁺

XX-21	XIX-21		LC-MS: m/z 874.4[M+H] ⁺
XX-22	XIX-22		LC-MS: m/z 896.2[M+H] ⁺
XX-23	XIX-23		LC-MS: m/z 1079.50 [M-H] ⁺
XX-24	XIX-24		LC-MS: m/z 1069.45 [M+H] ⁺

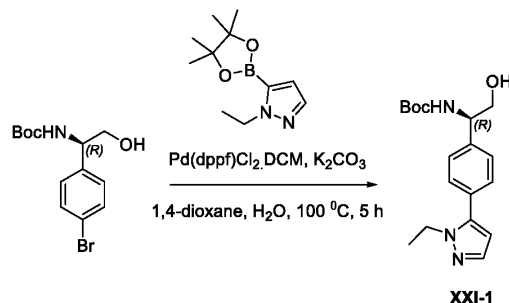
XX-25	XIX-25		LC-MS: m/z 1008.6 [M+H] ⁺
XX-26	XIX-26		LC-MS: m/z 952.30 [M+H] ⁺
XX-27	XIX-27		LC-MS: m/z 844.80 [M+H] ⁺
XX-28	XIX-28		LC-MS: m/z 1026.45 [M+H] ⁺

XX-29	XIX-29		LC-MS: m/z 988.20[M+H] ⁺
XX-30	XIX-30		LC-MS: m/z 1051.45 [M+H] ⁺
XX-31	XIX-31		LC-MS: m/z 1151.45 [M+H] ⁺
XX-32	XIX-32		LC-MS: m/z 1179.55 M+H] ⁺

XX-33	XIX-33		LC-MS: m/z 1158.3214[M+H] ⁺
XX-34	XIX-34		LC-MS: m/z 1026.35 [M+H] ⁺
XX-35	XIX-35		LC-MS: m/z 1039.65[M+H] ⁺
XX-36	XIX-36		LC-MS: m/z 1008.6[M+H] ⁺

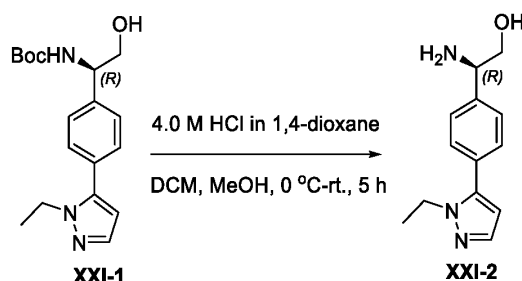
XX-37	XIX-37		LC-MS: m/z 1008.60 [M+H] ⁺
XX-38	XIX-38		LC-MS: m/z 1010.6 [M+H] ⁺
XX-39	XIX-39		LC-MS: m/z 981.6 [M+H] ⁺
XX-40	XIX-40		LC-MS: m/z 981.6 [M+H] ⁺

Synthesis of tert-butyl (R)-(1-(4-(1-ethyl-1H-pyrazol-5-yl)phenyl)-2-hydroxyethyl)carbamate (XXI-1):



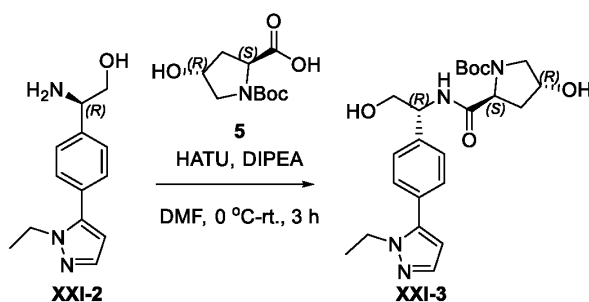
To a stirred solution of tert-butyl (R)-(1-(4-bromophenyl)-2-hydroxyethyl)carbamate (10.0 g, 31.63 mmol, 1.0 equiv.) and 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (8.43 g, 37.951 mmol, 1.2 equiv.) in 1, 4-dioxane (80.0 mL) and water (8.0 mL), was added potassium carbonate (13.11g, 94.87 mmol, 1.0 equiv.), and the mixture was purged with argon gas for 15 mins. Then Pd(dppf)Cl₂·DCM (2.61 g 3.190 mmol, 0.1 equiv.) was added, and the mixture was degassed again (5 min) and stirred at 100 °C for 5 h. After completion of reaction, the reaction mixture was cooled to RT, filtered through Celite[®] bed, and washed with EtOAc (2x30 mL). The filtrate was concentrated under reduced pressure, diluted with water (50 mL), and extracted with EtOAc (3x50 mL). The organic layers were collected, washed with brine (30 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to get the crude product which was purified by column chromatography (silica gel, 230-400 mesh, 50% EtOAc in hexane) to get the pure compound **XXI-1** (9.0 g; yield 86%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.29(d, *J* = 8.4 Hz, 1H), 7.41(s, 4H), 7.49 (s, 1H), 6.32(d, *J* = 1.6 Hz, 1H), 4.834 (t, *J* = 6.0 Hz, 1H), 4.60 - 4.58(m, 1H), 4.11(q, *J* = 7.2 Hz, 2H), 3.53 (t, *J* = 6.4 Hz, 2H), 1.38 (s, 9H), 1.293 (t, *J* = 7.2 Hz, 3H); LC-MS: *m/z* 332.2 [M+H]⁺.

Synthesis of (R)-2-amino-2-(4-(1-ethyl-1H-pyrazol-5-yl)phenyl)ethan-1-ol (XXI-2):



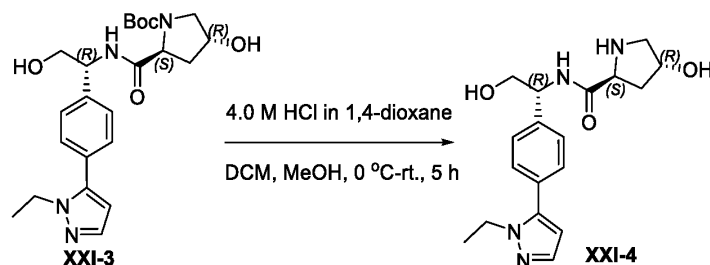
To a stirred solution of XXI-1 (8.5 g, 25.65 mmol, 1.0 equiv.) in DCM (15.0 mL) and MeOH (15 mL) at 0 °C was added 4.0 M HCl in 1,4- dioxane (25 mL), and the resulting mixture was stirred at rt for 5 h. The reaction mixture was concentrated directly under reduced pressure to get the crude product. Residual acid was stripped off by the addition of diethyl ether (2x10 mL), and the mixture was dried and concentrated to get the crude compound **XXI-2** (9.5 g) which was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.71 (s, 2H), 7.66(d, *J* = 8.4 Hz, 2H), 7.54-7.51(m, 3H), 6.38(s,1H), 4.36 -4.32(m, 1H), 4.14(q, *J* = 7.2 Hz, 2H), 3.78(d, *J* = 5.6 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H); LC-MS: *m/z* 232.1 [M+H]⁺

Step 3: Synthesis of tert-butyl (2*S*,4*R*)-2-((*R*)-1-(4-(1-ethyl-1*H*-pyrazol-5-yl)phenyl)-2-hydroxyethyl)carbamoyl)-4-hydroxypyrrolidine-1-carboxylate (XXI-3):



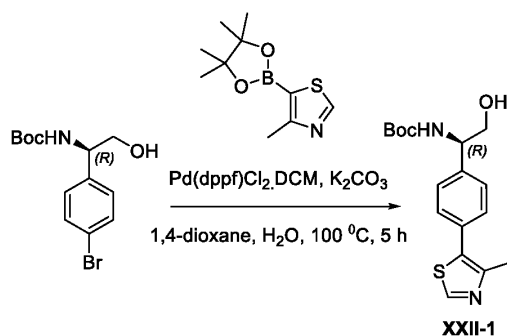
To a stirred solution of **XXI-2** (7.5 g, 28.01 mmol, 1.0 equiv.) in DMF (80 mL), diisopropylethylamine (7.24 g, 56.02 mmol, 2.0 equiv.) was added at 0 °C, and the reaction mixture was stirred for 30 mins at rt. Then (2*S*,4*R*)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (6.48 g, 28.01mmol, 1.0 equiv.) followed by HATU (9.88g, 42.01 mmol, 1.5 equiv.) were added to the reaction mixture, and the contents of the vessel were stirred for 3 h. After completion of reaction, the reaction mixture was quenched with ice-cold water (50 mL) and extracted with DCM (2x100 mL). The organic layers were collected washed with brine (50 mL), dried over anhydrous. sodium sulphate, filtered, and concentrated under reduced pressure to get the crude product which was purified by column chromatography (silica gel, 230-400 mesh, 5% MeOH in DCM) to get the pure compound **XXI-3** (9.5 g; yield 76%). ¹H NMR (400 MHz, DMSO-*d*₆): 8.29 - 8.25 (m, 1H), 7.49(d, *J* = 1.6 Hz, 1H), 7.44 -7.37(m, 4H), 6.31(d, *J* = 2.0 Hz, 1H), 4.99 - 4.98 (m, 1H), 4.90 - 4.86(m, 2H), 4.26 - 4.21 (m, 2H), 4.14 -4.08 (m, 2H), 3.65 -3.61 (m, 3H), 3.37- 3.34 (m, 1H), 3.33- 3.30 (m, 1H), 3.27 -3.09 (m, 1H), 2.05 – 2.15(m, 1H), 1.78 -1.85 (m, 1H), 1.26(s, 9H); LC-MS: *m/z* 445.3 [M+H]⁺

Synthesis of (2*S*,4*R*)-N-((*R*)-1-(4-(1-ethyl-1*H*-pyrazol-5-yl)phenyl)-2-hydroxyethyl)-4-hydroxypyrrolidine-2-carboxamide (XXI-4):



To a stirred solution of **XXI-3** (9.5 g 21.37 mmol, 1.0 equiv.) in DCM (20.0 mL) and MeOH (20.0 mL) at 0 °C was added 4.0 M HCl in 1,4- dioxane (40.0 mL), and the resulting mixture was stirred at rt for 5 h. The reaction mixture was concentrated directly under reduced pressure to get the crude product. The residual acid was stripped-off by the addition of diethyl ether (2x30 mL), and the mixture was dried and concentrated to get the crude compound **XXI-4** (9.0 g) which was directly forwarded for the next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.030(s, 1H), 6.655(s, 1H), 5.153-5.121(m, 1H), 4.641-4.596(m, 2H), 4.378-4.324(m, 2H), 3.896-3.736(m, 3H), 3.379-3.325(m, 1H), 2.002(m, 1H), 1.464-1.403(m, 1H) 1.403-1.399(m, 3H), 1.387-1.381(m, 6H); LC-MS: *m/z* 345.2[M+H]⁺.

Synthesis of tert-butyl (R)-(2-hydroxy-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamate (XXII-1):

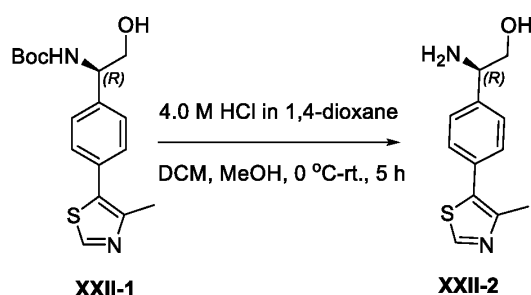


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To a stirred solution of tert-butyl (R)-(1-(4-bromophenyl)-2-hydroxyethyl)carbamate (10.0 g, 31.62 mmol, 1.0 equiv.) and 4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole (9.25 g, 41.11 mmol, 1.2 equiv.) in 1, 4-dioxane (80.0 mL) and water (8.0 mL), potassium carbonate (13.11g, 94.87 mmol, 3.0 equiv.) was added and the reaction mixture was purged with argon gas for 15 mins. Then Pd(dppf)Cl₂·DCM (2.58 g 3.16 mmol, 0.1 equiv.)

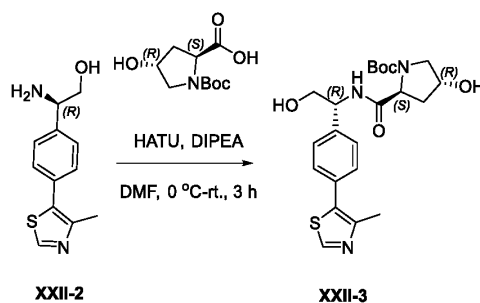
was added, and the reaction mixture was degassed again (5 min) and subsequently stirred at 100 °C for 5 h. The reaction mixture was cooled to RT, filtered through a Celite® bed, and washed with EtOAc (2x30 mL). The filtrate was concentrated under reduced pressure, diluted with water (50 mL), and extracted with EtOAc (3x50 mL). The organic layers were collected, washed with brine (30 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to get the crude product which was purified by column chromatography (silica gel, 230-400 mesh, 50% EtOAc in hexane) to get the pure compound **XXII-1** (8.9g; yield 84%). ¹H NMR (400 MHz, CDCl₃): δ 8.70 (s, 1H), 7.47-7.44 (m, 2H), 7.40-7.38 (m, 2H), 5.32 - 5.31 (m, 1H), 4.84 (bs, 1H), 3.94 - 3.89 (m, 2H), 2.55 (s, 3H), 2.12 - 2.22 (m, 1H), 1.47 (s, 9H); LC-MS: *m/z* 335.3 [M+H]⁺

Synthesis of (R)-2-amino-2-(4-(4-methylthiazol-5-yl)phenyl)ethan-1-ol (**XXII-2**):



To a stirred solution of **XXII-1** (8.9 g, 26.61 mmol, 1.0 equiv.) in DCM (15.0 mL) and MeOH (15 mL) at 0 °C, was added 4.0 M HCl in 1,4- dioxane (25 mL), and the mixture was stirred at rt for 5 h. The reaction mixture was concentrated directly under reduced pressure to get the crude product. The residual acid was stripped off by the addition of diethyl ether (2x10 mL), and the mixture was dried to get the crude compound **XXII-2** (5.3 g) which was directly forwarded for the next step without further purification. LC-MS: *m/z* 235.3[M+H]⁺

Synthesis of tert-butyl (2S,4R)-4-hydroxy-2-(((R)-2-hydroxy-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidine-1-carboxylate (**XXII-3**):

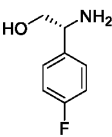
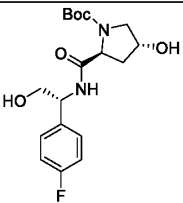
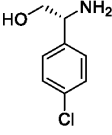
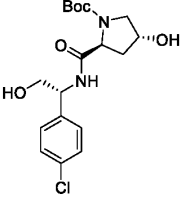


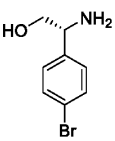
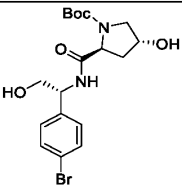
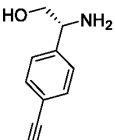
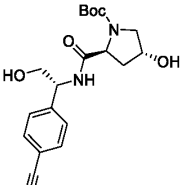
To a stirred solution of **XXII-2** (5.2 g, 19.20 mmol, 1.0 equiv.) in DMF (50 mL), diisopropylethylamine (4.96 g, 38.40 mmol, 2.0 equiv.) was added at 0 °C, and the reaction mixture was stirred for 30 mins at rt. Then (2S,4R)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (6.48 g, 28.01mmol, 1.5 equiv.) followed by HATU (6.77g, 28.80 mmol, 1.5 equiv.) were added to the reaction mixture, and the contents of the vessel were stirred for 3 h. After completion of reaction, the reaction mixture was quenched with ice-cold water (50 mL) and extracted with DCM (2x100 mL). The organic layers were collected, washed with brine (50 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to get the crude product which was purified by column chromatography (silica gel, 230-400 mesh, 5% MeOH in DCM) to get the pure compound **XXII-3** (5.3g; yield 62%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.98 (s, 1H), 8.27- 8.23 (m, 1H), 7.45 - 7.38 (m, 4H), 5.01-4.99(m,1H), 4.88 - 4.83 (m, 2H) 4.25 - 4.20 (m, 2H) 3.66 - 3.61(m, 2H) 3.36- 3.32 (m, 1H) 2.45(s, 3H) 2.09-2.07(m, 2H) 1.79-1.77(m, 1H) 1.41(m, 9H); LC-MS: *m/z* 448.3[M+H]⁺

The compounds listed in below **Table-12** were prepared by reacting appropriate amine with (2S,4R)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid with appropriate variations in reagents, solvents and reaction conditions using a procedure similar to the one described in Intermediate **XXII-3** to obtain desired amide product. The characterization data of the compounds are summarized herein the below table

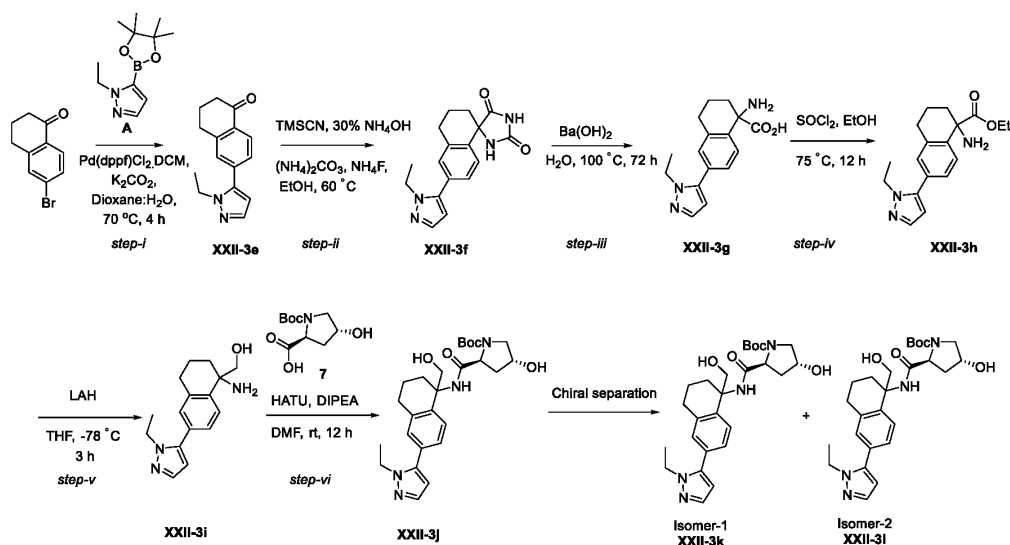
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Table-12

Int-No.	Amine	Intermediate Structure	Analytical Data
XXII-3a			LC-MS: <i>m/z</i> 369.1(M+H) ⁺
XXII-3b			LC-MS: <i>m/z</i> 385.1 (M+H) ⁺

XXII-3c			LC-MS: m/z 315.1 (M+2H) ⁺
XXII-3d			LC-MS: m/z 375.1 (M+H) ⁺

Synthesis of tert-butyl (2S,4R)-2-(((S)-6-(1-ethyl-1H-pyrazol-5-yl)-1-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamoyl)-4-hydroxypyrrolidine-1-carboxylate and tert-butyl (2S,4R)-2-(((S)-6-(1-ethyl-1H-pyrazol-5-yl)-1-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamoyl)-4-hydroxypyrrolidine-1-carboxylate (XXII-3k and XXII-3l):



Step-i: Synthesis of 6-(1-ethyl-1H-pyrazol-5-yl)-3,4-dihydronaphthalen-1(2H)-one (XXII-3e)

To a stirred solution of 6-bromo-3,4-dihydronaphthalen-1(2H)-one (5.00 g, 22.21 mmol, 1.0 equiv.) and 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (5.92 g, 26.65 mmol, 1.2 equiv.) in 1, 4-dioxane (40 mL) and water (10 mL), was added

potassium carbonate (9.21 g, 66.63 mmol, 3.0 equiv.) and the reaction mixture was purged with argon gas for 15 mins. Then Pd(dppf)Cl₂·DCM (1.81 g, 2.22 mmol, 0.1 equiv.) was added, and the reaction mixture was degassed again (5 min) and stirred at 70 °C for 4 h. After completion of reaction, the reaction mixture was cooled to RT, filtered through celite bed, and washed with EtOAc (2x20 mL). The filtrate was concentrated under reduced pressure, diluted with water (50 mL), and extracted with EtOAc (3x25 mL). Organic layers were collected, washed with brine (30 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to get the crude product which was purified by column chromatography (silica gel, 230-400 mesh, 50% EtOAc in hexane) to get the pure titled compound **XXII-3e** (5.3g); LC-MS: *m/z* 241.1 (M+H)⁺

Step-ii: Synthesis of 6'-(1-ethyl-1H-pyrazol-5-yl)-3',4'-dihydro-2'H-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (XXII-3f)

A suspension of 6-(1-ethyl-1H-pyrazol-5-yl)-3,4-dihydronaphthalen-1(2H)-one (**XXII-3e**) (3.5 g, 14.56 mmol, 1.0 equiv.), TMSCN (6.21 g, 62.62 mmol, 4.3 equiv.), (NH₄)₂CO₃ (15.47 g, 161.08 mmol, 11.06equiv) and NH₄F (9.55 g, 167.49 mmol, 11.50 equiv.) in ethanol (100 mL) and 30% aqueous NH₃ (45 mL) were heated at 60 °C for 6 h. After cooling to the room temperature, the reaction mixture was diluted with water and then compound was extracted with EtOAc. The organic layer was dried over Na₂SO₄ and then concentrated under reduced pressure to obtain titled compound **XXII-3f** (3.5g); LC-MS: *m/z* 311.1 (M+H)⁺

Step-iii: Synthesis of 1-amino-6-(1-ethyl-1H-pyrazol-5-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (XXII-3g)

To a suspension of 6'-(1-ethyl-1H-pyrazol-5-yl)-3',4'-dihydro-2'H-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (**XXII-3f**) (3.5 g, 11.27 mmol, 1.0 equiv) in 50 mL of water was added barium hydroxide octahydrate (11.59 g, 67.66 mmol, 6.0 equiv.). The reaction was heated at 100 °C for 72 h. After completion of reaction, the reaction mixture was acidified with 1M H₂SO₄ and then reaction mixture was filtered. The filtrate obtained was concentrated and lyophilized for 48 hr to obtain titled compound **XXII-3g** (2.3g); LC-MS: *m/z* 286.1 (M+H)⁺

Step-iv: Synthesis of ethyl 1-amino-6-(1-ethyl-1H-pyrazol-5-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (XXII-3h)

To a suspension of 1-amino-6-(1-ethyl-1H-pyrazol-5-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (**XXII-3g**) (1.0 g, 3.50 mmol, 1.0 equiv) in EtOH (50

mL) was added SOCl₂ (0.3 mL, 4.20 mmol, 1.2 equiv) at 0 °C. The reaction mixture was heated to reflux for 12 h before being evaporated to dryness. After completion of reaction, the reaction mixture was filtered over celite, water and brine wash were given to the filtrate and then dried over Na₂SO₄ and then concentrated under reduced pressure to obtain crude product. The crude
5 was purified by combi flash by combi flash eluting it with 0-40% EtOAc/Hexane to give pure compound **XXII-3h** (0.56g); LC-MS: *m/z* 313.1(M+H)⁺

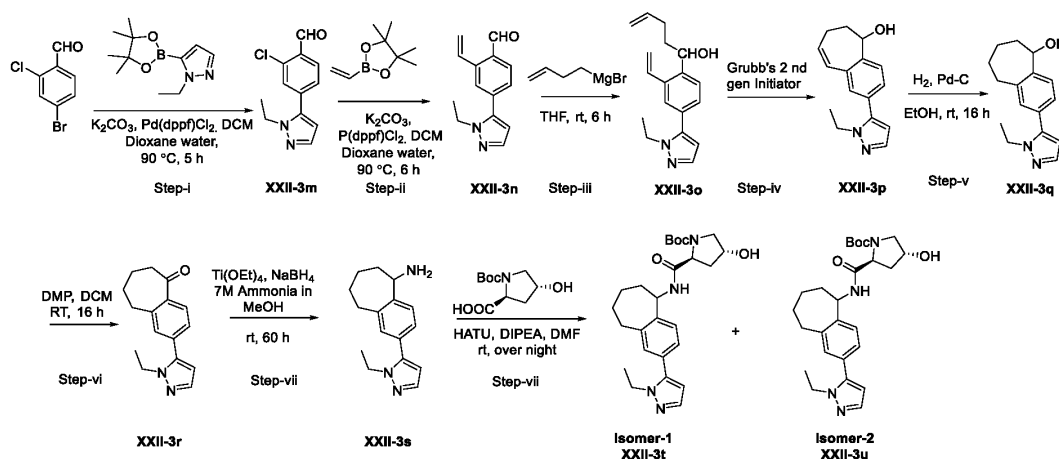
Step-v: Synthesis of (1-amino-6-(1-ethyl-1H-pyrazol-5-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (XXII-3i)

To a suspension of lithium aluminum hydride (0.34 g, 8.93 mmol, 5 equiv) in 6 mL of
10 THF at 0°C was added ethyl 1-amino-6-(1-ethyl-1H-pyrazol-5-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (**XXII-3h**) (0.56 g, 1.78 mmol, 1.0 equiv.). The mixture was stirred at -78 °C for 3 hr. After completion of reaction, the reaction mixture was quenched with saturated NH₄Cl solution and then compound was extracted with 10% MeOH-DCM. The organic layer was dried over Na₂SO₄, filtered and then concentrated under reduced pressure to
15 give a residue. The residue was purified by Combi flash, eluting it with 5-10% MeOH in DCM to get the titled compound **XXII-3i** (0.48g); LC-MS: *m/z* 272.1 (M+H)⁺.

Step-vi: Synthesis of tert-butyl ((2S,4R)-2-((6-(1-ethyl-1H-pyrazol-5-yl)-1-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamoyl)-4-hydroxypyrrolidine-1-carboxylate (XXII-3k and XXII-3l))

To a stirred solution of (2S,4R)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (**XXII-3i**) (0.41 g, 1.76 mmol, 1.0 equiv.) in DMF (10 mL) was added DIPEA (0.45 g, 3.53 mmol, 2.0 equiv.) and HATU (0.62 g, 2.65 mmol, 1.5 equiv.) while keeping the reaction mixture in an ice bath. After 15 min, (1-amino-6-(1-ethyl-1H-pyrazol-5-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (0.48 g, 1.76 mmol, 1.0 equiv.) was added, and the
25 reaction was stirred overnight at rt for 12 hr. After completion of the reaction, the reaction mixture was diluted with ice cold water and extracted with ethyl acetate (15 mLx3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by Combi flash, eluting with 7-10% MeOH in DCM to get the titled racemic compound **XXII-3j** (0.47 g); Isomers (isomer-
30 1(**XXII-3k**) and isomer-2 (**XXII-3l**)) were separated by using Regis 250 x 21.2mm , 5 micron column and Hexane / 0.1% DEA in Ethanol as solvent; LC-MS: *m/z* 484.1(M+H)⁺.

Synthesis of tert-butyl (2S,4R)-2-((2-(1-ethyl-1H-pyrazol-5-yl)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)carbamoyl)-4-hydroxypyrrolidine-1-carboxylate (XXII-3t) and tert-butyl (2S,4R)-2-((2-(1-ethyl-1H-pyrazol-5-yl)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)carbamoyl)-4-hydroxypyrrolidine-1-carboxylate (XXII-3u):



5

Step-i: Synthesis of 2-chloro-4-(1-ethyl-1H-pyrazol-5-yl)benzaldehyde (XXII-3m):

To a stirred solution of methyl 4-bromo-2-chlorobenzaldehyde (5.0 g, 22.78 mmol) in 1, 4 dioxane (50 mL) and water (20 mL) was added 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (7.6 g, 34.17 mmol), potassium carbonate (9.44 g, 68.34 mmol) and reaction mixture was purged with argon for 15 min. Then Pd(dppf)Cl₂·DCM (1.66 g, 2.27 mmol) was added, and reaction mixture was stirred at 90 °C for 5 hours. After completion of reaction, the reaction mixture was filtered through celite bed and quenched with ice cold water and extracted with ethyl acetate (15 mLx3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by Combi-flash, eluting with 50% ethyl acetate in hexane to afford titled compound **XXII-3m** (2.7 g, 50%) as light yellow color solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.37 (d, *J* = 0.8 Hz, 1H), 7.97 (d, *J* = 28.4 Hz, 1H), 7.7 (s, 1 H), 7.67 (dd, *J* = 1.6 Hz, 0.8 Hz, 2H), 7.57 (s, 1H), 6.58 (s, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H); LC-MS: *m/z* 234.95 (M+H)⁺

Step-ii: Synthesis of 4-(1-ethyl-1H-pyrazol-5-yl)-2-vinylbenzaldehyde (XXII-3n)

To a stirred solution of 2-chloro-4-(1-ethyl-1H-pyrazol-5-yl)benzaldehyde (**XXII-3m**) (2.8 g, 26.8 mmol) in 1, 4 dioxane (16 mL) and water (4 mL) was added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (2.07 g, 13.4 mmol), potassium carbonate (2.89 g,

26.85 mmol) and purged with argon for 15 min. Then Pd(dppf)Cl₂·DCM (0.65 g, 0.9 mmol) was added, and reaction mixture was stirred at 90 °C for 6 hour. After completion of reaction, the reaction mixture was filtered through celite bed and quenched with ice cold water and extracted with ethyl acetate (15 mLx3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by Combi-flash, eluting with 50% ethyl acetate in hexane to afford titled compound **XXII-3n** (1.5 g, 74%) as light yellow color solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.97 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 0.8 Hz, 1H), 7.69 – 7.63 (m, 2 H), 7.56 (d, *J* = 2.0 Hz, 1H), 6.54 (d, *J* = 2.0 Hz, 1H), 5.96 (dd, *J* = 17.6 Hz, 1.2 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H).

Step-iii: Synthesis of 1-(4-(1-ethyl-1H-pyrazol-5-yl)-2-vinylphenyl)pent-4-en-1-ol (XXII-3o)

To a stirred solution of 4-(1-ethyl-1H-pyrazol-5-yl)-2-vinylbenzaldehyde (2.4 g, 10.6 mmol) in THF was added but-3-en-1-ylmagnesium bromide (**XXII-3n**) (3.38 g, 21.21 mmol), mixture was stirred at rt for 6 hours. After the completion of reaction, the reaction mixture was quenched with ice cold ammonium chloride solution and extracted with ethyl acetate (15 mLx3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by Combi-flash, eluting with 50% ethyl acetate in hexane to afford titled compound **XXII-3o** (1.2 g, 40%) as light-yellow color solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.60 (d, *J* = 8.0 Hz, 1H), 7.51 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.38 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.13 – 7.606 (m, 1 H), 6.37 (d, *J* = 1.0 Hz, 1H), 5.85 – 5.74 (m, 2H), 5.38- 5.36 (m, 1H), 5.31 (d, *J* = 4.4 Hz, 1H), 5.04- 4.90 (m, 3H), 4.13 (q, *J* = 7.2 Hz, 2H), 2.18 – 2.08 (m, 2H), 1.67 – 1.61 (m, 2H), 1.31 (t, *J* = 7.2 Hz, 3H).

Step-iv: Synthesis of 2-(1-(4-(1-ethyl-1H-pyrazol-5-yl)-6,7-dihydro-5H-benzo[7]annulen-5-ol (XXII-3p)

To a stirred solution of 1-(4-(1-ethyl-1H-pyrazol-5-yl)-2-vinylphenyl)pent-4-en-1-ol (**XXII-3o**) (2.4 g, 10.6 mmol) in toluene was added grubbs 2nd generation initiator (0.15 g, 0.050 mmol), and reaction mixture was stirred at 50 °C for 6 hours. After the completion of reaction, the reaction mixture was passed through celite bed and organic layer was concentrated under reduced pressure to give a residue. The residue was purified by Combi-flash, eluting with 40% ethyl acetate in hexane to afford titled compound **XXII-3p** (0.8 g, 88%) as off-white

color solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.62 (d, $J = 7.6$ Hz, 1H), 7.49 (d, $J = 2.0$ Hz, 1H), 7.32 – 7.25 (m, 2H), 6.47 – 6.44 (m, 1H), 6.33 (d, $J = 1.6$ Hz, 1H), 5.98 – 5.93 (m, 1H), 5.42 (d, $J = 4.8$ Hz, 2H), 4.68 (q, $J = 4.4$ Hz, 1H), 4.13 (q, $J = 7.2$ Hz, 2H), 4.02 (dd, $J = 7.2$ Hz, 1.6 Hz, 2H), 2.45 – 2.42 (m, 2H), 2.10 – 1.90 (m, 2H), 1.31 (t, $J = 7.2$ Hz, 3H), 1.07 (s, 2H); LC-MS: m/z 255.15 ($\text{M}+\text{H}$) $^+$.

Step-v: Synthesis of 2-(1-ethyl-1H-pyrazol-5-yl)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-ol (XXII-3q)

To a stirred solution of 2-(1-ethyl-1H-pyrazol-5-yl)-6,7-dihydro-5H-benzo[7]annulen-5-ol (**XXII-3p**) (0.25g, 0.98 mmol) in EtOH was added Pd-C 20% (0.335 g, 3.14 mmol), and the reaction mixture was stirred at rt for 16 hour. After the completion of reaction, the reaction mixture was passed through celite bed and organic layer was concentrated under reduced pressure to give a titled compound **XXII-3q** (0.23 g, 91%) as off-white color solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.56 (d, $J = 8.0$ Hz, 1H), 7.48 (d, $J = 2.0$ Hz, 1H), 7.25 (dd, $J = 8.0$ Hz, 1.6 Hz, 1H), 7.17 (d, $J = 1.6$ Hz, 1H), 6.30 (s, 1H), 5.29 (s, 1H), 4.79 (d, $J = 9.6$ Hz, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 2.91 – 2.86 (m, 2H), 2.76 – 2.71 (m, 2H), 1.97 – 1.91 (m, 2H), 1.80 – 1.72 (m, 2H), 1.57 – 1.49 (m, 2H), 1.30 (t, $J = 7.2$ Hz, 3H); LC-MS: m/z 257.20 ($\text{M}+\text{H}$) $^+$.

Step-vi: Synthesis of 2-(1-ethyl-1H-pyrazol-5-yl)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (XXII-3r)

To a stirred solution of 2-(1-ethyl-1H-pyrazol-5-yl)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-ol (**XXII-3q**) (0.5g, 1.95 mmol) in DCM was added Dess–Martin periodinane (1.6 g, 3.75 mmol), and the reaction mixture was stirred at rt for 16 hour. After the completion of reaction, the reaction mixture was passed through celite bed and organic layer was washed with water and concentrated under reduced pressure to give a titled compound **XXII-3r** (0.22 g, 44%) as off-white color solid. LC-MS: m/z 255.10 ($\text{M}+\text{H}$) $^+$.

Step-vii: Synthesis of 2-(1-ethyl-1H-pyrazol-5-yl)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-amine (XXII-3s)

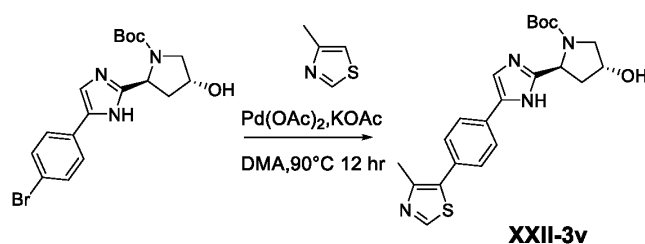
To a stirred solution of 2-(1-ethyl-1H-pyrazol-5-yl)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (**XXII-3r**) (0.05g, 0.19 mmol) in 10 mL of 7M Ammonia in MeOH was added titanium ethoxide (0.112 g, 0.5 mmol), and the reaction mixture was stirred at rt for 48 hour. After that NaBH_4 (0.03 g; 0.78 mmol) was added and stirred for 60 h at rt. After the

completion of reaction, the reaction mixture was poured in ice cold 2M HCl solution and extracted by EtOAc. Then acidic aqueous layer was basified by saturated sodium bicarbonate solution and extracted in EtOAc. Organic layer was concentrated under reduced pressure to give a titled compound **XXII-3s** (0.05 g, Crude) as yellow-white color solid.; LC-MS: m/z
 5 256.20 (M+H)⁺.

Step-viii: Synthesis of tert-butyl (2S,4R)-2-((2-(1-ethyl-1H-pyrazol-5-yl)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)carbamoyl)-4-hydroxypyrrolidine-1-carboxylate (XXII-3t) and tert-butyl (2S,4R)-2-((2-(1-ethyl-1H-pyrazol-5-yl)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)carbamoyl)-4-hydroxypyrrolidine-1-carboxylate (XXII-3u)

To a stirred solution of (2S,4R)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (0.05g, 0.22 mmol) in 10 mL of DMF was added DIPEA (0.08 g, 0.58 mmol), followed by HATU (0.07 g; 0.3 mmol) and the reaction mixture was stirred at rt for 0.5 hour. After that 2-(1-ethyl-1H-pyrazol-5-yl)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-amine(**XXII-3s**) (0.05 g; 0.019 mmol) was added and stirred overnight in rt. After the
 15 completion of reaction, the reaction mixture was poured in ice cold water and extracted by EtOAc. Organic layer was concentrated under reduced pressure and purified by 10% MeOH in DCM to give a titled compound (0.055 g, 60%) as yellow-white color solid. Isomer's (isomer-1(**XXII-3t**) and isomer-2 (**XXII-3u**)) were separated by using Regis 250 x 21.2mm , 5 micron column and Hexane / 0.1% DEA in Ethanol as solvent.LC-MS: m/z 469.20 (M+H)⁺.

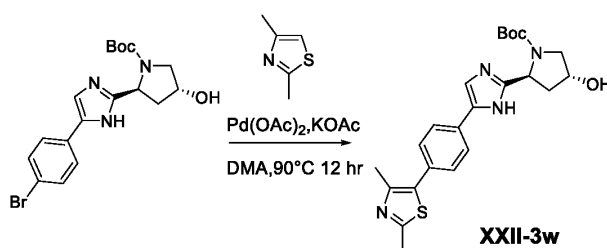
Synthesis of tert-butyl (2S,4R)-4-hydroxy-2-(5-(4-(4-methylthiazol-5-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (XXII-3v)



A mixture of tert-butyl (2S,4R)-4-hydroxy-2-(5-(4-(4-methylthiazol-5-yl)phenyl)-1H-imidazol-2-yl)pyrrolidine-1-carboxylate (1.5 g, 3.673 mmol, 1.0 equiv.), 4-methylthiazole
 25 (1.0 g, 11.020 mmol, 3.0 equiv.) and potassium acetate (0.721 g, 7.340mmol, 2.0 equiv.) in 15 mL of DMA was transferred to a sealed tube and degassed with argon for 30 min. Pd(OAc)₂(0.082 g, 0.360 mmol, 0.09 equiv.) was added to the reaction mixture, which was

then degassed for another 5 min. The reaction mixture was then heated at 90 °C for 12 h. After completion of reaction, the reaction mixture was allowed to cool to room temperature then diluted with ethyl acetate and filtered through a pad of celite. The organic layer was separated from the aqueous layer and dried over anhydrous sodium sulphate then concentrated under reduced pressure to get crude product. The crude was purified by combi-flash column chromatography using 30% ethyl acetate in hexane to afford the titled compound **XXII-3v** (1.5g). LC-MS: m/z 427.1 (M+H)⁺.

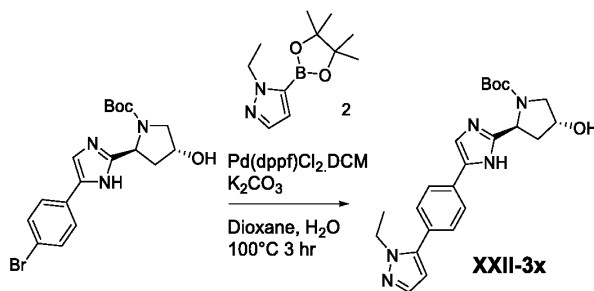
Synthesis of (3R,5S)-5-(5-(4-(2,4-dimethylthiazol-5-yl)phenyl)-1H-imidazol-2-yl)pyrrolidin-3-ol (XXII-3w):



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The intermediate XXII-3w was prepared by reacting tert-butyl (2S,4R)-2-(5-(4-bromophenyl)-1H-imidazol-2-yl)-4-hydroxypyrrolidine-1-carboxylate with 2,4-dimethylthiazole using a procedure similar to the one described in **Intermediate XXII-3v**. LC-MS: m/z 441.1 (M+H)⁺

Synthesis of tert-butyl (2S,4R)-2-(5-(4-(1-ethyl-1H-pyrazol-5-yl)phenyl)-1H-imidazol-2-yl)-4-hydroxypyrrolidine-1-carboxylate (XXII-3x):



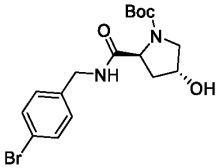
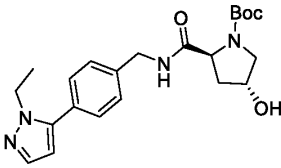
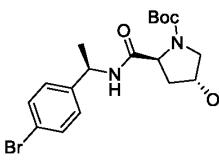
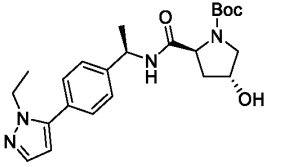
To a stirred solution of tert-butyl (2S,4R)-2-(5-(4-bromophenyl)-1H-imidazol-2-yl)-4-hydroxypyrrolidine-1-carboxylate (0.600 g, 1.47 mmol, 1.0 equiv.) and 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.392 g, 1.760 mmol, 1.2 equiv.) in 1, 4-dioxane (8 mL) and water (1.0 mL), potassium carbonate (0.609g, 4.40 mmol, 2.99 equiv.) was added and purged with argon gas for 15 mins. Then Pd(dppf)Cl₂·DCM (0.120 g 0.140 mmol,

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0.1 equiv.) was added, and the reaction mixture was degassed again (5 min) and subsequently stirred at 100 °C for 3 h. The reaction mixture was cooled to RT, filtered through a celite bed, and washed with EtOAc (2x30 mL). The filtrate was concentrated under reduced pressure, diluted with water (50 mL), and extracted with EtOAc (3x50 mL). Organic layers were collected, washed with brine (30 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to get the crude product which was purified by column chromatography (silica gel, 230-400 mesh, 50% EtOAc in hexane) to get the pure compound **XXII-3x** (0.58 g; yield 93.16%).

The compounds listed in below **Table-13** were prepared by reacting 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole with appropriate bromo compound with reagents, solvents and reaction conditions using a procedure similar to the one described in **Intermediate XXII-3x**. The characterization data of the compounds are summarized herein the below table.

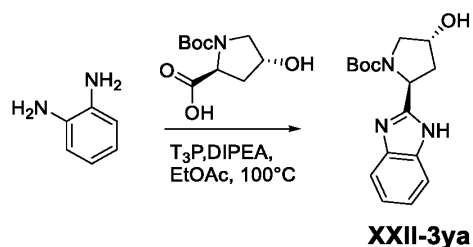
Table-13

Int. No.	SM used	Intermediate structure	Analytical data
XXII-3xa			LC-MS: m/z 415.2 (M+H) ⁺
XXII-3xb			LC-MS: m/z 429.0 (M+H) ⁺

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Synthesis of tert-butyl (2S,4R)-2-(1H-benzo[d]imidazol-2-yl)-4-hydroxypyrrolidine-1-carboxylate (XXII-3ya):

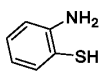
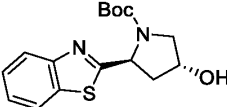


To a stirred solution of (2S,4R)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (1.026, 4.62 mmol, 1.0 equiv.) in DMF (10 mL) was added DIPEA (1.79 g, 13.87 mmol, 3.0 equiv.) and T₃P (50% solution DMF) (1.76 g, 5.54 mmol, 1.2 equiv.) while keeping the reaction mixture in an ice bath. After 15 min, benzene-1,2-diamine (0.500 g, 4.62 mmol, 1.0 equiv.) was added, and the reaction was stirred overnight at 100 °C. After the completion of reaction, the reaction mixture was diluted with ice cold water and extracted with ethyl acetate (15 mLx3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by Combi flash, eluting with 7-10% MeOH in DCM to get the titled compound (**XXII-3ya**) as brown sticky solid (0.70 g, 49.91%); LC-MS: *m/z* 304.1 (M+H)⁺.

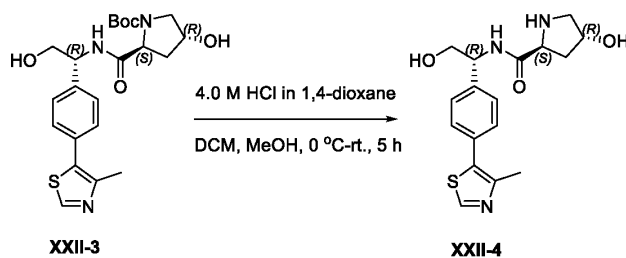
The compounds listed in below **Table-14** were prepared by reacting (2S,4R)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid with appropriate amine with reagents, solvents and reaction conditions using a procedure similar to the one described in the synthesis of **Intermediate XXII-3ya**. The characterization data of the compounds are summarized herein the below table.

Table-14

Int. No.	SM used	Intermediate structure	Analytical data
XXII-3yb			LC-MS: <i>m/z</i> 320.1 (M+H) ⁺

XXII-3yc			LC-MS: m/z 321.1 (M+H) ⁺
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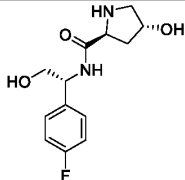
Synthesis of (2S,4R)-4-hydroxy-N-((R)-2-hydroxy-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (XXII-4):

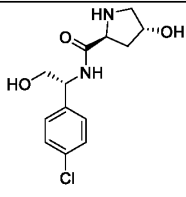
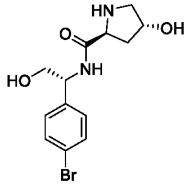
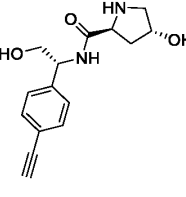
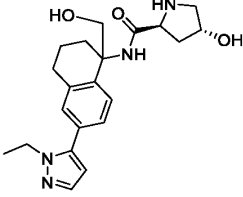
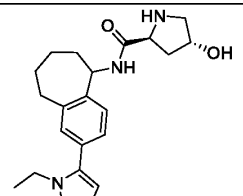
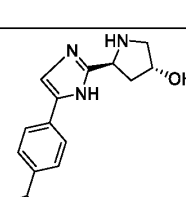


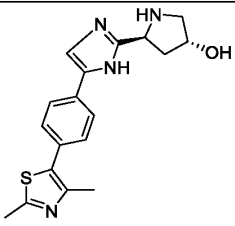
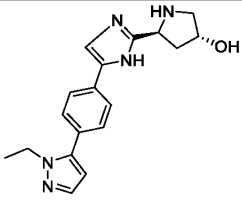
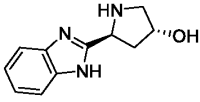
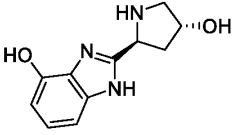
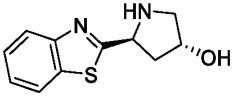
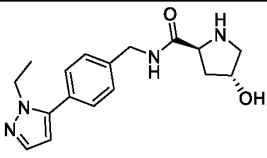
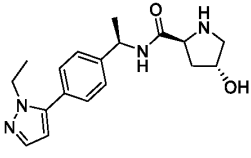
- 5 To a stirred solution of **XXII-3** (0.75 g 1.67 mmol, 1.0 equiv.) in DCM (5.0 mL) and MeOH (5 mL) at 0 °C was added 4.0 M HCl in 1,4- dioxane (10.0 mL), and the reaction mixture was stirred at rt for 5h. After completion of reaction, the reaction mixture was concentrated directly under reduced pressure to get the crude product. The residual acid was striped-off by the addition of diethyl ether (2x10 mL), and the mixture was dried to get the crude compound
- 10 **XXII-4** (0.6 g). LC-MS: m/z 348.1 [M+H]⁺.

The intermediate listed in below **Table-15** were prepared by a procedure similar to the one described in **Intermediate XXII-4** with 4N HCl in 1,4-dioxane as deprotecting reagent. The characterization data of the intermediate is summarized herein the below table.

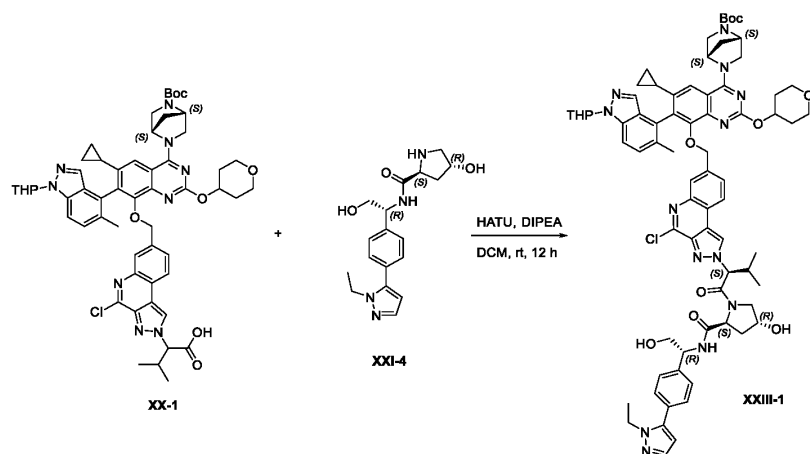
Table-15

Int-No.	Boc protected compound	Intermediate Structure	Analytical Data
XXII-5	XXII-3a		LC-MS: m/z 269.1 (M+H) ⁺

XXII-6	XXII-3b		LC-MS: m/z 285.1 (M+H) ⁺
XXII-7	XXII-3c		LC-MS: m/z 215.1 (M+2H) ⁺
XXII-8	XXII-3d		LC-MS: m/z 275.1 (M+H) ⁺
XXII-9	XXII-3k		LC-MS: m/z 385.20 (M+H) ⁺
XXII-10	XXII-3u		LC-MS: m/z 369.1 (M+H) ⁺
XXII-11	XXII-3v		LC-MS: m/z 327.0 (M+H) ⁺

XXII-12	XXII-3w		LC-MS: m/z 341.1 (M+H) ⁺
XXII-13	XXII-3x		LC-MS: m/z 324.2 (M+H) ⁺
XXII-14	XXII-3ya		LC-MS: m/z 204.10 (M+H) ⁺
XXII-15	XXII-3yb		LC-MS: m/z 220.1 (M+H) ⁺
XXII-16	XXII-3yc		LC-MS: m/z 221.1 (M+H) ⁺
XXII-17	XXII-3xa		LC-MS: m/z 315.2 (M+H) ⁺
XXII-18	XXII-3xb		LC-MS: m/z 329.0 (M+H) ⁺

Synthesis of *tert*-butyl (1*S*,4*S*)-5-(8-(((4-chloro-2-((*S*)-1-((2*S*,4*R*)-2-(((*R*)-1-(4-(1-ethyl-1*H*-pyrazol-5-yl)phenyl)-2-hydroxyethyl)carbamoyl)-4-hydroxypyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2*H*-pyrazolo[3,4-*c*]quinolin-7-yl)methoxy)-6-cyclopropyl-7-(5-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-4-yl)-2-((tetrahydro-2*H*-pyran-4-yl)oxy)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (XXIII-1):

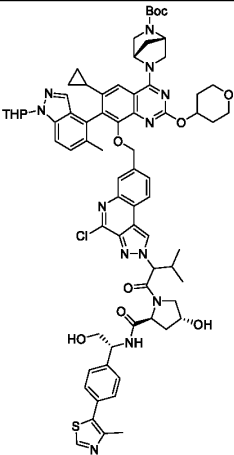
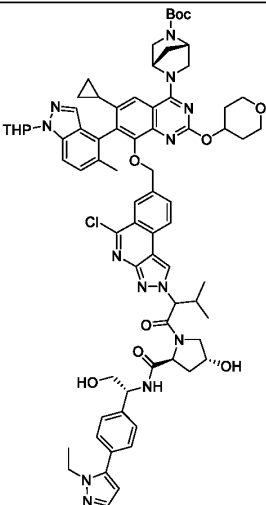


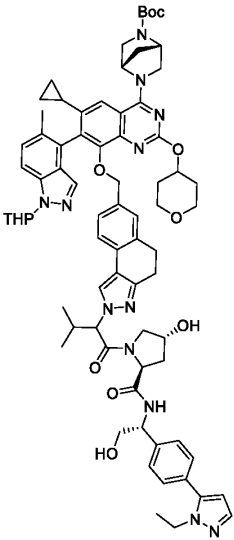
To a stirred solution of acid (**XX-1**) (0.525 g, 0.52 mmol, 1.0 equiv.) in DMF (10 mL) was added DIPEA (0.27 g, 2.1 mmol, 4.0 equiv.) and HATU (0.25 g, 1.03 mmol, 2.0 equiv.) while keeping the reaction mixture in an ice bath. After 15 min, amine (**XXI-4**) (0.22 g, 0.62 mmol, 1.2 equiv.) was added, and the reaction was continued overnight at rt. After the completion of reaction, the reaction mixture was diluted with ice cold water and extracted with ethyl acetate (15 mLx3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give the crude product. The crude product was purified by Combi flash, eluting with 7-10% MeOH in DCM to get the title compound (**XXIII-1**) as brown sticky solid (0.55 g, 75%); ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.21- 9.10 (m, 1H), 8.52- 8.48 (m, 1H), 8.25-8.19 (m, 1H), 8.19- 8.05 (m, 1H), 7.96 (s, 1H), 7.80- 7.60 (m, 2H), 7.51- 7.30 (m, 7H), 7.21- 7.16 (m, 2H), 5.83- 5.76 (m, 1H), 5.50- 5.38 (m, 1H), 5.35- 5.20 (m, 4H), 5.10- 4.95 (m, 1H), 4.90- 4.60 (m, 2H), 4.60- 4.40 (m, 3H), 4.40- 4.30 (m, 2H), 4.15- 3.95 (m, 2H), 3.90- 3.60 (m, 8H), 3.58- 3.45 (bs, 3H), 3.30-3.20 (m, 2H), 2.62- 2.55 (bs, 2H), 2.15 (s, 3H), 2.10- 1.90 (m, 5H), 1.75- 1.60 (bs, 3H), 1.60- 1.50 (bs, 3H), 1.48- 1.40 (bs, 9H), 1.40- 1.30 (m, 3H), 1.30- 1.20 (m, 3H), 1.10- 1.05 (m, 3H), 0.80- 0.65 (m, 5H); LC-MS: *m/z* 1339.6 [M+H]⁺.

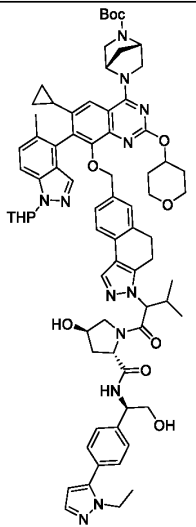
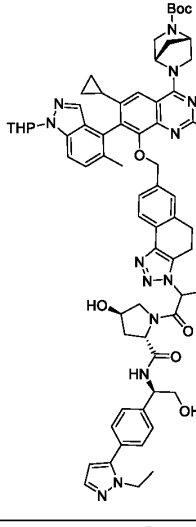
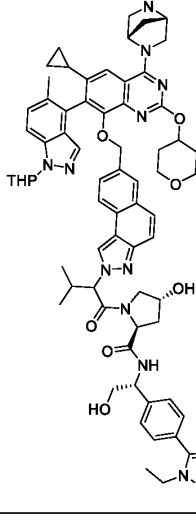
The intermediates **XXIII-2** to **XXIII-56** listed below in **Table-16** were prepared by procedures similar to the one described in the synthesis of **Intermediate XXIII-1** with

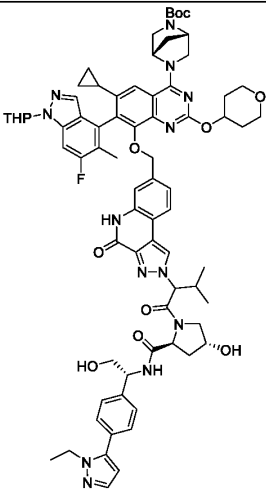
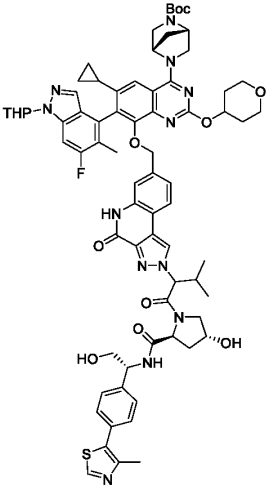
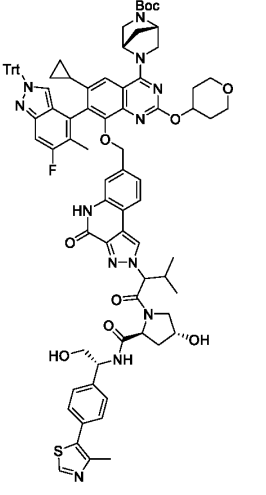
appropriate acid (SM-1) and amine (SM-2) with appropriate variations in reagents, solvents and catalyst. The characterization data of the intermediates are summarized in Table-16.

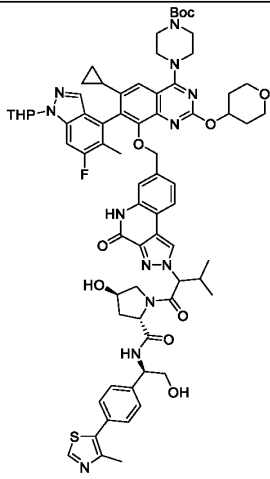
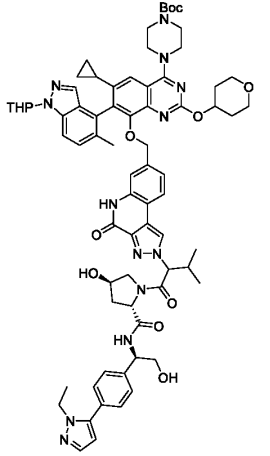
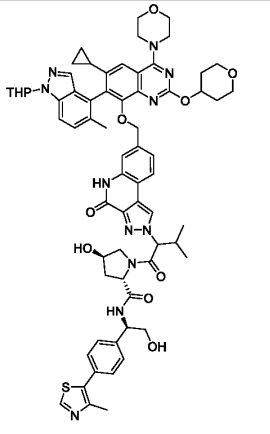
Table-16

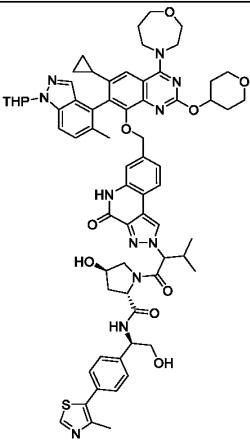
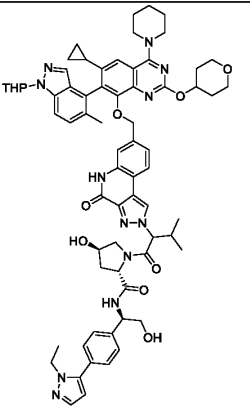
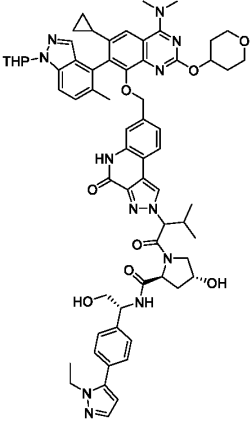
Int-No	Acid SM-1	Amine SM-2	Intermediate Structure	Analytical Data
XXIII-2	XX-1	XXII-4		LC-MS: m/z 1339.60 [M+H] +.
XXIII-3	XX-2	XXI-4		LC-MS: m/z 1339.20 [M+H] +.

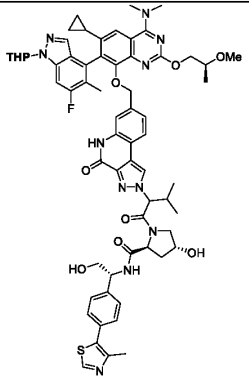
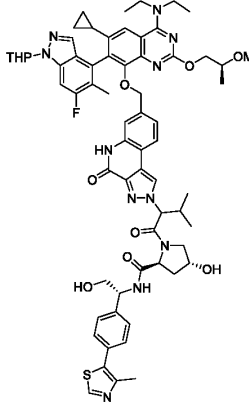
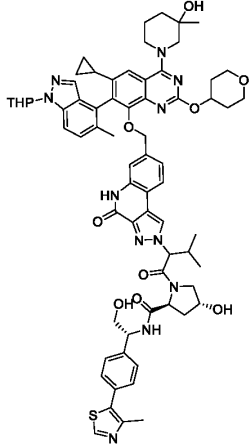
XXIII-4	XX-3	XXI-4		¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 8.50- 8.45 (bs, 1H), 8.15- 8.05 (m, 1H), 7.72- 7.70 (m, 1H), 7.55- 7.40 (m, 6H), 7.40- 7.35 (m, 3H), 7.35- 7.25 (m, 1H), 7.25- 7.17 (m, 1H), 6.65- 6.50 (m, 1H), 6.35- 6.30 (m, 2H), 5.90- 5.80 (m, 1H), 5.25- 5.10 (m, 5H), 5.10- 5.00 (m, 1H), 5.00- 4.80 (m, 3H), 4.65- 4.50 (m, 2H), 4.45- 4.40 (m, 1H), 4.40- 4.30 (m, 2H), 4.30- 4.20 (m, 1H), 4.19- 4.10 (m, 2H), 4.10- 4.00 (m, 1H), 3.95- 3.90 (m, 4H), 3.80- 3.70 (m, 4H), 3.65- 3.55 (m, 5H), 3.45- 3.55 (m, 3H), 3.15- 3.12 (m, 2H), 2.68- 2.67 (m, 5H), 2.50- 2.49(m, 2H), 1.70- 1.65 (m, 4H), 1.62- 1.50 (m, 3H), 1.41- 1.32 (m, 9H), 1.24- 0.98 (m, 3H), 0.74- 0.67 (m, 8H); LC-MS: <i>m/z</i> 1306.2 [M+H] ⁺ .
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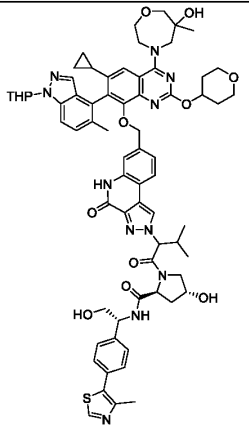
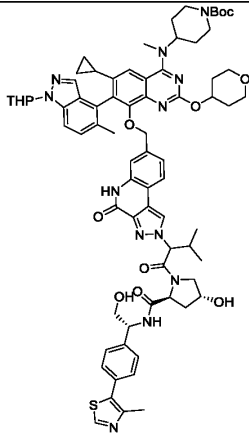
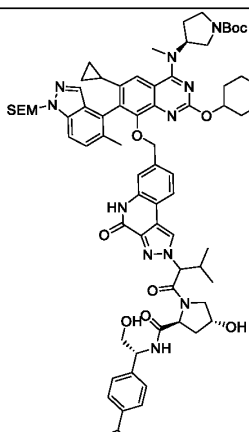
XXIII-5	XX-4	XXI-4	 Chemical structure of compound XXIII-5, featuring a complex polycyclic system with a Boc-protected piperidine, a THP-protected pyrazole, and a hydroxyl group.	LC-MS: m/z 1306.50 [M+H] ⁺ .
XXIII-6	XX-5	XXI-4	 Chemical structure of compound XXIII-6, featuring a complex polycyclic system with a Boc-protected piperidine, a THP-protected pyrazole, and a hydroxyl group.	LC-MS: m/z 1308.0 [M+H] ⁺ .
XXIII-7	XX-6	XXI-4	 Chemical structure of compound XXIII-7, featuring a complex polycyclic system with a Boc-protected piperidine, a THP-protected pyrazole, and a hydroxyl group.	LC-MS: m/z 1304.2 [M+H] ⁺ .

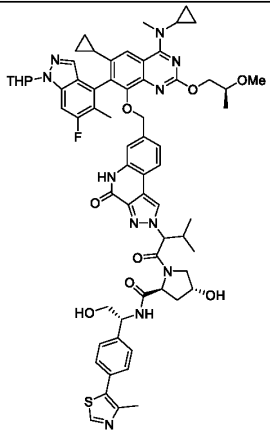
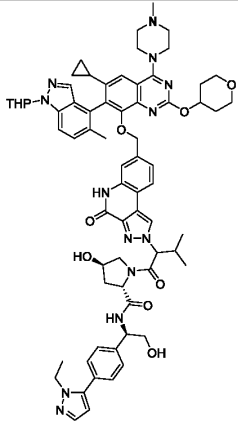
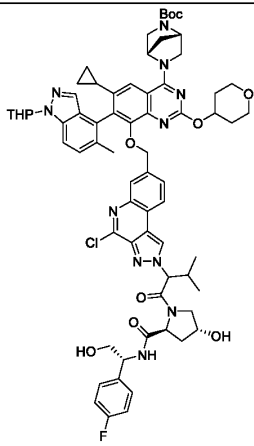
XXIII-8	XX-7	XXI-4		LC-MS: m/z 1338.55 [M+H] ⁺ .
XXIII-9	XX-7	XXII-4		LC-MS: m/z 1341.40[M+H] ⁺
XXIII-10	XX-8	XXII-4		LC-MS: m/z 1499.90[M+H] ⁺

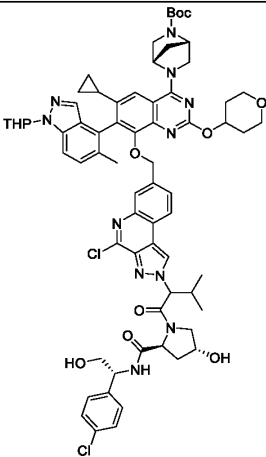
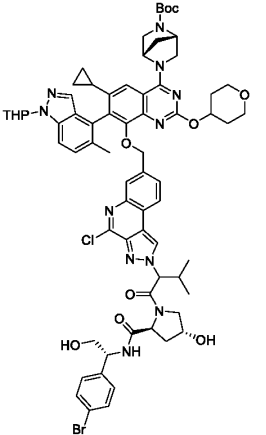
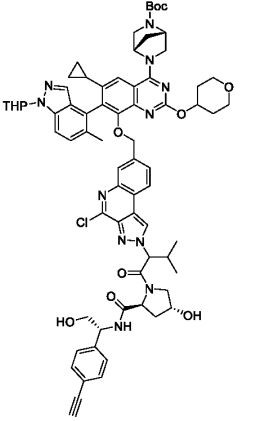
XXIII-11	XX-9	XXII-4	 Chemical structure of compound XXII-4: A complex molecule featuring a central pyrimidine ring system. It includes a THP-protected amine, a Boc-protected amine, a morpholine ring, a fluorinated phenyl group, a hydroxyl group, a carbonyl group, a hydroxyl group, a hydroxyl group, and a thiazole ring.	LC-MS: m/z 1329.50 $[M+H]^+$
XXIII-12	XX-10	XXI-4	 Chemical structure of compound XXI-4: A complex molecule featuring a central pyrimidine ring system. It includes a THP-protected amine, a Boc-protected amine, a morpholine ring, a hydroxyl group, a carbonyl group, a hydroxyl group, a hydroxyl group, and a thiazole ring.	LC-MS: m/z 1308.30 $[M+H]^+$
XXIII-13	XX-11	XXII-4	 Chemical structure of compound XXII-4: A complex molecule featuring a central pyrimidine ring system. It includes a THP-protected amine, a Boc-protected amine, a morpholine ring, a hydroxyl group, a carbonyl group, a hydroxyl group, a hydroxyl group, and a thiazole ring.	LC-MS: m/z 1212.40 $[M+H]^+$

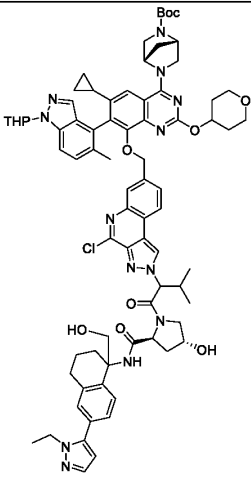
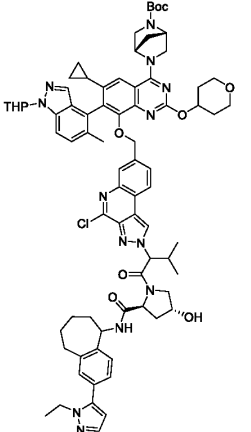
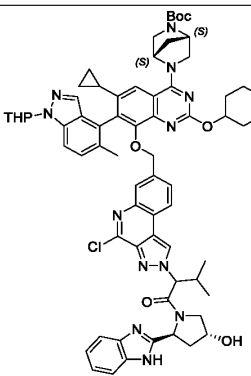
XXIII-14	XX-12	XXII-4	 Chemical structure of compound XXIII-14, featuring a complex polycyclic aromatic system with a THP group, a morpholine ring, and a thiazole ring, connected via a linker to a pyrazole ring, which is further connected to a chiral center with a hydroxyl group and a thiazole ring.	LC-MS: m/z 1127.10 $[M+H]^+$
XXIII-15	XX-13	XXI-4	 Chemical structure of compound XXIII-15, featuring a complex polycyclic aromatic system with a THP group, a morpholine ring, and a thiazole ring, connected via a linker to a pyrazole ring, which is further connected to a chiral center with a hydroxyl group and a thiazole ring.	LC-MS: m/z 1207.30 $[M+H]^+$
XXIII-16	XX-14	XXI-4	 Chemical structure of compound XXIII-16, featuring a complex polycyclic aromatic system with a THP group, a morpholine ring, and a thiazole ring, connected via a linker to a pyrazole ring, which is further connected to a chiral center with a hydroxyl group and a thiazole ring.	LC-MS: m/z 1167.00 $[M+H]^+$

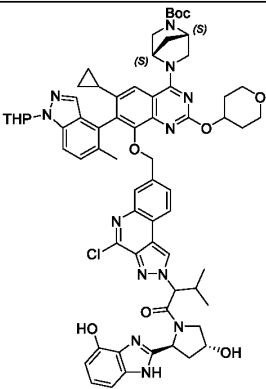
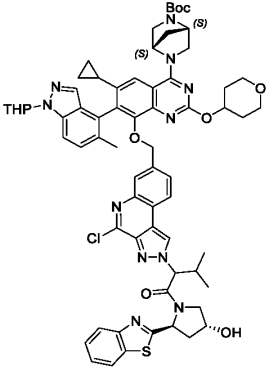
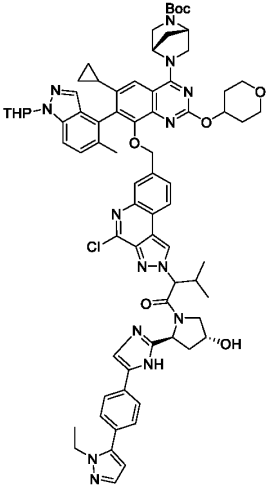
XXIII-17	XX-15	XXII-4	 Chemical structure of compound XXIII-17, featuring a complex polycyclic system with a thiazole ring, a pyridine ring, and a morpholine ring, connected by various functional groups including amides and ethers.	LC-MS: m/z 1176.40[M+H] ⁺
XXIII-18	XX-16	XXII-4	 Chemical structure of compound XXIII-18, featuring a complex polycyclic system with a thiazole ring, a pyridine ring, and a morpholine ring, connected by various functional groups including amides and ethers.	LC-MS: m/z 1204.50 [M+H] ⁺
XXIII-19	XX-17	XXII-4	 Chemical structure of compound XXIII-19, featuring a complex polycyclic system with a thiazole ring, a pyridine ring, and a morpholine ring, connected by various functional groups including amides and ethers.	LC-MS: m/z 1241.00[M+H] ⁺

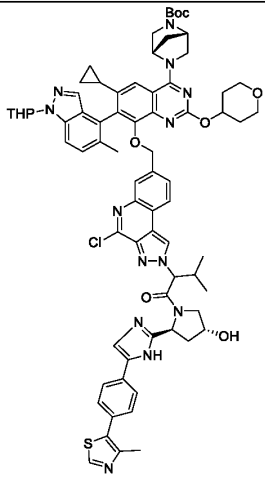
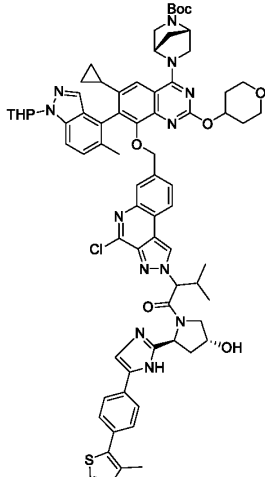
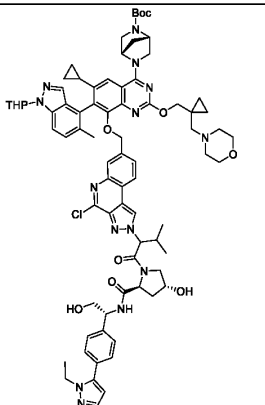
XXIII-20	XX-18	XXII-4	 Chemical structure of compound XXIII-20. It features a central pyrazole ring substituted with a THP group, a morpholine ring, and a complex side chain containing a pyrazole, a pyridine, and a thiazole moiety.	LC-MS: m/z 1256.55 (M+H) ⁺ .
XXIII-21	XX-19	XXII-4	 Chemical structure of compound XXIII-21. It features a central pyrazole ring substituted with a THP group, a morpholine ring, and a complex side chain containing a pyrazole, a pyridine, and a thiazole moiety.	LC-MS: m/z 1339.15[M+H] ⁺
XXIII-22	XX-20	XXII-4	 Chemical structure of compound XXIII-22. It features a central pyrazole ring substituted with a SEM group, a morpholine ring, and a complex side chain containing a pyrazole, a pyridine, and a thiazole moiety.	LC-MS: m/z 1371.6[M+H] ⁺

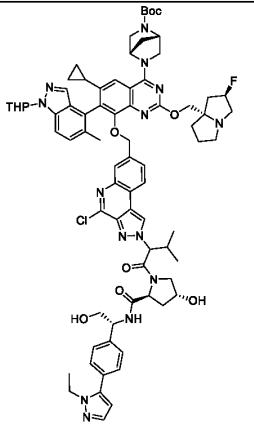
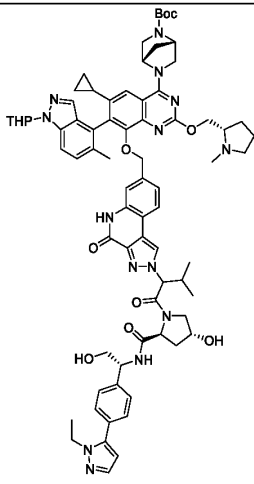
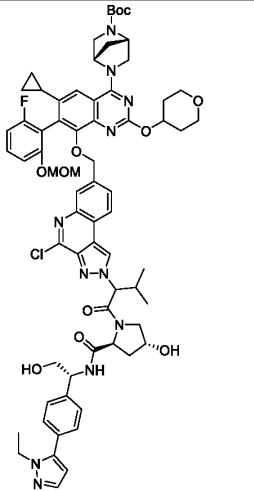
XXIII-23	XX-21	XXII-4	 Chemical structure of compound XXII-4: A complex molecule featuring a central pyrazole ring system. It includes a THP-protected amine, a fluorinated benzene ring, a methoxy group, a hydroxyl group, and a thiazole ring.	LC-MS: m/z 1203.8[M+H] ⁺
XXIII-24	XX-22	XXI-4	 Chemical structure of compound XXI-4: A complex molecule featuring a central pyrazole ring system. It includes a THP-protected amine, a morpholine ring, a hydroxyl group, and a thiazole ring.	LC-MS: m/z 1222.6[M+H] ⁺
XXIII-25	XX-1	XXII-5	 Chemical structure of compound XXII-5: A complex molecule featuring a central pyrazole ring system. It includes a THP-protected amine, a Boc-protected amine, a morpholine ring, a chlorine atom, and a fluorinated benzene ring.	LC-MS: m/z 1263.70 (M+H) ⁺

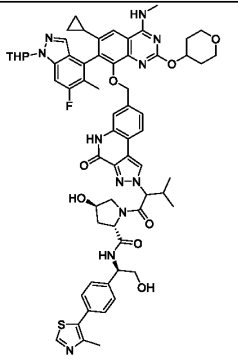
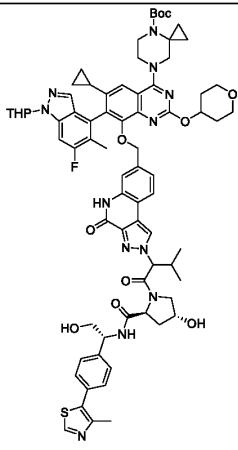
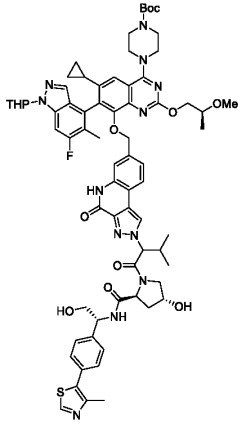
XXIII-26	XX-1	XXII-6		LC-MS: m/z 1278.60 (M+H) ⁺
XXIII-27	XX-1	XXII-7		LC-MS: m/z 1324.70 (M+H) ⁺
XXIII-28	XX-1	XXII-8		LC-MS: m/z 1267.60 (M+H) ⁺

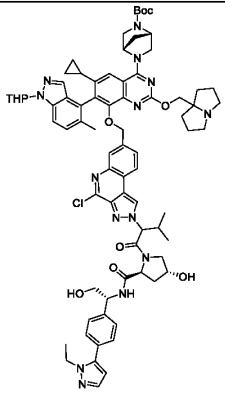
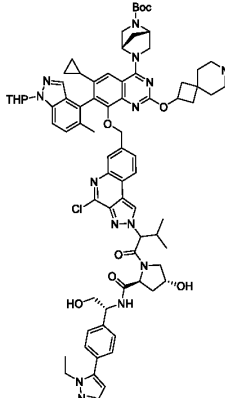
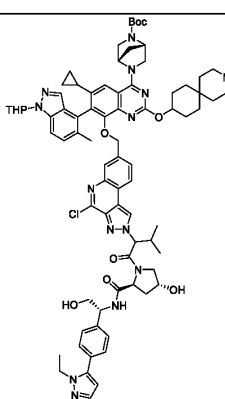
XXIII-29	XX-1	XXII-9		LC-MS: m/z 1360.80 (M+H) ⁺
XXIII-30	XX-1	XXII-10		LC-MS: m/z 1360.50 (M+H) ⁺
XXIII-31	XX-1	XXII-14		LC-MS: m/z 1197.40 (M+H) ⁺

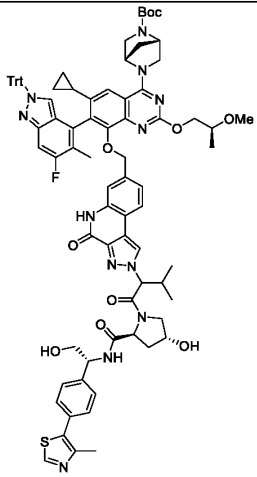
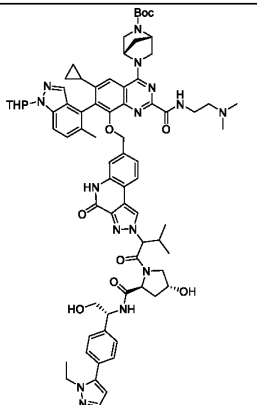
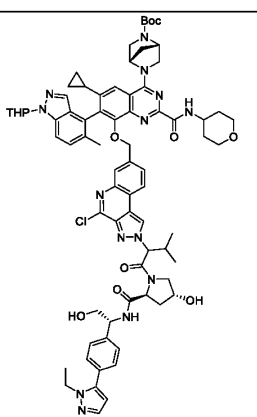
XXIII-32	XX-1	XXII-15		LC-MS: m/z 1213.40 (M+H) ⁺
XXIII-33	XX-1	XXII-16		LC-MS: m/z 1214.60 (M+H) ⁺
XXIII-34	XX-1	XXII-13		LC-MS: m/z 1317.55 (M+H) ⁺

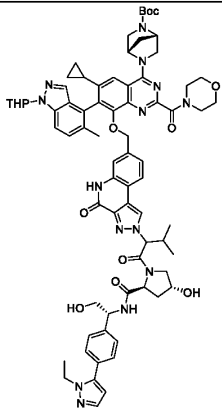
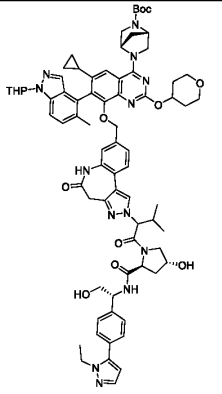
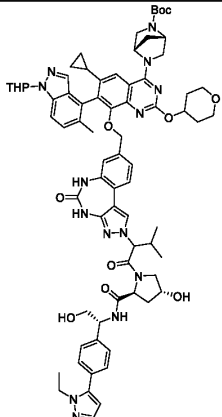
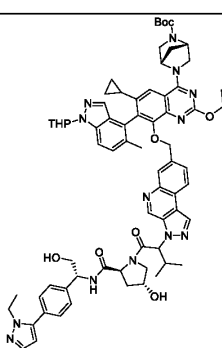
XXIII-35	XX-1	XXII-11		LC-MS: m/z 1320.45 (M+H) ⁺
XXIII-36	XX-1	XXII-12		LC-MS: m/z 1335.45 (M+H) ⁺
XXIII-37	XX-23	XXI-4		LC-MS: m/z 1405.90 [M-H] ⁺

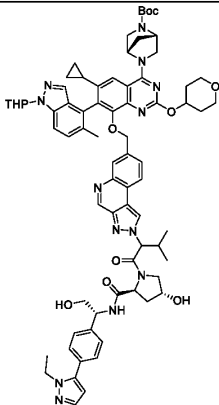
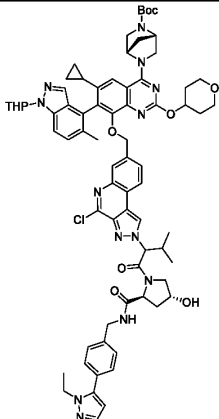
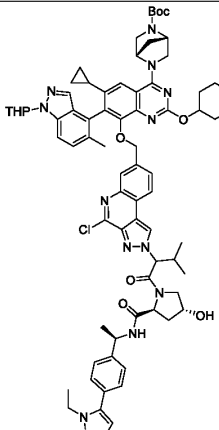
XXIII-38	XX-24	XXI-4	 Chemical structure of compound XXIII-38. It features a complex polycyclic aromatic system with a THP-protected nitrogen, a Boc-protected nitrogen, and a fluorinated pyrrolidine ring. The structure includes a central benzene ring with a chlorine atom and a nitrile group, and a side chain with a hydroxyl group and a pyridine ring.	LC-MS: m/z 1396.50 [M+H] ⁺
XXIII-39	XX-25	XXI-4	 Chemical structure of compound XXIII-39. It features a complex polycyclic aromatic system with a THP-protected nitrogen, a Boc-protected nitrogen, and a pyrrolidine ring. The structure includes a central benzene ring with a nitrile group and a side chain with a hydroxyl group and a pyridine ring.	LC-MS: m/z 1334.9 [M+H] ⁺
XXIII-40	XX-26	XXI-4	 Chemical structure of compound XXIII-40. It features a complex polycyclic aromatic system with a THP-protected nitrogen, a Boc-protected nitrogen, and a morpholine ring. The structure includes a central benzene ring with a chlorine atom and a nitrile group, and a side chain with a hydroxyl group and a pyridine ring.	LC-MS: m/z 1260.5 [M+H] ⁺

XXIII-41	XX-27	XXII-4	 Chemical structure of compound XXIII-41. It features a central pyrazole ring substituted with a THP group, a fluorophenyl group, and a morpholine ring. The pyrazole is also linked to a biphenyl system, which is further substituted with a hydroxyl group and a morpholine ring. The structure is complex, with multiple stereocenters and functional groups.	LC-MS: m/z 1174.40 $[M+H]^+$
XXIII-42	XX-28	XXII-4	 Chemical structure of compound XXIII-42. It features a central pyrazole ring substituted with a THP group, a fluorophenyl group, and a morpholine ring. The pyrazole is also linked to a biphenyl system, which is further substituted with a hydroxyl group and a morpholine ring. The structure is complex, with multiple stereocenters and functional groups.	LC-MS: m/z 1355.65 $[M+H]^+$
XXIII-43	XX-29	XXII-4	 Chemical structure of compound XXIII-43. It features a central pyrazole ring substituted with a THP group, a fluorophenyl group, and a morpholine ring. The pyrazole is also linked to a biphenyl system, which is further substituted with a hydroxyl group and a morpholine ring. The structure is complex, with multiple stereocenters and functional groups.	LC-MS: m/z 1317.65 $[M+H]^+$

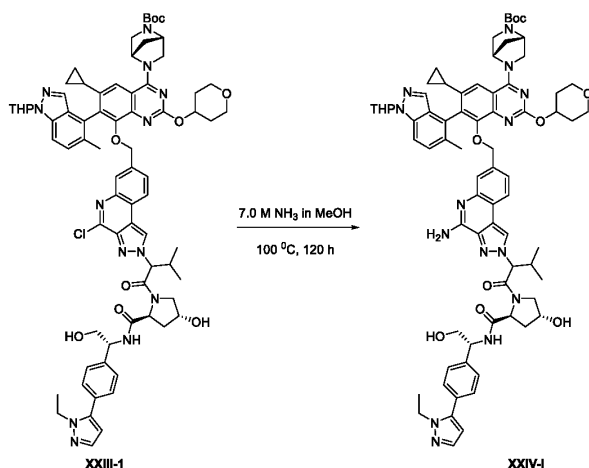
XXIII-44	XX-30	XXI-4	 Chemical structure of compound XXIII-44. It features a complex polycyclic aromatic system with a THP-protected nitrogen, a Boc-protected nitrogen, and a chlorine atom. The structure includes a pyridine ring, a pyrazole ring, and a hydroxyl group. The Boc group is attached to a nitrogen atom in a six-membered ring.	LC-MS: m/z 1377.05 $[M-H]^+$
XXIII-45	XX-31	XXI-4	 Chemical structure of compound XXIII-45. It features a complex polycyclic aromatic system with a THP-protected nitrogen, a Boc-protected nitrogen, and a chlorine atom. The structure includes a pyridine ring, a pyrazole ring, and a hydroxyl group. The Boc group is attached to a nitrogen atom in a six-membered ring.	LC-MS: m/z 1479.7 $[M+H]^+$
XXIII-46	XX-32	XXI-4	 Chemical structure of compound XXIII-46. It features a complex polycyclic aromatic system with a THP-protected nitrogen, a Boc-protected nitrogen, and a chlorine atom. The structure includes a pyridine ring, a pyrazole ring, and a hydroxyl group. The Boc group is attached to a nitrogen atom in a six-membered ring.	LC-MS: m/z 1179.55 $M+H]^+$

XXIII-47	XX-33	XXII-4		LC-MS: m/z 1488.65[M+H] ⁺
XXIII-48	XX-34	XXI-4		LC-MS: m/z 1352.55 [M+H] ⁺
XXIII-49	XX-35	XXI-4		LC-MS: m/z 1365.55[M+H] ⁺

XXIII-50	XX-36	XXI-4	 Chemical structure of compound XXIII-50, featuring a complex polycyclic aromatic system with a THP-protected nitrogen, a Boc-protected nitrogen, and a morpholine ring. The structure includes a central benzene ring substituted with a morpholine group and a complex side chain containing a pyrazole, a pyrrolidine, and a hydroxyl group.	LC-MS: m/z 1334.60[M+H] ⁺
XXIII-51	XX-37	XXI-4	 Chemical structure of compound XXIII-51, featuring a complex polycyclic aromatic system with a THP-protected nitrogen, a Boc-protected nitrogen, and a morpholine ring. The structure includes a central benzene ring substituted with a morpholine group and a complex side chain containing a pyrazole, a pyrrolidine, and a hydroxyl group.	LC-MS: m/z 1333.15 [M-H] ⁺
XXIII-52	XX-38	XXI-4	 Chemical structure of compound XXIII-52, featuring a complex polycyclic aromatic system with a THP-protected nitrogen, a Boc-protected nitrogen, and a morpholine ring. The structure includes a central benzene ring substituted with a morpholine group and a complex side chain containing a pyrazole, a pyrrolidine, and a hydroxyl group.	LC-MS: m/z 1335.60 [M+H] ⁺
XXIII-53	XX-39	XXI-4	 Chemical structure of compound XXIII-53, featuring a complex polycyclic aromatic system with a THP-protected nitrogen, a Boc-protected nitrogen, and a morpholine ring. The structure includes a central benzene ring substituted with a morpholine group and a complex side chain containing a pyrazole, a pyrrolidine, and a hydroxyl group.	LC-MS: m/z 1307.9 [M+H] ⁺

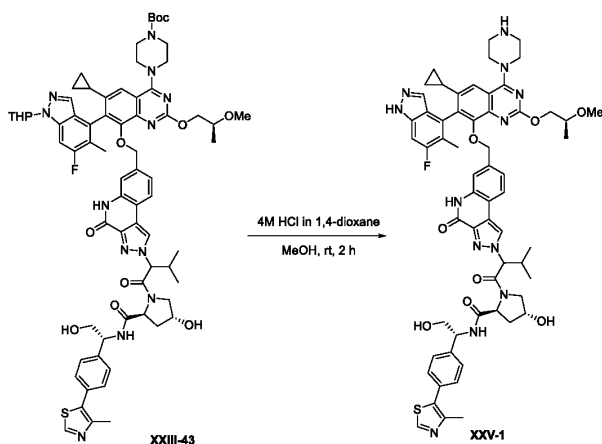
XXIII-54	XX-40	XXI-4		LC-MS: m/z 1307.9 [M+H] ⁺
XXIII-55	XX-1	XXII-17		LC-MS: m/z 1308.80[M+H] ⁺
XXIII-56	XX-1	XXII-18		LC-MS: m/z 1323.00[M+H] ⁺

Synthesis of tert-butyl (1S,4S)-5-(8-((4-amino-2-(1-((2S,4R)-2-(((R)-1-(4-(1-ethyl-1H-pyrazol-5-yl)phenyl)-2-hydroxyethyl)carbamoyl)-4-hydroxypyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2H-pyrazolo[3,4-c]quinolin-7-yl)methoxy)-6-cyclopropyl-7-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-2-(((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (XXIV-1):



A stirred solution of chloro intermediate **XXIII-1** (0.25 g, 0.187 mmol, 1.0 equiv.) in 7.0M NH₃ in MeOH (10 mL) was heated 100 °C for 120 h. After completion of reaction, the reaction mixture was concentrated under vacuum to get the titled crude product **XXIV-1** (0.25 g). LC-MS: *m/z* 1320.2 [M+H]⁺.

Synthesis of (2S,4R)-1-(2-(7-(((6-cyclopropyl-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-((S)-2-methoxypropoxy)-4-(piperazin-1-yl)quinazolin-8-yl)oxy)methyl)-4-oxo-4,5-dihydro-2H-pyrazolo[3,4-c]quinolin-2-yl)-3-methylbutanoyl)-4-hydroxy-N-((R)-2-hydroxy-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (XXV-1):

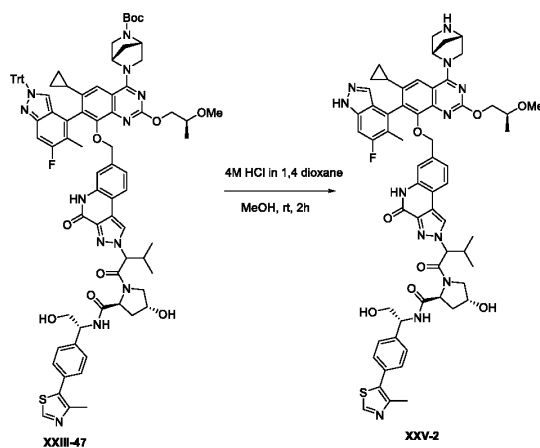


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To a stirred solution of **XXIII-43** (0.50 g, 0.37 mmol, 1.0 equiv.) in MeOH was added 4.0 M HCl in 1, 4 dioxane (5 mL), and the mixture was stirred for 2h at room temperature. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was precipitated with diethyl ether to get the title compound

5 **XXV-1** (0.40 g) as a mixture of four diastereomers; LC-MS: m/z 1133.30[M+H]⁺

Synthesis of (2S,4R)-1-(2-(7-(((4-(((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-6-cyclopropyl-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-((S)-2-methoxypropoxy)quinazolin-8-yl)oxy)methyl)-4-oxo-4,5-dihydro-2H-pyrazolo[3,4-c]quinolin-2-yl)-3-methylbutanoyl)-4-hydroxy-N-((R)-2-hydroxy-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**XXV-2**):



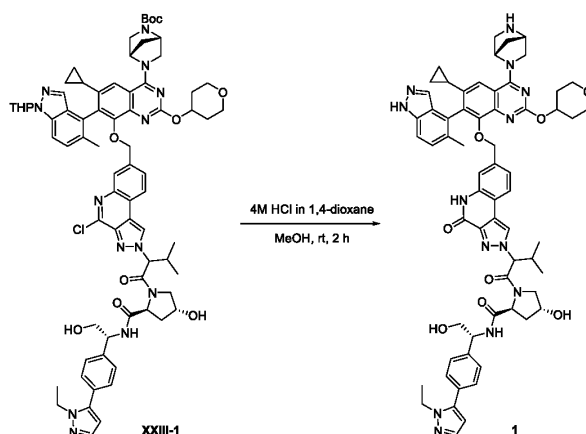
The above intermediate **XXV-2** was prepared using procedure similar to the one described in the synthesis of **Intermediate XXV-1** using **XXIII-47** as starting material; LC-MS: m/z 1145.30[M+H]⁺

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PREPARATION OF COMPOUNDS

Example-1: Synthesis of (2S,4R)-1-(2-(7-(((4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-6-cyclopropyl-7-(5-methyl-1H-indazol-4-yl)-2-((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-8-yl)oxy)methyl)-4-hydroxy-2H-pyrazolo[3,4-c]quinolin-2-yl)-3-methylbutanoyl)-N-((R)-1-(4-(1-ethyl-1H-pyrazol-5-yl)phenyl)-2-hydroxyethyl)-4-hydroxypyrrolidine-2-carboxamide (Compound-1)



To a stirred solution of **XXIII-1** (0.50 g, 0.37 mmol, 1.0 equiv.) in MeOH was added 4.0 M HCl in 1, 4 dioxane (5 mL), and the mixture was stirred for 2h at room temperature.

After the completion of the reaction, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was precipitated with diethyl ether to get the title compound **1** (0.40 g) as a mixture of four diastereomers. The mixture was purified by Prep-HPLC to provide the four pure diastereomers as formate salts (Prep HPLC condition: Column- Luna omega C18 (250 x 21.2mm, 5 micron), Mobile Phase-Formic acid in water(A), Acetonitrile (B)).

1a (Isomer-1 of **1**) ¹H NMR (400 MHz, CD₃OD): δ 8.64 (s, 1H), 8.56- 8.48 (m, 2H), 7.60- 7.12 (m, 11H), 6.93 (s, 1H), 6.53 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 6.02 (d, *J* = 2.0 Hz, 1H), 5.34- 5.20 (m, 4H), 5.00- 4.93 (m, 1H), 4.50- 4.40 (m, 4H), 3.95- 3.85 (m, 4H), 3.79 (d, *J* = 6.0 Hz, 1H), 3.76- 3.60 (m, 3H), 3.45- 3.40 (m, 3H), 2.82- 2.72 (m, 1H), 2.40- 2.30 (m, 2H), 2.19 (s, 3H), 2.18- 2.0 (m, 5H), 1.85- 1.75 (m, 2H), 1.50- 1.40 (m, 1H), 1.25 (t, *J* = 7.6 Hz, 3H), 1.20 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.67- 0.60 (m, 4H); LC-MS: *m/z* 1136.60 [M+H]⁺

1b (Isomer-2 of **1**) ¹H NMR (400 MHz, CD₃OD): δ 8.65 (s, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.50- 7.36 (m, 12H), 6.99 (s, 1H), 6.60 (d, *J* = 8.04Hz, 1H), 6.33 (d, *J* = 1.6 Hz, 1H), 5.34 (s, 2H),

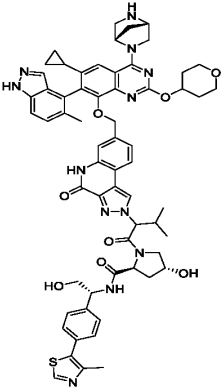
5.24- 5.19 (m, 2H), 5.10 (s, 1H), 4.60- 4.40 (m, 6H), 4.2 (q, $J = 7.2$ Hz, 3H), 4.05- 3.90 (m, 7H), 3.88 (d, $J = 6.8$ Hz, 3H), 3.65- 3.60 (m, 1H), 3.45- 3.40 (m, 3H), 2.82- 2.72 (m, 1H), 2.20 (s, 5H), 2.15- 2.00 (m, 6H), 1.85- 1.80 (m, 2H), 1.25- 1.20 (m, 3H), 0.86 (d, $J = 6.4$ Hz, 3H), 0.70- 0.60 (m, 4H); LC-MS: m/z 1136.69 $[M+H]^+$

5 **1c** (Isomer-3 of **1**) ^1H NMR (400 MHz, CD_3OD): δ 8.55 (s, 1H), 7.56- 7.37 (m, 8H), 7.28 (d, $J = 8.4$ Hz, 2H), 7.15 (d, $J = 8.4$ Hz, 2H), 7.11 (s, 1H), 6.44 (dd, $J = 8.04$ Hz, 1.6 Hz, 1H), 6.04 (d, $J = 2.0$ Hz, 1H), 5.40- 5.20 (m, 5H), 5.05 (t, $J = 7.6$ Hz, 1H), 4.71 (t, $J = 8.4$ Hz, 1H), 4.50- 4.40 (m, 4H), 4.05- 3.90 (m, 6H), 3.84 (d, $J = 6.4$ Hz, 3H), 3.70- 3.60 (m, 2H), 3.50- 3.40 (m, 2H), 2.40- 2.30 (m, 2H), 2.24 (s, 4H), 2.20- 2.10 (m, 4H), 1.90- 1.78 (m, 3H), 1.40- 1.35 (m, 3H), 1.21 (d, $J = 7.2$ Hz, 3H), 0.86 (d, $J = 6.8$ Hz, 3H), 0.65- 0.56 (m, 4H); LC-MS: m/z 1136.60 $[M+H]^+$

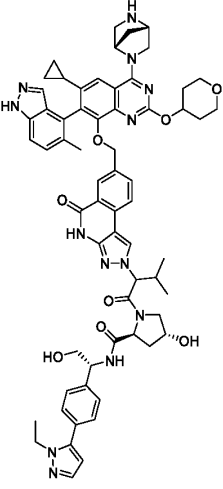
1d (Isomer-4 of **1**) ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.27 (s, 1H), 8.76 (s, 1H), 8.20 (d, $J = 8.4$ Hz, 1H), 7.60 (d, $J = 8.0$ Hz, 1H), 7.51- 7.43 (m, 8H), 7.37- 7.22 (m, 6H), 7.08 (s, 1H), 6.34 (d, $J = 2.0$ Hz, 1H), 6.27 (d, $J = 7.6$ Hz, 1H), 6.13 (d, $J = 1.6$ Hz, 1H), 5.25- 5.20 (m, 6H), 4.85- 4.60 (m, 2H), 4.32-4.20 (m, 3H), 4.02 (q, $J = 7.2$ Hz, 2H), 3.85- 3.60 (m, 13H), 2.12- 1.95 (m, 6H), 1.90- 1.87 (m, 1H), 1.85- 1.6 (m, 3H), 1.06 (d, $J = 6.8\text{Hz}$, 3H), 0.71 (d, $J = 6.4\text{Hz}$, 4H), 0.62- 0.60 (m, 4H); LC-MS: m/z 1136.6 $[M+H]^+$

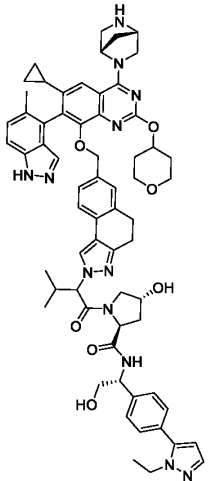
The Examples listed in below **Table-17** were prepared by a procedure similar to the one described in **Example 1** with 4N HCl in 1,4-dioxane as deprotecting reagent. The characterization data of the intermediates are summarized in Table-17.

Table-17

Compound no.	SM	Compound structure	Analytical Data
2 (mixture of four diastereomers)	XXIII -2		LC-MS: m/z 1139.60 $(M+H)^+$

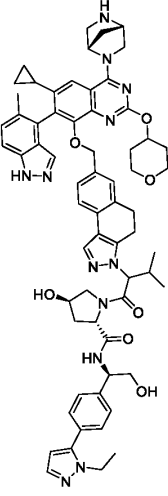
2a		Isomer-1 of compound 2	LC-MS: m/z 1139.60 (M+H) ⁺
2b		Isomer-2 of compound 2	LC-MS: m/z 1137.45 (M-H) ⁺
2c		Isomer-3 of compound 2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.1 (s, 1H), 11.3 (m, 1H), 9.0 (s, 1H), 8.19- 8.13 (m, 1H), 7.70 (d, <i>J</i> = 8.0 Hz, 1H), 7.66- 7.61 (m, 3H), 7.59- 7.50 (m, 3H), 7.48 (s, 1H), 7.46- 7.44 (m, 1H), 6.33 (d, <i>J</i> = 8.8 Hz, 1H), 5.25- 5.1 (m, 4H), 4.87 (d, <i>J</i> = 11.6 Hz, 2H), 4.39- 4.32 (m, 5H), 4.10- 3.90 (m, 1H), 3.80-3.61 (m, 4H), 3.55- 3.42 (m, 3H), 3.40-3.33(m, 3H), 3.31-3.32 (m, 2H), 2.51-2.50 (m, 1H), 2.47-2.44 (m, 2H), 2.33 (s, 1H), 2.14-2.12 (m, 4H), 1.99- 1.94 (m, 3H), 1.64- 1.62 (m, 3H), 1.34- 1.33 (m, 1H), 1.1 (dd, <i>J</i> = 17.2 Hz, 5.2 Hz, 4H), 0.72- 0.66 (m, 9H); LC-MS: m/z 1137.85 (M-H) ⁺
2d		Isomer-4 of compound 2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 13.0 (s, 1H), 11.31 (s, 1H), 9.0-8.90 (m, 1H), 8.8- 8.77 (m, 1H), 7.82-7.76-8.90 (m, 1H), 7.53-7.3 (m, 8H), 7.11-7.0 (m, 1H), 6.34-6.32 (m, 1H), 5.32-5.10 (m, 4H), 5.05-4.95 (m, 2H), 4.90-4.80 (m, 2H), 4.52-4.37 (m, 4H), 4.13-4.0 (m, 2H), 3.81- 3.75 (m, 4H), 3.70-3.53 (m, 3H), 3.52- 3.45 (m, 2H), 2.18-2.1 (m, 4H), 2.1-1.95 (m, 5H), 1.57-1.51 (m, 3H), 1.40-1.30 (m, 2H), 1.15-1.05 (m, 2H), 0.95-0.85 (m, 3H), 0.74-0.65 (m, 7H), 0.62-0.51 (m, 2H); LC-MS: m/z 1137.55 (M-H) ⁺

3 (mixture of four diastereomers)	XXIII -3		LC-MS: m/z 1137.1 $[M-H]^+$
3a		Isomer-1 of compound 3	1H NMR (400 MHz, CD_3OD): δ 8.43 (s, 1H), 7.69 (d, $J = 1.6$ Hz, 1H), 6.63 (d, $J = 8.0$ Hz, 1H), 7.59 (s, 2H), 7.53- 7.48 (m, 2H), 7.42 (d, $J = 8.8$ Hz, 1H), 7.31 (d, $J = 8.0$ Hz, 2H), 7.15 (d, $J = 8.4$ Hz, 2H), 6.83 (dd, $J = 8.0$ Hz, 2.0 Hz, 1H), 6.17 (d, $J = 2.0$ Hz, 1H), 5.74 (s, 1H), 5.60- 5.50 (m, 1H), 5.10- 5.00 (m, 2H), 4.80- 4.75 (m, 2H), 4.70- 4.64 (m, 2H), 4.50- 4.40 (m, 2H), 4.05- 3.55 (m, 14H), 2.73- 2.50 (m, 2H), 2.30 (s, 6H), 2.20- 1.85 (m, 6H), 1.65- 1.55 (m, 1H), 1.25 (t, $J = 7.2$ Hz, 3H), 1.19 (d, $J = 6.8$ Hz, 3H), 0.94 (d, $J = 6.4$ Hz, 3H), 0.80- 0.75 (m, 4H) ; LC-MS: m/z 1137.1 $[M-H]^+$. (isomer 1)
3b		Isomer-2 of compound 3	1H NMR (400 MHz, CD_3OD): δ 8.40 (s, 1H), 7.93 (s, $J = 1.6$ Hz, 1H), 7.65 (d, $J = 8.0$ Hz, 1H), 7.55- 7.37 (m, 10H), 6.95 (dd, $J = 8.0$ Hz, 1.6 Hz, 1H), 6.33 (d, $J = 2.0$ Hz, 1H), 5.50- 5.35 (m, 2H), 5.15- 5.00 (m, 2H), 4.85- 4.80 (m, 1H), 4.66 (s, 2H), 4.60 (t, $J = 8.4$ Hz, 2H), 4.50 (s, 2H), 4.18 (q, $J = 7.2$ Hz, 3H), 4.05- 3.92 (m, 4H),

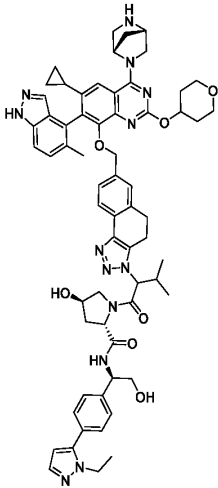
			3.87 (d, $J = 6.0$ Hz, 3H), 3.79- 3.55 (m, 5H), 2.75- 2.47 (m, 3H), 2.20 (s, 5H), 2.19- 2.00 (m, 4H), 1.90- 1.77 (m, 2H), 1.60- 1.50 (m, 1H), 1.36 (t, $J = 8.8$ Hz, 3H), 1.16 (d, $J = 6.8$ Hz, 3H), 0.88 (d, $J = 6.8$ Hz, 3H), 0.75- 0.60 (m, 4H) ; LC-MS: m/z 1137.1 [M-H] ⁺
3c		Isomer-3 of compound 3	¹ H NMR (400 MHz, CD ₃ OD): δ 8.53 (s, 1H), 8.28 (s, 1H), 7.73 (d, $J = 1.2$ Hz, 1H), 7.55- 7.35 (m, 8H), 7.25 (dd, $J = 6.4$ Hz, 2 Hz, 2H), 7.02 (s, 1H), 6.82 (dd, $J = 8.0$ Hz, 1.6 Hz, 1H), 6.11 (d, $J = 2.0$ Hz, 1H), 5.45- 4.96 (m, 7H), 4.74 (t, $J = 8.0$ Hz, 1H), 4.60 (s, 1H), 4.50- 4.37 (m, 2H), 4.05- 3.95 (m, 5H), 3.99 (d, $J = 6.8$ Hz, 2H), 3.80- 3.40 (m, 6H), 2.73- 2.65 (m, 1H), 2.40- 2.30 (m, 2H), 2.24 (s, 3H), 2.20- 1.80 (m, 6H), 1.40- 1.30 (m, 3H), 1.24 (t, $J = 7.2$ Hz, 3H), 1.18 (d, $J = 6.8$ Hz, 3H), 0.91 (d, $J = 7.6$ Hz, 3H), 0.65- 0.55 (m, 4H) ; LC-MS: m/z 1137.2 [M-H] ⁺
3d		Isomer-4 of compound 3	LC-MS: m/z 1137.1 [M-H] ⁺
4 (mixture of four diastereomers)	XXIII -4		LC-MS: m/z 1122.0 [M+H] ⁺

4a		Isomer-1 of compound 4	¹ H NMR (400 MHz, CD ₃ OD): δ 8.60-8.50 (m, 1H), 8.00- 7.90 (bs, 1H), 7.62-7.40 (m, 7H), 7.25- 7.15 (m, 5H), 6.63-6.61 (m, 1H), 6.35- 6.32 (m, 1H), 6.03 (s, 1H), 5.40- 5.30 (m, 2H), 5.25- 5.10 (m, 1H), 5.10- 4.95 (m, 1H), 4.72 (d, J = 10.8 Hz, 1H), 4.65 (t, J = 10.8 Hz, 1H), 4.52-4.48 (m, 3H), 4.38- 4.34 (m, 1H), 4.03-3.97 (m, 5H), 3.79- 3.73 (m, 4H), 3.57-3.55 (m, 3H), 2.85- 2.60 (m, 6H), 2.35- 2.0 (m, 11H), 1.60- 1.49 (m, 1H), 1.40- 1.37 (m, 1H), 1.24 (t, J = 6.8 Hz, 3H), 1.13 (d, J = 6.4 Hz, 3H), 0.88 (d, J = 6.4 Hz, 3H), 0.70 -0.66 (m, 5H); LC-MS: m/z 1122.0 [M+H] ⁺
4b		Isomer-2 of compound 4	¹ H NMR (400 MHz, CD ₃ OD): δ 8.60-8.45 (bs, 1H), 8.00 (s, 1H), 7.62- 7.40 (m, 10H), 7.18 (d, J = 8.0 Hz, 3H), 6.68 (d, J = 7.6 Hz, 1H), 6.38 (s, 1H), 6.32 (d, J = 2.0 Hz, 1H), 5.40- 5.3 (m, 2H), 5.15- 5.05 (m, 2H), 4.80- 4.75 (m, 2H), 4.62 (t, J = 8.0 Hz, 1H), 4.52-4.48 (m, 2H), 4.38-4.34 (m, 1H), 4.20 (q, J = 7.2 Hz, 1H), 4.10- 4.0 (m, 3H), 3.96- 3.90 (m, 1H), 3.87 (d, J = 6.0 Hz, 2H), 3.85- 3.80 (m, 1H), 3.61- 3.5 (m, 3H), 3.45- 3.40 (m, 1H), 2.84- 2.75 (m, 4H), 2.65- 2.55 (m, 1H), 2.38- 2.32 (m, 1H), 2.25- 2.18 (m, 6H), 2.17- 1.95 (m, 3H), 1.90- 1.80 (m, 2H), 1.56- 1.48 (m, 1H), 1.38- 1.31 (m, 4H), 1.12 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.4 Hz, 3H), 0.70 -0.64 (m, 4H); LC-MS: m/z 1122.0 [M+H] ⁺ .

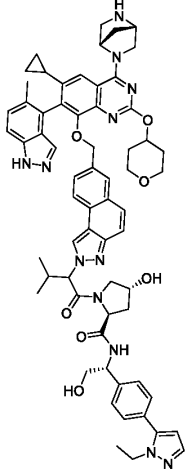
4c		Isomer-3 of compound 4	¹ H NMR (400 MHz, CD ₃ OD): δ 8.51-8.45 (bs, 2H), 7.97 (s, 1H), 7.55- 7.42 (m, 7H), 7.39- 7.30 (m, 3H), 7.28- 7.20 (m, 2H), 7.08 (d, <i>J</i> = 7.6 Hz, 1H), 6.56 (dd, <i>J</i> = 9.6, 1.6, 1H), 6.40- 6.30 (m, 1H), 6.06 (d, <i>J</i> = 2.0 Hz, 1H), 5.40- 5.30 (m, 2H), 5.14 (d, <i>J</i> = 11.2 Hz, 1H), 5.05- 5.04 (m, 1H), 4.76 (d, <i>J</i> = 11.2 Hz, 1H), 4.67 (t, <i>J</i> = 8.4 Hz, 1H), 4.50- 4.45 (m, 4H), 4.03- 4.99 (m, 4H), 3.82- 3.77 (m, 3H), 3.68- 3.65 (m, 2H), 3.38- 3.37 (m, 2H), 3.50- 3.40 (m, 1H), 2.80- 2.60 (m, 6H), 2.45- 2.00 (m, 12H), 1.95- 1.80 (m, 2H), 1.52- 1.30 (m, 2H), 1.25 (t, <i>J</i> = 7.2 Hz, 3H), 1.13 (d, <i>J</i> = 6.8 Hz, 1H), 0.87 (d, <i>J</i> = 6.8 Hz, 2H), 0.65-0.64 (m, 3H); LC-MS: <i>m/z</i> 1122.0 [M+H] ⁺
4d		Isomer-4 of compound 4	¹ H NMR (400 MHz, CD ₃ OD): δ 8.60 (bs, 2H), 7.99 (s, 1H), 7.58- 7.42 (m, 10H), 7.16 (d, <i>J</i> = 7.6 Hz, 1H), 6.64 (d, <i>J</i> = 7.6 Hz, 1H), 6.37 (s, 1H), 6.32 (d, <i>J</i> = 1.6 Hz, 1H), 5.40- 5.30 (m, 2H), 5.15 (d, <i>J</i> = 10.8 Hz, 1H), 5.08 (t, <i>J</i> = 6.0 Hz, 1H), 4.80- 4.70 (m, 2H), 4.60 (t, <i>J</i> = 8.0 Hz, 1H), 4.52- 3.90 (m, 3H), 4.20 (q, <i>J</i> = 7.2 Hz, 2H), 4.02- 4.00 (m, 3H), 3.87- 3.86 (m, 1H), 3.87 (d, <i>J</i> = 6.0 Hz, 2H), 3.85- 3.78 (m, 1H), 3.65- 3.50 (m, 3H), 3.45- 3.40 (m, 4H), 2.80- 2.75 (m, 4H), 2.60- 2.50 (m, 1H), 2.40- 2.30 (m, 1H), 2.25 (s, 6H), 2.10-1.95 (m, 2H), 1.90- 1.80 (m, 2H), 1.55- 1.49 (m, 1H), 1.38- 1.30 (m, 3H), 1.12 (t, <i>J</i> = 6.4 Hz, 3H), 0.84 (d, <i>J</i> = 6.4

			Hz, 3H), 0.71- 0.65 (m, 3H); LC-MS: m/z 1122.0 $[M+H]^+$.
5 (mixture of four diastereomers)	XXIII -5		LC-MS: m/z 1121.30 $[M+H]^+$
5a		Isomer-1 of compound 5	^1H NMR (400 MHz, CD_3OD): δ 8.41 (s, 1H), 7.77 (s, 1H), 7.55- 7.40 (m, 11H), 7.19 (d, J = 8.0 Hz, 1H), 6.65 (d, J = 6.8 Hz, 1H), 6.41 (s, 1H), 6.32 (dd, J = 4.0 Hz, 1.6 Hz, 1H), 5.40- 5.30 (m, 2H), 5.15- 5.00 (m, 2H), 4.90- 4.85 (m, 1H), 4.80- 4.75 (m, 1H), 4.65- 4.60 (m, 1H), 4.55- 4.52 (m, 3H), 4.45- 4.40 (m, 1H), 4.18 (q, J = 7.2 Hz, 2H), 4.05- 4.00 (m, 3H), 3.90- 3.80 (m, 3H), 3.80- 3.75 (m, 1H), 3.65- 3.50 (m, 2H), 3.15- 2.90 (m, 2H), 2.75- 2.70 (m, 2H), 2.50- 2.40 (m, 1H), 2.39- 2.25 (m, 4H), 2.20- 1.95 (m, 3H), 1.90- 1.85 (m, 2H), 1.80- 1.50 (m, 4H), 1.34 (t, J = 7.2 Hz, 3H), 1.12 (d, J = 6.8 Hz, 3H), 0.90- 0.85 (m, 1H), 0.77 (d, J = 6.8 Hz, 3H), 0.70 -0.60 (m, 4H); LC-MS: m/z 1121.30 $[M+H]^+$
5b		Isomer-2 of compound 5	^1H NMR (400 MHz, CD_3OD): δ 8.44 (s, 1H), 7.83 (s, 1H), 7.60- 7.15 (m, 13H), 6.70- 6.60 (m, 1H), 6.40- 6.35 (m, 1H),

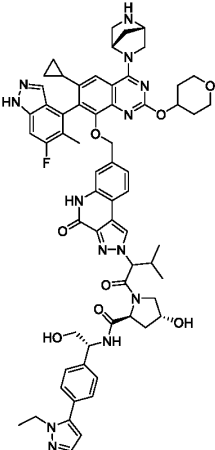
			6.28 (d, $J = 2.0$ Hz, 1H), 5.40- 5.30 (m, 3H), 5.20- 4.90 (m, 3H), 4.80- 4.45 (m, 7H), 4.35- 4.30 (m, 1H), 4.20- 3.95 (m, 4H), 3.90- 3.80 (m, 2H), 3.75- 3.65 (m, 2H), 3.60- 3.40 (m, 4H), 3.10- 2.70 (m, 8H), 2.50- 2.40 (m, 2H), 2.35- 2.10 (m, 3H), 2.10- 1.80 (m, 3H), 1.65- 1.50 (m, 2H), 1.35 (t, $J = 7.2$ Hz, 3H), 1.16 (d, $J = 6.8$ Hz, 3H), 0.95- 0.85 (m, 1H), 0.82 (d, $J = 6.8$ Hz, 3H); LC-MS: m/z 1121.20 $[M+H]^+$
5c		Isomer-3 of compound 5	^1H NMR (400 MHz, CD_3OD): δ 8.49 (s, 1H), 7.76 (s, 1H), 7.60- 7.35 (m, 10H), 7.16 (d, $J = 8.0$ Hz, 1H), 6.63 (d, $J = 9.2$ Hz, 1H), 6.37 (s, 1H), 6.31 (dd, $J = 6.8$ Hz, 1.6 Hz, 1H), 5.35- 5.30 (m, 2H), 5.15- 5.00 (m, 2H), 4.87- 4.81 (m, 3H), 4.65- 4.55 (m, 2H), 4.53- 4.40 (m, 3H), 4.19- 4.15 (m, 2H), 4.04- 3.99 (m, 3H), 3.90- 3.75 (m, 3H), 3.70- 3.35 (m, 4H), 3.20- 2.90 (m, 2H), 2.75- 2.65 (m, 3H), 2.45- 2.35 (m, 1H), 2.25- 2.10 (m, 7H), 2.05- 1.95 (m, 1H), 1.90- 1.75 (m, 2H), 1.60- 1.45 (m, 1H), 1.36 (t, $J = 7.2$ Hz, 3H), 1.12 (d, $J = 6.2$ Hz, 3H), 0.05- 0.85 (m, 3H), 0.77 (d, $J = 6.4$ Hz, 3H), 0.69-0.64 (m, 4H); LC-MS: m/z 1122.00 $[M+H]^+$
5d		Isomer-4 of compound 5	^1H NMR (400 MHz, CD_3OD): δ 8.51 (s, 2H), 7.80 (s, 1H), 7.60- 7.30 (m, 11H), 7.13 (d, $J = 8.0$ Hz, 1H), 6.34 (d, $J = 4.4$ Hz, 1H), 6.27 (s, 1H), 6.20 (d, $J = 2.0$ Hz, 1H), 5.31- 4.90 (m, 6H), 4.85- 4.55 (m, 3H), 4.52- 4.30 (m, 4H), 4.20- 3.85 (m,

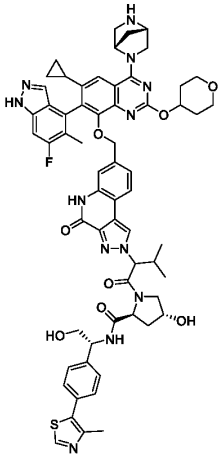
			9H), 3.70- 3.40 (m, 5H), 3.10- 2.85 (m, 2H), 2.80- 2.50 (m, 4H), 2.40- 1.80 (m, 9H), 1.68- 1.45 (m, 1H), 1.34 (t, $J = 7.2$ Hz, 3H), 1.30- 1.20 (m, 1H), 1.08 (d, $J = 6.4$ Hz, 3H), 0.82 (d, $J = 7.6$, Hz, 3H), 0.67- 0.64 (m, 1H); LC-MS: m/z 1122.70 $[M+H]^+$
6 (mixture of four diastereomers)	XXIII -6		LC-MS: m/z 1120.9 $[M-H]^+$.
6a		Isomer-1 of compound 6	^1H NMR (400 MHz, DMSO- d_6): δ 13.0 (s, 1H), 8.40- 8.35 (m, 1H), 8.25 (s, 2H), 7.54- 7.34 (m, 11H), 6.66 (d, $J = 7.6$ Hz, 1H), 6.45 (s, 1H), 6.26 (d, $J = 2.0$ Hz, 1H), 5.32 (d, $J = 9.2$ Hz, 1H), 5.06 (s, 2H), 4.85- 4.80 (m, 3H), 4.30- 4.20 (m, 1H), 4.08 (q, $J = 7.2$ Hz, 2H), 3.90- 3.75 (m, 4H), 3.70- 3.60 (m, 4H), 3.12- 3.00 (m, 7H), 2.85- 2.76 (m, 1H), 2.13- 1.90 (m, 11H), 1.80- 1.60 (m, 4H), 1.32- 1.20 (m, 4H), 1.08 (d, $J = 6.8$ Hz, 3H), 0.70 -0.55 (m, 6H); LC-MS: m/z 1120.4 $[M+H]^+$.
6b		Isomer-2 of compound 6	^1H NMR (400 MHz, DMSO- d_6): δ 13.0 (s, 1H), 8.48 (d, $J = 8.4$ Hz, 1H), 8.23 (s, 1H), 7.57- 7.30 (m, 12H), 6.69 (d, $J = 8.0$ Hz, 1H), 6.46 (s, 1H), 6.32 (d, $J = 1.6$ Hz, 1H),

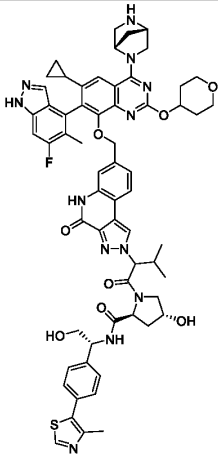
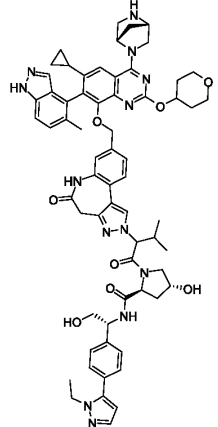
			5.27 (d, $J = 10.8$ Hz, 1H), 5.25- 5.03 (m, 4H), 4.95- 4.8 (m, 3H), 4.47 (t, $J = 7.6$ Hz, 1H), 4.30- 4.20 (m, 2H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.90- 3.85 (m, 4H), 3.84- 3.75 (m, 3H), 3.65- 3.60 (m, 3H), 3.10- 3.00 (m, 1H), 2.95- 2.85 (m, 2H), 2.80- 2.75 (m, 2H), 2.15- 2.10 (m, 4H), 2.10- 2.00 (m, 4H), 1.95- 1.90 (m, 1H), 1.85- 1.60 (m, 4H), 1.32 (t, $J = 6.8$ Hz, 3H), 1.09 (d, $J = 6.4$ Hz, 3H), 0.70 (d, $J = 6.8$ Hz, 3H), 0.65- 0.50 (m, 3H) ; LC-MS: m/z 1120.65 $[M+H]^+$
6c		Isomer-3 of compound 6	^1H NMR (400 MHz, DMSO- d_6): δ 13.0 (s, 1H), 8.48 (d, $J = 8.0$ Hz, 1H), 7.55- 7.35 (m, 12H), 6.65 (d, $J = 8.0$ Hz, 1H), 6.46 (s, 1H), 6.32 (d, $J = 1.6$ Hz, 1H), 5.38- 5.15 (m, 4H), 5.12 (d, $J = 4.0$ Hz, 1H), 5.05 (s, 1H), 4.88 (q, $J = 5.6$ Hz, 2H), 4.68 (d, $J = 7.6$ Hz, 1H), 4.47 (t, $J = 7.6$ Hz, 1H), 4.35- 4.20 (m, 2H), 4.12 (q, $J = 7.2$ Hz, 2H), 3.90- 3.80 (m, 1H), 3.80- 3.73 (m, 3H), 3.68- 3.47 (m, 4H), 3.15- 2.83 (m, 3H), 2.67 (q, $J = 2.0$ Hz, 2H), 2.11 (s, 3H), 2.10- 1.60 (m, 11H), 1.55- 1.43 (m, 1H), 1.32 (t, $J = 6.8$ Hz, 3H), 1.09 (d, $J = 6.4$ Hz, 3H), 0.70 (d, $J = 6.4$ Hz, 3H), 0.63 (d, $J = 6.0$ Hz, 3H) ; LC-MS: m/z 1120.9 $[M-H]^+$
6d		Isomer-4 of compound 6	^1H NMR (400 MHz, DMSO- d_6): δ 13.0 (s, 1H), 8.35 (d, $J = 8.4$ Hz, 1H), 7.55- 7.32 (m, 12H), 6.64 (d, $J = 9.2$ Hz, 1H), 6.48 (s, 1H), 6.26 (d, $J = 1.6$ Hz, 1H), 5.35- 5.30 (m, 2H), 5.25- 5.15 (m, 2H), 5.11 (d, $J = 3.2$ Hz, 1H), 5.05 (s, 2H), 4.92- 4.80 (m,

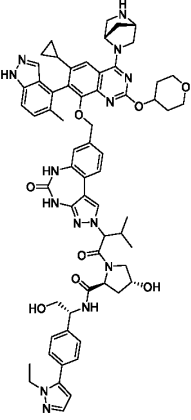
			2H), 4.72- 4.64 (m, 1H), 4.55- 4.48 (m, 1H), 4.26- 4.20 (m, 2H), 4.07 (d, $J = 7.2$ Hz, 2H), 3.94- 3.82 (m, 3H), 3.78- 3.70 (m, 3H), 3.66- 3.50 (m, 3H), 2.13- 2.08 (m, 5H), 2.07- 1.95 (m, 5H), 1.91- 1.84 (m, 2H), 1.75- 1.70 (m, 2H), 1.68- 1.63 (m, 2H), 1.50- 1.40 (m, 2H), 1.30- 1.25 (m, 5H), 1.08 (d, $J = 6.4$ Hz, 3H), 0.86 (t, $J = 6.8$ Hz, 3H), 0.7 (d, $J = 6.8$ Hz, 3H) ; LC-MS: m/z 1120.9 [M-H] ⁺
7 (mixture of four diastereomers)	XXIII -7		LC-MS: m/z 1120.0 [M-H] ⁺
7a		Isomer-1 of compound 7	¹ H NMR (400 MHz, CD ₃ OD): δ 8.78 (s, 1H), 8.51 (s, 1H), 7.96 (d, $J = 8.4$ Hz, 2H), 7.60- 7.30 (m, 10H), 7.34 (d, $J = 9.2$ Hz, 3H), 7.10- 7.04 (m, 3H), 6.96- 6.90 (m, 1H), 5.99 (d, $J = 2.0$ Hz, 1H), 5.36- 5.24 (m, 5H), 4.51- 4.44 (m, 4H), 4.04- 3.93 (m, 7H), 3.70- 3.60 (m, 3H), 2.85- 2.75 (m, 1H), 2.40- 2.25 (m, 2H), 2.19 (s, 6H), 2.15- 2.09 (m, 3H), 1.90- 1.80 (m, 3H), 1.55- 1.45 (m, 1H), 1.21 (d, $J = 7.6$ Hz, 6H), 0.95- 0.90 (m, 1H), 0.86 (d, $J = 6.4$ Hz, 3H), 0.75-0.60 (m, 3H); LC-MS: m/z 1120.0 [M-H] ⁺

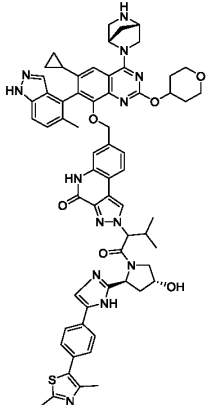
7b		Isomer-2 of compound 7	¹ H NMR (400 MHz, CD ₃ OD): δ 8.76 (s, 1H), 8.53 (s, 1H), 7.96 (d, <i>J</i> = 8.0 Hz, 1H), 7.60- 7.30 (m, 12H), 7.08 (s, 1H), 6.99 (d, <i>J</i> = 8.4 Hz, 1H), 6.33 (d, <i>J</i> = 2.0 Hz, 1H), 5.35- 5.28 (m, 3H), 5.13- 5.00 (m, 2H), 4.95 (t, <i>J</i> = 9.2 Hz, 1H), 4.60 (t, <i>J</i> = 7.6 Hz, 1H), 4.52- 4.45 (m, 3H), 4.36 (s, 1H), , 4.19 (q, <i>J</i> = 7.2 Hz, 2H), 4.05- 3.85 (m, 7H), 3.60- 3.40 (m, 4H), 2.80- 2.05 (m, 1H), 2.40- 2.30 (m, 1H), 2.19 (s, 6H), 2.10- 2.00 (m, 3H), 1.90- 1.75 (m, 3H), 1.55- 1.50 (m, 1H), 1.36 (t, <i>J</i> = 7.2 Hz, 3H), 1.20 (d, <i>J</i> = 6.8 Hz, 3H), 0.80 (d, <i>J</i> = 6.8 Hz, 3H), 0.70-0.60 (m, 4H); LC-MS: <i>m/z</i> 1119.9 [M-H] ⁺
7c		Isomer-3 of compound 7	¹ H NMR (400 MHz, CD ₃ OD): δ 8.70 (s, 1H), 8.52 (s, 1H), 7.79 (d, <i>J</i> = 8.0 Hz, 1H), 7.60- 7.10 (m, 12H), 7.11 (s, 1H), 6.02 (d, <i>J</i> = 1.6 Hz, 1H), 5.40- 5.30 (m, 3H), 5.10- 4.90 (m, 2H), 4.75- 4.45 (m, 6H), 4.03- 3.95 (m, 7H), 3.90- 3.52 (m, 8H), 3.50- 3.40 (m, 2H), 2.40- 2.00 (m, 11H), 1.90- 1.80 (m, 2H), 1.25- 1.15 (m, 6H), 0.83 (d, <i>J</i> = 6.8 Hz, 3H), 0.64 (d, <i>J</i> = 5.6 Hz, 3H); LC-MS: <i>m/z</i> 1119.9 [M-H] ⁺
7d		Isomer-4 of compound 7	¹ H NMR (400 MHz, CD ₃ OD): δ 8.77 (s, 1H), 8.50 (s, 1H), 7.93 (d, <i>J</i> = 8.4 Hz, 1H), 7.65- 7.38 (m, 13H), 7.08 (d, <i>J</i> = 12.4 Hz, 1H), 7.02- 6.95 (m, 1H), 6.33 (d, <i>J</i> = 2.4 Hz, 1H), 5.40- 5.34 (m, 4H), 5.10- 5.00 (m, 2H), 4.60 (s, 1H), 4.50- 4.44 (m, 3H), 4.24- 4.10 (m, 3H), 4.05- 3.80 (m, 8H), 3.70- 3.60 (m, 2H), 3.55- 3.45 (m, 3H),

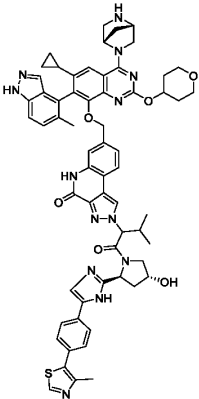
			2.80 (s, 1H), 2.42- 2.38 (m, 1H), 2.25 (s, 3H), 2.21 (s, 4H), 2.15- 2.10 (m, 2H), 1.90- 1.80 (m, 2H), 1.40- 1.30 (m, 3H), 1.20 (d, $J = 6.8$ Hz, 3H), 1.06 (d, $J = 6.4$ Hz, 3H), 0.80 (d, $J = 6.8$ Hz, 3H); LC-MS: m/z 1120.0 $[M-H]^+$
12 (mixture of four diastereomers)	XXIII -8		LC-MS: m/z 1154.35 $[M+H]^+$
12a		Isomer-1 of compound 12	LC-MS: m/z 1154.35 $[M+H]^+$
12b		Isomer-2 of compound 12	LC-MS: m/z 1154.35 $[M+H]^+$
12c		Isomer-3 of compound 12	LC-MS: m/z 1154.35 $[M+H]^+$
12d		Isomer-4 of compound 12	1H NMR (400 MHz, CD_3OD): δ 8.64 (s, 1H), 8.48 (s, 1H), 7.62 (d, $J = 8.4$ Hz, 1H), 7.54- 7.44 (m, 8H), 7.30 (d, $J = 0.8$ Hz, 1H), 7.21 (d, $J = 8.4$ Hz, 1H), 6.99 (s, 1H), 6.61 (dd, $J = 8.0$ Hz, 1.6 Hz, 1H), 6.33 (d, $J = 2.0$ Hz, 1H), 5.35- 5.25 (m, 4H), 5.21 (d, $J = 10.8$ Hz, 1H), 5.11- 5.05 (m, 1H), 4.97 (d, $J = 12.0$ Hz, 1H), 4.65 - 4.44 (m, 4H), 4.19 (q, $J = 7.2$ Hz, 2H), 4.18- 4.10 (m, 1H), 4.05- 3.87 (m, 7H), 3.69-3.65 (m, 1H), 3.51-3.42 (m, 3H), 2.80- 2.72 (m,

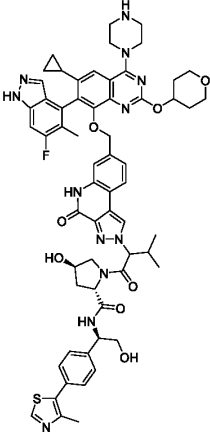
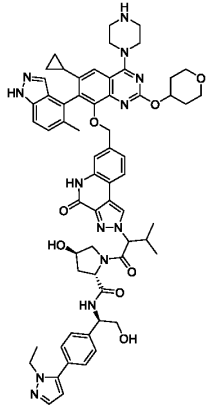
			1H), 2.42- 2.38 (m, 1H), 2.15-2.00 (m, 7H), 1.85- 1.79 (m, 2H), 1.36 (t, $J = 7.2$ Hz, 3H), 1.20 (d, $J = 6.8$ Hz, 3H), 0.86 (d, $J = 6.8$ Hz, 3H), 0.72- 0.60 (m, 4H); LC-MS: m/z 1154.35 $[M+H]^+$
13 (mixture of four diastereomers)	XXIII -9		LC-MS: m/z 1157.35 $[M+H]^+$
13a		Isomer-1 of compound 13	LC-MS: m/z 1157.35 $[M+H]^+$
13b		Isomer-2 of compound 13	LC-MS: m/z 1157.35 $[M+H]^+$
13c		Isomer-3 of compound 13	LC-MS: m/z 1157.35 $[M+H]^+$
13d		Isomer-4 of compound 13	1H NMR (400 MHz, CD_3OD): δ 8.90 (s, 1H), 8.65 (s, 1H), 8.56 (s, 2H), 7.62 (d, $J = 8.0$ Hz, 1H), 7.51- 7.44 (m, 7H), 7.30 (s, 1H), 7.21 (d, $J = 10.0$ Hz, 1H), 6.62 (d, $J = 8.0$ Hz, 1H), 5.35- 5.27 (m, 4H), 5.21 (d, $J = 10.8$ Hz, 1H), 5.10- 5.06 (m, 1H), 4.97 (d, $J = 10.8$ Hz, 1H), 4.64 - 4.51 (m, 4H), 4.08- 3.85 (m, 7H), 3.73-3.69 (m, 1H), 3.55-3.42 (m, 4H), 2.77- 2.70 (m, 1H), 2.51 (s, 3H), 2.45- 2.40 (m, 1H), 2.15-2.00 (m, 5H), 1.85- 1.75 (m, 2H), 1.48-1.40 (m, 1H), 1.20 (d, $J = 6.4$ Hz, 3H), 0.85 (d, $J =$

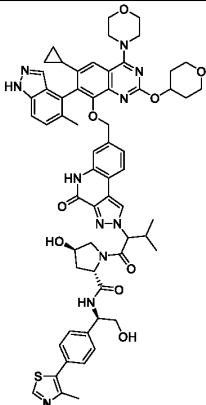
			6.4 Hz, 3H), 0.70-0.61 (m, 4H); LC-MS: m/z 1157.35 $[M+H]^+$
13a	XXIII -10		LC-MS: m/z 1157.35 $[M+H]^+$
32	XXIII -51		LC-MS: m/z 1149.55 $[M-H]$
32a		Isomer-1 of compound 32	LC-MS: m/z 1149.55 $[M-H]^+$
32b		Isomer-2 of compound 32	LC-MS: m/z 1149.55 $[M-H]^+$

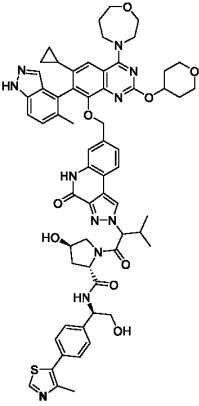
38(mixture of four diastereomers)	XXIII -52		LC-MS: m/z 1151.50 $[M+H]^+$
38a		Isomer-1 of compound 38	^1H NMR (400 MHz, CD_3OD): δ 8.54 (s, 1H), 7.91 (s, 1H), 7.54- 7.31 (m, 10H), 7.10 (d, J = 7.6 Hz, 1H), 6.42- 6.40 (m, 1H), 6.28 (s, 1H), 6.17 (d, J = 2.0 Hz, 1H), 5.29 (s, 2H), 5.09- 5.03 (m, 2H), 4.67 (t, J = 4.4 Hz, 1H), 4.6 (s, 1H), 4.45 – 4.42 (m, 2H), 4.30 (s, 1H), 4.10 (q, J = 7.2 Hz, 2H), 4.0 -3.92 m, 4H), 3.85 (d, J = 5.6 Hz, 2H), 3.74 - 3.68 (m, 1H), 3.58-3.45 (m, 4H), 2.40-2.30 (m, 2H), 2.17 (s, 3H), 2.10 – 2.02 (m, 3H), 1.90-1.70 (m, 3H), 1.52 – 1.45 (m, 1H), 1.45 -1.35 m, 2H), 1.13 (d, J = 6.4 Hz, 3H), 0.93 (d, J = 6.4 Hz, 3H), 0.72-0.60 (m, 4H); LC-MS: m/z 1151.40 $[M+H]^+$
38b		Isomer-2 of compound 38	^1H NMR (400 MHz, CD_3OD): δ 8.53 (s, 1H), 7.87 (s, 1H), 7.58- 7.41 (m, 9H), 7.09 (d, J = 8.0 Hz, 1H), 6.43 (dd, J = 9.6, 1.6 Hz, 1H), 6.33 (d, J = 2.0 Hz, 1H), 6.30 (s, 1H), 5.35 5.28 (m, 3H), 4.50 -4.40 (m, 2H), 4.02 -3.85 (m, 7H), 3.60- 3.50 (m, 2H), 2.1 – 2.0 (m, 6H), 1.92 -1.70 (m, 3H), 1.42 -1.30 (m, 16H), 1.11 (d, J = 6.4 Hz,

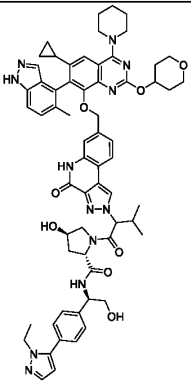
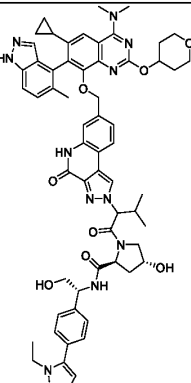
			3H), 0.94 – 0.89 (m, 6H), 0.75-0.6 (m, 5H); LC-MS: m/z 1151.50 $[M+H]^+$
38c		Isomer-3 of compound 38	LC-MS: m/z 1151.50 $[M+H]^+$
38d		Isomer-4 of compound 38	^1H NMR (400 MHz, CD_3OD): δ 8.53 (s, 1H), 7.87 (s, 1H), 7.58- 7.41 (m, 9H), 7.09 (d, J = 8.0 Hz, 1H), 6.43 (dd, J = 9.6, 1.6 Hz, 1H), 6.33 (d, J = 2.0 Hz, 1H), 6.30 (s, 1H), 5.35 5.28 (m, 3H), 4.50 -4.40 (m, 2H), 4.02 -3.85 (m, 7H), 3.60- 3.50 (m, 2H), 2.1 – 2.0 (m, 6H), 1.92 -1.70 (m, 3H), 1.42 -1.30 (m, 16H), 1.11 (d, J = 6.4 Hz, 3H), 0.94 – 0.89 (m, 6H), 0.75-0.6 (m, 5H); LC-MS: m/z 1151.50 $[M+H]^+$
160 (mixture of three diastereomers)	XXIII -36		LC-MS: m/z 1138.1 $[M-H]^+$
160a		Isomer-1 of compound 160	LC-MS: m/z 1138.1 $[M-H]^+$
160b		Isomer-2 of compound 160	LC-MS: m/z 1138.1 $[M-H]^+$
160c		Isomer-3 of compound 160	^1H NMR (400 MHz, DMSO-d_6): δ 13.00 (s, 1H), 11.31 (s, 1H), 8.73 (s, 1H), 8.43 (s, 3H), 7.82-7.30 (m, 12H), 7.13 (s, 1H), 6.35 (d, J = 8.4 Hz, 1H), 5.35-5.05 (m, 6H), 4.72-4.55 (m, 2H), 4.29-4.12 (m, 2H), 3.88-3.60 (m, 8H), 3.35-3.00 (m 6H),

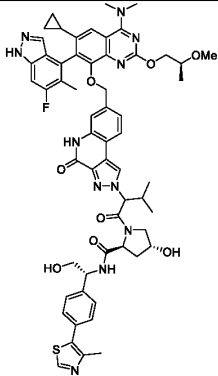
			2.67 (s, 3H), 2.41 (s, 3H), 2.18-2.15 (m, 1H), 2.13 (s, 3H), 2.09-1.95 (m, 3H), 1.85-1.50 (m, 3H), 1.38-1.32 (m, 1H), 1.02-0.95 (m, 3H), 0.71-0.45 (m, 7H); LC-MS: m/z 1138.1 $[M-H]^+$
161 (mixture of four diastereomers)	XXIII -35		LC-MS: m/z 1117.30 $[M+H]^+$.
161a		Isomer-1 of compound 161	LC-MS: m/z 1117.30 $[M+H]^+$.
161b		Isomer-2 of compound 161	LC-MS: m/z 1117.30 $[M+H]^+$.
161c		Isomer-3 of compound 161	LC-MS: m/z 1118.40 $[M+H]^+$.
161d		Isomer-4 of compound 161	1H NMR (400 MHz, DMSO- d_6): δ 13.00 (s, 1H), 12.06 (s, 1H), 11.30 (s, 1H), 8.99 (s, 1H), 8.74 (s, 1H), 8.33 (s, 2H), 7.83 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.58-7.32 (m, 9H), 7.14 (s, 1H), 6.35 (d, J = 9.2 Hz, 1H), 5.45-5.05 (m, 6H), 4.72-4.55 (m, 1H), 4.28-4.09 (m, 2H), 3.85-3.60 (m, 6H), 3.35-3.00 (m, 8H), 2.13 (s, 3H), 2.03-1.90 (m, 7H), 1.85-1.75 (m, 3H), 1.05-1.02 (m, 3H), 0.71-0.55 (m, 7H); LC-MS: m/z 1116.7 $[M-H]^+$

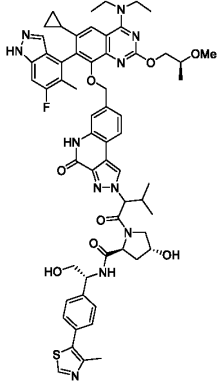
168	XXIII -11		LC-MS: m/z 1145.25 [M+H] ⁺
169 (mixture of four diastereomers)	XXIII -12		LC-MS: m/z 1124.25 [M+H] ⁺
169a		Isomer-1 of compound 169	LC-MS: m/z 1124.25 [M+H] ⁺
169b		Isomer-2 of compound 169	LC-MS: m/z 1124.25 [M+H] ⁺
169c		Isomer-3 of compound 169	¹ H NMR (400 MHz, CD ₃ OD): δ 8.64 (s, 1H), 8.55 (bs, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.52-7.37 (m, 8H), 7.34 (s, 1H), 6.99 (d, J = 1.2 Hz, 1H), 6.61 (dd, J = 8.0, 1.6 Hz, 1H), 6.33 (d, J = 2.0 Hz, 1H), 5.38- 5.30 (m, 1H), 5.26 (d, J = 11.6 Hz, 1H), 5.21 (d, J = 10.4 Hz, 1H), 5.10 (t, J = 6.0 Hz, 1H), 4.61-4.58 (m, 1H), 4.54-4.48 (m, 1H), 4.18 (q, J = 7.2 Hz, 2H), 4.04- 3.89 (m, 9H), 3.48-3.40 (m, 2H), 3.25-3.18 (m, 4H), 2.80-

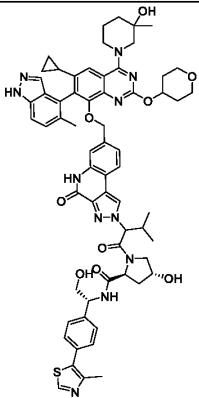
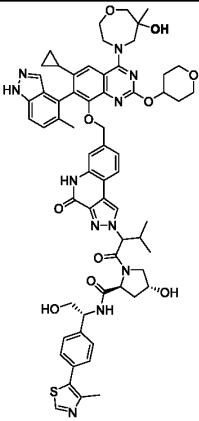
			2.72 (m, 1H), 2.28-2.00 (m, 11H), 1.89-1.78 (m, 2H), 1.33 (t, $J = 7.2$ Hz, 3H), 1.21 (d, $J = 6.8$ Hz, 3H), 0.86 (d, $J = 6.8$ Hz, 3H), 0.69-0.60 (m, 4H); LC-MS: m/z 1124.25 $[M+H]^+$
169d		Isomer-4 of compound 169	LC-MS: m/z 1124.25 $[M+H]^+$
170 (mixture of four diastereomers)	XXIII -13		
Mixture of 170 and 170b		Mixture of isomer-1 and isomer-2 of compound 170	LC-MS: m/z 1128.3 $[M+H]^+$
Mixture of 170c and 170d		Mixture of isomer-3 and isomer-4 of compound 170	^1H NMR (400 MHz, DMSO- d_6): δ 13.01 (s, 1H), 11.30 (s, 1H), 9.00 (s, 1H), 8.79 (s, 1H), 8.49-8.45 (m, 1H), 7.71 (d, $J = 8.0$ Hz, 1H), 7.52-7.35 (m, 7H), 7.25 (s, 1H), 7.14 (s, 1H), 6.39-6.35 (m, 1H), 5.22-5.13 (m, 3H), 4.88-4.83 (m, 2H), 4.49-4.30 (m, 2H), 3.89-3.70 (m, 13H), 3.48-3.20 (m, 3H), 2.47 (s, 3H), 2.14 (s, 3H), 2.10-2.01 (m, 2H), 1.89-1.60 (m, 3H), 1.39-1.33 (m, 1H), 1.12 (d, $J = 6.4$ Hz, 3H), 0.72-0.51 (m, 7H); LC-MS: m/z 1128.50 $[M+H]^+$

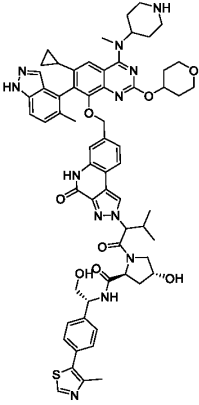
171 (mixture of four diastereomers)	XXIII -14		LC-MS: m/z 1142.1 $[M+H]^+$
171a		Isomer-1 of compound 171	LC-MS: m/z 1142.1 $[M+H]^+$
171b		Isomer-2 of compound 171	LC-MS: m/z 1142.1 $[M+H]^+$
Mixture of 171c and 171d		Mixture of Isomer-3 and isomer-4 of compound 171	^1H NMR (400 MHz, DMSO-d_6): δ 13.01 (s, 1H), 11.30 (s, 1H), 9.00 (s, 1H), 8.86 (s, 1H), 8.47 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.52-7.35 (m, 9H), 7.14 (s, 1H), 6.39-6.35 (m, 1H), 5.22- 5.13 (m, 4H), 4.88-4.78 (m, 3H), 4.46 (t, J = 8.0 Hz, 1H), 4.06-4.00 (m, 4H), 3.95-3.91 (m, 2H), 3.82-3.78 (m, 5H), 3.67-3.60 (m, 2H), 3.48-3.20 (m, 1H), 2.47 (s, 3H), 2.15 (s, 3H), 2.15-2.01 (m, 4H), 1.85-1.60 (m, 3H), 1.39-1.33 (m, 1H), 1.12 (d, J = 6.4 Hz, 3H), 0.72-0.51 (m, 7H); LC-MS: m/z 1142.10 $[M+H]^+$

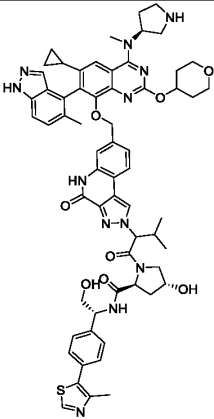
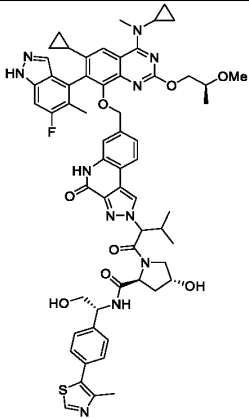
172 (mixture of four diastereomers)	XXIII -15		LC-MS: m/z 1124.1[M+H] ⁺
172a		Isomer-1 of compound 172	LC-MS: m/z 1124.1[M+H] ⁺
Mixture of 172b, 172c and 172d		Mixture of isomer-2, isomer-3 and isomer-4 of compound 172	¹ H NMR (400 MHz, CD ₃ OD): δ 8.64 (s, 1H), 8.48 (bs, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.52-7.32 (m, 9H), 6.97 (s, 1H), 6.60 (dd, J = 8.0, 1.6 Hz, 1H), 6.33 (d, J = 2.0 Hz, 1H), 5.38- 5.10 (m, 4H), 4.65-4.50 (m, 3H), 4.18 (q, J = 7.2 Hz, 2H), 4.04- 3.75 (m, 8H), 3.48-3.40 (m, 1H), 2.80-2.72 (m, 1H), 2.23 (s, 3H), 2.17-2.00 (m, 4H), 1.89-1.81 (m, 7H), 1.48-1.43 (m, 1H), 1.35 (t, J = 7.2 Hz, 3H), 1.21 (d, J = 6.8 Hz, 3H), 0.88-0.83 (m, 4H), 0.72-0.60 (m, 3H); LC-MS: m/z 1124.1 [M+H] ⁺
173 (mixture of four diastereomers)	XXIII -16		LC-MS: m/z 1081.3[M-H] ⁺
173a		Isomer-1 of compound 173	LC-MS: m/z 1083.4[M+H] ⁺

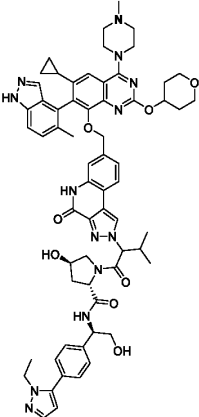
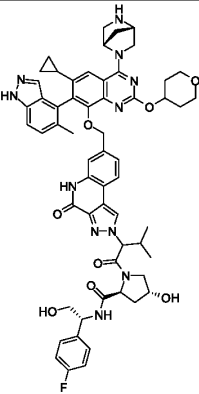
173b		Isomer-2 of compound 173	LC-MS: m/z 1083.4[M+H] ⁺
173c		Isomer-3 of compound 173	LC-MS: m/z 1083.4[M+H] ⁺
173d		Isomer-4 of compound 173	¹ H NMR (400 MHz, DMSO-d ₆): δ 13.01 (s, 1H), 11.30 (s, 1H), 8.79 (s, 1H), 8.52 (d, J = 8.0 Hz, 1H), 8.47 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.51-7.48 (m, 3H), 7.45-7.40 (m, 5H), 7.36 (d, J = 8.8 Hz, 1H), 7.15 (s, 1H), 6.40-6.30 (m, 2H), 5.22-5.11 (m, 4H), 4.92-4.75 (m, 2H), 4.49-4.32 (m, 2H), 4.46 (q, J = 7.2 Hz, 2H), 3.85-3.50 (m, 6H), 3.33 (s, 6H-merged with solvent water peak), 3.25-3.15 (m, 4H), 2.15 (s, 3H), 2.10-2.01 (m, 3H), 1.87-1.79 (m, 1H), 1.70-1.58 (m, 2H), 1.32 (t, J = 7.2 Hz, 3H), 1.11 (d, J = 6.8 Hz, 3H), 0.71 (d, J = 6.8 Hz, 3H), 0.68-0.51 (m, 4H); LC-MS: m/z 1083.4[M+H] ⁺
174 (mixture of four diastereomers)	XXIII -17		LC-MS: m/z 1092.35 [M+H] ⁺
174a		Isomer-1 of compound 174	LC-MS: m/z 1092.2[M+H] ⁺
174b		Isomer-2 of compound 174	LC-MS: m/z 1092.2[M+H] ⁺

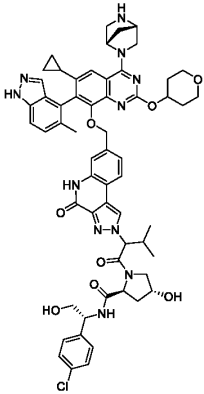
Mixture of 174c and 174d		Mixture of isomer-3 and isomer-4 of compound 174	LC-MS: m/z 1092.2[M+H] ⁺
175 (mixture of four diastereomers)	XXIII -18		LC-MS: m/z 1120.35 [M+H] ⁺
175a		Isomer-1 of compound 175	LC-MS: m/z 1120.35 [M+H] ⁺
175b		Isomer-2 of compound 175	LC-MS: m/z 1120.35 [M+H] ⁺
Mixture of 175c and 175d		Mixture of isomer-3 and isomer-4 of compound 175	¹ H NMR (400 MHz, CD ₃ OD): δ 8.90 (s, 1H), 8.63 (d, J = 4.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.49 (s, 3H), 7.46-7.39 (m, 3H), 7.16 (d, J = 10.2 Hz, 1H), 6.91 (d, J = 7.2 Hz, 1H), 6.56 (t, J = 7.2 Hz, 1H), 5.28-5.20 (m, 2H), 5.10-5.05 (m, 1H), 5.00 (d, J = 8.4 Hz, 1H), 4.62-4.60 (m, 2H), 4.55-4.50 (m, 1H), 4.42-4.38 (m, 2H), 4.02-3.72 (m, 10H), 3.43 (s, 3H), 2.80-2.72 (m, 1H), 2.50 (s, 3H), 2.08-2.02 (m, 4H), 1.48 (t, J = 7.2 Hz, 6H), 1.25-1.15 (m, 6H), 0.87-0.80 (m, 3H), 0.65-0.58 (m, 4H); LC-MS: m/z 1120.35 [M+H] ⁺

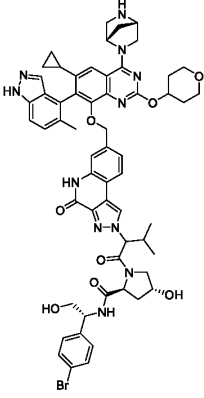
176 (mixture of four diastereomers)	XXIII -19		LC-MS: m/z 1156.2 $[M+H]^+$
176a		Isomer-1 of compound 176	LC-MS: m/z 1156.2 $[M+H]^+$
176b		Isomer-2 of compound 176	LC-MS: m/z 1156.2 $[M+H]^+$
176c		Isomer-3 of compound 176	LC-MS: m/z 1156.2 $[M+H]^+$
176d		Isomer-4 of compound 176	LC-MS: m/z 1156.2 $[M+H]^+$
177 (Mixture of eight diastereomers)	XXIII -20		LC-MS: m/z 1172.5 $[M+H]^+$
Mixture of 177a and 177b		Mixture of isomer-1 and isomer-2 of compound 177	LC-MS: m/z 1172.5 $[M+H]^+$
mixture of 177c and 177d		Mixture of isomer-3 and isomer-4 of compound 177	LC-MS: m/z 1172.5 $[M+H]^+$

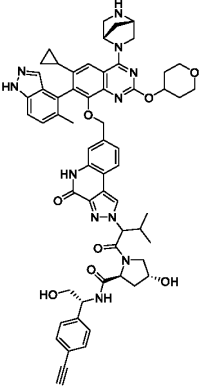
mixture of 177e and 177f		Mixture of isomer-5 and isomer-6 of compound 177	LC-MS: m/z 1172.5 [M+H] ⁺
mixture of 177g and 177h		Mixture of isomer-7 and isomer-8 of compound 177	LC-MS: m/z 1172.5 [M+H] ⁺
178 (mixture of four diastereomers)	XXIII -21		LC-MS: m/z 1155.45[M+H] ⁺
178a		Isomer-1 of compound 178	LC-MS: m/z 1155.45[M+H] ⁺
178b		Isomer-2 of compound 178	LC-MS: m/z 1155.45[M+H] ⁺
178c		Isomer-3 of compound 178	¹ H NMR (400 MHz, CD ₃ OD): δ 8.90 (s, 1H), 8.63 (s, 1H), 8.54 (s, 1H), 7.62-7.38 (m, 11H), 6.97 (s, 1H), 6.60 (d, J = 8.0 Hz, 1H), 5.35- 5.05 (m, 6H), 4.65-4.50 (m, 3H), 4.05-3.89 (m, 6H), 3.48-3.35 (m, 7H), 3.30-3.22 (m, 2H), 2.50 (s, 3H), 2.28-2.20 (m, 8H), 2.15-2.10 (m, 2H), 1.85-1.75 (m, 1H), 1.50-1.45 (m, 1H), 1.19 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H), 0.68-0.60 (m, 4H); LC-MS: m/z 1155.45 [M+H] ⁺
178d		Isomer-4 of compound 178	LC-MS: m/z 1155.45[M+H] ⁺

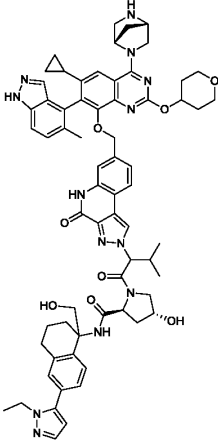
179 (mixture of four diastereomers)	XXIII -22		LC-MS: m/z 1138.7 [M+H]⁺
179a		Isomer-1 of compound 179	LC-MS: m/z 1138.7 [M+H]⁺
179b		Isomer-2 of compound 179	LC-MS: m/z 1138.7 [M+H]⁺
Mixture of 179c and 179d		Mixture of isomer-3 and isomer-4 of compound 179	LC-MS: m/z 1138.7 [M+H]⁺
180 (mixture of four diastereomers)	XXIII -23		LC-MS: m/z 1119.4[M+H]⁺
Mixture of 180a and 180b		Isomer-1 and 2 of compound 180	LC-MS: m/z 1119.4[M+H]⁺
mixture of 180c and 180d		Isomer-3 and 4 of compound 180	LC-MS: m/z 1119.4[M+H]⁺

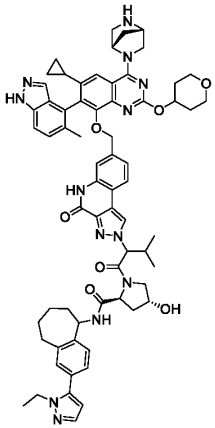
181 (mixture of four diastereomers)	XXIII -24		LC-MS: m/z 1138.25 [M+H] ⁺
181a		Isomer-1 of compound 181	LC-MS: m/z 1138.25 [M+H] ⁺
181b		Isomer-2 of compound 181	LC-MS: m/z 1138.25 [M+H] ⁺
181c		Isomer-3 of compound 181	LC-MS: m/z 1138.25 [M+H] ⁺
181d		Isomer-4 of compound 181	LC-MS: m/z 1138.25 [M+H] ⁺
196 (mixture of four diastereomers)	XXIII -25		LC-MS: m/z 1060.4 [M+H] ⁺
196a		Isomer-1 of compound 196	LC-MS: m/z 1060.4 [M+H] ⁺
196b		Isomer-2 of compound 196	LC-MS: m/z 1060.4 [M+H] ⁺

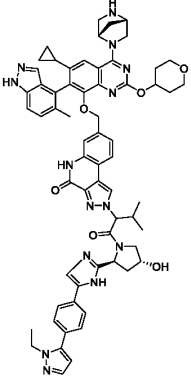
196c		Isomer-3 of compound 196	LC-MS: m/z 1059.3 $[M-H]^+$
196d		Isomer-4 of compound 196	31d (Isomer-4): 1H NMR (400 MHz, CD ₃ OD): δ 8.63 (s, 1H), 8.53 (s, 1H), 8.50 (s, 1H), 7.66-7.32 (m, 6H), 7.16-7.13 (m, 2H), 6.98-6.87 (m, 2H), 6.56-6.48 (m, 1H), 5.39-4.99 (m, 6H), 4.70-4.32 (m, 7H), 4.01-3.78 (m, 7H), 3.60-3.38 (m, 5H), 2.38-1.80 (m, 13H), 1.48-1.40 (m, 1H), 1.18 (d, J = 6.8 Hz, 3H), 0.85-0.59 (m, 7H); LC-MS: m/z 1060.4 $[M+H]^+$
197 (mixture of three diastereomers)	XXIII -26		LC-MS: m/z 1076.25 $[M+H]^+$
197a		Isomer-1 of compound 197	LC-MS: m/z 1076.25 $[M+H]^+$
197b		Isomer-2 of compound 197	LC-MS: m/z 1077.35 $[M+H]^+$
197c		Isomer-3 of compound 197	LC-MS: m/z 1076.4 $[M+H]^+$

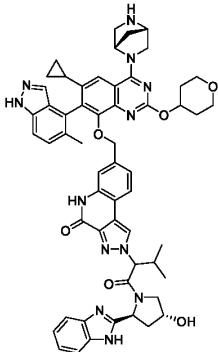
198 (mixture of four diastereomers)	XXIII -27		LC-MS: m/z 1120.5 $[M+H]^+$
198a		Isomer-1 of compound 198	^1H NMR (400 MHz, DMSO- d_6): δ 13.00 (s, 1H), 11.29 (s, 1H), 8.77-7.10 (m, 14H), 6.35-6.31 (m, 1H), 5.30-5.05 (m, 4H), 4.82-4.65 (m, 2H), 4.50-4.22 (m, 3H), 3.91-3.55 (m, 8H), 3.25-3.05 (m, 5H), 2.13 (s, 3H), 2.09-1.92 (m, 4H), 1.80-1.58 (m, 4H), 1.68-1.62 (m, 1H), 1.10-1.04 (m, 3H), 0.70 (d, J = 6.8 Hz, 3H), 0.69-0.48 (m, 4H); LC-MS: m/z 1120.5 $[M+H]^+$
198b		Isomer-2 of compound 198	^1H NMR (400 MHz, DMSO- d_6): δ 13.00 (s, 1H), 11.29 (s, 1H), 8.77-7.10 (m, 14H), 6.35-6.31 (m, 1H), 5.30-5.05 (m, 4H), 4.82-4.65 (m, 2H), 4.50-4.22 (m, 3H), 3.91-3.55 (m, 8H), 3.25-3.05 (m, 5H), 2.13 (s, 3H), 2.09-1.92 (m, 4H), 1.80-1.58 (m, 4H), 1.68-1.62 (m, 1H), 1.10-1.04 (m, 3H), 0.70 (d, J = 6.8 Hz, 3H), 0.69-0.48 (m, 4H); LC-MS: m/z 1120.5 $[M+H]^+$
Mixture of 198c and 198d		Mix of Isomer-3&4 of compound 198	^1H NMR (400 MHz, DMSO- d_6): δ 13.00 (s, 1H), 11.29 (s, 1H), 8.77-7.10 (m, 14H), 6.35-6.31 (m, 1H), 5.30-5.05 (m, 4H), 4.82-4.65 (m, 2H), 4.50-4.22 (m,

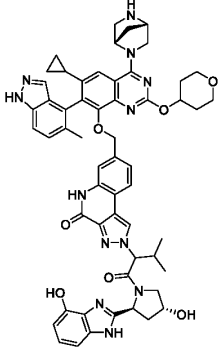
			3H), 3.91-3.55 (m, 8H), 3.25-3.05 (m 5H), 2.13 (s, 3H), 2.09-1.92 (m, 4H), 1.80-1.58 (m, 4H), 1.68-1.62 (m, 1H), 1.10-1.04 (m, 3H), 0.71-0.55 (m, 7H); LC-MS: m/z 1120.5 $[M+H]^+$
199 (mixture of three diastereomers)	XXIII -28		LC-MS: m/z 1066.2 $[M+H]^+$
199a		Isomer-1 of compound 199	LC-MS: m/z 1066.2 $[M+H]^+$
199b		Isomer-2 of compound 199	LC-MS: m/z 1066.2 $[M+H]^+$
199c		Isomer-3 of compound 199	1H NMR (400 MHz, CD ₃ OD): δ 8.63 (s, 1H), 8.55 (s, 1H), 8.50 (s, 1H), 7.66-7.32 (m, 9H), 7.16-7.13 (m, 2H), 6.98-6.97 (m, 1H), 6.56-6.50 (m, 1H), 5.88 (d, J = 2.0 Hz, 1H), 5.49-5.00 (m, 6H), 4.60-4.39 (m, 7H), 4.05-3.70 (m, 8H), 3.70-3.62 (m, 2H), 3.53-3.41 (m, 3H), 2.42-2.00 (m, 9H), 1.86-1.78 (m, 2H), 1.48-1.40 (m, 1H), 1.21-1.15 (m, 3H) 0.89-0.60 (m, 7H); LC-MS: m/z 1066.4 $[M+H]^+$

200 (mixture of three diastereomers)	XXIII -29		LC-MS: m/z 1176.5 $[M+H]^+$
200a		Isomer-1 of compound 200	LC-MS: m/z 1176.5 $[M+H]^+$
200b		Isomer-2 of compound 200	^1H NMR (400 MHz, CD ₃ OD) 8.64 (s, 1H), 8.49 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H) 7.55-7.39 (m, 8H), 7.26-7.20 (m, 2H), 6.98 (s, 1H), 6.60 (d, J = 8.0 Hz, 1H), 6.28 (d, J = 2.0 Hz, 1H), 5.38-5.18 (m, 4H), 4.60- 4.45 (m, 6H), 4.19 (q, J = 7.2 Hz 2H), 4.05-3.88 (m, 5H), 3.81-3.79 (m, 2H), 3.66-3.62 (m, 1H), 3.49-3.42 (m, 2H), 2.41-2.05 (m, 13H), 1.99-1.78 (m, 6H), 1.39 (t, J = 7.2 Hz 3H), 1.19 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H), 0.72-0.58 (m, 4H), LC-MS: m/z 1176.5 $[M+H]^+$
200c		Isomer-3 of compound 200	^1H NMR (400 MHz, CD ₃ OD) 8.64 (s, 1H), 8.52 (s, 1H), 7.52-7.31 (m, 9H), 7.26-7.20 (m, 3H), 6.83 (s, 1H), 6.47 (d, J = 8.0 Hz, 1H), 6.13 (d, J = 2.0 Hz, 1H), 5.38-5.18 (m, 4H), 4.60- 4.45 (m, 6H), 4.19 (q, J = 7.2 Hz 2H), 4.05-3.88 (m, 5H), 3.81-3.79 (m, 2H), 3.66-3.62 (m, 1H), 3.49-3.42 (m, 2H), 2.41-2.05 (m,

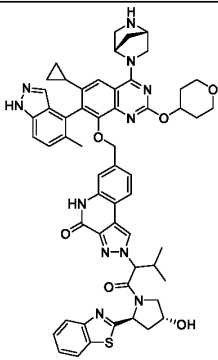
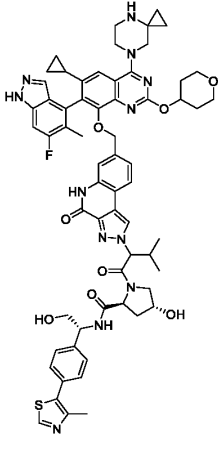
			13H), 1.99-1.78 (m, 6H), 1.39 (t, $J = 7.2$ Hz 3H), 1.19 (d, $J = 6.4$ Hz, 3H), 0.86 (d, $J = 6.8$ Hz, 3H), 0.72-0.58 (m, 4H), LC-MS: m/z 1176.5 $[M+H]^+$
201 (mixture of four diastereomers)	XXIII -30		LC-MS: m/z 1160.5 $[M+H]^+$
201a		Isomer-1 of compound 201	LC-MS: m/z 1160.55 $[M+H]^+$
201b		Isomer-2 of compound 201	LC-MS: m/z 1160.55 $[M+H]^+$
201c		Isomer-3 of compound 201	LC-MS: m/z 1160.50 $[M+H]^+$
201d		Isomer-4 of compound 201	^1H NMR (400 MHz, DMSO- d_6): δ 13.00 (s, 1H), 11.29 (s, 1H), 8.80 (d, $J = 7.2$ Hz, 1H), 8.21 (s, 1H), 7.71-7.14 (m, 9H), 6.35-6.31 (m, 2H), 5.30-5.05 (m, 4H), 4.72-4.10 (m, 6H), 3.90-3.51 (m, 5H), 3.25-3.05 (m, 6H), 2.14 (s, 3H), 2.09-1.60 (m, 12H), 1.38-1.30 (m, 3H), 1.12-0.98 (m, 3H), 0.71-0.50 (m, 7H); LC-MS: m/z 1160.5 $[M+H]^+$

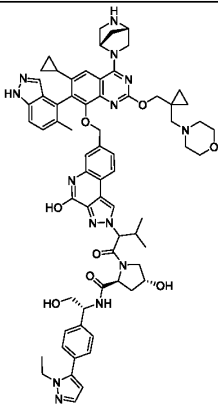
202 (mixture of four diastereomers)	XXIII -34		LC-MS: m/z 1116.48 $[M+H]^+$.
202a		Isomer-1 of compound 202	LC-MS: m/z 1116.48 $[M+H]^+$.
202b		Isomer-2 of compound 202	LC-MS: m/z 1115.5 $[M+H]^+$.
202c		Isomer-3 of compound 202	^1H NMR (400 MHz, DMSO- d_6): δ 13.00 (s, 1H), 11.31 (s, 1H), 8.76 (s, 1H), 8.22 (s, 2H), 7.95 (d, $J = 8.0$ Hz, 1H), 7.82-7.30 (m, 10H), 7.17-7.09 (m, 2H), 5.45-5.05 (m, 6H), 4.72-4.55 (m, 1H), 4.48-4.00 (m, 4H), 3.88-3.60 (m, 6H), 3.35-3.00 (m, 6H), 2.13 (s, 3H), 2.03-1.90 (m, 5H), 1.85-1.50 (m, 3H), 1.33 (t, $J = 7.2$ Hz, 3H), 1.20-1.05 (m, 3H), 0.71-0.45 (m, 7H); LC-MS: m/z 1113.45 $[M-H]^+$
202d		Isomer-4 of compound 202	^1H NMR (400 MHz, DMSO- d_6): δ 13.00 (s, 1H), 12.09 (s, 1H), 11.31 (s, 1H), 8.76 (s, 1H), 8.30 (s, 2H), 7.85 (d, $J = 8.0$ Hz, 1H), 7.82-7.30 (m, 10H), 7.17-7.09 (m, 2H), 5.45-5.05 (m, 6H), 4.72-4.55 (m, 1H), 4.48-4.00 (m, 4H), 3.88-3.60 (m, 6H), 3.35-3.00 (m, 6H), 2.13 (s, 3H), 2.03-1.90 (m, 5H), 1.85-1.50 (m, 3H), 1.33 (t, $J = 7.2$ Hz, 3H), 1.20-1.05 (m,

			3H), 0.71-0.45 (m, 7H); LC-MS: m/z 1113.45 $[M-H]^+$
203 (mixture of four diastereomers)	XXIII -31		LC-MS: m/z 993.55 $[M-H]^+$
203a		Isomer-1 of compound 203	^1H NMR (400 MHz, DMSO- d_6): δ 13.00 (s, 1H), 11.31 (s, 1H), 8.62 (s, 1H), 8.33 (s, 3H), 7.72-7.05 (m, 12H), 6.35-6.28 (m, 1H), 5.30-5.05 (m, 6H), 4.72-4.55 (m, 4H), 4.29-4.12 (m, 3H), 3.88-3.60 (m, 6H), 3.35-3.10 (m, 5H), 2.25-2.15 (m, 1H), 2.13 (s, 3H), 2.09-1.95 (m, 3H), 1.85-1.50 (m, 3H), 1.38-1.32 (m, 1H), 1.02-0.95 (m, 3H), 0.71-0.45 (m, 7H); LC-MS: m/z 993.55 $[M-H]^+$
203b		Isomer-2 of compound 203	^1H NMR (400 MHz, DMSO- d_6): δ 13.00 (s, 1H), 11.31 (s, 1H), 8.56 (s, 1H), 8.34 (bs, 3H), 7.60-7.24 (m, 11H), 6.89 (s, 1H), 6.56 (d, $J = 8.0$ Hz, 2H), 5.30-5.05 (m, 6H), 4.72-4.55 (m, 4H), 4.29-4.12 (m, 3H), 3.88-3.60 (m, 6H), 3.35-3.10 (m, 5H), 2.25-2.15 (m, 1H), 2.13 (s, 3H), 2.09-1.95 (m, 3H), 1.85-1.50 (m, 3H), 1.38-1.32 (m, 1H), 1.02-0.95 (m, 3H), 0.71-0.45 (m, 7H); LC-MS: m/z 993.55 $[M-H]^+$

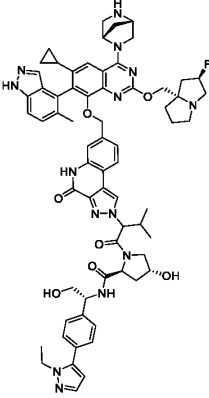
203c		Isomer-3 of compound 203	¹ H NMR (400 MHz, DMSO-d ₆): δ 13.00 (s, 1H), 11.31 (s, 1H), 8.71 (s, 1H), 8.35 (s, 3H), 7.64 (d, <i>J</i> = 8.0 Hz, 1H), 7.51-7.42 (m, 6H), 7.35 (d, <i>J</i> = 8.0 Hz, 1H), 7.18-7.10 (m, 3H), 6.34 (d, <i>J</i> = 8.0 Hz, 2H), 5.30-5.05 (m, 6H), 4.72-4.55 (m, 4H), 4.29-4.12 (m, 3H), 3.88-3.60 (m, 6H), 3.35-3.10 (m, 5H), 2.25-2.15 (m, 1H), 2.13 (s, 3H), 2.09-1.95 (m, 3H), 1.85-1.50 (m, 3H), 1.38-1.32 (m, 1H), 1.02-0.95 (m, 3H), 0.71-0.45 (m, 7H); LC-MS: <i>m/z</i> 993.55 [M-H] ⁺
203d		Isomer-4 of compound 203	¹ H NMR (400 MHz, DMSO-d ₆): δ 13.00 (s, 1H), 11.31 (s, 1H), 8.71 (s, 1H), 8.35 (s, 3H), 7.64 (d, <i>J</i> = 8.0 Hz, 1H), 7.51-7.42 (m, 6H), 7.35 (d, <i>J</i> = 8.0 Hz, 1H), 7.18-7.10 (m, 3H), 6.34 (d, <i>J</i> = 8.0 Hz, 2H), 5.30-5.05 (m, 6H), 4.72-4.55 (m, 4H), 4.29-4.12 (m, 3H), 3.88-3.60 (m, 6H), 3.35-3.10 (m, 5H), 2.25-2.15 (m, 1H), 2.13 (s, 3H), 2.09-1.95 (m, 3H), 1.85-1.50 (m, 3H), 1.38-1.32 (m, 1H), 1.02-0.95 (m, 3H), 0.71-0.45 (m, 7H); LC-MS: <i>m/z</i> 993.55 [M-H] ⁺
204 (mixture of four diastereomers)	XXIII -32		LC-MS: <i>m/z</i> 1099.35 [M-H] ⁺

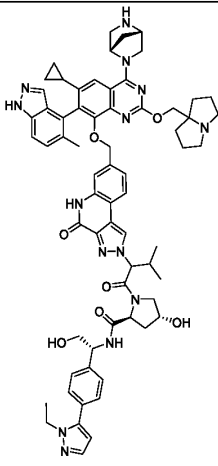
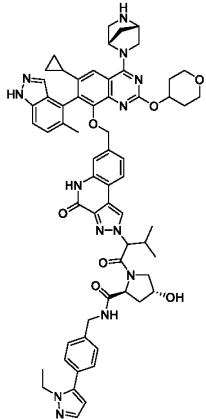
204a		Isomer-1 of compound 204	¹ H NMR (400 MHz, DMSO-d ₆): δ 13.00 (s, 1H), 11.31 (s, 1H), 8.23 (s, 3H), 7.70-7.34 (m, 4H), 7.16-6.84 (m, 3H), 6.58-6.25 (m, 2H), 5.32-5.05 (m, 5H), 4.72-4.10 (m, 5H), 3.98-3.60 (m, 7H), 3.35-3.10 (m 5H), 2.25-2.15 (m, 1H), 2.13 (s, 3H), 2.09-1.95 (m, 3H), 1.85-1.50 (m, 3H), 1.38-1.32 (m, 1H), 1.10-0.98 (m, 3H), 0.71-0.45 (m, 7H); LC-MS: <i>m/z</i> 1099.35 [M-H] ⁺
204b		Isomer-2 of compound 204	¹ H NMR (400 MHz, DMSO-d ₆): δ 13.00 (s, 1H), 11.31 (s, 1H), 8.71 (s, 1H), 8.35 (s, 3H), 7.70-7.34 (m, 4H), 7.16-6.84 (m, 3H), 6.58-6.25 (m, 2H), 5.30-5.05 (m, 5H), 4.72-4.10 (m, 5H), 3.98-3.60 (m, 7H), 3.35-3.10 (m 5H), 2.25-2.15 (m, 1H), 2.13 (s, 3H), 2.09-1.95 (m, 3H), 1.85-1.50 (m, 3H), 1.38-1.32 (m, 1H), 1.10-0.98 (m, 3H), 0.71-0.45 (m, 7H); LC-MS: <i>m/z</i> 1099.35 [M-H] ⁺
Mixture of 204c and 204d		Mix of Isomer-3&4 of compound 204	¹ H NMR (400 MHz, DMSO-d ₆): δ 13.00 (s, 1H), 11.31 (s, 1H), 8.71 (s, 2H), 8.64 (s, 1H), 7.70-7.34 (m, 4H), 7.16-6.84 (m, 3H), 6.58-6.25 (m, 2H), 5.30-5.05 (m, 5H), 4.72-4.10 (m, 5H), 3.98-3.60 (m, 7H), 3.35-3.10 (m 5H), 2.25-2.15 (m, 1H), 2.13 (s, 3H), 2.09-1.95 (m, 3H), 1.85-1.50 (m, 3H), 1.38-1.32 (m, 1H), 1.10-0.98 (m, 3H), 0.71-0.45 (m, 7H); LC-MS: <i>m/z</i> 1099.55 [M-H] ⁺

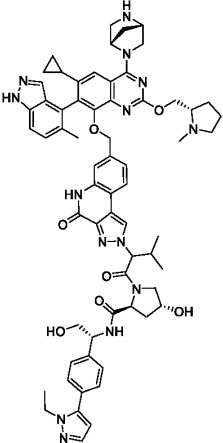
205 (mixture of four diastereomers)	XXIII -33		LC-MS: m/z 1012.30 $[M+H]^+$.
205a		Isomer-1 of compound 205	LC-MS: m/z 1012.30 $[M+H]^+$.
Mixture of 205b and 205c		Mix of Isomer-2&3 of compound 205	LC-MS: m/z 1012.35 $[M+H]^+$.
205d		Isomer-4 of compound 205	LC-MS: m/z 1012.30 $[M+H]^+$.
207 (mixture of four diastereomers)	XXIII -42		LC-MS: m/z 1171.45 $[M+H]^+$
207a		Isomer-1 of compound 207	LC-MS: m/z 1171.45 $[M+H]^+$
207b		Isomer-2 of compound 207	LC-MS: m/z 1171.45 $[M+H]^+$
207c		Isomer-3 of compound 207	LC-MS: m/z 1171.45 $[M+H]^+$
207d		Isomer-4 of compound 207	1H NMR (400 MHz, CD_3OD): δ 8.89 (s, 1H), 8.65 (s, 1H), 7.63-7.61 (d, J = 8 Hz, 1H), 7.48 (s, 4H), 7.42-7.40 (m, 2H), 7.32 (s, 1H), 7.23-7.20 (d, J = 12 Hz,

			1H), 6.98 (s, 1H), 6.65-6.63 (q, 1H), 5.32-5.29 (m, 2H), 5.22-5.19 (d, $J = 12$ Hz, 1H), 5.09-5.06 (t, 1H), 5.02-4.99 (m, 1H), 4.61-4.57 (t, 1H), 4.5 (s, 1H), 4.01 (s, 1H), 3.96-3.94 (m, 5H), 3.91-3.90 (m, 3H), 3.76-3.73 (m, 2H), 3.45-3.44 (m, 2H), 3.24 (s, 1H), 2.80-2.70 (m, 1H), 2.50 (s, 3H), 2.30-2.20 (m, 1H), 2.10-2.09 (m, 3H), 2.02 (m, 1H), 1.82-1.81 (m, 2H), 1.42-1.41 (m, 1H), 1.19-1.17 (m, 3H), 0.87-0.85 (d, $J = 8$ Hz, 3H), 0.80-0.78 (m, 5H), 0.70 (m, 1H), 0.61-0.59 (m, 3H); LC-MS: m/z 1171.45 $[M+H]^+$
208 (mixture of four diastereomers)	XXIII -37		LC-MS: m/z 1204.60 $[M-H]^+$
208a		Isomer-1 of compound 208	1H NMR (400 MHz, DMSO- d_6): δ 13.00 (s, 1H), 11.30 (s, 1H), 8.74-8.71 (m, 1H), 8.15-8.11 (m, 1H), 7.70-7.64 (m, 1H), 7.50-7.17 (m, 10H), 6.58-6.50 (m, 1H), 6.13 (m, 1H), 5.17-5.07 (m, 6H), 4.86-4.83 (m, 3H), 4.50 (m, 1H), 4.36-4.34 (m, 2H), 4.27-4.23 (m, 3H), 4.03-4.01 (m, 3H), 3.96-3.93 (m, 3H), 3.70 (m, 3H), 2.19-2.14 (m, 12H), 1.98 (m, 1H), 1.89 (m, 1H), 1.79 (m, 1H), 1.32 (m, 3H), 1.06-1.04 (m, 3H), 0.71-0.96 (m, 6H), 0.67-

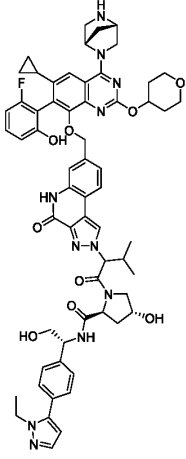
			0.53 (m, 4H), 0.42 (m, 2H), 0.25 (m, 2H) LC-MS: m/z 1204.60 [M-H] ⁺
208b		Isomer-2 of compound 208	LC-MS: m/z 1204.60 [M-H] ⁺
208c		Isomer-3 of compound 208	¹ H NMR (400 MHz, DMSO-d ₆): δ 13.00 (s, 1H), 11.20 (m, 1H), 8.77 (m, 1H), 8.48-8.46 (m, 1H), 8.16 (s, 1H), 7.72-7.18 (m, 12H), 6.56-6.54 (m, 1H), 6.32 (m, 1H), 4.90-4.87 (m, 2H), 4.45 (m, 2H), 4.31 (m, 4H), 4.22 (m, 4H), 4.13-4.11 (m, 2H), 4.03-4.02 (m, 2H), 3.98-3.94 (m, 3H), 3.80 (m, 2H), 3.70 (m, 2H), 3.64-3.61 (m, 4H), 3.34 (m, 4H), 2.53-2.51 (m, 1H), 2.20-2.10 (m, 7H), 1.90-1.87 (m, 1H), 1.33-1.30 (m, 3H), 1.25-1.05 (m, 2H), 0.71-0.66 (m, 7H), 0.52-0.40 (m, 3H), 0.20 (m, 2H) LC-MS: m/z 1204.60 [M-H] ⁺
208d		Isomer-4 of compound 208	¹ H NMR (400 MHz, DMSO-d ₆): δ 13.00 (s, 1H), 10.85 (s, 1H), 8.67-8.63 (m, 1H), 8.18-8.12 (m, 2H), 7.64-7.62 (d, 1H), 7.48-7.31 (m, 6H), 7.09 (s, 1H), 6.59-6.55 (m, 2H), 6.30 (s, 1H), 5.13-5.12 (m, 5H), 4.8-4.7 (m, 2H), 4.77 (s, 1H), 4.20-4.11 (m, 5H), 3.81-3.70 (m, 8H), 3.44-3.43 (m, 4H), 3.07 (m, 2H), 2.51-2.50 (m, 6H), 2.30-2.27 (m, 3H), 2.162 (s, 2H), 1.91-1.89 (m, 2H), 1.77 (m, 2H), 1.34-1.27 (m, 6H), 1.11-1.09 (m, 3H), 0.76-0.73 (m, 3H), 0.60-0.61 (m, 3H), 0.509 (m, 2H), 0.322 (s, 2H). LC-MS: m/z 1204.60 [M-H] ⁺

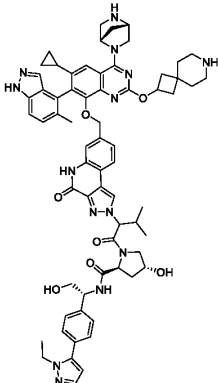
209 (mixture of four diastereomers)	XXIII -38		LC-MS: m/z 1192.58 [M-H] ⁺
Mixture of 209a and 209b		Mixture of Isomer-1 and 2 of 209	¹ H NMR (400 MHz, DMSO-d ₆): δ 12.98 (s, 1H), 11.21-11.18 (m, 1H), 8.74-8.71 (m, 1H), 8.33-8.28 (m, 5H), 8.14-8.12 (m, 1H), 7.69-7.15 (m, 4H), 6.49-6.47 (m, 1H), 5.25-5.23 (m, 2H), 5.09-5.03 (m, 5H), 4.86 (m, 3H), 4.50 (m, 1H), 4.28-4.25 (m, 2H), 4.03-4.01 (m, 3H), 3.97-3.96 (m, 4H), 3.87 (m, 2H), 3.815-3.78 (m, 5H), 3.08-2.90 (m, 6H), 2.67 (m, 2H), 2.33 (m, 4H), 2.13 (m, 2H), 2.01 (m, 4H), 1.94 (m, 2H), 1.76 (m, 3H), 1.32-1.22 (m, 2H), 1.06-1.05 (m, 2H), 0.72-0.70 (m, 4H), 0.65-0.61 (m, 2H) LC-MS: m/z 1192.58 [M-H] ⁺
209c		Isomer-3 of compound 209	LC-MS: m/z 1192.58 [M-H] ⁺
209d		Isomer-4 of compound 209	LC-MS: m/z 1192.58 [M-H] ⁺

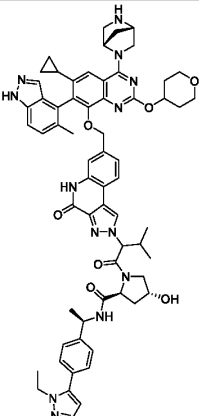
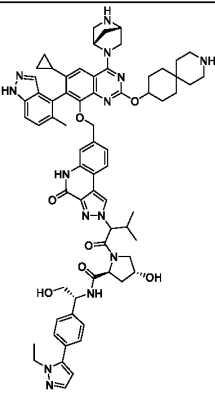
210 (mixture of four diastereomers)	XXIII -44		LC-MS: m/z 1174.59 [M-H] ⁺
210a		Isomer-1 of compound 210	LC-MS: m/z 1174.59 [M-H] ⁺
210b		Isomer-2 of 210	LC-MS: m/z 1174.59 [M-H] ⁺
210c		Isomer-3 of compound 210	LC-MS: m/z 1174.59 [M-H] ⁺
210d		Isomer-4 of compound 210	LC-MS: m/z 1174.59 [M-H] ⁺
211 (mixture of three diastereomers)	XXIII -55		LC-MS: m/z 1105.53 [M-H] ⁺
211a		Isomer-1 of compound 211	LC-MS: m/z 1105.53 [M-H] ⁺
211b		Isomer-2 of compound 211	LC-MS: m/z 1105.53 [M-H] ⁺
211c		Isomer-3 of compound 211	¹ H NMR (400 MHz, MeOD-d ₁): δ 13.00 (s, 1H), 8.63 (s, 1H), 7.59-7.14 (m, 10H), 6.91 (s, 1H), 6.49 (m, 1H), 6.03-6.02 (s,

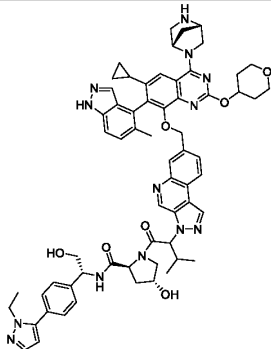
			1H), 5.36-5.17 (m, 4H), 4.68-4.65 (m, 3H), 4.59-1.34 (m, 6H), 4.04-3.84 (m, 6H), 3.70-3.50 (m, 3H), 3.49-3.38 (m, 3H), 2.35-2.04 (m, 11H), 1.80-1.48 (m, 4H), 1.24-1.18 (m, 5H), 0.93-0.86 (m, 3H), 0.69-0.54 (m, 4H), LC-MS: m/z 1105.53 [M-H] ⁺
212 (mixture of four diastereomers)	XXIII -39		LC-MS: m/z 1148.57 [M-H] ⁺
212a		Isomer-1 of compound 212	¹ H NMR (400 MHz, MeOD-d ₁): 8.54-8.52 (m, 2H), 7.55-7.10 (m, 10H), 6.06-6.05 (m, 2H), 5.37-5.35 (m, 6H), 4.59-4.52 (m, 4H), 4.01-3.84 (m, 4H), 3.65 (m, 3H), 2.76-2.67 (m, 6H), 2.24-2.19 (m, 8H), 2.05-2.01 (m, 5H), 1.62-1.42 (m, 4H), 1.37-1.10. (m, 6H), 0.93-0.55 (m, 8H) LC-MS: m/z 1148.57 [M-H] ⁺
212b		Isomer-2 of compound 212	¹ H NMR (400 MHz, MeOD-d ₁): 8.54-8.52 (m, 2H), 7.55-7.10 (m, 12H), 6.06-6.05 (m, 2H), 5.37-5.36 (m, 3H), 5.35 (m, 4H), 4.59-4.55 (m, 4H), 4.01-3.95 (m, 3H), 3.89-3.84 (m, 3H), 3.65-3.50 (m, 4H), 2.76-2.67 (m, 6H), 2.24-2.21 (m, 8H), 2.05-2.01 (m, 6H), 1.62-1.32 (m, 3H), 1.24-1.10 (m, 4H), 0.99-0.84 (m,

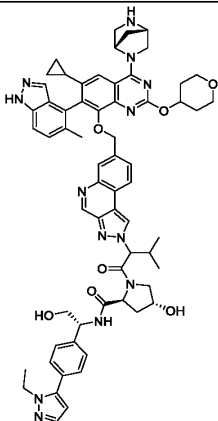
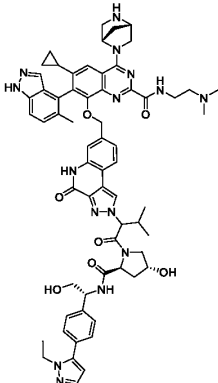
			4H), 0.79-0.55 (m, 4H) LC-MS: m/z 1148.57 [M-H] ⁺
212c		Isomer-3 of compound 212	¹ H NMR (400 MHz, MeOD-d1): 8.64 (m, 1H), 8.53-8.52 (m, 1H), 7.63-7.37 (m, 12H), 6.96 (m, 1H), 6.33-6.32 (m, 1H), 5.37-5.31 (m, 4H), 4.87 (m, 6H), 4.59-4.40 (m, 6H), 4.26-4.16 (m, 3H), 4.00-3.84 (m, 5H), 2.80-2.67 (m, 3H), 2.24-2.23 (m, 4H), 2.12-2.15 (m, 2H), 2.07-2.02 (m, 4H), 1.62-1.42 (m, 3H), 1.38-1.32 (m, 3H), 1.28-1.12 (m, 3H), 0.99-0.80 (m, 6H), 0.66-0.08 (m, 4H) LC-MS: m/z 1148.57 [M-H] ⁺
212d		Isomer-4 of compound 212	¹ H NMR (400 MHz, MeOD-d1): δ 13.00 (s, 1H), 8.68 (s, 1H), 8.62 (s, 1H), 7.59-7.35 (m, 10H), 6.94 (m, 1H), 6.54-6.52 (m, 1H), 6.33-6.36 (m, 1H), 5.36-5.09 (m, 6H), 4.51-4.47 (m, 4H), 4.21-4.13 (m, 4H), 4.02-3.87 (m, 6H), 2.77-2.67 (m, 5H), 2.26-2.12 (m, 6H), 2.05-1.96 (m, 6H), 1.85-1.62 (m, 3H), 1.46-1.32 (m, 4H), 1.28-1.16 (m, 3H), 0.93-0.81 (m, 5H), 0.79-0.64 (m, 4H), LC-MS: m/z 1148.57 [M-H] ⁺

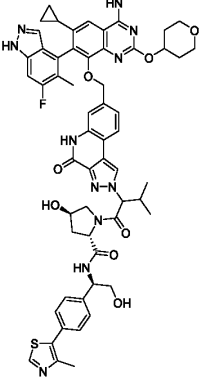
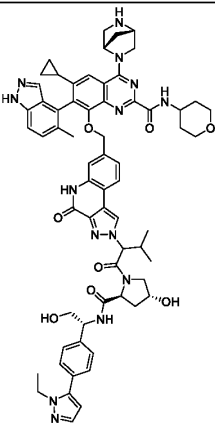
213 (mixture of four diastereomers)	XXIII -40		LC-MS: m/z 1115.50 [M-H] ⁺
213a		Isomer-1 of compound 213	¹ H NMR (400 MHz, MeOD-d ₁): δ 8.71-8.70 (m, 1H), 8.52 (m, 1H), 7.82-7.80 (m, 1H), 7.54-7.21 (m, 12H), 7.01-6.98 (m, 2H), 6.76-6.66 (m, 3H), 6.33-6.28 (m, 3H), 3.97-3.86 (m, 5H), 3.60-3.42 (m, 3H), 3.33-3.32 (m, 4H), 2.60(m, 3H), 2.34-2.03 (m, 8H), 1.80-1.77 (m, 4H), 1.38-1.16 (m, 6H), 0.87-0.71 (m, 11H) LC-MS: m/z 1115.50 [M-H] ⁺
213b		Isomer-2 of compound 213	¹ H NMR (400 MHz, MeOD-d ₁): δ 8.71 (s, 1H), 8.60-8.53 (m, 1H), 7.83-7.81 (m, 1H), 7.57-7.42 (m, 2H), 7.31-7.16 (m, 8H), 7.01-6.95 (m, 2H), 6.77-6.67 (m, 2H), 3.96 (m, 4H), 3.86-3.58 (m, 6H), 3.41-3.38 (m, 5H), 2.90-2.60 (m, 3H), 2.33-2.02 (m, 9H), 1.79-1.76 (m, 5H), 1.39-1.10 (m, 6H), 0.92-0.88 (m, 5H), 0.79-0.77 (m, 6H) LC-MS: m/z 1115.50 [M-H] ⁺
213c		Isomer-3 of compound 213	¹ H NMR (400 MHz, MeOD-d ₁): δ 8.71-8.70 (m, 1H), 8.50 (m, 1H), 7.83-7.81 (m, 1H), 7.80-7.43 (m, 5H), 7.29-7.22 (m,

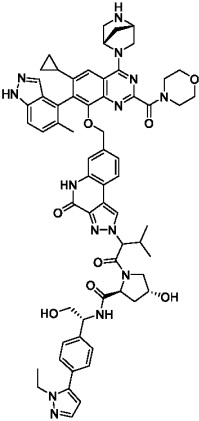
			5H), 7.01-6.99 (m, 1H), 6.77-6.67 (m, 3H), 5.29-5.20 (m, 5H), 4.02 (m, 3H), 3.91-3.87 (m, 3H), 3.80 (m, 4H), 3.65 (m, 2H), 3.47-3.44 (m, 4H), 2.67 (m, 2H), 2.12-2.05 (m, 5H), 1.78-1.76 (m, 4H), 1.36-1.30 (m, 3H), 1.25-1.11 (m, 4H), 0.90-0.89 (m, 3H), 0.77-0.72 (m, 5H) LC-MS: m/z 1115.50 $[M-H]^+$
213d		Isomer-4 of compound 213	1H NMR (400 MHz, MeOD- d_1): δ 8.71-8.70 (m, 1H), 8.47 (m, 2H), 7.82-7.80 (m, 1H), 7.54-7.40 (m, 5H), 7.29-7.22 (m, 2H), 7.01-6.99 (m, 1H), 6.75-6.68 (m, 2H), 6.33-6.32(m,1H), 5.30-5.19 (m, 6H), 4.62-4.47 (m, 5H), 4.21-4.14 (m, 3H), 4.04-4.05 (m, 2H), 3.97-3.80 (m, 4H), 3.71-3.65 (m, 3H), 3.49-3.40 (m, 2H), 2.45-2.39 (m, 2H), 2.14-2.03 (m, 4H), 1.81-1.74(m, 4H), 1.38-1.3 (m, 6H), 1.23-1.16 (m, 4H), 0.92-0.81 (m, 3H), 0.79-0.722 (m, 3H), LC-MS: m/z 1115.50 $[M-H]^+$
214 (mixture of four diastereomers)	XXIII-45		LC-MS: m/z 1174.59 $[M-H]^+$
214a		Isomer-1 of compound 214	LC-MS: m/z 1174.59 $[M-H]^+$

214b		Isomer-2 of compound 214	LC-MS: m/z 1174.59 [M-H] ⁺
214c		Isomer-3 of compound 214	LC-MS: m/z 1174.59 [M-H] ⁺
214d		Isomer-4 of compound 214	LC-MS: m/z 1174.59 [M-H] ⁺
215 (mixture of four diastereomers)	XXIII -56		LC-MS: m/z 1119.54 [M-H] ⁺
215a		Isomer-1 of compound 215	LC-MS: m/z 1119.54 [M-H] ⁺
215b		Isomer-2 of compound 215	LC-MS: m/z 1119.54 [M-H] ⁺
215c		Isomer-3 of compound 215	LC-MS: m/z 1119.54 [M-H] ⁺
215d		Isomer-4 of compound 215	LC-MS: m/z 1119.54 [M-H] ⁺
216 (mixture of four diastereomers)	XXIII -46		LC-MS: m/z 1202.62 [M-H] ⁺
216a		Isomer-1 of compound 216	LC-MS: m/z 1202.62 [M-H] ⁺

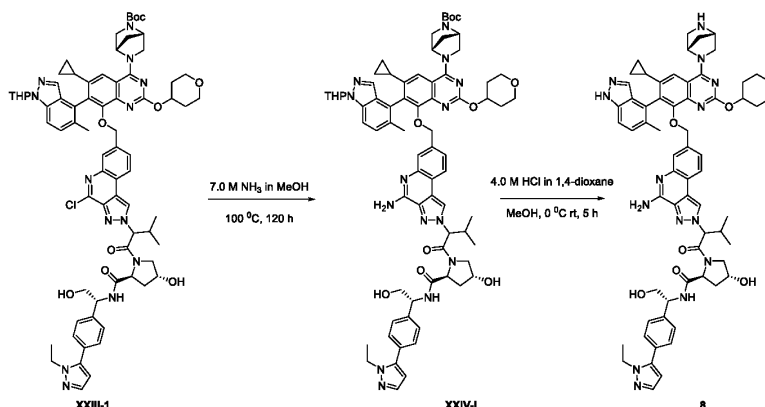
216b		Isomer-2 of compound 216	LC-MS: m/z 1202.62 [M-H] ⁺
216c		Isomer-3 of compound 216	LC-MS: m/z 1202.62 [M-H] ⁺
216d		Isomer-4 of compound 216	LC-MS: m/z 1202.62 [M-H] ⁺
217 (mixture of three diastereomers)	XXIII -53		LC-MS: m/z 1119.54 [M-H] ⁺
217a		Isomer-1 of compound 217	LC-MS: m/z 1119.54 [M-H] ⁺
217b		Isomer-2 of compound 217	LC-MS: m/z 1119.54 [M-H] ⁺
217c		Isomer-3 of compound 217	¹ H NMR (400 MHz, MeOD-d ₁): δ 9.54 (s, 1H), 8.58 (s, 1H), 8.05-8.03 (m, 1H), 7.78 (m, 1H), 7.53-7.29 (m, 9H), 7.00 (m, 1H), 6.32(d, 1H), 5.41-5.33 (m, 7H), 5.11 (m, 2H), 4.88(m, 1H), 4.77-4.57 (m, 6H), 4.19-4.17 (m, 3H), 3.96-3.87 (m, 6H), 3.50-3.49 (m, 2H), 2.28-2.19 (m, 6H), 2.04-2.02 (m, 4H), 1.42-1.31 (m, 5H), 1.24-1.22 (m, 3H), 0.93-0.89 (m, 5H), 0.69-0.65 (m, 3H), LC-MS: m/z 1119.54 [M-H] ⁺

218	XXIII -54		LC-MS: m/z 1119.54 [M-H] ⁺
219 (mixture of four diastereomers)	XXIII -48		LC-MS: m/z 1149.57 [M-H] ⁺
219a		Isomer-1 of compound 219	LC-MS: m/z 1149.57 [M-H] ⁺
Mixture of 219b and 219c		Mixture of Isomer-2 and 3 of 219	LC-MS: m/z 1149.57 [M-H] ⁺
219d		Isomer-4 of compound 219	¹ H NMR (400 MHz, MeOD-d ₁): δ 8.64 (s, 1H), 8.50 (s, 1H), 7.63-7.30 (m, 10H), 6.64-6.62 (m, 2H), 6.33-6.28 (m, 2H), 5.62 (m, 2H), 5.37-5.35 (m, 3H), 5.28-5.19 (m, 2H), 5.11-5.06 (m, 4H), 4.62-4.57 (m, 6H), 4.52-4.51 (m, 2H), 4.19-4.17 (m, 3H), 3.88-3.87 (m, 1H), 3.51-3.49 (m, 3H), 2.48 (m, 6H), 2.24-2.19 (m, 5H), 2.05-2.04 (m, 5H), 1.42-1.32 (m, 3H), 1.20-1.19 (m, 3H), 0.93-0.89 (m,

			3H), 0.86-0.84 (m, 4H) LC-MS: m/z 1149.57 $[M-H]^+$
220 (mixture of four diastereomers)	XXIII -41		LC-MS: m/z 1090.35 $[M+H]^+$
220a		Isomer-1 of compound 220	LC-MS: m/z 1090.35 $[M+H]^+$
220b		Isomer-2 of compound 220	LC-MS: m/z 1090.35 $[M+H]^+$
220c		Isomer-3 of compound 220	LC-MS: m/z 1090.35 $[M+H]^+$
220d		Isomer-4 of compound 220	LC-MS: m/z 1090.35 $[M+H]^+$
221 (mixture of four diastereomers)	XXIII -49		LC-MS: m/z 1163.50 $[M+H]^+$
221a		Isomer-1 of compound 221	LC-MS: m/z 1163.50 $[M+H]^+$
221b		Isomer-2 of compound 221	LC-MS: m/z 1163.50 $[M+H]^+$

221c		Isomer-3 of compound 221	LC-MS: m/z 1163.50 $[M+H]^+$
221d		Isomer-4 of compound 221	1H NMR (400 MHz, CD_3OD): δ 8.65 (s, 1H), 7.70-7.68 (d, J = 8 Hz, 1H), 7.55-7.53 (m, 2H), 7.52-7.50 (m, 3H), 7.46-7.43 (t, 3H), 7.39 (s, 1H), 7.17 (s, 1H), 6.32 (s, 1H), 5.64 (s, 1H), 5.22-5.19 (m, 2H), 5.10-5.08 (m, 2H), 4.78 (s, 3H) 4.50 (m, 4H) 4.19-4.17 (m, 2H), 4.07-4.05 (m, 2H), 3.98-3.88 (m, 2H), 3.86-3.83 (m, 2H), 3.83-3.81 (m, 2H), 3.60 (s, 1H), 3.48-3.45 (m, 2H), 2.40 (m, 1H), 2.26 (s, 3H), 2.14 (m, 1H), 2.05-2.03 (m, 1H), 1.85-1.81 (m, 2H), 1.55 (m, 1H), 1.50-1.41 (m, 2H), 1.34-1.32 (t, 3H), 1.20-1.18 (d, J = 8 Hz, 3H), 0.86-0.84 (d, J = 8 Hz, 3H), 0.79-0.77 (m, 2H), 0.75-0.74 (m, 3H); LC-MS: m/z 1163.50 $[M+H]^+$
222 (mixture of two diastereomers)	XXIII -50		LC-MS: m/z 1150.45 $[M+H]^+$
222a		Isomer-1 of compound 222	LC-MS: m/z 1150.45 $[M+H]^+$
222b		Isomer-2 of compound 222	LC-MS: m/z 1150.45 $[M+H]^+$

Example-2: Synthesis (2S,4R)-1-(2-(7-(((4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-6-cyclopropyl-7-(5-methyl-1H-indazol-4-yl)-2-((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-8-yl)oxy)methyl)-4-amino-2H-pyrazolo[3,4-c]quinolin-2-yl)-3-methylbutanoyl)-N-((R)-1-(4-(1-ethyl-1H-pyrazol-5-yl)phenyl)-2-hydroxyethyl)-4-hydroxypyrrolidine-2-carboxamide (Compound 8)



Step-1: Synthesis of tert-butyl (1S,4S)-5-(8-(((4-amino-2-(1-((2S,4R)-2-(((R)-1-(4-(1-ethyl-1H-pyrazol-5-yl)phenyl)-2-hydroxyethyl)carbamoyl)-4-hydroxypyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)-2H-pyrazolo[3,4-c]quinolin-7-yl)methoxy)-6-cyclopropyl-7-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-2-((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (XXIV-I)

A stirred solution of chloro intermediate **XXIII-1** (0.25 g, 0.187 mmol, 1.0 equiv.) in 7.0M NH₃ in MeOH (10 mL) was heated to 100 °C for 120 h. After completion of reaction, the reaction mixture was concentrated under vacuum to get the titled crude product **XXIV-1** (0.25 g) as a white gummy solid. LC-MS: *m/z* 1320.2 [M+H]⁺.

Step-2: Synthesis of (2S,4R)-1-(2-(7-(((4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-6-cyclopropyl-7-(5-methyl-1H-indazol-4-yl)-2-((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-8-yl)oxy)methyl)-4-amino-2H-pyrazolo[3,4-c]quinolin-2-yl)-3-methylbutanoyl)-N-((R)-1-(4-(1-ethyl-1H-pyrazol-5-yl)phenyl)-2-hydroxyethyl)-4-hydroxypyrrolidine-2-carboxamide (Compound 8)

Compound **8** was prepared by a procedure similar to the one described in **Example-1** with 4.0 M HCl in 1,4-dioxane as deprotecting reagent. The isolated product was purified by Prep-HPLC to provide the four pure diastereomers as formate salts (Prep HPLC condition:

Column- Luna omega C18 (250 x 21.2mm, 5 micron), Mobile phase-Formic acid in water(A), Acetonitrile (B). The characterization data of the compounds are summarized below.

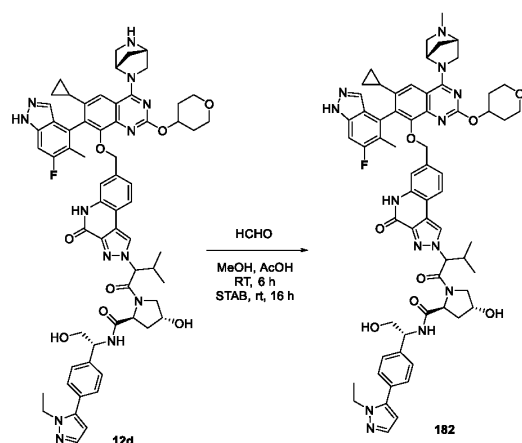
8a (Isomer 1 of compound **8**) : ^1H NMR (400 MHz, CD_3OD): δ 8.80 (s, 1H), 8.38 (bs, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.60-7.18 (m, 10H), 6.72 (d, J = 9.2 Hz, 1H), 6.15 (d, J = 1.6 Hz, 1H),
5 5.38- 5.20 (m, 4H), 4.72 (t, J = 8.4 Hz, 1H), 4.64- 4.49 (m, 5H), 4.10- 4.00 (m, 3H), 3.95- 3.86 (m, 4H), 3.80- 3.70 (m, 6H), 3.34 (s, 2H), 2.90- 2.75 (m, 1H), 2.50- 2.40 (m, 1H), 2.38- 2.22 (m, 4H), 2.15- 2.00 (m, 5H), 1.90- 1.75 (m, 3H), 1.22 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 8.8 Hz, 3H), 0.71- 0.60 (m, 5H) ; LC-MS: m/z 1135.0 $[\text{M}+\text{H}]^+$

8b (Isomer 2 of compound **8**) : ^1H NMR (400 MHz, CD_3OD): δ 8.79 (s, 1H), 8.45 (bs, 1H),
10 7.75- 7.36 (m, 10H), 7.26 (s, 1H), 6.71 (dd, J = 8.4 Hz, 1.6Hz, 1H), 6.33 (d, J = 1.6 Hz, 1H), 5.40- 5.25 (m, 5H), 5.10 (t, J = 7.2 Hz, 1H), 4.64- 4.59 (m, 3H), 4.52- 4.50 (m, 3H), 4.19 (q, J = 7.2 Hz, 2H), 4.06 (d, J = 11.2 Hz, 2H), 3.98- 3.85 (m, 5H), 3.70- 3.65 (m, 2H), 3.50- 3.40 (m, 1H), 2.85- 2.75 (m, 1H), 2.45- 2.40 (m, 2H), 2.25- 2.04 (m, 11H), 1.85- 1.75 (m, 3H), 1.65- 1.60 (m, 1H), 1.50- 1.44 (m, 1H), 1.21 (d, J = 6.4 Hz, 3H), 0.85 (d, J = 6.0 Hz, 3H), 0.71- 0.63
15 (m, 4H) ; LC-MS: m/z 1133.55 $[\text{M}-\text{H}]^+$

8c (Isomer 3 of compound **8**): ^1H NMR (400 MHz, CD_3OD): δ 8.65 (s, 1H), 8.46 (bs, 1H), 7.55- 7.20 (m, 9H), 7.04- 7.00 (m, 1H), 6.60 (d, J = 8.4 Hz, 1H), 6.14 (d, J = 2.0 Hz, 1H), 5.40- 5.20 (m, 4H), 5.10- 5.00 (m, 2H), 4.55- 4.45 (m, 3H), 4.25- 4.15 (m, 2H), 4.10- 3.80 (m, 7H), 3.70- 3.60 (m, 2H), 3.50 (s, 3H), 2.90- 2.70 (m, 1H), 2.25- 1.95 (m, 11H), 1.90- 1.75 (m, 2H),
20 1.40- 1.20 (m, 6H), 0.90- 0.80 (m, 3H), 0.70- 0.55 (m, 4H) ; LC-MS: m/z 1135.50 $[\text{M}+\text{H}]^+$.

8d (Isomer 4 of compound **8**) : LC-MS: m/z 1134.90 $[\text{M}-\text{H}]^+$

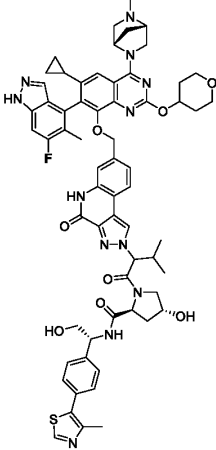
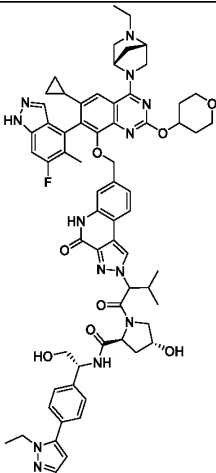
**Example-3: Synthesis of (2S,4R)-1-(2-(7-(((6-cyclopropyl-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2-((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-8-yl)oxy)methyl)-4-oxo-4,5-dihydro-2H-pyrazolo[3,4-
25 c]quinolin-2-yl)-3-methylbutanoyl)-N-((R)-1-(4-(1-ethyl-1H-pyrazol-5-yl)phenyl)-2-hydroxyethyl)-4-hydroxypyrrolidine-2-carboxamide (Compound-182)**

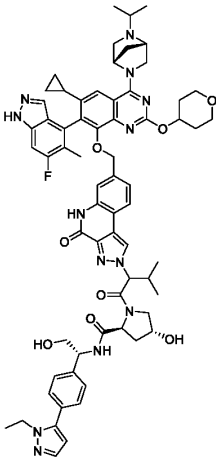


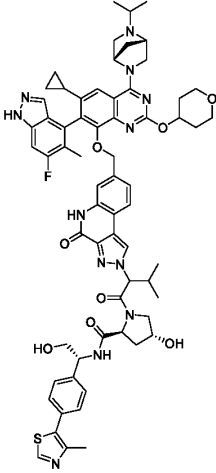
To a stirred solution of (2S,4R)-1-(2-(7-(((4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-6-cyclopropyl-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-8-yl)oxy)methyl)-4-oxo-4,5-dihydro-2H-pyrazolo[3,4-c]quinolin-2-yl)-3-methylbutanoyl)-N-((R)-1-(4-(1-ethyl-1H-pyrazol-5-yl)phenyl)-2-hydroxyethyl)-4-hydroxypyrrolidine-2-carboxamide (**Compound-12d**) (0.10 g, 0.09 mmol, 1.0 equiv.) in MeOH (20 mL) was added formaldehyde (0.005 g, 0.17 mmol, 2.0 equiv.) and the reaction was continued for 6 h at rt. After that STAB (0.074 g, 0.34 mmol, 4.0 equiv.) was added and reaction mixture was stirred at rt for 16 h. After completion of reaction, the reaction mixture was diluted with ice cold water and extracted with 10% MeOH in ethyl acetate (15 mLx3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep TLC plate, eluting with 7-10% MeOH in DCM to get the titled **compound -182** as white solid (0.015 g, 15%). ¹H NMR (400 MHz, CD₃OD): δ 8.64 (s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.55-7.35 (m, 5H), 7.36 (s, 1H), 7.18 (d, J = 6.0 Hz, 1H), 6.98- 6.97 (m, 1H), 6.60 (dd, J = 8.0 Hz, 0.8 Hz, 1H), 6.33 (d, J = 0.8 Hz, 1H), 5.36- 5.08 (m, 7H), 4.65 – 4.58 (m, 1H), 4.54 - 4.50 (bs, 1H), 4.25- 4.10 (m, 4H), 4.05 – 3.91 (m, 4H), 3.88 (d, J = 6.0 Hz, 2H), 3.52-3.39 (m, 4H), 3.10-3.05 (m, 2H), 2.80-2.70 (m, 2H), 2.55 (s, 3H), 2.21 (t, J = 8.0 Hz, 2H), 2.18-2.00 (m, 8H), 1.90- 1.77 (m, 2H), 1.65 – 1.60 (m, 2H), 1.41 - 1.36 (m, 9H), 1.19 (dd, J = 10.8 Hz, 6.4 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H), 0.67- 0.58 (m, 4H); LC-MS: m/z 1166.20 [M+H]⁺

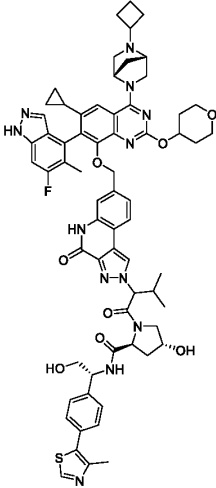
The compounds listed in below **Table-18** were prepared by a procedure similar to the one described in **Example-2** reacting appropriate aldehyde/keto reagent with compound-1 to get desired reductive aminated product. The characterization data of the intermediates are summarized herein the below table.

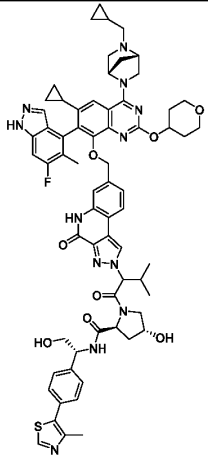
Table-18

Compound- No.	SM	Aldehyde/ Keto Reagent	Compound Structure	Analytical Data
183 (mixture of two diastereomers)	Mixture of 13c and 13d	HCHO		LC-MS: m/z 1171.3 [M+H] ⁺
183a			Isomer-1 of compound 183	LC-MS: m/z 1171.3 [M+H] ⁺
183b			Isomer-2 of compound 183	LC-MS: m/z 1171.3 [M+H] ⁺
184	Compound -12d			LC-MS: m/z 1181.4 [M+H] ⁺

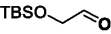
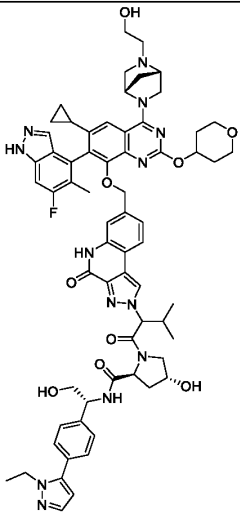
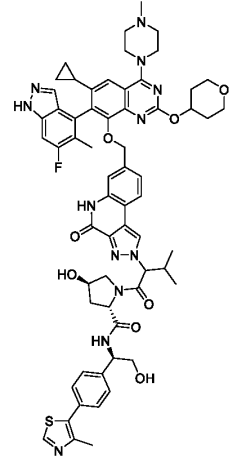
185	Compound -12d		 ¹H NMR (400 MHz, DMSO-<i>d</i>₆): δ 13.05 (s, 1H), 11.30 (s, 1H), 8.48 (d, <i>J</i> = 8.0 Hz, 1H), 7.72 (d, <i>J</i> = 8.0 Hz, 1H), 7.53 (s, 1H), 7.50 (d, <i>J</i> = 1.6 Hz, 1H), 7.48 (s, 1H), 7.43-7.40 (m, 3H), 7.35 (d, <i>J</i> = 9.6 Hz, 1H), 7.20 (bs, 1H), 7.14 (s, 1H), 6.66 (bs, 1H), 6.41 (d, <i>J</i> = 8.4 Hz, 1H), 6.32 (d, <i>J</i> = 2.0 Hz, 1H), 5.33 (t, <i>J</i> = 4.4 Hz, 1H), 5.31 (d, <i>J</i> = 4.8 Hz, 1H), 5.19-5.13 (m, 3H), 5.02 (bs, 1H), 4.95-4.84 (m, 2H), 4.76 (d, <i>J</i> = 11.6 Hz, 1H), 4.46 (d, <i>J</i> = 6.8 Hz, 1H), 4.35-4.30 (m, 1H), 4.12 (q, <i>J</i> = 7.2 Hz, 2H), 3.92-3.73 (m, 5H), 3.70-3.58 (m, 3H), 3.25-3.10 (m, 4H), 2.64- 2.59 (m, 2H), 2.09-1.98 (m, 8H), 1.91- 1.79 (m, 2H), 1.69-1.60 (m, 1H), 1.50- 1.40 (m, 1H), 1.32 (t, <i>J</i> = 7.6 Hz, 3H), 1.10 (d, <i>J</i> =
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				6.8 Hz, 3H), 1.07-1.02 (m, 6H), 0.80-0.55 (m, 7H); LC-MS: m/z 1194.2 $[M+H]^+$
186 (mixture of two diastereomers)	13A			LC-MS: m/z 1197.45 $[M+H]^+$
186a			Isomer-1 of compound- 186	LC-MS: m/z 1197.45 $[M+H]^+$
186b			Isomer-2 of compound- 186	^1H NMR (400 MHz, CD_3OD): δ 8.91 (s, 1H), 8.62 (s, 1H), 8.43 (s, 1H), 7.61 (d, $J = 8.4$ Hz, 1H), 7.50-7.42 (m, 6H), 7.32 (s, 1H), 7.20 (d, $J = 10.0$ Hz, 1H), 6.98 (s, 1H), 6.63-6.58 (m, 1H), 5.34-5.25 (m, 3H), 5.20 (d, $J = 10.4$ Hz, 1H), 5.08 (t, $J = 6.0$ Hz, 1H), 4.98-4.93 (m, 1H), 4.62-4.42 (m, 4H), 4.21-4.12 (m, 2H), 4.02-3.83 (m, 2H), 3.69-3.58 (m,

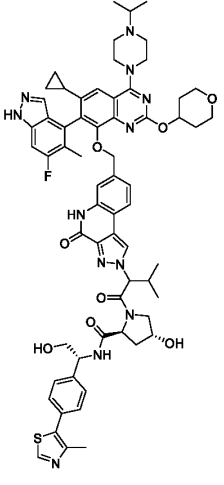
				1H), 3.50-3.38 (m, 3H), 2.80-2.70 (m, 1H), 2.51-2.47 (m, 4H), 2.42-2.21 (m, 3H), 2.18-2.00 (m, 7H), 1.85-1.75 (m, 2H), 1.48-1.30 (m, 9H), 1.22-1.15 (m, 3H), 0.88-0.79 (m, 3H), 0.70-0.58 (m, 4H); LC-MS: m/z 1197.45 $[M+H]^+$
187 (mixture of two diastereomers)	2A			LC-MS: m/z 1212.35 $[M+H]^+$
187a			Isomer-1 of compound-187	LC-MS: m/z 1212.35 $[M+H]^+$
187b			Isomer-2 of compound-187	1H NMR (400 MHz, CD_3OD): δ 8.97 (s, 1H), 8.64 (s, 1H), 8.50 (bs, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.50-7.44 (m, 5H), 7.33 (s, 1H), 7.19 (d, J = 10.0 Hz, 1H), 6.97 (s, 1H), 6.60

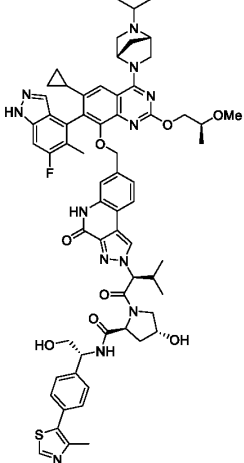
				(d, $J = 8.0$ Hz, 1H), 5.34- 5.20 (m, 4H), 5.08 (t, $J = 6.0$ Hz, 1H), 4.98- 4.93 (m, 1H), 4.62- 4.42 (m, 2H), 4.35-4.30 (m, 1H), 4.05-3.87 (m, 8H), 3.61-3.49 (m, 3H), 3.18-3.12 (m, 1H), 2.78-2.71 (m, 1H), 2.51 (s, 3H), 2.38-2.00 (m, 13H), 1.90-1.78 (m, 4H), 1.45-1.30 (m, 2H), 1.19 (d, $J = 6.8$ Hz, 3H), 0.85 (d, $J = 6.8$ Hz, 3H), 0.65-0.58 (m, 4H); LC-MS: m/z 1212.35 $[M+H]^+$
188 (mixture of two diastereomers)	2A			LC-MS: m/z 1211.50 $[M+H]^+$
188a			Isomer-1 of compound- 188	LC-MS: m/z 1211.50 $[M+H]^+$

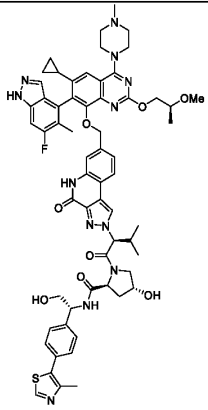
188b			Isomer-2 of compound-188	¹ H NMR (400 MHz, CD ₃ OD): δ 8.90 (s, 1H), 8.70 (s, 1H), 8.52 (bs, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.52-7.49 (m, 4H), 7.44 (s, 1H), 7.33 (s, 1H), 7.20 (d, J = 10.8 Hz, 1H), 7.00 (s, 1H), 6.61 (d, J = 8.0 Hz, 1H), 5.34- 5.20 (m, 6H), 5.08 (t, J = 6.0 Hz, 1H), 4.98- 4.93 (m, 2H), 4.62- 4.32 (m, 5H), 4.13 (d, J = 10.8 Hz, 1H), 4.03-3.87 (m, 6H), 3.55-3.40 (m, 4H), 2.98-2.90 (m, 2H), 2.78-2.71 (m, 1H), 2.50 (s, 3H), 2.18-2.03 (m, 7H), 1.85-1.78 (m, 2H), 1.45-1.30 (m, 2H), 1.19 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H), 0.71-0.60 (m, 6H), 0.48-0.45 (m, 2H); LC-MS: m/z 1211.50 [M+H] ⁺
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189	Compound -12d			LC-MS: m/z 1198.15 [M+H] ⁺
190 (mixture of four diastereomers)	Compound -168	HCHO		
190a			Isomer-1 of compound-190	LC-MS: m/z 1159.45 [M+H] ⁺
190b			Isomer-2 of compound-190	LC-MS: m/z 1159.45 [M+H] ⁺
190c			Isomer-3 of compound-190	¹ H NMR (400 MHz, CD ₃ OD): δ 8.90 (s, 1H), 8.63 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.50-7.47 (m, 4H), 7.44 (s, 1H) 7.41 (s, 1H), 7.35 (s, 1H), 7.20

				(d, $J = 10.0$ Hz, 1H), 6.99 (s, 1H), 6.64 (dd, $J = 8.0, 1.6$ Hz, 1H), 5.39- 5.28 (m, 3H), 5.20 (d, $J = 10.8$ Hz, 1H), 5.07 (t, $J = 6.0$ Hz, 1H), 5.02 (d, $J = 10.8$ Hz, 1H), 4.60 (t, $J = 7.0$ Hz, 1H), 4.53-4.49 (m, 1H), 4.02-3.85 (m, 11H), 3.50-3.40 (m, 2H), 2.85-2.70 (m, 5H), 2.51 (s, 3H), 2.50 (s, 3H), 2.25-2.00 (m, 8H), 1.85-1.80 (m, 2H), 1.19 (d, $J = 6.8$ Hz, 3H), 0.86 (d, $J = 6.8$ Hz, 3H), 0.72-0.60 (m, 4H); LC-MS: m/z 1159.45 $[M+H]^+$
190d			Isomer-4 of compound-190	LC-MS: m/z 1159.45 $[M+H]^+$

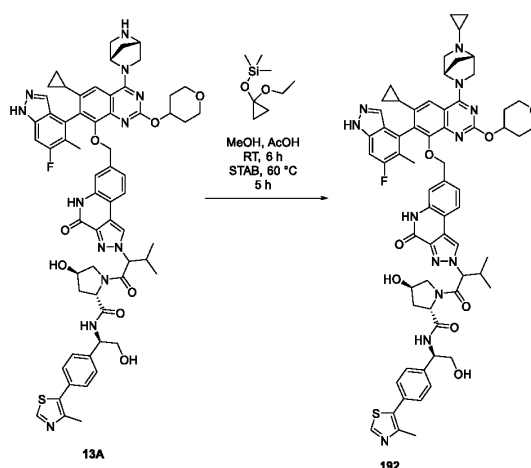
191 (mixture of four diastereomers)	Compound -168			LC-MS: m/z 1187.45 $[M+H]^+$
191a			Isomer-1 of compound- 191	LC-MS: m/z 1187.45 $[M+H]^+$
191b			Isomer-2 of compound- 191	LC-MS: m/z 1187.45 $[M+H]^+$
191c			Isomer-3 of compound- 191	^1H NMR (400 MHz, CD_3OD): δ 8.90 (s, 1H), 8.65 (s, 1H), 8.52 (bs, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.50-7.47 (m, 4H), 7.49 (s, 1H), 7.44 (s, 1H), 7.42 (s, 1H), 7.21 (d, J = 10.0 Hz, 1H), 6.99 (d, J = 0.8 Hz, 1H), 6.64 (dd, J = 8.0, 1.6 Hz, 1H), 5.39- 5.28 (m, 3H), 5.20 (d, J = 10.8 Hz, 1H), 5.07 (t, J = 6.0 Hz, 1H), 5.02 (d, J = 10.8 Hz, 1H), 4.60 (s, 2H), 4.53-4.49 (m, 1H), 4.02- 3.85 (m,

				11H), 3.51-3.40 (m, 2H), 3.01-2.92 (m, 5H), 2.51 (s, 3H), 2.25-2.00 (m, 8H), 1.85-1.80 (m, 2H), 1.25-1.18 (m, 9H), 0.87 (d, $J = 6.8$ Hz, 3H), 0.72-0.60 (m, 4H); LC-MS: m/z 1187.45 $[M+H]^+$
191d			Isomer-4 of compound-191	LC-MS: m/z 1187.45 $[M+H]^+$
206 (mixture of two diastereomers)	XXV-2			LC-MS: m/z 1188.50 $[M+H]^+$
206a			Isomer-1 of compound-206	LC-MS: m/z 1188.50 $[M+H]^+$
206b			Isomer-2 of compound-206	LC-MS: m/z 1188.50 $[M+H]^+$

224 (mixture of two diastereomer)	XXV-1			LC-MS: m/z 1147.40 [M+H] ⁺
224a			Isomer-1 of compound-224	LC-MS: m/z 1147.40 [M+H] ⁺
224b			Isomer-2 of compound-224	¹ H NMR (400 MHz, CD ₃ OD): δ 8.90 (s, 1H), 8.64 (s, 1H), 7.61-7.59 (d, J = 8 Hz, 1H), 7.48 (s, 4H), 7.42 (s, 1H), 7.38-7.37 (m, 2H), 7.23-7.21 (d, J = 8 Hz, 1H), 6.95 (s, 1H), 6.64-6.62 (m, 1H), 5.32-5.29 (d, J = 12 Hz, 1H), 5.22-5.19 (d, J = 12 Hz, 1H), 5.09-5.07 (m, 2H), 4.61-4.57 (m, 2H), 4.50 (s, 1H), 4.03-4.00 (m, 1H), 3.96-3.94 (m, 4H), 3.87-3.86 (d, J = 4 Hz, 2H), 3.80-3.77 (m, 1H), 3.42 (s, 3H), 3.00 (s, 4H), 2.70-2.60 (m, 1H), 2.63 (s, 3H), 2.50 (s, 3H), 2.05-2.02

				(m, 5H), 1.25-1.15 (m, 7H), 0.89-0.85 (m, 3H), 0.84-0.81 (m, 1H), 0.70-0.61 (m, 4H); LC-MS: m/z 1147.40 $[M+H]^+$
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Example-4: Synthesis of (2S,4R)-1-((2S)-2-(7-(((6-cyclopropyl-4-((1S,4S)-5-cyclopropyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-8-yl)oxy)methyl)-4-oxo-4,5-dihydro-2H-pyrazolo[3,4-c]quinolin-2-yl)-3-methylbutanoyl)-4-hydroxy-N-((R)-2-hydroxy-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (Compound-192)



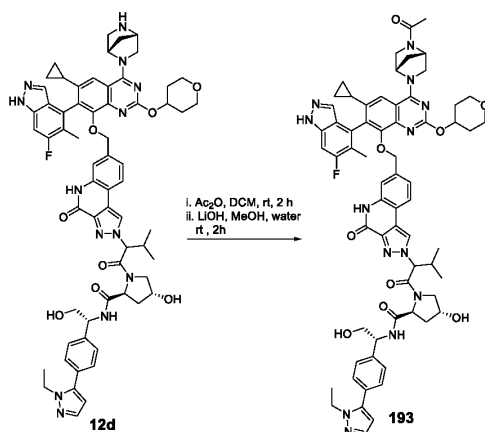
To a stirred solution of (2S,4R)-1-(2-(7-(((4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-6-cyclopropyl-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-8-yl)oxy)methyl)-4-oxo-4,5-dihydro-2H-pyrazolo[3,4-c]quinolin-2-yl)-3-methylbutanoyl)-N-((R)-1-(4-(1-ethyl-1H-pyrazol-5-yl)phenyl)-2-hydroxyethyl)-4-hydroxypyrrolidine-2-carboxamide (**13A**) (0.40 g, 0.35 mmol, 1.0 equiv.) in MeOH (2.5 mL) and acetic acid (0.04 g, 0.7 mmol, 2 eq) was added (1-Ethoxycyclopropyloxy) trimethyl silane (0.18 g, 1.05 mmol, 3.0 equiv.) and the reaction was continued for 6 h at RT. After that sodium triacetoxyborohydride (0.043 g, 0.7 mmol, 2.0 equiv.) was added and reaction mix was stirred at rt for 5 h at 60 °C. After completion of reaction, the reaction mixture was diluted with ice cold water and extracted with 10% MeOH in ethyl acetate (15 mLx3). The combined organic

layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep HPLC, to get the two isomers of titled compound (**compound-192**) as white solid Isomer I (0.06 g, 10%) and Isomer II (0.06 g; 10%).

Compound-192a (isomer-1): ^1H NMR (400 MHz, CD_3OD): δ 8.72 (s, 1H), 8.48 (s, 1H), 7.53 (s, 1H), 7.49 (bs, 1H), 7.31 (d, $J = 8.0$, 1H), 7.27 (d, $J = 8.0$ Hz, 2H), 7.19 (d, $J = 8.4$ Hz, 2H), 7.1-7.05 (m, 2 H), 6.73 (s, 1H), 6.40 (dd, $J = 8.4$ Hz, 1.2 Hz, 1H), 5.40 – 5.30 (m, 2H), 5.36-5.15 (m, 5H), 5.07 (t, $J = 6.0$ Hz, 1H), 5.03 – 4.99 (m, 2H) 4.4 (t, $J = 8.4$ Hz, 1H), 4.47 (bs, 1H), 4.24 – 4.21 (m, 1H), 3.99 – 3.97 (m, 3H), 3.89 – 3.84 (m, 4H), 3.54 (d, 3H), 3.23 – 3.22 (m, 2H), 2.80 – 2.70 (m, 1H), 2.40- 2.30 (m, 1H), 2.28 (s, 3H), 2.20 – 2.07 (m, 8H), 1.90 – 1.80 (m, 2H), 1.35 – 1.30 (m, 2H), 1.20 (d, $J = 6.4$ Hz, 3H), 0.84 (d, $J = 6.4$ Hz, 3H), 0.65 – 0.50 (m, 8H) ; LC-MS: m/z 1197.45 $[\text{M}+\text{H}]^+$

Compound-192b (isomer-2): ^1H NMR (400 MHz, CD_3OD): δ 8.89 (s, 1H), 8.63 (s, 1H), 8.38 (s, 1H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.54-7.53 (m, 2H), 7.49 (s, 3H), 7.44 (s, 1H), 7.35 (dd, $J = 4.4$ Hz, 0.8 Hz, 1H), 7.18 (d, $J = 9.2$ Hz, 1H), 6.96 (bs, 1H), 6.58 (dd, $J = 8.0$ Hz, 1.2 Hz, 2H), 5.36- 5.08 (m, 6H), 4.65 – 4.58 (m, 3H), 4.25 – 3.85 (m, 8H), 3.50 – 3.47 (m, 2H), 3.23 (bs, 2H), 2.80 – 2.70 (m, 1H), 2.50 (s, 3H), 2.20- 2.0 (m, 6H), 1.19 (d, $J = 6.8$ Hz, 3H), 0.85 (d, $J = 8.8$ Hz, 3H), 0.63- 0.54 (m, 7H); LC-MS: m/z 1197.45 $[\text{M}+\text{H}]^+$

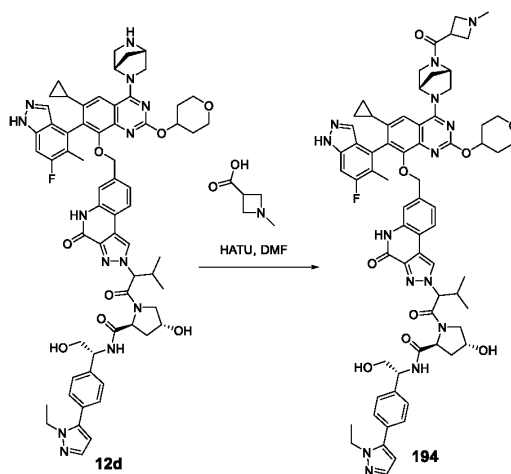
Example-5: Synthesis of (2S,4R)-1-((2S)-2-(7-(((4-((1S,4S)-5-acetyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-6-cyclopropyl-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-8-yl)oxy)methyl)-4-oxo-4,5-dihydro-2H-pyrazolo[3,4-c]quinolin-2-yl)-3-methylbutanoyl)-N-((R)-1-(4-(1-ethyl-1H-pyrazol-5-yl)phenyl)-2-hydroxyethyl)-4-hydroxypyrrolidine-2-carboxamide (Compound-193)



To a stirred solution of Compound-12d (0.02 g, 0.017 mmol) in DCM (5 mL) was added acetic anhydride (0.002 g, 0.02 mmol), and mixture was stirred at rt for 2 hours. After the completion of reaction, organic solvent was removed by high vacuum. Then the mixture was treated with LiOH (0.002 g; 0.04 mmol) in MeOH and water solution. After 2 h reaction
 5 was quenched with ice cold water and extracted with 2 butanol (5 mLx3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep TLC, eluting with 10% MeOH in DCM to afford titled compound (0.007 g, 36%) as off-white color solid.

¹H NMR (400 MHz, CD₃OD): δ 8.64 (s, 1H), 8.40 (bs 1H), 7.59-7.32 (m, 10H), 7.18 (d, *J* = 9.6 Hz, 1H), 6.96 (dd, *J* = 6.4, 0.8 Hz, 1H), 6.61-6.57 (m, 1H), 6.32 (d, *J* = 2.0 Hz, 1H), 5.40-5.28 (m, 3H), 5.22- 5.05 (m, 3H), 4.62- 4.28 (m, 6H), 4.22-4.15 (m, 2H), 4.05-3.80 (m, 10H), 3.65-3.60 (m, 1H), 3.52-3.49 (m, 2H), 2.80-2.70 (m, 1H), 2.30-2.03 (m, 11H), 1.88-1.79 (m, 2H), 1.36 (t, *J* = 7.6 Hz, 3H), 1.20 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.67- 0.58 (m, 4H); LC-MS: *m/z* 1194.25 [M+H]⁺

15 **Example-6: Synthesis of (2S,4R)-1-((2S)-2-(7-(((6-cyclopropyl-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-4-((1S,4S)-5-(1-methylazetidine-3-carbonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2-((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-8-yl)oxy)methyl)-4-oxo-4,5-dihydro-2H-pyrazolo[3,4-c]quinolin-2-yl)-3-methylbutanoyl)-N-((R)-1-(4-(1-ethyl-1H-pyrazol-5-yl)phenyl)-2-hydroxyethyl)-4-hydroxypyrrolidine-2-carboxamide (Compound 194)**

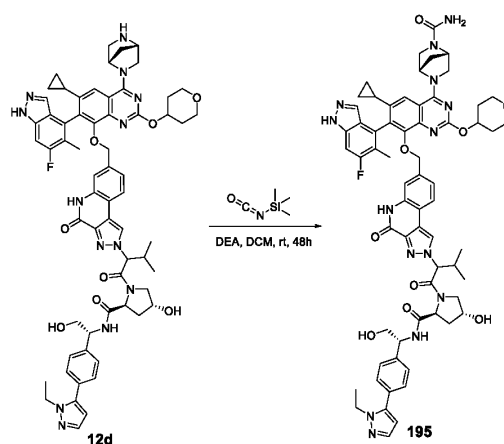


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To a stirred solution of **12d** (0.03 g, 0.026 mmol) in DCM (5 mL) and diethyl amine (0.010 gm) was added 1-methylazetidine-3-carboxylic acid (0.015 g, 0.13 mmol), and mixture was stirred at rt for 48 hour. After the completion of reaction, the mixture was quenched with

ice cold water and extracted with 2 butanol (5 mLx3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep TLC, eluting with 10% MeOH in DCM to afford titled compound **194** (0.007 g, 23%) as off-white color solid. LC-MS: *m/z* 1251.25 [M+H]⁺.

5 **Example-7: Synthesis of (1S,4S)-5-(6-cyclopropyl-8-((2-((S)-1-((2S,4R)-2-(((R)-1-(4-(1-ethyl-1H-pyrazol-5-yl)phenyl)-2-hydroxyethyl)carbamoyl)-4-hydroxypyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)-4-oxo-4,5-dihydro-2H-pyrazolo[3,4-c]quinolin-7-yl)methoxy)-7-(6-fluoro-5-methyl-1H-indazol-4-yl)-2-((tetrahydro-2H-pyran-4-yl)oxy)quinazolin-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxamide (Compound-195)**



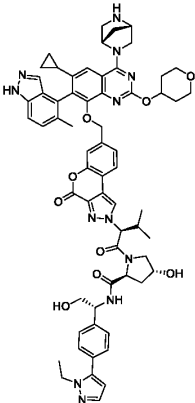
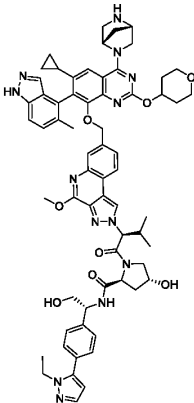
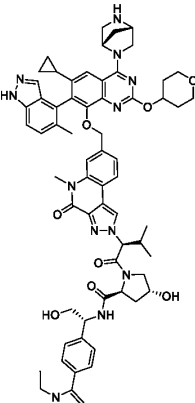
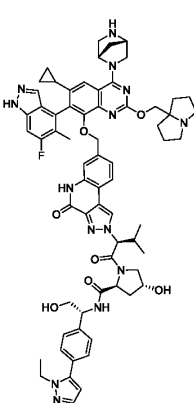
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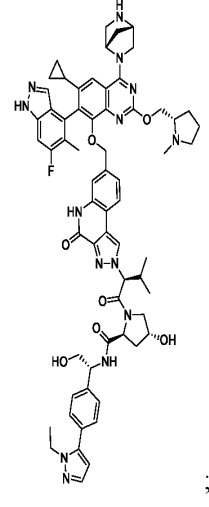
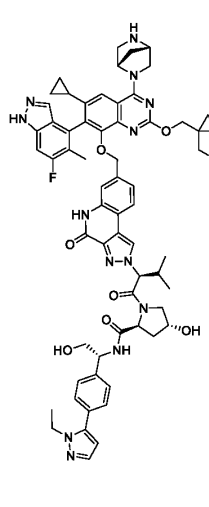
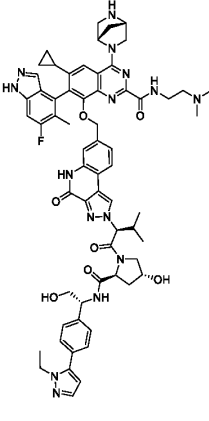
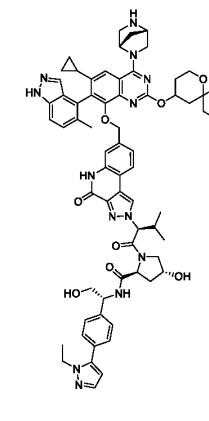
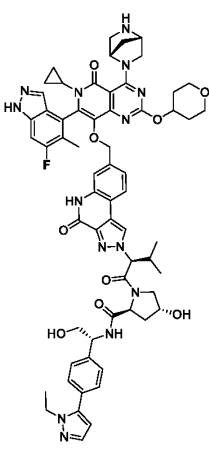
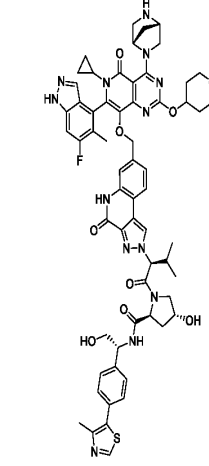
To a stirred solution of **Compound-12d** (0.03 g, 0.026 mmol) in DCM (5 mL) and diethyl amine (0.010 gm) was added isocyanato trimethyl silane (0.015 g, 0.13 mmol), and mixture was stirred at rt for 48 hours. After the completion of reaction, the mixture was quenched with ice cold water and extracted with 2 butanol (5 mLx3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep TLC, eluting with 10% MeOH in DCM to afford titled compound (0.007 g, 23%) as off-white colour solid.

¹H NMR (400 MHz, CD₃OD): δ 8.65 (s, 1H), 7.60-7.41 (m, 10H), 7.14 (d, *J* = 8.8 Hz, 1H), 6.89 (s, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.33 (d, *J* = 2.0 Hz, 1H), 5.45- 5.36 (m, 4H), 5.22- 5.05 (m, 3H), 4.62- 4.40 (m, 5H), 4.22-4.15 (m, 2H), 4.05-3.80 (m, 10H), 3.65-3.60 (m, 2H), 3.52- 3.49 (m, 2H), 2.80-2.70 (m, 1H), 2.30-2.03 (m, 9H), 1.88-1.80 (m, 2H), 1.36 (t, *J* = 7.6 Hz, 3H), 1.20 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.67- 0.58 (m, 4H); LC-MS: *m/z* 1197.50 [M+H]⁺

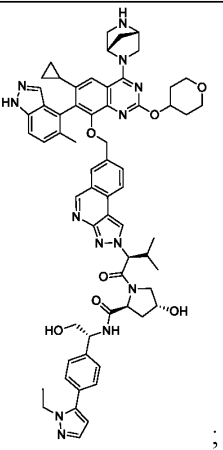
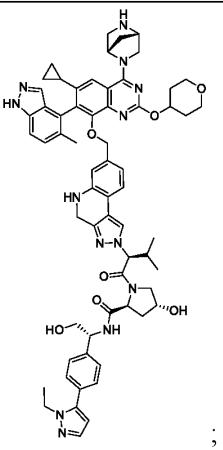
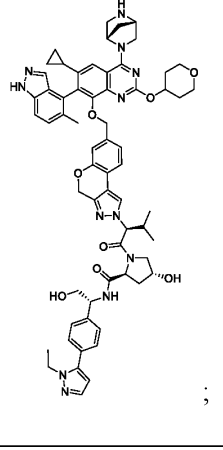
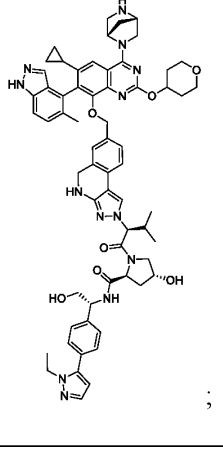
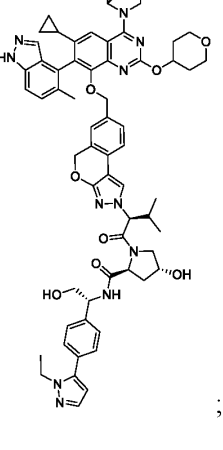
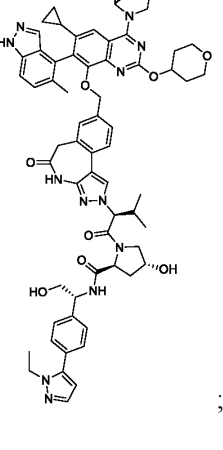
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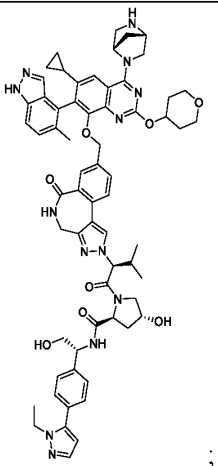
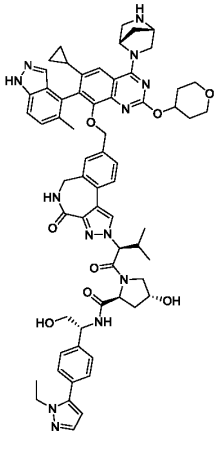
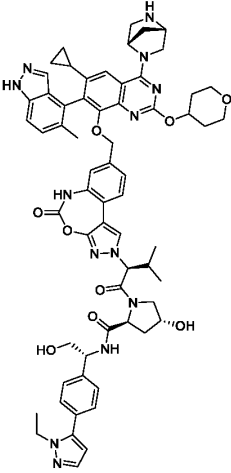
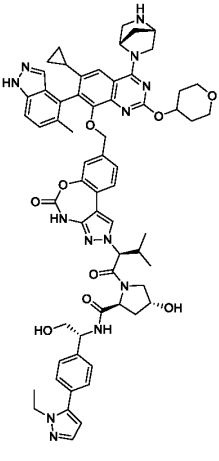
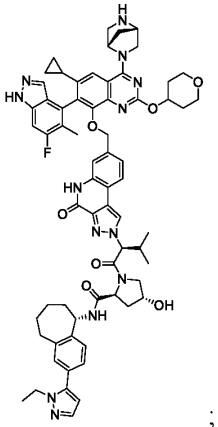
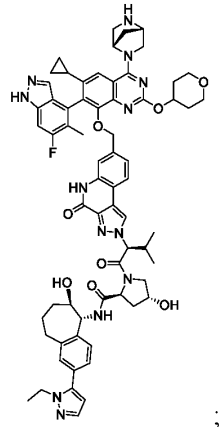
Although the present invention has been illustrated by certain of the preceding examples, it is not to be construed as being limited thereby; but rather, the present invention encompasses the generic area as hereinbefore disclosed. Various modifications and embodiments can be made without departing from the spirit and scope thereof. For example, 5 the compounds given below which can be prepared by following similar procedure as described in above Schemes/Examples with suitable modifications known to the one ordinary skilled in the art are also included in the scope of the present invention.

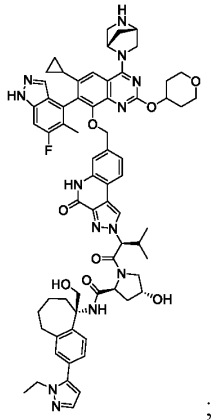
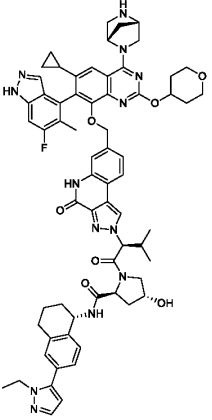
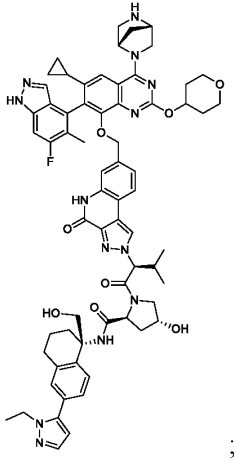
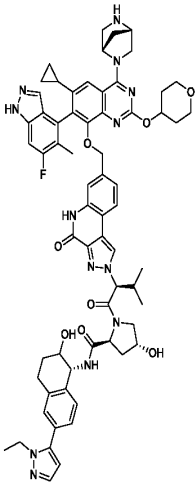
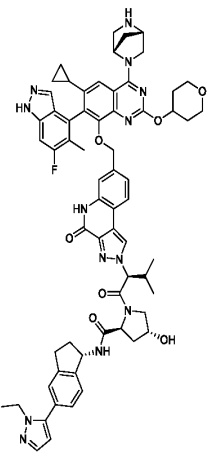
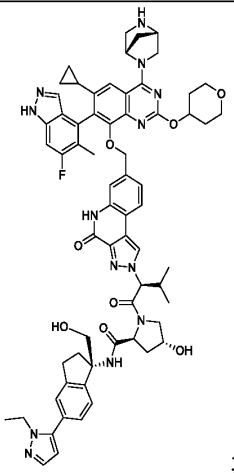
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11.		14.	

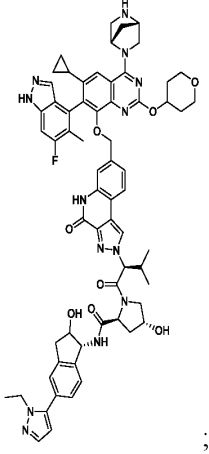
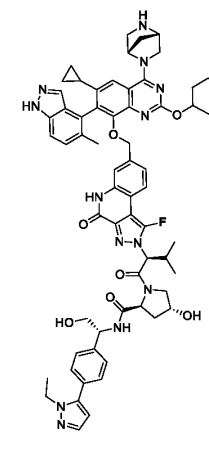
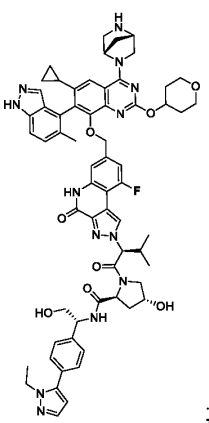
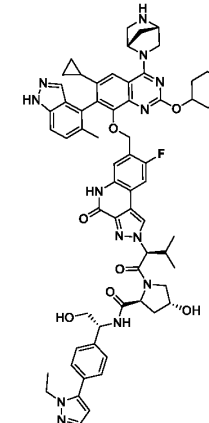
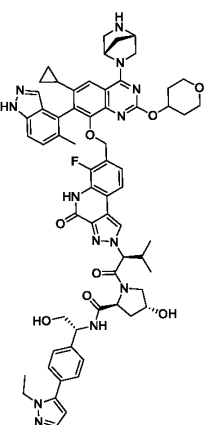
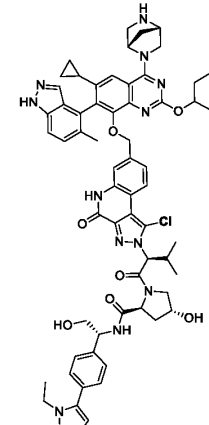
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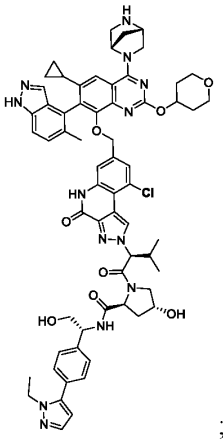
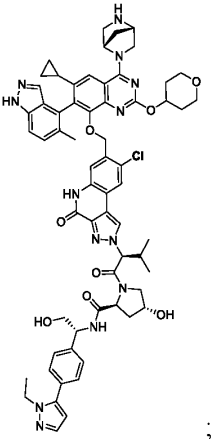
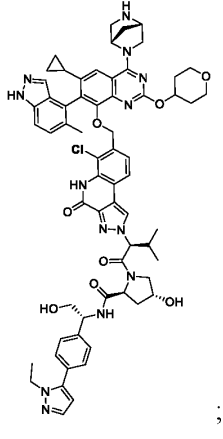
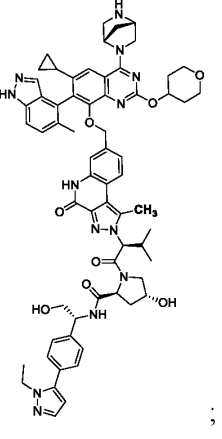
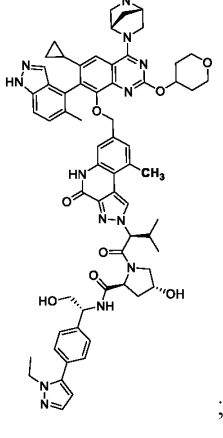
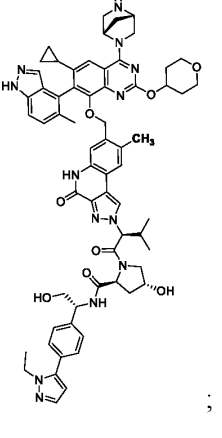
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25.		26.	

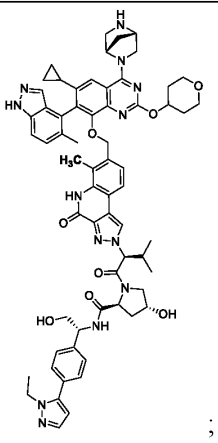
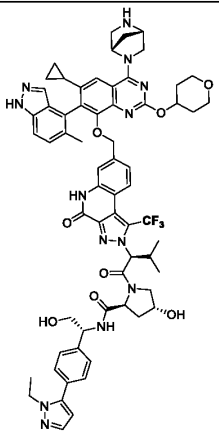
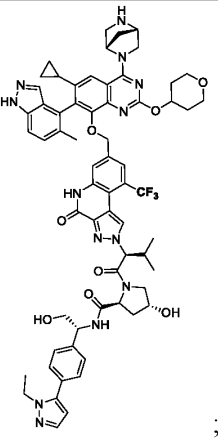
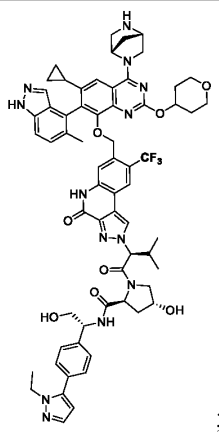
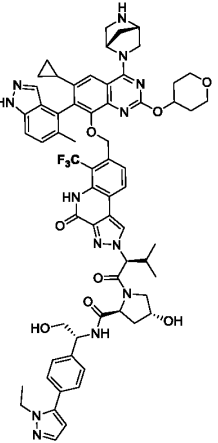
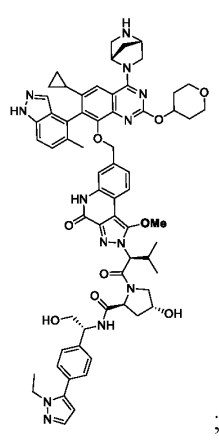
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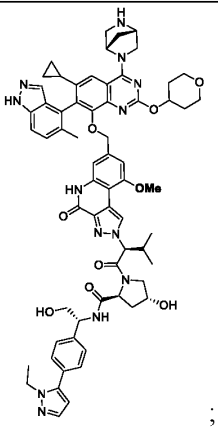
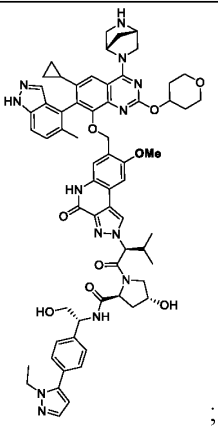
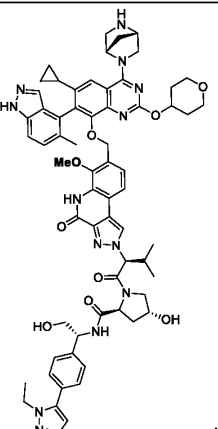
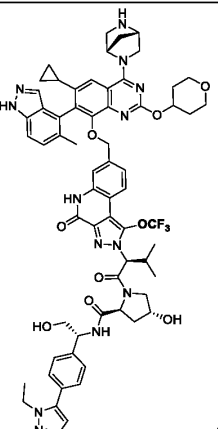
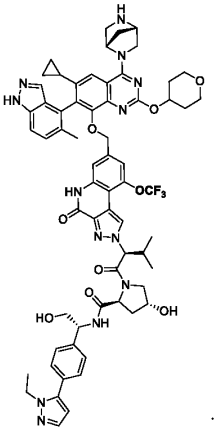
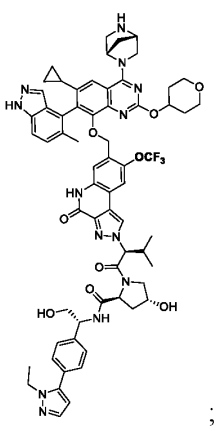
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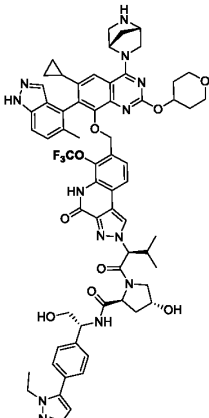
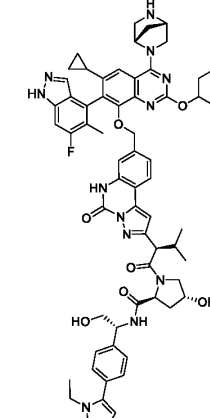
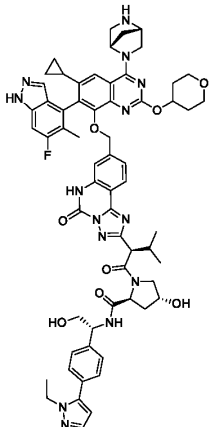
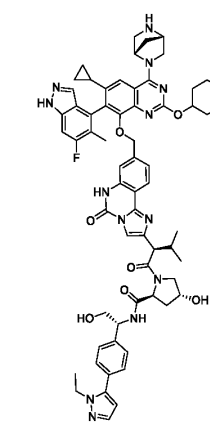
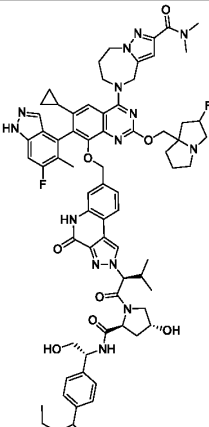
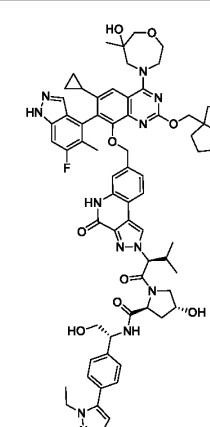
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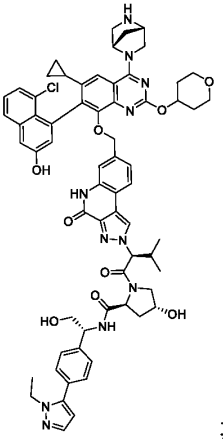
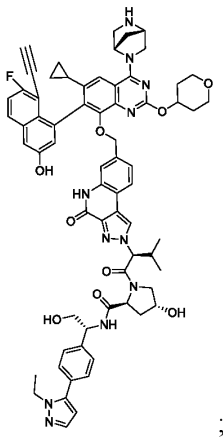
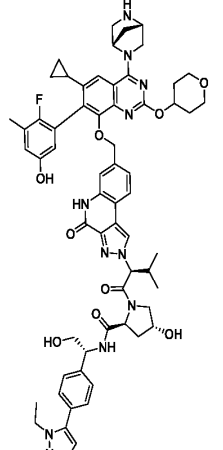
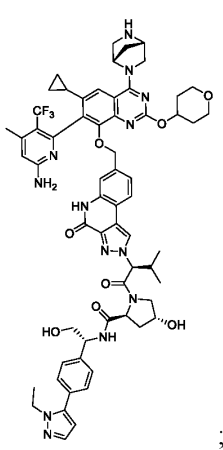
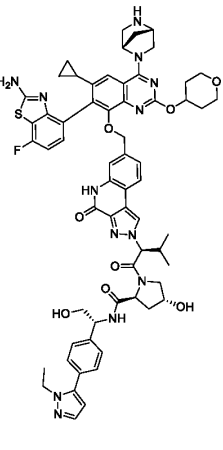
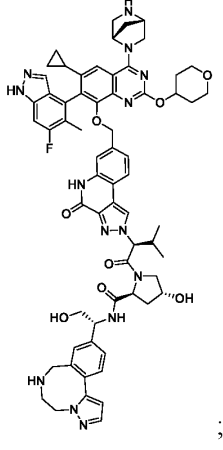
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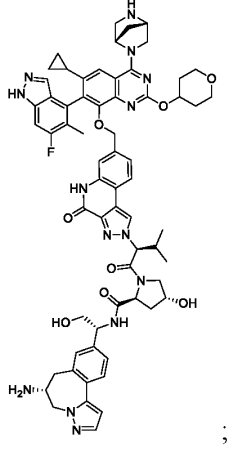
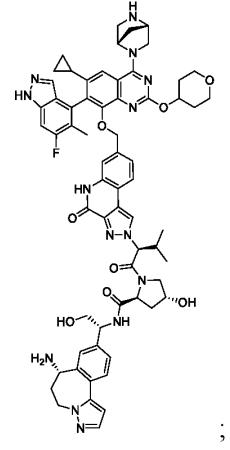
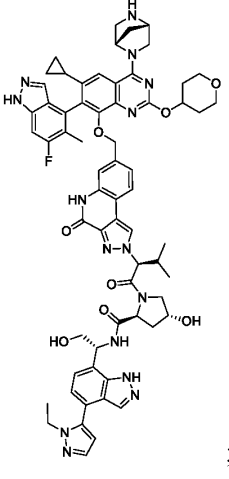
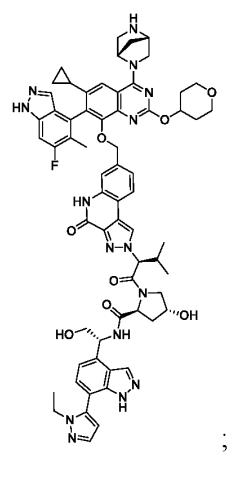
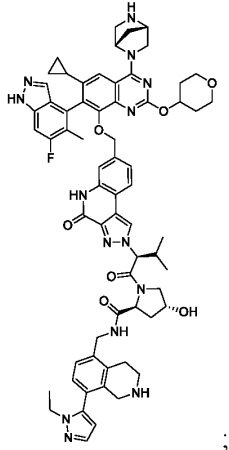
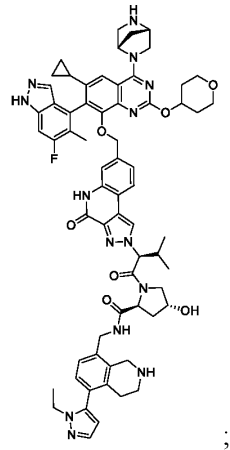
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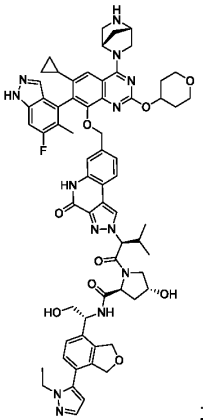
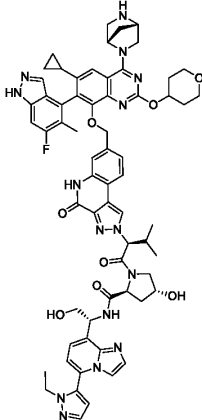
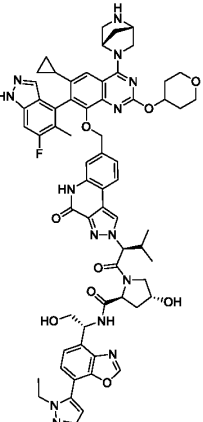
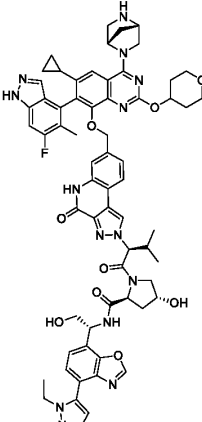
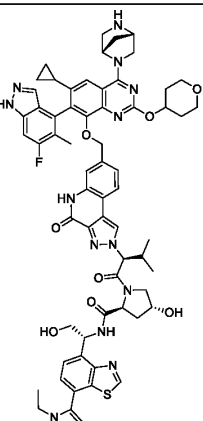
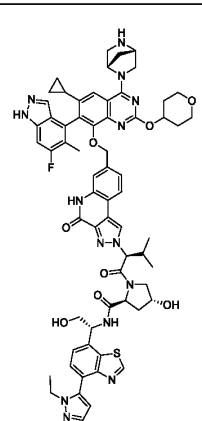
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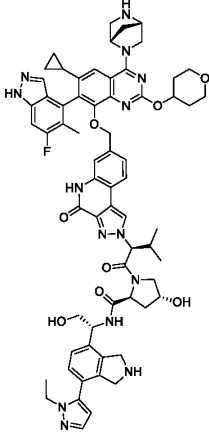
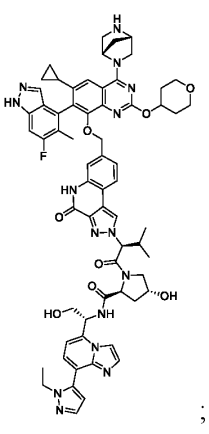
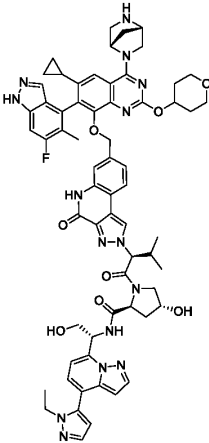
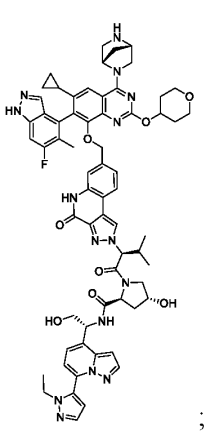
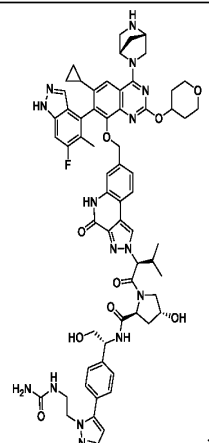
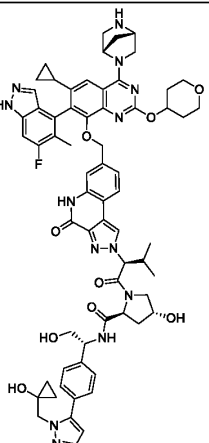
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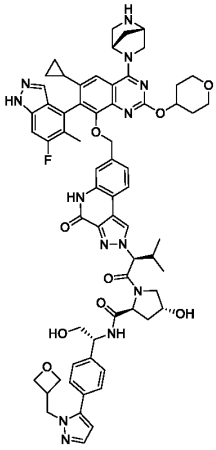
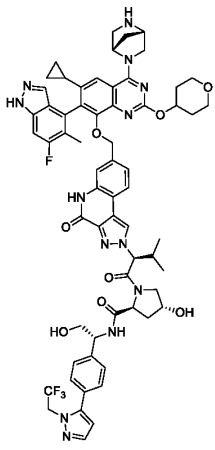
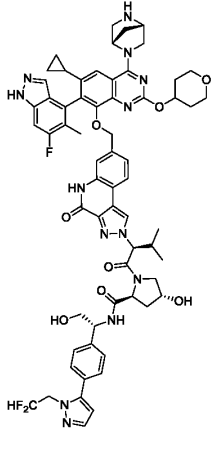
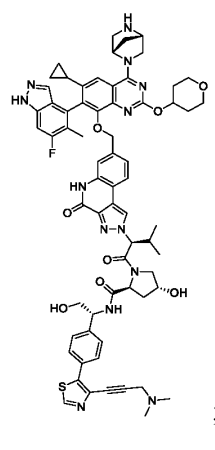
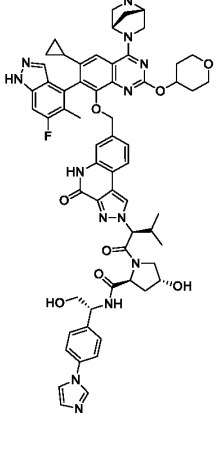
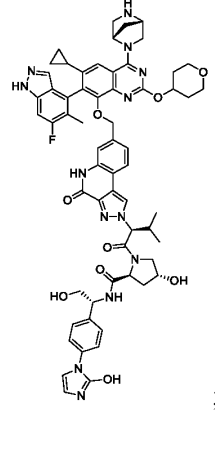
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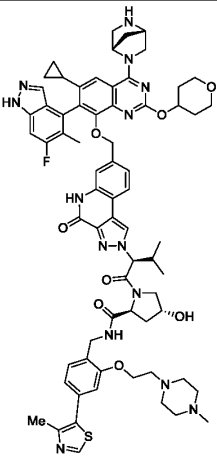
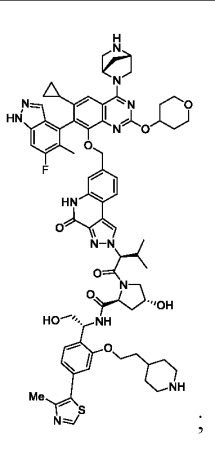
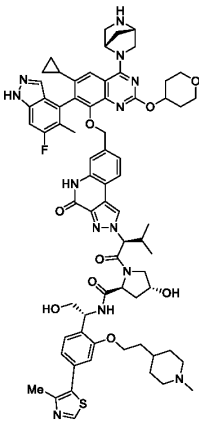
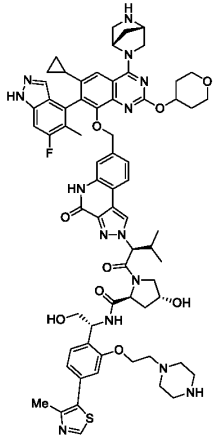
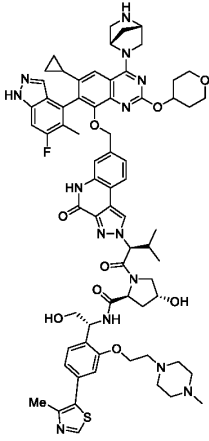
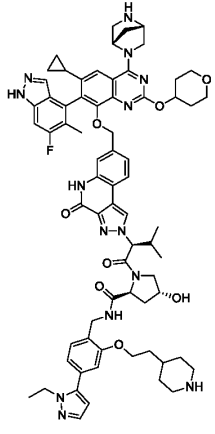
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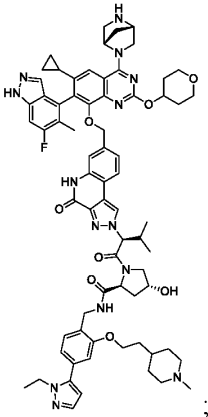
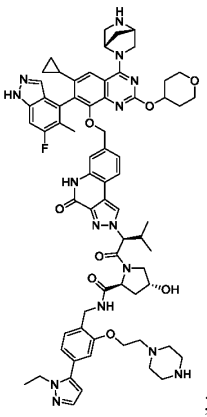
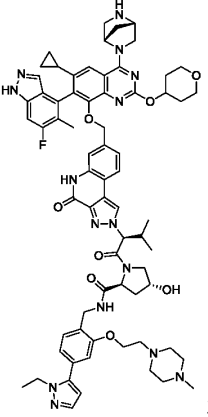
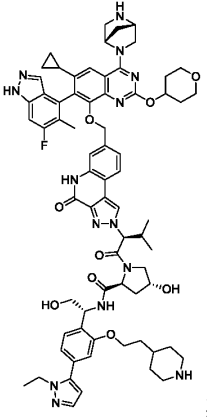
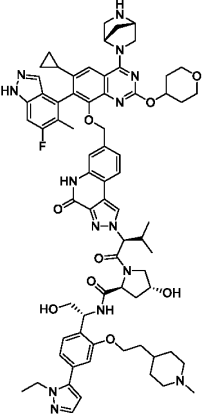
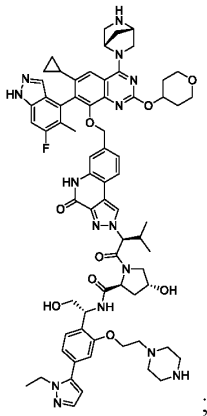
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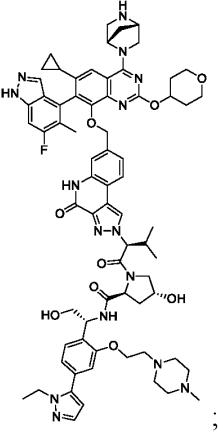
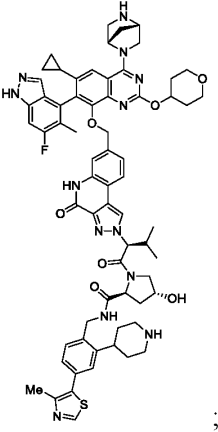
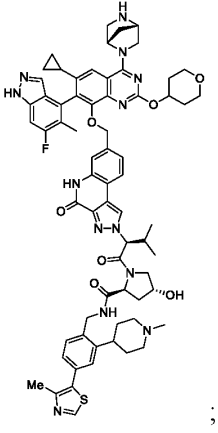
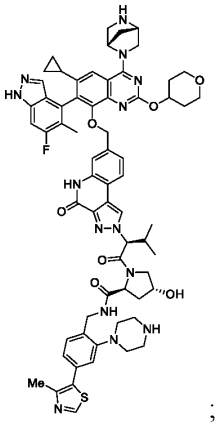
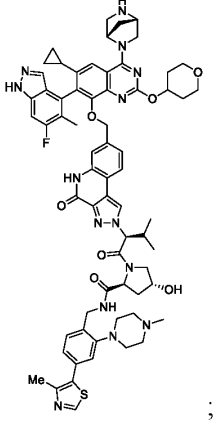
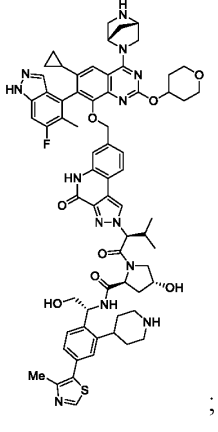
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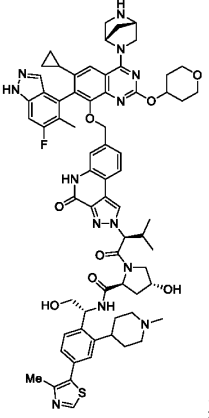
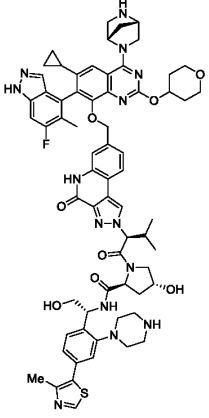
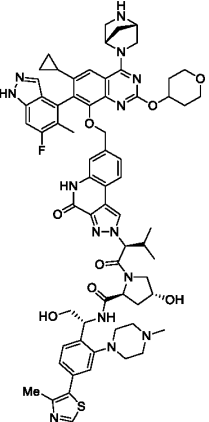
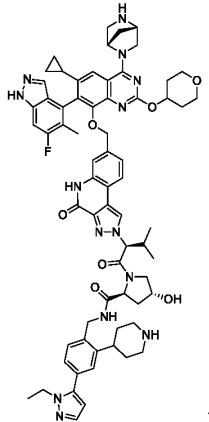
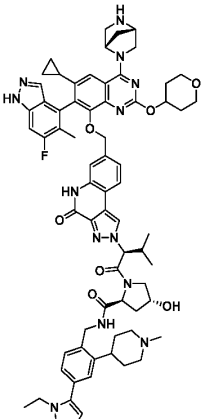
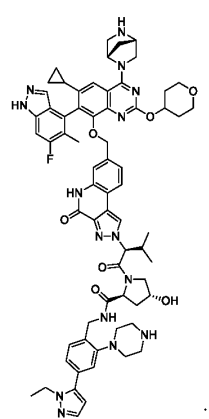
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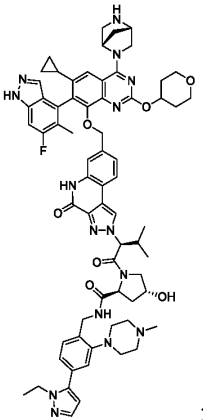
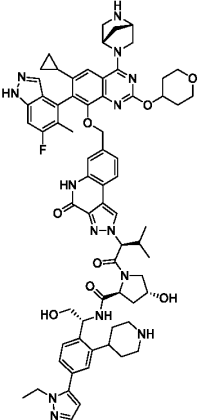
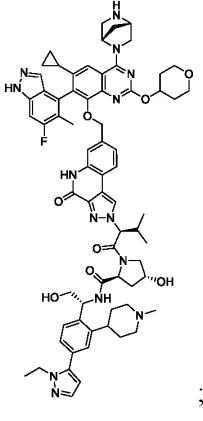
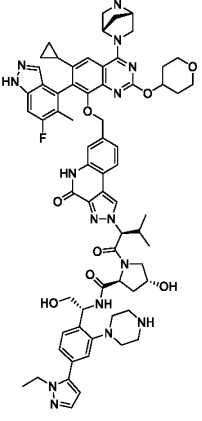
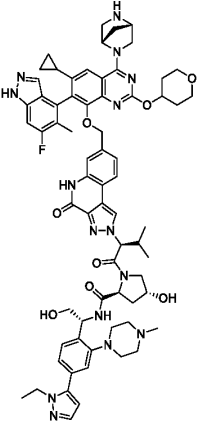
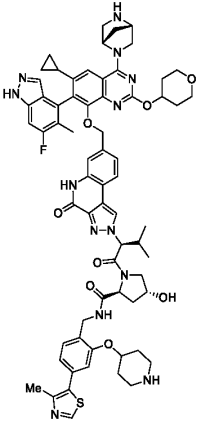
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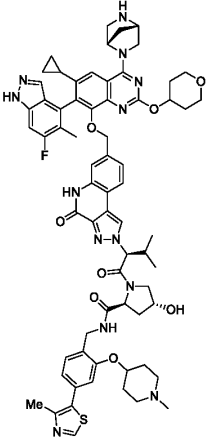
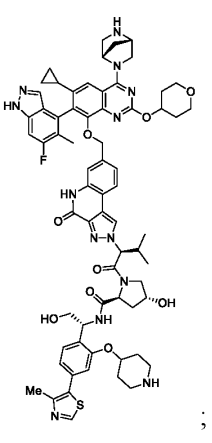
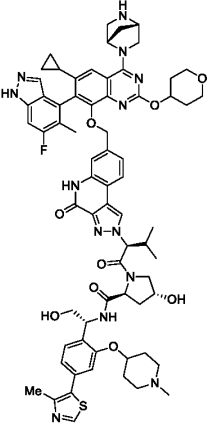
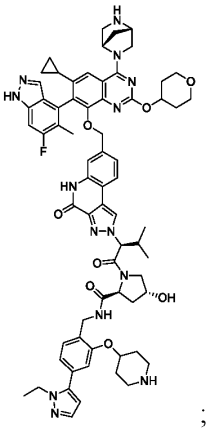
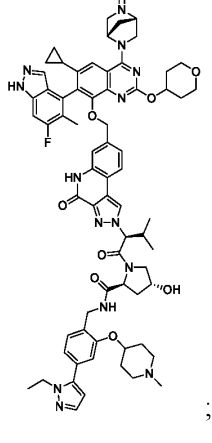
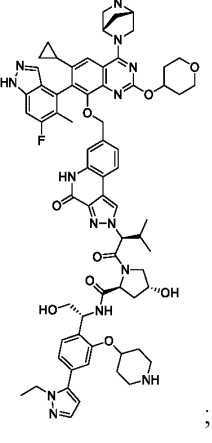
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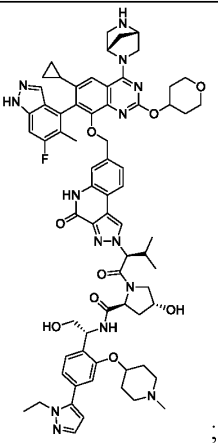
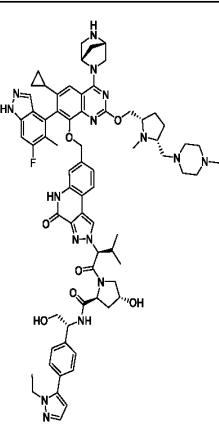
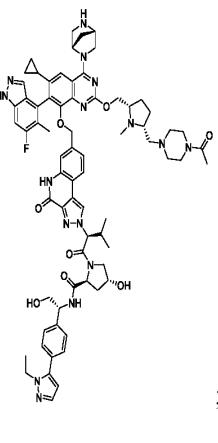
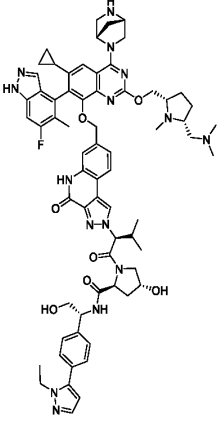
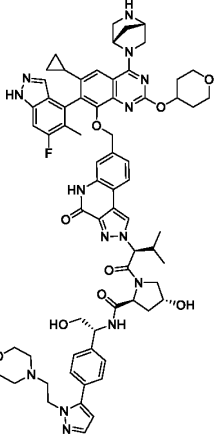
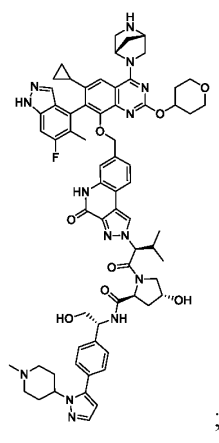
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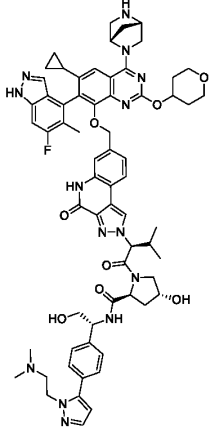
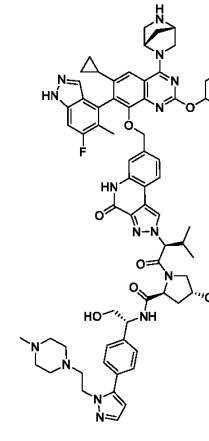
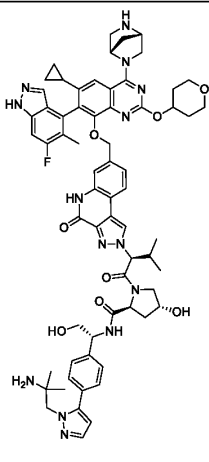
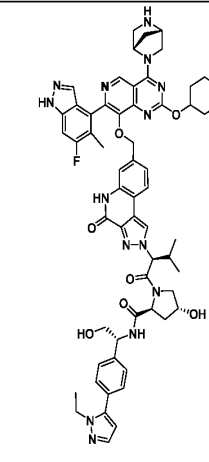
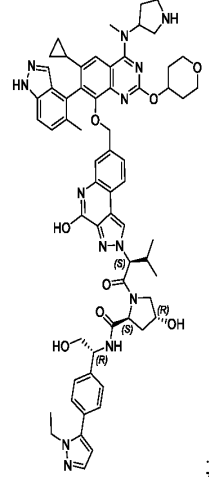
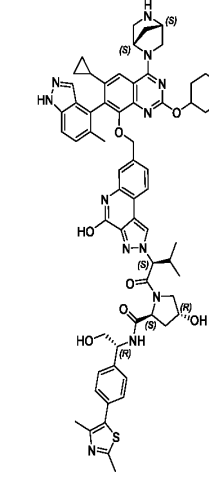
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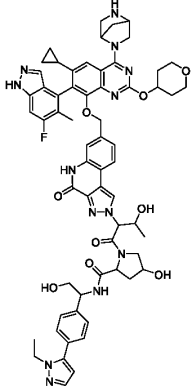
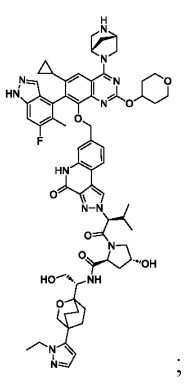
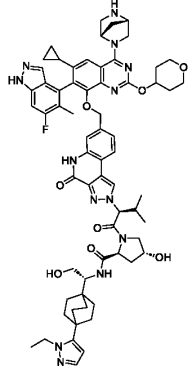
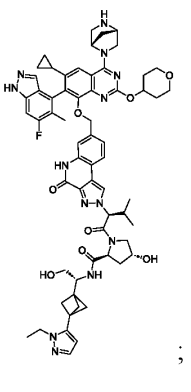
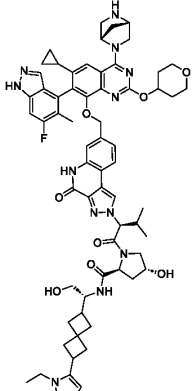
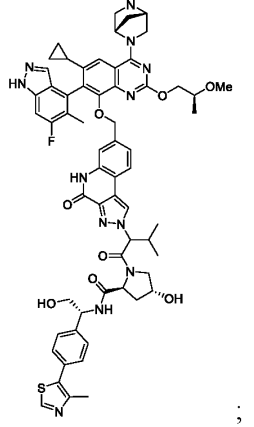
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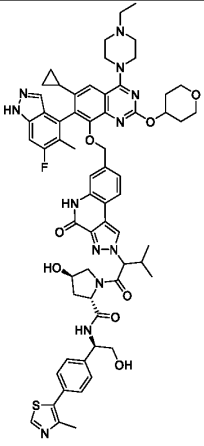
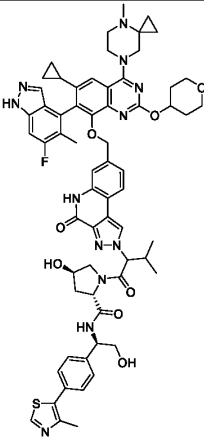
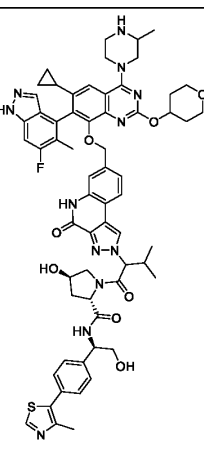
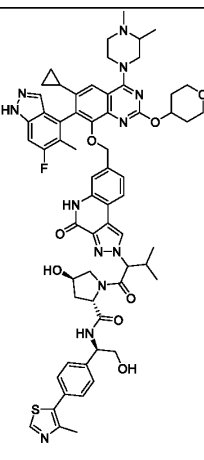
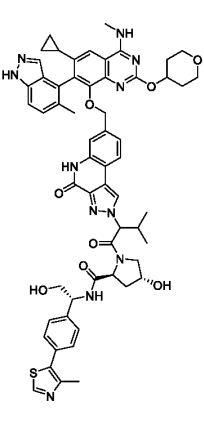
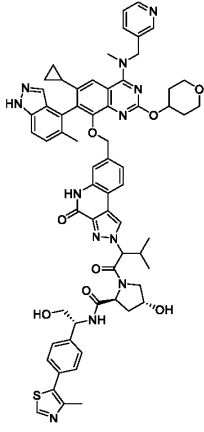
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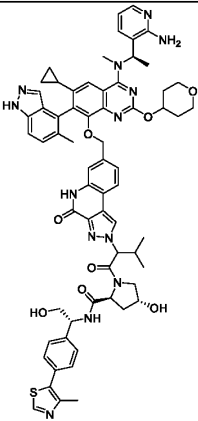
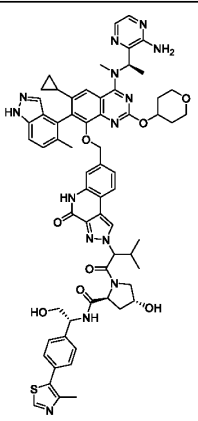
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157.		158.	
159.		162.	

163.		164.	
165.		166.	
167.		223	

225		226	
227		228	
229		230	

231		232	
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and

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

Biological Data:

Example 8: Determination of KRAS degradation in SW1990 cell lines by HiBit degradation assay

SW1990 HiBiT-KRAS G12D cells were plated at 7000 cells/well in a 96-well plate. Compounds of the present disclosure and positive controls were diluted in 10% DMEM complete media and applied to the plated cells resulting in a final concentration titration of 10 μ M to 4 nM in 1% DMSO. All assays were performed in triplicate. Cells were treated with compounds for 24 hours at 37 °C in an incubator containing 5% CO₂. Following treatment, 20 μ L of CellTiter-Fluor™ Cell Viability Assay (Promega cat. No. G6081) was added to the cells and incubated for 30 minutes at 37 °C to determine if compounds treatment led to a loss in cell viability after 24 hours, by capturing fluorescence on the BMG Labtech Clariostar instrument. After completion of the fluorescence read, Nano-Glo® HiBiT detection reagent (Promega cat. No. PRN3040) was prepared according to the manufacturer's instructions and 100 μ L reagent was added to each well followed by incubation at room temperature for 30 minutes. The luminescence was read in the BMG Labtech Clariostar instrument.

Selected compounds of the present invention were screened in the above-mentioned assay procedures for determination of D_{max} values and the results are summarized in below table A.

Table-A:

Compound No.	SW1990 HiBiT (D _{max} at 10 μM)	Compound No.	SW1990 HiBiT (D _{max} at 10 μM)
1a	10	191c	86
1c	59	192a	56
1d	91	192b	22
3c	16	193	79
3d	84	194	92
4a	16% @ 3.3 μM	195	56
4b	11	196a	33
4c	30	196c	>99
4d	86	196d	>99
5b	29	197a	15
5c	16	197c	91
5d	12	198a	35
6b	14	Mixture of 198c and 198d	81
7d	97	199b	38
8d	22	199c	97
12c	68	200c	45
12d	>99% @ 1.1 μM	201a	83
13c	38	201b	81
13d	>99% @ 0.37 μM	201c	91

32b	103	201d	93
38d	104	202c	15
160b	23	202d	53
160c	37	203a	12
161c	36	203b	14
161d	63	203c	80
169c	>99	203d	99
169d	43	Mixture of 204c and 204d	91
Mixture of 170c and 170d	43	205d	13
171b	56	206a	42
Mixture of 171c and 171d	51	206b	93
Mixture of 172b, 172c and 172d	63	207b	35
173d	85	207c	43
174a	51	208d	83
174b	46	209d	101
Mixture of 174c and 174d	31	210b	12

176c	23	210d	86
mixture of 177c and 177d	54	211a	14
mixture of 177e and 177f	53	211c	103
178c	96	212a	17
178d	51	212c	30
Mixture of 179c and 179d	>99	212d	100
181b	73	215d	96
181c	99	216b	26
182	>99% @ 0.3 μ M	216d	69
183a	82	217b	85
183b	112	219a	51
184	96	219d	112
185	>99	220a	27
186a	90	220c	82
186b	>99	220d	57
187a	76	221a	48
187b	76	221c	20
188a	77	221d	100
188b	83	222b	99

189	>99	224a	86
190c	99		

Example 9: Determination of KRAS degradation in MIAPaCa-2 cell lines by HiBit degradation assay

MIAPaCa-2 HiBiT-KRAS G12C cells were seeded at 4000 cells/well in a 96-well plate.

5 Compounds of the present disclosure and positive controls were diluted in 10% DMEM complete media and applied to the plated cells resulting in a final concentration range ranging from 10 μ M to 4 nM at 1% DMSO. All assays were performed in triplicate. Cells were incubated with compounds for 24 hours at 37 °C in an incubator containing 5% CO₂. Following treatment, 20 μ L of CellTiter-Fluor™ Cell Viability Assay (Promega cat. No. G6081) was

10 added on the cells and incubated for 30 minutes at 37 °C to determine if compounds treatment led to a loss in cell viability after 24 hours, by capturing fluorescence on the BMG Labtech Clariostar instrument. Post completion of the fluorescence read, Nano-Glo® HiBiT detection reagent (Promega cat. No. PRN3040) was prepared according to the manufacturer's instructions and 100 μ L reagent was added to each well followed by incubation at room

15 temperature for 30 minutes. The resultant luminescence was read in the BMG Labtech Clariostar instrument.

Selected compounds of the present invention were screened in the above-mentioned assay procedures for determination of D_{max} values and the results are summarized in below table B.

20 **Table-B:**

Compound No.	MiaPaCa-2 HiBiT (D _{max} at 10 μ M)	Compound No.	MiaPaCa-2 HiBiT (D _{max} at 10 μ M)
1d	>99	185	>99
12d	99	186b	>99
173d	>99% @ 3.3 μ M	188b	81
178c	15% @ 1.1 μ M	190c	>99

181c	99	191c	67
182	>99% @ 1.1 μ M	193	78
184	>99		

Example 10: Determination of KRAS degradation in SW620 (G12V) cell degradation assay by western blot

SW620 cells were seeded at 0.6×10^6 cells/well in 6-well plates. Compounds of the present disclosure and positive controls were diluted in 10% RPMI complete media and applied to the plated cells resulting in a final concentration range of 10 μ M to 2 nM at 1% DMSO. Cells were treated with compounds for 24 hours at 37 °C in an incubator containing 5% CO₂. Following treatment, PBS was added to the treated cells which were then scraped using a cell scraper and centrifuged at 12500 rpm for 15 min at 4 °C. After centrifugation, the pellets were resuspended with 1X RIPA lysis buffer for 60 min with intermediate vortex and centrifuged at 12500 rpm for 15 min at 4 °C. After this, the supernatant was collected and estimated protein concentration was determined using BCA kit. Twenty micrograms of protein were loaded per lane and resolved at 80 V for 2 hours. After the protein resolved, the gel was equilibrated in 1X transfer buffer with 20% methanol and processed for wet transfer by setting up the blotting paper, gel, nitrocellulose membrane (0.2 μ m) and blotting paper in a transfer cassette and set up the transfer for 1 hour at 80 V under cold conditions. Post transfer, the membrane was blocked using Intercept® blocking buffer (TBS) (Licor, Cat # 972-60001) for 1 hour at RT after which the primary antibody using K-RAS recombinant rabbit monoclonal antibody (Invitrogen :11H35L14 Ref# 703345) (1:1500) with housekeeping antibody β -Actin (Santa Cruz Biotechnology Cat# sc69879) (1:10000) was added for incubation overnight at 4 °C in the rocker. Primary antibody was then removed from the blots and washed twice with 1X TBST for 5 minutes. After washing, blots were incubated with the secondary antibody using Goat anti-Rabbit IgG (Licor; IRDye 800CW, Cat # 926-32211) (1:10000) and Goat anti-Mouse IgG (Licor; IRDye 680RD, Cat # 926-68070) for 1 hour at RT. After secondary antibody incubation, the blots were washed thrice with 1X TBST at 15 mins interval. Then, the blots were dried and scanned by LICOR Odyssey™ infrared scanner in the 800 and 700 channels.

Selected compounds of the present invention were screened in the above-mentioned assay procedures for determination of $D_{\max}$ values and the results are summarized in below table C.

Table-C:

Compound No.	SW620 ($D_{\max}$ at 10 μ M)	Compound No.	SW620 ($D_{\max}$ at 10 μ M)
1d	85	185	85
12d	73	186b	88
169c	95	188b	86
173d	89	189	86
178c	47% @ 1.1 μ M	190c	93% @ 3.3 μ M
181c	95% @ 3.3 μ M	191c	86% @ 3.3 μ M
182	89	193	85
183b	80	194	71% @ 3.3 μ M
184	80	208d	83

5

Example 11: Determination of KRAS degradation in NCI-H460 (Q61H) cell degradation by western blot

NCI-H460 cells were seeded at 0.2×10^6 cells/well in 6-well plates. Compounds of the present disclosure and positive controls were diluted in 10% RPMI complete media and applied to the plated cells resulting in a final concentration range of 10 μ M to 2 nM at 1% DMSO. Cells were treated with compounds for 24 hours at 37 °C in an incubator containing 5% CO₂. Following treatment, PBS was added to the treated cells and were scraped using cell scraper and centrifuged at 12500 rpm for 15 min at 4 °C. After centrifugation, the pellets were resuspended with 1X RIPA lysis buffer for 60 min with intermediate vortex and centrifuged at 12500 rpm for 15 min at 4 °C. The supernatant was then collected, and protein concentration estimated by BCA kit. Twenty micrograms of protein were loaded per lane and resolved at 80 V for 2 hours. After resolution of protein, the gel was equilibrated in 1X transfer buffer (cat# 1610734 Biorad) with 20% methanol and processed for wet transfer by setting up the blotting

paper, gel, nitrocellulose membrane (0.2 μ M) and blotting paper in a transfer cassette and set up the transfer for 1 hour at 80 V under cold conditions. Post transfer, the membrane was blocked using Intercept® blocking buffer (TBS) (Licor, Cat # 972-60001) for 1 hour incubation at RT and primary antibody added which included K-RAS recombinant rabbit monoclonal antibody (Invitrogen :11H35L14 Ref# 703345) (1:1500) as well as housekeeping antibody β -Actin (Santa Cruz Biotechnology Cat# sc69879) (1:10000) and incubated overnight at 4 °C in the rocker. Primary antibody was then removed from the blots and washed twice with 1X TBST for 5 minutes. After these rinses, blots were incubated with the secondary antibody using Goat anti-Rabbit IgG (Licor; IRDye 800CW, Cat # 926-32211) (1:10000) and Goat anti-Mouse IgG (Licor; IRDye 680RD, Cat # 926-68070) for 1 hour at RT. After secondary antibody incubation, the blots were washed thrice with 1X TBST at 15 mins interval. Then, the blots were dried and scanned by LICOR Odyssey™ infrared scanner in the 800 and 700 channels.

Selected compounds of the present invention were screened in the above-mentioned assay procedures for determination of $D_{\max}$ values and the results are summarized below table D.

Table-D:

Compound No.	NCI-H460 ($D_{\max}$ at 10 μ M)
1d	98
12d	98
181c	91
183b	84
186b	85
190c	92

Example 12: Determination of KRAS degradation in HCT-116 (G13D) cell degradation by western blot

HCT-116 cells were seeded at 0.4×10^6 cells/well in 6-well plates. Compounds of the present disclosure and positive controls were diluted in the 10% RPMI complete media and applied to the plated cells resulting in a final concentration range of 10 μ M to 1 nM 1% DMSO. Cells were treated with compounds for 24 hours at 37 °C in an incubator containing 5% CO₂. Following treatment, PBS was added to the treated cells and were scraped using cell scraper and centrifuged at 12500 rpm for 15 min at 4 °C. After centrifugation, the pellets were resuspended with 1X RIPA lysis buffer for 60 min with intermediate vortex and centrifuged at 12500 rpm for 15 min at 4 °C. After that the supernatant was collected and estimated protein concentration by BCA kit. 20 μ g of protein were loaded per lane and resolved at 80 V for 2 hours. Once the protein resolved, the gel is equilibrated in 1X transfer buffer with 20% methanol and processed for wet transfer by setting up the blotting paper, gel, nitrocellulose membrane (0.2 μ m) and blotting paper in a transfer cassette and set up the transfer for 1 hour at 80 V under cold conditions. Post transfer, the membrane was blocked using Intercept® blocking buffer (TBS) (Licor, Cat # 972-60001) for 1 hour incubation at RT and added the primary antibody i.e. RAS (G13D MUTANT) ANTIBODY 100 UL cat# PA578088 R (1:500) with housekeeping antibody β -Actin (Santa Cruz Biotechnology Cat# sc69879) (1:10000) and incubated overnight at 4 °C in the rocker. Next day, primary antibody was removed from the blots and washed twice with 1X TBST for 5 mins. After washes, blots were incubated with the secondary antibody using Goat anti-Rabbit IgG (Licor; IRDye 800CW, Cat # 926-32211) (1:10000) and Goat anti-Mouse IgG (Licor; IRDye 680RD, Cat # 926-68070) for 1 hour at RT. After secondary incubation, the blots were washed thrice with 1X TBST at 15 mins intervals. Then, the blots were dried and scanned by LICOR Odyssey™ infrared scanner in the 800 and 700 channels.

Selected compounds of the present invention were screened in the above-mentioned assay procedures for determination of D_{max} values and the results are summarized in below table E.

Table-E:

Compound No.	HCT-116 (D _{max} at 10 μ M)
1d	76
12d	76
181c	91% @ 3.3 μ M
183b	88% @ 3.3 μ M
190c	89

Example 13: Study on efficacy of compounds in AsPC-1 pancreatic adeno carcinoma xenograft model

5 Five to six weeks-old female athymic nude mice were inoculated with 2 million AsPC-1 cells on the right flank region. Mice were randomized based on the tumor volume and dosing was initiated when the mean tumor volumes were $\sim 216 \text{ mm}^3$. Compounds 1d and 12d were dosed intravenously at a once-a-week interval for three weeks. Animals were monitored daily for body weight loss and clinical signs of toxicity while the tumor volumes were measured

10 twice weekly. Compounds 1d (Isomer-4 of compound 1) and 12d (Isomer-4 of compound 12) were well tolerated at 10 mg/kg and 30 mg/kg once-weekly doses. Compound 1d treatment demonstrated dose dependent anti-tumor efficacy with %TGI values of 78% and 100% at 10 mg/kg and 30 mg/kg, respectively, illustrated in Figure 1. Compound 12d treatment demonstrated dose dependent anti-tumor efficacy with %TGI values of 70% and 94% at 10

15 mg/kg and 30 mg/kg, respectively, illustrated in Figure 1.

% Tumor growth inhibition by Compound 1d and 12d in AsPC-1 pancreatic adeno carcinoma xenograft model is summarized in below table F.

Table F:

Treatment	% Tumor Growth Inhibition (TGI)
Compound 1d, 10 mg/kg, Q7D, IV	78*

Compound 1d, 30 mg/kg, Q7D, IV	100**
Compound 12d, 10 mg/kg, Q7D, IV	70*
Compound 12d, 30 mg/kg, Q7D, IV	94**

Brown-Forsythe & Welch ANOVA tests: -*p<0.05; **p<0.01** compared to vehicle controls.

Incorporation by Reference

5 All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent were specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

Equivalents

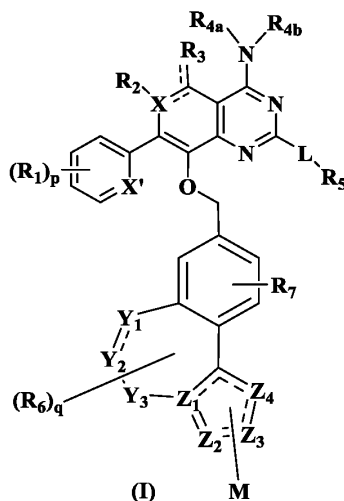
10 While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents and the specification, along with such variations.

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CLAIMS:

1. A compound of Formula (I)



or a pharmaceutically acceptable salt or stereoisomer or a tautomer thereof;

5 wherein,

R_1 at each occurrence, independently is hydrogen, (C₁-C₆)alkyl, hydroxy, halo, amino, halo(C₁-C₆)alkyl, and/or two R_1 adjacent to each other together with the C atoms to which they are attached form a phenyl or 5- to 6-membered heterocyclyl; wherein the phenyl and heterocyclyl are unsubstituted or substituted with 1, 2 or 3 substituents each independently
 10 selected from the group consisting of (C₁-C₆)alkyl, (C₂-C₄)alkynyl, halo, hydroxy, halo(C₁-C₆)alkyl, amino and cyano;

p is 1, 2, 3, or 4;

X and X' , independently, is C or N;

R_2 is hydrogen, cyclopropyl or absent;

15 R_3 is hydrogen or oxo;

R_{4a} and R_{4b} , independently, is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 5- to 10-membered heteroaryl(C₁-C₆)alkyl or 4- to 7-membered heterocyloalkyl, wherein the cycloalkyl and heteroarylalkyl are unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo, (C₁-C₆)alkyl and amino; and/or

R_{4a} and R_{4b} together with the nitrogen to which they are attached form a 4- to 14-membered heterocyclyl optionally containing one or two additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur; wherein the heterocyclyl is unsubstituted or substituted with 1, 2 or 3 groups each independently selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy, cyano and -C(O)-R_{4c}; wherein said alkyl is unsubstituted or substituted independently with one or more of halo, hydroxy, amino, cyano or (C₃-C₆)cycloalkyl; and/or

R_{4c} is hydrogen, amino, (C₁-C₆)alkylamino, 4- to 7-membered heterocycloalkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkyl or (C₁-C₆)alkylamino(C₁-C₆)alkyl; wherein the heterocycloalkyl and cycloalkyl are unsubstituted or substituted with 1, 2 or 3 groups each independently selected from the group consisting of halo, hydroxy and (C₁-C₆)alkyl;

L is -O-(CH₂)_m*, -C(O)-* or -C(O)-NH-*; wherein asterisk mark represents the point of attachment with R₅;

R₅ is (C₁-C₆)alkyl, (C₁-C₆)alkoxy, -(CH₂)_m-NR_cR_d, 5- to 14-membered heterocycloalkyl or (C₃-C₆)cycloalkyl; wherein the heterocycloalkyl and cycloalkyl are unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkyl, halo, amino and -(CH₂)_mNR_yR_z;

m is 0, 1, 2 or 3;

R_c and R_d, independently, is hydrogen or (C₁-C₆)alkyl; or R_c and R_d together with the N atom to which they are attached, form a 4- to 7-membered heterocycloalkyl;

R_y and R_z, independently is hydrogen or (C₁-C₆)alkyl; or R_y and R_z together with the N atom to which they are attached, form a 4- to 7-membered heterocycloalkyl; wherein the heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkyl, halo and (C₂-C₄)acyl;

R₆ at each occurrence, independently, is hydrogen, amino, (C₁-C₆)alkyl, (C₁-C₆)alkoxy or hydroxy; or two R₆ on the same carbon represent an oxo group;

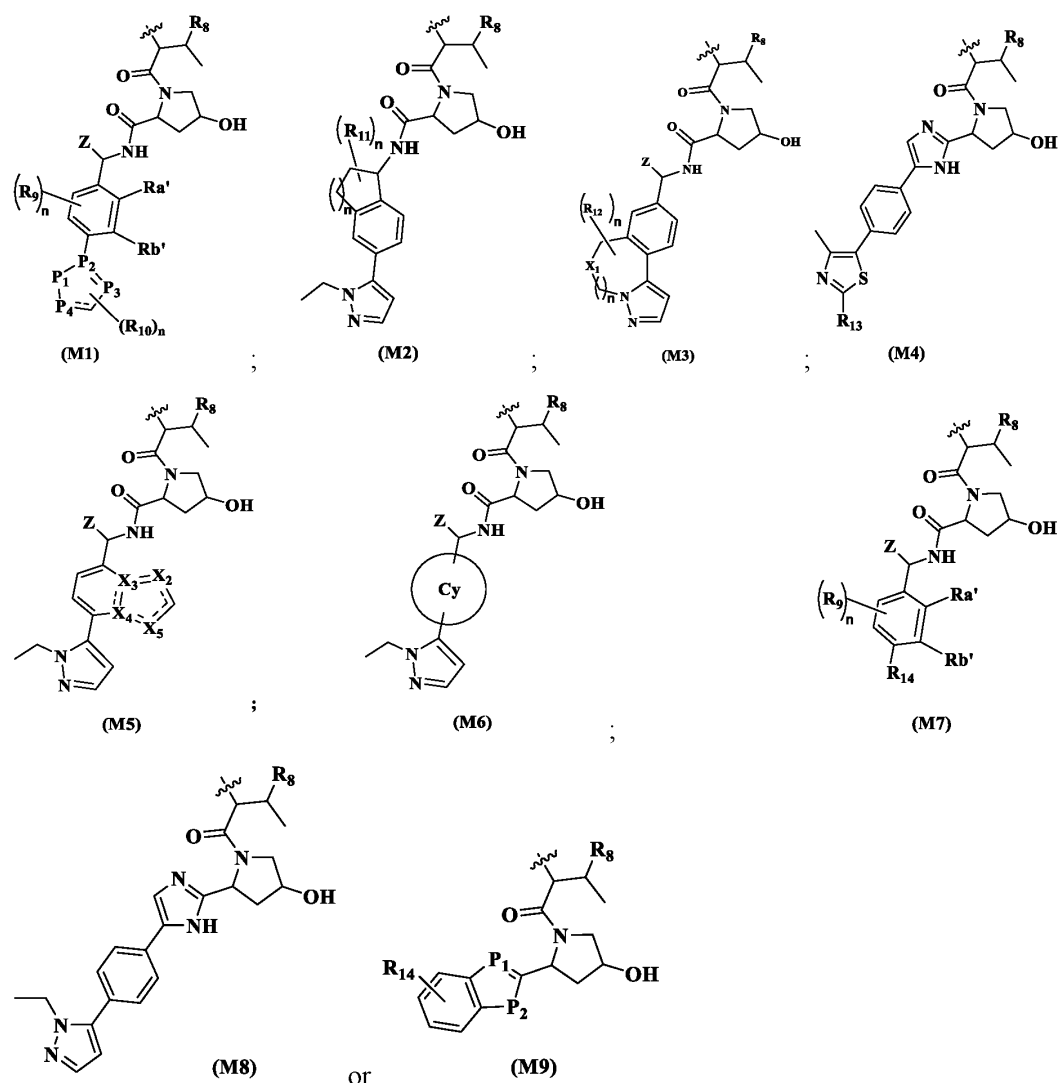
q is 1, 2 or 3;

Y₁, Y₂ and Y₃, independently, is a bond, C, N or O; wherein not more than one of Y₁, Y₂ or Y₃ is a bond;

Z_1 , Z_2 , Z_3 and Z_4 independently, is a C, $CR_{7'}$, NR_7 , or N; wherein at least two of Z_1 , Z_2 , Z_3 and Z_4 are N;

R_7 and $R_{7'}$ independently, is hydrogen, halo, (C_1-C_6) alkyl, halo (C_1-C_6) alkyl, (C_1-C_6) alkoxy or halo (C_1-C_6) alkoxy;

5 M is M1, M2, M3, M4, M5, M6, M7, M8 or M9;



wherein,

10 R_8 is (C_1-C_6) alkyl, hydroxy, halo or amino;

Z is hydrogen, (C_1-C_6) alkyl, halo or $-CH_2OH$;

R_a' and R_b' independently, is hydrogen, halo or (C₁-C₆)alkyl; or R_a' and R_b' together with the C atoms to which they are attached form a 5 to 6 membered heterocyclyl ring optionally containing one or two hetero atoms independently selected from the group consisting of O, S and N;

- 5 R₉ at each occurrence, independently, is hydrogen, 4- to 8-membered heterocycloalkyl, -O-heterocycloalkyl, -O-(C₁-C₆)alkyl;

wherein heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo or (C₁-C₆)alkyl;

- 10 wherein the alkyl in -O-(C₁-C₆)alkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkylamino or 5- to 8-membered heterocycloalkyl; wherein the heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo or (C₁-C₆)alkyl;

- 15 P₁, P₂, P₃ and P₄, independently, is C, N or S; wherein at least one of P₁, P₂, P₃ and P₄ is N;

R₁₀ is hydrogen, (C₁-C₆)alkyl, (C₂-C₄)alkynyl, hydroxy, 3- to 7-membered heterocycloalkyl or (C₃-C₆)cycloalkyl;

- 20 wherein the alkyl and alkynyl is unsubstituted or substituted with halo, cycloalkyl, -NH-(CO)-NH₂, -NR_mR_n or 4 to 6 membered heterocycloalkyl; wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkyl, hydroxy, halo or amino;

- 25 wherein 3- to 7-membered heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo, hydroxy or (C₁-C₆)alkyl;

R_m and R_n are independently hydrogen or (C₁-C₆)alkyl;

- 30 R₁₁ at each occurrence, independently, is hydrogen, hydroxy or (C₁-C₆)alkyl; wherein the alkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo or hydroxy;

R₁₂ at each occurrence, independently, is hydrogen or amino;

X₁ is C or N;

R₁₃ is hydrogen or (C₁-C₆)alkyl;

X₂, X₃, X₄ and X₅, each independently is C, CH or N; wherein one of X₃ or X₄ is always

5 N and the other is C;

R₁₄ at each occurrence, independently is hydrogen, halo, hydroxy, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl or (C₂-C₆)alkynyl;

Cy is (C₃-C₁₀)cycloalkyl or 3- to 10-membered heterocycloalkyl;

a dotted line [-----] indicates a bond or absent; and

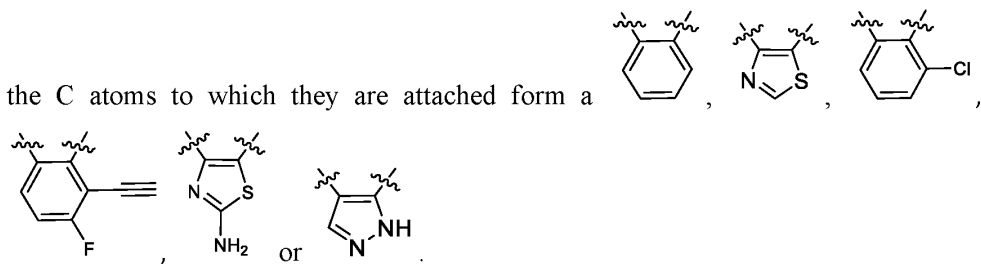
10 n is 1, 2 or 3.

2. The compound of claim 1, wherein R₁ at each occurrence is (C₁-C₆)alkyl, amino, hydroxy or halo.

3. The compound of claim 1, wherein two R₁ adjacent to each other together with the C atoms to which they are attached form a phenyl or 5- to 6-membered heterocyclyl; wherein the phenyl and heterocyclyl are unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from (C₁-C₆)alkyl, (C₂-C₄)alkynyl, halo and amino.

4. The compound of claims 1 and 3, wherein two R₁ adjacent to each other together with

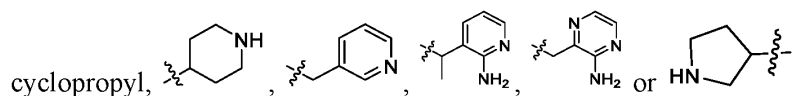
the C atoms to which they are attached form a



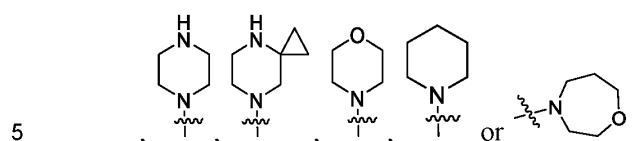
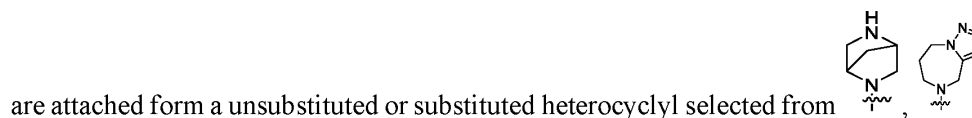
5. The compound of claim 1, wherein R₂ is cyclopropyl or absent.

6. The compound of claim 1, wherein R_{4a} and R_{4b}, independently, is (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 5- to 10-membered heteroaryl(C₁-C₆)alkyl or 4- to 7-membered heterocycloalkyl.

7. The compound of claims 1 and 6, wherein R_{4a} and R_{4b} independently, is methyl, ethyl,



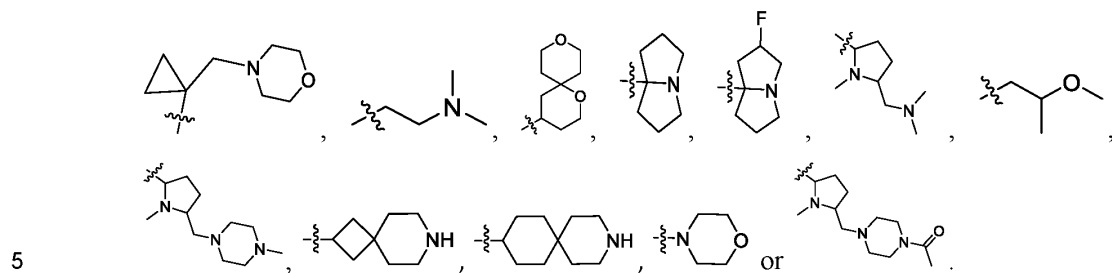
8. The compound of claim 1, wherein R_{4a} and R_{4b} together with the nitrogen to which they



9. The compound of claim 8, wherein the heterocyclyl is substituted with 1, 2 or 3 groups each independently selected from (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, hydroxy and $-C(O)-R_{4c}$; wherein said alkyl is substituted independently with one or more of halo, hydroxy or (C_3-C_6) cycloalkyl.
10. The compound of claim 9, wherein R_{4c} is amino, (C_1-C_6) alkylamino, (C_1-C_6) alkyl or unsubstituted or substituted 4- to 7-membered heterocycloalkyl; wherein the heterocycloalkyl is substituted with (C_1-C_6) alkyl.
11. The compound of claim 1, wherein L is $-O-$, $-O-(CH_2)_m-$, $-C(O)-$ or $-C(O)-NH-$; wherein asterisk mark represents the point of attachment with R_5 .
12. The compound of claims 1 and 11, wherein L is $-O-(CH_2)_m-$ wherein the asterisk mark represents the point of attachment with R_5 .
13. The compound of claim 1, wherein R_5 is (C_1-C_6) alkoxy, $-(CH_2)_m-NR_cR_d$ or 5- to 14-membered heterocycloalkyl; wherein the heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from (C_1-C_6) alkyl, halo, and $-(CH_2)_m-NR_yR_z$.
14. The compound of claim 13, wherein R_c and R_d are (C_1-C_6) alkyl; or R_c and R_d together with the N atom to which they are attached, form a 4- to 7-membered heterocycloalkyl.
15. The compound of claim 13, wherein R_y and R_z is (C_1-C_6) alkyl; or R_y and R_z together with the N atom to which they are attached, form a 4- to 7-membered heterocycloalkyl;

wherein the heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from (C₁-C₆)alkyl and (C₂-C₄)acyl.

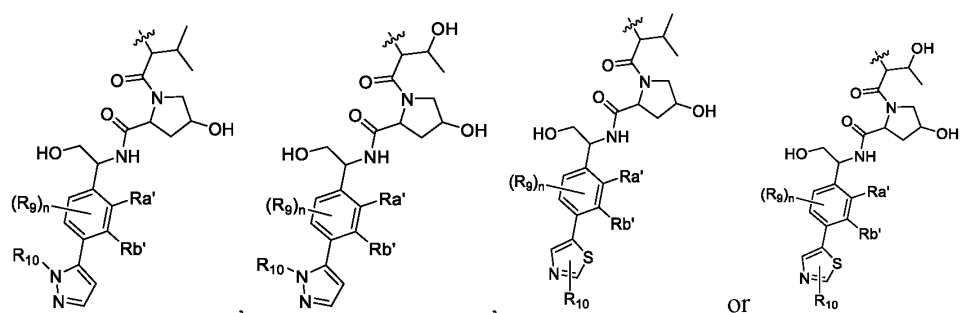
16. The compound of claims 1 and 13, wherein, R₅ is , , 



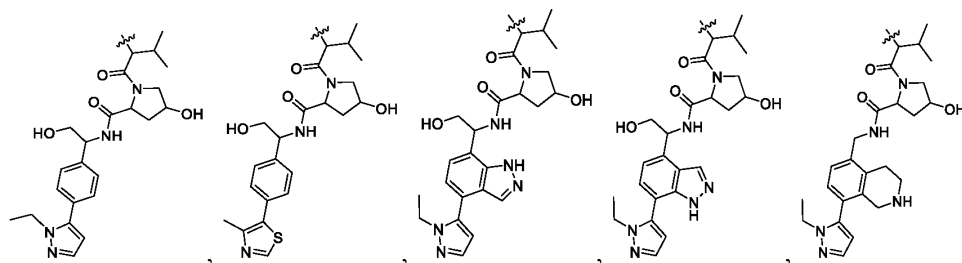
17. The compound of claim 1, wherein R₆ is hydrogen, amino, (C₁-C₆)alkoxy, or hydroxy; or two R₆ on the same carbon represent an oxo group.

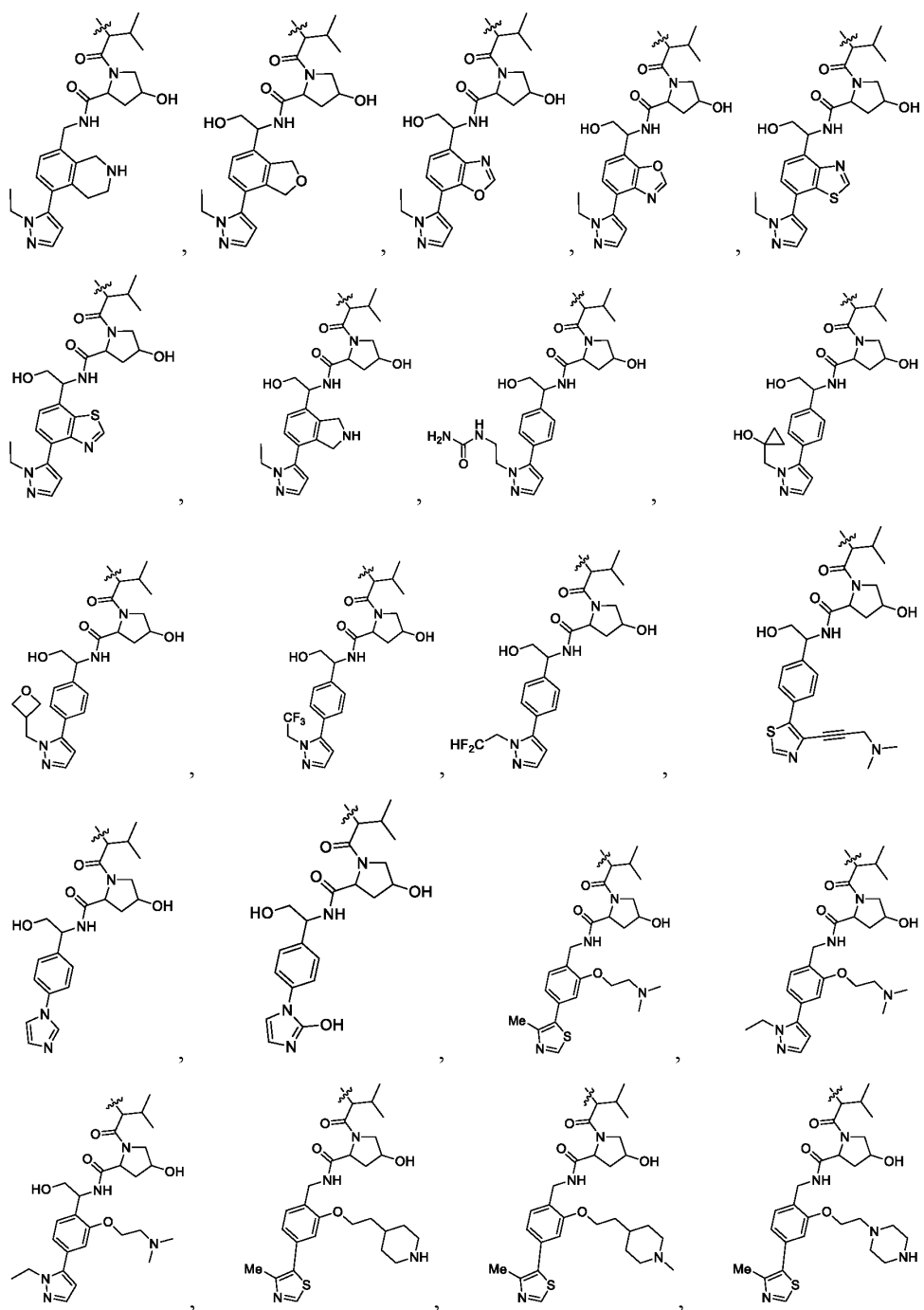
18. The compound of claim 1, wherein R₇ and R_{7'} are independently halo, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₁-C₆)alkoxy, or halo(C₁-C₆)alkoxy.

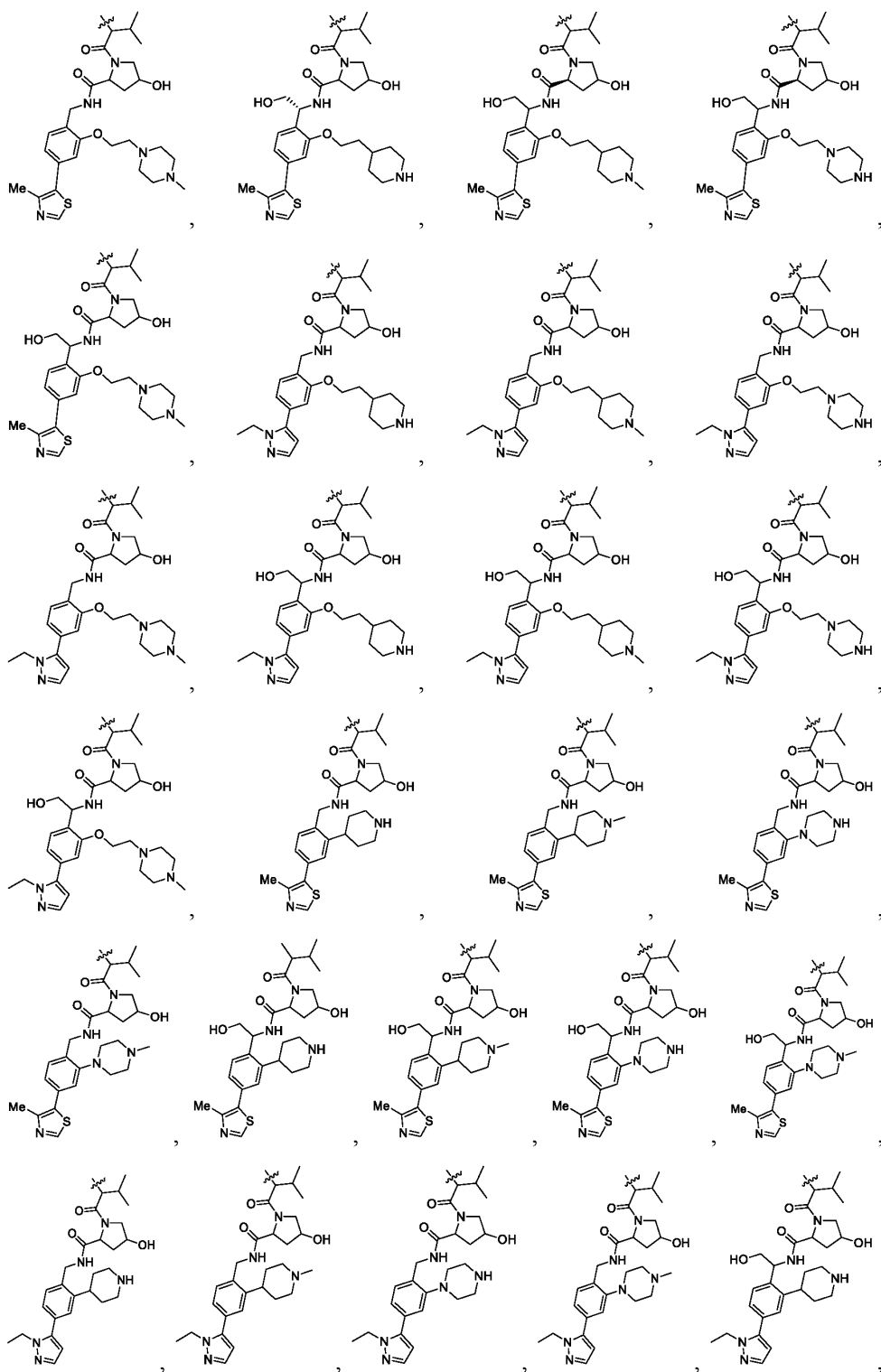
- 10 19. The compound of claim 1, wherein M1 is

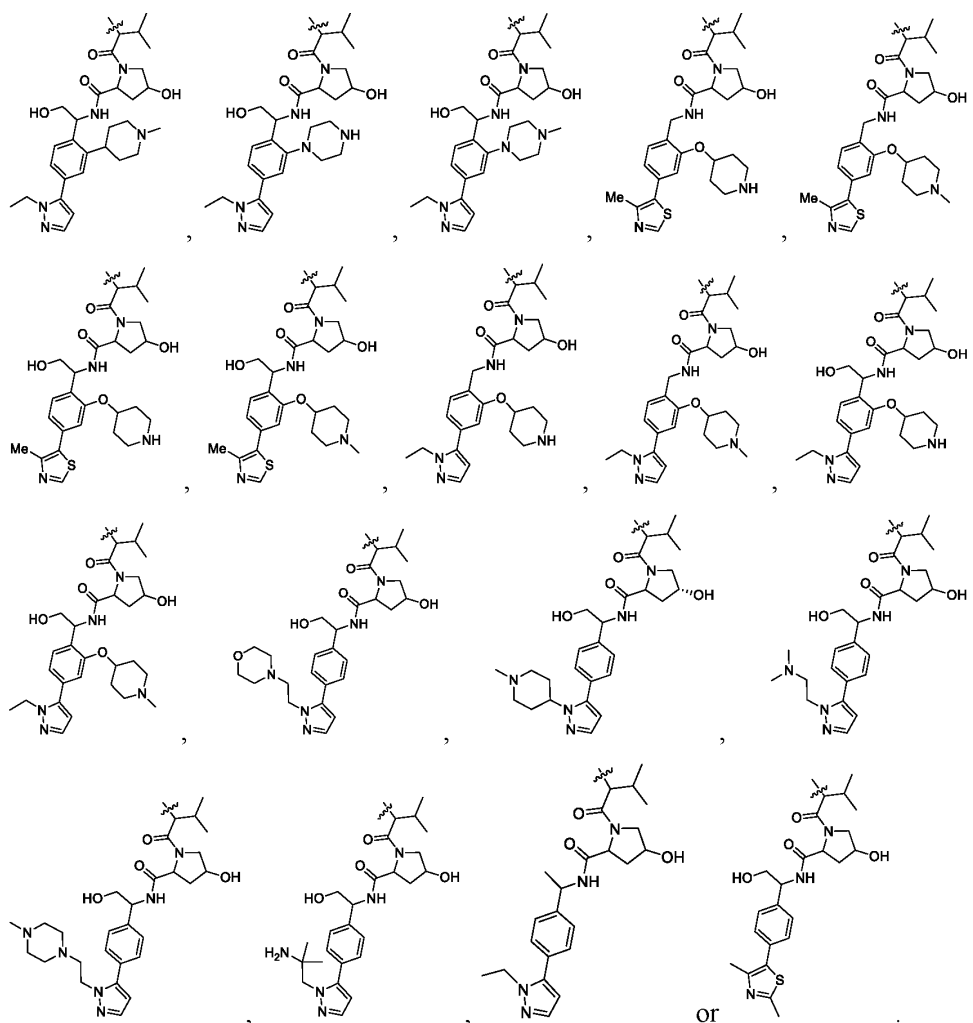


20. The compound of claims 1 and 19, wherein M1 is

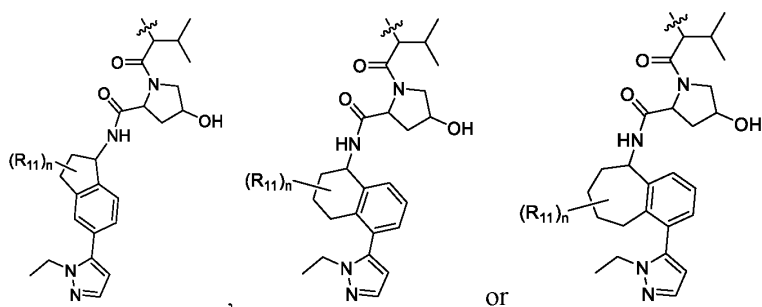




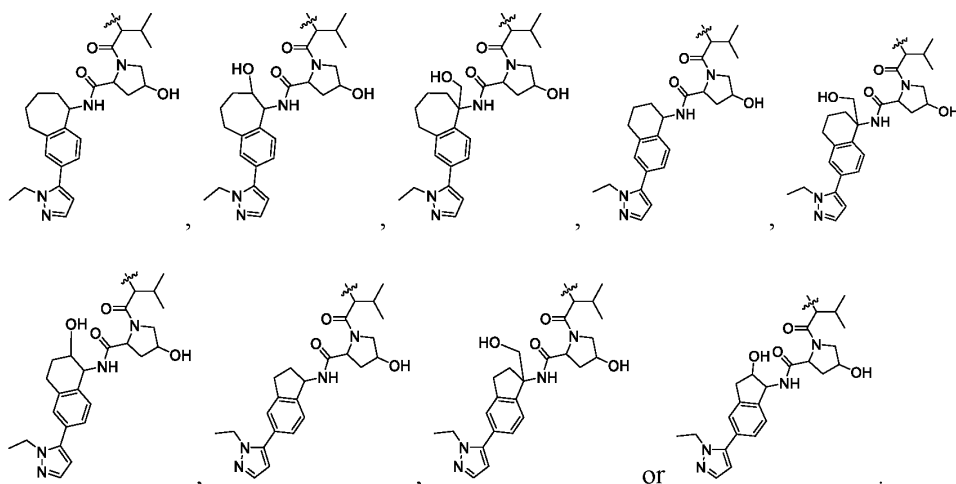




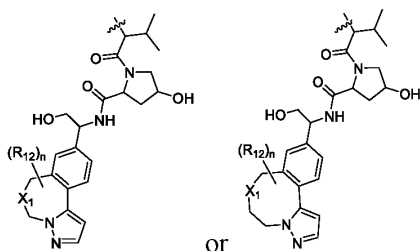
5 21. The compound of claim 1, wherein M2 is



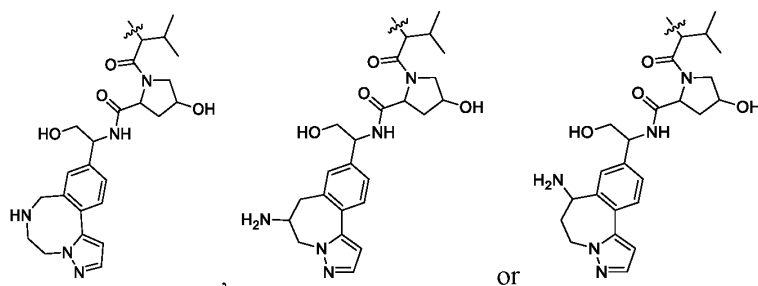
22. The compound of claims 1 and 21, wherein M2 is



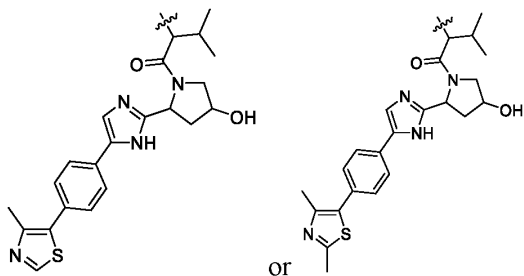
23. The compound of claim 1, wherein M3 is



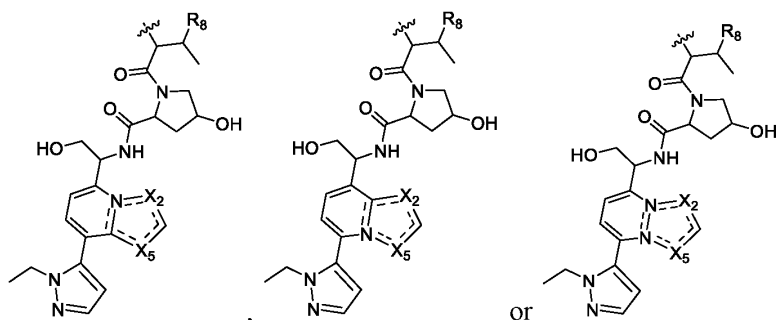
5 24. The compound of claims 1 and 23, wherein M3 is



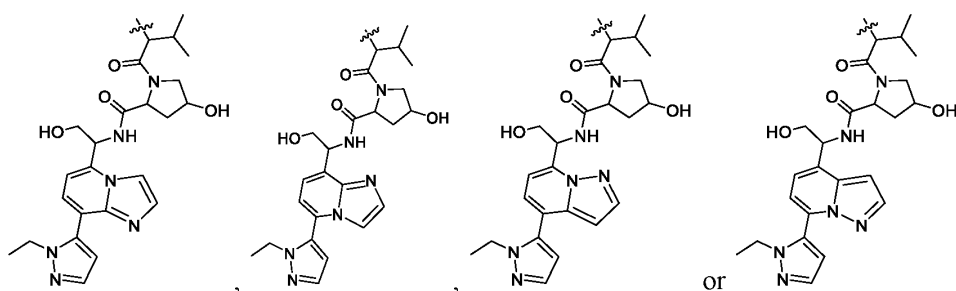
25. The compound of claim 1, wherein M4 is



26. The compound of claim 1, wherein M5 is

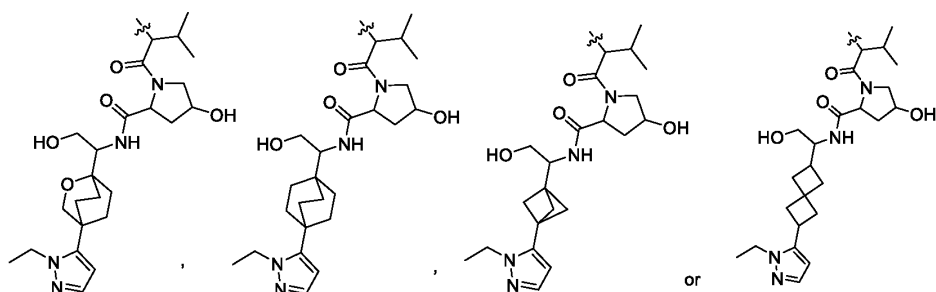


27. The compound of claims 1 and 26, wherein M5 is

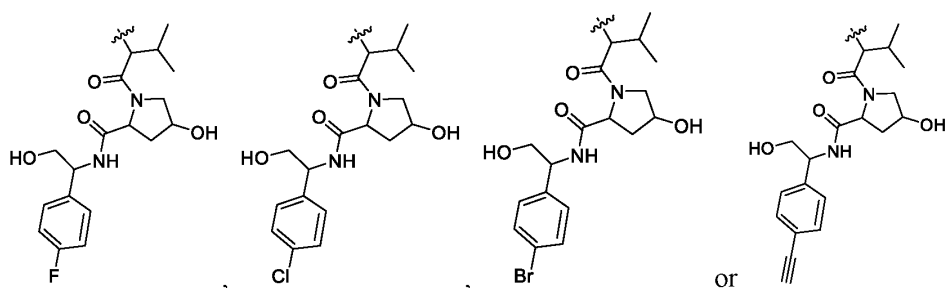


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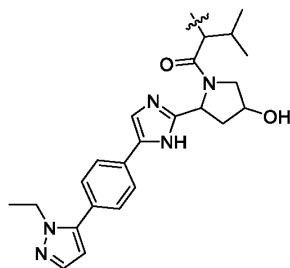
28. The compound of claim 1, wherein M6 is



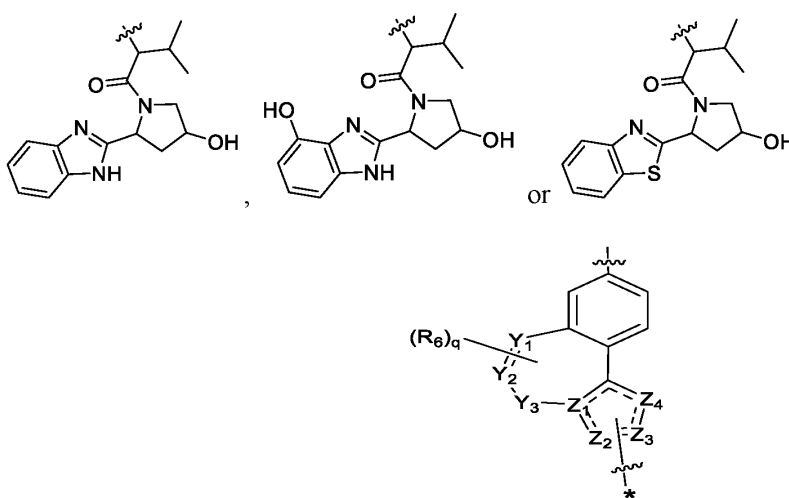
29. The compound of claim 1, wherein M7 is



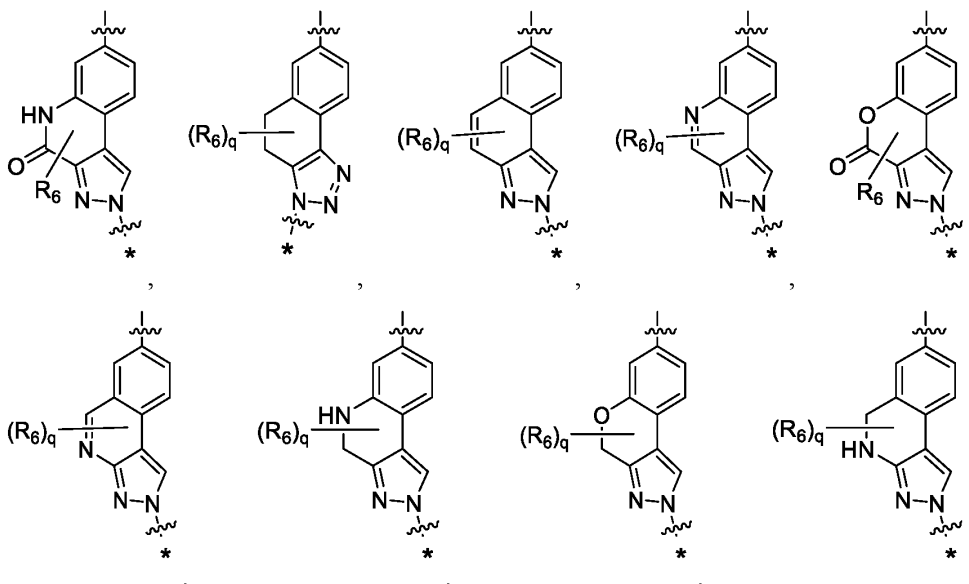
30. The compound of formula 1, wherein M8 is

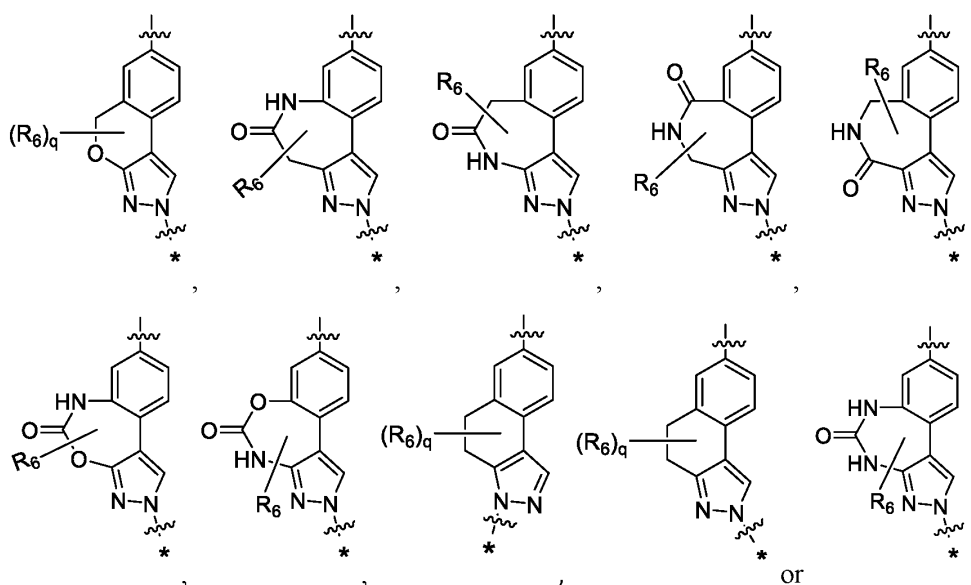


31. The compound of formula 1, wherein M9 is



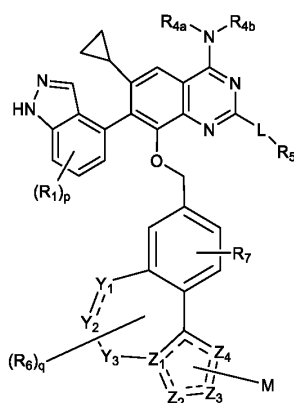
- 5 32. The compound of claim 1, wherein represents





wherein the asterisk mark represents the point of attachment with M.

33. The compound of claim 1, having a formula (IA):

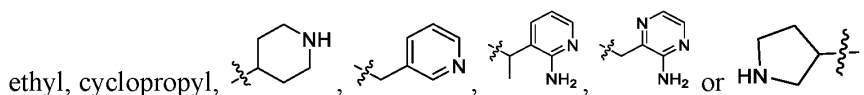


Formula (IA)

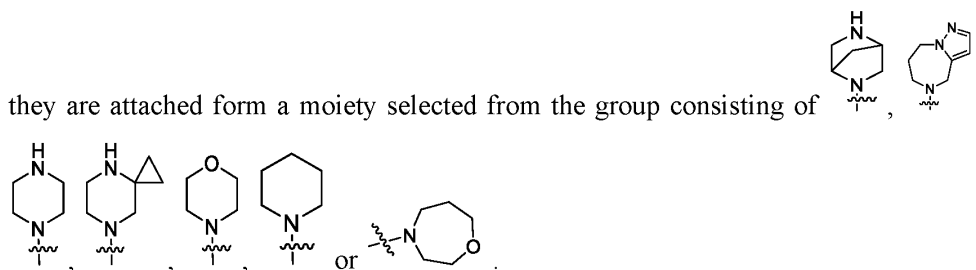
5

or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

34. The compound of claim 33, wherein R_1 is (C_1-C_6) alkyl, hydroxy or halo.
35. The compound of claim 33, wherein the R_{4a} and R_{4b} independently is (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl or 5- to 10-membered heteroaryl (C_1-C_6) alkyl.
36. The compound of claims 33 and 35, wherein R_{4a} and R_{4b} , independently, is methyl,

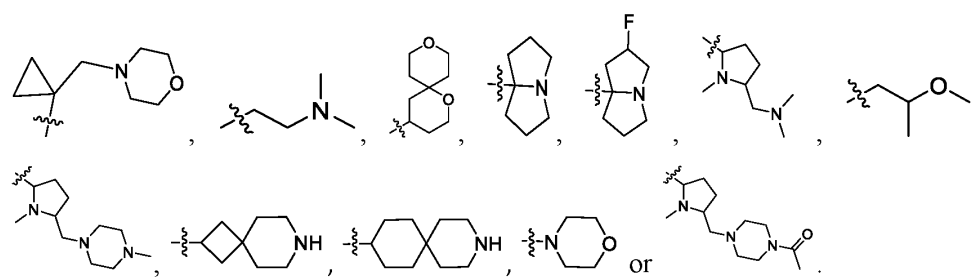


37. The compound of claim 33, wherein R_{4a} and R_{4b} together with the nitrogen to which



38. The compound of claim 33, wherein L is -O-, -C(O)-* or -O-CH₂-*; wherein asterisk
5 mark represents the point of attachment with R₅.

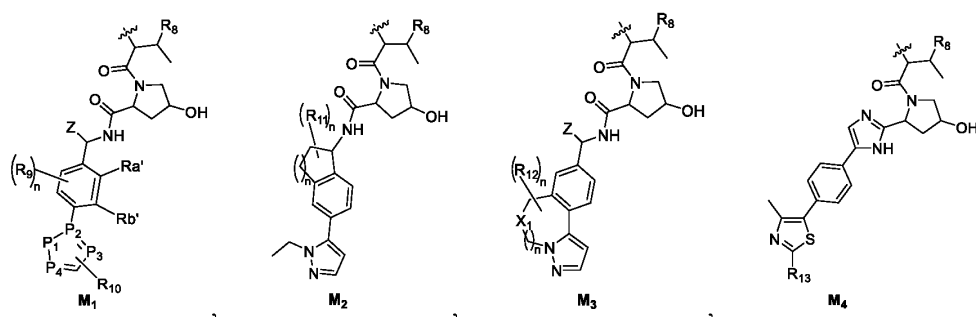
39. The compound of claim 33, wherein R₅ is , , or .

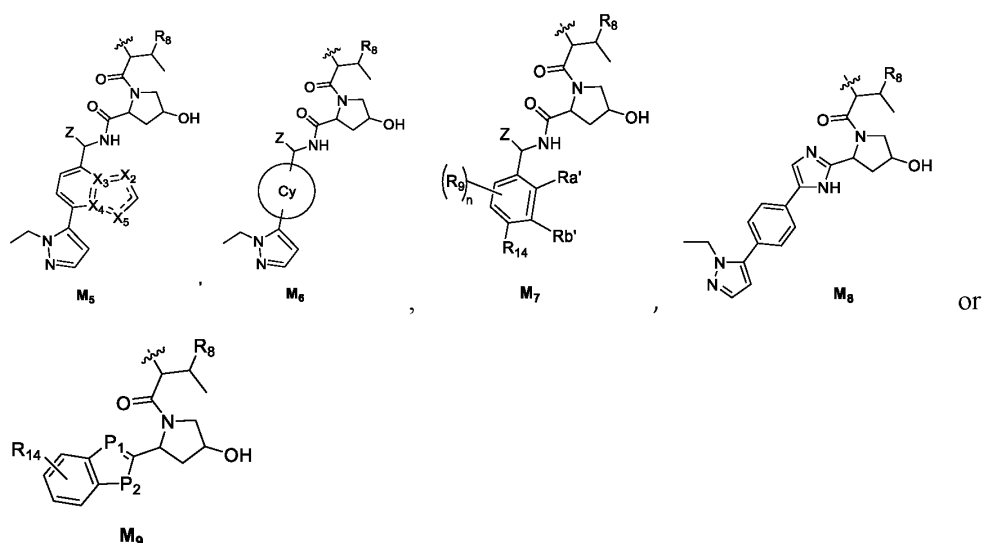


40. The compound of claim 33, wherein R₆ is hydrogen, amino, hydroxy or two R₆ on the same carbon represent an oxo group.

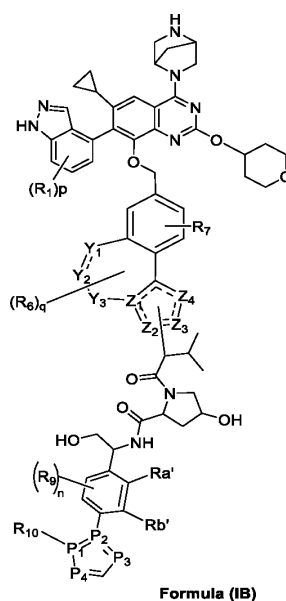
41. The compound of claim 33, wherein R₇ is hydrogen, halo, (C₁-C₆)alkyl or halo(C₁-C₆)alkyl.

42. The compound of claim 33, wherein M is M₁, M₂, M₃, M₄, M₅, M₆, M₇, M₈ or M₉;





43. The compound of claim 1, having formula (IB):



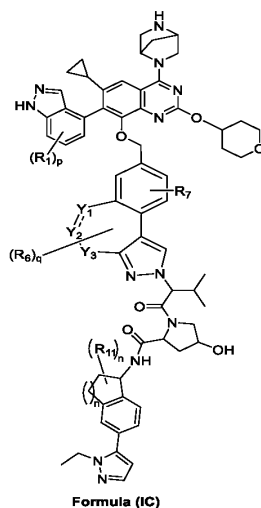
5 or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

44. The compound of claim 43, wherein R₁ is (C₁-C₆)alkyl, hydroxy or halo.

45. The compound of claim 43, wherein R₆ is hydrogen, amino, hydroxy or two R₆ on the same carbon represent an oxo group.

46. The compound of claim 43, wherein R₉ is hydrogen or (C₁-C₆)alkyl.

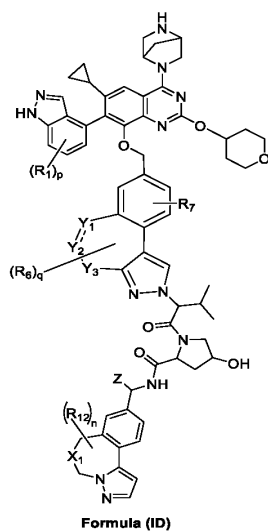
47. The compound of claim 43, wherein $R_{a'}$ and $R_{b'}$ together with the C atoms to which they are attached form 5- to 6-membered heterocycloalkyl or heteroaryl.
48. The compound of claim 43, wherein R_{10} is hydrogen or (C_1-C_6) alkyl.
49. The compound of claim 1, having formula (IC):



5

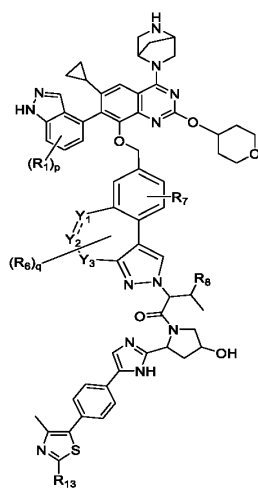
or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

50. The compound of claim 1, having formula (ID):



or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

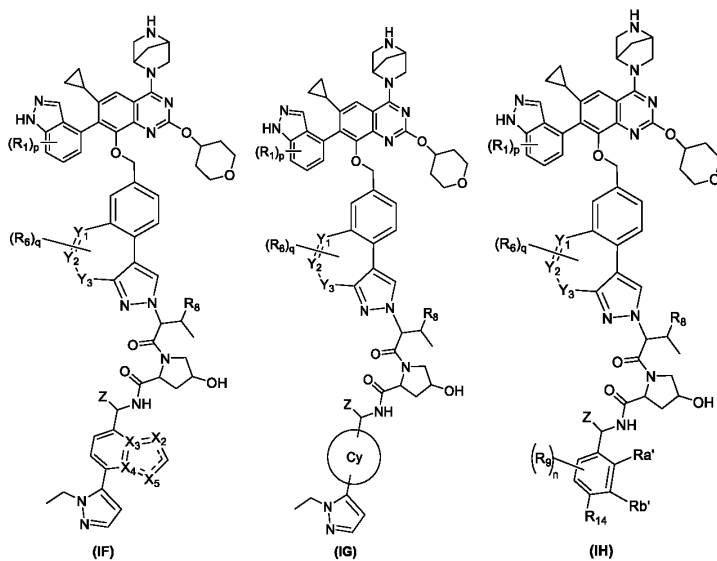
- 10 51. The compound of claim 1, having formula (IE)

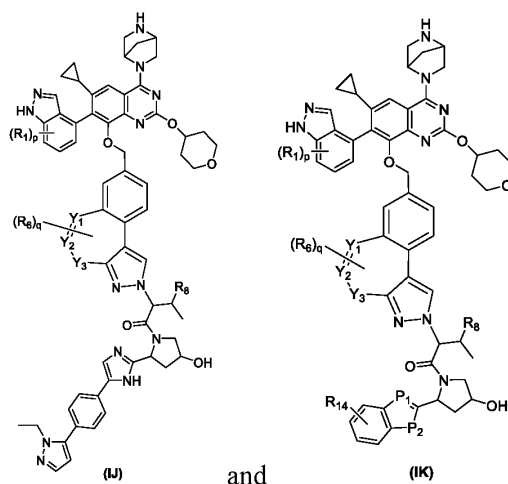


Formula (IE)

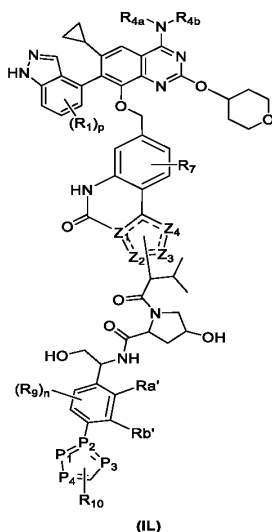
or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

52. The compound of claim 1, having structure of formula (IF), (IG), (IH), (IJ) and (IK):





53. The compound of claim 1, having structure of formula (II):



or a pharmaceutically acceptable salt or stereoisomer or a tautomer thereof;

5 wherein,

R₁ at each occurrence, independently is hydrogen, (C₁-C₆)alkyl, hydroxy, halo, amino, halo(C₁-C₆) alkyl and/or two R₁ adjacent to each other together with the C atoms to which they are attached form a phenyl or 5- to 6-membered heterocyclyl; wherein the phenyl and heterocyclyl are unsubstituted or substituted with 1, 2 or 3 substituents each independently
10 selected from the group consisting of (C₁-C₆)alkyl, (C₂-C₄)alkyne, halo, hydroxy, halo(C₁-C₆)alkyl, amino and cyano;

p is 1, 2, 3, or 4;

R_{4a} and R_{4b}, independently, is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, 5- to 10-membered heteroaryl(C₁-C₆)alkyl or 4- to 7-membered heterocycloalkyl, wherein the cycloalkyl and heteroarylalkyl are unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo, alkyl and amino; and/or

5 R_{4a} and R_{4b} together with the nitrogen to which they are attached form a 4- to 14-membered heterocyclyl optionally containing one or two additional heteroatoms selected from the group consisting of nitrogen, oxygen, and sulphur; wherein the heterocyclyl is unsubstituted or substituted with 1, 2 or 3 groups each independently selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy, cyano and -C(O)-R_{4c}; wherein said alkyl is
10 unsubstituted or substituted independently with one or more of halo, hydroxy, amino, cyano or (C₃-C₆)cycloalkyl; and/or

R_{4c} is hydrogen, amino, (C₁-C₆)alkylamino, 4- to 7-membered heterocycloalkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkyl or (C₁-C₆)alkylamino(C₁-C₆)alkyl; wherein the heterocycloalkyl and cycloalkyl are unsubstituted or substituted with 1, 2 or 3 groups each independently
15 selected from the group consisting of halo, hydroxy and (C₁-C₆)alkyl;

R₇ is hydrogen, halo, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₁-C₆)alkoxy or halo(C₁-C₆)alkoxy;

R_{a'} and R_{b'}, independently, is hydrogen, halo or (C₁-C₆)alkyl; or R_{a'} and R_{b'} together with the C atoms to which they are attached form a 5 to 6 membered heterocyclyl ring
20 optionally containing one or two hetero atoms independently selected from the group consisting of O, S, and N;

R₉ at each occurrence, independently, is hydrogen, 4- to 8-membered heterocycloalkyl, -O-heterocycloalkyl or -O-(C₁-C₆)alkyl;

wherein heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each
25 independently selected from the group consisting of halo or (C₁-C₆)alkyl;

wherein the alkyl in -O-(C₁-C₆)alkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkylamino or 5- to 8-membered heterocycloalkyl; wherein the heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo or
30 (C₁-C₆)alkyl;

P₁, P₂, P₃ and P₄ independently, is C, N or S; wherein at least one of P₁, P₂, P₃ and P₄ is N;

R₁₀ is hydrogen, (C₁-C₆)alkyl, (C₂-C₄)alkynyl, hydroxy, 3- to 7-membered heterocycloalkyl or (C₃-C₆)cycloalkyl;

5 wherein the alkyl and alkynyl is unsubstituted or substituted with halo, cycloalkyl, NH-(CO)-NH₂, NR_mR_n, or 4 to 6 membered heterocycloalkyl; wherein the cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1, 2 or 3 substituents each independently selected from the group consisting of (C₁-C₆)alkyl, hydroxy, halo or amino;

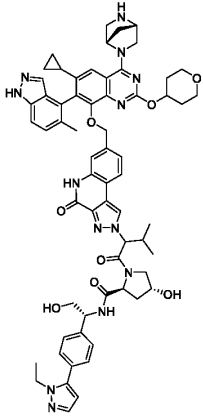
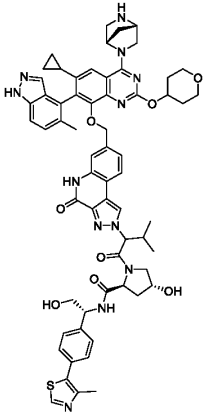
wherein 3- to 7-membered heterocycloalkyl is unsubstituted or substituted with 1, 2, or
10 3 substituents each independently selected from the group consisting of halo, hydroxy or (C₁-C₆)alkyl;

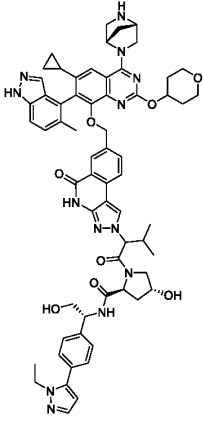
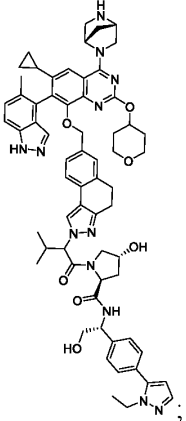
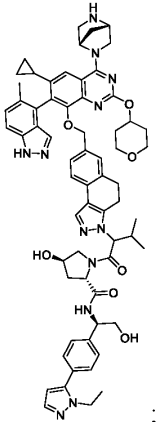
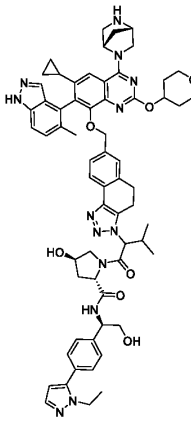
R_m and R_n are independently hydrogen or (C₁-C₆)alkyl;

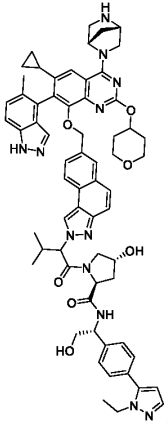
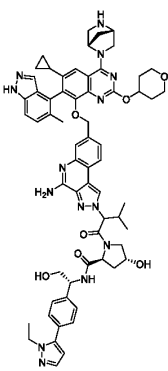
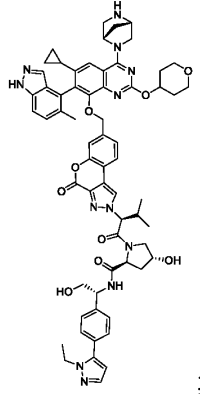
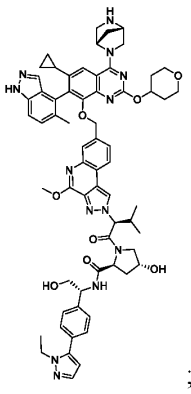
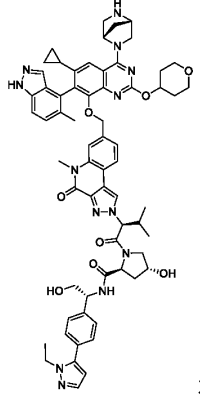
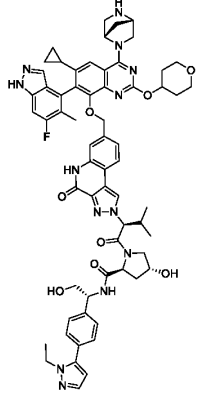
a dotted line [-----] indicates a bond or absent; and

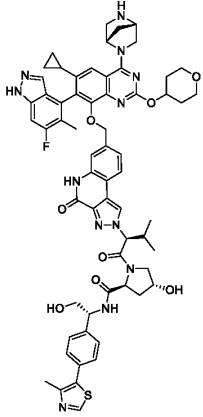
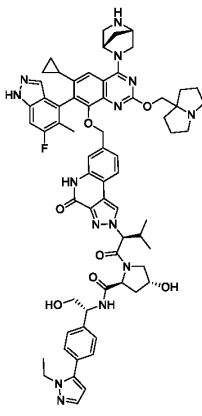
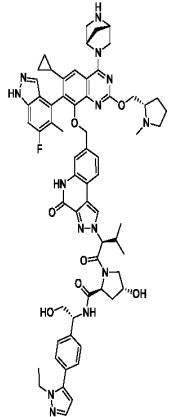
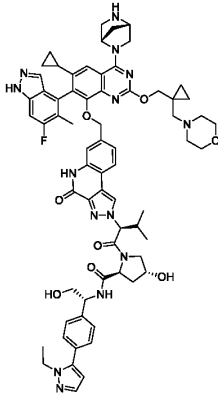
n is 1, 2 or 3.

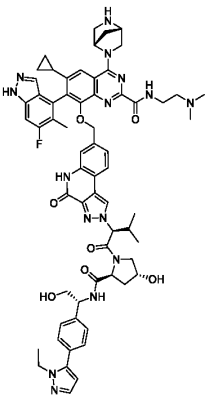
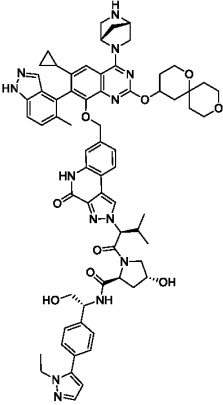
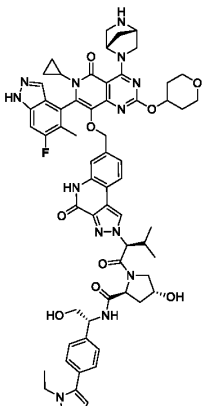
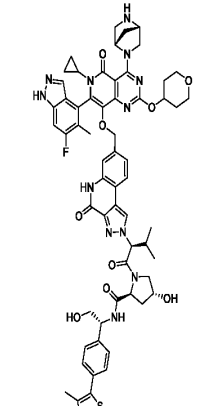
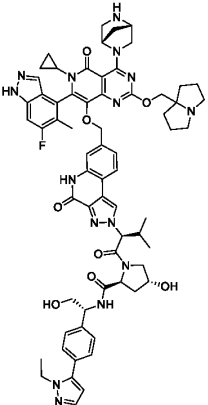
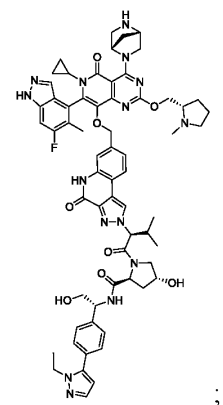
15 54. The compound of claims 1 to 53, wherein the compound is selected from:

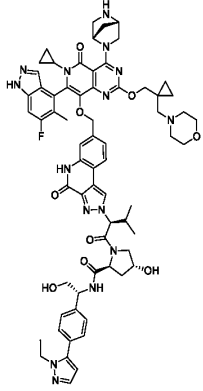
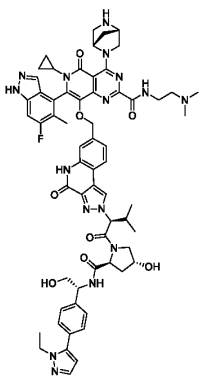
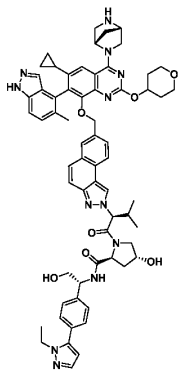
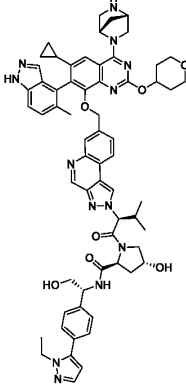
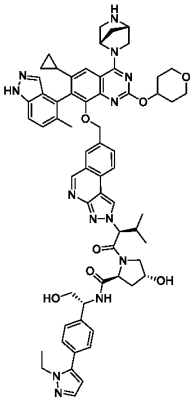
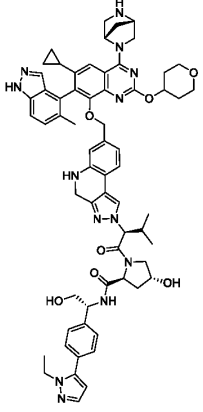
Comp. No	Compound structure	Comp. No	Compound structure
1.	 Isomer-1 of compound 1; Isomer-2 of compound 1;	2.	 Isomer-1 of compound 2; Isomer-2 of compound 2;

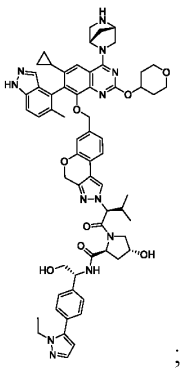
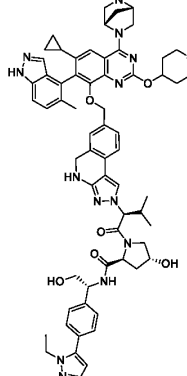
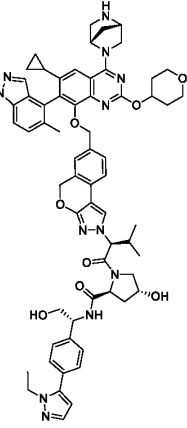
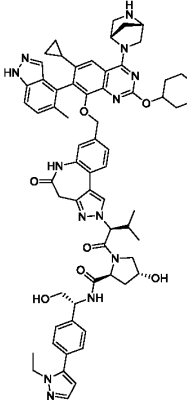
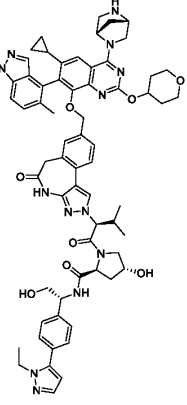
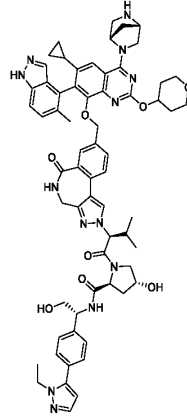
	Isomer-3 of compound 1; Isomer-4 of compound 1;		Isomer-3 of compound 2; Isomer-4 of compound 2;
3.	 Isomer-1 of compound 3; Isomer-2 of compound 3; Isomer-3 of compound 3; Isomer-4 of compound 3;	4.	 Isomer-1 of compound 4; Isomer-2 of compound 4; Isomer-3 of compound 4; Isomer-4 of compound 4;
5.	 Isomer-1 of compound 5; Isomer-2 of compound 5; Isomer-3 of compound 5; Isomer-4 of compound 5;	6.	 Isomer-1 of compound 6; Isomer-2 of compound 6; Isomer-3 of compound 6; Isomer-4 of compound 6;

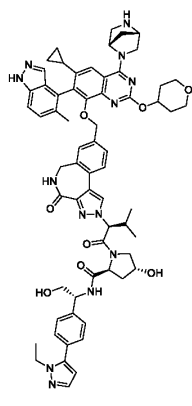
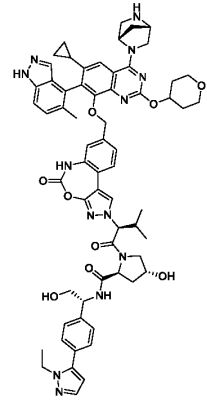
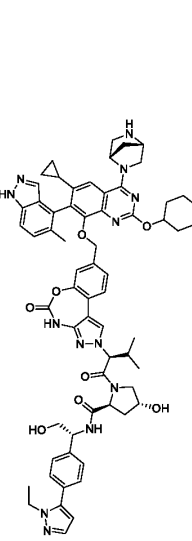
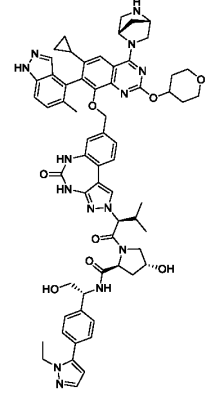
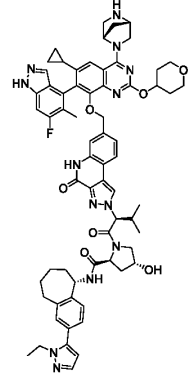
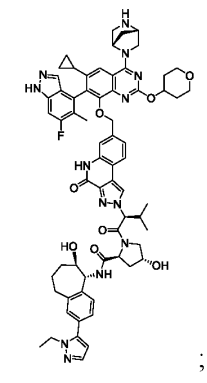
7.	 Isomer-1 of compound 7; Isomer-2 of compound 7; Isomer-3 of compound 7; Isomer-4 of compound 7;	8.	 Isomer-1 of compound 8; Isomer-2 of compound 8; Isomer-3 of compound 8; Isomer-4 of compound 8;
9.		10.	
11.		12.	

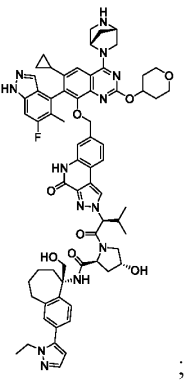
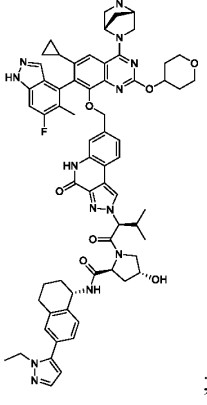
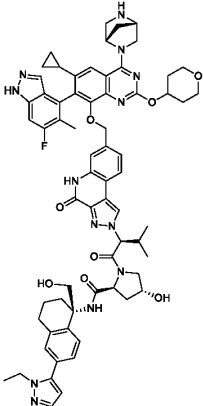
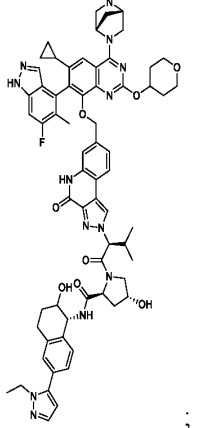
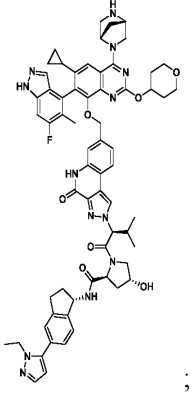
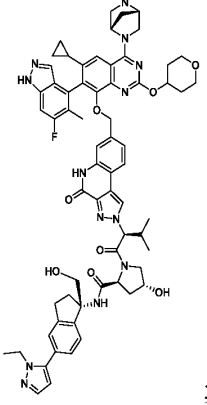
			Isomer-1 of compound 12 , Isomer-2 of compound 12 , Isomer-3 of compound 12 , Isomer-4 of compound 12 ,
13.	 Isomer-1 of compound 13 , Isomer-2 of compound 13 , Isomer-3 of compound 13 , Isomer-4 of compound 13 ,	14.	 Isomer-1 of compound 14 , Isomer-2 of compound 14 , Isomer-3 of compound 14 , Isomer-4 of compound 14 ,
15.	 Isomer-1 of compound 15 , Isomer-2 of compound 15 , Isomer-3 of compound 15 , Isomer-4 of compound 15 ,	16.	 Isomer-1 of compound 16 , Isomer-2 of compound 16 , Isomer-3 of compound 16 , Isomer-4 of compound 16 ,

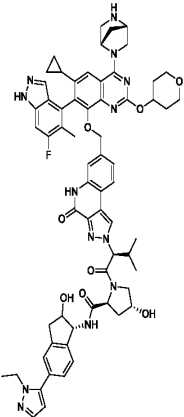
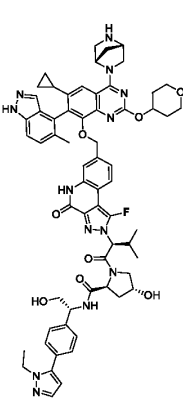
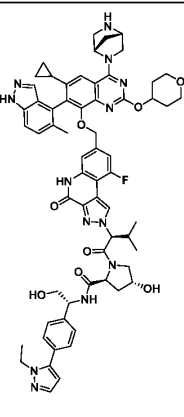
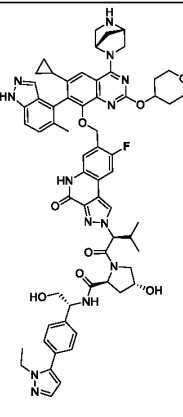
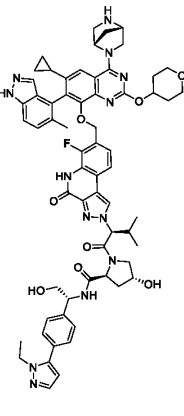
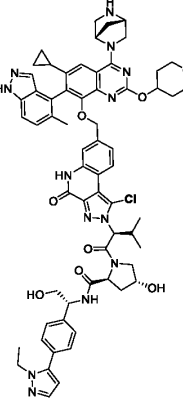
17.		18.	
19.		20.	
21.		22.	

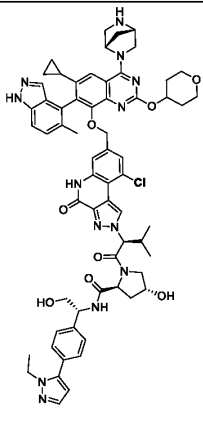
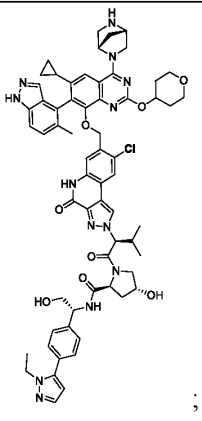
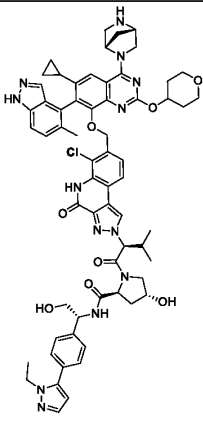
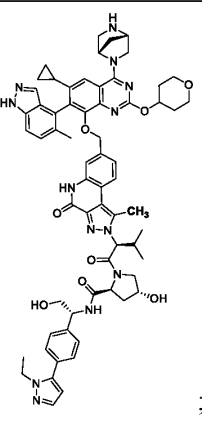
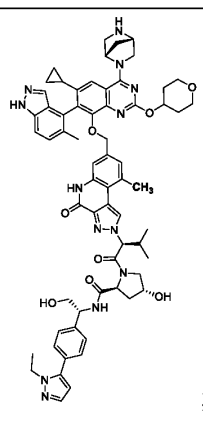
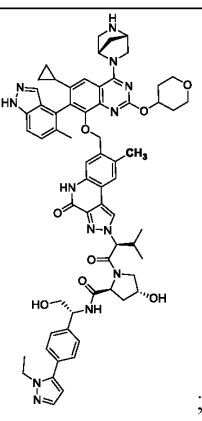
23.		24.	
25.		26.	
27.		28.	

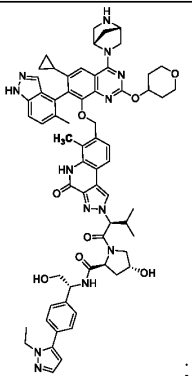
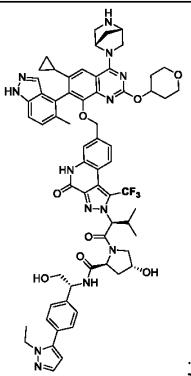
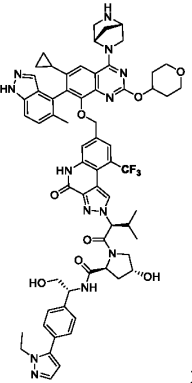
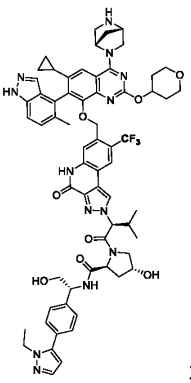
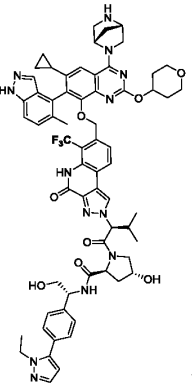
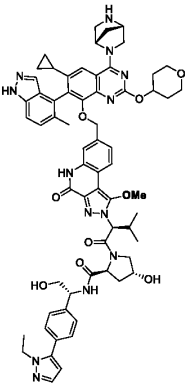
29.		30.	
31.		32.	 Isomer-1 of compound 32; Isomer-2 of compound 32;
33.		34.	

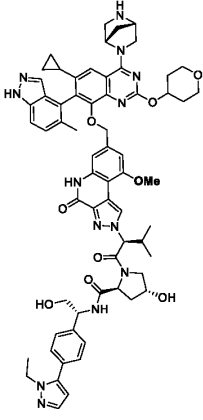
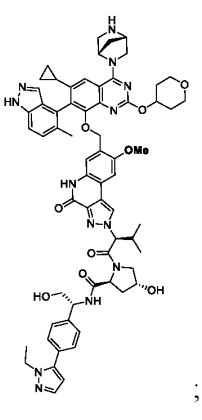
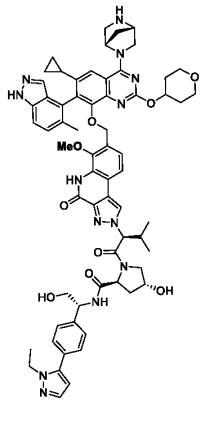
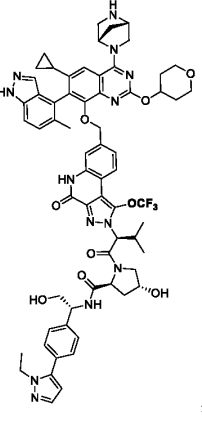
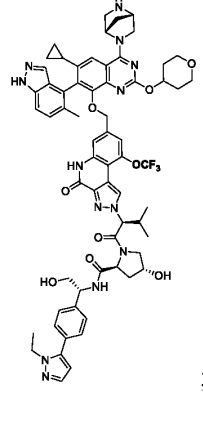
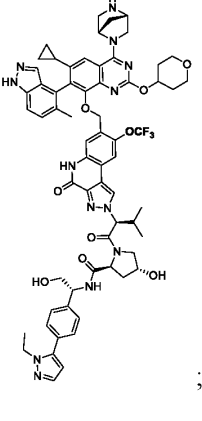
35.		36.	
37.		38.	 Isomer-1 of compound 38; Isomer-2 of compound 38; Isomer-3 of compound 38; Isomer-4 of compound 38;
39.		40.	

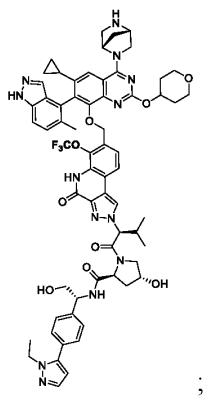
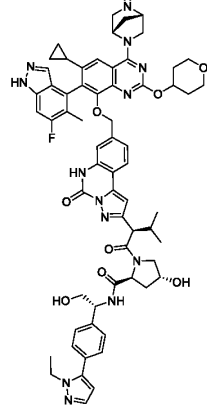
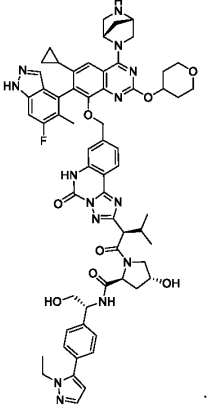
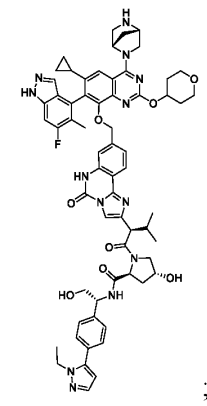
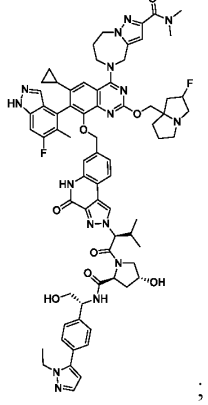
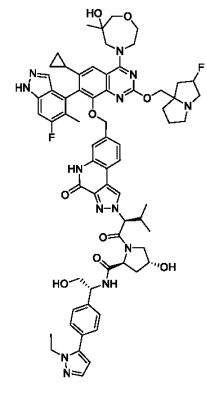
41.		42.	
43.		44.	
45.		46.	

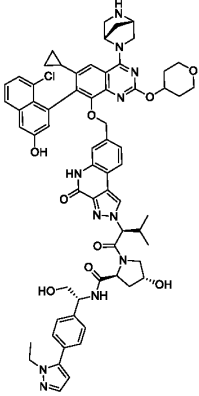
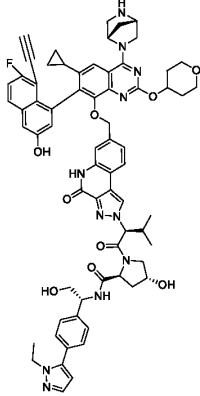
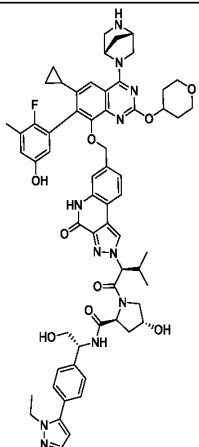
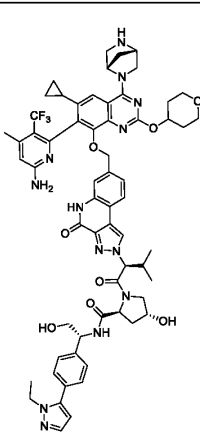
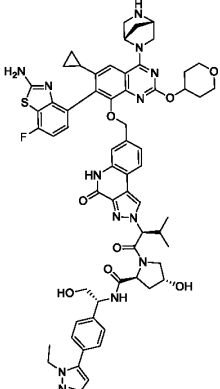
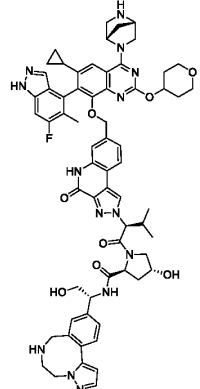
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51.		52.	

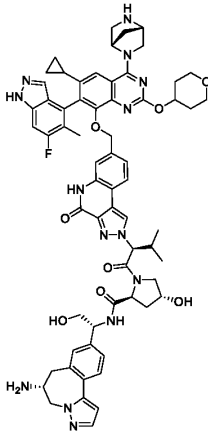
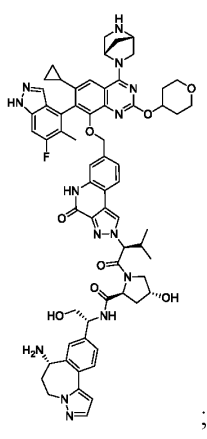
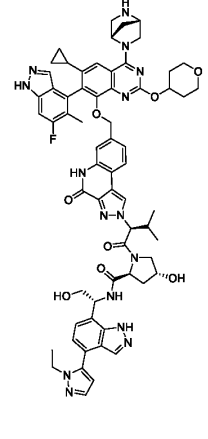
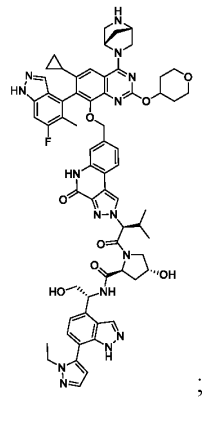
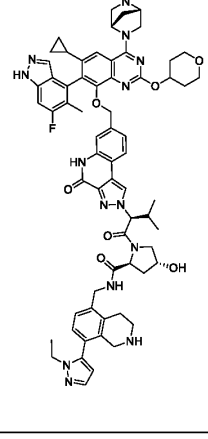
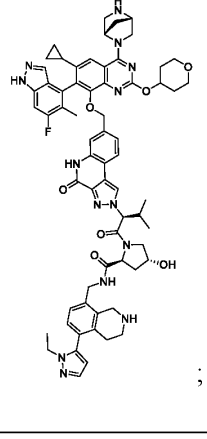
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57.		58.	

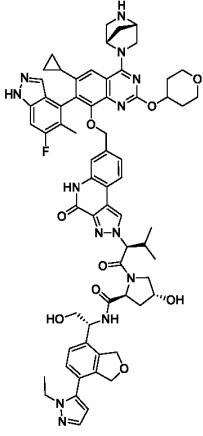
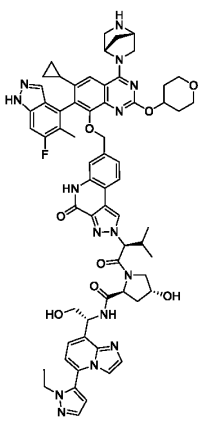
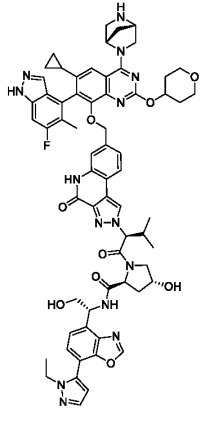
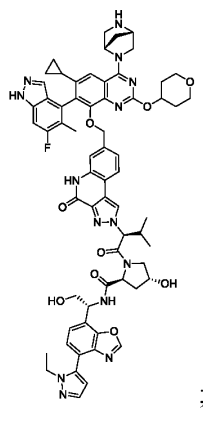
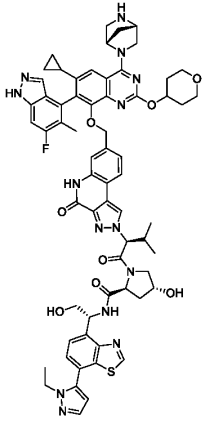
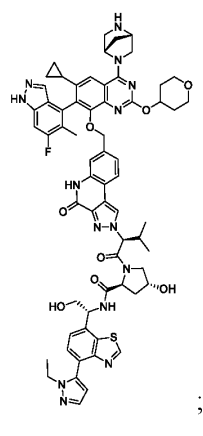
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63.		64.	

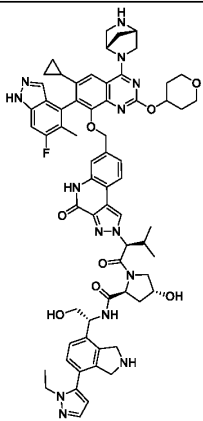
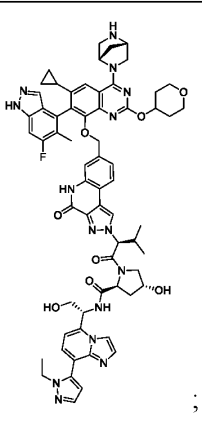
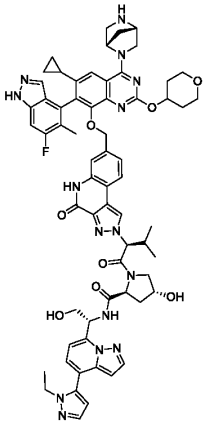
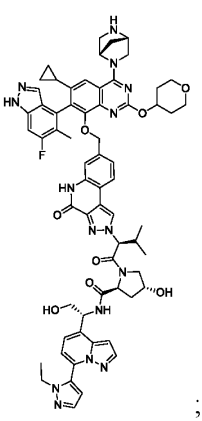
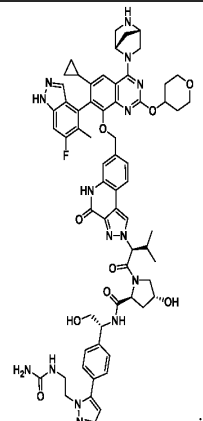
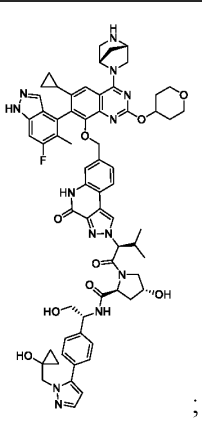
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69.		70.	

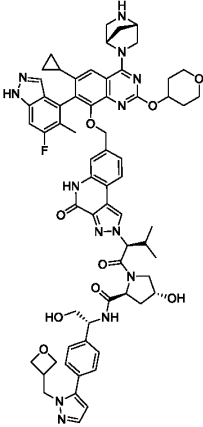
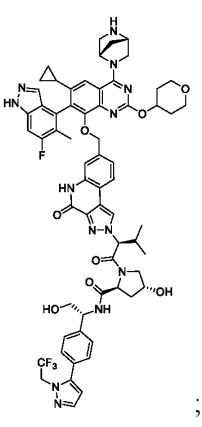
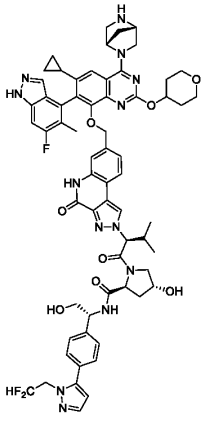
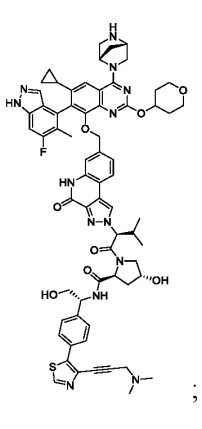
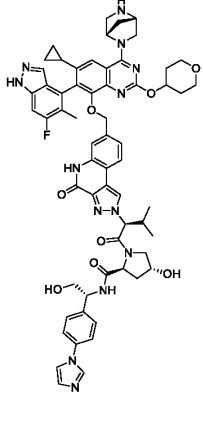
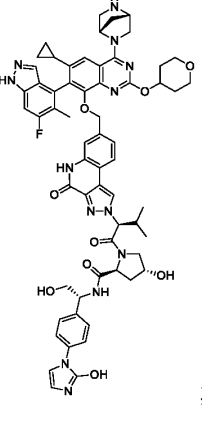
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75.		76.	

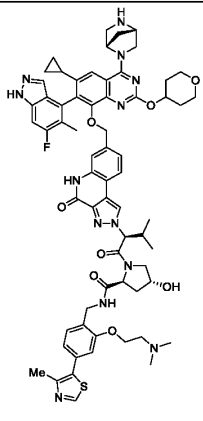
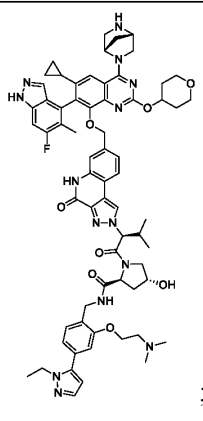
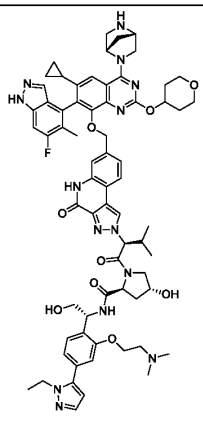
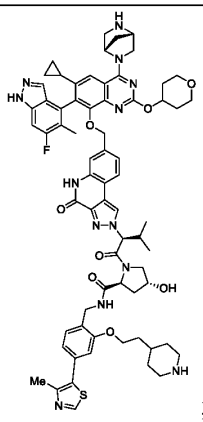
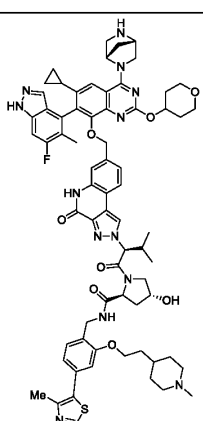
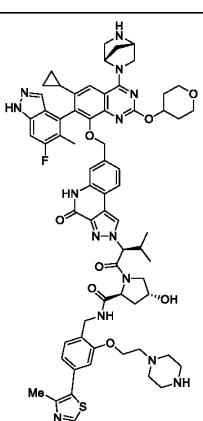
77.		78.	
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81.		82.	

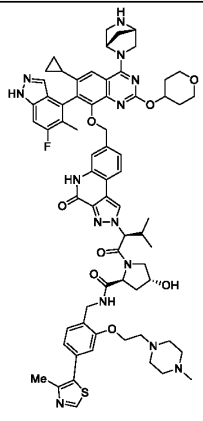
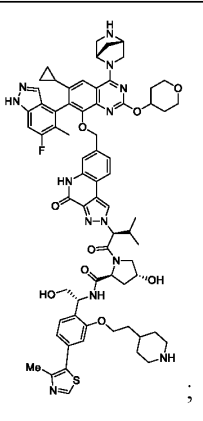
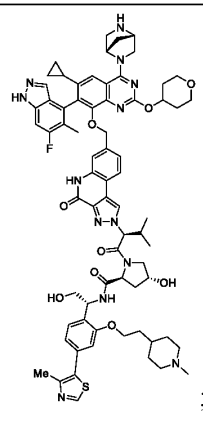
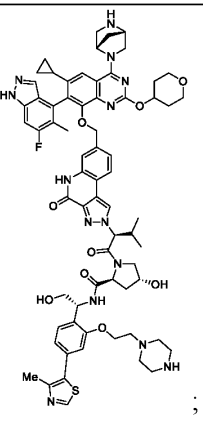
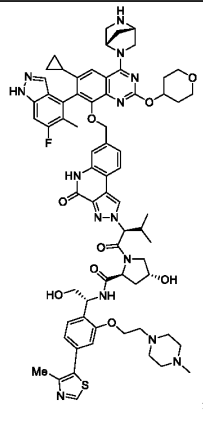
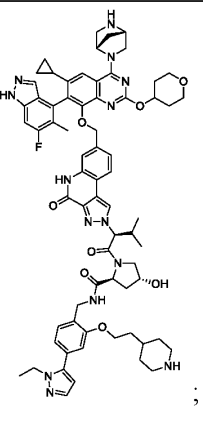
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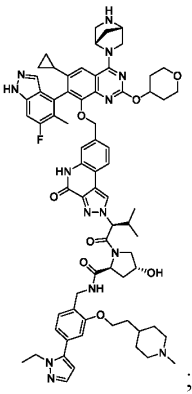
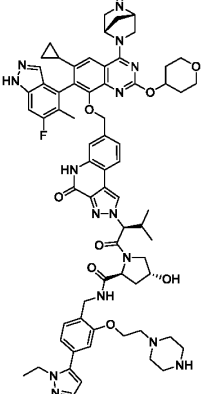
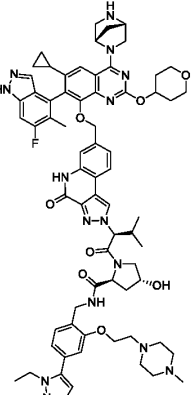
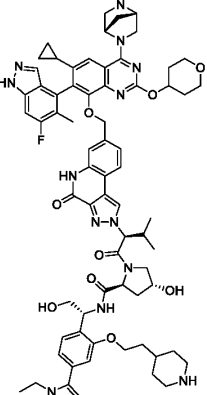
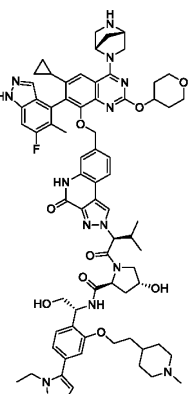
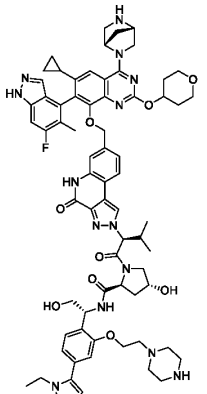
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93.		94.	

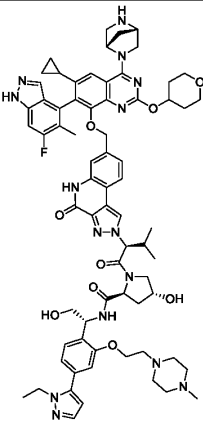
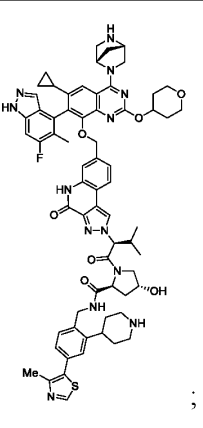
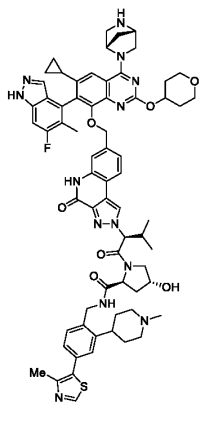
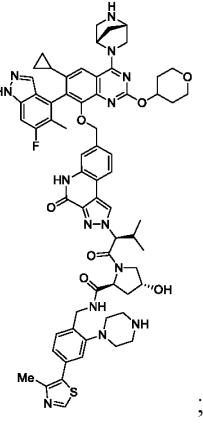
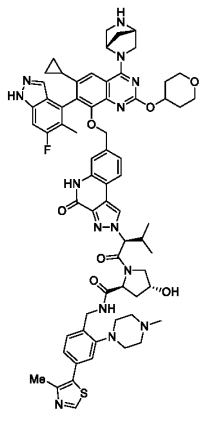
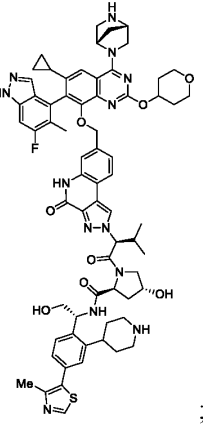
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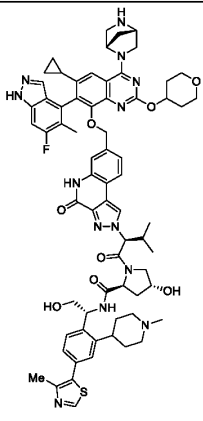
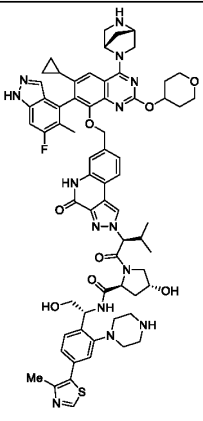
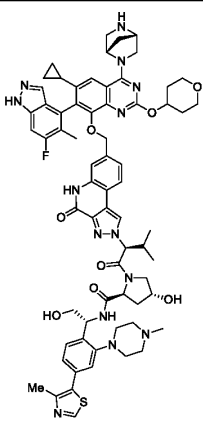
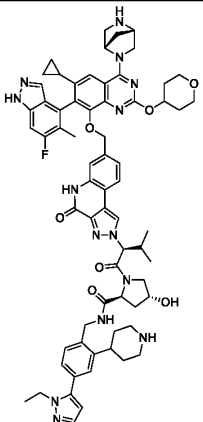
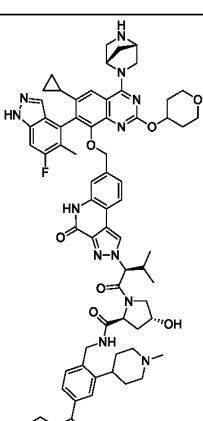
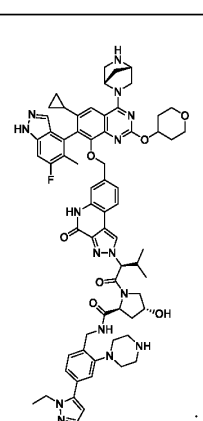
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105.		106.	

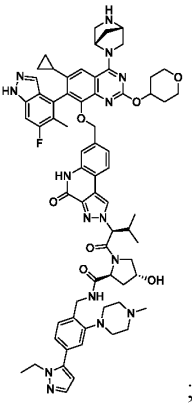
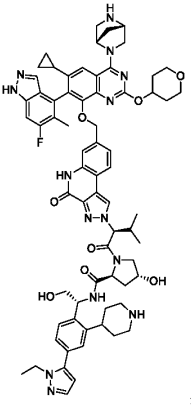
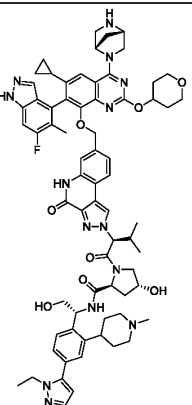
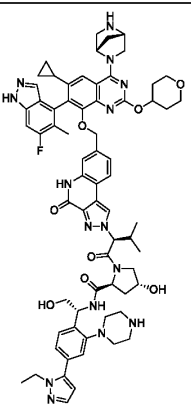
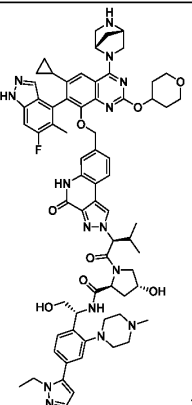
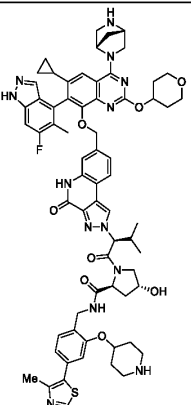
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111.		112.	

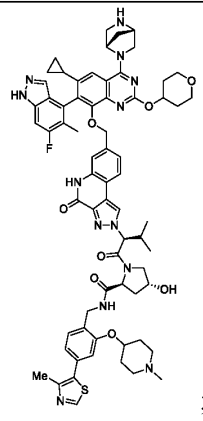
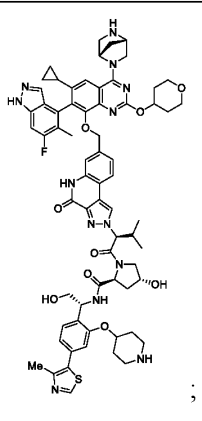
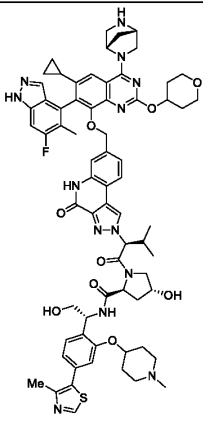
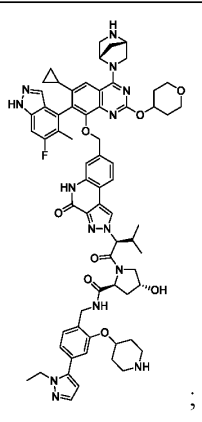
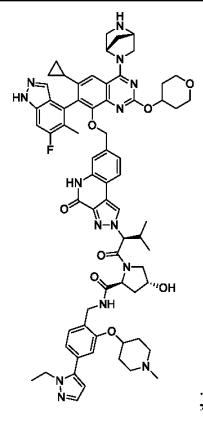
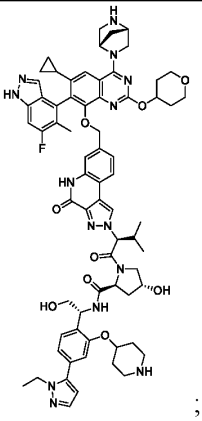
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119.		120.	
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123.		124.	

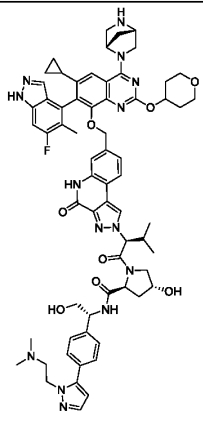
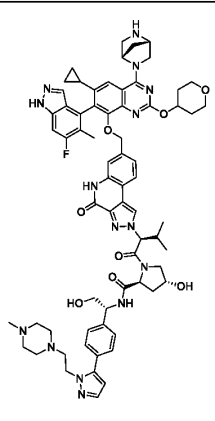
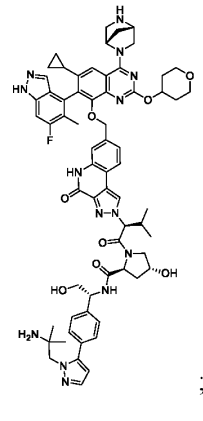
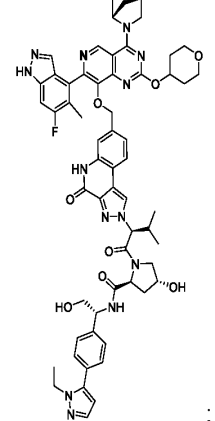
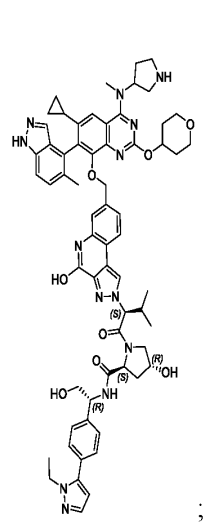
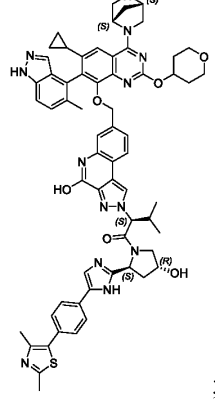
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129.		130.	

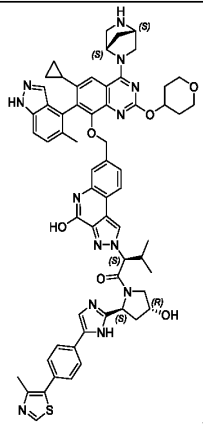
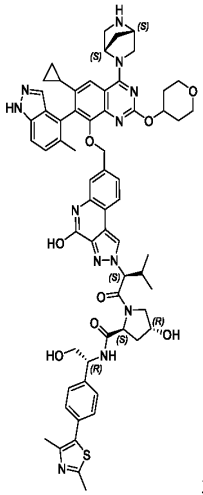
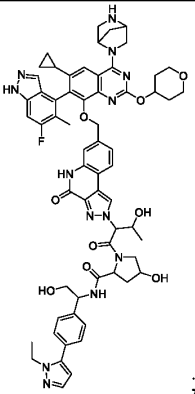
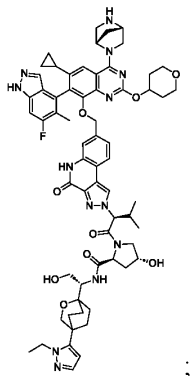
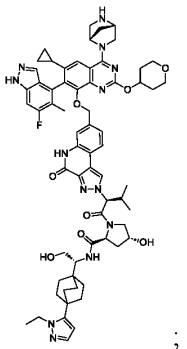
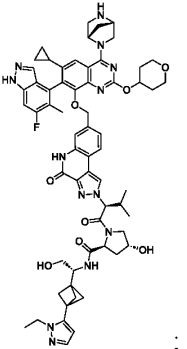
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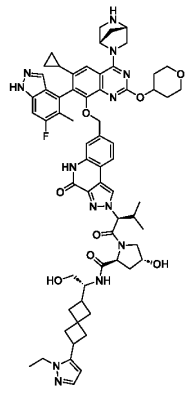
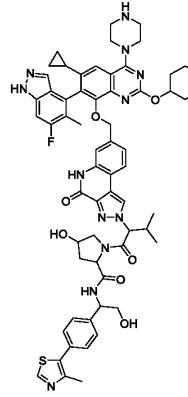
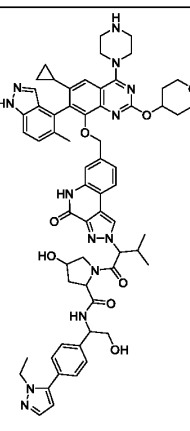
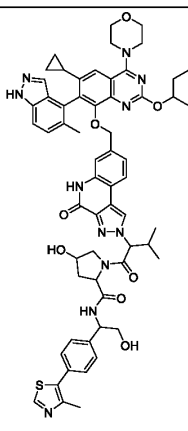
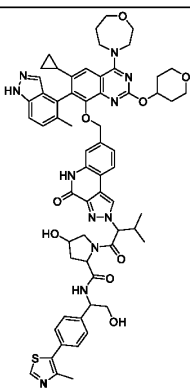
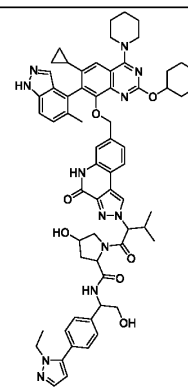
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141.		142.	

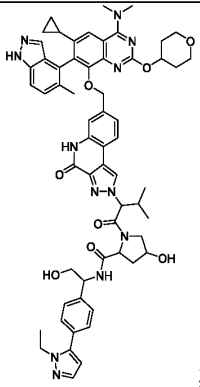
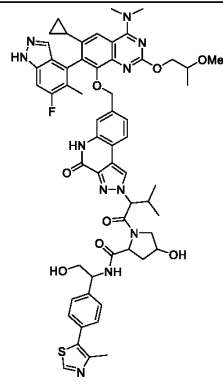
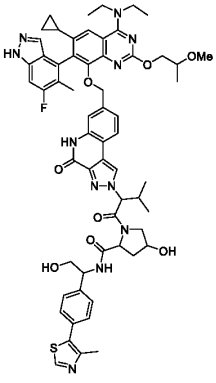
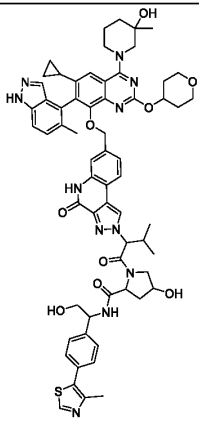
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147.		148.	

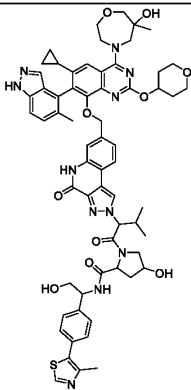
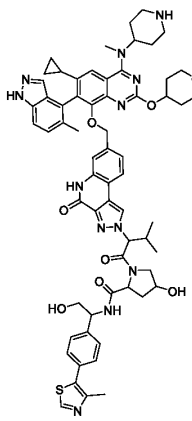
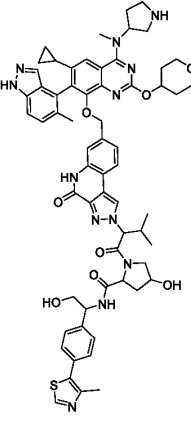
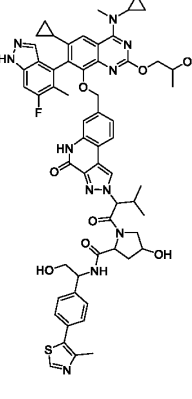
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152.	 ;
153.	 ;
154.	 ;

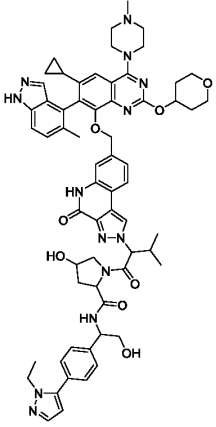
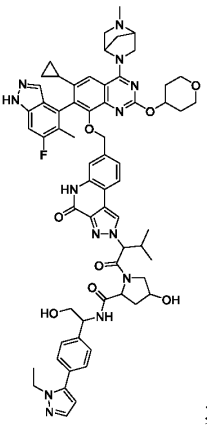
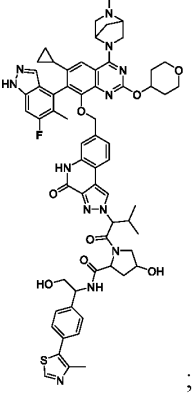
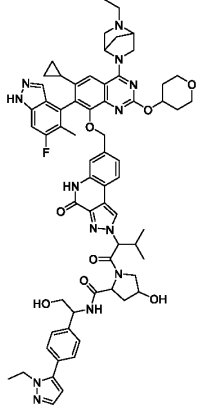
155.		156.	
157.		158.	
159.		160.	 Isomer-1 of compound 160; Isomer-2 of compound 160; Isomer-3 of compound 160;

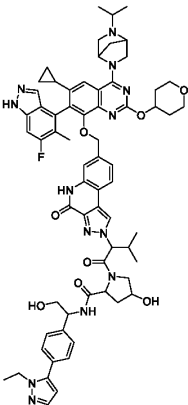
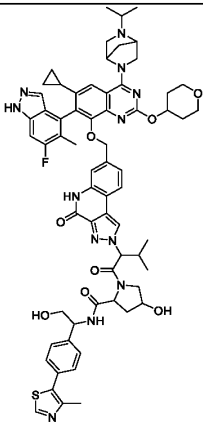
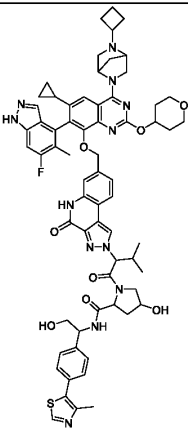
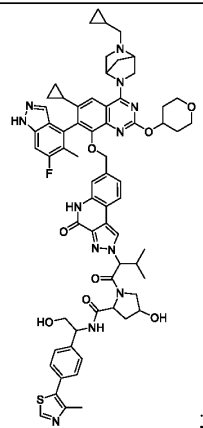
161.	 Isomer-1 of compound 161; Isomer-2 of compound 161; Isomer-3 of compound 161; Isomer-4 of compound 161;	162.	
163.		164.	
165.		166.	

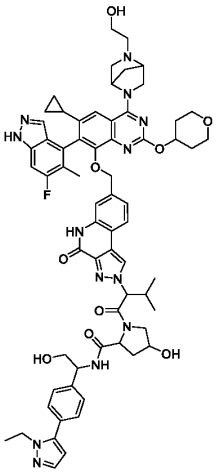
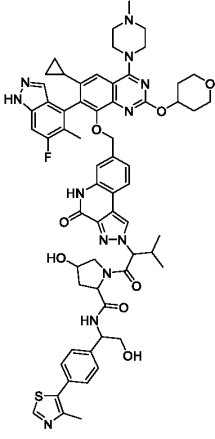
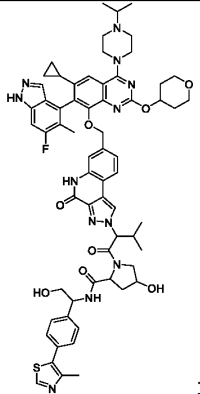
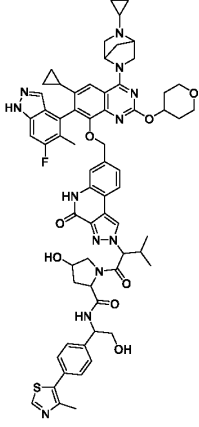
167.		168.	
169	 Isomer-1 of compound 169; Isomer-2 of compound 169; Isomer-3 of compound 169; Isomer-4 of compound 169;	170	 Isomer-1 of compound 170; Isomer-2 of compound 170; Isomer-3 of compound 170; Isomer-4 of compound 170;
171		172	

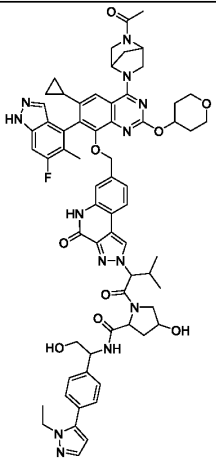
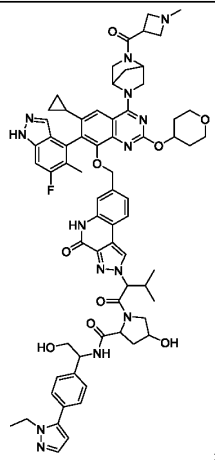
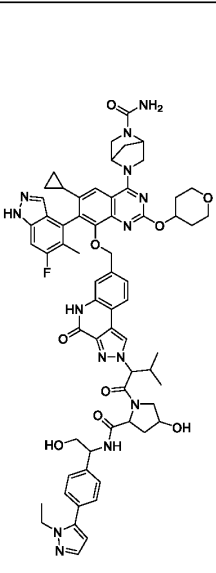
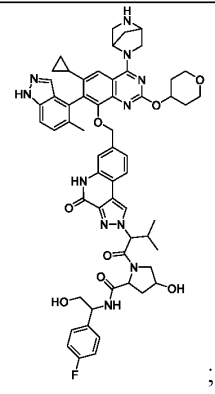
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173	 Isomer-1 of compound 173 ; Isomer-2 of compound 173 ; Isomer-3 of compound 173 ; Isomer-4 of compound 173 ;	174	 Isomer-1 of compound 174 ; Isomer-2 of compound 174 ; Isomer-3 of compound 174 ; Isomer-4 of compound 174 ;
175	 Isomer-1 of compound 175 ; Isomer-2 of compound 175 ; Isomer-3 of compound 175 ;	176	 Isomer-1 of compound 176 ; Isomer-2 of compound 176 ; Isomer-3 of compound 176 ;

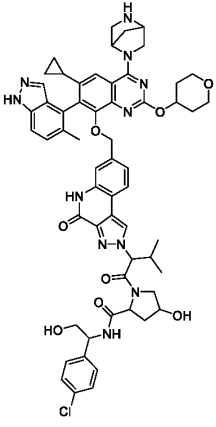
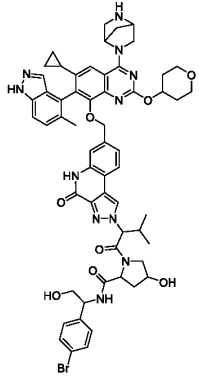
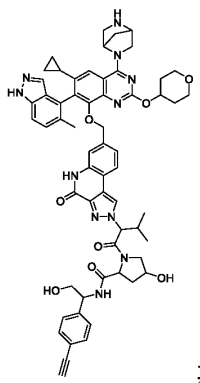
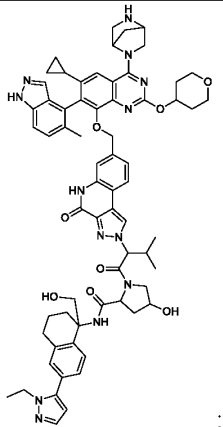
	Isomer-4 of compound 175 ;		Isomer-4 of compound 176 ;
177	 Isomer-1 of compound 177; Isomer-2 of compound 177; Isomer-3 of compound 177; Isomer-4 of compound 177; Isomer-5 of compound 177; Isomer-6 of compound 177; Isomer-7 of compound 177; Isomer-8 of compound 177;	178	 Isomer-1 of compound 178; Isomer-2 of compound 178; Isomer-3 of compound 178; Isomer-4 of compound 178;
179	 Isomer-1 of compound 179; Isomer-2 of compound 179;	180	 Isomer-1 compound 180; Isomer-1 compound 180;

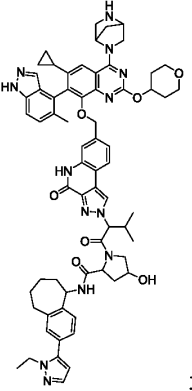
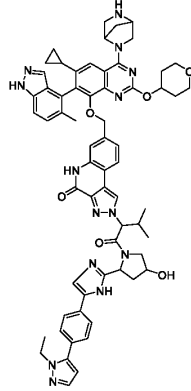
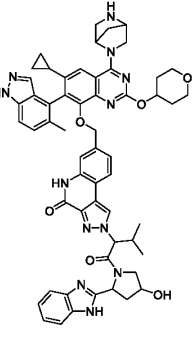
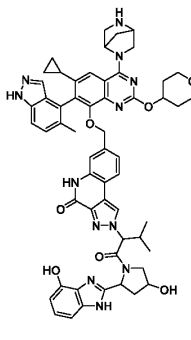
	Isomer-3 of compound 179 ; Isomer-4 of compound 179 ;		Isomer-1 compound 180 ; Isomer-1 compound 180 ;
181	 Isomer-1 of compound 181 ; Isomer-2 of compound 181 ; Isomer-3 of compound 181 ; Isomer-4 of compound 181 ;	182	 ;
183	 Isomer-1 of compound 183 ; Isomer-2 of compound 183 ;	184	 ;

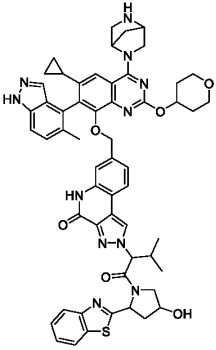
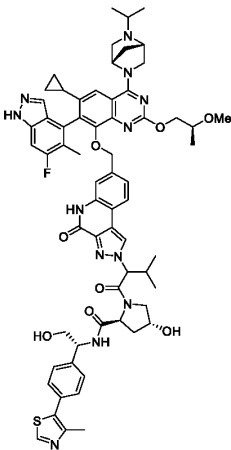
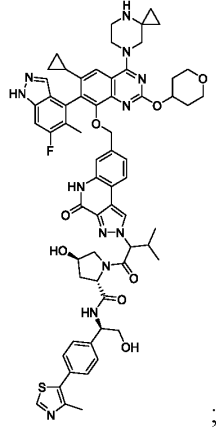
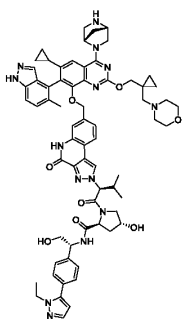
185		186	 Isomer-1 of compound 186; Isomer-2 of compound 186;
187	 Isomer-1 of compound 187; Isomer-2 of compound 187;	188	 Isomer-1 of compound 188; Isomer-2 of compound 188;

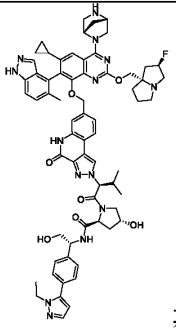
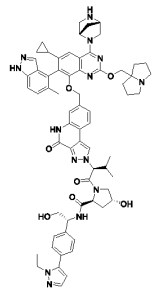
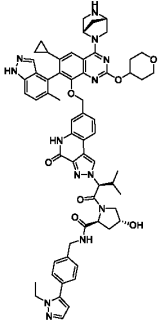
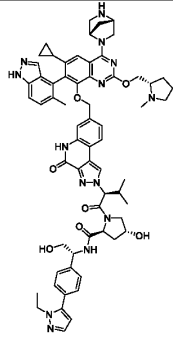
189	 Chemical structure of compound 189, featuring a complex polycyclic aromatic system with a fluorine substituent, a morpholine ring, and a hydroxymethyl group.	190	 Chemical structure of compound 190, featuring a complex polycyclic aromatic system with a fluorine substituent, a morpholine ring, and a hydroxymethyl group. Isomer-1 of compound 190; Isomer-2 of compound 190; Isomer-3 of compound 190; Isomer-4 of compound 190;
191	 Chemical structure of compound 191, featuring a complex polycyclic aromatic system with a fluorine substituent, a morpholine ring, and a hydroxymethyl group. Isomer-1 of compound 191; Isomer-2 of compound 191; Isomer-3 of compound 191; Isomer-4 of compound 191;	192	 Chemical structure of compound 192, featuring a complex polycyclic aromatic system with a fluorine substituent, a morpholine ring, and a hydroxymethyl group. Isomer-1 of compound 192; Isomer-2 of compound 192;

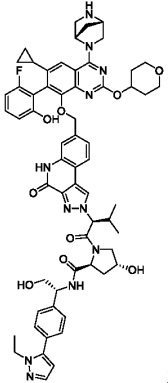
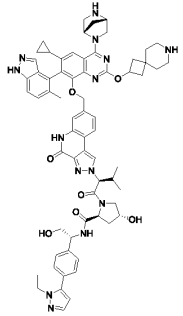
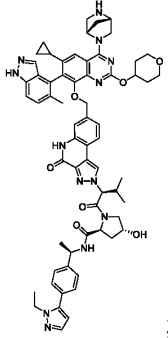
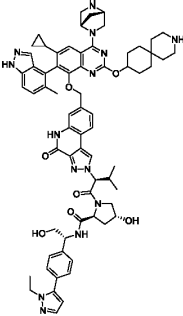
193	 Chemical structure of compound 193, featuring a complex polycyclic aromatic system with a fluorine substituent, a morpholine ring, and a hydroxyl group.	194	 Chemical structure of compound 194, featuring a complex polycyclic aromatic system with a fluorine substituent, a morpholine ring, and a hydroxyl group.
195	 Chemical structure of compound 195, featuring a complex polycyclic aromatic system with a fluorine substituent, a morpholine ring, and a hydroxyl group.	196	 Chemical structure of compound 196, featuring a complex polycyclic aromatic system with a fluorine substituent, a morpholine ring, and a hydroxyl group. Isomer-1 of compound 196; Isomer-2 of compound 196; Isomer-3 of compound 196; Isomer-4 of compound 196;

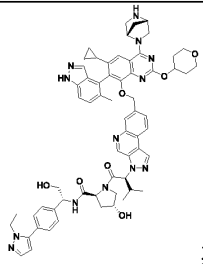
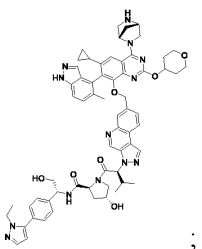
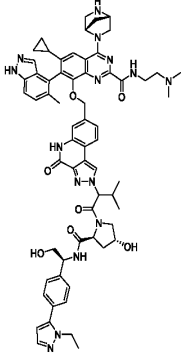
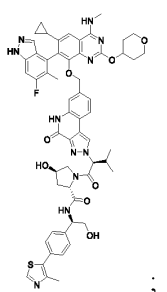
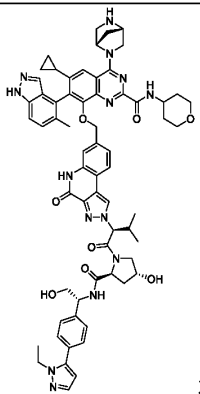
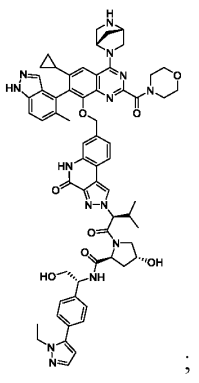
197	 Isomer-1 of compound 197; Isomer-2 of compound 197; Isomer-3 of compound 197;	198	 Isomer-1 of compound 198; Isomer-2 of compound 198; Isomer-3 of compound 198; Isomer-4 of compound 198;
199	 Isomer-1 of compound 199; Isomer-2 of compound 199; Isomer-3 of compound 199;	200	 Isomer-1 of compound 200; Isomer-2 of compound 200; Isomer-3 of compound 200;

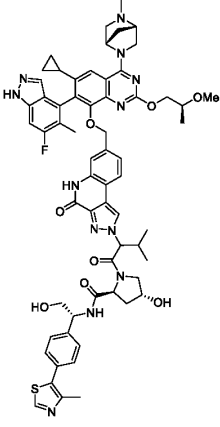
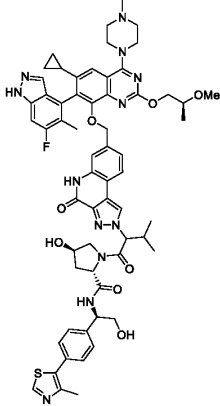
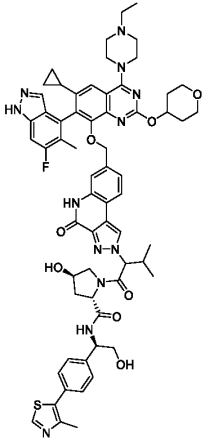
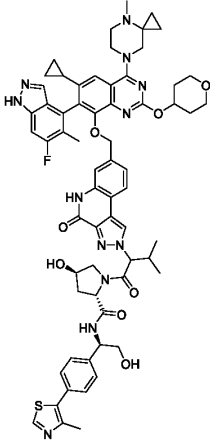
201	 Isomer-1 of compound 201; Isomer-2 of compound 201; Isomer-3 of compound 201; Isomer-4 of compound 201;	202	 Isomer-1 of compound 202; Isomer-2 of compound 202; Isomer-3 of compound 202; Isomer-4 of compound 202;
203	 Isomer-1 of compound 203; Isomer-2 of compound 203; Isomer-3 of compound 203; Isomer-4 of compound 203;	204	 Isomer-1 of compound 204; Isomer-2 of compound 204; Isomer-3 of compound 204; Isomer-4 of compound 204;

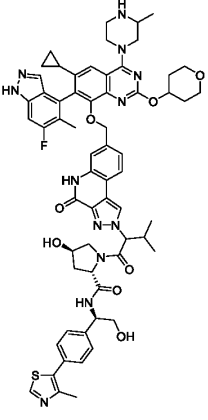
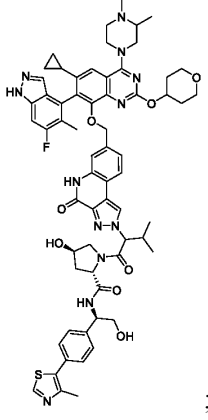
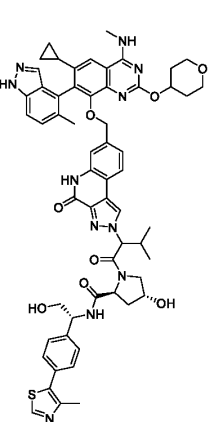
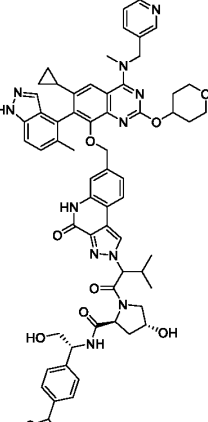
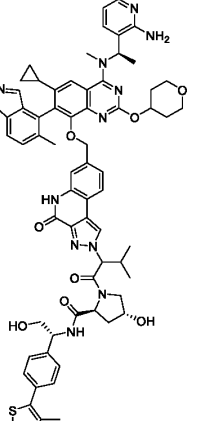
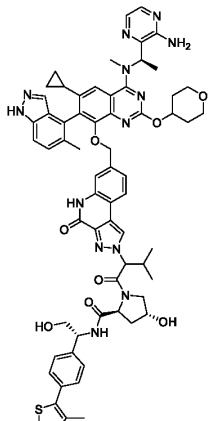
205	 Isomer-1 of compound 205; Isomer-2 of compound 205; Isomer-3 of compound 205; Isomer-4 of compound 205;	206	 Isomer-1 of compound 206; Isomer-2 of compound 206;
207	 Isomer-1 of compound 207; Isomer-2 of compound 207; Isomer-3 of compound 207; Isomer-4 of compound 207;	208	 Isomer-1 of compound 208; Isomer-2 of compound 208; Isomer-3 of compound 208; Isomer-4 of compound 208;

209	 Isomer-1 of compound 209; Isomer-2 of compound 209; Isomer-3 of compound 209; Isomer-4 of compound 209;	210	 Isomer-1 of compound 210; Isomer-2 of compound 210; Isomer-3 of compound 210; Isomer-4 of compound 210;
211	 Isomer-1 of compound 211; Isomer-2 of compound 211; Isomer-3 of compound 211;	212	 Isomer-1 of compound 212; Isomer-2 of compound 212; Isomer-3 of compound 212; Isomer-4 of compound 212;

213	 Isomer-1 of compound 213; Isomer-2 of compound 213; Isomer-3 of compound 213; Isomer-4 of compound 213;	214	 Isomer-1 of compound 214; Isomer-2 of compound 214; Isomer-3 of compound 214; Isomer-4 of compound 214;
215	 Isomer-1 of compound 215; Isomer-2 of compound 215; Isomer-3 of compound 215; Isomer-4 of compound 215;	216	 Isomer-1 of compound 216; Isomer-2 of compound 216; Isomer-3 of compound 216; Isomer-4 of compound 216;

217	 Isomer-1 of compound 217 ; Isomer-2 of compound 217 ; Isomer-3 of compound 217 ;	218	 Isomer-1 of compound 218 ; Isomer-2 of compound 218 ; Isomer-3 of compound 218 ;
219	 Isomer-1 of compound 219 ; Isomer-2 of compound 219 ; Isomer-3 of compound 219 ; Isomer-4 of compound 219 ;	220	 Isomer-1 of compound 220 ; Isomer-2 of compound 220 ; Isomer-3 of compound 220 ; Isomer-4 of compound 220 ;
221	 Isomer-1 of compound 221 ; Isomer-2 of compound 221 ; Isomer-3 of compound 221 ;	222	 Isomer-1 of compound 222 ; Isomer-2 of compound 222 ; Isomer-3 of compound 222 ;

	Isomer-1 of compound 221 ; Isomer-2 of compound 221 ; Isomer-3 of compound 221 ; Isomer-4 of compound 221 ;		Isomer-1 of compound 222 ; Isomer-2 of compound 222 ;
223	 ; A complex molecule featuring a central pyrazole ring substituted with a 4-fluorophenyl group, a 4-methoxyphenyl group, and a 4-(2-methyl-4-oxo-4,5-dihydro-1H-pyrazol-5-yl)phenyl group. It also includes a 4-(2-methyl-4-oxo-4,5-dihydro-1H-pyrazol-5-yl)phenyl group and a 4-(2-methyl-4-oxo-4,5-dihydro-1H-pyrazol-5-yl)phenyl group.	224	 ; A complex molecule featuring a central pyrazole ring substituted with a 4-fluorophenyl group, a 4-methoxyphenyl group, and a 4-(2-methyl-4-oxo-4,5-dihydro-1H-pyrazol-5-yl)phenyl group. It also includes a 4-(2-methyl-4-oxo-4,5-dihydro-1H-pyrazol-5-yl)phenyl group and a 4-(2-methyl-4-oxo-4,5-dihydro-1H-pyrazol-5-yl)phenyl group.
225	 ; A complex molecule featuring a central pyrazole ring substituted with a 4-fluorophenyl group, a 4-methoxyphenyl group, and a 4-(2-methyl-4-oxo-4,5-dihydro-1H-pyrazol-5-yl)phenyl group. It also includes a 4-(2-methyl-4-oxo-4,5-dihydro-1H-pyrazol-5-yl)phenyl group and a 4-(2-methyl-4-oxo-4,5-dihydro-1H-pyrazol-5-yl)phenyl group.	226	 ; A complex molecule featuring a central pyrazole ring substituted with a 4-fluorophenyl group, a 4-methoxyphenyl group, and a 4-(2-methyl-4-oxo-4,5-dihydro-1H-pyrazol-5-yl)phenyl group. It also includes a 4-(2-methyl-4-oxo-4,5-dihydro-1H-pyrazol-5-yl)phenyl group and a 4-(2-methyl-4-oxo-4,5-dihydro-1H-pyrazol-5-yl)phenyl group.

227		228	
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231		232	

and

or a pharmaceutically acceptable salt or stereoisomer or a tautomer thereof.

55. A pharmaceutical composition comprising the compound of any one of claims 1 to 54 or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof, and pharmaceutically acceptable carrier or an excipient.
56. The pharmaceutical composition of claim 55, for use in degrading a target protein in a subject, wherein the target protein is KRAS.
57. The pharmaceutical composition for use of claim 56, wherein the subject is afflicted with a disease or disorder dependent upon KRAS.
58. The pharmaceutical composition for use of claim 56, wherein the subject is afflicted with a disease or disorder dependent upon KRAS G12A, KRAS G12C, KRAS G12D, KRAS G12R, KRAS G12S, KRAS G12V, KRAS G13D or KRAS Q61H.
59. The pharmaceutical composition for use of claim 57, wherein the disease or disorder is a cancer selected from the group consisting of biliary tract malignancies, colon cancer, liver cancer, colorectal cancer, non-small cell lung cancer, small-cell lung cancer, pancreatic cancer, appendiceal cancer, melanoma, acute myeloid leukemia, small bowel cancer, ampullary cancer, germ cell cancer, cervical cancer, cancer of unknown primary origin, endometrial cancer, esophagogastric cancer, GI neuroendocrine cancer, ovarian cancer, sex cord stromal tumor cancer, hepatobiliary cancer, bladder cancer, lung cancer, prostate cancer, breast cancer, cervical carcinomas, testicular carcinomas, gastric cancer, head and neck cancer, hepatocellular cancer, laryngeal cancer, oral cancer, thyroid carcinomas, sarcomas, cardiac cancer, rhabdomyosarcoma, liposarcoma, myxoma, rhabdomyoma, fibroma, lipoma, teratoma, bronchogenic carcinoma, undifferentiated small cell cancer, adenocarcinoma, alveolar carcinoma, bronchiolar carcinoma, bronchial adenoma, lymphoma, chondromatous hamartoma, mesothelioma, gastrointestinal cancer, squamous cell carcinoma, leiomyosarcoma, stomach cancer, carcinoma, pancreas cancer, ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vasoactive intestinal peptide tumors (VIPoma), Kaposi's sarcoma, leiomyoma, hemangioma, neurofibroma, tubular adenoma, villous adenoma, hamartoma, genitourinary tract cancer, Wilm's tumor, nephroblastoma, leukemia, urethra cancer, transitional cell carcinoma, testis cancer, seminoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, interstitial cell carcinoma, fibroadenoma, adenomatoid tumors, hepatoma, hepatocellular carcinoma, cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, gall

- bladder carcinoma, ampullary carcinoma, bone cancer, osteogenic sarcoma, osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma, reticulum cell sarcoma, multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma, osteocartilaginous exostoses, benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma, giant cell tumors, nervous system cancer, skull cancer, granuloma, xanthoma, osteitis deformans, meningioma, meningiosarcoma, gliomatosis, brain cancer, astrocytoma, medulloblastoma, glioma, ependymoma, germinoma, pinealoma, glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors, spinal cord neurofibroma, neurofibromatosis type 1, gynecological cancer, uterus cancer, endometrial carcinoma, uterine carcinoma, uterine corpus endometrial carcinoma, pre-tumor cervical dysplasia, ovarian carcinoma, serous cystadenocarcinoma, mucinous cystadenocarcinoma, granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma, intraepithelial carcinoma, clear cell carcinoma, botryoid sarcoma, embryonal rhabdomyosarcoma, fallopian tubes carcinoma, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, myelodysplastic syndrome, Hodgkin's disease, non-Hodgkin's lymphoma, malignant melanoma, basal cell carcinoma, moles dysplastic nevi, dermatofibroma, keloids and neuroblastoma.
60. A method of degrading a target protein in a subject comprising administering to the subject in need thereof, a therapeutically effective amount of the compound according to any one of claims 1 to 54 or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.
61. The method of claim 60, wherein the target protein is KRAS.
62. The method of claim 60, wherein the target protein is KRAS G12A, KRAS G12C, KRAS G12D, KRAS G12R, KRAS G12S, KRAS G12V, KRAS G13D or KRAS Q61H.
63. A method of treating a disease or a disorder dependent upon KRAS in a subject comprising administering to the subject in need thereof, a therapeutically effective amount of a compound according to any one of claims 1 to 54 or a pharmaceutically acceptable salt or a stereoisomer or a tautomer thereof.

64. The method of claim 63, wherein the disease or disorder dependent upon KRAS is a cancer selected from the group consisting of biliary tract malignancies, colon cancer, liver cancer, colorectal cancer, non-small cell lung cancer, small-cell lung cancer, pancreatic cancer, appendiceal cancer, melanoma, acute myeloid leukemia, small
5 bowel cancer, ampullary cancer, germ cell cancer, cervical cancer, cancer of unknown primary origin, endometrial cancer, esophagogastric cancer, GI neuroendocrine cancer, ovarian cancer, sex cord stromal tumor cancer, hepatobiliary cancer, bladder cancer, lung cancer, prostate cancer, breast cancer, cervical carcinomas, testicular carcinomas, gastric cancer, head and neck cancer, hepatocellular cancer, laryngeal cancer, oral
10 cancer, thyroid carcinomas, sarcomas, cardiac cancer, angiosarcoma, rhabdomyosarcoma, liposarcoma, myxoma, rhabdomyoma, fibroma, lipoma, teratoma, bronchogenic carcinoma, undifferentiated small cell cancer, adenocarcinoma, alveolar carcinoma, bronchiolar carcinoma, bronchial adenoma, lymphoma, chondromatous hamartoma, mesothelioma, gastrointestinal cancer, squamous cell carcinoma,
15 leiomyosarcoma, stomach cancer, carcinoma, pancreas cancer, ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, VIPoma, adenocarcinoma, Kaposi's sarcoma, leiomyoma, hemangioma, neurofibroma, tubular adenoma, villous adenoma, hamartoma, genitourinary tract cancer, Wilm's tumor, nephroblastoma, leukemia, urethra cancer, transitional cell carcinoma, testis cancer, seminoma,
20 embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroadenoma, adenomatoid tumors, hepatoma, hepatocellular carcinoma, cholangiocarcinoma, hepatoblastoma, hepatocellular adenoma, gall bladder carcinoma, ampullary carcinoma, bone cancer, osteogenic sarcoma, osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, reticulum cell
25 sarcoma, multiple myeloma, malignant giant cell tumor chordoma, osteochondroma, osteochondrogenous exostoses, benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma, giant cell tumors, nervous system cancer, skull cancer, granuloma, xanthoma, osteitis deformans, meningioma, meningiosarcoma, gliomatosis, brain cancer, astrocytoma, medulloblastoma, glioma, ependymoma,
30 germinoma, pinealoma, glioblastoma multiforme, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors, spinal cord neurofibroma, neurofibromatosis type I, gynecological cancer, uterus cancer, endometrial carcinoma, uterine carcinoma, uterine corpus endometrial carcinoma, pre-tumor cervical dysplasia, ovarian carcinoma, serous cystadenocarcinoma, mucinous cystadenocarcinoma, granulosa

- 5 thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma, intraepithelial carcinoma, clear cell carcinoma, botryoid sarcoma, embryonal rhabdomyosarcoma, fallopian tubes carcinoma, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, myelodysplastic syndrome, Hodgkin's disease, non-Hodgkin's lymphoma, malignant lymphoma, malignant melanoma, basal cell carcinoma, moles dysplastic nevi, dermatofibroma, keloids and neuroblastoma.
65. The method of claim 64, wherein the cancer is pancreatic cancer.
66. The method of claim 64, wherein the cancer is lung cancer and non-small cell lung
10 cancer.
67. A compound of claims 1 to 54, for use as a medicament.
68. A compound according to any one of claims 1 to 54, for use in the treatment of a disease or disorder dependent upon KRAS, wherein the disease or disorder dependent upon KRAS is a cancer.
- 15 69. A compound according to any one of claims 1 to 54, for use in the treatment of a disease or disorder dependent upon KRAS G12A, KRAS G12C, KRAS G12D, KRAS G12R, KRAS G12S, KRAS G12V, KRAS G13D or KRAS Q61H.
70. Use of a compound of formula (I) or a pharmaceutical acceptable salt or a stereoisomer or a tautomer thereof according to any one of claims 1 to 54, in the manufacture of a
20 medicament for the treatment of a disease or disorder dependent upon KRAS; wherein the disease or disorder is a cancer selected from the group consisting of biliary tract malignancies, colon cancer, liver cancer, colorectal cancer, non-small cell lung cancer, small-cell lung cancer, pancreatic cancer, appendiceal cancer, melanoma, acute myeloid leukemia, small bowel cancer, ampullary cancer, germ cell cancer, cervical
25 cancer, cancer of unknown primary origin, endometrial cancer, esophagogastric cancer, GI neuroendocrine cancer, ovarian cancer, sex cord stromal tumor cancer, hepatobiliary cancer, bladder cancer, lung cancer, prostate cancer, breast cancer, cervical carcinomas, testicular carcinomas, gastric cancer, head and neck cancer, hepatocellular cancer, laryngeal cancer, oral cancer, thyroid carcinomas, sarcomas, cardiac cancer, angiosarcoma, rhabdomyosarcoma, liposarcoma, myxoma, rhabdomyoma, fibroma,
30 lipoma, teratoma, bronchogenic carcinoma, undifferentiated small cell cancer,

adenocarcinoma, alveolar carcinoma, bronchiolar carcinoma, bronchial adenoma,
lymphoma, chondromatous hamartoma, mesothelioma, gastrointestinal cancer,
squamous cell carcinoma, leiomyosarcoma, stomach cancer, carcinoma, pancreas
cancer, ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid
tumors, VIPoma, adenocarcinoma, Kaposi's sarcoma, leiomyoma, hemangioma,
neurofibroma, tubular adenoma, villous adenoma, hamartoma, genitourinary tract
cancer, Wilm's tumor, nephroblastoma, leukemia, urethra cancer, transitional cell
carcinoma, testis cancer, seminoma, embryonal carcinoma, teratocarcinoma,
choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroadenoma, adenomatoid
tumors, hepatoma, hepatocellular carcinoma, cholangiocarcinoma, hepatoblastoma,
hepatocellular adenoma, gall bladder carcinoma, ampullary carcinoma, bone cancer,
osteogenic sarcoma, osteosarcoma, fibrosarcoma, malignant fibrous histiocyto-
ma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma, reticulum cell sarcoma,
multiple myeloma, malignant giant cell tumor chordoma, osteochondroma,
osteochondrogenic exostoses, benign chondroma, chondroblastoma,
chondromyxofibroma, osteoid osteoma, giant cell tumors, nervous system cancer, skull
cancer, granuloma, xanthoma, osteitis deformans, meningioma, meningiosarcoma,
gliomatosis, brain cancer, astrocytoma, medulloblastoma, glioma, ependymoma,
germinoma, pinealoma, glioblastoma multiforme, oligodendroglioma, schwannoma,
retinoblastoma, congenital tumors, spinal cord neurofibroma, neurofibromatosis type
I, gynecological cancer, uterus cancer, endometrial carcinoma, uterine carcinoma,
uterine corpus endometrial carcinoma, pre-tumor cervical dysplasia, ovarian
carcinoma, serous cystadenocarcinoma, mucinous cystadenocarcinoma, granulosa-
thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma,
intraepithelial carcinoma, clear cell carcinoma, botryoid sarcoma, embryonal
rhabdomyosarcoma, fallopian tubes carcinoma, chronic myeloid leukemia, acute
lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases,
myelodysplastic syndrome, Hodgkin's disease, non-Hodgkin's lymphoma, malignant
melanoma, basal cell carcinoma, moles dysplastic nevi, dermatofibroma, keloids and
neuroblastoma.